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Short Communication

Simulation of Co-Crystal Solubility in the Mono-Solvents at Different Temperatures

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Abstract: This communication reports correlative models for the simulation of the solubility of co-crystals dissolved in mono-solvents at various temperatures. The trained models provided reasonably accurate results for three investigated co-crystals (as model co-crystals) by using Abraham, Hansen and Catalan parameters of the mono-solvents as input values.

Keywords: co-crystal, solubility, van't hoff model, mono-solvents, correlation, temperature

Physicochemical properties of active pharmaceutical ingredients (APIs), such as solubility and dissolution rate are an essential part of drug discovery and development investigations. Most of the candidate APIs have low solubility leading to poor bioavailability. To overcome this limitation, numerous methods have been recommended to increase solubility, such as co-crystal formation. Co-crystallization technology has caught much attention in the pharmaceutical industry and it can improve the properties of an API, such as solubility and dissolution rate.[1,2] In this technique, a homogenous (single phase) crystalline structure is made up of the connection of an API to a corfomer via non-covalent interactions, especially hydrogen bonding. It allows better products to be produced for the marketplace by improving the physical and chemical properties of API without any change in structure, contrary to the situation that happened during salt formation. The advantage of co-crystallization is that non-ionizable API molecules can form co-crystals against salt formation.[3]

Co-crystals consist of two molecules that are present in definite stoichiometric ratios, interacting with each other via non-covalent bonds, especially hydrogen bonding which has a unique crystalline pattern compared with its components.[4] Because of solution stability (co-crystals' ability to stay in solution without converting into crystals), solubility experiments and analysis of co-crystals have some challenges and time-consuming.[5,6] Thermodynamic analysis and modeling are possible after analyzing the final residual crystal from the saturated solutions to ensure the stability of the co-crystals in the solution.

Some experimental studies have been done to investigate the thermodynamic solubility of co-crystals in various solvents at different temperatures. The van't Hoff equation is a classic model to build up a mathematical model to correlate the solubility of a drug in a given mono-solvents at various temperatures (x_T). This could be considered as a disadvantage for the model since there is no possibility to extend its applicability for other mono-solvents. To cover this point, in a recent work,[7] the intercept and slope of the van't Hoff equation, (α and β) were correlated to the solvation parameters of the mono-solvents using a combination of Abraham solvation parameters (AP_i), Hansen solubility

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parameters (HP_i) and Catalan parameters (CP_i).[7] The numerical values of AP_i, HP_i and CP_i for the investigated solvents are listed in Table 1. The applicability of the model was tested on the solubility of a number of drugs in a number of mono-solvents at various temperatures[7] and also a number of salt forms of drugs.[8] The general form of the proposed model is:

$$\ln x_T = \left(\alpha_0 + \sum_{i=1}^{5} \alpha_{i,AP} AP_i + \sum_{i=1}^{3} \alpha_{i,HP} HP_i + \sum_{i=1}^{4} \alpha_{i,CP} CP_i \right) + \left(\frac{\beta_0 + \sum_{i=1}^{5} \beta_{i,AP} AP_i + \sum_{i=1}^{3} \beta_{i,HP} HP_i + \sum_{i=1}^{4} \beta_{i,CP} CP_i}{T} \right) \quad (1)$$

Table 1. Details of the employed parameters for the solvents

Solvent	Abraham parameters					
	c	*e*	*s*	*a*	*b*	*v*
Acetone	0.31	0.31	-0.12	-0.61	-4.75	3.94
Acetonitrile	0.41	0.08	0.33	-1.57	4.39	3.36
1-Butanol	0.17	0.40	-1.01	0.06	-3.96	4.04
Butanone	0.25	0.26	-0.08	-0.77	-4.86	4.15
Chloroform	0.19	0.11	-0.40	-3.11	-3.51	4.40
Ethanol	0.22	0.47	-1.00	0.33	-3.60	3.86
Ethyl acetate	0.33	0.37	-0.45	-0.70	-4.90	4.15
Methanol	0.28	0.33	-0.71	0.24	-3.30	3.55
1-Propanol	0.14	0.41	-1.00	0.25	-3.80	3.99
2-Propanol	0.10	0.34	-1.00	0.41	-3.80	4.03
		Hansen	parameters			
	δ_D	δ_P	δ_H	-	-	-
Acetone	15.50	10.40	7.00	-	-	-
Acetonitrile	11.59	12.95	16.34	-	-	-
1-Butanol	16.00	5.70	15.80	-	-	-
Butanone	16.00	9.00	5.10	-	-	-
Chloroform	17.80	3.10	5.70	-	-	-
Ethanol	15.80	8.80	19.40	-	-	-
Ethyl acetate	15.80	5.30	7.20	-	-	-
Methanol	15.10	12.30	22.30	-	-	-
1-Propanol	16.00	6.80	17.40	-	-	-
2-Propanol	13.00	10.40	15.70	-	-	-
		Catalan	parameters	-	-	-
	SP	*SdP*	*SA*	*SB*	-	-
Acetone	0.65	0.91	0.00	0.48	-	-
Acetonitrile	0.65	0.97	0.04	0.29	-	-
1-Butanol	0.67	0.66	0.34	0.81	-	-
Butanone	0.67	0.87	0.00	0.52	-	-
Chloroform	0.78	0.61	0.05	0.07	-	-
Ethanol	0.63	0.78	0.40	0.66	-	-
Ethyl acetate	0.66	0.60	0.00	0.54	-	-
Methanol	0.61	0.90	0.61	0.55	-	-
1-Propanol	0.66	0.75	0.37	0.78	-	-
2-Propanol	0.63	0.81	0.28	0.83	-	-

where α and β terms are the model constants. By including these parameters in the van't Hoff equation, the entropic and enthalpic changes during dissolution of a drug in the various mono-solvents are correlated with the mono-solvents' parameters and provide the capability of extension of the applicability of the model to other mono-solvents. The most significant ($p < 0.05$) independent variables obtained from the regression of the solubility data of three investigated co-crystals (stable co-crystal in solution after equilibration) in the mono-solvents at various temperatures[9-11] are:

For sulfamethazine-saccharin-form II:

$$\ln x_T = \left(4.773 + 6.243e + 0.267b - 0.237\delta_D + 0.119\delta_H\right) + \left(\frac{-2576.592 + 1443.957s - 210.292b - 31.340\delta_P}{T}\right) \quad (2)$$

$R = 0.997$, $F = 1837$, $N = 88$, $MPD = 6.0\%$.

For probenecid-4,4'-azopyridine:

$$\ln x_T = \left(11.086 - 16.603c - 0.308\delta_D + 8.245SP - 1.233SdP\right) + \left(\frac{174.824\delta_D - 27.476\delta_H - 7284.568SP - 2787.386SB}{T}\right) \quad (3)$$

$R = 0.999$, $F = 2170$, $N = 54$, $MPD = 3.2\%$.

For furosemide-4,4'-bipyridine-form II:

$$\ln x_T = \left(20.831 - 8.523c - 0.832\delta_D + 0.154\delta_H - 6.393SdP\right) + \left(\frac{333.909\delta_D - 96.192\delta_H - 8402.234SP - 2398.314SB}{T}\right) \quad (4)$$

$R = 0.999$, $F = 3327$, $N = 53$, $MPD = 2.5\%$ in which c, e, s and b are the AP_i parameters, δ_D, δ_H and δ_P are HP_i, SP, SdP and SB are CP_i parameters.[7] More details of Eqs. (2)-(4) including the correlation coefficient (R), F values, number of correlated data points (N) and the overall mean percentage deviation (MPD) are provided above. The MPD values were calculated using:

$$MPD = \frac{100}{N}\sum_{1}^{N}\left(\frac{\left|x_T^{Calculated} - x_T^{Observed}\right|}{x_T^{Observed}}\right) \quad (5)$$

and listed in Table 2 for the investigated co-crystals along with the corresponding values for the most common model, i.e. Apleblat equation collected from the literature.[9-11]

Careful examination of the listed MPD values in Table 2 revealed that the proposed model provides reasonably accurate correlations for the solubility of the investigated co-crystals. The model fits all solubility data of a co-crystal in different mono-solvents at various temperatures whereas Apelblat, van't Hoff and λh models fit the solubility of a co-crystal in a given solvent at various temperatures. Although the overall MPD of the proposed model is larger than that of the Apelblat model by a factor of two, however, the MPDs of both models lie within the experimental relative standard deviations, e.g. < 10%.

Concerning the above-mentioned results, it is recommended that the proposed model be used for the calculation of the solubility of co-crystals in mono-solvent systems at various temperatures. These calculations are required in the process design and scale-up investigations in the chemical industries. The main limitation of the proposed model is the unavailability of the AP_i, HP_i or CP_i for some organic solvents, such as 1,2-dichloroethane in this work and another issue is the solution stability of co-crystal which must be considered in each experiment.

Table 2. The mean percentage deviation (*MPD*) of the models for correlating the solubility of investigated co-crystals in the mono-solvents at various temperatures

Model	Proposed			Apelblat		
Solvent/Co-crystal	Sulfamethazine-saccharin-form II	Probenecid-4,4'-azopyridine	Furosemide-4,4'-bipyridine-form II	Sulfamethazine-saccharin-form II	Probenecid-4,4'-azopyridine	Furosemide-4,4'-bipyridine-form II
Acetone	3.4	1.8	1.8	1.1	0.6	1.2
Acetonitrile	4.3	4.1	3.6	1.8	0.9	3.1
1-Butanol	8.0	-[b]	2.6	1.4	-[b]	2.2
Butanone	3.0	-[b]	-[b]	0.7	-[b]	-[b]
Chloroform	7.3	-[b]	-[b]	0.8	-[b]	-[b]
1,2-Dichloroethane	-[a]	-[a]	-[a]	3.3	-[b]	-[b]
Ethanol	-[b]	2.0	3.0	-[b]	2.0	2.6
Ethyl acetate	-[b]	2.1	-	-[b]	2.1	-[b]
Methanol	3.8	-[b]	-[b]	2.4	-[b]	-[b]
1-Propanol	11.9	6.3	2.8	3.8	2.1	2.9
2-Propanol	5.3	3.3	1.3	2.5	3.2	1.0
Overall	5.9	3.3	2.5	2.0	1.8	2.2

a: The AP_i, HP_i or CP_i were not available. b: Solubility data were not available

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Conflict of interest

The authors declare that they have no conflict of interest.

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