Towards the development of a polymorphic control approach in sulfathiazole crystalization

This item was submitted to Loughborough University's Institutional Repository by the/an author.


Additional Information:

- This conference paper was published in BIWIC 2008 [© Shaker Publishing] which is available from: http://www.shaker.eu/

Metadata Record: https://dspace.lboro.ac.uk/2134/4750

Version: Accepted for publication

Publisher: © Shaker Publishing

Please cite the published version.
This item was submitted to Loughborough’s Institutional Repository (https://dspace.lboro.ac.uk/) by the author and is made available under the following Creative Commons Licence conditions.

For the full text of this licence, please go to: http://creativecommons.org/licenses/by-nc-nd/2.5/
Towards the development of a polymorphic control approach in sulfathiazole crystallization

M. R. Abu Bakar, C. D. Rielly, Z. K. Nagy*  
Department of Chemical Engineering, Loughborough University, Loughborough, Leicestershire, LE11 3TU, United Kingdom  
*E-mail: Z.K.Nagy@lboro.ac.uk

Controlling the formation of a specific polymorphic form of active pharmaceutical ingredients, particularly those that exhibit multiple polymorphic forms, during crystallization is critical for pharmaceutical manufacturers. This paper describes the construction of a phase diagram using Lasentec Focused Beam Reflectance Measurement (FBRM), which is an important step in the development of an approach for polymorphic control of sulfathiazole, an antimicrobial agent that is known to crystallize as a mixture of polymorphs. A preliminary work on mapping of different regions in the phase diagram, where various polymorphic forms were found, is also reported here. This study is part of a larger study on polymorphic control of pharmaceuticals through supersaturation control using Process Analytical Technology.

1. Introduction

Crystallizations of active pharmaceutical ingredients (APIs) particularly those that possess multiple polymorphic forms are amongst the most critical, yet least understood, pharmaceutical manufacturing processes. Statistically, 85% of APIs exhibit polymorphism and 50% have multiple polymorphic forms [1]. The polymorphs of a crystal can exhibit a variety of structures, which have different inter- and intramolecular interactions. Thus, they have different free energies and consequently different physico-chemical properties and mechanical behaviours [2]. These give an impact on the downstream process operations, such as isolation, filtering and drying, and affect the therapeutic properties of the final product. Due to this, pharmaceutical manufacturers often select a polymorphic form that has desirable characteristics that will assist in the efficient manufacturing and effective performance of the drug product. This underscores the importance to have a robust crystallization process that consistently produces the desired polymorphic form of the API.

The key to controlling crystallization of a polymorphic system is the ability to detect the onset of nucleation of each form and to detect and monitor possible transformations among the different forms. The use of Process Analytical Technology (PAT) tools such as focussed beam reflectance measurement (FBRM) and attenuated total reflectance ultraviolet-visible spectroscopy (ATR UV-Vis) will help in the in-situ detection and monitoring of nucleation and polymorphic transformations of APIs. The information could be used to implement an integrated methodology for crystallization processes that will be able to produce the desired final polymorphic form. The proposed approach will use a feedback control strategy, which will drive the process in the phase diagram by manipulating the operating temperature profile to achieve the desired polymorphic form. Similar approach has been proposed recently by Lin and co-workers [3]. Fig. 1 shows...
hypothetically the operating profile of the proposed approach on a phase diagram of a monotropic system with two polymorphs, form I and form II. In this case, form II is the desirable polymorph and in order to eliminate the presence of form I, the operating profile is driven in such a way that after the nucleation of an unknown polymorph or a mixture of the polymorphs, it is controlled to operate below the solubility curve of form I, but in the supersaturation region of form II. The approach could also be employed to the enantiotropic system.

The first step towards the implementation of the proposed polymorphic control approach is to construct the phase diagram of the compound of interest. A wide variety of measurement techniques have been applied to construct the phase diagram, i.e. to characterise the metastable zone width (MSZW) and solubility curve. FBRM, which measures the chord length distribution of the particles, has successfully been used to detect the MSZW since a sudden increase in the chord counts of FBRM indicates the onset of nucleation [4-6]. Besides the detection of nucleation events, it has been proved that FBRM can also be used to determine the solubility curve, since a reduction in the chord counts indicates the dissolution of crystals [4, 6].

Sulfathiazole, an antimicrobial agent, has been chosen as the model system in this study. In the crystallization of its polymorphs, Khoshkhoo and Anwar [7] found that the effect of solvent is more prominent than the effect of supersaturation, as exemplified by the formation of only form I in the crystallizations from propan-1-ol at all supersaturations, whereas from water, only forms II and III were obtained. Generally, most researchers found sulfathiazole as having a tendency to crystallize as mixtures of polymorphs [7-9]. Although this compound has been extensively and repeatedly investigated by various researchers, no work has been done so far in controlling the formation of its polymorphic forms during a crystallization process.

In this paper, the construction of a phase diagram for sulfathiazole in propan-1-ol-water mixtures using FBRM is presented. Since sulfathiazole tends to crystallize as a mixture of polymorphs, phase diagrams of the individual polymorphs would be difficult to construct. An alternative is to map different regions in a single phase diagram, where different polymorphic forms were found. The aim of this work is to provide information on process conditions, including cooling rate, solvent composition and initial solute concentration, in order to devise a systematic approach to consistently produce crystals with the desired polymorphic purity.
2. Experimental Section

2.1 Materials. Sulfathiazole was purchased from Sigma-Aldrich with a purity of 98%. The solvents used were water and propan-1-ol. The former was deionised water, whilst the latter was an analytical reagent grade solvent purchased from Fisher Scientific.

2.2 Apparatus. The crystallization experiments were performed in a jacketed 500 ml glass vessel. The temperature in the vessel was controlled with a PTFE thermocouple connected to a thermo fluid circulator bath (Huber Variostat CC-415 vpc). The temperature readings were recorded every 4 seconds on a computer by a control interface written in LabVIEW (National Instruments). An overhead stirrer with a PTFE three-blade marine type impeller was used to agitate the system at 215 rpm. A Focused Beam Reflectance Measurement (FBRM) probe (model D600, Lasentec) was inserted into the solution to measure chord length distributions. The distributions were collected every 10 seconds and averaged during collection. They were monitored using the FBRM control interface software (version 6.7). A schematic representation of the experimental set-up is shown in Fig. 2.

2.3 Construction of phase diagram. Solution of sulfathiazole was prepared to correspond to a solubility of 1.3 g of sulfathiazole per 100 g of propan-1-ol at 60°C [7]. In order to investigate the effect of kinetics on the metastable zone width of the system; it was made to undergo heating and cooling at various rates: 0.25, 0.5, 0.75 and 1 °C/min. For the subsequent experiments with different composition ratios of propan-1-ol: water, the same solute concentration was maintained by simultaneous addition of sulfathiazole and water to make up the chosen composition ratios. The solvents composition ratios chosen were 9:1, 8:2, 6:4, and 4:6. Two further sets of experiments were conducted using two different initial concentrations: 1.8 and 2.4 g per 100 g solvent. The FBRM probe was used as the tool to determine nucleation and saturation points of the system.

2.4 Mapping of polymorphs on the phase diagram. The same experiments as described in 2.3 were repeated for samples withdrawal. Three small set of experiments had been performed:-

2.4.1 Experiments at different cooling rates. In this set of experiments, the initial sulfathiazole concentration was 2.4 g per 100 g solvent. The solvent used was propan-1-ol: water mixture with a mass ratio of 4:6. The solutions were cooled at 0.25, 1.0 and 2.0 °C/min.

2.4.2 Experiments at different solvent compositions. In these experiments, the initial sulfathiazole concentration was 1.8 g per 100 g solvent. The solvent used was also propan-1-ol: water mixture, but in four different compositions by mass ratio; 1:0, 9:1, 8:2, and 6:4. The solutions were cooled at 0.75°C/min.

2.4.3 Experiments at different initial sulfathiazole concentrations. In this set of experiments, the initial sulfathiazole concentrations were 1.8 and 1.0 g per 100 g solvent. In both experiments, the
solvent used was propan-1-ol: water mixture with a mass ratio of 8:2. The solutions were cooled at 0.75°C/min. All samples were vacuum filtered and immediately dried in a hot air oven at 105°C for 15 minutes. They were then further dried in a vacuum oven at 70°C for 3 hours to remove residual water. The samples were finally characterized for their polymorphic form using optical microscopy and differential scanning calorimetry (DSC).

**Optical microscopy** - The crystals were visually examined using a Leica DMLM optical microscope and their images were captured and processed using Leica QWin (version 3.0, Leica Microsystems Digital Imaging).

**DSC** – The thermal behaviour of the crystals was examined using a TA Instruments Q10. About 8 mg of crystals was weighed into an aluminium pan and sealed hermetically. Analysis was carried out by heating the sample from 40 to 220°C at a heating rate of 10°C/min under constant purging of nitrogen at 40 ml/min. An empty aluminium pan was used as reference in all the runs.

### 3. Results and Discussion

#### 3.1 Construction of phase diagram.

FBRM was used to determine both the metastable zone limits and the solubility of sulfathiazole in propan-1-ol-water mixture. FBRM measured count data can be split into specific size ranges that allow the monitoring of a specific size range in which a change occurs. In this work, the fine counts in the 1-20 µm range were used to determine the nucleation points (i.e. the metastable zone limits) because it was found that the particles in that size range are more sensitive to the nucleation event as compared to the coarse counts in the 50-250 µm range [6]. The coarse counts, on the other hand, were used to determine the solubility points because the fine particles tend to dissolve before the coarser particles [6]. Fig. 3(a) shows the evolution of fine and coarse particles at cooling rates of 1.0, 0.75, 0.50 and 0.25 °C/min for sulfathiazole in 9:1 propan-1-ol: water mixture at an initial solute concentration of 1.26 g per 100 g solvent, corresponding to a literature solubility in pure propan-1-ol at 55°C [7].

![Fig. 3](image-url)

**Fig. 3:** The evolution of fine (1-20 µm) and coarse (50-250 µm) particles at various cooling rates for sulfathiazole in (a) 9:1 propan-1-ol:water mixture and (b) pure water.

In a separate experiment, sulfathiazole in a pure water system was heated and cooled at the rates of 0.10, 0.25, 0.40, 0.55 and 0.70°C/min at an initial solute concentration of 0.24 g per 100 g
water, corresponding to a literature solubility at 55°C. It was found that the nucleation points were difficult to determine due to the presence of noises as illustrated in Fig. 3(b). The noises were probably due to the nature of the fine particles formed from the water that are prone to adhere to the FBRM probe’s window. Even during dissolution, the number of fine particles did not return to the initial clear point baseline. This observation about the nature of a certain fine particles was also reported by Heath and co-workers and they suggested performing window cleaning regularly [10]. The noises, however, were less significant on the plot of the coarse particles as shown in Fig. 3(b). Therefore, in order to get the nucleation points for the system, the FBRM probe’s window should be cleaned with a lint-free tissue paper and acetone, whenever the counts readings at clear points were fluctuated or higher than the initial clear point baseline. Alternatively, each point should be determined from fresh solution.

Fig. 4(a) shows the plots of the obtained nucleation points and solubility curves from FBRM, such as shown in Fig. 3. In the plot, the solubility curves are represented by continuous lines. The solution/suspension was made to undergo at least 2 cooling/heating rates. The solubility points were found to be quite consistent, whereas the nucleation points follow the general trend that the faster the supersaturation generation i.e. the higher the cooling rate, the wider the metastable zone width. The metastable zone limits and solubility curves of the system at 3 different initial concentrations are plotted in Fig. 4(b). In order to avoid overcrowding in the plot, only data measured at a cooling rate of 0.25°C/min are shown.

![Graphs showing nucleation points and solubility curves.](image)

Fig. 4: Plots of the obtained nucleation points and solubility curves using FBRM for (a) the initial solute concentration of 1.3 g per 100 g solvent; and (b) the initial solute concentrations of 1.3, 1.8 and 2.4 g per 100 g solvent at cooling and heating rates of 0.25 and 0.50°C/min, respectively.

3.2 Mapping of polymorphs on the phase diagram.

3.2.1 Experiments at different cooling rates. In order to investigate if in this system, polymorphic form changes with the cooling rates, samples at the end of the experiments were withdrawn and analyzed. Fig. 5 below shows the microphotographs and DSC thermograms of the crystals formed at various cooling rates for 4:6 propan-1-ol: water mixture.
Based on the microphotographs shown in Fig. 5(a), there is no clear indication about the identity of the polymorph formed, since the crystals appear to exhibit multiple shapes. According to literature, form I is a rod- or needle-like, form II is a cuboid, form III is a truncated hexagon and form IV is a plate-like hexagon [11, 12]. The difference in size of the crystals, however, follows the general trend that the faster the cooling rate, the smaller the size of the crystals. As shown in Fig. 5(b), all samples produced a similar DSC thermogram profile, which indicates that they are having similar polymorphic purity. According to Lagas and Lerk [13], complete melting of form II at its melting temperature of 197°C can only be observed if the crystals were purely form II. If only the slightest amount of form I is present, form I (melts at 203°C) will crystallise during the melting process of form II at 198°C. Anwar and his co-workers [11] reported that form III transforms into form I in the temperature range of 150 to 170°C without showing any melting of form III at 175°C. These suggest that the crystals obtained at various cooling rates from 4:6 propan-1-ol: water mixture are a mixture of form I, II and III.

3.2.2 Experiments at different solvent compositions. Fig. 6 shows the microphotographs and the DSC thermograms of the crystals obtained from the experiments at different solvent compositions. The microphotographs in Fig. 6(a) show that with the exception of the crystals obtained from pure propan-1-ol, which appear to exhibit mainly a rod-like morphology, from all other solvent composition ratios, sulfathiazole crystallizes as mixture of polymorphs. This is verified by the DSC analysis, in which crystals obtained from both 9:1 propan-1-ol:water and 6:4 propan-1-ol:water were indicated to contain forms I, II and III. The DSC thermogram produced by 8:2 propan-1-ol: water, on the other hand, does not show a melting peak of form II. This may indicate that the crystals only consist of form III, or probably a mixture of form I and III. As indicated by their morphology, the crystals obtained from pure propan-1-ol were verified by the DSC as form I, since they produced only one melting peak, at 202°C (corresponding to the melting of form I).
3.2.3 Experiments at different initial sulfathiazole concentrations. The microphotographs and DSC thermograms of the crystals obtained at two different initial solute concentrations are presented in Fig. 7.

Although the crystals obtained from the lower initial solute concentration seem to have much more consistent crystal morphologies, the DSC analysis results, however, show that both initial solute concentrations in 8:2 propan-1-ol: water, produced crystals of form III, or probably a mixture of form I and III.

4. Conclusions

The phase diagram for sulfathiazole in propan-1-ol: water mixtures was constructed using FBRM. Since sulfathiazole tends to crystallize as mixture of polymorphs, individual phase
diagrams of the polymorph are hard to construct and therefore, mapping of different regions in the phase diagram, where different polymorphs were found, is the way forward. The outcomes of the preliminary works presented in this paper indicate the good prospect of the proposed approach. Works are underway for comprehensive polymorph characterization and data collection for complete mapping of polymorphic forms on the phase diagram.

5. References


Acknowledgements

Financial support provided by the Engineering and Physical Sciences Research Council (EPSRC), U.K., (grant EP/E022294/1) is gratefully acknowledged. One of the authors (MRAB) is grateful to the Malaysian Ministry of Higher Education for a scholarship.