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New prediction methods for solubility parameters based on molecular sigma profiles using pharmaceutical materials

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ABSTRACT

Solubility parameters have been applied extensively in the chemical and pharmaceutical sciences. Particularly attractive is calculation of solubility parameters based on chemical structure and recently, new *in silico* methods have been proposed. Thus, screening charge densities of molecular surfaces (i.e. so-called σ-profiles) are used by the conductor-like screening model for real solvents (COSMO-RS) and can be employed in a quantitative structure property relationship (QSPR) to predict solubility parameters. In the current study, it was aimed to compare both *in silico* methods with an experimental dataset of pharmaceutical compounds, which was complemented with own measurements by inverse gas chromatography. An initial evaluation of the total solubility parameters of reference solvents resulted in excellent predictions (observed versus predicted values) with R^2 of 0.855 (COSMO-RS) and 0.945 (QSPR). The subsequent main study of pharmaceutical compounds exhibited R^2 values of 0.701 (COSMO-RS) and 0.717 (QSPR). The comparatively lower prediction was to some extent due to the solid state of pharmaceuticals with known conceptual limitations of the solubility parameter and possible experimental bias. Total solubility parameters were also estimated by classical group contribution methods, which had comparatively lower prediction power. Therefore, the new *in silico* methods are highly promising for pharmaceutical applications.

1. Introduction

The choice of appropriate excipients is critical in pharmaceutical development and it should be based on considerable experimental work from early pharmaceutical profiling to preclinical and clinical formulation development (Kuentz et al., 2016). Any guidance to focus the selection process would considerably reduce resource investments and therefore, computational pharmaceutics is currently a thriving research field. One of the most widespread thermodynamic approaches with a long pharmaceutical history is the concept of the solubility parameter. This parameter is related to the cohesive energy density (CED), which in turn can be defined as energy of vaporization per unit volume (V):

$$\delta = (CED)^{1/2} = \sqrt{\frac{E_{coh}}{V}} = \sqrt{\frac{\Delta H_v - RT}{V}} \quad (1)$$

where E_{coh} is the cohesive energy in a condensed phase, ΔH_v is the enthalpy of vaporization, R is the gas constant, and T denotes the given temperature. This definition is according to Hildebrand and later Hansen proposed to split the cohesive energy density into different parts as follows (Hansen et al., 2007).

$$CED = \delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (2)$$

Thus, a total solubility parameter δ_t^2 can be expressed in terms of partial dispersive contribution, δ_d^2 a polar part, δ_p^2 and a part that accounts for hydrogen bonding, δ_h^2. A classical application of the Hansen solubility parameter (HSP) is in liquid solutions. The simplified view is here that two liquids are expected to mix spontaneously when the values of the HSP components for one liquid are close to another. Solid dispersions can be treated similarly in that miscibility of drug and excipient is assumed when their solubility parameters are reasonably close or equal (Greenhalg et al., 1999; Forster et al., 2001). Many other pharmaceutical applications exist and reviews were written by Hancock et al. (1997) and most recently by Jankovic et al. (2018).

Solubility parameters can be obtained by different methods and it is obvious that the classical calorimetric determination of ΔH_v is limited to volatile materials. Therefore, solid materials (e.g. polymers or drugs) require indirect experimental methods such as solubility experiments with a series of solvents that cover a broad range of partial solubility parameters (Hansen et al., 2007). Another method is inverse gas chromatography (iGC) (Adamska and Voelkel, 2005; Adamska et al.,

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2008; Adamska et al., 2016). Both of these indirect methods have in common that rather many experiments are needed to determine the total solubility parameter and even more solvents or probe gases must be employed to get suitable estimates for all partial solubility parameters. Therefore, *in silico* methods of solubility parameter estimation are more attractive for early pharmaceutical development since compound availability is generally limited and timelines are mostly ambitious.

Early calculation approaches to solubility parameters (Hansen and Skaarup, 1967; Hansen and Beerbower, 1971; Hansen et al., 2007) require some experimental input. A calculation from chemical structure alone was enabled by the group contribution methods according to Fedors (1974), Van Krevelen (1976) and Hoy (1970). More recently, a novel group contribution method for solubility parameter estimation has been presented for the specific application of hot melt extrusion (Just et al., 2013). However, this is rather an initial proposal for future updates to assign the molecular group contribution based on more data because there are currently only limited experimental values available. Other recent approaches are a determination of solubility parameters from molecular dynamics simulations (Gupta et al., 2011) or from quantitative structure property relationships (QSPR) (Gharagheizi, 2008; Goodarzi et al., 2010; Járvás et al., 2011; Koç and Koç, 2015). The latter QSPR relationships are based on selecting suitable molecular predictors regarding solubility parameter but this section is often rather arbitrary. Intriguing is the idea followed by Járvás et al. (2011) to select predictors form molecular surface charges that were calculated by quantum chemistry. The so-called σ-profiles are screening charge densities of molecular surfaces and form the basis of the conductor-like screening model for real solvents (COSMO-RS) (Klamt, 1995). Molecular interactions are treated in this theory based on surface segments with given screening charge σ. It is further assumed that surfaces are in close contact and only pair-wise surface interactions are considered (e.g. Coulomb interaction, hydrogen bond interaction, Van der Waals interaction, and a combinatorial term), while the three dimensional geometry is here neglected (Klamt, 2011). All models exhibit limitations and in case of COSMO-RS, non-equilibrium dynamic properties and systems near or beyond the critical point cannot be calculated directly. Moreover, properties of highly polar ions or tertiary amines may be calculated with rather low accuracy. It is possible to combine COSMO-RS with other approaches like QSPR or equation of state methodology (Panayiotou, 2003) to broaden applications and to improve calculation accuracy. COSMO-RS theory is currently maybe the most promising approach to link quantum chemistry with thermodynamic fluid phase calculations.

Since the quantum calculations are very computation-intensive, a fast approximation of σ-profiles was an important advancement for practical usage (Hornig and Klamt, 2005; Loschen and Klamt, 2012). This fast method is part of the so-called COSMOquick software and is based on the idea that new and big molecules can be composed of precalculated results from a large database. Once the σ-profiles are determined, the aforementioned COSMO-RS calculations or a QSPR approach provide two alternative ways to estimate solubility parameters as illustrated in Fig. 1 for the model compound paracetamol.

On the left hand side of Fig. 1 is the time-consuming quantum chemical calculation (QC) depicted, while the right part of the figure shows an approximation of the σ-profiles. A large database is here either directly used to get σ-profiles from existing structures or new compounds are estimated by molecular fragmentation. The reliability of the σ-profile estimation is quite accurate for most solvents as well as drugs (Loschen and Klamt, 2012).

The σ-profiles may not only be used by the COSMO-RS theory for thermodynamic calculations, but moments of this distribution can also just hold for molecular descriptors. Járvás et al. (2011) employed sigma moments as relevant independent parameters in their QSPR method to predict solubility parameters. It is alternatively possible to use the COSMO-RS theory to conduct a kind of virtual solubility screening (i.e. activity coefficient screening) to obtain the solubility parameter. The use of σ-moments has also been reported to expand the theory of Hansen solubility parameter with splitting the hydrogen bonding part into an acidic and basic molecular contribution (Stefanis and Panayiotou, 2012; Panayiotou, 2012). Thus, molecular surface screening charges have sparked new ideas of how to define and use solubility parameters.

The present work is motivated by applications in pharmaceutical profiling and early formulation development where resource-saving accurate *in silico* prediction of solubility parameters is of great interest. First a broad range of reference solvents is studied to assess the general suitability of the COSMO-RS and QSPR approach to predict Hansen solubility parameters. Subsequently, the accuracy of both approaches is evaluated for a set of 31 drugs (or drug-like compounds) and compared with literature data or results obtained from own iGC measurements. Finally, the suitability of the new approaches is discussed with respect to practical usage in pharmaceutics.

2. Materials and methods

2.1. Materials

Cyclosporin A, loratadine, simvastatin and zafirlukast were purchased from Carbosynth Ltd. (Compton – Berkshire, UK). Polar and non-polar solvents used in this study for the iGC measurements (decane, nonane, octane, acetone, acetonitrile, ethyl acetate, dichloromethane, methanol, ethanol and 1-butanol) and silanized glass wool were obtained from Sigma-Aldrich (Buchs, Switzerland). Heptane was bought from J.T. Baker (Deventer, the Netherlands).

For our experiments of total solubility parameter determination by iGC, the different drugs were first converted to the amorphous state except for zafirlukast that was already mostly amorphous as received, which was confirmed by X-ray powder diffraction (XRPD) using the D2 Phaser benchtop X-ray diffractometer from Bruker AXS Corp. (Karlsruhe, Germany). Thus, 2 g of cyclosporin A, loratadine, and simvastatin were molten in a stainless steel cup using a heating chamber (FED series) from Binder Ltd. (Tuttlingen, Germany). Temperature was selected individually for each drug 15 °C degrees below the melting point and was then carefully increased stepwise until liquefaction was observed. In the liquid state, the compounds were immediately quenched in liquid nitrogen so that a transparent glassy solid was obtained. The powder form was then obtained by manual milling using a mortar. All samples were stored at room temperature in a desiccator at low relative humidity. Successful amorphization was confirmed by XRPD measurements.

2.2. Methods

2.2.1. Inverse gas chromatography

Inverse gas chromatography (iGC) was used to analyze a solid that was packed into a chromatographic column as stationary phase. This stationary phase was flushed with an inert carrier gas that was helium in the present study. The principle of iGC is based on injecting various organic probe solvents with known characteristics into the flow of the carrier gas. The extent of interactions between the solid phase of interest and the probe gas is obtained by the net retention volume V_N:

$$V_N = \frac{j}{m} F (t_R - t_0) \frac{T}{273.15} \tag{3}$$

where T is the column temperature, F is the carrier gas flow rate at 1 atm and 273.15 K, m is the sample mass, t_R is the retention time of the absorbed probe gas and t_0 is the mobile phase hold up time and finally, j represents the James-Martin correction (that adjusts retention time for the pressure drop effect in the column bed). The calculated retention volume V_N was then used to estimate the weight fraction activity coefficient, Ω at infinite dilution: