Pharmaceutical Research, Vol. 25, No. 3, March 2008 (© 2007)
DOI: 10.1007/s11095-007-9394-1

Research Paper

Indomethacin–Saccharin Cocrystal: Design, Synthesis and Preliminary Pharmaceutical Characterization

Srinivas Basavoju,[1] Dan Boström,[2] and Sitaram P. Velaga[1,3]

Received December 15, 2006; accepted June 26, 2007; published online August 17, 2007

Purpose. To design and prepare cocrystals of indomethacin using crystal engineering approaches, with the ultimate objective of improving the physical properties of indomethacin, especially solubility and dissolution rate.

Materials and Methods. Various cocrystal formers, including saccharin, were used in endeavours to obtain indomethacin cocrystals by slow evaporation from a series of solvents. The melting point of crystalline phases was determined. The potential cocrystalline phase was characterized by DSC, IR, Raman and PXRD techniques. The indomethacin–saccharin cocrystal (hereafter IND–SAC cocrystal) structure was determined from single crystal X-ray diffraction data. Pharmaceutically relevant properties such as the dissolution rate and dynamic vapour sorption (DVS) of the IND–SAC cocrystal were evaluated. Solid state and liquid-assisted (solvent-drop) cogrinding methods were also applied to indomethacin and saccharin.

Results. The IND–SAC cocrystals were obtained from ethyl acetate. Physical characterization showed that the IND–SAC cocrystal is unique vis-à-vis thermal, spectroscopic and X-ray diffraction properties. The cocrystals were obtained in a 1:1 ratio with a carboxylic acid and imide dimer synthons. The dissolution rate of IND–SAC cocrystal system was considerably faster than that of the stable indomethacin γ-form. DVS studies indicated that the cocrystals gained less than 0.05% in weight at 98%RH. IND–SAC cocrystal was also obtained by solid state and liquid-assisted cogrinding methods.

Conclusions. The IND–SAC cocrystal was formed with a unique and interesting carboxylic acid and imide dimer synthons interconnected by weak N−H···O hydrogen bonds. The cocrystals were non-hygroscopic and were associated with a significantly faster dissolution rate than indomethacin (γ-form).

KEY WORDS: crystal engineering; dissolution rate; indomethacin; pharmaceutical cocrystals; poorly soluble drugs.

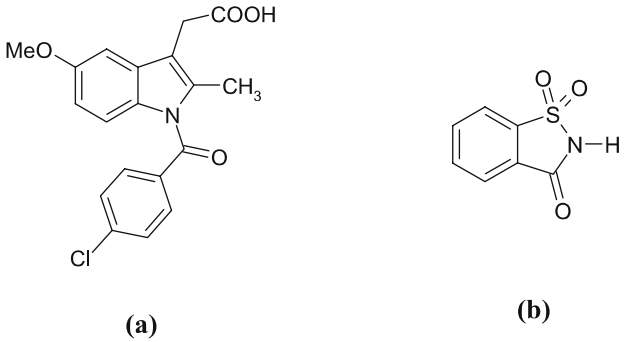
INTRODUCTION

One of the challenging tasks in the pharmaceutical industry is to discover ways of improving the physicochemical properties of active pharmaceutical ingredients (APIs). The solubility, dissolution rate, melting point, moisture sorption tendency, and compressibility of APIs and/or excipients affect the bioavailability, design, processing, manufacturing and stability of the resultant dosage form (1). APIs that permeate easily through mucous membranes but are poorly soluble (BCS class II) have poor bioavailability, and are consequently associated with difficulties in dosage form design and manufacturing. In such scenarios, in order to improve the solubility and thereby the dissolution rate, formulation scientists often turned to various basic approaches such as salt formation, changes in the solid state structure, complexation, encapsulation, etc. (2–4). Though salt formation is a widely implemented and convenient method of improving solubility, it suffers from some disadvantages such as a lack of ionizable groups on the APIs and the availability of only a limited number of nontoxic salt formers (5). Further, solid state manipulation approaches such as metastable phase formation or amorphization of APIs may increase the risk of phase conversion under normal storage conditions (6). When the chances of forming salts (ionic compounds) are limited and the inherent instability of amorphous or metastable solids is not desired, pharmaceutical cocrystallization is a promising alternative for improving the solubility and dissolution rate or manipulating other physical properties of APIs (7).

Pharmaceutical cocrystals are formed with an API (neutral or in the ionic form) and a benign cocrystal former that is solid under ambient conditions (8,9). The cocrystals

Electronic supplementary material The online version of this article (doi:10.1007/s11095-007-9394-1) contains supplementary material, which is available to authorized users.

[1] Department of Health Science, Luleå University of Technology, Luleå, S-971 87, Sweden.
[2] Energy Technology and Thermal Process Chemistry, Umeå University, Umeå, S-901 87, Sweden.
[3] To whom correspondence should be addressed. (e-mail: sitaram.velaga@ltu.se)



Scheme 1. Molecular structures of indomethacin (**a**), saccharin (**b**).

are designed from the first principles of crystal engineering by evaluating the robustness of the potential intermolecular interactions (*supramolecular synthons or hydrogen bonding motifs*) and following general hydrogen bonding rules (10–12). Recent publications provide some interesting examples of pharmaceutical cocrystals and practical guidelines for their design and synthesis (13–15).

Indomethacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid (Scheme 1), is a nonsteroidal drug with anti-inflammatory (NSAID), antipyretic and analgesic properties (Scheme 1a). It is widely prescribed for patients with moderate to severe rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and acute gouty arthritis (16). Indomethacin exists in polymorphic forms α and γ, the latter of which is thermodynamically stable at room temperature (17). Indomethacin (γ-form) is practically insoluble in water (2.5–4 μg/ml; it belongs to BCS class II) with a p*K*a of 4.5. Several methods of improving the solubility or dissolution rate of indomethacin have been proposed. One widespread method involves co-precipitation with hydrophilic polymers or cyclodextrins, resulting in an amorphous form of the drug (18,19). However, the tendency for amorphous indomethacin to transform to the stable γ-form even below $T_g = 42°C$ (i.e. at typical storage temperatures) compromises the solubility advantage, as well as raising serious product development and regulatory concerns (20). Pharmaceutical cocrystallization, on the other hand, offers stable crystalline solids with improved physical properties. Improvement of the physical properties of indomethacin by cocrystallization with a complementary cocrystal former is the subject of this manuscript. The cocrystal formed between indomethacin and the FDA-approved sweetener saccharin (Scheme 1b) appears to be a new cocrystalline phase (IND–SAC) and is one of the few cocrystals with saccharin that have been reported to date (21,22).

This paper describes the formation of the IND–SAC cocrystal, using crystal engineering strategies, and its pharmaceutical characterization. The physical state of IND–SAC cocrystals was characterized by IR, Raman, DSC, and PXRD. The IND–SAC crystal structure was determined by single-crystal X-ray diffraction. Pharmaceutical characterizations of IND–SAC included dissolution studies and DVS measurements. The IND–SAC cocrystal was also generated by solid state and liquid-assisted (23) grinding experiments.

MATERIALS AND METHODS

Indomethacin (γ-form) and cocrystal formers including saccharin were purchased from Sigma Aldrich, Stockholm, Sweden. The purity of these chemicals was >99.9%. All solvents (purity >99.8%) were also sourced from Sigma Aldrich, Stockholm, Sweden. All chemicals and solvents were used as received. Distilled water was used in the study.

Screening for Indomethacin Cocrystals

Several complementary cocrystal formers (see supplementary information) in suitable molar ratios were selected from a range of carboxylic acids, sugars and amino acids. The solution cocrystallization method was employed in the screening for cocrystals. A number of solvents, including ethanol, ethyl acetate, 1-propanol, 2-propanol, methanol, chloroform, acetone, acetonitrile and *N*,*N*-dimethylformamide, were used. IND–SAC was the only cocrystal obtained.

Cocrystallization of Indomethacin–Saccharin

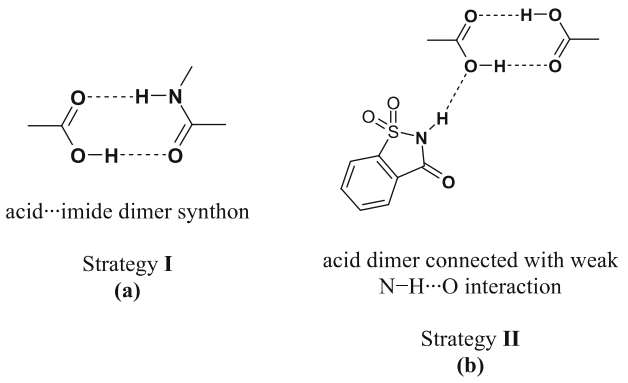
A 1:1 mixture of indomethacin (35.78 mg, 0.1 mmol) and saccharin (18.32 mg, 0.1 mmol) was added to 6–7 ml of ethyl acetate in a 25 ml conical flask and heated to aid dissolution. The solution was allowed to evaporate slowly in a controlled fume hood (temperature 22°C, air flow 0.54 m/s) to produce cocrystals. The resultant IND–SAC cocrystals were then scaled up to 14 g for further analyses.

Preliminary Characterization

The melting point of IND–SAC cocrystals was obtained using an Electro Thermal 1A9000 series digital melting point apparatus. Optical micrographs of cocrystals were taken under the Leica MZ6 polarizing microscope.

IR Spectroscopy

A Perkin Elmer 2000 FT-IR spectrophotometer was used in KBr diffuse reflectance mode (sample concentration 2 mg in 20 mg KBr) for collecting the IR spectra of the samples. It was equipped with an MCT detector. A total of 500 scans were collected over the range of 4,000–400 cm^{-1}



Scheme 2. Strategies involved in the design of IND–SAC cocrystal.

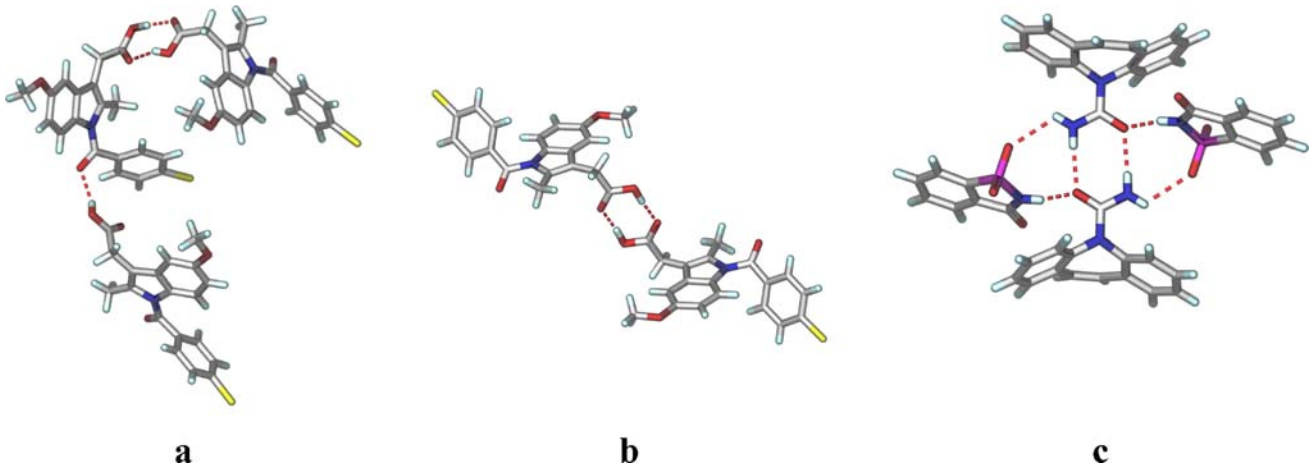


Fig. 1. Hydrogen bonding: **a** The indomethacin α-form. Two of the three symmetrically independent molecules form a carboxylic acid dimer synthon and the carboxylic acid group of the third molecule forms an O–H···O hydrogen bond with the amide carbonyl group of one of these two molecules. **b** The indomethacin γ-form. The two molecules form a robust acid dimer synthon. **c** The carbamazepine–saccharin (CBZ–SAC) cocrystal contains an imide dimer synthon and forms N–H···O hydrogen bonds with the saccharin molecule.

for each sample. Data were analyzed using Spectrum software (version 1.5, 24 Feb 1997).

Raman Spectroscopy

The Raman spectra were recorded on a Perkin Elmer NIR FT-Raman 1700X spectrometer equipped with an indium–gallium–arsenide (InGaAs) detector. An excitation wavelength of 1,064 nm of Nd: YAG laser radiation was used. A total of 50 scans were collected from 4,000–400 cm^{-1} for each sample. Data were analyzed using Spectrum software (version 1.5, 24 Feb 1997). Raman spectra for different samples are presented in the supplementary information.

Differential Scanning Calorimetry (DSC)

Thermal analyses of the samples were performed on a Thermal Advantage DSC Q1000 V9.8 Build 296 (TA instruments-Waters, LLC) module which was calibrated for temperature and cell constants using indium and sapphire. Samples (3–5 mg) were crimped in non-hermetic aluminium pans (30 μl) and scanned at a heating rate of 10°C/min in the range 25–300°C under a continuously purged dry nitrogen atmosphere (flow rate 50 ml/min). The instrument was equipped with a refrigerated cooling system. The data were collected in triplicate for each sample and were analyzed using TA Instruments Universal Analysis 2000 V4.3A software.

Powder X-ray Diffraction (PXRD)

Initially, the PXRD pattern of the IND–SAC cocrystals was collected on a Bruker D8Advance powder diffractometer with Cu Kα radiation (1.54056 Å). The diffractometer was equipped with a primary Göbel mirror and a super-speed VÅNTEC-1 detector (a position sensitive detector). The sample was enclosed in a capillary (0.7 mm) and spun in the diffractometer. The pattern was collected repeatedly under continuous scanning at a rate of 3°/min between 5° and 50° 2θ over 14 h. The scans were accumulated successively. The experimental PXRD patterns and simulated PXRD spectra from single crystal structure determinations were Rietveld refined using TOPAS R (version 2.1, 2003) software to confirm the composition of the material.

At a later stage, the PXRD patterns for the indomethacin, saccharin and cogrinding samples were collected on a Siemens DIFFRACplus 5000 powder diffractometer with Cu Kα radiation (1.54056 Å). The tube voltage and amperage were 40 KV and 40 mA, respectively. The divergence slit and antiscattering slit settings were variable for illumination of the 20 mm sample. Each sample was scanned between 5° and 50° 2θ with a step size of 0.02°. The instrument had previously been calibrated using a silicon standard.

Single Crystal X-ray Diffraction

The single crystal X-ray diffraction data of the crystals were collected on a Bruker Nonius Kappa CCD. The data set for the IND–SAC cocrystals was collected at 150 K using Mo Kα radiation ($\lambda = 0.71073$ Å). Lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program MAXUS. The crystal

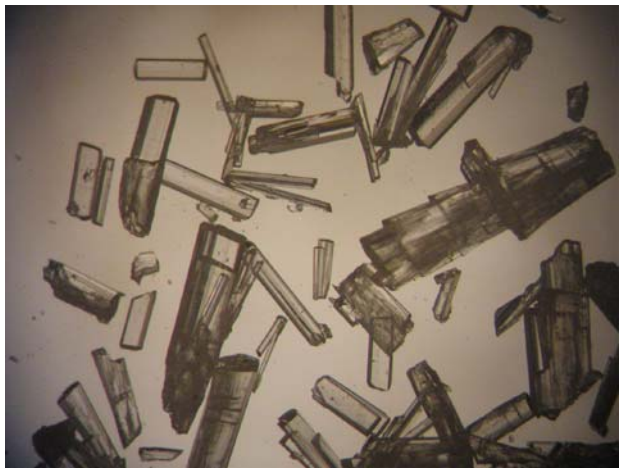


Fig. 2. Optical micrograph of IND–SAC cocrystals.

structure was solved by direct methods using SHELXS-97 and refined by full matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97 (24). N–H, O–H and $-CH_3$ group hydrogens on indole group were located from difference Fourier maps, and aromatic and aliphatic C–H hydrogens were generated by the riding model in idealized geometries. Table II gives the pertinent crystallographic data, and Table III gives the hydrogen-bond parameters.

Dissolution Studies

A previously reported HPLC method was used with minor modifications to determine the concentrations of indomethacin (25). A complete Perkin Elmer HPLC system, including a solvent delivery pump, a controller and a UV detector, was used in this study. A 25 cm C-18 (Restek, Ultra Aqueous) column containing particles with a diameter of 5 μm and a pore size of 4.5×150 mm was used for drug elution at room temperature. The mobile phase consisted of 75 vol of methanol and 25 vol of 0.2% phosphoric acid. The mobile phase was degassed and pumped at a flow rate of 1.5 ml/min. The injection volume of the solution was 80 μl. The drug was eluted isocratically and monitored with a UV detector operating at 319 nm. The assay run time and retention times for indomethacin were 10 and 5 min, respectively. The peak areas were integrated using Totalchrom Navigator 200-UV software (Version 6.2.0.0.0:B27). A calibration curve containing varied concentrations of indomethacin was drawn before the start of the dissolution studies.

For the dissolution studies, the samples were micronized and sieved using ASTM standard-mesh sieves (mesh size 125 μm). In each experiment, three 500 ml round-bottomed flasks containing 250 ml phosphate buffer (60 or 200 mM, pH 7.4) were equilibrated at 26.0°C (±1) in a laboratory oven (Memmert, Germany). The powdered samples of approximately (or corresponding to, for cocrystals) 1.2 g of

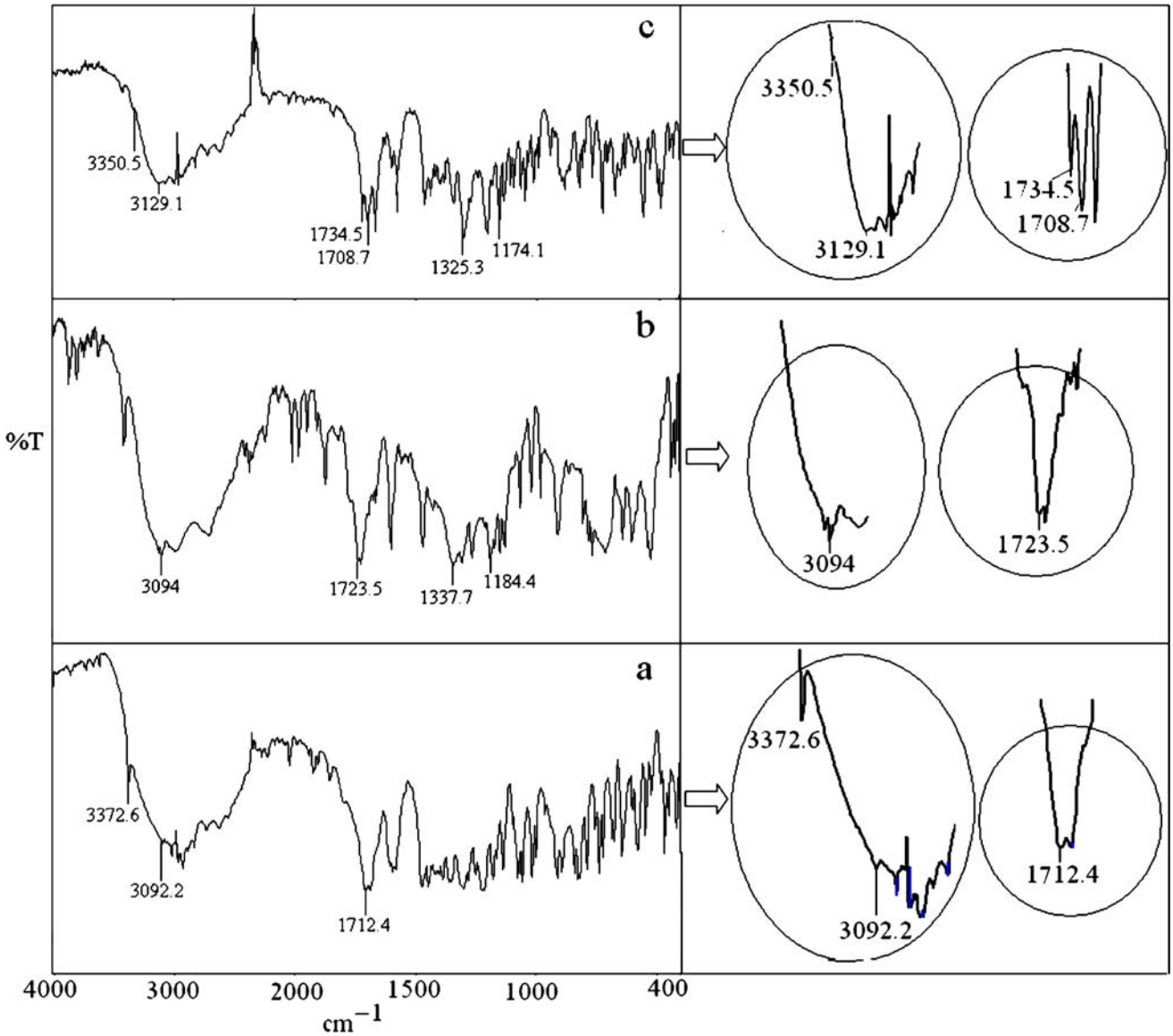


Fig. 3. IR spectra for **a** indomethacin; **b** saccharin; and **c** IND–SAC cocrystals.

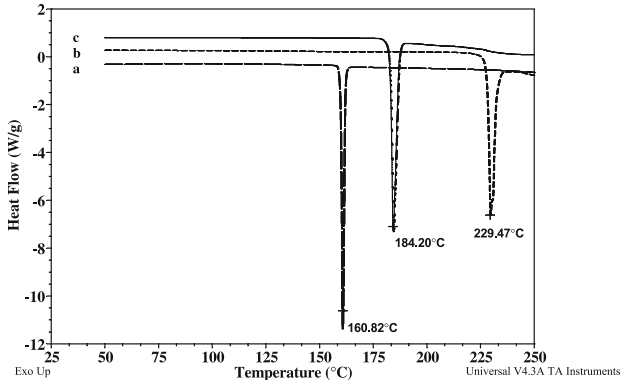


Fig. 4. DSC thermograms for **a** indomethacin; **b** saccharin; and **c** IND–SAC cocrystals.

indomethacin were added to the flasks, and the resulting slurry was stirred at 300 rpm on a magnetic stirrer. At specific time intervals over 2–3 days, an aliquot of the slurry was withdrawn from the three flasks and filtered through a 0.2 μm syringe filter (cellulose acetate membrane). A 20 μl sample of filtered aliquot was then injected directly into the HPLC column. The concentration of indomethacin in each sample was calculated from the standard graph. After the last aliquot had been collected, the remaining undissolved solids were collected by vacuum filtration, dried at room temperature and analyzed by PXRD. The pH of the filtrate was determined.

Dynamic Vapour Sorption (DVS) Studies

A DVS Advantage instrument (Surface Measurement systems, UK) was used for these studies. The high mass resolution (±0.1 μg) and excellent baseline stability allowed the instrument to measure the adsorption and desorption of very small amounts of the probe compound. All samples were initially dried for several hours under a continuous flow of air to establish the equilibrium dry mass. The relative humidity (RH) was then increased from 0 to 30% in 5% steps and then by 10 steps to 90% RH, followed by a 5% step to 98% RH. For the desorption cycle, the RH was decreased in a similar manner. The temperature was maintained at a constant 25 ± 0.1°C. The sorption isotherms were calculated from the equilibrium mass values.

Cogrinding Experiments

Cogrinding experiments were performed to check the feasibility of generating cocrystals using 'green chemistry' methodology and to assist in understanding the mechanism of cocrystal formation. A Retsch MM301 Mixer Mill, equipped with 10 ml stainless steel grinding jars, with one 5 mm and one 7 mm stainless steel grinding ball per jar, was used. All cogrinding experiments were performed at a rate of 30 Hz. The external temperature of the grinding jar has not exceeded ca 30°C.

Solid-State Grinding

A 1:1 mixture of indomethacin (143.2 mg, 0.4 mmol) and saccharin (73.27 mg, 0.4 mmol) were placed in a 10 ml grinding jar and coground for 15 min, 30 min or 60 min, using a fresh batch for each grinding period. The powder samples were then collected for PXRD.

Liquid-assisted (Solvent-Drop) Grinding

A 1:1 mixture of indomethacin (143.2 mg, 0.4 mmol) and saccharin (73.27 mg, 0.4 mmol) were placed in a 10 ml grinding jar, and one drop of solvent was added. The solvents

Table II. Crystallographic Data and Refinement Parameters of IND–SAC Cocrystal

Empirical Formula	$C_{26}H_{21}SClN_2O_7$
Formula Weight	540.97
Crystal System	triclinic
Space group [no.]	$P\bar{1}$ [2]
T [K]	150 (2)
a [Å]	7.1123 (2)
b [Å]	10.3751 (3)
c [Å]	16.6615 (3)
α/(°)	79.8437 (14)
β/(°)	86.524 (2)
γ/(°)	79.4256 (13)
Z	2
V [Å^3]	1189.14 (9)
D_{calc} [g/cm^3]	1.511
μ/mm^{-1}	0.301
F(000)	560
Theta range for data collection	3.14 to 30.41
Reflections collected	12,636
Unique reflections	7,192
Observed reflections	5,802
Parameters	354
R_1	0.0617
wR_2	0.1726
GOF	1.155
CCDC No.	639251

Table I. Melting Points and Enthalpy Values for Relevant Samples

Compound	Melting Point (T_{max}) (°C)	ΔH (kJ/mol)	Reported Melting Point (°C)
Indomethacin (γ-form)	160.82 (0.17)	39.99 (0.49)	162[20]
Indomethacin (α-form)	–	–	154.5–155.5[20]
Saccharin	229.47 (0.18)	26.77 (0.52)	227[b]
IND–SAC cocrystal	184.20 (0.15)	79.39 (0.52)	–

Standard deviation is indicated in the parentheses in columns 1 and 2. Superscripts indicate reference literature in column 4.
[b] From Sigma Aldrich catalogue

Table III. Hydrogen Bond Parameters in IND–SAC Cocrystal

D–H···A[a]	D···A (Å)	H···A (Å)	D−H···A (deg)
O2–H9···O1	2.659 (3)	1.68	171.50
N2–H17···O2	3.180 (3)	2.58	117.18
N2–H17···O7	2.859 (3)	1.89	160.07
C4–H1···O5	3.518 (3)	2.46	164.81
C9–H7···O5	3.628 (3)	2.76	136.51
C9–H8···O6	3.567 (3)	2.53	158.76
C12–H6···O6	3.621 (4)	2.58	160.46
C12–H5···O7	3.587 (3)	2.50	177.36
C15–H13···O5	3.621 (3)	2.57	163.06
C22–H18···O6	3.642 (3)	2.79	135.58
C23–H19···O1	3.311 (4)	2.59	123.37
C24–H20···O4	3.306 (4)	2.43	136.91

[a] All the C–H, N–H and O–H distances are neutron-normalized to 1.083, 1.009 and 0.983 Å, respectively.

used were ethyl acetate, ethanol, dichloromethane or water, since these represent solvents in which both or at least one component of the cocrystal dissolves. The mixture was ground for 15 min or 30 min in the mixer mill grinder using a fresh batch for each grinding period. The powder was then dried and collected for PXRD.

RESULTS AND DISCUSSION

Design Strategies for Indomethacin Cocrystals

A Cambridge Structural Database (CSD ConQuest version 5.27, Nov 2005, number of hits 355064) analysis revealed only four organic molecules of indomethacin; two of these are solvates of *tert*-butyl alcohol and methanol (refcodes BANMOT01 and BANMUZ) and the other two are the polymorphic forms α and γ (refcodes INDMET02 and INDMET03, respectively). The two solvates of indomethacin form tetramer synthons (O−H···O) in the crystal structures (26–28). The α-form comprises three symmetrically independent molecules, of which two form the carboxylic acid dimer synthon (Fig. 1a). In the γ-form, the asymmetric unit consists of only one molecule of indomethacin which forms the carboxylic acid dimer synthon (Fig. 1b). Examination of the crystal structures of indomethacin reveals that the carboxylic acid group is the main hydrogen bond donor–acceptor functionality; this group forms robust supramolecular synthons.

As the carboxylic acid group is the principal functional unit in the indomethacin molecule, several FDA-approved cocrystal formers with complementary functional groups (such as carboxylic acid, amide, pyridyl, hydroxyl, etc.) were selected for the cocrystallization experiments. The only one of these to form a cocrystal with indomethacin was saccharin. While the carboxylic acid homodimer synthon is present in indomethacin (α and γ), saccharin contains a strong hydrogen bond acceptor (C=O) and strong donors (N–H) to form a robust imide homodimer synthon in the crystal structure (29). In the process of generating the IND–SAC cocrystal, two possible supramolecular synthons were expected before crystallization (Scheme 2). The first strategy is the formation of a carboxylic acid···imide hetero synthon between the indomethacin and saccharin molecules (Scheme 2a). The second possibility is the formation of a carboxylic acid homodimer synthon of indomethacin with an interaction between this acid dimer and the saccharin N–H group, as seen in the carbamazepine–saccharin (CBZ–SAC) cocrystal in Fig. 1c (Scheme 2b) (30).

The second strategy seemed to be successful in forming the IND–SAC cocrystal, with the carboxylic acid dimer synthon interacting with the saccharin N–H group. Interestingly, saccharin also forms an imide dimer synthon to fulfill the hydrogen bonding possibilities. Further, the geometry of the carboxylic acid dimer synthon of indomethacin is devoid of all the steric hindrances to form the saccharin imide dimer synthon. Indeed, there are few examples in the CSD with the carboxylic acid dimer and imide dimer synthons (31). However, this is the first example of a cocrystal with an interaction (even though the connecting N–H···O is very weak) between the acid dimer and imide dimer synthons. Thus, this type of pattern can be expected in the pharmaceutical cocrystallization of compounds with imides, cyclic amide groups (lactam) or amide groups but without additional anti hydrogen atoms (–CONH–).

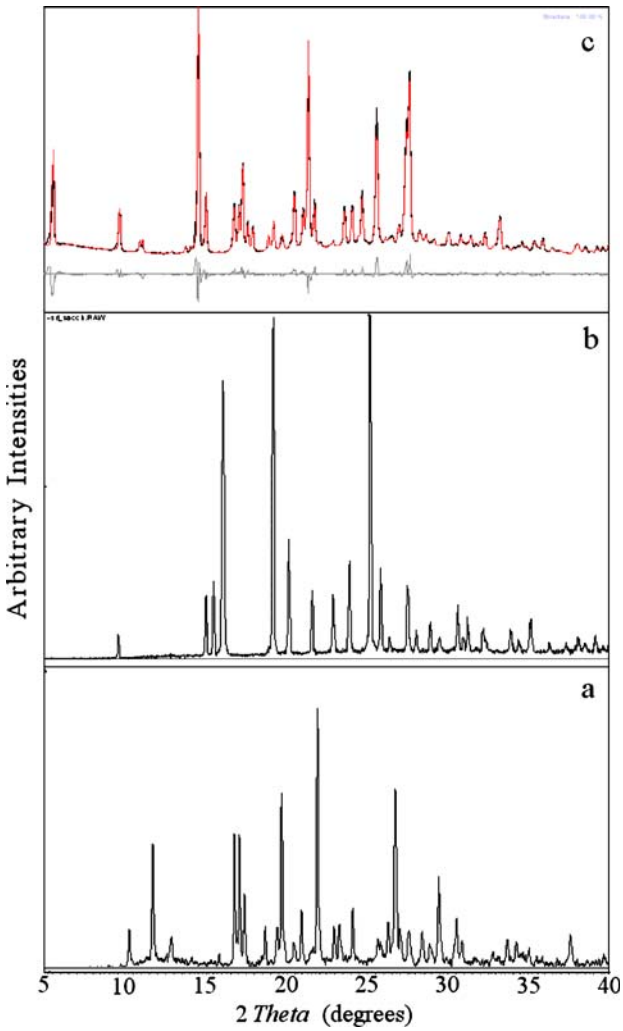


Fig. 5. PXRD patterns for **a** indomethacin; **b** saccharin; and **c** IND–SAC cocrystals showing a comparison of Rietveld–refined simulated (*red*), experimental (*black*) and difference (*gray*) patterns.

Preliminary Characterization of IND–SAC Cocrystals

The optical micrograph of IND–SAC cocrystals is shown in Fig. 2. IND–SAC cocrystals were colourless needle-shaped diffraction quality crystals and were obtained within two days. IND–SAC cocrystals were also obtained from other solvents such as ethanol, 1-propanol, 2-propanol, $CHCl_3$, acetonitrile and DMF upon slow evaporation. However, cocrystallization from methanol and acetone yielded a mixture of individual phases comprising cocrystals, the indomethacin α-form and saccharin. A clear sharp melting point at around 184°C was observed for the IND–SAC cocrystals. This lies in the region between the melting points of the individual native compounds, indomethacin (162°C) and saccharin (225–227°C). The distinct melting point of IND–SAC cocrystals indicate the formation of a new crystalline phase.

IR Spectroscopic Analysis

The IR spectra for indomethacin (γ-form), saccharin and IND–SAC cocrystals are presented in Fig. 3. The IR spectrum for indomethacin (γ-form) had peaks at 3,372.6 and 1,712.4 cm^{-1}, corresponding to carboxylic O−H and C=O stretch, respectively (Fig. 3a) (32). This indicates that indomethacin (γ-form) was the starting material in the cocrystallizations. The spectrum of pure saccharin had peaks corresponding to N−H and C=O stretch of the secondary amide at 3,094 and 1,723.5 cm^{-1} (Fig. 3b) (33,34). Additionally, asymmetric and symmetric stretching frequencies of the $-SO_2$ group were observed at 1,337.7 and 1,184.4 cm^{-1}, respectively (35).

The O–H stretching frequency of the carboxylic acid group of indomethacin and the N–H stretching frequency of the cyclic imide group of saccharin were observed at 3,350.5 and 3,129.1 cm^{-1}, respectively in IND–SAC cocrystals (Fig. 3c). This suggests that both molecules are present in the new phase. The decrease in the O−H stretching frequency from 3,372.6 cm^{-1} in indomethacin γ-form to 3,350.5 cm^{-1} in IND–SAC cocrystals implies that the O−H group is participating in a strong hydrogen bond. Subsequently, the increase in the N−H stretching frequency from 3,094 cm^{-1} in the imide dimer of saccharin to 3,129.1 cm^{-1} in IND–SAC cocrystals suggests that the N−H group is participating in a weak hydrogen bond. A hypsochromic shift in the saccharin C=O stretching frequency from 1,723.5 cm^{-1} to 1,734.5 cm^{-1} further explains the formation of IND–SAC cocrystals. The asymmetric and symmetric stretching frequencies of the $-SO_2$ group of saccharin were also observed in IND–SAC cocrystals at 1,325.3 and 1,174.1 cm^{-1}, respectively.

DSC Analysis

DSC experiments were carried out to study the thermal behavior of the IND–SAC cocrystals in relation to the individual components. The DSC traces and thermal data for indomethacin (γ-form), saccharin and IND–SAC cocrys-

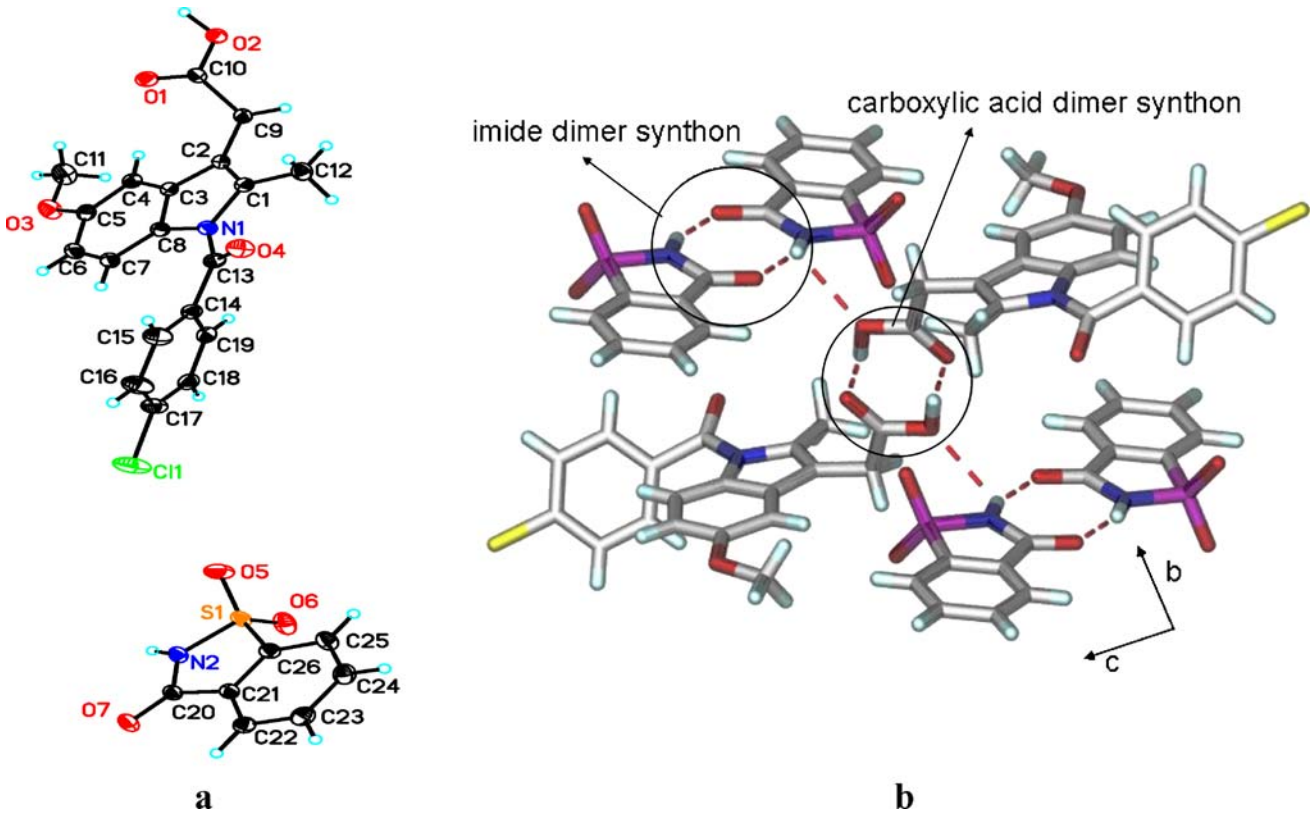


Fig. 6. ORTEP representation of the indomethacin–saccharin (IND–SAC) cocrystal. **a** Thermal ellipsoids are drawn at the 50% probability level. **b** Carboxylic acid dimer and imide dimer synthons in IND–SAC cocrystals.

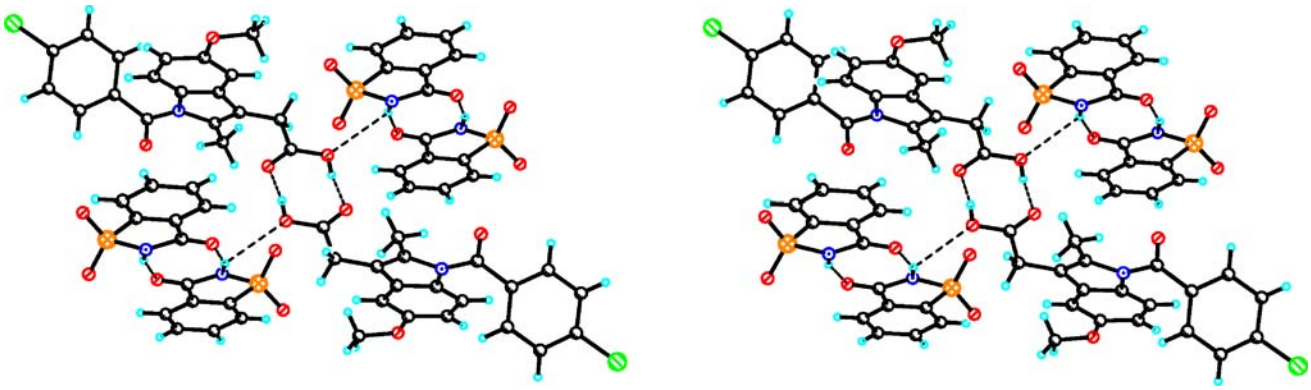


Fig. 7. Stereovision of IND–SAC cocrystals showing the perpendicular arrangement of acid and imide dimer synthons.

tals are presented in Fig. 4. Indomethacin showed a single melting transition with $T_{max} = 160.82°C$ and enthalpy (ΔH_f) = 39.99 kJ/mole (Fig. 4a and Table I). This indicates that indomethacin was in the γ-form (31). Saccharin showed a steep endothermic change, attributed to melting at 229.47°C with a ΔH_f of 26.77 kJ/mole, in agreement with reported thermal behavior (Fig. 4b) (36). The DSC thermogram for IND–SAC cocrystals showed a single endothermic transition attributed to the melting transition (T_{max} = 184.20°C, ΔH_f = 79.39 kJ/mole) (Fig. 4c). The T_{max} values for IND–SAC cocrystals and the individual components agreed with the measured melting range in the melting point determination. The thermal behavior of the cocrystals was distinct, with a different melting transition from that seen with either of the individual components; this suggests the formation of a new phase: IND–SAC cocrystals. A single endothermic transition for the IND–SAC cocrystals indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point.

PXRD Analysis

The PXRD patterns for indomethacin (γ-form), saccharin and IND–SAC cocrystals are depicted in Fig. 5a–c. The PXRD pattern for indomethacin was similar to that reported for the γ-form, supporting the interpretation of the DSC results (28). The PXRD of saccharin was in concurrence with the reported pattern (37). A different powder X-ray pattern for the IND–SAC cocrystals from those of the constituent indomethacin γ-form and saccharin confirms the formation of a new cocrystal phase. The recording of the initial small angles (5–8° 2θ) sufficiently identifies the distinct crystal form of IND–SAC cocrystals, which makes PXRD the method of first choice for fast identification of the new phases. The experimental and single-crystal simulated PXRD patterns of IND–SAC cocrystals were Rietveld refined to enable comparison of the spectra (Fig. 5c). The resemblance of the two patterns in this spectrum validates the respective methods and indicates the purity of the IND–SAC cocrystalline phase.

Crystal Structure Analysis

The IND–SAC cocrystal adopts the centrosymmetric triclinic $P\bar{1}$ space group, with one molecule each of indomethacin and saccharin in the asymmetric unit (Fig. 6a). The conformation of the indomethacin molecule in IND–SAC cocrystals is comparable to that of the one of the three symmetry independent molecules that is not participating in the acid dimer synthon of the α-form. In IND–SAC cocrystals, the dihedral angle between the mean planes passing through the C-atoms of the indole ring system and the *p*-chlorophenyl ring is 61.68° and in the γ-form it is 66.51°. In the α-form, these angles in the three symmetry independent molecules are 64.31°, 70.36° and 69.38°. The methoxy (–OCH_3) group of the indomethacin molecule in IND–SAC cocrystals is coplanar with the indole moiety (torsion angle C6–C5–O3–C11 = 175.57°), as occurs in the α and γ-forms of indomethacin.

The IND–SAC crystal structure analysis revealed that the indomethacin molecules form a carboxylic acid dimer (R_2^2 (8) motif) (O···O; 2.659(3), O–H···O; 171.50°) synthon centered at an inversion center and the saccharin molecules form an imide dimer (R_2^2 (8) motif) (N···O; 2.859(3), N–H···O; 160.07°) synthon (Fig. 6b). The carboxylic acid dimer and imide dimer synthons are arranged nearly perpendicular to each other to overcome the steric hindrance caused by the indole moiety and saccharin molecules (Fig. 7). In addition, repulsion between the oxygen atoms of the S=O group in the saccharin molecule and the carboxylic acid C=O group of the indomethacin molecule causes perpendicularity between the acid dimer and the imide dimer synthons. The two dimer

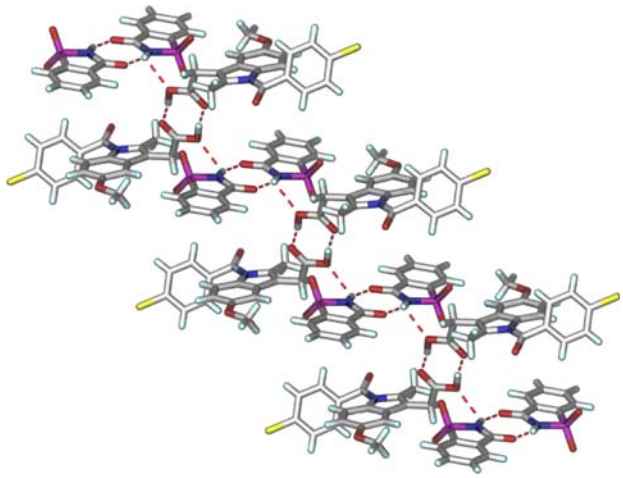


Fig. 8. Packing diagram of IND–SAC cocrystals. Note that both the carboxylic acid dimer and the imide dimer synthons are interconnected by weak N–H···O hydrogen bonds.

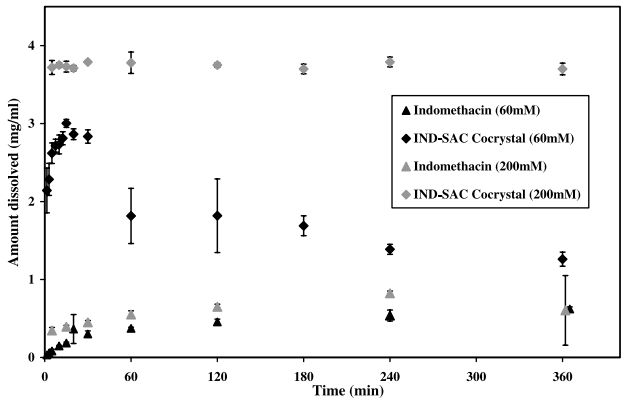


Fig. 9. Solubility and dissolution profiles for indomethacin and IND–SAC cocrystals, respectively. A phosphate buffer of pH 7.4 with different strengths (as indicated in the legend) is used as a dissolution medium.

synthons (acid and imide dimers) are interconnected by a weak N–H···O (N···O; 3.180(3), N–H···O; 117.18°) hydrogen bond which extends in one dimension along the *b*-axis (Fig. 8). This pattern is unique among all the crystal structures. These one-dimensional aggregates propagate into a second dimension *via* a weak C−H···Cl interaction along the *c*-axis. The overall structure is stabilized by the auxiliary C−H···O hydrogen bonds.

A few structural similarities between the indomethacin γ-form and IND–SAC cocrystals can be demonstrated. In the γ-form, the separation between the two alternative carboxylic acid dimers is 8.725 Å, along the *c*-axis (10 Å axis), whereas, in the IND–SAC cocrystals, the separation is 8.307 Å, along the *b*-axis (10 Å axis). In the γ-form, between the two carboxylic acid dimers, the *p*-chlorophenyl rings of the two inversion-related molecules stack with $\pi\cdots\pi$ (centroid to centroid, 3.922 Å) interactions whilst, in IND–SAC cocrystals, this space is occupied by saccharin molecules.

Dissolution Studies

Powder dissolution profiles for indomethacin (γ-form) and IND–SAC cocrystals at different strengths (60 and 200 mM) of phosphate pH 7.4 buffer at 26°C are shown in Fig. 9. The peak dissolution for powdered indomethacin (γ-form) was obtained after approx 250 min, which is indicative of its poor solubility. The time for peak dissolution was independent of buffer concentration. However, the dissolution rate for indomethacin (γ-form) was consistently higher in 200 mM buffer. The PXRD analysis of the solid filtrates obtained from both buffer concentrations demonstrate the stability of the γ-form. In fact, the pH of the system was not changed. The solubilities were 0.72 mg/ml (±0.1) and 1.3 mg/ml (±0.2) in 60 and 200 mM pH 7.4 phosphate buffers, respectively.

As shown by the dissolution profiles, in 60 mM pH 7.4 buffer, IND–SAC cocrystals dissolved instantaneously, followed by a period of intense precipitation with an instantaneous drop in the pH of the system to 6.8. The PXRD analysis of the filtered precipitates suggested amorphous phase with traces of crystalline solid (see supplementary information). It appears that the abrupt drop in the pH of the system triggered the dissociation of the cocrystals, resulting in the precipitation of a mixture of amorphous saccharin and/or indomethacin and traces of α-form of indomethacin. When the buffer strength was increased to 200 mM to stabilize the pH of the system, the dissolution of IND–SAC cocrystals was extremely rapid; peak concentrations (~3.7 mg/ml) were achieved before the first sampling. The system was observed to be stable in terms of holding the concentration of indomethacin at the same level for several hours. However, PXRD analysis of the undissolved solids indicated the disappearance of cocrystal peaks indicating phase in equilibrium is not cocrystal (see supplementary information). To completely understand the solubility behaviour of IND–SAC cocrystal, it is important to consider ionization of the ligand, complexation phenomenon and solution chemistry (38,39). In depth dissolution and solubility studies elucidating these aspects are currently under way in our laboratory. This preliminary study indicates that the dissolution rate of the cocrystal system in 200 mM pH 7.4 phosphate buffer was increased considerably (>50 times) compared with stable indomethacin γ-form.

DVS Studies

Dynamic vapour sorption and desorption isotherms for various samples are shown in Fig. 10. It was evident that IND–SAC cocrystals sorbed negligible water (<0.05%); less than the stable form of indomethacin (γ-form) at 95%RH. However, the trend was changed at RH beyond 95%: IND–SAC cocrystals sorbed more water than the γ-form and ultimately gained ≈0.1% at around 98%RH. These results indicate the IND–SAC cocrystals are nonhygroscopic. Further, the sortion–desorption curves suggest no solid state transformation or dissociation of the cocrystal under the experimental conditions.

Cogrinding Experiments

Cogrinding experiments, *viz*. solid state and liquid-assisted, were performed with two specific objectives: (1) to investigate the feasibility of forming IND–SAC cocrystals by 'green chemistry methods', (2) to obtain preliminary information about the formation mechanisms of IND–SAC in these experiments. PXRD spectra were collected before and after subjecting the mixture to solid state or liquid-assisted grinding for different time intervals (Fig. 11a–f). Room temperature solid state grinding of indomethacin (γ-form) and saccharin initiated conversion/

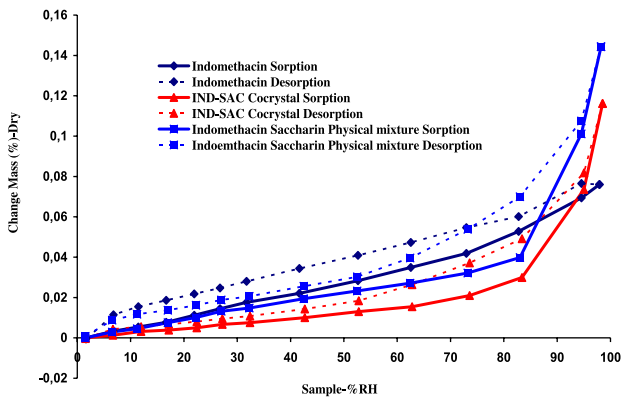
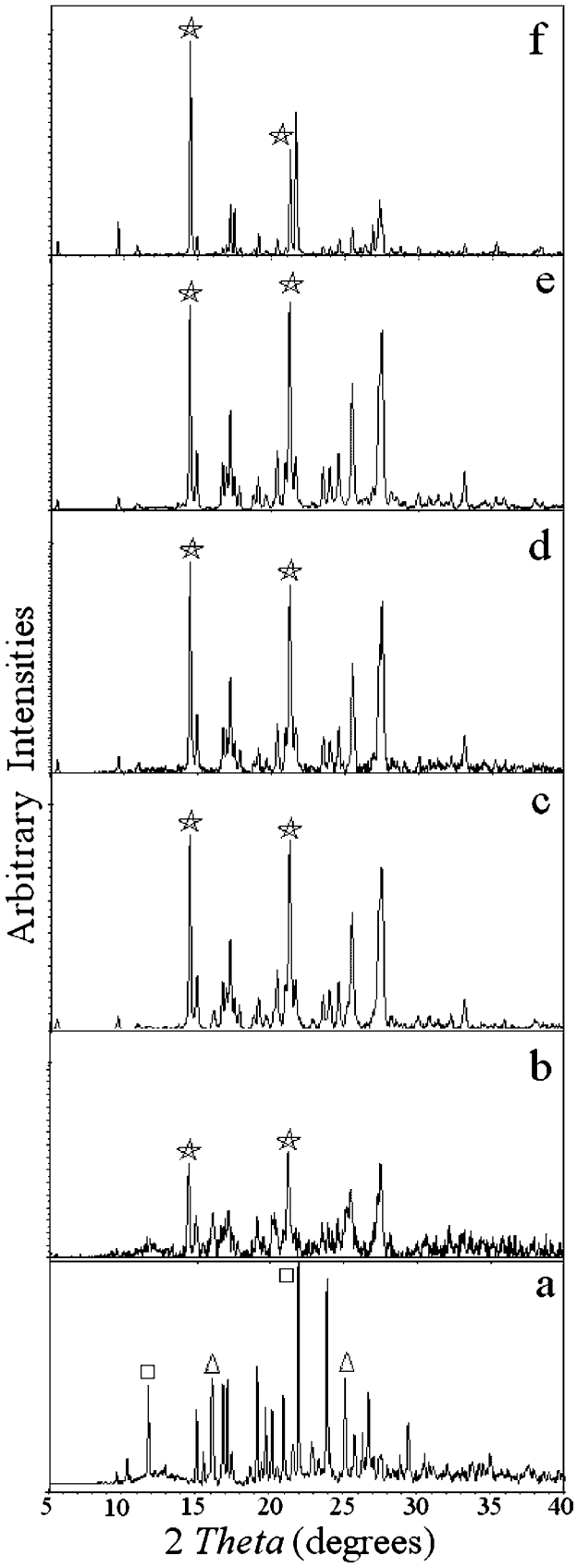


Fig. 10. DVS isotherm plots for different samples at 25°C.



◀ **Fig. 11.** PXRD patterns for indomethacin and saccharin cogrinding experiments at various time intervals. **a** Indomethacin and saccharin physical mixture. Solid state cogrinding after **b** 15 min; **c** 30 min; and **d** 1 h; **e** liquid–assisted cogrinding after 15 min and **f** Pure IND–SAC cocrystals from the solution method. Note that the PXRD pattern for the material ground for 15 min in the presence of dichloromethane or water also resembles (**c**). *Empty squares*, *empty triangles* and *empty stars* indicate the characteristic peaks of indomethacin, saccharin and IND–SAC, respectively.

formation of IND–SAC cocrystals within 15 min and pure IND–SAC cocrystals were eventually observed after 60 min (Fig. 11b–d). However, when one drop of dichloromethane or water (in which only one component is soluble) was added, predominantly IND–SAC cocrystals (with traces of reactants) were observed within 15 min. Whilst, in the presence of one drop of ethyl acetate or ethanol (in which both constituents are soluble), a pure IND–SAC cocrystal was obtained within 15 min (Fig. 11e).

This demonstrates that it is possible to generate IND–SAC cocrystals in a very 'environmentally friendly' manner using solid state and liquid-assisted grinding methods. The IND–SAC cocrystal is another example of a saccharin cocrystal that can be formed by both solution and cogrinding methods. The cocrystal formation was observed after 15 min of grinding the components as indicated by characteristic peaks (with low intensities) of IND–SAC cocrystal (Fig. 11b). The decrease in the intensities of the peaks indicates that the transformation to IND–SAC cocrystal by solid state grinding at room temperature (<30°C) is mediated by amorphous phase or disordered regions associated with increased molecular mobility (40–42). Interestingly, the addition of minute quantities of ethyl acetate or ethanol or water enhanced the transformation kinetics. This phenomenon of enhanced kinetics has also been observed with other cocrystals (23). Indeed, systematic studies to better understand cocrystal formation kinetics and mechanisms under ambient and subambient temperatures and in the presence of solvents or water are currently undergoing in our laboratory.

CONCLUSIONS

Pharmaceutical cocrystals of indomethacin with saccharin, a GRAS status sweetener, were designed employing crystal engineering strategies. IND–SAC cocrystals were prepared using both solution and solid state methods. The single crystal structure of IND–SAC cocrystals was determined. The IND–SAC cocrystal adopts the centrosymmetric triclinic $P\bar{1}$ space group, with one molecule each of indomethacin and saccharin in the asymmetric unit. In the IND–SAC crystal structure, indomethacin forms an acid dimer synthon and saccharin forms an imide dimer synthon. These two dimers interact with weak N−H···O hydrogen bond making the pattern unique. The IND–SAC cocrystal system had higher dissolution rate compared to indomethacin γ-form. The cocrystal was nonhygroscopic. The formation of IND–SAC cocrystals using cogrinding methods also offers a 'green chemistry' alternative to solution crystallizations. Further, phase transition to cocrystals in cogrinding has direct significance for the processing of dosage forms. In addition to ongoing comprehensive studies outlined previously, scaling up of production of IND–SAC cocrystals under

process analytical technologies (PAT) monitoring and the characterization of physical and technical properties of cocrystalline material are topics of our future work in this area.

ACKNOWLEDGEMENTS

We acknowledge 'Norbottensforskningsråd' and 'Kempestiftelserna' for the project grant (NoFo 05-011) and instrumental grant respectively. We thank Surface Measurement Systems, UK, for the DVS studies. We wish to thank Mr. Amjad Alhalaweh for his laboratory assistance with the dissolution studies.

SUPPORTING INFORMATION AVAILABLE

List of cocrystal formers used in the screening, Raman spectra, PXRD patterns for micronized IND–SAC cocrystal prior to the dissolution study and PXRD patterns for undissolved solids in 60 and 200 mM buffer concentrations in the dissolution study. Crystallographic information file for IND–SAC cocrystal can also be found.

REFERENCES

1. H. Brittain. *Polymorphism in pharmaceutical solids*, Marcel Dekker, New York, 1999.
2. S. M. Berge, L. D. Bighley, and D. C. Monkhouse. Pharmaceutical salts. *J. Pharm. Sci.* **66**:1–19 (1977).
3. S. R. Byrn, R. P. PfeifferJ. G. Stowell. *Solid State Chemistry of Drugs*, SSCI Inc, West Lafayete, IN, 1999.
4. A. T. M. Serajuddin. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* **88**:1058–1066 (1999).
5. P. H. StahlC. G. Wermuth. *Handbook of pharmaceutical salts*, Verlag Helvetica Chimica Acta; Zurich and Wiley-VCH, Weinheim, 2002.
6. A. M. Kaushal, P. Gupta, and A. K. Bansal. Amorphous drug delivery systems: Molecular aspects, design and performance. *Crit. Rev. in Ther. Drug Carrier Syst.* **21**:133–193 (2004).
7. D. P. McNamara, S. L. Childs, J. Giordano, A. Iarriccio, J. Cassidy, M. S. Shet, R. Mannion, E. O'Donnell, and A. Park. Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. *Pharm. Res.* **23**:1888–1897 (2006).
8. C. B. Aakeröy and D. J. Salmon. Building co-crystals with molecular sense and supramolecular sensibility. *Cryst. Eng. Comm.* **7**:439–448 (2005).
9. Ö. Almarsson and M. J. Zaworotko. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem. Commun. (Camb.)* 1889–1896 (2004).
10. M. C. Etter. Hydrogen bonds as design elements in organic chemistry. *J. Phys. Chem.* **95**:601–4610 (1990).
11. M. C. Etter. Hydrogen bond directed cocrystallization and molecular recognition properties of acyclic imides. *J. Am. Chem. Soc.* **113** (1991).
12. G. R. Desiraju. Supramolecular synthons in crystal engineering—a new organic synthesis. *Angew. Chem., Int. Ed. Engl.* **34**:2311–2327 (1995).
13. P. Vishweshwar, J. A. McMahon, J. A. Bis, and M. J. Zaworotko. Pharmaceutical co-crystals. *J. Pharm. Sci.* **95**:499–516 (2006).
14. A. V. Trask, W. D. Motherwell, and W. Jones. Physical stability enhancement of theophylline via cocrystallization. *Int. J. Pharm.* **320**:114–123 (2006).
15. S. L. Childs, L. J. Chyall, J. T. Dunlap, V. N. Smolenskaya, B. C. Stahly, and G. P. Stahly. Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic acids. Molecular complexes of fluoxetine hydrochloride with benzoic, succinic, and fumaric acids. *J. Am. Chem. Soc.* **126**:13335–13342 (2004).
16. J. R. Dipalma. *Basic Pharmacology in Medicine*, McGraw-Hill, New York, 1976.
17. P. A. Slavina, D. B. Sheena, E. E. A. Shepherda, J. N. Sherwooda, N. Feederb, R. Dochertyb, and S. Milojevic. Morphological evaluation of the γ-polymorph of indomethacin. *J. Cryst. Growth* **237–239**:300–305 (2002).
18. T. Matsumoto and G. Zografi. Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. *Pharm. Res.* **16**:1722–1728 (1999).
19. N. Bandi, W. Wei, C. B. Roberts, L. P. Kotra, and U. B. Kompella. Preparation of budesonide and indomethacin hydroxypropyl-beta-cyclodextrin (HPBCD) complexes using a single-step, organic-solvent-free supercritical fluid process. *Eur. J. Pharm. Sci.* **23**:159–168 (2004).
20. M. Yoshioka, B. C. Hancock, and G. Zografi. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *J. Pharm. Sci.* **83**:1700–1705 (1994).
21. R. D. B. Walsh, M. W. Bradner, S. Fleischman, L. A. Morales, B. Moulton, N. Rodriguez-Hornedo, and M. J. Zaworotko. Crystal engineering of the composition of pharmaceutical phases. *Chem. Commun.* 186–187 (2003).
22. R. Banerjee, P. M. Bhatt, N. V. Ravindra, and G. R. Desiraju. Saccharin salts of active pharmaceutical ingredients, their crystal structures, and increased water solubilities. *Cryst. Growth Des.* **5**:2299–2309 (2005).
23. T. Friščić, A. V. Trask, W. Jones, and W. D. S. Motherwell. Screening for inclusion compounds and systematic construction of three-component solids by liquid-assisted grinding. *Angew. Chem. Int. Ed.* **45**:7546–7550 (2006).
24. G. M. Sheldrick. *SHELX-97: Program for the Solution and refinement of Crystal Structures*, University of Göttingen, Germany, 1997.
25. S. Hess, U. Teubert, J. Ortwein, and K. Eger. Profiling indomethacin impurities using high-performance liquid chromatography and nuclear magnetic resonance. *Eur. J. Pharm. Sci.* **14**:301–311 (2001).
26. P. J. Cox and P. L. Manson. Indomethacin *tert*-butanol solvate at 120 K. *Acta Crystallogr.* **E59**:o1189–o1191 (2003).
27. X. Chen, K. R. Morris, J. J. Griesser, S. R. Byrn, and J. G. Stowell. Reactivity differences of indomethacin solid forms with ammonia gas. *J. Am. Chem. Soc.* **124**:15012–15019 (2002).
28. J. G. Stowell, S. R. Byrn, G. Zografi, and M. Yoshioka. Private Communication (2002).
29. J. L. Wardell, J. N. Low, and C. Glidewell. Saccharin, redetermined at 120 K: a three-dimensional hydrogen-bonded framework. *Acta Crystallogr.* **E61**:o1944–o1946 (2005).
30. S. G. Fleischman, S. S. Kuduva, J. A. McMahon, B. Moulton, R. D. B. Walsh, N. Rodriguez-Hornedo, and M. J. Zaworotko. Crystal engineering of the composition of pharmaceutical phases: multiple-component crystalline solids involving carbamazepine. *Cryst. Growth Des.* **3**:909–919 (2003).
31. The refcodes of the crystal structures with acid-dimer and imide-dimer or amide dimer synthons in the CSD: Acid-Imide: XUNHIX, XUNHUJ, GUGCUG, PAXNIL, YEJMOP. Acid-Amide: LORRIT, NUHYEU, TORQIA, TORQOG, WARXIW.
32. M. O'Brien, J. McCauley, and E. Cohen. Indomethacin. *Anal. Profiles Drug Subst.* **13**:211–238 (1984).
33. G. Jovanovski. Metal saccharinates and their complexes with N-donor ligands. *CCACAA* **73**:843–868 (2000).
34. Y. Hase. The infrared and raman spectra of phthalimide, *N*-D-phthalimide and potassium phthalimide. *J. Mol. Struct.* **48**:33–42 (2005).
35. G. Jovanovski. The SO2 stretching vibrations in some metal saccharinates: spectra-structure correlations. *Spectrosc. Lett.* **28**:1095–1109 (1995).
36. M. A. R. Matos, M. S. Miranda, V. M. F. Morais, and J. F. Liebman. Saccharin: a combined experimental and computational thermochemical investigation of a sweetener and sulfonamide. *Mol. Phys.* **103**:221–228 (2005).
37. Simulated PXRD pattern from single crystal X-ray diffraction obtained from CSD (Ref code: SCCHRN02).

38. S. J. Nehm, B. R. Spong, and N. R. Hornedo. Phase solubility diagrams of cocrystals are explained by solubility product and solution complexation. *Cryst. Growth Des.* **6**:592–600 (2006).
39. N. R. Hornedo, S. J. Nehm, K. F. Seefeldt, Y. P. Torres, and C. J. Falkiewicz. Reaction crystallization of pharmaceutical molecular complexes. *Mol. Pharm.* **3**:362–367 (2006).
40. K. J. Crowley and G. Zografi. Cryogenic griding of indomethaci polymorphs and solvates: assessment of amorphous phase formation and amorphous phase physical stability. *J. Pharm. Sci.* **91**:492–507 (2002).
41. B. C. Hancock and G. Zografi. The relationship between the glass transition temperature and water content of amorphous pharmaceutical solids. *Pharm. Res.* **11**:471–477 (1994).
42. A. Jayasankar, A. somwangthanaroj, Z. J. Shao, and N. R. Hornedo. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. *Pharm. Res.* **23**:2381–2392 (2006).