MODELING SOLUBILITY OF SOLIDS IN SUPERCRITICAL CARBON DIOXIDE USING q-CHRASTIL EQUATION

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Abstract. This work presents a generalization of Chrastil equation by using Tsallis´ statististical non-extensive entropy theory and the q-exponential function. A new model with three adjustable parameters (q-Chrastil) is proposed. A comparison between q-Chrastil and Chrastil equations was performed by modelling the solubility of 58 pharmaceuticals in supercritical CO_2. The results showed that both models provide deviations of about 15%, slightly higher than those obtained when models with a higher number of adjustable parameters were used. q-Chrastil equation is promising for modelling complex systems at higher temperatures and serves as a starting point for the development of new models.

Keywords: solubility of solids, supercritical carbon dioxide, semiempirical equations

1. Introduction

The use of supercritical fluids (SCFs) for the extraction of high-value compounds from natural sources or for particle production of active principle ingredients (API) has been extensively studied over few decades [1-5]. These processes exploit the particular gas-liquid properties of a SCF, such as liquid-like density and gas-like diffusivity and viscosity. Moreover, the product obtained is often free of residual organic solvent and if a non-flammable and non-hazardeous SCF is used, these techniques can be considered as "green" processes. Due to its mild critical properties, non-toxicity and environmentally friendly label, carbon dioxide is the most commonly utilized SCF [6].

In both SFE and precipitation processes, the solubility of the pure solid in the SCF should be known to evaluate the feasibility of the process. However, experimental determination of solubility of solids in sc-CO_2 is not an easy or inexpensive task. Therefore, models able to correlate and predict solubility of solids in sc-CO_2 are very desirable. Cubic equations of state and non-cubic equations of state (EOS) have been used to model solubility of solids in sc-CO_2 with and without cosolvents [7-9]. However, these equations require robust computational methods and the knowledge of several properties such as sublimation pressure, molar volume, critical temperature and pressure, and sometimes molecular parameters. These properties for pharmaceuticals are scarce in the literature and group contribution methods are usually applied introducing additional uncertainties in the use of these equations [10-11].

As an alternative to cubic and non-cubic EOS, semiempirical models can be applied to correlate and predict solubility of solid API in sc-CO_2. These models correlate experimental solubility data based on the density of the supercritical solvent and on the temperature of the binary system, and do not require pure solid properties. The main drawback is the semiempirical character, what means that solubility data are needed. Several equations have been presented by different authors, using from three to six parameters. Most of them are modifications of the Chrastil's equation with an increasing number of parameters [12-17]. However, an increase in the number of parameters does not correspond to a better performance and often the models become much more empirical.

The present work contributes to better understand modelling of solid API solubility in sc-CO_2 using semiempirical models, and a new model is proposed based on the Tsallis's statistical non-extensive entropy theory [18]. This new model used the *q*-exponential function to generalize Chrastil's equation for calculation of solubility of solid in binary systems.

2. Chrastil´s equation and definition of the proposed q-Chrastil´s model

Chrastil published in 1982 [12] one of the first semiempirical models to fit solubility data of solids in sc-CO_2. This equation (equation 1) was defined by taking into account the equilibrium between the solid and the SCF, forming a solvato-complex. Based on this assumption, a relationship between the solubility and the SCF density was established, including three adjustable parameters (*k*, A and B) that must be calculated by regressing experimental data against theoretical data.

$$S = \rho^k . \exp\left(\frac{A}{T} + B\right) \tag{1}$$

where *S* is the solubility of the solid in the SCF, *T* is the temperature, ρ is the density of the SCF and *k* is the association number of the solvato-complex.

As it can be seen in Equation 1, the exponential term comes from the Boltzmann's weight argument in the form of *exp(-E/RT)* where *E* is the energy, which is a mechanical non temperature dependent variable [18-19]. However, often empirical modifications are introduced in this type of exponential term considering that energy depends on temperature. The most common relationship considered between energy and temperature is the linear one. In this case, the following equation is used:

$$E = E_0 + E_1 T \tag{2}$$

Using Equation 2, the Boltzmann's weight argument becomes

$$\frac{E}{RT} = \frac{E_0}{RT} + \frac{E_1}{R} \tag{3}$$

Expressing $E_0/R = A$ and $E_1/R = B$, the exponential term of the Chrastil's equation is obtained.

However, several works have shown that the correct way to express the energy exponential term is based on the Tsallis's weight argument instead of Boltzmann's one, leading to an energy term independent of temperature [18, 20]. It should be noted when T rises to infinity, using Boltzmann's weight argument leads to an inconsistency: the exponential term should be equal to unity but with Chrastil's equation this term becomes the constant *exp(B)*.

To overcome this problem, we are proposing a generalised Chrastil's equation for calculating the solubility of solid in binary systems based on the Tsallis's statistical non-extensive entropy theory [21]. This theory has been applied in different areas of science, such as in the application of q-Weibull distribution to model hazard rate in problems of reliability engineering [22] or in the investigation of deviations from Arrhenius law in kinetics of chemical and biophysical processes [23].

The new q-Chrastil´s equation uses the definition of the *q*-exponential function expressed as follows [19]:

$$\exp_q x = \left[1 + (1-q)x\right]^{\frac{1}{1-q}}, \text{ if } \left[1 + (1-q)x\right] > 0 \tag{4}$$

or

$$\exp_q x = 0, \text{ if } \left[1 + (1-q)x\right] \leq 0 \tag{5}$$

Applying the q-exponential function it is possible to express q-Chrastil's equation as:

$$S = \rho^k . \exp_q\left(\frac{A_q}{T}\right) \tag{6}$$

where k, A_q and q are the only adjustable parameters. So, the q-Chrastil´s equation has the same three adjustable parameters as the original Chrastil´s equation, but without the theoretical inconsistency in the exponential term described above.

3. Procedure for calculation and comparison of the models.

In order to make a comparison between the new proposed model and the original Chrastil´s model, experimental solubility data of 58 API in pure sc-CO_2 were taken from different references, and were modelled with both equations, calculating the average absolute relative deviation (AARD):

$$AARD = \left(100/N\right) \cdot \sum_{i=1}^{N} \frac{\left|y_{cal} - y_{\exp}\right|}{y_{\exp}} \tag{7}$$

Table 1 shows the number of data points (N), and the temperature and pressure ranges for each system. Density of the sc-CO_2 was taken from NIST webbook [24]. It is important to say that all isotherms data were used together in the minimization procedure of the objective function in terms of the sum of relative deviation in solubility to estimate the parameters of the models, i.e., all parameters are considered to be roughly independent of the temperature. Newton´s method was used to perform the corresponding data regressions and estimation of the corresponding parameters for all the systems and models.

4. Results and discussion.

Table 2 shows the AARD calculated for each binary system with Chrastil and q-Chrastil models and the value of the parameter q.

According to the results, Chrastil and q-Chrastil fit the solubility data of solid APIs in sc-CO_2 with roughly the same deviation (around 15%). Moreover, both equations reproduce experimental data in the same way, as it can be observed in Figure 1, where both the experimental and the calculate data of solubility of ketoprofen in sc-CO_2 are depicted, in linear-linear, linear-log and log-log scales. As a matter of fact, the dotted line in the figure 1 is hidden by the continous line. Another point of interest is that the value of the parameter q is almost close to unity for all systems. If the parameter q tends to one, the q-exponential reduces to the original exponential, and as a consequence the q-Chrastil reduces to the original Chrastil´s equation. In fact, one can say that Chrastil´s equation is a particular case of the q-Chrastil's one when q equals one. Therefore, as q tends to unity for all binary systems investigated, we can say that the very close values of AARD for both systems are expected.

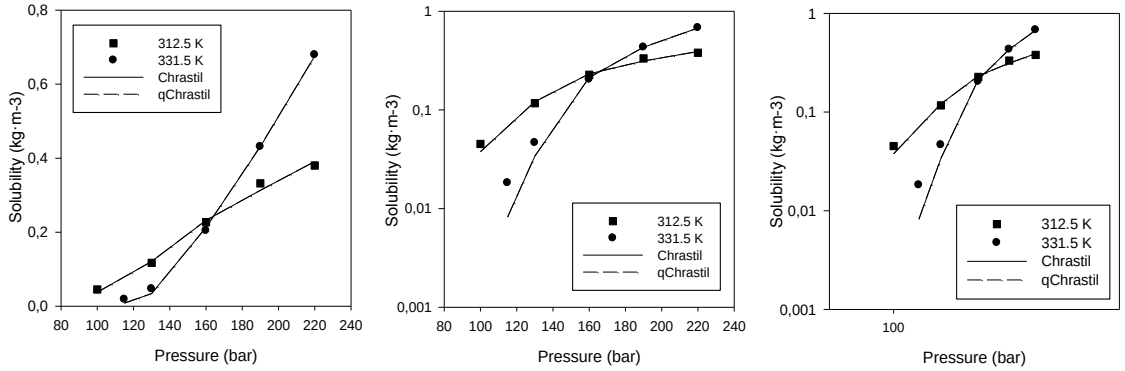

Figure 1. Prediction of the solubility of ketoprofen in sc-CO_2 with q-Chrastil and Chrastil with linear-linear, linear-log and log-log scales. Experimental data from [45].

In order to check the possibility of fixing the value of the parameter q for all these systems that would reduce the number of parameters of q-Chrastil's model from three to two, a simple correlation between parameter q and the temperature was looked for.

Table 1. Binary systems API-scCO$_2$ used to compare Chrastil's and q-Chrastil's equations.

Solid	Temperature range (K)	Pressure range (bar)	N	Ref.
2-Methylbenzoic acid	313-333	110-245	18	[25]
3-Methylbenzoic acid	313-333	110-245	18	[25]
3,5-Dinitrobenzoic acid	308-328	100-210	15	[26]
4-Aminoantipyrine	308-328	100-220	21	[27]
4-Methylbenzoic acid	313-333	110-245	18	[25]
Acetaminophen	313-353	80-300	10	[28]
Alpha-tocopherol	313-353	200-350	24	[29]
Aspirine	318-328	120-200	8	[30]
Astaxanthin	313-333	100-400	26	[31]
Atorvastatin	308-348	120-350	45	[32]
Beta-carotene	313-353	200-350	23	[29]
Budesonide	338-358	215-285	21	[33]
Caffeic acid	313-333	150-500	24	[34]
Caffeine	313-353	200-350	24	[35]
Cholesterol	313-333	100-250	22	[36]
Cholesterolbenzoate	308-328	120-270	20	[36]
Clofibric acid	308-328	100-220	21	[37]
Clozapine	318-348	120-355	27	[38]
Cyproterone acetate	308-348	120-350	40	[39]
Diflunisal	308-328	90-250	21	[40]
Exemestane	308-348	120-350	45	[41]
Fenofibrate	308-328	100-220	21	[37]
Flurbiprofen	303-323	80-250	27	[42]
Fluvastatin	308-348	120-350	45	[32]
Gemfibrozil	308-328	100-220	21	[37]
Hexadecanoic acid	308-318	130-225	10	[43]
Irgacure2959	308-328	100-260	21	[44]
Ketoprofen	312-331	100-220	10	[45]
Lamotrigine	308-348	120-355	45	[38]
Letrozole	308-348	120-350	45	[41]
Lycopene	313-333	200-400	19	[46]
Lidocaine	298-318	70-250	33	[47]
Lovastatin	308-348	120-350	45	[32]
Medroxyprogesterone acetate	308-348	120-350	40	[39]
Methimazole	308-328	120-350	40	[48]
Nabumetone	308-328	100-220	21	[49]
Naproxen	313-333	90-195	18	[50]
Nimesulide	313-333	130-220	8	[45]
Nitrendipine	333-373	100-300	42	[51]
Octadecanoic acid	308-318	130-225	10	[43]
Orto-hydroxybenzoic acid	308-328	80-200	49	[52]
PenicillinG	313-333	100-350	18	[53]
Penicillin V	315-335	80-280	24	[54]
Phenazopyridine	308-348	120-350	45	[48]
Procaine	298-318	70-250	28	[47]
Progesterone	308-328	105-240	40	[55]
Propanolol	308-348	120-350	45	[48]
Propyl p-hydroxybenzoate	308-328	80-230	18	[56]
p-toluenesulfonamide	308-328	80-210	15	[57]
Rosuvastatin	308-348	120-350	45	[32]
Simvastatin	308-348	120-350	45	[32]
Taxol	308-318	205-475	12	[58]
Testosterone	308-328	85-240	39	[55]
Tetradecanoic acid	308-318	100-225	11	[59]
Theobromine	313-353	210-345	23	[35]
Theophylline	313-353	200-350	22	[35]
Vitamine D2	313-353	200-320	19	[29]
Vitamine D3	313-353	200-350	23	[29]

Table 2. *AARD* calculated for the binary systems with Chrastil and q-Chrastil equations.

Solid	Chrastil	q-Chrastil	*q* value
2-Methylbenzoic acid	2.34	2.31	1.032
3-Methylbenzoic acid	3.49	3.37	1.037
3,5-Dinitrobenzoic acid	4.87	4.95	1.025
4-Methylbenzoic acid	2.67	2.59	1.043
4-aminoantipyrine	12.41	12.41	1.068
Acetaminophen	24.02	24.02	1.032
Alpha-tocopherol	3.82	3.73	1.077
Aspirine	6.08	6.08	1.057
Astaxanthin	52.98	52.49	1.036
Atorvastatin	8.86	10.26	1.026
Beta-carotene	26.69	29.75	1.027
Budesonide	11.86	11.82	1.047
Caffeic acid	56.75	57.26	1.041
Caffeine	5.16	4.43	1.070
Cholesterol	23.23	23.23	1.064
Cholesterolbenzoate	7.25	7.80	1.062
Clofibric acid	5.06	4.97	1.064
Clozapine	21.08	19.13	1.040
Cyproterone acetate	24.74	24.79	1.081
Diflunisal	21.08	21.01	1.039
Exemestane	33.46	33.46	1.023
Fenofibrate	8.90	7.99	1.064
Flurbiprofen	8.67	8.70	1.033
Fluvastatin	14.73	14.73	1.031
Gemfibrozil	7.83	7.49	1.051
Hexadecanoic acid	2.61	2.07	1.160
Irgacure 2959	3.49	3.37	1.035
Ketoprofen	11.72	11.72	1.047
Lamotrigine	5.74	5.75	1.076
Letrozole	38.46	39.09	1.025
Licopene	5.71	5.60	1.040
Lidocaine	34.45	34.46	1.044
Lovastatin	5.89	6.09	1.069
Medroxyprogesterone acetate	18.91	18.23	1.055
Methimazole	12.69	12.39	1.054
Nabumetone	11.55	11.55	1.045
Naproxen	9.77	9.80	1.059
Nimesulide	19.13	18.08	1.057
Nitrendipine	16.10	15.58	1.055
Octadecanoic acid	8.31	8.31	1.140
o-hydroxybenzoic acid	8.15	8.15	1.043
PenicillinG	25.43	25.65	1.035
Penicillin V	18.17	18.17	1.076
Phenazopyridine	15.46	15.59	1.051
Procaine	14.25	14.25	1.068
Progesterone	17.27	17.26	1.054
Propanolol	38.42	36.75	1.021
Propyl *p*-hydroxybenzoate	30.81	30.92	1.022
p-toluenesulfonamide	7.50	7.87	1.032
Rosuvastatin	6.96	6.84	1.047
Simvastatin	13.05	12.77	1.042
Taxol	4.34	4.28	1.057
Testosterone	23.48	23.51	1.038
Tetradecanoic acid	13.82	13.82	1.150
Theobromine	6.62	6.70	1.067
Theophylline	5.50	5.39	1.079
Vitamin D2	10.53	11.82	1.062
Vitamin D3	34.11	34.33	1.049
Average AARD	**15.45**	**15.42**	

The temperature effect on the parameter *q* was studied by plotting the average temperature of the experimental data for each system against 1/1-*q* (Figure 2). In this figure it can be seen that there is not a clear behaviour of the parameter *q* as a function of temperature. As a consequence, it is not possible to obtain a simple expression to correlate *q* as a function of temperature.

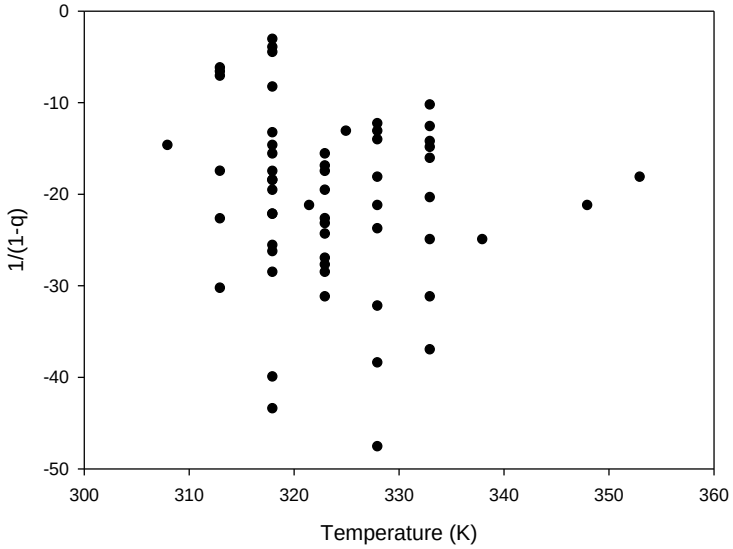

Figure 2. Temperature effect on parameter *q* for all binary systems.

However, it was observed that the value of the parameter *q* is around 1.15 for highly linear molecules (fatty acids) such as hexadecanoic, octadecanoic and tetradecanoic acids, differing of the common values found for molecules constituted by aromatic and/or polycyclic aliphatic rings (between 1.030 and 1.075). These results indicate the possibility of a dependence of the parameter *q* on the molecular structure of the solid and that a group contribution method could be developed to estimate this parameter, which would reduce the total number of parameters in the q-Chrastil´s equation.

5. Conclusions

A new semiempirical modified Chrastil equation with three adjustable parameters was proposed to fit solubility data of active principle ingredients in pure supercritical carbon dioxide. This model is a generalization of Chrastil´s equation by using Tsallis´ statistical non-extensive entropy theory and the q-exponential function. It was shown, by fitting experimental solubility data of 58 active pharmaceutical ingredients in supercritical carbon dioxide, that Chrastil and q-Chrastil models provide a similar deviation in terms of average absolute relative deviations (around 15%).

Further, it was shown that the adjustable parameter *q* does not depend on the temperature, although a relationship between the value of the parameter and the molecular structure of the solid was observed pointing to the possibility of developing a group contribution method to estimate the parameter *q*.

The original Chrastil´s equation can be seen as a particular case of the q-Chrastil model when parameter *q* tends to unity. The main advantage of using this q-model is the overcoming that the physical inconsistency of other models based on Boltzmann's weight argument because they expressed the energy exponential term based on the Tsallis's weight argument. Although the new q-Chrastil model proposed have shown deviations similar to the other models, it appears with a great potential for high complex systems and should be further explored mainly at higher temperatures.

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