A comparison between models based on cubic equations of state and density-based models for describing the solubility of solutes in CO_2

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1. INTRODUCTION

The poor dissolution behaviour of solid drugs in biological environment leads to a low bioavailability. However, the dissolution rate of such drugs can be enhanced dramatically by reduction of the particle size. At present, conventional micronization techniques such as milling and grinding, spray-drying, freeze-drying, high-pressure homogenization, ball and air jet milling have been utilized for particle size reduction. The disadvantages of these techniques are often degradation of the product, a broad particle size distribution and cumbersome solids handling. To overcome this, supercritical fluid (SCF) based particle size reduction processes are gaining in importance in material science and pharmaceutical technology. Reliable solubility data are essential for an accurate experimental design and for calculation of the concentration of supercritical solutions at different operating conditions. Today, models based on equations of state, together with different mixing rules, are most widely used to correlate and predict the solubility in SCFs. Therefore the accurate knowledge of the required solute data, such as critical parameters, acentric factor, solid molar volume, and sublimation pressure of the solutes is essential. However, the common estimation methods are mostly empirical and often lead to inconsistent and unreliable results.

Thus, due to the lack of information on these data, density-based models are often used for the correlation of experimental solubility data. In this paper, solubility data of S-Naproxen, of RS-Ibuprofen, of Phytosterol and of Salicylic acid in CO_2 is correlated by four different methods: two methods for the density-solubility correlation and two methods for the pressure-solubility correlation. In addition, the influence of solute data predicted by different estimation methods is investigated. Thereby, it turned out that for the solutes investigated, the equation of state based method is very sensitive to the values of the sublimation pressure.

2. MODELLING

2.1 Equation of State

Different cubic equations of state can be used to describe the experimental results of the solubility y_2 of an organic solid in a supercritical fluid. In the present investigation we used the original Peng–Robinson equation of state (PR-EoS) [1] to describe the solubility y_2.

$$p = \frac{R \cdot T}{(v-b)} - \frac{a(T)}{v^2 + 2bv - b^2} \tag{1}$$

In Eq. (1) p is the pressure, T the temperature, v the molar volume, and R the gas constant. The PR-EoS was applied to binary systems using the van der Waals mixing rules:

$$a = \sum_{i=1}^{k} \sum_{j=1}^{k} x_i x_j a_{ij} \quad a_{ij} = \sqrt{a_i \cdot a_j} \cdot 1 - k_{ij} \tag{2a}$$

$$b = \sum_{i=1}^{k} \sum_{j=1}^{k} x_i x_j b_{ij} \quad b_{ij} = \frac{b_{ii} + b_{jj}}{2} \cdot \left(1 - l_{ij}\right) \tag{2b}$$

The parameters a and b can be calculated from the critical properties of the pure components. The binary interaction parameters can be obtained by regressing the experimental data with the EoS and the mixing rules (see Eq. (2a), (2b)).

$$a = 0.45724 \frac{R^2 T_C^2}{p_C} \alpha(T, \omega) \quad \text{with} \tag{2c}$$

$$\alpha(T, \omega) = \left(1 + 0.37464 + 1.54226\omega - 0.26992\omega^2\right)\left(1 - \sqrt{T / T_C}\right))^2 \quad \text{and} \tag{2d}$$

$$b = 0.0778 \frac{R T_C}{p_C} \tag{2e}$$

In Eq. (2c) – (2e) ω is the acentric factor, and T_C and p_C the critical constants. This procedure requires the accurate knowledge of the various thermophysical data, such as critical parameters, acentric factor, solid molar volume, and sublimation pressure of the solutes [2,3]. The correlation which was used to calculate the solubility of the solute in the supercritical solvent is shown in Eq. (3). This equation is a result of the equifugacity condition between the solid and the fluid phase, under the assumption that the solubility of the solvent is negligible in the solid phase.

$$y_2 \left(p, T\right) = \frac{p_{2,sub} \left(T\right) \cdot \varphi_{2,sub}(p_{2,sub}, T)}{p \cdot \varphi_2 \left(p, T, y_2\right)} \exp\left(\frac{v_2 \left(p - p_{2,sub}\right)}{RT}\right) \tag{3}$$

In Eq. (3) to (5) the subscripts 1 and 2 refer respectively to the pure solvent and to the pure solute. In Eq. (3) $p_{2,\mathrm{sub}}$ is the saturation (sublimation) pressure of component 2 at temperature T, $\varphi_{2,\mathrm{sub}}$ is the fugacity coefficient at the saturation pressure, φ_2 is the fugacity coefficient for the solute in the SCF phase, and v_2 is the molar volume of the pure solid. Thereby, it is assumed that v_2 is independent on the pressure p. In this work φ_2 is calculated using the PR-EoS with mixing rules given in Eq. 2a and 2b, while $\varphi_{2,\mathrm{sub}}$ can be considered as unit. Thus, the calculation of the solubility y_2 therefore requires the knowledge of the solid saturation pressure ($p_{2,\mathrm{sub}}$), solid molar volume (v_2) and a reliable equation of state.
However, estimation methods for pharmaceutical compounds, polymers, biomolecules, and other complex molecules are mostly empirical and often lead to inconsistent and unreliable results [4]. Thus, due to the lack of information on these data, empirical density based models are often used.

2.2 Density based models

One of the most commonly used model, which correlates the solubility y_2 of a solute in a SCF to the fluids density has been proposed by Stahl et al. [5] and by Kumar and Johnston [6]:

$$\ln\left(y_2\right) = a + b \cdot \ln\left(\rho_{\mathrm{Red}}\right) \qquad \text{with} \quad \rho_{\mathrm{Red}} = \frac{\rho_1}{\rho_{1,\mathrm{C}}} \tag{4}$$

In Eq. (4) ρ_1 is the density of CO_2 at the equilibrium temperature T and pressure p, $\rho_{1,\mathrm{C}}$ the critical density of CO_2, and a and b are two empirical constants.

Mendez-Santiago and Teja [7] have shown that the following equation:

$$T \cdot \ln E = A + B \cdot \rho_1 \qquad \text{with: } E = \frac{y_2 \cdot p}{p_{2,\text{sub}}} \tag{5}$$

can be used to calculate the solubility of numerous solids in CO_2. Since the constants A and B are independent of temperature, the solubility data for binary systems at different temperatures should collapse to a single straight line when plotted in terms of $T \cdot \ln E$ vs. the solvents density. The lower limit of this linear behaviour is about half while the upper limit is around the twofold of the critical density of the solvent [7]. The fact that all isotherms collapse to a single line allows determining the self-consistency of experimental data and allows identifying data sets that are not consistent with other data.

3. ESTIMATION OF SOLUTE PROPERTIES

As mentioned above, it is necessary for the calculation of the solubility of a solute in a supercritical fluid using an EoS to have critical properties and acentric factors of all components, and molar volumes and sublimation pressures of the solid components. If some of these data are not available, estimation techniques must be employed. As shown in Fig. 1, there are a few methods, which use group or atomic contributions to estimate critical properties [8]. When neither critical properties nor acentric factors are available in literature, it is desirable to have the normal boiling point (T_b) of the compound since some estimation techniques require only T_b and molecular structure.

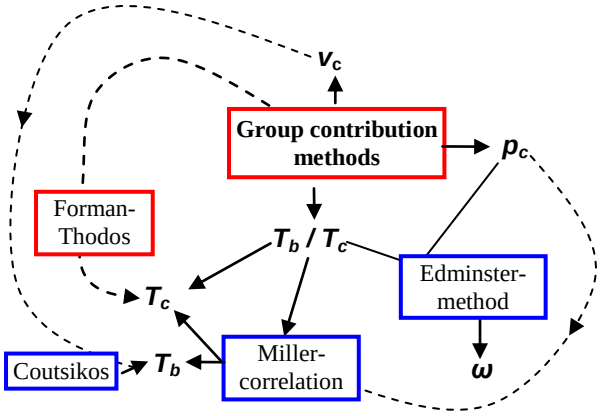

Fig. 1: Schematic representation of the various "ways" to use different estimation techniques [8] for calculating T_C, p_C and ω.

In Table 1 some important physical properties of the substances investigated are summarized.

Tab.1: Physical properties of the substances investigated.

solute	M / g/mol	T_M / K	Δh_i^{fus} / kJ/mol	v_i / m³/mol
RS-Ibuprofen	206.28	348.6	25.5	$1.88 \cdot 10^{-4}$
Salicylic acid	138.12	431.5	27.8	$9.59 \cdot 10^{-5}$
S-Naproxen	230.26	427.7	31.4	$1.78 \cdot 10^{-4}$
Phytosterol	414.72	411.5	18.9	$4.11 \cdot 10^{-4}$

3.1 Sublimation pressure data

Experimental sublimation pressure data were available in literature for RS-Ibuprofen [9], Salicylic acid and S-Naproxen [10]. However, no data has been reported for Phytosterol. Therefore, $p_{i,sub}$ was obtained using the Coutsikos correlation [11] for solids. This group-contribution model is based on the concept of the hypothetical liquid.

$$\ln(p_{i,sub}) = A + B/T + C \cdot \ln T + D \cdot T + E \cdot T^2 + (\Delta S_i / T) \cdot (1 - T_M / T) \qquad (6)$$

The five constants A to E can be estimated via the Abrams–Massaldi–Prausnitz equation, while for the entropy of fusion (ΔS_i) at the melting point (T_M) a simple group-contribution scheme is proposed [11]. In Fig. 2 the comparison between calculated and experimental data for RS-Ibuprofen and S-Naproxen are shown.

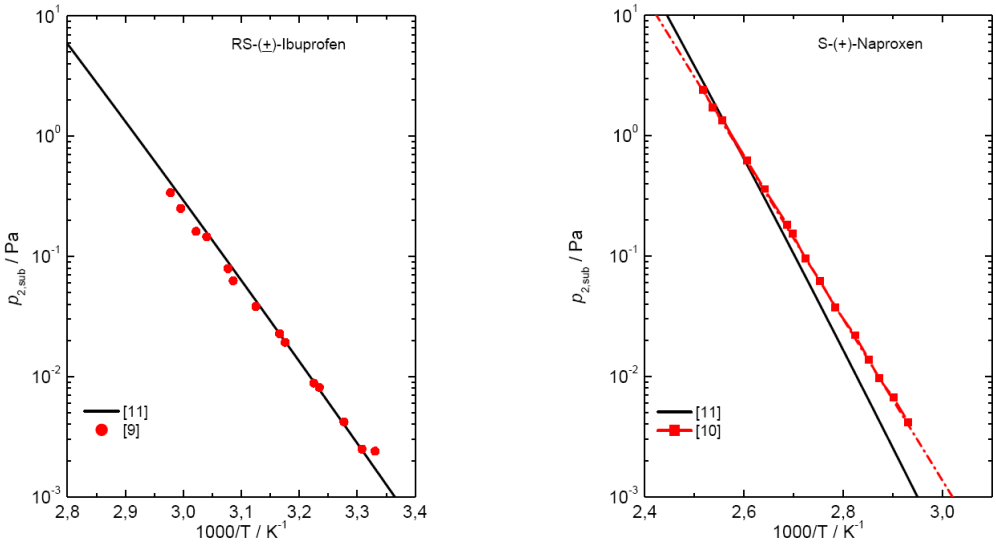

Fig. 2: Comparison between experimental and calculated sublimation pressure data.

In case of RS-Ibuprofen, the Coutsikos correlation represents the experimental data quite well. The relative deviation between experimental and calculated values increases from 2.3% at 313 K to 21% at 343 K. Much larger deviations between experimental and modelled values are found for S-Naproxen. For this substance, the relative deviation decreases from 656% at 313 K to 164% at 343 K. The deviations, obtained for Salicylic acid, are one order of magnitude larger than for S-Naproxen.

4. CORRELATION OF EXPERIMENTAL SOLUBILITY DATA

The influence of the system temperature and the solvents density are shown in Fig. 3 which shows the solubility of Phytosterol and of S-Naproxen as a function of CO_2 density. For both substances the experimental results show trends which are similar to those observed for other solids in the supercritical region. In agreement with Eq. (4) and as it is illustrated in Fig. 3, the logarithmic solubility-density relationship shows the expected linear behaviour for all isotherms. At constant temperature, the solubility of a solute increases almost linear with the solvents density and therewith solvent power. Fig. 3 also shows the pronounced temperature effect on the solubility in the region outside the retrograde region. In this region, the effect of the temperature on the solute sublimation pressure overlays the effect of the solvent density, resulting in an increase of the solute solubility with increasing temperature.

The lines depicted in Fig. 3 are calculated with Eq. (4) and demonstrate that there is a good correlation between calculated values and the experimental data. As can be seen from the ARD listed in Tab. 2, the experimental data are satisfactorily correlated with this empirical

correlation with an overall ARD of 3.6% for Phytosterol and of 3.2% for S-Naproxen. Similar results are obtained for Salicylic acid (6.8%) and RS-Ibuprofen (7.3%).

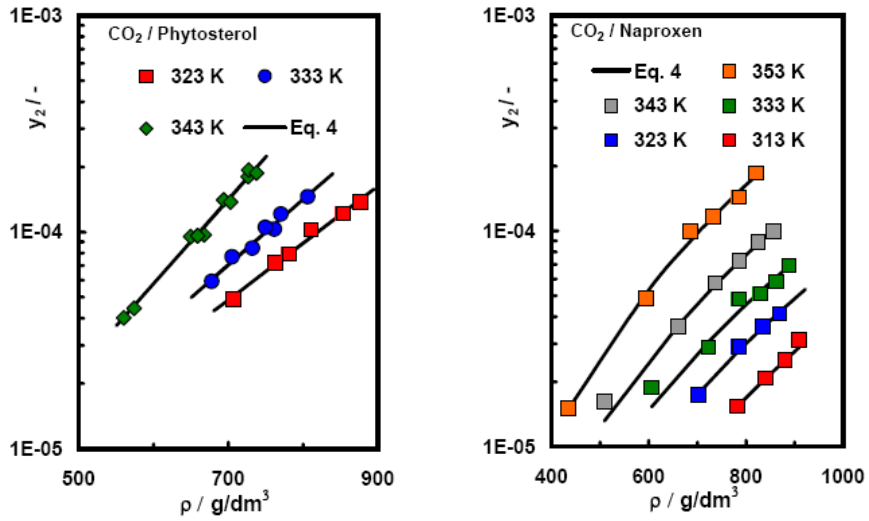

Fig. 3: Solubility versus solvent density for CO_2 / Phytosterol [12] and CO_2 / S-Naproxen [4].

To our knowledge, no other solubility data has been reported for Phytosterol [12]. However, it is shown in Fig. 4 that, according to Eq. 5, all isotherms collapse to a single straight line when plotted in terms of $T \cdot \ln E$ vs. the CO_2 density. This fact confirmed the consistency and reliability of these experimental solubility data.

For S-Naproxen, experimental solubility data for temperatures ranging from (308 to 348) K within the pressure range of (12 - 35) MPa are published in literature [13 – 15]. Although each individual set of data follows mostly a common trend, in some cases the published data exhibit different trends with respect to temperature or pressure [4].

As can be seen from Fig. 4, most of the solubility data published from different authors collapse to a single line. The solid line depicted in Fig. 4 is calculated with the experimental sublimation pressure of Perlovich et al. [10]. In addition, Eq. (5) was fitted to the enhancement factor data calculated with the sublimation pressure which was estimated with the Watson correlation [8]. This curve shows a significant deviation up to -35% which is the result of the noticeably higher values from the estimated sublimation pressure data. Applying the Coutsikos correlation [11] leads to significant higher values for E from around 10 - 12% (see also Fig. 2).

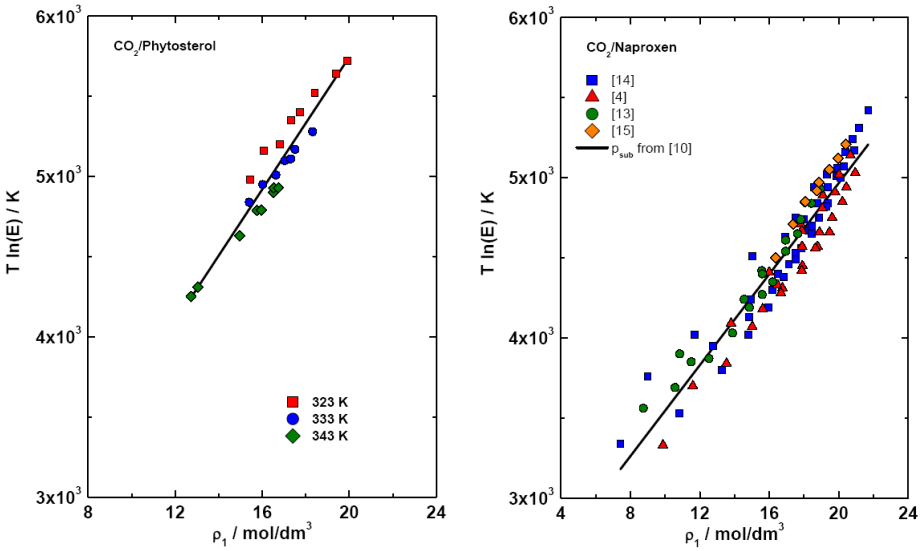

Fig. 4: $T \ln E$ versus solvent density for CO_2 / Phytosterol [12] and CO_2 / S-Naproxen.

As can be seen from the ARD values in Tab. 2, the experimental data for RS-Ibuprofen and for Salicylic acid can be satisfactorily correlated with Eq. 5 and an ARD of 10.5 and 7.7%. These lower deviations are mainly caused by the significant higher solubility of the substances in CO_2.

In addition to these empirical correlation approaches, we have employed two equations of state methods for the correlation of the solubility. While one can only correlate the solubility as function of the density with the empirical methods, one also can correlate the solubility as function of the pressure with an equation of state approach. The first one is based on the PR-EoS for the binary systems as described above. It is summarized in Tab. 2 that this approach leads to significant higher deviations than the density based models. Depending on the estimation method and the binary systems, the ARD values range from 10 to 77% which is one order of magnitude higher than for the Kumar & Johnston approach.

Tab. 2: Calculation results for the solute solubility in sc-CO_2 using various models. It should be noted that the first two are deviations in the density, the second two in pressure.

Solute	Kumar & Johnston ARD / %	Mendez-Santiago & Teja ARD / %	PR-EoS ARD / %	LK-EoS ARD / %
RS-Ibuprofen	7.3	10.5	16 – 33	
Salicylic acid	6.8	7.7	10 – 44	5
S-Naproxen	3.2	26	14 – 33	10
Phytosterol	3.6	25	37 – 77	7

$$\mathrm{ARD} = \frac{1}{N}\sum_{1}^{N}\frac{\left|y_{2,ber} - y_{2,\exp}\right|}{y_{2,\exp}} \cdot 100$$

The second method is based on an accurate non-cubic EoS (LK-EoS) for the supercritical solvent CO_2 [16]. Within this approach the properties of the solute enter by the sublimation pressure and the molar volume while the solvent enters by its fugacity as shown in Eq. (3).
The critical parameters of the pure solute do not need to be estimated by a group contribution method because we fit the attraction and co-volume equation of state parameter for the solute during the solubility correlation. For the same reason also no k_{ij} parameter is required. The total number of parameters fitted in this work is four namely two equation of state parameters of the pure solute and two parameters for the sublimation pressure. Since the sublimation pressure is required in the correlation of the solubility one can treat it as an adjustable parameter when fitting the model to solubility data. If solubility data are available for different temperatures one can build in a Clausius-Clapeyron-like temperature dependence of the sublimation pressure on the temperature:

$$p_{2,\mathrm{sub}} = p_0 \exp\left(-\frac{A_{\mathrm{sat}}}{T} + B_{\mathrm{sat}}\right) \qquad (7)$$

Here A_{sat} and B_{sat} are adjustable parameters and $p_0 = 1$ MPa is the unit pressure. The suitability of this approach has been demonstrated for various low volatile substances ranging from dyes in CO_2 and N_2O [17-19].The sublimation pressure obtained in this way from the solubility agrees well with experimental data where available and behaves systematically [17].

For Naproxen solubility three different correlation procedures are compared: (A) we correlate Eq. (7) to the available experimental data of the sublimation pressure [10], (B) we fit Eq. (7) to the literature data which are estimated with a group contribution of Coutsikos [11] and (C) we treat the sublimation pressure as adjustable property fitting the parameters of Eq. (7) during the solubility correlation. Phytosterol and salicylic acid are correlated by implementing Eq. (8) and fitting its parameters to the solubility isotherms. The value of the molar volume solute is fixed in all correlations to the value given in Tab. 1 and the compressibility of the solute is set to zero. The remaining four parameters are fitted to the data are the attraction parameter a and the co-volume parameter b of the solute. The resulting values are for fit (A) a = 883.735 K, b = 81.2094 $cm^3 \cdot mol^{-1}$, A_{sat} = 15442.4 K, B_{sat} = 25.9397, for fit (B) a = 892.276 K, b = 86.9116 $cm^3 \cdot mol^{-1}$, A_{sat}= 19194.7 K, B_{sat} = 35.8954, and for fit (C) a = 805.23 K, b = 53.4022 $cm^3 \cdot mol^{-1}$, A_{sat} = 11048.6 K, B_{sat} = 17.2568. The parameters obtained for Phytosterol are a = 660.357 K, b = 106.492 $cm^3 \cdot mol^{-1}$, A_{sat} = 11847.3 K, B_{sat} = 15.9749, and for Salicylic acid a= 987.828 K, b = 34.029 $cm^3 \cdot mol^{-1}$, A_{sat} = 9740.14 K, B_{sat} = 17.7586.

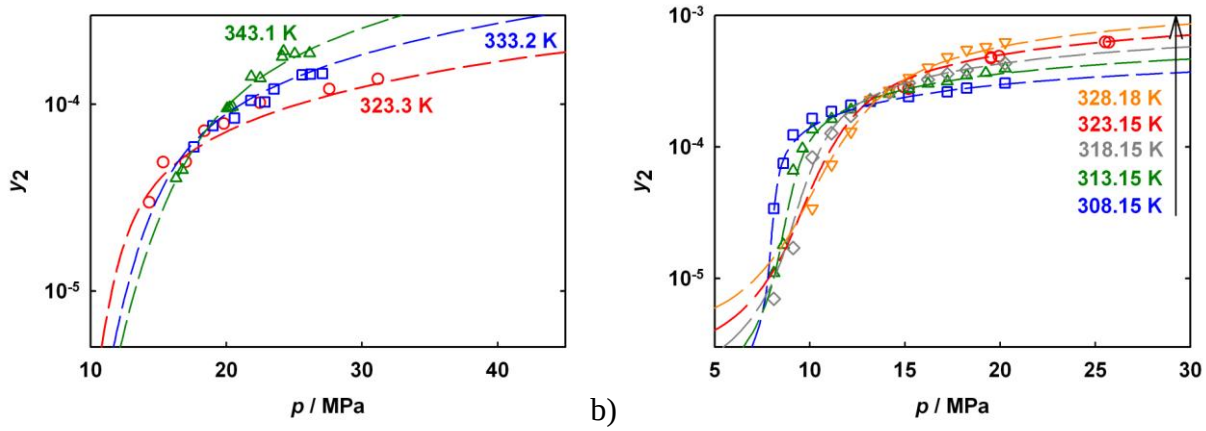

Fig. 5: Solubility correlation for a) Phytosterol and b) Salicylic acid [20-22].

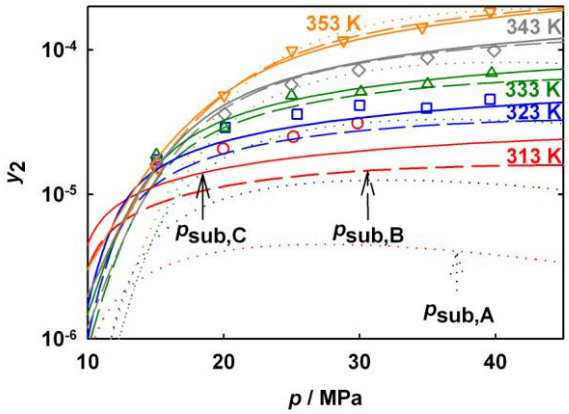

Fig. 6: Solubility correlation for Naproxen by three different correlation procedures as described in the text.

The correlation results are shown in Fig. 5 and 6. For Phytosterol as well as for Salicylic acid the correlation is very good over the complete temperature and pressure range. The correlation of the Naproxen solubility data turns out to be more difficult. It appears that the temperature dependence of the saturation pressure it not suitable to correlate all isotherms with equal accuracy. Even if the parameters of the saturation pressure curve (Eq. (7)) are treated as

adjustable parameters ($p_{sub,C}$) we get some deviation for the isotherm at 313 K. Using the saturation pressure estimated by the method of Coutsikos [11] ($p_{sub,A}$) we get even worse results. However, Naproxen seems to be an exception since for all other substances correlated with this method the agreement is well as in case of Phytosterol and Salicylic acid.

5. ACKNOWLEDGMENTS

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