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In Vitro Product Performance Testing of Oral Drug Products: View of the USP Expert Panel

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ABSTRACT

This is the last in a series of *Stimuli* articles developed by the USP Expert Panel New Advancements in Product Performance Testing charged with reviewing and proposing new approaches for drug performance testing in the US Pharmacopeia. The USP Expert Panel created working groups that focused on five major routes of administration, continuous manufacturing, and nanomaterials. The article reports the results of the working group that studied the performance tests for orally administered drug products. The goal of this article is to highlight current knowledge gaps and potential challenges associated with performance tests for certain orally administered drug products, and to stimulate public input on current practices and new advances for in vitro testing. The input received may inform the development or revision of *USP* general chapters.

INTRODUCTION

Although dissolution testing for oral products is well established, periodic review and timely assessments of current procedures and possible alternatives are required to support regulatory approval for new and generic drug products. To this end, USP established the Expert Panel New Advancements in Product Performance (EP-NAPPT) to review the status of drug performance tests regardless of their route of administration. As noted in the introductory article (*1*) for this series of papers, several working groups were created within the panel and were responsible for: 1) conducting a gap analysis to evaluate current compendial product performance tests; 2) providing recommendations for the adaption of current tests and possible development of innovative new approaches to performance testing; and 3) stimulating public comments about how USP can contribute to the establishment of best practices and standards for such tests.

This *Stimuli* article focuses on oral dosage forms and describes the limitations and challenges to develop dissolution methods to support QC and biorelevant purposes. The development of various oral dosage forms requires development of robust methods and unique techniques based on the release characteristics. This *Stimuli* article is arranged by specific types of solid oral dosage forms. For each dosage form there is a discussion of the limitations and points to consider for the development of quality control or biorelevant dissolution methods. It is the intent of this *Stimuli* article to generate public comments on how USP can update or create new compendial chapters.

IMMEDIATE-RELEASE DOSAGE FORMS

In vitro dissolution testing of solid oral dosage forms is well established in all pharmaceutical laboratories. It is widespread in routine use from early development to commercial stage for release testing, stability as well as

formulation development and regulatory acceptance for bioequivalence or biowaiver. Its design is well established and described in Dissolution <711>, Drug Release <724>, The Dissolution Procedure: Development and Validation <1092>, Oral Dosage Forms—Performance Tests <1711> and harmonized with *European Pharmacopoeia, Japanese Pharmacopoeia*, and ICH. Whether or not the dissolution profiles have been correlated with biological effectiveness, the standard dissolution test is a simple and inexpensive indicator of a product's physical consistency. However, several limitations associated with the test design (e.g., apparatus, medium, volume, and timepoints) or its applicability have been identified and are discussed in this *Stimuli* article.

Tablets

Current Approaches: Limitations and Challenges for Tablets

Although the in vitro dissolution testing for tablets is robust and well described, there are several aspects where the test is associated with limitations. Depending on its purpose, these limitations can be classified in four different categories: 1) artifact due to the test design; 2) high variability; 3) test conditions are time consuming; and 4) limited bio-relevance.

1. **Artifact:** A well-known hydrodynamic artifact for the dissolution of tablets that uses paddle is the "coning" (sticking/mounting) effect (*2*). It is an accumulation of particles near the bottom of the vessel due to insufficient agitation underneath the paddle. It can typically be easily circumvented by higher speed or peak vessels. However, the challenge resides in the balance of not impairing the discriminating power of the method and avoiding a strong artifact which can negatively impact the results. In general, poor hydrodynamics can also contribute to high variability.

2. **Variability:** High variability can, in some instances, be observed in dissolution testing, particularly at the beginning of the profiles during the ascending part of the release. It is important to differentiate if this observed variability is related to the product quality, or to the variation in dissolution method. The first can be estimated by the assessment of content uniformity and physical parameter variations (e.g., hardness, disintegration) while dissolution method variation can be estimated, for instance, by intermediate precision (e.g., %RSD higher than 5% at plateau is an indicator of poor reproducibility).

3. **Analytical test conditions and detection:** The analytical part of in vitro dissolution is often associated with a high burden in laboratory. Activities such as sampling, test preparation, time for equilibration, degassing and off-line measurements (e.g., HPLC) are all time consuming. There are several potential sources of variation associated with each step. On-line or at-line UV technology and detection can have the potential to significantly decrease the analytical burden.

Table 1. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Oral Drug Products—Immediate-Release Dosage Forms

Dosage Form	Limitations and Challenges
Disintegrating, eroding, and diffusing tablets	Biorelevance of the test Need of high amount of surfactant for poorly soluble compounds Variability and lack of reproducibility Artifacts (i.e., sticking, mounting) Analytical challenges (i.e., on-line versus off-line, stability, sampling frequency
Effervescent tablets	Biorelevance of the test Sample introduction Application of USP recommended methods for tablets named as effervescent that do not immediately disintegrate, but show CO_2 formation with the purpose of floating
Chewable tablets	Mechanical force needed for drug release may not be achievable by high agitation in both Apparatus 2 and Apparatus 3
Sublingual tablets	Biorelevance of the test (small saliva volume, drug release, and immediate absorption via the mucosa, swallowing of part of the dissolved drug) Analytical methods and sampling frequency need to enable short sample/measuring intervals when aiming to record a dissolution profile
Orally disintegrating tablets (ODT)	Biorelevance of the test Assessment of both disintegration and dissolution Taste masking may impact release profiles. Therefore, effectiveness may need to be demonstrated in vitro Analytical challenges due to flavorings (selectivity/specificity) Definition of ODT varies by region (< 30s for US, < 3 min elsewhere)

4. **Biorelevance:** Dissolution working conditions described in <711> and <1092> are very different from an in vivo environment, including the volume, media composition and pH, and mechanisms of agitation. Many dissolution methods developed using compendial equipment as a quality control tool for manufacturing cannot be correlated to in vivo performance. When a dissolution method is intended to be bio-indicative, the description of the method in the pharmacopeia could only allow limited options. Typically, a change in pH during the gastric passage or differences in ionic strength, buffers, enzymes and/or surfactants concentration in the gastrointestinal (GI) tract cannot be easily reflected in a 1 L vessel under sink condition with a rotating paddle. As a result, biorelevant methods often deviate from product quality methods described in USP.

Possible Alternatives or Surrogates: Points to Consider

1. **Artifact:** The purpose of the dissolution test is to measure the rate and extent of release of a drug from a formulation. The test should be sensitive to factors that matter such as clinical relevance, critical process parameters or aging, and insensitive to factors such as method variation or artifact. There have been several attempts over the years to overcome this intrinsic design flaw, e.g., apex vessels (*3*), tilted vessel (*4*), "mega" paddle (*5*), metal stripes, permanent in-line probes acting as baffles and the off-center paddle (*6*). A recent example of a good mitigation for the coning effect, the Apex Vessel (*3*) is presented as a reasonable alternative using method 1 or 2 as described in <711>.

2. **Variability:** While some of these potential sources of variance can be reduced or controlled by optimizing the method (e.g., degassing, detection method, elimination of artifacts), the sample size representation can also be increased by following an approach called as Real Time Release Testing (RTRT). RTRT allows for more process data collected using stratified sampling over the process (i.e., sampling at predefined intervals (*7, 8*).

3. **Analytical test conditions and detection:** Other detection techniques such as in-situ fiber optic absorbance and at-line/on-line near infrared analysis of materials or dosage forms instead of traditional HPLC have shown some benefit depending on the purpose (development) or the mode of manufacture.

4. **Biorelevance:** Appropriate in vitro conditions (e.g., media and hydrodynamics) that simulate in vivo conditions can lead to successful predictions of the in vivo performance and in vitro–in vivo correlations for oral formulations (*9*). Biorelevant dissolution testing can be used to guide formulation development, to identify food effects on the dissolution and bioavailability of orally administered drugs, and to identify solubility limitations and stability issues. To develop a biorelevant dissolution test for oral dosage forms, the physiological conditions in the GI tract that can affect drug dissolution are taken into consideration according to the properties of the drug and dosage form. A variety of biorelevant methods in terms of media and hydrodynamics to simulate the contents and the conditions of the GI tract are presented in the literature. Input is sought from investigators who develop in vitro dissolution methods for tablets to comment on current needs relating to the points above. Specifically, it would be useful to receive comments on potential development of testing strategies/methods that could be further developed as a new *USP* compendial test.

Capsules

General Considerations

Capsules follow similar purposes, requirements and procedures as tablets with regards to in vitro dissolution performance testing. Dissolution testing of capsules is well established and described along with tablets in <711>, <1092>, <1711>, and Disintegration and Dissolution of Dietary Supplements <2040>. Additionally, most of the requirements and procedures are harmonized with *European Pharmacopoeia, Japanese Pharmacopoeia*, and ICH. However, there are some important aspects that are still not harmonized, such as the use of enzymes to overcome gelatin capsule cross-linking, which is not accepted by the *Japanese Pharmacopoeia*. Dissolution testing of capsules is comparable to tablet dissolution with regard to the ability to indicate the physical consistency of a product and its correlation to biological performance. However, capsule dissolution has unique challenges that are not encountered in tablet dissolution. Chapter <1094> specifically addresses the dissolution of capsules and related quality attributes.

Current Approaches: Limitations and Challenges for Capsules

Dissolution testing for capsules made by using different capsule shells (hard or soft shells), different polymers [gelatin, hypromellose (HPMC), or the other polymers], and different type of fillers (solution, dispersion, or solid) can present different challenges and limitations. The capsule dissolution process generally involves three

stages: 1) rupture of the capsule shell; 2) release and dispersion of the capsule fill material; and 3) dissolution of the active ingredient in the medium. Different types of capsules may encounter limitations at different stages in the dissolution process.

Table 2. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Oral Drug Products—Capsules

Limitations and Challenges
Similar to the IR tablet formulations
Biorelevance to the test
Tailoring the in vitro hydrodynamics of standard apparatus to in vivo conditions (i.e., wetting and dispersion)
In vitro dissolution test is often sensitive to changes (cross-linking, gelling) that have no or un- certain in vivo relevance
Sinkers can have variable impact on results
Use of enzymes for gelatin cross-linking are not universally accepted; need for additional validation of methods for use with enzymes

1. **Hydrodynamics:** Once the capsule shell is opened or dissolved, the solid fill material can accumulate at bottom of the vessel if the hydrodynamic parameters are not optimized (see *Tablets Artifact* section above). For liquid filled soft capsules with hydrophobic based formulation, the release and dispersion of the capsule content is highly influenced by the agitation efficiency with which the capsule contents mix with dissolution media (*10*).

2. **Cross-linking and gelling:** Capsule dissolution is very sensitive to changes of the capsule shells. For gelatin capsules, gelatin cross-linking formed in storage can significantly affect the dissolution and result in abnormal drug release profiles. Many studies and publications have demonstrated the causes and mechanisms of the cross-linking that occurred on gelatin capsules including both hard and soft gelatin capsules. Dissolution testing of cross-linked capsules can result in significantly large variations such as slower release of the drug or no drug release. Chapters <711> and <2040> describe the use of enzymes in dissolution testing to overcome possible gelatin cross-linking. For HPMC capsules, the capsule opening in dissolution testing is significantly slower than gelatin capsules (*11*). During dissolution testing, the HPMC shell can form a gel-like material which can stick to the sinker in Apparatus 2 or clog the basket mesh in Apparatus 1. In the worst cases, the gelling material can hold some of the active drug and prevent it from fully releasing. Capsule gelling and its effects on dissolution have not been widely noted and studied. Another issue for some HPMC capsules is the presence of carrageenan, which can bind with certain ionic drugs or excipients and result in slower dissolution. The in vivo impact of this may be case specific.

3. **Use of enzymes:** Chapters <711> and <2040> allow the addition of enzymes to the dissolution medium when the capsules do not meet the dissolution acceptance criteria due to gelatin cross-linking. When the two chapters were revised in 2016, two additional enzymes, bromelain and papain, were added to cover the pH range between 4.0 and 6.8 where the two original enzymes pepsin and pancreatin have low enzyme activity. The new general chapter <1094> for capsule dissolution references <711> for adding enzymes to the dissolution medium to overcome cross-linking. Chapter <711> also provides guidance on the use of enzymes to overcome gelatin cross-linking when the dissolution medium contains surfactant. However, a much bigger challenge is how to demonstrate the presence of cross-linking in gelatin capsules (*12*). Both <711> and <1094> emphasize that enzymes should not be used in the absence of evidence of cross-linking. The use of enzymes for gelatin cross-linking is not universally accepted, for example, by Japan, which has been a big burden for international submission of new drug products and global marketing.

4. **Sinkers:** Sinkers are often used in dissolution testing of capsules primarily to prevent them from floating during the test. Floating can lead to changes in the local hydrodynamics around the dosage form resulting in variability in the dissolution data. It can decrease the surface area exposed to the dissolution medium or lead to irregular and additional movement of the dosage form. Over time, different sinker types have become commercially available and have been used at different laboratories. These include: 1) longitudinal sinkers that contact the capsule on the long axis; 2) lateral, helical-shaped sinkers that entwine the capsule and come in contact with it at the top and the bottom; and 3) screen enclosure, wire cage-like sinkers (Japanese sinker, or alternative sinker defined in <711>) that surrounds the whole capsule. A standard hand-made coil sinker using stainless steel wire has been recommended in the *USP* information chapter <1092> with a detailed preparation procedure, but it has not been widely adopted since there are commercially available sinkers.

   Studies on sinkers have shown that the geometry of different sinker shapes can affect dissolution rates

(*13*). The sinker size and weight are also important to avoid too much restriction of the expansion of the capsule in the sinker, and for overcoming the capsule flowing issue. Therefore, the sinker should be appropriate to the capsule dosage form and validated for the method. The same sinkers should be used for method transfer, or if a different sinker is used, it should be shown to produce equivalent results.

Possible Alternatives or Surrogates: Points to Consider

1. **Hydrodynamics:** When coning is a concern in dissolution testing of solid filled hard-shell capsules, increasing paddle speed may not be always an option to overcome it since the discrimination of the method may be reduced as a result. Instead, use of an alternative non-compendial method, such as Apex Vessel (previously known as peak vessels) (*3*) can be adopted. For testing of liquid filled soft capsules, hydrophobic based fill material can form a film on the surface of the dissolution medium after the capsule shell bursts. The choice of dissolution apparatus and agitation parameters can help with the dispersion of the capsule content and enhance the efficiency in helping the capsule contents mix with dissolution media. In such situations, Apparatus 3 could be employed as an alternative to Apparatus 1 and Apparatus 2, as it has different hydrodynamics that may assist in dispersing hydrophobic droplets to avoid the formation of layers and floating on the surface of the medium.

2. **Cross-linking and gelling:** Cross-linking is a significant potential disadvantage in gelatin capsule drug products. A tremendous amount of work and studies have been done to understand product formulation, to identify possible sources of cross-linking agents, and to take measures to eliminate or at least minimize the cross-linking problem. The use of enzymes to overcome the gelatin cross-linking has been accepted by most ICH countries except Japan. This has led to a recent trend in capsule formulation development for drug companies looking to market their products globally to increasingly use HPMC shells to allow them to register in Japan while avoiding the gelatin cross-linking issue without the need to use enzymes. However, as previously mentioned, a possible trade-off with the use of HPMC shells is gelling, which could prevent the full release of the drug during dissolution testing. In addition, during dissolution, HPMC capsule shells burst much slower than gelatin capsule shells. Therefore, HPMC capsules also show much greater variation in early time points of dissolution testing. It should be noted that there is little evidence that the delay in rupture time is relevant in vivo for most IR formulations. More studies need to be conducted to document the phenomena, to understand the mechanisms, and to develop solutions to making the use of enzymes more broadly applicable.

3. **Use of enzymes:** As previously mentioned, <7111> and <2040> allow the addition of four types of enzymes: pepsin, pancreatin, bromelain and papain, to the dissolution medium to overcome gelatin cross-linking. For the use of enzymes, the biggest challenge remains how to demonstrate and document the presence of cross-linking in gelatin capsules. Since there is no specific guidance in the current *USP* chapters on how to accomplish this, detailed procedures and methods with executable instructions should be developed and provided to help avoid inappropriate use of enzymes in the good manufacturing practice dissolution testing and/or as a solution for any failure that may not even be related to gelatin cross-linking. More effort towards international harmonization on the use of enzymes in dissolution testing is needed. These should either encompass acceptance by the *Japanese Pharmacopoeia* for the use of enzymes or finding other commonly acceptable solutions.

4. **Sinkers:** The standard hand-made coil sinker recommended in <1092> has not been widely adopted. The three types of the commercially available sinkers, including the longitudinal, lateral-helical-shaped, and Japanese basket-like sinker that have already been included in <711> should be considered for inclusion as alternatives. The latest version of <711> also includes the stationary basket as an alternative to the sinkers. With this inclusion, the modifications required to use the stationary basket on standard Apparatus 2 are becoming more commercially available, which may lead to its more widespread use. Input is sought from investigators who develop in vitro dissolution methods for capsules to comment on current needs in regard to the points mentioned above.

Granules, Powders, or Pellets Administered with Food or Beverages

General Considerations

Oral granules, often referred to as minitablets, and powders are commonly developed as a suitable and convenient dosage form primarily for pediatric (as they provide age-appropriate delivery and flexibility with respect to potency ranging) and geriatric applications. This

can be achieved by adjusting the number of minitablets or the amount of powder administered to the patient according to their age and/or weight specific dosing regimen. To administer the correct dose, the specified number of granules or the amount of powder is provided to the patient in separate containers such as stick packs or sprinkle capsules.

Additionally, due to the small size of these dosage forms, they can be easily administered with various soft food or in a liquid vehicle which makes them especially amenable, especially for children. Oral granules specifically, are often developed with a similar formulation approach as the adult dosage forms and therefore similar considerations with respect to controllable properties (i.e., active pharmaceutical ingredient [API] particle size) apply.

Because of the co-administration of the dosage form with food or beverages, understanding the potential interaction of the dosage form with the vehicle is crucial to evaluate the performance and should be taken into consideration when selecting appropriate vehicles for the drug product.

Table 3. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Oral Drug Products—Granules, Powders, or Pellets Administered With Food or Beverages

Limitations and Challenges
Addition of food into traditional dissolution apparatus can lead to variability and artifacts
Challenges for analysis of food
Dispersion of granules, floating to the surface

Current Approaches: Limitations and Challenges

For granules, powders or pellets, standard dissolution tests for release purposes can be developed by testing the drug product directly according to <711> and <1092>. When assessing the performance in the presence of food or beverages, the FDA draft guidance on "Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Consideration for Selection and in Vitro Methods for Product Quality Assessments" (*14*) and USP chapter <1711> present testing approaches to understand and select food vehicles that have no appreciable impact on the drug product performance. These food compatibility studies are normally carried out during dosage form development rather than as a standard quality control release test. If dosing with a beverage results in a solution, generally no dissolution testing needs to be performed, and only testing for chemical stability in the vehicle should be sufficient. However, if it results in a suspension, similar considerations as described in the section for oral suspensions should be followed where the dosage form suspended in the liquid vehicle should be tested during dissolution testing. Dissolution testing of oral granules and powders that are suspended in food is much more challenging. The introduction of food to the dissolution bath directly can lead to significant analytical challenges such as trapping of the drug product in the food leading to slow or incomplete dissolution which might not represent the actual in vivo behavior. As an alternative, the undissolved material can be removed from the vehicle and analyzed for both chemical stability and dissolution performance after washing. This approach is often not practical due to partial disintegration or dissolution of the drug product into the food which can result in incomplete recovery of the material. Additionally, inconsistencies in the washing step can further add variability to the measurement which makes direct comparison of dissolution behavior of granules or powders exposed to different foods difficult.

Possible Alternatives or Surrogates: Points to Consider

While studying the possible food vehicles directly via human in vivo studies gives the best indication of the impact of the vehicle on the performance of oral granules and powders, it is not practical to study all the potential vehicles in this manner. To cover the vast majorities of different foods that can potentially be used during dosing, evaluation of drug product performance in vehicles with varying properties (i.e., pH, water content, viscosity) can be executed. As an alternative to measuring dissolution of the granules or powders after contact with foods, the overall risk to the product performance when exposed to chemical environments covering the ranges observed in soft foods and beverages should be considered. This could include tests which evaluate both chemical and physical changes to the dosage form and the API directly. Potential observed changes can also give a good indication for the potential risks in release behavior of the dosage form.

Input is sought from investigators who develop methods for granules, powders, and/or pellets to comment on current needs relating to measuring dissolution after contact with food. Specifically, it would be useful to receive comments on potential development of testing strategies/methods which could further be developed as a new *USP* compendial test.

Oral Suspensions

General Considerations

The API is often available as an API powder in a suspension drug product. Therefore, particle size and size distribution, morphology and solid state characteristics such as crystalline or amorphous form, will directly affect the

dissolution performance. In addition to considering API solubility and exposed surface area of API particulates, particle characteristics and local hydrodynamics will also impact particle motion, sample and particle dispersal, relative velocity and thus dissolution rate in the dissolution test environment. Forces impacting vertical particle motion include: fluid and particle density, gravity, particle volume (or volume of the submerged solid), viscosity, fluid velocity (i.e., upward or downward), and particle size. Vertical particle motion will dictate whether a particle will be suspended or sedimented at any point in time. Particle wetting (for example, following reconstitution of powders) will also impact segregation and dispersal of particles, and whether the sample will act as discrete particles or as an aggregated mass during the dissolution test.

Table 4. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Oral Drug Products—Suspensions

Dosage Form	Limitations and Challenges
Ready-to-use oral suspensions, or powders, granules, or tablets for oral suspension	Biorelevance of the test Sample introduction Challenges around ensuring homogenous representative sample prepared and taken; sample placement in the vessel Sample filtration

Current Approaches: Limitations and Challenges for Capsules

The current <1711> and <1092> generally refer to the performance testing of suspensions along with other dosage forms.

The most common approach to performance testing of oral suspensions is to introduce a sample of suspension to the dissolution medium in Apparatus 2. Typically, a sample of the suspension is withdrawn by a syringe and introduced into the dissolution medium. The syringe is weighed before and after the introduction of the sample to the medium, and a known sample weight is analyzed.

The sample preparation method should be standardized for a particular product to ensure homogeneity of the sample and reproducibility of the test, in particular with respect to the sample agitation, considering acceleration, amplitude, frequency, and time-course of shaking (*15*). Introduction of bubbles should be avoided to promote sample homogeneity. Furthermore, the sample analyzed should be representative of the product as used by the patient. Therefore, patient/user instructions should be followed with respect to shaking the bottle and withdrawing the sample. When considering powders, tablets or granules for oral suspension, instructions for reconstituting the product should also be followed. The sample should represent one dosage unit or the highest unit dose as mentioned in <1711>.

In some cases, a product is recommended to be administered with certain liquids or soft foods (see *Granules, Powders, or Pellets* section above). This can involve essentially a particulate dosage form, whether the original dosage form is a powder/granules/suspension or whether it is, for example, a capsule containing pellets that is opened and mixed with food. Such manipulations are generally relevant to patients at extremes of age and others with swallowing difficulties. Dissolution/release testing of the product-vehicle mixture should be undertaken. Care should be taken in such instances to ensure relevant patient instructions are followed to prepare the product-vehicle mixture.

Rapid dissolution of immediate release suspension products can necessitate early sampling time points. Chapter <1092> suggests that sampling in the 5–10 min timeframe may provide useful information.

Lower agitation rates in the paddle apparatus (25–50 rpm) can be employed per <1092>; however, higher rates have been noted (50–100 rpm) in particular for more viscous preparations to prevent particulate sedimentation (*15*). Therefore, agitation rate is a parameter that should be understood and exploited to develop appropriately discriminating test methods.

The point of sample introduction to the vessel can vary between, for example, the bottom of the vessel or between the top of the blades and the medium surface. However, there are fluid recirculation zones in both the lower and upper regions of the vessel (*16*), therefore it is important that the sample introduction point should be standardized for a particular product as part of method development. The sample should be rapidly dispersed on introduction to the medium. In some cases, the paddle should be rotating with the addition of the sample.

Possible Alternatives or Surrogates: Points to Consider

Apparatus 4 is used for multiple injectable suspension products (FDA dissolution methods database) but appears to be less commonly used for oral suspensions. Potential advantages of Apparatus 4 in suspension performance testing include more repeatable and customizable drug loading within the cell, dispersal of sample among glass beads to mitigate against aggregation effects, a more uniform hydrodynamic environment, and a smaller local available volume which may aid discriminatory test method development.

Nanosuspensions present unique challenges particularly with respect to separation techniques, and the reader is referred to the relevant *Stimuli* article for specific information regarding such preparations.

Biorelevant and biopredictive testing: With respect to medium used for performance testing of oral suspensions, aspects relevant to medium selection for other oral immediate release products are also relevant to suspension products, with the additional consideration that the hydrodynamic impact of medium volume and viscosity is relevant to the particulate behavior from the beginning of the test (i.e., no disintegration step is required). Similarly, considerations relevant to testing of immediate release dosage forms in other apparatuses, including more bio-relevant non-compendial apparatuses, apply to performance testing of suspensions. Regardless of the apparatus used, the effect of the local environment on sample dispersal and particulate motion should be considered and its impact on the dissolution profile should be understood.

As the location of sample introduction, local fluid dynamics and particulate properties will impact particle motion behavior, in particular dispersal and suspension versus sedimentation behavior. Particle imaging methods may have a role in characterizing aggregation and dispersal behavior of suspensions during dissolution testing. Methods presented in the literature relevant to suspensions and other dosage forms include focused beam reflectance measurement (*17, 18*), shadowgraph imaging (*19, 20*), Qicpic (*21*), and camera-flow cell analysis (*22*). Consideration should also be given to employment of "macro" imaging methods for insight into general dosage form behavior during the test. Simulation of particulate motion in different hydrodynamic environments may also prove useful in understanding particulate dissolution behavior (*19, 20*).

Ultimately, for dissolution testing of oral suspension products or those forming oral suspensions (e.g., powders or granules), there are several critical steps in method development. Dissolution can occur quickly and establishing discriminating conditions can be challenging. Furthermore, due to the heterogeneous nature of a particulate suspension, combined with the general variability in the dissolution test environment, test repeatability can be problematic. Therefore, it is recommended that consideration be given to selection and standardization of sample preparation and location and method of introduction of the sample to the test environment. The impact of the agitation/flow rate and medium fluid properties on particulate wetting, sample and particulate dispersal, and particulate motion/sedimentation should be understood, and test methodology should be selected based on discriminatory and reproducibility capabilities.

Input is sought from investigators who develop methods for oral suspensions to comment on current needs relating to dissolution and biorelevant testing. Specifically, it would be useful to receive comments on potential development of testing strategies/methods which could be further developed as a new *USP* compendial test.

ORAL DOSAGE FORMS WITH MODIFIED-RELEASE PROFILE

General Considerations

In vitro dissolution/release studies are typically used to assess modified release (MR) formulation performance and the impact of formulation composition modification on the API release rate. API release is dependent on the drug product's composition and polymer properties. In addition, the release rate can be affected by the surrounding media, and therefore, changes within the GI tract based on regional physiological differences (e.g., pH, ionic strength, etc.) or changing conditions such as fed state.

Pharmaceutical development should establish the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate. The formulation should be tested under different dissolution conditions to determine its sensitivity/robustness to the expected physiological environment after administration.

Table 5. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Oral Drug Products—Modified-Release Dosage Forms

Dosage Form	Limitations and Challenges
Delayed-release capsules and tablets Extended-release capsules and tablets	Type of release medium (as buffer type [ion species and ionic strength] can have a huge impact on the dissolution of coating materials) Alcohol dose dumping Variability
Gastro-retentive tablets	Biorelevance of the test Buoyancy is critical in some formulations and should be incorporated in the test if possible Performance test needs to be tailored based on the mechanism of action to ensure appropriate gastro retentive properties (bioadhesive, floating, swelling, effervescent, raft forming)

Current Approaches: Limitations and Challenges

Current performance tests are described in <711> and <1711>. The release rate from MR products is tested in vitro by a dissolution test method. The development of a

suitable dissolution test method should be based on the physicochemical in vitro and in vivo characteristics of the active ingredient and the drug product considering the mechanism of release. The in vitro dissolution test must be capable of discriminating between batches, testing for batch-to-batch consistency, determining stability of the relevant release characteristics of the product over the proposed shelf life and storage conditions.

The MR product is tested in vitro under various conditions (i.e., media, pH), apparatus, agitation, as well as other factors. Gastro-resistance should also be tested at a higher pH (to address co-administration with food). Buffer type (ion species and ionic strength) can have a huge impact on the dissolution of coating materials. Buffering capacity of the media (pH of the medium to be controlled for media with a low buffering capacity), surfactants, and enzymes should be considered during the dissolution method development. The in vitro dissolution test should also be able to distinguish different dosing conditions (i.e., fasted versus fed state).

Robustness of the release profile is always an issue with such dosage forms, particularly with a view to preventing dose dumping. Alcohol-induced dose dumping of modified-release oral drug formulations that occurs when a significant amount of an API is prematurely released due to failure of the release controlling mechanism in the presence of alcohol is an issue of concern. Appropriate in vitro dissolution testing needs to be designed to simulate in vivo conditions with alcohol consumption for these cases. FDA and European Medicines Agency (EMA) have developed guidelines for testing oral MR dosage forms for their vulnerability to hydro-alcoholic media; FDA requires testing for 2 h with sampling every 15 min in up to 40% hydroalcoholic media while the EMA requirement is only up to 20% ethanol content and the time is not specified.

Furthermore, for hydrophilic matrix tablets, mechanical stress can be an issue when they are in a "swollen state" and need to pass the pylorus or the ileocecal valve.

Possible Alternatives or Surrogates: Points to Consider

Media (compendial: pharmacopeia buffers; biorelevant: mimicking the composition of the GI fluids) and apparatus (i.e., Apparatus 1, Apparatus 2, Apparatus 3, and Apparatus 4) able to simulate GI conditions and predict oral product performance have been developed (ref). In bio-predictive (biorelevant) dissolution testing of MR products, the physiological conditions within the GI tract that can affect drug release/dissolution are taken into consideration. These conditions include the properties of GI fluids (composition, volume, pH), gastric emptying, intestinal transit, GI motility and hydrodynamic patterns, GI enzymes, and the presence or absence of food. Implementation of biorelevant media should be considered where necessary, particularly when aiming to simulate fed state dosing conditions.

If GI stress/forces can impact drug release or robustness of the formulation, devices applying stress to the formulation (such as the stress test apparatus or similar devices) can be useful. Texture analysis after immersion of the dosage form in different types of media can also be useful for this purpose (combined quality assessment).

For delayed-release capsules and tablets, the use of biorelevant buffer system should be considered or at least buffer compositions should be specified in more detail.

Input is sought from investigators who develop methods for MR dosage forms to comment on current needs relating to dissolution and biorelevant testing. Specifically, it would be useful to receive comments on potential development of testing strategies/methods which could be further developed as a new *USP* compendial test.

VETERINARY DOSAGE FORMS

General Considerations

There are a number of oral dosage forms unique to veterinary medicine. Tablets and oral suspensions used in veterinary medicine are subject to *USP* monographs and may utilize similar drug release mechanisms as those associated with human medicine. Accordingly, sponsors generally should conduct the same performance tests as those described in the *USP* general chapters <701> and/or <711>. Oral animal drug products may also leverage the general concepts contained in Assessment of Solid Oral Drug Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution <1090>, although this chapter was not originally written with animal drug products in mind. Oral boluses are formulations unique to veterinary medicine, being designed to take advantage of the physiology of the rumen of species such as cattle, sheep, and goats. Several bolus products are also the subject of *USP* monographs, and a subset of these have disintegration or dissolution tests that follow <701> or <711>, respectively. Finally, Type A medicated articles are FDA-regulated products that must be diluted into animal feed prior to administration. Type A medicated articles are not considered dosage form drugs under Animal Drugs for Use in Animal Feeds <1152>. The few *USP* monographs that exist for Type A medicated articles do not include performance tests for routine use. In the past, development of performance tests for oral animal

drug products was frequently limited by the selection of solubilization media. This limitation is beginning to be overcome by species-specific media additions to chapters such as Solubility Measurements <1236>. We look forward to inclusion of media for additional species and methods appropriate for them.

Table 6. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Oral Drug Products—Veterinary Oral Dosage Forms

Dosage Form	Limitations and Challenges
Bolus, chewable, extended-release tablets	Biorelevance of test (species differences in GI physiology may affect in vivo solubility, dissolution, and bioavailability). One formulation may be indicated for multiple species. Media and conditions from <711> are not optimized for veterinary use.
Type A medicated articles and Type B and Type C medicated feeds	Usually no tests required

Current Approaches: Limitations and Challenges

When identifying appropriate performance test conditions for veterinary oral dosage forms, a determination should be made as to whether the conditions can adequately reflect the properties of the dosage form and detect critical changes in the formulation and manufacturing process. Biorelevance of the media and conditions selected may not always be considered when developing performance tests for orally administered animal drugs, and performance tests specifically designed for target species other than humans are not well represented in compendial standards. Much of the scarcity of species-specific tests can be attributed to an incomplete recognition of the species' GI physiology and fluid composition (*23*, *24*). Consequently, tests for oral dosage forms may not be optimized for biorelevance within the framework of veterinary medicine. Some of the factors that may differ between species (and even breeds) that could influence dissolution and disintegration of oral dosage forms include (*23*), pH and its gradients, GI transit time, food/diet, components such as bile salts present in the GI fluids (*25*, *26*), gastric fluid volume (*23*, *26*), and gastric fluid viscosity. These physiological differences can impact oral bioavailability primarily by influencing drug solubility and dissolution and should be considered during the development of performance tests (*23*, *26*), even if the test will only be used for quality control (*24*).

Some oral dosage forms may have indications for multiple target species. In those situations, optimization of the dissolution medium will depend both upon the drug physicochemical properties and perhaps different GI characteristics of each target animal species (*23*). For human drug quality control testing (*27*), it has been assumed that if batches of product showed similar in vitro performance, this would imply similar in vivo performance. This assumption may be inappropriate if a product is indicated for more than one target animal. Allowable formulation and manufacturing variability in one species may not necessarily translate to the same permissible limits for a different animal species. Depending on the robustness and discriminatory power of the tests, it is seldom clear if changes in dissolution or disintegration have significant species-specific adverse effects can be detected if only one set of general test conditions are used for quality control or by extension, if the same manufacturing defects or variability could differently affect species' physiological responses to a product.

Possible Alternatives or Surrogates: Points to Consider

Sometimes trade-offs should be considered between practicality and biorelevance to develop usable tests in a timely manner for commercial product release of oral dosage forms indicated for one or multiple target animals. Chapter <1236> now lists optimized media conditions for solubility measurements in animals, and these conditions may be adopted as a starting point for development of compendial performance test media for commercial animal drug products. When paired with appropriately designed and validated apparatus, the use of species-specific media may provide an opportunity to develop biorelevant in vitro test methods (*24*). Another possible source of information that could be used to provide direction for development may include FDA's Guidance for Industry #238 Modified Release Veterinary Parenteral Dosage Forms: Development, Evaluation, and Establishment of Specifications. Although this guidance covers parenterals, some of the descriptions of performance testing should apply to oral dosage forms equally.

Input is sought from investigators who develop methods for veterinary oral dosage forms to comment on current needs relating to dissolution testing.

SPECIAL DOSAGE FORMS

In recent years, special dosage forms, such as sensing tablets/capsules, which can measure multiple physiochemical properties such as pH, oxygen levels, pressure, and temperature when ingested were developed (*28*). These sensors are often used to measure properties of the human GI tract and help further

understanding of the biopharmaceutical parameters and predictions; however, these devices are not used for drug delivery. Rather than using dissolution to test the functionality, sensing accuracy and precision should be determined directly for the measured property.

Remote controlled capsules, which release drug from a reservoir after the capsule is electronically opened, have been utilized for targeted, site-specific drug delivery as well to study regional absorption (*29*). Drug release from such capsules can be triggered externally, for example via a radio-frequency signal. Measuring the release from these delivery systems should undergo the same considerations as mentioned in the previous sections of this manuscript.

Table 7. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Oral Drug Products—Veterinary Oral Dosage Forms

Dosage Form	Limitations and Challenges/Considerations
Sensing tablets/capsules: pH sensing tablets Pressure sensing tablets Temperature sensing tablets Sensor to test if dosage form was ingested (ingestion event marker)	Dosage form is not used for drug release, but rather to monitor physiological conditions of the GI tract. Dissolution is not an appropriate test to confirm functionality of the device.
Remote-controlled delivery capsules	Limited capabilities to test if the delivery will happen in the target region with offline methods

CONCLUSION

Performance testing of oral dosage forms provides valuable information during development and should be incorporated in the formulation design, optimization of the manufacturing process, and as a QC test. This *Stimuli* article was written to outline the specific challenges to develop product performance test methods for oral dosage forms. It is the objective of the authors that the challenges described herein will initiate research to develop product performance and product quality test methodologies which can be incorporated into future compendial chapters.

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NOTES

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"Modified release" is a term used when the rate and/or time of release of the drug substance is altered as compared to what would be observed or anticipated for an immediate-release product. Two modified-release profiles, delayed release and extended release, are recognized.

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