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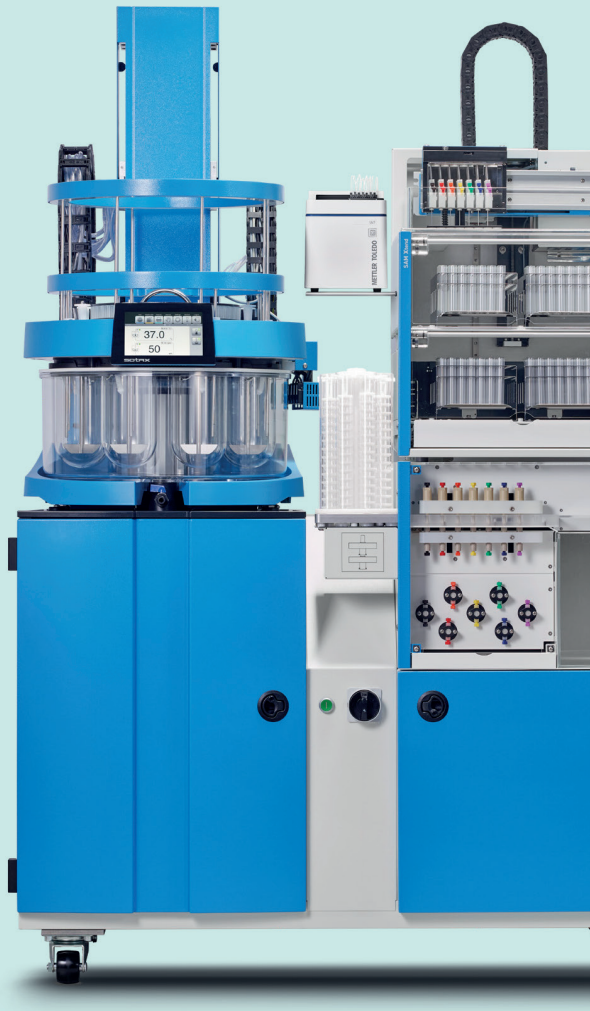

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Topics for the Next Issue

The February 2025 issue will include a *Stimuli* article on the apex vessel, amiodarone and metformin HCl tablets, simulated nasal fluid, highlights from the AAPS annual meeting, and the Q and A feature.

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STIMULI TO THE REVISION PROCESS

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Testing the In Vitro Product Performance of Inhalation and Nasal Drug Products: Views of the USP Expert Panel

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ABSTRACT

While inhalation and nasal drug products are available as various different drug-device combination products for the treatments of local and systemic diseases, their compendial performance testing has concerned with only delivered dose uniformity (DDU) and aerodynamic particle/droplet size distribution (APSD). This *Stimuli* article presents the views of the USP Expert Panel on New Advancements in Product Performance Testing (EP-NAPPT), providing the gap analysis and the recommendations for in vitro product performance testing for these local and systemic drug- device combination products. The gap analysis identified the following performance testing areas to be improved: 1) in vivo-predictive lung and nose delivery testing; 2) fast particle/droplet size testing; 3) spray pattern and plume geometry testing; 4) drug release/dissolution testing; and 5) in vitro product performance and physiologically based pharmacokinetic (PBPK) modeling. Recommendations were then made to each area for identification of testing needs and improved in vivo prediction.

INTRODUCTION

Science and technology in pharmaceutical product development continue to evolve, and many innovative and complex dosage forms have been approved for therapeutic use in patients. Considering the prohibitive costs of drug therapies in many diseases, demand for therapeutically equivalent generic products is also rising. Therefore, careful timely assessments, periodic reviews, and updates are essential to ensure that product performance tests in the USP are sufficient and relevant to support regulatory approvals of such new and generic drug products. As overviewed in the introductory article (*1*), the USP Expert Panel on New Advancements in Product Performance Testing (EP-NAPPT) has been charged to: 1) evaluate current compendial product performance tests; 2) conduct a gap analysis of the current status of product performance testing in USP; and 3) provide recommendations for the adaption of product performance tests and the development of innovative approaches.

Accordingly, the Inhalation and Nasal Drug Product Subcommittee of the EP-NAPPT presents this *Stimuli* article as the fourth article in the series, concerning in vitro product performance testing for inhalation and nasal drug products. The article describes the current USP framework and scope, the recent efforts by the Inhalation and Nasal Drug Product Subcommittee on the USP General Chapters Dosage Forms Expert Committee, EP-NAPPT's gap analysis for the USP product performance testing, and the subcommittee's recommendations.

CURRENT USP FRAMEWORK AND SCOPE

As listed in Table 1, *USP–NF* includes several general chapters on inhalation and nasal drug products (*2*). *Inhalation and Nasal Drug Products— General Information and Product Quality Tests* <5> (*3*) clarifies different types and names of the products and describes their general product quality tests (e.g., identification, assay, content uniformity, leachables, elemental impurities, impurities and degradation products, foreign particulate matter, water and co-solvent content, spray pattern, plume geometry, valve/pump delivery, net fill weight, leak rate, and microbial limits). *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* <601> (*4*) describes the performance quality tests of these drug-device combination products, specifically limited to delivered dose uniformity (DDU) and aerodynamic particle/droplet size distribution (APSD). Chapter <601> (*4*) has most widely been recognized and used to assess drug delivery to, and deposition within, the lung and the nose from the products. *Topical Aerosols* <603> (*5*) concerns drug aerosol products for topical delivery to sites other than lung or nose, such as skin, and thus, is not for inhalation and nasal drug products. The other applicable chapters, *Propellants* <602> (*6*) and *Leak Rate* <604> (*7*) concern propellants and leak tests for aerosol containers respectively, and thus are not performance quality tests. Therefore, unlike oral drug products, performance of inhalation and nasal drug products has been thought to depend only on aerosol or spray delivery and deposition, but not on post-delivery and deposition behaviors or events in the lung and the nose, such as drug release and dissolution.

Table 1. USP-NF General Chapters for Inhalation and Nasal Drug Products

Chapter type	Chapter	Title
General Tests and Assays	<5>	Inhalation and Nasal Drug Products—General Information and Product Quality Tests
	<601>	Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests
	<602>	Propellants
	<604>	Leak Rate
General Information Chapters	<1601>	Products for Nebulization—Characterization Tests
	<1602>	Spacers and Valved Holding Chambers Used with Inhalation Aerosols—Characterization Tests
	<1603>	Good Cascade Impactor Practices
	<1604>	Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Drug Products

Chapters *Products for Nebulization—Characterization Tests* <1601> (*8*), *Spacers and Valved Holding Chambers Used with Inhalation Aerosols— Characterization Tests* <1602> (*9*), *Good Cascade Impactor Practices* <1603> (*10*), and *Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Drug Products* <1604> (*11*) are informational (Table 1). They are useful to assess product quality and performance but are not mandatory for regulatory submissions. Almost identical to its *European Pharmacopoeia* counterpart (*12*), <1601> (*8*) describes the performance tests of products for nebulization, i.e., the measurements of drug delivery rate, DDU, and APSD for aerosol droplets.

Chapter <1602> (*9*) concerns add-on devices used with inhalation aerosols, i.e., spacers and valved holding chambers, and their characterization tests. Chapter <1603> (*10*) is a guide for good cascade impactor practices for quality maintenance; and <1604> (*11*) is a new chapter, currently being drafted, describing how to present APSD measurement data for inhalation drug products. Hence, <1603> (*10*) and <1604> (*11*) both ensure adequate performance testing of APSD described in <601> (*4*).

RECENT EFFORTS BY THE USP INHALATION AND NASAL DOSAGE FORM EXPERT SUBCOMMITTEE

The Inhalation and Nasal Drug Product Subcommittee on the USP General Chapters Dosage Forms Expert Committee has been active in responding to comments made by stakeholders and providing updates and clarifications to the chapters listed in *Table 1* (*13*). Chapter <5> (*3*) has undergone minor changes to its lists for consistency within the *USP–NF*. Chapter <601> (*4*) has had several major revisions, including 1) addition of APSD measurements for nasal aerosols and sprays; 2) removal of Marple-Miller impactor (Apparatus 2) and Multi-Stage Liquid Impinger (Apparatus 4) for APSD measurement; and 3) separation of its data presentation section as <1604> (*13*). Originating in the work by the Product Quality Research Institute (PQRI), <1603> (*10*) was published in 2021 to ensure the maintenance and quality of the cascade impaction equipment. In 2022, <601> (*4*) was revised in *PF* 48(5) (*15*) to provide thorough methodological clarifications in the DDU and APSD measurements including figures and tables. Finally, the joint subcommittee with the USP Statistics Expert Committee is in the process of responding to public comments made to <1604> (*11*) with additional revisions to reflect current FDA practices. Both chapter revisions are expected to appear in the *Pharmacopeial Forum* during 2022 or by the first half of 2023.

GAP ANALYSIS

Inhalation and nasal drug products have now been approved not only for local treatments of lung and nose diseases but also for treatments of systemic diseases, such as diabetes, schizophrenia, Parkinson's disease, migraine, and osteoporosis. Recognizing the need to address gaps in the compendial framework, the EP-NAPPT Inhalation and Nasal Drug Product Subcommittee reviewed these general chapters and their revisions by the USP Expert Subcommittee as well as recent scientific literature on performance testing for inhalation and nasal drug products from a compendial perspective. In addition, the EP-NAPPT Subcommittee also considered the FDA's Generic Drug User Fee Acts Amendments (GDUFA) program and its funding projects to identify more efficient approaches to test bioequivalence (BE) for approval of generic inhalation and nasal drug products (*16*). Following its development by the EP-NAPPT, the Inhalation and Nasal Subcommittee of the USP Expert Committee then reviewed and agreed to this gap analysis.

In Vivo-Predictive Lung and Nose Delivery Testing

For inhalation drug products, the *USP–NF* stipulates only the measurements of DDU and APSD in <601> (*4*) as performance tests (Table 2). In addition to the emitted dose, the total lung dose (TLD) and the fine ("respirable") particle dose (FPD) and/or fraction (FPF) are typically determined from the APSD profiles, alongside the mass median aerodynamic diameter (MMAD) and the measure of spread, e.g., geometric standard deviation (GSD), as described in chapter <1604> (*11*). While these methods were originally intended to ensure product quality, the TLD and FPD or FPF would become clinically meaningful, if predictive of in vivo lung delivery and deposition in humans. However, the 90-degree USP induction port is geometrically far simpler than the internal geometry of the mouth and throat of humans. Moreover, no patients inhale drug aerosols at a fixed inspiratory flow rate, as used in the DDU and APSD measurements (Table 2). Hence, use of in vivo-mimicking mouth-throat (MT) models and/or inspiratory maneuvers (inspiratory flow-time profiles) has been assessed as an alternative to better predict in vivo lung delivery, deposition, and their variations (*17–20*). A variety of "realistic" MT models differing in material and geometry/size (Figure 1) and inspiratory flow profiles of healthy and lung disease [e.g., chronic obstructive pulmonary disease (COPD)] subjects (Figure 2) have been proposed and tested (*18–20*). Even so, improved in vitro-in vivo correlations (IVIVCs) are yet to be formally acknowledged, presumably due to limited and rather imprecise in vivo lung delivery and deposition

Table 2. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Inhalation (Inh.) Drug Products

Dosage Form	Current Performance Test	Limitations of Current Performance Test	Analytical Challenges	Possible Alternatives or Surrogates	Limitations of Possible Alternatives	Recommendations
Inh. aerosol (suspension and solution); and inh. spray	<601> DDU (App- A); APSD (impactor)	• Performance measures (TLD, FPD/FPF, MMAD, and distribution) are not predictive of in vivo lung delivery, deposition, and their variations • Drug release / dissolution is not a subject of performance test[a] • Methods for IVIVC / IVIVR evaluation are not certain	• The USP induction port and the fixed inspiratory flow rate are "not realistic" • In vivo lung delivery and deposition by imaging are highly variable for use in IVIVC / IVIVR • Whether drug release/ dissolution affects in vivo performance is yet to be established[a]	• Use of in vivo-mimicking MT models and inspiratory maneuvers may enable better in vivo prediction • In vivo-relevant respirable aerosol release / dissolution test may enable better prediction of in vivo local and systemic exposure and their changes[a] • Model-based analysis (e.g., PBPK modeling) may be useful to identify critical attributes	• In vivo-predictive performance measures are uncertain • Imprecise in vivo lung delivery and deposition may preclude IVIVC / IVIVR • In vivo predictive release / dissolution test and model-based analysis are work-in-progress; their need is still being debated[a]	• In vivo-predictive MT model and inspiratory flow profiles are to be developed for DDU and APSD tests • In vivo predictive aerosol drug release / dissolution test is to be rationalized and established[a] • Use of the performance measures in modeling and simulation would be a desired goal
Inh. powder	<601> DDU (App-B); APSD (impactor)					
Inh. solution; solution for inh.; (Drug) for inh. solution	<1601> Rate, total mass, and APSD of nebulized aerosols					
Inh. suspension	<1601> Rate, total mass, and APSD of nebulized aerosols; primary PSD					

[a]*Not applicable for Inh. Solution; Solution for Inh.; and [Drug] for Inh. Solution.*

data in humans (Table 2). Scintigraphy-based imaging enables direct assessments of aerosol drug delivery to, and deposition within, the lungs of humans (*21*). However, inter-subject variability of whole and regional lung depositions [e.g., central-to-peripheral (C/P) ratio] is large (up to 80% of relative standard deviations), in part attributed to natural variability of airway geometry (*18, 9, 21*). By contrast, pharmacokinetics (PK)-based prediction of whole and regional lung depositions has been exercised through various PK modeling analyses including physiologically based PK (PBPK) modeling, as discussed in the section below. Even so, such PK model- predicted lung delivery and deposition have yet to be used as reference in vivo human data to validate and establish the methods of in vivo- predictive DDU and APSD measurements. Thus, in vivo-predictive DDU and APSD measurements are useful as in vitro performance tests for inhalation drug products; however, the issue seems to be rather a lack of relevant in vivo human data to properly assess IVIVCs (Table 2).

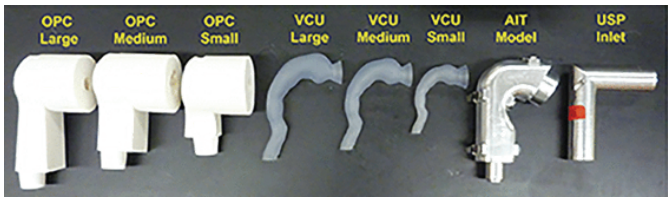

Figure 1. Various "realistic" mouth-throat (MT) models developed to test inhalation drug products, alongside the USP induction port (inlet), for DDU and APSD measurements. OPC, Oropharyngeal Consortium; VCU, Virginia Commonwealth University; AIT, Alberta Idealized Throat. Adapted from (18) with permission of the publisher.

For nasal drug products, DDU and APSD measurements are also performance tests in the *USP–NF* (Table 3). However, it is questionable whether APSD measurements with cascade impactors are valid as a product performance test, recognizing that the majority of particle/droplet size from nasal drug products are ≥10 µm, which exceeds the size measurable with compendial cascade impactors (*22, 23*). Rather, it would assess lung penetration as an off-target, if particles/droplets escaping from nasal deposition accurately enter the cascade impactors. Clearly, however, the 90-degree USP induction port would not capture drugs deposited in the nose; and patients never take drugs from nasal products at a fixed inspiratory/breathing rate (Table 3). Therefore, if the assessment of lung penetration continues to be needed, in vivo-relevant nose-throat models and inspiratory/breathing profiles are to be developed for this cascade impactor-based method. Alternatively, nasal cavity cast models can be used (Table 3). Approximately 40 anatomically relevant nasal cavity cast models that differ in material, modeling process, and geometry/size have in fact been tested by virtue of direct assessments of nasal delivery and deposition from products (*22, 23*). However, to date, no nasal cast model has been endorsed for use in regulation, as IVIVCs remain unproven (*22*). Like lung data, in vivo nasal deposition data in humans are rarely available and, if any, highly variable for use in IVIVC (*22*). Besides, in vivo-relevant inspiratory/breathing flow was not incorporated in the majority of the studies; how to determine and compare whole and regional nasal depositions is uncertain; and the regions of interest within the nasal cavity (e.g., turbinates, maxillary sinuses, and ethmoid regions) for clinical implications are hardly set. Even so, this approach (i.e., a nasal cast model with use of the in vivo-relevant inspiratory/breathing profiles) may be more meaningful as a performance quality test for nasal drug products (Table 3).

Fast Particle/Droplet Size Testing

Use of laser diffractometry (LD) to measure particle/droplet sizes and their distributions is described in <601> for nasal aerosol and spray drug products (Table 3), but

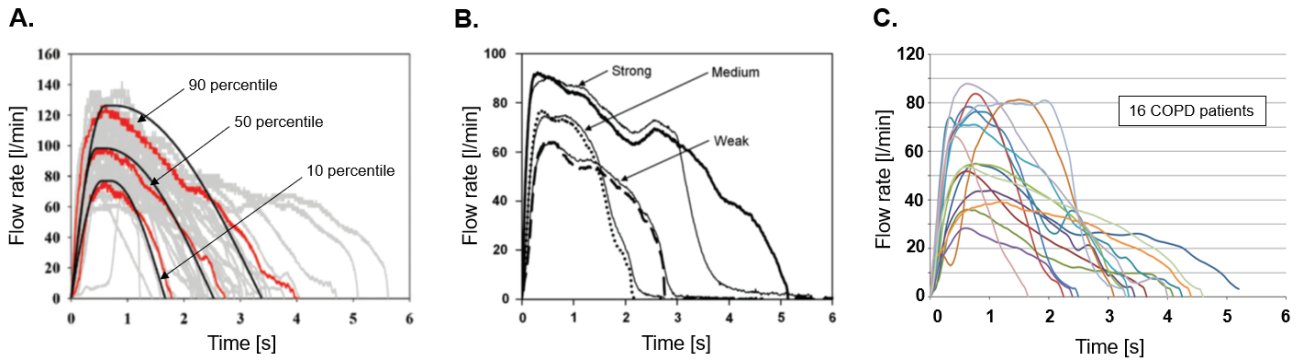

*Figure 2. Selected inspiratory flow rate vs. time profiles used to test inhalation drug products for DDU and APSD measurements. **A.** The 90th, 50th, and 10th percentiles were obtained from 20 healthy adults (18); **B.** "Strong", "Medium", and "Weak" profiles were the 95th, 50th, and 5th percentiles obtained from 74 healthy adults (19); and **C.** each inspiratory profile was obtained from individual COPD patients (20). Although adapted from (18-20) with permission from the publishers, these figures were redrawn by USP, partly since the Subcommittee believed the y-axis ticks on Fig. 2C was mislabeled in (20).*

Table 3. Gap Analysis and Recommendations by USP EP-NAPPT: USP-NF Performance Tests for Nasal Drug Products

Dosage Form	Current Performance Test	Limitations of Current Performance Test	Analytical Challenges	Possible Alternatives or Surrogates	Limitations of Possible Alternatives	Recommendations
Nasal aerosol; nasal spray (suspension and solution)	<601> DDU (App-A); P/DSD[a] (laser diffraction) or APSD (impactor)	• Performance measures (delivered dose, aerosol / droplet size, and distribution) are not predictive of in vivo nose delivery, deposition, and their variations SP-PG[b] is a quality test, but not implicated with performance • Drug release / dissolution is not a subject of performance test[c] • No performance test is listed	• The USP induction port and the fixed inspiratory / breathing flow rate are "not realistic" • In vivo nose delivery and deposition are rarely available and highly variable for use in IVIVC / IVIVR • P/DSD does not measure size of the drug but the formulation[c] • Whether SP-PG and aerosol drug release / dissolution affect in vivo performance is yet to be established	• Use of in vivo-mimicking inlet port and inspiratory / breathing profiles in APSD test may enable better prediction of lung penetration as an off-target • Nasal cast model may enable direct assessments of in vivo nose delivery, deposition, and their variations • MDRS measures drug-specific size and its distribution in nasal suspension, which may be in lieu of a clinical bioequivalence study[c] • SP-PG may be an attribute for in vivo performance • In vivo-relevant drug release / dissolution test may enable better prediction of in vivo local and systemic exposure and their changes[c] • Model- based analysis (e.g., PBPK modeling) may be useful to identify critical attributes	• In vivo predictive performance measures are uncertain • No nasal cast model has been endorsed for use in IVIVC / IVIVR • Imprecise in vivo nose delivery and deposition may preclude IVIVC / IVIVR • MDRS may not be sensitive to the in vivo performance changes; delivery and deposition-dependent outcomes are not examined[c] • SP-PG, in vivo-predictive release / dissolution test and model-based analysis are work- in-progress; their need is still being debated[c]	• In vivo- predictive inlet port and inspiratory / breathing profiles are to be developed for DDU and APSD tests • Nasal cast models need to be examined for regulatory use • MDRS is to be methodologically validated as a performance test[c] • More systematic investigation would be needed to identify critical attributes for nose deposition, including SP-PG • In vivo-predictive release / dissolution test is to be rationalized and established[c] • Use of the performance measures in modeling and simulation would be a desired goal
Nasal powder	<601> DDU (App- B); APSD (impactor)					
Nasal solution	-					

[a]*P/DSD: Particle/droplet size distribution.*
[b]*SP-PG: Spray pattern and plume geometry.*
[c]*Not applicable for nasal spray (solution) and nasal solution.*

not for inhalation drug products (*2*). While the method is much simpler, faster, and less labor-intensive than cascade impaction, careful methodological validation is essential to ensure that the measurements accurately reflect the distribution of drug mass in each size, as delivered to, and deposited within, the lung and the nose (Table 2) (*3, 24, 25*). In reality, however, the method measures the size distributions of particles/droplets that are not necessarily those of drugs due to the possibility of heterogenous drug compositions among the particles/droplets (Table 2 and Table 3). For inhalation aerosols—metered-dose inhalers (MDIs)—drug aerosol particle formation upon actuation is not instantaneous but rather dynamic due to a need for evaporation of propellants and volatile co-solvents (e.g., ethanol), if any. Thus, a location for laser diffraction (LD) sampling from aerosol emission of the products should be rightfully chosen with a proper rationale. Meanwhile, many inhalation powders—dry powder inhalers (DPIs)—formulate physical admixtures of drug and excipients (e.g., lactose); however, size distributions are reported without their distinction, thereby requiring post-sampling data processing to obtain drug-specific size distributions.

Even so, such size distributions are those for the particles/droplets passing through the laser beam, which is just a part of those emitted from the products. Therefore, it is pivotal to ensure that such a partial sampling still represents the entire populations of the particles/droplets for the product. Finally, the LD method measures volume-based size distributions so that APSDs are processed outcomes computed with an assumption of spherical shape and an allocation of a constant density

value, irrespective of particle/droplet size. With all these taken into consideration, the LD method may not be a product performance test in regulation to replace cascade impaction and may rather be suited to screening for formulation and/or device selection during inhalation drug product development. Similar conclusions can also be drawn for the use of other fast size testing methods, such as light scattering, laser Doppler, and time-of-flight methods, although several attempts have been made toward regulatory testing applications (*24, 25*).

For nasal aerosol and spray drug products, the LD method is a *USP–NF* product performance test to measure particle/droplet size distributions "for the delivered plume subsequent to delivery under specified experimental conditions" (*2*). Generally, particle/droplet size distributions are reported with the 10th (D_{10}), 50th (D_{50}), and 90th (D_{90}) percentiles of the cumulative volume-based size distribution, alongside the span of the distribution [$(D_{90} - D_{10})/D_{50}$] and the percentages of particles/droplets in a size <10 µm (to estimate lung penetration) (*2*).

Nevertheless, as is the case for testing inhalation drug products described above, such size distributions may not accurately reflect the distributions of drug mass in each size, especially for suspension aerosol and spray drug products (Table 3) (*24*). Besides, how particle/droplet size distribution and its changes influence regional drug deposition within the nasal cavity and thus, local or systemic therapeutic or adverse outcomes, remain still uncertain (Table 3). After all, particle/droplet size distribution alone is probably not a single independent attribute for regional deposition within the nasal cavity. Spray pattern and plume geometry, orientation/angle and insertion depth of dosing should also be involved as covariates (*24*). Thus, these different measures may need to be systematically understood, with respect to their impact on regional drug deposition within the nasal cavity.

Meanwhile, morphologically directed Raman spectroscopy (MDRS) is an emerging in vitro tool that can be used with suspension nasal spray drug products (*26*). MDRS measures the size and shape of particles in sprayed suspensions using its microscopic component and identifies drug particles by Raman spectra, apart from excipient particles. By so doing, drug-specific particle size distributions can be obtained, potentially as a product performance test (Table 3). Nevertheless, it should be noted that these drug-specific size distributions are not for the assessments of nasal delivery and deposition, but of post-delivery and deposition behaviors/events, such as drug release/dissolution, uptake/absorption, and local and systemic outcomes. The MDRS data were in fact submitted in the abbreviated new drug application (ANDA) for a generic nasal spray product of mometasone furoate suspension in lieu of a comparative clinical BE study (*26*). Subsequently, the FDA revised product-specific guidance for locally acting nasal suspensions, adding recommendations for an alternative approach to BE testing using the MDRS method and other similar advanced methods (*26*). Even so, the MDRS measures drug-specific particle size and its distribution in the entire sprayed formulations, but not those in different droplet sizes sprayed from the product. Hence, the method would not examine delivery-dependent or regional deposition-dependent outcomes, such as local pharmacological actions. Clearly, more experience and evidence would be needed to identify this emerging method for usefulness and thus inclusion as a product performance test for suspension nasal drug products in regulation (Table 3).

Spray Pattern and Plume Geometry Testing

Chapter <5> (*3*) in the *USP–NF* lists spray pattern and plume geometry to assess performance of the delivery system including valve, actuator, and pump, for inhalation and nasal aerosol and spray drug products (*2*). They are characterized by imaging methods with certain outcome measures, such as angle and width of spray plume, and ovality ratio and area of section of spray (*22, 23*). However, like the LD method for size measurements, these outcome measures are based on particles/droplets, but are not necessarily specific to drugs (Table 3). Moreover, these measures have not yet been proven to influence delivery and regional deposition, more than or equivalent to DDU and APSD, especially for inhalation aerosols/sprays. In the *USP–NF*, no general chapter describes the standardized methods for these measurements, although contract-based testing services are commercially available, typically using controlled mechanical actuation and sophisticated imaging analysis. Selection of relevant outcome measures and their acceptance criteria that provide discriminatory capability among products are also in need. Finally, inspiratory/breathing condition is generally absent in these tests, differing from a condition of actual use by patients. In patients, inhalation aerosols/sprays are taken with deep inspiration, and many nasal drug products also recommend inspiration during administration with or without one nostril closed.

For nasal drug products, spray pattern and plume geometry have both been shown to influence regional deposition within the nasal cavity (*21–23, 26*); however,

opinions in the literature differ. A nasal spray product with a wider plume angle (a greater area of spray) resulted in greater deposition in the anterior region of the nasal cast model than that with a narrower plume angle (*27*). On the other hand, wider plume angles paradoxically led to increased posterior nasal deposition for another nasal spray product (*28*). In these studies, however, whether other delivery properties, such as aerosol/spray size and its distribution, and dosing orientation/angle and insertion depth, remained unchanged to properly examine the impact of plume angle is uncertain. In fact, computational fluid dynamics simulation failed to show effects of plume angle on regional deposition within the nasal cavity (*29*). Therefore, it is highly likely that spray pattern and plume geometry are each not a single independent attribute. As discussed above, other delivery properties (aerosol/spray size and its distribution, and dosing orientation/angle and insertion depth) should also be involved as covariates, and therefore, systematic investigation is needed to identify their validity as a product performance test in regulation (Table 3).

Drug Release/Dissolution Testing

In the *USP–NF*, the performance tests for inhalation and nasal drug products are focused on the characterization of drug delivery and deposition from devices to the lung and the nose; and testing of drug release/dissolution is not stipulated, unlike the situation for oral drug products (*2*). To date, no compendial methods are available to test drug release/dissolution for inhalation and nasal drug products (Table 2 and Table 3). In 2008, the Inhalation Ad Hoc Advisory Panel for the USP Performance Tests for Inhalation Dosage Forms concluded through a literature review that compelling evidence suggesting a need for drug release/dissolution tests could not be found (*30*). It was noted though, that a USP standard for assessing drug release/dissolution for inhalation dosage forms may be considered in the future, if scientifically warranted, as a result of the development of novel products with modified or controlled drug release/dissolution (*30*). An interest then emerged in light of the BE assessment for approval of generic inhalation products of locally acting drugs, specifically poorly soluble corticosteroids (*16*). During GDUFA I, FDA supported several research projects to explore in vivo-predictive aerosol particle dissolution test methods for inhalation drug products as potentially more efficient in vitro approaches for BE demonstration (*16*). Attempts and discussions have also been active over the years among scientists and their consortiums and working groups toward the development and establishment of in vitro drug release/dissolution testing for inhalation drug products (*31–34*). Even so, as our knowledge is still limited with respect to the relationship between aerosol drug release/dissolution and clinical therapeutic or safety outcomes, the need and establishment of in vivo-predictive discriminatory drug release/dissolution test methods for inhalation drug products are yet to be substantiated for compendial use (Table 2).

The development of in vitro drug release/dissolution test methods for inhalation drug products is an ongoing research area with an initial focus on poorly soluble inhaled corticosteroids, such as fluticasone propionate (*16, 31–34*). It is important to consider the robustness and validation of the published methodologies that would be required for a standardized performance test method. The design of the test method (e.g., use of whole or "respirable" aerosol particles, or testing under sink or non-sink conditions) and the correlation of its outcome measures with clinical performance measures should be carefully considered as an in vivo-predictive method. Generally, the methods have used either the whole formulated dose or a certain (e.g., "respirable") fraction of the dose collected using cascade impactors or customized deposition/collection apparatus (*31–35*). Modifications were also made for sample introduction to the release/dissolution test systems (e.g., use of aerosol samples collected on filters or direct sample placement in a basket) to ensure reproducible and homogenous dispersion without aggregation or floating (*31–35*). The solvent media for release/dissolution were phosphate buffer, phosphate-buffered saline, or simulated lung lining fluids, and were used with different volumes (*31–35*). Drug release/dissolution of such an aerosolized fraction is recognized to be more likely predictive of in vivo release/dissolution in the lung, although drug aerosol particles with similar aerodynamic size may still exhibit different release/dissolution upon lung deposition due to different particle morphology (*36*). In reality, drug release/dissolution is affected by many factors, such as the size of the particles (as the dissolution rate is inversely related to the radius of the particles; especially for particles within the range of 1.5–10 µm), the drug solubility, the diffusion layer thickness, and the particle shape/morphology. Upon collection, several dissolution test systems have been employed in the literature, such as two-stage impinger, horizontal diffusion cell, static dissolution cell, shaking incubator, paddle dissolution apparatus (USP Apparatus 2), dialysis membranes, flow through cell apparatus (USP Apparatus 4), Transwell system, and Franz cell system and the dissolution model integrated with deposition and cell permeation (*31–35*). Even after this active research, no release/dissolution method has been endorsed for

compendial use as of yet. By contrast, attempts to develop in vivo-predictive release/dissolution tests for nasal drug products are scarce in the literature despite their similar use for poorly soluble corticosteroids.

Nevertheless, similar factors would be expected to be of interest for consideration, while drug release/dissolution of suspension droplets may also need to be assessed for nasal suspension spray products.

Implications of aerosol particle drug release/dissolution for systemic exposure and PK have been shown for poorly soluble corticosteroids; however, their implications for clinical therapeutic and safety outcomes remain unsubstantiated (*16, 31–34*). Hence, given the current advances in local and systemic use of inhalation and nasal drug products, there is an interest in how the GDUFA II program will progress, considering BE testing for approval of generic inhalation drug products. So, whether an in vitro drug release/dissolution test is necessary for these products as well as controlled release products pursued for approval in near future is still formally undecided to date (Table 2 and Table 3).

In Vitro Product Performance and PBPK Modeling

Model-based systemic PK profile analysis has been used to identify critical drug, product, and biological/physiological attributes primarily for systemic actions (e.g., oral drug products). Among several approaches, PBPK modeling is a powerful tool, because its model is physiologically relevant and can incorporate organ-specific parameter sets for healthy subjects or patients with disease, alongside drug properties, delivery, and delivery site-specific biopharmaceutical disposition (*37*). PBPK modeling could also establish a link between in vitro product quality attributes and in vivo clinical performance by IVIVC or relationship (IVIVR). Once this link is verified, critical product quality attributes can be identified to ensure clinical safety and efficacy performances, as expected by product design. Moreover, acceptable variations of such product quality attributes without causing changes in safety and efficacy outcomes could also be examined, which would then in theory enable the establishment of their specifications.

PBPK modeling has been increasingly used for inhalation drug products to understand not only systemic but also local lung exposure of drugs, given that their primary use is for local therapeutic actions (*38–43*). Nevertheless, lung delivery and regional deposition, drug release/dissolution, and lung absorption and disposition for inhalation drug products are highly complex, which makes their interpretations via PBPK modeling extremely challenging, especially for quantitative assessments (Table 2; *38–43*). To date, many different PBPK models have been proposed and all of them have sounded sensible (*38–43*); however, use of the parameter sets derived from the compendial DDU and APSD measurements has yet to be reported. Accordingly, DDU and APSD specifications have been established in most cases, based on the data obtained by experiments with limited batches of the product, from a product quality control perspective, and thus have no implication to clinical performance due to a lack of established IVIVC or IVIVR. Clearly, however, if PBPK modeling could be verified with use of the DDU and/or APSD parameters, DDU and APSD specifications would surely become more meaningful clinically. Likewise, aerosol drug release/dissolution in the lung could be kinetically critical (i.e., rate-limiting), especially for poorly soluble drugs. However, as addressed above, to date, no in vitro drug release/dissolution method has been established to be predictive of in vivo, and thus, incorporation of drug release/dissolution kinetic processes is quite limited in the literature (*42, 43*).

In contrast, support for the use of PBPK modeling for nasal drug products in humans is still scarce in the literature (*44*). However, recognizing that this drug delivery route is used not only for local actions but also for systemic actions, and may notably be used for drug delivery to the brain (*45*), it is predicted that efforts to quantitatively understand critical attributes for efficient local, systemic or brain drug delivery will be increasing through, for example, PBPK modeling (Table 3). Even so, as is the case for inhalation drug products, whether the compendial performance measures (DDU, APSD, and droplet size distribution) and possibly drug release/dissolution measures can be incorporated in such exercises for IVIVC or IVIVR remains uncertain.

Use of PBPK modeling to evaluate bioequivalence and therapeutic equivalence for inhalation and nasal drug products is just on the horizon. While these methodologies have great potential, there are significant knowledge gaps in this area. To address these gaps, FDA has included PBPK modeling in a list of GDUFA science and research policy initiatives since 2020, with a hope to help rationalize critical attributes for product performance and specifications of compendial performance measures (*16*). Thus, there is no doubt that such quantitative rationalization is desired; however, more research should be indispensable, including model verification and sensitivity analysis.

CONCLUSION

Inhalation and nasal drug products are available in a variety of drug-device combination products (e.g., aerosols, sprays, powders, and nebulization) and are approved not only for local treatments of lung and nose diseases, but also for treatments of systemic diseases. At present, DDU and APSD measurements are the performance tests for delivery and deposition in the *USP–NF*. However, the methods are not necessarily in vivo-predictive and, for nasal drug products, may not be valid. Therefore, alternative or additional methods have been exercised, which include delivery and deposition assessments with nasal cavity cast models, fast particle/droplet size measurements (by laser diffraction and MDRS), and spray pattern and plume geometry analyses. Various drug release/dissolution test methods have also been reported as potentially performance tests for inhalation drug products (but not for nasal drug products), with a notion that clinical outcomes of poorly soluble drugs like fluticasone propionate may be compromised due to solubility and/or dissolution after delivery and deposition. Finally, use of PBPK modeling is being extended to inhalation and nasal drug products with a hope to help identify product quality attributes pivotal for local lung or systemic clinical outcomes. This *Stimuli* article is a view of the Inhalation and Nasal Drug Product Subcommittee of the USP EP-NAPPT for each of these product testing methods with a review of the up-to-date knowledge and our recommendations for consideration in compendial use, if and where appropriate. The EP-NAPPT Subcommittee would like to receive valuable comments, suggestions, and opinions from stakeholders to further discuss the outcomes of this review process in the near future.

DISCLAIMER

FDA representatives participated in the USP Expert Panel on New Advancements in Product Performance Testing and in the drafting of this article. FDA's participation in the USP Expert Panel on New Advancements in Product Performance Testing and in drafting this article should not be construed as an endorsement of the approaches outlined in this article. No official support or endorsement by the FDA is intended or should be inferred.

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Demonstrating Discriminatory Power of a Dissolution Method Using DDDPlus: Case Study of an Extended-Release Formulation and Use in Regulatory Justifications

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ABSTRACT

Introduction: Dissolution testing is an important attribute that provides insight into in vivo performance, batch-to-batch uniformity and consistent clinical quality. Demonstrating discriminatory power of the dissolution method ensures that any changes in manufacturing processes or composition can be reflected through dissolution. Although discriminatory power is demonstrated through multiple experiments, modeling software such as Dose Disintegration and Dissolution Plus (DDDPlus) can be utilized. In the present case, for an extended-release formulation containing a class 3 (Biopharmaceutics Classification System) API, the regulatory agency indicated that the dissolution method lacked discriminatory power with respect to polymer content based on pilot test formulations in humans. Although formulations with varying polymer concentration showed differences in in vivo results, the in vitro dissolution were similar. DDDPlus was used to investigate the root cause for the lack of discriminatory power. **Methods:** A DDDPlus model was developed and validated using formulations with different polymer content. Simulated formulations with up to 70% less polymer content were used to test the model, and a cut-off for polymer content resulting in dissolution dissimilarity was determined. **Results:** When the polymer level was less than 50% of the original, similarity failure was observed, but formulations with higher polymer levels achieved similarity. This was attributed to the presence of highly soluble class 3 API in the formulation (> 50% w/w) coupled with a relatively low polymer level (20% w/w). This justification was accepted by the regulatory agency and further re-development of dissolution method was not necessary. **Conclusion:** This work opens new avenues for demonstrating discriminatory power of a dissolution method using software such as DDDPlus, which can reduce analytical workload, increase productivity, and speed up regulatory filings.

KEYWORDS: Discriminatory power, dissolution, DDDPlus, extended-release

INTRODUCTION

Dissolution is an important step that governs drug absorption, bioavailability, and efficacy. Because of this, dissolution testing of dosage forms plays a significant role in characterizing the in vivo performance of orally administered drug products. During the new chemical entity (NCE) development, dissolution testing in multiple pH conditions with biorelevant fluids (e.g., simulated intestinal fluids) is used to understand precipitation behavior and impact of food and/or proton pump inhibitors (PPI) (*1–3*). Subsequently, dissolution testing is used to bridge formulations between various clinical phases, scale-up, and commercial manufacturing (*4*). In the generic product development process, dissolution testing is widely used to establish bioequivalence between innovator and generic formulations and subsequently to support biowaivers and site transfers as well as scale-up and post-approval changes (SUPAC) (*5–7*). When dissolution is coupled with physiologically based pharmacokinetic and biopharmaceutic models (PBPK/PBBM), the results can predict in vivo performance (*7–9*). In addition, quality control (QC) dissolution methods are used during routine manufacturing to ensure product quality and batch-to-batch consistency (*7*).

Discriminatory power is a prerequisite for any dissolution method that is used for QC purposes, which is defined as the ability of the dissolution method to discriminate

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between batches manufactured with different critical process parameters (CPP), critical material attributes (CMA), or critical formulation variables (CFV) that may have impact on bioavailability, i.e., critical bioavailability attributes (CBA) (*10*). During the dissolution method development, discriminatory power is demonstrated through intentional formulation changes and corresponding dissolution evaluation. For example, the impact of active pharmaceutical ingredient (API) particle size, compression force, and polymer concentration on dissolution behavior can be evaluated. An ideal dissolution method should be able to discriminate changes in these parameters. Based on the outcome of discriminatory testing, appropriate ranges can be defined for the variables to assure desired in vivo performance. Recently, agencies such as the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) mandated demonstration of discriminatory power of the dissolution method by through its ability to reject nonbioequivalent batches (*11*). Absence of discriminatory power can result in an inability to detect changes in formulation variables, thus limiting utility of the dissolution method for QC purposes as well as predicting in vivo performance. Although discriminatory power of the dissolution method is routinely established through experimentation, modeling software such as Dose Disintegration and Dissolution Plus (DDDPlus) can be used to simulate experimental outcomes (*12*, *13*). Thus, in the present article, DDDPlus was used to demonstrate the discriminatory power of the dissolution method.

The test product in this study is an extended-release tablet containing an API belonging to class 3 of the Biopharmaceutics Classification System (BCS). The API has a drug load of more than 50% (w/w), with methocel K100M used as rate-controlling excipient (approximately 20% w/w). The regulatory agency indicated that the dissolution method lacks discriminating ability with respect to polymer content, considering the behavior of pilot test formulations in humans. The pilot test formulations resulted in bio-inequivalence (especially the upper 90% T/R ratio); however, no differences in dissolution results were observed. The agency recommended to re-develop the dissolution method and demonstrate discriminatory ability with intentional and meaningful variations of polymer content (±10–20% changes in the specified values). Multiple attempts were made to demonstrate the discriminatory power of the dissolution method, but none were successful. To investigate the root cause for the lack of discriminatory power, DDDPlus was used.

This study aims to demonstrate the utility of DDDPlus in establishing discriminatory power of a dissolution method for an extended-release formulation and for regulatory justification. Using a validated DDDPlus model, a threshold for polymer concentration that can result in a lack of dissolution similarity with pivotal test formulations may be identified, thereby demonstrating discriminatory power of the dissolution method. This approach to demonstrating discriminatory power using DDDPlus is considered novel and may be utilized in regulatory justifications.

METHODS

Materials

The solubility and other characteristics of API are presented in Table 1. The API was obtained from the local market for the determination of solubility. The API was formulated as extended-release formulation using methocel K100M (approximately 18% w/w) at drug load of more than 50% (w/w). All other excipients were conventional excipients such as PVP K-30, colloidal silicone dioxide, magnesium stearate, microcrystalline cellulose, dicalcium phosphate, and croscarmellose sodium.

Table 1. DDDPlus Model Input Parameters

Property	Model Input	Reference
Dosage form	CR polymeric matrix tablet	Controlled-release dosage form
Dimensions of dosage form	Tablet volume: 2.071 cm^3 Tablet surface area: 7.679 cm^2	Based on tooling information, oblong nature of dosage form
Solubility	pH 1.2: 329.6 mg/mL pH 3: 327.8 mg/mL pH 4.5: 326.8 mg/mL pH 6.8 (reference solubility): 329.4 mg/mL	In-house
Other properties	API density: 1.2 g/mL Diffusion coefficient: 1.201 $cm^2/s \times 10^5$ Log P: –0.82	Default values or ADMET Predicted values
Dissolution conditions	900 mL of 50 mM pH 6.8 phosphate buffer USP apparatus 2 at 75 rpm	Quality control media conditions
Dissolution model	Constant porosity model	Suitable dissolution model
Calibration constant	API: 0.0996 Polymer: 1.5	Optimized using reference formulation
Simulation length	600 min	Quality control media dissolution duration

CR: controlled release; API: active pharmaceutical ingredient; USP: United States Pharmacopeia.

The amount of methocel K100M that were used in various formulations for DDDPlus model development, validation, and application are presented below.

- *Model development:* Pivotal and pilot reference formulations – 317.5 mg (18% w/w)
- *Model validation:* Pivotal test formulation: 275 mg (20% w/w), pilot test 1: 280 mg (20.51% w/w), pilot test 2: 317 mg (22.56% w/w), batches manufactured intentionally with –20% polymer (220 mg, 16% w/w) and +20% polymer (330 mg, 24.2% w/w) relative to the pivotal test formulation
- *Model application:* Hypothetical batches manufactured with polymer content of –10% (247.5 mg), –20% (220 mg), –50% (137.5 mg), –60% (110 mg), and –70% (82.5 mg) relative to the pivotal test formulation

Dissolution Studies

Dissolution testing of all the batches was performed for QC purposes with 900 mL of 50-mM pH 6.8 phosphate buffer at 37 °C as the medium, using United States Pharmacopeia apparatus 2 at 75 rpm. Samples (5 mL) were collected at 0, 60, 150, 180, 240, 360, 480, and 600 mins, replaced with fresh medium, and analyzed by high-performance liquid chromatography (HPLC).

The DDSolver, an add-in for Microsoft Excel was used to calculate similarity factor (f_2) values for comparison of dissolution profiles. Twelve replicates were used for similarity factor calculations.

DDDPlus Modeling

DDDPlus (version 6, Simulations Plus, Lancaster, CA), was utilized to simulated in vitro dissolution for all formulations.

Model Development

A detailed modeling workflow for DDDPlus is described in Figure 1. The base model was developed using the input parameters listed in Table 1. The pH vs solubility profile (at pH 1.2, 4.5, 6.8) were input using an spd file. The default value of API density was used, and log P and the diffusion coefficient were calculated using ADMET Predictor (Simulations Plus). Considering the matrix formulation, CR polymeric matrix was selected as the dosage form. Oblong was chosen as dosage form shape, and the dimensions of tablet were entered to obtain tablet volume as 2.071 cm^3 and tablet surface area as 7.679 cm^2. Similar dimensions were utilized for all other trials during model development and validation. The same dissolution conditions were used to mimic QC testing (900 mL of 50-mM pH 6.8 phosphate buffer at 37 °C in USP apparatus 2 at 75 rpm for 600 mins). Constant porosity was selected as dissolution model. The base DDDPlus model was developed with reference formulation by entering the composition into the Formulation tab. During initial model development, calibration constants of the API and polymer were used to achieve the optimal fit between observed and predicted dissolution data.

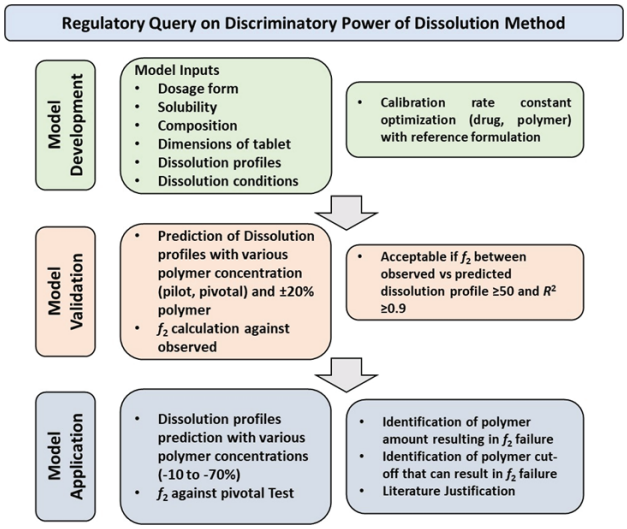

Figure 1. DDDPlus model workflow for demonstrating discriminatory power of a dissolution method.

Model Validation

A model validation exercise was performed with formulations containing different amounts of release-controlling polymer content. The pivotal test formulation (275 mg polymer), both pilot test formulations (280 and 317 mg), and two batches intentionally manufactured with ±20% polymer content (220 and 330 mg) were used. In the Formulation tab, the polymer amount was changed to account for formulation composition change. The simulations were ran, and the validation was performed using two metrics to compare the observed and predicted dissolution values: similarity factor (f_2) and regression coefficient (R^2) (*14*, *15*). Successful prediction is indicated by f_2 greater than 50 and R^2 greater than 0.9.

Model Application

To demonstrate discriminatory power, dissolution profiles were simulated in the validated model using simulated formulation compositions with polymer content of –10% (247.5 mg), –20% (220 mg), –50% (137.5 mg), –60% (110 mg), and –70% (82.5 mg) relative to the pivotal test formulation (275 mg). Similarity factors were used compare the observed and simulated dissolution profiles against the pivotal test formulation. A boundary of polymer content that resulted in f_2 failure with respect to the pivotal test formulation was identified.

RESULTS

Solubility and Dissolution

Across the pH conditions, the solubility values were found to be higher than 300 mg/mL (Table 1). Approximately 3.4 mL of aqueous fluids are required to dissolve a complete dose of 1000 mg, thereby confirming the highly soluble nature of the API. However, the API is formulated as an extended-release formulation controlled by methocel K100M. The release profiles of pilot and pivotal test and reference formulations are provided in Figure 2. The dissolution data indicate that release is controlled over a period of 10 h, after which almost complete release is achieved at the end of the dissolution.

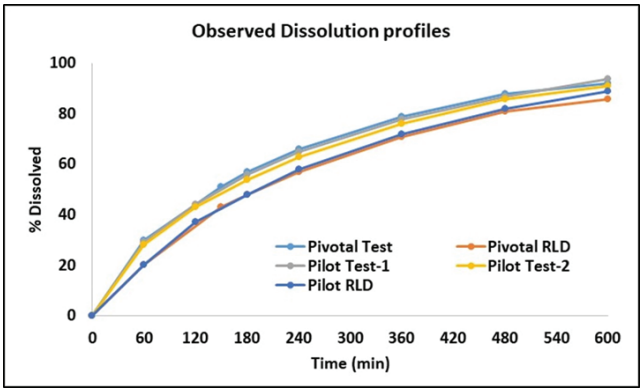

Figure 2. Observed dissolution profiles of various formulations. RLD: reference listed drug.

DDDPlus Modeling

Model Development

Critical aspects such as dosage form and tablet dimensions were considered appropriately in the developed DDDPlus model. The model was developed with pivotal and pilot reference formulations. Initial simulations indicated that the dissolution profiles of reference product were not predicted well and thus it was necessary to optimize the calibration constants of API and polymer. With the optimized calibration constants, the model predicted pivotal reference formulations well, as indicated in Table 2 and Figure 3. For both pilot and pivotal reference formulations, f_2 and R^2 values for the observed versus predicted profiles were considered similar, indicating the suitability of the model.

Model Validation

Results of the model validation exercise with various polymer levels are provided in Table 2 and Figure 3. Across all the predictions, f_2 and R^2 values indicated that the model was valid. Based on the regulatory agency query, additional batches with ±20% polymer content were manufactured, and dissolution profiles were generated. Predictions were performed for these batches as well (available as Supplemental Table S1), and the f_2 and R^2 values were more than 50 and 0.9, respectively, further indicating the validity of the model. Overall, the validation exercise was successful as the model was able to accurately predict dissolution profiles across formulations with varying levels of the polymer content.

Model Application

Results of DDDPlus simulations with varying polymer levels from –10% to –70% w/w are presented in Table 3 and in Figure 4. With decreasing polymer concentration, an increase in the dissolution rate was observed, as expected. When compared to the pivotal test formulation, f_2 values

Table 2. Model Validation for Pilot and Pivotal Test Formulations and Reference Products

Test Formulations												Reference Products							
Pivotal Test Formulation (275 mg polymer)				Pilot Test 1 Formulation (280 mg polymer)				Pilot Test 2 Formulation (317 mg polymer)				Pilot Reference Formulation (317.57 mg polymer)				Pivotal Reference Formulation (317.57 mg polymer)			
Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff
0	0	0	NA	0	0	0	NA	0	0	0	NA	0	0	0	NA	0	0	0	NA
60	30	32	2	60	29	32	3	60	28	31	3	60	20	30	10	60	20	30	10
150	51	51	0	120	44	46	2	120	43	44	1	120	37	42	5	150	43	47	4
180	57	56	-1	180	56	56	0	180	54	53	-1	180	48	52	4	180	48	52	4
240	66	65	-1	240	65	65	0	240	63	62	-1	240	58	60	2	240	57	60	3
360	79	79	0	360	78	79	1	360	76	76	0	360	72	73	1	360	71	73	2
480	88	92	4	480	87	92	5	480	86	87	1	480	82	84	2	480	81	84	3
600	92	100	8	600	94	100	6	600	91	98	7	600	89	94	5	600	86	94	8
f_2 = 83				f_2 = 78				f_2 = 87				f_2 = 65				f_2 = 64			
R^2 = 0.97				R^2 = 0.98				R^2 = 0.98				R^2 = 0.95				R^2 = 0.93			

Obs: observed release data; pred: predicted release data; f_2: similarity factor; R^2: regression coefficient.

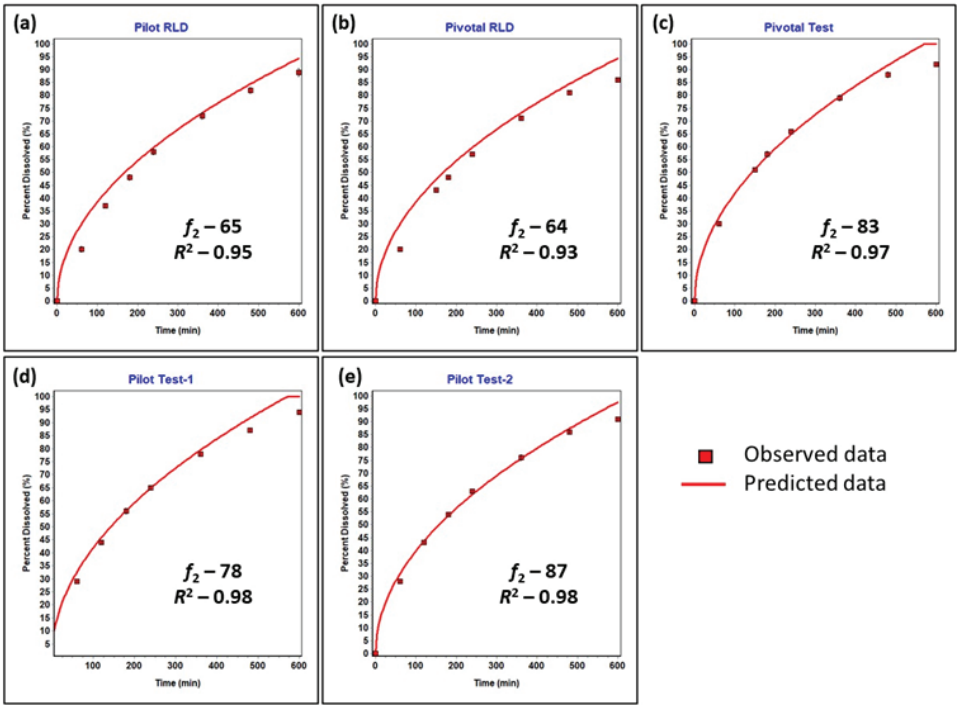

Figure 3. DDDPlus predictions for reference and test formulations. RLD: reference listed drug.

Table 3. Predicted Dissolution Data with Various Polymer Concentrations and f_2 Calculations

Time (min)	Pivotal Test Formulation (275 mg Polymer)			Time (min)	Simulated Formulations (%)				
	Obs (%)	Pred (%)	Diff		–10% polymer (247.7 mg)	–20% polymer (220 mg)	–50% polymer (137.5 mg)	–60% polymer (110 mg)	–70% polymer (82.5 mg)
0	0	0	NA	0	0	0	0	0	0
60	30	32	2	60	33	35	38	39	40
150	51	51	0	150	53	55	60	62	63
180	57	56	-1	180	58	60	65	67	69
240	66	65	-1	240	67	69	76	78	80
360	79	79	0	360	82	85	93	95	98
480	88	92	4	480	95	98	100	100	100
600	92	100	8	600	100	100	100	100	100
f_2 (obs vs pred) = 83				f_2	72 (vs obs) 80 (vs pred)	63 (vs obs) 67 (vs pred)	49 (vs obs) 51 (vs pred)	46 (vs obs) 47 (vs pred)	43 (vs obs) 44 (vs pred)

Obs: observed release data; pred: predicted release data; diff: difference

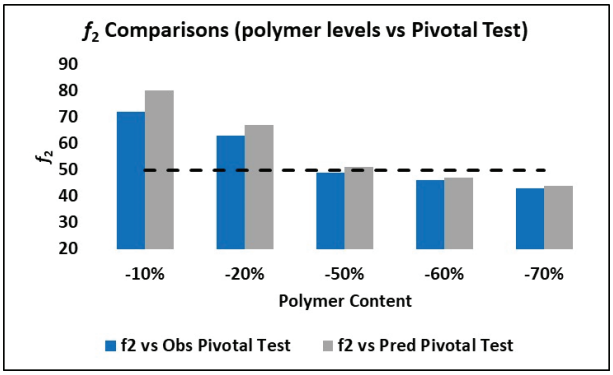

Figure 4. Dissolution similarity analysis between pivotal test and formulations with different polymer content. Obs: observed data; pred: predicted data.

indicated similar dissolution profiles for formulations with up to 20% less polymer content; however, the dissolution profiles were not similar for formulations with 50%, 60%, and 70% less polymer content.

These results indicate that when the polymer level is reduced beyond half of original formulation (i.e., beyond –50%), the dissolution method can discriminate between formulations, but polymer reductions up to 50% could not be discriminated on the basis of dissolution.

DISCUSSION

Demonstrating the discriminatory ability of a dissolution method can ensure manufacturing as well as clinical

quality (*16*, *17*). Identification of critical attributes as a part of discriminatory dissolution testing and integration through PBPK/PBBM modeling is an upcoming area (*10*). Such approaches can aid in development of patient-centric quality standards, thereby ensuring that patients receive drug products with acceptable quality.

In this study, a BCS class 3 API was formulated as an extended-release formulation with methocel K100M as rate-controlling polymer. Like any other controlled-release product, polymer content has been identified as critical attribute that can impact product performance. Although dissolution profiles were similar for the two pilot formulations in humans (Figure 2), some differences were observed in the bioequivalence study results between both formulations, wherein test 2 formulation exhibited slightly higher ratios than the test 1 formulation (Supplemental Table S2). Considering this, regulatory agency indicated that the dissolution method lacks discriminatory power and suggested to re-develop the dissolution method. As none of the formulation trails taken were successful to demonstrate discriminatory ability, a novel approach using DDDPlus was described in this article.

A DDDPlus model was developed using pivotal reference formulation through optimization of calibration rate constants for the API and polymer. The calibration constant is a fitted parameter that enables dissolution model to simulate the dissolution rate and extent for a particular ingredient. Further, constant porosity model was chosen as this options allows to turn on porosity vs time calculations to be off in the polymeric matrix model and assumes constant porosity throughout the dissolution process. The model validation consisted of testing the predictability of the model with various levels of polymers. The model validation results from Table 2 (and Supplemental Table S1) indicated that the observed and simulated profiles are similar, thus confirming the validity of the model. Typically, for PBPK or PBBM models, prediction error is utilized; however, in DDDPlus simulations, the metrics f_2 and R^2 were found to be appropriate and acceptable (*18*).

Using the validated model to demonstrate discriminatory ability, a range of virtual formulations with up to 70% reduced polymer content relative to the pivotal test formulation were simulated. Manufacturing a formulation with 50–70% less polymer content was not possible as tablet could not be formed, thus studying the observed dissolution is not feasible. Because of this limitation, it was not possible to validate the model against a failing result (i.e., failed f_2 vs pivotal test batch). In such cases, designing hypothetical formulations and studying their behavior through DDDPlus is an appropriate choice for demonstrating discriminatory power. When dissolution profiles of these formulations are compared against the pivotal test formulation (observed and simulated), those with less than half of the original polymer content resulted dissimilarity based on f_2 calculation. Thus, the dissolution method is considered to be discriminatory, but only at when the polymer concentration is reduced by half of the original amount and beyond (i.e. beyond -50%).

The reasons for lack of discriminatory power in the dissolution method, in this case at polymer ranges up to –50% of original amount, can be multi-fold. The API is BCS class 3 in nature, with a drug load of more than 50% (w/w) and polymer content of only 20% (w/w). Although drug release is controlled by polymer, a high drug load in a highly soluble API could explain the apparent lack of discriminatory power of the dissolution method. Literature from polymer manufacturer Colorcon also indicated that for a highly soluble drug like Metformin HCl manufactured with methocel K100M or K200M at a drug load of 50% (w/w), dissolution discriminatory power was not observed at polymer levels of 20–30% (w/w). High viscosity grade K200M did not result in a difference in dissolution; hence, the absence of an impact for lower viscosity grade polymer K100M is evident (*19*). These findings are in line with observations made in the present study. Our observations are also in line with other DDDPlus studies that were conducted to simulate in vitro dissolution for establishing IVIVC, develop biorelevant media, and gain mechanistic insight into drug absorption behavior through reduction of lab experiments (*12*, *13*, *20*).

As an additional point of consideration, the regulatory agency's concerns were based on pilot study results of only 15 subjects (Supplemental Table S2), and the upper confidence interval for the test 2 formulation was beyond 125% (leading to bioinequivalence), which needs to be interpreted with caution because wide confidence intervals may not represent actual in vivo variability. It can be seen from the pivotal test formulation study with 30 subjects that the 90% confidence intervals were further narrowed. Thus, there is no significant discrepancy between in vivo results and in vitro dissolution, and the dissolution method is adequate. This justification was accepted by the regulatory agency and redevelopment of dissolution method was not necessary.

Overall, this research is considered to be novel, as it highlights (1) the importance of the dissolution method's discriminatory power during pharmaceutical

development and (2) the application of DDDPlus for regulatory justifications to minimize analytical experimentation and enhance productivity. As an extension, integration of these dissolution data into PBPK or PBBM models can provide insight into in vivo behavior (*21*).

CONCLUSION

In the present work, a novel way of demonstrating the discriminatory power of a dissolution method for an extended-release formulation was developed, validated, and applied utilizing DDDPlus. This work highlights importance of utilizing in silico simulations to reduce the number of experiments, enhance productivity, and speed up regulatory submissions. This approach is particularly useful in cases where formulations cannot be manufactured due to practical considerations, yet dissolution method discrimination needs to be established. When such modeling tools are coupled with strong rationale and relevant literature references, they yield significant insight into dissolution behavior of the drug product. Extension of these dissolution data into PBPK or PBBM models can provide insight into in vivo behavior and correlate in vitro dissolution similarity with in vivo bioequivalence.

SUPPLEMENTAL MATERIAL

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

DISCLOSURES

This study was sponsored by Dr. Reddy's Laboratories Ltd. The authors have no other conflicts of interest.

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Mathematical Model Application for In Vitro Release Kinetics of Ranolazine Extended-Release Tablets

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ABSTRACT

Introduction: Mathematical models are vital tools in understanding drug release mechanisms and release kinetics of different dosage forms, which can be achieved by assessing dissolution release profiles. This study aimed to determine and compare the mechanism of drug release using in vitro data for ranolazine extended-release tablets. **Methods:** Seven formulations of ranolazine extended-release tablets (500 mg) were prepared using a wet granulation technique with matrix-forming polymers. Dissolution tests were conducted in 0.1 N hydrochloric acid using United States Pharmacopeia (USP) apparatus 2 operating at 50 rpm for 24 h. Drug release data were compared using different mathematical models (zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell) in DDsolver. **Results:** Formulation batch F5 and the reference product best fit the Korsmeyer–Peppas model, with a coefficient exponent value of 0.5, indicating Fickian drug release, and Higuchi square root diffusion-controlled mechanisms were noted for both of these formulations, where the fraction of drug released is proportional to the square root of time. **Conclusion:** Having a similar dissolution profile and diffusion-controlled drug release mechanism, formulation F5 tablets are considered interchangeable with the reference product.

KEYWORDS: drug release, mathematical models, dissolution

INTRODUCTION

Dissolution involves the solubilization of a solid substance in a specific solvent, resulting in mass transfer from solid to liquid phase (*1*). Drug release occurs when a drug is converted into the required product formulation and undergoes pharmacokinetic processes, including absorption, metabolism, distribution, and excretion, after appropriate administration via a suitable route, making it available to exhibit its therapeutic action.

IImmediate-release products allow the drug to disintegrate and dissolve without delay; modified-release products are designed to provide prolonged availability of the drug after administration (e.g., delayed and extended release). In the development of new formulations, in vitro dissolution studies are used to depict the drug release profile from pharmaceutical dosage forms (*2, 3*). Quantitative analytical evaluation of drug release from any dosage form is facilitated by applying appropriate mathematical formulas. Kinetic models consider the quantity of dissolved drug (C) from the dosage form over time (t), represented as $C = f(t)$ (*4*).

Ranolazine is used for the treatment of angina, and unlike other anginal drugs such as beta-blockers and nitrates, ranolazine alone does not significantly affect blood pressure or heart rate. Therefore, ranolazine is beneficial for patients with angina who do not achieve the desired response with maximum tolerated doses of other anti-anginal drugs (*5*). Extended-release formulations are used to release ranolazine continuously over a prolonged period, maintaining a therapeutic concentration range in plasma.

Mathematical models assist in evaluating drug release rates and diffusion behavior after administration, reducing the need for extensive experimentation to design effective treatment plans and refine dosing regimens (*6, 7*). These models provide a logical foundation by relating to the mechanism of mass transport associated with controlled drug release, thereby facilitating the rationalization of existing dosage forms and the development of novel forms. Successful drug delivery systems are known for their constituents, alignment, and geometrics. Some models consider the

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combined effects of drug diffusion, dissolution, and drug adsorption onto tablet components, leading to fragmentation into multiple dimensions. Drug release mechanisms are governed by various models, including zero-order, first-order, and Higuchi release by diffusion, Korsmeyer–Peppas release by semi-empirical diffusion, and Hixson–Crowell (cube root) release by erosion (*4, 8*). Statistical analyses are often used to determine the best-fitting mathematical model. Calculating the coefficient of determination (R^2) is a common method to evaluate the suitability of model equations. The model with the highest adjusted R^2 (R^2_adj) considered the best fit and is selected for further study. Other statistical-based methods, such as multivariate analysis of variance, one-way analysis of variance (ANOVA), and calculating the correlation coefficient may also be used for comparing and selecting models (*6, 9*).

In this study, ranolazine extended-release tablets were designed using various polymers in different ratios to achieve 85% release within 20 h with a once-daily dosage. In vitro dissolution behavior and mechanisms of release for the optimized formulations were assessed and compared with a reference product according to the Hixson–Crowell, Korsmeyer–Peppas, Higuchi square root, first-order, and zero-order release models.

METHODS

Materials

Ranolazine was provided as a gift by Natco Pharma Ltd (India). Other excipients used were received as gifts from Aurobindo Pharma Ltd (India), including microcrystalline cellulose (Avicel PH 101 and PH 200; FMC Biopolymer, NY, USA), lactose monohydrate (Granulac 200; Meggle USA, Inc, USA), hydroxypropyl methylcellulose (Methocel K15M and K100 CR; DOW Chemical Pacific Ltd, Singapore), carnauba wax (SP 63 XFP; Strahl & Pitsch LLC), and magnesium stearate (Peter Greven, China). All other ingredients and chemicals used were of analytical grade.

Formulation of Ranolazine Extended-Release Tablets

Formulation of ranolazine extended-release tablets was conducted using a wet granulation technique. Accurately weighed active ingredient and other excipients were mixed geometrically, sifted, and resifted using an ASTM 30 mesh sieve. Purified water was used as the granulation fluid. The wet mass was sifted using ASTM 10 mesh and then dried in a fluid bed processor at 50–55 °C to achieve a loss on drying (LOD) under 2% w/w. The dried granules were sifted using ASTM 20 mesh. The sifted and dried granules were further lubricated and compressed into oval-shaped tablets (16.50 × 6.50 mm) using a 20-station rotary compression machine (EP-400, Elizabeth, India). The compression force was adjusted to achieve tablet hardness between 140 and 180 N (14.276–18.355 kp).

Composition of the ranolazine extended-release tablets is detailed in Table 1. Physical properties of tablets, such as tablet average weight, dimensions (length and width), thickness, hardness, and friability, and chemical properties, such as assay, dissolution, and content uniformity, were evaluated.

Among the various trials of ranolazine extended-release tablets, seven optimized formulation batches were selected for further study based on the extent of release for a once daily dosing regimen using dissolution testing, including solid-state characterization, similarity index (f_2), and mathematical models of drug release mechanisms.

Table 1. Formulation Details of Ranolazine Extended-Release Tablets (500 mg)

Composition (mg)	Formulation Batch Numbers						
	F1	F2	F3	F4	F5	F6	F7
Ranolazine	500.000	500.000	500.000	500.000	500.000	500.000	500.000
Microcrystalline cellulose (PH 101)	37.500	37.500	18.750	37.500	31.250	21.875	12.500
Lactose monohydrate	9.375	9.375	9.375	9.375	9.375	9.375	9.375
Hypromellose (methocel K15M CR)	56.250	-	37.500	34.375	34.375	34.375	34.375
Hypromellose (methocel K100 CR)	-	56.250	37.500	21.875	21.875	21.875	21.875
Carnauba wax	-	-	-	-	6.250	15.625	25.000
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Microcrystalline cellulose (PH 200)	15.625	15.625	15.625	15.625	15.625	15.625	15.625
Magnesium stearate	6.250	6.250	6.250	6.250	6.250	6.250	6.250
Total	625.00	625.00	625.00	625.00	625.00	625.00	625.00

PH: pharmaceutical grade; CR: controlled release; dash (-) indicates not applicable.

Solid State Characterization

The drug substance, along with controlled tablet samples and accelerated stability study samples taken at 6 months (i.e., 40 ± 2 °C/75 ± 5% RH), were analyzed using x-ray powder diffraction (D8 Discover, Bruker, Germany).

Dissolution Method

The dissolution profile of ranolazine extended-release tablets was studied in 900 mL of 0.1 N hydrochloric acid. The dissolution test was conducted at 37 ± 0.5 °C using a United States Pharmacopeia (USP) type 2 (paddle) apparatus (TrustE-14, Electrolab India) operated at 50 rpm. Dissolution samples (5 mL) were collected at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h and filtered with a 0.45-µm membrane filter. To maintain sink conditions, the same volume of fresh dissolution solution was substituted for the collected samples. The samples were analyzed using a UV-visible spectrophotometer (2377, Electronics India) to measure the absorbance at 272 nm, the wavelength of maximum absorption (λmax).

Mathematical Modeling of Drug Release

Various mathematical models were used to characterize the drug release mechanism using in vitro dissolution data and DDSolver (Microsoft Excel add-in, version 1), as described below (*10*). The model with the highest R^2, lowest Akaike information criterion (AIC), and highest model selection criterion (MSC) is considered to be the best fit.

Zero-order model

According to pharmacokinetic principles, the release of a drug from any dosage form can be described by the equation: $Ct = C_0 + K_0 t$, where Ct is drug quantity released at time t, C_0 is drug quantity released at time $t = 0$, and K_0 is the rate constant. The zero-order equation suggests that the drug delivery system releases drug continuously following zero-order kinetics, resulting in a constant drug level in the blood throughout delivery. To determine if the drug release mechanism follows zero-order kinetics, data obtained from in vitro dissolution testing were plotted as cumulative drug release (% w/w) versus time (h).

First-order model

First-order kinetics can be described by the equation: $dC/dt = -K_1 C$, where K_1 represents the rate constant of the first order, expressed per hour. First-order kinetics implies that the reaction rate is directly proportional to the quantity of the drug, resulting in linear release. Rearranging and integrating the equation yields $\log C = \log C_0 - K_1 t/2.303$, where C_0 is initial drug concentration, and C is the percentage of drug residue at time t. To determine if the drug release mechanism follows first-order kinetics, data from in vitro dissolution testing were plotted as the log % of drug residue against time.

Higuchi square root model

In this era of advanced modified-release concepts, the Higuchi square root model has emerged as the most effective (*11*). The Higuchi model is based on the following assumptions: (i) the initial quantity of drug in the drug product is greater than the solubility of the matrix; (ii) perfect sink conditions are maintained; (iii) the diffusivity of the drug remains constant; and (iv) swelling of the polymer is negligible. The Higuchi square root equation is: $Q = A\sqrt{D(2C_0 - C_s)\,C_s\,t}$, where Q is the cumulative quantity of drug release at time t per unit area (A), C_0 is initial drug concentration, C_s is drug solubility in the matrix, and D is the diffusion coefficient of the drug.

This equation effectively describes the relationship in the dosage form until the drug is depleted, and it evaluates dissolution in a general mixed matrix dosage form, where the quantity of drug in the matrix is less than its solubility, and release occurs through a permeable structure. Thus, the equation can be expressed as: $Q = \sqrt{(D\delta/\tau)\,(2C_0 - \delta C_s)\,t}$, where δ represents the matrix porosity, D is the diffusion coefficient of the drug in the solvent, and τ represents the matrix tortuosity. Q, A, C_s, and t have the same significance as mentioned previously. Tortuosity is a measure of the radius in the matrix obtained by dividing the pores and channels. By simplifying the above equation, it can be presented as $Q = K_H \times t^{1/2}$, where K_H is the Higuchi constant of dissolution.

To determine if the drug release mechanism follows Higuchi kinetics, the obtained data were plotted as the percentage of cumulative drug release (Q) against the square root of time, where the slope represents the K_H constant.

Korsmeyer–Peppas model

When the drug release mechanism primarily follows the diffusion approach according to the Higuchi square root model, it is necessary to determine the type of diffusion exhibited by the drug release. The drug release data can be analyzed using the Korsmeyer–Peppas empirical equation: $M_t/M_\infty = Kkp.t^n$, where M_t/M_∞ represents the fraction of drug released at time t. By logarithmic conversion, it becomes $\log(M_t/M_\infty) = \log Kkp + n \log t$. In this equation, M_t denotes the quantity of drug released at time t, M_∞ denotes the quantity of drug released after

infinite time, n represents the exponent of diffusion, and Kkp represents the Korsmeyer drug release constant.

Hixson–Crowell model

The Hixson–Crowell model describes the release of a drug from delivery systems when there is variation in the surface area and the thickness of the particles (tablets) (*2*, *12–14*). According to this relationship, particle size is proportional to the cube root of particle volume. Based on this relation, the Hixson–Crowell equation for drug release from delivery systems is: $K_{HC}t = (W_0)^{1/3} - (W_t)^{1/3}$ where W_0 represents initial drug quantity (t = 0), W_t represents residual drug quantity at time t, and K_{HC} is the constant for Hixson–Crowell that defines the relationship between volume and surface area.

RESULTS AND DISCUSSION

Physical Properties

The physical properties of 500-mg ranolazine extended-release tablets are presented in Table 2. All tablets passed the weight variation test as per *British Pharmacopeia* (BP) criteria for tablets that are batch-formulated (*15*). For tablet weights of 250 mg or higher, no two tablets should deviate by 5% and no single tablet should deviate by 10%. Tablet weight for formulated tablets ranged from 625.3 (624.3–627.8) to 628.1 (622.7–628.9) mg. As per BP, for thickness and diameter (or length × width) values, an acceptable deviation from mean values is 0.02 and 0.06, respectively, and should not deviate by more than 5%. No significant deviation was observed for thickness and diameter within and across trial formulation batches. In addition, all batches were within acceptable limits for friability (< 1% weight loss) and hardness (140–180 N).

Solid State Characterization

The drug substance, along with controlled samples of tablets and accelerated stability study samples taken at 6 months (i.e., 40 ± 2 °C/75 ± 5% RH), were analyzed using the X-RD method. The details of the analysis are ranolazine active ingredient (Drug substance/API- batch no.: 11102440) that exhibits crystalline polymorphic form-I. All tested samples of ranolazine (Control sample tablets, batch no.: T501500; Accelerated stability condition (i.e., 40 ± 2 °C/75 ± 5% RH) and 6-month sample tablets, batch no.: T501500) consistently displayed crystalline polymorphic form-I only, indicating no polymorphic changes during formulation development and accelerated stability study. This minimizes the potential impact on the dissolution study of ranolazine extended-release tablets for further evaluation. The placebo batch no. P001 and Ranolazine standard batch no. WS1500012 were used for evaluation. The X-RD diffractogram for ranolazine is shown in Figure 1, the specific 2θ values obtained were as follows: 5.0747, 9.4872, 10.0242, 10.3704, 12.2540, 12.4977, 13.1542, 14.3537, 15.5913, 16.9239, 19.3507, 19.8194, 21.3927, 22.3922, 23.4267, 24.6624, 25.4281, 26.4974, 27.9187, 30.1472, 31.8108, 32.2975, 33.6066, 34.5555, 35.8669, 37.4801, and 38.6075.

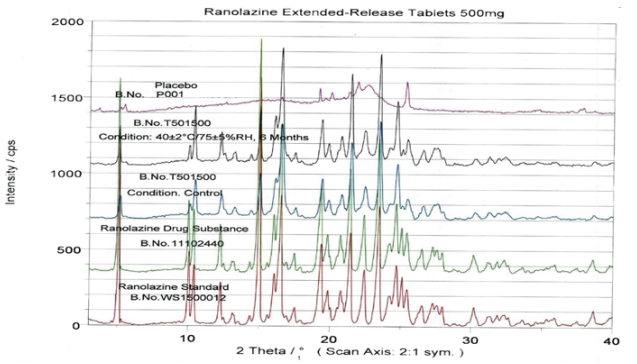

Figure 1. X-ray powder diffractogram shows stability of ranolazine extended-release tablets after 6 months of storage.

Dissolution Profiles

The dissolution profiles for formulation batches F1–F7 and the reference product are shown in Figure 2. The goal was to achieve 85% drug release within 20 h for a once-daily dosing regimen.

Table 2. Physical Properties of Ranolazine Extended-Release Tablets (500 mg)

Tablet Parameters	Formulation Batch Numbers						
	F1	F2	F3	F4	F5	F6	F7
Mean weight, mg (range)	627.4 (623.2– 628.9)	625.3 (624.3– 627.8)	627.6 (623.0– 627.9)	628.1 (622.7– 628.9)	627.2 (623.0–628.3)	626.7 (622.5–628.7)	627.4 (622.5–628.3)
Thickness, mm	4.90–5.16	4.87–5.11	4.85–5.17	4.91–5.14	4.80–5.05	4.91–5.14	4.95–5.28
Length, mm	16.51 ± 0.01	16.52 ± 0.01	16.50 ± 0.01	16.50 ± 0.01	16.50 ± 0.01	16.50 ± 0.01	16.50 ± 0.01
Width, mm	6.52 ± 0.01	6.52 ± 0.01	6.50 ± 0.01	6.51 ± 0.01	6.51 ± 0.01	6.50 ± 0.01	6.51 ± 0.01
Hardness, N	145–180	140–175	140–175	145–170	140–175	140–175	140–160
Friability, %	0.28	0.39	0.24	0.37	0.21	0.17	0.19

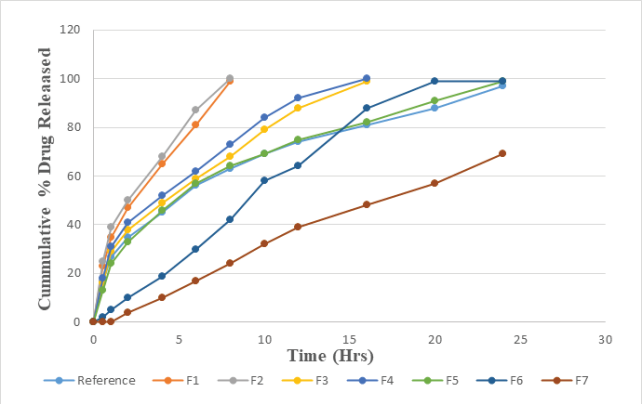

Figure 2. Comparison of in vitro dissolution profiles for the reference product and various formulations of ranolazine extended-release tablets (500 mg).

Ranolazine extended-release tablet batches F1 and F2 were formulated with a single rate-controlling polymer, i.e., hypromellose (Methocel K15M or K100 CR), which exhibited complete release within 8 h, which was not desirable. Batches F3 and F4 were formulated with a 1:1 (F3) and 3:2 (F4) combination of rate-controlling polymers, which exhibited complete release within 16 h.

Batches F5, F6, and F7 were formulated with Methocel K15M CR and K100 CR in a 3:2 ratio and carnauba wax added at 1% (F5), 2.5 % (F6), and 4% (F7). These batches exhibited controlled drug release; however, F7 showed poor release and F6 exhibited very controlled release, but F5 exhibited the required controlled release for 24 h.

In vitro dissolution profiles for batches F5 and F6 were further compared with reference product using the similarity factor index. The calculated similarity factors were 81.95 and 37.33, respectively. Thus, the dissolution profiles for batch F6 and the reference product are not considered to be similar.

Drug Release Mechanism

The suitability of batches F5 and F6 and the reference were checked with various mathematical dependent models (zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell).

As per summary data reflected in Table 3, F5 and the reference product did not fit well with the zero-order model (cumulative drug release vs. time), having a low R^2_adj value F6 had high R^2_adj (0.960), MSC (3.037), and AIC (71.412) values. The first-order model (log cumulative drug remaining vs. time) did not fit well either, having low R^2_adj, low MSC, and high AIC values.

F6 was compatible with the Hixson–Crowell cube root model (cube root of drug remaining vs. time), with high R^2_adj (0.966) and MSC (3.200) values but AIC was not low (69.620). F6 exhibited a small drug release by erosion-controlled drug release as signified by the high R^2. F5 and RP had high R^2_adj (0.983 and 0.971) and MSC (3.918 and 3.342) values but AIC values were not low (55.371 and 60.109).

Table 3. Statistical Evaluation of Goodness of Fit for Various Kinetic Release Models.

Product	Parameter	Zero-order	First-order	Higuchi	Korsmeyer–Peppas	Hixson–Crowell (cube root)
F5	K	5.154	0.134	21.164	24.674	0.036
	R^2_adj	0.475	0.949	0.983	0.993	0.905
	AIC	93.386	67.666	55.371	46.743	74.607
	MSC	0.462	2.8	3.918	4.703	2.169
	n	-	-	-	0.44	-
F6	K	4.84	0.089	18.702	7.608	0.025
	R^2_adj	0.96	0.934	0.872	0.972	0.966
	AIC	71.412	76.884	84.192	68.375	69.62
	MSC	3.037	2.54	1.875	3.313	3.2
	n	-	-	-	0.84	-
Reference	K	5.063	0.132	20.881	26.267	0.035
	R^2_adj	0.345	0.909	0.971	0.997	0.847
	AIC	94.217	72.539	60.109	37.493	78.232
	MSC	0.241	2.212	3.342	5.398	1.695
	n	-	-	-	0.41	-

K: rate constant; R^2_adj: coefficient of determination adjusted; AIC: Akaike information criterion; MSC: model selection criterion; n: exponential coefficient; dash (-) indicates not applicable.

The Korsmeyer–Peppas model (log cumulative % drug released vs. log time) had high R^2_adj values of 0.9943, 0.975, and 0.997 for F5, F6, and the reference, respectively, and high MSC values of 4.703, 3.313, and 5.398, respectively. The model had low AIC values of 46.743 and 37.493 for F5 and the reference, respectively, but F6 had a high AIC value of 68.375.

Aside from the Korsmeyer–Peppas model, the Higuchi square root model had the best fit for F5 and the reference, indicating that drug release was mostly via diffusion (Table 3).

The Korsmeyer–Peppas model exponent coefficient (n) describes the drug release as Fickian and non-Fickian. According to Lokhandwala et al., Fickian (case I) is diffusion-controlled drug release with an n of 0.45, whereas non-Fickian (anomalous) is n greater than 0.45 but less than 0.89; non-Fickian diffusion (case II transport) is n = 0.89, and non-Fickian (super case II transport) is n > 0.89. Drug release may be polymer relaxation/swelling-controlled, whereas anomalous drug release may follow both diffusion and erosion-controlled mechanisms (*9*). In the current study, n values for F5 and the reference were < 0.45, exhibiting Fickian diffusion, whereas F6 had n = 0.84, exhibiting non-Fickian (anomalous) diffusion.

Polymer-developed tablet formulations follow either drug release by diffusion or erosion of the matrix by filling its pores with water (*16, 17*). Hydrophilic polymers like hypromellose, where the matrix is initially penetrated by dissolution media, result in polymer swelling, causing disintegration of polymer linkages, leading to erosion.

Based on mathematical models, F5 and the reference fit the Higuchi square root and Korsmeyer–Peppas models, reflecting Fickian drug release governed by both diffusion (following Fick's law of diffusion proportional to the square root of time) and through a swollen matrix with water-filled pores. F6 fit the zero-order, Hixson–Crowell cube root, and Korsmeyer–Peppas models, showing non-Fickian (case II) drug release and polymer relaxation/swelling-controlled drug release. Anomalous drug release followed both diffusion and erosion-controlled mechanisms.

CONCLUSION

Matrix tablets containing 500 mg of ranolazine were formulated using polymers such as carnauba wax and hypromellose to achieve prolonged or extended-release profiles. The polymorphic form of ranolazine remained consistent throughout the development process, and stability testing indicated minimal influence on dissolution performance. Formulation batch F5 and the reference best fit the Korsmeyer–Peppas model, with a coefficient exponent value (n = 0.45) indicating Fickian drug release, and Higuchi square root diffusion-controlled mechanisms. Thus, Batch F5 and the reference product are considered to be interchangeable.

DISCLOSURES

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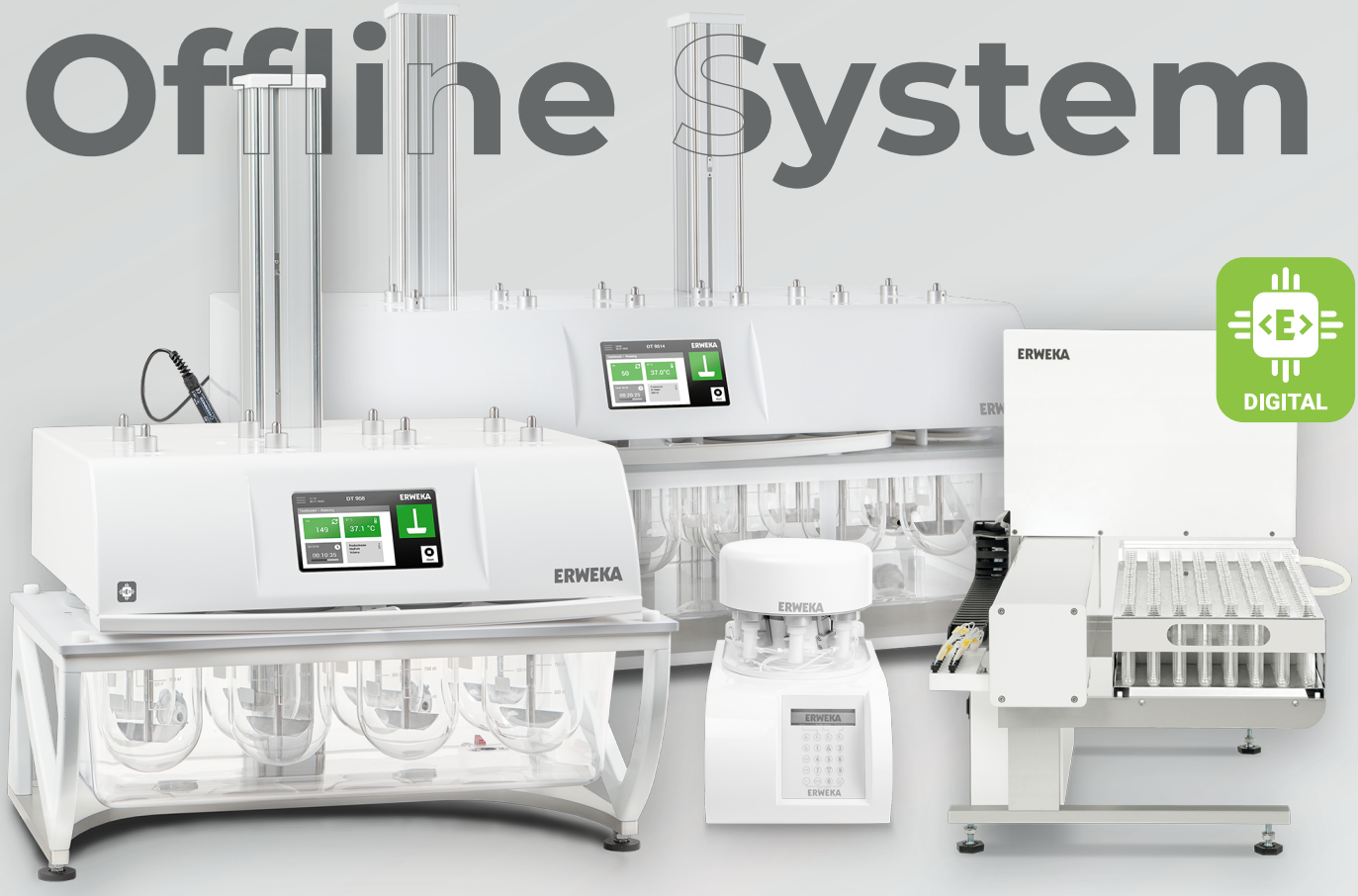

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Comparative In Vitro Release of Eletriptan Hydrobromide Formulations for Buccal Administration

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ABSTRACT

Introduction: Migraine is a neurological disease characterized by unilateral headache attacks that can last between 4-72 hours and accompanying different symptoms such as photophobia, phonophobia, osmophobia, nausea, vomiting, or movement sensitivity. Eletriptan hydrobromide (EHBR) has been recognized as a reliable and efficient treatment for severe to moderate migraine attacks, with or without aura. Buccal drug administration is the most preferred route of administration compared to other alternative routes of administration. Orally disintegrating tablets (ODT), orally disintegrating films (ODF), and in situ gel systems are popular dosage forms that can be used without the need for chewing or water when the medication is taken. With these features, they create important advantages for patients with dysphagia or problems with water intake. **Methods**: ODT, ODF, and in situ gel formulations were developed and evaluated in terms of dissolution profiles. **Results**: For the ODT formulation, more than 85% of the EHBR dissolved within the first 15 minutes. For the ODF formulation, 78% cumulative release was observed in the first 15-minutes. At the end of 4 hours, 93% cumulative drug release of EHBR from in situ gel was observed. **Conclusion**: Based on the results of these dissolution studies, ODT and ODF formulations for treatment of acute migraine attacks provide a rapid effect.

KEYWORDS: Eletriptan hydrobromide, orodispersible tablet, orodispersible film, in situ gel, dissolution

INTRODUCTION

Migraine is a neurological disorder characterized by unilateral headache attacks that can persist for 4–72 hours, accompanied by symptoms such as photophobia, phonophobia, osmophobia, nausea, vomiting, cranial allodynia, or sensitivity to movement. Patients strive for rapid control of all migraine symptoms to mitigate the impact of the condition on their professional, familial, and social obligations. Triptans are the primary treatment option for managing migraines. They function by activating 5-HT1B and 5-HT1D receptors, inducing vasoconstriction (*1*). They are particularly favored for patients who are unresponsive to nonspecific analgesics or experience severe pain, along with nausea and sensitivity to sound and light during migraine attacks, impeding their functionality (*2*, *3*).

Eletriptan hydrobromide (EHBR) was approved by the US Food and Drug Administration (FDA) on December 26, 2002 for the acute treatment of migraines in adults, with or without aura. EHBR is classified as a methylpyrrolidinyltryptamine substituted with a benzene sulfonyl derivative, and it falls under the category of organic compounds known as indoles (*4*). EHBR is a safe and effective solution for managing severe to moderate migraine headache attacks, demonstrating a favorable tolerability profile for both short- and long-term treatment in men and women of all ages. In a placebo-controlled trial focusing on a single migraine attack treated with EHBR, the medication was superior to placebo across all administered dosages (20, 40, and 80 mg) in providing headache relief within 2 hours (*5*). EHBR belongs to class I of the Biopharmaceutics Classification System (BCS), having high permeability and high solubility (*6*). The medication achieves 50% bioavailability after oral administration, with peak plasma concentrations (Tmax) reached within 1 hour. EHBR demonstrates approximately 85% protein binding. The need for an alternative route of drug administration arises due to the significant first-pass effect (*5*).

Although the oral route remains the predominant method for drug delivery, its prevalent limitations have prompted exploration into alternative administration routes. Consequently, the buccal route has garnered significant attention in research. Buccal drug delivery circumvents issues such as the first-pass effect, pre-systemic elimination by the gastrointestinal tract, and potential

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adverse drug reactions. Moreover, the ease of buccal administration positions it as a promising alternative to oral drug delivery, offering a viable option that ensures treatment compliance (*7*). Orally disintegrating tablets (ODT) are solid dosage forms that can dissolve in the mouth without the need for chewing or water when taken orally (8). With these characteristics, they offer significant advantages for patients with dysphagia or difficulties with water intake (*9*, *10*). Oral dispersible films (ODF) rapidly hydrate and dissolve upon placement in the mouth. The active ingredient is promptly released due to the formulations' quick dissolution facilitated by hydrophilic polymers present in ODF. Oral in situ gel, also referred to as environment-sensitive gel, represents an innovative dosage form utilized in drug delivery. Unlike conventional formulations, in situ gels are initially administered as low-viscosity solutions. Under specific environmental conditions, the polymer undergoes a conformational change, leading to gel formation. Consequently, this enhances the contact time and spreadability between the drug and the absorbent area (*4*).

From the patient's perspective, some currently available ODT products are excessively delicate and prone to breakage, whereas ODF formulations are sturdier, offering enhanced ease of administration and improved adherence. Many elderly patients encounter difficulties in swallowing solid dosage forms such as tablets or capsules. Despite ODT being designed for rapid disintegration in the mouth, concerns persist regarding the fear of swallowing solid tablets and the risk of choking, particularly for specific patient populations (*10*). The adoption of ODF has the potential to address the issue of swallowing difficulties and subsequently improve adherence. Moreover, in situ gelling formulations represent drug delivery systems that typically remain in a liquid state at room temperature and transition into a gel state upon application to the body, triggered by various stimuli like temperature changes, pH shifts, or alterations in ionic composition. These systems aim to reduce dosing frequency and enhance therapeutic outcomes for patients; however, developing such highly functional yet intricate dosage forms presents significant challenges (*11*). These innovative dosage forms have the potential to enhance patient adherence. Clinical research findings suggest a preference among patients for orally dissolving dosage forms over conventional solid oral dosage forms. From a clinical perspective, this innovative dosage form shows significant promise in addressing issues of inconvenience (*12*).

In the current study, ODF, ODT, and in situ gel dosage forms containing EHBR for migraine treatment were developed. This study aimed to compare the release of EHBR from these three different formulations.

METHODS

Materials

EHBR was gifted from Ali Raif Pharmaceutical Industry, Turkey. Acetonitrile was of HPLC grade from Merck. Potassium dihydrogen phosphate and ortho phosphoric acid were of analytical grade, also from Merck.

Analytical Method Development and Validation

Analysis and quantification of EHBR was determined using high pressure liquid chromatography (HPLC). The HPLC system used consists of a UV lamp, automatic sampler, degas unit, and column oven (Agilent 1100-1200 series). A C18 column (Kromasil, 250 × 4.6 mm, 5 µm) was used for analyses. For the phosphate buffer, acetonitrile mixture (65:35) was used as the mobile phase; 20 µL of sample was injected into the system at a flow rate of 1 mL/min, and 234 nm was used as the wavelength (*13*).

The HPLC method was validated for specificity, linearity, recovery, precision, repeatability, and stability in aqueous solution according to International Council for Harmonization (ICH) guidelines (*14*).

For linearity studies, stock solution was prepared by dissolving 10 mg EHBR in 100 mL of phosphate buffer. Solutions were prepared at concentrations of 5, 10, 15, 20, 25, and 30 µg/mL, by making the necessary dilutions with phosphate buffer from the stock solution. Three parallel samples were prepared for each concentration. The equation and correlation coefficient of the calibration curve for EHBR were obtained.

A calibration curve was created with solutions prepared at different concentrations. The concentrations of the standards prepared for the calibration curve were 5, 10, 15, 20, 25, and 30 µg/mL.

Samples at three concentrations (15, 20, and 25 µg/mL) were prepared for accuracy and recovery studies. Repeatability was studied by injecting six replicates of the EHBR solution in phosphate buffer at a concentration of 15 µg/mL. Solution stability was evaluated using solutions of EHBR in phosphate buffer at concentration of 15 µg/mL. The solutions were analyzed at 0, 24, and 48 h.

Solubility Study

Low aqueous solubility is the main problem encountered in the formulation development of new active substances, as well as in generic development. In addition, the active substance must be dissolved to be absorbed from the application site. For this reason, we examined the solubility

of EHBR in artificial saliva fluid and distilled water media (15 mL) (n = 6). An excessive amount of active ingredient was added to the prepared media and placed in a water bath preheated to 37 ± 0.5 °C and stirred with a magnetic stirrer. Samples (1 mL) samples were taken at 15, 30, 45, 60, and 90 minutes. The volume of medium was kept constant by adding 1 mL of solvent to the medium. The solubility study continued until a constant field value was reached in the samples taken. Using the area values obtained from the solubility study, the amount of EHBR was calculated using standard curve equations.

Dissolution Studies

Dissolution studies of ODT and ODF were carried out using United States Pharmacopeia (USP) dissolution apparatus type 2 (Varian VK7010).

For in situ gel formulations, studies were performed using a water bath with magnetic stirrer. A calculated amount of in situ gel formulation was placed in a dialysis membrane (12–14 kDa), then the membrane was closed from the top and bottom with the help of clamps.

For all formulations, pH 7.4 artificial saliva (250 mL) was used as the dissolution medium, with a 1-L vessel and a paddle of appropriate size for these vessels. The ambient temperature was set at 37 °C, and the stirring speed was set at 50 rpm. A 2-mL sample was taken from the medium at predetermined time intervals, the same amount of dissolution medium was added to maintain sink conditions. The samples were filtered through a 0.45-µm filter, then the amount of drug was determined with HPLC, and the in vitro release graph was drawn after the necessary calculations were made. The studies were carried out in six replicates.

Kinetic Modeling of Drug Release

Numerous kinetic models are available to characterize drug release from various dosage forms. Given the potential impact of formulation changes on drug release and subsequent in vivo performance, there is a continuous drive to develop tools that streamline product development, minimizing the reliance on extensive biostudies. Hence, leveraging in vitro drug dissolution data to forecast in vivo bioperformance is a rational approach. The in vitro drug release data were fitted into multiple kinetic models including zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson-Crowell to assess the release mechanism. The model demonstrating strong linearity, reflected by a high-value correlation, is deemed the most suitable to characterize the release kinetics of the formulations.

RESULTS AND DISCUSSION

Development and Validation of the Analytical Method

The EHBR calibration curve demonstrated linearity within the specified concentration range of 5–30 µg/mL. The equation of the calibration curve was y = 37.376x + 2.7775, and R^2 = 0.9998 (Fig. 1). Samples of the three given concentrations showed satisfactory recovery of EHBR. For concentrations of 15, 20, and 25 µg/mL, the mean recovery was found to be 101.58%, 100.78%, and 99.86%, respectively (Table 1). Thus, the method was found to be accurate as per ICH guidelines. The precision study results were suitable for guidelines outlined by ICH, demonstrating satisfactory outcomes, as shown in Table 2.

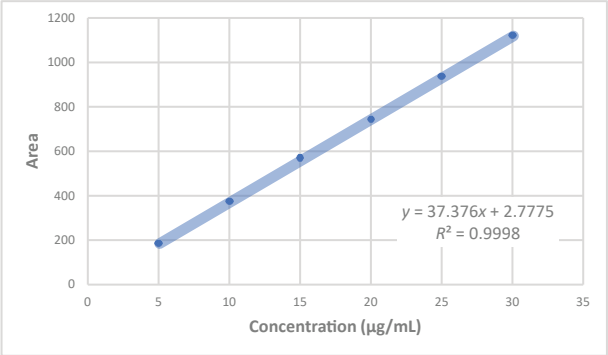

Figure 1. Calibration curve of eletriptan hydrobromide in phosphate buffer solution.

Table 1. Results of Accuracy Studies (n = 3)

Concentration	Sample	Area (AU)	Amount recovered (µg/mL)	Recovery%
15 µg/mL	1	572.43	15.24	101.61
	2	571.00	15.20	101.35
	3	573.46	15.27	101.79
	Average	**572.30**	**15.24**	**101.58**
	SD	**1.24**	**0.04**	**0.22**
	RSD %	**0.22**	**0.23**	**0.22**
20 µg/mL	1	755.63	20.14	100.71
	2	756.53	20.17	100.8
	3	756.49	20.17	100.83
	Average	**756.22**	**20.16**	**100.78**
	SD	**0.51**	**0.02**	**0.06**
	RSD %	**0.07**	**0.09**	**0.06**
25 µg /mL	1	934.97	24.94	99.76
	2	936.12	24.97	99.89
	3	936.62	24.98	99.94
	Average	**935.90**	**24.96**	**99.86**
	SD	**0.85**	**0.02**	**0.09**
	RSD %	**0.09**	**0.08**	**0.09**

RSD: relative standard deviation.

Table 2. Results of Precision Studies (15 µg/mL EBHR in Phosphate Buffer), n = 6.

Sample	Area (AU)	Mean Area (AU)	RSD %
1	572.43	571.71	0.18
2	571.00		
3	573.46		
4	571.07		
5	571.45		
6	570.88		

AU: arbitrary units; RSD: relative standard deviation.

The stability study data showed no noteworthy decrease in the amount of active substance at the end of 48 hours (Table 3).

Table 3. Results of Stability Studies (15 µg/mL EBHR in Phosphate Buffer)

Time	Area (AU)	Concentration (µg/mL)
0 h	566.24	15.08
24 h	552.46	14.71
48 h	548.79	14.61

AU: arbitrary units.

Solubility Studies

Solubility of EHBR in two different solution (distilled water and simulated saliva fluid) was evaluated. Findings were presented in Figure 2. The solubility of EHBR in artificial saliva was found to be substantially higher compared to its solubility in distilled water. This is thought to be due to the ions present in the saliva.

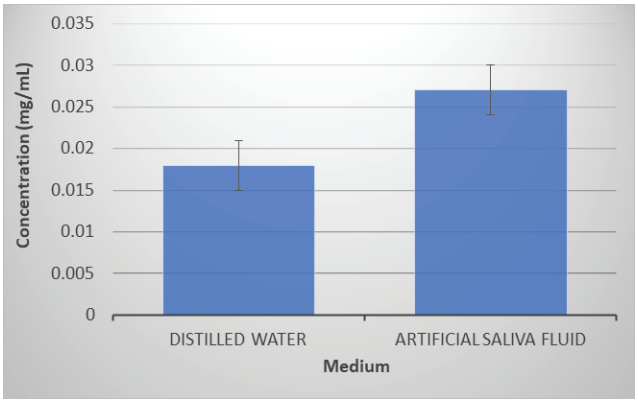

Figure 2. Results of solubility study. Error bars represent SD

Dissolution Studies

Dissolution profiles are presented in Figure 3. For the ODT formulation, more than 85% of EHBR dissolved within the first 15 minutes. These results indicate that ODT formulations can exert their effect rapidly, especially in situations where quick action is anticipated. For the ODF formulation, 78% of EHBR was released in the first 15 minutes, and complete drug release was achieved in 45 minutes.

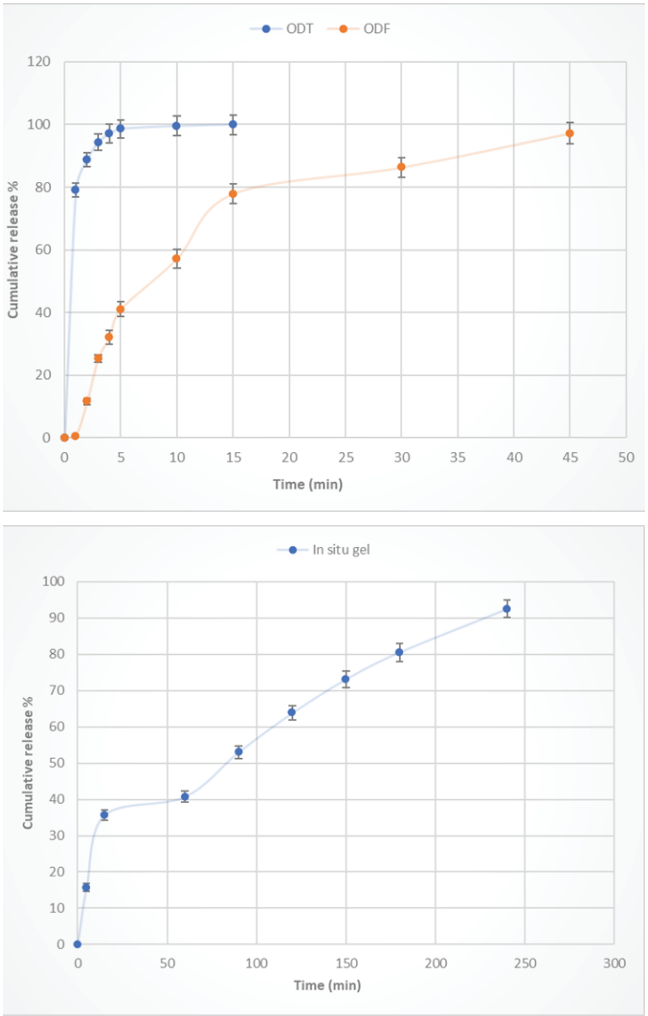

Figure 3. Dissolution profile of formulations for ODT and ODT (top) and in situ gel (bottom). Error bars represent standard deviation of n = 6. ODT: orodispersible tablet; ODF: orodispersible film.

Gel formulations generally exhibit slower drug release compared to colloidal systems. The drug is expected to be released by erosion of the gel system and diffusion from it. At the end of 4 hours, 93% cumulative drug release was observed.

Because ODT includes the use of excipients that can induce fast disintegration, it exhibited the fastest drug release. The results showed that creating a 3D network structure by using a polymer affected dissolution of the drug.

Kinetic Modeling of Drug Release

The dissolution study data were fitted into distinct kinetic models to evaluate their linearity, assessed through regression coefficients. Notably, each of the three formulations (ODT, ODF, and in situ gel) displayed

distinct behavior and mechanisms in drug release (Table 4). Specifically, the findings indicated that the first-order model best described the release kinetics for ODT and ODF, while the Higuchi model exhibited the best fit for the in situ gel.

Table 4. Results of Kinetic Modelling

Kinetic Model		ODT	ODF	In situ gel
Zero Order	R^2	-1.698	0.605	0.768
	k_0	10.305	2.765	0.455
First order	R^2	0.991	0.975	0.907
	k_1	1.442	0.078	0.01
Higuchi Model	R^2	0.132	0.930	0.972
	kH	37.119	15.865	5.934
Korsmeyer-Peppas Model	R^2	0.989	-0.005	0.968
	kKP	83.483	4.238	8.932
	n	0.082	0.656	0.415
Hixson-Crowell Model	R^2	0.059	0.972	0.893
	kHC	0.084	0.025	0.002
Best Fit Model		**Korsmeyer-Peppas**	**First order**	**Higuchi**

ODT: orodispersible tablet; ODF: orodispersible film.

CONCLUSION

This study compared the drug release profiles of ODT, ODF, and in situ gel formulations. Based on the results of these dissolution studies, ODT and ODF formulations for treatment of acute migraine attacks will provide a rapid effect.

ACKNOWLEDGEMENT

The authors acknowledge E. U. Pharmaceutical Sciences Research Center (FABAL) for allowing them to use its laboratory instruments.

DISCLOSURES

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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 We have Peak vessels in our lab and we would like to know if the performance verification procedure (PVT) is applicable to these vessels.

A Peak is a brand name from a specific manufacturer. The generic name of this type of vessel is apex vessel. There is no PVT procedure for apex vessels. The Dissolution Performance Verification Standard – Prednisone tablets was developed specifically for use with Apparatus 1 and Apparatus 2 as described in general chapter <711> Dissolution. The suitability of dissolution equipment should be verified using standard vessels.

Be aware that, as apex vessels are not standardized, their dimensions may vary from one supplier to another. When replacing a broken apex vessel, the replacement should come from the same supplier.

Typically apex vessels are the last option, and their use requires justification obtained with the sample under evaluation. Before using apex vessels simply increasing the rotation speed is a good place to start to see if problems with a dissolution method can be resolved.

Q We are doing a dissolution test with a tablet that has a very low label claim. The dissolution procedure states to use 900 mL of dissolution medium and quantification by spectrophotometric procedure. We are obtaining low absorbance values. Can we change the volume to 500 mL?

A If the dissolution method was developed using 900 mL, you cannot change any of the dissolution conditions without a justification. An alternative way of solving this problem is to use UV-Vis cells with a longer pathlength, like 5 cm or 10 cm. This approach would allow you to obtain higher absorbance values without making any changes to the dissolution procedure.

Q I am doing some research work in tablet disintegration. As it is widely known, tablets and capsules need to disintegrate within 15 and 30 min respectively to pass the USP disintegration test. I would like to know how the 15- and 30-min timing came about.

A The 15- and 30-minute criteria mentioned above is simply a suggestion. Actually, there is no established acceptance criteria for disintegration. The acceptance criterion for disintegration is formulation-dependent and must be justified with data obtained from the samples being evaluated.

Q What are the limits for enzymatic activity of pepsin to be used in dissolution?

A The limits for enzyme activity mentioned in general chapter <711> Dissolution describes the upper limit for enzyme activity in the dissolution medium. Because the activity of enzymes can vary from lot to lot, the activity of any enzyme to be used in dissolution testing must be determined prior to preparing the dissolution medium. Use the procedure referenced for each enzyme in the USP general chapter <711> Dissolution. Using the activity value determined experimentally, the weight of enzyme is calculated to obtain the appropriate activity per unit volume as stated in <711>.

Q USP General Chapter <711> states: "Time: Where a single time specification is given, the test may be concluded in a shorter period if the requirement for the minimum amount dissolved is met. Specimens are to be withdrawn only at the stated times, within a tolerance of ±2%." Is this point applicable for manual withdrawal or for automated sampling? What is the minimum time (single time) considered for the tolerance limit of ±2%., For example, if a single time specification is given at 15 minutes, then it is quite difficult to withdrawal within the specified tolerance limit.

A The tolerance for the sampling time of ±2% is applicable to both manual and automated sampling. If the sample is going to be taken at 15 minutes, the range to start the sampling is 15 ± 2%. Keep in mind that the dissolution process stops only when the dissolving particles are removed from the dissolution media. Consequently, sampling includes both removing the sample from the dissolution vessel and filtering the sample. As a result, early sampling time points can be challenging for both manual and automated sampling methods.

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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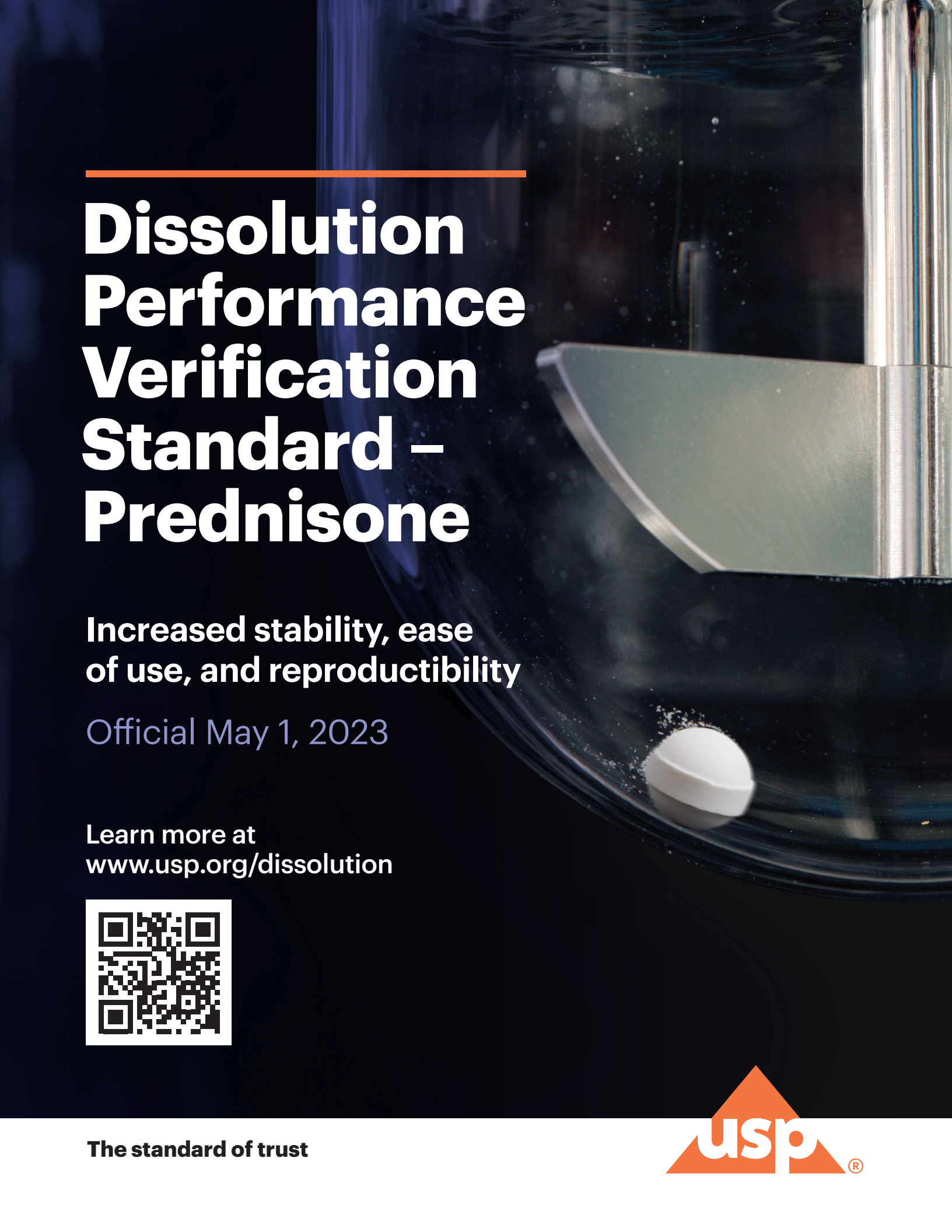

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Calendar of Events

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

November 26, 2024

PKUK Pre-Conference Workshop: Special Populations and DDI in GastroPlus®X
Location: Coppin Beech Hotel, Bracknell, UK
Registration: https://www.simulations-plus.com/events/pkuk-pre-conference-workshop-special-populations-and-ddi-in-gastroplus-x/

December 3, 2024

Complimentary Introduction to GPX™
Location: Online
Registration: https://www.simulations-plus.com/events/complimentary-introduction-to-gpx-3/

December 9–13, 2024

GastroPlus® X Immersive Experience Workshop
Location: Online
Registration: https://www.simulations-plus.com/events/gastroplus-x-immersive-experience-workshop-2/

March 11–12, 2025

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

- ***Fiber Optic UV: Better Dissolution Testing On Demand***
  https://www.distekinc.com/watch/fiber-optic-uv-better-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/
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Logan Instruments appoints Keith Hamman as President and CEO

October 7th, 2024

Somerset, NJ - Logan Instruments Corp. (Logan), a global provider of pharmaceutical formulation development and QC instruments used for studying API drug release characteristics of solid, semi-solid, transdermal, ophthalmic, suspensions, inhalation, and other critical dosage forms, has appointed Keith Hamman the new President and CEO. Mr. Hamman previously served as the Vice President and General Manager of Teledyne LABS and prior to that as President and COO of Hanson Research Corporation.

"With nearly 20-years of leadership experience serving the global pharma industry with high quality instrumentation, and a proven track record of putting customer needs first, Keith will drive Logan through the next growth phase and give us the fresh leadership perspective that we need," said Dr. Luke Lee, founder and former CEO. "I'm especially enthusiastic about our strategy of addressing more of the mature markets of the US & Europe while simultaneously providing a full suite of cost-effective products that serve the emerging markets of Asia, Middle East, Africa, and Latin America."

With the addition of Mr. Hamman, Dr. Lee will shift his focus away from day-to-day operations and serve as the Executive Chairman and Chief Engineer focused on the R&D technology pipeline to better support the changing dynamics in the pharma and biopharma spaces.

"I'm beyond thrilled to join Logan and carry the torch that Dr. Lee lit back in the 80s when he pioneered most of the technologies that are still used today. It's rare to find such a great, mature company that hasn't lost their entrepreneurial spirit and desire to accelerate growth by helping to improve the quality of medicines for all mankind," said Mr. Hamman.

About Logan Instruments Corp.

Headquartered in Somerset, NJ (USA) with manufacturing operations in NJ and multiple sites in Shanghai, China, Logan was founded in 1990 by Industrial Designer / Engineer Luke Lee and currently designs, manufactures, sells and supports high quality USP Apparatus 1-7 dissolution instruments; tablet disintegration, friability, and hardness testers; topical & transdermal diffusion and permeation testers; inhaler testers; nanoparticle & microsphere testers; as well as other tools for the pharmaceutical, biopharma, contract research, academia, government, and industrial research laboratory environments.

For more information on Logan's products and services, visit www.loganinstruments.com

Press inquiries: info@loganinstruments.com

Simulations Plus and the University of Southern California Secure NIH Grant to Develop New AI Drug Discovery Offerings

Partnership will advance the field of ligand-based virtual screening to improve drug design and optimization activities

Lancaster, CA - Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of biosimulation, simulation-enabled performance and intelligence solutions, and medical communications to the biopharma industry, announced the award of a new research grant from the National Institutes of Health (NIH), secured in partnership with the University of Southern California (USC) Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences. The grant will be used to evaluate novel computational methods that account for water-ligand interactions in drug discovery and that integrate with the Artificial Intelligence-driven Drug Design (AIDD) module in ADMET Predictor® to offer a first-of-its-kind ligand-based virtual screening (LBVS) solution for pharmaceutical companies.

For this award, Dr. Ian Haworth, Associate Professor and Vice Chair of Pharmacology and Pharmaceutical Sciences at the USC Mann School, and his lab will apply their previously developed algorithm (WATGEN) for the prediction of water positions in the unbound protein and protein-ligand complex. With support from the data scientists and software engineers at Simulations Plus, they will apply machine learning (ML) approaches to predict the pharmacophore features that will be used in ADMET Predictor's proprietary 3D shape and feature matching algorithm.

"Identifying chemicals with shapes and characteristics similar to those that bind drug targets has been invaluable in drug discovery and development. However, the retention or displacement of water molecules during formation of the protein-ligand interface plays a significant role in determining ligand binding. This has often been overlooked in existing software programs, including LBVS algorithms," said Dr. Noam Morningstar-Kywi , Scientist II at Simulations Plus and a key investigator for this grant. "Our goal is to develop new approaches that combine ML and validated 3D-based calculations to incorporate these essential water molecules into LBVS, enhancing current methods and enabling researchers to accelerate the discovery of better and more effective drugs."

Dr. Haworth added, "We will harness the power of structure-based approaches, including the detailed information of protein-ligand and protein-water interactions, and combine them with the speed and accuracy associated with ligand-based similarity scoring methods. This project is a powerful collaboration between industry and academia that drives research from the lab into real-world applications, promising exciting, tangible results that could transform the field."

The team at Simulations Plus will productize the updated methods into the ADMET Predictor platform and validate it by designing drugs against defined targets using the AIDD module. Selected compounds will be synthesized and tested experimentally to highlight the technology's applications.

"As a drug discovery scientist, I am particularly excited to apply the NIH funding towards this innovative technology to design and test new compounds against several clinically relevant targets. We have the potential to dramatically reduce the Design-Make-Test-Analyze (DMTA) cycle of drug discovery," said Dr. Jeremy Jones , Principal Scientist at Simulations Plus and principal investigator for this grant. "We are committed to driving impactful advancements that benefit our stakeholders and the global communities we serve, and we eagerly anticipate future collaborations that continue to create value and foster growth."

Simulations Plus Announces New Research Project with International Collaboration on Cosmetics Safety

Objective: Define best practices for use of novel PBK modeling strategies to support animal-free safety assessment of new chemicals

Lancaster, CA - Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of biosimulation, simulation-enabled performance and intelligence solutions, and medical communications to the biopharma industry, announced a newly funded research project with the International Collaboration on Cosmetics Safety (ICCS) to evaluate the use of physiologically based kinetic (PBK) modeling approaches to advance animal-free science for cosmetics and other non-pharmaceutical ingredients.

In a competitive bidding process, Simulations Plus was selected for its proposal to establish workflows for probabilistic PBK modeling of new chemicals based on pharmacokinetic (PK) analogs. Simulations Plus will review ICCS-provided data, select target-source pairs based on similarity criteria, build PBK models for source chemicals, and apply these in virtual populations to predict exposure for target chemicals. The results and best practices will be published.

"We are excited to partner with ICCS and its membership, which includes major cosmetics and consumer product companies, ingredient suppliers, trade and research organizations, and animal welfare NGOs. Our mutual goal is to expand the use of PBK models for the safety assessment of new chemicals developed in an animal-free paradigm," said Dr. Priyata Kalra , Senior Scientist at Simulations Plus and principal investigator for this collaboration. "Using data from ICCS, we will collaboratively develop a PBK-based read-across concept for various chemicals and exposure routes (intravenous, oral, dermal) across virtual populations of different species (humans and rodents). This partnership is expected to result in general workflows and guidance for implementing this approach in animal-free safety assessments."

"We have pioneered the integration of machine learning with PBK models, coupled with limited in vitro data, to accurately predict safety exposure levels in animals and humans," added Dr. Maxime Le Merdy , Director of PBPK Research and Collaborations at Simulations Plus. "We believe our expertise in this space, combined with ICCS's commitment to advancing animal-free research and development, will help drive innovation in the non-pharmaceutical markets we serve. As a recognized global leader in modeling and simulation, we look forward to collaborating on this important research project that will help establish best practices and a comprehensive framework as valuable guidance tools for companies and regulatory agencies."

Simulations Plus Releases ADMET Predictor® Version 12

Enhancements in key models power HT-PBPK simulations and AI-driven drug design with unprecedented performance and accuracy

Lancaster, CA - Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of biosimulation, simulation-enabled performance and intelligence solutions, and medical communications to the biopharma industry, announced the release of version 12.0 of ADMET Predictor® (AP12), its flagship machine learning (ML) modeling platform for the discovery, design, and optimization of new molecules.

AP12 includes:

- **Enhanced Models** : New and expanded models offer greater predictive accuracy, with an average 30% increase in training set sizes, for microsome and hepatocyte clearance, protein binding, biorelevant solubilities, MDCK-LE/PAMPA permeability, and more.
- **High-Throughput Pharmacokinetics (HTPK)** : New options for solution dosing, adjusted free fraction outputs, and species-specific simulations enhance the flexibility and precision of HTPK studies.
- **Artificial Intelligence-Driven Drug Design (AIDD)** : Integration of 3D shape matching and tissue sensitivities (based on tissue Kp values) as new objectives, facilitating innovative lead optimization processes.
- **New DILI Module** : Introduction of the first drug-induced liver injury (DILI) endpoint models to support high-throughput (HT) DILIsym® predictions in early drug development.
- **Boosted ANN Regression Models** and 37 new descriptors in ADMET Modeler™.
- **General Usability and Informatics Improvements.**

Dr. David Miller, Vice President of Cheminformatics said: "ADMET Predictor 12 features substantial advancements in the critical components required to build high-quality machine learning models. This upgraded version integrates new premium data, novel descriptors, and robust algorithms that will increase our customers' ability to predict with confidence. These enhancements reinforce our commitment to providing state-of-the-art tools for the scientific community."

"Based on feedback from our customers, we are improving the accuracy of essential models as well as extending the software's capabilities for integration and automation within existing workflows," added Dr. Eric Jamois, Director of Key Accounts and Strategic Alliances. "The advances embedded in AP12 deliver downstream benefits in HTPK, AIDD, and now, HT-DILI. We are constantly innovating to take drug discovery research to the next level and are very excited to introduce this new version to our growing user community."

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DISSOLUTION

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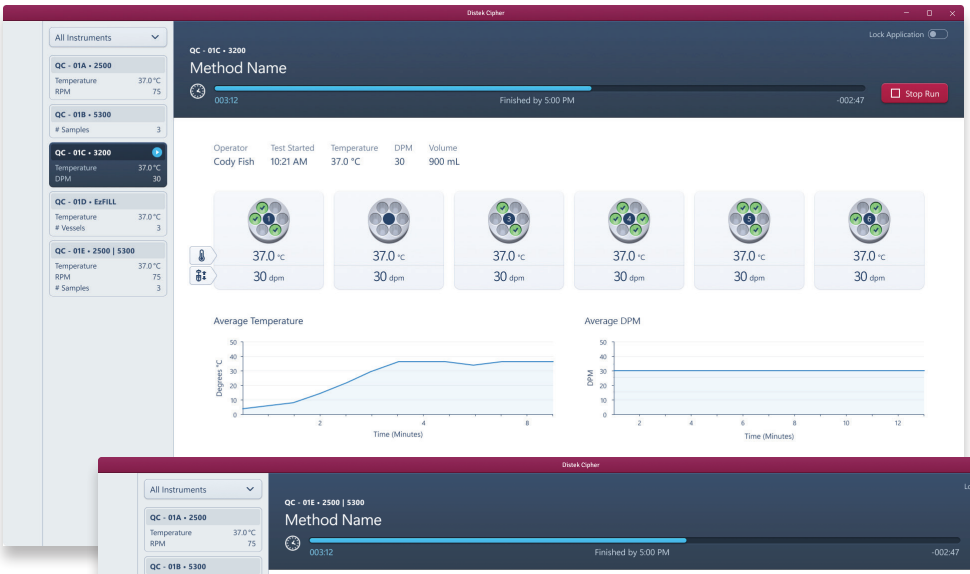

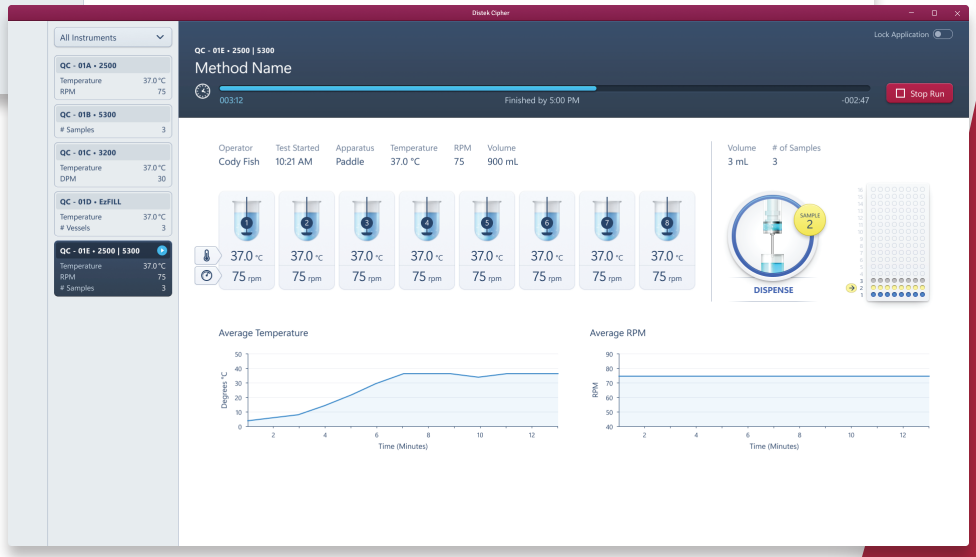

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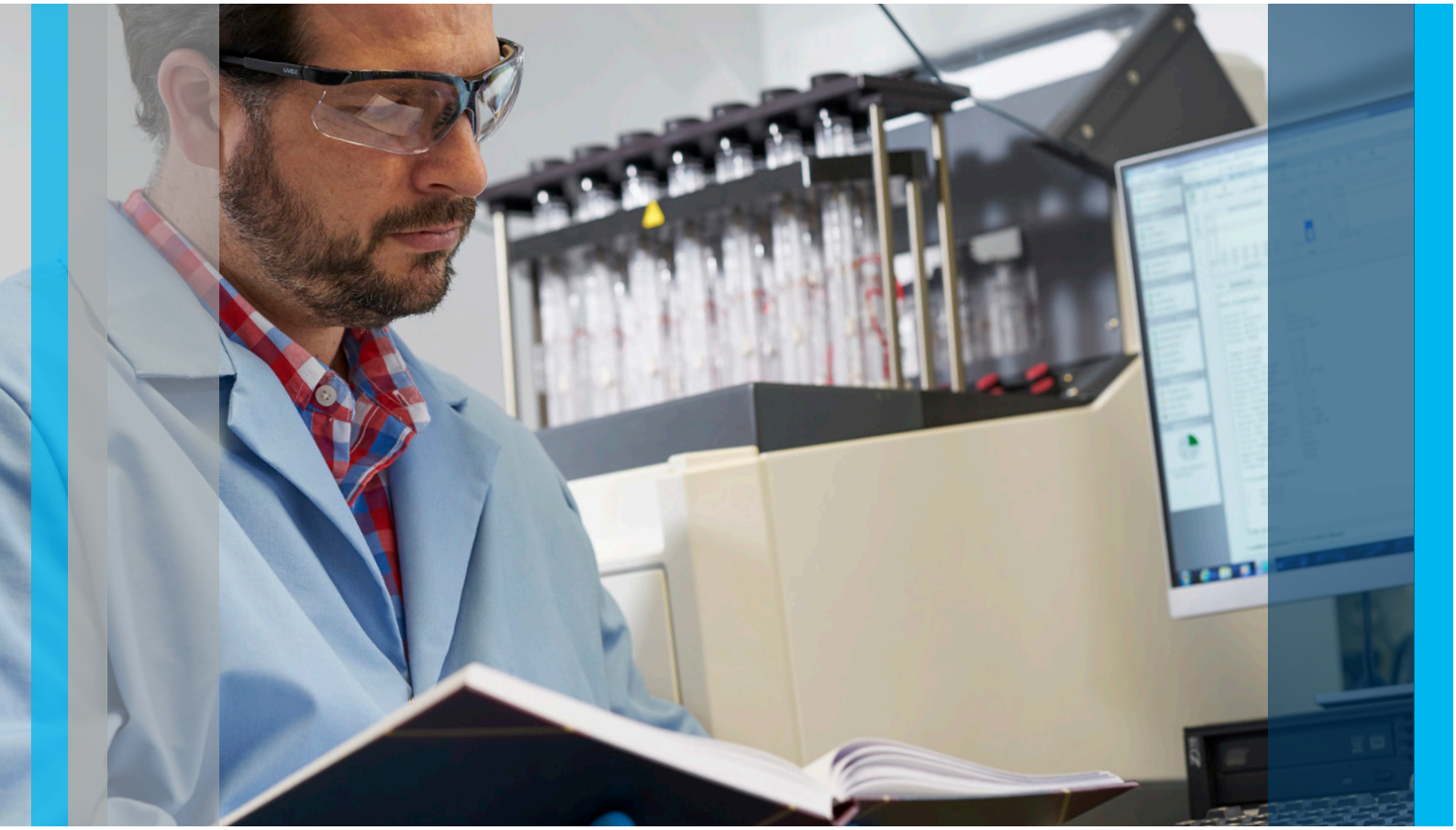

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