

Liquid–Liquid Equilibria Determination and Modeling of ATPS Based on PEG4000 and PVP29000 at 298.15 K and 0.1 MPa

Pedro Velho,* Afonso Madaleno, and Eugénia A. Macedo*

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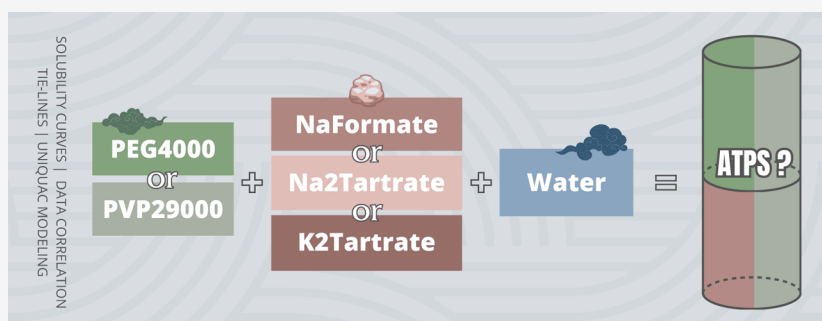
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ABSTRACT: Additionally to the known nontoxicity and eco-friendliness of aqueous two-phase systems (ATPS), polymeric ATPS, which are composed of at least one polymer [e.g., poly(ethylene glycol) or poly(vinylpyrrolidone)], provide extractive media with enhanced potential for drug delivery and biomolecule extraction. Nevertheless, the lack of liquid–liquid equilibria (LLE) data concerning these systems still limits their large-scale application and hampers proper thermodynamic modeling, delaying advancements in the design of novel materials and processes based on polymers. In this work, the LLE, *i.e.*, solubility curves and tie-line compositions, of the ATPS {PEG4000 (1) + NaFormate (2) + Water (3)} and {PVP29000 (1) + NaFormate or Na₂Tartrate or K₂Tartrate (2) + Water (3)} were determined at 298.15 K and 0.1 MPa. The estimation of tie-line composition using third-degree polynomials of liquid density (ρ) and electrical conductivity (κ) allowed to better understand the influence of composition on these thermophysical properties, and the tie-line data were successfully correlated using the models of Othmer–Tobias and Bancroft–Hubard, achieving determination coefficients (R^2) larger than 0.9575 and 0.9676, respectively. Moreover, the obtained compositions were effectively described using the UNiVersal QUAsi-Chemical (UNIQUAC) model, with standard deviations (σ) lower than 6.84×10^{-3} .

1. INTRODUCTION

Aqueous two-phase systems (ATPS), or aqueous biphasic systems, constitute a useful liquid–liquid extraction technique in which two completely or partially immiscible chemical compounds coexist due to the presence of a consolute (e.g., water). The least soluble component in the consolute is named as salting-out agent and causes phase splitting by competing for the consolute molecules.¹ The phase separation of ATPS has been increasingly studied given its promising potential for industrial application, particularly to what pertains their biocompatibility and nontoxicity (suitable for protein purification and cell culture^{2–5}), selectivity and extraction efficiency (advantageous for bioprocessing and biotechnology^{6,7}), and low environmental impact (crucial in waste treatment and recovery^{8–11}).

Polymeric ATPS are composed of at least one polymer [e.g., poly(ethylene glycol), poly(propylene glycol), and poly(vinylpyrrolidone)] and provide enhanced possibility for the development of drug delivery systems, allowing the controlled release and targeted delivery of pharmaceutical compounds, and

enhancing their therapeutic efficacy.^{12,13} Moreover, given their generally low ionic strength, these ATPS have also been successfully applied in the extraction of labile species, such as vitamins^{14–16} and antioxidants,^{17–20} aiming at the valorization of agricultural and industrial waste and providing an enhanced understanding of polymeric interactions with solvents and electrolytes.

To ease process simulation, the interactions between particles in two liquid phases in equilibrium are often described using excess Gibbs free energy thermodynamic models such as the non-random two-liquid (NRTL)²¹ and the UNiVersal QUAsi-Chemical (UNIQUAC).²² In the modeling of polymeric ATPS, UNIQUAC is often preferred to NRTL due to a stronger

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Table 1. List of Chemicals Used and Their Respective Suppliers, Purities, CAS Numbers, and Abbreviations

chemical	supplier	purity ^a /m % ^b	CAS	abbreviation ^c
dipotassium L-tartrate hemihydrate (C ₄ H ₄ K ₂ O ₆ ·0.5H ₂ O)	Thermo Scientific	>99.9	6100-19-2	K ₂ Tartrate
disodium tartrate dihydrate (C ₄ H ₄ Na ₂ O ₆ ·2H ₂ O)	VWR Chemicals	>99.9	6106-24-7	Na ₂ Tartrate
ethanol (CH ₃ CH ₂ OH)	Sigma-Aldrich	>99.0	64-17-5	EtOH
poly(ethylene glycol), ~ 4000 g·mol ⁻¹ (H(OCH ₂ CH ₂) _n OH)	Merck	>99.0	25322-68-3	PEG4000
poly(vinylpyrrolidone), ~ 29,000 g·mol ⁻¹ ((C ₆ H ₉ NO) _n)	Sigma-Aldrich	>99.0	9003-39-8	PVP29000
purified water (H ₂ O)	VWR Chemicals		7732-18-5	W
sodium formate (HCOONa)	VWR Chemicals	>99.0	141-53-7	NaFormate

^aProvided by the supplier. ^bm % refers to mass percentage. ^cIn the organic salts, abbreviations refer to anhydrous moieties.

theoretical basis²³ and easier application to polymers, so its use in the description of tie-line composition data is widespread for these systems.^{24–27} However, the lack of data concerning these systems still limits comprehensive modeling approaches and large-scale application of polymeric ATPS, delaying progress in the design of materials and processes based on polymers.

In this work, the liquid–liquid equilibria (LLE) (solubility curves and tie-line composition) of the ATPS {PEG4000 (1) + NaFormate (2) + Water (3)} and {PVP29000 (1) + NaFormate or Na₂Tartrate or K₂Tartrate (2) + Water (3)} were determined at 298.15 K and 0.1 MPa. Then, tie-line composition data were correlated with common empirical expressions and modeled using the UNiVersal QUAsi-Chemical (UNIQUAC) model.

2. EXPERIMENTAL SECTION

2.1. Chemicals. In Table 1, the list of chemical components used in this work, together with their respective commercial suppliers, purities, Chemical Abstracts Service (CAS) numbers, and abbreviations, are presented. No further pretreatments nor purification steps were carried out since these chemicals were recently purchased.

2.2. Apparatus and Experimental Procedure. Concerning the used apparatus, mass (*m*) was determined with an ADAM AAA 250 L balance with standard measurement uncertainty of 10⁻⁴ g, pH was assessed with a VWR pH 1100 L pH meter with standard measurement uncertainties of 0.001 and 0.1 K, and density (*ρ*) was determined using an Anton Paar DSA-4500 M densimeter with standard measurement uncertainties of 5 × 10⁻⁵ g·cm⁻³ and 0.1 K. Furthermore, equilibrium temperature (*T*) was kept at 298.15 ± 0.1 K using a thermoregulated bath OvanTherm MultiMix BHMSE, and electrical conductivities (*κ*) were evaluated using a Hanna EDGE EC conductivity meter, coupled with a platinum conductivity cell HI763100, with relative measurement uncertainty of 0.01. Finally, when needed, a VWR vortex VV3 and an IKA RO 10P magnetic stirrer were used to stir the samples.

2.2.1. Solubility Curve Determination. To determine the solubility curves of the studied ATPS at 298.15 K, a water-jacketed glass cell was coupled to an OvanTherm MultiMix BHMSE thermoregulated bath and to an IKA RO 10P magnetic stirrer. Then, the “cloud-point” method was applied, in which droplets of an aqueous solution of polymer (PEG4000: 47.38 m %; PVP29000: 38.39 m %) were added to titrate solutions of organic salts with known concentrations. The dropwise addition of the polymer solution was halted when persistent turbidity (“cloudiness”) was observed, and pure water was pipetted until a homogeneous solution was reattained. This procedure was repeated until enough data were collected to fully describe the solubility curve, and compositions were determined by weighing. Moreover, to validate the obtained data, the inverse

methodology was performed by titrating known polymeric solutions with aqueous solutions of organic salts (NaFormate: 51.99 m %; Na₂Tartrate: 20.13 m %; K₂Tartrate: 44.09 m %).

Then, the obtained solubility data were fitted to common empirical correlations, namely, the ones of Merchuk *et al.*²⁸ (eq 1), Hu *et al.*²⁹ (eq 2), and Han *et al.*³⁰ (eq 3).

$$w_1 = A_M \cdot \exp(B_M \cdot w_2^{0.5} - C_M \cdot w_2^3) \quad (1)$$

$$w_1 = A_U + B_U \cdot w_2^{0.5} + C_U \cdot w_2 + D_U \cdot w_2^2 \quad (2)$$

$$w_1 = \exp(A_A + B_A \cdot w_2^{0.5} + C_A \cdot w_2 + D_A \cdot w_2^2) \quad (3)$$

where *w*₁ and *w*₂ are, respectively, the mass fractions of components 1 and 2, *A*_M, *B*_M, and *C*_M are the adjustable parameters of the Merchuk *et al.*²⁸ correlation, *A*_U, *B*_U, *C*_U, and *D*_U are the adjustable parameters of the Hu *et al.*²⁹ correlation, and *A*_A, *B*_A, *C*_A, and *D*_A are the adjustable parameters of the Han *et al.*³⁰ correlation.

2.2.2. Homogeneous Zone Characterization. For each system, approximately 40 mixtures of 15 g were prepared in vials covering all the homogeneous (miscible) zone delimited by the solubility curve and by the axes. Then, triplicate measurements of liquid density (*ρ*) and electrical conductivity (*κ*) were conducted for these mixtures and the obtained thermophysical properties were correlated with their composition by fitting the data to third-degree polynomials, as eqs 4 and 5 show.

$$\rho = \sum_{i=1}^3 (a_i w_1^i + b_i w_2^i + c_i w_3^i) \quad (4)$$

where *a*_{*i*}, *b*_{*i*}, and *c*_{*i*} are the adjustable parameters of the third-degree polynomial for liquid density (*ρ*) correlation, and *w*₁, *w*₂, and *w*₃ are the mass fractions of the components 1, 2, and 3, respectively.

$$\kappa = \sum_{i=1}^3 (d_i w_1^i + e_i w_2^i + f_i w_3^i) \quad (5)$$

where *d*_{*i*}, *e*_{*i*}, and *f*_{*i*} are the adjustable parameters of the third-degree polynomial for electrical conductivity (*κ*) correlation, and *w*₁, *w*₂, and *w*₃ are the mass fractions of components 1, 2, and 3, respectively.

2.2.3. Tie-Line Composition Determination. Six mixtures of approximately 20 g were prepared in vials in the immiscible region of each ATPS by pipetting pure water and binary aqueous solutions of polymers (PEG4000: 47.38 m %; PVP29000: 38.39 m %) and organic salts (NaFormate: 51.99 m %; Na₂Tartrate: 20.13 m %; K₂Tartrate: 44.09 m %). Then, the capped and sealed vials were stirred in a VWR VV3 vortex for 2 min, left under further stirring for 6 h in an OvanTherm MultiMix BHMSE thermostatic bath at 298.15 K, and left settling overnight

(approximately 12 h) at the same temperature. Afterward, the liquid phases were separated using syringes, and mass (m), liquid density (ρ), electrical conductivity (κ), and pH were measured for each phase. All of these determinations were conducted in triplicate.

To determine the tie-line composition, the objective function (O.F.) of eq 6, which couples the third-degree polynomials, was minimized in each tie-line by iterating the mass fractions (w_i) of the ATPS constituents in each liquid phase while respecting the mass balance ($\sum w_i = 1$). This optimization relied on a quasi-Newtonian method with 10^6 maximum iterations.

$$\text{O. F.} = \alpha \cdot \sqrt{\frac{(\rho_{\text{corr}}(w_i) - \rho_{\text{exp}})^2}{\rho_{\text{exp}}}} + \beta \cdot \sqrt{\frac{(\kappa_{\text{corr}}(w_i) - \kappa_{\text{exp}})^2}{\kappa_{\text{exp}}}} \quad (6)$$

where ρ_{exp} and κ_{exp} refer, respectively, to the measured liquid density and electrical conductivity in each tie-line, ρ_{corr} and κ_{corr} to the calculated values of these properties using, respectively, eqs 4 and 5, and α and β are weighting factors. In this work, these factors were considered as $\alpha = 1$ and $\beta = 1$, following a common practice of the research group.^{31,32}

Then, the slope (TLS) and length (TLL) of each tie-line were determined using eqs 7 and 8, respectively.

$$\text{TLS} = \frac{w_1^{\text{top}} - w_1^{\text{bot}}}{w_2^{\text{top}} - w_2^{\text{bot}}} \quad (7)$$

$$\text{TLL} = \sqrt{(w_1^{\text{top}} - w_1^{\text{bot}})^2 + (w_2^{\text{top}} - w_2^{\text{bot}})^2} \quad (8)$$

where w_1 and w_2 are, respectively, the mass fractions of components 1 and 2. Top and bot refer, respectively, to the top and bottom phases.

3. CORRELATION AND MODELING OF TIE-LINE DATA

3.1. Models of Othmer–Tobias and Bancroft–Hubard.

In 1942, Othmer and Tobias³³ developed a new type of plot representation for the tie-line composition of ternary LLE data, which allowed to correlate the mass fraction of solvent in the solvent-rich phase with the one of diluent in the diluent-rich phase, as eq 9 shows.³³ Theoretically, this approach is able to describe all tie-lines with only two parameters for each system,³³ which is very useful for the interpolation of these compositions.³⁴

$$\log \left(\frac{1 - w_{1,\text{I}}}{w_{1,\text{I}}} \right) = n_{\text{OT}} \cdot \log \left(\frac{1 - w_{2,\text{II}}}{w_{2,\text{II}}} \right) + S_{\text{OT}} \quad (9)$$

where $w_{1,\text{I}}$ is the mass fraction of component 1 in phase I (rich in component 1), $w_{2,\text{II}}$ is the mass fraction of component 2 in phase II (rich in component 3), and n_{OT} and S_{OT} are the adjustable parameters of the Othmer–Tobias (OT) correlation.

In the same year, an alternative correlation was proposed by Bancroft and Hubbard,³⁵ as eq 10 shows. Similarly to the OT correlation, this model intended to ease phase composition representation in ternary systems containing two immiscible (or partially miscible) components.³⁵

$$\log \left(\frac{w_{2,\text{I}}}{w_{1,\text{I}}} \right) = n_{\text{BH}} \cdot \log \left(\frac{w_{2,\text{II}}}{w_{3,\text{II}}} \right) + S_{\text{BH}} \quad (10)$$

where $w_{1,\text{I}}$ and $w_{2,\text{I}}$ are, respectively, the mass fractions of components 1 and 2 in phase I (rich in component 1), $w_{2,\text{II}}$ and

$w_{3,\text{II}}$ are, respectively, the mass fractions of components 2 and 3 in phase II (rich in component 3), and n_{BH} and S_{BH} are the adjustable parameters of the Bancroft–Hubard (BH) correlation.

3.2. UNIQUAC. In 1975, Abrams and Prausnitz²² established a local composition model based on the two-fluid theory to describe LLE and vapor–liquid equilibria of mixtures: the UNiVersal QUAsi-Chemical (UNIQUAC) model. UNIQUAC considers that the total excess Gibbs free energy (G^{E}) of a mixture is given by the sum of a combinatorial (G_{C}^{E}) and a residual (G_{R}^{E}) contributions,²² as eq 11 shows.

$$G^{\text{E,UNIQUAC}} = G_{\text{C}}^{\text{E}} + G_{\text{R}}^{\text{E}} \quad (11)$$

The combinatorial contribution (G_{C}^{E}), which accounts for size and shape effects, is calculated using eq 12, while the residual one (G_{R}^{E}), which describes interactions among molecules, is given by eq 13.²²

$$\frac{G_{\text{C}}^{\text{E}}}{RT} = \sum_{i=1}^{n_{\text{species}}} \left[x_i \ln \left(\frac{\phi_i}{x_i} \right) \right] - \frac{Z}{2} \sum_{i=1}^{n_{\text{species}}} q_i x_i \ln \left(\frac{\theta_i}{\phi_i} \right) \quad (12)$$

$$\frac{G_{\text{R}}^{\text{E}}}{RT} = - \sum_{i=1}^{n_{\text{species}}} q_i x_i \ln \left(\sum_{j=1}^{n_{\text{species}}} \theta_j \tau_{ji} \right) \quad (13)$$

where x_i is the mole fraction of component i , n_{species} is the total number of species in solution, ϕ and θ are the average volume fraction and average local area fraction of component i , respectively, and Z is the lattice coordination number, which was considered equal to 10 following previous works.^{23,32,36}

The UNIQUAC volume (r) and area (q) parameters were calculated following eqs 14 and 15,³⁷ respectively, using the van der Waals volumes (V_{w} , in m^3/mol) and surface areas (A_{w} , in m^2/mol) determined by the Bondi method³⁸ for each chemical species.

$$r = \frac{V_{\text{w}}}{15.17 \times 10^{-6}} \quad (14)$$

$$q = \frac{A_{\text{w}}}{2.5 \times 10^5} \quad (15)$$

In eq 13, τ_{ij} refers to the UNIQUAC binary interaction parameters and is calculated from the interaction energies between species i and j (U_{ij}) using eq 16.²²

$$\tau_{ij} = e^{-Z/2(U_{ij} - U_{ij}^{\text{ref}})/RT} = e^{-Z/2\Delta U_{ij}/RT} \quad (16)$$

where ΔU_{ij} are adjustable parameters determined by minimizing the standard deviation (σ_x) from phase equilibria data, using eq 17, with the constraint of fulfilling the isoactivity criterion (IC) given by eq 18.²³

$$\sigma_x = \sqrt{\frac{\sum_{i=1}^{n_{\text{points}}} \sum_{j=1}^{n_{\text{species}}} (x_{ij}^{\text{corr}} - x_{ij}^{\text{exp}})^2}{n_{\text{points}} \cdot n_{\text{species}}}} \quad (17)$$

$$\text{IC} = \frac{\sum_{j=1}^{n_{\text{points}}} \sum_{i=1}^{n_{\text{species}}} (x_{ij}^{\text{corr},\text{I}} \gamma_{ij}^{\text{I}} - x_{ij}^{\text{corr},\text{II}} \gamma_{ij}^{\text{II}})}{n_{\text{points}} \cdot n_{\text{species}}} = 0 \quad (18)$$

where n_{points} is the number of data points in each system, n_{species} is the total number of chemical species, x_{ij}^{corr} and x_{ij}^{exp} are, respectively, the correlated and experimental mole fraction of species i in the data point j , and γ_{ij} is the activity coefficient of

Table 2. Solubility Data for the Studied ATPS at 298.15 K and 0.1 MPa^a

system	w_1	w_2	w_1	w_2	w_1	w_2
{PEG4000 (1) + NaFormate (2) + Water (3)}	0.592	0.112	0.275	0.159	0.055	0.243
	0.540	0.114	0.234	0.172	0.036	0.257
	0.494	0.120	0.203	0.183	0.024	0.267
	0.451	0.125	0.183	0.189	0.012	0.280
	0.410	0.131	0.164	0.198	0.009	0.292
	0.371	0.139	0.133	0.206	0.006	0.299
	0.360	0.143	0.116	0.213	0.002	0.311
	0.315	0.150	0.092	0.225	0.002	0.347
	0.294	0.154	0.067	0.2350		
	0.339	0.183	0.092	0.237	0.015	0.256
{PVP29000 (1) + NaFormate (2) + Water (3)}	0.299	0.191	0.081	0.239	0.010	0.260
	0.236	0.205	0.064	0.242	0.002	0.289
	0.195	0.213	0.048	0.246	0.001	0.318
	0.169	0.220	0.039	0.248	0.000	0.354
	0.137	0.227	0.029	0.251		
	0.116	0.232	0.020	0.254		
	0.419	0.044	0.1230	0.106	0.029	0.131
{PVP29000 (1) + Na ₂ Tartrate (2) + Water (3)}	0.308	0.065	0.104	0.111	0.019	0.134
	0.253	0.076	0.087	0.115	0.011	0.143
	0.223	0.083	0.071	0.119	0.004	0.154
	0.204	0.086	0.087	0.115	0.002	0.168
	0.168	0.095	0.051	0.124	0.001	0.175
	0.144	0.102	0.041	0.128	0.001	0.191
	0.550	0.050	0.050	0.132	0.009	0.148
{PVP29000 (1) + K ₂ Tartrate (2) + Water (3)}	0.341	0.080	0.045	0.134	0.006	0.150
	0.251	0.094	0.038	0.135	0.003	0.158
	0.142	0.110	0.032	0.137	0.002	0.163
	0.073	0.125	0.027	0.139	0.001	0.231
	0.068	0.127	0.019	0.142	0.001	0.296
	0.061	0.129	0.016	0.144	0.001	0.343
	0.053	0.131	0.012	0.146	0.001	0.440

^aThe relative (u_r) and standard (u) measurement uncertainties are $u_r(w) = 0.002$ and $u(T) = 0.1$ K.

species i in the data point j . I and II refer to the two liquid phases in equilibrium.

4. RESULTS AND DISCUSSION

4.1. Solubility Curves. Following the “cloud-point” method, the solubility data of ATPS {PEG4000 (1) + NaFormate (2) + Water (3)} and {PVP29000 (1) + NaFormate or Na₂Tartrate or K₂Tartrate (2) + Water (3)} were determined at 298.15 K and 0.1 MPa and can be observed in Table 2. Using these data, the solubility (or distribution) curves were drawn for each system, as Figure 1 shows, and it was observed that ATPS containing sodium formate (NaFormate) obtained smaller immiscible zones, which may be explained by its higher molar solubility in water (14.67 mol·kg^{−1} at 298.65 K³⁹) when compared to disodium tartrate (Na₂Tartrate, 2.30 mol·kg^{−1} at 298.15 K⁴⁰) and dipotassium tartrate (K₂Tartrate, 6.33 mol·kg^{−1} at 298.15 K⁴¹).

For the same reason, K₂Tartrate provided a slightly smaller liquid–liquid zone compared to Na₂Tartrate, for which the latter can be considered a stronger salting-out agent, respecting the Hofmeister or lyotropic series,⁴² which orders cations based on their salting-out potential. Yet, the effect of cations is generally less relevant given the larger polarizabilities of anions,^{43,44} so, in PVP-containing systems, the difference between formate- and tartrate-based systems is notoriously larger than the one between sodium- and potassium-based ones.

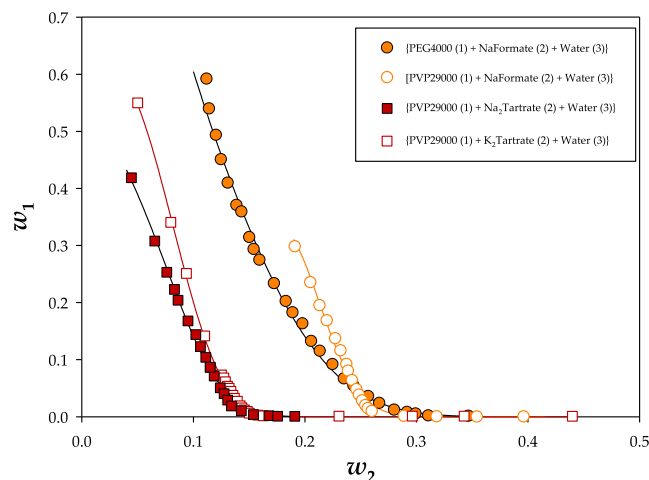


Figure 1. Determined solubility curves of the studied ATPS at 298.15 K and 0.1 MPa.

Surprisingly, Figure 1 also shows that poly(vinylpyrrolidone) (PVP), with a molar mass of 29,000 g·mol^{−1}, induced a smaller liquid–liquid immiscible zone than poly(ethylene glycol) (PEG), with a molar mass of 4000 g·mol^{−1}, for NaFormate-based systems. Although longer polymer chains generally imply lower solubilities in water (and larger immiscible zones), PVP is known to yield smaller heterogeneous regions than PEG, even at

significantly larger molar masses,²⁴ due to its larger hydrophilicity.^{24,45} This enhanced hydrophilic character is probably caused by the higher polarity of the amide group of PVP compared to the ether/hydroxyl groups in PEG.

To ease plot representation, the obtained solubility curves were correlated using the models of Merchuk *et al.*,²⁸ Hu *et al.*,²⁹ and Han *et al.*,³⁰ which are given by eqs 1–3, respectively. In Table 3, the obtained adjustable parameters and respective determination coefficients (R^2) can be observed, and it is notorious that the model of Han *et al.*³⁰ outperformed all others, generally achieving the largest values of R^2 . However, the model of Merchuk *et al.*,²⁸ which requires one less adjustable parameter than the others (3 instead of 4), is a close second, even providing the best fitting for the ATPS {PVP29000 (1) + NaFormate (2) + Water (3)}.

It must be noted that, in this work, the term “solubility curve” is not considered equivalent to “binodal curve” since the former refers to connecting solubility data points while the latter to joining tie-line composition data.⁴⁶ A complete overlap of these curves would only happen in the case of an equivalent number of data points and zero experimental error, which is considered impossible.

4.2. Homogeneous Zones. Before the tie-line composition was determined, it was necessary to characterize the homogeneous zone of each ATPS. Therefore, liquid density (ρ) and electrical conductivity (κ) at 298.15 K and 0.1 MPa were fitted to third-degree polynomials, following eqs 4 and 5, respectively. The obtained parameters and determination coefficients (R^2) can be observed in Table 4, while the thermophysical properties data can be found in Tables S1–S2, in the Supporting Information.

To ease data interpretation, the graphical representations of the third-degree polynomials of liquid density and electrical conductivity were conducted. As example, the obtained plots for the ATPS {PEG4000 (1) + NaFormate (2) + Water (3)} are shown in Figure 2, while the ones for {PVP29000 (1) + NaFormate or Na₂Tartrate or K₂Tartrate (2) + Water (3)} are presented, respectively, in Figures S1–S3, in the Supporting Information. As Figure 2 shows, liquid density always increased with growing mass fraction of salt (w_2), while electrical conductivity increased up to approximately $w_2 = 0.2$, decreasing afterward. Moreover, while liquid density remained practically unchanged for a constant content of salt despite the growing mass fraction of polymer (w_1), electrical conductivity generally presented a minimum at approximately $w_1 = 0.2$, increasing afterward. These observations are in general agreement with other works for aqueous binary mixtures containing salts^{40,47,48} or polymers.^{48,49}

4.3. Tie-Line Composition. To determine the composition of tie-lines at 298.15 K and 0.1 MPa, eq 6 was used, which considers the deviations between the experimental (found in Table S3, in the Supporting Information) and estimated (calculated using the third-degree polynomials) thermophysical properties. To do so, mass fractions were iterated until a minimum was found. Then, the slopes (STL) and lengths (TLL) of the tie-lines were determined using eqs 7 and 8, respectively. The obtained compositions of the liquid phases of each tie-line, together with the respective pH, STL, and TLL, are shown in Table 5. In the ATPS {PVP29000 (1) + Na₂Tartrate + Water (3)}, only five different tie-lines could be obtained.

As expected, the top phases (lower density) are polymer-rich, while the bottom ones (higher density) are salt-rich, presenting residual polymer content. Furthermore, mild pH values were

Table 3. Adjustable Parameters for the Correlation of Solubility Data for the Studied ATPS at 298.15 K and 0.1 MPa, and Respective Determination Coefficients (R^2)

system	Merchuk <i>et al.</i> ²⁸					Hu <i>et al.</i> ²⁹					Han <i>et al.</i> ³⁰				
	A_M	B_M	C_M	R^2		A_U	B_U	C_U	D_U	R^2	A_A	B_A	C_A	D_A	R^2
{PEG4000 (1) + NaFormate (2) + Water (3)}	8.12	-7.66	79.1	0.9966		4.39	-18.2	21.2	-8.51	0.9969	26.2	-171	313	-349	0.9992
{PVP29000 (1) + NaFormate (2) + Water (3)}	0.000	39.4	518	0.9932		5.85	-18.9	13.0	6.56	0.9804	-27.5	83.3	0.447	-280	0.9922
{PVP29000 (1) + Na ₂ Tartrate (2) + Water (3)}	0.687	-2.01	950	0.9964		0.0841	6.04	-23.2	47.3	0.9969	10.2	-112	319	-870	0.9983
{PVP29000 (1) + K ₂ Tartrate (2) + Water (3)}	0.708	-0.536	1093	0.9986		2.88	-14.8	20.8	-11.5	0.9779	16.2	-164	451	-1114	0.9993

Table 4. Adjustable Parameters and Respective Determination Coefficients (R^2) and Standard Deviations (σ) of the Third-Degree Polynomials for Liquid Density (ρ) and Electrical Conductivity (κ) at 298.15 K and 0.1 MPa^a

system	liquid density (ρ)										R^2	σ
	a_1	b_1	c_1	a_2	b_2	c_2	a_3	b_3	c_3			
{PEG4000 (1) + NaFormate (2) + Water (3)}	1214	1668	856.5	120.9	73.82	215.7	-216.0	72.36	-75.15		0.9999	0.578
{PVP29000 (1) + NaFormate (2) + Water (3)}	1078	1232	2004	-873.3	1926	-1849	1251	-5922	841.6		0.9993	1.34
{PVP29000 (1) + Na ₂ Tartrate (2) + Water (3)}	1380	1869	629	106.2	372.5	558	-265.6	-17.71	-189.5		0.9998	0.238
{PVP29000 (1) + K ₂ Tartrate (2) + Water (3)}	1418	1894	611.2	39.33	251.4	555.8	-231.3	-21.88	-169.7		0.9999	0.567
system	electrical conductivity (κ)										R^2	σ
	d_1	e_1	f_1	d_2	e_2	f_2	d_3	e_3	f_3			
{PEG4000 (1) + NaFormate (2) + Water (3)}	-96.72	-22.11	157.5	-54.98	-134.42	-212.2	428.5	-150.08	54.74		0.9987	0.120
{PVP29000 (1) + NaFormate (2) + Water (3)}	-53.79	33.33	96.57	-22.02	-265.6	-133.1	116.7	363.2	36.42		0.9986	0.123
{PVP29000 (1) + Na ₂ Tartrate (2) + Water (3)}	-127.4	-70.95	158.7	95.25	19.71	-189.5	32.44	59.99	30.79		0.9966	0.0231
{PVP29000 (1) + K ₂ Tartrate (2) + Water (3)}	-115.7	-54.97	212.9	36.54	-51.53	-314.5	60.78	55.53	101.9		0.9999	0.0422

^aThe standard (u) and relative (u_r) measurement uncertainties are $u(\rho) = 5 \times 10^{-5} \text{ g}\cdot\text{cm}^{-3}$, $u(T) = 0.1 \text{ K}$, and $u_r(\kappa) = 0.1$.

obtained (from 6.26 to 8.21), for which these ATPS provide safe extractive media for the separation of labile biomolecules, such as antioxidants and vitamins. Concerning tie-line lengths (TLLs), the longest were obtained for the system with PEG4000, for which this ATPS provides more distinct compositions in the top and bottom phases, which could yield enhanced selectivity in future partition studies. Moreover, even though all tie-line slopes (TLSs) were negative, this ATPS was the only one in which they generally increased (in absolute value) with TLL.

In Figure 3, the phase equilibria diagrams of {PEG4000 or PVP29000 (1) + NaFormate (2) + Water (3)} can be seen. Once again, the significantly larger heterogeneous zone of the PEG-based ATPS, due to the higher hydrophobicity (lower polarity) of this polymer, is notorious. When comparing these diagrams with the ones found in literature for {PEG6000⁵⁰ or PVP40000⁵¹ (1) + NaFormate (2) + Water (3)}, also at 298.15 K and 0.1 MPa, it was observed that longer polymeric chains promoted a notably wider heterogeneous zone, as Figure 3 shows. This was caused by a decrease in polarity (increase in hydrophobicity) of the polymers with growing length of the polymeric chain, which results in a lower solubility in water and ultimately in a larger immiscible zone, and agrees with other works on similar topics.^{52–54} Analogous results were obtained for the phase diagrams of {PVP29000 (1) + Na₂Tartrate or K₂Tartrate (2) + Water (3)}, as Figure 4 shows, with the literature-based data for {PVP3500 (1) + Na₂Tartrate (2) + Water (3)},⁵⁵ also at 298.15 K and 0.1 MPa, showing a significantly smaller heterogeneous zone due to larger polymer solubility. The ternary diagrams of the studied ATPS can be seen in Figures S4–S7, in the Supporting Information.

4.4. Othmer–Tobias and Bancroft–Hubard. The correlations of Othmer–Tobias,³³ given by eq 9, and Bancroft–Hubard,³⁵ expressed by eq 10, ease the graphical representation and interpolation of tie-line compositions, reducing the need to conduct additional experimental procedures. In this work, the original purpose of these empirical models is kept,⁴⁶ i.e., it is believed that they do not provide any information on the so-called “reliability”, “consistency”, or “quality” of the tie-lines, but only on the suitability of these mathematical expressions for tie-line interpolation. As Table 6 shows, these correlations yielded very satisfactory fittings of the experimental data, with the one of Bancroft–Hubard³⁵ generally providing larger determination coefficients (R^2). Nevertheless, both correlations were considered to properly describe the studied ATPS and convey good interpolation alternatives.

As Figure 5 illustrates, the systems {PVP29000 (1) + Na₂Tartrate or K₂Tartrate (2) + Water (3)} presented very similar correlation parameters, which was expected given their very similar solubility curves and salts. On the other hand, the results for {PVP29000 (1) + NaFormate (2) + Water (3)} were the most different, which was probably due to its more distinct phase diagram, as seen in Figure 3.

4.5. UNIQUAC Modeling. Even though the UNiVersal QUasi-Chemical (UNIQUAC)²² model was not originally developed to account for long-range interactions, it has widely been used to describe the LLE of electrolyte-containing systems,⁵⁶ such as ATPS with organic salts as salting-out agents.^{31,57,58} To do so, UNIQUAC requires two parameters relative to the volume and surface area of the studied molecules, which have been mostly iterated in the literature. Nevertheless, in this work, to preserve the physical meaning of the r and q parameters, they were calculated based on the van der Waals

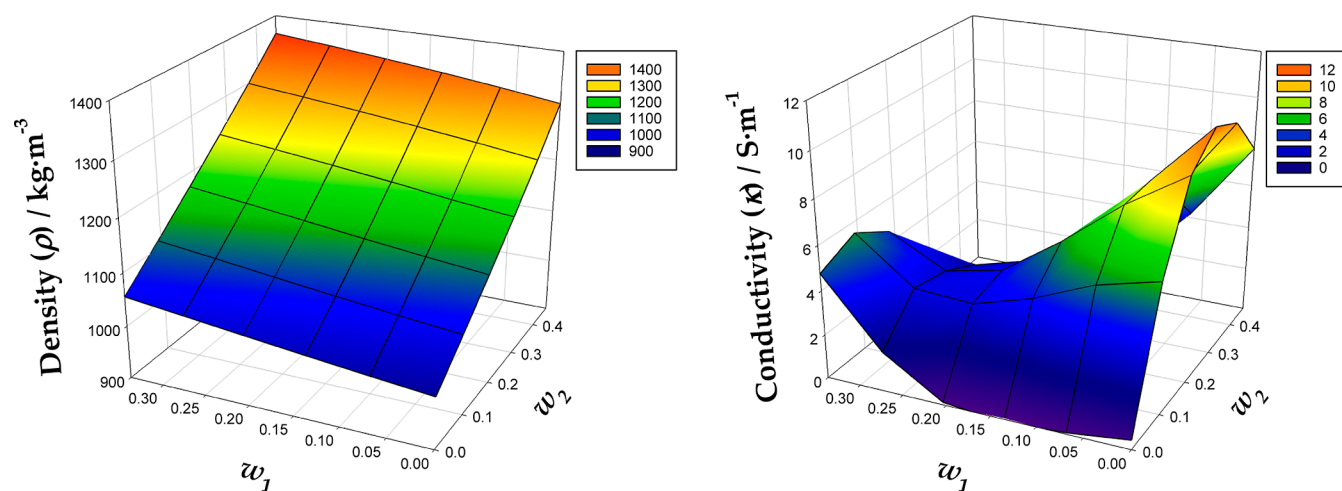


Figure 2. Graphical representation of the obtained third-degree polynomials for liquid density (ρ) (left) and electrical conductivity (κ) (right) for ATPS {PEG4000 (1) + NaFormate (2) + Water (3)} at 298.15 K and 0.1 MPa.

Table 5. Composition, pH, Tie-Line Slope (TLS), and Tie-Line Length (TLL) of the Determined Tie-Lines (TLs) for the Studied ATPS at 298.15 K and 0.1 MPa^a

system	# TL	feed		top phase			bottom phase			TLS	TLL
		w_1	w_2	w_1	w_2	pH	w_1	w_2	pH		
{PEG4000 (1) + NaFormate (2) + Water (3)}	1	0.0400	0.2809	0.3664	0.1350	8.13	0.0114	0.2966	8.21	−2.20	0.3900
	2	0.0586	0.2809	0.4200	0.1300	8.20	0.0004	0.3058	8.20	−2.39	0.4553
	3	0.0760	0.2809	0.4475	0.1237	8.12	0.0003	0.3170	8.20	−2.31	0.4875
	4	0.0958	0.2809	0.5105	0.1200	8.10	0.0001	0.3211	8.19	−2.54	0.5487
	5	0.1136	0.2809	0.5500	0.1164	8.08	0.0001	0.3259	8.18	−2.63	0.5885
	6	0.1330	0.2809	0.5900	0.1068	8.04	0.0000	0.3342	8.17	−2.59	0.6323
{PVP29000 (1) + NaFormate (2) + Water (3)}	1	0.0400	0.2691	0.1234	0.2264	7.40	0.0021	0.2842	7.55	−2.10	0.1344
	2	0.0582	0.2781	0.1540	0.2205	7.40	0.0020	0.3136	7.47	−1.63	0.1783
	3	0.0780	0.2843	0.1734	0.2156	7.41	0.0019	0.3332	7.41	−1.46	0.2079
	4	0.0945	0.2937	0.2040	0.2156	7.41	0.0017	0.3626	7.41	−1.38	0.2501
	5	0.1121	0.3020	0.2244	0.2107	7.42	0.0011	0.3920	7.41	−1.23	0.2876
	6	0.1300	0.3097	0.2448	0.2048	7.44	0.0009	0.4214	7.40	−1.13	0.3262
{PVP29000 (1) + Na ₂ Tartrate (2) + Water (3)}	1	0.0714	0.1800	0.2525	0.0808	6.42	0.0059	0.1564	6.49	−3.26	0.2579
	2	0.1158	0.1486	0.3267	0.0594	6.43	0.0051	0.1753	6.40	−2.78	0.3419
	3	0.1421	0.1337	0.3713	0.0495	6.39	0.0030	0.1832	6.37	−2.76	0.3917
	4	0.1627	0.1203	0.3960	0.0446	6.35	0.0020	0.1931	6.26	−2.65	0.4211
	5	0.2036	0.0958	0.4257	0.0396	6.40	0.0010	0.2079	6.30	−2.52	0.4568
	6	0.2036	0.0958	0.4257	0.0396	6.40	0.0010	0.2079	6.30	−2.52	0.4568
{PVP29000 (1) + K ₂ Tartrate (2) + Water (3)}	1	0.0501	0.1661	0.3001	0.0840	7.07	0.0090	0.1827	6.91	−2.95	0.3073
	2	0.0753	0.1803	0.3523	0.0789	7.33	0.0018	0.2097	6.90	−2.70	0.3758
	3	0.1011	0.1943	0.3998	0.0710	7.51	0.0000	0.2351	7.21	−2.44	0.4324
	4	0.1242	0.2099	0.4503	0.0630	7.43	0.0000	0.2641	7.39	−2.23	0.4913
	5	0.1494	0.2248	0.4976	0.0550	7.70	0.0000	0.3004	7.42	−2.03	0.5548
	6	0.1750	0.2409	0.5499	0.0501	7.79	0.0000	0.3343	7.55	−1.93	0.6191

^aThe standard (u) and relative (u_r) measurement uncertainties are $u(w) = 0.0002$, $u(T) = 0.1$ K, and $u_r(\text{pH}) = 0.001$.

volume (V_w) and surface area (A_w), respectively, using the Bondi method.³⁸

In Table 7, the calculated UNQUAC volume (r) and surface area (q) parameters are shown. Due to their large molar masses, the parameters of PEG4000 and PVP2900 were significantly higher than the ones of the other components. Moreover, NaFormate presented the smallest UNQUAC parameters of the salts, given its significantly smaller salt-anion. Therefore, the calculation of the UNQUAC parameters conveyed a fairer representation of reality compared to a simple optimization and is strongly advised in modeling studies.

The UNQUAC binary interaction energy parameters (ΔU_{ij}) obtained in the modeling of the tie-line compositions, together

with the respective standard deviations (σ), can be observed in Table 8. Even though UNQUAC requires the conversion of compositions to a mole basis, the obtained standard deviations are shown in mass basis in Table 8 given their enhanced intelligibility compared to mole basis. As Table 8 shows, low standard deviations ($\sigma < 6.84 \times 10^{-3}$) were obtained for the studied ATPS, with {PVP29000 (1) + K₂Tartrate (2) + Water (3)} attaining the lowest value ($\sigma < 1.16 \times 10^{-4}$). Hence, UNQUAC satisfactorily expressed the tie-line compositions of the studied ATPS, providing mathematical validation of the existence of an equilibrium between the two determined phases.

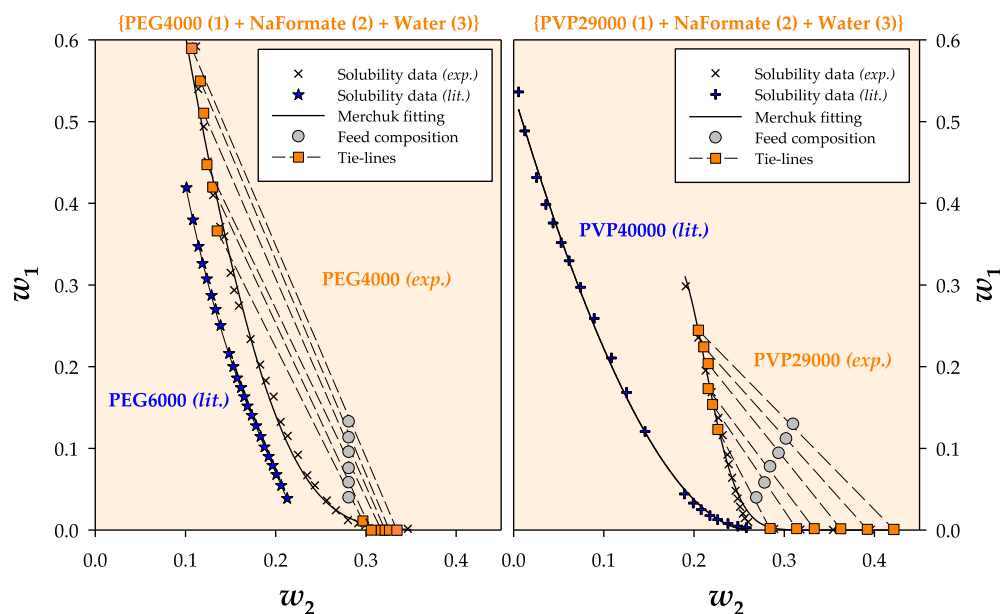


Figure 3. Experimental phase equilibria diagrams of ATPS {PEG4000 (1) + NaFormate (2) + Water (3)} (left) and {PVP29000 (1) + NaFormate (2) + Water (3)} (right) at 298.15 K and 0.1 MPa. Blue stars (left) and plus signs (right) refer, respectively, to the literature-based ATPS {PEG6000 (1) + NaFormate (2) + Water (3)}⁵⁰ and {PVP40000 (1) + NaFormate (2) + Water (3)}⁵¹ at 298.15 K and 0.1 MPa.

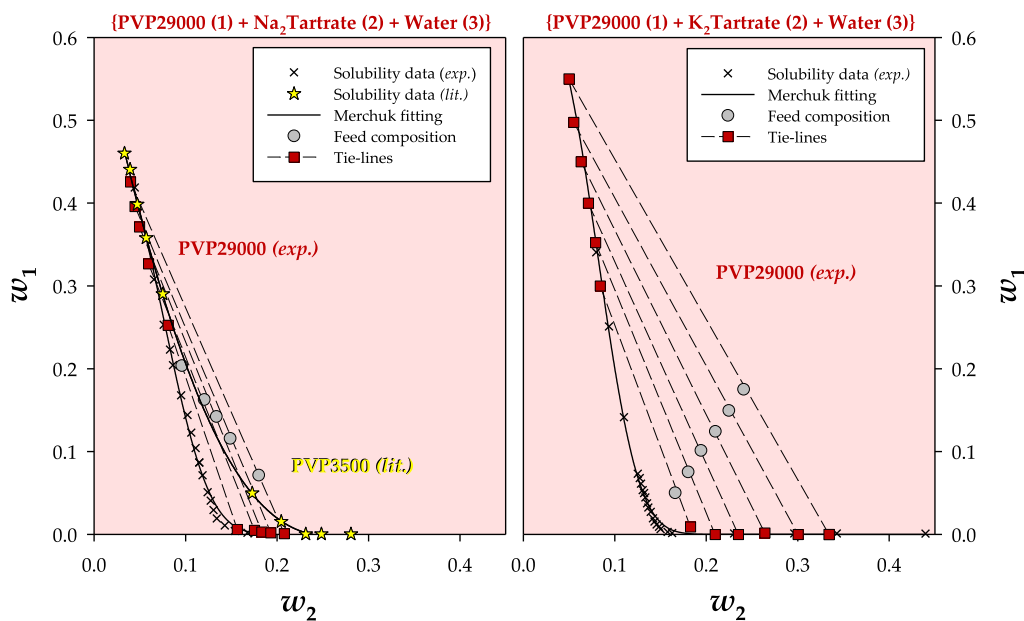


Figure 4. Experimental phase equilibria diagrams of ATPS {PVP29000 (1) + Na₂Tartrate (2) + Water (3)} (left) and {PVP29000 (1) + K₂Tartrate (2) + Water (3)} (right) at 298.15 K and 0.1 MPa. Yellow stars refer to the literature-based ATPS {PVP3500 (1) + Na₂Tartrate (2) + Water (3)}⁵⁵ at 298.15 K and 0.1 MPa.

Table 6. Adjustable Parameters and Respective Determination Coefficients (R^2) of the Othmer–Tobias³³ and Bancroft–Hubard³⁵ Correlations for the Tie-Line Compositions of the Studied ATPS at 298.15 K and 0.1 MPa

system	Othmer–Tobias ³³			Bancroft–Hubard ³⁵		
	n_{OT}	S_{OT}	R^2	n_{BH}	S_{BH}	R^2
{PEG4000 (1) + NaFormate (2) + Water (3)}	5.281	−3.984	0.9575	−4.379	−4.717	0.9777
{PVP29000 (1) + NaFormate (2) + Water (3)}	1.371	0.642	0.9808	−1.277	−0.623	0.9807
{PVP29000 (1) + Na ₂ Tartrate (2) + Water (3)}	2.319	−2.866	0.9674	−3.718	−7.443	0.9676
{PVP29000 (1) + K ₂ Tartrate (2) + Water (3)}	1.282	−1.091	0.9982	−1.427	−3.402	0.9985

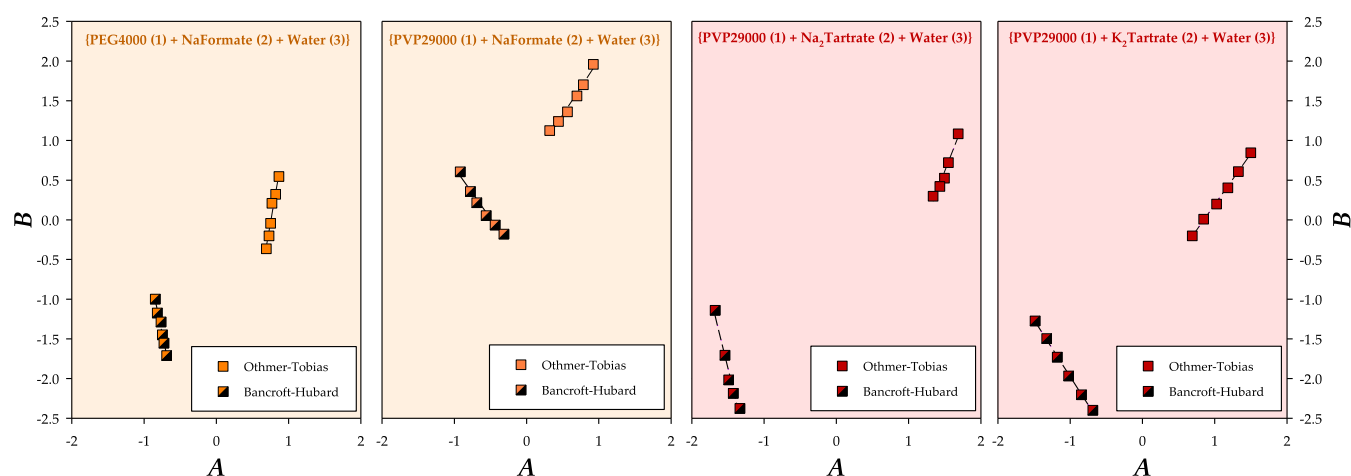


Figure 5. Othmer–Tobias³³ ($A = \log \left(\frac{1 - w_{2,II}}{w_{2,II}} \right)$, $B = \log \left(\frac{1 - w_{1,I}}{w_{1,I}} \right)$) and Bancroft–Hubard³⁵ ($A = \log \left(\frac{w_{2,I}}{w_{1,I}} \right)$, $B = \log \left(\frac{w_{2,II}}{w_{3,II}} \right)$) correlations of tie-line composition for the studied ATPS at 298.15 K and 0.1 MPa.

Table 7. Calculated UNIQUAC Volume (r) and Surface Area (q) Parameters for the Components of the Studied ATPS Using the Bondi's Method³⁸

component	r	q
PEG4000	149.38	130.04
PVP29000	1097.73	852.40
NaFormate	3.17	2.67
Na ₂ Tartrate	7.85	6.50
K ₂ Tartrate	11.26	8.13
Water	0.92 ⁵⁹	1.40 ⁵⁹

Table 8. Interaction Energy Parameters (ΔU_{ij}), in J·mol⁻¹, Obtained in the Correlation of the LLE Data of the Studied ATPS, at 298.15 K and 0.1 MPa, and Respective Standard Deviations in Mass Basis (σ) to the Experimental Data

{PEG4000 (1) + NaFormate (2) + Water (3)}				
	1 (j)	2	3	σ
1 (i)	0	-96.126	-841.33	6.84×10^{-3}
2	186.63	0	-756.20	
3	407.05	64.8230	0	
{PVP29000 (1)+ NaFormate (2) + Water (3)}				
	1 (j)	2	3	σ
1 (i)	0	521.10	-111.25	5.91×10^{-3}
2	827.18	0	-836.66	
3	827.34	213.82	0	
{PVP29000 (1)+ Na ₂ Tartrate (2) + Water (3)}				
	1 (j)	2	3	σ
1 (i)	0	-5.3160	-860.00	1.78×10^{-3}
2	55.714	0	-851.13	
3	385.84	106.64	0	
{PVP29000 (1)+ K ₂ Tartrate (2) + Water (3)}				
	1 (j)	2	3	σ
1 (i)	0	-669.98	-795.39	1.16×10^{-4}
2	90.802	0	-758.25	
3	430.05	-523.09	0	

5. CONCLUSIONS

The lack of data concerning the LLE of polymeric ATPS composed of poly(ethylene glycol) (PEG) or poly(vinylpyrrolidone) (PVP) has been limiting advancements in the design of novel materials and processes based on polymers.

For that reason, in this work, the LLE (solubility curves and tie-line compositions) of ATPS {PEG4000 (1) + NaFormate (2) + Water (3)} and {PVP29000 (1) + NaFormate or Na₂Tartrate or K₂Tartrate (2) + Water (3)} were determined at 298.15 K and 0.1 MPa. Using common empirical correlations, the solubility curves were adequately described and the interpolation of tie-line compositions was deemed satisfactory. Moreover, the estimation of tie-line composition using third-degree polynomials of liquid density (ρ) and electrical conductivity (κ) allowed to better understand the influence of composition on these thermophysical properties.

Finally, the calculation of the UNIQUAC parameters from the van der Waals volumes (V_w) and surface areas (A_w), determined following the Bondi method, provided a fairer model representation of the components of the studied ATPS, which allowed to successfully describe the obtained data and provide a mathematical validation to the existence of phase equilibrium.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jced.4c00055>.

Graphical representations of the ternary phase diagrams and third-degree polynomials (for the correlation of liquid density and electrical conductivity) and measured data of these thermophysical properties for the definition of third-degree polynomials and for the determination of tie-line compositions (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Pedro Velho – LSRE-LCM—Laboratory of Separation and Reaction Engineering—Laboratory of Catalysis and Materials, Faculty of Engineering, University of Porto, Porto 4200-465, Portugal; ALiCE—Associate Laboratory in Chemical Engineering, Faculty of Engineering, University of Porto, Porto 4200-465, Portugal; orcid.org/0000-0003-4802-7301; Email: velho@fe.up.pt

Eugénia A. Macedo – LSRE-LCM—Laboratory of Separation and Reaction Engineering—Laboratory of Catalysis and Materials, Faculty of Engineering, University of Porto, Porto 4200-465, Portugal; ALiCE—Associate Laboratory in

Chemical Engineering, Faculty of Engineering, University of Porto, Porto 4200-465, Portugal; orcid.org/0000-0002-0724-5380; Email: eamacedo@fe.up.pt

Author

Afonso Madaleno — LSRE-LCM—Laboratory of Separation and Reaction Engineering—Laboratory of Catalysis and Materials, Faculty of Engineering, University of Porto, Porto 4200-465, Portugal; ALiCE—Associate Laboratory in Chemical Engineering, Faculty of Engineering, University of Porto, Porto 4200-465, Portugal; orcid.org/0009-0000-6395-0677

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acs.jced.4c00055>

Notes

The authors declare no competing financial interest.

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