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110 **In Vitro Product Performance Testing of Oral Drug Products: View of the USP Expert Panel**
Nikoletta Fotaki, Deirdre D'Arcy, James Demuth, Andre Hermans, Xujin Lu, Ishai Nir, Emmanuel Scheubel, and Raymond Skwierczynski

122 **Magnesium Stearate – Its Importance and Potential Impact on Dissolution of Oral Solid Dosage Forms**
R. Christian Moreton

128 **Dissolution Testing Strategies for Large Sample Sizes and Applications in Continuous Manufacturing**
Martin Otava, Sylvaine Jacquart, and Stan Altan

136 **Life Cycle Application of AQbD for Formulation Development and Validation of a Dissolution Method for Nevirapine**
Rayza A. D. de Almeida, Maria Luiza R. A. de Oliveira, Ivone de J. N. Lopes, Diogo D. Nascimento, Camila A. Oliveira, and Livia D. Prado

145 **Question & Answer Section**
Margareth Marques and Mark Liddell

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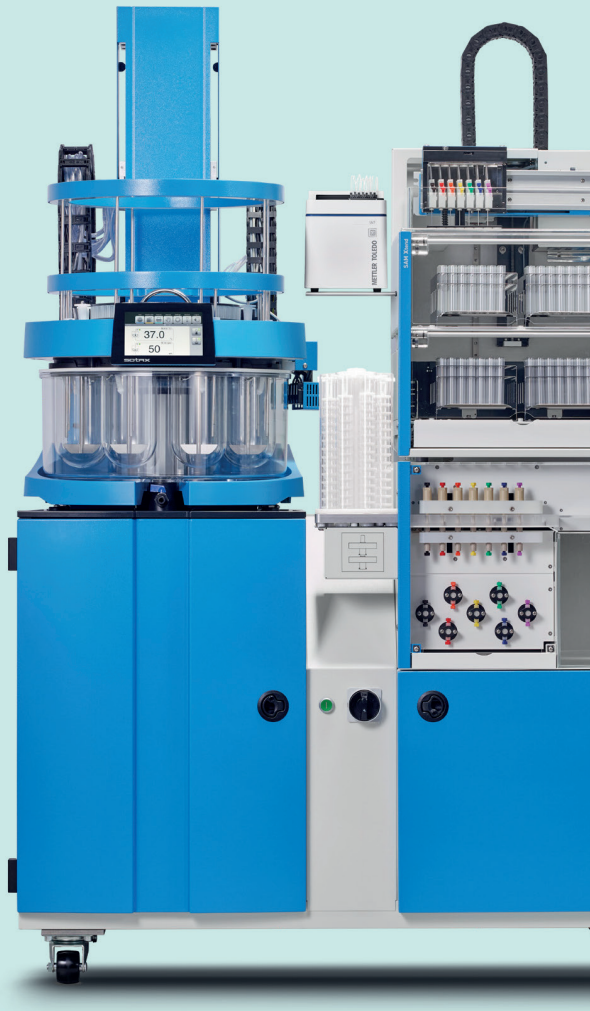

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Table of Contents

In This Issue

In Vitro Product Performance Testing of Oral Drug Products: View of the USP Expert Panel.....110

Magnesium Stearate – Its Importance and Potential Impact on Dissolution of Oral Solid Dosage Forms 122

Correction to "Highlights from the 2023 AAPS 360 Annual Meeting – In Vitro Release and Dissolution" ...126

Dissolution Testing Strategies for Large Sample Sizes and Applications in Continuous Manufacturing 128

Life Cycle Application of AQbD for Formulation Development and Validation of a Dissolution Method for Nevirapine 136

Question and Answer Section 145

Calendar of Events 149

Industry News.....151

Advertisers

Sotax..... Inside front cover
Copley.....109
Pharma Test 126
Eastern Analytical Symposium.....127
Logan.....135
Simulations Plus.....147
USP.....148
Erweka 150
Distek..... Back inside cover
Agilent Technologies .....Back outside cover

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The scope of articles is limited to dissolution or disintegration topics as the major focus. Articles on formulation development where dissolution is just one test of many should not be submitted.

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Topics for the Next Issue

The November 2024 issue will include a USP *Stimuli* article on in vitro performance of inhalation formulations, Dose Disintegration and Dissolution Plus (DDDPlus), ranolazine tablets, eletriptan hydrobromide buccal, glimepiride tablets, and the Q and A feature.

Research Editor
Vivian Gray
vagray@rcn.com

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

Nikoletta Fotaki[1], Deirdre D'Arcy[2], James Demuth[3], Andre Hermans[4], Xujin Lu[5], Ishai Nir[6], Emmanuel Scheubel[7], Raymond Skwierczynski[8]

[1]*Department of Life Sciences, Centre for Therapeutic Innovation, University of Bath, Bath, UK.*
[2]*School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Ireland.*
[3]*University of Wisconsin-Madison, Madison, WI, USA.*
[4]*Merck and Co., Inc., Rahway, NJ, USA.*
[5]*Bristol-Myers Squibb, New Brunswick, NJ, USA.*
[6]*Distek, Inc., North Brunswick, NJ, USA.*
[7]*F. Hoffmann-La Roche AG, Basel, Switzerland.*
[8]*Skwierczynski Consulting, Andover, MA, USA.*

Correspondence should be addressed to:
Antonio Hernandez-Cardoso,
US Pharmacopeia, 12601 Twinbrook Parkway
Rockville, MD 20852-1790
email: ahc@usp.org.

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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DISCLAIMERS

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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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Magnesium Stearate – Its Importance and Potential Impact on Dissolution of Oral Solid Dosage Forms

R. Christian Moreton[1]
[1]*FinnBrit Consulting, Waltham, MA, USA.*

e-mail: consulting@finnbrit.com

ABSTRACT

Magnesium stearate is the most commonly used lubricant in the formulation and manufacture of oral solid dosage forms (compressed tablets and powder-filled capsules). However, its chemical and physical properties can adversely impact the final dosage form by reducing the hardness of tablets and reducing dissolution of the active drug from both tablets and powder-filled capsules if used incorrectly. In addition, the potential for these negative aspects to occur in the formulation and manufacture of oral solid dosage forms is increased during scale up. This review article describes the advantages and disadvantages of magnesium stearate and explains how the properties of magnesium stearate can impact the manufacture and performance of the finished dosage form. A brief review of alternative lubricants for oral solid dosage forms is provided.

KEYWORDS: Magnesium stearate, excipients, dissolution, lubricants

INTRODUCTION

Chemically, magnesium stearate is the magnesium salt of stearic acid: $(C_{17}H_{35}COO)_2Mg$. Typically, magnesium stearate is far from such a straightforward chemical. It may be possible to produce a pure form of magnesium stearate, and it would likely work as a lubricant, but the material that is commercially available for pharmaceutical use typically contains a mixture of saturated long-chain fatty acids, notably including palmitic acid.

The range of fatty acids contained in a sample of magnesium stearate will reflect the source of the fatty acids used to manufacture the magnesium stearate: animal, vegetable, or synthetic. Vegetable source fatty acids are preferred for a variety of reasons, including the risk of transmissible spongiform encephalopathies (TSE) when using animal-sourced fatty acids. The detailed composition of magnesium stearate and other fatty acid magnesium salts in a particular sample is often unknown. In addition, magnesium stearate can exist as the anhydrous form or mono-, di-, or trihydrate forms. There may also be polymorphic or pseudo-polymorphic forms and different particle morphologies, all of which can impact its performance in a given formulation. For example, Koglin examined samples from different commercial sources and identified up to seven different forms of magnesium stearate (*1*).

The disadvantages of magnesium stearate became important after the introduction of dissolution testing in the early 1970s (the first dissolution specifications appeared in the *USP* in 1971). Before that, disintegration testing was the only in vitro performance test, and specification limits were typically quite broad. The potential impact of magnesium stearate on the compactibility of tablet blends was also known by that time.

WHY IS MAGNESIUM STEARATE SO POPULAR?

Given uncertainties as to the precise form of magnesium stearate, and its disadvantageous properties, why is it so popular? The reason is that magnesium stearate is arguably the best lubricant for tablets and powder-filled capsules. It is generally effective at low concentrations (typically 0.5–1.0%), and it has a good balance of the main lubricant functions, i.e., reduction in interparticle friction during consolidation and compaction, flow enhancement, lowering ejection force, and prevention of sticking to punches, capsule filling dosator pistons, or tamping pins. It also has a long history of use, certainly going back to the 19th century.

HOW MAGNESIUM STEARATE WORKS IN ORAL SOLID DOSAGE FORMS

Magnesium stearate is a boundary lubricant; it has a polar head (the magnesium ion) and a fatty acid tail. It achieves its effects by being adsorbed onto the other particles of the final powder blend to be tableted or filled into capsules, in effect forming a partial film around the blend of particles (*2*). Adsorption onto powder particles reduces cohesiveness and helps promote powder flow. This adsorption may also reduce the tendency of some materials to stick to the tablet punch or capsule dosing change parts. It may also adsorb onto metal surfaces and reduce the friction when powder moves across a metal surface, as in tablet ejection or capsule plug ejection. It may also lubricate moving metal surfaces. However, magnesium stearate can interfere with the compaction of materials if too much is included in the formulation or when mixed with other components for too long. This is due to the magnesium stearate forming a more complete film around the powder particles, which interferes with particle-particle bonding.

To work effectively as a lubricant in the formulation and manufacture of tablets and powder-filled capsules, magnesium stearate is prepared in very finely divided form; typically micronized. According to Allen and Luner, the particle size of magnesium stearate is typically < 20 µm (*3*). While this property may account, in part, for its advantageous performance in the formulation and manufacture of tablets and powder-filled hard gel capsules, it also gives rise to its disadvantages in reducing dissolution of active drugs under certain circumstances. In addition, its fine particle size and morphology (most often agglomerated lamellae) compounds its hydrophobicity because such particles can deagglomerate during pharmaceutical processing and spread over a greater surface area, such as during blending.

The agglomeration of fine particles is a well-known phenomenon in pharmaceutical processing. In general terms, for typical pharmaceutical powders, agglomeration becomes an increasing issue as the particle size of the powder particles is reduced below 50 µm. With such small particles, the van der Waals forces of attraction become larger than the gravitational forces that would cause the particles to separate. During processing, such as powder blending, there may be sufficient energy to cause the agglomerates of magnesium stearate to break up. The more energy that is input (longer blending times or more intense blending), the more the agglomerates will be broken up, and the resulting particles will adsorb onto the other particles of the blend, thereby partially coating the particles with hydrophobic magnesium stearate particles. At a certain point, the extent of magnesium stearate coverage of the other particles of the blend will be such that the penetration of water into the tablet matrix or capsule plug will be retarded, potentially impacting compaction of the tablet and dissolution of the active drug. This is shown in Figure 1.

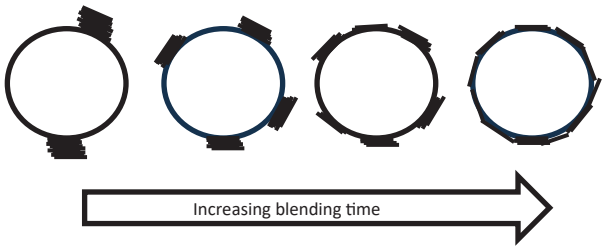

Figure 1. Diagram represents the effects of increased blending time on the formation of a magnesium stearate film on powder particles. The magnesium stearate is represented as the stacked lamellae.

In addition, if the amount of magnesium stearate is too great, even with shorter blending times, it will spread over the surface of the other components of the blend to such an extent that it can reduce the ability of water to penetrate into the tablet or capsule fill, and also into the granules contained in that fill, thereby reducing the rate of dissolution of the active ingredient (*4*). It will also reduce the compactibility of the tablet blend. The form of magnesium stearate (state of hydration, etc.) will also affect the formation of the hydrophobic film (*5*).

The formation of the magnesium stearate film is also the reason that over-lubrication with magnesium stearate causes reduced compactibility of tablet blends, resulting in softer tablets that are prone to capping and chipping during subsequent handling. The layer of adsorbed magnesium stearate interferes with the bonding between the other particles in the blend.

EFFECTS OF SCALE OF MANUFACTURE OF TABLETS AND POWDER-FILLED CAPSULES

When considering the impact of magnesium stearate on the dissolution of tablets and powder-filled capsules, the scale and intensity of mixing are important considerations. For example, Gunning reported that a reduction in dissolution, which occurred within minutes at large scale, required 30 hours blending to achieve a comparable reduction in dissolution at laboratory scale (*6*). From the author's experience in the late 1970s, working at the 2000-kg scale with an immediate-release capsule blend, and using a double cone tumbling blender, 5 minutes of final lubricant blend time gave acceptable dissolution, whereas 7 minutes gave dissolution results very close to

the lower limit, and potential failure. These results agree with those reported by Mehrotra et al., who found that high total shear impacted tablet hardness (*7*). However, for conditions of constant total shear, the shear intensity (intensity of mixing) only had a slight effect. This indicates that the total shear rather than the intensity of shear is important.

THE ANALYTICAL IMPACT OF MAGNESIUM STEARATE

The major impact of magnesium stearate in analytical terms is on the dissolution of drugs from the dosage form. Under certain circumstances, magnesium stearate can have a deleterious effect on the disintegration of dosage forms and the dissolution of drugs in vitro and possibly in vivo. This phenomenon has been known for many years, certainly in the 1970s for dissolution, and even earlier for disintegration testing. The adverse effect of magnesium stearate on dissolution from oral solid dosage forms is due to its propensity to adsorb onto the other components of the formulation during blending, as discussed above. Thus, it can create a hydrophobic 'coating' that retards the penetration of the dissolution medium into the formulation. The mechanism of this adsorption is due to electrostatic interactions owing to the small size of the magnesium stearate particle. Calahan et al. investigated the impact of different forms and sources of magnesium stearate on tablet manufacturing parameters and dissolution using a direct compression tablet formation (*8*). The authors reported differences in the optimum form that were related to the different parameters. Thus, the choice of magnesium stearate form and process parameters necessitates a compromise between the required tablet compaction or capsule filling process and the required dissolution from the finished dosage form.

INCOMPATIBILITY OF MAGNESIUM STEARATE AND DRUG MOLECULES

Chemical Incompatibility

Magnesium stearate is not chemically inert. When considering its chemical compatibility with drug molecules, it has the typical properties of a magnesium salt (and other salts of alkaline earth elements). Magnesium stearate is incompatible with esters, e.g., aspirin and enalapril, as it causes hydrolysis of the ester linkage. It may also facilitate certain other chemical interactions. It may facilitate the Maillard reaction between a primary amine and a reducing sugar. For example, again from the author's experience, during an excipient compatibility study of a primary amine drug, the Maillard reaction between the drug and lactose monohydrate was enhanced in the presence of magnesium stearate.

In addition, if the magnesium stearate contains unsaturated fatty acids, there is the possibility of the formation of an adduct with a primary amine; analogous to a Michaels addition. Thus, it is important to understand the chemical composition of the magnesium stearate, particularly the minor components.

Physical Incompatibility

Because magnesium stearate is an ionic salt, it can induce disproportionation of hydrochloride salts by exchange of ions, thus forming magnesium chloride, which is deliquescent. For example, John et al. reported on disproportionation of a drug hydrochloride salt occurring due to interaction with excipients including magnesium and sodium salts (e.g., magnesium stearate, sodium stearyl fumarate, and croscarmellose sodium) (*9*). However, the effects with magnesium stearate were greater than with the sodium salt excipients. The same authors also reported that disproportionation did not occur with neutral excipients or stearic acid. This disproportionation can impact susceptibility of the finished tablets to moisture uptake when stored at high humidity. This has implications for packaging, stability, and shelf-life of the finished product. In addition, the increased uptake of moisture by the finished tablets may cause premature activation of disintegrants, leading to soft tablets on storage and loss of disintegrant activity in use, which could cause a reduction in dissolution.

ALTERNATIVES TO MAGNESIUM STEARATE

Are there alternatives to magnesium stearate? The short answer is yes! However, they all have issues. Zinc stearate and calcium stearate have both been used as tablet and capsule lubricants, but have similar disadvantageous properties to, and show no clear advantages over, magnesium stearate. Many, but not all, alternatives to the stearate salts are also hydrophobic, and they all have other issues such as chemical incompatibilities and effectiveness as lubricants. For example, sodium stearyl fumarate is also an effective boundary lubricant and not hydrophobic (although not water-soluble at room temperature); however, it has the incompatibilities of a sodium salt. In addition, primary amines can interact with the olefinic double bond in the fumarate moiety to form an addition compound.

The so-called fluid film lubricants, such as stearic acid, hydrogenated castor oil, and hydrogenated vegetable oil type I work differently than boundary lubricants.

During compaction they melt, and the resultant oily film provides the lubricant effect. They also require higher concentration to achieve their lubricant effect. On removal of the compaction pressure, these lubricants re-solidify which is why they are prone to sticking, thus requiring the inclusion of an anti-adherent such as talc or fumed silica. There are other materials that have been used as lubricants, particularly for effervescent tablets, such as leucine and isoleucine, but they are not considered particularly effective, and have not been widely adopted.

POSSIBLE FUTURE DEVELOPMENTS

The ideal lubricant for the manufacture of tablets and powder-filled capsules would have all the beneficial properties of magnesium stearate but none of its drawbacks, such as hydrophobicity. Salpekar and Augsburger investigated the use of magnesium lauryl sulfate, which is water soluble, as a tablet lubricant (*10*). It was not as effective as magnesium stearate in that a higher concentration was required in the blend. Magnesium lauryl sulfate did not have the disadvantages of magnesium stearate (impacting dissolution or compressibility); however, it has not been commercialized. This may partly be due to its lachrymatory properties; it is highly irritant to the eyes and mucus membranes. Given its finely divided form, use of magnesium lauryl sulfate in pharmaceutical manufacturing areas would require significant personal protection measures. There is always the possibility of a new lubricant, but given the understanding surrounding magnesium stearate, it seems unlikely that any new lubricants will be introduced in the immediate future.

CONCLUSION

There is no ideal lubricant. Provided that there are no chemical compatibility issues, magnesium stearate is still arguably the best compromise for a lubricant from a tablet and capsule manufacturing perspective, despite some physical compatibility issues. Magnesium stearate will likely continue to be the most common lubricant for use in oral solid dosage forms for the foreseeable future. Despite its well-known disadvantages, the alternatives have their own drawbacks, and magnesium stearate is often the best compromise. However, when using it, it is necessary to understand its properties and limitations to produce robust formulations and consistent finished medicinal products. This understanding includes the balance between the level of incorporation, the scale of manufacture, and the extent of mixing to achieve sufficient lubrication to allow the tablet press or capsule filling machine to operate efficiently while avoiding any reduction in dissolution of the active drug, and the requirements for finished product packaging and shelf-life.

DISCLOSURES

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Correction to "Highlights from the 2023 AAPS 360 Annual Meeting – In Vitro Release and Dissolution"

In the May 2024 issue of *Dissolution Technologies*, there were errors in the authors' affiliations for the article by Patel et al, "Highlights from the 2023 AAPS 360 Annual Meeting – In Vitro Release and Dissolution" (DOI: 10.14227/DT310224P86). The corrected affiliation information is below.

Sanjaykumar Patel[1*] Jie Shen[2], Zhao Liu[1], Ishai Nir[3], Devin Janai Swiner[1], Hyunho Kang[1], Vivian A. Gray[4], Andre Hermans[1], and Tahseen Mirza[5]

[1]*Merck & Co., Inc., Rahway, NJ, USA.*
[2]*Northeastern University, Boston, MA, USA.*
[3]*Distek Inc., New Brunswick, NJ, USA.*
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Dissolution Testing Strategies for Large Sample Sizes and Applications in Continuous Manufacturing

Martin Otava[1*], Sylvaine Jacquart[2], and Stan Altan[3]
[1]*Manufacturing and Applied Statistics, Janssen-Cilag s.r.o., a Johnson & Johnson company, Prague, Czech Republic.*
[2]*Dissolution Sciences, Janssen Pharmaceutica NV, a Johnson & Johnson company, Beerse, Belgium.*
[3]*Manufacturing and Applied Statistics, Janssen Pharmaceutical LLC, a Johnson & Johnson company, Springhouse, PA, USA*

e-mail: motava@its.jnj.com

ABSTRACT

The potential advantages of larger sample sizes for dissolution testing through surrogate modeling in the context of continuous manufacturing and process analytical technology is the motivation for development of a statistically based batch release acceptance criterion. A common approach in conventional batch release is to measure at most 24 tablets in three subsequent stages and evaluate the results against the acceptance criteria of the United States Pharmacopoeia (*USP* <711> Dissolution). We describe two approaches for a statistically based release testing strategy for immediate-release dosage forms with $N > 24$: 1) generalization of *USP* <711> three-stage acceptance criteria for any sample size greater than 24, and 2) a tolerance interval approach. Both approaches are based on a sample-size independent criterion ensuring a known probability of passing *USP* <711> acceptance criteria. The proposed criteria can be applied to the entire batch or segmented portions of a single batch run.

KEYWORDS: Release testing, continuous manufacturing, large N, tolerance intervals, dissolution

INTRODUCTION

In vitro dissolution is an important quality attribute of pharmaceutical solid oral formulations, such as immediate-release tablets. It requires a time consuming and complex laboratory measurement method. Hence, there is motivation to develop surrogate models capable of predicting dissolution based on process analytical technology (PAT) tools and process parameters, as PAT measurements can be available online with little extra cost and for larger sample sizes (*1*, *2*). Dissolution testing for batch release is typically performed by using a three-stage evaluation against the acceptance criteria of the harmonized dissolution chapter of the *United States Pharmacopoeia*, *European Pharmacopoeia*, and *Japanese Pharmacopoeia*, henceforth referred to as *USP* <711> acceptance criteria (*3*). This involves assessment of six tablets at the first stage, six additional tablets in the second stage, and 12 additional tablets at the third stage. At most, 24 tablets are evaluated, but in practice a typical product rarely goes beyond stage 1, where only six tablets are evaluated. Continuous manufacturing and PAT have enabled the ability to analyze larger numbers of dosage units compared to the traditional batch manufacturing process. The development of surrogate models for dissolution can support a full realization of real-time release (RTR) and reduce the time to market. For example, such models can predict the dissolution for an entire sample of tablets collected for content uniformity testing. This would lead to a substantial increase in the amount of dissolution data to interpret, higher than what is currently included in the *USP* <711> acceptance criteria. There are no default acceptance criteria for dissolution testing applicable to large sample sizes. Hence, companies need to propose the release test and its acceptance criteria based on knowledge built during the drug product development cycle, considering regulatory guidelines, the company's own risk control practices, and the commercial and clinical needs of the product.

In this study, the development of two acceptance criteria for dissolution release testing for sample sizes greater than 24 are presented along with an assessment of their statistical risk properties. One attractive feature of the proposed approaches is probability-based flexibility to accommodate variable risk levels in relation to meaningful batch quality requirements. Moreover, increased sample size leads to higher precision in enabling the right release test decision.

This study focuses on *USP* <711> acceptance criteria for immediate-release dosage forms as a basis for

*Corresponding author

characterizing the release test performance using concepts developed by Garcia et al. and Bergum et al. for *USP* <905> testing of content uniformity (*4*–*6*). The aim is to develop an acceptance criteria rule that ensures a high probability of passing *USP* <711> acceptance criteria. The alternative approach directly assesses the desired quality level in a straightforward, interpretable way based on a tolerance interval approach. The risks and benefits for both approaches will be discussed.

USP <711>-BASED APPROACH

The evaluation of dissolution performance against *USP* <711> acceptance criteria can be understood as a demonstration test of quality. The inference applies only to the sample tested (*3*). Tablets are analyzed in stages, only moving to the next stage if the current stage fails. Success at any stage is considered to pass the overall acceptance criteria. Batch rejection only occurs if the dissolution results do not comply with the stage three acceptance criterion. Given the limitation on inference beyond the units tested with *USP* <711>, companies may develop their own dissolution test acceptance criteria, including the specification time point (Q-time point) and specification value (Q value). Internally developed acceptance criteria can be evaluated against the *USP* <711> test. Typically, we would expect to see company-developed acceptance criteria that afford greater protection against batch mean and variability shifts compared with the *USP* <711> test, partly as a consequence of larger sample sizes.

For immediate-release dosage forms, *USP* <711> acceptance criteria with a prespecified fixed Q value, expressed as a percentage of the labeled content of the dosage unit dissolved at a prespecified time point are as follows:

- Stage 1 (6 tablets): no tablet is less than Q + 5%
- Stage 2 (+6 tablets): mean of 12 tablets is equal or greater than Q, and no tablet is less than Q – 15%
- Stage 3 (+12 tablets): mean of 24 tablets is equal or greater than Q, not more than (NMT) two tablets are less than Q – 15%, and no tablet is less than Q – 25%.

Given that failure of Stage 1 and Stage 2 of *USP* <711> acceptance criteria do not result in batch rejection, the role of the first two stages is analogous to an 'early stopping rule', e.g., if the process is capable of producing product of such quality that all six samples are above Q + 5, then there is no need to further investigate the batch mean dissolution.

The probability of passing the *USP* <711> acceptance criteria can serve as a baseline to assess alternative company-developed acceptance criteria. As an example, probabilities of passing were calculated in relation to assumed true batch properties for a case where Q = 80%, including four levels of batch dissolution (mean % dissolved) across a broad range of standard deviation (SD). Figure 1 provides the operating characteristic curve for the four batch mean values (79%, 80%, 85%, and 90%) in relation to varying the magnitude of SD. A batch with a true mean of 79% and a low SD would generally fail *USP* <711> acceptance criteria; however, with a larger SD, the probability of passing is up to nearly 40%. This is mostly due to the stage 2 rule. A batch mean of 80%, equal to the Q value, has approximately 62% probability of passing *USP* <711> acceptance criteria when the SD is small (close to zero). This is a result of a 50% probability to pass the mean value criterion in stage 2 and an additional smaller probability to pass stage 3 (conditionally on failing stage 2). With increasing SD, the probability of rejection increases due to requirements on individual tablets. Finally, with a batch mean of 85% or above, there is a rather high probability of passing if SD is below 10%, and rapidly decreasing probability as SD increases above 10%.

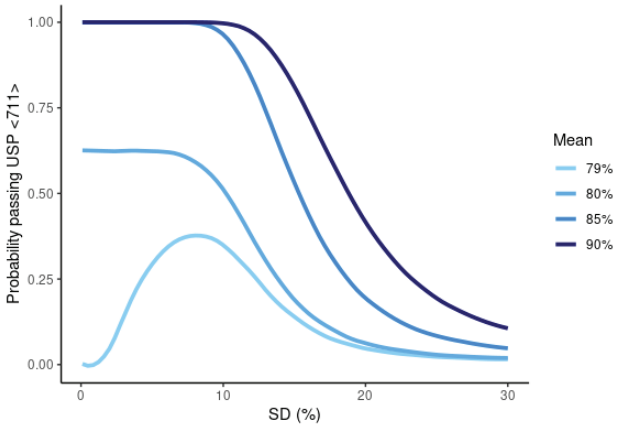

Figure 1. Probability of passing the USP <711> acceptance criteria depending on mean percent dissolved and standard deviation (SD), in an example where Q = 80%.

Extension of USP <711> Acceptance Criteria to Large Samples

Companies have commonly used *USP* <711> acceptance criteria as a release test, although the acceptance criteria were not designed with any probability-based assumption that permits risk calculations applicable to the batch being tested. However, the probability (i.e., assurance) of passing *USP* <711> acceptance criteria under given assumptions of batch quality can be used as a benchmark to evaluate competing acceptance criteria for large

sample sizes. Analogous discussions have been published in the context of *USP* <905> and content uniformity (*4*, *6*).

When extending acceptance criteria beyond $N = 24$, start with the stage 3 criterion of *USP* <711> (*3*):

1. *Sample Mean*: mean of 24 tablets (point estimate) is not less than Q;
2. *Individual Values at Q – 15*: NMT two tablets (function of *N*) are less than Q – 15%; and
3. *Individual Values at Q – 25*: no tablet is less than Q – 25%.

Condition 1: Sample Mean

Condition 1 of the *USP* <711> procedure imposes a requirement on the mean. It is a simple demonstration requirement and lacks any statistical claim of a known probability of meeting this requirement for some random batch at time of manufacture. It is reasonable to assume that the aim of *USP* <711> acceptance criteria is to ensure that the batch has a mean of at least Q.

In this regard, there are two approaches that can be followed. The first is to assess the point estimate of the mean directly against the threshold value. The second is to compare the lower confidence bound against the threshold. With increasing sample sizes, the two approaches are numerically close to each other, although the overall test performance of batches with true mean of percent dissolved close to the Q-value may be affected by the two approaches. The advantage of the confidence interval (CI) approach is that it effectively fails batches with true means of percent dissolved below Q. On the other hand, batches with means above Q have reduced probability to pass the criterion in comparison with a point estimate approach.

Condition 2: Individual Values at Q – 15%

To impose a requirement of high probability of compliance with *USP* <711> acceptance criteria, consider the proportion allowed below Q – 15% from stage 3 with $N = 24$, then generalize to larger sample sizes to arrive at a recommendation as described below. Note that variability is addressed on the SD scale rather than variance scale. The algorithm is given as follows.

1. Assume "worst-case mean" of Q. Note that a batch with a mean equal to Q has only 50% probability of passing the mean criterion. The following steps focus on the variability criterion only.
2. Calculate the probability under the normality assumption for various SDs to comply with Q – 15% criterion from *USP* <711> in stage 3 (see Fig. 2).
3. Choose the desired target probability p_1 to achieve as the baseline to calibrate against.
4. Find corresponding SD, denoted as SD_1, to achieve the target probability (e.g., $p_1 = 95\%$ gives $SD_1 = 8.275$; $p_1 = 90\%$ gives $SD_1 = 8.947$; see example below). SD_1 will be used to calibrate with stage 3 *USP* <711> acceptance criteria.
5. Select desired sample size (e.g., $N = 50$) and find the value of $k(N)$ (i.e., number of tablets < Q – 15%) such that p_1 for SD_1 is met for the chosen sample size.

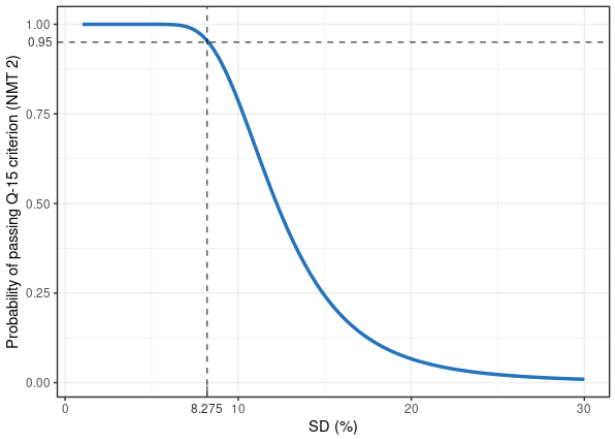

Figure 2. Probability of passing the condition that no more than (NMT) two measurements are below Q – 15% for a batch with mean percent dissolved of Q and standard deviation (SD) as on x-axis.

The following example is for a desired target probability to pass *USP* <711> acceptance criteria of 95% ($p_1 = 95\%$). The probability (*P*) to pass the criterion is simply $P(X \le 2)$, where the relevant binomial equation is given by $X \sim Binom\left(24, \Phi_{Q,sd}(Q-15)\right)$, where $\Phi_{Q,sd}(y)$ normal distribution function, *Q* is the mean, and *sd* is SD. Solve the binomial equation to find the highest SD, such that the $P(X \le 2) \ge 0.95$. As mentioned above, select $SD_1 = 8.275$ or lower to achieve ≥ 95%.

For a given sample size ($N = 50$) and SD_1, solve the binomial equation to obtain $k(N)$ where $P(X \le k) \ge 0.95$. The solution in this case is $k = 4$ tablets, i.e., allowing two extra tablets compared to standard *USP* <711> stage 3 acceptance criterion below Q – 15 (see supplemental table for tabulated values and instruction for use). Note that the solution is obtained assuming that the batch has a true mean equal to Q, as the calculation for $k(N)$ only aims at assessing variability. The mean check is part of condition 1.

Condition 3: Individual Values at Q – 25%

For condition 3, we can either assume the same criterion as for N = 24 (no individual value below Q – 25%) or consider an alternative analogous to condition 2: following the derivation of Q – 15% (condition 2), calculate how many values are allowed below Q – 25% as part of the acceptance criteria, denoted as $k_2(N)$. The acceptance criterion can be set as: NMT $k_2(N)$ below Q – 25%. In such case, the determination of $k_2(N)$ should be done directly from the normal distribution assumed for the condition 2 development to keep internal consistency of the acceptance criterion. However, to maintain a conservative approach and for simplicity, we suggest requiring no values less than Q – 25%, as a more stringent criterion.

Final criterion

In summary, the derivation described above leads directly to the formulation of the acceptance criterion for a sample size larger than 24. For given Q value, sample of size N has to fulfill:

1. *Sample Mean*: Mean of all tablets is above Q (point estimate or lower 95% confidence bound);
2. *Individual Values at Q – 15%*: $k(N)$ represents the number of tablets allowed below Q – 15% as a function of N; and
3. *Individual Values at Q – 25%*: no tablet can have a value below Q – 25%.

Drawbacks of Proposed Extension of USP <711>

The development of the *USP* <711> extension criterion has made multiple statistical as well interpretational assumptions either explicitly or implicitly. These assumptions are summarized below, and the drawbacks of this approach are discussed.

Normality Assumption

The normality assumption is necessary to derive rules to satisfy conditions 2 and 3. However, if the normal distribution is assumed and evaluated for N = 24 for *USP* <711> acceptance criteria, the same SD_1 is not derived for conditions 2 and 3 following the steps given previously (i.e., to achieve NMT two below for condition 2 and none below for condition 3). Because of this difference in SD_1 obtained by each condition, only condition 2 is used for SD_1 determination, whereas condition 3 is only used to safeguard against heavy-tailed distributions. Lack of clarity on which SD should be used for condition 3 led to the recommendation of no single value below Q – 25%, but the problem is more profound; it questions whether normality should be used for calibration or some other distribution.

At the same time, using larger sample sizes in the hundreds to thousands with the normality assumption would lead to decreasing probabilities to pass condition 3 with SD_1 for p_1 = 95%. With N = 200, the probability of passing condition 3 is only around 80% probability (if the batch mean is at Q%). In practice, such a large SD is not expected to be obtained, so the actual risk of failure due to condition 3 is expected to be very low. Still, it is a drawback of the statistical approach given.

Role of Q Value Selection

The developed framework assumes that the true (but unknown) batch mean percent dissolved is not too close to 100%. Note that an atypical dissolution readout can arise from two different causes: actual slower/faster dissolution properties of the tablet or off-target content. The latter can vary both below and above 100%, affecting proportionately of the percent dissolved at the defined Q time point, but the former results in skewed distribution of percent dissolved at Q time point at the tablet level, as there is more potential variability for slower dissolution than for faster dissolution, which is bounded by tablet content. The combination of these properties would cause issues with normality and affect the SD calculations needed to derive the table for Q – 15% criterion. For typical choices of immediate-release dosage forms with Q between 75–85%, with typical SD values, the proposed framework will work sufficiently well, but it needs to be clearly understood that it is an approximate solution that may not work with Q values closer to 100% (note that such large Q is unrealistic in practice).

Granularity and Choice of p_1

The p_1 target value is typically not achieved exactly, especially for smaller sample sizes with resulting $k(N)$ < 10 tablets. At various sample sizes, the actual overall properties of the criterion would differ somewhat.

For example, changing p_1 from 95% to 93% would have achieved same result for N = 50, i.e., $k(N)$ = 4 tablets due to the granularity of the criterion. The dependence of $k(N)$ on choice of p_1 is more pronounced for large sample sizes. For N = 1000 tablets, $k(1000)$ = 51 tablets for p_1 = 93%, or 45 tablets for p_1 = 95%. Thus, conformance to the chosen p_1 is sample size dependent.

The choice of p_1 allows a company the flexibility to set the acceptable risk level. Hence, it should not be chosen arbitrarily or according to a default strategy but based on scientific assessment and internal business practices.

Performance

The overall performance of the extended framework is shown in Figure 3. The black line represents the curve for $N = 24$ with $k(24) = 2$ tablet, and the dashed lines represent varying criteria based on sample size. The proposed criteria are more conservative than the traditional *USP* <711> criteria used directly. That is expected given that *USP* <711> is a demonstration test, whereas the extended criteria lead to a confidence level of passing the demonstration test. However, the resulting curves are rather far from the desired ideal curve (i.e., step function with respect to the black reference line: at probability of 1 when reference curve is above p_1 and immediately dropping to zero when the reference line crosses below p_1). Sample sizes well above 100 would be required to achieve performance close to the desired step function.

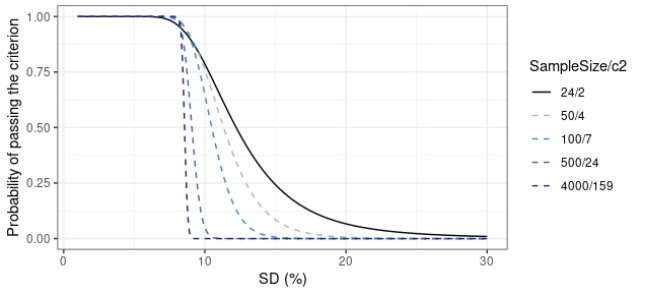

Figure 3. Probability of passing the various criteria: solid line refers to USP <711> acceptance criterion of stage 3 NMT than two values below Q – 15 with N = 24; dashed lines represent larger samples (N = 50, 100, 500, and 4000) with corresponding k(N) values (4, 7, 24, and 159, respectively). c2: condition 2 of respective criterion; NMT: not more than; SD: standard deviation.

DIRECT QUALITY (TOLERANCE INTERVAL) APPROACH

As shown in previous sections, building the criteria directly around *USP* <711> acceptance criteria is rather cumbersome. An alternative approach to large N criteria is to start from a patient-centric perspective and simplify criteria to a single threshold decision rule.

An approach based on tolerance intervals (TIs) can be employed to ensure that the quality of the product is above a required threshold with a prespecified degree of confidence. Analogous reasoning has been proposed for large sample considerations for *USP* <905> (*7*). A further simplification is that for dissolution, only a one-sided tolerance limit is needed.

There are several advantages of such an approach. Firstly, the tolerance limit implementation is relatively simple. Following Krishnamoorthy and Mathew, the *p*% content and (1 – α)% confidence lower tolerance bound, is calculated according to the equation (*8*): $\bar{x} - K \cdot s$, where *K* is the TI constant.

$$K = \frac{t_{n-1,1-\alpha,\ell}}{\sqrt{n}}.$$

K is equal to the (1 – α)% quantile of the non-central t-distribution with n-1 degrees of freedom and non-centrality parameter $\ell = z_p\sqrt{n}$ divided by $\sqrt{n}$; *n* is sample size; z_p is the p^{th} quantile of the standard normal distribution, $\bar{x}$ is the sample mean, and *s* is the sample SD.

Note that *K* is used in this section to distinguish TI constant from the lowercase *k*(*N*) used in the previous section.

The formula may be too complicated to be implemented for release in commercial manufacturing quality systems. However, given that for a single product, both α and p will be fixed, the *K* value can be precalculated for varying sample sizes. Then, the formula is given by $\bar{x} - K(N) \cdot s$, with *K*(*N*) denoting dependence of the constant K on the sample size *N*.

Finally, the calculated tolerance bound is compared with a certain threshold that defines the required quality. The criterion is single-stage, and the sample size is already considered in the calculation, so the acceptance criterion is independent of the sample size.

There are two TI-based approaches to consider, one is based on quality of individual values and the other is based on an extension of the *USP* <711> stage 3 acceptance criterion.

Individual Tablet Quality

Conceptually the simplest, yet the most stringent, approach to a direct quality assessment would be an individual tablet quality requirement. This approach is related to a known probability of compliance with the *USP* <711> acceptance criteria assuming the same Q value. A high proportion of the tablets being above the Q value implies high probability of compliance.

To show a concrete example, let Q = 80%, *p* = 95%, and 1 – α = 90%, and consider various levels of the true underlying dissolution mean and SD. Results for *N* = 50 are shown in Figure 4 and discussed in detail here; sample sizes of 24 and 200 are shown in supplemental figures. In contrast to *USP* <711> acceptance criteria shown in Figure 1, a criterion based on the TI limit has entirely different behavior: lower SD values and a certain distance above Q = 80 are needed for compliance (due to the inclusion of the lower bound as part of the criterion). Naturally, this is caused by the requirement of having individual tablet readouts above a certain threshold. Note that the curve shows a clear step-function-like behavior.

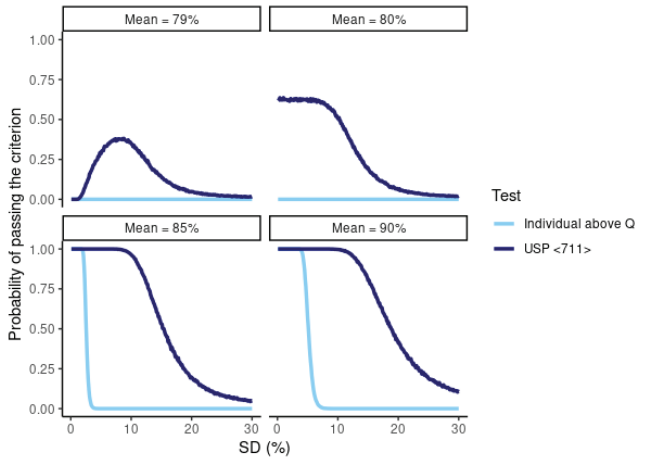

Figure 4: Comparison of the 90% confidence, 95% coverage tolerance interval above the Q = 80% mean value versus USP <711> acceptance criteria for batches of N = 50 across a range of mean values and standard deviation (SD). Sample sizes of 24 and 200 are shown in supplemental figures.

A drawback of this approach is considerable conservativeness of the criterion when compared to *USP* <711> acceptance criteria in the sense of rejecting batches that exhibit large probability of compliance with *USP* <711>. Hence, it can only be applied if there is a clear requirement for individual values to be above the Q value.

USP <711>-Based Quality

A variation of the direct quality approach is deriving the TI threshold and coverage directly from *USP* <711> acceptance criteria. The stage 3 criterion allows two out of 24 tablets to be below Q – 15%, which translates into 8.33% of tablets. Extrapolating this to the population using a threshold of Q – 15% with p = 92% content and $1 - \alpha$ = 95% confidence, TI would align with the properties of *USP* <711> acceptance criteria. To ensure a sufficiently large probability to pass *USP* <711> acceptance criteria for a batch passing TI criterion, the coverage needs to be increased above 92%. Empirically, p = 97.5% has been shown to provide good performance.

Note that when using Q – 15%, an additional acceptance criterion must be added. The population statement above Q – 15% does not guarantee the mean above Q, so the point estimate or the lower confidence bound of the mean value of the observed tablets must be above the Q value. Essentially, a use of confidence limit requirement instead of point estimate will eliminate the possibility of batches below Q passing the criterion in small samples and will penalize batches with a mean value just above the Q value.

Results for N = 50 are shown in Figure 5, including the point estimate and confidence interval for the mean value criterion (sample sizes of 24 and 200 are shown in supplemental figures). An SD of approximately 10% is the threshold where the batches start to occasionally fail *USP* <711> acceptance criteria. With a 95%/97.5% parametric one-sided TI, there is only a small probability for batches with SD > 10% to pass the criterion. At the same time, the criterion is much less conservative than the approach using Q = 80%, as discussed in previous sub-section.

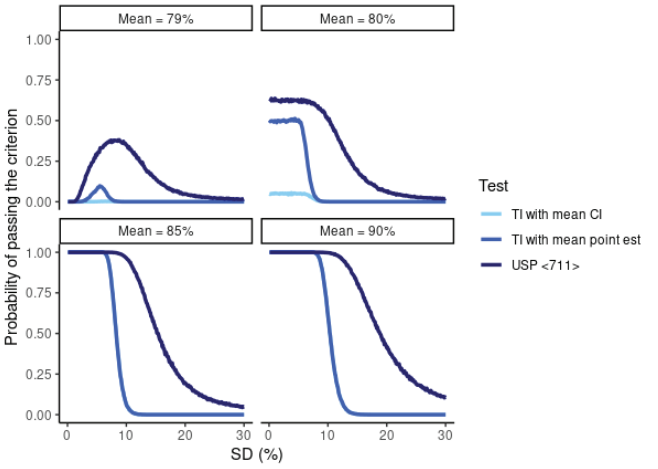

Figure 5: Comparison of the USP <711> acceptance criteria with a double criterion of 95% confidence, 97.5% coverage tolerance interval (TI) above Q – 15% and mean above Q. The plot shows batches of N = 50 across a range of mean values and standard deviation (SD). When only two lines are displayed, the point estimate and confidence interval (CI) based testing fully overlaps. Sample sizes of 24 and 200 are shown in supplemental figures.

DISCUSSION

This study presents two statistical approaches to developing acceptance criteria applicable to dissolution release testing of large sample sizes (N > 24). The first approach is an extension of the *USP* <711> acceptance criteria to large N sample sizes, including a strict requirement on individual tablets. The second approach is based on a TI criterion with two different options. The operating characteristic curves were compared in relation to *USP* <711> acceptance criteria, considering the practical implementation, ease of interpretation, and quality protection of both approaches.

The simplicity of the TI-based criterion is an advantage, and it has good small sample size properties when the true batch mean percent dissolved is close to the Q threshold. The most important criterion is the direct link to quality, unlike the fairly complex relationship for the approach based on an extension of *USP* <711> acceptance criteria. The TI-based approach is recommended as a practical release strategy, affording good product quality protection to the patient.

The TI-based option that requires individual tablet quality specifications looks at the problem from a strict individual tablet quality requirement perspective. This criterion is overly conservative and generally requires lower SD than the *USP* <711> test to be successful. Although there may be circumstances related to operational considerations and patient risk requirements where this option may be considered, this approach is generally not recommended.

The TI-based option that is based on extension of stage 3 *USP* <711> acceptance criteria has good calibration properties and is not overly conservative. Hence, it may generally be a good choice for an acceptance criterion rule for dissolution assessment of large samples. Additionally, such an approach is consistent with the development of content uniformity testing (*9*).

Immediate-release dosage forms were used in this study; however, the approaches can be adapted to testing of other dosage forms.

CONCLUSION

The proposed approaches contain a probabilistic metric that controls the risk level and can be applied to large sample sizes in applications such as continuous manufacturing. The first approach extends *USP* <711> acceptance criteria to a large sampling procedure, controlling the risk with parameter p_1. Risk control with respect to batch parameters for two TI-based approaches are maintained via the content and confidence parameters. Different values may be assessed to achieve a desired risk level and level of calibration against *USP* <711> acceptance criteria as appropriate for a given situation.

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DISCLOSURES

All authors are employees of Johnson & Johnson and the manuscript has been written as part of their employment. No other financial support or conflicts of interest have been declared by the authors.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

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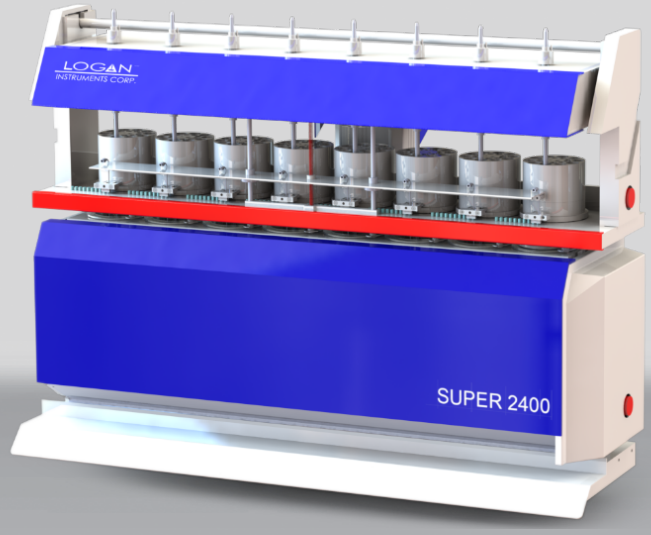

This system precisely delivers, preheats, and degasses media into 8 dry-heat vessels removing the added complication of a water bath. Each vessel has bottom and side cameras to record the dissolution for subsequent viewing and result verification. After the test is over, the vessels automatically empty the media, they are then sprayed, washed, and blow-dried, ready for the next 9 batches of test samples.

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Life Cycle Application of AQbD for Formulation Development and Validation of a Dissolution Method for Nevirapine

Rayza A. D. de Almeida[1], Maria Luiza R. A. de Oliveira[1], Ivone de J. N. Lopes[1], Diogo D. Nascimento[1], Camila A. Oliveira[1], and Livia D. Prado[1*]

[1]Laboratório de Desenvolvimento e Validação Analítica, Instituto de Tecnologia em Fármacos (Farmanguinhos), Fundação Oswaldo Cruz, Rua Sizenando Nabuco, Rio de Janeiro, Brazil.

e-mail: liviaderis@gmail.com

ABSTRACT

Introduction: Dissolution plays a vital role as an in vitro test in the pharmaceutical product life cycle. For the evaluation of an appropriate dissolution test, analytical quality by design (AQbD) principles can provide increased confidence when deciding whether the product is of the expected quality. **Methods**: This study applied AQbD concepts for dissolution method development for nevirapine 200-mg tablets. Solubility tests were performed. The analytical target profile (ATP) was established for the dissolution and the quantification methods. Risk assessment was carried out through the construction of an Ishikawa diagram to identify the critical method parameters. Robustness was evaluated using a fractional factorial design and validation tests were conducted. **Results**: Nevirapine showed pH-dependent solubility and near-sink conditions were observed at pH 2.0. The ATP considered the targets for specificity, range, accuracy, and precision. The dissolution method was able to differentiate formulation attributes and changes in critical process parameters. The method showed robustness after 45 minutes, and pH control was the key element in ensuring analytical performance. Validation tests proved method specificity, linearity, accuracy and precision. **Conclusion**: This study demonstrated the application of AQbD to a dissolution method, making it possible to evaluate the discriminative power, robustness and to define the specification.

KEYWORDS: Nevirapine; dissolution; analytical target profile; design of experiments

INTRODUCTION

Nevirapine is a non-nucleoside reverse transcriptase inhibitor that is effective when used as part of combination therapy for the treatment of human immunodeficiency virus-1 infection (*1*, *2*). Nevirapine is a weak base whose conjugate acid has a pKa of 2.8 and the solubility depends strongly on the pH of the solution (*3*, *4*). Due to its low water solubility and high permeability, nevirapine is classified as a class II drug in the Biopharmaceutics Classification System (BCS). BCS class II compounds exhibit dissolution rate-limited bioavailability (*4*, *5*).

Dissolution is an important quality control test to evaluate the in vitro release performance of pharmaceutical dosage forms and represents a critical quality attribute of drug products (*6*–*8*). Dissolution tests frequently support the formulation development process to evaluate the stability of a drug product and ensure batch-to-batch consistency (*9*, *10*). The quality by design (QbD) approach strongly emphasizes the role of dissolution testing in evaluating critical process parameters that can affect dosage form performance (*11*). In this context, it is essential to have a dissolution methodology with sufficient discriminatory power to characterize potential differences, and such dissolution methodology should be a combination of justified parameters like media buffer pH, media volume, and mixing speed (*12*–*17*).

Regulatory guidelines have been published to present the steps for developing a dissolution method. If a method is described in a pharmacopeial monograph, its suitability

*Corresponding author

for the intended pharmaceutical product should be assessed (*18–20*). Therefore, the discriminative power can be determined prior to the analytical validation step. Also, international guidelines recommend performing a robustness assessment during method development (*21*). For dissolution, robustness is conventionally evaluated for the quantification method, varying parameters related to spectrophotometric or chromatographic methods (*22–24*). However, International Conference of Harmonization (ICH) Q2(R2) guideline addresses robustness as a performance characteristic associated with the reasoning for selecting dissolution parameters such as media pH and volume (*21*).

Analytical quality by design (AQbD) principles have been applied in the development of analytical methods, especially for chromatographic methods (*25–32*). AQbD strategy begins with the definition of an ATP and includes several steps to identify critical method attributes and parameters (CMAs and CMPs, respectively), develop or optimize experimental procedures (design of experiment [DoE] process), and determine method robustness. AQbD gained attention for enabling the development of robust and cost-effective procedures with regulatory flexibility and control strategies designed for life cycle monitoring. The significance of AQbD has been described in ICH Q14 guideline (*33*).

To our knowledge, few studies have been reported on the application of AQbD for dissolution methods to ensure adequate performance throughout the product life cycle. Furthermore, no study has presented ATP with the performance characteristics of dissolution and quantification methods, and a limited number of studies show the application of DoE for dissolution conditions (*34–36*). In this study, a dissolution method for immediate-release nevirapine 200-mg tablets was developed using AQbD elements to provide a robust and suitable method. Analytical validation was carried out to prove the suitability of the method.

METHODS

Chemical and Reagents

Materials used in experiments included: nevirapine reference standard (USP), nevirapine API (manufacturers A and B [manufacturer names were not disclosed due to confidentiality reasons), acetonitrile HPLC grade (J.T Baker), ethanol HPLC grade (Supelco), orthophosphoric acid (Merck), sodium phosphate monobasic monohydrate (Merck), hydrochloric acid (Êxodo), acetic acid (Biograde), and potassium phosphate monobasic (Êxodo).

Four nevirapine 200-mg tablet formulations were used, each one with variations in relation to the API manufacturer (A or B), hardness, or disintegrant amount. Sample N1 is the current formulation registered by the Brazilian regulatory agency (Anvisa), which was used as a reference product. The characteristics of the formulations were: N1 (API manufacturer A, 142 N hardness, 5% disintegrant), N2 (API manufacturer B, 154 N hardness, 5% disintegrant), N3 (API manufacturer B, 228 N hardness, 5% disintegrant), and N4 (API manufacturer B, 128 N hardness, 0% disintegrant).

Solubility Studies

Nevirapine suspensions in hydrochloric acid (HCl) 0.1 M pH 1.2, sodium phosphate buffer pH 2.0 (dissolution medium for nevirapine tablets described in the *United States Pharmacopeia* [USP]), acetate buffer pH 4.5 (preparation according to *USP*), and potassium phosphate buffer pH 6.8 (preparation according to USP) were maintained under agitation (100 rpm) at 37 °C using an IKA KS4000i (Germany) for determination of solubility by shake-flask method (*37*). Three independent experiments were carried out for each medium. Aliquots (10 mL) were taken at 2, 6, 12, and 24 h, filtered using a 0.22-µm PTFE syringe filter, and diluted for further quantification. The samples were quantified by high-performance liquid chromatography (HPLC) based on analytical curves in the range of 0.05–0.30 mg/mL. The HPLC method used was a previously developed and validated stability indicating method. A Metrohn (Switzerland) 780 potentiometer was used to determine the pH of all solutions.

Filter Suitability for Dissolution Test

Two PTFE syringe filters (Agilent UHMWPE 35 µm and BioNaky 0.22 µm) were evaluated. Leachability was tested by comparing chromatograms of the dissolution media before and after filtration. To evaluate if the dissolved API binds to the filter membrane, 10 mL of the standard solution was filtered, and the signal variation was calculated by comparing the peak area of the chromatogram with that of the unfiltered solution. Filtration efficiency was evaluated by taking a 20-mL aliquot from the dissolution vessel 5 minutes after adding formulation N2 to 900 mL of dissolution medium at 37 °C and 50 rpm. The sampled volume was divided into three parts. The first was immediately evaluated. The second and third parts were placed in an ultrasound bath for 5 and 10 minutes, respectively, after which the samples were evaluated by HPLC. The dissolution medium used was sodium phosphate buffer pH 2.0. The HPLC method used was the same as described for the quantification of dissolution test.

Analytical Target Profile (ATP) and Risk Assessment for Identification of Critical Method Parameters and Attributes (CMPs and CMAs)

The ATP was prepared based on the quality target product profile (QTPP) previously developed by the authors (unpublished data), in which dissolution was considered as a critical quality attribute (CQA). Risk assessment was conducted, with the elaboration of an Ishikawa diagram, to recognize the CMPs that can affect the final performance of the dissolution test, related to the CMAs (*38*).

Dissolution Test and Profile Comparison

Dissolution profiles were obtained for formulations N1, N2, N3, and N4 in a Varian (USA) VK7010 dissolution apparatus according to the method described in the *USP* (n = 6) (*37*). A USP apparatus 2 (paddle) at 50 rpm was used with 900 mL of 0.1-M sodium phosphate buffer pH 2.0 as dissolution medium. The bath temperature was set at 37 °C. Samples (10 mL) were drawn at 5, 10, 15, 30, 45, 60, and 90 minutes and filtered with a 35-µm Ultra High Molecular Weight Polyethylene (UHMWPE) filter. The percentage of drug dissolved was corrected in relation to the volume collected at each time point, and the absorbance was determined using a HPLC method. The HPLC system consisted of a Shimadzu (Japan) with an LC-20AT pump, CTO-20AC column oven, SIL-20A auto sampler, SPD-M20A PDA detector, and CBM-20A system controller. Chromatographic conditions included an X Terra C18 column (150 x 3.9 mm, 5 µm) at ambient temperature, mobile phase of water: acetonitrile (77:23 v/v), flow rate of 1.0 mL/min, detection at 214 nm, and injection volume of 20 µL.

Dissolution efficiency (DE) was obtained from the area under the curve (AUC) of the dissolution profile (*39*). The DE results were studied with analysis of variance (ANOVA) at 95% confidence level. In addition, two-way ANOVA was performed considering the percentage dissolved as the random variable and formulation and time as class variables (*40*).

Design of Experiment (DoE) for Robustness Evaluation

Robustness of the dissolution method was evaluated with batch N2 (n = 6) by carrying out a fractional factorial design (2^{4-1}). The DoE was created in Protimiza Experiment Design Software (http://experimental-design.protimiza.com.br). Four variables (X factors) were adopted: pH of the dissolution medium, volume of dissolution medium, degassing in the preparation of the dissolution medium, and sampling type (manual or automatic). Table 1 presents such variables and their respective levels. Percentage of API dissolved at each sampling time point (Y factor) was evaluated as the response. Effects were evaluated at 95% and 90% significance levels.

Table 1. Design of Experiment (DoE) Factors and Levels

Test no.	Coded Values				Real Values			
	X1	X2	X3	X4	X1	X2	X3	X4
1	-1	-1	-1	-1	1.9	800	No	Automatic
2	1	-1	-1	1	2.1	880	No	Manual
3	-1	1	-1	1	1.9	920	No	Manual
4	1	1	-1	-1	2.1	920	No	Automatic
5	-1	-1	1	1	1.9	880	Yes	Manual
6	1	-1	1	-1	2.1	880	Yes	Automatic
7	-1	1	1	-1	1.9	920	Yes	Automatic
8	1	1	1	1	2.1	920	Yes	Manual

X1: medium pH; X2: medium volume (mL); X3: degassing; X4: sampling type.

Validation of the Quantification Method

The quantification method used in the dissolution test was validated according to international guidelines. Specificity, linearity, precision, and accuracy were evaluated (*21*, *41*). Solution stability was also verified. Specificity was determined through injection of standard solutions (concentration = 0.0135 mg/mL) and placebo solutions obtained after a dissolution run and proper dilution. The placebo was composed of all constituents of the N2 formulation without nevirapine. Placebo interference was calculated (*37*). The linearity was evaluated through dilution of the nevirapine stock solution (concentration = 0.054 mg/mL) into dissolution medium at six concentrations levels (20%, 40%, 60%, 80%, 100%, and 120%) of the drug working concentration (0.0135 mg/mL). The determination of accuracy was accomplished by adding known amounts of nevirapine to the placebo solution to obtain the concentrations at 80%, 100%, and 120% levels. Each concentration was prepared in triplicate, and the percentage of recovery was calculated. The repeatability and the intermediate precision on consecutive days were established by performing the dissolution test with sample collection at 45 minutes. Relative standard deviations (RSD) were calculated.

The stability of nevirapine in 0.1-M phosphate buffer pH 2.0 was evaluated under storage condition at room

temperature. Samples were collected at 0 h, 6 h, 24 h, 48 h, and 72 h, filtering into the vial using a 0.22-µm PTFE syringe filter. Standard solution and sample solution were evaluated.

RESULTS AND DISCUSSION

Solubility Studies

Nevirapine exhibits pH-dependent solubility (Table 2), which has been reported in the literature (*42*, *43*). The dose/solubility ratio was found to be greater than 250 only in pH 1.2 medium. This result suggests that nevirapine has low solubility in the other media (pH 4.5 and 6.8). RSD was lower than 5%, indicating low variation between replicates and indicating reliability of the results. The sink condition was calculated, and it requires that drug solubility be greater than three times the total concentration of drug in the dissolution vessel (*37*). Sink condition was not achieved for buffer pH 4.5 and 6.8 because the dissolution should be performed in 900-mL vessels; near sink conditions were observed at pH 2.0. It is possible to perform the dissolution test in non-sink conditions; however, the method may have robustness problems (*44*). Therefore, it is necessary to assess whether small changes in dissolution conditions will have an impact on the amount of drug dissolved.

Table 2. Equilibrium Solubility (mg/mL) of Nevirapine in Different Media

Time (h)	pH 1.2	pH 2.0	pH 4.5	pH 6.8
0	2.14 (0.42)	0.56 (0.60)	0.12 (0.21)	0.11 (1.41)
2	2.18 (0.97)	0.57 (2.26)	0.12 (0.24)	0.11 (0.90)
6	2.19 (1.68)	0.57 (1.84)	0.12 (0.07)	0.11 (0.23)
12	2.13 (0.20)	0.56 (1.12)	0.12 (0.18)	0.11 (0.50)
24	2.17 (0.58)	0.56 (0.60)	0.12 (0.21)	0.11 (1.41)

Values are mean (relative SD).

Filter Suitability for Dissolution Test

The filtration step is fundamental in drug dissolution tests and should be evaluated during method development (*45*). In this study, tests were carried out to assess leaching, efficiency, and adsorption (*6*). No new peaks were observed in the chromatograms of the filtered medium, thus no leachability occurred for the 35-µm UHMWPE and 0.22-µm PTFE filters. Also, drug adsorption was not observed on the filter membranes: 0% variation in peak area between the filtered and unfiltered samples. In the filtration efficiency test, the samples kept in an ultrasound bath showed no significant increase in the nevirapine peak area (0% for the 35-µm UHMWPE filter and 1% for the 0.22-µm PTFE filter). The filter suitability tests showed that the 35-µm UHMWPE filter for sample collection and the 0.22-µm hydrophilic PTFE syringe filter used for sample preparation are suitable.

ATP and Risk Assessment for Identification of CMP and CMA

The established ATP for nevirapine tablet dissolution method must present the performance characteristics of the method with the intended target to guarantee the application throughout the life cycle (*21*, *33*, *37*, *46*). The scientific literature presents several papers with the application of AQbD and definition of ATP for chromatographic methods (*29–31*, *47*, *48*). However, there are no studies that define the ATP for dissolution methods, considering the performance characteristics. For the ATP established in this work (Table 3), we considered the performance characteristics for the dissolution and quantification methods as defined in the ICH Q2R2 (*21*).

The dissolution method must have adequate discriminative power for nevirapine 200-mg tablets. AQbD principles begin with elaboration of the ATP from an identified CQA. As dissolution is a CQA for the nevirapine 200-mg tablet, as previously established in the QTTP by the authors (unpublished data), the ATP link to the CQA was established. Understanding of the analytical procedure and link to the CQA allowed the definition of performance characteristics that ensure the quality of the measured dissolution result (Table 3).

A risk assessment was carried out through the construction of an Ishikawa diagram to define the CMP that may have a potential impact on the CMA and consequently on the performance of the dissolution method (Fig. 1). The Ishikawa diagram is the most adopted tool for the risk assessment of cause-effect phenomena (*49*, *50*). The percentage of API dissolved at each time point of the dissolution profile has been previously identified as a CMA. Factors related to people, equipment, measurement, and milieu are not considered CMAs, as they are controlled in the laboratory routine, such as training analysts in standard operating procedures, qualification of equipment, and control of the environmental conditions. As the method used is described in USP, some method parameters, such as apparatus, were not considered for the DoE study (*37*). Robustness was evaluated with the most critical factors, i.e., medium pH and volume, degassing, and type of sampling.

Dissolution Profiles

The dissolution profiles of the formulations are shown in Figure 2. Batches N1 and N2 represent the reference

Table 3. Analytical Target Profile for Dissolution Method for Nevirapine Tablets

Performance Parameter	Dissolution Test		Quantification Test	
	Target	Rationale	Target	Rationale
Selectivity and specificity	Statistically significant difference between batches (*21*)	Parameter assessed based on *USP* <1092> (*37*); discriminatory power demonstration.	No interference from excipients and dissolution medium (≤ 2%) (*37*)	Parameter assessed based on *USP* <1092> (*37*); API quantification shall not to be affected by the presence of other substances
Range	Not applicable (*21*)	Not applicable (*21*)	Interval between the upper and lower concentrations of the API observed in the dissolution profile (*37*)	Parameter assessed based on *USP* <1092> (*37*); stated range for intended use of the procedure
Accuracy	Not applicable (21)	Not applicable (*21*)	95–105% recovery (*37*)	Parameter assessed based on *USP* <1092> (*37*) and ICH Q2R2 (*21*) to ensure quality reportable results
Precision	RSD of ≤ 10% at time points with < 85% dissolved and ≤ 5% for time points > 85% (*37*)	Parameter assessed based on *USP* <1092> (*37*) to ensure quality reportable results	RSD ≤ 5% at specification time point (*37*)	Parameter assessed based on *USP* <1092> (*37*) and ICH Q2R2 (*21*) to ensure quality reportable results

CQA: critical quality attributes; RSD: relative standard deviation; USP: United States Pharmacopeia; API: active pharmaceutical ingredient; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

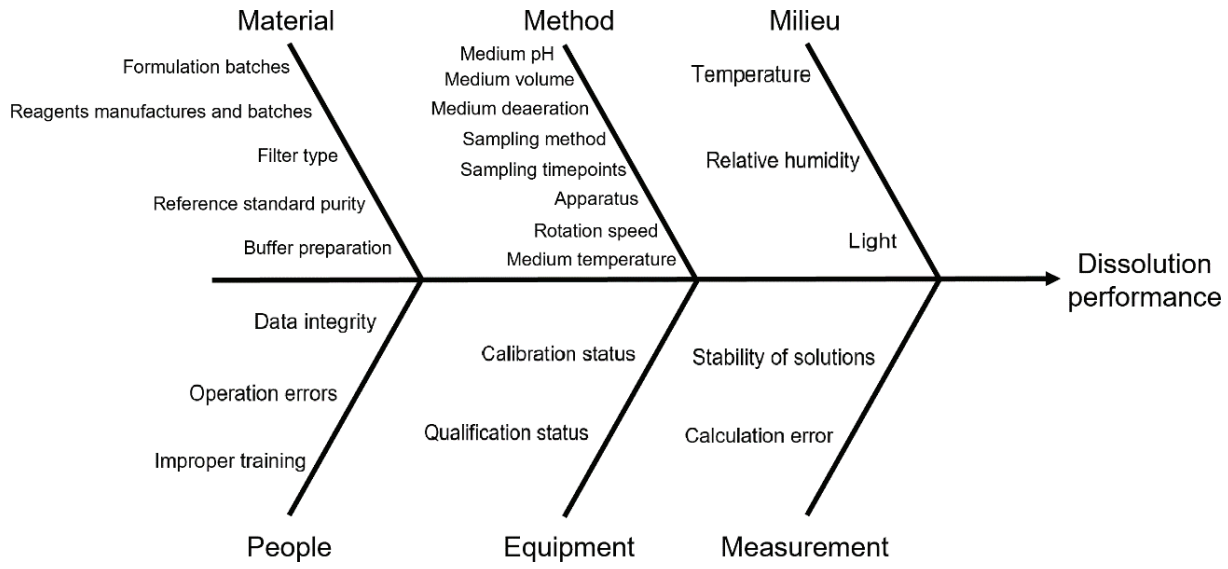

Figure 1. Ishikawa diagram used to identify critical method parameters for dissolution performance.

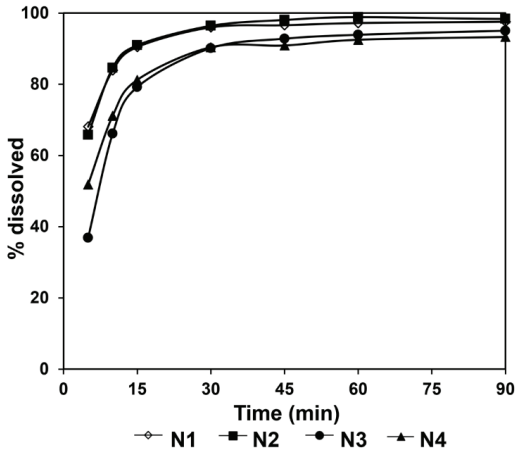

Figure 2. Dissolution profile of nevirapine batches N1, N2, N3, and N4.

product and the formulation with the API from manufacturer B, respectively. Batches N1 and N2 showed very fast dissolution (> 85% within 15 minutes), thus, the similarity of the profiles and the compliance with the ATP (i.e., link to CQA) was confirmed. Batches N3 and N4 showed fast dissolution (85% in 30 minutes), with the type of dissolution profile being different from batches N1 and N2, which proves the discriminative power of the method (selectivity for dissolution method described in the ATP). Because the calculation of the similarity factor (f_2) loses its discriminative power when very fast profiles are observed, and the difference between the dissolution of the formulations was proven by the difference in the profile types, f_2 was not calculated; however, the DE and ANOVA were used for comparison.

DE obtained for N1, N2, N3, and N4 were 88%, 89%, 78%, and 79%, respectively. By increasing hardness and reducing the amount of disintegrant in the formulation, the DE was lower. Comparison of DE values revealed a statistically significant difference ($p < 0.05$) between the formulations, thereby proving the discriminatory power of the method. DE is closely related to the performance of the formulations. It is then possible to evaluate the behavior of the formulations in comparison with each other and with the ideal 100% release.

Considering the DE results, it can be concluded that, this dissolution method is also relevant in the context of QbD, as it differentiates formulation attributes and changes in critical process parameters. A *p*-value < 0.05 indicated a statistical difference between the dissolution profiles. During drug development, several experimental formulations were produced to evaluate the discriminative power of the method and to evaluate the production process. In this case, it was found that the tablet disintegration in the vessel was important for the discriminative power of the dissolution method. Therefore, the previously described deliberate changes to the formulations were made.

Batch N2, the final test formulation with the API from manufacturer B, had acceptable RSD values for the dissolved amount of 5%, 3%, 2%, 2%, 2%, 3%, and 2% at times points of 5, 10, 15, 30, 60, and 90 minutes, respectively. This result is in accordance with precision of the dissolution method described in the ATP, as the RSD was ≤ 5%.

DoE for Robustness

Assessment for robustness of the dissolution method must involve evaluating the impact of small variations on the percentage dissolved. Robustness is traditionally determined by varying one factor at a time (*51*). In this study, DoE was performed with factors selected from the construction of the Ishikawa diagram. pH and volume can be critical due to possible analytical errors in the preparation of the medium, and the type of sampling and degassing are also essential for the application of the method in the quality control routine. Thus, these factors were selected.

The effects of variables (X factors) on responses (Y) were evaluated according to Table 4. Comparison of the pH was statistically significant ($p < 0.05$) for Y1 versus Y4. The pH factor was the CMP that had the most impact on the responses; the pH decrease caused an increase in the percentage dissolved of nevirapine between 5 and

Table 4. Main Effects and p-Values Obtained from Fractional Factorial Design

	Y1 Effect	p-value	Y2 Effect	p-value	Y3 Effect	p-value	Y4 Effect	p-value	Y5 Effect	p-value	Y6 Effect	p-value	Y7 Effect	p-value
Average	56.54	< 0.0001	76.35	< 0.0001	84.63	< 0.0001	91.0	< 0.0001	92.71	< 0.0001	93.5	< 0.0001	94.292	< 0.0001
X1	-15.17	< 0.0001	-13.79	< 0.0001	-12.25	< 0.0001	-3.8	0.0048	-2.00	0.1056	-1.67	0.1515	-1.250	0.2456
X2	0.75	0.6764	0.21	0.8958	-0.42	0.8341	-1.2	0.3705	-1.17	0.3403	-1.83	0.1155	-1.333	0.2160
X3	3.50	0.0563	2.13	0.1861	0.08	0.9666	0.7	0.6077	-1.08	0.3756	-1.58	0.1725	-0.333	0.7551
X4	-3.75	0.0415	-1.71	0.2861	-1.25	0.5306	1.2	0.3705	0.42	0.7322	0.08	0.9421	0.750	0.4838

X1: medium pH; X2: medium volume; X3: degassing; X4: sampling type; Y1: % dissolved at 5 min; Y2: % dissolved at 10 min; Y3: % dissolved at 15 min; Y4: % dissolved at 30 min; Y5: % dissolved at 45 min; Y6: % dissolved at 60 min; Y7: % dissolved at 90 min.

30 minutes. The use of degassed medium favored the dissolution of nevirapine during the first 5 minutes of the test ($p < 0.1$). The type of sampling also had an effect at 5 minutes ($p < 0.05$), with automatic sampling resulting in a higher percentage dissolved. The initial time points are expected to have greater variation and less robustness (*52*).

Establishing a control strategy is part of the AQbD approach and should be derived from data collected during method development phase (*33*). For the nevirapine dissolution method, pH control is the key element for proper method performance throughout the life cycle. Therefore, the medium must be carefully prepared with a pH of 2.0. In addition, for an adequate specification of the dissolution method, a time point of 45 minutes is recommended, as this time is the beginning of the plateau and presents robustness, demonstrated by the DoE (*19, 20*). The current specification described in *USP* is 60 minutes, but a 45-minute specification allows the reduction of testing time in quality control.

Validation of the Quantification Method

The specificity was demonstrated because no interference of excipients was observed. The quantification method showed good linearity at the concentration range of 20–120%. Correlation coefficient was $R^2 = 0.9999$ (*41*).

The accuracy of the method was considered adequate (between 95% and 105%) (*37*). Recovery results were 99% at 80% level (with replicate values of 98.9%, 99.2%, and 98.7%); 99% at 100% level (with replicate values of 99.4%, 98.8%, and 99.3%); and 99% at 120% level (with replicate values of 99.1%, 99.3%, and 99.2%). Repeatability and intermediate precision were evaluated, and RSD was ≤ 2% (with replicate values for analyst A of 92.5%, 89.3%, 93.5%, 97.2%, 98.6% ,and 95.7% and for analyst B of 97.1%, 97.0%, 97.8%, 93.4%, 100.5%, and 102.4%), demonstrating good precision (*37*). RSD obtained for repeatability was 3.6% and for intermediate precision was 3.8%.

The stability of nevirapine in 0.1-M sodium phosphate buffer pH 2.0 was evaluated up to 72 h. The RSD for the standard solution and sample solution was 1.2% (recovery of 101%) and 1.1% (recovery of 103%), respectively, being below the 2% acceptance limit (*37*). Thus, the solutions can be stored, prior to quantification, for up to 72 h at room temperature.

CONCLUSION

In this work, a systematic approach to development of the dissolution method for nevirapine tablets was demonstrated. The AQbD process was carried out including the definition of ATP and the use of experimental design as a multivariate approach for robustness. The suitability of the pharmacopoeia method with discriminative power for the product was demonstrated. The DoE allowed identifying the pH as the CMP to be controlled during the life cycle of the method. The quantification and dissolution methods can be used as a routine quality control test once the analytical validation has proven their performance. This study can be used as a reference for the development and evaluation of dissolution methods in the pharmaceutical industry, bringing scientific knowledge closer to regulatory requirements.

DISCLOSURES

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Q+A Question & Answer Section

*The following questions have been submitted by readers of Dissolution Technologies. Margareth R. Marques, Ph.D., and Mark Liddell, Ph.D., United States Pharmacopeia (USP), authored responses to each of the questions. *Note: These are opinions and interpretations of the authors and are not necessarily the official viewpoints of the USP. E-mail for correspondence: mrm@usp.org.*

Q In the validation of a dissolution procedure, for the precision evaluation, what is the appropriate precision technique? a) Sampling the same vessel six times and injecting each one of them into the HPLC system; b) Using six different vessels, but pooling the sampling results into one solution and injecting six times into the HPLC system; or c) Using six different vessels, sampling from each vessel, and injecting each of the six samples into the HPLC system.

A According to <1092> The Dissolution Procedure: Development and Validation the precision evaluation typically consists of three main components: repeatability of analysis, intermediate precision, and reproducibility. Ultimately, it is up to your organization to decide which approach to take to verify each of the three components for both the standard solution, the spiked placebo, and the sample solution obtained from a well-characterized dosage form. Keep in mind that the approach used to demonstrate precision may vary depending on the type of solution (e.g., standard solution vs. dissolution sample solution) that is being evaluated. The procedure should be as close as possible to the one used in the routine analysis of dissolution samples solutions obtained from a well-characterized final dosage form.

Q In a dissolution procedure with multiple sampling points at different time intervals, how should we carry out a verification study? As an example, the USP monograph for tamsulosin hydrochloride capsules, in buffer stage, requires sampling at 2, 3, and 8 h. What time point should be chosen for the precision evaluation?

A The validation of any parameter in a dissolution method is done considering the entire dissolution profile and is not determined based on the expected acceptance criteria. Keep in mind that the dissolution test for tamsulosin hydrochloride capsules is formulation dependent. Each formulation is going to have its own specific and discriminative dissolution test. This is the reason for multiple dissolution tests in the USP monograph for tamsulosin hydrochloride capsules.

Q Is there an upper limit for dissolution test? If the assay range for a particular product is 95–105% and one of the dissolution results is 135% and the average of six dissolution results is 103%, what could be the possible reasons for this high dissolution value?

A There is no upper limit for dissolution tests. Dissolution results cannot be compared with assay results. Dissolution and assay tests measure different parameters of the product, and the sample is treated in a totally different manner for each of these tests.

If dissolution results above 100% are observed, an investigation should be conducted to identify possible reasons for high results. Here are some examples of parameters that could be investigated:

- Filter validation: material, type (syringe filter, canula tip filter, etc.), pore size, and construction of filters.
- Sampling methodology: is the sample withdrawn at the appropriate time and at the appropriate position within the dissolution vessel?
- Interference of other components in the formulation or the dissolution media components used in the dissolution test.
- Uniformity of dosage unit range for the batch being evaluated.
- Cleaning method validation for dissolution equipment and sampling. If using an autosampler, carryover from previous runs should be considered

Q Some dissolution test media contain sodium dodecyl sulfate. This reagent is commercially available with different purities, like 85%, 93%, or 99%. Which quality grade should be used in dissolution test?

A This question should be addressed as part of the dissolution method validation. Ideally, it is recommended to use the highest quality grade of the surfactant to minimize possible interference in the quantitative determination of the amount of drug released from the dosage form and to minimize variability in the composition of the dissolution media.

Q If the six dissolution results fail stage 1 (S1) (Acceptance Table 1 in *USP* general chapter <711> Dissolution) but are within the limits of stages 2 and 3 (S2 and S3), should an out of specification results investigation be done or shall the test continue with S2 and S3?

A The three stages described in Acceptance Table 1 are part of the evaluation of routine dissolution results for immediate-release dosage forms. A batch is considered out of specification if it fails S3. Then, and only then, should an investigation for out of specification results be initiated.

Q If enzymes are added to the dissolution medium when there is evidence of cross-linking, should a verification be done?

A The use of enzymes in the dissolution medium when there is evidence of cross-linking in gelatin capsules should be evaluated as part of the dissolution method validation procedure. See *USP* general chapters <1092> The Dissolution Procedure – Development and Validation and <1094> Capsules – Dissolution Testing and Related Quality Attributes for more information related to this topic.

Q Section 1.2.2 Stability in *USP* general chapter <1092> The Dissolution Procedure: Development and Validation states: "The solution containing the drug substance is stored under conditions that ensure stability. The stability of this solution is analysed over a specified period of time (for at least the time of the entire dissolution procedure), using a freshly prepared solution at each time interval for comparison. The acceptable range for solution stability is influenced by the drug concentration and is typically between 98% and 102% of the expected final concentration." We understood that expected final concentration means the concentration at the final time point. For dissolution methods with multiple time points, e.g., extended release formulations, is this assumption correct?

A Section 1.2.2 is a subsection of 1.2 Determining Solubility and Stability of Drug Substance in Various Media. This section is preparatory work before the dissolution method is even considered; therefore, the reference to the concentration range of 98–102% of the expected concentration does indeed refer to the final expected concentration at the end of the dissolution experiment. Keep in mind that the stability of any solutions used in a dissolution test should be established considering the entire test time, including the quantitative step. This means that the time required to carry out the quantitative analysis step must also be considered and is likely to be longer than the last sampling point of the dissolution method. All solutions used during the dissolution test (sample solutions, all standard solutions, dissolution medium, diluent, etc.) must have an expiry date and storage conditions defined based on dissolution method development and validation data. This information must be stated clearly in the final version of the dissolution method.

Q *USP* general chapter <711> Dissolution states: "If the dosage form containing gelatin does not meet the criteria in the appropriate *Acceptance Table* (see *Interpretation*, *Immediate-Release Dosage Forms*, *Extended-Release Dosage Forms*, or *Delayed-Release Dosage Forms*) because of evidence of the presence of cross-linking, the dissolution procedure should be repeated with the addition of enzymes to the medium, as described below, and the dissolution results should be evaluated starting at the first stage of the appropriate *Acceptance Table*. It is not necessary to continue testing through the last stage (up to 24 units) when criteria are not met during the first stage testing, and evidence of cross-linking is observed." Does this mean that once a capsule drug product has gone through S1, S2, and S3 and does not meet Acceptance Table limits, the test with enzymes must be only done in Stage 1?

A No. If the capsules failed the dissolution test at any stage because of the presence of cross-linking, the test may be stopped, dissolution medium with the appropriate enzyme in the appropriate amount is prepared, and, using new capsules, the test is repeated starting at S1 and carried out through S2 and S3 if needed, with enzymes in the dissolution media. The use of enzymes is justified only

when failures are observed during the specific testing stage **and** there is evidence of cross-linking.

Q In the USP monograph for Ursodiol Tablets, the dissolution medium is simulated intestinal fluid TS, prepared without pancreatin, and adjusted with 0.1 N sodium hydroxide or 0.1 N hydrochloric acid to a pH of 8.0. The preparation of the simulated intestinal fluid TS in the Test Solutions section of USP directs to adjust the pH of this test solution to 6.8. Which pH should be used in the dissolution test of ursodiol tablets?

A The simulated intestinal fluid preparation instruction in the Test Solutions section of the *USP–NF* are general test solution preparation instructions. The instructions in USP monograph supersedes the general preparation instructions in any other sections of the *USP–NF*. Therefore, the simulated intestinal fluid TS for the use in the dissolution test of ursodiol tablets should be prepared according to the instructions in the monograph, i.e., the pH should be adjusted to 8.0 as stated in the dissolution medium description of the monograph.

Q+A

Every issue of *Dissolution Technologies* features a Question and Answer section. This section is designed to address general dissolution questions submitted by our readers.

Please send your questions to:
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Calendar of Events

August 20, 2024

Complimentary Introduction to GPX™ Workshop for New-to-GastroPlus® Users
Location: Online
Registration: https://simulations-plus.learnupon.com/store/3864001-gpx100vr-complimentary-introduction-to-gastroplus-x-for-new-to-gp-users-aug2024

September 30–October 2nd, 2024

Introductory GastroPlus® X Workshop
Location: The Universities at Shady Grove, Rockville, MD
Registration: https://simulations-plus.learnupon.com/store/3881633-gpx101ip-introductory-gastroplus-x-workshop-in-person-oct-2024

October 20–23, 2024

PharmSci 360 AAPS Meeting
Location: Salt Palace Convention Center, Salt Lake City, UT, USA
For information, visit https://www.aaps.org/pharmsci/annual-meeting

November 18–20, 2024

Eastern Analytical Symposium and Exhibition
Location: Crowne Plaza Princeton-Conference Center, Plainsboro, NJ, USA
For information, visit eas.org

November 21, 2024

Dissolution Discussion Group Quarterly Online Meeting—Dissolution method development guidance using QbD
Location: DDG Online Meeting at 10:30 am ET
Registration: https://www.agilent.com/chem/dissolution-webinars

March 11–12, 2024

M-CERSI workshop "Role of In Vitro Dissolution Studies for Predictive Insight into In Vivo Performance and Biopharmaceutics Risk Mitigation"
Location: Universities at Shady Grove (USG; Rockville, Maryland), Building II
Registration: www.pharmacy.umaryland.edu/centers/cersievents/2025dissolution

On Demand Events

- ***Simplifying Dissolution Automation with In-Situ Fiber Optic UV***
  https://www.distekinc.com/watch/webinar-simplifying-dissolution-automation-with-in-situ-fiber-optic-uv/
- ***Clarifying 21 CFR Part 11 & Data Integrity Requirements for Dissolution Testing On Demand***
  www.distekinc.com/watch/clarifying-21-cfr-part-11-and-data-integrity-for-dissolution-testing/
- ***Ocular Administration (OCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-ocular-administration-ocat-virtual/
- ***Oral Cavity Administration (OCCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-oral-cavity-administration-occat-virtual/
- ***Pulmonary Administration (PCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-pulmonary-administration-pcat-virtual/
- ***GastroPlus® ADR – 4 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™)***
  https://www.simulations-plus.com/events/gastroplus-adr-4-course-bundle-tcat-ocat-occat-pcat/
- ***GastroPlus® ADR – 5 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™ / Injectables)***
  https://www.simulations-plus.com/events/gastroplus-adr-5-course-bundle-tcat-ocat-occat-pcat-injectables/
- ***Transdermal Administration (TCAT™) in GastroPlus®***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-transdermal-administration-tcat-virtual/
- ***Injectables (IM, SQ, IA) in GastroPlus® Including Biologics and LAIs***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-injectables-incl-lai-biologics-virtual/

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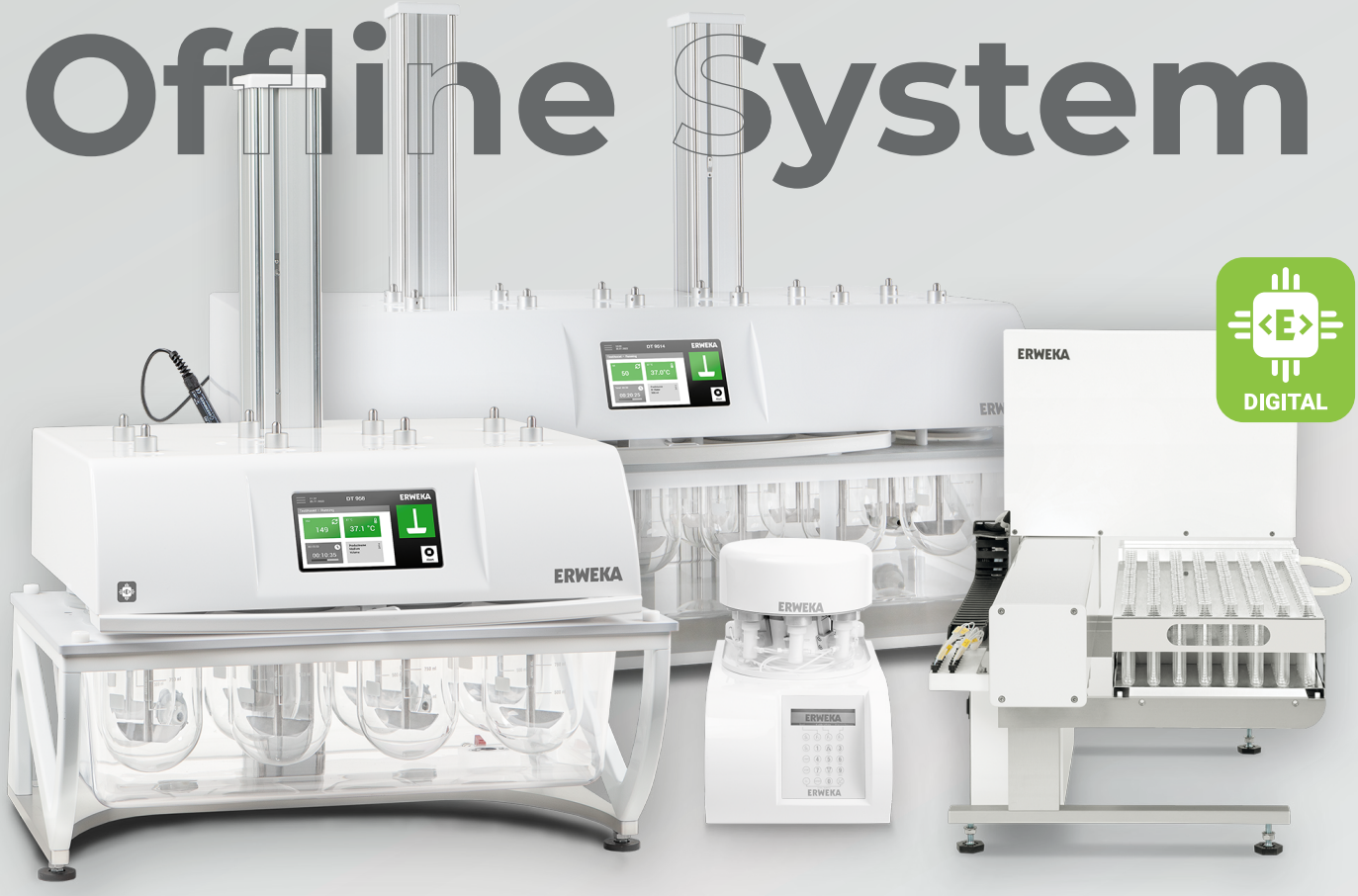

Easy to use dissolution testing with automated sampling.

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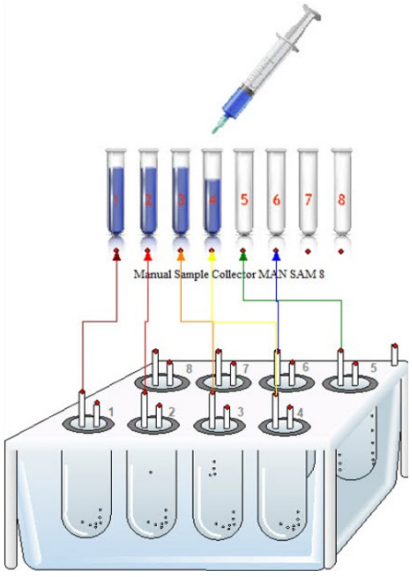
Industry News

IDIS Dissolution Data Management Software Enhances Compliance in Automation

The IDIS Tablet Dissolution software provides an open architecture allowing users to control a wide range of dissolution testers, spectrophotometers with unique HPLC automation. New features in newly released V4 provide greater compliance in automation.

Bath Control

It is now possible to control only the dissolution tester to provide traceability, with acquisition of metadata from the bath at infinitely definable times.



Dissolution Tester USP 711

We introduced a manual sample collector to enable customers to configure audible and written prompts to appear at the sampling times to meet regulatory requirements for sampling.

Automating Spectroscopy Limit Tests

IDIS is now capable of performing spectroscopy limit test and other types of analysis that uses spectrophotometers. These tests can be configured by users in IDIS and the results organized in IDIS reports. This allows spectrophotometers from Agilent, Jena, Mettler, PerkinElmer, Shimadzu, and Thermo to be used for a wide range of laboratory applications when controlled by IDIS.

Windows Active Directory Integration

IDIS users can now be authenticated using windows Active Directory authentication. When used across multiple sites, IDIS networking can search and find IDIS groups to add users into IDIS to perform analysis.

To learn more about Automated Lab Systems, visit our website, www.auto-labsystems.co.uk

For more information, please contact info@auto-labsystems.co.uk

Simulations Plus Releases GastroPlus® X, The Next Generation PBPK/PBBM Modeling and Simulation Software

Redesigned platform offers ease-of-use, enhanced software engineering, and significant productivity gains for users

Simulations Plus, Inc. (Nasdaq: SLP), a leading provider of modeling and simulation solutions for the pharmaceutical, biotechnology, chemicals, and consumer goods industries, has announced the release of GastroPlus® X.

Branded as GPX™, this new platform represents the next generation of physiologically based pharmacokinetics/biopharmaceutics (PBPK/PBBM) modeling and simulation software. Utilizing proven top-rated science, advanced models, refined algorithms, and integrated machine learning (ML) technology, GPX offers an entirely updated user experience with an intuitive interface, streamlined workflows, and faster processing.

"GPX is truly a culmination of a long-term collaboration with our partners to understand how we can better support their program needs and enable critical scientific thinking," said Neil Miller , Vice President of Simulation Sciences at Simulations Plus. "Our development process included significant external user testing, and we sought partners' feedback throughout the entire development cycle. This resulted in a completely redesigned, intuitive, flexible platform that follows our customers' research and thought processes instead of requiring them to fit their processes to the software."

"For more than 25 years, we have remained laser-focused on providing the best science and algorithms on the market. Our commitment to continuous innovation and improvement is why GastroPlus remains the preferred platform for predicting a wide array of applications, including gastrointestinal absorption for oral products, first-in-human outcomes, and food effects," said John DiBella , President of PBPK Solutions at Simulations Plus. "GPX offers increased functionality that other programs cannot provide, such as true polypharmacy simulations mimicking real-world scenarios. We believe the intuitive design, workflows, and data handling will help us expand our addressable market globally by significantly shortening the learning curves for new users, improving the productivity of experienced modelers, and enhancing critical communication with health authorities. As our clients consider the implications of the FDA's newly established Quantitative Medicine Center of Excellence, GPX will provide robust support for their regulatory interactions. GPX is truly the most exciting development in PBPK science to launch in many years."

GPX is designed to be a comprehensive PBPK/PBBM modeling and simulation platform, allowing users to handle everything from early discovery high-throughput PK simulations and drug-drug interactions (DDIs) to population predictions and more all in the same place. Utilization of a single PBPK/PBBM platform, with reusable assets and templates, reduces the time spent on tedious tasks like model setup, importing and exporting data, and reformatting plotted modeling results.

GPX offers flexible deployment options, allowing for both local installation and seamless integration with cloud environments, providing users with the freedom to choose the best setup for their needs.

GPX is available for licensing now. For more information, please contact Renee Bouche at 661-723-7723 or renee.bouche@simulations-plus.com.

Simulations Plus Acquires Pro-ficiency, Creating a One-of-a-Kind Platform Spanning the Drug Development Continuum

Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of modeling and simulation software and services for pharmaceutical safety and efficacy, has announced the acquisition of Pro-ficiency Holdings, Inc. and its subsidiaries ("Pro-ficiency"), a leader in providing simulation-enabled performance and intelligence solutions for clinical and commercial drug development. Simulations Plus acquired Pro-ficiency from QHP Capital, L.P. (management company for NovaQuest Private Equity) ("QHP Capital") and Pro-ficiency's minority shareholders for approximately $100 million in cash.

The transaction expands Simulations Plus' presence across the drug development continuum from establishing pre-clinical protocols to product commercialization, providing pharmaceutical and biotech companies with an end-to-end offering that now includes clinical trial operations, medical affairs, and commercial market launches. Pro-ficiency's suite of software and services, developed with artificial intelligence (AI) technologies, is a highly complementary and synergistic addition to Simulations Plus' platform by expanding its capabilities to enhance clinical trial and launch training, data analytics, and outcomes.

"We are thrilled to announce the expansion of our suite of drug discovery and R&D solutions with this strategic acquisition of Pro-ficiency," said Shawn O'Connor, Chief Executive Officer of Simulations Plus. "This transaction brings together two businesses, each with complementary expertise and services that are grounded in science and focused on applying advanced technologies like AI to enhance actionable data analytics. Together, we will continue to assist our clients in improving their drug development return on investment and patient care delivery. With the integration of Pro-ficiency's immersive simulation-enabled learning, data-driven insights, and medical communications platforms, we are approximately doubling our total addressable market by unlocking the significant growth potential of a $4 billion market opportunity, which is incremental to our $4 billion biosimulation market.

"This acquisition not only deepens our client engagement capabilities and relationships but also presents meaningful cross-selling opportunities to our shared customer base in life sciences. By further expanding our portfolio of critical solutions for efficacious and cost-efficient drug development and commercialization, we believe this acquisition gives us a distinct competitive advantage and will significantly enhance our ability to drive innovation and success within the sector. Furthermore, the transaction is expected to be accretive to our fiscal 2025 EPS," concluded O'Connor.

Michael Raymer, Chief Executive Officer of Pro-ficiency, added, "We are excited to join the Simulations Plus team, which has a well-established and recognized leadership position in modeling and simulations within the pharmaceutical and biotech community. Both teams approached this transaction with a growth mentality. We look forward to leveraging Simulations Plus' specialized offerings and business development infrastructure to expand our combined market reach. Finally, our operations are complementary, our cultures are aligned, and together we believe we can elevate the performance of our mutual clients as well as attract new ones with our end-to-end solutions."

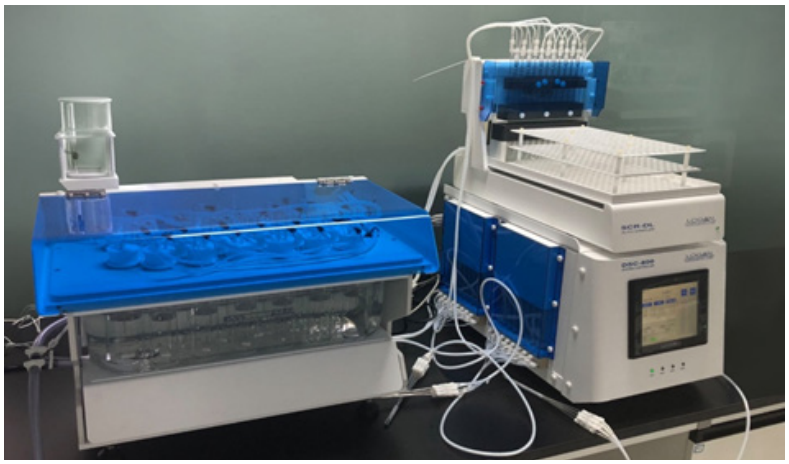
QHP Capital made its original investment in Pro-ficiency in 2021. Pro-ficiency completed the acquisitions of Fugitive Labs, LLC in 2022 and Compass Group Partners in 2023. "We are very pleased with the growth and innovation we have seen these past few years at Pro-ficiency and we are excited to see them continue to improve clinical development as part of the Simulations Plus offering," said Michael Sorensen, Partner at QHP Capital.

For more information, please contact Renee Bouche at 661-723-7723 or renee.bouche@simulations-plus.com.

Logan Instruments Launches Innovative Microsphere Release Testing System

According to the SDi Global Assessment Report 2022, Logan Instruments ranked third in the dissolution testing global market. Logan Instruments specializes in pharmaceutical testing equipment, offering a wide range of products including dissolution testers, physical testing systems, topical/transdermal testing systems, and, increasingly, inhaler testing systems.

Logan Instruments Corp. proudly announces the release of its latest innovation, the **Microsphere Release Testing System**. This cutting-edge product is set to revolutionize the testing and development of microsphere dosage forms, addressing the growing need for advanced drug delivery systems. Microsphere dosage forms have gained significant attention and application in recent years due to their numerous advantages, including improved drug solubility, controlled release, enhanced drug stability, and increased selectivity. These attributes contribute to better patient convenience and adherence, making microspheres an essential component in modern pharmaceutical formulations.



Enhanced Stability: Polymer materials and advanced preparation processes improve the stability of peptide drugs both in vivo and in vitro.

Increased Bioavailability: By reducing metabolism in the liver or gastrointestinal tract, microspheres enhance drug bioavailability.

Targeted and Slow Release: Microspheres can be passively or actively targeted to specific organs, providing prolonged efficacy, and stable blood concentrations.

Non-toxicity and Biodegradability: The polymers used in microspheres are biodegradable, ensuring they are excreted without accumulating in the body, reducing the risk of toxicity.

Improved Patient Compliance: Microspheres reduce the frequency of injections, making medication regimens more manageable for patients.

Microsphere formulations can be used for a variety of drug delivery routes, including nasal, ocular, oral, and non-intestinal. The **Microsphere Release Testing System** is designed to meet the complex and technical challenges associated with the preparation and handling of microspheres, especially in sterile dosage forms.

Logan Instruments' **Microsphere Release Testing System** provides a comprehensive solution for researchers and pharmaceutical companies, offering precision and reliability in the development and validation of microsphere-based drugs. With this new apparatus, Logan Instruments continues to lead the way in advancing pharmaceutical testing technologies.

For more information about the **Microsphere Release Testing System**, please visit www.loganinstruments.com or contact us at infoDT@loganinstruments.com.

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For more information about the NanoDis System, visit: www.agilent.com/chem/nanodis

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