Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics

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Library of Congress Control Number: 2007924356

ISBN-13: 978-0-387-69149-7 e-ISBN-13: 978-0-387-69154-1

Printed on acid-free paper.

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Practical Aspects of Solubility Determination in Pharmaceutical Preformulation

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Introduction

Solubility is one of the most important physicochemical properties studied during pharmaceutical preformulation. For liquid dosage form development, accurate solubility data are essential to ensure the robustness of the finished product. For solid dosage forms, solubility data are important in determining if an adequate amount of drug is available for absorption *in vivo*. If a compound has a low aqueous solubility, it may be subject to dissolution rate-limited or solubility-limited absorption within the gastrointestinal (GI) residence time (Lobenberg et al., 2000). The importance of solubility, in biopharmaceutical terms, is highlighted by its use in the biopharmaceutics classification system (BCS) described by Amidon et al. (1995). This system defines low solubility compounds as those whose aqueous solubility in 250 mL of pH 1-7.5 aqueous solution is less than the total dose. Solubility data are also used to estimate the maximum absorbable dose (MAD) (Johnson and Swindell, 1996). MAD is a conceptual tool that relates the solubility requirement for oral absorption to the dose, permeability and GI volume and transit time. It is defined as:

$$\text{MAD (mg)} = \text{S (mg/mL)} \times K_a \text{ (1/min)} \times \text{SIWV (mL)} \times \text{SITT (min)}$$

where S is solubility at pH 6.5 reflecting typical small intestine condition; K_a is the trans-intestinal absorption rate constant determined by a rat intestinal perfusion experiment; SIWV is the small intestine water volume, generally considered to be 250 mL; and SITT is the small intestine transit time, typically about 270 min.

Solubility is influenced by many variables including temperature, pH (for ionizable compounds), solvents used for the solubility determination, state of the

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solid, common ions in the medium, and so on. For poorly soluble compounds, determining solubility in the presence of various solubilizing agents presents a special set of challenges.

The aims of this chapter are to summarize solubility determination methods commonly used in pharmaceutical preformulation and to discuss various factors to be considered in designing and carrying out these solubility studies.

Experimental Methods

Saturation Shake-Flask Method

The shake-flask method is based on the phase solubility technique that was developed 40 years ago and is still the most reliable and widely used method for solubility measurement today (Higuchi and Connors, 1965). The method can be divided into five steps: sample preparation, equilibration, separation of phases, analysis of the saturated solution and residual solid, and data analysis and interpretation (Yalkowsky and Banerjee, 1992, Winnike, 2005).

Sample Preparation

A solubility sample is typically prepared by adding an excess amount of solid to the solubility medium in a stoppered flask or vial. The amount added does not need to be accurately measured. While it is important to ensure that enough material is added so the sample is a suspension, it is also important not to add too much material to significantly alter the properties of the solubility medium including its pH.

Equilibration

Depending on the type of agitation used, the drug substance properties, amount of material used, and the equilibration method used, the time to reach equilibrium varies. With good agitation, samples generally reach equilibrium reasonably quickly, often within 24 hours. However, for poorly soluble compounds, the equilibration time may be unrealistically long due to the poor dissolution rate that is further depressed as the equilibrium process advances and the concentration in solution gets closer to the solubility. One way to speed up the process is to increase the effective surface area for dissolution. This can be achieved by either vortexing or sonicating samples prior to equilibration. Creating a supersaturated solution may also be helpful in overcoming the problem of a slow dissolution rate. This can be achieved by adding a certain amount of amorphous material to the samples, or by cycling the sample temperature to higher and lower temperatures during the equilibration process.

Another challenge for determining solubility of poorly soluble compounds is their poor wettability and their tendency to float. Ways to get around this problem include using small glass microspheres (Glassperlen) to de-aggregate the particles with agitation or sonication, and adding an amount of sodium

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dodecyl sulfate below the critical micelle concentration to serve as a wetting agent (Lötter et al., 1983).

There is no better way to accurately determine the end point for equilibration than by performing an actual analysis. Saturation or equilibrium is considered to be achieved when multiple samples assayed after different equilibration time periods give the same apparent solubility. If solid-state form transitions occur during equilibration, the equilibration time may be longer, especially if the solubility differences between various forms are small. To ensure that equilibrium is indeed reached, it is a good idea to demonstrate that the same equilibrium state (solubility) can be reached from different directions; for example, from undersaturation and supersaturation as well as from constant temperature or from temperature variation by means of temperature cycling.

Separation of Phases

Filtration and centrifugation both have been commonly employed to separate the saturated solution from the solute phase. Filtration is easily accomplished, but filter sorption can be a significant source of error. Generally, filter sorption is more significant for hydrophobic and poorly soluble compounds, and obviously it is directly proportional to the filter surface area. Typically, pre-rinsing the filter with a few milliliters of the saturated solution can remedy the problem. However, in some extreme cases where the solubility of the compound is very low, a much larger volume may be needed to saturate the filter adsorption sites.

Centrifugation or ultracentrifugation may be preferable for certain samples that are difficult to filter. Solubility samples in co-solvent systems with high viscosity are such examples. If the solute is less dense than the solubility medium, it will float on the surface, making it difficult to sample the solution. This may be particularly problematic for compounds with low solubility where a single particle carried over to the solution may cause significant overestimation of the true solubility.

Theoretically, the solid should always be separated from the saturated solution at the equilibrium temperature. Obviously this is more important when equilibrium is reached quickly. For poorly soluble compounds, equilibrium is typically reached slowly, thus filtration at ambient temperature may not introduce a significant error.

Centrifugal filter devices such as the UniPrep® filter have become commercially available in recent years, making it possible to combine both approaches (Glomme et al., 2004; Winnike, 2005).

Analysis of the Saturated Solution and Residual Solid

High performance liquid chromatography (HPLC) is the most commonly used analytical tool for the analysis of saturated solutions. Its advantage over the ultraviolet method is that it can detect impurities and any instability. A generic gradient method can be made readily available that is stability-indicating enough for multiple compound analyses without the need to make major adjustments in the column or mobile phase.

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