Bilayer tablets with carbamazepine as a biphasic quick/slow delivery system

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INTRODUCTION

Bilayer compacting technology has gained more popularity in recent years because bilayer tablets offer several advantages over the conventional tablets (1, 2). The purpose of this study was to develop and characterize three formulas of bilayer tablets with carbamazepine (200 mg), a model drug of the class II Biopharmaceutical Classification System, as a biphasic quick/slow delivery system. The sustained release layer was composed by the drug and one of three matrices, such as Kollidon® SR (inert), Protanal® CR 8223 (hydrophilic) and Lubritab® (lipidic). The rapid release layer was kept constant and contained the drug and Ac-Di-Sol® (superdisintegrant).

EXPERIMENTAL METHODS

Materials

The raw materials used were carbamazepine (Acofarma®, antiepileptic and anticonvulsant drug), Ac-Di-Sol® (FMC BioPolymer; croscarmellose sodium), Kollidon® SR (BASF SE; a mixture of polyvinyl acetate and polyvinylpyrrolidone - 8:2 w/w), Protanal® CR 8223 (FMC Biopolymer; sodium alginate) and Lubritab® (JRS Pharma; hydrogenated vegetable oil).

Manufacture of tablets

Three types of bilayer tablets (Table 1), with a target weight of 320 mg (± 16 mg), were prepared using a single-punch compression machine (Korsch 9048-71, Germany) with 10 mm diameter punches, as follows: the first layer with a weight of 160 mg (100 mg carbamazepine + 60 mg Ac-Di-Sol®), responsible for the rapid drug release, was obtained by compaction; the second layer, with a weight of 160 mg (100 mg carbamazepine + matrix excipient), responsible for the sustained drug delivery, was then added to the compacted first layer and tablets were obtained by compaction of the two layers.

Characterization of the tablets

Weight uniformity (mean ± standard deviation (SD), n = 10), analytical balance Mettler AG 204, Mettler Toledo, Switzerland), thickness (mean ± SD, n = 10, electronic digital caliper, model number Z22855, Powerfix®, Germany) and hardness (mean ± SD, n = 10, tablet hardness tester Erweka TBH 28, Erweka GmbH, Germany) were evaluated in the obtained tablets. Friability was determined by submitting 10 previously weighed tablets to falling shocks for 4 min in a friabilator (EF-1W, Electrolab, India), set at 25 rpm/min. After 4 min, the tablets were reweighed and friability was calculated.

Tensile strength (mean ± SD, n = 10) was assessed using equation 1, as it takes into account the dimensions of the tablets.

\[ \text{Tensile strength} = \frac{P}{\pi \times D \times t} \] (1)

Where P is the hardness (N), D and t are the diameter (mm) and thickness (mm) of the tablet, respectively.

In vitro release studies

The in vitro drug release studies (mean ± SD, n = 6) were performed using a dissolution apparatus (AT7, Sotax, Switzerland) according to the paddle method at 100 rpm (3). The dissolution medium consisted of 900 mL of sodium lauryl sulfate solution 1% (w/v) at 37.0±0.5 ºC (3). The collection times were 15, 30, 45, 60, 120, 180, 240, 360, 480 minutes, and the volume of the collected samples was 10.0 mL (without volume replacement). The samples were filtered and the carbamazepine concentration was determined with an UV-VIS spectrophotometer (V-650, Jasco, Japan). A drug calibration curve was previously prepared (λ=288 nm; y=45.4144x+0.0444; R²=0.9991) (3).

Table 1. Bilayer tablets composition (mg).

<table>
<thead>
<tr>
<th>Formula 1 (F1)</th>
<th>Formula 2 (F2)</th>
<th>Formula 3 (F3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid release layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ac-Di-Sol®</td>
<td>60</td>
<td>Ac-Di-Sol®</td>
</tr>
<tr>
<td>Sustained release layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>60</td>
<td>Protanal® CR 8223</td>
</tr>
</tbody>
</table>
The dissolution profiles of tablets were compared using the similarity factor ($f_2$) calculated as follows (4):

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

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.

Differential scanning calorimetry (DSC)
DSC thermograms of samples were recorded using a differential scanning calorimeter (DSC 200 F3 Maia®, Netzsch, Germany) with automatic sample changer, using a sample size of 6 mg. The temperature was ramped from 20 to 300 °C at a constant scanning speed (10 °C/min). The samples were contained in crimped aluminum pans under a flow of nitrogen at 40 mL/min.

RESULTS AND DISCUSSION
Bilayer tablets, containing 200 mg of carbamazepine, with uniform aspect and suitable physical properties (weight uniformity, thickness and tensile strength) were produced (Table 2). However, the obtained tablets presented a friability value greater than 1.0%.

In vitro dissolution tests showed at 480 minutes a mean carbamazepine release from 62.7 to 91.4% (Figure 1). As can be seen, the amount of drug released during 2 h was very similar for all formulations.

Regarding the results of $f_2$, the tablets obtained from inert and lipidic matrices showed similar dissolution profiles ($f_2 > 50$).

The DSC thermograms (Figure 2) revealed that there is no incompatibility between the drug and the excipients. The thermogram of carbamazepine (A) showed a sharp endothermic peak at 189.5°C corresponding to its melting point.

CONCLUSION
The bilayer tablets allowed a quick release of the carbamazepine contained in the rapid release layer and a slow release of the same drug contained in the sustained release layer. The inert and lipidic matrices showed similar dissolution profiles ($f_2 > 50$).

ACKNOWLEDGEMENTS
Kollidon® SR, Protanal® CR 8223 and Lubritab® were kindly supplied by BASF SE, FMC Biopolymer and JRS Pharma, respectively.

**REFERENCES**


**Table 2. Physical properties of the bilayer tablets.**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Tensile strength (N/mm²)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>315±2</td>
<td>3.33±0.02</td>
<td>1.56±0.17</td>
<td>1.09</td>
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<tr>
<td>F2</td>
<td>319±1</td>
<td>3.03±0.03</td>
<td>1.67±0.10</td>
<td>1.79</td>
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<tr>
<td>F3</td>
<td>317±1</td>
<td>3.25±0.02</td>
<td>1.42±0.17</td>
<td>1.58</td>
</tr>
</tbody>
</table>