

Dissolution Method Development for Poorly Soluble Compounds

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INTRODUCTION

Developing dissolution methods for poorly soluble compounds has been a consistent challenge for the pharmaceutical scientist. Because of inherently slow dissolution, poorly soluble compounds are good candidates for developing in vitro-in vivo correlations (IVIVCs) if intestinal permeability is high and drug dissolution is the controlling mechanism for the release of drug from the dosage form. (1) At the time of the dissolution assay development, however, in vivo human data is normally not available. Instead, prior to the human clinical studies, dissolution data must usually be generated without the benefit of comparative rankings between formulations or lots, estimated in vivo absorption rates, or any other information that could be used to guide the development of a discriminating dissolution test.

To determine appropriate dissolution conditions *a priori* in order to get an IVIVC is a topic of great interest. Some progress has been made in identifying media to simulate the gastrointestinal milieu (2,3), and while appropriate for small studies during formulation development, such media are impractical for QC testing because of the expense of the components. A universal dissolution medium made of affordable components guaranteed to generate an IVIVC will perhaps be identified in the future, but in the meantime, we must deal with the poorly soluble compounds typical of today's drug discovery programs.

Dissolution problems with poorly soluble compounds generally fall into two categories. First, extent of release is too low, i.e. one cannot get 100% of the dosage form dissolved. Second, rate of release is too slow, i.e. one cannot get dissolution fast enough for a convenient test. This article presents the equations that govern extent and rate, and strategies to affect each variable within the equations will be discussed. It is assumed that the dissolution test will be utilized for quality control, and that what is desired is a test that will dissolve a large fraction of the dose in a reasonable amount of time.

FACTORS AFFECTING DISSOLUTION EXTENT

Equation [1] describes factors controlling extent of dissolution.

$$\text{Maximum Dissolvable Dose} = V \times C_s / \text{Sink} \quad [1]$$

where,

V = Dissolution medium volume

C_s = Saturated solubility of the compound in the medium

Sink = Sink condition factor

To increase the maximum dissolvable dose, one needs to increase the dissolution media volume, change the media to increase the saturation solubility of the compound, or reduce the dissolution sink requirements.

Media Volume

There are several ways to increase the dissolution media volume. Using 4-liter vessels is relatively uncommon, but they are available from vendors. This offers a potential 4-fold enhancement in maximum dissolvable dose over the standard 1-liter vessels.

The flow-through apparatus (USP 4) allows flow rates exceeding 50 ml/min (3 L/hr). Although these volumes can provide the theoretical capacity for complete extent of dissolution, for slowly dissolving compounds a limiting dissolution rate can be reached. One then ends up merely diluting the sample concentration to a point at which it becomes difficult to detect analytically. Using reasonable flow rates and long assay times, this apparatus can provide a significant increase in the volume.

Media replacement is a strategy used for implant and could theoretically be applied to other dosage forms. With this technique, the dosage form is dropped into a limited volume of dissolution media. After given time periods, the entire volume is replaced with fresh media. These tests can occur on the order of days or weeks, but require that the dosage form remains intact so that when the media is replaced, one does not lose undissolved drug particles.

Saturation Solubility

The standard way to affect the saturation solubility of drug in the dissolution media is to change the media, typically by adjusting the pH, adding a surfactant, or in rare cases, using non-aqueous solvents.

pH

If the compound is ionizable, adjusting the pH of the dissolution media is a very effective way to increase solubility. Examples of solubility as a function of pH for a free base and a free acid are shown in Figure 1. One defines an intrinsic solubility (C_i) as the solubility of the neutral compound. At pHs approaching the pK_a , more and more of the compound is ionized and the overall solubility increases. For singly ionizable compounds, the equations that govern solubility are:

$$\text{Free Base: } C_{\text{Total}} = C_i \times (1 + 10^{(pK_a - \text{pH})})$$

$$\text{Free Acid: } C_{\text{Total}} = C_i \times (1 + 10^{(\text{pH} - pK_a)})$$

Because of the exponential change in overall solubility (C_{Total}) as the positive difference between the media pH and the compound's pK_a increases, one can achieve orders of magnitude increase in solubility by adjusting pH.

Surfactants

Two factors to consider when evaluating surfactants are cost and concentration needed. If the dissolution assay is to be run in a Quality Control setting, choosing an inexpensive surfactant will be important to keep overall assay costs down. Examples of inexpensive surfactants are sodium dodecyl sulfate or SDS (also referred to as sodium lauryl sulfate or SLS) for an anionic surfactant,

cetyltrimethylammonium bromide or CTAB for a cationic surfactant, and the polysorbates or Tweens for a non-ionic surfactant.

To get any substantial solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration or CMC. The CMC will depend upon, among other things, the surfactant itself and the ionic strength of the media. The amount of surfactant needed depends on the CMC and the degree to which the compound partitions into the surfactant micelles. Since there is not a good method to predict these factors *a priori*, solubility at different surfactant concentrations should be measured if for no other reason than to define appropriate sink conditions. Because of the nature of the compound/micelle interaction, there is typically a linear dependence between solubility and surfactant concentration above the CMC, as shown in Figure 2.

If the compound is ionizable, surfactant concentration and pH may be varied simultaneously, and the combined effect can substantially change the solubilization ability of the dissolution media. Figure 3 (page 8) shows an example of the solubility of a free base as a function of SDS concentration at both pH 3 and pH 6.8.

Non-aqueous Solvents

The use of non-aqueous solvents for dissolution media is unconventional. From a practical point of

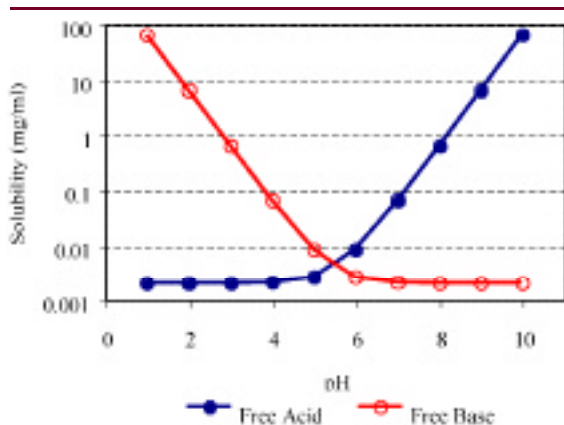


Figure 1: Solubility as a function of pH for a free acid and a free base.

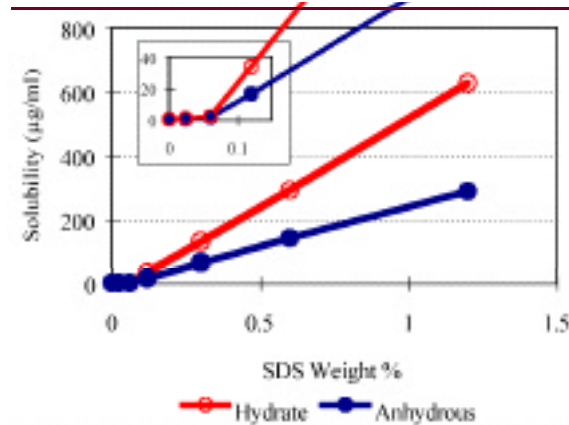


Figure 2: Solubility versus surfactant concentration for two crystal forms of a compound demonstrating linearity above the critical micelle concentration of 0.06% SDS.

Poorly Soluble Compounds... *continued*

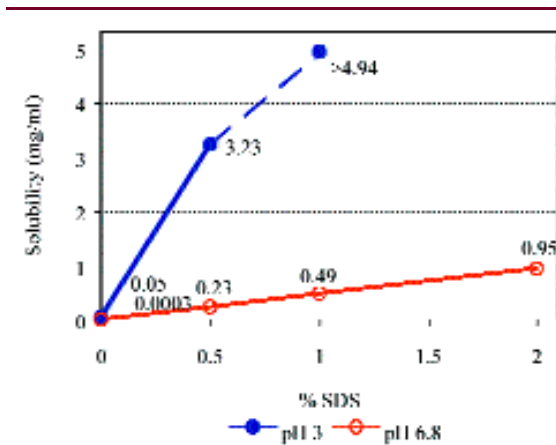


Figure 3: Solubility of a free base versus surfactant concentration at two pHs.

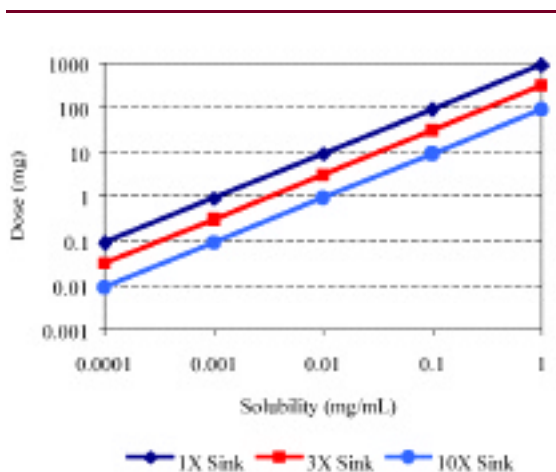


Figure 4: Maximum dose soluble in 900mL of dissolution media for various sink conditions.

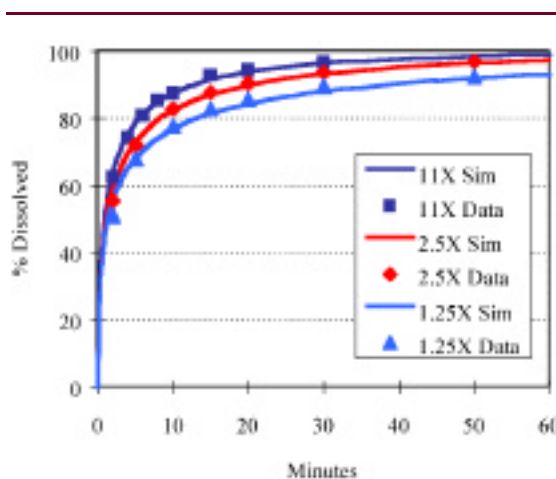


Figure 5: Dissolution data and simulation of a suspension under various sink conditions. Compound has 77µg/mL solubility and 5.4µm mean particle size.

view, if such a medium is filed with the regulatory authorities, one will probably be expected to show that conventional tactics for getting adequate solubility and dissolution do not work. One also has to deal with the waste disposal problem since often non-aqueous media cannot be merely neutralized and poured down the drain. However, if aqueous-based methods for achieving solubility have been exhausted, use of hydro-alcoholic media may be the best alternative. For example, the USP24-NF19 monograph for cortisone acetate tablets lists 30% isopropanol, 70% 0.01 N HCl as the dissolution media, and water/alcohol mixtures have been used as media for drug release testing of topical formulations using the Franz-diffusion cell apparatus.(4)

Sink Conditions

Sink conditions refer to the excess solubilizing capacity of the dissolution medium. Most sources recommend at least 3X (three times the volume needed to completely solubilize the dose) and some sources recommend 5X and even 10X. But how much is really needed?

The relationship between maximum soluble dose in 900 ml vs. solubility is shown in Figure 4 for sink conditions of 1X, 3X, and 10X. If you have rigidly defined sink conditions for your dissolution media, by relaxing the criteria, you can get a quick enhancement in the maximum solubilized dose. The effect on dissolution rate may or may not be significant, depending on the particle size of the drug. Figure 5 shows actual data and a simulation for a compound with solubility of 77 mg/mL and relatively small particle size. Decreasing sink from 11X to 1.25X results in only an 8% change in the extent of dissolution at 30 minutes. As a caution, though, the larger the particle size, the greater the difference in dissolution rates as the sink conditions decrease.

FACTORS AFFECTING DISSOLUTION RATE

Equation [2] describes factors controlling the rate of drug dissolution. The equation is based on the Brunner modification of the Noyes-Whitney equation and assumes that there is a stagnant thin film around the dissolving particle. The rate of mass lost from the particle is given by:

$$-d[\text{Mass}]/dt = (D \cdot S/h) \times (C_S - C_B) \quad [2]$$

where,

D = Diffusion coefficient of compound in the medium

S = Surface area

h = Stagnant film layer thickness
 C_s = Saturated solubility of the compound at the particle/media interface
 C_B = Concentration of the compound in the bulk medium

To enhance the dissolution rate, one needs to increase the diffusion coefficient, increase the surface area, decrease the stagnant diffusion layer thickness, or increase the saturation solubility. Solubility has already been discussed, so we deal with the other variables below.

Diffusion Coefficient

The diffusion coefficient of the solute is inversely proportional to solvent viscosity and the molecular size of the solute to some power, depending on the theory:

$$D \propto 1/[\eta \times (V_A)^x]$$

where

η = Solvent viscosity

V_A = Solute molecular volume

To increase the diffusion coefficient, one would have to either decrease the solvent viscosity, which is difficult to do since aqueous solutions already have a relatively low viscosity, or reduce the solute molecular size, which of course is inherent to the compound. This variable is therefore difficult to affect in a way that would significantly increase dissolution rate.

Note that by adding surfactants to enhance solubility, one actually decreases the effective diffusion coefficient, since as the solute partitions into the micelles, the effective molecular size of the diffusing species increases dramatically. The effective diffusion coefficient of the solute with micelles present has been estimated by summing the mole fractions of free drug and drug in micelles times the respective diffusion coefficients:

$$D_{\text{eff}} = D_{\text{free}} \times X_{\text{free}} + D_{\text{micelle}} \times (1 - X_{\text{free}})$$

The overall dissolution rate may increase with added surfactant, however, because of the dramatic increase in the saturation solubility 'CS'.

Surface Area

Fundamental particle surface area is a property of the drug in the dosage form. Reducing the particle size of the drug substance increases surface area and can significantly enhance the dissolution rate. This is illustrated in *Figure 6* for suspensions of a compound with 77 mg/ml solubility. For a dosage form like a compressed tablet, the important drug surface area is that which is directly exposed to the dissolution medium. Increasing the agitation can help the formulation

disintegration process, thereby exposing drug to medium. *Figure 7* illustrates the increased dissolution rate for a series of tablet formulations as paddle agitation is increased from 50 to 75 rpm. For the USP 2 (paddle) apparatus, increased agitation can reduce or eliminate the coning effect at the bottom of the dissolution vessel, which also helps expose drug particles to dissolution media.

Another factor that can affect surface area is the extent of media deaeration. If air bubbles partially cover the surface of the drug particles, that portion of the surface will not be exposed to dissolution media and therefore will not dissolve. This problem is of course not unique to poorly soluble drugs, and media deaeration has been the topic of a few publications. (5,6)

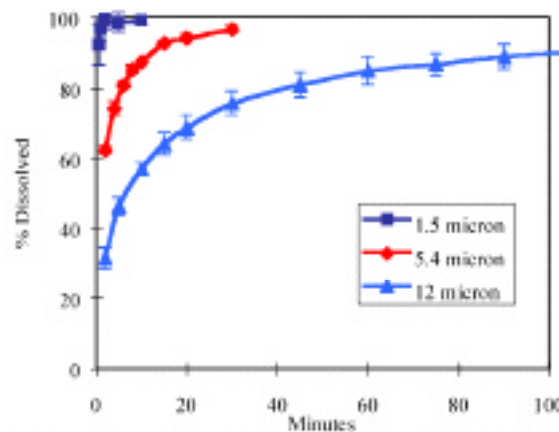


Figure 6: Dissolution of milled and micronized drug suspensions showing particle size effect for a compound with 77µg/mL solubility

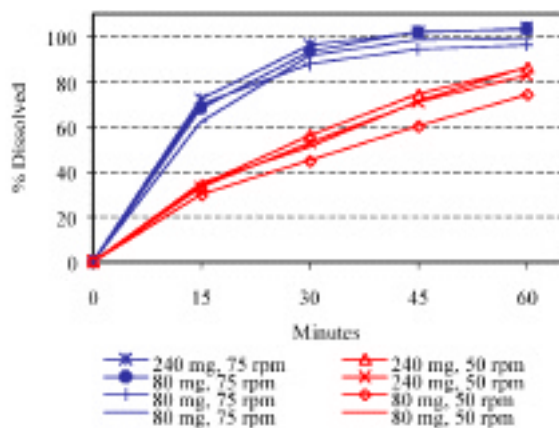


Figure 7: Agitation effects on dissolution for several tablet formulations.

Poorly Soluble Compounds... .. continued

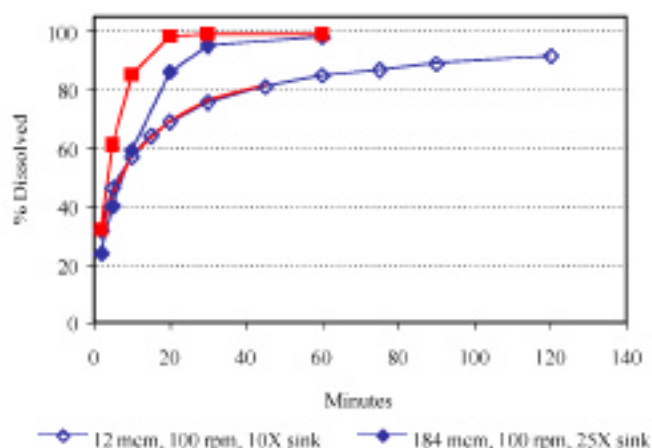


Figure 8: Agitation effects on large and small particle size suspensions consistent with reduction in diffusion layer thickness.

Diffusion Layer

The diffusion layer model assumes that there is a stagnant thin film with thickness 'h' around the dissolving particle. In certain situations, increasing the agitation reduces the stagnant film thickness and results in an increase in the dissolution rate. Figure 8 illustrates this point consistent with the diffusion layer model. Suspensions of a drug with mean particle sizes of 12 and 184 microns were added to a dissolution flask, with paddle speeds of 100 and 150 rpm. The 12 mm particle size material showed no change in the dissolution rate, whereas the 184 mm size material showed a significant increase. For the 12 mm size material, particles are easily suspended and carried along as the media stirs. Relative to the motion of the media, the particles see limited agitation, and so increasing the agitation rate has no effect on the dissolution rate. The larger particles, on the other hand, exhibit some slip velocity or drag when suspended in the media which can reduce the stagnant diffusion layer thickness 'h'. The initial 100 rpm agitation rate was necessary to prevent the larger particles from settling to the bottom of the dissolution vessel. At 100 rpm, significant drag already occurs since the dissolution rate is already faster than the 12 mm material. As the rotation rate increases, the drag increases, the stagnant diffusion layer decreases, and the dissolution rate increases for the larger particle suspension.

If the solid is ionizable, another factor that can affect dissolution rate is the buffer capacity of the media. The rate equation [2] is derived assuming a linear concentration gradient across the diffusion layer between saturation solubility at the solid surface and the bulk concentration. If an acid-base reaction occurs within the diffusion layer, the concentration gradient is no longer linear. The greater the extent of the acid-base reaction, the steeper the concentration gradient at the solid surface and the faster mass flux. (7,8) In certain instances, increasing the buffer concentration (and thereby the buffer capacity of the media) increases the extent of that

acid-base reaction within the diffusion layer. This has the effect of speeding up the dissolution rate.

CONCLUSION

Understanding the physicochemical properties of the drug is crucial for determining the most effective strategy for enhancing dissolution. Typically, the greatest enhancement in dissolution of poorly soluble compounds is made by changing the dissolution medium to increase compound solubility. Surfactants and pH changes are very effective ways to increase solubility. It is important to note that no matter what new, innovative, and clever dissolution methods are developed in the future to deal with poorly soluble compounds, they will have to affect one or more of the variables discussed above in a way to affect extent and/or rate of dissolution. For example, the PEAK™ vessel can increase dissolution rate by removing the coning effect in the round bottom vessel, thereby increasing the effective drug surface area exposed to dissolution media. At a recent workshop, a colleague suggested helping the dissolution process by increasing the bath temperature, which would affect solubility. This has its own set of problems, i.e., regulatory acceptance and perhaps increase drug degradation, but nevertheless is a potential strategy. One might also design a different agitation device or increase sink conditions by using a partitioning phase to remove compound from an aqueous phase. In any case, increasing dissolution rate or extent will have to change one of the aforementioned variables.

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