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Modeling Solubility of Acetylsalicylic Acid in Aspen Plus

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Abstract

Acetylsalicylic acid is one of the most exchanged pharmaceuticals in the world. However, it was scarcely studied when it was in solution. Solubility of acetylsalicylic acid in ethanol, acetone, propylene glycol, and 2-propanol were determined in the temperature range between 270-360 K using Aspen Plus V14 as for binary systems. Three thermodynamic models (NRTL, UNIFAC, and UNIQUAC) of Aspen Plus were used for the simulations and the results were validated based on previous experimental work by Maia and Giulietti (2008). The results showed that ethanol, propylene glycol, and 2-propanol had excellent agreement between modeled and experimental solubility values, while acetone had little discrepancy, highlighting the need for extensive modeling. The NRTL thermodynamic model outperformed others, especially in ethanol. Temperature-dependent solubility was determined in all solvents, with 2-propanol showing significant similarity between actual and simulated data. Propylene glycol and ethanol gave similar results to the experiments till 310 K and showed slight deviation at high temperatures. This study highlights the relevance of solvent-specific factors and accurate modeling for solubility prediction, providing useful information for medical and chemical applications.

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1. Introduction

Solubility knowledge is crucial in the pharmaceutical industry since it allows scientists to select the optimal solvent medium for a drug or combination of drugs and helps overcome problems encountered when preparing pharmaceutical solutions.[1,2] These solutions can be used to create a liquid dosage form, to verify the quality of bulk medications, to extract ingredients from synthetic or natural sources, and beyond.[3-5] Acetylsalicylic acid, also known as 2-acetoxybenzoic acid or aspirin is a drug known as an analgesic, which also includes antipyretics, anti-inflammatories, and platelet aggregation inhibitors (Fig. 1).[6,7] It is also becoming evident that aspirin use on a regular basis may help prevent colorectal cancer.[8,9]

Ability of aspirin to inhibit thromboxane synthesis, which prevents the development of both brain and heart thrombi, has led to countless reports on the advantages of a low dose for the secondary prophylaxis of numerous cardiovascular diseases, including sbrain stroke and myocardial infarction.[10,11]

Therefore, it is important to study the solubility of aspirin to get more information on its crystallization, purification and behavior in different conditions. The solubility of aspirin in water is at around 2-4 mg/ml. Its solubility changes dramatically by adding sodium hydroxide or calcium hydroxide to the mixture, or by raising the temperature.[12] In comparison to water, aspirin dissolves better in ethanol, ethyl ether, chloroform, sodium hydroxide solution, and sodium carbonate solution.[13] The solubility of aspirin in ethanol, acetone, propylene glycol, and 2-propanol was analyzed by Maia and Giulietti.[14] They discovered that the solubility increased for four solvents as the temperature rose. They claimed that up to a temperature of 326.3 K, acetylsalicylic acid had the highest solubility in acetone. Additionally, they evaluated the Nývlt model's capacity for correlating experimental data, and showed a fair agreement with experimental data reported in the literature.[14] Huang *et al*.[15] investigated the use of polar cosolvents to significantly boost polar organic compounds' solubilities in supercritical CO_2. They used a dynamic saturation approach to determine aspirin's solubility in methanol- and ethanol-modified supercritical CO_2. The results showed that the solubility of aspirin could be increased by up to 14 times, according to experimental findings, by adding 3.0 moles% methanol or

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ethanol. Mota *et al.*[16] calculated the solubilities of acetanilide, acetylsalicylic acid, adipic acid, ascorbic acid, hydroquinone, ibuprofen, paracetamol, and stearic acid in alcohols, ketones, alkanes, esters, acids, aromatics, and chlorinated solvents. The behavior of hydrogen bonds was specifically taken into consideration by treating each associated group separately and accounting for numerous group substitutions. Using a single binary interaction parameter with an average absolute deviation, accurate correlations were obtained.

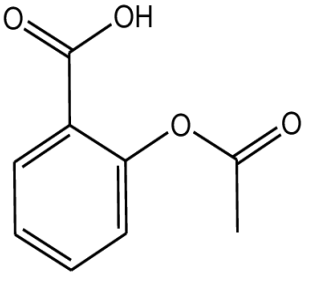

Fig. 1 Aspirin structure.

Our efforts represent a detailed study designed to improve our understanding of aspirin solubility. It builds on seminal research by Maia and Giulietti (2008), which included pioneering studies quantifying aspirin solubility and relating it to the Nývlt model. Our main goal is to study the subtleties of aspirin's dissolution behavior in various solvents using advanced modeling approaches. The present work aims at modeling and predicting of solubility of aspirin in four commonly used solvents, namely, ethanol, acetone, propylene glycol, and 2-propanol based on Aspen Plus.

2. Methods

Aspen Plus is a simulation tool with a variety of applications in petrochemistry, industry, polymers, electrolytes, pharmaceuticals, metallurgy and other chemical processes. The solubility of aspirin was determined using Aspen Plus V14 for the binary system. The components are acetylsalicylic acid as a solute, 2-propanol, acetone, ethanol and ethylene-glycol-mono-propyl-ether as a solvent were used with their pure component properties taken from Aspen Pure 40 database. The solubility of aspirin was analyzed for each solvent using NRTL, UNIFAC and UNIQUAC thermodynamic models. The obtained results were collected, plotted in Origin and Excel, and discussed in further detail. The NRTL and UNIQUAC models are applicable for characterizing the vapor-liquid equilibrium (VLE), liquid-liquid equilibrium (LLE), and enthalpic properties of extremely non-ideal systems. These models are acceptable to simulate highly non-ideal systems under low-pressure conditions.

The first method applied is the "Non-random Two-liquid" (NRTL) approach. It has been chosen because it can handle a wide range of components found in solutions. Renon and Prausnitz[17] were the first to provide a detailed explanation of the NRTL model. They demonstrated its usefulness in calculating (vapor + liquid) and (liquid + liquid) equilibrium for a wide range of mixtures. This model relies on the idea of molecular local composition, which can be expressed as follows in Equation (1).[17]

$$\ln\gamma_i=\frac{\sum_{j=1}^{\delta}\chi_i\tau_{ji}G_{ji}}{\sum_{k=1}^{\delta}\chi_kG_{ki}}+\sum_{j=1}^{\delta}\left(\frac{\chi_jG_{ij}}{\sum_{k=1}^{\delta}\chi_kG_{kj}}\left(\tau_{ij}-\frac{\sum_{m=1}^{\delta}\chi_m\tau_{mj}G_{mj}}{\sum_{k=1}^{\delta}\chi_kG_{kj}}\right)\right), \quad (1)$$

$G_{ij}=\exp(-\alpha_{ij}\tau_{ij})$;

$\tau_{ij}=\frac{(g_{ij}-g_{jj})}{RT}$;

$\alpha_{ij}=\alpha_{ji}\ (i\neq j)$

where δ is the number of components; x represents the mole fraction; R is the gas constant; T is the equilibrium temperature; γ_i is the activity coefficient of the i component; G_{ij} is a dimensionless interaction parameter depending on the energy interaction parameter g_{ij} and the non-randomness factor (α_{ij}). To determine the activity coefficient, a formula that applies to the balance between solid and liquid states and is derived from thermodynamic principles, can be expressed in the following manner, as shown in Equation (2).[18]

$$\ln x\gamma=-\frac{\Delta_{fus}H}{R}\left(\frac{1}{T}-\frac{1}{T_m}\right) \quad (2)$$

where x is the experimental mole fraction of solute in different solvents; γ is the activity coefficient of solute in different solvents; T_m is the melting temperature of the solute; T is the equilibrium temperature; $\Delta_{fus}H$ is the enthalpy of fusion for solute.[18]

The second method applied is UNIFAC (UNIQUAC functional group activity coefficients). The UNIQUAC model, discusses below) is expanded upon by the UNIFAC activity coefficient model. The same theory used by UNIQUAC for molecules is also used in UNIFAC. The method can be used for polar and nonpolar systems. As the UNIFAC model operates as a group-based approach, it possesses predictive capabilities.[19] All the group parameters and group binary parameters that have been published are conveniently stored within the Aspen Physical Property System. The equation for the original UNIFAC/UNIQUAC liquid activity coefficient model is made up of a combinatorial and residual term, as shown in Equations (3) and (4).[19]

$$\ln\gamma=\ln\gamma_i^c+\ln\gamma_i^r \quad (3)$$

$$\ln\gamma_i^c=\ln\left(\frac{\Phi_i}{x_i}\right)+1-\frac{\Phi_i}{x_i}-\frac{Z}{2}\left[ln\frac{\Phi_i}{\theta_i}+1-\frac{\Phi_i}{\theta_i}\right] \quad (4)$$

where γ is the activity coefficient; Φ_i is molecular volume fraction; Θ_i is surface fraction; Z is coordination number, x_i is mole fraction of liquid.

The third method is UNIversal QUAsiChemical (UNIQUAC). The model is frequently used to calculate activity coefficients for multicomponent systems. The rationale is that UNIQUAC may be used for systems with greater size differences since it contains two instead of three changeable parameters, which are less temperature-dependent.[20] The UNIQUAC model is described by the following Equation (5).[20]

$$ln\gamma_i = ln\frac{\Phi_i}{x_i} + \frac{Z}{2}q_i ln\frac{\theta_i}{\Phi_i} - q_i' lnt_i' - q_i' \sum_j \theta_j' \tau_{ij} \Big/ t_j' + l_i + q_i' - \frac{\Phi_i}{x_i}\sum_j x_j l_j \quad (5)$$

where q_i is area parameter; τ and t are binary interaction parameters at given temperature; l is component.

3. Results and discussion

In this article, a thorough study aimed at modeling the solubility of acetylsalicylic acid (aspirin) in several solvents is described. The main goal is to improve our understanding of aspirin solubility using sophisticated modeling techniques, building on the earlier work of Maia and Giulietti (2008) who provided useful experimental data on the solubility of aspirin in various solvents and correlated solubility using the Nývlt model. In this study, as noted above, three well-known models—NRTL, UNIFAC, and UNIQUAC—were used to simulate aspirin's solubility in the same set of solvents by harnessing the computing capability of Aspen Plus. The results provide a thorough insight of the aspirin's complicated solubility behavior, as seen in Fig. 2. The results as shown in Fig. 2 demonstrate that for ethanol, propylene glycol, and 2-propanol, the simulated solubility values and the experimental data showed remarkable agreement. This high level of agreement indicates that our simulation models accurately reflect the solubility behavior of aspirin in these solvents. However, the case of acetone is a notable exception, as there is a small but consistent discrepancy between experimental and modeled solubility levels. This discrepancy highlights the need for more careful modeling of the specific solvation properties of aspirin in acetone. The NRTL model stands out among the three simulation models used, accurately reflecting the experimental results for most solvents. The NRTL model offers an accurate description of solubility behavior with significantly lower errors than other models, especially for ethanol.

Another noteworthy component of our results is the temperature dependence of solubility. Solubility increases with increasing temperature in all solvents studied, which is consistent with the general understanding. Notably, the 2-

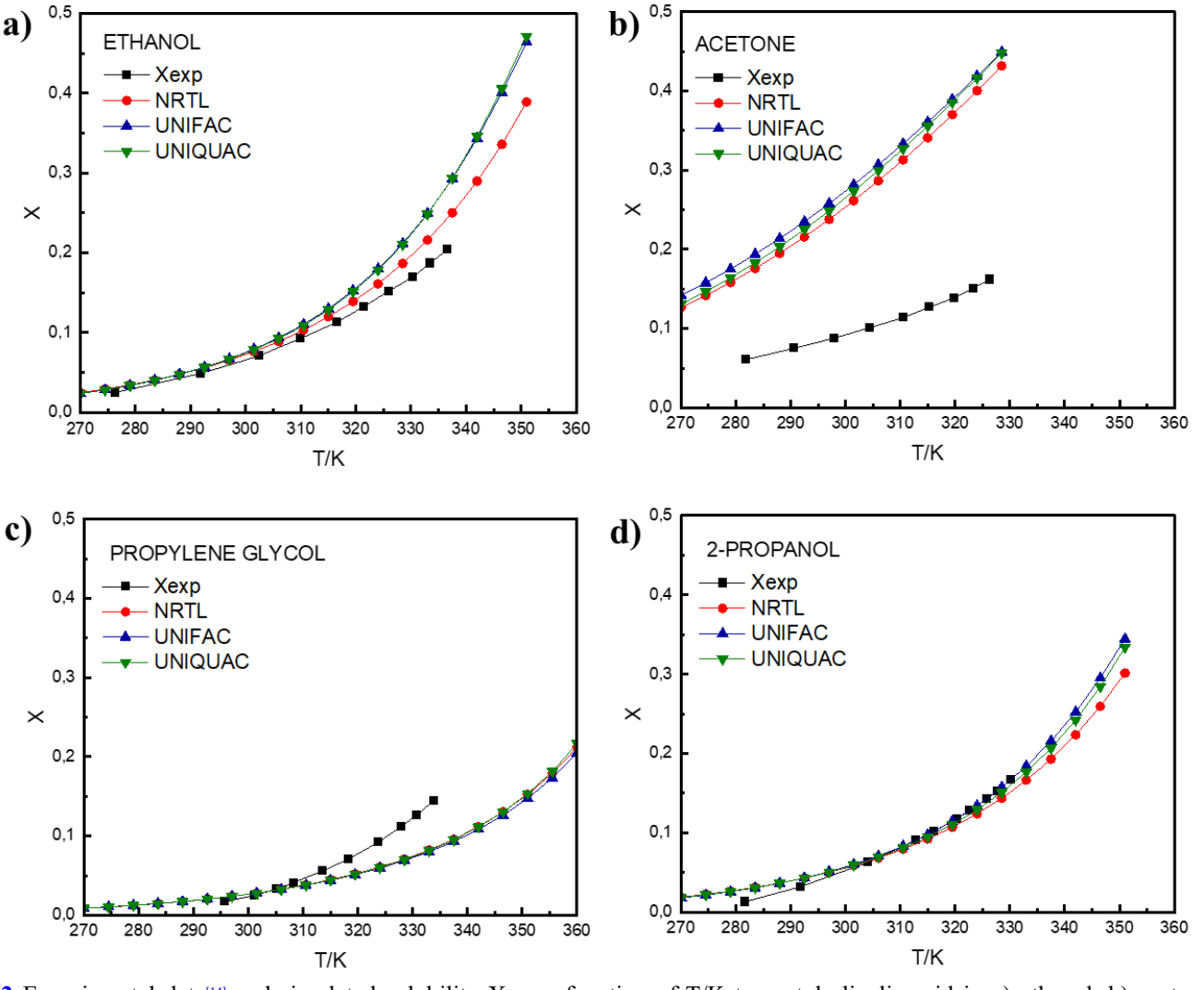

Fig. 2 Experimental data[14] and simulated solubility X as a function of T/K to acetylsalicylic acid in a) ethanol, b) acetone, c) propylene glycol, and d) 2-propanol using Aspen Plus with NRTL, UNIFAC, UNIQUAC models.

propanol shows a very significant correlation between actual and simulated data, highlighting the viability of our models in identifying this temperature-dependent behavior. The results obtained from all three models - NRTL, UNIFAC and UNIQUAC - are quite comparable for propylene glycol. The accuracy of these models in simulating aspirin solubility in propylene glycol, especially at temperatures up to 310 K, is confirmed by the agreement between experimental and simulated solubility values. However, above 310 K there is a significant discrepancy between the experimental and calculated results. The behavior of ethanol is also interesting; although the experimental and calculated data are approximately the same up to 310 K, differences begin to appear at higher temperatures. The NRTL model, which consistently provides an excellent fit to the experimental data, stands out as the most accurate among the three simulation models in this case. In contrast, the UNIFAC and UNIQUAC models show better agreement with the experimental results for 2-propanol. These findings highlight the importance of considering specific solvent properties when selecting an appropriate model for accurate solubility prediction.

In Fig. 3a thorough examination of the solubility of acetylsalicylic acid in several solvents is presented. Aspen Plus simulations using the NRTL, UNIFAC and UNIQUAC models are shown in panels (b), (c) and (d), respectively, while panel (a) presents the experimental solubility data.[14] Our research shows that the solubility trends seen in the simulated models created with Aspen Plus closely match the outcomes of the experiments. All simulation models consistently show that the solubility of acetylsalicylic acid in acetone is high. Propylene glycol, which has the lowest solubility, is followed by 2-propanol and ethanol as the top three solvents for dissolving aspirin. As a result, the following list summarizes the order of solubility of acetylsalicylic acid in the solvents studied: acetone > ethanol > 2-propanol > propylene glycol. In addition, our studies show that increasing temperature increases solubility in all solvents, as observed in both experimental and computational models. Comparison with Table 1 shows that the solubility values for acetylsalicylic acid obtained from Aspen Plus simulations in ethanol, propylene glycol and 2-propanol are almost consistent with the experimental results. However, it is worth noting that acetone solubility values have minor variations, which may be due to potential data errors in the Aspen database, as mentioned earlier, for the solubility parameters. In summary, Fig. 3 shows the solubility behavior of acetylsalicylic acid in several

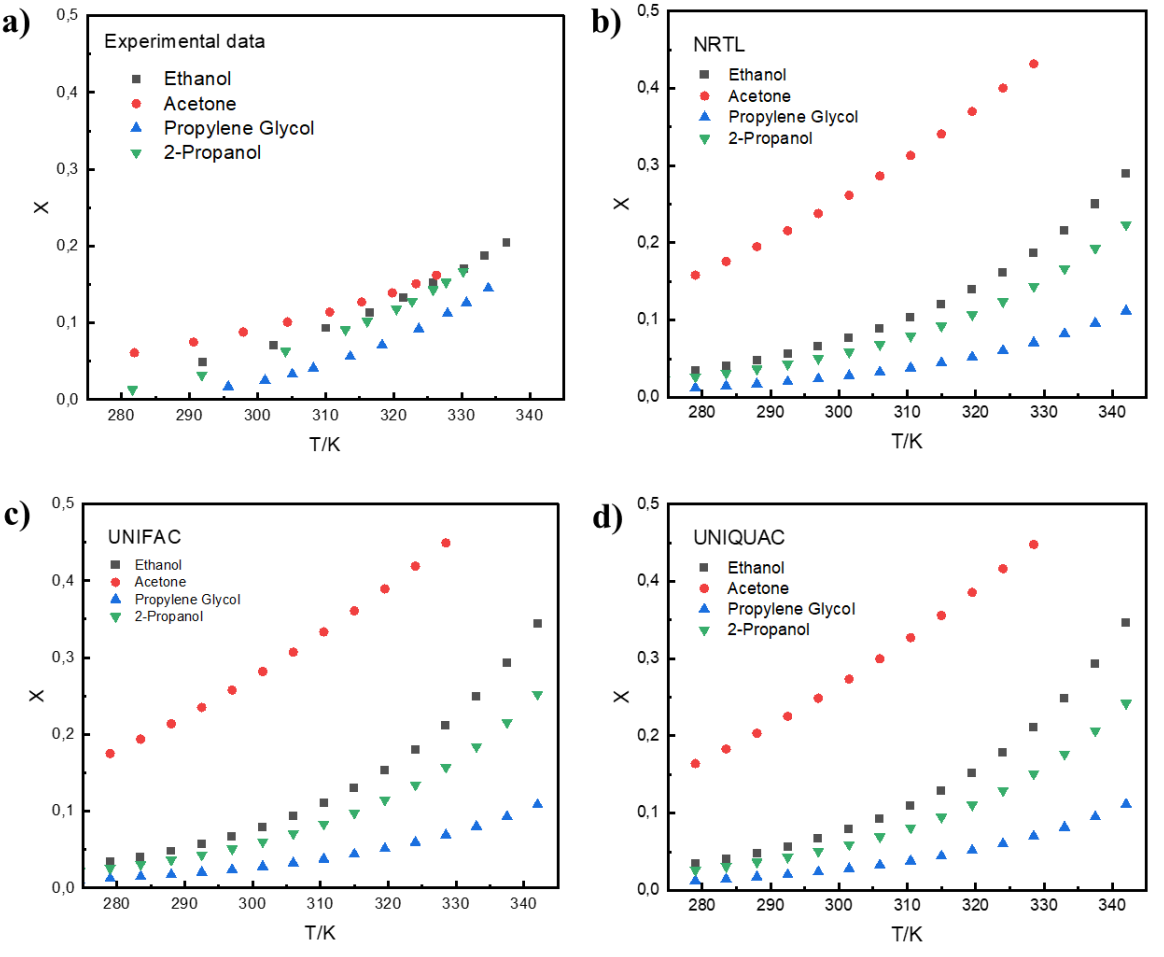

Fig. 3 Solubility of acetylsalicylic acid in different solvents - a) experimental data [14], b) simulated by Aspen Plus with NRTL model, c) simulated by Aspen Plus with UNIFAC model, d) simulated by Aspen Plus with UNIQUAC model.

Table 1. Experimental data[14] and simulated solubility of acetylsalicylic acid in various solvents using Aspen Plus with NRTL, UNIFAC, UNIQUAC models.

Ethanol								Acetone							
T/K	Xexp	T/K	NRTL	T/K	UNIFAC	T/K	UNIQUAC	T/K	Xexp	T/K	NRTL	T/K	UNIFAC	T/K	UNIQUAC
291,9	0,049	274,5	0,02937	274,5	0,02854	274,5	0,02841	281,9	0,061	270	0,12681	270	0,14196	270	0,13087
302,4	0,071	279	0,03465	279	0,03403	279	0,03384	290,6	0,075	274,5	0,14184	274,5	0,15792	274,5	0,14677
310	0,093	283,5	0,04077	283,5	0,04047	283,5	0,0402	297,9	0,088	279	0,1582	279	0,1752	279	0,16413
316,5	0,113	288	0,04784	288	0,04803	288	0,04766	304,4	0,101	283,5	0,17596	283,5	0,19383	283,5	0,18299
321,5	0,133	292,5	0,05602	292,5	0,05688	292,5	0,05639	310,6	0,114	288	0,19516	288	0,21383	288	0,20337
325,9	0,152	297	0,06546	297	0,06726	297	0,06662	315,3	0,127	292,5	0,21582	292,5	0,23517	292,5	0,22526
330,4	0,17	301,5	0,07634	301,5	0,0794	301,5	0,0786	319,8	0,139	297	0,23795	297	0,25785	297	0,24866
333,4	0,187	306	0,08887	306	0,09363	306	0,09265	323,3	0,151	301,5	0,26157	301,5	0,28182	301,5	0,27351
336,6	0,204	310,5	0,10331	310,5	0,11031	310,5	0,10915	326,3	0,162	306	0,28664	306	0,30704	306	0,29975
		315	0,11993	315	0,12988	315	0,12855			310,5	0,31313	310,5	0,33346	310,5	0,32729
		319,5	0,13909	319,5	0,15288	319,5	0,15143			315	0,34098	315	0,36098	315	0,35601
		324	0,16118	324	0,17992	324	0,17848			319,5	0,37011	319,5	0,38953	319,5	0,38579
		328,5	0,18669	328,5	0,21174	328,5	0,21053			324	0,40042	324	0,41902	324	0,4165
		333	0,21618	333	0,24914	333	0,24851			328,5	0,43178	328,5	0,44933	328,5	0,44797
		337,5	0,25033	337,5	0,2929	337,5	0,2934								
		342	0,28995	342	0,34355	342	0,34589								
		346,5	0,33591	346,5	0,40095	346,5	0,40582								
		351	0,38906	351	0,46373	351	0,47133								
Propylene Glycol								**2-Propanol**							
T/K	Xexp	T/K	NRTL	T/K	UNIFAC	T/K	UNIQUAC	T/K	Xexp	T/K	NRTL	T/K	UNIFAC	T/K	UNIQUAC
295,7	0,017	270	0,00861	270	0,0089	270	0,00877	281,6	0,013	270	0,01896	270	0,01805	270	0,01859
301,1	0,025	274,5	0,01028	274,5	0,01056	274,5	0,01043	291,8	0,032	274,5	0,02245	274,5	0,02161	274,5	0,0221
305,1	0,033	279	0,01223	279	0,01249	279	0,01236	304,1	0,063	279	0,02651	279	0,0258	279	0,0262
308,2	0,041	283,5	0,01451	283,5	0,01473	283,5	0,01461	312,9	0,091	283,5	0,03122	283,5	0,0307	283,5	0,03097
313,6	0,056	288	0,01715	288	0,01733	288	0,01722	316,1	0,102	288	0,03667	288	0,03645	288	0,03653
318,3	0,071	292,5	0,02023	292,5	0,02034	292,5	0,02025	320,4	0,118	292,5	0,04296	292,5	0,04316	292,5	0,04298
323,7	0,092	297	0,0238	297	0,02382	297	0,02376	322,7	0,128	297	0,05023	297	0,05099	297	0,05048
327,9	0,112	301,5	0,02794	301,5	0,02784	301,5	0,02783	325,8	0,143	301,5	0,05861	301,5	0,06013	301,5	0,05919
330,7	0,126	306	0,03273	306	0,03248	306	0,03254	327,7	0,153	306	0,06826	306	0,07079	306	0,0693
333,9	0,145	310,5	0,03827	310,5	0,03784	310,5	0,03799	330,2	0,167	310,5	0,07938	310,5	0,0832	310,5	0,08106
		315	0,04469	315	0,04402	315	0,04431			315	0,09219	315	0,09768	315	0,09472
		319,5	0,05211	319,5	0,05117	319,5	0,05163			319,5	0,10695	319,5	0,11456	319,5	0,11065
		324	0,06072	324	0,05943	324	0,06014			324	0,12398	324	0,13426	324	0,12924
		328,5	0,07071	328,5	0,069	328,5	0,07005			328,5	0,14365	328,5	0,15726	328,5	0,15099
		333	0,08233	333	0,08013	333	0,08163			333	0,16641	333	0,18415	333	0,17654
		337,5	0,09589	337,5	0,09311	337,5	0,09523			337,5	0,19282	337,5	0,21558	337,5	0,20664
		342	0,11177	342	0,10831	342	0,11129			342	0,22353	342	0,25231	342	0,2422
		346,5	0,1305	346,5	0,12625	346,5	0,13042			346,5	0,25938	346,5	0,29509	346,5	0,28428
		351	0,15273	351	0,14759	351	0,15345			351	0,30135	351	0,34456	351	0,33394
		355,5	0,1794	355,5	0,17327	355,5	0,18157								
		360	0,21184	360	0,20468	360	0,21659								

solvents, demonstrating the consistency of experimental and simulated data and highlighting the role of temperature on solubility. It also emphasizes the importance of carefully checking data when working with modeling software such as Aspen Plus, especially when data discrepancies may arise.

4. Conclusion

Aspen Plus platform can generally be used to forecast the best way to formulate a certain medicine using a variety of solvents and compositions. If the medicine isn't already a part of the databank, its skeleton molecular editor in Aspen Plus can characterize it with a few details about its physical characteristics, such as melting point, boiling point, or density. The calculated data in Aspen plus for the binary system almost coincides with the experimental solubility of aspirin in different solvents. For ethanol, propylene glycol, and 2-propanol, excellent agreement between simulation and experimental results is found, while investigating the solubility of aspirin in several solvents using extensive simulation. The acetone case clearly showed the need for more accurate modeling. Notably, the NRTL model generally outperforms others, especially when it comes to ethanol. Our study revealed the effect of temperature on solubility, demonstrating a consistent trend for solubility to increase with temperature for all solvents examined. These observations highlight the importance of accurate modeling and are useful for real-world applications.

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Conflict of Interest
There is no conflict of interest.

Supporting Information
Not applicable.

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