Cyclodextrins as excipients in solid oral dosage forms

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To my Parents, 
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Publications

This section presents all publications published within the scope of the Doctoral Thesis.

- **Articles published in international peer-reviewed journals**


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- Communications in international congresses

1. Jaime Conceição. Helena Maria Cabral-Marques, José Manuel Sousa Lobo. Cyclodextrins in tablet and capsule formulations. In: 5th European Conference on Cyclodextrins (EUROCD 2017) held at the Faculty of Pharmacy of the University of Lisbon, from 3 to 6 October 2017. (abstract and poster presentation)

2. Jaime Conceição, Oluwatomiode Adeoye, Helena Maria Cabral-Marques, José Manuel Sousa Lobo. Hydroxypropyl-β-cyclodextrin and β-cyclodextrin as tablet direct compression fillers. In: 29th International Carbohydrate Symposium (ICS 2018) held at the Faculty of Sciences of the University of Lisbon, from 14 to 19 July 2018. (abstract, flash communication and poster presentation)

3. Jaime Conceição, Oluwatomiode Adeoye, Helena Cabral-Marques, José Manuel Sousa Lobo. Cyclodextrins, Pharmaceutical Technology and Medicinal Products. In: 1st International Congress on the History of Science in Education held at the University of Trás-os-Montes and Alto Douro (UTAD), on 30 and 31 May and 1 June 2019. (abstract and oral communication)


7. **Jaime Conceição**, Oluwatomide Adeoye, Helena Cabral-Marques, Angel Concheiro, Carmen Alvarez-Lorenzo, José Manuel Sousa Lobo. Hydrophilic and hydrophobic cyclodextrins as excipients in quick/slow release bilayer tablets. In: 20th International Cyclodextrin Symposium (ICS2020), Giardini Naxos, Italy, May 26-29, 2020. (abstract (**Appendix II**) and short presentation accepted for publication; due to the ongoing spread of Corona (SARS-CoV-2) virus, the Meeting was postponed to 7 to 10 June, 2021)

- Communications in national congresses

1. **Jaime Conceição**, Helena Maria Cabral-Marques, José Manuel Sousa Lobo. Cyclodextrins in drug delivery systems: Pharmaceutical applications. In: 9th iMed.ULisboa and 2nd i3DU Postgraduate Students Meeting held at the Faculty of Pharmacy of the University of Lisbon, on 13 and 14 July 2017. (abstract and poster presentation)
2. **Jaime Conceição**, Helena Maria Cabral-Marques, José Manuel Sousa Lobo. Cyclodextrins in drug delivery systems: Methods to enhance complexation efficiency and regulatory aspects. In: 12th National Meeting (Glupor-12) of the Group of Carbohydrates of the Portuguese Chemistry Society held at the University of Aveiro, from 11 to 13 September 2017. (abstract and poster presentation)

3. **Jaime Conceição**, Oluwatomi Adeoye, Helena Maria Cabral-Marques, José Manuel Sousa Lobo. Cyclodextrins as non-complexing excipients of the tablets. In: 10th iMed.ULisboa Postgraduate Students Meeting and 3rd i3DU Meeting held at the Faculty of Pharmacy of the University of Lisbon, on July 24 and 25, 2018. (abstract and poster presentation)

4. **Jaime Conceição**, Oluwatomi Adeoye, Helena Maria Cabral-Marques, José Manuel Sousa Lobo. Oral solid formulations containing cyclodextrins as excipients. In: Annual Meeting of the Applied Molecular Biosciences Unit-UCIBIO held at the Faculty of Sciences and Technology of NOVA University of Lisbon (FCT NOVA), on September 28 and 29, 2018. (flash communication and poster presentation)

5. **Jaime Conceição**, Xián Farto-Vaamonde, Alvaro Goyanes, Oluwatomi Adeoye, Ángel Concheiro, Helena Cabral-Marques, José Manuel Sousa Lobo, Carmen Alvarez-Lorenzo. Formulation of fast-disintegrating 3D printed tablets of carbamazepine containing hydroxypropyl-β-cyclodextrin and cellulose ethers as excipients. In: 11th iMed.ULisboa Postgraduate Students Meeting and 4th i3DU Meeting held at the Faculty of Pharmacy of the University of Lisbon, on July 15, 2019. (abstract and poster presentation)
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Abstract

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic central cavity that present several industrial applications. As far as Pharmaceutical Technology is concerned, these compounds are mainly used by the formulation scientists as multifunctional excipients to improve certain properties of drugs such as low in vitro dissolution, low bioavailability and unpleasant taste.

In this Thesis, cyclodextrins were used as complexing and non-complexing excipients in four types of tablet formulations, i.e., in uncoated tablets, three-dimensional (3D) printed tablets, orodispersible tablets and bilayer tablets. Three cyclodextrins were studied, namely β-cyclodextrin, hydroxypropyl-β-cyclodextrin and triacetyl-β-cyclodextrin. In addition, carbamazepine, an antiepileptic and anticonvulsant agent, was used as a model of a poorly soluble drug with poor flowability.

Concerning the uncoated tablets, the ability of hydroxypropyl-β-cyclodextrin and β-cyclodextrin to act as tablet fillers for direct compression was studied evaluating their flow properties, compaction behaviour by using an instrumented alternative tableting machine, and the influence on carbamazepine release characteristics. Moreover, these properties of the cyclodextrins were compared with those from other commonly used direct compression fillers. The obtained results highlighted that: i) the studied cyclodextrins can be used as tablet fillers for direct compression; ii) hydroxypropyl-β-cyclodextrin showed better properties than β-cyclodextrin mainly at the level of the physics of compression (higher values of plasticity index and lubrication efficiency) and of the drug release characteristics (faster and greater dissolution rate and shorter disintegration time); and iii) lactose monohydrate and hydroxypropyl-β-cyclodextrin displayed the best results. As there are people intolerant to lactose, hydroxypropyl-β-cyclodextrin, although its cost is higher, can be considered a good substitute for lactose.

3D printed tablets (also named printlets) are innovative solid dosage forms comprising several therapeutic and technological advantages. Taking these features into consideration, the feasibility of using cyclodextrins to prepare for the first time orodispersible and immediate release 3D printed tablets was explored via semisolid extrusion of wet masses of hydroxypropyl-β-cyclodextrin, carbamazepine and cellulose ethers (hydroxypropyl methylcellulose and croscarmellose sodium). Four main conclusions were obtained: i) hydroxypropyl-β-cyclodextrin was used for the first time to prepare 3D printed formulations (printlets); ii) micro-extrusion 3D printing was revealed as an innovative approach to in situ formation of carbamazepine/hydroxypropyl-β-cyclodextrin complexes; iii) orodispersible and immediate release printlets were successfully prepared with suitable physical and drug release properties for oral delivery; and iv) small changes in cellulose ethers ratio allowed fine tuning of drug release profile.
The development of orodispersible tablets for poorly soluble and poorly flowable drugs via direct compression is still a formulation challenge. In this way, orodispersible tablets of carbamazepine were developed by combining hydroxypropyl-β-cyclodextrin that form inclusion complexes to improve wetting and release properties, and directly-compressible five-in-one co-processed excipients (Prosolv® ODT G2 and F-Melt® type C) able to promote rapid disintegration and solve the poor flowability typical of inclusion complexes. The obtained results showed that orodispersible tablets containing carbamazepine/hydroxypropyl-β-cyclodextrin complex can be prepared by direct compression through the addition of co-processed excipients. The simultaneous use of co-processing and cyclodextrin technologies rendered orodispersible tablets with an in vitro disintegration time in accordance with the European Pharmacopoeia requirement and with a fast and complete drug dissolution. Therefore, the combination of hydrophilic cyclodextrins and five-in-one co-processed excipients may help addressing the orodispersible tablets formulation of poorly soluble drugs with poor flowability, by direct compression and with the desired release properties.

In the last experimental section, the combination of hydrophilic and hydrophobic cyclodextrins to prepare bilayer tablets that can perform as quick/slow biphasic release systems of carbamazepine was studied. This formulation approach is of particular interest for treatments that require a rapid action followed by sustained therapeutic levels. Hydroxypropyl-β-cyclodextrin was chosen as complexing agent in the rapid release layer. Differently, triacetyl-β-cyclodextrin was tested as controlling release agent in the sustained release layer. Furthermore, croscarmellose sodium was utilized as superdisintegrant in the rapid release layer, and sodium stearyl fumarate was applied as anti-adherent lubricant in both layers. The results highlighted the feasibility of the combination of carbamazepine/hydroxypropyl-β-cyclodextrin inclusion complex with croscarmellose sodium in the rapid release layer to achieve fast dissolution for the first 30-45 min, and triacetyl-β-cyclodextrin as controlling release agent in the sustained release layer of the bilayer tablets to obtain a prolonged release during 720 min. On this wise, combinations of hydrophilic and hydrophobic cyclodextrins may help addressing the formulation of poorly soluble drugs in bilayer tablets as fast/slow biphasic release systems.

In conclusion, the outcomes obtained in this Thesis showed that cyclodextrins are multifunctional excipients in 3D printed tablets, orodispersible tablets and bilayer tablets. Additionally, these compounds can act as tablet fillers for direct compression.

**Keywords:** β-cyclodextrin; hydroxypropyl-β-cyclodextrin; triacetyl-β-cyclodextrin; carbamazepine; tablet formulation.
Resumo

As ciclodextrinas são oligossacáridos cíclicos, com uma superfície externa hidrófila e uma cavidade central hidrófoba, que apresentam diversas aplicações industriais. No que diz respeito à Tecnologia Farmacêutica, estes compostos são utilizados principalmente pelos cientistas de formulação como excipientes para melhorar determinadas propriedades dos fármacos como, por exemplo, a baixa dissolução in vitro, a baixa biodisponibilidade e o sabor desagradável.

Nesta Tese, as ciclodextrinas foram utilizadas como excipientes complexantes e não complexantes em quatro tipos de comprimidos, a saber, comprimidos não revestidos, comprimidos obtidos por impressão 3D, comprimidos orodispersíveis e comprimidos de dupla camada. Estudaram-se três ciclodextrinas, designadamente a β-ciclodextrina, a hidroxipropil-β-ciclodextrina e a triacetil-β-ciclodextrina. Adicionalmente, a carbamazepina, um agente antiepilético e anticonvulsivante, foi utilizada como modelo de um fármaco pouco solúvel com más propriedades de escoamento.

Em relação aos comprimidos não revestidos, estudou-se a aptidão da hidroxipropil-β-ciclodextrina e da β-ciclodextrina de atuarem como diluentes de compressão direta, avaliando as suas propriedades de escoamento, comportamento durante a compactação através de uma máquina de compressão alternativa instrumentada, e a influência nas características de libertação da carbamazepina. Além disso, estas propriedades das ciclodextrinas foram comparadas com as de outros diluentes de compressão direta muito utilizados. Os resultados obtidos evidenciaram que: i) as ciclodextrinas estudadas podem ser utilizadas como diluentes de compressão direta; ii) a hidroxipropil-β-ciclodextrina apresentou melhores propriedades do que a β-ciclodextrina, principalmente ao nível da física da compressão (valores mais elevados de índice de plasticidade e de eficácia de lubrificação) e das características de libertação do fármaco (dissolução mais rápida e superior, e menor tempo de desagregação); e iii) a lactose mono-hidratada e a hidroxipropil-β-ciclodextrina apresentaram os melhores resultados. Como existem pessoas intolerantes à lactose, a hidroxipropil-β-ciclodextrina, apesar do seu preço superior, pode ser considerada um bom substituto para a lactose.

Os comprimidos obtidos por impressão 3D são formas farmacêuticas sólidas inovadoras que apresentam diversas vantagens terapêuticas e tecnológicas. Com base nestas potencialidades, investigou-se a viabilidade do uso de ciclodextrinas para preparar pela primeira vez comprimidos orodispersíveis e de libertação imediata obtidos por impressão 3D por extrusão semissólida de massas húmidas de hidroxipropil-β-ciclodextrina, carbamazepina e éteres de celulose (hidroxipropilmetilcelulose e croscarmelose sódica). Quatro conclusões principais foram obtidas: i) a hidroxipropil-β-ciclodextrina foi utilizada pela primeira vez para preparar comprimidos obtidos por impressão 3D; ii) a impressão 3D por extrusão semissólida foi revelada como uma abordagem inovadora para a formação in situ de complexos de inclusão de carbamazepina/hidroxipropil-β-ciclodextrina; iii) os comprimidos orodispersíveis e de libertação imediata obtidos por impressão 3D apresentaram propriedades físicas e de libertação do fármaco adequadas para a administração oral; e iv) pequenas alterações na proporção dos éteres de celulose permitiram ajustar adequadamente o perfil de dissolução do fármaco.
O desenvolvimento de comprimidos orodispersíveis por compressão direta, contendo fármacos pouco solúveis e com más propriedades de escoamento, ainda constitui um desafio de formulação. Assim, desenvolveram-se comprimidos orodispersíveis de carbamazepina combinando a hidroxipropil-β-ciclodextrina, capaz de formar complexos de inclusão de modo a melhorar as propriedades de molhabilidade e de libertação do fármaco, e excipientes coprocessados cinco-em-um de compressão direta (Prosolv® ODT G2 e F-Melt® tipo C) capazes de promover uma desagregação rápida e de melhorar o mau escoamento típico dos complexos de inclusão. Os resultados obtidos mostraram que os comprimidos orodispersíveis, contendo o complexo de inclusão carbamazepina/hidroxipropil-β-ciclodextrina, podem ser preparados por compressão direta através da adição dos excipientes coprocessados. O uso simultâneo de excipientes coprocessados e de ciclodextrinas permitiu preparar comprimidos orodispersíveis com um tempo de desagregação in vitro de acordo com o requisito da Farmacopeia Europeia e com uma rápida e completa dissolução do fármaco. Deste modo, a combinação de ciclodextrinas hidrófilas e excipientes coprocessados cinco-em-um poderá ajudar na formulação de comprimidos orodispersíveis, contendo fármacos pouco solúveis com más propriedades de escoamento, por compressão direta e com as características de libertação desejadas.

Na última parte experimental, explorou-se a combinação de ciclodextrinas hidrófilas e hidrófobas para preparar comprimidos de dupla camada capazes de atuarem como sistemas de libertação bifásica rápida/lenta de carbamazepina. Esta abordagem de formulação é de particular interesse para tratamentos que requerem uma ação rápida seguida de níveis terapêuticos prolongados. A hidroxipropil-β-ciclodextrina foi utilizada como agente complexante na camada de libertação rápida. De modo diferente, a triacetil-β-ciclodextrina foi testada como agente modulador da libertação na camada de libertação prolongada. Ademais, a croscarmelose sódica foi utilizada como superdesagregante na camada de libertação rápida, e o fumarato de estearilo e sódio foi testado como lubrificante antiaderente nas duas camadas. Os resultados evidenciaram a viabilidade: i) da combinação do complexo de inclusão carbamazepina/hidroxipropil-β-ciclodextrina com a croscarmelose sódica na camada de libertação rápida para se obter uma dissolução rápida durante os primeiros 30-45 minutos; e ii) da triacetil-β-ciclodextrina como agente modulador da libertação na camada de libertação prolongada dos comprimidos de dupla camada para se alcançar uma libertação do fármaco durante 720 minutos. Desta forma, a combinação de ciclodextrinas hidrófilas e hidrófobas poderá ajudar na formulação de comprimidos de dupla camada como sistemas de libertação bifásica rápida/lenta de fármacos pouco solúveis.

Em suma, os resultados obtidos nesta Tese demonstraram que as ciclodextrinas são excipientes multifuncionais em comprimidos obtidos por impressão 3D, comprimidos orodispersíveis e comprimidos de dupla camada. Além disso, estes compostos podem ser utilizados como diluentes de compressão direta dos comprimidos.

**Palavras-chave:** β-ciclodeextrina; hidroxipropil-β-ciclodeextrina; triacetil-β-ciclodeextrina; carbamazepina; formulação de comprimidos.
Graphical abstract

Fillers for direct compression

Bilayer tablets

Cyclodextrins as excipients in tablet formulations

3D printed tablets

Orodispensible tablets
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1. INTRODUCTION

This Doctoral Thesis in Pharmaceutical Sciences - Pharmaceutical Technology Speciality, entitled “Cyclodextrins as excipients in solid oral dosage forms”, is divided into four main chapters, namely:

i) Introduction, where the outline and main goals of the Thesis are presented;

ii) Cyclodextrins, which contains two published review manuscripts concerning the theoretical background of the Thesis theme;

iii) Experimental Section, where four research manuscripts published are described;

iv) and Conclusion, which integrates all the obtained results as well as their relevance in the pharmaceutical field.

This Thesis aimed to study and explore the applications of cyclodextrins as excipients in solid oral dosage forms. Tablets were studied as a model of a solid oral dosage form, since they are the most used dosage form in therapy mainly due to their good stability and accurate dosing. Therefore, the following six specific objectives were established:

i) to perform a state of the art review concerning the cyclodextrins as drug carriers in Pharmaceutical Technology highlighting their history, properties and pharmaceutical applications with typical examples;

ii) to carry out a critical review of cyclodextrins as excipients in tablet formulations emphasising their principal pharmaceutical applications, the most relevant technological aspects in pharmaceutical formulation development and their actual regulatory status;

iii) to study the ability of cyclodextrins to act as tablet fillers (non-complexing excipients) for direct compression, evaluating their flow properties, compaction behaviour and the influence on drug release characteristics from uncoated tablets;

iv) to explore for the first time the use of cyclodextrins to prepare three-dimensional (3D) printed tablets (printlets) of poorly soluble drugs via semisolid extrusion;

v) to develop orodispersible tablets of poorly soluble drugs via direct compression by combining cyclodextrins that form inclusion complexes to improve wetting and release properties, and directly-compressible five-in-one co-processed excipients able to promote rapid disintegration and solve the poor flowability typical of inclusion complexes;

vi) and to investigate the combination of hydrophilic and hydrophobic cyclodextrins to prepare bilayer tablets that can perform as quick/slow biphasic release systems of a poorly soluble drug.

In order to achieve these goals, three cyclodextrins were tested, specifically β-cyclodextrin, hydroxypropyl-β-cyclodextrin and triacetyl-β-cyclodextrin. In addition, carbamazepine (C₁₁₃H₁₂₂N₂O), an antiepileptic and anticonvulsant agent, was used as a model of a poorly soluble drug with poor flowability.
2. CYCLODEXTRINS

2.1. Cyclodextrins as drug carriers in Pharmaceutical Technology: The state of the art
2.1.1. Abstract

**Background:** Cyclodextrins (CDs) are versatile excipients with an essential role in drug delivery, as they can form non-covalently bonded inclusion complexes (host-guest complexes) with several drugs either in solution or in the solid state.

**Methods:** The main purpose of this publication was to carry out a state of the art of CDs as complexing agents in drug carrier systems. In this way, the history, properties, and pharmaceutical applications of the CDs were highlighted with typical examples. The methods to enhance the complexation efficiency (CE) and the CDs applications in solid dosage forms were emphasized in more detail.

**Results:** The main advantages of using these cyclic oligosaccharides are as follows: i) to enhance solubility/dissolution/ bioavailability of poorly soluble drugs; ii) to enhance drug stability; iii) to modify the drug release site and/or time profile; and iv) to reduce drug side effects (for example, gastric or ocular irritation). These compounds present favourable toxicological profile for human use and therefore there are various medicinal products containing CDs approved by regulatory authorities worldwide. On the other hand, the major drawback of CDs is the increase in formulation bulk, once the CE is, in general, very low. This aspect is particularly relevant in solid dosage forms and limits the use of CDs to potent drugs.

**Conclusion:** CDs have great potential as drug carriers in Pharmaceutical Technology and can be used by the formulator in order to improve the drug properties such as solubility, bioavailability and physico-chemical stability. Additionally, recent studies have shown that these compounds can be applied as active pharmaceutical ingredients.

**Keywords:** cyclodextrins; complexation; drug carriers; solid dosage forms; dissolution; bioavailability.
2.1.2. Introduction

With the view to select the best drug candidates for development, physicochemical criteria such as solubility, chemical and physical stability, hygroscopicity, and thermal characteristics need to be studied as soon as possible and balanced against other important parameters such as Pharmacology or Pharmacokinetics (1-3).

The Biopharmaceutics Classification System (BCS), proposed by Amidon and his collaborators (4), is an important tool in the pharmaceutical field that classifies drugs in four classes according to their water solubility and intestinal permeability (Fig. 1) (4, 5). The poor oral bioavailability arising from poor water solubility (class 2 and 4 drugs of the BCS) should make drug development harder (6). According to the literature, up to 75% of new candidates in drug development have low solubility (7, 8), and around 40% of the marketed drugs are poorly soluble (9, 10).

The need for solubility enhancement through formulation is a well-known but still problematic issue (11-13), because drugs with low aqueous solubility are prone to low and variable oral bioavailability and, hence, to variability in therapeutic effect (13). The drugs that have water solubility less than 10 mg/mL (over the pH range of 1 - 7 at 37 °C) show the potential bioavailability problems (14). Currently, there are several approaches that are utilized to improve the solubility of poorly water-soluble drugs, such as: i) pH modification and salt forms (15, 16); ii) co-solvency and surfactant solubilisation (17, 18); iii) amorphous forms, solid dispersions, and cocrystals (19, 20); iv) polymeric micelles (21, 22); v) size reduction and nanonization (10, 14); vi) solid lipid nanoparticles (23, 24); vii) liposomes and proliposomes (25, 26); viii) microemulsions and self-emulsifying drug delivery systems (27, 28); and ix) cyclodextrin (CD) complexation (29, 30).

![Fig. 1. Biopharmaceutics Classification System. Adapted from (4).]
CDs are cyclic oligosaccharides largely used as "molecular capsules" in the pharmaceutical (31, 32), cosmetic (33, 34), chemical (35, 36), food (37-39), textile (40, 41), agricultural (42), and environmental (43, 44) industries/fields. In the pharmaceutical area, these compounds are mainly used as excipients in order to solubilize several poorly soluble drugs through the formation of water-soluble drug-CD complexes (45). In addition, CDs complexation generally improves physico-chemical stability, reduces the side effects (for instance, gastric or ocular irritation) or reduces or eliminates unpleasant taste and odour, prevents drug-drug interactions, and converts liquid drugs into powders (29, 46-49). These excipients have great potential and are used in drug delivery systems for oral, parenteral, dermal, ocular, buccal and sublingual, rectal, nasal, and pulmonary drug delivery (46).

The main purpose of this publication was to carry out a state of the art of CDs as complexing agents in drug carrier systems. In this way, the history, properties, and pharmaceutical applications of the CDs were highlighted with typical examples. The methods to enhance the complexation efficiency (CE) and the CDs applications in solid dosage forms were emphasized in more detail.

2.1.3. Cyclodextrins
2.1.3.1. Historical perspective

Although CDs are considered by scientists and regulators as a new group of excipients, they have been reported in literature more than one hundred years ago (50). CDs were first isolated by Antoine Villiers (1854-1932) in 1891 as a digest of *Bacillus amylobacter* on potato starch, and the main events of their history are shown in Table I.

CDs are cyclic carbohydrates formed during the bacterial (*Bacillus macerans*) degradation of starch by CD glucosyltransferase enzyme (CGTase), and they present a hydrophilic outer surface and a hydrophobic central cavity that can trap or encapsulate other molecules (Fig. 2) (14, 51, 52).

According to Grégorio Crini (52), the CDs history can be divided into five quite distinct periods, namely: i) the first period, from 1891 to 1911, covers their discovery by Antoine Villiers and characterization by Franz Schardinger; ii) from 1911 to 1935 came a period of doubt and disagreement, in particular between the laboratories of Hans Pringsheim and of Paul Karrer; iii) the third period, from 1935 to 1950, was marked by the results obtained by Karl Freudenberg, and Dexter French; iv) the period of exploration between 1950 and 1970 focused on inclusion complexes with the work of Friedrich Cramer in the forefront; and v) the period of utilization has been in progress since 1970 and CDs found numerous industrial applications.
Table I. Historical perspective of CDs and achievements.

<table>
<thead>
<tr>
<th>Year</th>
<th>Occurrence</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>1891</td>
<td>Villiers published his discovery of cellulose (cyclodextrin)</td>
<td>(53)</td>
</tr>
<tr>
<td>1903</td>
<td>Schardinger isolated and purified α- and β-CDs</td>
<td>(54)</td>
</tr>
<tr>
<td>1911</td>
<td>Schardinger did lay the foundation of CD chemistry</td>
<td>(55)</td>
</tr>
<tr>
<td>1924</td>
<td>Methylination of CDs first described</td>
<td>(32)</td>
</tr>
<tr>
<td>1935</td>
<td>Freudenberg and Jacobi discovered γCD</td>
<td>(56)</td>
</tr>
<tr>
<td>1935-1955</td>
<td>Research on structure and function of CDs complexes by Freudenberg, Cramer, French, Rundle, Saenger, Bender, and Breslow</td>
<td>(57-60)</td>
</tr>
<tr>
<td>1953</td>
<td>The first CD patent was issued in Germany to Freudenberg, Cramer, and Plieninger</td>
<td>(61)</td>
</tr>
<tr>
<td>1954</td>
<td>Cramer’s book on inclusion complexes was published</td>
<td>(62)</td>
</tr>
<tr>
<td>1957-1965</td>
<td>glucose units. First fundamental review on CDs containing first misinformation on toxicity of CD was published</td>
<td>(63, 64)</td>
</tr>
<tr>
<td>1960-1970</td>
<td>First analytical methods of CDs were developed</td>
<td>(65)</td>
</tr>
<tr>
<td>1965</td>
<td>Higuchi and Connors published their article about phase-solubility profiles</td>
<td>(66, 67)</td>
</tr>
<tr>
<td>1969</td>
<td>Launch DDS Research Institute of ALZA Co. in Kansas University</td>
<td>(68)</td>
</tr>
<tr>
<td>1975</td>
<td>First publication on CD polymers by M. Furu</td>
<td>(29, 69)</td>
</tr>
<tr>
<td>1976</td>
<td>Manufacturing of natural CDs using alkaline CGTase in Japan</td>
<td>(68)</td>
</tr>
<tr>
<td>1976</td>
<td>Approval in Japan of the first pharmaceutical product with PGE2/βCD (Prostarmon E™ sublingual tablets)</td>
<td>(31, 32, 70)</td>
</tr>
<tr>
<td>1978</td>
<td>Approval of natural CDs as food additives in Japan</td>
<td>(68)</td>
</tr>
<tr>
<td>1981</td>
<td>First International CD Symposium organized in Budapest (Hungary)</td>
<td>(71)</td>
</tr>
<tr>
<td>1981</td>
<td>First CD book is published</td>
<td>(29)</td>
</tr>
<tr>
<td>1983-1985</td>
<td>Braun and Müller (Europe) and Pitha (USA) filed for patents on hydroxypropyl-β-CD</td>
<td>(32)</td>
</tr>
<tr>
<td>1983</td>
<td>First suggestion of self-association of parent CDs by K. Miyajima</td>
<td>(29, 72)</td>
</tr>
<tr>
<td>1985</td>
<td>The first patent registering the pharmacological benefits of the complexation of analgesics compounds in CDs</td>
<td>(73)</td>
</tr>
<tr>
<td>1987</td>
<td>Approval of benexate HCl/βCD capsules in Japan</td>
<td>(68)</td>
</tr>
<tr>
<td>1988</td>
<td>Approval of piroxicam/βCD tablets (Brexin®) in Europe</td>
<td>(70)</td>
</tr>
<tr>
<td>1990</td>
<td>Stella and Rajewski filed for a patent on sulfobutyl ether-βCD</td>
<td>(32)</td>
</tr>
<tr>
<td>1990</td>
<td>Approval of hydroxypropyl-βCD containing cosmetics in Japan</td>
<td>(68)</td>
</tr>
<tr>
<td>1994</td>
<td>αCD and βCD listed in Japanese Pharmaceutical Excipients</td>
<td>(68)</td>
</tr>
<tr>
<td>1997</td>
<td>Approval of itraconazole/hydroxypropyl-βCD oral solution (Sporanox®) in United States</td>
<td>(74)</td>
</tr>
<tr>
<td>1997</td>
<td>Founding of CD Society in Japan</td>
<td>(68)</td>
</tr>
<tr>
<td>1997</td>
<td>First monograph on βCD appeared in the European Pharmacopoeia</td>
<td>(75)</td>
</tr>
<tr>
<td>2001</td>
<td>Approval of sulfobutyl ether-βCD containing injections in United States</td>
<td>(68)</td>
</tr>
<tr>
<td>2005</td>
<td>Publication of “Nanomaterial Cyclodextrin”</td>
<td>(68)</td>
</tr>
<tr>
<td>2006</td>
<td>First CD Workshop in Japan</td>
<td>(68)</td>
</tr>
<tr>
<td>2008</td>
<td>Approval of sugammadex (Bridion®) in Europe</td>
<td>(76)</td>
</tr>
<tr>
<td>2010</td>
<td>Approval of sugammadex (Bridion®) in Japan</td>
<td>(76)</td>
</tr>
<tr>
<td>2011</td>
<td>Launch DDS Research Institute of Sojo University (Kumamoto)</td>
<td>(68)</td>
</tr>
<tr>
<td>2015</td>
<td>Approval of sugammadex (Bridion®) in United States</td>
<td>(76)</td>
</tr>
</tbody>
</table>
2.1.3.2. Natural cyclodextrins

The four main chemical groups of carbohydrates are monosaccharides, disaccharides, oligosaccharides, and polysaccharides (77). CDs are enzymatically modified starches with a wide range of applications and they are cyclic oligosaccharides, containing a minimum of six D-(+)-glucopyranose units attached by α-1,4-linkages (78,79). They are produced by the action of the CGTase on a medium containing starch (78, 79). CGTase is a unique enzyme able of converting starch or starch derivates into CDs via the cyclization reaction (80, 81).

Three native/natural/parent CDs available on the market are alpha-cyclodextrin (αCD), beta-cyclodextrin (βCD), and gamma-cyclodextrin (γCD), consisting of 6, 7 and 8 glucose units respectively (Fig. 3, Table II) (82). These compounds are crystalline, homogeneous, and non-hygroscopic substances (71).

![Fig. 2. CDs structural characteristics. Adapted from (31).](image)

![Fig. 3. Chemical structures of the CDs monomer (A) and βCD (B). Adapted from (50).](image)
<table>
<thead>
<tr>
<th></th>
<th>αCD</th>
<th>βCD</th>
<th>γCD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of glucose units</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>(71)</td>
</tr>
<tr>
<td>Chemical names</td>
<td>Cyclohexaamylose</td>
<td>Cycloheptaamylose</td>
<td>Cyclooctaamylose</td>
<td>(82)</td>
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<tr>
<td></td>
<td>Cyclomaltohexaose</td>
<td>Cyclomaltoheptose</td>
<td>Cyclomaltooctaose</td>
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<td></td>
<td>Alfadex</td>
<td>Betadex</td>
<td>Gammadex</td>
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<tr>
<td>Other names</td>
<td>α-Schardinger dextrin</td>
<td>β-Schardinger dextrin</td>
<td>γ-Schardinger dextrin</td>
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<td>CAS Registry Number</td>
<td>10016-20-3</td>
<td>7585-39-9</td>
<td>17465-86-0</td>
<td>(83)</td>
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<tr>
<td>Molecular weight (g/mol)</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
<td>(14)</td>
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<td>Chemical formula</td>
<td>C_{36}H_{60}O_{30}</td>
<td>C_{42}H_{70}O_{35}</td>
<td>C_{48}H_{80}O_{40}</td>
<td>(84)</td>
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<tr>
<td>Physical appearance</td>
<td>White powder</td>
<td>White powder</td>
<td>White powder</td>
<td>(85)</td>
</tr>
<tr>
<td>Odour</td>
<td>Odourless</td>
<td>Odourless</td>
<td>Odourless</td>
<td>(85)</td>
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<tr>
<td>Water solubility (g/100 mL at 25 °C)</td>
<td>14.5</td>
<td>1.85</td>
<td>23.2</td>
<td>(86)</td>
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<td>Water molecules in cavity</td>
<td>6</td>
<td>11</td>
<td>17</td>
<td>(87)</td>
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<tr>
<td>Crystal forms (from water)</td>
<td>Hexagonal plates</td>
<td>Monoclinic parallelograms</td>
<td>Quadratic prisms</td>
<td>(71)</td>
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<tr>
<td>Moisture content (%, w/w)</td>
<td>10.2</td>
<td>13-15</td>
<td>8-18</td>
<td>(88)</td>
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<tr>
<td>Specific rotation [α]_{D} 25 °C</td>
<td>150±0.5</td>
<td>162.5±0.5</td>
<td>177.4±0.5</td>
<td>(71)</td>
</tr>
<tr>
<td>Inner cavity diameter (Å)</td>
<td>4.7-5.3</td>
<td>6.0-6.5</td>
<td>7.5-8.3</td>
<td>(89)</td>
</tr>
<tr>
<td>Outer diameter cavity (Å)</td>
<td>14.6</td>
<td>15.4</td>
<td>17.5</td>
<td>(89)</td>
</tr>
<tr>
<td>Cavity height (Å)</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
<td>(50)</td>
</tr>
<tr>
<td>Cavity volume (Å³)</td>
<td>174</td>
<td>262</td>
<td>427</td>
<td>(80)</td>
</tr>
<tr>
<td>pKa at 25 °C</td>
<td>12.332</td>
<td>12.202</td>
<td>12.081</td>
<td>(90)</td>
</tr>
<tr>
<td>Log P_{octanol/water} at 25 °C</td>
<td>-13</td>
<td>-14</td>
<td>-17</td>
<td>(91)</td>
</tr>
<tr>
<td>Gibbs free energy of dissolution (kJ/mol)</td>
<td>15</td>
<td>20</td>
<td>14</td>
<td>(92)</td>
</tr>
<tr>
<td>Diffusion constant at 40 °C</td>
<td>3.443</td>
<td>3.224</td>
<td>3.000</td>
<td>(90)</td>
</tr>
<tr>
<td>Surface tension (mN/m)</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>(88)</td>
</tr>
<tr>
<td>Hydrogen donors</td>
<td>18</td>
<td>21</td>
<td>24</td>
<td>(91)</td>
</tr>
<tr>
<td>Hydrogen acceptors</td>
<td>30</td>
<td>35</td>
<td>40</td>
<td>(91)</td>
</tr>
<tr>
<td>Melting temperature range (°C)</td>
<td>255-260</td>
<td>255-265</td>
<td>240-245</td>
<td>(93)</td>
</tr>
<tr>
<td>Oral bioavailability in rats</td>
<td>1%</td>
<td>0.6%</td>
<td>0.02%</td>
<td>(94-96)</td>
</tr>
<tr>
<td>Hydrolysis by α-amylase</td>
<td>Negligible</td>
<td>Slow</td>
<td>Fast</td>
<td>(97, 98)</td>
</tr>
<tr>
<td>Current usage</td>
<td>Oral and parenteral formulations</td>
<td>Oral, buccal, rectal, dermal, and ocular formulations</td>
<td>Dermal and oral (food) formulations</td>
<td>(45)</td>
</tr>
</tbody>
</table>
CDs are toroidal compounds with a truncated cone shape possessing secondary hydroxyl groups on the C-2 and C-3 atoms located on one side of the torus (wider side), while the primary hydroxyl groups on C-6 are located on the opposite, narrower side of the torus (99). The CH groups carrying the protons H-1, H-2, and H-4 are located on the outside of the molecule, thus the outer surface of CDs are hydrophilic (99). The interior of the torus presents a much lower polarity than water, then it can be seen as a hydrophobic cavity, which is lined by two rings of CH groups (H-3 and H-5) and by a ring of glucosidic “ether oxygens” (O-4), with H-6 situated near the cavity (100, 101). These properties allow several kinds of drugs (“guests”) to be encased originating non-covalently bonded inclusion complexes (102, 103).

Practical use of natural CDs as drug carriers is limited by their low aqueous solubility, especially that of βCD (104). For example, βCD is about seven-fold less soluble than αCD and fourteen-fold less than γCD (105). This is partially attributed to the formation of internal hydrogen bonds between secondary hydroxyl groups, thereby diminishing the capacity of βCD molecules to create hydrogen bonds with contiguous water molecules (32). γCD has the highest water solubility, largest hydrophobic cavity, and the most favourable toxicological profile (83). However, it is described that this CD in parenteral formulations sometimes forms visible aggregates in aqueous solutions (106).

According to the dimensions, αCD complexes low molecular weight compounds or molecules with aliphatic side chains, βCD complexes aromatics and heterocycles, and γCD can include compounds with high molecular weight like macrocycles and steroids (107, 108).

### 2.1.3.3. Cyclodextrin derivatives

In general, CD derivatives are divided into three groups, namely hydrophilic, hydrophobic, and ionisable (Table III) (68, 104, 109-111). These compounds have been developed with various types of substituents in distinct positions and with several average degrees of substitution to extend physicochemical properties and inclusion ability of natural CDs (48, 65, 112).
### Table III. Characteristics of CDs derivatives. Adapted from (68, 110, 111, 113).

<table>
<thead>
<tr>
<th>Derivative</th>
<th>Abbreviation</th>
<th>Water solubility</th>
<th>Possible use</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrophilic derivatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated βCD</td>
<td></td>
<td>Soluble in cold water</td>
<td>Oral, dermal, mucosal</td>
<td>(114, 115)</td>
</tr>
<tr>
<td>Randomly-methylated-βCD</td>
<td>MEβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,6-di-O-methyl-βCD</td>
<td>DMβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per-O-methyl-βCD</td>
<td>TMβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylated DM-βCD</td>
<td>DMAβCD</td>
<td>Soluble</td>
<td>Parenteral</td>
<td></td>
</tr>
<tr>
<td><strong>Hydroxy alkylated βCD</strong></td>
<td></td>
<td>Soluble</td>
<td>Oral, dermal, parenteral, mucosal</td>
<td>(88, 104, 115-120)</td>
</tr>
<tr>
<td>2-hydroxyethyl-βCD</td>
<td>2-HEβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-hydroxypropyl-βCD</td>
<td>HPβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-hydroxypropyl-βCD</td>
<td>3-HPβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3-dihydroxypropyl-βCD</td>
<td>2,3-DHPβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Branched βCD</strong></td>
<td></td>
<td>Soluble</td>
<td>Oral, mucosal, parenteral</td>
<td>(115, 123, 124)</td>
</tr>
<tr>
<td>Glycosyl-βCD</td>
<td>G1βCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maltosyl-βCD</td>
<td>G2βCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucuronyl-glucosyl-βCD</td>
<td>GUGβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydrophobic derivatives</strong></td>
<td></td>
<td>Insoluble</td>
<td>Oral, parenteral, sustained release of water-soluble drugs</td>
<td>(125-127)</td>
</tr>
<tr>
<td>Alkylated βCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,6-di-O-ethyl-βCD</td>
<td>DEβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per-O-ethyl-βCD</td>
<td>TEβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acylated βCD</td>
<td></td>
<td>Insoluble</td>
<td>Oral, dermal, sustained release of water-soluble drugs</td>
<td>(128)</td>
</tr>
<tr>
<td>per-O-acetyl-βCD</td>
<td>TAβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per-O-butanyloxy-βCD</td>
<td>TBβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per-O-valeryl-βCD</td>
<td>TVβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per-O-octyl-βCD</td>
<td>TOβCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ionisable derivatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anionic βCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-carboxymethyl-O-ethyl-βCD</td>
<td>CMEβCD</td>
<td>Soluble at pH &gt; 4</td>
<td>Oral, dermal, mucosal, delayed release</td>
<td>(129, 130)</td>
</tr>
<tr>
<td>β-CD · sulphate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfoctyl ether-βCD</td>
<td>SBEβCD</td>
<td>Soluble</td>
<td>Oral, mucosal</td>
<td>(131, 132)</td>
</tr>
<tr>
<td>β-CD · phosphate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al · βCD · sulphate</td>
<td></td>
<td>Insoluble</td>
<td>Sustained release</td>
<td></td>
</tr>
<tr>
<td>Octakis-S-(2-carboxyethyl)-octathio-γCD octasodium salt</td>
<td>Sugammadex (Bridion®)</td>
<td>Soluble</td>
<td>Parenteral</td>
<td>(76)</td>
</tr>
<tr>
<td><strong>Cationic βCD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethyl-ammonium-βCD</td>
<td>TMAβCD</td>
<td></td>
<td>Sustained release</td>
<td>(90)</td>
</tr>
<tr>
<td>Drug-CD conjugate</td>
<td></td>
<td></td>
<td>Delayed release (site-specific release)</td>
<td>(90)</td>
</tr>
</tbody>
</table>
Whereas that CDs exhibit eighteen (αCD), twenty-one (βCD), or twenty-four (γCD) substitutable hydroxyl groups, the number of possible derivatives is infinite (133). The derivatizations purpose can be (133): i) to enhance the solubility of the CD derivative (and its complexes); ii) to enhance the fitting and/or the association between the CD and its guest, with simultaneous stabilization of the guest, decreasing its reactivity and mobility; iii) to attach specific (catalytic) groups to the binding site such as in enzyme modelling; or iv) to create insoluble, immobilized CD-containing structures, polymers such as for chromatographic purposes.

The hydrophilic or ionisable CDs are mainly used to increase the absorption of drugs, while hydrophobic CDs may act as sustained-release agents of water-soluble drugs, integrating peptides and proteins (128). Anionic CDs show improved characteristics for drug inclusion comparing with natural CDs, that is, they have greater solubility in water and greater cavity, they form stronger inclusion complexes with polar guests or guests bearing positive charge at a given pH, enabling the release of drugs controlled by pH (134).

It should be noted that CD-polymers have been investigated due to their enormous versatility, as their molecular weight, architecture (linear vs. branched), and pendant ligands can be promptly tuned (135, 136). CD-polymers maintain the CDs capability to form inclusion complexes, which can be even increased due to cooperative effects (137, 138). CD polymers can be prepared through different processes, such as (139): i) condensation of CDs with bi- or multifunctional cross-linkers like epichlorohydrin, biepoxides, diisocyanates or polyacids; ii) anchoring of CDs to polymer chains; and iii) polymerization of acrylic/vinyl derivatives of CDs with other monomers. However, the most common synthetic method is cross-linking the CD monomers with epichlorohydrin (137).

2.1.3.4. Inclusion complex formation

The formation of an inclusion complex (host-guest complex) may occur in solution and in the solid state, and after administration, it dissociates, releasing the drug into the organism in a quick and uniform mode (101). CDs can form complexes with several kinds of compounds like inorganic, organic, or organometallic that can be radical, cationic, anionic, or neutral molecules (140). Inclusion constitutes a true molecular encapsulation and no covalent bonds are created or broken during complex formation (141, 142). The driving forces that lead to the CD complexation are electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding, and charge-transfer interaction (143).
Overall, there are four energetically favourable connections that help shift the equilibrium to form the inclusion complex, namely (107): i) the displacement of water molecules from the CD cavity; ii) the increased number of hydrogen bonds formed as the displaced water returns to the larger pool; iii) a decrease of the repulsive connections between the hydrophobic guest and the aqueous environment; and iv) a raise in the hydrophobic interactions as the guest inserts itself into the apolar CD cavity.

The formation of an inclusion complex depends on several factors, such as (107, 144): i) sizes of the CD and the drug or some major functional groups within the guest moiety; ii) thermodynamic connections between the different components of the system (CD, guest, and solvent); iii) structure of added substituent to the CD derivative; and iv) location of substituent within the CD molecule.

There are two essential parameters that can be determined for the inclusion process (145, 146): i) the complexation strength or stability/equilibrium constant \( K_C \) defined by Fig. 4 and Eq. 1, where \([CD]\) and \([D]\) are the concentrations of free CD and free drug molecule, respectively; and ii) the lifetime \( \tau \) of the complex, also defined in Fig. 4, measured when the equilibrium is perturbed. The constants \( k_f \) and \( k_r \) are the forward and reverse rate constants, respectively, and \( k_{obs} \) (Eq. 2) is the observed rate constant for the reestablishment of the equilibrium after it is perturbed. \( k_f \) is a second order rate constant while \( k_r \) is a first order rate constant (145).

\[
K_C = \frac{k_f}{k_r} = \frac{[D-CD]}{[D][CD]}
\]

\[
K_{obs} = k_f ([CD] + [D]) + k_r
\]

**Fig. 4.** The interaction of drug (D) with a cyclodextrin (CD) to form an inclusion complex (D-CD) of 1:1 stoichiometry with a binding constant of \( K_C \). Adapted from (145).
In general, as can be seen in Eqs. 3 and 4, higher order complexes are formed in a stepwise fashion where a 1:1 complex is formed in the first step, 1:2 (or 2:1) complex in the next step, and so forth (45).

\[
D + CD \leftrightarrow D - CD \tag{3}
\]

\[
D - CD + CD \leftrightarrow D - CD_2 \tag{4}
\]

Thereafter, the \(K_C\) can be written as shown in Eqs. 5 and 6 (45).

\[
K_{1:1} = \frac{[D-CD]}{[D][CD]} \tag{5}
\]

\[
K_{1:2} = \frac{[D-CD_2]}{[D-CD][CD]} \tag{6}
\]

Considering the thermodynamic point of view, the Gibbs free energy \((\Delta G^0)\) of complexation can be calculated from Eq. 7, where \(R\) is the gas constant, \(T\) is the absolute temperature, \(\Delta H^0\) is the standard enthalpy of complexation, and \(\Delta S^0\) is the standard entropy of complexation (92).

\[
\Delta G^0 = -RT\ln K_{1:1} = \Delta H^0 - T\Delta S^0 \tag{7}
\]

Various values of \(K_C\) of 0 to about 100,000 M\(^{-1}\) have been described for CD complexes, with 0 meaning to absence of binding (147-150). Very weak binding is characterized by a \(K_C\) less than 500 M\(^{-1}\), while weak, moderate, strong, and very strong binding are characterized by \(K_C\) in the ranges of 500-1000 M\(^{-1}\), 1000-5000 M\(^{-1}\), 5000-20,000 M\(^{-1}\), and greater than 20,000 M\(^{-1}\), respectively (30). József Szejtli (46) proposed that a \(K_C\) value bigger than 10,000 M\(^{-1}\) meaningly decreases bioavailability due to the inability of the complex to dissociate.

The general requirements for the drug candidate for inclusion complexation are as follows (14, 151): i) its melting point should be below 250 and 270 °C; ii) the molecule should present less than five condensed rings; iii) it should have polarity lower than that of water;
and iv) its molecular weight should be between 100 and 400 g/mol. However, bigger molecules can form complexes with CD if one portion of the molecule is included into the CD cavity.

In order to improve the solubility and dissolution of the drugs, the CD complexation is a suitable approach for the drugs which shows that the aqueous solubility is less than 0.1-0.05 mg/mL (14). Therefore, the drugs of classes 2 and 4 of the BCS are the most eligible for CD complexation (14).

It should be noted that CDs can form non-inclusion complexes, that is, the hydroxyl groups on the outer surface are able to form hydrogen bonds with other compounds and CDs can form water-soluble complexes with lipophilic water-insoluble molecules (32, 152, 153). For example, the catalytic effect on the degradation of β-lactam antibiotics has been associated with non-inclusion β-lactam-CD complex formation (153). In another study, αCD formed both inclusion and non-inclusion complexes with dicarboxylic acids and the two types of complexes coexisted in aqueous solutions (154).

2.1.3.5. Inclusion complexes in solution

In aqueous solutions, CDs form inclusion complexes by replacing water molecules located within the relatively hydrophobic central cavity with some lipophilic drug moiety (152, 155). Drug-CD complexes are continuously forming and dissociating with lifetimes in the range of milliseconds or less (145).

Szejtli (71) suggested that in aqueous solutions, water molecules occupy the slightly apolar CD cavity via energetically unfavourable polar-apolar interactions and consequently can be promptly substituted by suitable “guest molecules” that show lower polarity than water. The dissolved CD acted as a “host molecule” and the “driving force” of the complex formation was the replacement of the high-enthalpy water molecules by these guests (71).

The most frequently claimed stoichiometric ratio for CD complexes is 1:1 (156). Nevertheless, other ratios are recognised, and the most usual of these possibly is 1:2 (156).

The analytical characterization of drug-CD interactions is essential, however, it is not a simple assignment and often requires the use of numerous analytical techniques, whose results have to be interpreted together (93).

The real challenges for the analytical analysis of CDs are as follows (65): i) in most cases have no own ultraviolet absorbance appropriate for detection; ii) influence wavelength and absorbance value of ultraviolet and visible spectra of a guest molecule and matrix components; iii) normally interfere with analytical reagents and change chemical reactions; iv) the hydroxypropyl-β-CD (HPβCD) or the sulfobutyl ether-β-CD (SBEβCD) are composite
mixtures of many isomers; v) can interact with components of solvents, eluents, and buffer additives utilized in separation techniques as well as with the column surface; and vi) frequently self-assemble, aggregate in aqueous solutions originating sample preparation and detection problems.

The stoichiometry of drug-CD complexes and the values of their $K_C$ are often acquired from phase-solubility profiles (Fig. 5), that is, plots of drug solubility versus CD concentration (66, 157, 158). The phase-solubility technique was developed by Higuchi and Connors (66), and it is based on research associated to how complexes of diverse complexing agents such as caffeine, polyvinylpyrrolidone, and some aromatic acids influence the drugs aqueous solubility (66, 67). Phase solubility profiles are classified into A and B types: A type diagrams designate the formation of soluble inclusion complexes while B type indicate the formation of inclusion complexes with poor solubility (159). The $B_S$ type corresponds to complexes with limited solubility and the $B_I$ profile indicates the presence of insoluble complexes (159). On the other hand, the A-type profiles are subdivided into $A_L$ (linear increase of drug solubility as a function of CD concentration), $A_P$ (positively deviating isotherms), and $A_N$ (negatively deviating isotherms) subtypes (159). βCD habitually presents B-type diagrams due to its poor water solubility while HPβCD and SBEβCD generally originate soluble complexes (A-type profiles) (159).

![Fig. 5. Phase-solubility diagrams. Adapted from (158).](image-url)
Linear phase solubility profiles (A-type) denote that the complex is first order regarding the CD \( n = 1 \) and first or higher order in relation to the drug \( m \geq 1 \) (155). In this situation, the apparent drug solubility \( S_{\text{tot}} \) will be expressed by Eq. 8, where \( S_0 \) is the drug inherent solubility in the aqueous complexation medium (155).

\[
S_{\text{tot}} = S_0 + m[D_m - CD]
\]  

(8)

If one drug forms a complex with one CD, so the slope of the linear phase-solubility diagram will be calculated by the Eq. 9, where \( K_{1:1} \) is the stability constant for the complex (155).

\[
\text{Slope} = \frac{S_0K_{1:1}}{S_0K_{1:1} + 1}
\]  

(9)

It should be noted that this method does not demonstrate if a given drug forms inclusion complex with CD, but only how the CD effects the drug (155). Phase-solubility studies are conducted in aqueous solutions saturated with the drug where formation of higher-order complex aggregates is more probable than in diluted unsaturated solutions (155).

Several review papers about the analytical characterization of CD complexes in solution and/or in the solid state have been published (65, 93, 160-167). According to Paola Mura (93), the principal analytical methods utilized for characterization of CD inclusion complexation in solution are as follows: i) spectroscopic methods (ultraviolet-visible, circular dichroism, fluorescence, nuclear magnetic resonance (NMR), and electron spin resonance); ii) electroanalytical methods (polarography, voltammetry, potentiometry, and conductimetry); iii) separation methods (high performance liquid chromatography (HPLC) and capillary electrophoresis); iv) polarimetry; and v) isothermal titration calorimetry. Spectroscopic techniques, and especially NMR, have a crucial role in the characterization of inclusion complexes in solution (93).

2.1.3.6. Inclusion complexes in solid state

The technique utilized to prepare the solid complex can affect the characteristics of the obtained product (160). Currently, the main methods used to prepare the CD inclusion complexes are as follows (14, 49, 168-174): i) methods in the solid state (milling/co-grinding
method, supercritical fluid technology or microwave irradiation); ii) methods in the semi-solid state (kneading method); and iii) methods in solution (co-precipitation technique, solvent evaporation method, neutralization precipitation method, lyophilization/freeze-drying method or atomization/spray-drying method).

The importance of water molecules in drug-CD inclusion complex formation in aqueous solutions has been extensively studied, however in the solid state it has not been studied enough (167). It should be noted that a full characterization of the formation of a drug-CD inclusion complex in solution does not demonstrate its presence also in the solid state (160). Furthermore, the techniques that can be applied for preparing solid complexes can influence the final product properties (160).

The principal analytical methods for the characterization of drug-CD solid systems are the following (160): i) thermal analysis methods (differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and hot stage microscopy (HSM)); ii) X-ray diffraction (single crystal X-ray diffraction and powder X-ray diffraction); iii) spectroscopic methods (Fourier-transform infrared (FTIR) spectroscopy, attenuated total reflectance-FTIR spectroscopy, and Raman spectroscopy); and iv) scanning electron microscopy (SEM). DSC with X-ray diffraction methods are considered the methods of choice (160).

2.1.3.7. Methods to enhance the complexation efficiency

If one drug forms a complex with one CD, so the CE (Eq. 10) will be equal to the drug intrinsic solubility ($S_0$) times the $K_C$ (175). Thus, increased CE can be obtained by increasing either $S_0$ or $K_C$, or by increasing $S_0$ and $K_C$ simultaneously (176, 177).

$$CE = K_C S_0 = \frac{[D-CD]}{[CD]}$$

(10)

CE is obtained from the slope of the phase-solubility profiles (Fig. 5), and for 1:1 D-CD complexes is calculated from Eq. 11 (45).

$$CE = S_0 K_{1:1} = \frac{Slope}{(1 - Slope)}$$

(11)

The drug-CD molar ratio can be calculated from the CE through Eq. 12 (45).

$$D : CD = 1 \div \left( \frac{CE + 1}{CE} \right)$$

(12)
Eq. 13 displays the correlation between the relative increase in formulation bulk (RIFB) and molecular weights of the CD ($MW_{CD}$) and the drug ($MW_{Drug}$), and the CE value (31).

$$RIFB = \frac{MW_{CD}}{MW_{D}}\left(1 + \frac{1}{CE}\right) \quad (13)$$

The CE value can vary from zero, when no complexation is detected, to infinity, when every CD present in solution forms a complex with the drug (45). The CE value in aqueous media is seldom superior than 1.5 being its mean value of about 0.3 (178).

For various reasons such as cost, formulation bulk, and toxicology, the CD amount that can be incorporated in pharmaceutical formulations is restricted (152, 176). In addition, the CE value is, generally, very low and the CD molecular weight is quite high (152). In this way, the main methods that can be used to increase the CE (Fig. 6) play an important role in order to reduce the amount of CD (45, 47, 175, 179, 180).

**Fig. 6.** Methods to enhance CE. Adapted from (45, 47, 175, 179, 181).
2.1.3.7.1. pH adjustment of the complexation medium

The pH control and the CD complexation are generally utilized solubilization methods in formulating ionizable drugs (182). Un-ionized species typically forms a more stable complex with CD than its ionic counterpart, so it is frequently assumed that the un-ionized species is primarily responsible for the complex formation and the consequent increase in solubility (177).

Concerning both complexation and pH control for an ionizable drug, four species (free un-ionized drug \( D_u \), free ionized drug \( D_i \), un-ionized drug-CD complex \( D_u - CD \) and ionized drug-CD complex \( D_i - CD \)) are in equilibrium, and the total concentration of the drug \( D_{\text{tot}} \) is exposed in Eq. 14 (182).

\[
\left[D_{\text{tot}}\right] = [D_u] + [D_i] + [D_u - CD] + [D_i - CD]
\]

Several studies have been published using a joint strategy of pH adjustment and CD complexation (177, 183-203). For example, HPβCD solubilization of sulfisoxazole could be enhanced by drug ionization through pH adjustments (202).

2.1.3.7.2. Formation of multicomponent complexes with hydroxy acids, hydroxylamines and amino acids

Salt formation is a powerful technique in order to increase the solubility and dissolution rates of acidic and basic drugs (16). The term “multicomponent” has been utilized for describing either CDs complexes of mixture of diverse substances (204, 205) or self-organized assemblies with amphiphilic compounds (including amphiphilic CDs) (206). Hydroxy acids, hydroxylamines, and amino acids can be used for enhancing the CE and ternary systems distinctly signifies superiority over binary systems in terms of CE, solubility, \( K_c \), and formulation bulk.

Multicomponent complex formation in the presence of hydroxy acids (for example, tartaric, citric, ascorbic, gluconic, malic, lactic, and treonic acids) is an advantageous method for improving the solubilizing power of CDs and consequently reducing their amount (105). Concomitant complexation and salt formation with these acids meaningly enhance the solubilizing power, allowing to reduce the CD amount in the formulation (105). However, a number of requirements should be mentioned (105): i) drug solubility should be less than 0.1 mg/mL and should be enhanced by salt formation with hydroxy acids; ii) the \( K_c \) value
should be at least $10^3 \text{ M}^{-1}$; and iii) the amino group should have a pKa value greater than or equal to 5.0.

Salt formation with different hydroxy acids and CDs in the multicomponent complexes has been studied to improve the solubility of basic drugs and the solubility of classic binary complexes (207-218). For example, ternary systems with citric acid enabled a significant increase in complexing and solubilizing ability towards the econazole nitrate with respect to the binary ones, indicating a synergistic effect between SBEβCD and citric acid and the formation of highly soluble ternary complexes (219).

Several therapeutic drugs have acidic groups, such as nonsteroidal anti-inflammatory agents; hypoglycemic sulfonylurea derivatives; diuretics; and choleric like bile acids (220). In these drugs, certain hydroxylamines (for example, monoethanolamine, diethanolamine, and triethanolamine) enhanced the solubility and stability of classic binary complexes (202, 221-223). For instance, complexation between ascorbic acid, HPβCD, and triethanolamine, individually and in combination, was previously studied (221). The obtained results showed a pronounced enhancement of aqueous stability of acid ascorbic with the triethanolamine association complex, while this effect was lower with the HPβCD inclusion complex (221).

The use of amino acids, such as lysine, cysteine, valine, glycine, isoleucine, and arginine, as multicomponent complex formation with acidic drugs had been studied, due to their potential ability to simultaneously interact with both the drug, via electrostatic interactions, and CD, via hydrogen bonding (224). It has been demonstrated that CDs and amino acids have a synergistic effect on acidic drugs aqueous solubility (225-230). Recently, the influence of arginine on the complexing and solubilizing power of randomly-methylated-βCD (MEβCD) towards oxaprozin was examined (231). The results of phase-solubility studies showed that addition of arginine improved the MEβCD complexing and solubilizing power of about 3.0 and 4.5 times, respectively, in comparison with the binary complex (231). In other study, Aiassa et al. (232) prepared multicomponent complexes of chloramphenicol and βCD with glycine or cysteine. The results demonstrated that multicomponent complexes can enhance the chloramphenicol solubility as well as reducing the reactive oxygen species production (232).

2.1.3.7.3. Formation of multicomponent complexes with water-soluble polymers

Water-soluble polymers have been widely used in pharmaceutical formulations (141, 233). These compounds can interact with drugs via electrostatic bonds (ion-to-ion,
ion-to-dipole, and dipole-to-dipole bonds), but other kinds of forces like van der Waals' forces and hydrogen bonds, can normally contribute in the complex formation (234).

Thorsteinn Loftsson (235) proposed the use of three different categories of polymers, namely: i) water-soluble natural polymers (for example, inulin, pectins, sodium alginate, agar, casein, and gelatin); ii) water-soluble semi-synthetic polymers (for example, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl ethylcellulose, hydroxypropyl ethylcellulose, hydroxypropyl methylcellulose phthalate, carboxymethylcellulose, and sodium carboxymethylcellulose); and iii) water-soluble synthetic polymers (for example, polyethylene glycols, polyvinyl derivatives, and several copolymers of acrylic acid). Particularly preferred polymers are sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone (235).

The polymers increase the $K_C$ of the drug-CD complexes through formation of ternary drug-CD-polymer complexes (152). In general, in average 40 to 50% less CD is needed when a polymer is present (152). It is described that the maximum CE is normally achieved at polymer concentrations between 0.1 and 1% (w/v) (141, 152, 176).

Several studies have been published about the influence of water-soluble polymers with CDs on solubility/dissolution/bioavailability of drugs, such as acetazolamide (233, 236-238), benznidazole (239, 240), bisacodyl (241), celecoxib (242), delta-9-tetrahydrocannabinol (243), dexamethasone (244), efavirenz (245), finasteride (246), gemfibrozil (247), glibenclamide (248), glyburide (249), hydrocortisone (233, 250-252), irbesartan (253), isradipine (254), methazolamide (255), modafinil (256), naproxen (257, 258), nifedipine (259), nimesulide (260), piroxicam (261), prazepam (233, 237), RS-8359 (a monoamine oxidase-A inhibitor) (262), sulfamethoxazole (233, 237), triclosan (263, 264), tropicamide (265), vinpocetine (266-268), and zaleplon (269). Moreover, water-soluble polymers enhance the βCD water solubility (270-272) and also increase the bioadhesion of the inclusion complexes to the biological membranes (273-275).

2.1.3.7.4. Cosolvents and metal complexes

The cosolvency is a common method to increase the drugs water solubility (18). The usual cosolvents are ethanol, propylene glycol, glycerine, and polyethylene glycol (PEG) (17, 18, 276-280). They enhance the nonpolar drugs solubility by decreasing the aqueous mixture polarity (281). Combined effects of cosolvency and inclusion complexation on drug solubility have been extensively investigated (281-287). For example, the combined
approach of cosolvency and complexation occasioned a significant increase in the carbamazepine total apparent solubility (282). Zung et al. (283) observed synergistic effects of cosolvency and complexation in solubilizing pyrene by using a series of alcohols. However, it should be noted that some researchers have stated that cosolvents reduce drug solubility in the complex (190, 288).

Generally, deprotonation and complexation of secondary hydroxyl groups of CDs to metal ions leads to the formation of sandwich-type complexes in which partly or fully deprotonated CD molecules are connected through a multinuclear metallomacrocycle ring (181, 289). In order to obtain a stable aqueous liquid formulation of a non-fluorinated topical quinolone, the evaluation of the combined use of Mg$^{2+}$ ions and HPβCD was studied (290). In this work, Mg$^{2+}$ and HPβCD showed a synergetic effect, such that the solubility of drug increased a remarkable 500-fold (290).

2.1.3.7.5. Combination of two or more methods

In addition to the methods previously described for increasing the CE of the CDs, an increase in the CE with even greater expression can be promoted by combining two or more strategies. For instance, in order to increase the mebendazole aqueous solubility, HPβCD was used in combination with polymers (polyvinylpyrrolidone or hydroxypropyl methylcellulose) and different acids (citric or tartaric) (291). The results showed that the best condition for increasing solubility and limiting degradation of drug was to heat a combination of mebendazole, HPβCD, tartaric or citric acid and hydroxypropyl methylcellulose (0.1%, w/v) in a water-bath at 95 °C for 60 min (291). In another study, Laura Ribeiro et al. (292) showed that the increase in vinpocetine solubility, as well as a rise on CE, resulted from a synergistic effect in presence of CDs (βCD and SBEβCD), tartaric acid and polymers (hydroxypropyl methylcellulose and polyvinylpyrrolidone).

2.1.3.8. Absorption, distribution, metabolism and excretion, and toxicity

CDs present very low oral bioavailability (< 4%) and they are metabolized in the gastrointestinal tract, principally by bacterial digestion, to form oligosaccharides, monosaccharides, and gases such as hydrogen, carbon dioxide and methane (29). However, MEβCD (log $K_{ow}$ approximately -6) has bigger oral bioavailability (about 12%) in rats (91).

The CD degradation rate in the gastrointestinal tract can be hampered by inclusion complex formation (97). CDs are resistant to β-amylases, but they are slowly hydrolysed by
α-amylases (29). For example, αCD and βCD are principally stable toward α-amylase in saliva while γCD is quickly digested by salivary and pancreatic α-amylase (98).

CDs do not promptly permeate biological membranes via passive diffusion, because they are oligosaccharides with molecular weight between 972 and 2163 g/mol, present very low octanol-water partition coefficients, and they have several hydrogen bond donors and acceptors (31, 91, 293-295). Depending on the quantity, CDs can affect the permeability of tissues and therefore the drug bioavailability by topical route such as nasal, rectal, dermal, and ocular (296).

After absorption, CDs distribute to numerous tissues and organs including the kidney, urinary bladder, liver, adrenal gland, and others (94-96). The kidney has the highest level of CDs of all tissues (297). Subsequently, CDs are quickly ($t_{1/2} \approx 2$ h in humans) excreted unchanged in urine after intravenous injection without tubular reabsorption (298). No CD accumulation is observed in patients with normal excretion levels (298).

The safety profiles and toxicology of CDs have been studied by several authors (115, 297, 299-303). CDs commonly have a rather favourable toxicological profile, particularly in comparison to other excipients like surfactants, polymers, and organic solvents (115, 297, 299). At high doses (bigger than 1000 mg/kg/day), CDs can cause reversible diarrhoea and cecal enlargement in animals, and hence also in humans to some small extent (296).

When administered intravenously βCD demonstrates a more pronounced haemolytic activity than αCD or γCD (the less haemolytic), furthermore its low water solubility leads to its recrystallization in the kidneys resulting in nephrotoxic effect (304). The in vitro haemolytic activity of CDs is described in the order βCD > αCD > HPβCD > γCD >> hydroxypropyl-γCD (HPγCD) ≥ hydroxypropyl-αCD (HPαCD) in erythrocytes freshly collected from human and P388 murine leukemic cells (305).

Several safety studies demonstrate that three natural CDs (αCD, βCD, and γCD) and some chemically modified CDs (HPβCD, 2,6-di-O-methyl-βCD, and SBEβCD) can be used in oral formulations (115). On the other hand, αCD, HPβCD, and SBEβCD are suitable for parenteral preparations (115).

2.1.3.9. Pharmaceutical applications

The pharmaceutical applications of CDs have been known for decades (306). In Fig. 7, the main advantages and drawbacks of the CDs use are illustrated (14, 48, 75, 90, 106, 144).
Concerning the published review articles about pharmaceutical/biomedical applications of CDs, it is possible to observe that CDs and their inclusion complexes can be used in the preparation of solid, liquid, and semi-solid dosage forms for oral (90, 307), parenteral (88, 308), pulmonary (309-311), nasal (200, 312, 313), buccal (314-316), sublingual (317-319), rectal (320, 321), vaginal (322, 323), ocular (238, 324), and dermal (75, 325) administration. In addition, CDs can be used in the microparticles (326, 327), nanoparticles (328-330), liposomes (331, 332), protein formulations (333, 334), and gene therapy (85, 335).

CDs are used in immediate release formulations and in modified release preparations. The incorporation of CDs into polymeric matrices can modify drug release by a diversity of mechanisms (336). CDs can increase drug release by the following mechanisms (336): i) improving the aqueous solubility of drugs; ii) acting as channelling agents and promoting erosion of the matrix; iii) acting as wicking agents; or iv) increasing the concentration of diffusible species. On the other hand, adding CDs to polymeric matrices can decrease drug release by (336): i) complexing drug, indeed increasing its molecular weight and hence decreasing its diffusivity; ii) reducing the concentration of diffusible species by forming poorly soluble complexes; iii) reducing the concentration of diffusible species by forming drug-CD complexes; or iv) acting as cross-linking agents and reducing polymer mesh size.

The utility of CDs for increasing oral bioavailability was investigated by Carrier et al. (30). Twenty eight studies were examined and usually detected factors involved the following (30): i) use of pre-formed complex rather than physical mixtures; ii) drug hydrophobicity (log P bigger than 2.5); iii) low drug solubility (typically less than 1 mg/mL);
iv) moderate $K_C$ value (less than 5000 M$^{-1}$); v) low dose of drug (less than 100 mg); and vi) low CD:drug ratio (less than 2:1).

It should be noted that recently numerous researchers are investigating the CD potential as active pharmaceutical ingredients for the treatment of different clinical situations such as hypercholesterolemia, cancer, and Niemann-Pick disease type C (92, 337). In addition, CDs derivatives can be effective blockers of pore-forming toxins and utilized as inhibitors of toxins and anti-infectives (338).

Sugammadex is a novel drug, which reverses neuromuscular blockade with a mechanism that differs from the commonly used acetylcholinesterase inhibitors (339). After approval in Europe in 2008 and Asia in 2010, sugammadex (Bridion®) has newly been approved in the United States of America and Canada (76). Sugammadex ($C_{72}H_{112}O_{48}S_8$) is a modified γCD with a molecular weight of 2178 g/mol and after intravenous injection, instantly binds free intravascular rocuronium or vecuronium (76), with $K_C$ of 25,000,000 M$^{-1}$ and 10,000,000 M$^{-1}$, respectively, i.e., the affinity for rocuronium is 2.5 times higher (340).

2.1.3.9.1. Solid dosage forms

Tablets and capsules are solid dosage forms widely used in the market for administering active pharmaceutical ingredients due to their stability and ease of administration (341, 342). The three requirements for the formulation of a solid dosage form with CDs are as follows (47): i) the dose:solubility ratio must be equal to or less than 250 mL; ii) the upper limit of the drug dose and excipients per tablet is approximately 800 mg; and iii) drug dissolution from the tablet must be satisfactorily quick to avoid dissolution rate-limited drug absorption.

Table IV shows examples of studies performed with CDs in solid pharmaceutical dosage forms (tablets, orally disintegrating tablets, effervescent tablets, bilayer tablets, osmotic pump tablets, mucoadhesive buccal tablets, minitablets, and capsules). After the analysis, the main uses of CDs in these drug delivery systems are the following: i) to increase solubility/dissolution/bioavailability of poorly soluble drugs (class 2 and 4 drugs of the BCS); ii) to modify the release of drugs (for example, sustained release and pulsatile delivery); iii) to increase physico-chemical stability of drugs; iv) to be used as an osmotic pump agent; and v) to reduce bad tastes of drugs. In addition, some studies demonstrated that βCD can be used as a direct compression excipient because of its very good flowing behaviour (343-345).
Concrete examples of studies with different types of solid dosage forms containing CDs will be briefly described. Wang et al. (346) studied the pharmacokinetic behaviour of orally disintegrating tablets containing perphenazine-HPβCD inclusion complex in rabbits and evaluated their bioequivalence with conventional tablets. The orally disintegrating tablets presented quicker absorption and higher peak concentration when compared with conventional tablets, which suggested that orally disintegrating tablets could be promising oral formulations for perphenazine (346).

The therapeutic applications of cilostazol are limited by its low aqueous solubility (less than 5 µg/mL) and high biovariability (347). In order to increase the solubility and bioavailability of drug, inclusion complexes with βCD were prepared and orally disintegrating tablets were formulated (347). The spray-dried complexes displayed greater solubility and quicker dissolution compared to plain drug, and the prepared tablets with low disintegration time and fast dissolution showed to be a promising drug delivery system with improved bioavailability and better patient compliance (347).

Mura et al. (348) developed two kinds of mucoadhesive buccal tablets of clonazepam to supply a local or systemic delivery. Tablets were prepared by direct compression with combinations of polymers (348). In vitro permeation studies from coated tablets exhibited that clonazepam loading as MEβCD-coground enabled a 5-times increase in drug flux and permeability (348). The results demonstrated that the complexation with MEβCD was a successful strategy to increase the clonazepam performance from buccal tablets for local or systemic action (348).

Benznidazole is used to treat Chagas disease, but it has poor aqueous solubility, which results in low bioavailability (349). In order to overcome this situation, stable effervescent tablets using an inclusion complex of drug with CD were developed (349). HPβCD originated the highest improvement in the drug aqueous solubility (349). Additionally, the effervescent matrix of the tablets was effective in improving the dissolution behaviour of drug complexed with CD (349).

The effect of aging on the physicochemical stability of glibenclamide-βCD systems and tablets prepared with CD-complexed drug was studied by Babu and Pandit (350). The dissolution rate of the kneaded mixture, inclusion complex, and tablets prepared with the inclusion complex was unaffected on storage for 4 years (350).

The effect of SBEβCD as solubilizing agent for testosterone and as osmotic pump agent was studied and compared with HPβCD and a sugar mixture (osmotic agent only) (351). The drug release was expressively quicker with SBEβCD than with HPβCD or the sugar mixture (351). In this study, it was established that SBEβCD can be used for the development of osmotic pump tablets for poor solubility drugs (351).
Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-βCD were developed in order to circumvent the low bioavailability and short half-life of drug (352). The studies showed that about 30% of drug was released after 2h at gastric pH, and about 90% of drug was released within the subsequent 3h in jejunal fluid (352).

Spironolactone is an aldosterone antagonist that has a low and erratic bioavailability due to poor aqueous solubility which restricts its dissolution rate (353). To overcome this situation, the spironolactone-βCD complex was formulated as a 1:4 ratio (353). In vitro studies displayed that there was an eight-fold increase in the drug solubility for the spironolactone-βCD complex compared with spironolactone (353). In addition, capsules containing 125 mg of spironolactone-βCD (equivalent to 25 mg of drug) were manufactured, and dissolution studies using simulated gastric fluid revealed that after 30 min 99.6 (±2.84)% of the drug had dissolved compared with 47.8 (±2.76)% for Aldactone® tablets (353).

Miller et al. (354) made practical considerations in development of solid dosage forms that contain CDs. If a preformed complex is not required, a physical mixture can be prepared by conventional blending methods and can be tableted directly or granulated prior to tableting (354).

The principal drawback to pharmaceutical application of CDs is their formulation bulk (45). In this way, in solid dosage forms, CDs can only be utilized as complexing excipients for potent drugs or for drugs with medium potency and with suitable CE value (45).
Table IV. Examples of studies with solid dosage forms containing CDs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cyclodextrin(s)</th>
<th>Dosage form</th>
<th>References</th>
</tr>
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<td>Tablet</td>
<td>(355)</td>
</tr>
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<td>βCD</td>
<td>Tablet</td>
<td>(356)</td>
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<tr>
<td>Amlodipine</td>
<td>βCD</td>
<td>Bilayer buccal tablet</td>
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<tr>
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<td>HPβCD</td>
<td>Orally disintegrating tablet</td>
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<td>αCD, βCD, γCD, HPβCD, MEβCD</td>
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<td>(359)</td>
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<td>Carvedilol</td>
<td>βCD</td>
<td>Tablet</td>
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<td>βCD</td>
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<td>Clofazimide</td>
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<td>Orally disintegrating tablet</td>
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<td>Clonazepam</td>
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<td>Table</td>
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<td>Clozapine</td>
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<td>(367)</td>
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<tr>
<td>Diltiazem hydrochloride</td>
<td>βCD, diethyl-βCD, triethyl-βCD</td>
<td>Tablet</td>
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<td>Gemfibrozil</td>
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<td>Tablet and capsule</td>
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<td>Itraconazole</td>
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<td>Lorazepam</td>
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</table>
2.1.3.9.2. Parenteral preparations

Excipients are used in parenteral formulations in order to improve or maintain drug solubility (solubilizers) and/or stability (buffers, antioxidants, chelating agents, cryo- and lyoprotectants) (403). Excipients are also essential to guarantee safety (antimicrobial preservatives), diminish pain and irritation upon injection (tonicity agents), and control or extend drug delivery (polymers) (403).

The possible application of CDs in parenteral formulations has been studied by several researchers (88, 404). In parenteral formulations, CD inclusion complexes can be used with the following advantages (14): i) to improve the solubility of the drug; ii) to reduce drug-induced haemolysis and muscular tissue damage; iii) to enhance drug stability; and iv) suspensions for parenteral use can be prepared by reducing the drug to a fine powder containing the CD complex.

The ideal CD derivative to be used as parenteral drug carrier should have the following characteristics (405): i) very soluble in water at room temperature; ii) inexpensive; iii) available in high purity; iv) non-toxic, even at high doses, in chronic treatment; v) powerful solubilizer for numerous lipophilic drugs; vi) stable to heat sterilization and upon storage in solution; vii) non-reacting with cholesterol and phospholipids or other cell membrane components; viii) pharmacologically inert; and ix) biodegradable in the circulation and eliminated as small molecular metabolites.

αCD, βCD, and MEβCD present nephrotoxicity at relatively low doses after parenteral administration and consequently they are not appropriate for intravenous application (296). On the other hand, HPβCD and SBEβCD are considered safe (296).

The CD effect on the aqueous solubility and chemical stability of \(O\)-(4-dimethylaminoethoxycinnamoyl)fumagillol was studied by Kim et al. (203) with the purpose of preparing an effective parenteral formulation. The drug solubility was improved by the combination of pH adjustment and HPβCD complexation, and the stability of lyophilized drug-HPβCD complex was also enhanced after storage (203).

Miconazole is an antimycotic drug with basic character that presents a very poor water solubility (less than 1.03 μg/mL) (211). It was found a synergistic effect on drug solubility between CDs (HPβCD or SBEβCD) and lactic acid, and the obtained results suggested that it is possible to develop a parenteral solution of miconazole without surfactant (211).
2.1.3.9.3. Emulsions and beads

Emulsions are commonly used in formulations applied on skin, however they are thermodynamically unstable liquid/liquid dispersed systems (304). The principal interest in using CDs to stabilize emulsions is that their irritant potential is very weak comparing to traditional surfactants (406).

Multiple emulsions are complex polydispersed systems where both oil-in-water (o/w) and water-in-oil (w/o) emulsion exist concurrently which are stabilized by hydrophilic and lipophilic surfactants respectively (407). These preparations, which can contain drugs dissolved in each phase, constitute very attractive drug delivery systems (408). They also could represent a controlled release system for drugs incorporated in the internal phase(s), and they could be used for either oral (oil-in-water-in-oil (o/w/o)) or dermal administration (o/w/o or water-in-oil-in-water (w/o/w)) (409). The CDs use in their formulation is particularly stimulating because it permits the reduction in the high amount of traditional surfactant (409).

The interactions between CDs with components of the vegetable oils (more particularly with triglycerides) allow stabilising simple or multiple emulsions but also to form particles called “beads” (142). Very rich in oil, this lipid carrier presents an important potential for the encapsulation of highly lipophilic compounds and their delivery for pharmaceutical (oral and topical routes) and cosmetic applications (142, 410). The preparation mechanisms, formulations, and methods, the in vitro and in vivo properties of beads were reviewed by Aburahma (411), Hamoudi and Bochot (412), Liu and Yi (413), and Hamoudi et al. (142).

Different oils whether vegetable (soybean oil, sweet almond oil, wheat germ oil or borage oil), synthetic (Silicon® 200 fluid 10, 50 or 100 cSt) or mineral (Primol® 352 and Marcol® 82) have been examined to form beads with natural CDs (414, 415). Among all of the combinations that formed beads, αCD and soybean oil are the most investigated due to their ability to produce beads with suitable surface characters and high drug load (414, 416-418). Morphologically, the beads are minispheres composed of partially crystalline CDs matrices surrounding micro-domains of oil (410). The diameter of freshly prepared beads using αCD-soybean oil is approximate 1.6 ± 0.2 mm and the water content is nearly 70% (410). After the removal of water from the beads, the oily content in the bead is as high as 80% (w/w) and the CD content around 20% of the weight (410).

Several works have been published about the potential of CDs combined to soybean oil-based formulations with lipophilic drugs, such as adapalene (419), berberine hydrochloride (420), indomethacin (418, 421), isotretinoin (414), and progesterone (417).
2.1.3.9.4. Microparticles and nanoparticles

In general, microparticles typically refer to particles with diameter between 0.1 and 100 μm and nanoparticles to particles with diameter between 1 and 100 nm (422). The first studies on the role of CDs in microparticle preparation were carried out by Loftsson et al. (327). Afterwards, many studies have been made with CD microparticles for oral (423), ocular (326), and pulmonary (424) drug delivery, and with antibodies (425).

The use of CD nanoparticles for drug delivery applications have been studied by various authors (328-330, 426-429). For instance, three main approaches are used in order to load the drug into the amphiphilic CD nanoparticles (112, 430, 431): i) use of preformed drug-amphiphilic CD complexes; ii) incubation between amphiphilic CDs and drug in the same solvent prior to the formation of nanoparticles; and iii) preparation of nanoparticles directly from preformed drug-amphiphilic CD complexes and loaded further by the addition of excess drug solution in the organic phase.

The benefits of CD nanoparticles are diverse, such as reduce dosage frequency, allow target site delivery, reduce toxic side effects, and control the release (329). For example, CD nanoparticles can be used as efficient carriers for antifungal drugs (432), anticancer drugs (112, 328, 433), and proteins and peptides (330).

2.1.3.9.5. Cyclodextrin-based nanogels

Nanogels present the advantages of hydrogels with those that are characteristic to their nanoscale size (434). Therefore, the nanogel network can host and protect drug molecules, as well as control their release (435). Nanogels with CDs are promising tools for the delivery of drugs and other applications in the biomedical field, due to their unique set of properties that ideally fit the conditions of drug transport via systemic routes of administration (436). For instance, sustained release aqueous eye drops of dexamethasone based on CD nanogels were studied by Moya-Ortega et al. (437). In this study, γCD units were cross-linked in the form of nanogels by means of an emulsification/solvent evaporation process (437). The nanogel eye drops (containing 25 mg dexamethasone per mL) were tested in rabbits and compared to the commercially available product Maxidex® (suspension with 1 mg dexamethasone per mL) (437). The maximum dexamethasone concentration in the aqueous humour (2 h after application) was 136 ± 24 mg/mL after application of the nanogel eye drops, and only 44.4 ± 7.8 μg/mL after application of Maxidex® (437). Moreover, the nanogel eye drops were well tolerated with no signs of irritation, redness or other toxic effects (437).
2.1.3.9.6. Cyclodextrin-based nanosponges

Nanosponges are a class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities (438). These systems have been developed for drug delivery, since their use can solubilize poorly water-soluble drugs and provide sustained release as well as increase the drug's bioavailability (438). Well-known examples of nanosponges are titanium-based nanosponges (439), hyper-crosslinked polystyrene nanosponges (440), and CD-based nanosponges (441).

Nanosponges are generally prepared from βCD because, among the natural CDs, βCD has the highest complexing ability and stability with crosslinking agents (438).

Principal applications of CD-based nanosponges include the following: i) improvement of drug solubility (442, 443); ii) modulation of drug release (444, 445); iii) efficient carriers for anticancer drugs (446); and iv) stability enhancement (441, 447, 448).

βCD cross-linked nanosponges were prepared by condensation reaction in order to encapsulate, store, and release calcium carbonate for prolonged period (449). This cross-linking enhanced the stability, in vitro release, and the encapsulation of calcium (449).

2.1.3.9.7. Liposomes

Liposomes are phospholipid vesicles with diameter between 50 and 100 nm with bilayer membrane structure (427). The entrapment of hydrophobic drugs in the aqueous core of liposomes as soluble inclusion complexes with CDs has been projected as an interesting strategy in 1994, thus obtaining drug-in-CD-in-liposome (DCL) systems (450). The encapsulation of the drug-CD inclusion complexes into liposomes combines the advantages offered by both systems: CDs increase drug solubility and bioavailability, and liposomes prevent drug-CD complexes dissociation due to dilution by the plasma or the facile renal excretion of CDs (332). Moreover, DCL is shown to be capable of increasing drug solubility and permeation across the skin, consequently improving drug bioavailability through transdermal route (451).

DCL systems have been studied with several drugs, such as doxorubicin (452), indomethacin (453), prilocaine (454), tretinoin (455), and vincristine (456). There are two mechanisms of drug release from DCL (332): i) one is that drug-CD complexes are transported from inner aqueous phase to lipid bilayers, and then the whole inclusion complexes are released; and ii) the other way is the release of free drug, which is in equilibrium with the inclusion complexes in inner aqueous phase of DCLs. Whether the
release process follows one route or the other, the lipid bilayer barrier should be overcome at first (453).

2.1.3.9.8. Peptide and protein delivery

Researchers have described successful interactions between CDs and proteins, such as enzymes, peptides, and amino acids (333). Protein aggregation is the most common manifestation of instability during drug development (457). In this way, CDs have been tested as antiaggregant agents, and this ability depends on the cavity and on the hydrophobicity and charge of the chains on the cavity (458).

CDs are utilized in nasal drug delivery as absorption improving compounds to enhance the bioavailability of peptide and protein drugs (313). The most effective CDs in animal experiments are the methylated derivatives, dimethyl-βCD and MEβCD, which are active at low concentrations (2% to 5%) (313). Nevertheless, large species differences between rats, rabbits, and humans exist for the nasal absorption improvement by CDs (313). Based on toxicological studies of the local effects of CDs on the nasal mucosa, dimethyl-βCD and MEβCD are considered safe nasal absorption enhancers (313).

Oligopeptide drugs, such as an ACTH(4-9) analogue (459) and the luteinizing hormone-releasing hormone analogues, buserelin (460) and leuprolide (461), are absorbed after nasal administration, but overall their nasal bioavailability is low (313). With CDs their nasal absorption can be improved significantly (313).

The nasal bioavailability of polypeptides and proteins is much smaller than that of oligopeptides (462). Consequently, CDs have been used as absorption enhancers for calcitonin (463), glucagon (464), insulin (465-470), and recombinant human granulocyte colony-stimulating factor (313, 471, 472).

2.1.3.9.9. Site-specific drug delivery (colon and brain)

Colon-specific drug delivery systems are used for the treatment of a variety of local diseases like ulcerative colitis, Crohn’s disease, irritable bowel syndrome, chronic pancreatitis, and colonic cancer (473). Furthermore, the colon can be a potential site for the systemic absorption of numerous drugs to treat non-colonic conditions (473).

Drugs which are destined to be incorporated into a colon-specific delivery system should fulfill one or more of the following physico-chemical/therapeutic criteria (474, 475): i) the drugs should show local effects in the colon to treat intestinal diseases; ii) these drugs may reveal a sub-optimal absorption in the upper gastrointestinal tract; and iii) a high
likelihood of the drug’s degradation in the stomach by the acidic environment or by enzymes.

Recently, Vieira et al. (476), through an in vivo study, showed that oral administration of diclofenac-βCD prodrug conjugate lead to the absorption of the drug diclofenac in the colon. Thus, the feasibility of this new CD prodrug to target and release diclofenac specifically in the colon following oral administration was established (476).

Redox brain-targeting chemical delivery systems were developed in the early 1980s to address the challenge of brain-targeted delivery due to the presence of a blood-brain barrier (477). The access of xenobiotics to the central nervous system is restricted because the blood-brain barrier is a diffusion barrier, which impedes influx of most molecules from blood to brain (478).

Brain-targeting chemical delivery systems exploit the idea that a lipophilic molecule that can cross the blood-brain barrier and enter the brain, can become “locked in” behind the blood-brain barrier if it is converted there into a hydrophilic molecule (477). This is attained via a specific tregetour moiety that undergoes enzymatic transformation resulting in a drastic change of lipophilicity (477).

Brain-increased delivery of testosterone using a chemical delivery system complexed with HPβCD was studied by Anderson et al. (479). The results suggested that testosterone can be efficiently delivered to the central nervous system with minimal peripheral effect, and the delivery of T-CDS1 (a testosterone chemical delivery system) to the central nervous system can be enhanced via complexation with HPβCD (479).

### 2.1.3.9.10. Gene delivery

Gene therapy has enormous promise for the treatment of an extensive variety of clinical situations (480). However, there are requirements for a vehicle for oligonucleotide delivery, such as (481): i) biodegradable and non-cytotoxic when intact in vivo; ii) metabolism products non-cytotoxic in vivo; iii) non-immunogenic; iv) relatively inexpensive formulation procedure; v) preparation should not involve biohazardous procedures; vi) possibility of scaling-up formulation process; vii) may be formulated with various methods; viii) formulation protocol should not alter on functionality; ix) enables storage for months to years; x) maximal entry into cellular sites possible; xi) maximal entry into intracellular (especially nucleus) sites; xii) control over clearance rates from the bloodstream possible; xiii) preparation with a relatively high oligonucleotide/vehicle component(s) ratio; xiv) provides protection against enzymatic degradation; and xv) provides protection against biomechanical degradation.
CDs can be attractive to gene delivery applications because not only of their binding affinity to nucleic acids but also of their capability to attenuate the cytotoxicity of other gene carriers (85). The main approaches of employing CDs for applications in gene delivery are shown in Fig. 8 (85).

The use of CD-containing polymers for gene delivery began in 1999 (482). CD-based polyrotaxanes and polypseudorotaxanes (PPRXs) have inspired interesting and rapid development of supramolecular biomaterials for drug and gene delivery (483). CD-based supramolecular polymers have attracted increasingly attention as effective drug and gene carriers, because of their attractive characteristics, such as low toxicity, sliding, dethreading, and ease to modify (483).

Comparing to other cationic non-viral vectors employed for siRNA delivery, CDs are excellent alternatives as they can be prepared in the size range of 50-200 nm and can serve as adapter molecules; wherein, different molecules, for example, modified adamantanes can be easily ‘plugged’ into the cone of the CD to offer additional functionality (484).

The Agrawal team was one of the first to study the use of CDs and their derivatives in facilitating cellular uptake of oligonucleotides (485, 486) and in modulating oligonucleotide-induced immune stimulation (487). One example of polymer modified with CDs for gene delivery was performed by Motoyama et al. (480). In this study, the authors studied whether PPRXs of PEG-grafted αCD/polyamidoamine dendrimer conjugate (PEG-α-CDE) with CDs have the potential for the novel sustained release systems for plasmid DNA (480). The obtained results suggested that the PEG-α-CDE/CD PPRX systems are useful for novel sustained DNA release systems (480).

Fig. 8. Major approaches of employing CDs for applications in gene delivery. Adapted from (85).
2.1.3.9.11. CDs and drug permeation through biological membranes

Loftsson and his co-workers have published review papers about the effects of CDs on drug delivery through biological membranes (91, 488-490). CDs improve drug delivery through biological membranes by increasing drug permeation through the unstirred water layer (UWL), that is, by increasing the availability of dissolved drug molecules juxtaposed to the membrane surface (91). Regularly, the UWL is the principal drug permeation barrier, particularly in the case of small-molecular-weight lipophilic drugs (489). CDs only increase drug permeation when UWL is present at the membrane exterior (91, 489). This UWL can comprise mucus or an aqueous vehicle like o/w creams or hydrogels, or simply as unstirred aqueous donor phases in in vitro tests (91).

CDs do not increase drug permeation from vehicles that do not form an UWL like ointments and w/o creams (91). The effect also depends on the physicochemical characteristics of the drug, that is, higher improvement is achieved for drugs that are poorly soluble in water and that form inclusion complexes with $K_C$ values between about 50 M$^{-1}$ and 5000 M$^{-1}$ (91, 489). In addition, it is very significant to optimize drug vehicles in relation to the CD amount (91, 489).

2.1.4. Regulatory aspects

It is an established fact that excipients, while pharmacologically inert, bear the utmost relevance for the efficacy of a drug product in obtaining optimal results from a pharmaceutical formulation developed to serve the well-being of humans (491).

In many pharmacopoeias, monographs on CDs are found (31, 106). At the moment, in the European and United States pharmacopoeias, the three natural CDs and HPβCD (Hydroxypropylbetadex) are official (65). Additionally, two other CDs are approved as excipients in medicinal products for human used, namely the HPγCD and the MEβCD (65).

The first monograph on Betadex was published in 1997 in the European Pharmacopoeia, and βCD is the most popular and well-investigated CD (75). In 2000-2004, αCD, βCD, and γCD were announced into the generally recognized as safe (GRAS) list of the Food and Drug Administration (FDA) for use as a food additive (296). SBEβCD and HPβCD are cited in the FDA's list of inactive pharmaceutical ingredients (296). In Japan, natural CDs have monographs in the Japanese Pharmacopoeia and are recognized as food additives (68). In addition, CDs have monographs in the Handbook of Pharmaceutical Excipients and Japanese Pharmaceutical Excipients.
The regulatory status of CDs is continuously evolving and recently, European Medicines Agency (EMA) published a background review for CDs used as excipients (32, 296). A consensus seems to be built among regulators that CDs are excipients and not integral to the drug, however numerous points of view have been assumed and elucidation related to this topic can be division- and product-specific (31, 70).

Table V highlights the list of approved commercial products which are available on the market, including CDs, drug and trade names, dosage form and therapeutic indication, company and country. It should be noted that CDs are available in numerous pharmaceutical dosage forms (solid, liquid, and semi-solid) in many countries. This fact evidences the importance of CDs as excipients in Pharmaceutical Technology.
Table V. Commercial products containing CDs. Adapted from (50, 76, 106, 112, 151, 339, 492).

<table>
<thead>
<tr>
<th>CD</th>
<th>Drug (Trade name)</th>
<th>Dosage form (Therapeutic indication)</th>
<th>Company (Country)</th>
</tr>
</thead>
<tbody>
<tr>
<td>αCD</td>
<td>Alprostadil (Caverject®)</td>
<td>Intravenous (I.V.) solution (erectile dysfunction)</td>
<td>Pfizer (USA)</td>
</tr>
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<td></td>
<td>Alprostadil (Prostavasin®)</td>
<td>I.V. solution and infusion (chronic arterial disease)</td>
<td>Ono (Japan), Schwarz (Germany, USA)</td>
</tr>
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<td></td>
<td>Alprostadil (Rigidur®)</td>
<td>I.V. solution (erectile dysfunction)</td>
<td>Ferring (Denmark)</td>
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<td></td>
<td>Cefotiam hexetil hydrochloride (Pansporin T®)</td>
<td>Tablet (bacterial infections)</td>
<td>Takeda (Japan)</td>
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<td></td>
<td>OP-1206 (Opalmon®)</td>
<td>Tablet (ischemic symptoms)</td>
<td>Ono (Japan)</td>
</tr>
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<td>βCD</td>
<td>Aceclofenac (Acerap®)</td>
<td>Tablet (osteoarthritis, muscular pain, gout, rheumatoid arthritis)</td>
<td>Taj Pharm. (India)</td>
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<td>Benexate hydrochloride (Ulgut®)</td>
<td>Capsule (peptic ulcer, gastritis)</td>
<td>Teikoku (Japan)</td>
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<td></td>
<td>Benexate hydrochloride (Lommie®)</td>
<td>Capsule (peptic ulcer, gastritis)</td>
<td>Shionogi (Japan)</td>
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<td>Betahistine (Betahist®)</td>
<td>Tablet (Vertigo Ménière's syndrome)</td>
<td>Geno Pharm. (India)</td>
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<td>Cefditoren (Meiact®)</td>
<td>Tablet (bacterial infections)</td>
<td>Meiji Seiko (Japan)</td>
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<td>Cetirizine (Zyrtec®)</td>
<td>Chewable tablet (allergies, hay fever, urticaria)</td>
<td>Losan Pharma (Germany)</td>
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<td>Chlordiazepoxide (Transillum®)</td>
<td>Tablet (anxiety, neurosis, psychosis)</td>
<td>Gador (Argentina)</td>
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<td>Chlorpheniramine maleate + acetaminophen (Cold Remedy Soothing®)</td>
<td>Tablet (fever and allergies)</td>
<td>Foshan Dezhong Pharm. (China)</td>
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<td>Cholecalciferol (Natures Aid Vitamin D3®)</td>
<td>Tablet (vitamin D deficiency)</td>
<td>Nature's Aid (United Kingdom)</td>
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<td>Dexamethasone (Glymesason®)</td>
<td>Ointment (eczema, dermatitis, pruritus, psoriasis, insect bite)</td>
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<td>Dextromethorphan (Rynathisol®)</td>
<td>Tablet (cough)</td>
<td>Synthelabo (Italy)</td>
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<td>Diphenhydramine hydrochloride + chlorotheophylline (Stada-Travel®)</td>
<td>Chewable tablet (nausea, vomiting)</td>
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<td>Ethinylestradiol + drospirenone (Yaz®)</td>
<td>Tablet (oral contraception)</td>
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<td>Flutarizine (Fluner®)</td>
<td>Tablet (migraine occlusive peripheral vascular disease)</td>
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<td>Garlic oil (Xund®, Tegra®, Allidex®, Garlessence®)</td>
<td>Solution (throat disinfectant)</td>
<td>Bipharm, Hermes (Germany)</td>
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<td>Iodine (Mena-Gargle®)</td>
<td>Drug (ostearthrosis, rheumatoid arthritis, ankylosing spondylitis)</td>
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<td>Meloxicam (Mobilit®)</td>
<td>Tablet (suppository)</td>
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<td>Metronidazole (Metrogel®)</td>
<td>Gel (rosacea infection)</td>
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<td>Nicotine (Nicorette®)</td>
<td>Sublingual tablet (nicotine replacement therapy)</td>
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<td>Nicotine (Nicogum®)</td>
<td>Chewable gum (smoking cessation therapy)</td>
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<td>Nimesulide (Nimedex®)</td>
<td>Tablet (acute pain, primary dysmenorrhea)</td>
<td>Novartis (Europe)</td>
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<td>Nitroglycerin (Nitopen®)</td>
<td>Sublingual tablet (coronary artery disease, hypertensive emergencies)</td>
<td>Nippon Kayaku (Japan)</td>
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<td>Norfloxacin + tinidazole (Entronor-TZ®)</td>
<td>Tablet (diarrhea, protozoal infections)</td>
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<td>Omeprazole (Omepeta®)</td>
<td>Tablet (stomach ulcers, Zollinger-Ellison syndrome)</td>
<td>Betapharm (Germany)</td>
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<td>PGE2 (Prostanaron E®)</td>
<td>Sublingual tablet (induction of labour)</td>
<td>Ono (Japan)</td>
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<td>Piroxicam (Brexin®)</td>
<td>Tablet (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis)</td>
<td>Chiesi (Italy)</td>
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<td></td>
<td>Piroxicam (Cycladol®)</td>
<td>Tablet (suppository, oral powder (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis)</td>
<td>Chiesi (Italy)</td>
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<td>Piroxicam (Flugene®)</td>
<td>Suppository (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis)</td>
<td>Ache (Brazil)</td>
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<td>Rofecoxib (Rofizgel®)</td>
<td>Tablet (osteoarthrosis, rheumatoid arthritis, ankylosing spondylitis)</td>
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<td>Thiamosol (Vitaseptol®)</td>
<td>Ophthalmic solution (eye infections)</td>
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<td>Tiaprofenic acid (Surgamyld®)</td>
<td>Tablet (inflammatory and rheumatic diseases)</td>
<td>Roussel-Maestrelli (Italy)</td>
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<td>γCD</td>
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<td>Topical solution (androgenic alopecia)</td>
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<td>Cisapride (Prepulsid®)</td>
<td>Suppository (gastroesophageal reflux disease)</td>
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<td>Diclofenac sodium (Dyloject®)</td>
<td>I.V. solution (mild, moderate or severe pain)</td>
<td>Javelin Pharmaceuticals (Europe)</td>
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<td>Diclofenac sodium (Voltaren® Ophtha)</td>
<td>Ophthalmic solution (eye inflammation)</td>
<td>Novartis (Switzerland)</td>
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<td>Hydrocortisone (Dexacort®)</td>
<td>Mouthwash solution (aphthous ulceration, lichen planus, and other mucosal disorders)</td>
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<td>Indomethacin (Indocid®)</td>
<td>Ophthalmic solution (ocular pain, eye inflammation, inhibition of myosis during surgery)</td>
<td>Chauvin (France)</td>
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<td>Itraconazole (Sporanox®)</td>
<td>Oral solution and i.v. solution (fungal infections)</td>
<td>Janssen (Europe and USA)</td>
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<td>Levothyroxine sodium (Leventa®)</td>
<td>Oral solution (thyroid replacement therapy in dogs with hypothyroidism)</td>
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<td>Mitomycin (Mitozytrex®)</td>
<td>I.V. infusion (tumours, leukemias, Hodgkin's disease, non-Hodgkin's lymphoma)</td>
<td>Novartis (Switzerland)</td>
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<td>Mitomycin (MitoExtra®)</td>
<td>I.V. infusion (tumours, leukemias, Hodgkin's disease, non-Hodgkin's lymphoma)</td>
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<td>Telavancin (Vibativ®)</td>
<td>I.V. perfusion (nosocomial pneumonia, bacterial infections)</td>
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<td>HPβCD</td>
<td>Amiodarone hydrochloride (Nexterone®)</td>
<td>I.V. solution (ventricular tachycardia, ventricular fibrillation)</td>
<td>Baxter Healthcare (USA)</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole (Abilify®)</td>
<td>Intramuscular (I.M.) solution (schizophrenia)</td>
<td>Bristol-Myers Squibb (USA), Otsuka Pharm. Co. (Japan)</td>
</tr>
<tr>
<td></td>
<td>Carfilzomib (Kyprolis®)</td>
<td>I.V. perfusion (multiple myeloma)</td>
<td>Amgen (Europe)</td>
</tr>
<tr>
<td></td>
<td>Maropitant (Cerenia®)</td>
<td>I.V. solution (nausea and acute vomiting in dogs)</td>
<td>Pfizer Animal Health (USA)</td>
</tr>
<tr>
<td></td>
<td>Voriconazole (V/Fend®)</td>
<td>I.V. solution (fungal infections)</td>
<td>Pfizer (USA)</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone mesylate (Geodon®)</td>
<td>I.M. solution (schizophrenia)</td>
<td>Pfizer (Europe and USA)</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone mesylate (Zeldox®)</td>
<td>I.M. solution (schizophrenia)</td>
<td>Pfizer (Europe and USA)</td>
</tr>
<tr>
<td>SBEβCD</td>
<td>Amiodarone hydrochloride (Nexterone®)</td>
<td>I.V. solution (ventricular tachycardia, ventricular fibrillation)</td>
<td>Baxter Healthcare (USA)</td>
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<tr>
<td></td>
<td>Aripiprazole (Abilify®)</td>
<td>Intramuscular (I.M.) solution (schizophrenia)</td>
<td>Bristol-Myers Squibb (USA), Otsuka Pharm. Co. (Japan)</td>
</tr>
<tr>
<td></td>
<td>Carfilzomib (Kyprolis®)</td>
<td>I.V. perfusion (multiple myeloma)</td>
<td>Amgen (Europe)</td>
</tr>
<tr>
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<td>Maropitant (Cerenia®)</td>
<td>I.V. solution (nausea and acute vomiting in dogs)</td>
<td>Pfizer Animal Health (USA)</td>
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<td></td>
<td>Voriconazole (V/Fend®)</td>
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<td></td>
<td>Ziprasidone mesylate (Geodon®)</td>
<td>I.M. solution (schizophrenia)</td>
<td>Pfizer (Europe and USA)</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone mesylate (Zeldox®)</td>
<td>I.M. solution (schizophrenia)</td>
<td>Pfizer (Europe and USA)</td>
</tr>
<tr>
<td>MEβCD</td>
<td>Chloramphenicol (Clorocil®)</td>
<td>Ophthalmic solution (bacterial infections)</td>
<td>Oftalder (Portugal)</td>
</tr>
<tr>
<td></td>
<td>17β-Estradiol (Aerodiol®)</td>
<td>Nasal spray (hormone replacement)</td>
<td>Servier (France)</td>
</tr>
<tr>
<td>HPγCD</td>
<td>Diclofenac sodium (Voltaren®)</td>
<td>Ophthalmic solution (ocular pain, eye inflammation, inhibition of myosis during surgery)</td>
<td>Novartis (France)</td>
</tr>
<tr>
<td></td>
<td>Tc-99m Teboroxime (CardioTec®)</td>
<td>I.V. solution (radioactive imaging agent)</td>
<td>Bracco (USA)</td>
</tr>
<tr>
<td>Sugammadex (modified γCD)</td>
<td>Bridion®</td>
<td>I.V. solution (reversal of neuromuscular blockade)</td>
<td>Merck Sharp &amp; Dohme (Europe)</td>
</tr>
</tbody>
</table>
2.1.5. Conclusion

CDs are cyclic oligosaccharides with hydrophilic outer surface and hydrophobic central cavity that were first isolated by Antoine Villiers (1854-1932) in 1891. Afterwards, these compounds have been studied by several scientists and currently constitute versatile excipients that are used to formulate solid, semi-solid, and liquid dosage forms in order to obtain immediate and/or modified drug delivery. Moreover, these multifunctional excipients are used in site-specific drug delivery (for example, colon and brain), gene delivery, peptide and protein delivery, and in drug delivery systems such as microparticles, nanoparticles, and liposomes. The main advantages of using these cyclic oligosaccharides are as follows: i) to enhance solubility/dissolution/bioavailability of poorly soluble drugs (class 2 and 4 drugs of the BCS); ii) to enhance drug stability; iii) to modify the release site and/or time profile; and iv) to reduce drug side effects (for example, gastric or ocular irritation). Therapeutic uses of CDs as drug carrier systems have significant impact on the treatment of many diseases, including cancer (328, 433, 493), arthritic illnesses (494), and fungal infections (495).

After analysing sixty studies described in the literature (Table IV), it is possible to affirm that CDs are used in solid pharmaceutical dosage forms like tablets, orally disintegrating tablets, effervescent tablets, bilayer tablets, osmotic pump tablets, mucoadhesive buccal tablets, minitablets, and capsules.

It should be noted that the major drawback of CDs is the increase in formulation bulk, once the CE is, in general, very low. This aspect is particularly relevant in solid dosage forms and limits the use of CDs to potent drugs. On the other hand, tablets with a large diameter make swallowing difficult and decrease the patient's compliance to therapy. All tablet conditions, including the size, number and surface coating, affect swallowing behaviours (496). In this way, the methods used to increase the CE (pH adjustment of the complexation medium; use of hydroxy acids, hydroxylamines, amino acids, water-soluble polymers, cosolvents and metal complexes; and combination of two or more of these methods) have an important role in reducing the amount of CD. For instance, in average 40 to 50% less CD is needed when a water-soluble polymer is present (152).

CDs have monographs in principal pharmacopoeias (European Pharmacopoeia, United States Pharmacopoeia-National Formulary, and Japanese Pharmacopoeia) and present favourable toxicological profile for human use. Thus, there are various medicinal products containing CDs approved by regulatory authorities around the world.
In relation to scientific publications with CDs in the pharmaceutical field, a prudential estimate gives figures of over 1000 articles in international scientific journals and about 30-40 review papers, books, and book chapters every year in the last years (160).

This review highlighted the state of the art of CD technology with typical examples. Thus, it is possible to conclude that CDs have great potential as drug carriers in Pharmaceutical Technology and can be used by the formulator in order to improve the drug properties such as solubility, *in vitro* dissolution, bioavailability, and physico-chemical stability. Additionally, recent studies have shown that these compounds can be applied as active pharmaceutical ingredients for the treatment of many diseases as hypercholesterolemia, cancer, and Niemann-Pick type C disease. After approval in Europe (2008), Asia (2010), and United States (2015), sugammadex (Bridion®) is a modified γCD that is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium.

2.1.6. List of abbreviations

**BCS** - Biopharmaceutics Classification System
**CD(s)** - Cyclodextrin(s)
**CE** - Complexation efficiency
**CGTase** - Cyclodextrin glucosyltransferase
**DCL(s)** - Drug-in-cyclodextrin-in-liposome(s)
**DSC** - Differential scanning calorimetry
**EMA** - European Medicines Agency
**FDA** - Food and Drug Administration
**FTIR** - Fourier-transform infrared spectroscopy
**GRAS** - Generally recognized as safe
**HPLC** - High performance liquid chromatography
**HPαCD** - Hydroxypropyl-α-cyclodextrin
**HPβCD** - Hydroxypropyl-β-cyclodextrin
**HPγCD** - Hydroxypropyl-γ-cyclodextrin
**HSM** - Hot stage microscopy
**I.M.** - Intramuscular
**I.V.** - Intravenous
**K_C** - Stability constant(s) or equilibrium constant(s)
**MEβCD** - Randomly-methylated-β-cyclodextrin
**NMR** - Nuclear magnetic resonance
2.1.7. Acknowledgements

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2.1.8. References


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2.2. Cyclodextrins as excipients in tablet formulations

This manuscript describes the main applications of cyclodextrins in tablet formulations and highlights the most relevant technological aspects in the pharmaceutical development.
2.2.1. Highlights

- Cyclodextrins are complexing excipients in tablets mainly for potent drugs.
- Methods to enhance the complexation efficiency decrease the cyclodextrin quantity.
- Inclusion complex flow properties play a crucial part in the tablet manufacture process.
- Commercial tablets containing cyclodextrins are available on the market.
- 3D printed tablets can be developed containing cyclodextrins as excipients.
2.2.2. Abstract

This manuscript aims to provide a critical review of cyclodextrins as excipients in tablet formulations, highlighting: i) the principal pharmaceutical applications of cyclodextrins; ii) the most relevant technological aspects in pharmaceutical formulation development; and iii) the actual regulatory status of cyclodextrins. Moreover, several illustrative examples are presented.

Cyclodextrins can be used as complexing excipients in tablet formulations for low-dose drugs. By contrast, for medium-dose drugs and/or when the complexation efficiency is low, the methods to enhance the complexation efficiency play a key part in reducing the cyclodextrin quantity. In addition, these compounds are used as fillers, disintegrants, binders, and multifunctional direct compression excipients of the tablets.

**Keywords:** cyclodextrins; complexation; tablets; formulation; pharmaceutical regulation.
2.2.3. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides that are produced from starch or starch derivatives using CD glycosyltransferase. These compounds were first isolated by Antoine Villiers in 1891 and they have been recognized as pharmaceutical excipients because they can form non-covalently bonded inclusion complexes (host-guest complexes) with several drugs either in solution or in the solid state (Fig. 1A) (1). Regarding the chemical structure, CDs comprise (α-1,4)-linked α-D glucopyranose units, have a lipophilic central cavity and a hydrophilic outer surface, and are shaped like a truncated cone, bucket-like or doughnut-shaped (Fig. 1B) (2).

Fig. 1. A) The interaction of drug (D) with a cyclodextrin (CD) to form an inclusion complex (D-CD) of 1:1 stoichiometry with a stability/equilibrium constant of $K_C$; and B) Chemical structure of the hydroxypropyl-β-cyclodextrin. Adapted from (1).

The three natural CDs are alpha-cyclodextrin (αCD; alfadex), beta-cyclodextrin (βCD; betadex), and gamma-cyclodextrin (γCD; gammadex), containing 6, 7 and 8 glucose units, respectively. CD derivatives are divided into three groups, specifically hydrophilic (for instance, 2-hydroxypropyl-β-CD (HPβCD)), hydrophobic (for instance, 2,6-di-O-ethyl-β-CD), and ionisable (for instance, sulfobutyl ether-β-CD (SBEβCD)).

CDs are used in the pharmaceutical industry for different purposes such as (3, 4): i) to enhance the aqueous solubility, dissolution, and bioavailability of drugs; ii) to increase drug physicochemical stability and improve shelf-lives of medicinal products; iii) to modify drug release site and/or time profile; iv) to minimize adverse drug reactions such as
gastrointestinal and ocular irritation; v) to reduce or eliminate unpleasant taste and smell; vi) to prevent drug-drug or drug-excipient interactions; and vii) to convert liquid drugs into microcrystalline or amorphous powders. Additionally, CDs can be used as drug substances such as sugammadex (Bridion®; Merck Sharp & Dohme), which is a modified γCD available in 100 mg/mL solution for injection. According to the summary of product characteristics (5), there are two therapeutic indications: i) for the reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults; and ii) for the paediatric population, sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2-17 years.

All these applications are based on inclusion complex forming ability of CDs. The binding or stability/equilibrium constant ($K_C$) of an inclusion complex ($D$-$CD$) of 1:1 stoichiometry can be calculated from Eq. 1, where $[D$-$CD]$, $[D]$, and $[CD]$ are the concentrations of inclusion complex, free drug substance, and free CD, respectively (6). $Slope$ is the slope of the phase-solubility profile and $S_0$ is the concentration of drug without CD. For complexes with low-to-mid $K_C$ value, binding of drug to plasma proteins will primarily determine the pharmacokinetics (7). By contrast, for complexes with high $K_C$ value and low protein binding, significant decrease in distribution volume and enhanced excretion of unmetabolized drug are observed (7).

$$K_C = \frac{[D$-$CD]}{[D][CD]} = \frac{\text{Slope}}{S_0(1\text{-Slope})}$$  \hspace{1cm} (1)

For 1:1 drug-CD complexes, the complexation efficiency (CE) can be calculated from Eq. 2 (8).

$$CE = S_0K_C = \frac{[D$-$CD]}{[CD]} = \frac{\text{Slope}}{(1\text{-Slope})}$$  \hspace{1cm} (2)

Oral delivery is the most common route for drug administration. Tablets are solid dosage forms that were discovered in 1843 by William Brockedon through the publication of British Patent Number 9977 about “shaping pills, lozenges and black lead by pressure in dies” (9). This pharmaceutical dosage form is the most used in the market because it
presents high-precision dosing, chemical, physical and microbiological stability, manufacturing efficiency, and good patient compliance (9, 10).

According to the European Pharmacopoeia 9 (11), in force since January 2017, there are ten types of tablets for oral administration: i) uncoated tablets; ii) coated tablets; iii) effervescent tablets; iv) soluble tablets; v) dispersible tablets; vi) orodispersible tablets; vii) gastro-resistant tablets; viii) modified release tablets; ix) tablets for use in the mouth; and x) oral lyophilizates. In addition, there are other types of tablets described in the literature such as bilayer/multilayer tablets and mini-tablets.

A medicinal product is a physical system whose properties depend, among others, on the individual contributions of drug(s) and excipients. Regarding the tablet formulation process, the pharmaceutical technologist can use several types of excipients such as fillers, lubricants (glidants and anti-adherents), binders, disintegrants, wettings, colourings, absorbents, buffers, sweeteners, and flavourings. Furthermore, in the pharmaceutical industry, there are co-processed and high functionality excipients that result from the combination of two or more excipients. For instance, the PROSOLV® EASYtab SP from JRS Pharma is a unique four-in-one system combining the strengths of frequently used excipients: microcrystalline cellulose (96%, w/w) as a binder-filler, colloidal silicon dioxide (2%, w/w) as a glidant, sodium starch glycolate (1.2%, w/w) as a superdisintegrant, and sodium stearyl fumarate (0.8, w/w) as a lubricant. The manufacturer states that these components maintain their chemical identities while synergistically providing increased functional performance.

The phenomena that occur during the preparation of tablets are collectively called compaction and this is divided into two phases: compression (i.e., volume reduction and particle rearrangement) and consolidation (i.e., interparticulate bond formation) (9). The major manufacturing processes of tablets are: i) direct compression; ii) wet granulation; iii) dry granulation; and iv) other processes (for example, lyophilisation and moulding technologies).

The aim of this article was to perform a critical review of CDs as excipients in tablet formulations. It should be noted that the last review article concerning CDs in solid dosage forms was published in 2007 (12). In this way, it was our objective to summarize the current state of knowledge and to emphasize the prospects for future research.

2.2.4. Functional applications of CDs in tablet formulations

As can be seen in Fig. 2, CDs have enormous potential as excipients in tablet formulations, because they can be used with different pharmaceutical applications. It should
be emphasized that the CD principal application is to enhance the dissolution and bioavailability of poorly soluble drugs belonging to classes 2 (low solubility and high permeability) and 4 (low solubility and low permeability) of the Biopharmaceutics Classification System (BCS).

Examples of studies with CDs as excipients in tablet formulations are illustrated in Table I. Analysing the literature it is possible to affirm that: i) these compounds are studied in various types of tablets such as uncoated tablets, coated tablets, orally disintegrating tablets (ODTs), effervescent tablets, modified release tablets, bilayer/multilayer tablets, osmotic pump tablets, mucoadhesive buccal tablets, and mini-tablets; and ii) the principal used CDs are αCD, βCD, γCD, HPβCD, randomly-methylated-βCD, SBEβCD, βCD-epichlorohydrin polymer, diethyl-βCD, triethyl-βCD, hydroxyethyl-βCD, dimethyl-βCD, triacetyl-βCD, and O-carboxymethyl-O-ethyl-βCD. Concrete examples will be given in more detail below.

Temporally, it can be stated that the foundations of dissolution research started in 1897 with the studies performed by Arthur Amos Noyes and Willis Rodney Whitney. The development of a relationship between dissolution and bioavailability occurred between 1950 and 1980, the emphasis on dissolution as a prognostic tool of oral drug absorption occurred between 1980 and 2000, and from 2000 to the present day dissolution in the framework of the BCS was verified (13). The drug dissolution process of solid dosages

---

**Fig. 2.** Principal CD applications in tablet formulations.
is theoretically defined by Noyes-Whitney equation as demonstrated in Eq. 3, where $dC/dt$ is the dissolution rate, $D$ is the diffusion coefficient, $S$ is the surface area, $h$ is the diffusion layer thickness, $Cs$ is the solubility of the substance, and $Ct$ is the concentration of the dissolved substance at time $t$.

$$\frac{dC}{dt} = \frac{DS}{h}(C_s - C_t)$$

(3)

To enhance the dissolution and bioavailability of carbamazepine, an anticonvulsant drug with poor aqueous solubility, tablets containing 50 mg of drug complexed with HPβCD in the presence of hydroxypropyl methylcellulose were prepared by direct compression (14). The results demonstrated an increased dissolution rate and a greater and faster absorption of the carbamazepine from complex tablets compared with commercial tablets (14).

As previously reported by Miller et al. (12), it is described in the literature that very often even the physical mixture of drug and CD increases the solubility of the drug owing to the instant complex formation upon contact with water. Thus, in these cases, the use of CD as a filler should be considered and a wetting agent (for example, sodium lauryl sulphate and polysorbate 80) and a superdisintegrant (for example, croscarmellose sodium, sodium starch glycolate or crospovidone) can be added as dissolution enhancers. However, it is necessary to study whether there is an interaction between the added excipient and the CD.

As for the release of the drug(s), the pharmaceutical dosage forms are divided into immediate release or conventional release dosage forms and modified release dosage forms. In turn, the modified release dosage forms include the sustained release dosage forms, the delayed release dosage forms, and the sequential release dosage forms (11). Hydrophobic (for example, diethyl-βCD and triacetyl-βCD) and ionisable (for example, O-carboxymethyl-O-ethyl-βCD) derivatives of βCD are used in the formulation of sustained release or delayed release tablets, respectively. O-carboxymethyl-O-ethyl-βCD seems to cause delayed dissolution not because of the presence of the ionisable carboxymethyl groups but rather due to the presence of the hydrophobic ethyl groups (15). Besides that, CDs are non-invasive platforms for targeted drug delivery (16). Rehman et al. (17) investigated the ability of βCD and chitosan as components in tablet matrix formulations to maximize the release of ibuprofen under conditions simulating the colon by employing a wet granulation method. Formulations with equal amounts of βCD and ethyl cellulose were the most stable carrier systems and displayed better ibuprofen release profiles than the formulations containing chitosan.
Recently, the effect of CD complexes on the chemical stability of drugs was reviewed by Popielec and Loftsson (18). It was established that CD complexation can hamper hydrolysis, oxidation, photodegradation, isomerization, and enzyme catalysed degradation of dissolved drugs in aqueous solution (18). For instance, the addition of βCD as an excipient to tablets improved the stability of limaprost, a prostaglandin E₁ derivative (19). Nevertheless, it should be noted that some drugs that are stabilized by CDs in aqueous solutions are destabilized by the same CDs in solid dosage forms (18).

Many taste-masking methods such as physical barrier coatings, chemical modification (for example, the complexation of drugs with CDs), and sensory masking have been developed (20). By way of example, the intensely bitter taste of aceclofenac, a nonsteroidal anti-inflammatory drug, was masked by complexing with HPβCD on ODTs (21). Taste evaluation of tablets in human volunteers revealed considerable taste masking with the degree of bitterness below a threshold value. This aspect is of importance because it promotes therapeutic compliance.

The guideline on good pharmacovigilance practices (22), published by the European Medicines Agency (EMA) in 2017, defines an adverse drug reaction as a response to a medicinal product that is noxious and unintended. CDs are used to minimize drug side effects such as gastric/intestinal and ocular irritation. Naproxen is a nonsteroidal anti-inflammatory drug with poor water solubility and undesirable gastrointestinal toxicity such as gastrointestinal intolerance and ulceration when given orally. To overcome this situation, Piao et al. (23) developed tablets with enteric coatings containing naproxen inclusion complexes with HPβCD to deliver the drug into the colonic region.

In tablet formulations, CDs have been used as a direct compression filler (for example, βCD), disintegrating agent (for example, CD polymer), binder (for example, βCD), and osmotic pump agent (for example, SBEβCD). For instance, Garcia-Fernandez et al. (24) developed a new multifunctional direct compression excipient based on citric acid-βCD polymer in its water-insoluble (PCD-I) and soluble (PCD-S) forms. Other excipients such as binders, lubricants or disintegrants were not added during the studies. The results highlighted the multifunctional excipient properties of PCD-I/PCD-S polymers, i.e., good flow and compression properties, no signs of toxicological symptoms, and modulable disintegration time.

In the past years, several scientific studies involving CDs in bilayer tablets and ODTs have been described in the literature. Bilayer (and multilayer) tablets offer several advantages over the conventional tablets like layers with different drug release profiles, separation of chemically incompatible ingredients, patient compliance, and combination therapy (25). For example, amlodipine bilayer buccal tablets of a hydroxypropyl
methylcellulose matrix system containing Carbopol®-βCD as the drug layer and ethyl cellulose as the non-swellable backing layer were developed (26). Amlodipine is a dihydropyridine calcium antagonist with poor water solubility and bioavailability, and high photosensitivity (26). The presence of inclusion complexes in the tablet improved permeation owing to its enhanced dissolution at the site of biointerface of tablet and buccal mucosa (26).

ODTs provide several advantages over conventional tablets such as suitability for patients with swallowing difficulties, mainly in the geriatric and paediatric population, and faster onset of action (27). The Food and Drug Administration (FDA) (28) establishes that ODTs should present the following attributes: i) tablet weight ≤ 500 mg; ii) friability percentage ≤ 1.0%; iii) disintegration time ≤ 30 s; iv) acceptable and palatable taste for the patient population; v) content uniformity, drug release and stability as applicable to tablet dosage form; and vi) pharmacokinetics similar to the conventional tablet dosage form (bioequivalent). For instance, ODTs of clozapine, a potent antipsychotic that belongs to class 2 of the BCS, and complexes with HPβCD, were prepared by an evaporation method (29). Tablets (140 mg) developed by direct compression showed suitable technological characteristics and a higher in vitro dissolution rate and bioavailability compared with the commercial tablets (29).

Regarding future developments, three-dimensional (3D) printed tablets can be developed containing CDs as excipients. This technology has gained more attention in pharmaceutical manufacturing since the FDA approved the first 3D printed tablet Spritam® (levetiracetam) to treat epilepsy in August 2015 (30). In addition, 3D printing is a layer-by-layer, automated process that can produce complex, personalized products on demand (30). At this moment, there are no studies published in the literature concerning 3D printed tablets with CDs. Another future possibility is the development of tablets containing CDs with a sensor that digitally tracks whether patients have ingested their medication. For example, the FDA approved to Otsuka Pharmaceutical and Proteus® a digital medicine system named Abilify MyCite® (31) - a drug-device combination product comprising aripiprazole tablets embedded with an ingestible event marker sensor.
<table>
<thead>
<tr>
<th>Drug and quantity per tablet (mg)</th>
<th>Therapeutic class</th>
<th>CD</th>
<th>Application aim</th>
<th>Inclusion complex method of preparation</th>
<th>Tablet type</th>
<th>Tablet manufacturing process</th>
<th>Tableting machine</th>
<th>Tablet weight (mg)</th>
<th>Tablet diameter (mm)</th>
<th>Observations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine besylate (10)</td>
<td>Calcium channel blocker</td>
<td>βCD</td>
<td>↑ dissolution and ↑ permeation</td>
<td>Kneading</td>
<td>Bilayer buccoadhesive</td>
<td>Direct compression</td>
<td>Hydraulic pellet press, Technosearch Instruments Thane</td>
<td>~166</td>
<td>10</td>
<td>• The βCD presence did not change bioadhesion force and swelling behaviour significantly. • The different weight ratios of chitosan:βCD did not appear to significantly influence the drug release profile.</td>
<td>(26)</td>
</tr>
<tr>
<td>Amoxicillin trihydrate (n.s.)</td>
<td>Antibiotic</td>
<td>βCD</td>
<td>Release rate-controlling polymer</td>
<td>Sustained release mucoadhesive</td>
<td>Direct compression</td>
<td>Single-punch</td>
<td>~130</td>
<td>~7.45</td>
<td>• A high CD concentration seemed to hamper the effervescence raising the disintegration time of tablets and also making the formulations more vulnerable to variations in atmospheric relative humidity. • Drug solubility was increased up to 95 times by complexation with HPβCD in the presence of 0.1% hydroxypropyl methylcellulose. The dissolution and bioavailability of complex tablets were increased compared with commercial tablets.</td>
<td>(32)</td>
<td></td>
</tr>
<tr>
<td>Benznidazole (100)</td>
<td>Antiparasitic</td>
<td>HPβCD</td>
<td>↑ dissolution</td>
<td>Kneading</td>
<td>Effervescent</td>
<td>Direct compression</td>
<td>Eccentric press, FABB</td>
<td>1250</td>
<td>16</td>
<td>• Drug solubility was increased up to 95 times by complexation with HPβCD in the presence of 0.1% hydroxypropyl methylcellulose. The dissolution and bioavailability of complex tablets were increased compared with commercial tablets. • The complex tablets, in the presence of sodium carboxymethyl cellulose, increased drug dissolution rate, and were shown to have more effective antimicrobial activity than commercial tablets.</td>
<td>(33)</td>
</tr>
<tr>
<td>Carbamazepine (50)</td>
<td>Anticonvulsant</td>
<td>HPβCD</td>
<td>↑ dissolution and ↑ bioavailability</td>
<td>Co-evaporation</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>Single-punch, Korsch EK-0</td>
<td>n.s.</td>
<td>15</td>
<td>• Complexation revealed to be an optimal strategy to improve the performance of drug from tablets aimed for local or systemic action in terms, respectively, of increased release rate and permeation properties.</td>
<td>(14)</td>
</tr>
<tr>
<td>Cefpodoxime proxetil (n.s.)</td>
<td>Antibiotic</td>
<td>HPβCD</td>
<td>↑ dissolution</td>
<td>Kneading</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>Single stroke punching</td>
<td>~220</td>
<td>12</td>
<td></td>
<td>(34)</td>
</tr>
<tr>
<td>Cilostazol (50)</td>
<td>Antiplatelet and vasodilator</td>
<td>βCD</td>
<td>↑ dissolution</td>
<td>Spray-drying</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>Rotary press, Rimek</td>
<td>450</td>
<td>10</td>
<td></td>
<td>(35)</td>
</tr>
<tr>
<td>Clonazepam (0.5 and 1.0)</td>
<td>Benzodiazepine</td>
<td>Randomly-methylated-βCD</td>
<td>↑ dissolution and ↑ permeation</td>
<td>Co-grinding, kneading and co-evaporation</td>
<td>Mucoadhesive buccal</td>
<td>Direct compression</td>
<td>Hydraulic pump</td>
<td>n.s.</td>
<td>13</td>
<td></td>
<td>(36)</td>
</tr>
<tr>
<td>Drug and quantity per tablet (mg)</td>
<td>Therapeutic class</td>
<td>CD</td>
<td>Application aim</td>
<td>Inclusion complex method of preparation</td>
<td>Tablet type</td>
<td>Tablet manufacturing process</td>
<td>Tableting machine</td>
<td>Tablet weight (mg)</td>
<td>Tablet diameter (mm)</td>
<td>Observations</td>
<td>References</td>
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<tr>
<td>Clozapine (12.5)</td>
<td>Atypical antipsychotic</td>
<td>HPβCD</td>
<td>↑ dissolution and ↑ bioavailability</td>
<td>Co-evaporation</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>Rotary press, GLZP-10A</td>
<td>140</td>
<td>8.5</td>
<td>• Tablets showed a higher dissolution rate and bioavailability compared with the commercial tablets.</td>
<td>(29)</td>
</tr>
<tr>
<td>Eslicarbazepine acetate (800)</td>
<td>Anticonvulsant</td>
<td>βCD</td>
<td>↑ dissolution and ↑ bioavailability</td>
<td>Co-evaporation</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>Rotary press, Jaguar, General Machinery Corporation</td>
<td>1200</td>
<td>16</td>
<td>• Tablets showed low disintegration time, higher in vitro drug release and higher bioavailability compared with the marketed tablets. • A simple blending of chitosan and SBEβCD retarded the release of eslicarbazepine acetate from tablets. The slow release of the drug was reflected in in vivo absorption after oral administration to rats.</td>
<td>(37)</td>
</tr>
<tr>
<td>Famotidine (n.s.)</td>
<td>Histamine H&lt;sub&gt;2&lt;/sub&gt; receptor antagonist</td>
<td>SBEβCD</td>
<td>Slow-release agent</td>
<td>Slow release</td>
<td>Direct compression</td>
<td>Hydraulic press</td>
<td>190</td>
<td>10</td>
<td>• The release of drug from buccal tablets comprising inclusion complex and hydroxypropyl methylcellulose demonstrated a complete and sustained release of the drug associated with an enhanced buccal permeation.</td>
<td>(38)</td>
<td></td>
</tr>
<tr>
<td>Felodipine (5)</td>
<td>Calcium channel blocker</td>
<td>HPβCD</td>
<td>↑ dissolution and ↑ permeation</td>
<td>Lyophilization</td>
<td>Buccoadhesive (sustained release)</td>
<td>Direct compression</td>
<td>Single-punch, Cadmach</td>
<td>115</td>
<td>8</td>
<td>• The highest significant release was achieved from the lyophilized ternary complex containing 100 mg of drug in presence of polyvinylpyrrolidone. The relative bioavailability of the gum tablet was found to be 166.06% compared to Nalfon® 200 mg capsules.</td>
<td>(39)</td>
</tr>
<tr>
<td>Fenoprofen calcium (200)</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>βCD</td>
<td>↑ dissolution and ↑ bioavailability</td>
<td>Lyophilization</td>
<td>Three-layered gum</td>
<td>Direct compression</td>
<td>Single-punch, Royal Artist</td>
<td>1800</td>
<td>17</td>
<td>• The CD polymer improved the disintegration and the dissolution rate, and increased the hardness of the tablets and provided good stability of dissolution profile.</td>
<td>(40)</td>
</tr>
<tr>
<td>Furosemide (20)</td>
<td>Diuretic</td>
<td>CD polymer</td>
<td>Disintegrant</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>Shimadzu hydraulic press</td>
<td>~254</td>
<td>13</td>
<td>• CD polymer was used advantageously in direct compression systems as a binder-disintegrant.</td>
<td>(41)</td>
<td></td>
</tr>
<tr>
<td>Furosemide (20)</td>
<td>Diuretic</td>
<td>CD polymer</td>
<td>Binder and disintegrant</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>Shimadzu hydraulic press</td>
<td>250</td>
<td>13</td>
<td></td>
<td>(42)</td>
<td></td>
</tr>
<tr>
<td>Drug and quantity per tablet (mg)</td>
<td>Therapeutic class</td>
<td>CD</td>
<td>Application aim</td>
<td>Inclusion complex method of preparation</td>
<td>Tablet type</td>
<td>Tablet manufacturing process</td>
<td>Tableting machine</td>
<td>Tablet weight (mg)</td>
<td>Tablet diameter (mm)</td>
<td>Observations</td>
<td>References</td>
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<tr>
<td>Glipizide (5)</td>
<td>Sulfonylurea</td>
<td>βCD</td>
<td>↑ dissolution and ↑ bioavailability</td>
<td>Trituration</td>
<td>Compression-coated</td>
<td>Wet granulation (core tablet)</td>
<td>Single-punch, Shanghai Pharmaceutical Machinery Factory</td>
<td>418</td>
<td>11</td>
<td>• The compression-coated tablets with glipizide/βCD and hydroxypropyl cellulose in the outer layer displayed a zero-order controlled release function. • Tablets produced by spray granulation, fluid bed processing and co-evaporation-granulation had almost identical dissolution profile in water and 0.1% sodium lauryl sulphate.</td>
<td>(43)</td>
</tr>
<tr>
<td>Glyburide (5)</td>
<td>Sulfonylurea</td>
<td>HPβCD</td>
<td>↑ dissolution</td>
<td>Co-evaporation, spray granulation and fluid bed processing</td>
<td>Immediate release</td>
<td>Granulation, spray granulation and fluid bed processing</td>
<td>Mini tablet press, Kambart, Cadmach Machinery</td>
<td>122 to 371.3</td>
<td>6 and 9</td>
<td>• The drug release from the mini-tablets showed no dependency on the amount of water used in the formation of the complexes.</td>
<td>(44)</td>
</tr>
<tr>
<td>Ibuprofen (1.54)</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>βCD</td>
<td>↑ dissolution</td>
<td>Kneading and suspension/solution with different processes of drying (air stream, spray-drying and lyophilization)</td>
<td>Mini-tablet</td>
<td>Direct compression (manually)</td>
<td>Universal mechanical press, Lloyd Instruments LR 50 K</td>
<td>10</td>
<td>2.5</td>
<td>• βCD improved the hardness of tablets without increasing the disintegration time. • The inclusion complexes enhanced the solubility of drug and improved its antifungal activity. Tablet containing inclusion complexes prolonged the residence time and the drug release on the vaginal mucosa.</td>
<td>(45)</td>
</tr>
<tr>
<td>Ibuprofen sodium (100)</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>βCD</td>
<td>Filler</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>Single-punch, Erweka EKO</td>
<td>400</td>
<td>12</td>
<td>• βCD improved the hardness of tablets without increasing the disintegration time. • The inclusion complexes enhanced the solubility of drug and improved its antifungal activity. Tablet containing inclusion complexes prolonged the residence time and the drug release on the vaginal mucosa.</td>
<td>(46)</td>
<td></td>
</tr>
<tr>
<td>Itraconazole (100 mg of complex)</td>
<td>Antifungal</td>
<td>SBEβCD</td>
<td>↑ dissolution and ↓ side effects</td>
<td>Lyophilization</td>
<td>Vaginal bioadhesive sustained release</td>
<td>Direct compression</td>
<td>Single-punch, Korsch EK-0</td>
<td>200</td>
<td>8</td>
<td>• Tablets containing the CD complex showed a higher in vitro dissolution rate and bioavailability compared with the tablets containing drug alone. • The use of HPβCD at a molar ratio of 1:10 showed a considerable positive effect on the taste masking of the drug.</td>
<td>(47)</td>
</tr>
<tr>
<td>Ketoconazole (10)</td>
<td>Antifungal</td>
<td>HPβCD</td>
<td>↑ dissolution and ↑ bioavailability</td>
<td>Kneading</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>Hydraulic press</td>
<td>~76</td>
<td>4</td>
<td>• Tablets containing the CD complex showed a higher in vitro dissolution rate and bioavailability compared with the tablets containing drug alone. • The use of HPβCD at a molar ratio of 1:10 showed a considerable positive effect on the taste masking of the drug.</td>
<td>(48)</td>
</tr>
<tr>
<td>Levocetirizine hydrochloride (5)</td>
<td>Antihistamine</td>
<td>HPβCD</td>
<td>↑ palatability</td>
<td>Co-evaporation</td>
<td>Effervescent</td>
<td>Direct compression</td>
<td>Single-punch, Erweka GmbH</td>
<td>350</td>
<td>13</td>
<td>• βCD as a tableting excipient improved the stability of drug in tablets of the lyophilized composites (with βCD).</td>
<td>(49)</td>
</tr>
<tr>
<td>Limprostat alfadex (50)</td>
<td>Prostaglandin E1 analogue</td>
<td>βCD</td>
<td>↑ stability</td>
<td>Lyophilization</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>VELA, Kikusui Selsakusho</td>
<td>n.s.</td>
<td>6.5</td>
<td></td>
<td>(19)</td>
</tr>
<tr>
<td>Drug and quantity per tablet (mg)</td>
<td>Therapeutic class</td>
<td>CD</td>
<td>Application aim</td>
<td>Inclusion complex method of preparation</td>
<td>Tablet type</td>
<td>Tablet manufacturing process</td>
<td>Tableting machine</td>
<td>Tablet weight (mg)</td>
<td>Tablet diameter (mm)</td>
<td>Observations</td>
<td>References</td>
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<tr>
<td>Lorazepam (4)</td>
<td>Benzodiazepine</td>
<td>HPβCD</td>
<td>↑ dissolution</td>
<td>Lyophilization</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>Eight-station single rotary, Cadmach Machinery</td>
<td>n.s.</td>
<td>7</td>
<td>Tablets containing complexes prepared with CD had significant improvement in the release profile of lorazepam as compared to tablets containing lorazepam without CD.</td>
<td>(50)</td>
</tr>
<tr>
<td>Lornoxicam (16: 8 + 8)</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>HPβCD</td>
<td>↑ dissolution</td>
<td>Lyophilization</td>
<td>Bilayer</td>
<td>Direct compression</td>
<td>Single-punch</td>
<td>400 (200 + 200)</td>
<td>n.s.</td>
<td>Lornoxicam/HPβCD freeze-dried product in 1:2 (drug/CD) showed the highest dissolution and was used in the drug rapid release layer.</td>
<td>(51)</td>
</tr>
<tr>
<td>Meclizine hydrochloride (25)</td>
<td>Antihistamine</td>
<td>HPβCD</td>
<td>↑ dissolution</td>
<td>Kneading</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>16 station rotary, Cadmach, Manesty</td>
<td>200</td>
<td>9.5</td>
<td>The solubility and dissolution rate of drug were significantly improved by complexation with HPβCD. The prepared formulation showed better release than a marketed tablet.</td>
<td>(52)</td>
</tr>
<tr>
<td>Melatonin (2)</td>
<td>Hormone</td>
<td>αCD, βCD, γCD, HPβCD, sulphated βCD, HPCαCD and HPCγCD</td>
<td>↑ dissolution</td>
<td>Co-evaporation</td>
<td>Hydrophilic matrix</td>
<td>n.s.</td>
<td>Hydraulic press, Maassen type MP 150</td>
<td>200</td>
<td>10</td>
<td>Melatonin was released faster from the drug/CD complexes than from the rest matrix systems.</td>
<td>(53)</td>
</tr>
<tr>
<td>Meloxicam (7.5)</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>HPβCD</td>
<td>↓ unpleasant taste and ↑ dissolution</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>Hand hydraulic press machine, Specac P/N 15011/25011</td>
<td>200</td>
<td>9.5</td>
<td>Tablets containing the mixture of resinate and drug/HPβCD complexes provided complete drug dissolution and masked the bitter taste.</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>Metformin hydrochloride (50)</td>
<td>Biguanide</td>
<td>Triacetetyl-βCD</td>
<td>Sustained-release</td>
<td>Spray-drying and grinding</td>
<td>Sustained release</td>
<td>Direct compression</td>
<td>Perkin-Elmer hydraulic press</td>
<td>825</td>
<td>10</td>
<td>Different sustained-release effects were obtained by varying the relative amounts of drug-CD as co-ground or spray-dried product.</td>
<td>(55)</td>
</tr>
<tr>
<td>Naproxen (n.s.)</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>HPβCD</td>
<td>↓ dissolution and ↓ side effects</td>
<td>Kneading</td>
<td>Colonic-release</td>
<td>Direct compression</td>
<td>Rotary tablet press, Korea Machine</td>
<td>330</td>
<td>9</td>
<td>The tablet with enteric coatings which contained inclusion complex and disintegrants could be useful to deliver naproxen to the lower small intestine and upper colon with increased dissolution and reduced intestinal tissue damage.</td>
<td>(23)</td>
</tr>
<tr>
<td>Natamycin (25 mg of complex)</td>
<td>Macrolide antimycotic</td>
<td>γCD</td>
<td>↑ dissolution, ↑ stability and ↓ side effects</td>
<td>Lyophilization</td>
<td>Vaginal bioadhesive</td>
<td>Direct compression</td>
<td>Single-punch, Korsch EK-0</td>
<td>50</td>
<td>5.5</td>
<td>The complexation improved the aqueous solubility of drug without modifying its antimycotic activity.</td>
<td>(56)</td>
</tr>
<tr>
<td>Drug and quantity per tablet (mg)</td>
<td>Therapeutic class</td>
<td>Inclusion complex method of preparation</td>
<td>Tablet type</td>
<td>Tablet manufacturing process</td>
<td>Tableting machine</td>
<td>Tablet weight (mg)</td>
<td>Tablet diameter (mm)</td>
<td>Observations</td>
<td>References</td>
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<tr>
<td>Oxaprozin (100)</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>Randomly-methylated-βCD</td>
<td>Cofusion</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>Hydraulic press</td>
<td>n.s.</td>
<td>n.s.</td>
<td>• The tablets containing the drug as co-fused system with CD, l-arginine and sepiolite nanoclay were more effective than the marketed tablet in terms of faster and more intense pain-relieving effect in the treatment of adjuvant-induced arthritis. (57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine (2)</td>
<td>Antipsychotic</td>
<td>HPβCD</td>
<td>Co-evaporation</td>
<td>Orally disintegrating</td>
<td>Direct compression</td>
<td>Rotary press, GLZP-10A, Beijing gylongli sci. &amp; tech. Co.</td>
<td>80</td>
<td>6</td>
<td>• Tablets with inclusion complexes showed least disintegration time and improved drug dissolution profile. (58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridostigmine bromide (60)</td>
<td>Cholinesterase inhibitor</td>
<td>βCD</td>
<td>Kneading</td>
<td>Dispersible</td>
<td>Direct compression</td>
<td>Single rotary press, ZDY-8, Shanghai Far-east Pharmaceutical Machinery Co.</td>
<td>400</td>
<td>12</td>
<td>• Tablets with desirable taste, short disintegration time and rapid dissolution rate were prepared using inclusion complexes. Pharmacokinetic results demonstrated that developed tablets and the commercial tablets were bioequivalent. (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valsartan (n.s.)</td>
<td>Angiotensin II receptor antagonist</td>
<td>βCD</td>
<td>Kneading</td>
<td>Press-coated</td>
<td>Direct compression</td>
<td>Mini Press I, Karnavati</td>
<td>370-420</td>
<td>12</td>
<td>• Press-coated pulsatile release tablets of valsartan with improved dissolution rate were developed. (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinpocetine (20)</td>
<td>Cerebral vasodilator</td>
<td>βCD and SBEβCD</td>
<td>Lyophilization</td>
<td>Sustained release matrix</td>
<td>Direct compression</td>
<td>Instrumented single-punch press, Specac Ltd.</td>
<td>200 and 300</td>
<td>8</td>
<td>• Multicomponent complexes were prepared and formulated in hydroxypropyl methylcellulose matrix tablets. The dissolution rate and oral bioavailability of drug were significantly improved. (61)</td>
<td></td>
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</tr>
<tr>
<td>Zaleplon (10)</td>
<td>Sedative-hypnotic</td>
<td>Randomly-methylated-βCD</td>
<td>Spray-drying</td>
<td>Immediate release</td>
<td>Direct compression</td>
<td>Single-punch, Korsch EK-0</td>
<td>200</td>
<td>10</td>
<td>• The drug dissolution from the mannitol tablets loaded with the drug-randomly methylated-βCD-hydroxypropyl methylcellulose ternary system was completed after 5 min. (62)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.2.5. Functional requirements of CD in tablet formulations

2.2.5.1. Drug quantity (therapeutic dose) per tablet

According to Jambhekar and Breen (6), there are three requirements for the formulation of a solid dosage form with CDs: i) the dose:solubility ratio must be ≤ 250 mL; ii) the upper limit of the drug dose and excipients per tablet is approximately 800 mg; and iii) drug dissolution from the tablet must be satisfactorily quick to avoid dissolution rate-limited drug absorption.

The major drawback of CDs in tablet formulations is their formulation bulk (1). This aspect limits the use of CDs in these delivery systems to potent drugs (low-dose drugs). The formulation bulk, resulting from CDs elevated molecular weight (for example, SBEβCD has 2163 g/mol), and drugs exhibiting low CE (Eq. 2) will frequently be too large for a single dose tablet (8). The relative increase in formulation bulk (RIFB) increases when the molecular weight of the CD (MW<sub>CD</sub>) increases and the CE decreases, as can be seen from Eq. 4 where MW<sub>D</sub> is the molecular weight of the drug (63).

\[
\text{RIFB} = \frac{\text{MW}_{\text{CD}}}{\text{MW}_{\text{D}}} \left(1 + \frac{1}{\text{CE}}\right)
\]

In general, the tablet weight ranges from 60-100 mg (diameter approximately 6 mm) to 900-1000 mg (diameter approximately 16 mm). Tablets with high weight and diameter cause difficulties in swallowing, which leads to a decrease in therapeutic compliance, especially in paediatrics and geriatrics and chronic treatments. In addition, some types of tablets should present low weight such as, for instance, buccal tablets (about 150 mg) (64). In this way, for medium-dose drugs and/or when the CE is low, the main methods that can be used to increase the CE play a key part in reducing the CD amount in the pharmaceutical formulation. These methods are as follows (8): i) pH adjustment of the complexation medium; ii) formation of multicomponent complexes with hydroxy acids (for example, tartaric, lactic, citric, and α-ketoglutaric acids), hydroxylamines (for example, monoethanolamine, diethanolamine, and triethanolamine), and amino acids (for example, lysine, cysteine, valine, glycine, isoleucine, and arginine); iii) formation of multicomponent complexes with water-soluble polymers (for example, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone); iv) use of co-solvents (for example, ethanol, propylene glycol, glycerine, and polyethylene glycol) and metal complexes; and v) combination of two or more of these methods. By way of example, sodium carboxymethylcellulose was used as a water soluble polymer to increase the
complexation of cefpodoxime proxetil by HPβCD (34). The drug dissolution rate and antimicrobial activity of complex tablets were higher when compared with commercial tablets (34).

### 2.2.5.2. Flow properties of the prepared complexes

Analysing the studies described in the literature, it can be stated that the principal methods used to prepare the CD inclusion complexes in tablet formulations are as follows: i) methods in the solid state (milling/co-grinding); ii) methods in the semi-solid state (kneading); and iii) methods in solution (co-precipitation, solvent evaporation, lyophilisation/freeze-drying and atomization/spray drying).

The flow properties are very important in the development of solid dosage forms and are used to predict the compression ability of a powder, granule or pellet. A material shows an excellent flow when presenting the following characteristics (11): i) angle of repose ≤ 25-30°; ii) flow time ≤ 10.0 s/100 g; iii) ability to settle ≤ 20 mL; iv) Carr’s index (C.I) or compressibility index ≤ 10%; and v) Hausner’s ratio (HR) ≤ 1.11. The C.I and the HR can be calculated from Eqs. 5 and 6, respectively, where $d_0$ is the is the apparent density before tapping (bulk density), $d_{10}$ is the apparent density after 10 taps, and $d_{500}$ is the apparent density after 500 taps (65, 66).

\[
\text{C.I} \,(\%) = \left( \frac{d_{500} - d_0}{d_{500}} \right) \times 100 \tag{5}
\]

\[
\text{HR} = \frac{d_{500}}{d_{10}} \tag{6}
\]

Salústio et al. (45) studied the flow properties of inclusion complexes of ibuprofen and βCD obtained by two complexation methods, namely suspension/solution (with water removed by air stream, spray- and freeze-drying) and kneading. All studied materials have shown poor flow properties and a glidant had to be added to the formulations to prepare mini-tablets. Another study indicated good compressibility and flow properties of the lorazepam complexes with HPβCD prepared by kneading, spray-drying, and lyophilisation (50). Thus, in our opinion, the flow properties of the prepared inclusion complex should be evaluated to predict the compressibility and to avoid tableting problems (e.g. variation in tablet weight and drug content).

Direct compression is the preferred manufacture method of tablets by the pharmaceutical industry because it has fewer steps compared to granulation processes, it
is the most economical, and it can be used for moisture or heat sensitive materials. However, this method requires that materials present the following properties: i) sufficient density; ii) constant flow; iii) agglutination and cohesion capacity; and iv) absence of friction, i.e., no adherence to the surfaces. Therefore, direct compression can only be used for inclusion complexes with good flow properties and compressibility or in situations by adding a direct compression filler (for example, microcrystalline cellulose, lactose monohydrate, calcium hydrogen phosphate, and mannitol) or a co-processed excipient (for example, MicroceLac® 100 that comprises 75% alpha-lactose monohydrate and 25% microcrystalline cellulose). It should be noted that direct compression is the most described manufacturing process in the literature to prepare tablets containing CDs. Nevertheless, sometimes the compression chamber (die) filling is done by manual mode and this is not suitable for industrial application.

If the complex does not show good flow properties and compressibility, other manufacturing processes should be considered such as wet granulation, dry granulation or another process. Gyanani et al. (44) demonstrated that spray granulation is a simple and cost-effective process for low-dose poorly soluble drugs, whereas fluid bed processing is appropriate for poorly soluble drugs with a moderate dose. By contrast, for drugs with high doses, if multiple dose units are suitable for administration, then fluid bed processing can be considered.

2.2.5.3. Regulatory status of CDs

The principal pharmacopoeias worldwide include monographs of CDs (for example, the European Pharmacopoeia and the United States Pharmacopoeia-National Formulary) or monographs of compounds with CDs (for example, Alprostadil Alfadex in the Japanese Pharmacopoeia). In addition, these compounds exhibit favourable toxicological profiles for human use (67). Concerning CDs that can be used in tablet formulations for oral administration, βCD (betadex), HPβCD (hydroxypropyl betadex), and SBEβCD (betadex sulfobutyl ether sodium) are the most commonly described in the literature.

In 2014, the EMA published a document on “Background review for CDs used as excipients” (68). In relation to oral products, βCD, γCD, HPβCD, and SBEβCD are applied. Table II displays examples of commercial tablets containing CDs, including drug and trade names, pharmaceutical dosage form, therapeutic indication, manufacturer and region. It should be noted that: i) only three CDs are present, i.e., βCD (the CD with higher pharmaceutical application), αCD and HPβCD; and ii) the first pharmaceutical product
containing CDs was approved in Japan in 1976 as sublingual tablets with PGE₂-βCD (Prostarmon E®).
### Table II. Examples of commercial tablets containing CDs.

<table>
<thead>
<tr>
<th>CD</th>
<th>Drug (trade name)</th>
<th>Dosage form (therapeutic indication)</th>
<th>Company (region)</th>
</tr>
</thead>
<tbody>
<tr>
<td>αCD</td>
<td>Cefotiam hexetil hydrochloride (Pansporin T&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (bacterial infections)</td>
<td>Takeda (Japan)</td>
</tr>
<tr>
<td></td>
<td>OP-1206 (Opalmon&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (ischemic symptoms)</td>
<td>Ono (Japan)</td>
</tr>
<tr>
<td></td>
<td>Aceclofenac (Acerap&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (osteoarthritis, muscular pain, gout, rheumatoid arthritis)</td>
<td>Taj Pharm. (India)</td>
</tr>
<tr>
<td></td>
<td>Betahistine (Betahist&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (Vertigo Ménière's syndrome)</td>
<td>Geno Pharm. (India)</td>
</tr>
<tr>
<td></td>
<td>Cefditoren (Meiact&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (bacterial infections)</td>
<td>Meiji Seiko (Japan)</td>
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<tr>
<td></td>
<td>Cetirizine (Zyrtec&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Chewable tablet (allergies, hay fever, urticaria)</td>
<td>Losan Pharma (Germany)</td>
</tr>
<tr>
<td></td>
<td>Chlordiazepoxide (Transillium&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (anxiety, neurosis, psychosis)</td>
<td>Gador (Argentina)</td>
</tr>
<tr>
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<td>Chlorpheniramine maleate + acetaminophen (Cold Remedy Soothing&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (fever and allergies)</td>
<td>Foshan Dezhang Pharm. (China)</td>
</tr>
<tr>
<td></td>
<td>Cholecalciferol (Natures Aid Vitamin D3&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (vitamin D deficiency)</td>
<td>Natures Aid (United Kingdom)</td>
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<td>Dextromethorphan (Rynathisol&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (cough)</td>
<td>Synthelabo (Italy)</td>
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<tr>
<td></td>
<td>Diphenhydramine hydrochloride + chlorotheophylline</td>
<td>Chewable tablet (nausea, vomiting)</td>
<td>Stada (Germany)</td>
</tr>
<tr>
<td></td>
<td>(Stada-Travel&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethinylestradiol + drospirenone (Yaz&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (oral contraception)</td>
<td>Bayer (USA)</td>
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<tr>
<td>βCD</td>
<td>Flunarizine (Fluer&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (migraine occlusive peripheral vascular disease)</td>
<td>Geno Pharm. (India)</td>
</tr>
<tr>
<td></td>
<td>Meloxicam (Mobitil&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet, suppository (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis)</td>
<td>Medical Union Pharm. (Egypt)</td>
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<td></td>
<td>Nicotine (Nicorette&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Sublingual tablet (nicotine replacement therapy)</td>
<td>Pharmacia (Sweden)</td>
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<tr>
<td></td>
<td>Nimesulide (Nimexed&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (acute pain, primary dysmenorrhea)</td>
<td>Novartis (Europe)</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin (Nitropen&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Sublingual tablet (coronary artery disease, hypertensive emergencies)</td>
<td>Nippon Kayaku (Japan)</td>
</tr>
<tr>
<td></td>
<td>Norfloxacin + tinidazole (Entronor -TZ&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (diarrhoea, protozoal infections)</td>
<td>Sydler (India)</td>
</tr>
<tr>
<td></td>
<td>Omeprazole (Omebeta&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (stomach ulcers, Zollinger-Ellison syndrome)</td>
<td>Betapharm (Germany)</td>
</tr>
<tr>
<td></td>
<td>PGE&lt;sub&gt;2&lt;/sub&gt; (Prostarmon E&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Sublingual tablet (induction of labour)</td>
<td>Ono (Japan)</td>
</tr>
<tr>
<td></td>
<td>Piroxicam (Brexin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis)</td>
<td>Chiesi (Italy)</td>
</tr>
<tr>
<td></td>
<td>Piroxicam (Cycladol&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet, suppository, oral powder (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis)</td>
<td>Chiesi (Italy)</td>
</tr>
<tr>
<td></td>
<td>Rofecoxib (Rofzegel&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis)</td>
<td>Wockhard (India)</td>
</tr>
<tr>
<td></td>
<td>Tiaprofenic acid (Surgamy&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (inflammatory and rheumatic diseases)</td>
<td>Roussel-Maestrelli (Italy)</td>
</tr>
<tr>
<td></td>
<td>Perindopril tert-butylamine (Perindopril Erbumine&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (hypertension, heart failure and cardiac events prevention)</td>
<td>Sandoz (Europe)</td>
</tr>
<tr>
<td></td>
<td>Voriconazole (Vorzu&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tablet (fungal infections)</td>
<td>Ranbaxy (India)</td>
</tr>
</tbody>
</table>

<sup>®</sup> Indicates the trade name of the drug.
2.2.6. Conclusion

CDs are complexing excipients in tablet formulations mainly for potent drugs. For medium-dose drugs and/or when the CE is low, the methods to enhance CE play a key part in reducing the CD quantity in the formulation.

The principal CD application in tablets is to enhance the dissolution and bioavailability of poorly soluble drugs. Additionally, CDs can be used by the pharmaceutical technologist for other purposes, for example to modify or control the release of a drug or to increase drug stability and taste.

Inclusion complex flow properties play a crucial part in tablet manufacture process. Direct compression is the most utilized method; however, sometimes the filling of the compression chamber is done manually.

Recently, several studies concerning CDs in ODTs and bilayer/multilayer tablets have been published. Regarding future developments, 3D printed tablets and tablets with sensors could be developed containing CDs as excipients. Finally, CDs are present in commercial tablets and there are CD monographs in several pharmacopoeias.

2.2.7. List of abbreviations

3D - Three-dimensional
BCS - Biopharmaceutics Classification System
CD(s) - Cyclodextrin(s)
CE - Complexation efficiency
Cᵰᵢ - Carr's index
EMA - European Medicines Agency
FDA - Food and Drug Administration
HPβCD - Hydroxypropyl-β-cyclodextrin
HR - Hausner's ratio
Kᵦ - Binding or stability/equilibrium constant
ODT(s) - Orally disintegrating tablet(s)
RIFB - Relative increase in formulation bulk
SBEβCD - Sulfobutyl ether-β-cyclodextrin
αCD - Alpha-cyclodextrin
βCD - Beta cyclodextrin
γCD - Gamma-cyclodextrin
2.2.8. Acknowledgements

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2.2.9. References

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3. EXPERIMENTAL SECTION

3.1. Hydroxypropyl-β-cyclodextrin and β-cyclodextrin as tablet fillers for direct compression

A suggested running head: Cyclodextrins as fillers for direct compression.
3.1.1. Abstract

Cyclodextrins are cyclic carbohydrates widely used as complexing and non-complexing excipients in drug delivery systems. The purpose of this work was to study the ability of hydroxypropyl-β-cyclodextrin and β-cyclodextrin to act as tablet fillers for direct compression. In this way, several parameters of the cyclodextrins were evaluated, namely: i) the flow properties such as angle of repose, flow time, Carr's index and Hausner's ratio; ii) the compaction behaviour, specifically the energies and forces exerted during tableting, the plasticity index, the lubrication efficiency, and compression profiles (force/time and work/displacement of the upper punch); and iii) the influence on carbamazepine release characteristics from uncoated tablets, i.e., dissolution rate and disintegration time. In addition, these properties of the cyclodextrins were compared with those from other commonly used direct compression fillers (lactose monohydrate, mannitol, calcium hydrogen phosphate dihydrate, and microcrystalline cellulose) and co-processed excipients (microcrystalline cellulose/mannitol and lactose monohydrate/cellulose).

Three main conclusions can be drawn: i) the studied cyclodextrins can be used as tablet fillers for direct compression; ii) hydroxypropyl-β-cyclodextrin showed better properties than β-cyclodextrin mainly at the level of the physics of compression (higher values of plasticity index and lubrication efficiency) and of the drug release characteristics (faster and greater dissolution rate and shorter disintegration time); and iii) lactose monohydrate and hydroxypropyl-β-cyclodextrin displayed the best results. As there are people intolerant to lactose, hydroxypropyl-β-cyclodextrin, although its cost is higher, can be considered a good substitute for lactose.

**Keywords:** cyclodextrins; flow; compaction; dissolution; disintegration.
3.1.2. Introduction

Cyclodextrins (CDs) are cyclic carbohydrates with a hydrophilic outer surface and a hydrophobic central cavity that are widely used as complexing and non-complexing excipients in Pharmaceutical Technology to formulate solid, semi-solid, and liquid pharmaceutical dosage forms (1, 2). The principal pharmaceutical application of the CDs is to enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs, i.e., drugs belonging to Class 2 (low solubility and high permeability) and 4 (low solubility and low permeability) of the Biopharmaceutical Classification System (3). In addition, these compounds can be used in other drug delivery systems such as microspheres/microcapsules (4), nanoparticles (5) and liposomes (6), and as active pharmaceutical ingredients (7).

The oral drug delivery and tablets are, respectively, the route of administration and the pharmaceutical dosage form most commonly used in therapeutics (8). In tablet formulations, CDs can be used with different pharmaceutical applications such as (9): i) to enhance drug dissolution and bioavailability of poorly soluble drugs; ii) to modify/control the release of drugs; iii) to increase physicochemical drug stability; iv) to mask the bitter taste of drugs; v) to minimize adverse drug reactions; vi) to act as a tablet excipient such as filler, disintegrant, binder or multifunctional direct compression agent; and vii) to act as an osmotic pump agent.

The three main manufacturing processes of tablets are direct compression, wet granulation, and dry granulation (10). Direct compression is the first choice for the pharmaceutical industry, since it has fewer steps, is cheaper compared to granulation processes, and does not use heat and humidity which is an advantage for thermolabile and hydrolytic active pharmaceutical ingredients respectively (11). However, excipients play a relevant role in direct compression and their flow, compressibility, and compaction properties are fundamental for the success of the tablet formulation (12).

Pharmaceutical technologists can use several types of excipients in the tablet formulation such as fillers, binders, disintegrants, lubricants (anti-adherents and glidants), wetting agents, colourings agents, absorbents, buffers, sweeteners, and flavourings (9, 13). Moreover, there are co-processed excipients, i.e., high functionality compounds resulting from the combination of two or more excipients by a physical process (14).

Based on the previous considerations, the aim of the present work was to study the ability of hydroxypropyl-β-cyclodextrin (HPβCD) and β-cyclodextrin (βCD) to act as tablet fillers for direct compression. In this way, several parameters of the CDs were evaluated, namely: i) the flow properties such as angle of repose, flow time, Carr’s index (C.I), and
Hausner's ratio (HR); ii) the compaction behaviour, specifically forces, energies, plasticity index (PI), lubrication efficiency (R), and compaction profiles (force/time and work/displacement of the upper punch); and iii) the influence on carbamazepine (CBZ) release characteristics (dissolution rate and disintegration time) from uncoated tablets. Furthermore, these properties of the CDs were compared with other direct compression fillers (lactose monohydrate, mannitol, calcium hydrogen phosphate dihydrate, and microcrystalline cellulose) and co-processed excipients (microcrystalline cellulose/mannitol and lactose monohydrate/cellulose). HPβCD (Hydroxypropyl-betadex) and βCD (Betadex) were selected because they can be used orally and have regulatory acceptance (15). CBZ (C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O), an anticonvulsant agent belonging to Class 2 of the Biopharmaceutical Classification System, with poor flowability and compressibility properties was selected as a model drug (16).

It should be highlighted that: i) there are few studies published in the literature concerning βCD and HPβCD as non-complexing excipients of tablets; and ii) this work is innovative because it compared the flow properties, the compaction behaviour, and the influence on drug release characteristics of the two commonly CDs used in oral solid formulations with six excipients especially designed for direct compression.

3.1.3. Materials and Methods
3.1.3.1. Materials

CBZ (Acofarma\textregistered), HPβCD (Kleptose\textsuperscript{®} HP oral grade - high average molar degree of substitution (MS = 0.85); Roquette\textsuperscript{®}), βCD (Kleptose\textsuperscript{®}; Roquette\textsuperscript{®}), lactose monohydrate (Tablettose\textsuperscript{®} 100; Meggle Excipients & Technology), mannitol (Pearlitol\textsuperscript{®} 300 DC; Roquette\textsuperscript{®}), calcium hydrogen phosphate dihydrate (Emcompress\textsuperscript{®} Premium; JRS Pharma), microcrystalline cellulose (Vivapur\textsuperscript{®} 102; JRS Pharma), microcrystalline cellulose (90%, w/w)/mannitol (10%, w/w) (Avicel\textsuperscript{®} HFE-102; FMC Health and Nutrition), lactose monohydrate (75%, w/w)/cellulose (25%, w/w) (Cellactose\textsuperscript{®} 80; Meggle Excipients & Technology), sodium stearyl fumarate (Pruv\textsuperscript{®}; JRS Pharma), and sodium lauryl sulfate (Acofarma\textsuperscript{®}) were used.

3.1.3.2. Methods
3.1.3.2.1. Moisture determination

For each material, a 1.5 g sample was used, and the moisture content was determined (n = 3; mean ± standard deviation (SD)) in an infrared moisture determination balance (A&D Company, AD-4713, Japan) at 80 °C for 5 min.
3.1.3.2.2. Particle size determination by optical microscopy

For each sample, the average Martin's diameter, i.e., the diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas, was determined on 250 particles through an optical microscope (Nikon, Alphaphot YS, Japan) at ×10 magnification (17). Previously, the calibration of the micrometer of the eyepiece was performed with a scale micrometer (0-1mm/100, Nikon, Japan).

3.1.3.2.3. Scanning electron microscopy analysis

Scanning electron microscopy (SEM) images were obtained for all materials using a field emission microscope (JEOL, JSM-7001F, Japan) at the accelerating voltage of 15 kV. The coating with gold/palladium with a thickness of 25 nm was carried out using a coating system (Polaron, E5100, England).

3.1.3.2.4. Flow properties

For each material, apparent volumes (n = 3; mean ± SD) were evaluated using a Tap Density Tester (Electrolab, ETD-1020, India) at 250 taps per min. 250 mL cylinders and sample weights of 75 g (microcrystalline cellulose and microcrystalline cellulose/mannitol excipient) or 100 g (other materials) were used. Afterwards, the values of apparent volume were used to calculate bulk and tapped densities, the ability to settle, Cril and HR by the Eqs. 1, 2, 3, 4 and 5 respectively, where m is the sample weight, \( V_0 \) is the apparent volume without compaction, \( V_{10} \) is the apparent volume after 10 taps, \( V_{500} \) is the apparent volume after 500 taps, \( V_{1250} \) is the apparent volume after 1250 taps, \( d_0 \) is the apparent density without compaction (bulk density), \( d_{10} \) is the apparent density after 10 taps, \( d_{500} \) is the apparent density after 500 taps, and \( d_{1250} \) is the apparent density after 1250 taps (tapped density) (17-20).

\[
\text{Bulk density (g/mL)} = \frac{m}{V_0} \quad (1)
\]

\[
\text{Tapped density (g/mL)} = \frac{m}{V_{1250}} \quad (2)
\]

\[
\text{Ability to settle (mL)} = V_{10} - V_{500} \quad (3)
\]
\[
C.I. \, (\%) = \left( \frac{d_{500} - d_0}{d_{500}} \right) \times 100
\]  
\[
HR = \frac{d_{500}}{d_{10}}
\]

The angle of repose (\(n = 3\); mean ± SD) and the flow time (\(n = 3\); mean ± SD) were evaluated with a granulate flow tester (Erweka, GTB, Germany) (17). The tested diameter of the funnel and sample weights were 25 ± 0.01 mm (nozzle 3) and 25 g respectively (17).

3.1.3.2.5. Preparation of tablets

For all formulations, CBZ and filler were blended in a Turbula® shaker-mixer (Willy A. Bachofen Maschinenfabrik, T2C, Switzerland) for 15 min. Afterwards, the anti-adherent lubricant (Pruv®) was added and blended for 3 min in the same mixer. No other excipients such as disintegrants, binders or wetting agents were used.

Tablets, with a target weight of 500 ± 25 mg and a hardness value of 65 ± 15 N, were prepared by direct compression in automatic mode at speed 1 (out of the 10 positions available in the machine; namely, the lowest compression rate) using an instrumented alternative tableting machine (Dott.Bonapace, CPR-6, Italy). The punches had 11 mm diameter with plane surface and the preparation was performed at room temperature. Eight formulations (batches of 100 g) were studied and the tablets composition is presented in Table I.

<table>
<thead>
<tr>
<th>Component / Formula</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
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<td>397.5</td>
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<td>397.5</td>
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</table>
### 3.1.3.2.6. Compaction physics

With software Cosalt-write, Cosalt-read, and FIMA Compression Data Analysis, it was possible to measure the energies (n = 6; mean ± SD) and forces (n = 6; mean ± SD) during compaction and to register the compression curves (force/time and work/displacement of the upper punch).

The PI (n = 6; mean ± SD), according to Stamm and Mathis (21), and R (n = 6; mean ± SD) were evaluated using the Eqs. 6 and 7 respectively, where $F_S$ is the exerted force by the upper punch, $F_I$ is the applied force in the lower punch, $E_{LA}$ is the apparent net energy, i.e., the energy effectively expended in obtaining one tablet, $E_S$ is the total energy supplied by the upper punch, and $E_{EXP}$ is the expansion energy, i.e., the energy lost by instantaneous elastic recovery.

\[
\text{PI} \, (\%) = \frac{E_{LA}}{E_S} \times 100 = \left(\frac{E_S - E_{EXP}}{E_S}\right) \times 100
\]  

\[
R = \frac{F_I}{F_S}
\]

The time periods of the force/time cycle of compaction were evaluated (n = 6; mean ± SD) according to the following definitions (22): i) the dwell time is the time between the points corresponding to 90% maximum force of the upper punch; ii) the contact time with the compression force is the time between the points corresponding at 10% maximum force of the upper punch; and iii) the consolidation time corresponds to the necessary time to reach maximum force.

### 3.1.3.2.7. Physical characterization of the tablets

Weight uniformity variation (n = 10; mean ± SD, analytical balance Mettler Toledo, AE 200, Switzerland), thickness (n = 10; mean ± SD, electronic digital caliper Powerfix®, model number Z22855, Germany), and hardness (n = 10; mean ± SD, tablet hardness tester Erweka, TBH 28, Germany) of the obtained tablets were evaluated.

Friability was determined by submitting ten previously weighed tablets to falling shocks for 4 min in a friabilator (Electrolab, EF-1W, India), set at 25 rpm. After 4 min, the
tablets were weighed, and the percentage of friability was calculated according to the Eq. 8, where \( W_0 \) is the initial weight of the tablets and \( W_f \) is the weight of tablets after the test.

\[
\text{Friability (\%)} = \left( \frac{W_0 - W_f}{W_0} \right) \times 100
\]  \hspace{1cm} (8)

The tensile strength (\( n = 10; \text{mean} \pm \text{SD} \)) was calculated according to Fell and Newton (23) through Eq. 9, where \( P \) is the hardness (N), \( D \) and \( t \) are the diameter (mm) and thickness (mm) of the tablet respectively.

\[
\text{Tensile strength} = \frac{2P}{\pi Dt}
\]  \hspace{1cm} (9)

### 3.1.3.2.8. Drug content in tablets

For each formula, three tablets were triturated individually using a mortar and pestle. The resulting powder was dissolved in water containing sodium lauryl sulphate (1%, w/v) and sonicated for 15 min at 37 °C in an ultrasonic bath (Bandelin Sonorex, RK100H, Germany). An aliquot was withdrawn, suitably diluted, and filtered through a 25 mm syringe filter (0.45 µm polytetrafluoroethylene (PTFE) membrane, VWR International, United States of America). Afterwards, the drug content (\( n = 3; \text{mean} \pm \text{SD} \)) was determined at 288 nm using an ultraviolet-visible (UV-VIS) spectrophotometer (Jasco, V-650, Japan).

### 3.1.3.2.9. Disintegration test

Disintegration times (\( n = 6 \)) were measured using a tablet disintegration tester (Electrolab, ED-2L, India) in 750 mL purified water at 37 ± 2 °C. Disintegration baskets with six cylindrical transparent tubes (apparatus A) and disks were used (17).

### 3.1.3.2.10. Dissolution testing

The \textit{in vitro} drug release studies (\( n = 6; \text{mean} \pm \text{SD} \)) were performed using a dissolution apparatus (Sotax, AT7, Switzerland) according to the paddle method at 75 rpm (24). The dissolution medium consisted of 900 mL of water containing sodium lauryl sulphate (1%, w/v) at 37.0 ± 0.5 °C (24). The collection times were 2.5, 5, 7.5, 10, 15, 30, 45, 60, 90, 120, and 180 min, and the volume of the collected samples was 1.0 mL (without
volume replacement). Aliquots were filtered with a 25 mm syringe filter (0.45 µm PTFE membrane, VWR International, United States of America) and suitably diluted with the dissolution medium, and the drug concentration was determined with an UV-VIS spectrophotometer (Jasco, V-650, Japan) at 288 nm (24). A drug calibration curve was previously prepared wherein standards were sonicated for 15 min at 37 ºC in ultrasonic bath (Bandelin Sonorex, RK100H, Germany), and the coefficient of determination ($R^2$) was determined.

The dissolution profiles were compared using the similarity factor ($f_2$) calculated as shown in Eq. 10, where $n$ is the number of time points, $R_j$ is the mean percent reference drug dissolved at time $j$ after initiation of the study, and $T_j$ is the mean percent test drug dissolved at time $j$ after initiation of the study (25). The evaluation of the $f_2$ was based on the following conditions: i) seven-time points were considered (zero excluded), i.e., from 2.5 min to 45 min inclusive; ii) the time points were the same for all formulations; and iii) not more than one mean value of > 85% dissolved for any of the formulations. An $f_2$ value between 50 and 100 indicates that the two dissolution profiles are similar (26).

$$f_2 = 50 \times \log \left[ \frac{100}{\sqrt{\sum_{j=1}^{n} (R_j - T_j)^2}} \right]$$

(10)
3.1.4. Results
3.1.4.1. Technological characteristics of the materials

The results of the physical and mechanical properties of the studied materials are shown in Table II. Bulk densities of the substances ranged from 0.318 g/mL (Vivapur® 102) to 0.880 g/mL (Emcompress® Premium) and tapped densities from 0.446 g/mL (Vivapur® 102) to 1.049 g/mL (Emcompress® Premium). The studied materials showed acceptable (Vivapur® 102 and Avicel® HFE-102), good (HPβCD, βCD, Tablettose® 100 and Cellactose® 80), and excellent (Pearlitol® 300 DC and Emcompress® Premium) flow properties, except CBZ which exhibited poor flow (CRI = 31.2% and HR = 1.37) (17). Comparing the two studied CDs, both demonstrated similar characteristics; however, HPβCD presented a lower flow time (less than half) than βCD.

The average Martin’s diameter ranged from 57 (CBZ) to 225 µm (Pearlitol® 300 DC). In relation to moisture content, the obtain values were less than or equal to 8%; CDs had the highest percentages and HPβCD (5.96%) presented a smaller value than βCD (8.11%).

SEM images of the CBZ and excipients are shown in Fig. 1. The materials exhibited different particle morphologies and sizes. Cellactose® 80 and Emcompress® Premium had a very evident spherical shape. Tablettose® 100 and Pearlitol® 300 DC showed agglomerates with a rough and structured surface, and granular powder aspect respectively. CBZ, βCD, HPβCD, Vivapur® 102, and Avicel® HFE-102 presented irregular shapes and sizes.
Table II. Apparent densities, flow properties, Martin's diameter, and moisture content.\(^a\)

<table>
<thead>
<tr>
<th>Parameter / Material</th>
<th>CBZ</th>
<th>HPβCD</th>
<th>βCD</th>
<th>Tablettose® 100</th>
<th>Pearlitol® 300 DC</th>
<th>Emcompress® Premium</th>
<th>Vivapur® 102</th>
<th>Avicel® HFE-102</th>
<th>Cellactose® 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density (g/mL)</td>
<td>0.530±0.016</td>
<td>0.418±0.002</td>
<td>0.652±0.002</td>
<td>0.575±0.007</td>
<td>0.676±0.013</td>
<td>0.880±0.016</td>
<td>0.318±0.005</td>
<td>0.388±0.011</td>
<td>0.426±0.006</td>
</tr>
<tr>
<td>Tapped density (g/mL)</td>
<td>0.780±0.010</td>
<td>0.503±0.002</td>
<td>0.813±0.000</td>
<td>0.714±0.004</td>
<td>0.758±0.012</td>
<td>1.049±0.010</td>
<td>0.446±0.000</td>
<td>0.499±0.004</td>
<td>0.519±0.001</td>
</tr>
<tr>
<td>Ability to settle (mL)</td>
<td>49±4</td>
<td>14±3</td>
<td>18±1</td>
<td>14±1</td>
<td>7±1</td>
<td>10±1</td>
<td>45±3</td>
<td>26±4</td>
<td>14±0</td>
</tr>
<tr>
<td>Carr's index (%)</td>
<td>31.2±1.3</td>
<td>13.1±0.8</td>
<td>17.8±0.4</td>
<td>18.8±1.2</td>
<td>9.7±1.2</td>
<td>14.9±1.2</td>
<td>26.9±1.3</td>
<td>21.8±1.9</td>
<td>16.9±0.8</td>
</tr>
<tr>
<td>Hausner's ratio</td>
<td>1.37±0.02</td>
<td>1.07±0.01</td>
<td>1.14±0.01</td>
<td>1.10±0.01</td>
<td>1.05±0.01</td>
<td>1.10±0.01</td>
<td>1.26±0.02</td>
<td>1.17±0.02</td>
<td>1.07±0.0</td>
</tr>
<tr>
<td>Flow time (s/100g)</td>
<td>n.d.</td>
<td>0.8±0.0</td>
<td>1.9±0.2</td>
<td>1.1±0.2</td>
<td>0.4±0.0</td>
<td>0.4±0.0</td>
<td>4.6±1.0</td>
<td>3.2±0.3</td>
<td>1.2±0.0</td>
</tr>
<tr>
<td>Angle of repose (º)</td>
<td>n.d.</td>
<td>33.7±0.5</td>
<td>27.4±0.9</td>
<td>28.8±0.1</td>
<td>26.3±0.3</td>
<td>23.5±0.6</td>
<td>38.6±0.6</td>
<td>31.5±1.4</td>
<td>31.3±1.0</td>
</tr>
<tr>
<td>Martin's diameter (µm)</td>
<td>57</td>
<td>137</td>
<td>90</td>
<td>86</td>
<td>225</td>
<td>141</td>
<td>107</td>
<td>90</td>
<td>103</td>
</tr>
<tr>
<td>Moisture (%)</td>
<td>0.34±0.07</td>
<td>5.96±0.39</td>
<td>8.11±0.48</td>
<td>0.40±0.11</td>
<td>0.28±0.12</td>
<td>0.33±0.11</td>
<td>3.47±0.21</td>
<td>3.40±0.31</td>
<td>2.18±0.28</td>
</tr>
</tbody>
</table>

\(^a\) n.d. means not determined
3.1.4.2. Compaction and properties of the tablets

As can be seen from Fig. 2 and Table III, tablets with uniform aspect and suitable physical properties were obtained. However, tablets presented a friability value greater than 1.0%. The CBZ content in tablets ranged from 97.4 ± 3.5 (formula I) to 100.9 ± 0.7% (formula II).

The values of tensile strength ranged from 0.38 to 1.06 N/mm$^2$, and the tablets obtained from formulation VIII ($< F_S$ value) showed the lowest tensile strength value. All the analysed formulas presented a value of $R < 0.94$. Values of $R$ lower than 0.8 indicate an inadequate lubrication, as verified for formulations III, IV, and VIII (27, 28).
The values of PI, calculated according to Stamm and Mathis, were greater than 69.8% and formulations II, IV, and V presented similar values. HPβCD presented the highest value (PI = 87.7%).

All the obtained compaction profiles showed the same configuration. In Fig. 3, an example of the force/time (a) and work/displacement of the upper punch (b) compression profiles is shown. Concerning the time periods of the force/time compaction curve, it should be noted that: i) the dwell time was around 30 ms, except for formulation V which exhibited 22.7 ms; ii) the consolidation time ranged from 73.9 to 102.1 ms; iii) the contact time with compaction force ranged between 124.3 and 156.4 ms; and iv) formulas I and VIII demonstrated the highest values of contact and consolidation times.

![Fig. 2. Physical aspect of the tablets: a) Formula I; b) Formula II; c) Formula III; d) Formula IV; e) Formula V; and f) Formula VIII.](image-url)
Table III. Compaction forces and energies, R, PI, time periods of the force/time compression cycle, physical properties, drug content, and disintegration time of the tablets.

<table>
<thead>
<tr>
<th>Parameter / Formulas</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>510±2</td>
<td>500±15</td>
<td>500±6</td>
<td>487±6</td>
<td>502±2</td>
<td>508±4</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>4.92±0.02</td>
<td>4.28±0.03</td>
<td>4.12±0.02</td>
<td>3.94±0.08</td>
<td>3.13±0.01</td>
<td>4.97±0.01</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>72±3</td>
<td>76±16</td>
<td>51±10</td>
<td>58±9</td>
<td>57±8</td>
<td>33±3</td>
</tr>
<tr>
<td>Tensile strength (MPa)</td>
<td>0.85±0.04</td>
<td>1.03±0.21</td>
<td>0.72±0.14</td>
<td>0.85±0.13</td>
<td>1.06±0.14</td>
<td>0.38±0.04</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>2.9</td>
<td>1.7</td>
<td>2.1</td>
<td>7.1</td>
<td>1.9</td>
<td>3.9</td>
</tr>
<tr>
<td>FS (N)</td>
<td>7450±80</td>
<td>6110±370</td>
<td>13,370±200</td>
<td>25,640±550</td>
<td>14,520±260</td>
<td>4290±120</td>
</tr>
<tr>
<td>F (N)</td>
<td>6450±50</td>
<td>4930±230</td>
<td>10,340±180</td>
<td>19,380±500</td>
<td>13,700±220</td>
<td>3310±80</td>
</tr>
<tr>
<td>R</td>
<td>0.87±0.00</td>
<td>0.81±0.01</td>
<td>0.77±0.00</td>
<td>0.76±0.00</td>
<td>0.94±00</td>
<td>0.77±0.01</td>
</tr>
<tr>
<td>ES (J)</td>
<td>7.77±0.21</td>
<td>4.16±0.45</td>
<td>8.74±0.47</td>
<td>15.67±0.75</td>
<td>6.60±0.44</td>
<td>4.61±0.13</td>
</tr>
<tr>
<td>EXP (J)</td>
<td>0.96±0.15</td>
<td>1.14±0.21</td>
<td>1.61±0.31</td>
<td>4.75±0.48</td>
<td>1.72±0.41</td>
<td>0.60±0.06</td>
</tr>
<tr>
<td>ELA (J)</td>
<td>6.81±0.10</td>
<td>3.02±0.26</td>
<td>7.13±0.21</td>
<td>10.93±0.45</td>
<td>4.88±0.14</td>
<td>4.01±0.13</td>
</tr>
<tr>
<td>PI (%)</td>
<td>87.7±1.5</td>
<td>72.7±2.2</td>
<td>81.7±2.7</td>
<td>69.8±2.1</td>
<td>74.2±4.5</td>
<td>87.1±1.3</td>
</tr>
<tr>
<td>Consolidation time (ms)</td>
<td>90.5±7.6</td>
<td>76.8±4.7</td>
<td>81.5±0.9</td>
<td>79.4±1.6</td>
<td>73.9±1.8</td>
<td>102.1±1.5</td>
</tr>
<tr>
<td>Dwell time (ms)</td>
<td>33.4±3.2</td>
<td>29.7±1.1</td>
<td>32.9±3.8</td>
<td>32.7±2.5</td>
<td>22.7±3.0</td>
<td>33.0±1.1</td>
</tr>
<tr>
<td>Contact time (ms)</td>
<td>155.8±10.9</td>
<td>130.5±4.4</td>
<td>136.2±1.1</td>
<td>143.8±1.8</td>
<td>124.3±2.2</td>
<td>156.4±2.0</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>97.4±3.5</td>
<td>100.9±0.7</td>
<td>100.1±0.7</td>
<td>99.8±0.4</td>
<td>100.4±0.3</td>
<td>99.4±0.5</td>
</tr>
<tr>
<td>Disintegration time (s)</td>
<td>545</td>
<td>1080</td>
<td>143</td>
<td>1058</td>
<td>&gt;10,800</td>
<td>40</td>
</tr>
</tbody>
</table>
Fig. 3. Compaction profiles obtained from one tablet of formula I: a) Force (kN)/time (s); and b) Progressive work (J)/displacement of the upper punch (mm).
3.1.4.3. Drug release characteristics

As shown in the Fig. 4, in vitro dissolution tests showed at 180 min a mean CBZ release from 13 ± 5 to 108 ± 4%. A drug calibration curve was obtained (y = 45.761x + 0.0049; R² = 0.9998) and the dissolution profiles were not similar (f₂ < 50) (26). Nevertheless, for formulas I and III, II and IV, and III and VIII, the f₂ values were 47.5, 47, and 40.5 respectively.

Disintegration times of the tablets (Table III) were less than or equal to 18 min, except for formula V (Emcompress® Premium) which presented a value greater than 3 h. Formulas II and IV showed similar disintegration times and the formula VIII had a faster disintegration (40 s). Comparing the influence on drug release characteristics of the CDs, HPβCD (formula I) presented a faster and greater dissolution rate and a shorter disintegration time (about half) than βCD (formula II).

Fig. 4. Drug dissolution profiles from the uncoated tablets in distilled water containing sodium lauryl sulphate (1%, w/v) at 37 °C.
3.1.5. Discussion

Previously, some researchers used CDs as non-complexing excipients of the tablets, i.e., as fillers, binders or disintegrants (29, 30). For instance, Zimmer et al. (31) analysed the feasibility of the βCD as a diluent in the formulation of orally disintegrating tablets containing ibuprofen. The results showed that the higher concentration of βCD improved the hardness of tablets without increasing the disintegration time. The same conclusion was obtained by Late and Banga (32). Another study showed the potential use of HPβCD as an excipient for orally disintegrating tablets containing alpha-tocopheryl acetate, an oily drug (33). In addition, tablets, prepared by the moulding process, showed high hardness and rapid disintegration both in vitro and in vivo (33). Recently, Garcia-Fernandez et al. (34) developed a new multifunctional direct compression excipient based on citric acid-βCD polymer in its water-insoluble (PCD-I) and soluble (PCD-S) forms. The outcomes emphasized the multifunctional excipient properties of PCD-I/PCD-S polymers, that is to say, good flow and compression properties, no signs of toxicological symptoms, and modulable disintegration time.

In this study, the functionalities of the βCD and HPβCD as direct compression tablet fillers were studied and compared with six excipients especially designed for direct compression. These CDs were selected because they are often used as complexing and non-complexing excipients in oral solid formulations and present regulatory acceptance by the medicine authorities worldwide (15).

In a first step, the material flow properties were evaluated because they are extremely important in pharmaceutical industry for blending, tablet compaction, uniformity in drug content, and in scale-up processes (35, 36). A material presents good flow when it shows the following characteristics (17-20): i) angle of repose less than or equal to 35º; ii) flow time less than or equal to 10.0 s/100 g; iii) Cr less than or equal to 15%; iv) HR less than or equal to 1.18; and v) ability to settle less than or equal to 20 mL. It should be noted that these parameters are not intrinsic properties of a material and can be influenced by size and shape, surface area, moisture content, and cohesiveness (37). All materials presented acceptable/good/excellent flow properties. Nevertheless, CBZ showed poor flow (cohesive material) and it was not possible to determine the angle of repose and the flow time with the nozzle corresponding to aperture size of 25 mm (17). HPβCD presented a lower flow time (less than half) than βCD; this aspect can be explained by the fact that hydroxypropyl-betadex had lower values of ICr, HR, and moisture content, and higher Martin's diameter than betadex. Concerning the moisture content, Crouter and Briens (38) observed that the flowability decreased with increasing moisture content for four excipients.
(microcrystalline cellulose, carboxymethyl cellulose, polyvinylpyrrolidone, and potato starch). According to the SEM images, materials displayed different particle morphologies and sizes. The obtained flow properties values are concordant with SEM analysis and the determined average Martin's diameter, i.e., materials with higher particle size flow better than materials with minor particle size. Generally, particles larger than 250 µm are frequently free-flowing and particles smaller than 100 µm are cohesive and flow problems will probably happen as with CBZ (average Martin's diameter = 57 µm) (39).

Afterwards, uncoated tablets were prepared by direct compression and the study of the physical compression was performed. However, for formulas VI (Vivapur® 102) and VII (Avicel® HFE-102), it was not possible to prepare tablets with a target weight of 500 ± 25 mg with suitable hardness. It should be emphasized that the flowability of the excipient-CBZ mixtures was suitable for preparing the tablets by direct compression in automatic mode at speed 1 using the instrumented alternative tableting machine. Each prepared tablet contained 100 mg of CBZ and sodium stearyl fumarate (Pruv®), an inert and poorly water-soluble compound but with hydrophilic character, was used as anti-adherent lubricant (0.5%, w/w) because with this concentration, we obtained previously suitable lubrication (R = 0.912 ± 0.004) (40) and reduced interference in the drug dissolution rate and in the disintegration time of the tablets (41). Lubrication is perfect or suitable when the R value is 1 or greater than 0.9 respectively (27, 28).

In the pharmaceutical market, there are immediate release and sustained release tablets containing 100, 200, 300, and 400 mg of CBZ. In general, microcrystalline cellulose, croscarmellose sodium or sodium starch glycolate, anhydrous colloidal silicon dioxide, and magnesium stearate are, respectively, the filler, the disintegrant, the glidant, and the anti-adherent lubricant most used in the formulas for immediate release of the drug.

Although the friability value was greater than 1.0%, tablets showed adequate physical characteristics for their use in the laboratory. In addition, the values of tensile strength are close to 1 MPa, with exception for formula VIII. It should be noted that tensile strengths down to 1 MPa may be sufficient for small batches where the tablets are not subjected to large mechanical stresses (42). On the other hand, a tensile strength greater than 1.7 MPa usually assures that a tablet is mechanically strong enough to withstand commercial manufacture (42).

The instrumentation of the tablet press is crucial for basic research in compression physics, as it facilitates product development, optimization and scale up, and allows monitoring and control of production (43). Regarding the compaction behaviour, it can be stated that: i) all obtained compaction profiles showed the same configuration; ii) from the values of the $F_s$ (Table III), it was possible to differentiate the tested materials, i.e.,
formulations III, IV, and V presented the highest values, and formulations I, II, and VIII showed the lowest values; and iii) HPβCD exhibited the highest value of the PI (87.7%) and an appropriate R value (0.87). It is known that the materials with higher percentage of plasticity show a better aptness for compaction (compression + consolidation) (13).

The performance of a drug is primarily influenced by the disintegration and dissolution behaviour of the powder compact (44). The drug dissolution rate after 3 h and the disintegration time of the tablets for formulation V were 13% and > 3 h respectively. Calcium hydrogen phosphate dihydrate (Emcompress® Premium) is a water-insoluble filler and this property may explain this aspect (44, 45). It should be pointed out that drug contents in tablets (Table III) ranged from 97.4 to 100.9% and the addition of a superdisintegrant (for instance, croscarmellose sodium, sodium starch glycolate, and crospovidone) and a wetting agent (for example, sodium lauryl sulphate and polysorbate 80) to formula V can enhance the dissolution rate and decrease the disintegration time. For instance, Ferrari et al. (46) affirm that the physical mixture of a practically insoluble drug with a superdisintegrant is a valid approach to the improvement of dissolution. In addition, in general, disintegrants performed better when formulated with insoluble fillers than with soluble fillers (45). As far as the disintegration times are concerned, it can be stated that according to the pharmacopoeial standards and specifications, the uncoated tablets must have a disintegration time less than or equal to 15 min. Based on this specification, only formulas I, III, and VIII met this requirement. As the disintegration time was low (<3 min) for formulas III and VIII, Tablettose® 100 and Cellactose® 80 can be used, for instance, as diluents in soluble and dispersible tablets. On the other hand, in the dissolution test, the pharmacopoeial specification for CBZ tablets states that not less than 75% of the labelled amount of CBZ should be dissolved in 60 min (24). According to this criterion, only formulas I, III, IV, and VIII complied with this specification. Formula I showed better properties at the level of the CBZ release characteristics than formula II and this aspect can be explained by the fact that βCD (aqueous solubility at 20 °C = 1.85 g/100 mL) has lower solubility than HPβCD, a water highly soluble βCD derivative (aqueous solubility at 25 °C = 65 g/100 mL).

Considering the economic point of view and the information provided by the manufacturers, although HPβCD is more suitable as filler in comparison with βCD, HPβCD (600 €/kg) has higher cost than βCD (16 €/kg). By contrast, the other fillers present a more attractive price for its industrial application, i.e., for instance, the price (€/kg) for Tablettose® 100, Vivapur® 102, Cellactose® 80, and Emcompress® Premium are, respectively, 2.87, 4.5, 5.07 and 5.5.

Overall, formulas III, IV, and VIII showed suitable results, however: i) formula III presented a friability value of 2.1% and a R value less than 0.8 (R = 0.77) which indicates
inadequate lubrication (27, 28); ii) formula IV had high values of $F_S$, $E_{LA}$, and friability, and low value of $R$; and iii) formula VIII had high value of friability, and low values of $R$ and tensile strength.

3.1.6. Conclusion

Three main conclusions can be drawn from the results obtained in the present work: i) the studied CDs can be used as tablet fillers for direct compression; ii) HPβCD showed better properties than βCD mainly at the level of the physics of compression (higher values of PI and $R$) and of the drug release characteristics (faster and greater dissolution rate and shorter disintegration time); and iii) lactose monohydrate and HPβCD displayed the best results. As there are people intolerant to lactose, HPβCD, although its cost is higher, can be considered a good substitute for lactose.

3.1.7. List of abbreviations

CBZ - Carbamazepine
CD(s) - Cyclodextrin(s)
$C_{ri}$ - Carr's index
$E_{EXP}$ - Expansion energy
$E_{LA}$ - Apparent net energy
$E_S$ - Total energy supplied by the upper punch
$f_2$ - Similarity factor
$F_I$ - Applied force in the lower punch
$F_S$ - Exerted force by the upper punch
HPβCD - Hydroxypropyl-β-cyclodextrin
HR - Hausner's ratio
MS - Average molar degree of substitution
PI - Plasticity index
PTFE - Polytetrafluoroethylene
$R$ - Lubrication efficiency
$R^2$ - Coefficient of determination
SD - Standard deviation
SEM - Scanning electron microscopy
UV-VIS - Ultraviolet-visible
βCD - β-cyclodextrin
3.1.8. Acknowledgements

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3.1.9. References


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3.2. Hydroxypropyl-β-cyclodextrin-based fast dissolving carbamazepine printlets prepared by semisolid extrusion 3D printing

Hydroxypropyl-β-cyclodextrin-based fast dissolving carbamazepine printlets prepared by semisolid extrusion 3D printing

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\textsuperscript{e} Fohlia Ltd., 3 Bournes Road, Ashford, Kent TN24 0SW, United Kingdom
3.2.1. Highlights

- Hydroxypropyl-β-cyclodextrin was used for the first time to prepare three-dimensional (3D) printed formulations (printlets).
- Orodispersible and immediate release printlets were successfully prepared.
- Small changes in cellulose ethers ratio allowed fine tuning of drug release profile.
3.2.2. Abstract

This work aimed to explore for the first time the use of cyclodextrins to prepare printlets of poorly soluble drugs, such as carbamazepine, which require fine dose adjustment and rapid release. Orodispersible (flash) and immediate release formulations were 3D printed via semisolid extrusion of wet masses of hydroxypropyl-β-cyclodextrin (HPβCD) and cellulose ethers and regulating tablet porosity. Rheology of the wet masses allowed identifying printable compositions. Printing robustness was assessed evaluating weight, dimensions, hardness, drug content, and microstructure. Drug crystallinity, printlet disintegration and dissolution profiles were also characterized.

The results highlighted the feasibility of using HPβCD as excipient in printlets of poorly soluble drugs, and the possibilities of tuning drug release profiles through small changes in cellulose ethers nature and ratio. Semisolid extrusion-based 3D printing was revealed as a feasible approach to in situ form carbamazepine-HPβCD complexes and to produce printlets with suitable physical and drug release properties for oral delivery.

**Keywords:** 3D printed tablets; semisolid extrusion; carbamazepine; hydroxypropyl-β-cyclodextrin; flash formulation; additive manufacturing.
3.2.3. Graphical abstract
3.2.4. Introduction

The three-dimensional (3D) printing technologies are being widely explored in a variety of biomedical fields such as tissue engineering (1) and diagnostics (2). In Pharmaceutical Technology, the additive manufacturing has become one of the most revolutionary and powerful tools because of its inherent advantages compared to traditional solid forms manufacturing technologies (3-5), such as rapid and on-demand production of complex configurations (sizes and internal/external geometries); accurate control of the spatial distribution of the active pharmaceutical ingredient/s within the dosage form; and production of small batches of personalized medicines with the most adequate drug dose (particularly for age- or pharmacogenetic-adjustments), excipients (considering intolerances, allergies or religious issues) and release profiles for each patient.

Currently, there are five main 3D printing technologies used in the pharmaceutical field, namely (4, 6): i) binder jet printing; ii) selective laser sintering (SLS); iii) fused deposition modelling (FDM); iv) semisolid extrusion; and v) stereolithography (SLA). In 2015, the Food and Drug Administration (FDA) approved a 3D printed orodispersible tablet, Spritam® (levetiracetam), which opened a new chapter for the manufacture of pharmaceuticals (7). The technology used, binder jet printing, resembles the traditional way of powder-wet granulation for tableting and has not been developed to manufacture personalized formulations. A similar technology that uses a laser to sinter the particle together, SLS, has not been adapted for personalized medicine either (8). FDM requires the use of hot melt extrusion for the preparation of filaments which may result in drug degradation (9); and excipients used in SLA are not approved for human consumption (10). Differently, semisolid extrusion, also known as 3D micro-extrusion, relies on the layer-by-layer deposition of semisolids (gels or pastes) through a syringe-based tool-head (11). Compared to other 3D printing technologies, this technology requires normally simple preparation steps, mild processing conditions avoiding drug degradation, and can use generally recognized as safe (GRAS) excipients (12, 13).

There are few reports on immediate release 3D printed tablets (printlets) prepared using semisolid extrusion which rely normally on highly water-soluble polymers or high proportions of disintegrants (14, 15). Cyclodextrins and their polymers are widely used in pharmaceutics in order to increase drug solubility and bioavailability (16, 17). However, to the best of our knowledge, the use of cyclodextrins as drug solubilizing agents or even as hydrophilic fillers has not been explored in printlets in spite of its extended use for solid drug formulation (18, 19).
The aim of this work was to explore the feasibility of using cyclodextrins to prepare for the first time personalized orodispersible (flash) and immediate release printlets of carbamazepine (CBZ). CBZ is a Biopharmaceutics Classification System (BCS) class 2 drug used as antiepileptic and anticonvulsant for the treatment of seizure disorders and neuropathic pain (20). The treatments with this drug may benefit from fine dose adjustment, and current formulations do not cover paediatric needs (21). The needs of drug dose personalization could be overcome by means of 3D printing. Thus, the hypothesis of our work is that personalized, rapid release CBZ solid formulations can be prepared by combining the feasibility of regulating formulation size, dose and porosity through 3D printing, with the capability of hydroxypropyl-β-cyclodextrin (HPβCD) to act as soluble filler and to form inclusion and non-inclusion complexes with a wide variety of hydrophobic drugs (16). Thus, to carry out the work, first mixtures of CBZ and HPβCD with various cellulose ethers were wetted with hydroalcoholic solutions to obtain wet masses that enable in situ drug/HPβCD complex formation and have suitable rheological properties for semisolid extrusion 3D printing. A 3D printing protocol was implemented to obtain pore-controlled matrices with high surface area of contact with the dissolution medium. Printlets were characterized using a variety of techniques, including relevant pharmacopeial assays for oral solid dosage forms.

3.2.5. Materials and Methods
3.2.5.1. Materials

CBZ (molecular weight (MW) 236.3 g/mol) was from Acofarma® (Spain). HPβCD (Kleptose® HP oral grade; high average molar substitution (MS) = 0.85; MW 1480.7 g/mol) was from Roquette® (France). Hydroxypropyl methylcellulose (HPMC) as Methocel™ E4M Premium (methoxyl 28.6%; hydroxypropoxyl 9.5%; viscosity 2% in water 3853 mPa·s) and Methocel™ F4M Premium (methoxyl 30.0%; hydroxypropoxyl 7.5%; viscosity 2% in water 4970 mPa·s) were from Colorcon® (United Kingdom (UK)). Polyvinylpyrrolidone (PVP) Plasdone® K-25 with average MW 34,000 was from ISP Technologies, INC. (United States of America (USA)). Sodium carboxymethylcellulose Blanose™ CMC 9M31F PH (degree of substitution (DS) 0.88; viscosity 2% in water 2520 mPa·s) was from Ashland UK Ltd. (UK). Croscarmellose sodium (Ac-Di-Sol® SD-711; DS 0.72) was from FMC Corporation (USA). Sodium lauryl sulphate (Acofarma®, Spain), ethanol absolute (VWR Chemicals, France), and distilled water were also used.
3.2.5.2. Methods

3.2.5.2.1. Preparation of wet masses

Two wet masses were selected, after several trials, to prepare orodispersible (formulation I) and immediate release (formulation II) printlets (Table I). The masses were prepared as follows: i) HPMC F4M (0.625 g, binder) was added slowly to moistening liquid (water:ethanol: 90:10 vol/vol; 10 mL) and dispersed using a dual-speed mixer (IKA®, RW 20 DZM, Germany) at 200 rpm for 15 min. The resulting gel was stored in a tightly closed container at 4 °C for 12 h; ii) separately, CBZ (1.1875 g) was mixed with HPβCD (3.5625 g) in a mortar for 2 min; iii) 1.150 g of the previously prepared gel was added into the mortar containing the CBZ/HPβCD mixture and blended until homogeneous aspect (approx. 2 min); iv) the disintegrant (0.125 g of Ac-Di-Sol® powder; only for formulation I) or the binder agent (0.125 g of HPMC F4M powder; only for formulation II) was added into the mortar and mixed (approx. 2 min more); and v) more moistening liquid was added, if needed (up to 100 µL), in order to properly perform the malaxation. All formulations contained the same percentage (24%, w/w dry formulation) of CBZ.

Table I. Composition of the printlets.

<table>
<thead>
<tr>
<th>Raw materials</th>
<th>Dry formulations (%)</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>24.0</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>HPβCD</td>
<td>72.1</td>
<td>72.1</td>
<td></td>
</tr>
<tr>
<td>HPMC F4M</td>
<td>1.4</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Ac-Di-Sol® SD-711</td>
<td>2.5</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

3.2.5.2.2. Preparation of the 3D printed tablets

The wet masses were immediately transferred to a 5 mL extrusion syringe with a tapered extrusion tip (0.58 mm orifice), and placed into the 3D bioprinter (Regemat 3D S.L., Spain) with a fan attached (Fig. 1). With the used software (Regemat 3D Designer), cylindrical-geometry printlets were designed as follows: 15 mm diameter; 3 mm height; diagonal (45°) infill pattern; 1 mm pore size; 0.58 mm layer height; 3 mm/s flow speed; and total layers 5. Finally, printlets were placed in an oven at 40 °C for 12 h.
Fig. 1. The 3D printing setup with an extrusion syringe loaded with the wet mass containing carbamazepine (CBZ; chemical structure in the figure). The insert shows the detail of the mass flowing from the tip during the second layer of the printlet design.

3.2.5.2.3. Rheological characterization of wet masses

Samples of wet masses were taken from the syringe immediately before printing and mechanically analysed using a rheometer (Anton Paar, MCR 302, Austria) fitted with a H-PTD 200 Peltier hood and a disposable measuring aluminium plate (15 mm in diameter). The gap and the temperature were fixed at 1 mm and 20 ºC, respectively. The test consisted in five steps in amplitude sweep mode recording G’ (storage modulus) and G” (loss modulus) to evaluate the self-healing, as follows (22, 23): i) 0.5% shear strain at 1 Hz for 300 s (data points every 12 s); ii) 100% shear strain at 1 Hz for 120 s; iii) 0.5% shear strain at 1 Hz for 300 s; iv) 100% shear strain at 1 Hz for 120 s; and v) 0.5% shear strain at 1 Hz for 300 s. For each mass composition, at least four replicates were evaluated.

3.2.5.2.4. Characterization of the 3D printed tablets
3.2.5.2.4.1. Physical properties

Diameter and thickness of the printlets (n = 10) were measured using a digital calliper (Powerfix®, Z22855). The weight (n = 10) was recorded with an analytical balance (RADWAG, AS220.R2), the breaking force (n = 5) was determined using a tablet hardness tester (Erweka, TBH 28), and the friability (n = 10) was evaluated in a friabilator (Electrolab, EF-1W) set at 25 rpm for 4 min.
3.2.5.2.4.2. Scanning electron microscopy

Scanning electron microscopy (SEM) images of surface (top and bottom) and cross-section of the printlets were taken with a high resolution Schottky environmental scanning electron microscope (FEI Quanta 400 FEG ESEM). All samples were visualized after sputter coating with Au/Pd thin film (∼20 nm) using the SPI-Module™ Sputter Coater equipment.

3.2.5.2.4.3. Drug content

Three printlets of each formulation were placed in separate volumetric flasks (250 mL) with distilled water containing sodium lauryl sulphate (1%, w/v) and stirred for 30 min in a hotplate stirrer (IKA®, C-MAG HS 7) (24). Afterwards, samples of solution were filtered through 0.45 μm polytetrafluoroethylene (PTFE) membranes, and suitably diluted. CBZ concentration was determined from absorbance at 288 nm (spectrophotometer Jasco, V-650, Japan) using a calibration curve in the 0.00444 to 0.02664 mg/mL range.

3.2.5.2.4.4. Differential scanning calorimetry

Differential scanning calorimetry (DSC) curves of raw materials (drug and excipients), formulation blends before printing, and the printlets formulations (ground to a fine powder) were recorded in a DSC Q200 (TA instruments, USA) integrated with a refrigerator cooling system and Universal Analysis 2000 software. Samples (5-6 mg) were heated from 40 to 250 °C at 10 °C/min under nitrogen flow (50 mL/min).

3.2.5.2.4.5. X-ray diffraction

Samples of CBZ and excipients, formulation blends and printlets (ground to a fine powder) were examined. The X-ray powder diffraction (XRD) patterns were obtained at 25 °C with an X-ray diffractometer (Philips Analytical PW 3050/60 X'Pert PRO) equipped with X'Celerator detector and with automatic data acquisition (X'Pert Data Collector software), using monochromatized Cu-Kα radiation as incident beam. The intensity and voltage applied were, respectively, 30 mA and 40 kV. The angular range of data acquisition was 7-42° 2θ, with a step size of 0.017° and 19.685 s of scan step time.
3.2.5.2.4.6. Disintegration test

Disintegration times (n = 3) were measured using a tablet disintegration tester (Electrolab, ED-2L) in distilled water at 37 ± 2 °C. In addition, the time that a printlet floating on distilled water (25 mL) in a Petri dish required to completely disintegrate was also measured (n = 3) (25). The images of the disintegration process were recorded through a smartphone (Samsung, Galaxy S6).

3.2.5.2.4.7. CBZ release test

Drug release tests from printlets (n = 3) were performed using a paddle dissolution tester (Sotax, AT7) at 75 rpm in 900 mL of distilled water containing sodium lauryl sulphate (1%, w/v) at 37.0 ± 0.5 °C, according to the United States Pharmacopeia (USP) 41 - National Formulary (NF) 36 (26) for the dissolution test of CBZ oral solid dosage forms. Pure CBZ (50 mg) dissolution rate was similarly monitored. After 2.5, 5, 7.5, 10, 12.5, 15, 30, 45, and 60 min, samples of the medium (3.0 mL, without volume replacement) were taken, filtered through 0.45 μm PTFE membranes, and suitably diluted with dissolution medium. CBZ concentration was determined from absorbance at 288 nm (spectrophotometer Jasco, V-650).

3.2.6. Results and Discussion

3.2.6.1. Printlets preparation

The main challenge of semisolid extrusion is to obtain wet masses that combine adequate flowability through the nozzle, high consistency once deposited on the platform to withstand the weight of the next layer without deformation, and the desired drug release profiles after drying. Indeed, most research on printlets has been focused on sustained release formulations (12, 27). The reports on rapid release formulations are much scarcer and rely on drug dispersions in highly water-soluble polymers or drug mixtures with high proportions of disintegrants (12, 14, 15, 28, 29). Differently, in the present study we hypothesized that the hydrophilic HPβCD (not yet tested for semisolid extrusion 3D printing) may facilitate the wetting of the strands and increase the apparent solubility of CBZ, which in turn should contribute to accelerate more the release. CBZ/HPβCD 1:1 inclusion complex formation has been previously reported (30), and it was also shown that HPβCD may perform as soluble tablet filler for direct compression and accelerates tablet disintegration and release rate of CBZ (31).
Additionally, other components were chosen among common approved pharmaceutical excipients. Since recently, a variety of cellulose derivatives are being evaluated to prepare 3D printed structures (32, 33), and specifically cellulose ethers are gaining attention as components of printlets. For example, a high viscosity variety of HPMC was evaluated as gelling component in the semi-extrusion printing of a naftopidil salt, showing that an increase in the proportion of HPMC causes a delay in drug release (34). Lower viscosity HPMC varieties have been investigated for gastro-floating tablets printed covering a wide range of infilling percentages as a way of trapping air and improve buoyancy (35). Cellulose ethers, such as hydroxypropyl cellulose, have been also suitable to prepare capsules by FDM to encapsulate a variety of compounds (36).

During the preparation of the printlets, four principal aspects were studied, namely: i) the binder agent: HPMC E4M, HPMC F4M, sodium carboxymethylcellulose, and PVP K25; ii) the wetting liquid: several ethanol/water in different ratios mixtures were evaluated; iii) the effect of the croscarmellose sodium (disintegrant) on the disintegration time and resistance to crushing of the printlets; and iv) the printing parameters such as size, pore size, perimeters, total layers of the printlets, infill pattern, flow speed, infill speed, and travel speed. Thus, first a batch of masses was prepared keeping constant the amount of CBZ and HPβCD, but varying the binder. PVP K25 masses flew without difficulty through the extrusion tip but led to brittle printlets, and thus it was discarded for further experiments. Oppositely, HPMC E4M and sodium carboxymethylcellulose rendered too hard wet masses and were also discarded. Differently, HPMC F4M allowed preparing homogenous mixtures without formation of lumps.

Lump formation was avoided by dispersing first the amount used as binder (0.625 g HPMC F4M) into the moistening liquid (water:ethanol 90:10 vol/vol; 10 mL) under mechanically stirring (15 min) followed by storage in a tightly closed container at 4 °C for 12 h. This hydration period allowed the complete swelling of this amount of cellulose ether, rendering a soft, shear-thinning hydrogel that, in a subsequent step, homogeneously integrated CBZ and HPβCD during mixing in the mortar for 2 min. It should be also noted that the proportion of ethanol in the moistening liquid played a relevant role; in the absence of ethanol, the wet mass was very viscous and did not dry sufficiently rapid after 3D printing, which resulted in the collapse of the structure. Differently, ethanol content above 20% caused the mass to become dry too rapidly, even during the mixing in the mortar, particularly after the addition of the final components (the disintegrant Ac-Di-Sol® for formulation I or more HPMC F4M for formulation II). Thus, the compromise in drying time was reached using water:ethanol 90:10 vol/vol. It was also expected that the presence of ethanol facilitated the kneading of CBZ and HPβCD and the inclusion complex formation through
partial solubilization of the drug. Also relevantly, the final components (Ac-Di-Sol® and HPMC F4M) were added as powder since the presence of non-solubilized materials has been shown to increase the consistency of the wet masses and improve the printability (13). Overall, the excipients were selected with the ultimate view of fabricating printlets with fast release characteristics and good appropriate properties for their handling.

Two formulations of cyclodextrin-CBZ printlets were successfully 3D printed by semisolid extrusion with the compositions shown in Table I: formulation I intended to be orodispersible, and formulation II for immediate drug release. SEM images (Fig. 2) show in detail the pore structure of the printlets which was designed to provide a rapid disintegration and CBZ release. Distance between strands was set in 1 mm to allow free movement of the release medium. For both formulations, the strands had smooth surface, which confirmed that the components were homogenously distributed. Certain bending of the printed strands may be due to the diagonal infill pattern chosen for the design. As recently reported for Carbopol®-based pastes, 45 ° weaving angle may cause certain areas to lack support for the next layer filament weight (13). This issue could be solved printing with 60 or 90 ° weaving angle.

Fig. 2. SEM images of A) top, B) bottom and C) cross-section of the formulation I; and D) top, E) bottom and F) cross-section of the formulation II.
3.2.6.2. Rheological properties of wet masses

Although there is still a paucity of information on the most adequate properties that the pastes for 3D micro-extrusion should have, several studies have evidenced the close relationship between the paste's rheology and its performance as 3D ink in terms of consistency and homogeneity of the strand and printing resolution (13). Thus, to gain an insight into that relationship, once the selected wet masses were loaded in the printer syringe, a portion was poured on the plate of the rheometer and the dependence of $G'$ and $G''$ on applied strain was recorded (Fig. 3). The amplitude sweep tests were recorded under strain conditions that mimic rest-like situation in the syringe barrel (0.5% strain) and then maximum stress (100% strain) during delivery through the syringe tip for 3D printing. These conditions were cyclically applied to obtain information about the recovery of the consistency once the wet mass was deposited on the printing platform and about the feasibility of using the same mass for successive printing of several printlets.

![Rheological properties of wet masses used to obtain formulations I and II.](image-url)
The chosen protocol was similar to that previously proposed for evaluating self-healing materials (22) and stimuli-responsive gels for 3D printing (23). The applied strain range (from 0.5 to 100%) was much larger than that previously evaluated for related wet masses (13) in order to cover the most extreme situations that the mass may have to face up to during printing.

The rheological properties of formulation I masses were very sensitive to small changes in water content. Interestingly, optimum printing (in terms of resolution of the printed architecture) was observed for masses exhibiting G'' values (close to $10^5$ Pa) above G' already at low strains (rest-like conditions). Thus, under angular frequency of 1 Hz (6.28 rad/s) cross-over of G' and G'' did not occur, and G' was always lower than G'' during the time of study. This means that for this wet mass the viscous- or liquid-like behaviour predominates over the solid-like component. The application of a large strain caused a step decrease in both moduli, mainly in G' (up to $10^3$ Pa). The G'' values dropped to $10^4$ Pa. When the strain returned to 0.5%, the moduli increased their values in a time-dependent manner. The increase in G'' was progressive, while for G' an initial jump was observed followed by a progressive recovery. Complete recovery was not attained in the five minutes period. Application of another strain cycle led to similar profiles. A little excess in water caused a remarkable decrease in G' values under low strain. Oppositely, a slight shortness in wetting led to a remarkable increase in both moduli also under low strain conditions. Interestingly, the behaviour under 100% strain was not affected by small changes in wetting liquid content. The rheological patterns observed for the wet masses of formulation I agree well with the behaviour recently reported for wet masses prepared with swellable Avicel®; the higher the Avicel® proportion, the higher the frequency required for the elastic (G') component to overcome the G'' values under low strain conditions, and also the lower the percentage of strain recovery after flow (13).

Differently, formulation II masses under low strain conditions (0.5% shear strain) had G' values slightly above G'' values; both being in the $10^5$ to $10^6$ Pa range. This finding indicates that the wet mass behaved as a gel-like system, which should be favoured by its higher content in the hydrophilic HPMC F4M (approx. 0.75 g in less than 10 mL liquid available for wetting). Sudden application of a large (100%) strain resembling the delivery through the small diameter nozzle caused a brusque drop in both moduli, which was greater than two orders of magnitude in case of G'. The G'' values dropped to $10^4$ Pa. Cessation of the strain (mimicking the rest stay on the printing platform) allowed the mass to recover the initial rheological behaviour (i.e. the high consistency) almost completely in few seconds. For formulation II, the first step of rapid recovery was more intense than for formulation I. Formulation II mass withstood a second strain cycle, exhibiting again good self-healing
behaviour. Successive batches of formulation II masses showed excellent reproducibility in their rheological properties and ideal quick recovery.

It should be noted that the main difference between both formulations is that in formulation I the hydrophilic HPMC F4M has been replaced in part by the disintegrant croscarmellose sodium (Ac-Di-Sol® powder). Croscarmellose is a cross-linked derivative of carboxymethyl cellulose sodium which swells to a large extent (4- to 8-fold) once in contact with water (37). In the wet mass, the amount of free water available for swelling is clearly below the amount that the Ac-Di-Sol® powder could uptake. Therefore, small changes in the water content may cause remarkable changes in the conformation of this polymer network. Previous reports highlighted that the behaviour of swellable excipients is strongly dependent on small changes in the flow conditions during extrusion, which may affect the quality of the printed designs (13).

3.2.6.3. Drug state after printing

DSC and XRD analysis were carried out to gain an insight into the formation of drug-cyclodextrin complexes (38). It should be noted that a CBZ/HPβCD 1:3% w/w ratio, i.e. 24% of CBZ and 72% of HPβCD, was used to prepare the printlets (Table I). This means that the CBZ/HPβCD molar ratio was approximately 2:1.

DSC curves of the pure materials, physical mixtures, and printlets are displayed in Fig. 4. CBZ showed a principal sharp endothermic peak at 192 °C corresponding to its melting point. In addition, at 176 and 179 °C, CBZ displayed, respectively, an endothermic and an exothermic peak due to a polymorphic transition (39). During heating, the endotherm at 176 °C corresponded to the melting of form III, which was followed by immediate recrystallization to form I, and subsequent melting of form I at 192 °C. HPβCD, HPMC F4M and Ac-Di-Sol® SD-711 presented a large endothermic band ranging between 40-50 and 100-130 °C due to the loss of adsorbed water molecules (40).

Considering the physical mixtures, the endothermic peak of the CBZ was observed indicating the non-formation of inclusion complexes. On the other hand, the DSC scans of printlet formulations displayed a broad endotherm in the 150-180 °C interval. The melting enthalpy referred to the content in CBZ was ca. 50% lower in the case of formulation I and 65% lower for formulation II than for pristine CBZ. This decrease in melting enthalpy agrees well with the likelihood of the drug to form complexes (41). As mentioned above the HPβCD molar amount available to form inclusion complexes was half of the total number of moles of the drug. The higher content of formulation II in HPMC F4M may have favoured the complex formation yield and also the formation of solid dispersions.
The XRD patterns of the analysed samples confirmed the remanence of part of CBZ in the crystalline state (Fig. 5). The XRD pattern of pristine CBZ revealed relevant diffraction peaks at 13.02, 14.95, 15.25, 15.82, 18.65, 19.43, 20.31, 23.36, 23.87, 24.68, 24.90, 26.65, 27.10, 27.50, and 27.58° 2θ. The highest peak of CBZ was observed at 15.25° 2θ (4050.57) in agreement with previous reports (42). As expected, for HPβCD, HPMC F4M and Ac-Di-Sol® SD-711 only broad amorphous halos were observed.

The diffraction patterns of formulations mixtures (kneaded without wetting) with the pure materials showed less intense diffraction peaks which can be explained, among other factors, by the dilution of the pure crystalline component (43). In the case of the printlets, the peaks intensity decreased even more which may correlate with the lower crystallinity observed by DSC, although overlapping with excipients peaks and baseline made differences between spectra E, F, G and H barely perceptible. In any case, DSC findings suggest that CBZ coexists both as crystalline and amorphous states in the printlets, which should facilitate subsequent release.
3.2.6.4. Printlets properties

Main physical properties of the printlets as well as their drug content and disintegration time are summarized in Table II. The relative standard deviations of the weight variation results were below 7.5% for both formulations, fulfilling the requirements of the European Pharmacopoeia for tablets (44). The robustness of the 3D printing was verified through the reproducibility of printlets diameter and thickness, as well as in the CBZ content which was close to the nominal dose and in all cases inside the 95.0-105.0% limits. This means that no drug loss occurred during semisolid extrusion. Although the friability of the printlets was above the 1.0% limit, they still showed suitable physical characteristics for handling.
Table II. Weight, diameter, thickness, breaking force, friability, drug content, and disintegration time of the printlets.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation I</th>
<th>Formulation II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>211 ± 13</td>
<td>217 ± 15</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>15.41 ± 0.31</td>
<td>15.33 ± 0.24</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>2.20 ± 0.15</td>
<td>2.24 ± 0.19</td>
</tr>
<tr>
<td>Breaking force (N)</td>
<td>25 ± 3</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>98.3 ± 2.9</td>
<td>103.6 ± 1.6</td>
</tr>
<tr>
<td>Disintegration timea (s)</td>
<td>167</td>
<td>450</td>
</tr>
<tr>
<td>Disintegration timeb (s)</td>
<td>540 ± 11</td>
<td>1140 ± 15</td>
</tr>
</tbody>
</table>

* a Pharmacopeial method; b Petri dish method

Two methods were employed to quantify the disintegration time: the pharmacopeial method placing the printlets immersed in a large volume of medium in the oscillating basket, and the Petri dish method using a limited volume of liquid resembling more static conditions in the mouth. Disregarding the method, formulation I disintegrated in a much shorter time than formulation II; formulation I required less than 3 min using the basket and 9 min in the Petri dish vs. formulation II that required 7.5 min in the basket and 19 min in the Petri dish. According to the European Pharmacopoeia (44), orodispersible tablets should disintegrate within 3 min and uncoated tablets disintegrate within 15 min. Therefore, formulation I accomplished the requirements for orodispersible formulations, while formulation II disintegration time matched that of oral uncoated tablets. Moreover, a relationship between the breaking force of the printlets and the disintegration time was observed, i.e., the most brittle tablets (formulation I) showed a shorter disintegration time. As previously reported (25), the Petri dish method renders higher disintegration times because there is no stirring. The complete disintegration of the formulation I printlets into fine particles is shown in Fig. 6.
In vitro dissolution tests were carried out using as release medium distilled water containing sodium lauryl sulphate (1%, w/v). Both formulations completed CBZ release in less than 60 min (Fig. 7), and thus complied the USP 41 - NF 36 specifications for CBZ tablets since not less than 75% of the CBZ amount was dissolved in 60 min. CBZ dissolution rate was remarkably faster from formulation I compared to formulation II. For instance, at 15 min, formulations I and II led to, respectively, 98.9% and 55.8% CBZ released. These results correlated well with the disintegration times, and the differences are due to a small change in the printlets compositions; namely, in formulation I the binder (HPMC F4M) was partially replaced by the disintegrant Ac-Di-Sol® SD-711. The dissolution profile of CBZ fine powder was slower as expected from its low solubility (45), but complete since the medium ensured sink conditions with the presence of the surfactant. Faster release from the printlets clearly indicates the beneficial effect of the chosen excipients on drug solubility. Moreover, the printlets released CBZ even faster than tablets prepared by direct compression of CBZ/HPβCD 1:4 w/w mixtures, which under the same conditions released 65 ± 6% at 15 min and 80 ± 6% at 30 min (31).
3.2.7. Conclusion

HPβCD has been shown to be a suitable component for the manufacture of fast release printlets of CBZ (BCS class 2 drug). The semisolid extrusion-based 3D printing was revealed as an innovative approach to in situ formation of drug-cyclodextrin complexes and to produce personalized CBZ printlets with adequate physical and drug release properties. Therefore, HPβCD can be included into the list of excipients suitable for 3D printing manufacture of medicines. Relevantly, small changes in the ratio between hydrophilic (HPMC) and swellable (croscarmellose sodium) cellulose ethers caused remarkable changes in the wet masses rheology, which in turn determined printability. Also, the cellulose ethers ratio had a direct impact on the printlets disintegration and also on drug release rate. In sum, 3D printing of combinations of cyclodextrins and cellulose ethers as porous architectures may help addressing the formulation and therapy personalization demands of BCS class 2 drugs.
3.2.8. List of abbreviations

3D - Three-dimensional
BCS - Biopharmaceutics Classification System
CBZ - Carbamazepine
DS - Degree of substitution
DSC - Differential scanning calorimetry
FDA - Food and Drug Administration
FDM - Fused deposition modelling
G' - Storage modulus
G'' - Loss modulus
GRAS - Generally recognized as safe
HPMC - Hydroxypropyl methylcellulose
HPβCD - Hydroxypropyl-β-cyclodextrin
MS - Average molar degree of substitution
MW - Molecular weight
NF - National Formulary
PTFE - Polytetrafluoroethylene
PVP - Polyvinylpyrrolidone
SEM - Scanning electron microscopy
SLA - Stereolithography
SLS - Selective laser sintering
UK - United Kingdom
USA - United States of America
USP - United States Pharmacopeia
XRD - X-ray powder diffraction

3.2.9. Acknowledgements

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3.2.10. References


3.3. Orodispersible carbamazepine/hydroxypropyl-β-cyclodextrin tablets obtained by direct compression with five-in-one co-processed excipients

A suggested running head: CBZ/HPβCD orodispersible tablets.
3.3.1. Abstract

The development of orodispersible tablets (ODTs) for poorly soluble and poorly flowable drugs via direct compression is still a challenge. This work aimed to develop ODTs of poorly soluble drugs by combining cyclodextrins that form inclusion complexes to improve wetting and release properties, and directly-compressible co-processed excipients able to promote rapid disintegration and solve the poor flowability typical of inclusion complexes. Carbamazepine (CBZ) and hydroxypropyl-β-cyclodextrin (HPβCD) were used, respectively, as a model of a poorly soluble drug with poor flowability and as a solubilizing agent. Specifically, CBZ - an antiepileptic and anticonvulsant drug - may benefit from the studied formulation approach, since some patients have swallowing difficulties or fear of choking and are non-cooperative. Prosolv® ODT G2 and F-Melt® type C were the studied five-in-one co-processed excipients. The complex was prepared by kneading. Flow properties of all materials and main properties of the tablets were characterized.

The obtained results showed that ODTs containing CBZ/HPβCD complex can be prepared by direct compression through the addition of co-processed excipients. The simultaneous use of co-processing and cyclodextrin technologies rendered ODTs with an in vitro disintegration time in accordance with the European Pharmacopoeia requirement and with a fast and complete drug dissolution. In conclusion, the combination of five-in-one co-processed excipients and hydrophilic cyclodextrins may help addressing the ODT formulation of poorly soluble drugs with poor flowability, by direct compression and with the desired release properties.

**Keywords:** orally disintegrating tablets; direct compression; carbamazepine/hydroxypropyl-β-cyclodextrin complexes; Prosolv® ODT G2; F-Melt® type C.
### 3.3.2. Introduction

Several approaches have been proposed to overcome the low solubility of the active pharmaceutical ingredients (APIs) belonging to Class 2 or 4 of the Biopharmaceutics Classification System (BCS). The use of co-crystals, salts, amorphous forms, particle size reduction, solid dispersions, and self-emulsifying systems has been widely explored (1, 2). Cyclodextrins (CDs), through the formation of inclusion complexes, are primarily used to increase the solubility, dissolution, and bioavailability of the APIs and are present as excipients in several medicinal products for human use (3-5). Additionally, CDs can form non-inclusion complexes and self-assembled aggregates suitable for preparing a variety of drug delivery systems (6-8). Recently, we developed three-dimensional (3D) printed tablets (printlets) via semisolid extrusion containing carbamazepine (CBZ)/hydroxypropyl-β-cyclodextrin (HPβCD) complexes and cellulose ethers, namely hydroxypropyl methylcellulose and croscarmellose sodium (9). HPβCD showed to be a suitable excipient for developing fast dissolving printlets while semisolid extrusion enabled in situ formation of drug-CD complexes.

Orodispersible tablets (ODTs), also referred to as orally disintegrating or fast-disintegrating tablets, are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed (10). Compared to conventional tablets, ODTs have the advantages of improving the patient’s compliance because they can be easily swallowed without drinking or chewing, thereby minimizing swallowing problems or fear of choking (11-13). In this way, ODTs can be used in paediatric, geriatric, dysphagic, bedridden, psychiatric or neurologic patients. Moreover, ODTs may enhance the bioavailability of some APIs as well as provide a faster onset of action favoured by pre-gastric absorption. Compared to oral liquid dosage forms, ODTs assure dose accuracy and are more stable. Due to these reasons, ODTs have been studied by several researchers. For instance, Petrovick et al. (14) developed ODTs containing solid lipid pellets and metformin hydrochloride with immediate drug release profile and taste-masked properties. In another study, ODTs of clozapine/HPβCD complexes were developed by direct compression showing higher in vitro dissolution rate and bioavailability compared with the commercial tablets (15).

ODTs can be manufactured by wet or dry granulation, lyophilization (freeze-drying), spray-drying, or moulding; nevertheless, the simplest and most cost-effective method is direct compression (16-18). Direct compression can be used for thermolabile and moisture-sensitive APIs, but the flow and compaction properties of the formula’s constituents are crucial for the quality of the tablets.
Co-processed excipients, a combination of two or more excipients that does not lead to the formation of covalent bonds, may overcome some limitations of the tablet formulations such as poor flowability and compressibility, high moisture sensitivity, poor disintegration properties, insufficient mechanical strength, low dilution potential, weak blending characteristics, and inadequate organoleptic properties (19-21). These high-functionality excipients have properties that are not achievable through simple blending (10). Additionally, co-processed excipients simplify the formulation and manufacturing processes, since less excipients are needed resulting in fewer components to handle, test, and inventory (22, 23). Examples of the first co-processed excipients are microcrystalline cellulose and calcium carbonate, cellulose and lactose, and glucomannan and galactomannan (24). Nowadays, there are co-processed excipients with three (e.g., CombiLac®), four (e.g., Prosolv® EASYtab SP), and five individual components (e.g., F-Melt® type C) that perform as directly-compressible excipients (25, 26). Examples of co-processed excipients for use in directly compressed ODT formulations include Prosolv® ODT G2, F-Melt® type C, Ludiflash®, Pharmaburst® 500, and SmartEx® QD-100 (17). There are also co-processed excipients for sustained release formulations, such as RetaLac® that comprises hypromellose and alpha-lactose monohydrate.

The development of ODTs by direct compression for poorly soluble and poorly flowable APIs, with fast disintegration and suitable hardness, is still a formulation challenge (27, 28). The hypothesis of our work is that ODTs of poorly soluble APIs can be prepared by direct compression combining CDs that form inclusion complexes and thus improve the wetting and the release properties, and directly-compressible co-processed excipients that may solve the poor flowability typical of inclusion complexes as well as promoting a rapid disintegration. CBZ and HPβCD were used, respectively, as a model of a poorly soluble API with poor flowability and as a solubilizing agent. Specifically, CBZ - a BCS class 2 drug used as antiepileptic and anticonvulsant for the treatment of seizure disorders and neuropathic pain - may benefit from this formulation approach, since existing formulations do not cover paediatric and geriatric needs and some patients have swallowing difficulties and are non-cooperative (29). Thus, the work was carried out in the following steps: i) to perform phase solubility studies of CBZ/HPβCD in aqueous solution; ii) to prepare CBZ/HPβCD complexes by kneading and to characterize them in the solid state; iii) to evaluate the flow properties of the inclusion complex, physical mixture, pure co-processed excipients, and final formulations; iv) to prepare ODTs by direct compression containing the obtained complex and two five-in-one co-processed excipients (Prosolv® ODT G2 and F-Melt® type C); and v) to characterize the obtained tablets, in particular their disintegration time and drug dissolution rate. From a practical point of view, a poor flow of formula components, a
low solubility of APIs, and slow disintegration in the oral cavity are three major challenges for scientists involved in the research and development of ODTs.

3.3.3. Materials and Methods

3.3.3.1. Materials

CBZ (Acofarma®, Spain; molecular weight (MW) of 236.3 g/mol), HPβCD Kleptose® HP oral grade - high average molar degree of substitution (MS = 0.85) and MW of 1480.7 g/mol (Roquette®, France), Prosolv® ODT G2 (JRS Pharma, United States of America (USA)), F-Melt® type C (Fuji Chemical Industries, Japan), Pruv® (JRS Pharma, USA), sodium lauryl sulphate (Acofarma®, Spain), ethanol absolute (VWR® Chemicals, France), and methylene blue (Difco Laboratories, United Kingdom) were used. Water was purified using reverse osmosis (Milli-Q, Millipore, Spain).

Prosolv® ODT G2 comprises mannitol (67.1%, w/w; water-soluble filler), microcrystalline cellulose (20.8%, w/w; water-insoluble filler), crospovidone (5.4%, w/w; superdisintegrant), fructose (4.8%, w/w; sweetener), and colloidal silicon dioxide (2.0%, w/w; glidant agent). Differently, F-Melt® type C comprises mannitol (64.9%, w/w; water-soluble filler), microcrystalline cellulose (17.7%, w/w; water-insoluble filler), crospovidone (8.1%, w/w; superdisintegrant), xylitol (4.8%, w/w; sweetener), and anhydrous dibasic calcium phosphate (4.0%, w/w; water-insoluble filler).

3.3.3.2. Methods

3.3.3.2.1. Phase solubility studies

Phase solubility studies were performed in triplicate in Milli-Q water according to Higuchi and Connors method (30). An excess amount of CBZ (10 mg) was added to 5 mL aqueous solutions containing different concentrations of HPβCD (0-24 mM). Subsequently, samples were tightly closed and mechanically shaken at 25 °C/200 rpm for 72 h in an incubating mini shaker (VWR®, model 230 volt, USA). Aliquots were centrifuged during 90 min at 25 °C/5000 rpm (Eppendorf®, model 5804 R, Germany) and suitably diluted with ethanol/water medium (50:50, v/v). The CBZ concentration was determined from absorbance measurements at 288 nm (Agilent 8453, USA) (31). A drug calibration curve in ethanol/water solution (50:50, v/v) was previously prepared (y = 50.6980x + 0.0033), in the 0.002 to 0.020 mg/mL range with a coefficient of determination \((R^2)\) of 0.9992, and the validation of the analytical method was properly performed. The stability constant \((K_C)\) and the complexation efficiency \((CE)\) were calculated (n = 3; mean ± standard deviation (SD))
from the slope of the linear plot of the phase solubility diagram according to Eqs. 1 and 2, where \( S_0 \) is the concentration of CBZ without HPβCD (32).

\[
K_c = \frac{\text{slope}}{S_0 (1 - \text{slope})} \quad (1)
\]

\[
CE = \frac{\text{slope}}{(1 - \text{slope})} \quad (2)
\]

3.3.3.2.2. Preparation of inclusion complex and physical mixture

The complex of CBZ/HPβCD in a molar ratio 1:1 (batches of 10 g) was prepared by kneading as follows (33): i) about 3 mL of water/ethanol solution (90:10, v/v) was progressively added in a mortar containing the HPβCD (8.62 g) to perform the wetting; ii) afterwards, CBZ (1.38 g) was added gradually and well blended in the mortar in order to obtain a homogeneous viscous paste; iii) the obtained complex was dried at room temperature for 48 h; and iv) finally, the complex powder was grinded in a mortar and sieved through a mesh size of 180 µm. Additionally, a physical mixture of CBZ/HPβCD 1:1 molar ratio (batches of 10 g) was also prepared by spatulation according to the geometric dilution method.

3.3.3.2.3. Characterization of CBZ/HPβCD complex

3.3.3.2.3.1. Differential scanning calorimetry

Differential scanning calorimetry (DSC) curves of pure materials (CBZ and HPβCD), CBZ/HPβCD physical mixture, and CBZ/HPβCD complex were recorded in a differential scanning calorimeter (TA Instruments, model Q200, USA). Samples of 6 mg were heated from 40 to 250 °C at 10 °C/min under a nitrogen flow of 50 mL/min. The obtained data were analysed with TA Instruments Universal Analysis 2000 software.

3.3.3.2.3.2. X-ray diffraction

The X-ray powder diffraction (XRD) patterns of CBZ, HPβCD, CBZ/HPβCD physical mixture, and CBZ/HPβCD complex were recorded using an X-ray diffractometer (Philips
Analytical PW 3050/60 X’Pert PRO, Netherlands) in the 2θ range of 7-42° with a step size of 0.017° and 19.685 s of scan step time using monochromatized Cu-Kα radiation as incident beam (30 mA/40 kV). The obtained data were analysed with OriginPro® 2019 analysis and graphing software.

3.3.3.2.3.3. Scanning electron microscopy

Scanning electron microscopy (SEM) images of CBZ, HPβCD, CBZ/HPβCD physical mixture, and CBZ/HPβCD complex were obtained with a high resolution Schottky environmental scanning electron microscope (FEI Quanta 400 FEG ESEM, USA). Samples were coated with Au/Pd thin film (~15 nm) by the SPI-Module™ Sputter Coater apparatus (USA).

3.3.3.2.3.4. Assay of drug content

Portions of CBZ/HPβCD inclusion complexes and physical mixtures were added, in triplicate, to volumetric flasks (250 mL) with distilled water containing sodium lauryl sulphate (1%, w/v) and then kept under magnetic stirring (Heidolph, model MR Hei-Tec, Germany) until complete dissolution. The solutions were filtered through 0.45 μm polytetrafluoroethylene (PTFE) syringe filters (VWR International, USA) and suitably diluted (31). The CBZ content was determined from absorbance measurements at 288 nm (Jasco, model V-650, Japan) (31).

3.3.3.2.3.5. Dissolution studies

In vitro release studies (n = 3; mean ± SD) were performed with pure CBZ (25 mg) or its equivalent amount of CBZ/HPβCD complex and of physical mixture (total weight of 182 mg) in a dissolution apparatus (Sotax, model AT7, Switzerland). The paddle method at 75 rpm in 900 mL distilled water containing sodium lauryl sulphate (1%, w/v) maintained at 37.0 ± 0.5 °C was used (31). After 1, 2.5, 5, 7.5, 10, 12.5, 15, 30, 45, and 60 min, 3.0 mL samples were taken without volume replacement, filtered through 0.45 μm PTFE membranes (VWR International, USA), and suitably diluted with the dissolution medium. CBZ concentration was determined from absorbance measurements at 288 nm (Jasco, model V-650, Japan) (31).
3.3.3.2.4. Evaluation of the flow properties

The flow properties of the inclusion complex, physical mixture, pure co-processed excipients, and formulas II and IV (Table I) were assessed. The Carr’s index (n = 3; mean ± SD) and the Hausner’s ratio (n = 3; mean ± SD) were evaluated using a tap density tester (Electrolab, model ETD-1020, India) and the USP II method of testing (250 taps per minute) (10, 34). The used sample weight for pure excipients was 100 g; in contrast, for the inclusion complex, the physical mixture, and formulas II and IV, a sample weight of 50 g was used. Furthermore, the angle of repose (n = 3; mean ± SD) and flow time (n = 3; mean ± SD) were also determined through a flow tester (Erweka, model GTB, Germany) using a sample of 25 g and an outlet nozzle with 25 mm diameter (10, 34).

3.3.3.2.5. Preparation of the ODTs

For all formulations (batches of 150 g), pure CBZ or inclusion complex or physical mixture and co-processed excipient were blended in a Turbula® WAB mixer (model T2C, Switzerland) for 15 min. Then, the lubricant was added and blended for 3 min in the same mixer. Six formulas of ODTs containing 25 mg of CBZ or its equivalent amount of CBZ/HPβCD complexes and of physical mixtures (Table I), with a target weight of 500 ± 25 mg and a target hardness value of 100 N, were prepared by direct compression using a single-punch compression machine (Korsch, 9048-71, Germany) with 13 mm diameter punches. Two five-in-one co-processed excipients (Prosolv® ODT G2 and F-Melt® type C) were studied, and sodium stearyl fumarate (Pruv®, 0.5%, w/w) was used as an anti-adherent lubricant (34-36).

Table I. ODTs composition.

<table>
<thead>
<tr>
<th>Component / Formula</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>25</td>
<td>-</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inclusion complex (with 25 mg of CBZ)</td>
<td>-</td>
<td>182</td>
<td>-</td>
<td>182</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Physical mixture (with 25 mg of CBZ)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>182</td>
<td>182</td>
</tr>
<tr>
<td>Prosolv® ODT G2</td>
<td>472.5</td>
<td>315.5</td>
<td>-</td>
<td>-</td>
<td>315.5</td>
<td>-</td>
</tr>
<tr>
<td>F-Melt® type C</td>
<td>-</td>
<td>-</td>
<td>472.5</td>
<td>315.5</td>
<td></td>
<td>315.5</td>
</tr>
<tr>
<td>Pruv®</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>
3.3.3.2.6. ODTs characterization

3.3.3.2.6.1. Physical properties

For the weight uniformity assessment, tablets were randomly selected and weighed (n = 20; mean ± SD) using an analytical balance (Mettler Toledo, model AG245, Switzerland). The diameter and thickness of the tablets (n = 20; mean ± SD) were measured with a digital calliper (Powerfix®, model number Z22855, Germany). The tablet breaking force (n = 10; mean ± SD) was measured using a tablet hardness tester (Erweka, model TBH 28, Germany).

3.3.3.2.6.2. Drug content

Tablets (n = 3; mean ± SD) were added to 250 mL of sodium lauryl sulphate aqueous solution (1%, w/v) and kept under magnetic stirring (Heidolph, model MR Hei-Tec, Germany) until complete dissolution (31). Afterwards, samples were filtered through a 0.45 μm syringe filter PTFE membrane (VWR International, USA), suitably diluted, and the CBZ concentration was determined from absorbance measurements at 288 nm (Jasco, model V-650, Japan) (31).

3.3.3.2.6.3. Wetting time and water-absorption ratio

The wetting time (n = 3; mean ± SD) was measured using three circular Whatman® filter papers of 7 cm in diameter, which were placed in a Petri dish of 9 cm diameter containing 10 mL of a methylene blue solution (0.1%, w/v). One tablet was positioned on the surface of the filter paper, and the time required for water to reach the upper surface of the tablet was noted as the wetting time (37).

The water-absorption ratio (WAR) was calculated from Eq. 3, where \( W_b \) is the weight of the tablet before placing in the Petri dish and \( W_a \) is the weight of the wetted tablet.

\[
WAR = \left( \frac{W_a - W_b}{W_b} \right) \times 100
\] (3)
3.3.3.2.6.4. Disintegration tests

The *in vitro* disintegration tests of the tablets (*n* = 6) were performed using a disintegration tester (Electrolab, model ED-2L, India) containing distilled water which was maintained at 37 ± 2 °C (10). One tablet was placed in each of the six tubes of the basket and discs were added (10).

3.3.3.2.6.5. Dissolution testing

*In vitro* release studies (*n* = 3; mean ± SD) of the tablet formulations were performed in a dissolution apparatus (Sotax, model AT7, Switzerland) according to the paddle method at 75 rpm in 900 mL distilled water containing sodium lauryl sulphate (1%, w/v) at 37.0 ± 0.5 °C (31). Aliquots of the solution (3 mL; without volume replacement) were withdrawn at predetermined time intervals, i.e., at 1, 2.5, 5, 7.5, 10, 12.5, 15, 30, 45, and 60 min, filtered through 0.45 μm PTFE membranes (VWR International, USA), and suitably diluted. Subsequently, the CBZ concentration was determined from absorbance measurements at 288 nm (Jasco, model V-650, Japan) (31).

3.3.4. Results and Discussion

3.3.4.1. Inclusion complexes

CBZ, used for the treatment of epilepsy and other neurological and psychiatric disorders, was studied as a model of a poorly soluble API with poor flowability (34). Additionally, as current CBZ formulations do not cover paediatric and geriatric needs, some patients have swallowing difficulties and are non-cooperative, compliance could be enhanced by means of ODTs that increase adherence to therapy (29, 38, 39). Due to the suitable flow properties for direct compression, broad regulatory acceptance by the regulatory authorities of medicinal products and by pharmacopoeias, lower MW and price relative to other derivatives (e.g., sulfobutyl ether-β-cyclodextrin), and toxicological profile suitable for oral use, HPβCD was used as a hydrophilic complexing agent in order to increase the drug solubility and dissolution rate (34, 40). Prosolv® ODT G2 and F-Melt® type C were used as directly-compressible high-functionality excipients. These products are two examples of the most modern and functional co-processed excipients for ODT formulation, development, and manufacture, since they are a unique combination of five ingredients.

The phase solubility studies (*Fig. 1*), performed according to the Higuchi and Connors method, showed the following: i) the CBZ complexation with HPβCD increased the
aqueous solubility of the API; ii) an A-type profile was obtained \((R^2 = 0.9863)\), which means that the formation of the complexes is of first order in relation to the CD; iii) as the obtained slope was less than 1, it can be assumed that CBZ forms complexes with HPβCD in a 1:1 molar ratio; iv) the obtained \(K_C\) and CE values were, respectively, \(272 \pm 7 \text{ M}^{-1}\) and \(0.326 \pm 0.047\). The \(K_C\) value was slightly lower than that reported by some researchers \((444.1 \text{ M}^{-1})\) (41); on the other hand, the \(S_0\) value \((146 \pm 3 \mu\text{g/mL})\) was in line with the value described in the literature \((< 200 \mu\text{g/mL})\) (42).

The kneading method was used for the preparation of CBZ/HPβCD complex in a molar ratio 1:1, because this procedure is quite inexpensive, requires low quantity of wetting liquid, no waste is produced, the yield of inclusion formation is high, and the scaling up is feasible (33). However, this method has some disadvantages such as the risk of incomplete complex formation and amorphization (33, 43). For instance, the solvent evaporation technique was more effective in terms of norfloxacin solubilization than the kneading method (43). A water/ethanol solution (90:10, v/v) was used as moistening liquid to facilitate CBZ solubilization and the solvent removal that occurs afterward (9).

DSC together with XRD are considered the methods of choice for the characterization of drug-CD complexes in the solid state (44). DSC curves (Fig. 2) demonstrated the formation of the complex, since the physical mixture displayed two endothermic peaks while the complex only showed a broad peak at lower temperature than pure CBZ. The CBZ and HPβCD presented characteristic DSC scans similar to those previously described in the literature (41, 45, 46). As far as pure CBZ is concerned, a small

![Fig. 1. Phase solubility diagram of CBZ/HPβCD in aqueous solutions at 25 °C.](image-url)
endothermic peak at 176 °C was observed, which is typical of the transition of the β-form to the α-form with melting at 192 °C and calculated enthalpy of 104.7 J/g. In addition, HPβCD interfered in the CBZ crystallization transitions in the physical mixture, i.e., the CD changed the transformation mode of the β-form to the α-form, since a decrease in the enthalpy of melting of the α-form was observed (calculated enthalpy of 1.7 J/g). Similar effect was noted with hydroxypropyl methylcellulose on the CBZ crystallization, and this decrease indicates that part of the β-form that melted at 176 °C cannot be converted to the α-form due to a disruption of the crystallization caused by the excipient (46).

Through the analysis of the XRD patterns (Fig. 3), it was possible to observe that CBZ and HPβCD presented, respectively, crystalline and amorphous natures (47). The diffraction pattern of the physical mixture exhibited a lower intensity of the diffraction peaks, and overlapping of some CBZ peaks were observed. In contrast, CBZ/HPβCD complex showed a decrease in peaks intensity in relation to the physical mixture, and some CBZ peaks disappeared, i.e., at 14.9465, 20.5370, 24.6796, and 27.4967° (2θ).

![Fig. 2. DSC curves of CBZ (A); HPβCD (B); CBZ/HPβCD physical mixture (C); and CBZ/HPβCD complex (D).](image-url)
Particle morphology of the CBZ, HPβCD, CBZ/HPβCD physical mixture, and CBZ/HPβCD complex was studied by SEM (Fig. 4A). The physical mixture contains, as expected, CBZ and HBβCD particles; in contrast, the inclusion complex has a distinctive morphology with smaller size which means that a different solid entity was obtained. However, it should be noted that the complex was ground and sieved during its preparation process.

The CBZ content in the inclusion complex and in the physical mixture was, respectively, 102.3 ± 2.5% and 96.7 ± 8.1%. The API content in the inclusion complex showed that no drug loss occurred during the kneading method. In Fig. 4B, a fast and high in vitro dissolution rate was noticed for the CBZ/HPβCD complex; differently, the physical mixture and pure drug showed slower dissolution rate.
Fig. 4. A) SEM images of CBZ (A); HPβCD (B); CBZ/HPβCD physical mixture (C); and CBZ/HPβCD complex (D); and B) Drug dissolution profiles from the inclusion complex, physical mixture, and pure CBZ powder (25 mg) in distilled water containing sodium lauryl sulphate (1%, w/v) at 37 °C.

3.3.4.2. Flow properties

The flow properties of raw materials are critical for direct compression tableting and the quality of the final tablets (e.g., variation in tablet weight and drug content) (6). The Carr’s index, Hausner’s ratio, flow time, and angle of repose of the inclusion complex, physical mixture, pure co-processed excipients (Prosolv® ODT G2 and F-Melt type C), and of formulas II and IV are summarized in Table II. The CBZ/HPβCD complex showed poor flow (Carr’s index > 25% and Hausner’s ratio > 1.25). The angle of repose and the flow time through the outlet nozzle with 25 mm diameter could not be determined. Differently, the physical mixture in 1:1 molar ratio presented good flow properties. As reported previously (34), CBZ and HPβCD displayed, respectively, poor and good flow properties. Thus, although the formation of the inclusion complex enhances the dissolution of poorly soluble APIs, the flow characteristics are often poor, and this aspect makes the preparation of ODTs by direct compression very difficult. In addition, in certain cases to overcome this aspect, the filling of the compression chamber (die) is done by manual mode and this is not suitable for industrial application (6). For instance, Salústio et al. (48) prepared ibuprofen/βCD complexes by two different methods (kneading and suspension/solution with water removed by air stream, spray- and freeze-drying), and the complexes also displayed poor flow abilities, implying that glidant agents must be added to pharmaceutical formula. In another study, indomethacin/βCD complexes presented also poor flowability (49). By contrast, the
two five-in-one co-processed excipients showed good flow properties, which is in line with literature, as well as formulas II and IV. Even though the complex is used in the formulas in 36.4% (w/w), the addition of a directly-compressible co-processed excipient improved the flow properties of the blend allowing the preparation of the ODTs via direct compression. Moreover, the presence of Pruv® (0.5%, w/w) as anti-adherent lubricant did not affect the flowability (34-36). As mentioned by Al-Khattawi and Mohammed (27), compressed ODTs have a maximum dose capacity approaching 30-40% of the tablet weight due to difficulty in retaining fast disintegration and suitable hardness above this level.

Table II. Flow properties of CBZ/HPβCD inclusion complex, physical mixture, co-processed excipients, and ODTs formulas.

<table>
<thead>
<tr>
<th>Parameter / Sample</th>
<th>Inclusion complex</th>
<th>Physical mixture</th>
<th>Prosoolv®</th>
<th>F-Melt®</th>
<th>Formula II</th>
<th>Formula IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr’s index (%)</td>
<td>29.9 ± 1.6</td>
<td>14.2 ± 1.3</td>
<td>19.8 ± 0.4</td>
<td>18.6 ± 0.5</td>
<td>22.3 ± 0.7</td>
<td>22.1 ± 0.1</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.33 ± 0.03</td>
<td>1.07 ± 0.01</td>
<td>1.17 ± 0.01</td>
<td>1.13 ± 0.01</td>
<td>1.14 ± 0.01</td>
<td>1.14 ± 0.01</td>
</tr>
<tr>
<td>Flow time (s/100g)</td>
<td>n.d.</td>
<td>0.7 ± 0.2</td>
<td>2.0 ± 0.0</td>
<td>1.2 ± 0.0</td>
<td>3.2 ± 0.2</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>Angle of repose (%)</td>
<td>n.d.</td>
<td>30.6 ± 0.8</td>
<td>26.2 ± 1.0</td>
<td>27.2 ± 0.6</td>
<td>28.0 ± 0.5</td>
<td>28.9 ± 1.0</td>
</tr>
</tbody>
</table>

n.d. - not determined

3.3.4.3. ODTs properties

ODTs were manufactured with a target hardness value of 100 N. The mean values of the physical properties (weight, diameter, thickness, and hardness) of the tablets as well as their drug content, wetting time, WAR, and disintegration time are summarized in Table III. The physical appearance of the obtained tablets by direct compression through a single-punch compression machine is shown in Fig. 5A.

Table III. Physical properties, drug content, wetting time, WAR, and disintegration time of the ODTs.

<table>
<thead>
<tr>
<th>Parameter / Formula</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>508 ± 2</td>
<td>505 ± 3</td>
<td>508 ± 3</td>
<td>506 ± 3</td>
<td>508 ± 4</td>
<td>502 ± 6</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>13.13 ± 0.02</td>
<td>13.11 ± 0.03</td>
<td>13.14 ± 0.02</td>
<td>13.11 ± 0.03</td>
<td>13.16 ± 0.03</td>
<td>13.24 ± 0.04</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.25 ± 0.02</td>
<td>3.50 ± 0.02</td>
<td>3.19 ± 0.02</td>
<td>3.62 ± 0.05</td>
<td>3.19 ± 0.03</td>
<td>3.21 ± 0.08</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>104 ± 3</td>
<td>102 ± 4</td>
<td>106 ± 3</td>
<td>101 ± 3</td>
<td>100 ± 6</td>
<td>100 ± 6</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>101.9 ± 2.1</td>
<td>99.2 ± 1.1</td>
<td>100.9 ± 1.1</td>
<td>101.9 ± 2.2</td>
<td>100.3 ± 4.3</td>
<td>101.0 ± 2.3</td>
</tr>
<tr>
<td>Wetting time (s)</td>
<td>31 ± 2</td>
<td>29 ± 2</td>
<td>31 ± 2</td>
<td>30 ± 4</td>
<td>30 ± 1</td>
<td>30 ± 1</td>
</tr>
<tr>
<td>Water-absorption ratio (%)</td>
<td>80.3 ± 1.9</td>
<td>78.5 ± 1.3</td>
<td>78.5 ± 2.8</td>
<td>77.5 ± 2.5</td>
<td>53.4 ± 1.5</td>
<td>53.5 ± 2.2</td>
</tr>
<tr>
<td>Disintegration time (s)</td>
<td>60</td>
<td>60</td>
<td>53</td>
<td>50</td>
<td>180</td>
<td>150</td>
</tr>
</tbody>
</table>
The disintegration time is a critical quality attribute of ODTs. In all cases, disintegration times were as follows: i) less than or equal to 180 s, fulfilling the specifications of the European Pharmacopoeia 9.0, since ODTs must disintegrate within 3 min using water as the liquid medium (10); ii) similar for the two co-processed excipients although the F-Melt® type C has a higher amount of crospovidone (cross-linked polyvinylpyrrolidone) - a superdisintegrant and dissolution enhancer that improves release characteristics through predictable swelling without gel formation - than Prosolv® ODT G2 (8.1% versus 5.4%, w/w) (50); iii) the presence of the inclusion complex in the formulas (36.4%, w/w) did not interfere in this parameter; and iv) the CBZ/HPβCD physical mixture (formulas V and VI) showed higher disintegration times than the inclusion complex (formulas II and IV) and the pure CBZ (formulas I and III). It should be noted that there are differences in relation to the disintegration time of the ODTs between the European Pharmacopoeia (≤ 180 s), the United States Pharmacopeia/National Formulary (≤ 60 s), and the Food and Drug Administration (FDA) guidance (approximately 30 s or less) (10, 31, 51).

The method used to determine the wetting time and the WAR is depicted in Fig. 5A. All tablet formulations presented similar wetting time values, approx. 30 s (Table III). The obtained WAR values ranged from 53.4 to 80.3%; ODTs with the pure CBZ and the inclusion complexes presented similar and higher values than the tablets with the physical mixture.

As can been see in Fig. 5B, ODTs with CBZ/HPβCD complexes (formulas II and IV) exhibited faster and greater drug dissolution rates than ODTs with pure CBZ (formulas I and III) and with physical mixtures (formulas V and VI). These results are in agreement with the DSC, XRD, and dissolution assays previously described, and show clearly the technological advantage of the use of CDs as complexing agents to accelerate the dissolution of poorly soluble APIs. At 60 min, a mean CBZ release from 95.3 ± 0.3 to 102.3 ± 0.9% was observed. As far as the formulas with the inclusion complexes are concerned, it can be stated that the largest differences occurred during the initial 2.5 min, as formula IV with F-Melt® type C displayed higher CBZ dissolution rate than formula II with Prosolv® ODT G2, i.e. at 1 and 2.5 min, formula II released, respectively, 38.4 ± 5.0% and 74.1 ± 3.0%; on the other hand, at 1 and 2.5 min, formula IV released, respectively, 53.4 ± 3.6% and 96.8 ± 3.5%.

Among all formulations studied, formulation IV showed the highest dissolution rate (96.8 ± 3.5% drug release within 2.5 min). Considering other studies reported in the literature, similar results were obtained by Rao et al. (52) for fast dissolving tablets by direct compression (formulation B8) of CBZ/βCD complex, croscarmellose sodium (superdisintegrant), microcrystalline cellulose (water-insoluble filler), mannitol (water-soluble filler), aspartame (sweetener), talc (glidant agent), and magnesium stearate.
(anti-adherent lubricant), which displayed 99.89% drug release in 4 min. However, our formulation is simpler, as it has fewer constituents (half), reducing the number of manufacturing steps and improving overall operational costs. Therefore, our developed formulas with five-in-one high functionality excipients may constitute a technological advantage for industrial manufacturing allowing to achieve a time- and cost-saving process.

During the first 12.5 min, ODTs prepared with the physical mixture showed lower dissolution rates than the tablets with the pure CBZ. Thus, the dissolution results, obtained under sink conditions due to the presence of the surfactant (sodium lauryl sulphate (1%, w/v)), are well in line with those of the disintegration test.

![Fig. 5. A) Physical appearance (A; units in cm) of the ODTs from formula IV and pictures showing one tablet in a Petri dish before (B) and after (C) the water reaches its upper surface; and B) CBZ dissolution profiles from the ODTs in distilled water containing sodium lauryl sulphate (1%, w/v) at 37 ºC.](image)

Finally, it should be pointed out that the simultaneous use of the CDs and co-processed excipients in ODTs formulation has an additional advantage in terms of palatability and acceptability promoting the patient compliance, i.e., the complexation diminishes the bitter taste of drugs (53); and, in general, co-processed excipients exhibit a positive organoleptic profile compared to pure microcrystalline cellulose (Avicel® PH-102) (19).
3.3.5. Conclusion

The low solubility of the APIs (BCS Classes 2 and 4), the poor flow of the raw materials, and the formulation of ODTs via direct compression are great challenges for the pharmaceutical technologists. Thus, to overcome these aspects, in this work, a new formulation approach was developed, namely the following: i) the preparation of inclusion complexes was performed in order to enhance the solubility and dissolution of APIs, and ii) five-in-one co-processed excipients were used to improve the flow properties of the inclusion complex, allowing the preparation of the tablets by direct compression, as well as to obtain disintegration times in accordance to pharmacopeial specifications. In conclusion, the combination of five-in-one co-processed excipients and hydrophilic CDs may help addressing the ODT formulation of poorly soluble APIs with poor flowability, by direct compression and with the desired release properties.

3.3.6. List of abbreviations

3D - Three-dimensional
API(s) - Active pharmaceutical ingredient(s)
BCS - Biopharmaceutics Classification System
CBZ - Carbamazepine
CD(s) - Cyclodextrin(s)
CE - Complexation efficiency
DSC - Differential scanning calorimetry
FDA - Food and Drug Administration
HPβCD - Hydroxypropyl-β-cyclodextrin
Kc - Stability constant
MS - Average molar degree of substitution
MW - Molecular weight
ODT(s) - Orodispersible tablet(s)
PTFE - Polytetrafluoroethylene
R² - Coefficient of determination
S₀ - Intrinsic solubility of the drug
SD - Standard deviation
SEM - Scanning electron microscopy
USA - United States of America
WAR - Water-absorption ratio
XRD - X-ray powder diffraction
3.3.7. Acknowledgements

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3.3.8. References


40. Background review for cyclodextrins used as excipients. London, United Kingdom: European Medicines Agency (EMA), Committee for Human Medicinal Products (CHMP); 2014.


3.4. Carbamazepine bilayer tablets combining hydrophilic and hydrophobic cyclodextrins as a quick/slow biphasic release system
3.4.1. Highlights

- Hydroxypropyl-β-cyclodextrin and triacetyl-β-cyclodextrin were used as excipients in carbamazepine bilayer tablets.
- Carbamazepine/hydroxypropyl-β-cyclodextrin inclusion complex associated to croscarmellose sodium enabled fast dissolution.
- Changes in triacetyl-β-cyclodextrin concentration allowed fine tuning of drug release profile.
- Fast/slow biphasic release systems were successfully developed and characterized.
3.4.2. Abstract

This work aimed at exploring the combination of hydrophilic and hydrophobic cyclodextrins to prepare bilayer tablets that can perform as quick/slow biphasic release systems of a poorly soluble drug. This formulation approach is of particular interest for treatments that require a rapid action followed by sustained therapeutic levels. Carbamazepine (CBZ), an antiepileptic and anticonvulsant agent, was used as a model of a Biopharmaceutics Classification System Class 2 drug. Hydroxypropyl-β-cyclodextrin (HPβCD) was chosen as complexing agent in the rapid release layer. Differently, triacetyl-β-cyclodextrin (TAβCD) was tested as controlling release agent in the sustained release layer. Croscarmellose sodium was utilized as superdisintegrant in the rapid release layer, and sodium stearyl fumarate was applied as anti-adherent lubricant in both layers. Bilayer tablets were characterized through several techniques.

The results highlighted the feasibility of the combination of CBZ/HPβCD inclusion complex with croscarmellose sodium in the rapid release layer to achieve fast dissolution for the first 30-45 min, and TAβCD as controlling release agent in the sustained release layer of the bilayer tablets to obtain a prolonged release during 720 min. In conclusion, combinations of hydrophilic and hydrophobic cyclodextrins may help addressing the formulation of poorly soluble drugs in bilayer tablets as a fast/slow biphasic release system.

**Keywords:** bilayer tablets; carbamazepine; hydroxypropyl-β-cyclodextrin; triacetyl-β-cyclodextrin; rapid/sustained release.
3.4.3. Graphical abstract

Rapid release layer

- CBZ (poorly soluble drug)
- HPβCD (solubilizing agent)
- Croscarmellose sodium (disintegrant)
- Sodium stearyl fumarate (lubricant)

Sustained release layer

- CBZ (poorly soluble drug)
- TAβCD (controlling release agent)
- Sodium stearyl fumarate (lubricant)

Bilayer tablets

In vitro quick/slow release

186
3.4.4. Introduction

Modified-release dosage forms comprise sustained-release, delayed-release and pulsatile-release dosage forms (1). Sustained release preparations are widely used in therapy to minimize the frequency of dosage forms administration, thus improving patient compliance; to reduce the oscillations in plasma drug concentrations; to decrease the possibility of adverse reactions or toxic effects; to avoid saturation of the absorption process; and to provide greater economy (2-4).

Fast/slow biphasic release systems are useful in certain clinical situations, i.e., when a therapeutic effect needs to be achieved quickly and then a prolonged release phase should maintain the therapeutic effects and avoid repeated administration (5-7). Examples of active pharmaceutical ingredients (APIs) that may benefit from this type of release include nonsteroidal anti-inflammatory, analgesic, anxiolytic, sedative, hypnotic, antihypertensive, antihistaminic, and anti-allergic agents (5-7). In order to achieve a rapid API release, superdisintegrants and dissolution enhancers, such as croscarmellose sodium, sodium starch glycolate, crospovidone and soy polysaccharides, are commonly used. Differently, to obtain a prolonged API release, hydrophilic and hydrophobic (lipidic and inert) matrix excipients are normally utilized. Concerning the solid dosage forms, multifunctional and multiple unit systems, containing for example mini-tablets, capsules or granules in a hard capsule, bilayer or multilayer tablets, and tablets/capsules with specific coatings and fill materials (e.g. powders, granules, pellets, microparticles and nanoparticles) have been tested to obtain combined fast/slow release patterns (8-10).

Bilayer tablets play an important role in pharmacotherapy due to a confluence of factors including advanced release strategies, patient compliance and combination therapy (9, 11). Consequently, this solid dosage form presents three main advantages compared to conventional monolayer tablets, that is, two chemically incompatible ingredients (APIs or excipients) can be formulated in a single unit; two APIs or the same API with different release profiles can be delivered (for example, immediate release and sustained release); and increased efficacy of the API due to their synergistic effect (12-14). For example, Nguyen et al. (15) prepared bilayer gastroretentive tablets based on hydrophobic polymers, including Kollidon® SR - a polyvinyl acetate and povidone sustained release agent - which showed excellent tableting properties for direct compression. In another study, sustained release bilayer tablets of ibuprofen and phenylephrine hydrochloride were successfully developed and characterized using different viscosity grades of hydroxypropyl methylcellulose as sustained release matrix, lactose as soluble filler, colloidal silicon dioxide as glidant agent, and stearic acid as anti-adherent lubricant (16). Also, it should be pointed
that there are tablets with more than two layers (named as multilayer tablets) (12) and 3D printed bilayer tablets (17).

Cyclodextrins (CDs) are cyclic oligosaccharides largely used as multifunctional excipients in the pharmaceutical field (18, 19). Their derivatives are classified in three main groups, namely hydrophilic, hydrophobic and ionisable (20, 21). The hydrophilic CDs, such as hydroxypropyl-β-cyclodextrin (HPβCD), are mainly used to increase the solubility, dissolution and bioavailability of poorly soluble APIs, while hydrophobic CDs, such as triacetyl-β-cyclodextrin (TAβCD), may act as sustained-release agents (22, 23). In addition, a few of these compounds can be used as APIs. For instance, sugammadex (Bridion® 100 mg/mL, solution for injection) is a modified γ-cyclodextrin that is able to reverse neuromuscular block induced by rocuronium or vecuronium (24, 25).

The hypothesis of our work is that bilayer tablets of poorly soluble APIs showing quick/slow release patterns can be prepared combining hydrophilic HPβCD as solubilizing excipient (complexing agent) and superdisintegrants in the rapid release layer, and hydrophobic TAβCD in the sustained release layer as matrix excipient (non-complexing agent). Croscarmellose sodium was utilized as superdisintegrant in the rapid release layer, and sodium stearyl fumarate was applied as anti-adherent lubricant in both layers. The proposed formulation approach has the advantages of using well-known excipients and that only two compression steps are required, without additional technological processing (such as encapsulation or combination of different dosage forms, i.e. capsules and granules or tablets).

Carbamazepine (CBZ) was studied as a model of a Biopharmaceutics Classification System Class 2 API (low solubility and high permeability). Explicitly, CBZ, an antiepileptic and anticonvulsant API utilized both in adults and children, usually by oral route as tablets (conventional or sustained release), capsules (sustained release), chewable tablets, and suspension, may benefit from this formulation approach, since it has a narrow therapeutic index, a short half-life, slow and irregular absorption, and unpredictable fluctuations in the plasma levels leading to the occurrence of intermittent side-effects and/or a potential fall to subtherapeutic levels (3, 26, 27). Furthermore, CBZ administration three or four times daily is an inconvenience and may affect compliance; therefore, the development of fast/sustained release formulations may overcome this drawback by providing better tolerability, efficacy and higher quality of life for the patients (28, 29). To the best of our knowledge, there has been no attempt to explore the potential of the combinations of hydrophilic and hydrophobic CDs to develop CBZ bilayer tablets as a fast/slow drug release system. The composition of the rapid release layer was fixed, while series of sustained release layers were prepared varying the total content in TAβCD. The TAβCD flowability
was characterized, and release profiles were recorded for each layer in separate and after bilayer tablets preparation. Bilayer tablets provided, in all cases, a burst of 50% of the drug dose followed by tunable sustained release profiles of the remaining 50% for several hours.

3.4.5. Materials and Methods
3.4.5.1. Materials

CBZ (Acofarma®, Spain; molecular weight (MW) 236.3 g/mol), HPβCD (Roquette®, France; Kleptose® HP oral grade - Average molar degree of substitution (MS) = 0.85; MW 1480.7 g/mol), TAβCD (Sigma-Aldrich, China; MW 2017.75 g/mol), VIVASOL® (JRS Pharma, Germany; croscarmellose sodium), Pruv® (JRS Pharma, Germany; sodium stearyl fumarate), sodium lauryl sulphate (Acofarma®, Spain) and ethanol 96% (v/v) (Manuel Vieira & Cª (Irmão) Sucrs, Lda, Portugal) were used.

3.4.5.2. Methods
3.4.5.2.1. Preparation of CBZ/HPβCD inclusion complex

Inclusion complexes of CBZ/HPβCD in a molar ratio 1:1 were prepared by a kneading method as previously reported (30). A water/ethanol solution (90:10, v/v) was used as a moistening liquid (31).

3.4.5.2.2. Evaluation of the flow properties and moisture content of the TAβCD

The Carr’s index (n = 3; mean ± standard deviation (SD)) and the Hausner’s ratio (n = 3; mean ± SD) of the TAβCD were evaluated using a tap density tester (Electrolab, ETD 1020, India) through 250 ± 15 taps per min (1). The used sample weight was 50 g. Moreover, the angle of repose (n = 3; mean ± SD) and flow time (n = 3; mean ± SD) were also assessed by a flow tester (Erweka, GTB, Germany) using a sample of 25 g and an outlet nozzle with 25 ± 0.01 mm diameter (1).

The moisture content of the TAβCD (n = 3; mean ± SD) was also determined with an infrared moisture determination balance (A&D Company, AD-4713, Japan) in 1.5 g sample at 80 ºC for 5 min (32).
3.4.5.2.3. Preparation of the bilayer tablets

First, CBZ/HPβCD complex and VIVASOL® were blended in an automatic mixer (Turbula® WAB, T2C, Switzerland) for 15 min. In separate, pure CBZ and TAβCD (Table I) were also mixed in the same blender during the same time. Finally, the lubricant (Pruv®) was added to the two previous mixtures and blended for 3 min in the same mixer.

Six formulas of bilayer tablets with cylindrical geometry (Table I), with 100 mg of CBZ and a target hardness value of 100 N, were prepared using a single-punch compression machine (Korsch 9048-71, Germany) and 13 mm diameter punches. Briefly, the first layer with 50 mg of CBZ + 11, 22, 33, 44, 55 or 66% (w/w relative to the total weight of the sustained release layer as independent tablet) of TAβCD + 0.5% (w/w) of Pruv®, responsible for the slow drug release, was obtained by compaction; and the second layer, with a weight of 382 mg (364 mg of CBZ/HPβCD complex containing 50 mg of CBZ + 16 mg of VIVASOL® + 2 mg of Pruv®), responsible for the rapid drug release, was then added to the compacted first layer and tablets were obtained by compaction of the two layers. The contents of the layers were weighed on an analytical balance (Mettler Toledo, AG245, Switzerland), and the filling of the compression chamber was performed manually. The volume of the compression chamber was adjusted by the position of the lower punch according to the weight of the tablets; on the other hand, the hardness of the tablets was defined by the displacement of the upper punch. It should be noted that the rapid release layer was kept constant for all formulas; contrarily, the weight of the sustained release layer varied, since TAβCD was used at six different proportions.

Table I. The qualitative and quantitative composition of the CBZ bilayer tablets.

<table>
<thead>
<tr>
<th>Rapid release layer</th>
<th>364</th>
</tr>
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<tbody>
<tr>
<td>CBZ/HPβCD inclusion complex (with 50 mg of CBZ)</td>
<td></td>
</tr>
<tr>
<td>VIVASOL®</td>
<td>16</td>
</tr>
<tr>
<td>Pruv®</td>
<td>2</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>382</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Sustained release layer / Formula</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>TAβCD</td>
<td>6</td>
<td>14</td>
<td>25</td>
<td>39</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>Pruv®</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.45</td>
<td>0.6</td>
<td>0.75</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>56.3</td>
<td>64.3</td>
<td>75.4</td>
<td>89.45</td>
<td>111.6</td>
<td>147.75</td>
</tr>
</tbody>
</table>
3.4.5.2.4. Characterization of the bilayer tablets

3.4.5.2.4.1. Physical properties

The mass (n = 20; mean ± SD) was evaluated with an analytical balance (RADWAG®, AS 220.R2, Poland). Diameter and thickness of the tablets (n = 20; mean ± SD) were measured using a digital calliper (fixPOINT®, RS232C, Germany).

The crushing strength of ten tablets of each formula was measured using a tablet hardness tester (Erweka, TBH 28, Germany). The obtained hardness value corresponded to the force required to cause the bilayer tablet rupture.

3.4.5.2.4.2. Scanning electron microscopy

Scanning electron microscopy (SEM) image of a side view of a bilayer tablet obtained from formula VI was taken with a high resolution Schottky environmental scanning electron microscope (FEI Quanta 400 FEG ESEM, United States of America (USA)). The sample was visualized after sputter coating with Au/Pd thin film (∼15 nm) using the SPI-Module™ Sputter (USA). The backscattered electron image was obtained in the topographic mode at 15 kV.

3.4.5.2.4.3. Drug content

Bilayer tablets of each formula were individually placed in a 500 mL volumetric flask with distilled water containing sodium lauryl sulphate (1%, w/v) with magnetic stirring (Barnstead Thermolyne CIMAREC®, SP131320-33, USA) until complete dissolution (~6 h) (33). Afterwards, samples of solution were filtered through 0.45 µm filters (VWR International, USA), suitably diluted, and the concentration of CBZ determined with a double-beam spectrophotometer (Jasco, V-650, Japan) at 288 nm using a calibration curve (y = 45.761x + 0.005) in the 0.00444 to 0.02664 mg/mL range with a coefficient of determination (R²) of 0.9998 (33). All measurements were made in triplicate, and data are reported throughout as mean ± SD.

3.4.5.2.4.4. Differential scanning calorimetry

A differential scanning calorimeter (TA Instruments, Q200, USA) was used to analyse the samples (5-6 mg) by heating from 40 to 280 °C at 10 °C/min. Nitrogen was used as a purge gas at a rate of 50 mL/min. The obtained data were analysed with TA Instruments Universal Analysis 2000 software.
3.4.5.2.4.5. X-ray diffraction

The X-ray powder diffraction (XRD) patterns were obtained in an X-ray diffractometer (Philips Analytical PW 3050/60 X’Pert PRO, Netherlands) using a Cu-Kα X-ray source. The intensity and voltage applied were 30 mA and 40 kV respectively. The angular range of data acquisition was 7 - 42° 2θ, with a stepwise size of 0.017° and 19.685 s of scan step time. The obtained data were analysed with OriginPro® 2020 analysis and graphing software.

3.4.5.2.4.6. Dissolution testing and data modelling

In vitro release profiles were obtained using a dissolution apparatus (Sotax, AT7, Switzerland). In each assay, bilayer tablets were placed at the bottom of the vessel in 900 mL distilled water containing sodium lauryl sulphate (1%, w/v) under constant paddle stirring (75 rpm) at 37 ± 0.5 °C (33). After 1, 3, 5, 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, 600 and 720 min, 1.0 mL samples were removed without volume replacement, filtered through 0.45 μm filters (VWR International, USA), suitably diluted, and CBZ concentration was determined using a double-beam spectrophotometer (Jasco, V-650, Japan) at 288 nm (33). Tests were performed in triplicate under sink conditions, and data were reported throughout as mean ± SD. In addition, the in vitro dissolution profiles from the rapid layer and from the sustained release layers as independent monolayer tablets were also evaluated.

The dissolution profiles from bilayer tablets were compared through calculation of the similarity factor ($f_2$) according to the Eq. 1, where $n$ is the number of time points, $R_j$ is the mean percent reference drug dissolved at time $j$ after initiation of the study, and $T_j$ is the mean percent test drug dissolved at time $j$ after initiation of the study (34). The evaluation of the $f_2$ was based on the following conditions (34): i) eleven-time points were considered (zero excluded), i.e., from 1 min to 240 min inclusive; ii) the time points were the same for all formulations; and iii) not more than one mean value of > 85% dissolved for any of the formulations.

$$f_2 = 50 \times \log \left[ \frac{100}{\sqrt{\sum_{j=1}^{n} (R_j - T_j)^2 \over n}} \right]\ (1)$$
To analyse the mechanism of CBZ release from the sustained release layers as independent monolayer tablets, the release data were fitted to Eq. 2 (zero-order model) (35), 3 (Higuchi model) (36, 37), and 4 (Korsmeyer-Peppas model) (38, 39), where $M_t$ is the amount of drug dissolved in time $t$, $M_0$ is the initial amount of drug, $K_0$ is the zero-order release constant, $K_H$ is the Higuchi rate constant, $K_K$ is the release constant and $n$ is the release exponent which characterizes the mechanism of drug release (40, 41). The $R^2$ value was used as indicator of the best fitting for each of the models. Furthermore, in order to analyse the release exponent ($n$), the release data obtained from the sustained release layers of the bilayer tablets were fitted to the Korsmeyer-Peppas model.

$$M_t = M_0 + K_0 t$$  \hspace{1cm} (2)  

$$M_t = M_0 + K_H t^{0.5}$$  \hspace{1cm} (3)  

$$M_t = M_0 + K_K t^n$$  \hspace{1cm} (4)  

3.4.6. Results and Discussion

In this study, an innovative formulation approach towards CBZ bilayer tablets was developed, i.e., HPβCD, a hydrophilic CD easily soluble in water, was used as complexing agent of CBZ in the rapid release layer, and TAβCD, a hydrophobic CD practically insoluble in water, was tested as matrix excipient (non-complexing agent) in the sustained release layer. It should be noted that Horiuchi et al. (42) prepared theophylline tablets having one fast-release layer of hydrophilic (β-cyclodextrin) complexes, and one slow-release layer of hydrophobic and ionizable complexes (heptakis-(2,6-di-O-ethyl)-β-cyclodextrin and carboxymethyl-ethyl-β-cyclodextrin) (42). Differently, our formulation approach involved: i) only two types of CDs (hydrophilic and hydrophobic); and ii) TAβCD was used as sustained release excipient (non-complexing agent), i.e. a physical mixture of this CD with the drug was directly used to prepare the tablets, being a time- and cost-saving process.

HPβCD and TAβCD have already been studied together, as far as we know, they have never been used as excipients in CBZ bilayer tablets. For instance, Fernandes et al. (43) studied the release behaviour of nicardipine/HPβCD and nicardipine/TAβCD complexes in powders (not in bilayer tablets) in pH 1.2 and pH 6.8 media as well the oral bioavailability in rabbits. The results highlighted that the formulations composed of hydrophilic and hydrophobic CDs inclusion complexes could be useful in oral administration of nicardipine to reach prolonged action, improved bioavailability and reduced side-effects (43).
According to a previous study, inclusion complexes of CBZ/HPβCD 1:1 molar ratio were successfully prepared by a kneading method (30). A fast and high in vitro dissolution rate was noted for the CBZ/HPβCD complex; differently, the physical mixture and pure drug showed slower dissolution rate (30). At 1 min, a drug release of 96.8 ± 5.7% was noticed for 182 mg of CBZ/HPβCD complex containing 25 mg of CBZ in 900 mL of distilled water containing sodium lauryl sulphate (1%, w/v) at 37 ºC (30).

The flow properties of the TAβCD were evaluated according to the pharmacopeial methods (1). Analysing the obtained results, it can be stated that this hydrophobic CD showed poor flowability, since Carr’s index and Hausner's ratio values were 25.7 ± 0.6% and 1.27 ± 0.00 respectively. The flow time and the angle of repose were not determined, as the material did not flow through the 25 ± 0.01 mm diameter nozzle. Regarding the moisture content, TAβCD presented a low value (0.58 ± 0.13%). Thus, it can be used in the formulation of solid oral dosage forms containing APIs susceptible to hydrolytic degradation.

Six formulas of bilayer tablets were successfully prepared through a single-punch compression machine (Table I). The rapid release layer was kept constant for all formulas; in contrast, the weight of the sustained release layer varied, since TAβCD was studied at six different proportions, i.e., at 11, 22, 33, 44, 55 and 66% (w/w relative to the total weight of the sustained release layer as independent tablet). This means that the TAβCD/CBZ molar ratio ranged approximately from 1:4 to 1:71.

Croscarmellose sodium (VIVASOL®), a cellulose-based superdisintegrant, was added at a concentration of 4% (w/w) in the fast release layer because in previous studies this excipient provided appropriate disintegration time during the development of HPβCD-based orodispersible CBZ printlets by semisolid extrusion 3D printing (31). Additionally, croscarmellose sodium is one of the most efficient superdisintegrants in pharmaceutical technology (44, 45). On the other hand, sodium stearyl fumarate (Pruv®) was used as anti-adherent lubricant at a concentration of 0.5% (w/w) in agreement with previous studies with uncoated (32) and orodispersible (30) tablets. In addition, as opposed to magnesium stearate, Pruv® offers several advantages such as improved API compatibility, robustness to over-lubrication, no adverse effect on bioavailability, and improved appearance of effervescent solutions (46).

The physical properties (weight uniformity, diameter, thickness and hardness) and drug content of the bilayer tablets are summarized in Table II. Tablets were produced with a target hardness value of 100 N, and with small weight variations and uniform diameter and thickness. Concerning the drug content, the obtained values varied within the range 100 ± 5%.
Table II. Physical properties and drug content of the bilayer tablets.

<table>
<thead>
<tr>
<th>Parameter / Formula</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>427 ± 3</td>
<td>438 ± 3</td>
<td>453 ± 3</td>
<td>464 ± 4</td>
<td>483 ± 3</td>
<td>521 ± 5</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>13.07 ± 0.02</td>
<td>13.06 ± 0.03</td>
<td>13.08 ± 0.02</td>
<td>13.06 ± 0.02</td>
<td>13.10 ± 0.03</td>
<td>13.06 ± 0.02</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.01 ± 0.03</td>
<td>2.97 ± 0.04</td>
<td>2.77 ± 0.04</td>
<td>3.04 ± 0.02</td>
<td>2.93 ± 0.03</td>
<td>3.28 ± 0.02</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>98 ± 4</td>
<td>101 ± 9</td>
<td>100 ± 4</td>
<td>100 ± 4</td>
<td>99 ± 7</td>
<td>102 ± 3</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>102.7 ± 1.7</td>
<td>98.8 ± 0.3</td>
<td>98.6 ± 0.7</td>
<td>98.8 ± 0.4</td>
<td>101.6 ± 1.6</td>
<td>101.2 ± 0.9</td>
</tr>
</tbody>
</table>

SEM images (side view) of bilayer tablets obtained from the formula VI (Fig. 1) allowed for visualizing the two layers. Compaction caused small and thin cracks in the tablet structure.

![SEM image of a bilayer tablet obtained from formula VI (side view). In the upper part is the sustained release layer and in the lower part is the rapid release layer.]

**Fig. 1.** SEM image of a bilayer tablet obtained from formula VI (side view). In the upper part is the sustained release layer and in the lower part is the rapid release layer.

The drug crystallinity and the possibility of materials interactions before and after compaction were investigated by differential scanning calorimetry (DSC) and XRD. DSC curves of pure materials (CBZ, HPβCD, TAβCD, VIVASOL® and Pruv®) and of rapid release and sustained release layers before and after compaction are shown in Fig. 2. CBZ, HPβCD and croscarmellose sodium showed thermograms similar to those previously reported (30, 31). In relation to CBZ, a small and a large endothermic peak were observed at 176 °C and 192 °C, respectively (30, 31). TAβCD presented two endothermic peaks, i.e., a small one around 195 °C and a large one at 222.5 °C. Corti et al. (4, 47) previously described a similar thermal behaviour, i.e., the TAβCD instantly started losing the weakly hydrogen-bonded water (as shown by the broad initial endothermic band), transforming into a lower melting anhydrous polymorph which melts at 191.8 °C and then recrystallizes into a higher melting...
form with melting endotherm peak at 219.8 °C. Differently, Pruv® displayed three endothermic peaks (around 113, 137 and 200 °C) and an exothermic peak at 248 °C. DSC scans of the rapid release layer before and after compaction were similar to each other, making it possible to affirm that compaction had no effect. In addition, thermograms demonstrated the formation of the complex, since pure CBZ displayed two endothermic peaks while the rapid release layers showed only a broad peak at lower temperature. Thus, the disappearance of the CBZ melting peak could be due to drug amorphization, as a consequence of the kneading treatment with the amorphous HPβCD. It should be highlighted that when guest molecules are incorporated in the CD cavity, their melting, boiling or sublimation points frequently shift to a different temperature or disappear within the temperature range where the CD is decomposed (48).

As far as sustained release layers are concerned, the mixtures presented similar thermogram both before and after compaction, and the two endothermic peaks of CBZ at around 176 and 192 °C were clearly revealed, although with small attenuation in intensity. Overall, compaction did not alter drug crystallinity and there was no incompatibility between the constituents of the sustained release layer.

![Fig. 2. DSC curves of CBZ (A); HPβCD (B); TAβCD (C); VIVASOL® (D); Pruv® (E); rapid release layer (physical mixture before compaction) (F); rapid release layer (after compaction) (G); sustained release layer of the formula V (physical mixture before compaction) (H); and sustained release layer of the formula V (after compaction) (I).](image-url)
As can be seen from the XRD patterns (Fig. 3), CBZ, TAβCD and Pruv® presented crystalline natures due to the presence of several sharp peaks. The XRD pattern of pristine TAβCD revealed relevant diffraction peaks at 8.3, 8.6, 8.8, 9.0, 11.9, 12.1, 15.1, 17.2, 18.1, 19.4, 21.2, 22.5, 22.8, 23.1 and 24.2° 2θ. The TAβCD crystalline character was previously described; however, we observed the major diffraction peaks at 2θ of 8.8, 17.2 and 22.5° and not at 2θ of 7.6, 10.1 and 20.2° (49). The highest peak of TAβCD was observed at 8.8° 2θ. Otherwise, HPβCD and VIVASOL® showed amorphous natures (30, 31). Regarding the rapid release layer, the XRD patterns before and after compaction were similar, and a reduction of the intensity as well as the disappearance of some CBZ peaks were noted. This aspect could be due to CBZ (partial) amorphization as a consequence of the kneading treatment with the amorphous HPβCD, together with the further dilution within the amorphous excipient VIVASOL® (30). The presence of some residual peaks evidenced that CBZ coexists both as crystalline and amorphous states. The sustained release layer before and after compaction displayed also similar XRD patterns revealing that compaction had no negative effect on the drug and there were no incompatibilities between the constituents because principal CBZ peaks remained unaltered. These results were in agreement with those of the DSC assays described above.

The in vitro CBZ profiles from the rapid layer and from the sustained release layers as independent monolayer tablets are shown in Fig. 4. The tablets obtained from the rapid release layer showed a fast CBZ dissolution. At 15 and 30 min, a drug dissolution rate of 86.8 ± 2.9 and of 94.8 ± 1.3% was observed respectively. At 45 min, a total release (100.6 ± 2.5%) was noted. Regarding the tablets obtained from the sustained release layer of the various studied formulas, a slow CBZ release was noticed, and the largest difference in the dissolution profiles was observed between 360 and 720 min. At 720 min, a CBZ release from 31.5 ± 1.1 to 53.6 ± 2.2% was seen.
Fig. 3. XRD patterns of CBZ (A); HPβCD (B); TAβCD (C); VIVASOL® (D); Pruv® (E); rapid release layer (physical mixture before compaction) (F); rapid release layer (after compaction) (G); sustained release layer of the formula V (physical mixture before compaction) (H); and sustained release layer of the formula V (after compaction) (I).

Fig. 4. CBZ dissolution profiles from the rapid release layer and sustained release layers as independent tablets in distilled water containing sodium lauryl sulphate (1%, w/v) at 37 ºC.
Drug release profiles evidenced fast/slow release patterns (Fig. 5). As expected, at the early phase, the six formulas of bilayer tablets showed a similar drug dissolution rate, i.e., about 50% of the CBZ was dissolved during the first 30-45 min, which corresponded to the dose in the rapid release layer. These results agreed with the dissolution profile of the rapid release layer as independent tablet previously described in Fig. 4. Moreover, the combination of CBZ/HPβCD inclusion complex with croscarmellose sodium superdisintegrant proved to be an appropriate formulation approach to achieve fast dissolution. After the initial 30-45 min, a prolonged drug release profile was recorded for 720 min. At 720 min, the CBZ release ranged from 69.4 ± 1.1 to 103.0 ± 0.7%. The CBZ release rate was markedly slowed down when the amount of TAβCD increased. In this way, TAβCD demonstrated to be a suitable controlling agent in the sustained release layer. It should be noted that this hydrophobic CD was used at six different proportions (w/w relative to the total weight of the sustained release layer as independent tablet), i.e., at 11 (formula I), 22 (formula II), 33 (formula III), 44 (formula IV), 55 (formula V) and 66% (formula VI).

The prolonged CBZ release was more pronounced in the monolayer tablets obtained from the sustained release layers than in the bilayer tablets. Thus, the rapid release layer of the bilayer tablets influenced the CBZ release from the sustained release layer. A possible explanation for this issue may be the presence of the VIVASOL® and the hydrophilic CD in the rapid release layer, since both improve the wetting and the release properties, i.e.: i) croscarmellose sodium is a superdisintegrant that due its fibrous nature possesses a wicking effect allowing rapid capillary transport into the tablet matrix (44, 45); and ii) HPβCD is an effective solubilizing excipient (complexing agent) for poorly soluble drugs (30), and a functional soluble filler (non-complexing agent) with suitable disintegration properties (32).

**Fig. 5.** CBZ dissolution profiles from the bilayer tablets in distilled water containing sodium lauryl sulphate (1%, w/v) at 37 °C.
An $f_2$ value between 50 and 100 suggests that the two dissolution profiles are similar, i.e., the differences in dissolution results at each sampling time are 10% or less (34). Analysing the obtained results (Table III), all formulas of bilayer tablets showed a similar dissolution profile during the first 240 min (not more than one mean value of > 85% dissolved), except formulas I and IV ($f_2 = 48$), I and V ($f_2 = 46$), and I and VI ($f_2 = 42.5$).

Table III. Similarity factor ($f_2$) values calculated for all formulas.

<table>
<thead>
<tr>
<th>Formula</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>57.5</td>
<td>54.0</td>
<td>48.0</td>
<td>46.0</td>
<td>42.5</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>79.5</td>
<td>67.0</td>
<td>61.5</td>
<td>54.5</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>-</td>
<td>-</td>
<td>75.0</td>
<td>69.0</td>
<td>59.5</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>84.5</td>
<td>68.5</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>76.5</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

The release data obtained from the sustained release layers as independent monolayer tablets were fitted to zero-order, Higuchi and Korsmeyer-Peppas models (Table IV). The values for the release rate constants ($K_0$, $K_H$, $K_K$), the initial amount of drug ($M_0$), the $R^2$, and the release exponent ($n$) were considered. Overall, the best model for the data was the Korsmeyer Peppas ($R^2$ value). Nevertheless, the zero-order model fitted well in some cases (for example, for tablets of the sustained release layers obtained from formulas I, II and III), and Korsmeyer-Peppas and Higuchi models showed the same $R^2$ value for tablets of the sustained release layer obtained from formula V.

In relation to release exponent ($n$), values between 0.45 and 0.89 (anomalous non-Fickian transport) and higher than 0.89 (super case-II transport) were observed. By contrast, if $n = 0.45$ signifies Fickian diffusion, and $n = 0.89$ designates a case-II relaxational release transport, i.e., polymer relaxation controls drug release (5, 7).

Table IV. Fitting of the kinetic models for sustained release layers as independent monolayer tablets.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Zero-order model</th>
<th>Higuchi model</th>
<th>Korsmeyer-Peppas model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K_0$</td>
<td>$M_0$</td>
<td>$R^2$</td>
</tr>
<tr>
<td>I</td>
<td>0.075</td>
<td>1.427</td>
<td>0.998</td>
</tr>
<tr>
<td>II</td>
<td>0.063</td>
<td>2.849</td>
<td>0.992</td>
</tr>
<tr>
<td>III</td>
<td>0.055</td>
<td>2.959</td>
<td>0.995</td>
</tr>
<tr>
<td>IV</td>
<td>0.048</td>
<td>4.761</td>
<td>0.971</td>
</tr>
<tr>
<td>V</td>
<td>0.046</td>
<td>5.181</td>
<td>0.935</td>
</tr>
<tr>
<td>VI</td>
<td>0.044</td>
<td>3.369</td>
<td>0.947</td>
</tr>
</tbody>
</table>
The release data obtained from the sustained release layers of the bilayer tablets were also fitted to the Korsmeyer-Peppas model, since 45 min (> 49.8% of dissolution) to 720 min (103.0% maximum dissolution) (Table V). As the $n$ values were less than 0.45 (cylindrical geometry), the API release was controlled by pseudo-Fickian diffusion (50). As mentioned by Lopes et al. (5), it should be noted that the analysis of the results applying the mathematical models is purely empirical, and no definitive conclusions can be drawn concerning the dominant mass transport mechanisms.

Table V. Fitting of the kinetic model for all formulas of the bilayer tablets.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Korsmeyer-Peppas model</th>
<th>$n$</th>
<th>$K_\infty$</th>
<th>$M_0$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>0.193</td>
<td>32.369</td>
<td>-8.178</td>
<td>0.982</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>0.234</td>
<td>21.820</td>
<td>-0.510</td>
<td>0.992</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>0.293</td>
<td>12.458</td>
<td>12.980</td>
<td>0.997</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>0.237</td>
<td>15.741</td>
<td>11.414</td>
<td>0.998</td>
</tr>
<tr>
<td>V</td>
<td></td>
<td>0.107</td>
<td>50.914</td>
<td>-26.334</td>
<td>0.986</td>
</tr>
<tr>
<td>VI</td>
<td></td>
<td>0.200</td>
<td>12.041</td>
<td>24.168</td>
<td>0.986</td>
</tr>
</tbody>
</table>

3.4.7. Conclusion

Bilayer tablets exhibiting quick/slow release patterns were successfully developed using HPβCD as main component of the fast release layer and TAβCD as the controlling release agent in the slow release layer. The CBZ complexation with the HPβCD, together with the addition of the croscarmellose sodium superdisintegrant, allowed complete dissolution of 50% CBZ dose in the first 30-45 min. In addition, by adjusting the TAβCD proportion in the sustained release layer, CBZ release could be prolonged for 720 min. In conclusion, combinations of hydrophilic and hydrophobic CDs may help addressing the formulation of poorly soluble drugs in bilayer tablets as a fast/slow biphasic release system.

3.4.8. List of abbreviations

- **API(s)** - Active pharmaceutical ingredient(s)
- **CBZ** - Carbamazepine
- **CD(s)** - Cyclodextrin(s)
- **DSC** - Differential scanning calorimetry
- **$f_2$** - Similarity factor
- **HPβCD** - Hydroxypropyl-β-cyclodextrin
- **$K_0$** - Zero-order release constant
3.4.9. Acknowledgements

Jaime Conceição is grateful to Fundação para a Ciência e a Tecnologia (FCT, Portugal) and PhD Programme in Medicines and Pharmaceutical Innovation (i3DU) for funding this work through the grant [PD/BD/127813/2016]. This work was also supported by the Applied Molecular Biosciences Unit-UCIBIO which is financed by national funds from FCT/MCTES (UID/Multi/04378/2019). André Vilaranda, Andreia Vale, Matilde Rodrigues, Sónia Guerra and Yohanna Gabrieli are acknowledged for the help during the preparation of the bilayer tablets. JRS Pharma is acknowledged for supplying free samples of VIVASOL® and Pruv® excipients. We are also thankful to Materials Centre of the University of Porto (CEMUP) for the expert assistance with SEM analysis.

3.4.10. References


4. CONCLUSION

Cyclodextrins (CDs) are cyclic oligosaccharides composed of α-(1,4) linked glucopyranose subunits that can have several pharmaceutical applications (1-3). In this Thesis, CDs were studied as excipients in four types of tablet formulations, namely in uncoated tablets, where they acted as fillers for direct compression (section 3.1), orodispersible and immediate release three-dimensional (3D) printed tablets (section 3.2), orodispersible tablets (ODTs) along with five-in-one co-processed excipients (section 3.3), and bilayer tablets as quick/slow biphasic release systems (section 3.4).

Three CDs were studied, i.e., two hydrophilic (β-cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (HPβCD)) and one hydrophobic (triacetyl-β-cyclodextrin (TAβCD)). Moreover, carbamazepine (CBZ) was used as a model of a poorly soluble active pharmaceutical ingredient (API) with poor flowability.

In section 2.1, the state of the art of CDs as drug carriers in Pharmaceutical Technology was revisited (4). Thus, it is possible to state that: i) CDs are versatile excipients that are used to formulate solid, semisolid and liquid dosage forms in order to obtain immediate and/or modified API release; ii) the main advantages of using these cyclic oligosaccharides in Pharmaceutical Technology are to enhance solubility/dissolution/bioavailability of poorly soluble APIs (class 2 and 4 drugs of the Biopharmaceutics Classification System); to enhance physical-chemical stability of APIs; to modify the API release site and/or time profile; and to reduce API side effects (for example, gastric or ocular irritation); iii) CDs are complexing and non-complexing excipients in solid oral pharmaceutical dosage forms like tablets, ODTs, effervescent tablets, bilayer tablets, osmotic pump tablets, mucoadhesive buccal tablets, minitablets and capsules; iv) the major drawback of CDs is the increase in formulation bulk, once the complexation efficiency (CE) is, in general, very low. This aspect is particularly relevant in solid dosage forms and limits the use of CDs to potent drugs. In this way, the methods used to increase the CE (pH adjustment of the complexation medium; use of hydroxy acids, hydroxylamines, amino acids, water-soluble polymers, cosolvents and metal complexes; and combination of two or more of these methods) have an important role in reducing the amount of CD; v) CDs have monographs in principal pharmacopoeias (European Pharmacopoeia, United States Pharmacopoeia - National Formulary and Japanese Pharmacopoeia) and present favourable toxicological profile for human use. Therefore, there are several medicinal products containing these compounds as excipients approved by regulatory authorities around the world. It should be noted that the revised monograph of sulfobutylbetadex sodium was published in Supplement 9.8 of the European Pharmacopoeia whose
implementation date was July 1, 2019; and vi) these compounds can be applied as APIs for the treatment of many diseases like hypercholesterolemia, cancer and Niemann-Pick type C disease (5).

A critical review of CDs as excipients in tablet formulations was performed in section 2.2 (6). The main obtained conclusions were the following: i) the principal application of CDs in tablets is to enhance the dissolution and bioavailability of poorly soluble APIs; ii) CDs can be used as complexing excipients in tablet formulations for low-dose APIs; iii) these compounds are also used as fillers, disintegrants, binders and multifunctional direct compression excipients of the tablets; and iv) the flow properties of the inclusion complex play a crucial part in the tablet manufacturing process mainly by direct compression. Therefore, these properties should be evaluated during the pharmaceutical formulation development.

HPβCD and βCD as tablet fillers for direct compression were studied in section 3.1 (7). Three main conclusions can be drawn from the obtained results: i) the studied CDs can be used as tablet fillers for direct compression; ii) HPβCD showed better properties than βCD mainly at the level of the physics of compression (higher values of plasticity index and lubrication efficiency) and of the drug release characteristics (faster and greater dissolution rate and shorter disintegration time); and iii) lactose monohydrate and HPβCD displayed the best results. As there are people intolerant to lactose, HPβCD, although its cost is higher, can be considered a good substitute for lactose as soluble filler for direct compression. Particularly, it should be highlighted that Asian populations present a high prevalence of lactose intolerance due to the high prevalence of lactase deficiency (8-10).

3D printing or additive manufacturing is an innovative technology to produce small-batch personalized medicinal products (11, 12), and a promising tool in bioavailability enhancement of poorly water-soluble APIs (13). As such, in section 3.2, HPβCD was used for the first time to prepare 3D printed tablets (printlets) (14). The results highlighted the feasibility of using HPβCD as main excipient in printlets of poorly soluble APIs, and the possibilities of tuning API release profiles through small changes in cellulose ethers nature and ratio. In addition, semisolid extrusion-based 3D printing was revealed as a feasible approach to in situ form CBZ/HPβCD complexes and to produce printlets with suitable physical and drug release properties for oral delivery. Regarding the major technological challenges for the development of 3D printed tablets via semi-solid extrusion, the batch-to-batch variability and the low mechanical resistance (friability and hardness) of the produced printlets should be mentioned.

The hypothesis that ODTs of poorly soluble APIs can be prepared by direct compression combining CDs that form inclusion complexes and thus improve the wetting
and the release properties, and directly-compressible five-in-one co-processed excipients that may solve the poor flowability typical of inclusion complexes as well as promoting a rapid disintegration was tested in section 3.3 (15). Thus, a new formulation approach was developed, namely: i) the preparation of inclusion complexes was performed in order to enhance the solubility and dissolution of APIs; and ii) five-in-one co-processed excipients (Prosolv® ODT G2 and F Melt® type C) were used to improve the flow properties of the CBZ/HPβCD inclusion complex, allowing the preparation of the tablets by direct compression, as well as to obtain disintegration times in accordance to pharmacopoeial specifications. In conclusion, the combination of five-in-one co-processed excipients and hydrophilic CDs may help addressing the ODT formulation of poorly soluble APIs with poor flowability, by direct compression and with the desired release properties.

Finally, in section 3.4, the combination of hydrophilic and hydrophobic CDs to prepare bilayer tablets that can perform as quick/slow biphasic release systems of a poorly soluble API was explored, since this formulation approach is of particular interest for treatments that require a rapid action followed by sustained therapeutic levels (16). Bilayer tablets exhibiting quick/slow release patterns were successfully developed using HPβCD as main component of the fast release layer (complexing agent), and TAβCD as the controlling release agent in the slow release layer (non-complexing agent). The CBZ complexation with the HPβCD, together with the addition of the croscarmellose sodium superdisintegrant, allowed complete dissolution of 50% CBZ dose in the first 30-45 min. Additionally, by adjusting the TAβCD proportion in the sustained release layer, CBZ release could be prolonged for 720 min. In summary, combinations of hydrophilic and hydrophobic CDs may help addressing the formulation of poorly soluble APIs in bilayer tablets as a fast/slow biphasic release system.

In sum, the six specific objectives established for this Thesis were achieved. The obtained outcomes showed that CDs are multifunctional excipients in 3D printed tablets, ODTs and bilayer tablets. Furthermore, these compounds can act as tablet fillers for direct compression.
4.1. List of abbreviations

3D - Three-dimensional
API(s) - Active pharmaceutical ingredient(s)
CBZ - Carbamazepine
CD(s) - Cyclodextrin(s)
CE - Complexation efficiency
HPβCD - Hydroxypropyl-β-cyclodextrin
ODT(s) - Orodispersible tablet(s)
TAβCD - Triacetyl-β-cyclodextrin
βCD - β-cyclodextrin

4.2. References

1. Fernández MA, Silva OF, Vico RV, de Rossi RH. Complex systems that incorporate cyclodextrins to get materials for some specific applications. Carbohydr Res. 2019;480:12-34.


Appendices

Appendix I. Abstract and poster presentation, entitled "Formulation of orodispersible carbamazepine/hydroxypropyl-β-cyclodextrin tablets with five-in-one high functionality excipients for direct compression", accepted for publication in the 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology. Due to the ongoing spread of Corona (SARS-CoV-2) virus, the World Meeting was postponed to 11 to 14 May, 2021.

Formulation of orodispersible carbamazepine/hydroxypropyl-β-cyclodextrin tablets with five-in-one high functionality excipients for direct compression

Jaime Conceição1; Oluwatomiade Adeoye2; Helena Cabral-Marques3; Angel Concheiro4; Carmen Alvarez-Lorenzo5; José Manuel Sousa Lobo6

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INTRODUCTION
The hypothesis of this work is that orodispersible tablets (ODTs) of poorly soluble active pharmaceutical ingredients (APIs) can be prepared by direct compression combining cyclodextrins (CDs) that form inclusion complexes and thus improve the wetting and the release properties, and directly-compressible five-in-one co-processed excipients that may solve the poor flowability typical of inclusion complexes as well as promoting a rapid disintegration (1). Carbamazepine (CBZ) and hydroxypropyl-β-cyclodextrin (HPβCD) were used, respectively, as a model of a poorly soluble API with poor flowability and as a solubilizing agent.

EXPERIMENTAL METHODS
Materials
CBZ (Acofarma®), HPβCD Kleptose® HP oral grade (Roquette®), Provicol® ODT G2 (IRS Pharma), F-Melt® type C (Fuj Chemical Industries), Pruv® (IRS Pharma), sodium lauryl sulphate (Acofarma®), ethanol absolute (VWR® Chemicals), and methylene blue (Difco Laboratories) were used.

Phase solubility studies
Phase solubility studies were performed in Milli Q water (25 °C/200 rpm/72 h) according to Higuchi and Connors method. The stability constant (Kc), the complexation efficiency (CE) and the concentration of CBZ without HPβCD (Sc) were calculated.

Preparation and characterization of the CBZ/HPβCD complex
The complex of CBZ/HPβCD in a molar ratio 1:1 was prepared by kneading. In addition, a physical mixture of CBZ/HPβCD 1:1 molar ratio was also prepared by spulation according to the geometric dilution method. Differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM), drug content and in vitro dissolution studies were performed.

Evaluation of the flow properties
The flow properties (Carr’s index, Hausner ratio, flow time and angle of repose) of CBZ/HPβCD inclusion complex, physical mixture, co-processed excipients and ODTs formulas II and IV (Table 1) were assessed according to the European Pharmacopoeia 9.0.

Preparation of the ODTs
Six formulas of ODTs containing 25 mg of CBZ or its equivalent amount of CBZ/HPβCD complexes and of physical mixtures were prepared by direct compression using a single-punch compression machine (Korsch, 9048-J) with 11 mm diameter punches (Table 1).

ODTs characterization
Physical properties (weight uniformity, diameter, thickness and hardness), drug content, wetting time, water-absorption ratio, disintegration time in distilled water and in vitro dissolution tests were performed.

<table>
<thead>
<tr>
<th>Component / Formula</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
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<tr>
<td>CBZ</td>
<td>25</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Inclusion complex (with 25 mg of CBZ)</td>
<td>-</td>
<td>182</td>
<td>-</td>
<td>182</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Physical mixture (with 25 mg of CBZ)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>182</td>
<td>182</td>
<td>-</td>
</tr>
<tr>
<td>Provicol® ODT G2</td>
<td>472.5</td>
<td>315.5</td>
<td>-</td>
<td>315.5</td>
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<tr>
<td>F-Melt® type C</td>
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<td>-</td>
<td>472.5</td>
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<tr>
<td>Pruv®</td>
<td>2.5</td>
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<td>2.5</td>
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<td>2.5</td>
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</tr>
<tr>
<td>Total weight (mg)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
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</table>

Table 1. ODTs composition.
RESULTS AND DISCUSSION

The phase solubility studies showed: i) the CBZ complexation with HPβCD increased the aqueous solubility of the API; ii) an A2-type profile was obtained; iii) the obtained Kc and CE values were, respectively, 272 ± 7 M⁻¹ and 0.326 ± 0.047; and iv) the S₃ value was 146 ± 3 μg/mL. The CBZ content in the inclusion complex and in the physical mixture was, respectively, 102.3 ± 2.5% and 96.7 ± 8.1%. A fast and high in vitro dissolution rate was noticed for the CBZ/HPβCD complex; differently, the physical mixture and pure drug showed slower dissolution rate. DSC, XRD and SEM studies evidenced the formation of the inclusion complex.

The determined flow properties of the samples are shown in Table 2. The CBZ/HPβCD complex showed poor flow. In contrast, the other analyzed samples presented good flow. The mean values of the physical properties of the ODTs, as well as its drug content, wetting time, water-absorption ratio and disintegration time are summarized in Table 3. The disintegration times were less than or equal to 180 s, fulfilling the specifications of the European Pharmacopoea 9.0, and similar for the two five-in-one co-processed excipients. The presence of the inclusion complex in the formulas (56.4%, w/w) did not interfere in this parameter. Moreover, the CBZ/HPβCD physical mixture (formulas V and VI) exhibited higher disintegration times than the inclusion complex (formulas II and IV) and the pure CBZ (formulas I and III).

As can be seen in Figure 1, ODTs with CBZ/HPβCD complexes displayed faster and greater drug dissolution rates than ODTs with pure CBZ and with physical mixtures.

CONCLUSION

The preparation of inclusion complexes was performed to enhance the solubility and dissolution of the API, and five-in-one co-processed excipients were used to improve the flow properties of the inclusion complex, allowing the preparation of the tablets by direct compression, as well as to obtain disintegration times in accordance to pharmacopeial specifications (1). In conclusion, the combination of five-in-one co-processed excipients and hydrophilic CDs may help addressing the ODT formulation of poorly soluble APIs with poor flowability, by direct compression and with desired release properties.

ACKNOWLEDGEMENTS

Jaime Conceição is grateful to Fundação para a Ciência e a Tecnologia (FCT, Portugal) and PhD Programme in Medicines and Pharmaceutical Innovation (iSDU) for funding this work through the grant [PD/BD/127813/2016]. To IFS Pharma and Fuji Chemical Industries for supplying free samples of the excipients.

REFERENCES


<table>
<thead>
<tr>
<th>Parameter / Sample</th>
<th>Inclusion complex</th>
<th>Physical mixture</th>
<th>Prosolv® ODT G2</th>
<th>F-Melt® Type C</th>
<th>Formula II</th>
<th>Formula IV</th>
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<tr>
<td>Carr’s index (%)</td>
<td>29.9 ± 1.6</td>
<td>14.2 ± 1.3</td>
<td>19.8 ± 0.4</td>
<td>18.6 ± 0.5</td>
<td>22.3 ± 0.7</td>
<td>22.1 ± 0.1</td>
</tr>
<tr>
<td>Haunton ratio</td>
<td>1.33 ± 0.03</td>
<td>1.07 ± 0.01</td>
<td>1.17 ± 0.01</td>
<td>1.13 ± 0.01</td>
<td>1.14 ± 0.01</td>
<td>1.14 ± 0.01</td>
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<tr>
<td>Flow time (s/100g)</td>
<td>n.d.</td>
<td>0.7 ± 0.2</td>
<td>2.0 ± 0.0</td>
<td>1.2 ± 0.0</td>
<td>3.2 ± 0.2</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>Angle of repose (%)</td>
<td>n.d.</td>
<td>30.6 ± 0.8</td>
<td>26.2 ± 1.0</td>
<td>27.2 ± 0.6</td>
<td>28.0 ± 0.5</td>
<td>28.9 ± 1.0</td>
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</table>

Table 2. Flow properties of the samples. n.d. - not determined.

<table>
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<tr>
<th>Parameter / Formula</th>
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<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
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<tr>
<td>Weight (mg)</td>
<td>508 ± 2</td>
<td>505 ± 3</td>
<td>508 ± 3</td>
<td>506 ± 3</td>
<td>508 ± 4</td>
<td>502 ± 6</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>13.11 ± 0.02</td>
<td>13.11 ± 0.03</td>
<td>13.14 ± 0.02</td>
<td>13.11 ± 0.03</td>
<td>13.16 ± 0.03</td>
<td>13.24 ± 0.04</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.25 ± 0.02</td>
<td>3.50 ± 0.02</td>
<td>3.19 ± 0.02</td>
<td>3.62 ± 0.05</td>
<td>3.19 ± 0.03</td>
<td>3.21 ± 0.08</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>104 ± 3</td>
<td>102 ± 4</td>
<td>106 ± 3</td>
<td>101 ± 3</td>
<td>100 ± 6</td>
<td>100 ± 6</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>101.9 ± 2.1</td>
<td>99.2 ± 1.1</td>
<td>100.9 ± 1.1</td>
<td>101.9 ± 2.2</td>
<td>100.3 ± 4.3</td>
<td>101.0 ± 2.3</td>
</tr>
<tr>
<td>Water-absorption ratio (%)</td>
<td>80.3 ± 1.9</td>
<td>78.5 ± 1.3</td>
<td>78.5 ± 2.8</td>
<td>77.5 ± 2.5</td>
<td>53.4 ± 1.5</td>
<td>53.5 ± 2.2</td>
</tr>
<tr>
<td>Disintegration time (s)</td>
<td>60</td>
<td>60</td>
<td>53</td>
<td>50</td>
<td>180</td>
<td>150</td>
</tr>
</tbody>
</table>

Table 3. Physical properties, drug content, wetting time, water-absorption ratio and disintegration time of the ODTs.
INTRODUCTION

The hypothesis of the work is that orodispersible tablets (ODTs) of poorly soluble active pharmaceutical ingredients (APIs) can be prepared by direct compression using cyclodextrins (CDs) that form inclusion complexes and thus improve the wetting and the release properties, combined with directly-compressible fluid-vic one-co-processed excipients that may solve the poor flowability typical of inclusion complexes as well as promoting a rapid disintegration [1]. Carbamazepine (CBZ) and hydroxypropyl-β-cyclodextrin (HPβCD) were used, respectively, as a model of a poorly soluble API with poor flowability and as a solubilizing agent.

EXPERIMENTAL METHODS

Phase solubility studies were performed in MilliQ water (25 °C ± 2°C rpm 72 h) according to Higuchi and Connors method. The solubility constant (Ks), the complexation efficiency (CE) and the concentration of CBZ without HPβCD (C0) were calculated.

The complex of CBZ:HPβCD in a molar ratio 1:1 was prepared by grinding. In addition, a physical mixture of CBZ:HPβCD 1:10 molar ratio was also prepared by spolution according to the geometric dilution method. Differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM), drug content and in vitro dissolution studies were performed.

The flow properties (Car's index, Hausner ratio, flow time and angle of repose) of CBZ:HPβCD inclusion complex, physical mixture, co-processed excipients and ODTs formulae II and IV (Table 1) were assessed according to the European Pharmacopoeia 9.0. Six formulas of ODTs containing 25 mg of CBZ or its equivalent amount of CBZ:HPβCD complex and of physical mixtures were prepared by direct compression using a single-punch compression machine (Korsch, 604B FT) with 12 mm diameter punches (Fig. 1).

Physical properties (weight uniformity, diameter, thickness and hardness), drug content, wetting time, water-absorption ratio, disintegration time in distilled water and in vitro dissolution tests were performed.

RESULTS

The phase solubility studies showed that the CBZ complexation with HPβCD increased the aqueous solubility of the API (Fig. 1) an A-type profile was obtained, it obtained the Ks and CE values were, respectively, 272 ± 7.42 M-1 and 0.236 ± 0.047, and in the D5 value was 146 ± 2.3 μg/ml. The CBZ content in the inclusion complex and in the physical mixture was, respectively, 102.3 ± 2.9% and 96.7 ± 8.1%. A fast and high in vitro dissolution rate was noticed for the CBZ:HPβCD complex; differently, the physical mixture and pure drug showed slower dissolution rate (Fig. 1). DSC (Fig. 2), XRD (Fig. 3) and SEM (Fig. 4) studies evidenced the formation of the inclusion complex.

The determined flow properties of the samples are shown in Table 2. The CBZ:HPβCD complex showed poor flow. In contrast, the other analyzed samples presented good flow. The mean values of the physical properties of the ODTs, as well as their drug content, wetting time, water-absorption ratio and disintegration time are summarized in Table 3. The disintegration times were less than or equal to 180 s, fulfilling the specifications of the European Pharmacopoeia 9.0, and similar for the two fluid-one-co-processed excipients. The presence of the inclusion complex in the formulae (III, IV) that did not interfere in this parameter. Moreover, the CBZ:HPβCD physical mixture (formulae IV and V) exhibited higher disintegration times than the inclusion complex (formulae IV and V) and the pure CBZ (formulae I and III). As can be seen in Fig. 5, ODTs with CBZ:HPβCD complexes displayed faster and greater drug dissolution rates than ODTs with pure CBZ and with physical mixtures.

CONCLUSIONS

The preparation of inclusion complexes was performed to enhance the solubility and dissolution of the API, and fluid-vic one-co-processed excipients were used to improve the flow properties of the inclusion complex, allowing the preparation of tablets by direct compression, as well as to obtain disintegration times in accordance to pharmacopoeial specifications [1]. In conclusion, the combination of five one-co-processed excipients and hydrophilic CDs may help addressing the ODT formulation of poorly soluble APIs with poor flowability, by direct compression and with desired release properties.

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ACKNOWLEDGEMENTS

Jaime Conceição is grateful to Fundação para a Ciência e a Tecnologia (FCT, Portugal) and PhD Programme in Medicines and Pharmaceutical Innovation (SDC) for funding this work through the grant FCT-IF/00172/2012. This work was also supported by the Applied Molecular Biocatalysis Unit (CMUM), which is financed by national funds from FCT/MCTES (UID/CTM/04129/2019). To JRS Pharma and Fuj Chemical Industries for supplying free samples of the excipients. We are also thankful to Biomaterias Centre of the University of Porto (CEBIM) for the expert assistance with IOM analysis.

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Appendix II. Abstract accepted for publication, entitled “Hydrophilic and hydrophobic cyclodextrins as excipients in quick/slow release bilayer tablets”, in order to perform a short presentation in the 20th International Cyclodextrin Symposium (ICS2020). Due to the ongoing spread of Corona (SARS-CoV-2) virus, the Meeting was postponed to 7 to 10 June, 2021.

Hydrophilic and hydrophobic cyclodextrins as excipients in quick/slow release bilayer tablets

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This study aimed to formulate carbamazepine (CBZ) bilayer tablets as quick/slow release systems using hydroxypropyl-β-cyclodextrin (HPβCD) as solubilizing agent in the rapid release layer, and triacetetyl-β-cyclodextrin (TΑβCD) as controlling release agent in the sustained release layer [1, 2]. CBZ, an anticonvulsant and anti-epileptic agent, was studied as a model of a Biopharmaceutics Classification System Class 2 drug. Croscarmellose sodium (VTASOL®) was utilized as superdisintegrant in the rapid release layer, and sodium stearyl fumarate (Pruv®) was applied as anti-adherent lubricant. Phase solubility studies of CBZ with HPβCD were performed in water (25 °C/200 rpm/72 h). The CBZ/HPβCD complex (molar ratio 1:1) was prepared by kneading and characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), scanning electron microscopy (SEM), drug content and in vitro dissolution studies. Afterwards, six formulas of bilayer tablets were prepared using a single-punch compression machine, as follows: the first layer with 50 mg of CBZ + 11, 22, 33, 44, 55 or 66% (w/w relative to the total weight of the sustained release layer) of TΑβCD + 0.5% (w/w) of Pruv®, responsible for the sustained drug delivery, was obtained by compaction; and the second layer, with a weight of 382 mg (364 mg of CBZ/HPβCD complex containing 50 mg of CBZ + 16 mg of VTASOL® + 2 mg of Pruv®), responsible for the rapid drug release, was then added to the compacted first layer and tablets were obtained by compaction of the two layers. Physical properties of the bilayer tablets were evaluated as well as their drug content and in vitro dissolution profiles during 12 h. Moreover, SEM, DSC and XRD analysis were performed. Bilayer tablets exhibiting quick/slow release patterns were successfully developed and characterized using HPβCD as main component of the fast release layer and TΑβCD as slow-release agent in the sustained release layer.

Acknowledgments
Fundaçao para a Ciência e a Tecnologia and i3DU PhD Programme by the grant [PD/BD/127813/2016].

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Cyclodextrins as excipients in solid oral dosage forms