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Expert Review

The Science of USP 1 and 2 Dissolution: Present Challenges and Future Relevance

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Abstract. Since its inception, the dissolution test has come under increasing levels of scrutiny regarding its relevance, especially to the correlation of results to levels of drug in blood. The technique is discussed, limited to solid oral dosage forms, beginning with the scientific origins of the dissolution test, followed by a discussion of the roles of dissolution in product development, consistent batch manufacture (QC release), and stability testing. The ultimate role of dissolution testing, "to have the results correlated to *in vivo* results or *in vivo in vitro* correlation," is reviewed. The recent debate on mechanical calibration *versus* performance testing using USP calibrator tablets is presented, followed by a discussion of variability and hydrodynamics of USP Apparatus 1 and Apparatus 2. Finally, the future of dissolution testing is discussed in terms of new initiatives in the industry such as quality by design (QbD), process analytical technology (PAT), and design of experiments (DOE).

KEY WORDS: biorelevant methods; dissolution; *in vitro–in vivo* correlation; quality by design; variability.

INTRODUCTION

This paper explores the advantages and disadvantages of the current methodology in light of recent challenges. While acknowledging its limitations, a case is made that the current dissolution test for drug product performance has value.

The scope of this paper includes information on current issues, but it is not a tutorial on dissolution testing. The focus is on USP Apparatus 1 (baskets) and 2 (paddles) because these two systems constitute the bulk of dissolution testing in the pharmaceutical industry (1).

The paper is organized by contemporary dissolution topics. Presented first is a description of the current challenges the paper will address. The challenges generally are divided into two classes, biorelevance and variability. Challenges covered by each subheading are discussed, followed by a brief section on the origin of the method procedure governed by *United States Pharmacopeia* chapter on Dissolution <711> (1). The intent is to demonstrate the scientific basis of current industry practice. Then, a review of dissolution by application exposes both the value and limitations of the technique as an analytical tool. Application to formulation development, quality control, and *in vitro–in vivo* correlations (IVIVC) is covered. Next, variability inherent to dissolution testing is explored in the context of the challenges. A discussion is presented on calibration, including use of physical measurements and calibrator tablets, plus error associated with experimental conditions or analyst technique. It should be noted that recently the calibrator tablets were renamed by USP as Performance Verification Standards; however, since this is a new development, we have kept the term calibrator tablets throughout this paper. Hydrodynamics is the final section under dissolution method variability. The future of dissolution testing is discussed in sections on process analytical testing (PAT), design of experiments (DOE), and quality by design (QbD). Finally, the utility and future of the technique are summarized.

Challenges

Both biorelevance and technique variability are used to challenge the validity of dissolution testing. The basis for each challenge is presented below.

The most significant challenge for many dissolution methods used as a nominal performance measure stems from the lack of biorelevance. Scientists have stated that developing a dissolution method and setting associated specifications that are not linked to *in vivo* performance may limit the value of testing (2–7). It is not difficult to see that the vortex in the current design of USP apparatus is not the same as in a churning stomach. The majority of dissolution testing is carried out in a simple salt medium at a particular pH. The gastrointestinal lumen is significantly different, containing a plethora of biomolecules and salts in a changing pH

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environment. A lack of a biorelevant (physiologically based) dissolution system and specification often leads to data that are disconnected from *in vivo* results (2,3,7,8). Examples are cited where the dissolution method is either overly or not sufficiently discriminating (2,7,9). Few cases have been found where the method is appropriately discriminating (10). A dissolution method that is developed solely as a quality control tool for manufacturing is much less desirable than one that has bearing on patient safety or efficacy. If measurements have no bearing on the pharmacokinetic impact, then testing is not controlling the most important aspect of performance (2,3,7,8). Calls for better method development with biorelevant specifications are the result (2,3,6,7).

Variability associated with dissolution testing is another area receiving a great deal of attention. Many studies demonstrate the source and extent of variability (2–4,8,11–14). These sources can be divided into four subsets. The first is the physical or mechanical setup of the test. Tolerances allowed in operating the apparatus are defined by the USP (1). The definitions are designed to allow the apparatus to function with acceptable method variability, but even when operating within these limits, different dissolution profiles for the same drug product may result. Other physical factors are not controlled by the USP description but have an effect. Among the parameters in this class are shaft or basket wobble, vessel/shaft tilt, shaft centering, shaft height in vessel, and rotational speed (3,13). Vessel roundness, surface uniformity, or other hydrodynamic effects fall into this class and impact results (3–5,11,14,15). Even small changes in basket mesh size seem to have an influence on results (14). Another class of variability arises from operational differences. Parameters in this group are incidental vibration, the extent of degassing, inconsistent tablet placement in vessels, and inconsistent use of clips or sinkers (3,11–13). The third class of variability comes indirectly from performance differences in calibrator tablets that are real (8,16,17), operator induced, or from excipient deposition (18). As the name implies, calibrator tablets are used to verify overall system precision to qualify apparatus and control system variability. However, different disintegration mechanisms between calibrator and sample tablets are cited as a source of variability (3). Proposed remedies for calibrator tablet variability are mechanical calibration (3,13,19), project-specific manufacturer calibrator tablets possessing similar processing and mechanistic disintegration qualities (3,6), or non-USP apparatus (4,5,20). The fourth source of variability comes from manufacturing and is due to lot-to-lot or tablet-to-tablet processing or handling differences of the drug product (3,6,16). It includes particle size distribution and polymorph changes during drug substance manufacture. Changes in excipient characteristics are known to impact results (7). The variability from this cause is independent of the method but is reflected in the results. Sorting out the origin among all the potential sources of variability can be problematic.

Scientific Origins of Dissolution

Scientific Origins

Initially, the dissolution test was used primarily as a formulation development tool and as a quality control test for determining that the dosage would dissolve. To this day, dissolution is the only test that indicates if a dosage form will dissolve in the patient. The disintegration test was the first test designed to do this, but it has obvious limitations. Although a tablet or capsule can disintegrate into smaller particles, if it does not dissolve, it is not available to be absorbed in the small intestine.

Dissolution, as a general dosage performance test, was primarily linked to changes in the drug product formulation and the critical process parameters that can affect dissolution. During the process validation of tablet manufacturing, dissolution testing is performed on tablets at the target hardness and at the high and low extremes.

Dissolution is still a critical test to determine the effects of aging of the product on stability. Changes in tablet hardness, moisture, or other excipient changes can affect dissolution. Capsule cross-linking can have a significant effect on dissolution of samples on stability. In many respects, this continues to be the most compelling reason to have an effective dissolution test for testing a solid oral dosage product.

Some of the basic aspects of the dissolution test have their origins in general conditions in the human body. The test is conducted at 37°C. The paddle or basket rotation is designed to produce reproducible hydrodynamics that can be consistent from lab to lab. The real physical purpose of the agitation is to remove the drug-saturated layer of dissolution from around the dosage and replace it with fresh medium without causing a significant physical change in the dosage. The use of a 900-mL volume was determined in order to be enough to establish sink conditions (at least three times saturation) for most active pharmaceutical ingredients. Dissolution media were developed to mimic the pH of the gastrointestinal tract. At one time, simulated intestinal fluid had a pH of 7.4. This was changed to a pH of 6.8 in the mid-90s, because it was determined that this more closely represents the intestinal pH (21).

Dissolution Testing within the USP

The basic dissolution test in USP chapter <711> Dissolution describes the apparatus, the dissolution procedure, and product specifications. The old chapter <724> described Apparatus 3 through 7, while Apparatus 1 and 2 were described in chapter <711>. The newer editions of the USP have now combined Apparatus 1 through 4 in chapter <711>. The dissolution procedures have been harmonized in the pharmacopeias internationally, although there are some sections that remain unique to each pharmacopeia. The USP chapter <1088> describes the procedure for *in vitro–in vivo* evaluation of dosage forms, and chapter <1092> presents the development and validation of the dissolution procedure. The dissolution test has evolved over time and will continue to be improved as it is called upon to give more data that are relevant to dosage performance in the patient.

The FDA and Dissolution Testing in History

The FDA has placed much importance on the dissolution test and reviews the USP monograph dissolution tests for consistency with the dissolution conditions in the approved

product's New Drug Application. Most solid oral dosage forms are required to have a dissolution test, and it is not uncommon to have a drug recall due to a failed dissolution test. Part of the approval process of an NDA solid oral dosage is the FDA evaluation of the dissolution method.

Members of the FDA helped to develop the Biopharmaceutical Classification System (BCS). This has led to the development of guidances related to dissolution testing that are available on the FDA website.

Utility and Basic Goals of the Test—Formulation Development

Formulators consider the dissolution test to be a very powerful tool. The test can be used to show the dependence of dissolution rate on the presence and concentration of certain excipients and on manufacturing variables. There is abundant literature on the use of dissolution as a comparative test that can show a formulation change. A select few will be highlighted in this section of the paper.

As early as 1976, Khan and Rooke (22) described the effect of disintegration type upon the relationship between compression force and dissolution efficiency. The discussion compared three common disintegrants, sodium carboxymethyl cellulose, sodium starch glycolate, and a cation-exchange resin to then less commonly known excipients as insoluble sodium carboxymethyl cellulose, casein formaldehyde, calcium carboxymethyl cellulose, and a cross-linked polyvinylpyrrolidone. They concluded that the disintegrant type has a pronounced effect on the dissolution rate. In this work, the paddle was used at 50 rpm with water as the medium. The study also cited a 1963 publication of Levy *et al.* (23) that correlated an increase in compression force with starch-containing formulations.

Chowhan and Palagyi (24) explored the issues of hardness and the effect of the dissolution rate. This study showed how hardness was increased by partial moisture loss in compressed tablets. Several factors were investigated including type and percentage of excipient, water solubility, hygroscopicity of excipients or drug, and the influence of frequently used binders. They concluded that since the dissolution is related to moisture content of the granulation and the hardness of the tablets at the time of compression, the dissolution specification would ensure that the tablets meet the moisture and hardness requirements. It was recommended that the moisture content of the granulation and initial hardness be used as in-process controls. In this work, the paddle was used at 120 rpm with water or 7.4 phosphate buffer as the medium.

In 1981 Taborsky-Urdinola *et al.* (25) published a paper that won an APHA Research award. The importance of the paper was the proof that packaging type and storage conditions in multiple and unit dose containers markedly affect the dissolution results of model Prednisone tablets. A conclusion was that relabeling repackaged tablets with the expiration date of the original container was invalid. The dissolution conditions were paddle at 50 rpm using water as the medium.

Chowhan and Chi (26) continued his research and in 1985 described the role of lubricants and their effect on dissolution results. Two lubricants, magnesium stearate and sodium stearyl fumarate, were compared under identical mixing conditions to determine drug–excipient interactions. The conclusions were that sodium stearyl fumarate did not exhibit drug–excipient interactions, whereas magnesium stearate did exhibit significant drug–excipient interactions that adversely affected the disintegration time and dissolution rate.

Changes in surface area and dissolution rate were illuminated by Sunada *et al.* (27) in 1989. The changes in surface area during the dissolution process were measured, and the relationship between the surface producing rate constant and the initial particle size of sieved samples was estimated. There was also the simulation of the dissolution process based on the changes in surface area and the surface producing rate constant. The paddle speed was 250 rpm in water.

In the 1990s, the use of dissolution as an indicator of aging began. Chowhan (28) discussed the complexity of aging as related to selected factors other than the packaging and storage conditions. Factors such as the hygroscopicity of the superdisintegrants; method of disintegrant incorporation; granulation moisture content; effect of high or low humidity on the type of disintegrant (e.g., dibasic calcium phosphate dihydrate and tribasic calcium phosphate); effect of the use of lactose, dextrose, or MMC; and gelatin shell cross-linking were all evaluated. It was concluded that guidelines calling for accelerated conditions could give a good indication of aging issues.

Babu and Pandit (29) described how stability of glibenclamide was enhanced by complexation with β-cyclodextrin. The dissolution rate was employed as an indicator of aging using the paddle at 100 rpm and pH 7.4 phosphate buffer.

Dissolution rate was one of the important parameters measured when differentiating forms I and II (R, S) of propranolol hydrochloride. Bartolomei *et al.* (30) showed that dissolution rates of the two polymorphs were different using the paddle at 50 rpm with 0.1 N hydrochloric acid medium; the test was run at 20°C and 37°C.

The effects of temperature and humidity on the physical properties of piroxicam tablets were shown by Sarisuta *et al.* (31). The tablets containing various fillers (lactose or mannitol) were studied after storage for 12 weeks at 40°C and 52% relative humidity (RH) and 40°C and 96% RH. The physical properties of the tablets were measured every 2 weeks. Dissolution was measured using the paddle at 50 rpm with simulated gastric fluid as the medium. The dissolution rate decreased from week to week, regardless of the filler used. It was explained that the decrease in dissolution was due to moisture sorption by the tablet ingredients, which led to the formation of a saturated solution of water-soluble substances. Consequently, crystal growth and swelling of polymeric material occurred. This yielded a continuous structure of larger crystals so the exposed surface area was significantly reduced, hence the dissolution rate decreased.

In 1999 Rohrs *et al.* (32) showed the effect of croscarmellose sodium disintegrant on delavirdine mesylate. In the presence of high humidity, the water presumably acted as a reaction medium and a plasticizer for croscarmellose sodium, facilitating protonation of the carbonyl sites on the disintegrant. The important finding is that this reaction could very well occur with any acid salt of a free base. A change in inter-particle bonding can explain the reduction in tablet deaggregation during dissolution. The dissolution was performed using the paddle at 50 rpm, and the medium was 0.05 M phosphate buffer at pH 6 with 0.6% sodium dodecylsulfate surfactant.

The effect of powder substrate composition on the dissolution rate of methyclothiazide liquisolid compacts was

illustrated by Spireas *et al.* (33). Dissolution rates were increased by optimizing carrier-to-coating ratios in methyclothiazide liquisolid tablets containing a 5% *w/w* drug solution in polyethylene glycol 400 with difference excipient ratios. The dissolution conditions used were the paddle at 50 rpm and a medium of 0.1 N hydrochloric acid.

The influence of excipients, especially binders, on the dissolution rate of paracetamol tablet formulations was shown by Abebayo *et al.* (34). The effect of binders, namely breadfruit and cocoyam starch mucilage binders, was related to their surface tension and viscosity. The dissolution test used the basket at 50 rpm and pH 5.8 phosphate buffer.

Numerous articles on the subject of extended-release formulation information show that there is variability in the dissolution rate with the change of matrix ingredients and ratios (35–38). In the references cited, as in many cases, the paddle was used in the dissolution test.

In the last 30–40 years, the dissolution test with USP paddle and basket apparatus has been used extensively to provide information to the formulators regarding critical process variables. Only a limited amount of the literature is shown here as the literature is full of examples of *in vitro* release testing used to determine change in the formulation or manufacturing process. The power of the dissolution test is undisputed in assisting product development from early phases to monitoring stability.

QC Testing for Batch Manufacturing Consistency and Specification Setting

Product Batch Release

The value of *in vitro* dissolution testing as a quality control tool is demonstrated by its long history of regulatory acceptance. Dissolution testing has been included in the USP since 1970 and continues to be an important test today as evidenced by the large number of monographs that include dissolution requirements (over 600 as of 2006) (39). This points to an important benefit for drug manufacturers—dissolution testing fulfills a regulatory requirement.

Although the primary purpose of the dissolution test specification is to distinguish between acceptable and unacceptable batches, it is also used as a measure of batch-to-batch consistency of the manufacturing process. In this case, the method may be developed to be sensitive to manufacturing variables determined to influence drug release (40).

Stability and Shelf Life

Dissolution testing is also the primary method used to demonstrate stability of drug product performance throughout its shelf life. Although not specified by name in the guidance, dissolution testing fulfills the ICH Q1A (R2) requirement that stability studies include testing of drug attributes that influence "product quality, safety and/or efficacy" and that are susceptible to change over time (41). Dissolution has proven to be a valuable tool to indicate changes in such characteristics as crystallinity (42), glass transition temperature and pore structure of polymeric excipients (43), polymorphism (44), gelatin capsule cross-linking (45), and moisture content (32). This information can be used to make informed decisions on selection of formulation, manufacturing process, and packaging.

Setting Specifications, Establishing Product History, Post-Approval Manufacturing Changes

The dissolution test plays an important role in setting drug product specifications. The dissolution specification includes the specific dissolution procedure as well as acceptance criteria; it is intended to show that manufactured product is bioequivalent to pivotal clinical lots and confirm it was manufactured within acceptable values of critical manufacturing variables. Conformance to the acceptance criteria can be used to determine stability of the drug and to justify waiver of additional clinical studies following certain post-approval changes (46–48). Following approval, dissolution data for manufactured lots form a product history from which the "true" capability and variability of the process can be derived. This information may be used as justification for revised acceptance criteria (49).

Recently, the dissolution test has been criticized for not being predictive of bioavailability because methods do not mimic GI conditions closely enough (45). The lack of predictivity is not necessarily a limitation of the test, but may result from inappropriate selection of acceptance criteria or specific analytical conditions. In some applications, an overly sensitive dissolution test is desirable. For example, the FDA guidance on dissolution testing of immediate-release (IR) solid oral drugs (40) includes a procedure for manufacturing bioequivalent product lots with different *in vitro* dissolution to identify and establish an acceptable range for critical manufacturing variables. As for the question of biorelevance, because the goal of the dissolution procedure is to establish equivalence with acceptable clinical lots, the procedure need only be predictive of bioavailability. For this purpose, mimicking the gastrointestinal tract is not relevant. Ensuring that the procedure is predictive should be addressed during a rational method development following QbD principles.

Tests for Similarity and Difference

Because the comparison of dissolution profiles is used to evaluate the effects of formulation changes, the stability of product performance over time, and lot-to-lot manufacturing consistency and to demonstrate bioequivalence, it is important to understand the strengths and weaknesses of the various methods used for comparing them. Coming up with an objective data-based means of deciding if dissolution profiles are similar or different is a challenge. Because a dissolution profile is a plot of *cumulative* percent drug released (i.e., each data point is dependent on the previous data point) *versus* time, the underlying assumption of data independence is violated, precluding the use of statistical tests of difference (50). The use of exploratory data analysis methods, such as overlapping confidence intervals at individual time points as a test of similarity, becomes problematic when they overlap at some, but not all, of the time points.

Mathematical comparison methods such as f_1 and f_2 (51,52) utilize differences between average reference and test profiles at each sampling interval to provide a single number with which to quantify the similarity or difference between them. The mathematical comparator f_2 (similarity factor) (51), which is recommended by the FDA (40,46–48), has the advantage of being easy to calculate. However, this technique is sensitive to the number of dissolution time points after the plateau is reached (52) and does not account for vessel-to-vessel variability, and there does not appear to be a well-defined basis for the "sameness" threshold of f_2=50 (50). More importantly, because f_2 is a sample statistic and is not based on a known population, the probability of type I (rejecting similar profiles as dissimilar) and type II (accepting dissimilar profiles as being similar) error is unknown (50,53,54). A modification to this method, in which f_2 is calculated for each individual dosage unit, has been used to allow the inter-vessel variability to be expressed (54). The use of bootstrapping to simulate confidence intervals has been used with highly variable data to avoid making false conclusions (52,55).

Model-dependent methods involve fitting the reference dissolution profile data to a mathematical function (known physical curve); similarity of a test profile is evaluated in terms of difference between the mean model parameters of the reference and test curves (56). Models that have been used include zero-order (54,56), first-order (54,57), Hixson–Crowell (54,57), Higuchi (54,57), quadratic (57), Weibull (54,56–58), Gompertz (57,58), Probit (58), exponential (58), and logistic (57,58). These methods have the advantage of taking into account variance and covariance of the data sets, and sampling time points for the reference and test profiles do not have to be the same. However, it is not always possible to find a model that adequately fits the data. Selection of an inappropriate model curve can yield misleading results, resulting in incorrect conclusions, so it is important to run a lack-of-fit test on the reference data prior to comparing model parameters (59).

Statistical multivariate methods using multivariate ANOVA have also been used (60,61). These do take into account variability and correlation structure of cumulative percent-released-*versus*-time data. An advantage is that they can be used to make estimates of type I and type II errors.

In Vitro and *In Vivo* Relationships and Bioequivalence Challenges in Dissolution Method Development

IVIVCs were introduced as the desire of both industry and regulatory agency to reduce development time, cost, and regulatory burden (62). Recognizing that dissolution rate, aqueous solubility, and gastrointestinal permeability are the key parameters that control the rate and extent of drug absorption, Amidon *et al.* (63) proposed a Biopharmaceutics Classification Scheme (BCS) in 1995. Later, FDA classified drug substances into four groups: class I—high solubility, high permeability; class II—low solubility, high permeability; class III—high solubility, low permeability; class IV—low solubility, low permeability (48,64). For rapidly dissolving class I drugs, because of their high solubility and high permeability characteristics, the *in vivo* dissolution is not the rate-limiting step, so IVIVC may not be possible (63–65). In addition, since gastric emptying is the key factor in determining the plasma profile, if the excipients in the drug product alter the gastric-emptying rate, bioinequivalent products will be the result. For class II drugs, on other hand, dissolution may be the limiting step of the drug absorption, therefore, an IVIVC may be expected (21,62). More research is needed to develop and validate *in vitro* dissolution methods for class II drugs so that they can be used to predict *in vivo* dissolution (66). For class III drugs, permeability is the limiting step of the absorption, and a limited IVIVC may be expected, and finally, for class IV drugs, IVIVC is difficult. The drug will have both limited dissolution and permeability so it will be difficult, at best, to develop a dissolution model unless the permeability is borderline low.

Currently, there are four levels of IVIVC defined in FDA guidances (62,67–72). Level A correlation is a point-to-point relationship between *in vitro* dissolution and the *in vivo* pharmacokinetic data (73). It is generally linear and is reviewed as a predictive and preferred approach (62,73,74). In the case of a level A correlation, *in vitro* dissolution data can serve as a surrogate for *in vivo* performance. For a class I drug, IVIVC is generally not likely, but when formulated as an extended-release product and the solubility and permeability of the drug is site-independent, a level A correlation is expected (75,76). For a class II drug formulated as an extended-release product, and the solubility and permeability of the drug are site-independent, a level A correlation is also likely; however, if the permeability is site-dependent, IVIVC is unlikely (75). Level B correlation applies the principles of statistical moment analysis. It compares the mean *in vitro* dissolution time to either the mean residence time or the mean *in vivo* dissolution time (77,78), so it does not reflect the actual *in vivo* plasma concentration curve. Therefore, level B correlation alone cannot support biowaivers. A level C correlation represents a single-point relationship between a dissolution parameter (e.g., $t_{50\%}$, $t_{90\%}$) and a pharmacokinetic parameter (e.g., AUC, T_{max}, C_{max}). This correlation does not reflect the entire plasma-concentration–time curve or dissolution profile (62,79); therefore, it is considered the lowest correlation level. However, Level C correlation can provide useful information in early formulation development. For a class I drug, if the permeability is site-dependent, a level C correlation is expected (76). A multiple level C correlation compares one or more pharmacokinetic parameters of interest (e.g., C_{max}, AUC) to the amount of drug dissolved at several time points of the dissolution profile. This level of correlation may support a biowaiver if the correlation has been established over the entire dissolution profile with one or more pharmacokinetic parameters of interest. If a multiple level C correlation is possible, then it is likely that a level A correlation is possible as well, and the latter is the preferred correlation. In addition, level D correlation, which is a qualitative a rank-order correlation, has been described in an FDA guidance (62). This correlation can be useful in drug development but cannot support regulatory application.

Compared with immediate-release (IR) products (80,81), more attention has been given to the application of IVIVC for controlled-release oral dosage formulations (82–85), where formulation technology controls the release rate, thus drug release is the rate-limiting factor in the absorption process. For BCS class II drugs with immediate-release (IR) formulations, because of the intricacy of gastric emptying as

well as the low resolution of plasma data at early time points (0–3 h), a meaningful level A correlation seems unlikely and few publications have been made so far. However, Lue *et al.* (86) and Buch *et al.* (87) recently applied biorelevant dissolution media (BDM) in the investigation of the IVIVC of class II, immediate-release (IR) compounds. The application of IVIVC to non-oral products, such as parenteral depots or injectable dosage forms, has also been investigated (72,88–93). It is worthwhile to mention that for IR drugs, *in vitro–in vivo* relationship (IVIVR) was suggested by Polli (94) to describe the relationship of the *in vitro* dissolution to *in vivo* performance. IVIVR approach has been applied to metoprolol, piroxicam, and ranitidine (65,95).

Dissolution Development for IVIVC or IVIVR

A properly defined and executed dissolution method development process is the key activity to having a successful dissolution method that can be correlated or related to the *in vivo* release. The ideal of a level A correlation may not be obtainable, but some level of IVIVC or IVIVR should be obtainable for BCS class II drugs and extended-release oral dosages. If the drug product does not demonstrate this, one can expect a question about the dissolution method development from the FDA. The most common barriers to achieving an IVIVR are the following: (1) The dissolution of the drug is not the rate-limiting step in the dissolution and absorption/cell permeability process (i.e., the drug is class I, III, or IV). (2) The drug has a high first-pass metabolism that increases the variability of the *in vivo* data. (3) The drug product formulation critical process parameters and critical quality attributes are not well defined, resulting in a variable product.

So how does one start the dissolution method development process? First, as much information as possible must be known about the active pharmaceutical ingredient (API) including the solubility in various pH solutions and organic solvents, the pK_a, octanol–water partition coefficient, membrane permeability, polymorphism, and so forth. Once this information is known, the choice of the dissolution medium can be more easily determined by eliminating possible problem areas. The dissolution medium should not be near the pK_a of the API. There should be at least three to ten times the volume of media than the volume required to dissolve the amount of API is the highest dose. The salt chosen to prepare the dissolution medium can have an impact on the pH of the medium and the robustness of the method based on the buffering capacity at the chosen pH. The closer the medium pH is to the pK_a of the buffer and the higher the concentration, the more resistant the medium will be to pH change. The counterions in the medium can also have an effect on the dissolution of the API and the excipients based on the common-ion effect.

When the API has a low solubility in aqueous media and sink conditions are difficult to achieve, the use of surfactants is acceptable. The most common of the surfactants is sodium lauryl sulfate (SLS), also called sodium dodecyl sulfate (SDS). Other typical surfactants can be found in the USP chapter on dissolution development <1092>. Where capsule shell cross-linking is observed, the use of enzymes within certain concentrations is acceptable. The use of inclusion complexes with cyclodextrins has also been proposed. The use of hydroalcoholic media is discouraged, although it can be used as a last resort.

Biorelevant media have been developed by various groups to simulate a more natural environment (21,96). The use of bile salts, lecithin, phosphate buffers, and other salts are used to mimic both the fasted and fed state. An acidic pH around 1–2 is preferred for the gastric conditions. The more neutral pH range of 4.0–6.8 is preferred for the intestinal conditions.

The analytical finish is the final step in the dissolution method. Generally, the use of a UV/Visible spectrophotometer is acceptable for quantitation of the amount of API dissolved in the dissolution medium. This can give data in a relatively short time, where most chromatographic methods run over several hours. Some reasons for not using a UV spectrophotometer are (1) interference from the placebo, dissolution medium or capsule shell at the analytical wavelength, (2) low-dose drug or a weak chromophore that does not have a significant absorbance, (3) more that one API in one dosage unit, and (4) the final formulation has not been selected and the excipients may have potential interference.

The universal method of choice that has both selectivity and sensitivity is HPLC. Even so, with the advent of new dosage forms, biomolecules, and highly potent compounds, this traditional analytical technique has been challenged when the analyte is a poor chromophore. The detectability of the API can be improved by using an evaporative light-scattering detector (ELSD), electrochemical detector (ECD), refractive index detector (RI), or LCMS with post-column derivatization (97).

In summary, IVIVC can be used in drug development, in setting dissolution specifications, and to support biowaivers. However, IVIVC cannot be applied to every drug; therefore, it creates challenges for pharmaceutical scientists in developing relevant dissolution methods and setting meaningful product specifications.

Mechanical (Physical Parameter Check) *Versus* Chemical Calibration with Calibrator Tablets

The ASTM E55.03 Technical Subcommittee on Pharmaceutical Standards has approved a new standard E2503 titled "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus." Even more recently, the FDA has issued a draft guidance that offers a mechanical calibration alternative to the industry. These documents present the mechanical calibration approach of checking key physical parameters instead of using USP calibrator tablets. There is support for both the ASTM mechanical approach and the USP standard, which requires a combination of mechanical checks and chemical calibration. Both approaches have positive and negative aspects, which are being debated among pharmaceutical companies, dissolution apparatus vendors, contract laboratories, the USP, and the FDA (98).

The most significant physical parameter affecting dissolution rate and reproducibility is the rotational speed (rpm) of the paddle or basket. This parameter influences the hydrodynamics within the vessel. The temperature of the medium has a significant effect on the dissolution, although it is typically set at 37°C and not evaluated as a parameter than can be changed. The equipment alignment quality, which includes the vertical positioning of the shaft and the center of

the shaft within the vessel, can affect the dissolution rate. This typically causes the dissolution rate to be higher when compared to equipment that is well aligned. The other parameters that have some affect on the dissolution hydrodynamics, and therefore the dissolution rate, include basket or paddle height and wobble, vessel shape and smoothness, basket mesh size (opening size), and presence or absence of basket clips. Additionally, as the equipment ages, the quality of these conditions can change.

Other factors are not presently addressed by mechanical calibration. During deaeration, the formation of small bubbles on the dosage form can impede access of the medium and have an impact on dissolution rate. Techniques used to deaerate dissolution media have different levels of effectiveness and can influence the rate of re-aeration (99). Vibration from the lab environment can have significant impact on dissolution and is the primary reason for the implementation of the USP tablet calibration program in 1978 (100). In addition, aspects of the vessel shape that are not addressed by the mechanical standard can have an impact on dissolution rates and variability (101). Finally, the cumulative effects of multiple variations of the mechanical parameters that are close to the specification limits are not addressed (102).

In addition to the above variables, inconsistencies in the technique of the analysts performing the test can affect dissolution rate and reproducibility. Sampling cannula position, especially sampling depth, can affect the dissolution. There is analyst-to-analyst variability in manual sampling, while automated sampling can eliminate this issue. One area of inconsistency from lab to lab concerns whether the rotation of the apparatus is stopped before the dosage is dropped into the vessel. Other questions that should be addressed during a method transfer are as follows: (1) Do you drop all dosages at the same time and sample at the same time? (2) How long do you wait after deaeration and pouring before starting the dissolution experiment? This can influence both re-aeration and evaporation. (3) For dissolution profile calculations, do you account for the media loss and amount removed?

Calibrator Tablets

The original purpose of the calibrators was for standardization of the dissolution apparatus from lab to lab so that dissolution results would be independent of the equipment manufacturer. Even though there was a USP monograph with apparatus requirements, as dissolution apparatus were introduced to the market, it was still possible to have apparatus variability that could significantly affect dissolution rate. The calibrator tablet made it possible to test the effect of all these combined variations in a holistic approach. Calibrator tablets are sensitive to vibration and can give results on the cumulative effects of many different parameters.

So why is the calibrator tablet in question? Throughout the history of the USP calibrators, dissolution bath failures have been associated with individual tablets that have called into question their utility in assessing dissolution equipment conformance. Is the failure due to the dissolution apparatus or the calibrator tablet? Usually it is not the apparatus or the calibrator tablet, but analyst error. The Calibrator tablet manufacturing process has changed and has shown lot-to-lot differences and stability issues.

Calibrator tablets may show an apparent change in apparatus performance and induce a real change in downstream data. For example, when the same apparatus is calibrated at two different times using two lots of calibrator tablets, performance differences between calibrator tablet lots may lead to the false conclusion that a change occurred in the apparatus. Small corrections to the apparatus may be done as maintenance, resulting in a measurable performance difference in drug product testing.

Overall, the debate over mechanical calibration *versus* the use of the calibrator tablets is an example of the continuous improvement process and evolution of the dissolution methodology.

Variability Related to Hydrodynamic Artifacts or Fluid Flow in the Vessel

Primary Factors

The dissolution test is an important tool that has been used to support formulation development, to set quality control standards (68) and specifications, to predict *in vivo* drug performance, and so forth. However, variability due to the individual dosage form, deviations or systematic errors in the system setup, and fluid flow dynamics in the dissolution apparatus have been reported. In this section, we will focus our discussion on the latter cause.

Numerous studies have been carried out to investigate the cause of variance seen in the dissolution test in an effort to understand and ultimately minimize it. Researchers have shown that the biases of dissolution apparatus (e.g., vessels) and operational characteristics disrupt the hydrodynamics in the dissolution vessels, which subsequently influences the reproducibility of the test. Variations were seen from test to test within laboratories and between laboratories (18,103,104). Three primary factors that affect the hydrodynamics of dissolution are vessel shape and contour (15,105), operational characteristics, and drug dispersion pattern and settling location in the vessel.

Geometric Irregularities of the Vessel

Although it is believed that commercially available vessels have the correct physical parameters (i.e., inner diameter of the cylindrical portion, depth from the flange top to the inner bottom, and flange diameter), the vessel inner shapes vary widely from vessel to vessel (105). Tanaka *et al*. (101) studied the influence of the vessel inner shape on dissolution rate using USP Prednisone Calibrator tablets. Their results show that vessel shape varies even among conventional vessels. The irregular inner shape includes the deviation from circularity for the inner cylinder, deviation from cylindricity for the entire cylindrical shape, and deviation from concentricity for the center of the sphere. Due to these irregularities, the liquid flow dynamics was altered and resulted in large variation of the test results. This research suggests that there should be better control of vessel geometry. Besides vessel inner shape irregularities, vessel contour imperfections and wide geometric tolerances were reported to be another cause of large variability in the dissolution test (15); therefore, additional control over the

vessel specifications of oblique taper, eccentricity, and flatness are necessary.

Operational Characteristics

The impact of the physical parameters of the dissolution apparatus on the dissolution test has also been studied. The physical parameters discussed here include the type of dissolution apparatus, paddle design, basket mesh size, agitation speed, fluid-flow velocity and pattern, media temperature, deaeration method, sinkers, vibration, and so forth.

As expected, the dissolution rate increases with an increase in agitation speed, and study results confirm this (15,20). The effect of dissolution apparatus type on drug release was also investigated. Wu *et al.* (106) studied the dissolution rate of theophylline (class 1, high solubility and high permeability) and naproxen (class 2, low solubility and high permeability) tablets using both USP basket and paddle methods at various rotational speeds. The paddle method provided higher dissolution rates than the basket method. In both basket and paddle apparatus, drug release and mass transfer coefficients increased and the film thickness decreased with increased agitation intensity. The study results also showed that a larger paddle size resulted in a higher percentage of drug dissolved, an increased mass transfer coefficient, and a lower film thickness. In summary, hydrodynamic conditions affect the mass transfer rate and ultimately the dissolution rate. Studies conducted by Baxter *et al.* (107) confirm that that any modification to standard USP Apparatus 2, such as agitator clearance, speed, and type, could have significant impact on the hydrodynamics and, ultimately, the dissolution rate measurement. The computational fluid dynamics (CFD) model was applied by D'Arcy (108) to study the relationship between the velocity in the dissolution apparatus and the dissolution rate. The fluid velocity profiles between the paddle and basket apparatus were compared. The CFD simulations revealed variations in the velocity and flow patterns inside the dissolution apparatus as well as between two USP apparatus (basket and paddle). This study shows that the magnitude of the flow velocities inside the basket is similar to, though a bit lower, those at the base of the paddle apparatus at the same rotation speed. At 50 rpm and 100 rpm, the velocities in the base of the vessel of the basket apparatus were found to be the lowest, followed by those within the basket, and the velocities at the base of the paddle vessel were the highest. D'Arcy's experiment illustrates that in the basket method, fluid enters axially at the base, flows upwards, and exits at the sides. Other studies conducted by McCarthy *et al.* (12,109,110) using a CFD model confirmed the influence of paddle rotation speed on mixing. This research clearly shows that sufficient speed is required to reach complete mixing in a short time, which suggests that dissolution rate measurements obtained at very early sampling points (>1 min) may vary greatly. A recent study (12) revealed that fluid velocity (dead zone) is negligible at the center of the vessel base, while velocity significantly increases 8–10 mm away from the center.

Besides the influence of the dissolution apparatus, rotation speed, flow velocity, and impeller size, other operating conditions such as dissolution medium temperature, vibration, basket mesh size, and attachment have also been investigated. Crist and Spisak (14) studied the dissolution test using the USP 10-mg Prednisone calibration tablet, and the results show that the subtle variations in temperature at 37±0.5°C did not have an impact on the Prednisone dissolution rate, while the high external vibration frequency resulted in failing results. The authors also compared basket attachments, such as USP clip-type and unofficial o-ring attachment, as well as the basket mesh size. They found a 12% difference in drug release between two basket attachment devices. The percentage of drug released using the JP 36-mesh basket was slightly lower than results obtained using the USP 40-mesh basket. The authors believe that the design of the 36-mesh basket, which has larger wire and fewer openings, caused the particles to be retained in the basket longer and subsequently led to lower dissolution results.

Deaeration of the dissolution medium provided more precise results in one study (103), while in another study (105), the percentage of drug released in non-deaerated media was higher than results in deaerated media. The effects of sink shapes on dissolution profiles were studied by Soltero *et al.* (111); the use of longitudinal type sinkers gave fast, complete dissolution and less variable results than use of lateral type sinkers.

Cone Formation in USP Apparatus

Besides the impact of physical parameters of the dissolution apparatus on the test, many unexplained variances have been reported while testing USP dissolution calibrators using USP Apparatus 2 (14,104,105,111). The formation of a dense mass was observed at the bottom center of USP Apparatus 2 where slow shear and limited agitation are available; therefore, it was suspected to be the cause of the dissolution variations (20).

This dense mass of particles was related to the dosage forms and their disintegration patterns. Ultrasound pulse echo (112), particle image velocimetry (113), and computational fluid dynamics (109,113) confirmed the presence of the dead zone at the bottom of the USP vessel underneath the paddle. Collins and Nair (114) performed dissolution studies of two disintegrating tablets, acetaminophen and naproxen sodium, using USP Apparatus 1 and 2 as well as Peak™ vessels. Their results showed that in the case of acetaminophen tablets, no significant difference in dissolution profiles was observed using USP Apparatus 1 and Peak™ vessels, while a significant dissolution rate difference ($p<0.05$) between USP 2 and Peak™ vessels was detected in the initial 10 min. In the case of naproxen sodium tablets, with Apparatus 1 and Peak™ vessels, no significant difference was seen in these two type of vessels, and only a slight difference was observed at the initial 10 min; while a 10–20% difference in release rate between USP Apparatus 2 and Peak™ vessels was reported throughout the entire range of sampling points. Their work confirmed that cone formation in Apparatus 2 slowed down the dissolution rate.

A dosage form containing high amounts of insoluble excipients is expected to form a dense mass at the bottom of the vessel. This cone formation was observed for both poorly and highly soluble drugs, but it has more impact on poorly soluble drugs (20). This dead-zone phenomenon does not have significant effect in the case of USP Apparatus 1 (15) because the dosage is placed in the basket instead of being

dropped at the bottom of vessel as in Apparatus 2. However, variance due to the basket mesh size in Apparatus 1 could cause some variability in the dissolution test since some of the disintegrated particles can fall through the basket and settle at the bottom where there is less agitation. In order to eliminate this dead-zone mostly seen in Apparatus 2 and, hence, to improve the reproducibility of the dissolution test, several modifications to USP Apparatus 2 were suggested and investigated. They are the tilted vessel (20), the Peak™ vessel with a cone-shape molded into the bottom of the vessel (20,106,115), metal strip (111), crescent-shaped spindles (116), mega-paddle (117), and various propeller shapes. A flow-through cell apparatus was also suggested as an alternative. These modifications, in essence, changed the flow hydrodynamics in the vessel either by displacing the unstirred disintegrated particles away from the center of the vessel or by shortening the distance between the drug and the bottom of paddle, allowing more interaction between the surfaces of the drug with moving medium. Because of these changes, dissolution rates increased and variations decreased. Of the aforementioned modifications, the Peak™ vessel drew much attention. An increase in agitation intensity to minimize or eliminate cone formation is another alternative to the modifications to USP Apparatus 2, but caution should be taken not to lose the discriminating power of the dissolution test simply by increasing the paddle rotation speed.

In summary, the physical parameters of the dissolution apparatus have impact on the variability of the dissolution test. The modifications to dissolution Apparatus 2 eliminated cone formation under the paddle, which reduced the variability seen in the conventional USP apparatus, but caution should be taken to balance the dissolution rate, variance, and discriminating capability of the test.

PROCESS ANALYTICAL TECHNOLOGY, DESIGN OF EXPERIMENTS, AND QUALITY BY DESIGN

Quality by design (QbD) is a relatively new and developing initiative in the pharmaceutical industry that has significant potential for improving dissolution testing. QbD is meant to provide robust manufacturing through knowledge gained from deliberate manipulation of process parameters (design space) during development. Often, statistical algorithms, or a design of experiments (DOE), are used to acquire this understanding efficiently. The results allow appropriate manufacturing process parameters to be set to maximize the chance of acceptable finished goods. In-line testing to monitor and ensure process control is termed process analytical technology (PAT). These tools are widely recognized and increasingly applied by pharmaceutical companies. It is relevant for dissolution testing because historically, methods have not been developed with this detailed information. It seems certain that dissolution will improve as a quality control measure because of greater understanding of critical process parameters. Similarly, as QbD is applied in formulation development, more physiologically relevant dissolution methods are expected. Despite current criticisms of the technique, the landscape is clearly changing, and in general, increased dissolution method quality seems imminent. These concepts are discussed below in more detail.

The Application of QbD Principles to Dissolution Method Development and Formulation Development

A significant challenge to the future use of USP Apparatus I and II has come from the application of quality by design principles to pharmaceutical development. As part of the FDA "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century" initiative, the agency has promoted the use of quality by design principles to decrease variability and assure consistently high quality of drug products. Under this new paradigm, quality is "built in" through the development of processes for which inputs and outputs critical to product quality are identified and the relationship between them is understood, rather than by conformance to end-product release specifications (118). With prior knowledge and experimentation (e.g., a multivariate model relating clinical performance), these critical process inputs (CPIs) can be used to identify and control sources of product performance variability (8). By continuous real-time monitoring of the critical outputs (critical quality attributes [CQAs]), the process can be adjusted in real time as needed to ensure product quality (119).

The fact that the dissolution profile of a drug product is influenced by so many disparate material and process inputs (e.g., raw material particle size, compression pressure, moisture) and that it can be a predictor of *in vivo* drug performance make it a potentially powerful CQA for method development. Using a quality-by-design approach, a design specification including intended use of the procedure and performance objectives (e.g., less than 20% released at 30 min, greater that 80% at 10 h, 12-h duration), is agreed upon *a priori* (8,120). A structured approach, such as statistical design of experiments, is used to identify the relationship between *in vivo* release profiles and method conditions (medium, apparatus, sampling procedure, etc.), and the response surface (*in vitro* release profiles). This information (e.g., Pareto chart of factors and interactions between factors) is used to identify critical method parameters for controlling the release profile and the ability of the method to predict drug bioavailability (121,122). A similar procedure can be used in formulation development to identify CPIs (material/intermediate attributes, manufacturing parameters, etc.) that influence the release profile of the product and which can be controlled to ensure final drug product quality (123,124).

PAT Techniques as Surrogates for Dissolution Testing

As defined by the FDA, PAT is a quality-by-design risk mitigation tool that continuously and automatically monitors CQAs throughout the manufacturing process. Data generated by PAT can provide feedback for real-time adjustment of critical parameters and attribute-based endpoints to ensure quality of final product throughout a manufacturing run (125) and increase efficiency by reducing or eliminating batches that do not meet quality specifications. The larger volume of in-process data provides greater confidence in conclusions drawn from statistical analysis and the construction of more robust multivariate models. Because real-time QC is performed during manufacture, the need for end-product testing may be eliminated.

Within this framework, dissolution testing would not be considered an ideal technique (non-destructive, little or no sample preparation, rapid) for use in PAT (125). In order to capture the dissolution profile information in real time, several methods have been designed as PAT surrogates for dissolution testing. Near infrared spectroscopy is a non-destructive and rapid technique that has been used to predict the time to 50% dissolution ($t_{50\%}$) (126), as well dissolution profiles (127,128). Terahertz pulsed imaging, a non-destructive and thermally non-stressing spectroscopic technique used to accurately measure and map the coating thickness of individual tablets, has been used to predict mean dissolution dime of drug product (129).

Despite the potential value of dissolution testing, its use has also been challenged as being of limited utility due to (1) a lack of biorelevance (i.e., not mimicking the gastrointestinal tract, thus not a relevant indicator of drug performance); (2) IVIVC based on clinical studies not typical of intended use (normal healthy subjects as opposed to target patient population, no other medications used) (7,118,130,131); and (3) not being predictive of *in vivo* performance (8). Although some of these arguments have merit based on the way dissolution tests have been developed and applied in the past, these problems can be remedied using quality by design tools such as statistical design of experiments and PAT in the development of dissolution methods and in conducting IVIVC studies. It should be noted that the purpose of the dissolution procedure is to distinguish product lots with acceptable and unacceptable bioavailability. Although FDA and USP discourage use of organic modifiers and limit the use of surfactants in media (132), presumably to maximize biorelevance, the actual criteria used to establish IVIVC are based only on the strength of the relationship between *in vitro* and *in vivo* responses to drug dissolution over time. The question of whether the dissolution procedure mimics the GI tract does not appear to be an issue. Therefore, it could be argued that the development of dissolution methodology with biorelevant conditions should not be a regulatory requirement.

Dissolution Design of Experiment (DOE)

Design Space

The ICH Q8A guidance describes the creation of a design space for pharmaceutical products. The aim of pharmaceutical development is to design a quality product and a manufacturing process that consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. The principle and procedure described in Q8A could be applied to analytical methods. The design space of an analytical method is established using a set of statistically designed experiments known as "design of experiments" or DOE. DOE is defined as a structured, organized method for determining the relationship between factors affecting a process and the output of that process. DOE is the most logical, rational, and scientific way of collecting data. In the case of an analytical method, the process is the analytical method. Robustness of an analytical method can also be studied using the DOE process (133–135).

The robustness of an analytical method is a measurement of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Robustness is traditionally determined by varying one factor at a time. For example, if the method calls for a pH of 6.8, one can vary the pH of the media from 6.6 to 7.0. It would take 128 experiments to determine the effect of seven variables if the variables are changed one at a time. Additionally, the major disadvantage of varying one factor at a time is that the interactions between factors are ignored. With a modified multifactor experimental design, otherwise called a Plackett–Burman design, up to seven variables can be evaluated using eight experiments, and 8–11 variables can be evaluated using 11 experiments. These designs have two levels per factor, which are varied in a very specific and symmetric way. Each factor effect can be estimated using all of the data collected. The procedure for determining the robustness using DOE involves the following steps:

- Define the response (dependant variable). This could be the dissolution result, assay value, system suitability parameters, and so forth.
- Identify the factors (independent variables) to be investigated. This could be analytical wavelength, medium pH, medium buffer concentration, paddle speed, bath temperature, or other HPLC parameters.
- Define low and high values for the independent variables. Usually they are the high and low limits of the specification. This will be the design space of the method if the method turns out to be robust.
- Discrete factors like analyst, equipment, and column can also be part of the design. The high-low values could be arbitrary assigned.

The results of Plackett–Burman design experiments can be further evaluated using other statistical tools like the normal probability plot to evaluate the robustness of the method. The results may lead to the addition of more experiments to evaluate parameter interactions further. This

Table I. Biorelevance of the Dissolution Test

Challenges	Possible remedies
Composition of media	pH should be within physiological range. Exceptions: alcohol use and high surfactant concentration occur with special dosage forms.
Clinically relevant specifications	Use of QbD and IVIVC/R will contribute to specifications that have meaning with *in vivo* performance.
Poorly soluble products	Use of surfactants (with justification), equipment designs that simulate sink conditions.
Method development	Learning critical parameters in early phases and applying the knowledge in developing discriminating methods, heavy use of DOE.

Table II. Variability in the Dissolution Test

Challenges	Remedies
Equipment operation	Increase knowledge of sources of variability and provide controls (e.g., vibration and vessel symmetry).
Formulation	Increase understanding of release mechanisms with use of *in vitro* release tests as an ultimate tool for indicating changes.
Manufacturing	Increase in-line testing of product components, develop adjunct testing such as NIR, particle size, disintegration.
Stability changes	Understand in-depth the mechanism of changes on stability.

type of statistical evaluation of DOE results will enable the analyst to identify the "critical analytical parameter" of the method. If the method is not robust, it does not mean that the method should be abandoned. The conditions should be controlled, and a precautionary statement should be included in the method. A well-designed DOE experiment can pinpoint the critical analytical parameters.

CONCLUSION

From its conception to the present day, the modern dissolution method has proven useful in many roles. Despite its success, biorelevance and variability are valid criticisms of the technique. Tables I and II briefly summarize some of the challenges and possible remedies.

Although success has been achieved, the development of dissolution methods with IVIVC has not consistently occurred. More effort and expertise need to be exercised in this area. With the advent of the BCS, QbD, and other tools, the situation is changing. More emphasis is being placed on early and fundamental scientific understanding rather than a last minute check on IVIVC in late stage pharmaceutical development. There is an expectation that the changing paradigm in method development will lead to an increased incidence of IVIVC. More complex methods or apparatus may be developed to aid in IVIVC discovery. However, these approaches must be balanced against the needs of a quality control laboratory. Methods that are labor-intensive, complex, time consuming, or costly may be impractical. It is desirable, but less critical, in early stages to establish IVIVC because formulations change as drug candidates move into later stages of development. However, it is important to gain insight into the controlling factors of an IVIVC early in the drug development process. A change in emphasis on and attention to IVIVC seems to be occurring widely in the pharmaceutical industry, and an increase in the frequency of IVIVC in dissolution methodology is expected. The future holds significant promise for more routine establishment of IVIVC.

The variability of the technique comes from several sources such as tolerances in the USP-defined apparatus, operation, calibration, and manufacturing. Efforts are underway to control more tightly the variance due to the USP apparatus tolerances and calibration in general. There is a high degree of expectation that these efforts will be effective in reducing method variance from these sources. Operational variance may be controlled through analyst training and definition of method parameters, such as degassing. Variance due to manufacturing is not related to method variance, but it may affect the results. This situation makes comprehension of method variance more difficult. Analysts should look at all sources of variance in developing effective, mature dissolution methods. The variance of the technique is expected to decrease in the future.

The dissolution technique will continue to add value to the pharmaceutical industry as a performance test. The method is currently evolving through the scientific process and is in a state of transition. In the near future, dissolution method variance will be reduced, and biorelevance will increase for this mainstay technique.

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