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Acceptable Analytical Practices for Dissolution Testing of Poorly Soluble Compounds

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This article, based on material from a 2003 PhRMA workshop on acceptable analytical practices, provides guidance for developing dissolution testing for poorly soluble compounds. The first article from the workshop, about phased method validation, was published in November. Future articles will cover analytical method equivalency and justification of specifications.

Dissolution testing of poorly soluble compounds in immediate-release (IR) solid dosage forms poses many challenges. These challenges include developing and validating the test method, ensuring that the method is appropriately discriminatory, and addressing the potential for an *in vivo–in vitro* relationship (IVIVR) or correlation (IVIVC). The objectives of dissolution testing, in general, vary during the life cycle of a dosage form. The primary objective during Phases 0 and I is to develop a method to clearly establish the mechanism of *in vitro* drug release and solubilization. During Phases II and III, the objective shifts to identifying a test method that can provide an IVIVR, IVIVC, or other biorelevant information. At registration and beyond, the goal is to identify a quality control (QC) dissolution test method to verify process and product consistency.

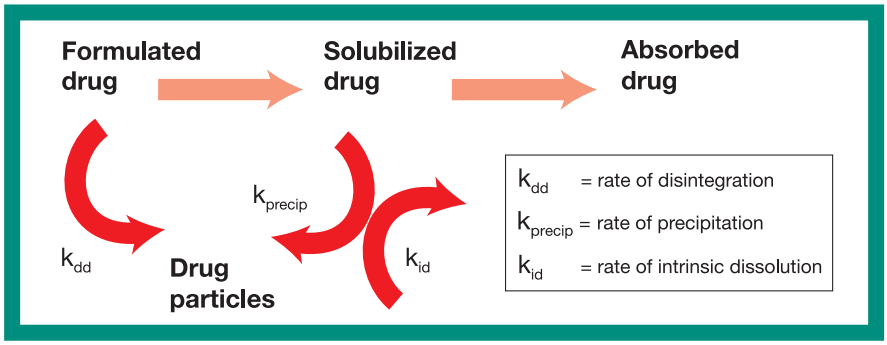

Figure 1: This diagram depicts the process of drug dissolution in a dosage form. When $k_{dd} > k_{id}$, dissolution is *intrinsic dissolution controlled*, and physical attributes of the active pharmaceutical ingredient are important. When $k_{dd} < k_{id}$, dissolution is *disintegration controlled*, and the cohesive properties of the formulation are important. When $k_{dd} \approx k_{id}$, dissolution is *intrinsic dissolution* and *disintegration controlled*, and both cohesive and physical properties may be important.

It is preferable to identify a dissolution test method that can evaluate both product consistency and bioavailability. This goal, however, remains a significant challenge for pharmaceutical formulation and analytical scientists, and frequently is not achievable. The literature, including regulatory positions, provides little guidance about addressing these challenges for poorly soluble compounds.

To collate acceptable practices and provide more guidance, the Analytical Technical Group of the Pharmaceutical Research and Manufacturers of America (PhRMA) included dissolution testing of poorly soluble compounds in the PhRMA Acceptable Analytical Practices Workshop held in September 2003 (1–2). Representatives from PhRMA member companies met to discuss the topic, share current practices, and agree on acceptable practices that represent good science and meet current regulatory requirements. The group also identified areas in which strategies need to be developed. This article presents the output of these discussions by providing a general overview of dissolution testing and highlighting the relevant issues and test modifications needed to test the dissolution of poorly soluble compounds.

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Why *in-vitro* dissolution testing?

Characterizing the drug-release mechanism by establishing an *in vitro* dissolution test method (or an appropriate alternative method) to measure product performance is particularly important for poorly soluble compounds. Dissolution testing historically has been a key tool during the development stages of a compound as well as for commercial manufacturing. For a development compound, dissolution testing is used primarily to help develop and evaluate new formulations by evaluating the rate of drug release from dosage forms, evaluating the stability of these formulations, monitoring product consistency, assessing formulation changes, and establishing IVIVRs or IVIVCs. For a commercial product, dissolution testing is used primarily to confirm manufacturing and product consistency, to evaluate the quality of the product during its shelf life, and to assess postapproval changes and the need for bioequivalency studies (3).

A dissolution test measures the rate of release of the drug. The objective is to develop a discriminatory method that is sensitive to variables that affect the dissolution rate. Such variables may include characteristics of the active pharmaceutical ingredient (API) (*e.g.,* particle size, crystal form, bulk density), drug product composition (*e.g.,* drug loading, and the identity, type, and levels of excipients), the drug product manufacturing process (*e.g.,* compression forces, equipment), and the effects of stability storage conditions (*e.g.,* temperature, humidity). Although it also is desirable to develop a dissolution test that establishes an IVIVC or an IVIVR, that kind of correlation between observed changes in *in vitro* dissolution rate to meaningful *in vivo* product performance quality remains a key challenge, as will be explained below.

Classifying drugs according to dissolution and permeability properties

Mechanism of dissolution. The dissolution test determines the cumulative amount of drug that goes into solution as a function of time. As shown in Figure 1, dissolution of drug from a dosage form involves at least two consecutive steps: liberation of the solute or drug from the formulation matrix (disintegration), followed by dissolution of the drug (solubilization of the drug particles) in the liquid medium. The overall rate of dissolution depends on the slower of these two steps. The relative difference in rates should be carefully considered when designing the dissolution method.

The cohesive properties of the formulated drug play a key role in the first step of dissolution. For solid dosage forms, these properties include disintegration and erosion, whereas for semisolid or liquid formulations, the dispersion of lipids or partitioning of the drug from the lipid phase is the key factor. If the first step of dissolution is rate-limiting, then the rate of dissolution is considered to be *disintegration controlled*. Careful assessment of the intrinsic rate of dissolution and the effect of various aspects of the formulation (*e.g.,* release profiles from precompressed granules, impact of compression force, porosity, and lubrication) can reveal the relative contribution of the disintegration step to the overall dissolution of the drug.

In the second step of dissolution—solubilization of the drug particles—the physicochemical properties of the drug such as its chemical form (*e.g.,* salt, free acid, free base) and physical form (*e.g.,* amorphous or polymorph, and primary particle size) play an important role. If this latter step is rate limiting, then the rate of dissolution is *intrinsic dissolution controlled*. This is the case for most poorly soluble compounds in IR formulations. For poorly soluble compounds in solubilized formulations, *in vivo* precipitation also may need to be considered when developing a dissolution test method, in particular for establishing an IVIVR or IVIVC.

The biopharmaceutics classification system (BCS) to define poorly soluble compounds. In addition to classifying drugs according to their disintegration and solubilization properties, drugs also may be classified by additional factors such as permeability. A classification system that uses permeability is the biopharmaceutical classification system (BCS), which is based on estimates of the contribution of solubility, permeability, and dissolution to oral drug absorption from IR dosage forms. First described in 1995, the BCS and its principles have been used in several guidances issued by the Food and Drug Administration (3–6).

BCS categories depend on a few key definitions, including *low-solubility, high permeability,* and *rapidly dissolving*:

- Based on the BCS, *low-solubility compounds* are compounds whose highest dose is not soluble in 250 mL or less of aqueous media from pH 1.2 to 7.5 at 37 °C. For a low-solubility compound, the highest dosage strength divided by the lowest solubility in the pH range 1.2–7.5 would be greater than 250. Solubility is primarily a property of the API and its salt form. Solubility usually is determined by measuring the concentration of a saturated solution after equilibration at 37 °C for 1 to 24 h. The equilibration time depends on the test duration time as well as the physical and chemical stability (*e.g.,* conversion of salt to free base *in vitro*) of the drug.
- *High permeability* is defined as human absorption of 90% or more of the administered dose (6).
- A *rapidly dissolving* IR drug product is defined as one for which no less than 85% of the label claim is dissolved within 30 min, as tested using either USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in pH 1.2 (0.1 N HCl or simulated gastric fluid USP, without enzyme), pH 4.5 buffer, and pH 6.8 buffer (or simulated intestinal fluid USP). (See discussion below in "Apparatus selection.")

Using these definitions, drugs fall into one of four BCS categories that describe the drug's permeability and absorption properties as well as its dissolution.

Class I: High solubility, high permeability compounds.

Class II: Low-solubility, high-permeability compounds. For these compounds, which are likely to demonstrate *intrinsic dissolution-limited absorption* (*i.e.,* the rate of drug solubilization is much lower than the rate of drug absorption), it may be possible to establish an IVIVR or IVIVC.

Class III: High solubility, low permeability compounds.

Class IV: Low-solubility, low permeability compounds. These compounds are likely to have *solubility-* and *permeability-limited absorption*.

Dosage form type and design affect dissolution testing

These key compound properties of dissolution, solubility, and permeability (along with other factors such as dose, bioavail-

ability, stability, and processability) will dictate the formulation design of a new product. In turn, considering the formulation design and mechanism of drug release from the product is critical in developing a dissolution test method.

In the case of *intrinsic dissolution-limited absorption* (*i.e.,* the disintegration of the dosage form is rapid, but dissolution is slow) a formulation approach commonly used is to reduce the particle size of the API. Small particle size, however, creates challenges in developing a dissolution test method. Small particles (*e.g.,* in formulations in which the drug is milled down to nanometer dimensions) can pass through filters and subsequently dissolve. In these cases, the use of smaller-pore filters, centrifugation, ultracentrifugation, or high wavelength UV detection may be needed. In addition, as the saturation solubility in the dissolution test media approaches 1X (defined as the *solubility limit*), small variations in assay parameters have an increasing effect on dissolution assay variability.

Also, in the case of *solubility-limited absorption (intrinsic-solubility controlled)*, a formulation approach commonly used is to enhance the transient solubility of the API. This approach includes using different salt forms of the API, using surfactants in the formulation, using solubilized liquid formulations in hard or soft gelatin capsules, and using noncrystalline materials. With transient solubility enhancement, one may have to consider that there may be a kinetic trade off between absorption and precipitation *in vivo*. In the case of *disintegration-controlled absorption,* the compound has a better solubility profile, but the two steps of dissolution may be competing and be very similar to each other. In either case, understanding the two steps of drug dissolution and which one is rate-limiting aids in designing the dissolution test (*e.g.,* media selection).

Dissolution test design

Before human clinical studies are conducted, dissolution data usually must be generated without the benefit of comparative rankings between formulations or lots, estimated *in vivo* human absorption rates, or any other information that could guide the development of a discriminating dissolution test. When developing a dissolution test for poorly soluble compounds early in drug development, therefore, the process should focus on assessing relevant physical and chemical properties of the API and the drug product's dosage form design, because these will guide the choice of the dissolution medium and apparatus.

This strategy for designing a dissolution test will change, however, in later stages of drug development, because of the evolving purpose of the dissolution test as well as the availability of additional data. For example, with the accumulation of both *in vivo* and *in vitro* experience during a product's development cycle, the early-phase dissolution test method should be critically reevaluated and potentially simplified for final QC testing. And in some cases, the data acquired will demonstrate the usefulness of alternative methods to replace dissolution testing. As the data become available for IR formulations that contain Class I drugs (*e.g.,* if the 85% of the drug dissolves in 15 min in pH 1.2, 4.5, and 6.8 buffers), a disintegration method can be justified and substituted for a dissolution test.

Media selection. The choice of medium will depend on the purpose of the dissolution test. For batch-to-batch quality testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of the drug product to ensure that sink conditions are met. The term *sink conditions* is defined as the volume of medium at least greater than three times that required to form a saturated solution of a drug substance. A medium that fails to provide sink conditions may be justifiable, however, if it is shown to be more discriminating or if it provides reliable data which otherwise can only be obtained with the addition of surfactants. On the other hand, when the dissolution test is used to indicate the biopharmaceutical properties of the dosage form, it is more important that the proposed biorelevant test closely simulate the environment in the gastrointestinal (GI) tract than necessarily produce sink conditions.

The dissolution characteristics of oral formulations should first be evaluated using test media within the physiologic pH range of 1.2–6.8 (1.2–7.5 for modified-release formulations) because low-solubility drugs include those with adequate aqueous solubility at either acidic (*e.g.,* amines) or neutral (*e.g.*, organic acids) pH levels. During method development, it may be useful to measure the pH of the test medium before and after a run to see if the pH changes during the test.

Selecting the most appropriate medium for routine QC testing is based on discriminatory capability, ruggedness, stability of the analyte in the test medium, and relevance to *in vivo* product performance where possible. Aqueous media without any surfactants are preferred, but aqueous media with surfactants may be used to increase the probability of establishing an *in vivo* relationship.

For some low-solubility compounds, adequate dissolution cannot be obtained with aqueous solutions within physiologic pH ranges. For these compounds, an aqueous solution containing a surfactant may be used to enhance drug solubility. Commonly acceptable ionic or nonionic surfactants include sodium lauryl sulfate (SLS), polyoxyethylenesorbitan monolaurate (Tween), cetyltrimethylammoniumbromide (CTAB), polyoxyl castor oil (Cremophor), hexadecyltrimethylammonium bromide (HTAB), polyethylene glycol tert-octylphenyl ether (Triton), nonylphenol ethoxylate (Tergitol), cyclodextrins, and lecithin. In general, nonionic detergents (*e.g.,* Tween) are considered more biologically relevant, and thus are often the first choice when considering the addition of a surfactant. A surfactant can be used as either a wetting agent or, when the critical micelle concentration (CMC) is reached, to solubilize the drug substance.

The need for surfactants, as well as their type and concentration, should be justified. The amount of surfactant needed for adequate drug solubility depends on the surfactant's CMC and the degree to which the compound partitions into the surfactant micelles. The surfactant's CMC depends, in turn, on the surfactant itself and the ionic strength of the base medium. Because of the nature of the compound and micelle interaction, typically a linear dependence exists between solubility and surfactant concentration above the CMC. If a compound is ionizable, surfactant concentration and pH may be varied simultaneously, and the combined effect can substantially change the solubility characteristics of the dissolution medium. Using an

aqueous-organic solvent mixture as a dissolution medium is discouraged; however, if an IVIVR or IVIVC is demonstrated that cannot be accomplished with a purely aqueous medium, an aqueous-organic solvent may be considered. The acceptability of such an aqueous-organic solvent media based dissolution method should be discussed with regulatory agencies early in product development.

Apparatus selection. Physical and chemical properties of the API (*e.g.,* solubility and stability) as well as the formulation concept play a key role in selection of the dissolution test apparatus, especially for poorly soluble compounds. Dissolution testing is conducted on equipment that has demonstrated suitability, such as that described in the *United States Pharmacopeia* (*USP*) under the general chapters of ⟨Dissolution⟩ and ⟨Drug Release⟩ (7). The basket method (USP Apparatus 1) is routinely used for solid oral dosage forms such as capsules or tablets at an agitation speed of 50 to 100 rpm, although speeds of up to 150 rpm have been used. The paddle method (USP Apparatus 2) also is used frequently for solid oral dosage forms such as tablets and capsules, but at 50 or 75 rpm. Both the paddle and the basket methods can accommodate media volumes ranging from 500 to 1000 mL with the standard vessel and 2000 to 4000 mL with larger vessels. Higher vessel volumes can be advantageous for low-solubility compounds. For highly potent, low dosage drugs, the use of 100 to 250 mL vessels should be explored.

The reciprocating cylinder (USP Apparatus 3) and the flow-through cell (USP Apparatus 4) also may offer advantages for some low-solubility dosage forms. Apparatus 3 can be used to estimate the drug release profile in the GI tract by using a series of different media in the vessels. Apparatus 4 may be more useful if certain ruggedness aspects can be improved by the vendors. By design, both the reciprocating cylinder and the flow-through cell allow for a controlled pH and volume change of the dissolution medium throughout the test. However, USP Apparatus 3 and 4 or other modified configurations are most often limited to use in product development and characterization. Flexibility in the selection of the apparatus during development facilitates understanding of the dissolution mechanism. Once the dissolution mechanism is understood, attention is focused on developing a method that is compendially acceptable and that may demonstrate an IVIVR or IVIVC. The superiority of a new or modified apparatus design should be proven in comparison to the compendial apparatus. The effect of hydrodynamics such as speed, axial velocity, vessel contours, currents, eddies, surface area, positioning, paddle shape, cage, and sinkers, should be considered during method development.

Discriminatory power

The discriminatory power of the dissolution method is the method's ability to detect changes in the drug product. Demonstrating the discriminatory power of the dissolution method is both challenging and important, particularly in monitoring API or formulation parameters critical for optimal product performance of the poorly soluble compound. Ideally, the dissolution test conditions should discriminate product changes that may affect biopharmaceutical product performance. However, unless an IVIVR or IVIVC exists for the product, variations in dissolution behavior may or may not reflect variations in the product's *in vivo* performance.

To determine if a dissolution method can discriminate product changes, the method must be challenged. The most common way to challenge the discriminatory power of the method is to test formulations with differences resulting from changes in the characteristics of the API (*e.g.,* particle size, crystal form, bulk density), drug product composition (*e.g.,* drug loading, and identity, type, and levels of excipients), the drug product manufacturing process (*e.g.,* dosage form, equipment variables), and stability conditions (*e.g.,* temperature, humidity). In conducting the challenge, the change in the drug product is evaluated versus the change in the dissolution data. If the data show a measurable difference for the key variables, then the method may be considered a discriminating test for critical manufacturing variables. The choice of experimental design to evaluate the critical variables will depend on the design of the dosage form, the manufacturing process, and intrinsic properties of the API. These experiments should be designed on a case-by-case basis in consultation with the formulation and manufacturing scientists. It is important to remember, however, that differences in the dissolution rates as a result of changing selected variables may or may not reflect *in vivo* product performance.

As mentioned previously, the purpose of the dissolution test method evolves through the various stages in drug development. Therefore, the test method should be re-evaluated and optimized (if needed) after human bioavailability data become available from the clinical trials. During further method development, optimization, and before selection of the final method, formulations used in the late-phase clinical trials are tested using various test medium compositions (*e.g.,* pH, ionic strength, surfactant composition). The effect of hydrodynamics on the rate of dissolution of the formulations also should be evaluated by varying the apparatus agitation speed of the dissolution apparatus. If a non-bioequivalent batch is discovered during a bioequivalency study, the dissolution methodology should be further optimized to allow for the differentiation of non-bioequivalent batches from the bioequivalent batches by dissolution specification limits, if possible. This will ensure batch-to-batch consistency within a range that guarantees comparable biopharmaceutical performance *in vivo*. Once a discriminating method is developed, the same method should be used to release product batches for future clinical trials, if possible. The biorelevant method may not always be feasible, and may or may not be the same as the QC method.

Validation and acceptance criteria. Acceptable practices for performing validation during early phases of development (8) and establishing acceptance criteria (9) for an *in vitro* dissolution test are described in other AAPs developed by the PhRMA Analytical Technical Group.

In vitro–in vivo relationships and *in vitro–in vivo* correlations

A common consideration of dissolution tests for low-solubility compounds is the opportunity to establish a method that allows for an *in vivo–in vitro* prediction. A distinction must be made between *in vivo–in vitro* relationships (IVIVRs) and cor-

relations (IVIVCs). A *relationship* is a broad term encompassing qualitative and even semi-quantitative associations between *in vivo* data and an *in vitro* metric. A *correlation,* on the other hand, is a predictive mathematical model, which, as outlined in the FDA guidance requires an evaluation of predictability and a degree of validation (6). A description of IVIVC levels A, B, and C appears in the FDA guidance (10).

It is well accepted that an IVIVC should be explored for extended release formulations in which the formulation technology controls the release rate. For immediate-release (IR) formulations of BCS Class II compounds (low-solubility, high permeability), it may be possible to establish an IVIVC if the API dissolution rate controls absorption. However, given the typical low resolution of data points on the time axis of the *in vivo* plasma curves within the 0–3 h time frame, as well as the convolution with gastric emptying, it is unlikely that a meaningful Level A correlation can be routinely developed for an IR dosage. If an IVIVC were established, it would likely be a Level C correlation relating a single point on the dissolution curve with a pharmacokinetic metric.

For Level C, however, each study leg contributes only one data point to the overall relationship, so developing a meaningful correlation requires a broad range of exposures covering "good" and "bad" formulations, and more than likely, integration of data across multiple bioavailability studies. As a consequence, there is a good deal of inherent variability associated with a Level C approach, and a rank-order qualitative relationship (*i.e.,* an IVIVR) may be the best that one can hope to achieve.

Current practices and hurdles for IVIVR and IVIVC. Very few IVIVRs for IR formulation were reported at the PhRMA workshop. In practice, IVIVRs for IR formulations typically have followed from unexpected pharmacokinetic study results in which dissolution testing did not necessarily predict the outcome. In these cases, it was only after differences between *in vivo* formulation performances were discovered that an effort was made to find dissolution conditions that provided a rank ordering. The new dissolution method was used to test subsequent formulations, and hence the dissolution method and IVIVR tended to evolve with the formulation development. The IVIVRs reported were used to qualitatively assess changes in formulation composition, process changes, and changes in dissolution observed on stability.

Although it would be ideal to have a single dissolution test method for IVIVR/IVIVC and QC purposes, this is not required and may not be feasible in most cases. In most cases, IVIVR test methods are not usable for QC, either because the extent of dissolution is too low, or because the methodology is too complicated to be practical for routine QC testing.

Although Level A correlations have a clearly defined regulatory benefit to the industry, lower level correlations (B and C) do not. As a result, the utility of Level B and C correlations generally is limited to establishing guidance for early formulation development, or providing a qualitative or, at most, a semi-quantitative method for evaluating formulation changes or stability changes during later-phase development. The industry tends, therefore, to establish Level B and C relationships rather than correlations for immediate-release solid oral dosage forms, because the term *correlation* brings with it connotations of requiring extensive validation and evaluation of predictability. This is compounded by the lack of clarity regarding the validation requirements and little perceived regulatory benefit (such as biowaivers, both during development and postapproval) of Level B and C IVIVCs.

Areas of discussion for IVIVR and IVIVC. During the PhRMA workshop, significant questions and opportunities were identified for further exploration and research. For example, in a typical QC dissolution test, more than 75–80% of the drug has dissolved at the final evaluation time point. In contrast, a dissolution test for a poorly soluble compound may show an IVIVR, but with a very low extent of dissolution (*e.g.,* $< 50\%$). Will such a test always be relegated to being a "development tool," or do circumstances exist in which it would be acceptable to use such a test for QC purposes?

In addition, formulation strategies for poorly soluble compounds can result in nontraditional *in vitro* profiles. Many formulation strategies rely on creating a transient supersaturated state *in vivo* that increases the concentration gradient across the intestinal wall, thereby increasing mass flux. The concentration reduction occurs by two pathways, absorption and precipitation. The relative rates of these two processes can significantly influence bioavailability. If precipitation is an important component of the *in vivo* behavior of a formulation, to achieve an IVIVR, the *in vitro* test method will have to account for precipitation. These methods are not nearly as well developed as traditional dissolution methods and need further attention.

The role of animal surrogates for developing and validating IVIVRs and IVIVCs has not been fully described. An understanding of drug and formulation properties (either robust or significantly affected by differences between species physiology) is needed. In addition, it is not clear whether formulation comparison in animals could ever be definitively substituted for human data for regulatory purposes.

Alternative methods to dissolution testing

The standard dissolution test measures a combination of cohesive properties and the API's intrinsic rate of solubilization. Under certain rate-controlling conditions, however, alternative measures may better reflect the critical performance characteristics of a drug product. For example, the International Conference on Harmonization has proposed (in its Q6A guidance) the use of disintegration testing as a surrogate for conventional compendial dissolution tests for highly soluble drug substances in which the intrinsic rate of solubilization is rapid and the overall drug release rate is dominated by the cohesive properties of the formulation (11). This concept has been further supported in FDA's guidance on biowaivers for rapidly dissolving drugs (6).

Available guidance regarding alternative test methods for poorly soluble compounds, on the other hand, is limited. The use of alternative methods, however, should be appropriate for low-solubility compounds, if the use is based on a scientific rationale resulting from a good understanding of the mechanism that controls the formulation's drug release. APIs that exhibit good solubility at gastric pH levels should receive allowances similar to those granted for BCS Class I and III products, *i.e.,* it may be justifiable to characterize these drugs by disintegration testing alone.

APIs that are poorly soluble at gastric pH levels (whether or not they are soluble in water or at more neutral pH levels) require additional considerations. First, if the dominant mechanism controlling the drug release is the API's intrinsic solubilization, physical properties of the API (*e.g.,* particle size, distribution, surface area) may serve as a more relevant predictor of drug release. Certain formulations lend themselves to this consideration better than others, such as:

- formulations in which the cohesive properties are minimal or nonexistent (*e.g.,* powder in a bottle, API in a capsule, and API suspensions for oral, intravenous or intramuscular administration)
- formulations in which the API's physical properties are very carefully controlled in the manufacturing process (*e.g.,* products produced using nano-milling and spheronization)
- formulations for which it has been demonstrated that the rate of disintegration is very rapid relative to API solubilization.

In one recent example of such an alternative approach, particle size was the definitive drug release criterion for a nano-milled formulation that demonstrated rapid aqueous release from a solid dosage form.

Another common formulation with unique advantages for poorly soluble compounds is the liquid filled capsule (LFC), in which the drug has been dissolved in solubilization aids, and offers a true solution to both the patient and the dissolution bath. The mechanism for drug release is likely to be the rupture of the capsule, and would justify the use of disintegration as a surrogate for the QC dissolution test. In such a case, the API's physical characteristics are insignificant, as long as the manufacturing process is robust with regard to ensuring drug dissolution and the product is robust with regard to maintaining the API dissolved for its intended shelf life. Where interest exists in developing an IVIVR to support the design of an LFC formulation, common challenges include, but are not limited to, the potential for *in vivo* precipitation of the API and the effect of the liquid vehicle components on API permeation.

Finally, other analytical techniques emerging as surrogates for dissolution testing are Raman and near-infrared spectroscopies (12). Both provide a combination of chemical and physical signatures (*e.g.,* porosity, and particle size) of a formulation, which may be correlated to the dissolution properties of a drug formulation. The application of these technologies will likely require extensive correlation to standard dissolution approaches to justify replacing dissolution testing.

In general, the use of an alternative test method may be easily justified or may require extensive data. For specific dosage forms such as LFCs or API in a capsule, disintegration or measurement of API physical properties, respectively, may be appropriate and require minimal justification as a surrogate to dissolution testing. More commonly, for final dosage forms, the use of an alternative test will likely require the application of a traditional dissolution test along with the alternative method to establish the correlation that justifies using the alternative method. The extent of the data needed will depend on the scientific understanding of the release mechanism as well as how dominant the release mechanism is relative to other potential factors that contribute to the drug release profile. Alternative methods will likely need to be applied during product development, including key stability monitoring, and proposing the alternative method to replace conventional dissolution either at registration or post launch, depending on when confidence in the alternative test is established.

Summary

Identifying a single dissolution or appropriate physical test method to provide a measure of product consistency as well as bioavailability remains a significant challenge for dosage forms containing poorly soluble compounds. Dissolution test method development should consider the design and matrix (cohesive properties of formulated drug) of the dosage form as well as the physicochemical (intrinsic) properties of the active pharmaceutical ingredient. The design of the dissolution test method also depends on its purpose. For example, the test may facilitate formulation screening at the early development stage and evaluating manufacturing process parameters at the later stages. The dissolution test media selection should be justified for pH (recommended range pH 1.2–7.5) as well as surfactant type (ionic *versus* non-ionic) and level. USP Apparatus I and II are commonly used for dissolution testing of commercially available products of poorly soluble compounds, whereas other apparatus have been used primarily for development. Acceptance criteria for the dissolution test are established or adjusted when the product moves into later stages of development.

The industry develops dissolution tests to understand the mechanism of drug release and to confirm process and product consistency according to regulatory requirements. In certain cases, such as in nanosized, microemulsions, and microparticulate formulations, unless the dissolution test relates to *in vivo* product performance, alternative methods to monitor product quality and consistency may be more meaningful. By using *in vitro* dissolution tests, the industry generally seeks to establish *in vivo–in vitro* relationships (IVIVRs) as opposed to *in vivo–in vitro* correlations (IVIVCs), because the latter have poorly defined validation requirements, challenges of predictability, and extensive added cost with questionable benefit. In particular, a lack of success has been seen across the industry in successfully establishing an IVIVC for immediate-release oral dosage forms. This situation is not expected to improve until there is a better definition of the necessary validation requirements and a perceived regulatory relief through biowaivers.

When an IVIVR or IVIVC is established, however, the IVIVR/IVIVC dissolution method does not have to be the same as the quality control method—and generally is not the same—because of the scope and limitations of IVIVR and IVIVC methods. Opportunities exist for further research into areas such as determining the value of a QC dissolution method in which less than 75–80% of the drug is dissolved, accounting for precipitation when this is an important component of the *in vivo* behavior of the formulation, and determining the role of animal surrogates in validating IVIVRs and IVIVCs.

Because the dissolution test measures a combination of cohesive properties of the formulation and the intrinsic properties of the API, in certain rate-controlling conditions, alternative test methods (such as disintegration and spectroscopy) may

be more appropriate to measure the critical performance characteristics of the formulation. In some cases, the use of alternative methods to dissolution may be easily justified, whereas in others, extensive data may be required to establish the correlation that justifies their use as a surrogate for the dissolution test. The industry currently has limited experience with the use of alternative methods and advancements in this area are expected to be very useful.

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