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Hansen solubility parameter as a tool to predict cocrystal formation

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ABSTRACT

The objective of this study was to investigate whether the miscibility of a drug and coformer, as predicted by Hansen solubility parameters (HSPs), can indicate cocrystal formation and guide cocrystal screening. It was also our aim to evaluate various HSPs-based approaches in miscibility prediction. HSPs for indomethacin (the model drug) and over thirty coformers were calculated according to the group contribution method. Differences in the HSPs between indomethacin and each coformer were then calculated using three established approaches, and the miscibility was predicted. Subsequently, differential scanning calorimetry was used to investigate the experimental miscibility and cocrystal formation. The formation of cocrystals was also verified using liquid-assisted grinding. All except one of the drug-coformers that were predicted to be miscible were confirmed experimentally as miscible. All tested theoretical approaches were in agreement in predicting miscibility. All systems that formed cocrystals were miscible. Remarkably, two new cocrystals of indomethacin were discovered in this study. Though it may be necessary to test this approach in a wide range of different coformer and drug compound types for accurate generalizations, the trends with tested systems were clear and suggest that the drug and coformer should be miscible for cocrystal formation. Thus, predicting the miscibility of cocrystal components using solubility parameters can guide the selection of potential coformers prior to exhaustive cocrystal screening work.

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1. Introduction

New solid forms of a drug can be developed to have unique physicochemical and mechanical properties that can offer significant advantages over other forms in the processing, stability and in vivo performance of the drug. Consequently, solid form screening, a routine activity in the pharmaceutical industry, is used to exploit the physicochemical property advantage and to fulfill regulatory requirements. The discovery of new solid forms is also one way of strengthening a company's patent portfolio (Trask, 2007; Vippagunta et al., 2001). In this context, pharmaceutical cocrystals have attracted phenomenal interest in recent years for their potential for improving the physicochemical properties of drug substances (Schultheiss and Newman, 2009). Therefore, cocrystal screening has become an integral part of solid form screening activities in drug development.

Cocrystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry, which are solids at room temperature and are held together by weak interactions, mainly hydrogen bonding (Aakeroy and Salmon, 2005). These characteristics distinguish cocrystals from other solid forms such as salts, solvate/hydrate, eutectic mixtures and solid solutions. Table 1 summarizes the fundamental differences and similarities among eutectic mixtures, solid solutions and cocrystals.

Over the years, cocrystal screening methodology has advanced from being empirically based to a more efficient and rational basis (Childs et al., 2008). Cocrystal screening methods can broadly be categorized as solid-based and liquid-based (Table 2). While solid-based methods often rely on the stoichiometric ratio of the reactants for cocrystal formation, the liquid-based methods can be either stoichiometric (slow evaporative crystallization, spray drying) (Alhalaweh and Velaga, 2010) or non-stoichiometric (slurry and reaction crystallization)(Alhalaweh and Velaga, 2010; Rodriguez-Hornedo et al., 2006; Zhang et al., 2007). It has however been shown that slurry-based methods are more suitable than other methods for scale-up purposes (Gagnière et al., 2009). Furthermore, the prediction of structure and formation of cocrystals using Cambridge structural database and computational methods has also been presented (Fabian, 2009; Issa et al., 2009; Karamertzanis et al., 2009).

By definition, cocrystals are miscible systems at a molecular level. It is therefore hypothesized that an indication of the miscibil-

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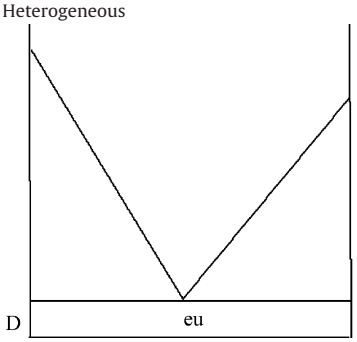
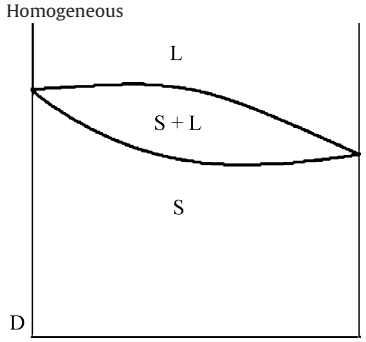
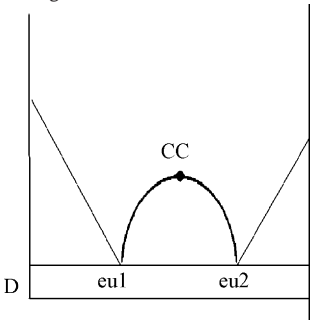
Table 1
Description of distinguishing characteristics of cocrystals (cc) from eutectic (eu) mixtures and solid solutions. S = solid; L = liquid.

Characteristics	Eutectic mixture	Solid solution	Cocrystal
State of the material	Crystalline	Amorphous	Crystalline
Number of phases	Multiple	Single	Single
Stoichiometry	Vague	Vague	Well-defined
Uniformity	Heterogeneous	Homogeneous	Homogeneous
Phase diagram in solid-state			

ity of the component molecules in the solid state could predict the likelihood of cocrystal formation, which would be useful in cocrystal screening. It is known that cocrystals can form via eutectic melt, but the proposed miscibility concept has not been considered in a similar sense (Chadwick et al., 2007; Lu et al., 2008).

The concept of a solubility parameter (δ) was introduced by Hildebrand and Scott, who proposed that materials with similar δ values would be miscible (Hildebrand and Scott, 1964). The Hansen solubility parameter (HSP) model, which was developed later, is based on the concept of dividing the total cohesive energy into individual components (dispersion, polar and hydrogen bonding) (Hansen, 1967a). This concept is well established in the areas of coating, and the paint and plastic industry (Hansen, 1967b; Krauskopf, 2004). HSPs have been widely used to predict liquid–liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surfaces (Hansen, 2007). In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions (Greenhalgh et al., 1999). Further, it has been suggested that HSPs could predict the compatibility of pharmaceutical materials, and their use is recommended as a tool in the pre-formulation and formulation development of tablets (Hancock et al., 1997; Johnson and Zografi, 1986; Rowe, 1988). The Flory–Huggins lattice theory has also been used to estimate the miscibility of various drugs with polymers (Marsac et al., 2006, 2009).

This study investigated whether the miscibility of a drug and its coformer components, as predicted by theoretical miscibility tools, could be used to predict the formation of cocrystals. Indomethacin was selected as the model active pharmaceutical ingredient (API). The HSPs of the coformers and indomethacin were calculated using group contribution methods. The miscibility of indomethacin with a coformer was predicted using three established miscibility tools (Bagley et al., 1971; Greenhalgh et al., 1999; Van Krevelen and Hoftyzer, 1976). Based on the prediction of miscibility, laboratory screening for cocrystals was conducted using thermal methods and liquid-assisted grinding (LAG). The discovered cocrystals were scaled-up and preliminarily characterized using high performance liquid chromatography (HPLC), thermal methods, Raman spectroscopy and powder X-ray diffraction (PXRD).

Table 2
Solid-based and liquid-based cocrystal screening and preparation methods. DSC, differential scanning calorimetry.

Liquid-based methods	Solid-based methods
Slow evaporative crystallization	Melt crystallization (hot stage microscopy and DSC)
Slurry conversion	Solid-state grinding
Reaction cocrystallization	Melt extrusion
Cooling crystallization	
Liquid-assisted grinding	
Sonication	
Supercritical fluids	
Spray drying	

1.1. Theory and miscibility models

The solubility parameters (i.e. cohesion energy parameters) can be used to predict the physicochemical properties (such as solubility, melting point, etc.) of a material (Hancock et al., 1997). The cohesive energy is the sum of the forces (van der Waals interactions, covalent bonds, hydrogen bonds and ionic bonds) that hold the material intact. Cohesive energy can also be defined as the energy needed to break all these interactions, allowing atoms or molecules to detach and resulting in solid to liquid/gas or liquid to gas transformations (Hancock et al., 1997). The cohesive energy per unit volume is termed the cohesive energy density (CED). The CED can be used to calculate the solubility parameter (δ) based on regular solution theory restricted to non-polar systems, as follows (Hildebrand and Scott, 1964):

$$\delta = (\mathrm{CED})^{0.5} = \left(\frac{\Delta E_V}{V_m}\right)^{0.5} \quad (1)$$

where ΔE_V is the energy of vaporization, and V_m is the molar volume. δ is measured in units of $(J/cm^3)^{0.5}$, $MP_a^{0.5}$ or $(cal/cm^3)^{0.5}$ where one $(cal/cm^3)^{0.5}$ is equivalent to 2.0421 $MP_a^{0.5}$ or $(J/cm^3)^{0.5}$.

Attempts have been made to extend the Hildebrand and Scott approach to include polar systems and strongly interacting species such as pharmaceuticals. One of the most widely accepted approaches, using HSPs, proposes that the total force of the various interactions can be divided into partial solubility parameters, i.e. dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h). These partial solubility parameters represent the possibility of intermolecular interactions between similar or different molecules. The total solubility parameter (δ_t), also called the three-dimensional solubility parameter, can be defined as follows:

$$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5} \quad (2)$$

Various theoretical and experimental methods based on solubility, calorimetry, sublimation, vaporization, inverse gas chromatography and group contribution methods have been used to estimate the HSPs of a material (Hansen, 2007). The group contribution

method is a commonly used theoretical method that only requires knowledge of the compound's chemical structure to calculate the HSPs (Subrahmanyam et al., 1996).

The partial solubility parameters, δ_d, δ_p and δ_h can be calculated using the combined group contribution methods of Van Krevelen–Hoftyzer and Fedors (Fedors, 1974; Van Krevelen and Hoftyzer, 1976) as follows:

$$\delta_d = \frac{\sum_i F_{d_i}}{\sum_i V_i} \quad (3)$$

$$\delta_p = \frac{\left(\sum_i F_{p_i}^2\right)^{0.5}}{\sum_i V_i} \quad (4)$$

and

$$\delta_h = \left(\frac{\sum_i E_{h_i}}{\sum_i V_i}\right)^{0.5} \quad (5)$$

where i is the structural group within the molecule, F_{d_i} is the group contribution to the dispersion forces, F_{p_i} is the group contribution to the polar forces, F_{h_i} is the group contribution to the hydrogen-bonding energy, and V_i is the group contribution to the molar volume.

The miscibility of compounds has been estimated using various approaches, all of which are based on the general principle of 'like dissolves like'. In other words, compounds with similar δ values are likely to be miscible. Van Krevelen and Hoftyzer have determined the miscibility of two compounds using the $\Delta\bar{\delta}$ factor, which can be calculated as follows:

$$\Delta\bar{\delta} = \left[(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2\right]^{0.5} \quad (6)$$

Krevlen and others then suggested that good miscibility will be achieved if $\Delta\bar{\delta} \leq 5\,MP_a^{0.5}$ (Güner, 2004; Van Krevelen, 1990). Further, Bagley et al. noticed that the effects of δ_d and δ_p are thermodynamically similar, while the effect of δ_h is different in nature from both (Bagley et al., 1971). Consequently, they introduced the volume-dependent solubility parameter, δ_v, where

$$\delta_v = (\delta_d^2 + \delta_p^2)^{0.5} \quad (7)$$

Subsequently, the $R_{a(v)}$ factor was used to determine the miscibility of two compounds:

$$R_{a(v)} = \left[4(\delta_{v2} - \delta_{v1})^2 + (\delta_{h2} - \delta_{h1})^2\right]^{0.5} \quad (8)$$

The two-dimensional plot of δ_v against δ_h is called a Bagley diagram. This diagram has been used in various applications including investigations into the miscibility of components, and predicting the duration of intestinal absorption for various drugs (Albers, 2008; Breitkreutz, 1998). In a study investigating drug/polymer miscibility, it was observed that the two components are miscible if $R_{a(v)} \leq 5.6\,MP_a^{0.5}$ (Albers, 2008).

Recently, Greenhalgh et al. used the difference in total solubility parameter between the drug and the carriers ($\Delta\delta_t$) as a tool to predict miscibility, as demonstrated in Eq. (9).

$$\Delta\delta_t = \left|\delta_{t2} - \delta_{t1}\right| \quad (9)$$

where t1 and t2 are carrier and drug respectively. In their work, which included many API/carrier systems, the authors demonstrated a general trend indicating that materials with $\Delta\delta_t < 7\,MP_a^{0.5}$ are miscible, while systems with $\Delta\delta_t < 7\,MP_a^{0.5}$ are immiscible (Greenhalgh et al., 1999).

2. Material and methods

2.1. Materials

All solvents (purity >99.8%) and chemicals (purity >99.0%) were purchased from Sigma–Aldrich, Sweden, and were used as received.

2.2. Cocrystal preparation and screening

2.2.1. Differential scanning calorimetry (DSC)

Physical mixtures of 2:1, 1:1, and 1:2 molar ratios of drug and coformers were prepared by thorough mixing using a mortar and pestle. The mixtures were tested for miscibility (eutectic mixture formation) and cocrystal formation using DSC (details of the method are presented in Section 2.4).

2.2.2. Liquid-assisted grinding (LAG)

A 1:1 molar ratio of indomethacin and the coformer was weighed and placed in a 10 ml Retsch grinding jar. In some cases, a 2:1 molar ratio was also tested. The mixture was ground for 30 min in a Retsch grinder (Mixer Mill MM301, Retsch GmbH & Co., Germany) at an operating frequency of 30 Hz, after adding 1 drop of ethyl acetate.

2.2.3. Reaction crystallization (RC)

A total of approximately 170 mg of indomethacin and cinnamic acid in a 1:1 molar ratio was stirred in 1 ml of ethyl acetate for 5 days at room temperature. Similar conditions were applied for indomethacin and 4,4′-bipyridine except that the molar ratio was 2:1. Solids were filtered, dried and analyzed by thermal analysis, Raman spectroscopy and PXRD.

2.3. High-performance liquid chromatography (HPLC)

The chemical stability and content of indomethacin in the cocrystal were determined by HPLC (series 200 binary LC pump and 200 UV–vis detector, TotalChrom software, PerkinElmer, Wellesly, MA). The drug was separated over a C18 column (Dalco Chrometch, 5 μm, 150 mm × 4.6 mm). The HPLC analysis was conducted at room temperature with a flow rate of 1 mL/min. UV detection at 319 nm was used and the mobile phase was phosphoric acid 0.2% (w/v) and MeOH, in proportions of 25:75.

2.4. Differential scanning calorimetry (DSC)

A Q1000 differential scanning calorimeter (TA instruments) was used in this study. It was equipped with a refrigerated cooling system and was calibrated for temperature and enthalpy using indium. Samples (3–5 mg) were crimped in non-hermetic aluminum pans and scanned at a heating rate of 10 °C/min, unless otherwise stated, under a continuously purged dry nitrogen atmosphere (flow rate 50 mL/min).

2.5. Powder X-ray diffraction (PXRD)

PXRD patterns of the samples were collected on a Siemens DIFFRACplus 5000 powder diffractometer with CuKα radiation (1.54056 Å). The tube voltage and amperage were set at 40 kV and 40 mA, respectively. The monochromator slit was set at 20 mm sample size. Each sample was scanned between 5° and 40° in 2θ with a step size of 0.01° at 1 step/s. The sample stage was spun at

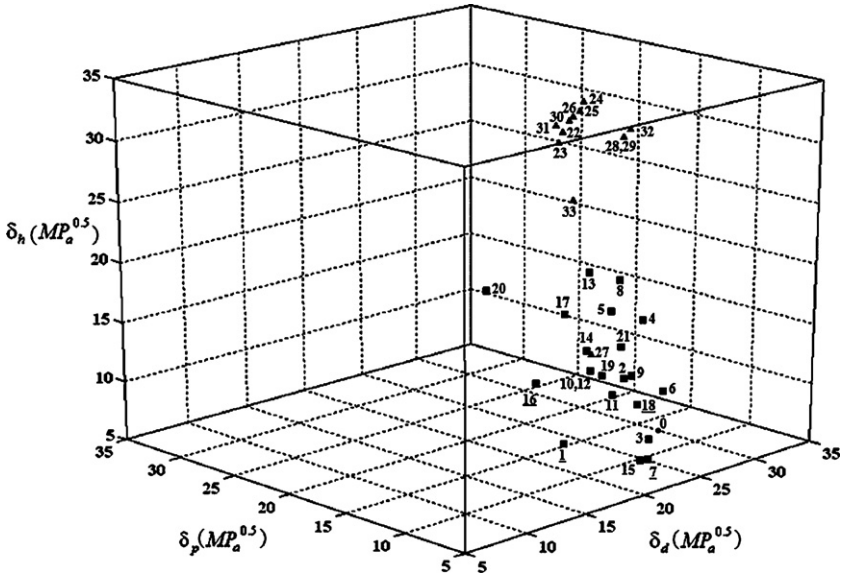


Fig. 1. Positions of indomethacin and coformers within the Hansen diagram. Numbers are used to indicate the compounds as follows: 0 = indomethacin; 1 = 4,4′-bipyridine; 2 = 4-aminobenzamide; 3 = 4-aminobenzoic acid; 4 = 4-hydroxybenzamide; 5 = 4-hydroxybenzoic acid; 6 = benzoic acid; 7 = cinnamic acid; 8 = citric acid; 9 = cyclamic acid; 10 = fumaric acid; 11 = glutaric acid; 12 = maleic acid; 13 = malic acid; 14 = malonic acid; 15 = neotame; 16 = nicotinamide; 17 = oxalic acid; 18 = saccharin; 19 = succinic acid; 20 = urea; 21 = vanillic acid; 22 = arabinose (furanose form); 23 = arabinose (pyranose form); 24 = fructose (furanose form); 25 = fructose (pyranose form); 26 = glucose; 27 = glycine; 28 = lactose; 29 = maltose; 30 = mannitol; 31 = mannose; 32 = sucrose; and 33 = tartaric acid. (▲) Immiscible coformers and (■) miscible coformers with indomethacin. Underlining numbers indicate the coformers form cocrystal with indomethacin.

30 rpm. The instrument was calibrated prior to use, using a silicon standard.

2.6. Raman spectroscopy

Raman spectra of cocrystals and their components were collected via backscattering geometry, using a Holoprobe Research 785 Raman Microscope (Kaiser Optical System Inc.). The laser, with a power of 400 mW, was focused on the samples with a spot size of 10 μm diameter through a standard 10× microscope objective. The spectra were collected with a data point acquisition time of 5 s. The spectral range and spectral resolution were 100–3200 cm^{-1} and 4 cm^{-1}, respectively. Spectra are presented as intensity (counts) versus Raman shift (cm^{-1}).

3. Results and discussion

3.1. Miscibility of the components

The experimental screening for cocrystals of indomethacin was conducted using solvent evaporation method in our earlier study (evaporation of under-saturated equimolar solutions of drug and coformers at room temperature) (Basavoju et al., 2008). Diverse set of thirty three coformers used in this study included those used in the previous study. Several of these coformers are diverse and have complementary functional groups with the ability to form hydrogen bonds with the drug. The HSPs for indomethacin and the coformers were calculated using the group contribution method following the combined models of Fedors and Van Krevelen–Hoftyzer (Supplementary information, Table S1). The HSPs calculations for indomethacin are given in Table 3 as an example. The HSPs were then used to study the miscibility of indomethacin and the coformers using methodology developed by Van Krevelen–Hoftyzer, Bagley and Greenhalgh (Bagley et al., 1971; Greenhalgh et al., 1999; Van Krevelen and Hoftyzer, 1976). The values for $\Delta\bar{\delta}$, $R_{a(v)}$ and $\Delta\delta_t$ were calculated for each drug/coformer system using Eqs. (6), (8), and (9), respectively. The calculated values are presented in the supplementary information (Table S2).

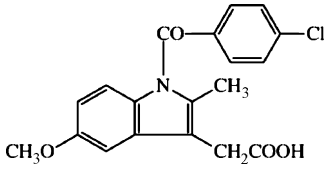
The approaches we employed for predicting miscibility have been well studied (Bagley et al., 1971; Greenhalgh et al., 1999; Van Krevelen and Hoftyzer, 1976). Notably, Van Krevelen and Hoftyzer translated HSPs data into three-dimensional (3-D) plots, while Bagley and co-workers simplified the data to two-dimensional (2-D) plots. In a recent study, the Hildebrand solubility parameter was used to calculate δ_t for various materials, and a correlation between $\Delta\delta_t$ and experimental miscibility was established (Greenhalgh et al., 1999). In discussing the limitations of the approach, the authors stated that the miscibility could be better predicted using HSPs than the Hildebrand solubility parameter, since HSPs consider the relative contribution of the various types of force independently. Hence, HSPs were used in this study.

The correlation plots for the differences in the HSPs ($\delta_{d2} - \delta_{d1}$, $\delta_{p2} - \delta_{p1}$ and $\delta_{h2} - \delta_{h1}$) and ($\delta_{v2} - \delta_{v1}$) versus $\Delta\bar{\delta}$ and $R_{a(v)}$ are presented in the supplementary information (Figs. S1 and S2). It was found that $\Delta\bar{\delta}$ and $R_{a(v)}$ correlated well with $\delta_{h2} - \delta_{h1}$, as the correlation coefficients were 0.99 and 0.97, respectively, while other plots showed poor correlation. These results suggest a contribution of hydrogen bonding to the miscibility.

The distribution of HSPs for the indomethacin/coformer systems is presented in a 3-D plot (Hansen diagram) and a 2-D plot (Bagley diagram) in Figs. 1 and 2, respectively. The coformers are further classified according to the observations of Greenhalgh et al. in Table 4. Twenty-two of thirty-three coformers were predicted to be miscible according to the criterion of Greenhalgh et al. (i.e. $\Delta\delta_t < 7\,MP_a^{0.5}$; Table 4). The predicted miscible drug coformers were verified experimentally using DSC for miscibility and cocrystals formation. DSC has been widely used to determine the miscibility of drugs and polymers or excipients (Greenhalgh et al., 1999; Forster et al., 2001; Marsac et al., 2006), using the formation of a eutectic mixture of the components or depression of the melting point as signs of miscibility. DSC thermograms showing the eutectic melt point for a drug/coformer system at various ratios are presented in Fig. 3 as an example, and the eutectic onset temperatures for miscible systems are presented in Table 5.

The experimentally confirmed miscible systems were found to cluster in one region in the Hansen and Bagley diagrams

Table 3
Calculation of HSPs and molar volume for indomethacin according to the Hoftyzer–Van Krevelen method.



Group	Frequency	F_{d_i} ($J^{1/2}$ cm$^{3/2}$ mol^{-1})	F_{p_i} ($J^{1/2}$ cm$^{3/2}$ mol^{-1})	F_{h_i} (J/mol)	V_m [a] (cm^3/mol)
$-CH_3$	2	840	0	0	67
$-CH_2-$	1	270	0	0	16.1
=CH–	3	600	0	0	40.5
>C=	5	350	0	0	−27.5
Phenylene (o, m, p)	1	1270	12,100	0	52.4
–Cl	1	450	302,500	400	24
–O–	1	100	160,000	3000	3.8
–CO–	1	290	592,900	2000	10.8
–COOH	1	530	176,400	10,000	28.5
–N<	1	20	640,000	5000	−9
Ring closure 5 or more atoms	2	380	0	0	32
Conjugation in ring for each double bond	4				−8.8
Σ		5100	1,883,900	20,400	229.8
$\delta_d = \frac{\sum_i F_{d_i}}{\sum_i V_i}$		22.19 $MP_a^{0.5}$			
$\delta_p = \frac{\left(\sum_i F_{p_i}^2\right)^{0.5}}{\sum_i V_i}$		5.97 $MP_a^{0.5}$			
$\delta_h = \left(\frac{\sum_i E_{h_i}}{\sum_i V_i}\right)^{0.5}$		9.42 $MP_a^{0.5}$			
$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5}$		24.84 $MP_a^{0.5}$			
$\delta_v = (\delta_d^2 + \delta_p^2)^{0.5}$		22.98 $MP_a^{0.5}$			

[a] Molar volume is calculated according to Fedors (1974).

(Figs. 1 and 2), while the immiscible systems were clustered separately. All drug/coformer systems with $\Delta\delta \leq 5.0\,MP_a^{0.5}$ were miscible, in agreement with previous studies (Güner, 2004; Van Krevelen, 1990). However, several systems that were experimentally miscible were not predicted by this condition. Similarly, a study by Albers on a limited number of systems suggested that two substances will be miscible if the distance between them in the Bagley plot, $R_{a(v)}$, is $\leq 5.6\ MP_a^{0.5}$ (Albers, 2008). However, in this study, several indomethacin/coformer systems that did not meet this criterion were experimentally miscible. These deviations could be partly related to differences in the characteristics of the materials, i.e. small molecular organics versus polymers in the earlier studies.

The fact that most of the drug/coformer systems with $\Delta\delta_t < 7\,MP_a^{0.5}$ showed eutectic/melting point depression (Tables 4 and 5) indicates that the miscibility predicted by Greenhalgh correlated well with that determined by DSC. However, glycine was immiscible with indomethacin experimentally, despite a $\Delta\delta_t = 0.03\,MP_a^{0.5}$ and appearing in the cluster with miscible systems in the Hansen and Bagely diagrams (Figs. 1 and 2). While the molecular rigidity of glycine could be the reason for this, deviations in the $\Delta\delta_t$ approach in predicting miscibility have been reported (Greenhalgh et al., 1999).

Sucrose was also tested experimentally as a model for systems with $\Delta\delta_t > 10\,MP_a^{0.5}$. In the DSC thermograms for drug/sucrose ($\Delta\delta_t > 10\,MP_a^{0.5}$) two distinct melting endotherms corresponding

Table 4
Classification of coformers following the miscibility criteria reported in Greenhalgh et al. (1999) and the experimental results from DSC.

$\Delta\delta_t$ ($MP_a^{0.5}$)	Coformers	Miscibility, as tested by DSC
<7	Cinnamic acid, neotame, 4,4′-bipyridine, benzoic acid, glutaric acid, fumaric acid, maleic acid, succinic acid, nicotinamide, 4-aminobenzoic acid, malonic acid, cyclamic acid, vanillic acid, saccharin, oxalic acid, 4-hydroxybenzoic acid, urea, citric acid, malic acid, 4-aminobenzamide, 4-hydroxybenzamide, and glycine	All miscible except glycine[a]
>10	Tartaric acid, arabinose (pyranose), arabinose (furanose), lactose, maltose, mannitol, mannose, glucose, fructose (pyranose), fructose (furanose) and sucrose[b]	Most not tested

[a] Glycine is immiscible even though $\Delta\delta_t = 0.03\,MP_a^{0.5}$.
[b] Sucrose is immiscible with the drug as confirmed by DSC.

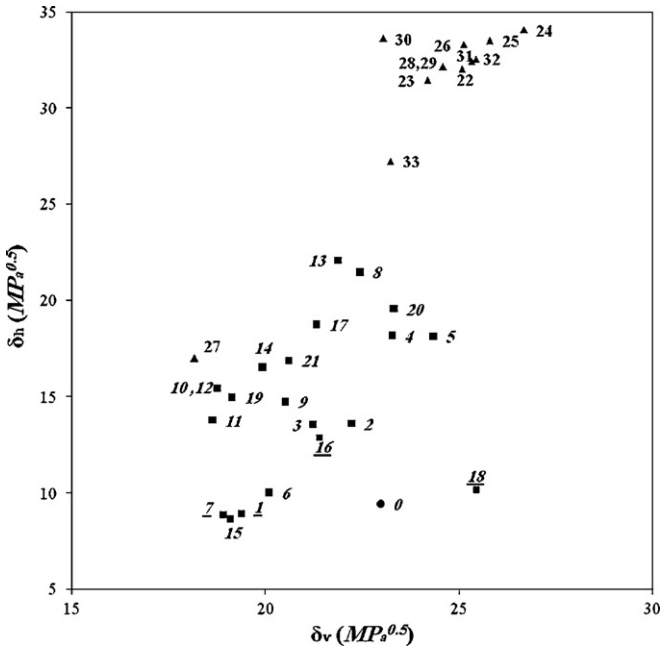


Fig. 2. Positions of indomethacin and coformers within the Bagley diagram. The miscible indomethacin/coformer systems are identified by a circle. Numbers are used to indicate coformers (see Fig. 1). (▲) Immiscible coformers and (■) miscible coformers with indomethacin. Underlining numbers indicate the coformers form cocrystal with indomethacin.

to drug and coformer melting were observed, indicating a lack of miscibility (Fig. S3, Supplementary information).

These results are partly in agreement with the findings of another study in which a combination of Hoy and Hoftyzer/Van Krevelen methods were used to calculate the HSPs (Forster et al., 2001). Using a set of drug/polymers including indomethacin, the authors demonstrated that systems with $\Delta\delta_t < 2\,MP_a^{0.5}$ were miscible, while others containing sucrose, lactose, mannitol or glucose with $\Delta\delta_t > 10\,MP_a^{0.5}$ were immiscible, in line with our results. However, as indicated in several studies, systems with $\Delta\delta_t$ in the range of 5 or 7–10 $MP_a^{0.5}$ may still be immiscible and multiple experimental tools may be required to verify miscibility.

Table 5
Coformers tested for eutectic and cocrystal formation using DSC. The melting temperatures of the coformers were determined experimentally using DSC.

Cocrystal formers tested	Cocrystal former onset melting temperature (°C)	Eutectic melt onset temperature (°C)	Cocrystal[a]
4,4′-Bipyridine	111.5	96.3	Yes
4-Aminobenzamide	182.4	132.6	No
4-Aminobenzoic acid	187.7	133.7	No
4-Hydroxybenzoic acid	214.9	141.4	No
Benzoic acid	122.1	102.2	No
Cinnamic acid	133.3	110.9	Yes
Citric acid	155.2	149.8	No
Cyclamic acid	179.3	152.5	No
Fumaric acid	280.0	157.8	No
Glutaric acid	95.5	92.3	No
Glycine	243.0	No	No
Maleic acid	143	133.6	No
Malic acid	130.2	102.7	No
Malonic acid	134.5	128.1	No
Neotame	75.0	72.1	No
Nicotinamide	128.4	98.8	Yes
Oxalic acid	189.5	139.3	No
Saccharin	228.0	147.7	Yes
Succinic acid	187.8	148.5	No
Urea	134.3	123.1	No
Vanillic acid	209.3	144.6	No

[a] The results are based on limited experimental conditions and screening methods used in the study. It might be possible that more cocrystals could be identified from miscible systems using other methods/conditions.

3.2. Miscibility and cocrystal formation

DSC has recently been used by others to screen for cocrystals (Lu et al., 2008). They found that the eutectic melt formed by heating the physical mixture of cocrystal components recrystallizes to the cocrystal form and melts, independently of the ratios of the components. Though this is a rapid screening method, interpretation of results may not be straight forward or this might fail to identify cocrystal if it shows low crystallization tendency.

In our study, four coformers (nicotinamide, saccharin, 4,4′-bipyridine and cinnamic acid) formed cocrystals with indomethacin according to the DSC. An example DSC thermogram of cocrystal formation from indomethacin and saccharin is presented in Fig. 4. The thermal behavior of indomethacin and three of these coformers (saccharin, 4,4′-bipyridine and cinnamic acid) was similar, suggesting cocrystal formation. Cocrystal formation

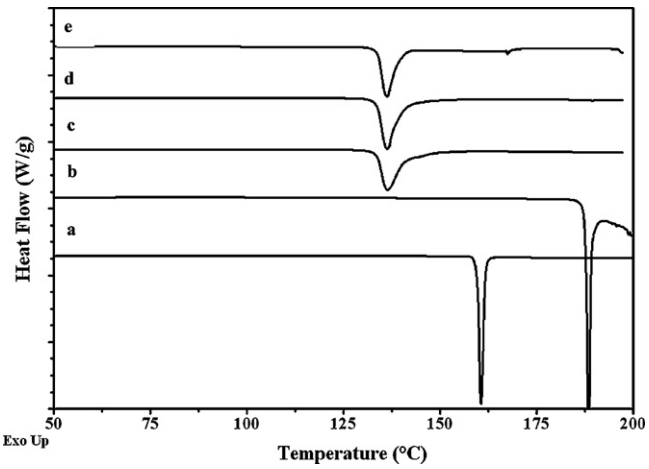


Fig. 3. DSC thermograms showing the eutectic melt point but no cocrystal formation, using indomethacin/4-aminobenzoic acid as an example. (a) Indomethacin gamma form, and (b) 4-aminobenzoic acid and a physical mixture of indomethacin and 4-aminobenzoic acid at ratios of (c) 2:1, (d) 1:1, and (e) 1:2.

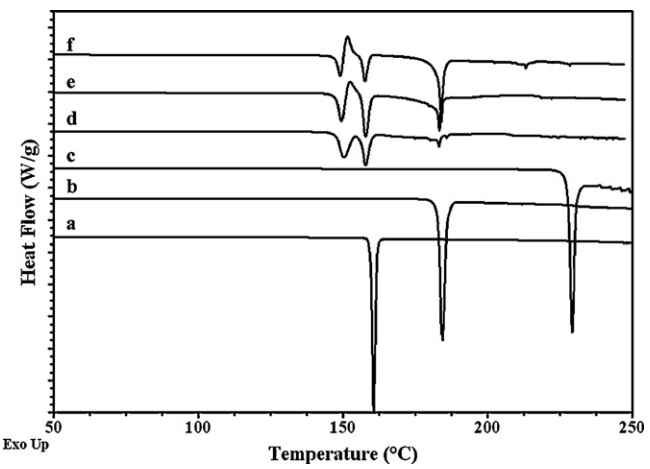


Fig. 4. DSC thermograms showing the eutectic melt point and cocrystal formation, using indomethacin/saccharin as an example. a) Indomethacin gamma form, b) INDSAC cocrystal in pure form, c) saccharin and a physical mixture of indomethacin and saccharin at ratios of d) 2:1, e) 1:1, and f) 1:2.

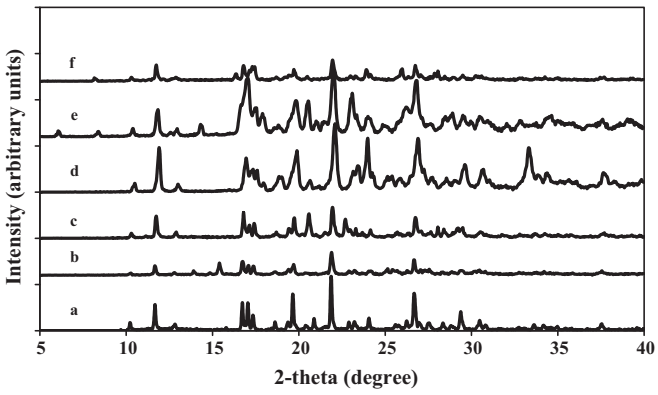


Fig. 5. PXRD patterns of (a) indomethacin gamma form, and resulting materials from LAG experiments with (b) 4-aminobenzoic acid, (c) 4-aminobenzamide, (d) malonic acid, (e) neotame, and (f) benzoic acid. A mixture of phases was also found with other coformers listed in Table 5 after LAG experiments (data not shown).

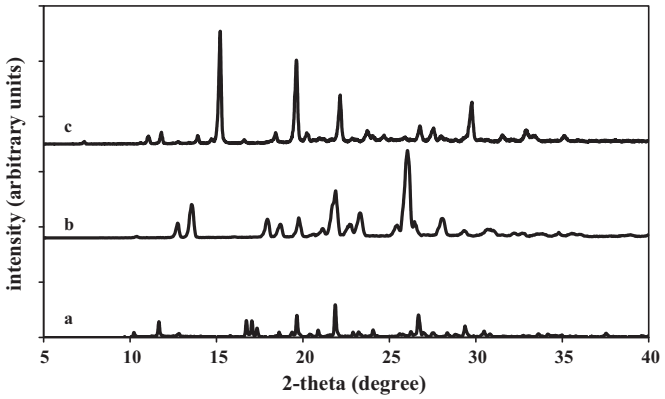


Fig. 7. PXRD patterns of (a) indomethacin gamma form, (b) 4,4′-bipyridine, and (c) indomethacin-4,4′-bipyridine cocrystals prepared by slurry crystallization in ethyl acetate. Peak heights of the 4,4′-bipyridine pattern were minimized for clarity.

for the indomethacin/nicotinamide mixture was only observed at low heating rates (i.e. 0.5 °C/min), indicating an influence of kinetics on cocrystal formation.

LAG screening for cocrystals of indomethacin and the coformers listed in Table 5 confirmed that, in addition to the known cocrystal-forming coformers (i.e. saccharin and nicotinamide), cinnamic acid and 4,4′-bipyridine were able to form cocrystals with indomethacin, as confirmed by different characterization tools. The remaining coformers did not form cocrystals, even though they were found experimentally to be miscible with the drug. The gamma form of indomethacin was found in these reaction mixtures in the LAG experiments (Fig. 5). One of the findings of the study was that sugars were both predicted and tested to be immiscible and failed to form cocrystals with indomethacin. Sugar-based drug cocrystals have not to date been reported; immiscibility between drugs and sugar could explain this.

The new cocrystals were scaled-up in a pure form using slurry crystallization and were characterized by HPLC, DSC, Raman spectroscopy and PXRD. The HPLC analysis confirmed the chemical stability of the drug. Further, indomethacin likely forms 1:1 and 2:1 cocrystals with cinnamic acid and 4,4′-bipyridine, respectively (based on grinding experiments). The melting points of these cocrystals were different from those of the starting materials (S4 and S5, Supplementary information). Further, these cocrystalline phases had distinctly different PXRD patterns from those of the individual drug and coformers. Figs. 6 and 7 present the PXRD patterns for cocrystals of indomethacin with cinnamic acid and 4,4′-bipyridine, respectively. Numerous shifts in the vibrational modes of indomethacin and the coformers were observed in the Raman spectra for the cocrystals (Fig. S6, Supplementary information). A thorough characterization and crystal structures of these new cocrystals are under investigation and will be discussed in details in our future work.

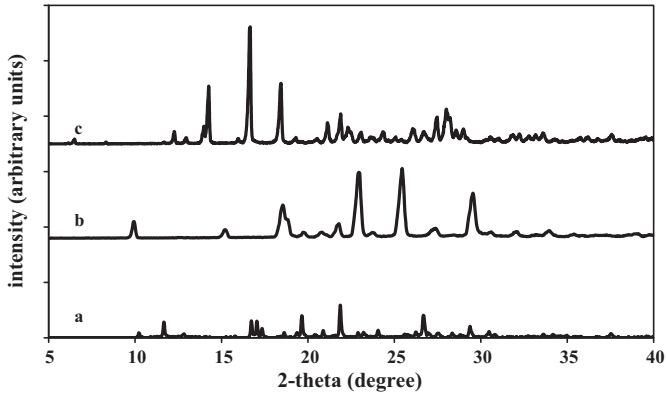


Fig. 6. PXRD patterns of (a) indomethacin gamma form, (b) cinnamic acid, and (c) indomethacin-cinnamic acid cocrystals prepared by slurry crystallization in ethyl acetate. Peak heights of the cinnamic acid pattern were minimized for clarity.

To further examine our hypothesis, $\Delta\delta_t$ was used to estimate the miscibility of 22 and 25 coformers with piroxicam and carbamazepine, respectively, which are known to form cocrystals. It was found that most of the drug/coformer systems had a $\Delta\delta_t$ value that was less than 7 (Fig. 8). The exceptions were camphoric acid and caprylic acid (7.72 $MP_a^{0.5}$ and 10.85 $MP_a^{0.5}$, respectively) with piroxicam, and tartaric acid (10.56 $MP_a^{0.5}$) with carbamazepine. This further endorses Greenhalgh's suggestion that drug/carrier systems with $\Delta\delta_t$ in the range of 7–10 $MP_a^{0.5}$ will be partially miscible (Greenhalgh et al., 1999). It can be deduced that the cocrystal-forming coformers are miscible with these drugs.

In summary, most of the cocrystal-forming coformers investigated in the study were miscible with the drug but not all miscible drug/coformer systems formed cocrystals. Miscible systems can fail to form cocrystals for many reasons, such as lack of hydrogen bonding complementarity, preferred packing patterns, conformational flexibility, molecular shape and size, and stability. Alternatively, though appear less likely, immiscible systems could form cocrystals as a result of strong intermolecular interactions and packing. However, based on the trends observed in our study, it is reasonable to suggest that miscibility of the components is necessary for cocrystal formation. In order to generalize these observations, drugs with different physicochemical profiles and diverse cofomers need to be tested. We are applying these concepts to wider range of substances in our ongoing studies.

3.3. Theoretical and computational models

A good correlation between the shape and polarity of model molecules and cocrystal formation has recently been demonstrated (Fabian, 2009). It has also been proposed that computational methods that rely on lattice energy calculations can predict the structure and formation of cocrystals; these methods are claimed to be superior to chemically intuitive supramolecular synthon-based approaches (Issa et al., 2009; Karamertzanis et al., 2009; Thakur and Desiraju, 2008). An approach using lattice energy calculations has also been applied for predicting stoichiometric cocrystals (Cruz-Cabeza et al., 2008). However, this method does not reliably predict

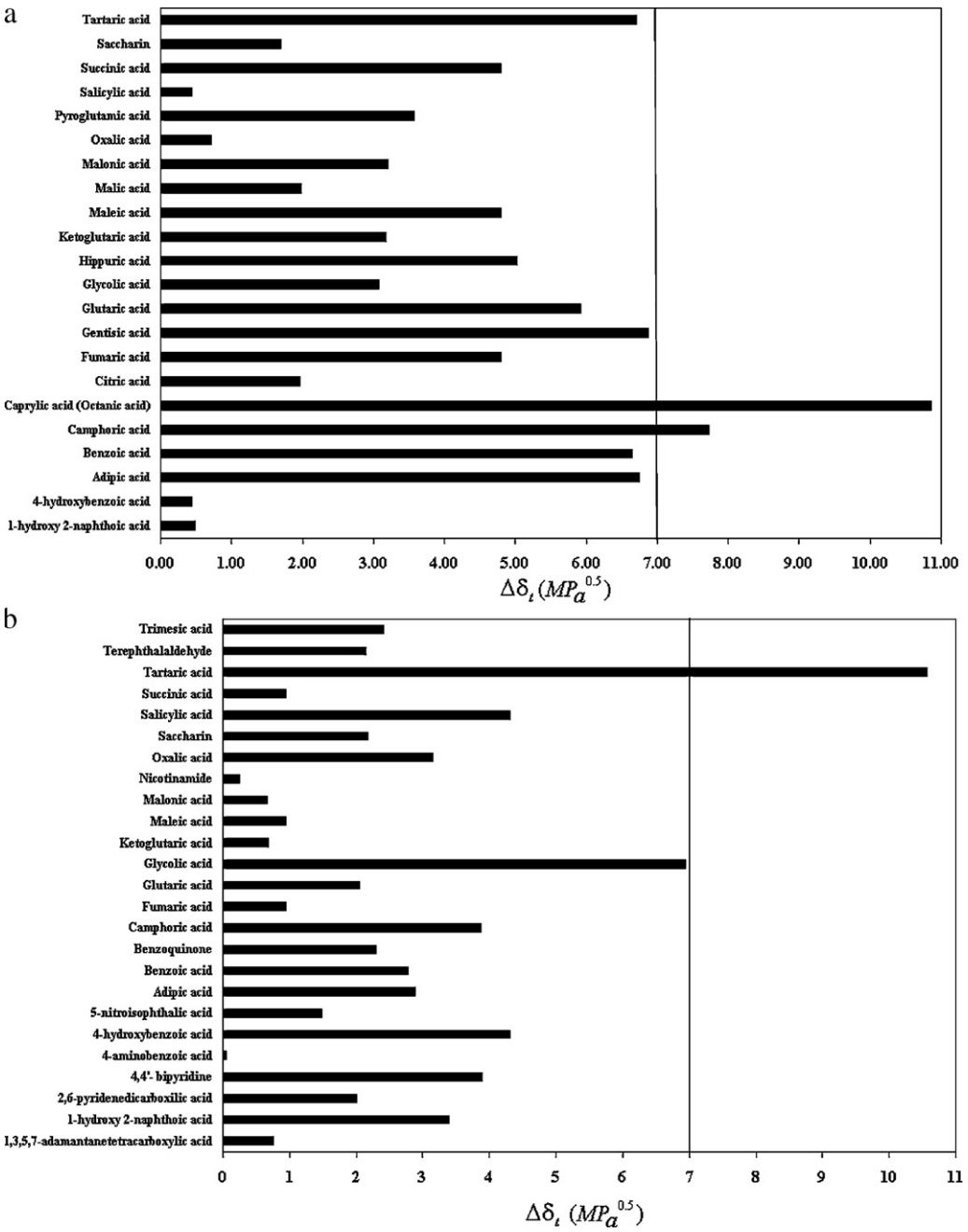


Fig. 8. Differences in the total HSPs of (a) piroxicam and (b) carbamazepine with known cocrystal-forming coformers. The range of $\pm 7\ MP_a^{0.5}$ is marked as an indicator of miscibility according to Greenhalgh et al.

the formation of cocrystals if the predicted lattice energy is not large enough. These methods often rely on the accuracy of the calculation methods and require crystal structure information which may not always be available. Thus, although some potential has been demonstrated, it could be a long time before we can rely on computational methods alone as beneficial tools in cocrystal screening research. In contrast, the solubility parameter approach discussed here is relatively simple, and only requires knowledge of the chemical structure of the components, which is readily available. The model-based approaches may not provide absolute prediction of cocrystal formation but they can potentially guide screening work and rationalize the screening outcomes. Interestingly, there is a direct relationship between the crystal lattice energy of a material (U) and its solubility parameter (δ), as $\delta = (U/V_m)^{0.5}$ (Florence and Attwood, 2006).

4. Conclusions

The overall aim of this study was to investigate whether the miscibility predicted by HSPs can be used to predict cocrystal formation.

Using the group contribution method to calculate partial solubility parameters and Van Krevelen–Hoftyzer, Bagley and Greenhalgh approaches to predict miscibility, 21 of 33 coformers tested were predicted and confirmed to be miscible with indomethacin. Of these miscible systems, four coformers formed cocrystals with indomethacin, including two that were previously unknown. The new cocrystals were scaled-up in pure form and were thoroughly characterized. The results from all three miscibility tools rationalized the miscibility and cocrystal formation better than any other single tool. The differences in HSPs between indomethacin and

coformers correlated well with hydrogen bonding forces but not with other forces.

The investigated approaches were effective in predicting the miscibility of the drug and the coformers. Most of the cocrystal-forming components were miscible but not all miscible components formed cocrystals in the systems tested. Thus, the miscibility between cocrystal components appears to be necessary for cocrystal formation. However, it should be interesting to see if these predictions and trends hold with the wide range of coformers and drug compound types that we are currently working on. The proposed HSPs-based approach would be useful for short listing potential coformers prior to complex laboratory screening experiments, leading to greater efficiency in cocrystal screening programs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2011.01.030.

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