Calculation of drug-polymer mixing enthalpy as a new screening method of precipitation inhibitors for supersaturating pharmaceutical formulations

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Graphical Abstract
Abstract

Supersaturating formulations are widely used to improve the oral bioavailability of poorly soluble drugs. However, supersaturated solutions are thermodynamically unstable and such formulations often must include a precipitation inhibitor (PI) to sustain the increased concentrations to ensure that sufficient absorption will take place from the gastrointestinal tract. Recent advances in understanding the importance of drug-polymer interaction for successful precipitation inhibition have been encouraging. However, there still exists a gap in how this newfound understanding can be applied to improve the efficiency of PI screening and selection, which is still largely carried out with trial and error-based approaches. The aim of this study was to demonstrate how drug-polymer mixing enthalpy, calculated with the Conductor like Screening Model for Real Solvents (COSMO-RS), can be used as a parameter to select the most efficient precipitation inhibitors, and thus realise the most successful supersaturating formulations. This approach was tested for three different Biopharmaceutical Classification System (BCS) II compounds: dipyridamole, fenofibrate and glibenclamide, formulated with the supersaturating formulation, mesoporous silica. For all three compounds, precipitation was evident in mesoporous silica formulations without a precipitation inhibitor. Of the nine precipitation inhibitors studied, there was a strong positive correlation between the drug-polymer mixing enthalpy and the overall formulation performance, as measured by the area under the concentration-time curve in in vitro dissolution experiments. The data suggest that a rank-order based approach using calculated drug-polymer mixing enthalpy can be reliably used to select precipitation inhibitors for a more focused screening. Such an approach improves efficiency of precipitation inhibitor selection, whilst also improving the likelihood that the most optimal formulation will be realised.
1. Introduction

A large proportion of active pharmaceutical ingredients (APIs) currently in development are classified as poorly soluble, with numbers quoted for the total percentage varying from 40% to 90% (Loftsson, 2010). Given that drugs must be sufficiently solubilized in the gastrointestinal (GI) tract to be absorbed into systemic circulation, poorly soluble drugs represent a challenge for successful oral delivery (Brouwers, 2009). In response, a wide range of formulation techniques have been developed to enhance the apparent solubility of the API in the intestinal lumen (Zheng, 2012). These options can improve absorption due to the generation of a supersaturated solution of the API in the GI tract, i.e. above the equilibrium solubility, which increases the driving force for absorption through the GI mucosa into the systemic circulation (Brouwers, 2009; Taylor and Zhang, 2016). Supersaturation is an energetically unfavorable state, and is at best metastable (Taylor and Zhang, 2016). Due to this, there is an innate tendency for the supersaturated solution to return to a lower energy state, through precipitation. Therefore, to derive maximum benefit from supersaturation of the API, such formulations often include a precipitation inhibitor to sustain the period over which the API remains in solution (Price, 2018). This formulation approach is often referred to as the “spring and parachute” model (Guzman, 2007). In this model, the ‘parachute’ is the precipitation inhibitor that inhibits or slows the precipitation of the API from the supersaturated ‘spring’ generated by the formulation.

Currently, the mechanistic details of precipitation inhibition are not fully understood, and the specific molecular properties that yield efficient precipitation inhibitors have not yet been clarified. Given this uncertainty, a variety of hypotheses for the molecular mechanisms of precipitation inhibition have been proposed (Warren, 2010; Price, 2018). Additionally, it appears that precipitation inhibition is also an API-specific process. Therefore, there may be no single mechanism that describes all cases of precipitation inhibition. For example, some studies show polymer hydrophobicity to be a critical property in precipitation inhibition (Prasad, 2016), some suggest that hydrogen bond interactions play a pivotal role (Warren, 2010), while yet others propose that polymer surface coverage is an important factor (Schram, 2015). In all likelihood, multiple precipitation inhibition mechanisms may contribute to the observed effect, with the balance depending on the specific properties of both the API and the precipitation inhibitor.

The current lack of clear mechanistic understanding makes selection of precipitation inhibitors rather inefficient and time consuming, due to overreliance on ‘trial and error’ based experimental approaches. Typically PI screening is carried out by generating supersaturation with a solvent-shift, in which API is dissolved in high concentrations in a favourable solvent (e.g. DMSO), which is then added to an aqueous phase to generate supersaturation. Analytical techniques such as UV spectroscopy, HPLC or nephelometry are then applied to track changes in
concentration of API in solution or precipitation over time. These concentration time profiles are then used to provide a measure of PI effectiveness (Price et al., 2018). One of the recent developments in this area is the µDISS™ profiler, which applies in situ UV probes in combination with liquid handling to study supersaturation and precipitation in real time. Using this approach, Palmelund and colleagues assessed the precipitation of 6 different BCS II drugs in combination with two polymers, PVP and HPMC (Palmelund et al., 2016). But despite recent advances in this area, the experimental selection of precipitation inhibitors remains both lengthy and costly. In addition to the time and cost resources involved, this approach is unlikely to lead to certain identification of the most effective precipitation inhibitor, but rather to “one that works”. To date, most supersaturating formulations incorporate one of a standard set of polymers, such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS), polyvinylpyrrolidone (PVP) or hydroxypropyl methyl cellulose (HPMC) (Warren, et al. 2010; Price, 2018). To overcome these drawbacks, there have recently been various attempts to establish a more mechanistic rational for precipitation inhibitor selection, as reviewed by Price et al. (Price, 2018). One of the more recent advances is the use of experimental tools that can design new precipitation inhibitors based on a mechanistic understanding of the specific interaction between the precipitation inhibitor and the API on a structural, molecular basis (Mosquera-Giraldo, 2016; Ting, 2016). Unfortunately, such de novo processes often require complex syntheses that yield novel excipients, which are impractical due to the need for toxicological studies to qualify them for use in pharmaceuticals. Therefore, more work is required to establish an efficient and rational precipitation inhibitor selection process using excipients that are already approved for pharmaceutical use. To bridge the gap between mechanistic understanding of precipitation inhibition and the realities of selecting precipitation inhibitors during pharmaceutical development, a more practical and robust approach is required. Such an approach, that can incorporate understanding of the importance drug-polymer interactions with a quick and efficient screening process, would be very useful. For this purpose, the Conductor like Screening Model for Real Solvent (COSMO-RS), which was developed by Klamt (Klamt, 1995, 2003), is a highly interesting prospect. COSMO-RS combines quantum mechanical molecular calculations with fluid-phase thermodynamics. The first step is to calculate screening charge distributions of a molecule of interest in a continuum, based on density functional theory (DFT) (Kohn and Sham, 1965). The so-called ‘sigma profiles’ that are obtained from these calculations are then used in COSMO-RS, where statistical thermodynamics is applied to estimate the chemical potential and further characteristics of the system, such as solubility and partition coefficients. COSMO-RS has previously been used as a screening tool to calculate the solubility of early-development APIs in a database of excipients for pre-clinical formulations (Pozarska, 2013). However, further pharmaceutical applications have been limited, possibly due to the fact that the rate determining step, the quantum chemical calculations, are computationally very
intensive. From a screening perspective, this is a significant drawback. A practical alternative to facilitate application of COSMO-RS theory for screening purposes is the software package COSMOquick. COSMOquick removes the need for the time-consuming quantum chemical calculations of molecular surface charges, whilst still carrying out the remaining COSMO-RS calculations to derive chemical potential. This is achieved by additively combining fragments of previously calculated sigma profiles stored in a database to compute a new sigma profile for molecules of interest (Hornig and Klamt, 2005). The COSMOquick approach has been recently applied pharmaceutically by the Kuentz group for the calculation of solubility parameters for a wide-range of molecules (Niederquell, et al. 2018). Another application of the COSMOquick software is in co-crystal screening approaches, which uses the calculated excess enthalpy of interaction between and API and a co-former to assess the likelihood of co-crystal formation (Loschen, 2016).

Figure 1. Chemical potential, and in turn a wide-range of thermodynamic properties, can be derived from sigma profiles using COSMO-RS theory. Sigma profiles can be obtained by two ways, either through de novo quantum chemical calculations or through an additive combination of previously calculated molecular fragments stored in
a large database. The former approach is applied in the full COSMO calculation, whilst the latter is applied in the software package COSMOquick (bottom).

To consider precipitation inhibition fundamentally, it is assumed that an interaction between API and polymer must be present. This interaction could take many forms (e.g. London, dipolar, hydrogen bonding and Coulombic forces) or combinations thereof. It can be hypothesized that the more efficient the interaction between the drug and polymer, the more effective the inhibition process (Price, 2018). However, this may be difficult to calculate, since the API and precipitation inhibitor must interact in a complex aqueous environment. We propose a simplified approach, in which the mixing (or excess) enthalpies of drug and excipient are calculated using COSMOquick. This estimated enthalpy is then used to rank potential precipitation inhibitors based on the strength of their molecular interaction with the API. It is hypothesized that this novel in silico protocol can be used to screen potential precipitation inhibitors allowing for a more focused selection to be carried out, thus significantly reducing the experimental burden of screening inhibitors by trial and error and ensuring the selection of an optimal inhibitor.

2. Materials and Methods

2.1. Materials

Crystalline dipyridamole (DPD), crystalline glibenclamide (GB), crystalline fenofibrate (FF) (thermodynamic polymorphs),poly(ethylene glycol) (PEG), poly(methyl methacrylate) (PMMA), Pluronic® (PLR), HPMC, PVP, chitosan (CH), reagent grade acetone, HPLC grade acetonitrile and HPLC grade methanol were all purchased from MilliporeSigma (St Louis, MO, USA). AQOAT (HPMCAS-MF) was purchased from ShinEtsu (Japan). Parteck® SLC was a gift sample from Merck KGaA (Germany). Eudragit (Eu) RL and EPO were obtained from Evonik (Germany).

Powder to make biorelevant dissolution medium, Fasted Simulated Intestinal Fluid (FaSSIF), was purchased from Biorelevant.com (UK).
### Table 1: Selected APIs and their relevant properties

<table>
<thead>
<tr>
<th>API</th>
<th>MWt [g/mol]</th>
<th>cLog P</th>
<th>cPka</th>
<th>Number of H-bond donors</th>
<th>Number of H-bond acceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole</td>
<td>505</td>
<td>1.5</td>
<td>6.6 (basic)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>361</td>
<td>5.3</td>
<td>-</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>494</td>
<td>4.7</td>
<td>4.3 (acidic)</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

*Calculated with ChemAxon*
2.2 Experimental

2.2.1 Thermodynamic Solubility

API (2-3mg) was accurately weighed into a Uniprep® syringeless filter (5mL; 0.45µm). 2 mL of FaSSIF (Galia, et al. 1998), composed of simulated intestinal fluid powder (FaSSGF, FaSSIF & FeSSIF Powder) dissolved in a pH 6.5 phosphate buffer, was added and the samples agitated at 450 rpm for 24 hours at 37 °C. The pH was checked at 7 hours and adjusted with 0.1 N NaOH or 0.1 N HCl, if deviation greater than +/- 0.05 pH units were observed. The final pH was also recorded after 24 hours.

Samples were filtered after 24 hours and the filtrates were diluted with acetonitrile and water (1:4) to avoid precipitation from the saturated solution. Samples were analyzed with UPLC (Thermo Dionex Ultimate 3000, Thermo Fisher, MA, USA) to determine the API concentration. API concentrations were determined by comparing the peak area to a standard calibration curve of nine standard concentrations (Equation 1). Three quality control samples of known concentrations were also prepared and used to check the robustness of the calibration curve. The analysis was carried out in duplicate.

$$C[\mu\text{g mL}^{-1}] = \frac{\alpha(A) F(A)}{m}$$  (1)

- \(C\) = concentration of sample
- \(\alpha(A)\) = peak area for analyte/mL
- \(m\) = gradient of the calibration curve
- \(F(A)\) = dilution factor for analyte

2.2.2 Partec SLC® Loading Procedure

All API-loaded silica samples were prepared using the solvent impregnation rotary evaporator method (Laine, et al. 2016) as follows: A solution (10 mg/mL) of API in acetone was added to Partec SLC (1:2 w/w API/Partec SLC®) under magnetic stirring for 15 minutes. The suspension was then transferred to a rotary evaporator, and solvent was removed under reduced pressure at 40° C. After complete removal of solvent, the powder was left to dry in the rotary evaporator under reduced pressure for 2 hours.
2.2.3 Loading Content Determination
To determine the % (w/w) of API in the mesoporous silica, the loaded samples were dispersed in acetone. Samples were taken after 1 hour, centrifuged, and filtered before being quantified with UPLC. The percentage API content was calculated relative to the mass of loaded samples dispersed within the acetone. The study was performed in triplicate.

2.2.4 Combination of API Loaded Silica with Precipitation Inhibitor
API loaded silica was combined with precipitation inhibitors as a physical mixture using a mortar and pestle in the mass ratio of 1:1. This results in an API:silica:PI ratio of 1: 2: 3.

2.2.5 FaSSIF Mini-dissolution Experiment
Around 5 mg of API (or the equivalent of API-loaded silica) was weighed accurately into a glass vial. To this, 5 mL of FaSSIF was added. The vials were agitated at 37 °C for 2 hours. Samples were taken at 2, 15, 60 and 120 minutes, filtered, diluted if appropriate, and analyzed with UPLC (Thermo Dionex Ultimate 3000, Thermo Fisher, MA, USA). Residues were collected via centrifugation and analyzed for crystallinity with powder X-ray diffraction (PXRD). This was carried out on API, API + polymer samples, API loaded silica and API loaded silica + polymers. The mini-dissolution trials were conducted in duplicate for all samples.

2.2.6 Powder X-Ray Diffraction (PXRD)
Samples were prepared between X-ray amorphous films and measured in transmission mode using Cu-Kα1-radiation and a Stoe StadiP 611 KL diffractometer equipped with Dectris Mythen1K PSD. The measurements were evaluated with the software WinXpow 3.03 by Stoe, Crystallographica Search/Match Version 3.1.0.2 and the ICDD PDF-4+ 2014 Database and Igor Pro Version 6.34 by Wavemetrics Inc. Finger/Cox/Jephcoat. Angular range: 1-65°; PSD-step width: 2° 2θ; angular resolution: 0.015 °2θ; measurement time: 15 s/step, 0.25 h overall.
2.2.7 COSMO-RS Calculations

COSMOquick (COSMOlogic, Germany, Version 1.6) was used to calculate excess enthalpy of interaction between API and polymer. APIs and PIs were entered in smiles notation. Polymer structures were approximated as trimers, since the quantum chemical calculations cannot capture the full complexity of large molecules like polymers. Furthermore, this was not deemed critical to the study as the hypothesis was related to local molecular interactions, which are assumed to be sufficiently captured by trimer forms of the polymer. Ratio of API:PI was set at 1:3 to align with the ratios used in the formulations, and the temperature was set at 37 °C.

COSMOquick calculates sigma profiles of the API and precipitation inhibitor molecules based on an additive-combination approach against a database of previously calculated quantum chemical sigma profiles (Loschen, 2006). Once sigma profiles are generated, several equations are performed to derive the energy required to combine the sigma profile of the API and PI. First, a sigma surface segment of the PI must be removed from the surface in order to make room for a new API segment, this requires energy associated with removing pre-existing contacts between precipitation inhibitor segments, -µs(σ'). Second, a new API segment must be added to the precipitation inhibitor sigma surface, this involves forming new interactions between API and PI, with related energy costs and gains associated with the two segments interacting, E(σ, σ'). This value is called the COSMO-RS interaction energy and, importantly, is calculated such that all binding modes (electrostatic, hydrogen bonding, van der Waals and combinatorial) are considered in the equation. (See appendix 3, Equations 1-3). Once a value for the sigma potential is reached, thermodynamic calculations provide the chemical potential of mixing the API and PI (See appendix 3, Equation 4). From the chemical potential, a wide range of further thermodynamic properties can be calculated. In the current approach enthalpy of interaction, ΔHmix, also referred to as the enthalpy change of mixing, was calculated as a rank order parameter to assess the propensity of the drug to interact with excipient. As addressed in the introduction, this approach represents a substantial simplification of the more complex solid-liquid equilibrium in aqueous medium. A similar approach has been previously applied to screen co-formers in co-crystal selection and details can be inferred from the literature (Abramov, 2012; Klamt, 1993).

In this study, the excess enthalpy of interaction between API and precipitation inhibitor is referred to as the “COSMO-Rank”. According to the working hypothesis, the more negative the calculated excess enthalpy of interaction, the higher the COSMO-Rank and thus the better the inhibition of precipitation of the API. For a full description of the calculations carried out within the software package, readers are referred to Klamt, 1993, 2002 and 2005, and Loschen, 2006.
2.2.8 Spearman’s Rank Correlation Coefficient

Spearman’s rank correlation coefficient is a non-parametric method that allows statistical rank correlation to be carried out between two sets of rankings. In this instance, Spearman’s rank correlation coefficient analysis was applied to the COSMO-rank and the rank order of the formulation performance. For the latter, AUC$_{0-120}$ of the dissolution profiles was selected as the best overall descriptor of formulation performance and was calculated using Equation 2.

\[ AUC_{0-120} = \sum \left( \frac{C_n + C_{n+1}}{2} \right) \times \left( t_{n+1} - t_n \right) \]  (2)

\( C \) = concentration (µg/mL)

\( T \) = time (minutes)

\( n \) = sampling point at time, \( t \)

Spearman’s rank correlation coefficient was calculated by Rstudio (R version 2.15.12) using the code

```r
corr <- cor.test(x=FILENAME$VARIABLE1, y=FILENAME$VARIABLE2, method = 'spearman')
```

2.2.9 UPLC Method

UPLC analysis was performed using a Thermo Dionex Ultimate 3000 (Thermo Fisher, MA, USA) equipped with a diode array detector (Thermo Fisher, MA, USA). Chromatographic separation was achieved on an Acquity UPLC BEH column C8 (2.1 x 50 mm, 1.7 µm, Waters, MA, USA). The mobile phases A and B consisted of water:formic acid 99:1 (v:v) and acetonitrile:formic acid 99:1 (v:v), respectively. Gradient and flow rate is shown in Table 2.

System management, data acquisition and processing were performed with the Chromeleon™ software package, version 7.2 (Thermo Fisher, MA, USA)

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Flow Rate (mL/min)</th>
<th>% (v:v) Mobile Phase A</th>
<th>% (v:v) Mobile Phase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.83</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2. UPLC gradient and flow rates
3. Results

3.1. Dissolution Profile of Crystalline API

The thermodynamic solubilities of dipyridamole, glibenclamide and fenofibrate are shown in Table 3. All three compounds are classified as “poorly soluble” in FaSSIF, pH 6.5 (Amidon, 1995).

Table 3. Thermodynamic solubilities of dipyridamole, glibenclamide and fenofibrate in FaSSIF, pH 6.5 at 37°C

<table>
<thead>
<tr>
<th>Compound</th>
<th>FaSSIF Thermodynamic Solubility (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole</td>
<td>19.6 ± 0.7</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>8.1 ± 0.1</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>14.0 ± 0.3</td>
</tr>
</tbody>
</table>

For all three compounds, the thermodynamic solubility was approached over the duration of the FaSSIF dissolution test (Figure 2). The rate of approach differed among the APIs, which may be related to differences in particle size and morphology. The average concentration of glibenclamide slightly exceeded the measured solubility after 2 hours of dissolution, but this was not statistically significant. Furthermore, some variation in glibenclamide FaSSIF thermodynamic solubility has been recorded in the literature, with values ranging from 8-10 µg/mL. This is in accordance with the observed dissolution behaviour (Fagerberg, 2010; Fagerberg 2012; Wei, 2006).
**Figure 2.** FaSSIF dissolution profiles (2 h) of dihydramide (a), glibenclamide (b) and fenofibrate (c). The thermodynamic solubility of the respective API is represented by the dashed line in each figure.

### 3.2. Loading onto Mesoporous Silica

Successful loading of APIs onto mesoporous silica was confirmed with PXRD by showing a successful shift from the crystalline (pure API) to the amorphous solid-state form after loading onto the mesoporous silica. The absence of Bragg diffraction patterns is indicative of an amorphous material (**Figure 3**).

Loading content was similar (~30% w/w) for all three compounds, as determined by UPLC (**Table 4**).
Figure 3. PXRD diffraction patterns of the pure API (black) and API loaded onto mesoporous silica (red) for dipyridamole (a), glibenclamide (b) and fenofibrate (c).

Table 4. API loaded silica total API content

<table>
<thead>
<tr>
<th>API</th>
<th>% Loading of API onto mesoporous silica (w/w %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole</td>
<td>30.1 ± 0.1</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>29.4 ± 0.1</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>29.7 ± 0.3</td>
</tr>
</tbody>
</table>

Delivering the API in the amorphous form significantly improved the dissolution performance in FaSSIF for all three compounds (Figure 4). As seen in figure 4, dipyridamole, glibenclamide and fenofibrate showed 4, 25 or 3-fold...
supersaturation relative to the thermodynamic solubility, respectively. However, all three profiles also show precipitation and a decrease in concentration towards the thermodynamic solubility within around 30 minutes.

**Figure 4.** Dissolution profiles of pure API (●), and API loaded onto mesoporous silica (●) for dipyridamole (a), glibenclamide (b) and fenofibrate (c) in FaSSIF, pH 6.5 at 37°C

### 3.3 Precipitation Inhibitor Screening: Calculation of Excess Enthalpy

The COSMO-RS *in silico* screening protocol was based on calculation of the enthalpy of interaction between each of the APIs with different potential precipitation inhibitors. Results are summarized in Figure 5. According to the hypothesis, the more negative the calculated enthalpy of interaction, the higher the ‘COSMO Rank’. A COSMO rank of 1 thus indicates the best potential for successful precipitation inhibition. By contrast, the more positive the enthalpy of interaction, the less likely the polymer is to be of use as a precipitation inhibitor. Of the inhibitors studied experimentally, Eudragit EPO, was predicted to be the best precipitation inhibitor for both dipyridamole and glibenclamide, whereas for fenofibrate, PMMA was assigned the highest COSMO rank. For all three compounds, chitosan was assigned COSMO rank 9, reflecting its high calculated enthalpy of interaction, which was hypothesized to translate into poor precipitation inhibition performance.
Figure 5. COSMO-RS Screen: calculated excess enthalpy of interaction between dipyridamole (a), glibenclamide (b) and fenofibrate (c) with a range of potential precipitation inhibitors. Polymers studied experimentally to test the correlation are highlighted as dark bars: Eudragit EPO, Pluronic (PLR), PEG, HPMCAS, PVP, HPMC, Eudragit RLPO, PMMA and Chitosan.

### 3.4 Dissolution data for API loaded onto mesoporous silica with precipitation inhibitor added

Each of the loaded mesoporous silica samples were physically combined with a selection of polymers (HPMCAS, HPMC, PVP, PEG, Eudragit EPO, Pluronic, PMMA, Eudragit RLPO and Chitosan) such that the final ratio of API: PI was 1:3, w/w (API : PI : Silica; 1 : 3 : 2, w/w). Therefore, table 5 shows the final % API content in the formulations after combination with the precipitation inhibitors. The final API concentrations are similar to conventional supersaturating formulations that require precipitation inhibitors.

<table>
<thead>
<tr>
<th>API</th>
<th>% Loading of API onto mesoporous silica (w/w %)</th>
<th>Final API Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole</td>
<td>30.1 ± 0.1</td>
<td>15.1</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>29.4 ± 0.1</td>
<td>14.7</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>29.7 ± 0.3</td>
<td>14.9</td>
</tr>
</tbody>
</table>
To assess the predictive power of the COSMO calculation, dissolution in FaSSIF was carried out for each of the API-loaded mesoporous silica samples in combination with each of the selected precipitation inhibitors. (Figures 6-8)

**Figure 6.** Dissolution profiles in FaSSIF for dipyridamole (▲), dipyridamole loaded mesoporous silica (●) and dipyridamole loaded mesoporous silica with precipitation inhibitors selected from the COSMO-RS screen. (a): Eudragit EPO (□), Pluronic (X), PEG ( ); (b): HPMC (△), HPMCAS (○), Eudragit RLPO (○) and (c): PMMA (●), PVP (●) and Chitosan (+). The order of the listed inhibitors corresponds to the rank order in the COSMO screen (i.e. Eudragit EPO COSMO rank #1 – Chitosan COSMO rank #9).
**Figure 7.** Dissolution profiles in FaSSIF for glibenclamide (†), glibenclamide loaded mesoporous silica (■) and glibenclamide loaded mesoporous silica with precipitation inhibitors selected from the COSMO-RS screen. (a): Eudragit EPO (□), Pluronic (X), PEG (×); (b): HPMCAS (○), HPMC (□), Eudragit RLPO (△) and (c): PMMA (*), PVP (●) and Chitosan (+). The order of the listed inhibitors corresponds to the rank order in the COSMO screen (i.e. Eudragit EPO COSMO rank #1 – Chitosan COSMO rank #9).
Figure 8. Dissolution profiles in FaSSIF for fenofibrate (▲), fenofibrate loaded mesoporous silica (●) and fenofibrate loaded mesoporous silica with precipitation inhibitors selected from the COSMO-RS screen. (a): PMMA (+), Pluronic (X), PEG (▲); (b): Eudragit EPO (△), Eudragit RLPO (○), PVP (●) and (c): HPMCAS (○), HPMC (●) and Chitosan (+). The order of the listed inhibitors corresponds to the rank order in the COSMO screen (i.e. PMMA COSMO rank #1 – Chitosan COSMO rank #9).

3.7 Spring-Parachute Plots

The performance of the precipitation inhibitor is rated in terms of its ability to sustain supersaturation. To reflect this, the data in Figure 9 indicates the maximum concentration ('Spring') achieved compared to the concentration at the end of the assay ('Parachute').
Figure 9. Maximum concentration, ‘Spring’, (dark bars) versus the concentration at the end of the dissolution experiment at 120 minutes, ‘Parachute’, (light bars) for dipyridamole (a), glibenclamide (b) and fenofibrate (c) loaded mesoporous silica in combination with a range of precipitation inhibitors during FaSSIF dissolution, with decreasing COSMO-rank for the respective API from left to right.

3.6 Spearman’s Rank Correlation Analysis

The overall formulation performance was assessed by calculating the AUC of the dissolution profiles for each system (Equation 2). Statistical analysis was then carried out to determine the correlation between COSMO-rank and formulation performance, with a higher AUC indicating a better formulation performance (Table 6-8).
Table. 6 Spearman’s rank correlation coefficient analysis: dipyridamole

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Calculated Enthalpy (kJ/mol)</th>
<th>AUC (µg·mg mL⁻¹)</th>
<th>COSMO Rank</th>
<th>Dissolution Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit EPO</td>
<td>-6.84</td>
<td>29000</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PLR</td>
<td>-3.45</td>
<td>14000</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>PEG</td>
<td>-3.08</td>
<td>8600</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>HPMC</td>
<td>-2.12</td>
<td>19000</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>-2.01</td>
<td>13000</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Eudragit RLPO</td>
<td>-1.55</td>
<td>6600</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>PMMA</td>
<td>-1.46</td>
<td>5800</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>PVP</td>
<td>-1.23</td>
<td>5300</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Chitosan</td>
<td>1.28</td>
<td>5100</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Spearman’s Rank Correlation Coefficient 0.91 Significance 0.001 P < 0.05

Table. 7 Spearman’s rank correlation coefficient analysis: glibenclamide

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Calculated Enthalpy (kJ/mol)</th>
<th>AUC (µg·mg mL⁻¹)</th>
<th>COSMO Rank</th>
<th>Dissolution Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit EPO</td>
<td>-4.96</td>
<td>11000</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PLR</td>
<td>-4.70</td>
<td>7200</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PEG</td>
<td>-3.92</td>
<td>960</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>HPMC</td>
<td>-2.17</td>
<td>6000</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>-1.55</td>
<td>6100</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Eudragit RLPO</td>
<td>-1.03</td>
<td>2100</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>PMMA</td>
<td>-0.72</td>
<td>2000</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>PVP</td>
<td>-0.64</td>
<td>600</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Chitosan</td>
<td>1.44</td>
<td>100</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Spearman’s Rank Correlation Coefficient 0.81 Significance 0.01 P < 0.05
Table 8 Spearman’s rank correlation coefficient analysis: fenofibrate

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Calculated Enthalpy (kJ/mol)</th>
<th>AUC (µg·mg mL⁻¹)</th>
<th>COSMO Rank</th>
<th>Dissolution Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMMA</td>
<td>-2.07</td>
<td>10000</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>PLR</td>
<td>-1.24</td>
<td>9000</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>PEG</td>
<td>-1.21</td>
<td>5200</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Eudragit EPO</td>
<td>-0.62</td>
<td>19000</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Eudragit RLPO</td>
<td>-0.37</td>
<td>13000</td>
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<td>2</td>
</tr>
<tr>
<td>PVP</td>
<td>-0.26</td>
<td>5400</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>HPMCAS</td>
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</tr>
<tr>
<td>HPMC</td>
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<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Chitosan</td>
<td>1.88</td>
<td>1700</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Spearman’s Rank Correlation Coefficient: 0.63  
Significance: 0.08  
P < 0.05

Given that dissolution performance for PEG formulations appears to consistently deviate from the correlation of COSMO rank with dissolution performance for all three APIs, the statistical analysis was re-run without PEG. For all samples, the correlation improved, with the Spearman’s rank correlation coefficients for dipyridamole and glibenclamide both increased to 0.98 (0.0004, p<0.05), indicating a strong positive correlation. For fenofibrate, removing PEG from the set also improved the Spearman’s rank coefficient to 0.8 (0.022, p<0.05) and passes the significance criterion. The results suggest that PEG may behave as an outlier in the COSMO calculations.

4. Discussion

In silico tools are an attractive option for bridging the gap between our current understanding of precipitation inhibitors and practical selection of inhibitors to be used in supersaturating formulations in pharmaceutical development. In this work, we applied the COSMO-RS model as a novel in silico screening tool to successfully predict the formulation performance of a wide range of precipitation inhibitors in formulations of glibenclamide, fenofibrate and dipyridamole. Specifically, it was hypothesized that free enthalpy of mixing (API-polymer) could be used as a parameter for ranking inhibitors, from highest potential for successful precipitation inhibition to lowest, based on the theoretical interaction between the inhibitor and the API. For all three compounds a strong positive correlation was observed between the rank assigned based on the calculated free enthalpy of mixing and the overall formulation performance.
The Importance of Enabling Formulations

The experimental thermodynamic solubility values for dipyridamole, glibenclamide and fenofibrate in FaSSIF are in line with values previously reported in the literature (Table 2) (Leigh, 2012; Fagerberg, 2012 and Buch, 2010). All three compounds represent Biopharmaceutical Classification System (BCS) II APIs (Amidon, 1995). This low solubility, coupled with the incomplete dissolution of the drugs in biorelevant media (Figure 2), signals the potential for oral absorption and bioavailability risks during development (Zheng, 2012). The selected APIs represent a typical range of molecular weights, charge, hydrophobicity and number of hydrogen bond donors and acceptors typical for poorly soluble drugs. Therefore, all three APIs are model candidates for absorption enhancement by formulation with enabling formulations. Indeed, there are already many examples in the literature of combining each of these APIs with enabling formulations such as lipid-based formulations, addition of surfactants to the formulation and formulations containing high-energy forms of the API such as solid dispersions (Thongnopkoon, 2016; Guo, 2011; Zecevic, 2018; Thei, 2017; Taniguchi, 2013).

Mesoporous Silica: A Model Supersaturating Formulation

In the current approach, mesoporous silica was selected as a model supersaturating formulation. Mesoporous silica stabilizes the amorphous API via nano-encapsulation in the pores, which have an approximate mean diameter of 4 nm. Upon contact with an aqueous environment, the drug is released in a molecularly dispersed fashion and thus supersaturation is generated (Ditzinger, F.D. and Price, D.J, 2018). Both fenofibrate and glibenclamide have previously been formulated with mesoporous silica in the literature. Van Speybroeck and co-workers reported that, after successfully loading onto ordered mesoporous silica, glibenclamide was completely released within 30 minutes, compared to just 60% release at 120 minutes for the commercial formulation, Daonil (Van Speybroeck, 2011). Furthermore, the improved in vitro dissolution performance translated into an improved in vivo performance in rats, with the extent of absorption fourfold higher for glibenclamide loaded silica than the commercial formulation (Van Speybroeck, 2011).

Mesoporous silica has also been demonstrated to improve both in vitro and in vivo performance of fenofibrate versus commercially available products (Van Speybroeck, 2010; Ahern, et al. 2013; Uejo, et al. 2013; Hong, et al. 2014; Bukara, et al. 2016; O’Shea, 2017; Dressman, 2015). Furthermore, fenofibrate was the API chosen for the first proof of concept clinical trial of mesoporous silica in man (Bukara, 2016). In that study, which compared fenofibrate loaded silica with the commercially available micronized Lipanthyl® formulation, a 77% increase in
25 \( C_{\text{max}} \), a reduced \( t_{\text{max}} \) and a 54 % increase \( \text{AUC}_{0-24h}/\text{dose} \) for fenofibrate loaded silica was observed, demonstrating that loading this API onto mesoporous silica can increase both the rate and extent of absorption.

Given this pre-established success with mesoporous silica for glibenclamide and fenofibrate, successful loading onto silica, as demonstrated by the solid-state shift from crystalline to amorphous, was expected for both compounds (Figure 3). Furthermore, the loading efficiency and extent of supersaturation was in line with previous examples in the literature (Table 4; Figure 4) (O’Shea, 2017; Van Speybroeck, 2011). In contrast, for dipyridamole, which has been formulated with other enhancing approaches such as solid dispersions, there have not yet been any published reports of formulation with mesoporous silica. For this molecule, a successful loading was also confirmed by the change in solid-state from crystalline to amorphous (Figure 3). Additionally, supersaturation was generated, and the observed loading efficiency obtained was in line with typical loading values reported in the literature (Table 4; Figure 4) (McCarthy, 2015).

For all three APIs, loading onto mesoporous silica resulted in the typical ‘spring’ profile in the FaSSIF dissolution curves (Figure 4). First reported by Guzman (Guzman, 2007), the presence of short-lived supersaturation followed by precipitation is typical for delivery of the compound in the amorphous form, such as with mesoporous silica. This is related to the metastable nature of the supersaturated state, which is returned to a thermodynamically more favorable state via the precipitation of the supersaturated API (Taylor and Zhang, 2016). The dissolution profiles of the three API-loaded silica confirm the need for a precipitation inhibitor, or a “parachute”, to maintain the API concentration in solution over physiologically relevant time scales.

Precipitation Inhibitor Selection with COSMO-RS

Given the current lack of understanding surrounding structure-inhibition relationships, selection of precipitation inhibitors has typically been empirical, requiring a large amount of experimental screening (Price, 2018). Such time-consuming experimental approaches have been reported in the literature for fenofibrate. Petrusevska et al. employed a high-throughput screening protocol that coupled a solvent-shift approach with off-line chromatography to screen a wide-range of precipitation inhibitors for fenofibrate (Petrusevska, 2013). In the study, it was determined that surfactant-based inhibitors were the most optimal for fenofibrate, as opposed to the cellulosic polymers, which proved to be optimal for carbamazepine (Petrusevska, 2013). Interestingly, the top performing polymers highlighted in the current study were not included in the high-throughput screen, which further indicates that, in addition to the large resource costs involved in experimental screening, the most optimal inhibitors may be missed due to practical limitations on the number of inhibitors that can be screened.
experimentally. This problem is especially pronounced when, instead of conducting a high-throughput experimental precipitation inhibitor screen, two to three “usual suspects” are selected for experimental screening. In this approach, polymers such as PVP, HPMCAS or HPMC are often selected and individually screened in combination with the supersaturating formulation of interest, after which the most successful polymer of the three is selected. This approach introduces a large amount of uncertainty as to whether the most efficient formulation has been realized (He, 2010; O’Shea 2017; Laine, 2016; Vora, 2016).

To reduce the resources required for precipitation inhibitor screening, it would be highly desirable to replace experimental with in-silico tools. Using the COSMO-RS screening protocol described herein, drug-polymer mixing enthalpy can be calculated for an API in combination with ~50 potential precipitation inhibitors in as little as two minutes. This represents a significant time-saving versus traditional experimental screening. During early pharmaceutical development, time can be the most critical factor in the success of failure of a project, so such savings are highly attractive. Furthermore, there is no limit to the number of molecules that can be included in the database. All potential inhibitors can be assessed using enthalpy of interaction as a rank-order parameter, which is designated the “COSMO Rank” (Figure 5 a-c). This is related to the hypothesis that the more negative the enthalpy, the higher the chance of successful precipitation inhibition based on interaction between API and PI. This hypothesis is links back to the principle that interactions between the API and PI are essential to efficient precipitation inhibition, which has been demonstrated in many studies (Price, 2018).

Even without considering the dissolution data generated in these studies, the rank order proposed by the COSMO-RS screen already points towards promising results. For example, in a study by Chauhan and co-workers, it was reported that Eudragit EPO and HPMC were able to sustain supersaturated solutions of dipyridamole significantly longer than all other polymers studied (Eudragit S100, Eudragit RL100, PEG and PVP). Both the in silico prediction and the dissolution studies carried out in our studies reflect these findings. Interestingly, PVP, which is often used as a first-line candidate in precipitation inhibitor selection, did not perform well as a precipitation inhibitor in the study by Chauhan (Chauhan, 2013). The COSMO calculation for dipyridamole (Figure 5a) was able to identify that PVP would not be a suitable polymer ($\Delta H = +1.28 \text{ kJ/mol}$) for dipyridamole.

Correlation of COSMO-Rank with Dissolution Performance

In addition to the general observation that the COSMO-RS calculated excess enthalpy of interaction appears to be a useful rank-order parameter for the selection of precipitation inhibitors, a statistical analysis of the correlation between the COSMO-RS rank and the dissolution data was also conducted (Tables 4-6). Comparing these two
parameters with Spearman’s rank correlation coefficient analysis, the correlation between the rank order predicted by COSMO-RS and the rank order observed in the dissolution experiments was determined to be 0.91 (0.001, p<0.05), 0.81 (0.01, p<0.05) and 0.61 (0.076, p<0.5) for dipyridamole, glibenclamide and fenofibrate, respectively. For dipyridamole and glibenclamide, the very strong positive correlation between COSMO prediction and formulation performance demonstrated that the COSMO-RS screening protocol can be used to select the most optimal precipitation inhibitors whilst avoiding the costly and time-consuming experimental screening. For fenofibrate, the correlation observed between the predictions and the results was lower. Furthermore, the significance in the Spearman’s rank correlation coefficient analysis was greater than 0.05 for fenofibrate, which introduces uncertainty as to the conclusions that can be drawn based on the analysis. However, when PEG was excluded from the analysis, all correlations improved substantially and the correlation coefficient for fenofibrate (0.8) reached statistical significance (p<0.05). It thus seems that PEG may be an outlier in terms of the COSMO predictions, although this would have to be tested with more APIs to be sure. We note that a strong positive correlation was independently achieved for each API, which suggests that the presented approach can be applied robustly and reliably.

In addition to the area under the curve of the dissolution profile, one can also consider how well the API sustains the API in solution by addressing the differences between the peak, ‘spring’, concentration and the final, ‘parachute’, concentration. As shown in figure 9, there is a good correlation between how well an inhibitor sustains the initial ‘spring’ concentrations and the COSMO-rank. By combining both the AUC of the dissolution profiles and spring-parachute behavior of an inhibitor, a broad landscape of precipitation inhibitor performance can be seen, which aligns well with the COSMO-RS predictions.

From a mechanistic perspective, the COSMO approach is highly attractive. Specifically, to calculate the energy required to combine the quantum sigma surfaces of the API and PI, the sigma potential (psσ'), the energy of forming new contacts between the two must be considered, this is reflected in the COSMO-RS energy term, \( E(\sigma,\sigma') \). This term significantly improves the mechanistic applicability of the approach, as all potential modes of interaction between API and PI are considered: hydrogen bond interactions, coulombic interactions and van de Waals interactions (see Appendix 3).

As recently reviewed by our group (Price et al., 2018) the majority of precipitation inhibitors sustain supersaturated API in solution via interactions. Although varying from system to system, the most common interactions are hydrogen bond interactions and hydrophobic interactions. For example, in accord with our findings, there have been a number of papers that show the successful precipitation inhibition of supersaturated APIs by Eudragit EPO, this is based on its ability to interact strongly via both hydrogen bonding and hydrophobic
interactions. For example, Higashi and co-workers studied the effect of Eudragit EPO in combination with the poorly soluble drug mefenamic acid with 2D NOESY NMR (Higashi, 2014). The team found that the successful precipitation inhibition of Eudragit EPO was related to hydrophobic interactions between the aromatic portion of the API and the EPO polymer backbone; as well as a hydrophilic hydrogen bond interaction between the aminoalkyl groups of EPO and the carbonyl groups of the API. Such interactions are also possible with dipyridamole, fenofibrate and glibenclamide.

Furthermore, considering the precipitation inhibitors that did not perform well, one can relate the calculation, dissolution performance and potential points of interaction from a mechanistic perspective. One of the interesting cases here is the lack of successful inhibition of dipyridamole precipitation by PVP. As previously mentioned, PVP is one of the polymers most commonly used as a precipitation inhibitor. However, PVP has been shown to be ineffective in sustaining dipyridamole in solution, this was also identified by the COSMO-screen and is reflected in the dissolution performance of the formulation in this study. Chauhan and colleagues demonstrated that no interaction takes place between PVP and Dipyridamole in the solid state (Chauhan et al., 2013), this is in line with the results in the current study as well as the fact that the COSMO-calculated enthalpy of interaction was positive and thus unfavorable.

Ultimately, these robust mechanistic calculations increase the successful prediction of API-PI interaction and thus precipitation inhibition, as reflected in the strong positive correlations achieved between the COSMO-rank and the final formulation performance. For a full overview of the COSMO-RS equations, see appendix 3.

Assumptions and Limitations of the Proposed In Silico Screening Protocol

Our approach, which utilized excess enthalpy calculations to screen precipitation inhibitors, does not take into consideration the impact of water on the interaction between the API and PI. It has been repeatedly suggested that for a precipitation inhibitor to successfully sustain drug in solution, it must interact with both the API and the water in the medium or GI tract (Ting, 2016; Schram, 2015; Price, 2018). To exclude consideration of water’s role in mediating API interactions with the precipitation inhibitor becomes especially problematic when considering polymers that have very high hydrophobicity or hydrophilicity, as demonstrated by Schram and co-workers (Schram, 2015; Schram, 2016). From the data presented in this study, it is clear that the COSMO prediction for PEG did not correlate to the overall dissolution performance. Furthermore, PEG was the only clear outlier in the correlation for all three samples. This may be due to the aforementioned potential problem: PEG is very hydrophilic and is expected to bind and interact preferentially with water. This reduces the direct interaction with
the API and therefore the desired precipitation inhibitor performance is not realized. The effect of removing PEG from the dataset is pronounced for all three compounds, such that when the Spearman’s rank correlation coefficient analysis was repeated without PEG, the correlation between COSMO-rank and dissolution-rank significantly improved to 0.98 (0.0004, p<0.05) for dipyridamole and glibenclamide, and to 0.8 (0.022, p<0.05) for fenofibrate. Due to this, the COSMO-RS protocol should be applied with the foresight that outliers and exceptions may be possible for very hydrophobic and hydrophilic inhibitors.

Another limitation of the COSMO-RS in-silico approach is the focus on local molecular interactions, whereas any supramolecular effects are neglected. Although factors such as molecular weight, viscosity and diffusivity of the precipitation inhibitors play an important role in precipitation inhibition (Warren, 2010, Price, 2018), insufficient information regarding these factors is available for many of the polymers. There are two main hypotheses with respect to the importance of these parameters to precipitation inhibition. The first, and lesser reported, states that molecular weight and viscosity affect precipitation inhibition via changes in the diffusion kinetics of both the drug and polymer in solution (Warren, 2010). Such effects cannot be taken into account by the COSMO-RS approach at the moment. The second, and more widely reported hypothesis, relates to an increasing number of binding sites when molecular weight and viscosity are increased (Warren, 2010). Such binding sites increase when a polymer is at least to some extent swollen in aqueous medium, but such swelling and the theta condition of the polymer in aqueous medium is an aspect that was not considered in the presented in silico screening. It would thus be beyond the scope of this approach to determine the effect of viscosity or molecular weight with the current COSMO-RS protocol. Finally, to complement the enthalpic considerations of interaction of PI with API, there are also entropic considerations that are not easily considered using the current COSMO-RS approach, therefore, for some API-precipitation inhibitor combinations, where the interaction is entropically unfavorable, the COSMO-RS approach may fail to predict the experimental result. Of course, it is also possible that the interaction is entropically favorable e.g. in the case of disruption of supramolecular structuring of polymers in aqueous solution, as previously reported (Schram, et al. 2015).

5. Conclusions

In this work, we describe a novel in silico screening protocol for the selection of precipitation inhibitors for supersaturating formulations. The protocol uses the COSMO-RS model to calculate excess enthalpy of interaction between API and precipitation inhibitors, which is then used as a rank-order parameter to select potential precipitation inhibitors. Conceptually, such an approach may be applied for any enabling formulation...
that requires precipitation inhibitors, for example HME or SDD, but further work is required to validate this cross-formulation applicability. Despite the simplifications and assumptions in the presented COSMO-RS protocol, strong positive correlations were obtained between the rank-order prediction and formulation performance for the APIs studied. Furthermore, given the high-throughput and high-speed nature of the in-silico calculations, the screening protocol is very attractive as a score-card approach for the design of enabling formulations for poorly soluble APIs in the pharmaceutical industry. Ultimately, this study highlights how in-silico tools can be used to improve efficiency of precipitation inhibitor selection as well as the likelihood that the most optimal formulation will be realized.

Acknowledgements:

We would like to thank Axel Becker and Michael Lange (Merck KGaA, Darmstadt) for their helpful discussions and input into developing understanding of COSMO-RS and the applications currently applied.

Funding:

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Appendix 1: List of Polymers Used in the Screening Protocol

Alginic Acid Gum
Cellulose Acetate Pthalate (CAP)
Chitosan
Eudragit EPO
Eudragit L100
Eudragit RL100
Hydroxyethyl methyl cellulose (HEMC)
Hydroxypropyl methyl cellulose (HPMC)
Hydroxypropyl methyl cellulose acetate succinate (HPMCAS)
Hydroxyethyl cellulose (HEC)
Lactose
Locust Bean Gum
Mannitol
Methyl Cellulose
Polyethylene glycol (PEG)
Polyglycolide (PGA)
Polyactide (PLA)
Polyactide-co-polyglycolide (PLGA)
Pluronic
Poly(methyl methacrylate) (PMMA)
Polyvinyl acetate (PVAc)
Polyacetylene
Polyether Polyol
Polyethylene Imine
Polyvinyl acetate-co-poly(methyl methacrylate) (PVAc-PMMA)
Polypropylene glycol (PPG)
Poly(vinyl alcohol) (PVA)
Poly(vinyl alcohol)-co-polyvinylpyrrolidone (PVA-PVP)
Polyvinylpyrrolidone (PVP)
Sodium Carboxymethyl Cellulose (SCMC)
Sorbitol
Vitamin E TPGS

Appendix 2: Control Data Crystalline API + Polymers
FaSSIF dissolution of crystalline API in combination with each of the selected polymers from the COSMO-RS screen showed little to no co-solvency effects. Fenofibrate, out of the three compounds, showed some enhancement in combination with all polymers versus dissolution of Fenofibrate alone. *(Figure 6)*

*Figure 8.* FaSSIF Dissolution Profiles for DPD (a), GB (b) and FF (c) in the crystalline form (■) and in combination with Eudragit EPO (○), Pluronic (X), PEG (▲); 4-6 (b): HPMCAS (○), HPMC (●), Eudragit RLPO (○); and 7-9 (b): PMMA (♦), PVP (●) and Chitosan (+).

**Appendix 3: COSMO-RS Equations**
Equation 1, Electrostatic interaction:

\[ E_{\text{Coulomb}}(\sigma) = \frac{\alpha}{2}(\sigma + \sigma')^2 \]

Where \( \alpha \) is an adjustable parameter that is calculated \textit{in situ} via parameterization, and \( \sigma \) and \( \sigma' \) are the solute and solvent segment, respectively.

Equation 2, Hydrogen bond interactions:

\[ E_{\text{hb}}(\sigma) = c_{\text{hb}} T \max\{0, \sigma_{\text{acc}} - \sigma_{\text{hb}}\} \min\{0, \sigma_{\text{don}} + \sigma_{\text{hb}}\} \]

Where \( \sigma_{\text{acc}} \) and \( \sigma_{\text{don}} \) are the sigma profile densities of the hydrogen bond acceptor and donor, respectively. \( c_{\text{hb}} \) and \( \sigma_{\text{hb}} \) are the adjustable parameters corresponding to the hydrogen bond prefactor and the hydrogen bond threshold, respectively. This equation is constructed with minimum and maximum thresholds to ensure that the screening charges exceed the required values for hydrogen bonding to occur.

Equation 3, van der Waals interactions:

\[ E_{\text{vdw}} = \sum_k \gamma_k A_k \]

Where the dispersion energy, \( E_{\text{vdw}} \), is related to the surface area of the contact point, \( A \), on the specific element, \( k \), and on an adjustable prefactor, \( \gamma \).

Equation 4, \( \mu \) calculation:

\[ \mu_x(\sigma) = -kT \ln \int p_x(\sigma') \exp\left[ \frac{E(\sigma,\sigma') - \mu_x(\sigma')}{RT} \right] d\sigma' \]

Where \( p_x(\sigma') \) is the sigma profile of the system, \( k \) is an element specific parameter, \( T \) is the temperature and \( R \) is the universal gas constant.

Equation 5, \( \mu_{\text{mix}} \) calculation:

\[ \mu_{\text{mix}} = \sum_x p^x(\sigma) \mu_x(\sigma) + \mu_{\text{ex}}^S \]

References


