

A new method for the reproducible generation of polymorphs: two forms of sulindac with very different solubilities

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Polymorphism of drugs has been the subject of intense interest in the pharmaceutical industry for over forty years. Although identical in chemical composition, polymorphs differ in bioavailability, solubility, dissolution rate, chemical and physical stability, melting point, colour, filterability, density, flow properties, and many other properties. The difference in solubility is particularly important for pharmaceuticals, as it can affect drug efficacy, bioavailability and safety. Despite significant investment in processes to find all the possible polymorphs of active pharmaceutical ingredients (APIs), new polymorphs can suddenly appear without warning. Polymorphs tend to convert spontaneously from less stable to more stable forms, and, therefore, it is best to discover and characterize the stable form as early as possible. Ideally the most stable polymorph will be found while the drug candidate is still in the discovery process, so that this is the form used for subsequent testing. The most stable polymorph will be the least soluble and solubility may be a limiting factor in the efficacy of the API. Despite the huge importance of polymorphism in the properties of materials, however, there is no method that can produce all the stable polymorphs of a compound, or even one that can provide confidence that the most stable polymorph has been obtained. Here we describe a new method, 'potentiometric cycling for polymorph creation (PC)²', which is able to generate the most stable polymorph in aqueous solution. This new method has been applied to sulindac, a non-steroidal anti-inflammatory drug, which also shows promise in anticancer treatment, producing two polymorphs of this API, including a new more stable one. By adjusting the conditions, this method is able to produce either polymorph exclusively.

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1. Introduction

A new method, 'potentiometric cycling for polymorph creation (PC)²', to generate multiple polymorphs in aqueous solution is described. In a study of the solubility of sulindac, two different polymorphs, characterized by powder X-ray crystallography, were found to have similar packing motifs, similar calculated energies but distinct structures. Despite the similarity of the structures, the intrinsic solubilities of the polymorphs differ by a factor of seven, which is much larger than earlier measurements of polymorph solubilities, and suggests that polymorphs may have a much greater solubility range than most precedent suggests. By adjusting the conditions, the method is able to produce either polymorph exclusively.

Polymorphism of drugs has been the subject of intense interest in the pharmaceutical industry for over 40 years. Although identical in

chemical composition, polymorphs differ in bioavailability, solubility, dissolution rate, chemical and physical stability, melting point, colour, filterability, density and flow properties, amongst other things. The difference in solubility can affect drug efficacy, bioavailability and safety. Despite significant investment to find all the possible polymorphs of active pharmaceutical ingredients (APIs), new polymorphs can suddenly appear without warning. Polymorphs tend to convert from less stable to more stable forms. Therefore, it is best to work with the most stable polymorph, even though this will be the least soluble.

When polymorphic conversion occurs it may be impossible to reproduce the less stable form. Abbott lost a quarter of a billion dollars in a year when a new polymorph of Ritonavir, an AIDS drug, appeared in their production lines, first at a production plant in North Chicago and then at a plant in Italy (Rouhi, 2003). Despite their efforts to stop the new form appearing, in a few days the new polymorph was dominating the product coming off the lines. This new polymorph was thermodynamically more stable than the old one and

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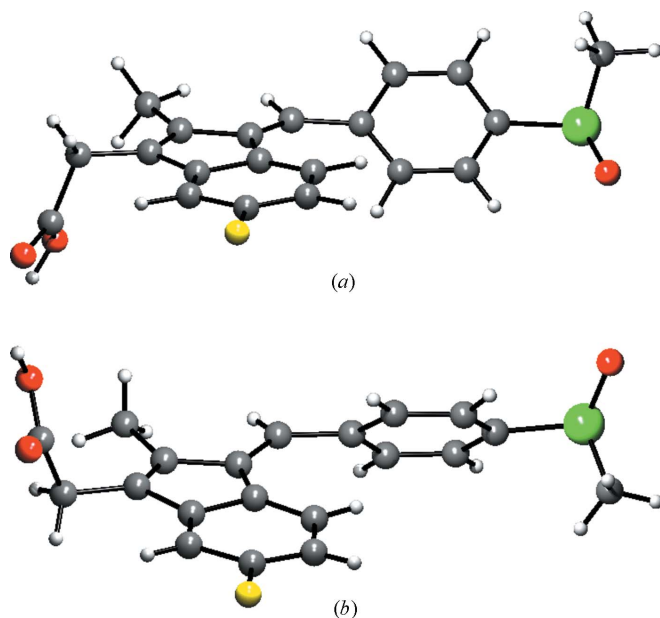


Figure 1
Molecular configurations of sulindac: (a) Form I and (b) Form II. C atoms are shown in grey, H atoms in white, O atoms in red, fluorine in yellow and sulfur in green.

had half of the solubility. Ritonavir was taken from the market and millions were spent trying to obtain the first form again. The company finally reformulated the drug in the second polymorphic form as a liquid gel capsule that required refrigeration. Similar cases have been reported (Rouhi, 2003; Goho, 2004). New forms may appear as a result of a change in the equipment used to dry the final drug substance, whilst materials are being stored and even with no recorded change in the storage conditions. The appearance of a new

polymorphic form of an API is a major concern for pharmaceutical companies.

A new method to generate polymorphs in aqueous solution has been discovered, using a development of a potentiometric acid–base titration described by Stuart & Box (2005) and developed commercially by Sirius. The titration method was designed to measure the intrinsic solubility of ionizable compounds and to ensure that thermodynamic equilibrium is reached in a short time.

When an ionizable compound dissolves in water, the pH of the solution shifts. Small changes in the pH of the solution may change a supersaturated solution into a subsaturated one. Careful control of the pH of the solution by addition of acid and base, and precise monitoring of the resultant pH, allow the equipment to determine if the changes in the pH of the solution are due to more compound dissolving, indicating a subsaturated solution, or due to the compound precipitating, indicating a supersaturated solution. Repeated cycling between these two states is possible by tiny adjustments to the pH of the solution by addition of acid and base. Each change makes the solution cross the precise concentration of saturation, and many measurements of this state may be made in a short time. This process is called ‘chasing equilibrium’ (Stuart & Box, 2005) and allows the rapid measurement of the thermodynamic intrinsic solubility of the solute.

We have applied this process to measure the aqueous solubility of sulindac, a non-steroidal anti-inflammatory drug, which also shows

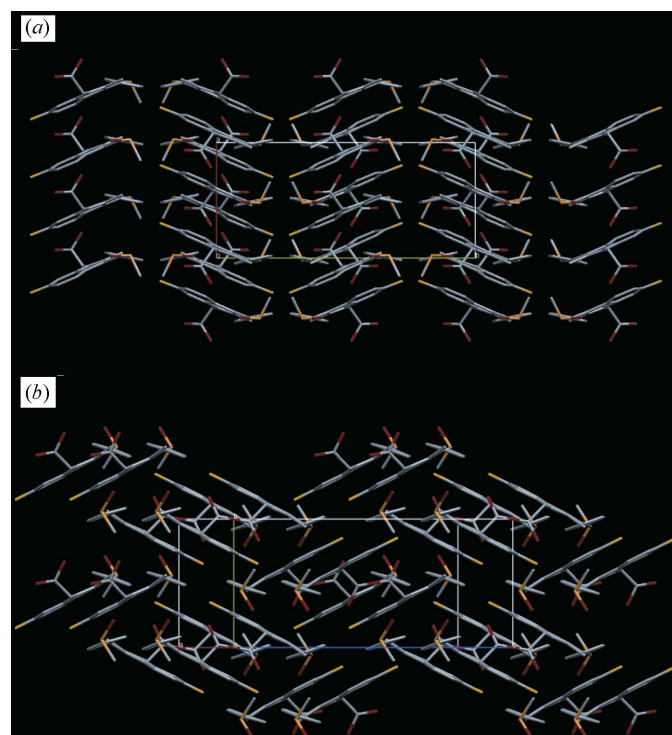
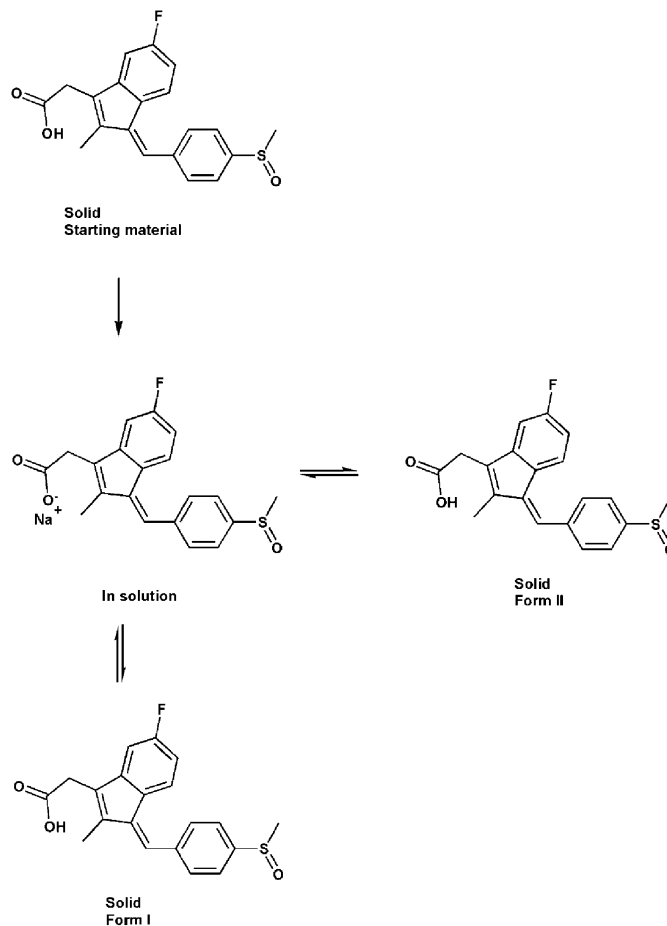
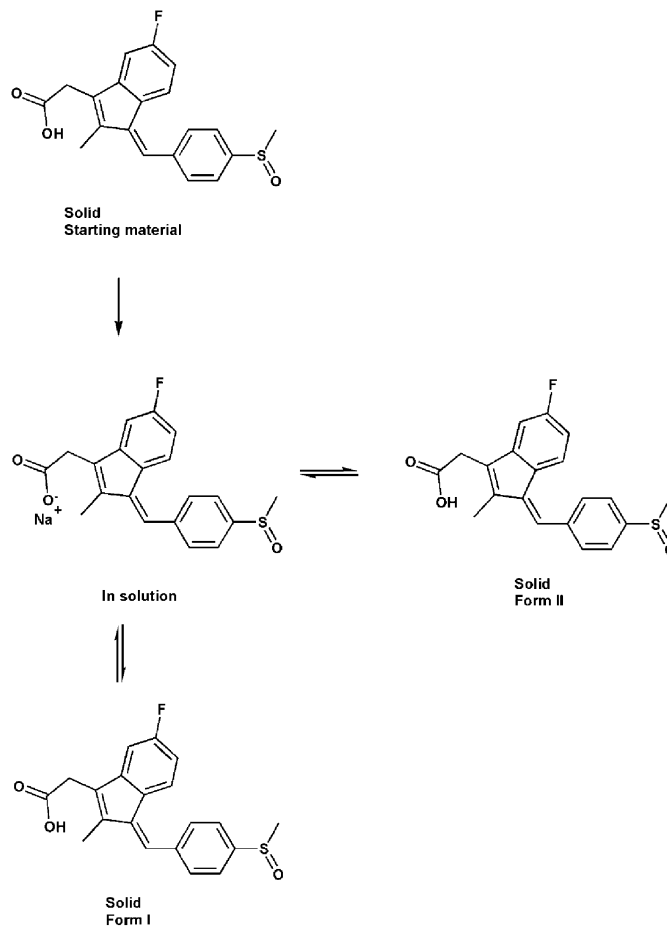


Figure 2
Crystal packing of both polymorphs of sulindac: (a) Form I and (b) Form II.



promise as an anticancer treatment (Giardello *et al.*, 1993). At first, the experiment produced measurements following the usual pattern, and the readings converged on an intrinsic solubility of $70 \mu\text{g ml}^{-1}$.

However, after about 20 min, there was a dramatic change in the measurements, and the readings jumped from oscillating around $70 \mu\text{g ml}^{-1}$ to oscillating around $10 \mu\text{g ml}^{-1}$. This experiment was repeatable, and it was possible to create one form of solid sulindac (Form I) by stopping the experiment before the 20 min transition, and to create a sample of the other form (Form II) by running the experiment for a longer time. Raman spectroscopy was used to follow the transformation *in situ*. This technique demonstrated that two different solid materials were being formed, but could not give detailed information about their structures.

The two solid forms could be different hydrates, or different salts of sulindac. We characterized them using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), infrared spectroscopy (IR), Raman spectroscopy, and X-ray crystallography.

Powder X-ray patterns were obtained for both forms. The powder pattern for Form I matched a pattern reported in the Cambridge Structural Database (CSD; Bruno *et al.*, 2002) (refcode DOHREX; Koo *et al.*, 1985). We were able to obtain a crystal of this substance, and a further X-ray experiment confirmed that it corresponded to this previously reported crystal structure of sulindac.

The powder X-ray pattern for the less soluble structure, Form II, does not correspond to anything in the CSD.¹ The DSC and TGA measurements confirmed that, like Form I, it had no solvent in the crystal structure, and so it was not simply a different hydrate of sulindac. We were unable to grow crystals of this form that were suitable for single-crystal X-ray crystallography, but we were fortunate that it was possible to solve the crystal structure of Form II from the powder X-ray diffraction pattern, using the simulated annealing algorithm implemented in *DASH* (David *et al.*, 1998). The model suggested by *DASH* was then refined against the data using the Rietveld method as implemented in the *GSAS* (Larson & Von Dreele, 2000) program suite. This gave a fully acceptable final fit and structural model, with $\chi^2 = 2.792$, $R_{\text{wp}} = 0.0505$ and $R_p = 0.0381$. R_{Bragg} was 0.0749. Final lattice parameters in the $P2_1/c$ setting were $a = 12.6858$ (3), $b = 8.1894$ (2), $c = 17.7934$ (5) Å, $\beta = 106.011$ (3)°, $V = 1776.83$ (6) Å³.

Fig. 1 shows the conformation of the individual sulindac molecules in the two crystal structures. The molecules are drawn so that the planar fused six- and five-membered rings are in the same orientation for both, illustrating how the relative positions of the acid group at one end and the sulfoxide at the other differ. Fig. 2 shows the crystal packing of the two forms.

In common with previous studies (Threlfall, 2003) the new polymorph of sulindac is less soluble than the original one. The factor of seven between the intrinsic solubilities is unusually large. A recent survey of polymorph pairs showed few ratios larger than two (Pudipeddi & Serajuddin, 2005). Our result suggests that polymorphs may have much more diverse solubility than is usually considered.

In conclusion, this new approach, provides a reproducible method of preparing two different polymorphs of an API. The new polymorph, characterized using Raman spectroscopy, IR, DSC, TGA and powder diffraction, shows a substantially lower solubility than the original polymorph, and this could have a significant impact on the manufacture and the formulation of this material.

¹ The CIF file for sulindac Form II can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi> (code CCDC 637252). Supplementary data for this paper are also available from the IUCr electronic archives (Reference: KK5012). Services for accessing these data are described at the back of the journal.

2. Experimental section

Solubility measurements. The apparatus used to perform the solubility determinations was a GLpKa titrator and a D-PAS spectrometer controlled from a computer running *Refinement Pro* and *CheqSol* software (Sirius Analytical Instruments Ltd). All experiments were performed in 0.15 M KCl solution under nitrogen atmosphere, at 298.2 (1) K, using standardized 0.5 M HCl and 0.5 M KOH solutions.

Differential scanning calorimetry. Differential scanning calorimetry was performed on powdered samples using a Metler Toledo DSC 821e, with Metler Toledo *STARe* software. Around 5–10 mg of each sample was run in a sealed aluminium pan with a hole pierced in the lid. Each run was carried out under nitrogen purge at a heating rate of 283 K min⁻¹.

Thermogravimetric analysis. Thermogravimetric analysis (TGA) was carried out on powdered samples (5–10 mg) using a Metler MT5 balance. Data were processed using Metler Toledo *STARe* software.

Powder X-ray diffraction. X-ray powder diffraction was performed using Co $K\alpha_1$ radiation ($\lambda = 1.79$ Å) on a Stoe Stadi-P diffractometer operating in Debye–Scherrer geometry. The sample was contained in a 0.7 mm-diameter borosilicate capillary (Lindemann glass). Data sets with relatively high signal–noise ratios suitable for structure solution were collected at 290 K (approximate counting time 24 h per data set). For the Rietveld refinement, suitable constraints on bond lengths, angles and planar groupings were employed, which were taken from the single-crystal study. These constraints were applied to all atoms, including H atoms, which were included at calculated distances and allowed to refine. A single ADP was employed.

Single-crystal X-ray diffraction. Single crystals were immersed in perfluoropolyether oil, mounted on thin glass fibres and placed in a low-temperature N₂ stream. Crystals were examined on a Nonius KappaCCD diffractometer using thin-slice κ and ω scans at 150 (2) K utilizing Mo $K\alpha$ radiation. Low temperatures were achieved using an Oxford Instruments Cryostream cooler. Data for this sample were corrected for absorption anomalies using the *SORTAV* utility. Structures were solved by direct methods using *SHELXTL* software. Refinements were made on F^2 with all non-H atoms refined anisotropically and H atoms were treated using a riding model (Sheldrick, 1998). The data have been deposited in the CSD.

Raman spectroscopy. A Raman RXN1 analyser from Kaiser Optical Systems Inc. was used to monitor the experiments in real time.

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