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Research Article

# DISSOLUTION ASPECTS FOR LOW SOLUBILITY DRUG PRODUCTS

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**ABSTRACT**

Dissolution testing plays a key role during the drug product development and commercial manufacturing. During the development stages of a drug product, dissolution testing is used to evaluate the rate of drug release from formulations and assess their stability and formulation changes. The bioavailability of the low soluble drugs can be improved by several formulation approaches. The most common method of increasing solubility (either a weak acid or weak base) is to induce salt formation. Even if the salt formation has no significant effect on the solubility, the salt dissolution rate will often be enhanced owing to the difference in the pH of the thin diffusion layer surrounding the drug particle. The dissolution rate can also be increased by reducing the size of solid drug particles, which leads to an increased surface area available for dissolution. In this review describe roles of dissolution testing during drug development, manufacturing, and post approval changes, followed by reviewing some important issues relevant to the Biopharmaceutics Classification System (BCS) classification and delivery of poorly soluble drugs.

**Keywords:** Dissolution testing, BCS, Low solubility drugs, Characterization, Dissolution media

## INTRODUCTION

Recent progress in the use of combinatorial chemistry and high-through put screening techniques to identify orally active drugs, the probability that poorly soluble compounds will make their way into development will likely remain in the foreseeable future [1,2].We have been relying heavily on formulation approaches to address issues relating to poor drug absorption of these compounds [3,4]. However, rational formulation design based on pharmaceutical properties of drugs is far from a reality. Among many factors, our lack of predictive dissolution testing invite often contributes to long and costly formulation development processes.

### Roles Of Dissolution Testing

Dissolution testing plays a key role during the drug product development and commercial manufacturing. During the development stages of a drug product, dissolution testing is used to evaluate the rate of drug release from formulations and assess their stability and formulation changes. In addition, it is employed to establish an invitro and in vivo correlation (IVIVC) in order to predict bioavailability or bioequivalence of drug products. For release of drug products, dissolution testing is used to ensure manufacturing and product consistency. For instance, for an immediate-release (IR) product, a single-point release criterion is often used, such as 0-80% in 30 min. In certain circumstances, a complete dissolution profile comparison rather than a single-point assessment is used [5]. Dissolution testing is also used in granting biowaivers of low strengths and for post approval manufacturing changes. The BCS guidance [6] employs dissolution testing to demonstrate rapid dissolution of immediate-release solid oral dosage forms so that a biowaiver can be granted.

The continued use of dissolution as a quality control tool is based on the belief articulated by USP that the dissolution test is in general overly sensitive to formulation differences. As a result, dissolution tests used for quality control emphasize the selection of discriminatory media and conditions. In comparison, dissolution tests for predicting bioavailability/bioequivalence require the choice of biorelevant media and conditions. Although it is desirable to have a single dissolution test that can be applied for both evaluation of invivo performance and assurance of product consistency, identifying such a dissolution test remains a significant challenge, particularly for dosage forms containing poorly soluble drugs [7, 8].

### Fomulation Of Low Solubility Drugs

### Definition of low solubility

In August 2000, the U.S. FDA issued Guidance for Industry covering the BCS [6]. The BCS is a scientific framework for classifying a drug substance on the basis of its equilibrium aqueous solubility and intestinal permeability [9]. When combined with the invitro dissolution characteristics of a drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate. These three factors govern the rate and extent of oral drug absorption for IR solid oral dosage forms [6]. The BCS defines four classes of drug substances on the basis of their solubility and permeability characteristics. From the BCS guidance, the criterion for high solubility uses the ratio of the highest strength to the minimum aqueous solubility in the pH range of 1.0–7.5 at 37°C. This ratio has a unit of volume and is referred to as the dose solubility volume. It is the volume needed to dissolve the strength across the entire pH range. If the dose solubility volume is ≤250 mL, the drug substance is considered highly soluble. However, if the dose solubility volume is >250 mL, the drug substance is considered poorly soluble. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 oz.) of water.

Class 1- High Solubility, High Permeability
Class 2 - Low Solubility, High Permeability
Class 3 - High Solubility, Low Permeability
Class 4 - Low Solubility, Low Permeability

The permeability classification is based on the extent of intestinal absorption of a drug substance in humans or measurements of the rate of mass transfer across the human intestinal membrane. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable. An IR drug product is characterized as a rapidly dissolving product when not less than 85% of the labeled amount of the drug dissolves within 30 min using USP Apparatus 1 at 100 rpm or USP Apparatus 2 at 50 rpm in a volume of 900 mL or less with each of the following media: (a) acidic media, such as 0.1 N HCl or USP-simulated gastric fluid (SGF) without enzymes; (b) a pH 4.5 buffer; and (c) a pH 6.8 buffer or USP-simulated intestinal fluid (SIF) without enzymes. Otherwise, the drug product is considered to be a slowly dissolving product. We will use the BCS definition to define low solubility drugs. However, we recognize that the BCS definition is conservative because it is used to waive regulatory bioequivalence studies for Class I drugs [10]. There are two reasons why the BCS definition for solubility is too conservative. The first reason is because of the need to show high solubility across the range of pH from 1.0 to 7.5. On the basis of the ionizable groups, the solubility of weak bases is higher in a stomach than that in the small intestine. A low solubility at high pH may not be a barrier to absorption of weak bases because the absorption may be complete before the drug enters the low

solubility, high pH GI region. On the other hand, low solubility at low pH may not be a problem of weak acids as high solubility and high permeability at distal small intestine are sufficient for their complete absorption. For example, many nonsteroidal anti-inammatory drugs, although classified as low solubility according to the BCS, have the bioavailability over 90% [11].

The second reason is that for the low solubility drugs, the in vitro aqueous solubility is not reflective of the in vivo gastrointestinal (GI) tract solubility. The solubility of lipophilic drugs is generally better in an in vivo environment because of the presence of bile salts or lecithin micelles. Recent studies have shown that solubility in biorelevant medium can be 1.1–160 times greater than the aqueous solubility of BCS Class II drugs, ranging from griseofulvin to danazol [12].

## Formulation Of Low Solubility Drugs

Some drugs classified as low solubility drugs on the basis of in vitro measures of aqueous solubility may have acceptable in vivo solubility because of either pH dependence or solubility in GI fluids. If these drugs with acceptable in vivo solubility are BCS Class II [6], they would then be expected to have acceptable oral bioavailability from standard solid oral dosage forms. For BCS Class II drugs that are shown to have low bioavailability owing to their poor solubility and inability to dissolve rapidly, the selection of formulation is often of great importance in developing a successful product for oral administration of Class II drugs. The bioavailability of these drugs can be improved by several formulation approaches. The most common method of increasing solubility (either a weak acid or weak base) is to induce salt formation. Even if the salt formation has no significant effect on the solubility, the salt dissolution rate will often be enhanced owing to the difference in the pH of the thin diffusion layer surrounding the drug particle. The dissolution rate can also be increased by reducing the size of solid drug particles, which leads to an increased surface area available for dissolution. A typical micronization method such as an air-jet mill can reduce the particle size to 2–5μm. Further reduction requires the use of ball-milling media in aqueous suspension [13]. This technology can reduce the crystalline particle size to 100–250 nm, providing a considerable increase in dissolution rate.

Another method of improving bioavailability for these poorly soluble drugs is to prepare an amorphous formulation, since an amorphous form allows faster dissolution of the drug in comparison to its corresponding crystalline form. An amorphous formulation is prepared by incorporating the drug in its amorphous form into a carrier matrix (polyvinylpyrrolidone and polyethylene glycol) using various techniques such as spray drying and melt extrusion [4]. However, it should be noted that amorphous solids are non equilibrium solid phases and hence are generally less stable relative to their corresponding crystalline phases.

Lipid formulations are another option for solubilization of poorly soluble drugs. These formulations include oil-based systems, water-insoluble self-emulsifying drug delivery systems (SEDDS), water-soluble SEDDS, and systems that contain very little oil that disperses to form micellar solutions [4]. The major advantage of the lipid delivery system is that the drug can be present in a stable liquid solution. This eliminates the time required to dissolve solid particles. Furthermore, the lipids used in the formulation may facilitate the transport of the drug substance across the intestinal membrane and further improve the absorption of drugs from lipid formulations [4]. However, one possible concern associated with this type of formulation is drug precipitation on dilution as well as unexpected phase transformation to a more stable polymorphic form [14]. In addition to the methods described above, the solubility of poorly soluble drugs can also be improved using solubilizing agents such as cyclodextrins. Cyclodextrins solubilize these poorly soluble compounds by forming water-soluble inclusion complexes with them. However, the dosage level can be limited by the use of this solubilizing agent, since there is a potential concern with regard to the toxicity of some commercially available cyclodextrins.

## Development Of Dissolution Method

FDA is encouraging sponsors to use quality-by-design (QbD) in the development of their drug products. QbD means designing and developing formulations and manufacturing processes to ensure a predefined quality and understanding how formulation and manufacturing process variables influence product quality [15].

**QbD consists of the following elements:**

- Define target product quality profile.
- Design and develop product and manufacturing processes to meet the target product quality profile.
- Identify and control critical raw material attributes, process parameters, and sources of variability.
- Monitor and adapt processes to produce consistent quality over time.

Because in vivo drug dissolution and release is an essential step in delivering the drug to its site of action, it should be included in the target product quality profile of solid oral dosage forms. Under the QbD system, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variable, while end-product testing, including in vitro dissolution, conforms the quality of the product. In the context of dissolution, QbD implies establishing the relationships among raw material properties (such as particle size), formulation variables (excipient levels and grade), process parameters (such as compression force and blending time), and the target product quality profile. Efficient implementation of QbD requires a biorelevant dissolution test during product development. In a QbD system, product attributes such as particle size or polymorphic form that are previously monitored indirectly via a QC dissolution test are monitored and controlled through the design and control of the manufacturing process. Thus, under QbD, dissolution testing development should mainly focus on its clinical relevance.

The following steps are crucial for designing a dissolution test for poorly soluble drug products:

1. Classification and characterization

- Measure solubility as a function of pH
- Classify a drug substance according to BCS
- Consider formulation factors

2. Determination of appropriate medium and volume
3. Selection of appropriate dissolution apparatus and operating speed
4. Determination of appropriate acceptance criteria

## Classification And Characterization

The first step is to know the BCS classification of the drug and use this information to help design formulations and evaluate the possibility of IVIVC. For a poorly soluble drug dosed in an immediate release product, the disintegration of the dosage form is generally rapid and the oral drug absorption is mainly limited by dissolution rate and/or permeation rate (permeability), where permeation rate refers to the flux of drug across the intestinal membrane. The rate of dissolution and the uptake rate of permeation determine the concentration of drug in the GI tract. However, the concentration in the GI tract is also limited by the solubility of the drug. When the rate of dissolution is far more than the uptake rate of permeation, the drug concentration in the GI fluid approaches its solubility limit. Therefore, poor dissolution can be caused either by particle size and/or solubility (Cs).

To emphasize the importance of solubility, [1] referred to the dissolution/solubility-limited case as solubility-limited absorption. The dissolution/particle size-limited case is still called dissolution limited absorption. As a result, permeability, solubility, and/or dissolution can limit the absorption of poorly absorbable drugs. For poorly soluble drugs with dissolution-limited absorption, the formulation approach commonly used to overcome slow dissolution is to increase surface area by reducing the particle size. The in vitro dissolution testing can be predictive of evaluating the effect of particle size reduction. However, a very small particle size could complicate the development of a dissolution test as small particles can pass through filters and subsequently dissolve. In this situation, the use of small pore filters, centrifugation, ultracentrifugation, or

high wavelength UV detection may be needed [8]. For poorly soluble drugs with solubility-limited absorption, possible formulation approaches are to use amorphous materials, lipid formulations, or one of the other technologies stated earlier. These formulation technologies and their potential failure modes will affect the selection of a dissolution test. In formulations using amorphous materials, a possible conversion of amorphous to crystalline state during the dissolution testing should be considered. An example of such an issue is the troglitazone data presented by Dressman [16]. Troglitazone dissolution in the fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) is predictive of the food effect observed in invivo pharmacokinetic studies. However, the dissolution profile in FaSSIF demonstrates a maximum. This maximum is due to recrystallization of the drug substance during the dissolution process into a less soluble crystalline form. This peak was not seen in the FeSSIF dissolution medium, indicating the role of medium components on the rate of nucleation of the less soluble form.

For lipid-based formulations where the drug is in solution, dissolution testing is not used to evaluate drug dissolution. Instead, it is employed to measure product capsule disruption and possible drug emulsification or precipitation on dilution. Nevertheless, of invitro sink condition is maintained, the precipitation that might occur invivo will not be observed in vitro. Therefore, we need to be cautious when we develop dissolution testing for lipid-based formulations.

**Dissolution Media**

**Quality Control Dissolution Media**

The choice of dissolution medium will depend on the purpose of the dissolution test. For batch-to batch quality control testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of a drug product to ensure that sink conditions are met. However, under certain circumstances, a medium that fails to provide sink conditions may be justifiable [8]. If the pH-dependent solubility indicates that the drug has a low solubility only in a particular pH range, the most likely media for an appropriate quality control dissolution test is an aqueous buffer at pH values that lead to high solubility. This approach becomes problematic when the pH with high solubility is greater than 6.8, because this condition is not relevant to in vivo dissolution. Nevertheless, in FDA OGD's dissolution database, out of about 300 dissolution methods, 19 use a pH higher than 7.2 and 10 use pH greater than 6.8 but less than or equal to 7.2. The use of pH outside physiologically relevant pH should be strongly discouraged. Surfactants can be used in a biorelevant manner by choosing a surfactant that matches solubility in more expensive simulated biological fluids. However, surfactants are more often used in a quality control setting for drugs whose solubility (even invivo solubility) is too low to establish the sink condition. Noory et al. [17] discuss some method development strategies and provide justification for the use of particular surfactants. Surfactants that have been used in the FDA-approved dissolution methods include SLS, Tween, CTAB, and Tris buffer, with SLS being by far the most commonly used surfactant. In general, it is desirable to use as little surfactant as possible to reach sink conditions. If too much surfactant is used, a dissolution test may not be able to detect changes in polymorphic form or particle size, as suggested in ICH Q6A.

**Biorelevant Dissolution Media**

Although dissolution testing is currently used primarily for quality control, it is desirable to have a dissolution test that is predictive of invivo performance. Therefore, there has been recent interest in developing biorelevant media whose properties match those of human gastric or intestinal fluids [18]. Vertzoni et al. [19] proposed a fasted state simulating gastric fluid (FaSSGF).

The use of FaSSGF improves the predictability of dissolution for a weak base, but not for a neutral drug. A comparison of the invitro dissolution data in biorelevant media within vivo data shows that it is possible to simulate food effects and shows differences in absorption between products of the same drug with the physiologically relevant media (FaSSIF, FeSSIF, and milk) [20].

**Apparatus and Dissolution Conditions**

For immediate-release products, the most commonly used dissolution apparatus are the USP Apparatus 1 (basket) and USP Apparatus 2 (paddle). Usually, the Apparatus 1 is operated at 100 rpm and the Apparatus 2 at 50 rpm. However, it was suggested that the Apparatus 2 is operated at 75 rpm to reduce coning [21]. By itself, the rotation speed would not be expected to affect the extent of dissolution of a low solubility drug because solubility is a thermodynamic property. However, once the solubility is addressed via selection of pH and surfactant, selection of the appropriate rotation speed raises similar issues to those found for higher solubility drugs. The rotation speed can be set on the basis of matching in vivo hydrodynamics, selecting the most sensitive speed, or selecting the speed that minimizes variability in the test method. In a recent article [22], the effect of hydrodynamics on both low solubility and high solubility drugs were evaluated, and the low solubility drug was slightly more sensitive to perturbations. In this article, the low solubility drug was still able to dissolve greater than 90% in 45 min in a media of 1000 mL borate buffer, pH 8.0, containing 0.1% Tween®80.

Other USP apparatus, the reciprocating cylinder (USP Apparatus 3) and the flow-through cell (USP Apparatus 4), are not commonly used for release testing but may be valuable for use in a biorelevant dissolution method during product development. The Apparatus 3 is believed to have hydrodynamic flow patterns that are more representative to those in vivo found [23]. The flow through cell allows removal of dissolved drug that would saturate media in other closed apparatus and thus gets much closer to the invivo situation that a truly low solubility drug encounters.

**Acceptance Limit**

After dissolution conditions are identified for a dissolution test, the dissolution specification is not complete until an acceptance limit is set. Three categories of dissolution test acceptance limits for immediate-release drug products are described in the 1997 FDA Guidances for Industry for immediate-release [5] and sustained-release drug products [24].

- Single-point specification as a routine quality control test. (For highly soluble and rapidly dissolving drug products.)
- Two-point specifications for slowly dissolving or poorly water soluble drugs (BCS Class II), a two-point dissolution specification, one at 15 min to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 min) to ensure 85% dissolution, is recommended to characterize the quality of the product.
- Profile comparison.

Although the FDA guidance for IR dissolution [5] suggests that a two-point limit be used for low solubility drugs, in practice almost all low solubility drugs in IR formulations have a single-point acceptance limit. For regulatory approvals of new drug applications (NDAs)/abbreviated new drug applications (ANDAs) for solid oral dosage forms, sponsors are required to develop appropriate invitro dissolution testing. For NDAs, the dissolution specifications are currently based on acceptable clinical, pivotal bioavailability, and/or bioequivalence batches. For ANDAs, the dissolution specifications are generally the same as that of the reference-listed drug (RLD). The specifications are then confirmed by testing the dissolution performance of the generic drug product from an acceptable bioequivalence study batch (es). If the dissolution of the generic product is substantially different from that of the RLD but the product is bioequivalent in an invivo study, a different dissolution specification for the generic product may be set [5].

**Future Development**

Industry and regulatory scientists have made every effort in developing dissolution tests to meet at least two objectives: a quality control tool to assure batch-to-batch consistency and an invitro surrogate for product performance that can guide formulation development and ascertain the need for bioequivalence tests. Since conditions that are optimum for the quality control purpose may not be applicable for establishing an IVIVC, it may be beneficial to

develop and use two kinds of dissolution tests: one for quality control and the other for invivo performance, to meet different objectives. The quality control test is sensitive enough to relevant product changes that ensure the high quality and consistent performance of products, while the dissolution test for IVIVC can predict in vivo performance of drug products and thus reduce unnecessary human studies, accelerate drug development, and hasten validation of post approval changes. Currently, the regulatory dissolution method is generally drug or drug product specific. Each drug product uses a different dissolution method, resulting in the development of IVIVC on a trial and error basis [7]. Therefore, dissolution data gathered from thousands of dissolution tests can rarely be used to gain dissolution knowledge that helps to understand the invivo performance of drug products. Furthermore, there is really no strong scientific and regulatory reason that immediate-release solid oral products of similar drugs cannot use a comparable dissolution method for predicting in vivo bioavailability and bioequivalence. Therefore, we should develop appropriate biorelevant dissolution testing methods, and academia, industry, and regulatory agencies should put more emphasis on devising predictive dissolution testing.

## CONCLUSION

The need to develop predictive dissolution methods for low solubility drugs is growing. The use of surfactants in the dissolution media is widely accepted in quality control dissolution methods. Characterization of the drug solubility in SGF/SIF provides insight into whether the levels of surfactant are similar to the solubilization found in vivo. Regulatory challenges include how to evaluate proposed dissolution methods that are used for both product quality control and invivo performance prediction. The dissolution tests provide useful information at several stages of drug development. Although scientists wish to establish in vitro–in vivo correlations between release of drug from the formulation and drug absorption, the limited knowledge of the complex composition and hydrodynamics of the gastrointestinal fluids remains a real hurdle. The experience gained so far indicates that the design of a unique dissolution test to be used reliably as a prognostic tool of oral drug absorption will not appear in the near future.

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