Determination of the Intrinsic Dissolution Rate (IDR) from a Powder and using a Miniaturized Wood's Apparatus

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INTRODUCTION

The objective of this study was to investigate the properties of several of the polymorphs of sulfathiazole using a novel powder intrinsic dissolution rate (IDR) approach[1], and to relate the powder IDR values to results obtained with new miniaturized disk IDR apparatus[2] and to solubility of sulfathiazole.

MATERIALS AND METHODS

Small Volume Dissolution Apparatus

The µDISS Profiler*PLUS*™ instrument (*p*ION INC), Fig. 1a, used in these dissolution measurements employs eight fiber optic dip probes each with its own dedicated photodiode array (PDA) spectrometer. Each probe is positioned centered in the vial holding a magnetic stirrer in 1-3 mL media at 37° ±0.5°C maintaining a stirring speed of 100 ±2 RPM. Some of the challenges of traditional dissolution testing methods that use external sampling of the test solutions are avoided by using *in situ* fiber optic dip probes, since the concentration measurements are performed directly in the dissolution media and allowing the processed results to be plotted in "real time." Interference due to background turbidity is minimized by a spectral second derivative method. Full spectral scans of all channels takes less than one second. The baseline noise is ±0.0002 absorbance units. The Mini-IDR compression system (Heath Scientific, UK) in Fig. 1b was used to make miniaturized pellets.

Ionization constants of sulfathiazole were measured with Gemini Profiler™ (*p*ION INC) having a unique capability of measuring pK_a values in the presence of precipitation.

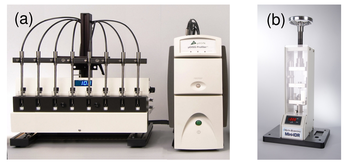


Fig. 1 µDISS Profiler*PLUS*™ from *p*ION INC (a). The Mini-IDR™ apparatus from Heath Scientific, UK (b) can be used to make pellets with 5 - 10 mg of API, instead of the "traditional" 100 – 700 mg.

Polymorphism

Polymorphism, the ability of a compound to adopt multiple solid-state arrangements, is critical to pharmaceutical drug development and formulation. Thermodynamics dictates that a given modification be the most stable under a set of conditions; whereas the rest are metastable under the same conditions (Fig. 2, a). Stable and metastable forms exhibit distinct pharmaceutical advantages and limitations. For example, stable forms exhibit prolonged phase stability while metastable forms may have desirable dissolution properties. Fig. 2, b illustrates some of the features of crystal growth leading to different polymorphic forms.

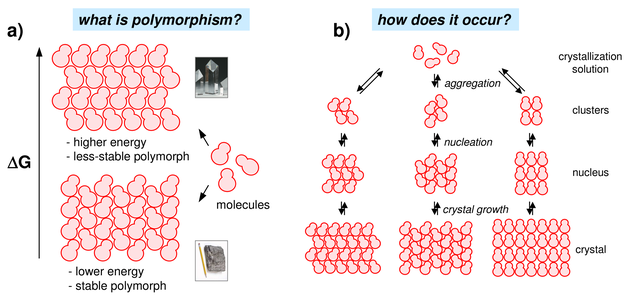
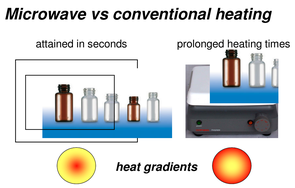


Fig. 2. Examples of differences between higher and lower energy polymorphs (G is Gibbs free energy) and crystal growth steps leading to a formation of various polymorphic forms.

The FDA now requires that all new drugs be rigorously screened for polymorphism. Selective growth of polymorphs is therefore essential to the rational design of suitable drug formulation. In this work the microwave technology[3] (Fig. 3) was used to grow three different polymorphs (forms I, III and V) of sulfathiazole (Fig 4.).



Microwave advantages

- energy efficient
- rapid superheating
- improved operational control
- uniform heating
- minimal or no decomposition
- rapid supersaturation
- lower nucleation barriers
  - favor the growth of metastable polymorphs

Fig. 3. Some advantages of microwave method over conventional heating approach for producing polymorphs[3].

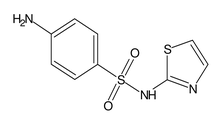


Fig. 4. Sulfathiazole, an antibacterial drug with 5 different polymorphic forms reported in the literature[4].

RESULTS AND DISCUSSION

Powder X-Ray Diffraction Data of Sulfathiazole Polymorphs

Fig. 5 shows powder X-ray diffraction data confirming that three different forms of sulfathiazole (Fig.5) were synthesized. The XRPD patterns were collected on a Bruker D8 Powder X-Ray Diffractometer at room temperature. All the data were acquired with same collection parameters, immediately after the crystals were harvested from a microwave experiment. The diffraction profiles were overlaid on literature patterns to identify the polymorph obtained in the microwave experiment. In addition, polymorphic purity and identity was verified with DSC experiments (results not shown).

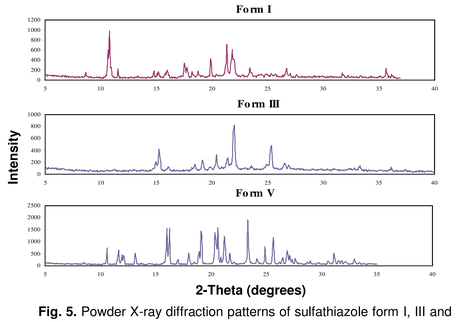


Fig. 5. Powder X-ray diffraction patterns of sulfathiazole form I, III and V. The nomenclature used for identifying the polymorphs was taken from Cambridge Structural Database.

Dissolution Profiles of Sulfathiazole

Dissolution behavior of sulfathiazole was studied in USP (*Vol. 25*) buffers at pH 4.5 and 6.8. The measured pK_a values of this amphoteric compound were 7.19 and 1.98 (25° C and 0.15 M ionic strength) suggesting that about 100% and 80% of the drug were in its neutral form at pH 4.5 and 6.8 respectively. Fig. 6 combines powder dissolution profiles of all studied polymorphic forms of sulfathiazole. The miniaturized disk dissolution apparatus[2] was used for IDR measurement of the most stable form (III).

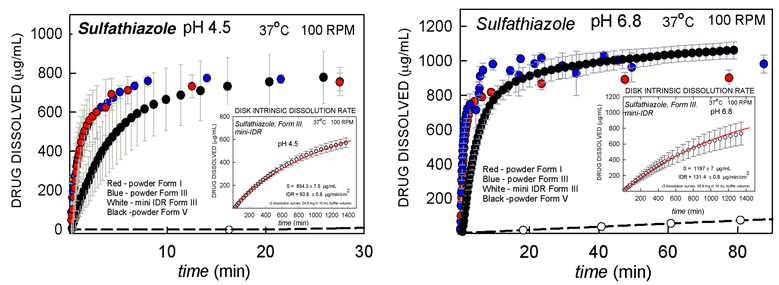


Fig. 6. Dissolution profiles of powdered sulfathiazole form I, III and V at pH 4.5 (a) and at pH 6.8 (b), 37ºC and 100 rpm rotation speed. The open circles expended in the inserts show dissolution profile of miniaturized disk of most stable form III with constant exposed area.

It can be seen that all dissolution profiles reach saturation at about 800 µg/mL (pH 4.5) or 1000 (pH 6.8) showing no significant difference in solubility between polymorphic forms. This unexpected result could indicate that metastable form I changed to the stable form III during or even before the dissolution studies. Such a phenomenon was described in ref. 5. Tables 1 and 2 summarize the data presented in Fig. 6.

Table 1. Data obtained by analyzing the dissolution profiles at pH 4.5 (Fig. 6, a)

Polymorph	Solubility (SD) µg/mL	IDR (SD) µg/min/cm²	Specific surface Area cm²/mg	Radius µm	D%
Form III (stable) mini-disk	845 (8)	94 (1)	0.12 (cm²)		16
Form III (stable) powder	843 (10)	93 (1)	1.2 (0.1)	20	68
Form I (metastable) powder	791 (36)	87 (4)	1.8 (0.2)	13	67
Form V (metastable) powder	872 (287)	96 (32)	0.7 (0.2)	34	68

Table 2. Data obtained by analyzing the dissolution profiles at pH 6.8 (Fig. 6, b)

Polymorph	Solubility (SD) µg/mL	IDR (SD) µg/min/cm²	Specific surface area cm²/mg	Radius µm	D%
Form III (stable) mini-disk	1197 (7)	131 (1)	0.071 (cm²)		33
Form III (stable) powder	1012 (26)	111 (3)	1.2 (0.2)	19	70
Form I (metastable) powder	930 (18)	102 (2)	1.7 (0.1)	14	82
Form V (metastable) powder	1203 (30)	132 (3)	0.5 (0.1)	47	80

Solubility obtained from the initial slope of the dissolution profile in IDR runs correlated well with solubility of form III determined in powder dissolution experiments. According to ref. 1, metastable form V has the same melting point (175° C) as the stable form III. That could explain the similarity in solubility between these two forms.

A new approach[1] enabling the derivation of *disk* IDR from the *powder* dissolution profiles was applied to get the *powder* IDR results presented in column 3 of Table 1 and 2. It should be noted that despite the vast difference in the dissolution rate (see Fig. 6, 7) between powder and disk methods, the *powder* IDR agreed well with miniaturized *disk* IDR values while reducing amount of required compound and speeding up the assay.

Specific surface area was estimated by fitting the powder dissolution profiles with integrated Noyes-Whitney equation[1] and effective radius of the particles was calculated based on mono dispersed spherical particle approximation[6]. This analysis revealed that form V has an area per unit mass about half of that of form III, which would lead to the slower power dissolution rate.

CONCLUSIONS

This study demonstrated the successful application of a new method to simultaneously determine two important properties of the polymorphs of sulfathiazole: (a) intrinsic dissolution rate, and (b) pH-dependent solubility.

Powder IDR measurements can be used in the early stages of drug development because they use up to 10,000 times less API than traditional Wood's rotating disk apparatus and are much faster. Powder dissolution IDR results for sulfathiazole correlated extremely well with miniaturized disk IDR data.

The small volume powder dissolution apparatus (µDISS Profiler*PLUS*) can be used to study solvation properties of polymorphs in early stages of the drug discovery process.

Analysis of the specific surface area can indicate the morphological difference between various polymorphic forms even when differences in solubility and IDR are practically indistinguishable.

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