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Solubility measurement of polymorphic compounds via the pH-metric titration technique

Ann F. Fioritto *, Shobha N. Bhattachar, James A. Wesley

Research Formulations, Pharmaceutical Sciences, Pfizer Global R&D, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

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Abstract

In drug development, the thermodynamically most stable form of a compound is preferred because metastable forms are prone to transform to the stable form during processing, formulation, or storage [Guillory, J.K., 1999. Generation of polymorphs, hydrates, solvates, and amorphous solids. In: Brittain, H.G. (Ed.), Polymorphism in Pharmaceutical Solids. Marcel Dekker, New York, pp. 183–226]. It is therefore important to discover and characterize the stable form as early as possible. One of the most important properties to determine is thermodynamic solubility. However, due to compound and time constraints this solubility value is usually not determined until late in discovery. This report explores the ability of the pH-metric titration method to measure intrinsic solubility of the stable form of compounds that exist in one or more polymorphic forms. One metastable form and the stable form of eight compounds were examined. Intrinsic solubility was measured via pH-metric titration. The technique was performed on a larger scale in order to monitor polymorphic form changes by powder X-ray diffraction. Shake-flask solubility and corresponding X-ray diffraction data of each form was also determined. The results of this study indicate that, in general, when starting with a metastable polymorph, the pH-metric titration method is able to achieve the solubility of the stable form by the third titration, while the traditional shake-flask solubility method is unable to consistently determine the stable form solubility.

Keywords: Solubility; Intrinsic; Polymorphs; Potentiometric; Titration

1. Introduction

In the pharmaceutical industry, the need for accurate solubility measurements of ionizable molecules is prevalent, extending from discovery through development. Early in discovery, solubility is typically measured using high throughput kinetic solubility measurements, which are designed to rapidly screen hundreds of compounds to determine if they have sufficient solubility for *in vitro* biological assays. However, these kinetic solubility values tend to be higher than thermodynamic solubility values since kinetic measurements are typically made from non-equilibrated solutions prepared from DMSO-solvated compounds (Lipinski, 2003). Later in discovery, precise thermodynamic solubility values are measured using crystalline material, since it is this solubility value that affects absorption, distribution, metabolism, and excretion (ADME) properties and formulation aspects of compounds (Glomme et al., 2005). Although crystalline material is used for this solubility measurement, it must be pointed out that at this stage the polymorphic form of this material is not typically identified as the stable form or a metastable form.

Determination of thermodynamic solubility is a much more rigorous exercise than determination of kinetic solubility. Thermodynamic solubility is generally determined by shaking solid compound in the solvent of interest over a period of 24 h or more (until equilibrium is achieved), filtering off the excess undissolved solid, and measuring the dissolved drug concentration in the filtrate. If the undissolved solid phase is the most stable form of the compound, the measured solubility value is the true equilibrium solubility of the compound in the solvent at the temperature of measurement. The most stable form of the compound will have the least solubility compared to the apparent solubility of any metastable or amorphous forms in which the compound might exist. However, it is not uncommon for the most stable form of the compound to appear later in development. Depending on the solubility of the compound and its dose, this can result in costly delays due to its impact on bioavailability and formulation (Morissette et al., 2003).

* Corresponding author. Tel.: +1 734 622 2089; fax: +1 734 622 7711.
E-mail address: Ann.Fioritto@pfizer.com (A.F. Fioritto).

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Therefore, it is clear that once a compound with desirable activity has been identified in early discovery screens, it is important to determine the thermodynamic solubility of the stable form as early as possible. With the current paradigm of reduced costs and shortened timelines, solubility measurements that do not demand much compound or operator time are highly valuable. This report explores the utility of the pH-metric titration technique in this context. This technique has been previously described in detail (Avdeef, 1998). It is suitable for intrinsic solubility measurement and subsequent pH-solubility profile determination of ionizable compounds. To determine the thermodynamic solubility of a poorly soluble ionizable compound at a single pH, the best compound-sparing methods use at least 1 mg of compound, whereas, an entire pH-solubility profile may be determined with the same amount of compound using the pH-metric technique (Glomme et al., 2005). The theoretical basis for the pH-metric intrinsic solubility measurement is that any undissolved compound present in the titration mixture will shift the titration curve. The extent of this shift is a function of the amount of undissolved compound present in the titration mixture according to Eq. (1), where S_0 is the intrinsic solubility of the compound, ΔpK_a is the pK_a shift caused by the presence of undissolved compound in the titration mixture, and C is the total molar concentration of compound in the titration mixture.

$$-\log S_0 = \Delta pK_a - \log(C/2) \quad (1)$$

Good correlation between the intrinsic solubility derived from pH-metric titration and traditional shake flask solubility measurements has been reported, allowing acceptance of pH-metric titration data in regulatory submissions by the FDA (Avdeef et al., 2000). This report investigates the unique ability of the pH-metric titration system to measure the intrinsic solubility of the stable form of compounds that exhibit polymorphism, regardless of which polymorphic form is studied. Eight compounds that exist in one or more polymorphic forms were chosen for this study. One metastable form and the stable form of each compound were examined. Intrinsic solubility was measured for each form by cycling the compounds through three consecutive potentiometric titrations using the pH-metric titration technique. The technique was then simulated on a larger scale in order to collect enough precipitate to follow possible polymorphic form changes by powder X-ray diffraction analysis. In addition, shake-flask solubility and corresponding powder X-ray diffraction data of each polymorphic form was determined.

2. Experimental

2.1. Materials

Eight ionizable compounds were chosen for this study (Table 1). The selected compounds were known to exist in at least two polymorphic forms. Acetaminophen, Acetazolamide, Chlorpropamide, Sulfamethoxazole, and Sulfathiazole were obtained from Sigma (St. Louis, MO). Furosemide was obtained from ICN Biochemicals (Aurora, OH). Premafloxacin was obtained from Pfizer Inc. (Kalamazoo, MI). One proprietary compound, Pfizer Compound X, was also supplied by Pfizer Inc. (Ann Arbor, MI).

Table 1
Materials, required parameters for pH-metric titration, and polymorphic forms used

Compound	MW	pK_a	Compound type	Stable form	Metastable form	Solubility ratio (metastable/stable)	No. of known forms
Acetaminophen	151.16	9.42[a]	MA	I	II	1.3[e]	3[j]
Acetazolamide	222.25	7.2[b]	MA	A(II)	B(I)	1.1[f]	2[k]
Chlorpropamide	276.74	4.87[a]	MA	A	B	1.2[g]	3[l]
Furosemide	330.75	10.63, 3.52[c]	DA	A(I)	B(II)	1.0[f]	3[m]
Pfizer Compound X	416.48	2.66[a]	MA	A	B	3.0[h]	2[h]
Premafloxacin	403.45	6.31, 9.66[a]	MA, MB	III	I	23.1[f]	3[n]
Sulfamethoxazole	253.28	5.75[a]	MA	A(I)	B(II)	1.2[f]	4[o]
Sulfathiazole	255.31	7.14[d]	MA	III	I	1.7[i]	4[p]

[a] Determined by capillary electrophoresis.
[b] Parasrampuria (1993).
[c] Avdeef et al. (2000).
[d] Zhou et al. (2005).
[e] Sohn (1990).
[f] Pudipeddi and Serajuddin (2005).
[g] Burger (1975).
[h] Pfizer, unpublished data.
[i] Yu (1995).
[j] Burger (1982).
[k] Griesser et al. (1997).
[l] Simmons et al. (1973).
[m] Matsuda and Tatsumi (1990).
[n] Schinzer et al. (1997).
[o] Price et al. (2005).
[p] Anwar et al. (1989).