Dissolution Technologies

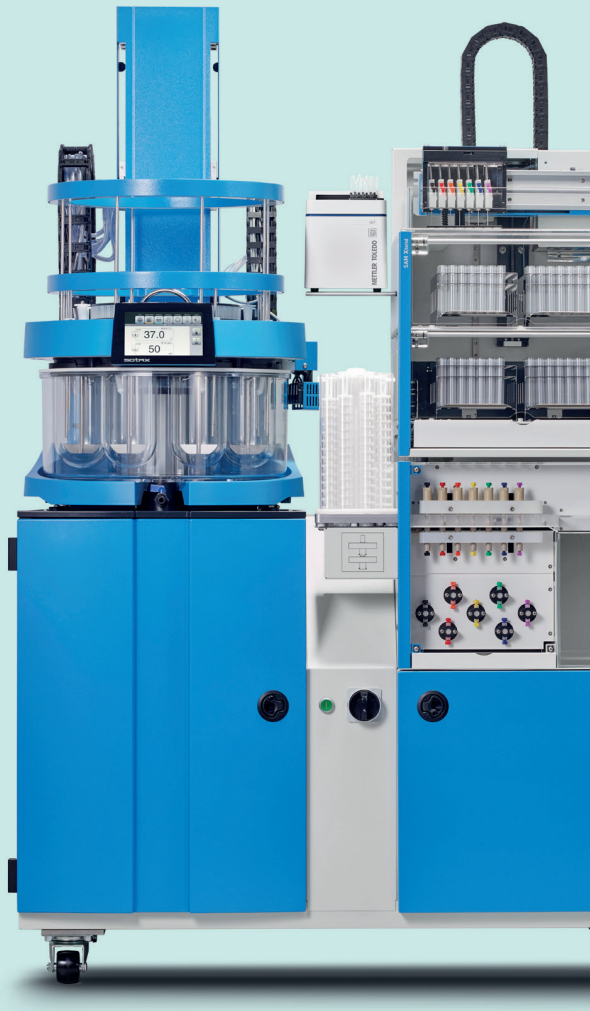
www.dissolutiontech.com Volume 29, Issue 3 | August 2022

ATF Xtend™ —
Fully Automated Dissolution
Testing System

sotax

Dissolution.
100 % Unattended.

Schedule your virtual DEMO today!



The new ATF Xtend™ – Automating the dissolution test does not need to be complex.

Controlled media preparation with vacuum degassing, recorded vessel filling, and robust system cleaning have been added to the proven Xtend™ semi-automated dissolution platform.

With a focus on efficient capture of data flows, this simplified take on automated disso is ready for global deployment!

Solutions for Pharmaceutical Testing

sotax.com

Table of Contents

In This Issue

Advertisers

To Submit Articles

Please check the website for instructions, the articles are peer-reviewed and are submitted through the PeerTrack™ website, https://www.editorialmanager.com/dt.

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

For inquiries and prescreening, e-mail vagray@rcn.com

***Dissolution Technologies* is indexed in:**

Science Citation Index Expanded®
Journal Citation Reports®/ Science Edition
International Pharmaceutical Abstracts
Chemical Abstracts (CAS)
SCOPUS
EMBASE
CrossRef

Topics for the Next Issue

The **August 2022** issue will include trouble-shooting methods, a USP Stimuli on parenterals, bioequivalence testing in Peru, value of generic comparisons, amlodipine besylate tablets, hydrochlorothiazide tablets, a book review, and the Q and A feature.

Research Editor
Vivian Gray
vagray@rcn.com

Publisher's Information

PURPOSE: *Dissolution Technologies* is a peer-reviewed quarterly publication reporting current information on dissolution testing. It provides an international forum for open exchange of information on various dissolution topics.

CORRESPONDENCE: Send all correspondence to: *Dissolution Technologies*, Inc., 9 Yorkridge Trail, Hockessin, DE 19707. Phone (302) 235-0621, e-mail: vagray@rcn.com. Website: www.dissolutiontech.com

STAFF: Founder, Cynthia Brown; Managing Director, Vivian Gray; Associate Editor, Valerie Clark; Research Editor, Vivian Gray; Communications, Michael Larson; Circulation Manager, Sandra Larson; Layout, Michele Arnold; Publication, Printing, and Distribution Services, Archer Print Group, Sellersville, Pennsylvania.

ISSN 1521-298X

Dissolution Technologies is indexed in:
Science Citation Index Expanded®
Journal Citation Reports®/ Science Edition
International Pharmaceutical Abstracts
Chemical Abstracts (CAS)
SCOPUS
EMBASE
CrossRef

Dissilio™ TXeco

Simply smart – make your everyday work easier.

- 100% USP/EP compliant
- user-friendliness
- smart features
- system design for the future
- ISO 9001:2015 quality standards

Made in Germany

https://riggtek.de

„Dissilio“ SMART FEATURES

intiutive 7“ touchscreen control for easy operation, can be operated with gloves on

easy, intuitive operation and real time monitoring via your PC with the innovative „Browser Interface“ without any software installation

optional CFR-compliance with individual user permissions, commenting of audit-trail and electronic signature etc.

secure and self align vessel positioning with protective vessel ring and orientation mark

various accessories available like Rotating Cylinders, Small Volume, Intrinsic, Immersion-Cell, Teflon-Coating, Automatic-Tablet-Drop

convenient screw-in accessories like paddles and basket for easy method change, automatic height adustment between paddles and baskets

smart storage compartments for dissolution accessories like paddles and baskets integrated as standard

modern interfaces like LAN and USB available, Parent-Child-functionality, optional automatic periodic Backup to USB or FTP and optional control via Autosampler „Sampilio“

robust and corrosion resistant design with compact footprint and height, individual clutches enable each individual shaft to be raised, lowered or engaged independent of the drive head

self-priming heater controlled by PT100 for highest temperature precision, optional cooling version to cool down to 5°C for fast releasing products (DTX8 only) or „ENERGY-Package“ for enhanced energy saving

certificaton of shafts, vessels, paddles and baskets as standard (serial numbered with Certificate of Conformance)

one piece leak-proof waterbath with rounded edges and drain tap for easy emptying and cleaning

6 to 8 (DTX8) or 12 to 16 (DTX16) test station unit configurations available, compatible to use RIGGTEK vessels and other brands vessels – for easy method transfer from competitive instruments! Of course also in Amber or with other special vessels

All these specifications and features have one target – make your everyday work easier. And they ensure, that the „Dissilio“ is your ideal partner for both R&D and quality control applications in dissolution testing, your everyday workhorse or your innovative partner in research. The „Dissilio“ is flexible to fit to your individual needs, innovative to drive your progress and prepared to replace easily the prior Dissolution Tester from any brand. Rely on precision, passion and experience in engineering „Made in Germany“ – rely on your „Dissilio“! Ask for your individual offer.

sales@riggtek.de

RIGGTEK
Dissolution Test Systems

dx.doi.org/10.14227/DT290322P122

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts.

Overview of the Activities of the USP Expert Panel on New Advancements in Product Performance Testing

Raymond D. Skwierczynski,[a] Vivian Gray,[b] James De Muth[a]

[a]*USP Expert Panel New Advancements in Product Performance Tests.*

[b]*USP Expert Committee Dosage Forms.*

Correspondence should be addressed to:
Margareth R. C. Marques, Senior Principal Scientist,
Science-General Chapters, US Pharmacopeia,
12601 Twinbrook Parkway, Rockville, MD 20852-1790
email: mrm@usp.org

ABSTRACT

The purpose of this paper is to provide an overview of the activities of the USP Expert Panel on New Advancements in Product Performance testing.

INTRODUCTION

The USP Expert Panel (EP) on New Advancements in Product Performance Testing was created by the 2015–2020 USP Expert Committee on Pharmaceutical Dosage Forms near the end of 2019 to explore new advances in drug product performance testing. The original charge to the EP was to provide recommendations for the adaptation of product performance tests and for the development of innovative approaches applicable to novel dosage forms in *USP* monographs and general chapters, as well as to evaluate current compendial product performance tests (dissolution, disintegration, and drug release) while considering the latest developments in the field. Furthermore, the EP was charged with conducting a gap analysis of USP's status quo regarding performance testing of commercially available drug and dietary supplement dosage forms versus emerging drug delivery systems, and the demand for performance tests applicable to innovative dosage forms. Finally, the EP was required to draft a *Stimuli* article, recommending possible chapter revision(s) and new chapter development. The panel will lead and cooperate with USP staff on the organization of activities for stakeholders' engagement, such as round tables and workshops.

The purpose of this paper is to provide an overview of the article series developed by the EP for pharmaceutical stakeholder and regulator consideration. In doing so, this article will provide a brief history of performance testing and summarize the current state of USP performance testing. The article will describe how the EP was structured to achieve its mandate and will discuss some of the challenges revealed by the aforementioned gap analysis.

HISTORY OF PERFORMANCE TESTING

The Dissolution Test is the most frequently required performance test in the *USP–NF*. It originated in the late 1800s when pill absorption was discovered to be related to dissolution. In 1895, Caspari wrote in a *Treatise on Pharmacy*, "... the composition of compressed tablets should be such that they will readily undergo disintegration and solution in the stomach" (*1*). Only a few years later, in 1897, the Noyes Whitney Equation was published (*2*). As early as the 1930s, experiments with in vitro–in vivo correlations using disintegration were performed and published (*3*). By 1937, tablets had begun to appear as an important dosage form, with disintegration testing found in the British Pharmacopoeia (BP) in 1945 and in the USP in 1950.

During the 1950s, it became known that disintegration was insufficient as evidenced by a *USP–NF* statement that

"disintegration does not imply complete solution of the tablet or even the active ingredient" (*4*).

To ensure drug effectiveness as well as safety, the Kefauver-Harris Drug Amendment was passed in 1962. At that time, the Pharmaceutical Manufacturers Association (PMA) Quality Control Section's Tablet Committee did a survey of 76 products because of concerns that some products disintegrated well but did not absorb. Also, there were product failures noted when the dissolution time was long. The survey found problems in those drugs with solubility less than 30 µg/mL of water—a recommendation was considered that dissolution should be required for drugs with less than 1% solubility instead of disintegration.

During the late 1960s, generic drug approvals were granted, and by 1973, bioequivalence regulations were in place. From the 1960s onward, instrumental analysis with drugs in biological fluid began, and a new generation of pharmaceutical scientists applied physical chemistry to pharmacy (this is attributed to Higuchi) (*5–7*). In 1960, a publication showed that incidence of local irritation and absorption rate of acetylsalicylic acid is a function of its dissolution rate (*8*).

Digoxin tablets were found to have different dissolution rates that were related to differences in plasma levels (*9*). This observation, in 1972, was considered a "game changer" as it was the single most significant medical occurrence of bioavailability problems. At the time, the "Griffin beaker" (a 400-mL beaker with a stirrer) was used for dissolution testing. It was determined that the main culprits for formulation problems were shellac coating and magnesium stearate.

USP scientists began to identify the need for dissolution testing. In 1967, a *USP–NF* Joint Panel on Physiologic Availability was set up to evaluate mechanisms to help assure drug effectiveness. This panel provided the following recommendations:

1. testing to demonstrate the rate at which active ingredients dissolve from the dosage form;
2. the rotating basket would be the most suitable method based on the results of non-disintegrating salicylic acid tablets; and
3. testing should include individual dosage units necessary to ensure uniformity of performance within a batch and should consider high within-lot variability.

A description of the dissolution apparatus known as "Pernarowski's basket" (officially adopted by USP as *Apparatus 1* in 1970) was published in 1967 by the *USP–NF* Joint Panel, although Pernarowski himself claimed that an obscure scientist developed the basket apparatus in Krasnoyarsk, Russia in 1922 (*10*).

PERFORMANCE TEST DEVELOPMENT AND EVOLUTION

The very first water bath was used in 1968 and was a 100-gallon glass-walled container. The equipment was pioneered by what at the time was called the USP Drug Standards Laboratory (DSL). Tim Grady, Bill Hanson, and William Mader were the key scientists who developed the tester currently used today (*11*).

During the 1970s–80s, dissolution test and equipment refinement took place. The *USP–NF* Joint Panel on Physiologic Availability that was established in 1967 advocated for the identification of candidate articles for the first 12 official dissolution tests that used *Apparatus 1* in 1968 (*12*). By the 1970s, there were 12 official *USP* monographs using the basket apparatus. The paddle method (USP *Apparatus 2*) was adopted in 1978. This apparatus was based on the round-bottom organic synthesis flask.

In 1975, regulations began to require bioequivalence and bioavailability with in vitro bioequivalence coming into play. Generic products were the driver for this initiative. Dissolution was seen as the only compendial test that assured the drug would be liberated from the dosage form and available for in vivo absorption.

In 1976, USP in joint leadership with the National Formulary (NF) adopted a new policy that advocated for the inclusion of dissolution tests in all tablet and capsule monographs; however, conditions and specifications were not uniform and sometimes absent. Also, there was a lack of industry cooperation.

By 1980, only about 72 *USP* monographs had dissolution tests. To remedy this situation, in 1975 USP enacted its "First Case" dissolution policy, which was a comprehensive policy for dissolution standards for tablets and capsules, which stated that "all tablet and capsules are subject to a dissolution standard of not less than 75% of label content is dissolved in not more than 45 min in 900-mL water at 37°, *Apparatus 1* (basket) at 100 rpm and *Apparatus 2* (paddle) at 50 rpm for all other cases."

The text of the policy stated, "The public interest warrants no further delay in assuring reliable release of

active ingredients from dosage forms." The policy meant automatic application of "First Case" requirements to every tablet and capsule monograph. All articles were presumed to conform unless USP was notified to the contrary. An earlier specification of 60% dissolution at 20 min was considered but discarded. By 1985, dissolution tests in monographs jumped from 70 to 400, with the majority as "First Case" conditions.

The preface to *USP XXI* (1985) contained the following words: "Experience has demonstrated that where a medically significant difference in bioavailability has been found among supposedly similar articles, a dissolution test has been efficacious in discriminating among these articles." The preface continued as follows—"There is no known medically significant bioinequivalence problem with articles where 75% is dissolved in water at 37° in 45 min." This was when highly soluble and highly permeable drugs were the majority. Eventually this wording was dropped out of the preface.

In the 1990s, the FDA pushed for profile testing: "The value of the dissolution test is significantly enhanced as a function of time with profiles instead of single points" and comparison of dissolution profiles using the F2 equation was introduced (*13*).

During the 1990s, there were several other changes initiated: 1) removal of disks from disintegration; 2) FDA directive stating that chewable tablets and soft gel capsules are no longer exempt from dissolution testing; 3) pooled dissolution instated for multi-component, highly soluble articles with a known track record and methodology included pooling six sample aliquots in one flask; 4) replace 0.1 N HCl media with 0.01 N HCl, viewed as more discriminating media and more environmentally friendly; 5) the FDA began to push for the specifications of 80% in 30 min rather than 75% in 45 min; 6) the FDA began to push for 100 rpm paddle speeds for immediate release products to be reduced to 50 rpm, 75 rpm in some cases; and 7) the FDA discourages use of water as a dissolution medium.

Today dissolution testing is generally recognized as the gold standard for performance testing.

CURRENT STATUS OF USP PERFORMANCE TESTING

USP provides five official chapters on the applicable quality standards for pharmaceutical products based on a taxonomy for the route of administration. These standards are presented in the first five chapters of the *USP–NF*:

<1> Injections and Implanted Drug Products (Parenterals)—Product Quality Tests

<2> Oral Drug Products—Product Quality Tests

<3> Topical and Transdermal Products—Product Quality Tests

<4> Mucosal Drug Products—Product Quality Tests

<5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests

Each of these chapters provide product quality tests, such as identification, assay, content uniformity, and impurity testing. Based on the route of administration, each chapter includes additional quality tests. Performance testing that assesses the release and availability of the drug substance from the dosage form is also provided but often in general terms. For example, Oral Drug Products—Product Quality Tests <2> states that Dissolution <711> or Drug Release <724> should be performed to assess the performance of a solid oral dosage form, but details of the test method are not provided. These performance tests have historically served as a quality control test at the time of product release or demonstration of stability over the product's shelf life.

Details of the performance test method and acceptance criteria can usually be found in the specific *USP–NF* monograph, if one exists (*14*). The USP and FDA dissolution databases provide information on the test method conditions (*15*, *16*). Additional *USP* chapters provide some guidance for performance tests for the five routes of administration. These chapters are presented in *Table 1*.

Ophthalmics, which represent a unique class of products, are discussed in *USP* chapters Ophthalmic Preparations—Quality Tests <771> and performance tests currently presented in Ophthalmic Products—Performance Tests <1771>. Performance tests for ophthalmic products are required for those with an extended- release mechanism, usually administered by injection or by a small surgery procedure.

DEVELOPMENT OF THE TACTICAL PLAN TO ACHIEVE THE OBJECTIVES

Members of the EP were recruited from the pharmaceutical industry, academia, and the FDA. A list of EP members and their affiliations is given in *Table 2*. The initial focus of the EP in May 2019 was to discuss emerging trends regarding drug delivery technologies. During subsequent meetings, characterization methods were

Table 1. Current USP Chapters Addressing Quality and Performance Testing

Quality Tests	Performance Tests
<1> Injections and Implanted Drug Products (Parenterals)—Product Quality Tests <2> Oral Drug Products—Product Quality Tests <3> Topical and Transdermal Products—Product Quality Tests <4> Mucosal Drug Products—Product Quality Tests <5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests	<1001> Performance Test for Parenteral Dosage Forms <701> Disintegration <711> Dissolution <724> Drug Release <1711> Oral Dosage Forms—Performance Tests <1087> Apparent Intrinsic Dissolution-Dissolution Test Procedures for Rotating Disk and Stationary Disks <1088> In vitro and In vivo Evaluation of Oral Dosage Forms <1090> Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution <1092> The Dissolution Procedure: Development and Validation <1094> Capsules—Dissolution and Related Quality Attributes <2040> Disintegration and Dissolution of Dietary Supplements <724> Drug Release <1724> Semisolid Drug Products—Performance Tests <1004> Mucosal Drug Products—Performance Tests <601> Inhalation and Nasal Drug Products Aerosols, Sprays, and Powders—Performance Quality Tests

Table 2. EP Membership and Working Group Assignments

Name	Affiliation	Workgroup Assignments
Om Anand, Ph.D.	FDA, USA	Topicals, Inhalation
Matthew Burke, Ph.D.	GlaxoSmithKline, USA	Parenterals, Nanomaterials
Carrie Coutant, Ph.D.	Eli Lilly & Co., USA	Orals, Cont. Manufacturing
Deirdre Darcy, Ph.D.	Trinity College Dublin, Ireland	Parenterals,* Orals
James E. De Muth, Ph.D.	University of Wisconsin, USA	Topicals, Mucosals, Inhalation
Raafat Fahmy, Ph.D.	FDA, USA	Cont. Manufacturing, Nanomaterials
Nikoletta Fotaki, Ph.D.	University of Bath, UK	Orals,* Inhalation
Andre Hermans, Ph.D.	Merck & Co, Inc., USA	Orals, Cont. Manufacturing
Gregory Hunter, Ph.D.	FDA, USA	Parenterals, Orals
Sandra Klein, Ph.D.	University of Greifswald, Germany	Mucosal,* Parenterals, Orals
Christina Lee, Pharm.D.	FDA, USA	Topicals, Mucosals
Hanlin Li, Ph.D.	Vertex Pharmaceuticals, USA	Cont. Manufacturing,* Orals
Kevin Li, Ph.D.	University of Cincinnati, USA	Topicals, Mucosals
Xujin Lu, Ph.D.	Bristol-Myers Squibb, USA	Cont. Manufacturing, Nanomaterials
John Mauger, Ph.D.	University of Utah, USA	Topical,* Orals
Masahiro Sakagami, Ph.D.	Virginia Commonwealth University, USA	Inhalation,* Mucosals
Emmanuel Scheubel, Ph.D.	F. Hoffmann-La Roche AG, Switzerland	Orals, Inhalation
Vivek Shah, M.S.	SOTAX Corp., USA	Parenterals, Orals
Raymond Skwierczynski, Ph.D.	Tremeau Pharmaceuticals, Inc., USA	Chair, Expert Panel
Matthias Wacker, Ph.D.	National University of Singapore, Singapore	Nanomaterials,* Injections
Kevin Warner, Ph.D.	Alucent Biomedical, Inc., USA	Topical,* Mucosals
Hao Xu, Ph.D.	Zoetis, USA	Parenterals, Topicals, Mucosals

**Working group chair.*

discussed and how these topics would influence how the EP would organize to meet its objectives. In-person meetings were held at USP headquarters in Rockville, MD in October and December 2019. The December meeting followed the workshop "Advancements in In-Vitro Performance Testing of Drug Products" where members heard presentations from USP staff and experts on drug performance testing and received input from stakeholders (*17*). In addition to reviewing information presented at the workshop, the EP discussed emergent technologies in major categories of dosage form performance testing and determined a plan and timeline for incorporating these technologies into a written USP standard.

The primary deliverable from the December 2019 meeting was a tabular framework for the gap analysis. The framework consisted of these points: 1) route of delivery; 2) dosage form; 3) current performance test for each dosage form, its limitations, and analytical challenges; 4) possible alternatives to or surrogates for the current performance test for each dosage form; and 5) recommendations.

It became quickly apparent that the magnitude of the gap analysis and subsequent *Stimuli* article was an enormous task. A decision was made to divide the charge into manageable pieces. Seven working groups were created to discuss and explore current and potential future tests that may be used for pharmaceutical performance tests.

Five of the working groups focused on the five aforementioned routes of administration (parenterals, orals, topical/transdermals, mucosal products, and inhalation and nasal products). Two additional groups were created to look at continuous manufacturing and nanomaterials.

Each EP member was assigned to at least two working groups, so information, thought processes, and designs could be shared amongst the various working groups. Working group assignments and chairs are also presented in *Table 2*.

Each working group was commissioned to complete a gap analysis and subsequent *Stimuli* article for their respective area. This approach provided the flexibility to have as many as seven focused *Stimuli* articles to cover the charge to the EP. Each group was also permitted to adjust the framework of the gap analysis and the format of their *Stimuli* article in order to facilitate public commentary from subject-matter experts and stakeholders who are familiar with the specific route or topic.

STATUS OF STIMULI ARTICLES

The first *Stimuli* article on nanomaterials has already been presented in *PF* 47(6) (*18*). The *Stimuli* article on continuous manufacturing will appear in *PF* 48(4) (*19*). The five working groups on the routes of delivery are progressing with their gap analyses. Publication of their *Stimuli* articles in *PF* is targeted for 2022 and 2023.

There are several common themes and visionary points emerging from the gap analyses. One is the desire to have performance tests be clinically relevant in addition to being discriminatory. Another is the desire to incorporate modeling, such as in vivo-predictive mouth-throat models and inhalation profiles for aerodynamic particle size distribution tests, and the predictive modeling for real-time release during continuous manufacturing.

As was mentioned in the nanomaterials *Stimuli* article, guidance on the selection of appropriate testing methodology, method development, and validation of release assays is needed for nanomaterial dosage forms. A similar gap analysis identified the need for a general systematic method development approach for various injectable dosage forms.

The examples above are not intended to be comprehensive. The details of the current state of performance testing, its gaps, and EP recommendations will, of course, be provided in each *Stimuli* article. The ultimate purpose of these *Stimuli* articles is to provide information to stakeholders and to provide opportunities to discuss and respond to the information and recommendations. Such feedback can range from support of the findings to challenges of their validity or feasibility. All comments are gratefully accepted and will be considered by the EP and the USP Dosage Forms Expert Committee as they work to prepare future standards for drug performance testing. Additional thoughts on the topics are also encouraged.

CONFLICT OF INTEREST STATEMENT

The authors did not declare any perceived or actual conflicts of interest related to the subject matter of this *Stimuli* article. The views presented in this article do not necessarily reflect those of the organizations for which the authors work. No official support or endorsement by these organizations is intended or should be inferred.

REFERENCES

1. Caspari C. "A Treatise on Pharmacy", 1895, Lea Bros., Philadelphia, 344.
2. Noyes AA, Whitney WR. *J. Am. Chem. Soc*. 1897;19:930.
3. Morgan T. "History of Dissolution Calibration", *Dissolution Technolog*., 1995;2(4):3–9. DOI:10.14227/DT020495P3.
4. Krämer J, Grady T, Gajendran J. Chapter 1 "Historical Development of Dissolution Testing", Pharmaceutical Dissolution Testing. Dressman J, Krämer J, eds. Taylor and Francis, Boca Raton, FL, 2005.
5. Higuchi WL, Hiestand EN. *J. Pharm Sci*, 1963;52:67–71.
6. Higuchi WL, Rowe EL, Hiestand EN. *J. Pharma Sci*. 1963;52:162–164.
7. Higuchi WL. *J Pharm Sci*. 1967;56:315–327.
8. Levy and Hayes. *New England J. of Medicine*, 1960;262:1053.
9. Fraser, Leach, and Paston. *The Lancet*, September 1972;541.
10. Pernarowski M. Chapter 3, "Dissolution Methodology", Dissolution Technology, eds. Leeson and Carstensen, Academy of Pharmaceutical Science, Washington, DC, 1974.

11. Grady T. “An early look at dissolution testing, including equipment, calibration, and acceptance criteria”, Dissolution Technolog., 2014;21(3):20–21. DOI:10.14227/DT210314P20.
12. In vitro and In vivo Evaluation of Oral Dosage Forms <1088>.
13. Shah V and Williams R. “Roles of Dissolution Testing: regulatory, industry and academic perspectives-role of dissolution testing in regulating pharmaceuticals”, *Dissolution Technolog*., 1999;6(3):7–8. DOI:10.14227/DT060399P7.
14. *USP–NF*, official as of October 1, 2021.
15. USP Dissolution Methods Database. https://www.usp.org/resources/dissolution-methods-database (accessed January 2, 2022).
16. United States Food and Drug Administration Dissolution Database. https://www.accessdata.fda.gov/scripts/cder/dissolution/ (accessed January 2, 2022).
17. Hermans A, et. al. Workshop Report USP Workshop on Advancements in In-Vitro Performance Testing of Drug Products. *Dissol. Technol.*, 2020;27(2). dx.doi.org/10.14227/DT270220P52.
18. Testing the In-Vitro Product Performance of Nanomaterial-Based Drug Products: View of the USP Expert Panel. *Pharmacopeial Forum*. 2021;47(6).
19. In vitro performance tests for continuous manufacturing: the impact on the current compendial framework from the view of the USP New Advancements in Product Performance Testing Expert Panel. *Pharmacopeial Forum*. 2022;48(4).

Auxiliary Information- Please check for your question in the FAQs before contacting USP.

dx.doi.org/10.14227/DT290322P128

The Combination of Liqui-Mass System and Pelletization to Improve Pharmaceutical Properties of Hydrochlorothiazide

Matthew Lam* **and Ali Nokhodchi**
Pharmaceutics Research Laboratory, School of Life Sciences, University of Sussex, Brighton, UK.

e-mail: m.lam@sussex.ac.uk

ABSTRACT

Liqui-Pellet technology has recently been developed and has shown to be promising in achieving a rapid drug release rate with water insoluble drugs. At present, only naproxen and ketoprofen have been applied to an oral solid dosage form for immediate release. The present investigation aims to explore the drug release performance of the poorly water-soluble hydrochlorothiazide (HCTZ) using the Liqui-Pellet technology. Various non-volatile co-solvents such as Tween 80, PG, Kolliphor EL, and PEG 200 were used to make HCTZ Liqui-Pellet formulations to investigate the influence of Liqui-Pellet technology on the drug release profile. Saturation solubility studies showed HCTZ was most soluble in PEG 200 (156 mg/mL), which is also reflected in the drug release data where HCTZ Liqui-Pellet containing PEG 200 had the most enhanced drug dissolution profile. A binary mixture of carriers consisting of Avicel PH-101 and Neusilin US2 was investigated, as this mixture has been shown to improve drug release rate in a previous study. Surprisingly, the binary mixture of carriers did not improve the drug release rate in this study. The best formulation reached 100% drug release at approximately 40 min. Other physicochemical analysis tests showed the Liqui-Pellets' flow property, robustness, and size distribution are generally acceptable and pose no major issue in terms of manufacturing. In conclusion, the Liqui-Mass system combined with extrusion-spheronization is a viable approach to enhance HCTZ dissolution.

KEYWORDS: Liqui-Pellet, Liqui-Mass system, dissolution enhancement, pelletization, co-solvent, dissolution

INTRODUCTION

Liqui-Pellet is produced by using Liqui-Pellet technology, which is also termed as Liqui-Mass technology. It is a newly developed technology that was patented and first appeared in the scientific literature in 2019 (*1*). It is considered to have the potential to contribute to the next generation of oral dosage forms. Recent studies have displayed Liqui-Pellet technology as a promising approach to enhance drug release rate performance, while having beneficial considerations for industrial manufacturing (*2, 3*). Liqui-Pellet comes from complementary concepts from liquisolid technology with pelletization technology. It should be made clear that the Liqui-Pellet technology is fundamentally different from liquisolid technology in that it uses Liqui-Mass system instead of liquisolid system (*4*). A liquisolid system is defined as a dry non-adherent and free-flowing powdered admixture, containing liquid medication and carrier along with coating materials. A Liqui-Mass system, on the other hand, contains considerably more liquid co-solvent, which usually makes the admixture wet and cohesive. It becomes flowable when the wet mass is converted into pellets (*4*). This key difference is the reason why Liqui-Pellet can achieve a fast drug release performance that is superior to liquisolid compact along with features that make it easy to manufacture, particularly the flow property (*2 ,3, 5*).

To appreciate the implication of Liqui-Pellet, it is prudent to understand that inadequate bioavailability of a drug is a major concern in the pharmaceutical industry. It has long been revealed that a large percentage of drugs on the market and in the development pipeline have poor bioavailability and poor dissolution rates, due to poor water solubility (*6*). An estimated 60% of synthesized drugs have poor solubility in gastrointestinal fluids, and around 90% of drugs in development are poorly water-soluble (*7*). Hence, energy and money have been invested into trying to overcome this global challenge.

In this study, hydrochlorothiazide (HCTZ), which has

* Corresponding author.

poor solubility in water, is used as the drug candidate for the Liqui-Pellet enhanced release dosage form. HCTZ is a thiazide diuretic and is used in the treatment of oedema, chronic heart failure, and high blood pressure (*8*). According to sources from the Clarke Analysis of Drugs and Poison, HCTZ is practically insoluble in water (*9*). HCTZ solubility is around 0.556 mg/mL at pH 6, which is considered to be very slightly soluble, making HCTZ a suitable drug model for this investigation (*10*).

Previous studies on Liqui-Pellet technology have shown that naproxen Liqui-Pellets have the potential for remarkable enhanced drug release, which is superior to liquisolid formulation (*2*, *3*, *5*). Naproxen is a weakly acidic water-insoluble drug; however, by applying Liqui-Pellet technology, it is able to achieve 100% drug release within 20 min at pH 1.2 despite being practically insoluble in such acidic conditions (*2*). Since this technique has the potential to be applied to a wide range of drugs with poor water solubility, it is considered a promising drug delivery platform. The technique itself can omit processes that require a high level of heat, making it suitable for heat-sensitive drugs along with being designed with sustainable technology in mind, which further adds to its potential value as a new drug delivery platform.

Liqui-Pellet has demonstrated that it is capable of overcoming the major disadvantages of liquisolid formulation such as poor flowability and the end product being too bulky for actual use in patients, particularly in high dose drugs (*2*, *3*, *6*, *11–15*). Furthermore, it carries key inherent advantages such as the ability to achieve a high liquid load factor and to exist as a multi-unit dosage form. It is also simple to apply, cost-efficient, and the typical excipients used are considered safe and widely available in the market (*11*). The pelletization aspect of the technology allows good flowability, potential to combine incompatible drugs or drugs with different release profiles in the same dose unit, flexibility for modification via coating technology, and reduced risk of side effects due to dose dumping in film-coated formulation (*16*, *17*).

It has been stated that the Liqui-Pellet technology has the potential to be manufactured at an industrial level given the excellent flow property, high liquid load factor, end product size, and drug releasing performance, which the liquisolid technology is lacking. Although there are other technologies attempting to overcome the same issue of poor dissolution rate of water-insoluble drugs, those other technologies may require advanced techniques or sophisticated machinery to prepare, may not be as cost-efficient, or may not perform as well (*11*). Such methods include altering crystalline drug into its amorphous state, micronization, solid dispersion, nanosuspension, salt formation, self-emulsifying drug delivery system, co-grinding, and inclusion of drug solution in a soft gelatin capsule (*18*, *19*).

With the array of advantages of this newly developed technology, there is much to investigate including studying its performance on a wide range of APIs. This led to the current study where it was investigated whether Liqui-Pellet technology can improve the dissolution of poorly water-soluble HCTZ.

MATERIALS AND METHODS

Materials and Chemicals

HCTZ was acquired from Spectrum Chemical MFG Corp (USA). Excipients used in making the formulation included microcrystalline cellulose (Avicel PH-101 and Avicel PH-102, FMC corp., UK); colloidal silicon dioxide (Aerosil 300, Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (Primojel, DFE Pharma, Goch, Germany); synthetic magnesium alumino-metasilicate (Neusilin US2, Fuji Chemicals, Japan); polysorbate 80 (Tween 80, Acros, Netherlands); propylene glycol (PG) (SAFC, Spain); polyethylene glycol 200 (PEG 200, Fisher Scientific, Leicester, UK), and macrogol glycerol ricinoleate 35 (Kolliphor EL, BASF SE, Ludwigshafen, Germany). All other reagents and solvents were of analytical grades.

Solubility of Hydrochlorothiazide (HCTZ) in Non-volatile Co-Solvents

Saturation solubility studies of HCTZ were carried out in four different non-volatile co-solvents: Tween 80; PG; Kolliphor EL, and PEG 200. Pure API drug crystals were added in excess in 10 mL of specified non-volatile co-solvent to create the saturated solutions. The vial was then subjected to mechanical agitation (shaking speed of 40 rpm) and constant temperature (37 °C) using a bath shaker (OLS Aqua Pro, Grant Instruments Ltd, UK) for 96 h. A pre-heated filter with a pore size of 0.22 µm (Merck Millipore Ltd., Ireland) was used in the filtration of the supernatant. The sample was then subjected to dilution with methanol and concentration was determined via UV/vis spectrophotometer (Biowave II, Biochrom Ltd., UK) at a wavelength 272 nm. Each test was carried out in triplicates.

Preparation of HCTZ 12.5-mg Liqui-Pellet and Physical Mixture Pellet

All of the formulations using the Liqui-Pellet approach were made in a similar method except for the variation in parameters such as carrier composition, choice of non-volatile co-solvent, and the amount of granulating liquid

(Table 1). The liquid medication was made by blending a known amount of active pharmaceutical ingredient (API) with a known amount of non-volatile co-solvent, using the mortar and pestle mixing technique. The liquid medication was then blended into a known amount of carrier, which is either completely Avicel PH-101, completely Avicel PH-102 or a mixture of Avicel PH-102 and Neusilin US2 at ratio of 1:1. All formulations contained 5.5% w/w sodium starch glycolate superdisintegrant (Primojel) and carrier to coating ratio of 20:1. The coating material incorporated was colloidal silicon dioxide (Aerosil 300). With the exception of the physical mixture pellet, all Liqui-Pellet formulations had 34% w/w of a specified non-volatile co-solvent and a liquid load factor (L_f) of 0.79.

The liquid medication, carrier material, and Primojel were blended for 2 min at 125 rpm (Caleva Multitab, Caleva Process Solutions Ltd, UK). The Primojel was incorporated into the admixture intragranularly, as previous studies showed this was better at promoting disintegration than extragranular incorporation (*13*). A stated quantity of liquid used for granulation (deionized water) was added gradually to achieve good rheological property for extrusion. The length of time of mixing the admixture with deionized water was 5 min. Aerosil 300 was then added into the admixture and further blended for 5 min before being extruded. Once a sample was extruded, it underwent spheronization at an almost constant setting of 4000 rpm, which could be reduced to 2000 rpm depending on the likelihood of agglomeration. The duration of spheronization depended on the extrudate's plastic property and was shortened if the formulation was prone to agglomeration or lengthened to ensure good spherical pellets. The wet pellets were then subjected to drying in an oven under 40 °C overnight to evaporate excess water.

Flowability Studies

Physical mixture pellet and all of the Liqui-Pellet formulations flow properties were assessed using three approaches, which includes flow rate in grams per second, angle of repose (Flowability tester, Copley Scientific, UK and Digimatic height gage, Mitutoyo, Japan) and Carr's compressibility index using the tapped density tester (SVM D-63150, Erweka, Germany). Flow rates were measured by recording sample mass in grams and the time in seconds of pellets flowing through a 10-mm diameter orifice funnel. The angle of repose test was carried out by placing specified formulation in a funnel and letting a heap of sample form on a circular test platform. Utilizing the Digimatic height gauge and micrometer, the height and diameter of the heap of the sample was measured. These measurements were used to calculate the angle of repose. Carr's compressibility index (CI%) was determined from the poured and tapped densities using CI equation. Tapped density was calculated using the data generated from tapped density tester, which was set to tap 100 times. All measurements were done in triplicates and standard deviation of the mean was calculated.

Friability Studies

The robustness of all formulations was examined using the friability test. The weight of 3 g of the specified sample and 3 g of glass beads were placed in a friabiliator drum (D-63150, Erweka, Germany). The friabilator drum was

Table 1. Composition of All Formulations

Formulation	Amount of granulating liquid (mL) per 20 g admixture of API and excipient	Non-volatile co-solvent	Carrier composition	Carrier (mg)	Coating material (mg)	Total weight of 12.5 mg HCTZ Liqui-Pellet (mg)
Physical mixture pellet	22.50	-	100% Avicel PH-102	104.37	5.22	133.34
F-1	2.46	Tween 80	100% Avicel PH-102	104.37	5.22	202.84
F-2	2.46	Tween 80	100% Avicel PH-101	104.37	5.22	202.84
F-3	2.46	PG	100% Avicel PH-102	104.37	5.22	202.84
F-4	2.46	Kolliphor EL	100% Avicel PH-102	104.37	5.22	202.84
F-5	2.46	PEG 200	100% Avicel PH-102	104.37	5.22	202.84
F-6	7.39	PEG 200	100% Avicel PH-102	104.37	5.22	202.84
F-7	7.39	Kolliphor EL	50% Avicel PH-101 and 50% Neusilin US2	104.37	5.22	202.84
F-8	12.32	PEG 200	50% Avicel PH-101 and 50% Neusilin US2	104.37	5.22	202.84

Note - All Liqui-Pellet formulations contain 12.5 mg of HCTZ, non-volatile co-solvent concentration of 34% w/w, Lf of 0.79, Primojel ~5.5% w/w, and carrier to coating material is at a ratio of 20:1.
API: active pharmaceutical ingredient; HCTZ: hydrochlorothiazide.

enclosed to stop the sample of pellets from leaving the container. The friabilator drum was then set to rotate 100 times in 4 min. The percentage weight loss of the sample was then calculated using the weight of the sample before and after the friability test.

Particle Size Analysis

The particle size distribution was examined on all formulations using the sieve method. Specified formulation of Liqui-Pellet weighing 5 g was placed in a sieve (Test sieve, Retsch, Germany) of sizes 2000, 1000, 850, 500, and 250 µm. The sieves were stacked with the largest sieve size on top and the smallest sieve size at the bottom and placed on a mechanical shaker (AS 200, Retsch, Germany). The mechanical shaker was set to vibrate with an amplitude of 60 for 1 min, then an amplitude of 40 for 4 min. The size distribution of Liqui-Pellet was determined based on the pellet fraction between 250 and 2000 µm and presented as the percentage of total pellet weight.

In-Vitro Drug Dissolution Test

The drug release rate of all formulations was examined using USP dissolution apparatus II (708-DS Dissolution Apparatus and Cary 60 UV-Vis, Agilent Technologies, USA). The dosage form subjected to the dissolution test was a hard-shell capsule filled with specified Liqui-Pellet formulation or physical mixture pellet. Each capsule contained an equivalent to 12.5 mg of HCTZ. Dissolution test vessels contained 900 mL of dissolution medium, which was kept at 37.3 ± 0.5 °C and paddle agitation was 50 rpm. The dissolution medium used was HCl buffer solution with a pH of 1.2 without enzymes, which were used to mimic pH in gastric fluid. The parameters were based on United States Food and Drug Administration (FDA) draft guidance for HCTZ/metoprolol oral tablets (*20*). The cumulative drug release was examined using the UV/Vis spectrophotometer method, which read absorbance at a wavelength of 272 nm every 5 min for 1 hour then 10 min for another hour. Preliminary work using Beers Lambert calibration curve (Fig. 1) was applied to dissolution test data to determine the concentration of HCTZ.

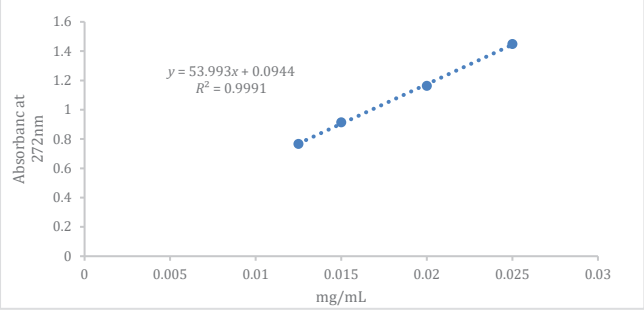


Figure 1. Beers Lambert calibration curve of hydrochlorothiazide at pH 1.2.

Model-independent analysis was used to compare the dissolution profiles of the various formulations. This included difference factor (f_1) and similarity factor (f_2), as described by Moore and Flanner (*21*). Such mathematical analysis has been recommended by the FDA and can be seen in various guidance documents (*22, 23*). In general, when the f_1 value is between 0 and 15 and the f_2 value is between 50 and 100, this indicates equivalence of the two dissolution profiles (*24*). Details of the equations can be found in various literature (*25–28*).

RESULTS AND DISCUSSION

Solubility of HCTZ in Non-Volatile Co-Solvents

The data obtained from the saturation solubility test (Table 2) indicate that HCTZ is most soluble in PEG 200 (156 mg/mL) compared to the other non-volatile co-solvents. This indicates that HCTZ is freely soluble in PEG 200, making it the most suitable liquid non-volatile co-solvent candidate for HCTZ Liqui-Pellets. This is because it is generally considered that the non-volatile co-solvent in which an API is most soluble in would exhibit the fastest drug release rate. This is due to reduced API in the ordered crystalline form and more in the solubilized or molecularly dispersed state, resulting in increased surface area for drug release (*29*).

Table 2. Solubility of Hydrochlorothiazide in Various Liquid Vehicles at 37 °C (n = 3)

Non-volatile solvent	Concentration, mg/mL (mean ± SD)	Inference
Tween 80	27.46 ± 1.31	Sparingly soluble
PG	11.35 ± 4.94	Sparingly soluble
Kolliphor EL	95.93 ± 5.81	Soluble
PEG 200	155.92 ± 6.33	Freely soluble

SD, standard deviation

The next non-volatile co-solvent in which HCTZ is most soluble in followed by PEG 200 is Kolliphor EL, then Tween 80, and finally PG. Despite the solubility test results, formulations F-1 (Tween 80) and F-4 (Kolliphor EL) have a very similar drug dissolution profile even though data indicate HCTZ is more soluble in Kolliphor EL than Tween 80. Therefore, it should be noted that API solubility is not the only factor that can influence the drug dissolution rate. Other physicochemical characteristics of the liquid vehicle such as lipophilicity, viscosity, polarity, chemical structure, and molecular mass may affect the drug release (*6*). Nevertheless, in general, drug solubility in a liquid vehicle does greatly influence drug release profile.

Flowability Studies

The data from flowability studies are shown in Table 3. According to the data obtained from the angle of repose test, all formulations have excellent flowability. As for CI,

Table 3. Formulation Flow Properties and Friability Data

Formulation	Flow Rate, g/sec	Angle of repose	Carr's CI%	Inference According to Angle of Repose	Inference According to Carr's CI%	% Weight Loss
Physical mixture pellet	7.73 ± 0.21	24.38 ± 0.73	11.62 ± 0.00	Excellent	Good	0.91
F-1	6.93 ± 0.10	27.57 ± 1.00	8.83 ± 0.00	Excellent	Excellent	0.10
F-2	6.28 ± 0.61	28.19 ± 0.84	11.71 ± 1.56	Excellent	Good	0.02
F-3	6.33 ± 0.19	26.38 ± 0.77	15.16 ± 0.00	Excellent	Good-fair	0.60
F-4	6.31 ± 0.33	28.86 ± 0.60	11.12 ± 0.00	Excellent	Good	0.20
F-5	6.00 ± 0.18	27.96 ± 0.46	9.80 ± 1.70	Excellent	Excellent	0.81
F-6	7.93 ± 0.15	25.26 ± 0.14	8.84 ± 0.00	Excellent	Excellent	0.05
F-7	7.27 ± 0.09	24.42 ± 0.49	11.40 ± 0.00	Excellent	Good	0.00
F-8	7.63 ± 0.20	23.41 ± 0.43	11.77 ± 0.00	Excellent	Good	0.14

Data are mean ± standard deviation (SD) (n = 3).
CI%: compressible index.

the inference of flowability is slightly more dispersed; there are excellent, good, and good-fair flow properties. In general, the flow properties of all of the formulations do not raise any concerns in terms of the potential to be manufactured at an industrial scale. This is supported in the previous studies on Liqui-Pellet where flowability was also not a major issue (*2*, *3*, *12–14*, *30*). It also marks a big leap forward in the powder-solution approach to solid oral dosage forms, because the high amount of non-volatile co-solvent historically gave rise to a manufacturing issue. This is due to the liquid in the powder contributing to a surface-surface interaction, which causes the admixture to be too cohesive, rendering it unsuitable for large-scale manufacturing. This is also the reason why there is currently no product in the market that uses classical liquisolid technology.

With the combination of the nanosized silicon dioxide coating material (Aerosil 300) and the spherical characteristic of the pellet, flow properties are not an issue for Liqui-Pellets as it is for liquisolid formulation. The coating material reduces the wetness of the pellet, thereby reducing interfacial tension among the Liqui-Pellets and its surroundings. This consequently improves the flow property. Hence, this suggests that coating material plays an important role in Liqui-Pellet smooth flow properties.

Also, the fact that the pellets that are produced are spherical in shape, the round edges reduce the surface area of particles interacting with one another. This reduces surface-to-surface interactions such as van der Waals forces between particles and effectively reduces cohesive force, resulting in a smooth flow property.

Friability Studies

All formulations pass the friability test as the percentage weight loss is below 1% (Table 3). This indicates that all formulations have acceptable robustness. In general, Liqui-Pellet has shown a good level of robustness since it was first introduced in the scientific literature in 2019 (*12*). In addition, it has been stated in Muley et al. review paper that pellet dosage forms are less friable (*31*).

Particle Size Studies

All formulations generally have a reasonably narrow pellet size distribution, with a particle size below 2000 µm. Formulations F-1, F-4, F-5, F-7, and F-8 are mostly within 500 µm, and formulations F-2, F-3, and F-6 are mostly within 850 µm (Fig. 2). Narrow size distribution is ideal for manufacturing as it will reduce weight and content variation when filled into a capsule.

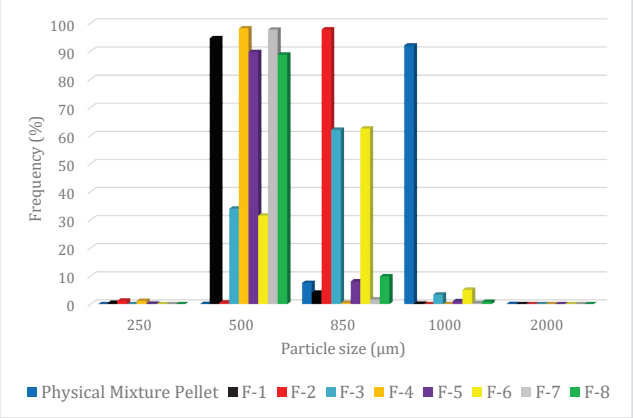


Figure 2. Particle size distribution of hydrochlorothiazide formulations.

It is worth pointing out that the size distribution of pellets is rather difficult to control. It has been stated in the literature that numerous factors can influence pellet size when prepared using the extrusion-spheronization technique. Such factors include API and excipients size

(*32–37*); extruder types; extrusion speed; properties of extrusion screen; spheronization speed (*38*); duration of spheronization time (*39-42*); and spheronization load (*40, 41, 43*). Overall, all of the pellet sizes are within the range that is expected, and most formulations achieved narrow size distribution.

In-Vitro Dissolution Test

According to the dissolution profiles shown in Figure 3, formulation F-5 (containing PEG 200 non-volatile co-solvent) showed the fastest drug release rate, where 100% drug release is achieved in approximately 40 min. This drug release profile is considered rapid because more than 85% of the drug is released within 30 min (*44*). In fact, this Liqui-Pellet formulation has faster drug release than technology such as solid dispersion. HCTZ solid dispersion from a study by Khan et al (*45*) achieved approximately 90% drug release after 45 min (USP apparatus I at 100 rpm in 900 mL 0.1 HCl), which is slower than Liqui-Pellet, suggesting Liqui-Pellet could be a competitive technology.

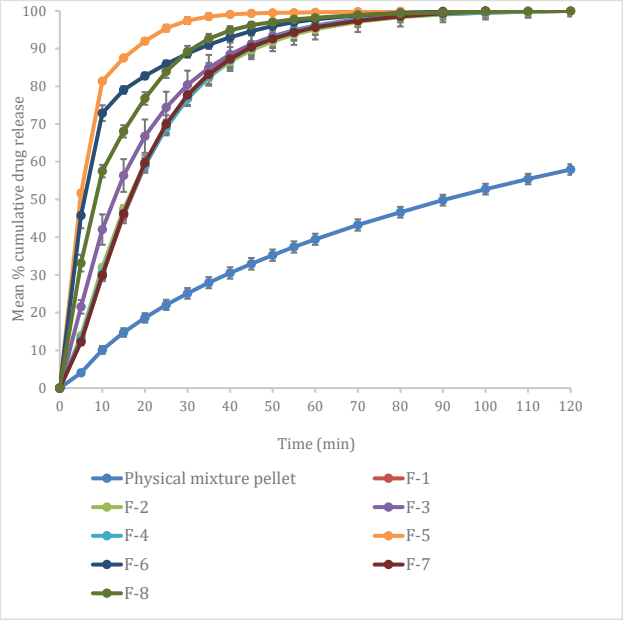


Figure 3. Dissolution profiles of physical mixture pellet and Liqui-Pellet hydrochlorothiazide formulations at pH 1.2.

The two next fastest drug release Liqui-Pellet formulations were F-6 (7.39 mL granulating liquid) and F-8 (12.39 mL granulating liquid). F-6 composition is the same as F-5 (best formulation) (Table 1), except the water content used during the mixing and extrusion-spheronization process was different. The water content used is higher in F-6 (7.39 mL) than F-5 (2.46 mL). According to the dissolution profile in Figure 3, the increased water content in F-6 resulted in a slightly slower drug release rate than F-5. Such influence on drug release rate by water content is supported in a previous study on Liqui-Pellet technology, which investigated the effect of water content on Liqui-Pellet physicochemical properties (*14*). It was observed that a reduction of water content effectively reduces cohesive strength within the Liqui-Pellet structure, improving its propensity for disintegration, thus enhancing dissolution (*14*). Despite F-6 showing a slightly slower drug release rate than F-5, F-6 is more mechanically robust than F-5, which is shown in the friability studies (Table 3). This suggests that formulation scientists will need to adjust water content when manufacturing Liqui-Pellets to compromise between drug release performance and mechanical robustness of the dosage form.

According to Sarkar and Liew (*46*), the improved disintegration property with reduced water content can be explained in terms of microcrystalline cellulose (MCC) aggregates. MCC constitutes aggregates of small subunits that are held together by hydrogen bonding. To cause the de-aggregation of the MCC subunit, the mentioned hydrogen bond must first be broken. This would suggest that when less amount of polar deionized water is used in the blending stage, there would be less de-aggregation. As a result, the MCC should have a larger particle size. Throughout the granulation and extrusion process with this larger particle of MCC, along with less moistening liquid content, there will be less surface tension and van der Waals forces. The resultant extrudate and pellet will have reduced internal cohesive strength, leading to improved disintegration for a faster drug release rate.

Formulation F-8, which has a different carrier composition and more water content than F-5, showed a slower drug dissolution profile than F-5 (f_1= 38.95, f_2= 37.25). This is interesting because F-8 contains Neusilin US2 and Avicel PH-102 as part of the carrier material. It has been observed in previous work on Liqui-Pellet technology that Neusilin US2 significantly improves the drug dissolution rate of effervescent Liqui-Pellet (*2,3*). However, Neusilin US2 does not seem to have the same effect as the HCTZ Liqui-Pellet in this study.

In general, the three best performing formulations (F-5, F-6, and F-8) all contain PEG 200 as the non-volatile co-solvent. Formulations containing PEG 200 have the fastest drug release rate among all of the other formulations with a different liquid vehicle. This is supported by the saturation solubility studies, where HCTZ is most soluble in PEG 200 among the different non-volatile co-solvents. The solubility test data indicate that HCTZ is considered freely soluble in PEG 200 (156 mg/mL), which is a suitable liquid vehicle for HCTZ.

It can be clearly seen that formulations F-1, F-2, F-4, and F-7 have almost identical drug dissolution profiles. Avicel

PH-102 is used for F-1 and Avicel PH-101 is used for F-2; both have an almost identical drug dissolution profile (f_1 = 1.89, f_2 = 90.53), indicating that the two different Avicel do not have any major effect on the drug release rate.

Formulations F-1 (containing Tween 80) and F-4 (containing Kolliphor EL) have almost identical drug release profiles despite containing different non-volatile co-solvents. This is unusual because HCTZ showed markedly different solubility in Tween 80 (~27.46 mg/mL) and Kolliphor EL (~95.93 mg/mL). Usually, it would have been expected that the liquid vehicle that can dissolve more API gives a faster drug release rate. Such results serve as another reminder that the drug dissolution results may not always correlate to the saturation solubility test data. Other physicochemical characteristics of the liquid vehicle such as lipophilicity, viscosity, polarity, chemical structure, and molecular mass may too affect drug release rate (*6*).

Formulations F-4 and F-7 are very similar in terms of composition. Both formulations have almost identical drug dissolution profiles (f_1 = 1.02, f_2 = 96.42). The key difference in these formulations is that F-7 contains a binary carrier (Neusilin US2 and Avicel PH-102) and around three times more water content used during the production compared to F-4. Previous studies on Liqui-Pellet have shown that Neusilin US2 can markedly improve drug release rate; however, this is not the case for F-7. Perhaps the larger amount of water content levels out the fast drug releasing influence of Neusilin US2, resulting in F-7 having a similar drug release rate as F-4. The reason why water content is increased in F-7 relative to F-4 is that the Neusilin US2 in F-7 seems to require greater water content for the Liqui-Pellet to be successfully produced.

Overall, it is possible to achieve enhanced drug release of HCTZ using Liqui-Pellet formulations. However, there is room for optimization to bring out the potential of how fast HCTZ can be released in the Liqui-Pellet dosage form. Further investigation is currently undergoing to realize the potential of enhanced release HCTZ Liqui-Pellet.

CONCLUSION

Liqui-Pellet is proven a viable approach for dissolution enhancement of HCTZ. It is found that among the non-volatile co-solvents used in this study, PEG 200 is the most suitable. HCTZ Liqui-Pellet is able to achieve 100% drug release in approximately 40 min and is considered as a rapid releasing dosage form. However, there is potential for further improvement as the formulation is yet to be optimized. Water content has been shown to affect the drug dissolution rate as expected; therefore, it is a crucial parameter to consider in Liqui-Pellet technology during production. Formulation containing the binary mixture of carriers (Avicel PH-101 and Neusilin US2) surprisingly did not show improvement in drug release rate; however, this could be due to high water content overlapping the influence of Neusilin US2. Avicel PH-101 and PH-102 did not show a significant difference in drug dissolution performance. The use of HCTZ Liqui-Pellet shows no issue in flowability, robustness, and particle size distribution, which reflects the potential industrial manufacturing feasibility. Overall, Liqui-Pellet seems like a commercially viable option for the rapid drug-releasing dosage form of poorly water-soluble drugs.

CONFLICTS OF INTEREST

This technology is protected by international patent WO2020/021254 (filed July 24, 2019, published January 30, 2020).

FUNDING

The authors disclosed no financial support related to this article.

REFERENCES

1. Lam, M.; Nokhodchi, A. Pharmaceutical methods and compositions. International patent WO/2020/021254, January 30, 2020. World Intellectual Property Organization website. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020021254 (accessed July 19, 2022).
2. Lam, M.; Asare-Addo, K.; Nokhodchi, A. Rapid releasing naproxen Liqui Pellet using effervescent agent and neusilin. *Iran J. Basic Med. Sci*. **2021**, *24* (1), 108–115. DOI: 10.22038/ijbms.2020.51697.11729
3. Lam, M.; Asare-Addo, K.; Nokhodchi, A. Liqui-Tablet: the innovative oral dosage form using the newly developed Liqui-Mass technology. *AAPS PharmSciTech*. **2021**, *22* (3), 85. DOI: 10.1208/s12249-021-01943-w.
4. Lam, M.; Ghafourian, T.; Nokhodchi, A. Liquisolid system and Liqui-Mass system are not the same. *AAPS PharmSciTech* **2020**, *21* (3), 105. DOI: 10.1208/s12249-020-01650-y.
5. Tiong, N.; Elkordy, A. A. Effects of liquisolid formulations on dissolution of naproxen. *Eur. J. Pharm. Biopharm*. **2009**, *73* (3), 373–384. DOI: 10.1016/j.ejpb.2009.08.002.
6. Spireas, S.; Sadu, S. Enhancement of prednisolone dissolution properties using liquisolid compacts. *Int. J. Pharm*. **1988**, *166* (2), 177–188. DOI: 10.1016/S0378-5173(98)00046-5.
7. Loftsson, T.; Brewster, M. E. Pharmaceutical applications of cyclodextrins: basic science and product development. *J. Pharm. Pharmacol*. **2010**, *62*, 1607–1621. DOI: 10.1111/j.2042-7158.2010.01030.x.
8. Joint Formulary Committee. *British National Formulary*. Royal Pharmaceutical Society: London. https://www.pharmpress.com/product/MC_BNF/british-national-formulary (*accessed February 2, 2022*).

9. Moffat, A. C.; Osselton, M. D.; Widdop, B. *Clarke's Analysis of Drugs and Poisons*, 4th ed.; Pharmaceutical Press: London, UK, 2011.
10. Baka, E.; Comer, J. E.; Takács-Novák, K. Study of equilibrium solubility measurement by saturation shake-flask method using hydrochlorothiazide as model compound. *J. Pharm. Biomed. Anal*. **2008**, *46* (2), 335–341. DOI: 10.1016/j.jpba.2007.10.030.
11. Nokhodchi, A.; Hentzschel, C. M.; Leopold, C. S. Drug release from liquisolid systems: speed it up, slow it down. *Expert Opin. Drug Deliv*. **2011**, *8* (2), 191–205. DOI: 10.1517/17425247.2011.548801.
12. Lam, M.; Ghafourian, T.; Nokhodchi, A. Liqui-Pellet: The emerging next-generation oral dosage form which stems from liquisolid concept in combination with pelletization technology. *AAPS PharmSciTech*. **2019**, *20* (6), 231. DOI: 10.1208/s12249-019-1441-9.
13. Lam, M.; Ghafourian, T.; Nokhodchi, A. Optimising the release rate of naproxen liqui-pellet: a new technology for emerging novel oral dosage form. *Drug Deliv. Transl. Res*. **2020**, *10* (1), 43–58. DOI: 10.1007/s13346-019-00659-6.
14. Lam, M.; Commandeur, D.; Maniruzzaman, M.; Tan, D. K.; Nokhodchi, A. The crucial effect of water and co-solvent on Liqui-Pellet pharmaceutical performance. *Adv. Powder Technol*. **2020**, *31* (5), 1903–1914. DOI: 10.1016/j.apt.2020.02.025.
15. Lam, M.; Nokhodchi, A. Producing High-Dose Liqui-Tablet (Ketoprofen 100 mg) for Enhanced Drug Release Using Novel Liqui-Mass Technology. *J. Pharm. Innov*. **2021**, 1–13. DOI: 10.1007/s12247-021-09561-6.
16. Reynolds, A. D. A new technique for production of spherical particles. *Manuf. Chem*. **1970**, *41*, 40.
17. Bechgaard, H.; Nielsen, G. H. Controlled-release multiple-units and single-unit doses a literature review. *Drug Dev. Ind. Pharm*. **1978**, *4* (1), 53–67. DOI: 10.3109/03639047809055639.
18. Hancock, B. C. Disordered drug delivery: destiny, dynamics and the Deborah number. *J. Pharm. Pharmacol*. **2002**, *54* (6), 737–46. DOI: 10.1211/0022357021778989.
19. Gullapalli, R. P. *Soft gelatin capsules (softgels). J. Pharm. Sci*. **2010**, *99* (10), 4107–4148. DOI: 10.1002/jps.22151.
20. *Draft Guidance on Hydrochlorothiazide/Metoprolol Succinate*. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).
21. Moore, J. W.; Flanner, H. H. Mathematical comparison of dissolution profiles. *Pharm. Technol*. **1996**, *20*, 64–74.
22. *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.
23. *SUPAC-MR: Modified Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.
24. Adams, E.; De Maesschalck, R.; De Spiegeleer, B.; Vander Heyden, Y.; Smeyers-Verbeke, J.; Massart, D. L. Evaluation of dissolution profiles using principal component analysis. *Int. J. Pharm*. **2001**, *212* (1), 41–53. DOI: 10.1016/S0378-5173(00)00581-0.
25. O'Hara, T.; Dunne, A.; Butler, J.; Devane, J. A review of methods used to compare dissolution profile data. *Pharm. Sci. Technol. Today* **1998**, *1* (5), 214–223. DOI: 10.1016/S1461-5347(98)00053-4.
26. Costa, P. An alternative method to the evaluation of similarity factor in dissolution testing. *Int. J. Pharm*. **2001**, *220* (1-2), 77–83. DOI: 10.1016/S0378-5173(01)00651-2.
27. Yuksel, N.; Kanik, A. E.; Baykara, T. Comparison of in vitro dissolution profiles by ANOVA-based, model-dependent and -independent methods. *Int. J. Pharm*. **2000**, *209* (1-2), 57–67. DOI: 10.1016/S0378-5173(00)00554-8.
28. Costa, P.; Sousa Lobo, J. M. Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci*. **2001**, *13* (2), 123–133. DOI: 10.1016/S0928-0987(01)00095-1.
29. Spireas, S.; Sadu, S.; Grover, R. In vitro release evaluation of hydrocortisone liquisolid tablets. *J. Pharm. Sci*. **1998**, *87* (7), 867–872. DOI: 10.1021/js970346g.
30. Lam, M.; Nokhodchi, A. Factors affecting performance and manufacturability of naproxen Liqui-Pellet. *Daru* **2020**, *28* (2), 567–579. DOI: 10.1007/s40199-020-00362-9.
31. Muley, S.; Nandgude, T.; Poddar, S. Extrusion – spheronization a promising pelletization technique: In-depth review. *Asian J. Pharm. Sci*. **2016**, *11* (6), 684–699. DOI: 10.1016/j.ajps.2016.08.001.
32. Barrau, J. P.; Bataille, B.; Duru, C.; Jacob, M.; Cassanas, G. [Interest of the wetting/granulometric yield relationship in extrusion/spheronization: application to four varieties of lactose] [Article in French]. *Pharm. Acta Helv*. **1992**, *67*, 124–128.
33. Bianchini, R.; Vecchio, C. Oral controlled release optimization of pellets prepared by extrusion-spheronization processing. *Farmaco* **1989**, *44* (6), 645–654.
34. Fielden, K. E.; Newton, J. M.; Rowe, R. C. A comparison of the extrusion and spheronization behaviour of wet powder masses processed by a ram extruder and a cylinder extruder. *Int. J. Pharm*. **1992**, *81* (2-3), 225–233. DOI: 10.1016/0378-5173(92)90014-S.
35. Fielden, K. E.; Newton, J. M.; Rowe, R. C. The influence of lactose particle size on spheronization of extrudate processed by a ram extruder. *Int. J. Pharm*. **1992**, *81* (2-3), 205–224. DOI: 10.1016/0378-5173(92)90013-R.
36. Newton, J. M.; Chow, A. K.; Jeewa, K. B. The effect of excipient source on spherical granules made by extrusion/spheronization. *Pharm. Technol*. **1993**, *17*, 166.
37. Wan, L. S. C.; Heng, P. W. S.; Liew, C. V. Spheronization conditions on spheroid shape and size. *Int. J. Pharm*. **1993**, *96* (1-3), 59–65. DOI: 10.1016/0378-5173(93)90212-X.

38. Vervaet, C.; Baert, L.; Remon, J. P. Extrusion-spheronisation a literature review. *Int. J. Pharm*. **1995**, *116* (2), 131–146. DOI: 10.1016/0378-5173(94)00311-R.
39. Malinowski, H. J.; Smith, W. E. Use of factorial design to evaluate granulations prepared by spheronization. *J. Pharm. Sci*. **1975**, *64* (10), 1688–1692. DOI: 10.1002/jps.2600641023.
40. Chariot, M.; Frances, J.; Lewis, G. A.; Mathieu, D.; Luu, R. P. T.; Stevens, H. N. E. A factorial approach to process variables of extrusion-spheronisation of wet powder masses. *Drug Dev. Ind. Pharm*. **1987**, *13* (9-11), 1639–1649. DOI: 10.3109/03639048709068685.
41. Hasznos, L.; Langer, I.; Gyarmathy, M. Some factors influencing pellet characteristics made by an Extrusion/Spheronisation process Part I.: Effects on size characteristics and moisture content decrease of pellets. *Drug Dev. Ind. Pharm*. **1992**, *18* (4), 409–437. DOI: 10.3109/03639049209043861.
42. Ku, C. C.; Joshi, Y. M.; Bergum, J. S.; Jain, N. B. Bead manufacture by extrusion/spheronization-a statistical design for process optimization. *Drug Dev. Ind. Pharm*. **1993**, *19* (13), 1505–1519. DOI: 10.3109/03639049309069323.
43. Hellén, L.; Yliruusi, J. Process variables of instant granulator and spheroniser: III. Shape and shape distributions of pellets. *Int. J. Pharm*. **1993**, *96* (1-3), 217–223. DOI: 10.1016/0378-5173(93)90230-D.
44. *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Silver Spring, MD, 2017.
45. Khan, A.; Iqbal, Z.; Shah, Y.; Ahmad, L.; Ismail; Ullah, Z.; Ullah, A. Enhancement of dissolution rate of class II drugs (Hydrochlorothiazide); a comparative study of the two novel approaches; solid dispersion and liqui-solid techniques. *Saudi Pharm. J.* **2015**, *23* (6), 650–657. DOI: 10.1016/j.jsps.2015.01.025.
46. Sarkar, S.; Liew, C. V. Moistening liquid-dependent de-aggregation of microcrystalline cellulose and its impact on pellet formation by extrusion-spheronization. *AAPS PharmSciTech* **2014**, *15* (3), 753–761. DOI: 10.1208/s12249-014-0098-7.

The new DT 951x and ZT 730 with AirBasket

NEW!

DIGITAL

Digital high volume dissolution testing with up to 14 test stations

- Intuitive user interface with the new TestAssist for easy dissolution testing
- New AirLift system for easy raising and lowering of the dissolution head
- Up to 14 test stations, upgradeable at any time

Cable-free automated disintegration testing

- Automatic determination of the disintegration time
- Acid proof
- Sealed, can be easily cleaned in a dishwasher

For **live online demos** contact us at **sales@erweka.com**

More info about the DT 951x and the ZT 730 at **www.erweka.com**

ERWEKA America Inc.
31 Northfield Avenue
Edison, 08837, NJ
United States

sales.usa@erweka.com
+1 (732) 662-1143

ERWEKA
www.erweka.com

dx.doi.org/10.14227/DT290322P138

Contribution of Multivariate Analysis to the In Vitro Dissolution Profile for Testing Clopidogrel Drugs Similarity

El Khabbaz Choukri[1], El Orche Aimen[2*], Cheikh Amine[3], Bouchafra Houda[4], Moulay El Abbes Faouzi[5], Cherrah Yahya[3,5], Boussen Ratiba[1], and Mustapha Bouatia[6]

[1]Laboratory of Nanotechnology Materials and Environment, Mohammed V University; Faculty of Sciences, Rabat, Morocco.
[2]Team of Analytical & Computational Chemistry, Nanotechnology and Environment, Faculty of Sciences and Techniques, University of Sultan Moulay Slimane, Beni Mellal, Morocco.
[3]Abulcasis University of Health Sciences, Cheikh Zaid Hospital, Rabat, Morocco.
[4]Laboratory of Drug Science, Biomedical Research and Technology, Faculty of Medicine and Pharmacy, Hassan I University, Casablanca, Morocco.
[5]Laboratory of Pharmacology and Toxicology, Bio Pharmaceutical and Toxicological Analysis Research Team, Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco.
[6]Laboratory of Analytical Chemistry & Bromatology, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Rabat, Morocco.

e-mail: aimen.elorche@gmail.com

ABSTRACT

A novel approach to test the similarity of clopidogrel batches by comparing drug dissolution profiles, based on the combination of principal component analysis with hierarchical cluster analysis (PCA-HCA), is presented. Dissolution curves corresponding to five brands of clopidogrel drugs, taken as model drugs, were prepared by measuring the dissolution rate in pH 1.2, 4.5, and 6.8). The dissolution data were analyzed by similarity factor (f_2) calculation and the PCA-HCA method, and the results were compared. Unlike the f_2 test, the PCA-HCA approach reflects the variability inside the individual dissolution patterns, which it is also sensitive to profile variations (form and size). The comparison between the PCA-HCA results with those of f_2 tests gives approximately similar results, knowing that PCA-HCA represents, in general, a more discriminative criterion.

KEYWORDS: Clopidogrel, dissolution, similarity, multivariate analysis

INTRODUCTION

Clopidogrel belongs to the second class of the biopharmaceutical classification system (BCS) with low solubility and high permeability; its solubility is very sensitive to the pH value (*1*). It is an inactive prodrug that is absorbed from the intestine and subsequently metabolized in active moiety (*2*). It is extensively used for reducing the risk of atherosclerotic events associated with platelet aggregation, stroke, and vascular-related death (*3*). Clopidogrel is dedicated for patients with acute coronary syndrome and those with atherosclerosis who have suffered from a myocardial infarction, stroke, or have peripheral artery disease (*4*).

Generally, clopidogrel requires metabolic activation in the liver. Up to 85% of the absorbed drug can be converted by carboxylesterases to a predominant metabolite carboxylic acid derivative that is considered inactive (*5*). The active metabolite clopidogrel is available in low quantity, whereas the remaining types of clopidogrel are hydrolyzed to an inactive acid derivate compound by esterase paraoxonase-1 (*6*).

The efficacy of clopidogrel can be affected by inter-individual variability in drug treatment. This variability is attributed to the clopidogrel P2Y12 receptor polymorphism; the hepatic metabolism variable is essential for its biotransformation and low oral bioavailability (*7*). This later can be related to its low solubility and further impact on intestinal absorption. These factors may be the main reasons behind the clinical limited effectiveness of this drug (*8*). As clopidogrel faces protonation in the stomach, only the non-ionized form can be absorbed in the intestine where factors such as solubility, limitation, and precipitation in the intestinal pH can limit the protonation process (*9*). Furthermore, efforts

*Corresponding author

to improve dissolution of clopidogrel in the intestines, the primary site of drug absorption, are needed and remain a challenge for clopidogrel management (*10*).

Clopidogrel was genericized after its pharmaceutical patent expired in May 2012. Several generic drugs are now available on the international market. It is critically important to demonstrate that these preparations are bioequivalent to the original drug in view of the above-mentioned elements. For this reason, the pharmaceutical industries try to respect as much as possible the similarity in excipients composition compared to those used in the reference product and attempt to have a similar manufacturing process to minimize the sources of variability between the generic and the originator drug (*5*).

However, more importantly, the commercially available salts of clopidogrel (bisulfate, besylate, hydrogen sulfate, etc) differ on their physicochemical properties. For instance, the bisulfate clopidogrel form of salt has been reported to have poor stability and degrades under moisture and heat conditions (*6*).

Clopidogrel base is a white to off-white powder with chemical formula $C_{16}H_{16}ClNO_2S$ ((αS)-a-(2-Chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester), and it has a molecular weight of 321.826 g/mol. It is soluble in methanol, sparingly soluble in methylene chloride, and practically insoluble in ethyl ether (*4*). The pKa value of clopidogrel is about 4.56 ± 0.20 (*11*). Similar to all bases, clopidogrel is practically insoluble in water at neutral pH, and it is freely soluble at pH 1. This feature is one of the reasons why the hydrogen sulfate salt is the preferred form of the active ingredient (*12*). The interaction site for salt formation is at the pyridine nitrogen, which is only capable of forming salts with extremely strong acids. Clopidogrel bisulfate has six different polymorphs and one amorphous form, but only I and II forms are used in pharmaceutical formulations (*13*). Polymorphic I (first) form has a melting point range between [198 and 200] °C, while the II (second) form has a melting point between [176 and 178] °C (*11*).

In pharmaceutical development, comparative study of the dissolution kinetics of an originator and a generic drug has an important place in early development. Later on, the dissolution test is a key parameter of quality control and is used to assess reproducibility between batches of drug products. Combined with other pharmaco-technical tests, dissolution studies ensure the quality, efficiency, and safety of drug products use.

The in vitro dissolution study, as a routine quality control test, must be robust, reproducible, and discriminatory to ensure consistent product quality and to detect alterations in product quality that may affect the in vivo drug performance (*14*).

The objective of this work is to evaluate the dissolution profile of five generic brands of clopidogrel available on the Moroccan market with the originator brand in three different pH dissolution media (pH 1.2, 4.5, and 6.8), with pH 4.5 being close to pKa of the base. Subsequently, the dissolution data will be analyzed to determine and compare similarity using the similarity factor (f_2) calculation and the PCA-HCA approach.

MATERIALS AND METHODS

API Reference and Various Drug Products

The Standard of clopidogrel bisulfate was provided by Medispray, India.

The reference product, Plavix (R), and five generic products (T1–T5) of clopidogrel (75-mg tablets) were purchased from the Moroccan market. All of them are formulated with the bisulfate salt form of clopidogrel. Information on the generic drugs studied is provided in Table 1.

Table 1. General Information about Generic Bisulfate Clopidogrel (75 mg) Products Used in This Study

Generic Name	Batch No.	Expiry Date	Code
Pedovex	ET11/17	05/2022	C01
Agreter	CRR1S0290318	02/2023	C02
Pedovex	AAIH001125	02/2020	C03
Ceruvin	AALH009032	04/2023	C04
Agrel	7010818070	12/2020	C05

Preparation of Buffer Solutions

Three buffer solutions were prepared as dissolution media according to *United States Pharmacopeia* (USP) requirements (15). The first buffer solution was prepared at pH 1.2, which consisted mainly of a mixture of potassium chloride solution (0.2 M) and hydrochloric acid (0.2 M). The second buffer solution was prepared at pH 4.5, which consisted mainly of a mixture of sodium acetate tri-hydrate and acetic acid (2 M). The third buffer solution was prepared at pH 6.8, which consisted of a mixture of monobasic phosphate monobasic phosphate (0.2 M) and a solution of sodium hydroxide (0.2M).

Preparation of Standard Solution

A standard solution of clopidogrel bisulfate was prepared according to USP requirements (*15*). A sample (20.83

mg) of clopidogrel bisulfate was dissolved in 25 mL of methanol, the solution was diluted with the previously prepared media, obtaining a solution with a concentration of 0.0830 mg/mL, and the solution was filtered before characterization within the spectrophotometer.

Dissolution Test

The dissolution test was performed according to the USP guideline (*15*).

In vitro dissolution tests were performed using a SOTAX AT7 Smart semi-automated dissolution tester with the paddle setting (USP apparatus 2), 50 rpm ± 4%, 900 mL of dissolution media, 37 ± 0.5 °C. Six tablets of the finished product were weighed. After the stabilization of the conditions of the apparatus, the tablets were placed in the vessel at the same time to carry out the dissolution test according to the protocol. Samples (xx mL) were collected at 5, 10, 15, 20, 30, 45, and 60 minutes.

The amount dissolved was determined by UV absorption spectroscopy at a wavelength of 240 nm in a filtered portion of the solution under test in comparison with the standard solution. All samples were analyzed with a JENWAY 6705 UV/VIS spectrophotometer.

Comparison of Profiles

The similarity factor (f_2) analysis is the simplest and most widely applicable among the studied methods for comparing dissolution profiles. Moore and Flanner proposed a model-independent mathematical approach to compare the dissolution profile using the difference and similarity factors, f_1 and f_2, respectively, but f_1 is neither described nor requested in the majority of the international guidelines (*16*).

The f_2 is inversely proportional to the average of the difference squared between two dissolution profiles, emphasizing the larger difference among all time points. The f_2 measures the proximity between the two profiles without taking into account the shape. f_2 has been widely accepted since the regulatory interest is in knowing whether the dissolution profiles of the test and reference products are similar or not.

When the two profiles are identical, $f_2 = 100$. The agencies have established a standard of f_2 between 50 and 100 to indicate acceptable similarity between two dissolution profiles. The value of 50 corresponds to a mean difference of 10% between the curves.

For pharmaceuticals dissolving to 85% or greater within 15 minutes, the profile comparison is not necessary.

For a dissolution profiles comparison, at least 12 units should be used for each profile determination, the average of which are used to estimate f_2. The percentage coefficient of variation at the early point (first or before 10 minutes) should not be greater than 20%, and at the other time points it should not be greater than 10%. Because f_2 values are sensitive to the number of dissolution time points, only one measurement should be considered after 85% dissolution, per EMA and US-FDA reference tests.

For the scope of this work, the f_2 was calculated using only 6 tablets for each formulation. The value obtained will give an analysis trend of the similarity between the profiles and will allow for comparison between the adapted approach and other methods.

Multivariate Data Analysis

Th Principal component (PC) analysis (PCA) is one of the most widely used methods of exploratory multivariate data analysis (*17, 18*). It is used to explore multidimensional data sets composed of quantitative variables. PCA can be considered as a projection method that allows to project the observations from the p-dimensional space of the p variables to a k-dimensional space ($k < p$) such a quantity of information is preserved (the information is here measured through the total variance of the scatterplot) on the first dimensions. If the information associated with the first two or three axes represents a sufficient percentage of the total variability of the scatterplot, then the observations can be represented on a two- or three-dimensional graph, which greatly facilitates the interpretation (*18*). The main objective of PCA is to study the similarity between individuals and the link between variables. PCA is performed in the dissolution data tables (the variables are the sampling times (column), and the individuals are the tablets of each drug (row)).

The number of significant PCs to retain can be obtained by various means, including cross-validation, by setting a threshold at the minimum explained variance, or by evaluating the residual variance (*19*). Observing the shape of the PCs is also a useful index. In this work, the total variability explained by the PCs was used with an increasing number of PCs until the optimal number of factors resulted in a low residual variance. In our study the first three PCs were selected arbitrary to be used as variables for the hierarchical ascending classification (HCA) analysis.

The HCA is an iterative classification method of simple principle (*20*). The HCA principle is to gather individuals according to a criterion of similarity defined beforehand, which will be expressed in the form of a 2 × 2 similarity matrix, expressing the similarity between two individual data points at a time. The main function of HCA is to group samples so that those belonging to the same cluster are more similar than samples from other groups.

The HCA is usually displayed as a dendrogram (*21*). This dendrogram represents a hierarchy of partitions. We can then choose a partition by truncating the tree at a given level of similarity, the level depending either on the user's constraints (the user knows how many classes he/she wants to obtain), or on more objective criteria.

In general, there are several calculation methods used for clustering analysis, among them we find the McQuitty's linkage method. This method has been considered as the best clustering algorithm (*22*). Based on McQuitty's linking method, the distance is calculated with the following distance matrix:

$$dmj = \frac{dkj - dij}{2}$$

Where *dmj* is the distance (*d*) between clusters *m* and *j*, *m* is the merged cluster that consists of clusters *k* and *i*, so *m* = (*k*, *i*); *dkj* is the distance between clusters *k* and *j*; and *dij* is the distance between clusters *i* and *j*.

A flow chart of the main procedures applied to develop this study is presented in Figure 1.

The PCA analysis was performed using Unscrambler software 10.4, and the HCA analysis was performed using Minitab 17 statistical software.

RESULTS AND DISCUSSION

The dissolution results are presented in Figure 2. The raw dissolution data are given in Tables 2–4.

The dissolution results at pH 1.2 showed that the dissolved quantity (*Q*) exceeded 85% within 15 min for the reference product (R) and for the generics T1–T3; however, *Q* did not exceed 85% for generics T4 and T5. The f_2 values for T4 and T5 versus R was calculated for the time points 5, 10, and 15 minutes. At pH 4.5, $_Q$ of the five generics did not exceed 85% after 15 min. The absence of complete dissolution could be attributed to the lower solubility of the drug in pH 4.5 compared to pH 1.2. The f_2 values for this pH reveal that only two generics are similar to R (f_2 between 50 and 100) whereas three generics are not ($f_2 < 50$). At pH 6.8, Q decreased for solubility reasons. The calculation of f_2 shows that three generics are similar to R and two were not.

In summary, the comparative study using f_2 analysis showed that only one generic was similar to the originator in all three pH values; two generics were similar at pH 1.2 and 6.8; one generic was similar at pH 1.2 and 4.5; and one generic was not similar to the originator at any pH value. These results do not exclude the in-vivo performance of the drug, but only indicate an in-vitro difference with respect to the behavior between the formulations.

The PCA and PCA-HCA were used to evaluate the similarity between the test and reference drugs. The purpose of these exploratory methods is to investigate the similarity between the samples and the relations between the batches. In both methods, the times within each formulation are closely linked together (i.e., dissolution at

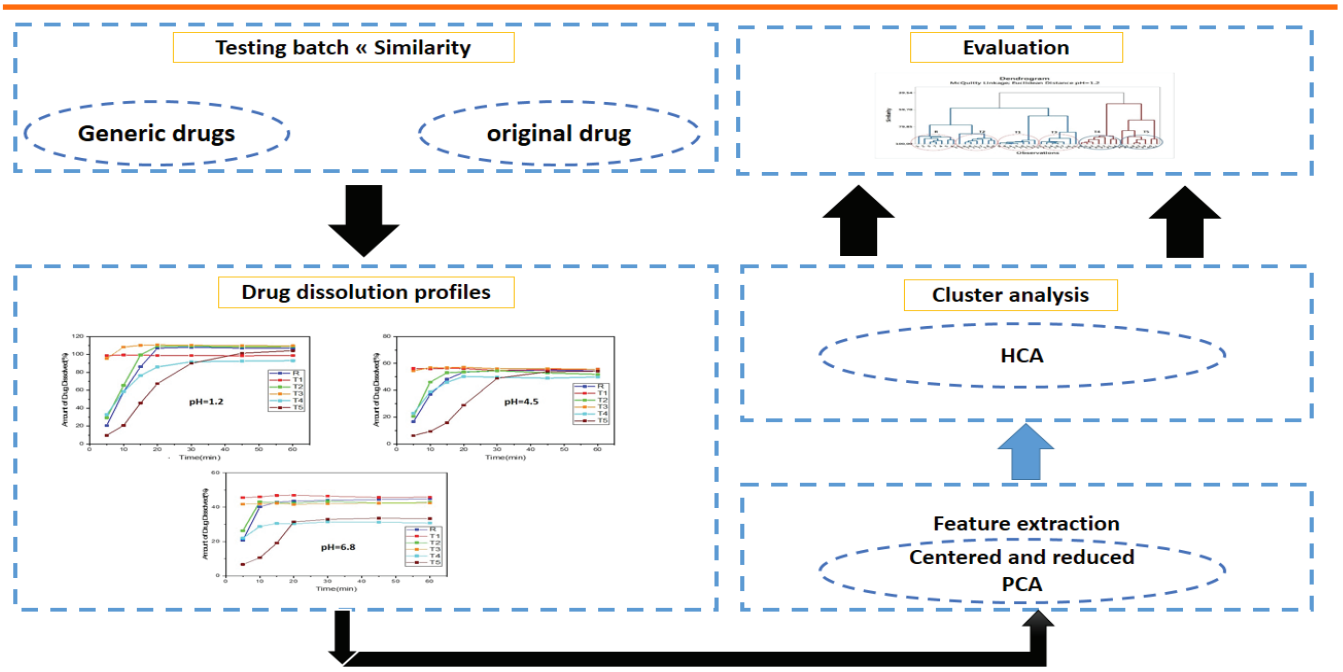


Figure 1. Principal steps employed to study the similarity of the drugs. HCA: hierarchical ascending classification; PCA: principal component analysis.

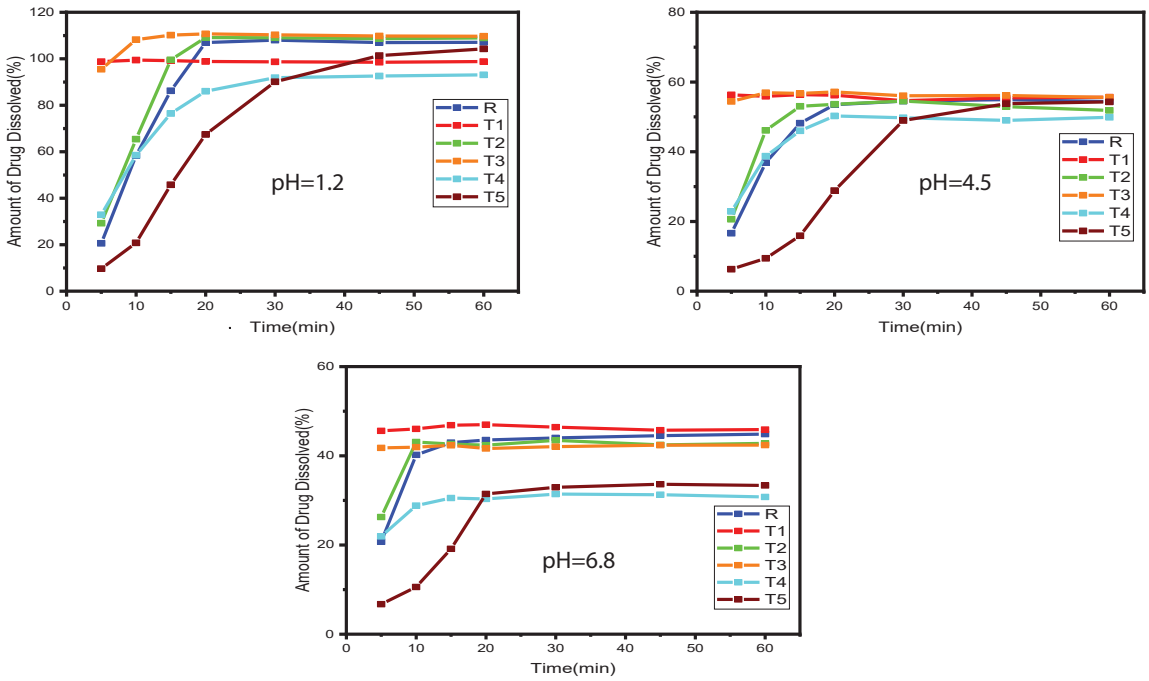


Figure 2. In vitro dissolution profiles of clopidogrel in pH 1.2, 4.5, and 6.8. R: reference; T: test.

time 2 depends on dissolution at time 1 etc...), with the exception of generic T5 with a larger dispersion of various times.

Application of the PCA on the obtained data by the dissolution at pH 1.2 (Fig. 3) shows that the first two PCs present 92% of the total data variability. The score plot PC1-PC2 shows that samples of batch R and T2 are very close to each other, which means that they present the same response pattern regarding the product amount released at different times. This plot also shows that T4 and R are not linked; T1, T3, T5, and R do not have the same response pattern; T1 and T3 are linked; and T1 and T5 are not linked.

PCA analysis at pH 4.6 shows that the first two PCs correspond to 89% of the total data variability. The score plot shows that the samples of batch R and T2 contribute in the same way along the PC1-PC2 axis, which means that they present a similar response behavior, while batch T1 and T2 have a similar response behavior along the PC1-PC2 axis. The T4 and T5 batches do not present the same response behavior compared to R, as they are far from each other.

The results found by the PCA at pH 6.8 reveal that the projection of the weights of the six batches on the first two PCs, which represent 96% of the total variability of the dissolution data, allow us to conclude that T1, T2, and T3 are similar to R because they contribute identically with the PC1 axis whereas T4 and T5 do not present the same pattern of response because they are very distant from R. These results are considered consistent with those found by the statistical approach based on the calculation of the similarity factor which shows that batches T4 and T5 do not have the same dissolution profile as R.

The observation of the results of PCA-HCA in form of dendrogram (Fig. 4) at pH 1.2 obtained on the data generated by PCA (PC1, PC2, and PC3) demonstrates the existence of two main clusters, the left one being sub-clustered in two. Cutting this tree at a certain height produces the desired partition, which is fixed at 50% of similarity. It shows that the four batches T1, T2, T3, and R belong to the first class, and batches T4 and T5 belong to the second class. In term of dissolution rate, T4 and T5 exhibit the slowest dissolution. In the first class, two subgroups exist: R and T2 in first subgroup and T1 and T3 in the second subgroup, this corresponds to faster dissolution. Congruent with the f_2 calculation, the approach developed by PCA-HCA shows that T4 is also not similar to R. The difference is due to the fact that only three points are used and the main difference between R and T4 is located after 15 minutes.

For the results found by the PCA-HCA approach on dissolution results at pH 4.5, there are two main clusters if we set the partitioning index at 50%, which allows us to conclude that all batches are similar to the reference except for the batch T5. However, starting from a

Table 2. Dissolution Results of Clopidogrel in pH 1.2

Sample	Time (min)						
	5	10	15	20	30	45	60
R	26.176691	55.6357511	80.7889512	95.312461	106.41956	106.185813	105.886698
R	23.359757	58.5757602	77.7934234	90.3707965	100.324724	104.328553	104.03467
R	26.2512013	57.9519204	78.2496579	93.2663544	102.51699	105.851828	105.093868
R	18.1797553	53.4659225	78.1528227	92.5087918	102.034715	105.724333	105.32183
R	27.143719	58.2657052	81.174836	95.9384778	104.768767	104.539283	103.792411
R	31.0628171	65.9786475	86.2069197	94.8544856	102.505016	104.038771	103.678424
T1	99.3608238	99.7068229	100.173411	99.4606212	99.3053808	99.0879402	98.870153
T1	98.5587479	99.9897163	99.2535027	98.9110565	98.6339947	99.1349706	98.5971019
T1	100.220627	99.488543	99.3406819	98.8053847	98.4643472	98.5723093	98.3585515
T1	95.6385171	97.918727	97.7232804	97.7232804	98.5050667	97.9838759	99.1565552
T1	99.5335082	100.295687	100.210518	99.866046	99.7150569	99.3065724	99.9870182
T1	99.3535523	99.6712441	99.1304882	99.1815688	98.6420992	98.4954722	99.5189211
T2	18.6649956	51.522327	91.889027	108.52311	108.570029	107.915138	108.448592
T2	33.9326252	66.7640827	92.9713254	108.140296	109.020878	108.506374	108.408401
T2	39.2121018	70.155704	103.650175	109.436483	109.343779	108.752314	109.721804
T2	25.1170693	67.8015686	108.598658	110.849031	110.340883	110.413475	110.340883
T2	34.4555317	67.2998164	91.1821825	108.717643	108.694705	108.670184	109.344108
T2	23.5682527	68.616491	109.71277	109.840462	109.532786	109.081203	109.347937
T3	92.2637903	102.292329	104.710033	106.628905	106.743693	106.306415	106.212533
T3	89.1030825	106.572384	107.832428	108.206243	107.162699	106.86168	106.292921
T3	93.9338695	104.414292	107.253408	107.578061	106.723393	106.354636	107.224265
T3	94.8671575	107.838646	109.731782	109.240969	109.100737	109.030621	109.170853
T3	88.5699995	103.113422	105.021287	105.754005	106.071695	104.821437	104.458335
T3	96.5457046	105.349692	106.52899	107.070644	106.770726	106.540352	106.170891
T4	31.0049567	59.1824205	77.4348137	86.2547246	91.6888101	92.5982165	92.8610288
T4	36.7072952	62.7435471	80.7909712	89.9155772	92.4198898	92.2187607	92.2505526
T4	27.8921975	53.5756089	73.9074582	81.5204393	90.8353283	92.3790104	92.6395599
T4	33.4129366	61.5241895	79.7101974	89.8820324	93.7658239	93.8891189	94.9987736
T4	37.2040637	59.3965408	75.4064135	86.9267922	91.3040694	92.3307794	93.0594493
T4	31.0761955	54.9504844	71.9863758	82.5439735	92.374553	93.4448191	94.447321
T5	8.95298226	20.8322634	39.8997207	58.5972689	77.6485151	100.319456	103.232307
T5	9.34335762	18.5687268	40.0652599	56.9072326	89.7742785	100.630686	103.996209
T5	9.77177873	21.8595864	44.6479319	68.8145605	90.4293022	101.113517	105.633148
T5	10.6067178	19.3147022	48.3194924	67.6996682	85.6394255	102.728026	106.590967
T5	8.97586903	22.7722344	57.4939611	76.5753826	99.3996829	103.415908	103.968283
T5	10.4278478	21.521736	44.6300154	76.5099336	98.7470258	101.463436	104.033182

R: Reference; T: Test

partitioning index equal to 56% we obtain three clusters, the first cluster contains R, T2, and T4, a second cluster contains T1 and T3, and a third contains T5. These results show that the batches T2 and T4 are closer to R than the others. Going ahead, we find that the formulation T2 is closer to R than T4. This finding agrees with the statistical calculation that showed batches T2 and T4 have a f_2 of 67.27 and 65.62, respectively. Dissolution at pH 4.5 showed many differences, which is probably because this pH is close to the pKa of clopidogrel, increasing the possible influence of the composition of the formulation on the dissolution and slight pH changes.

For the results obtained by PCA-HCA at pH 6.8, we obtained similar results as for pH 1.2: two classes in case of a partition index at 50%. Clusters are linked with

Table 3. Dissolution Results of Clopidogrel in pH 4.5

Sample	Time (min)						
	5	10	15	20	30	45	60
R	13.0540835	29.7437513	42.7998127	51.5458289	53.5138309	54.3777299	52.5908149
R	13.6611738	38.6519439	48.5752688	53.3229238	54.7444184	54.5123196	52.7967303
R	18.7497174	37.6370495	50.7126876	54.4981011	54.105686	54.8303518	55.0732541
R	17.2708514	38.2197545	48.6142484	53.4916648	53.9714106	55.6505212	55.1707753
R	20.0250862	41.0396009	49.3141837	54.336442	54.9638685	55.1204513	55.0427074
R	16.891162	35.8236698	49.0513352	53.7113839	55.7566948	55.1308759	55.5214345
T1	56.1950191	54.4913353	55.8015995	56.131718	54.1975185	55.1728996	55.2584354
T1	56.6481775	56.4085932	57.2354569	57.7297427	54.9587187	56.2679577	55.2986261
T1	57.8472904	56.9512219	56.385176	56.3901833	55.5840175	55.5086813	55.8357451
T1	57.4306511	56.2721077	57.7616635	57.0996387	55.692836	57.347898	57.8444166
T1	55.4649328	56.770681	56.127295	56.535059	54.6878092	54.1332051	55.5801458
T1	54.1908626	54.429672	54.8216144	53.3521015	52.7393526	54.2082148	53.9787322
T2	21.2930303	46.9671389	53.7633622	54.0056683	55.4199266	53.7811724	52.3064476
T2	20.9845011	40.8448634	52.1698015	53.3343117	53.9534841	52.1924699	50.9754984
T2	22.8249256	52.2815871	53.2205078	52.0675764	54.1557498	52.697707	51.4002264
T2	15.3720222	39.4292369	51.8805749	53.0334765	53.5714973	52.3417355	52.1111552
T2	18.5054352	44.6167083	52.9560833	53.8921998	54.5133855	53.1282975	51.9037114
T2	24.7273058	52.5472805	54.129275	55.2315581	55.6237102	53.4419665	52.28153
T3	53.8603636	56.3366105	56.3383836	57.4470649	55.6291114	55.4728498	56.0227575
T3	55.477883	57.4114675	56.6109702	57.570717	56.3743325	56.2953788	55.4242033
T3	53.9855224	56.5822749	56.8159586	56.7352951	55.2534039	55.6414194	54.6334535
T3	54.4573453	56.8423385	56.9218383	57.0808379	56.3653399	56.2063403	56.1268406
T3	54.4765349	57.3957666	57.5499414	57.7023616	57.4626561	57.534809	56.2082045
T3	54.2968565	56.930685	56.1550156	56.2289197	55.1509547	55.6079532	55.0699403
T4	23.5365516	40.4225745	42.9918906	51.138198	50.4292411	48.8369825	50.5477411
T4	23.4706072	36.0394738	44.5806182	49.5298844	49.1502128	49.0922356	49.1136668
T4	25.3030005	43.8252408	50.1593143	52.2477829	50.9491082	48.6719769	50.1717993
T4	21.7225417	39.0352441	46.46664	50.8764793	49.4065328	50.3048334	50.1415061
T4	20.4239202	37.2999073	45.7184336	49.9591781	48.7895861	48.0206856	50.3269422
T4	22.6994803	35.6743678	46.0241544	47.7250558	49.653665	48.9605153	48.9803451
T5	6.32333934	9.61630612	20.5938867	31.7451395	44.7876856	52.3003836	53.3966486
T5	5.83974903	8.02702439	11.0652722	21.9904693	37.1464156	53.3063427	53.3889848
T5	6.47107325	10.5453066	13.7334939	32.242254	52.051805	53.6176206	54.320188
T5	5.95671141	8.73651007	13.6607248	26.2095302	53.5309799	54.5634765	55.3577047
T5	6.95567327	9.3010174	17.213974	33.1560346	54.8707771	54.7166457	53.8629949
T5	6.17266009	10.3381065	19.0446787	27.70245	51.2585783	54.2360954	55.406219

R: Reference; T: Test

dissolution rate, the first cluster contains R, T1, T2, and T3, whereas the other cluster contains T4 and T5, which demonstrates that the batches T1, T2, and T3 have a similar relationship with R while the batches T4 and T5 do not. Again, the first cluster could be divided in two subgroups, R and T2 in one subgroup and T1 and T3 in the second. These results are exactly the same as those obtained by the statistical analysis, which shows that T1, T2, and T3 have a value of $f_2 > 50\%$ compared to the T4 and T5, which have an f_2 less than 50%.

These results have reported a certain similarity and complementarily between the in vitro dissolution method and other statistical methods for assessing similarity. The latter could be used to support the dissolution results especially in cases where the factor is very close to 50

Table 4. Dissolution Results of Clopidogrel in pH 6.8

Sample	Time (min)						
	5	10	15	20	30	45	60
R	17.6307533	40.2915767	43.3936915	44.4380687	44.4588828	44.7686453	43.7756911
R	17.2743217	36.9135803	42.0075697	42.6099936	43.495484	43.2301595	45.3922723
R	19.2273943	40.8945145	44.0669511	44.3907458	45.0091269	45.3270799	46.2333711
R	21.0715282	40.2668245	42.287382	42.8646842	44.5965906	44.8852417	46.328497
R	24.5485943	41.3835398	43.593238	44.3408985	43.4941993	45.1011419	44.1119731
R	24.5038041	41.4839273	42.3600807	42.52431	42.9687185	43.831417	43.2876795
T1	44.7082201	44.7292555	48.804451	46.6463045	48.0997666	45.5233402	47.686341
T1	46.0170824	49.0740006	45.9057898	46.4973343	47.3719492	45.9505487	45.9638555
T1	46.6645255	46.1026891	49.1350004	50.0006298	47.00032326	45.8739415	46.5971052
T1	47.1031821	45.7987863	46.5234506	46.8133164	45.7987863	46.9582492	45.9437192
T1	45.7267538	46.7578235	47.0606524	46.7852435	47.9461546	46.236845	45.6783657
T1	43.263989	43.6899355	43.7043872	45.0757826	42.2417175	43.8781886	43.3506995
T2	23.6526395	42.8591916	42.5963845	41.4762494	42.9288996	42.2394316	42.9713654
T2	25.7214079	43.8899308	42.9150577	41.8032419	42.1100729	41.5690501	42.0140146
T2	24.8735614	42.0535524	42.6471982	41.961031	41.2780405	41.5849891	41.8895553
T2	33.8525341	44.6970688	42.3523046	43.6712345	48.2142152	43.96433	44.2574255
T2	24.0243902	42.6563139	42.9745231	43.4355603	43.7484796	43.0477682	43.2146043
T2	25.4389748	42.4238422	42.3056699	41.902447	42.4957037	42.2346068	42.3982914
T3	41.9852646	42.2458338	42.3789202	42.1355122	42.0174855	42.2724511	41.6574517
T3	42.1978174	41.8286216	42.7172183	41.720881	42.1037637	42.982183	41.7429906
T3	41.8320376	41.7158375	41.7234458	41.1130495	40.9978869	41.8648918	42.3590881
T3	41.1328949	41.3777336	41.5001529	41.1328949	41.5001529	41.7449916	42.1122496
T3	41.3304055	41.8458067	43.11184	41.9887007	42.7460035	42.7505676	43.3758603
T3	42.0887615	42.6020562	42.6090781	41.7380219	42.9959801	42.6259304	43.127288
T4	21.6528354	28.9608099	33.5744373	30.7330015	32.8794714	33.0306977	31.3829286
T4	20.0617305	31.5517568	29.776532	30.0892688	31.0906918	30.7080884	30.4252945
T4	26.0692665	28.9189786	30.4461414	32.2649275	31.6749447	31.3866896	30.6027591
T4	18.8858169	27.4969666	29.3561921	29.845462	31.6068335	31.5089795	30.7261478
T4	24.606346	27.8751623	31.2232658	29.6719724	31.3408294	30.1851514	31.3583273
T4	20.2733913	28.205287	28.815137	29.3230706	29.8277077	30.7191326	30.0491217
T5	6.5582978	9.44678267	16.4599395	28.8018579	32.8389123	33.5679013	34.0875336
T5	6.59879493	9.04813929	11.8938696	31.4920614	32.3214933	32.1290284	33.1537892
T5	6.49856556	9.92981981	24.1821174	31.7023437	33.1683059	35.5557718	33.1881044
T5	6.92188011	10.9510342	15.0834999	32.6464793	32.9564142	32.9564142	33.2663492
T5	7.25574645	13.4225467	31.4760357	32.6394672	32.8600021	34.945299	33.81283
T5	6.55303432	10.6839308	15.7226594	31.3574828	33.4297209	32.5152433	32.5259338

R: Reference; T: Test

and where bioequivalence is not required. The main issue would be to understand the reason of those dissimilarities and the possible impact in vivo. Furthermore, the selection of the most appropriate media to reflect in vivo behavior is mandatory. A similarity in all pH could be seen as a promising indication of absence of differences in vivo whereas a difference in one only one condition could be inconclusive. For instance, one formulation that was not equivalent in one pH successfully passed bioequivalence. The reason for this difference could be linked with formulation composition and/or interaction between some excipient and dissolution media or excipients and API. For example, it is well documented that sodium croscarmellose interact with basic components as a function of pH value and its ionization (*23*, *24*).

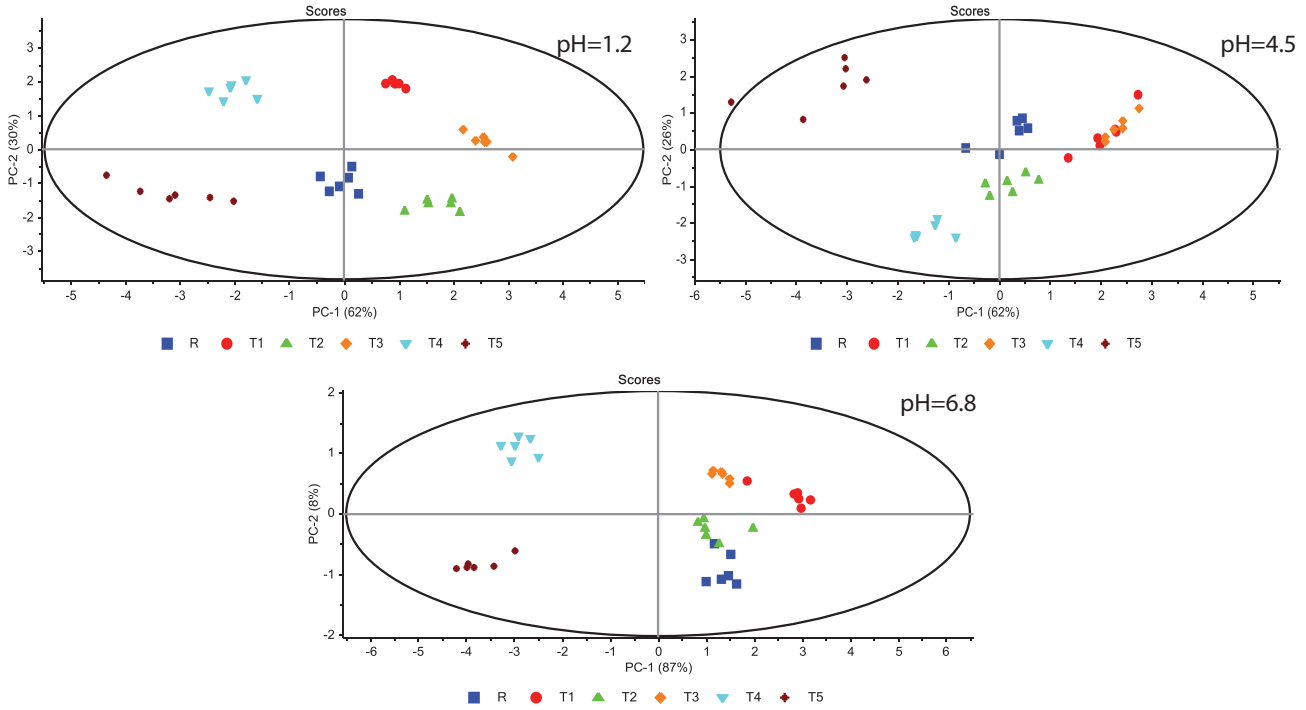


Figure 3. Score plot of PC1 versus PC2. Top left (pH 1.2): PC-2: 30%, PC-1: 62%. Top right (pH 4.5): PC-2: 25%, PC-1: 62%. Bottom (pH 6.8): PC-2: 8%, PC-1: 87%. PC: principal component.

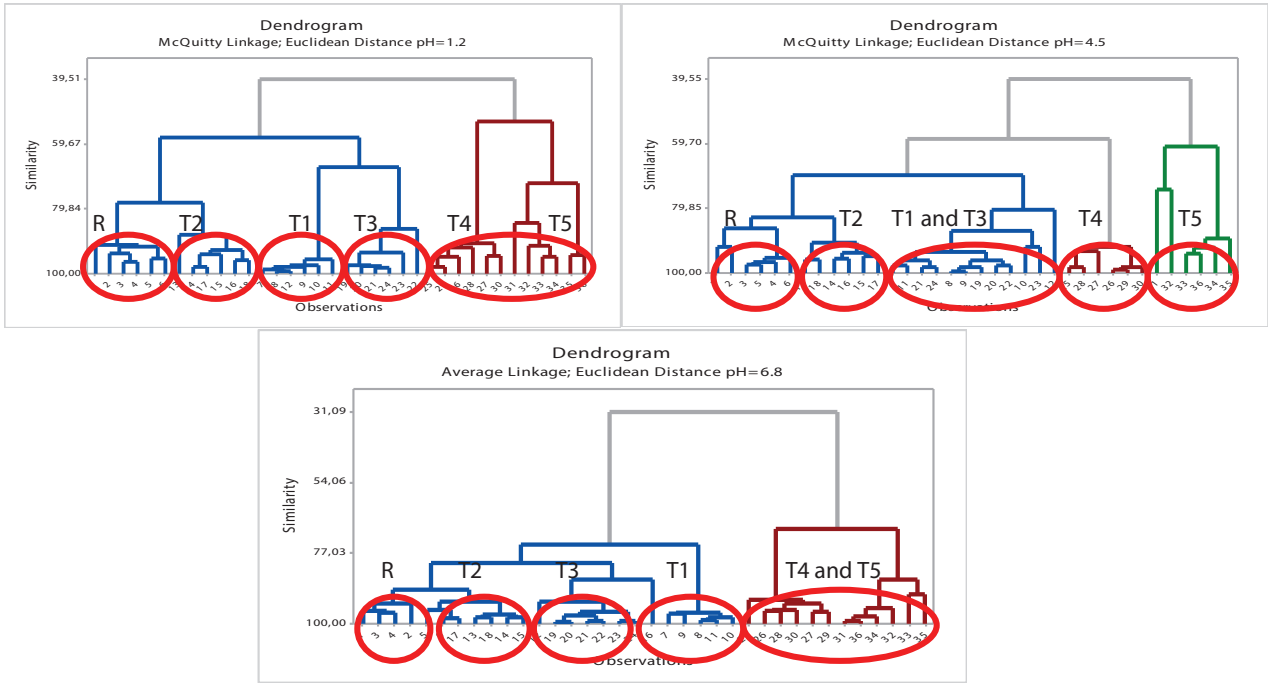


Figure 4. Hierarchical clustering analysis (HCA) generated by the three principal components of the principal component analysis (PCA); R: reference; T: test.

Furthermore, these results reinforce the utility of bioequivalence as a tool for assessing the quality of generic drugs in vivo. Inconclusive results on in vitro dissolution tests could not always preclude absence of bioequivalence. However, nonequivalent in vivo dissolution behavior could have considerable clinical consequences and should prompt the authorities to carry out the necessary investigations to guarantee the quality of the products placed on the market.

Overall, the current dissolution study was able to discriminate between formulations. One formulation was similar to the reference in all pH levels, and all other formulations showed a difference in at least one pH compared to the reference.

The PCA-HCA method allowed for cluster-based analysis of formulations to estimate the overall similarity of the formulation not only based on the distance between formulations but also on the global dissolution curve including the shape.

In contrast to the f_2 calculation, the PCA-HCA approach provides a simple graphical and analytical method for assessing drug similarity by employing robust mathematical and statistical procedures. Moreover, this approach can use all data sets obtained by the dissolution test, regardless of the dissolved drug quantity and data variability. This is extremely advantageous, as it allows a better appreciation of the dissolution behavior of the compared batches.

CONCLUSION

The dissolution test was used in this work to compare the in vitro dissolution profile and more precisely the amount released of the active ingredient between the originator and five different generic products of clopidogrel in three dissolution media (pH 1.2, 4.5, 6.8). The f_2 calculation gives an idea of the similarity between the generic drugs and their originator. This technique could be complemented by other analyses such as PCA and HCA to provide additional evidence of similarity.

CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

FUNDING

The authors disclosed no financial support for this article.

REFERENCES

1. Qureshia, M. J.; Phina, F. F.; Patrob, S. Enhanced solubility and dissolution rate of clopidogrel by nanosuspension: formulation via high pressure homogenization technique and optimization using Box Behnken design response surface methodology. *J. Appl. Pharm. Sci*. **2017**, *7* (2), 106–113. DOI: 10.7324/JAPS.2017.70213.
2. Sangkuhl, K.; Klein, T. E.; Altman, R. B. Clopidogrel pathway. *Pharmacogenet. Genomics* **2010**, *20* (7), 463–465. DOI: 10.1097/FPC.0b013e3283385420.
3. Bhatt, D. L.; Fox, K. A.; Hacke, W.; Berger, P. B.; Black, H. R.; Boden, W. E.; Cacoub, P.; Cohen, E. A.; Creager, M. A.; Easton, J. D.; et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N. Engl. J. Med*. **2006**, *354* (16), 1706–1717. DOI: 10.1056/NEJMoa060989.
4. Oldenburg, P. J. Clopidogrel. In *Reference Module in Biomedical Sciences*; Elsevier, 2018; p B9780128012383982000. DOI: 10.1016/B978-0-12-801238-3.98129-7.
5. Zaid, A. N.; Al Ramahi, R.; Bustami, R.; Mousa, A.; Khasawneh, S. Comparative fasting bioavailability of two clopidogrel formulations in healthy Mediterranean volunteers: an in vitro-in vivo correlation. *Drug Des. Devel. Ther*. **2015**, *9*, 2359. DOI: 10.2147/DDDT.S78658.
6. Abd-Elhakeem, E.; Teaima, M. H. M.; Abdelbary, G. A.; El Mahrouk, G. M. Bioavailability enhanced clopidogrel-loaded solid SNEDDS: development and in-vitro/in-vivo characterization. *J. Drug Deliv. Sci. Technol*. **2019**, *49*, 603–614. DOI: 10.1016/j.jddst.2018.12.027.
7. Jarvis, B.; Simpson, K. Clopidogrel: a review of its use in the prevention of atherothrombosis. *Drugs* **2000**, *60* (2), 347–377. DOI: 10.2165/00003495-200060020-00012.
8. Lassoued, M. A.; Sfar, S.; Bouraoui, A.; Khemiss, F. Absorption enhancement studies of clopidogrel hydrogen sulphate in rat everted gut sacs. *J. Pharm. Pharmacol*. **2012**, *64* (4): 541–552. DOI: 10.1111/j.2042-7158.2011.01434.x
9. Bali, D. E.; Osman, M. A.; El Maghraby, G. M. Enhancement of dissolution rate and intestinal stability of clopidogrel hydrogen sulfate. *Eur. J. Drug Metab. Pharmacokinet*. **2016**, *41* (6), 807–818. DOI: 10.1007/s13318-015-0311-4.
10. El-Laithy, H. M.; Badawi, A.; Abdelmalak, N. S.; Elsayyad, N. M. E. Stabilizing excipients for engineered clopidogrel bisulfate procubosome derived in situ cubosomes for enhanced intestinal dissolution: stability and bioavailability considerations. *Eur. J. Pharm. Sci*. **2019**, *136*, 104954. DOI: 10.1016/j.ejps.2019.06.008.
11. Sonje, V. M.; Kumar, L.; Meena, C. L.; Kohli, G.; Puri, V.; Jain, R.; Bansal, A. K.; Brittain, H. G. Atorvastatin Calcium. In *Profiles of Drug Substances, Excipients and Related Methodology*; Elsevier, 2010; Vol. 35, pp 1–70. DOI: 10.1016/S1871-5125(10)35001-1.
12. Lestari, M. L. A. D.; Suciati; Indrayanto, G.; Brittain, H. G. Clopidogrel bisulfate. In *Profiles of Drug Substances, Excipients and Related Methodology*; Elsevier, 2010; Vol. 35, pp 71–115. DOI: 10.1016/S1871-5125(10)35002-3.
13. Alam, S.; Patel, S.; Bansal, A. K. Effect of sample preparation method on quantification of polymorphs using PXRD. *Pharm. Dev. Technol*. **2010**, *15* (5), 452–459. DOI: 10.3109/10837450903286511.

14. Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action. EMA/CHMP/CVMP/QWP/336031/2017; Committee for Medicinal Products for Human use (CHMP), Committee for Medicinal Products for Veterinary use (CVMP), Quality Working Party (QWP), European Medicines Agency, August 10, 2017.
15. Buffer solutions. In *The United States Pharmacopeia and National Formulary USP 41–NF 36*; The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2020.
16. Moore, J. W.; Flanner, H. H. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. *Pharm. Technol*. **1996**, *20*, 64–74.
17. El Orche, A.; Bouatia, M.; Yanisse, S.; Labjar, H.; Mouhsin, M.; Bouha, M.; Oubenali, M.; Mbarki, M. Evaluation of the capability of horizontal ATR-FTMIR and UV-visible spectroscopy in the discrimination of virgin olive oils from the Moroccan region of Beni Mellal-Khenifra. *J. Spectrosc*. **2020**, *2020*, 1–9. DOI: 10.1155/2020/9317350.
18. Bro, R.; Smilde, A. K. Principal component analysis. *Anal. Methods* **2014**, *6* (9), 2812–2831. DOI: 10.1039/C3AY41907J.
19. Maggio, R. M.; Castellano, P. M.; Kaufman, T. S. A new principal component analysis-based approach for testing "similarity" of drug dissolution profiles. *Eur. J. Pharm. Sci*. **2008**, *34* (1), 66–77. DOI: 10.1016/j.ejps.2008.02.009.
20. Chelcea, S. Agglomerative 2-3 Hierarchical Classification: Theoretical and Applicative Study. **2007**, 241. https://tel.archives-ouvertes.fr/tel-00156809
21. Stanimirova, I.; Daszykowski, M. Exploratory analysis of metabolomic data. In *Comprehensive Analytical Chemistry*; Jaumot, J., Bedia, C., Tauler, R., Eds.; Elsevier, 2018; Vol. 82, pp 227–264. DOI: 10.1016/bs.coac.2018.08.005.
22. Gavioli, A.; de Souza, E. G.; Bazzi, C. L.; Schenatto, K.; Betzek, N. M. Identification of management zones in precision agriculture: an evaluation of alternative cluster analysis methods. *Biosyst. Eng*. **2019**, *181*, 86–102. DOI: 10.1016/j.biosystemseng.2019.02.019.
23. Gary Hollenbeck, R.; Mitrevej, K. T.; Fan, A. C. Estimation of the extent of drug-excipient interactions involving croscarmellose sodium. *J. Pharm. Sci*. **1983**, *72* (3), 325–327. DOI: 10.1002/jps.2600720333.
24. Zarmpi, P.; Flanagan, T.; Meehan, E.; Mann, J.; Fotaki, N. Biopharmaceutical understanding of excipient variability on drug apparent solubility based on drug physicochemical properties. Case study: superdisintegrants. *AAPS J*. **2020**, *22* (2), 46. DOI: 10.1208/s12248-019-0406-y.

2022 EASTERN ANALYTICAL SYMPOSIUM

EMBRACING ANALYTICAL DIVERSITY

FOR A SUSTAINABLE FUTURE

Crowne Plaza Princeton Conference Center
Plainsboro, NJ
November 14–16, 2022

3 DAY TECHNICAL PROGRAM
Cutting edge research from field experts

3 DAYS OF EXPOSITION
Newest analytical equipment and services

4 DAYS OF SHORT COURSES
In-depth practical applications

NETWORKING OPPORTUNITIES
Career & technical speed mentoring sessions

EASTERN ANALYTICAL SYMPOSIUM & EXPOSITION

EAS.ORG

SUBMIT YOUR WORK!
Poster and oral presentation submission opens March 1, 2022

dx.doi.org/10.14227/DT290322P150

Predictive Dissolution Models for Real-Time Release Testing: Development and Implementation – Workshop Summary Report

Nikolay Zaborenko[1*], Tessa M. Carducci[2], Alexander Ryckaert[3], Haritha Mandula[4], Matthew J. Walworth[1], Casey J. Smith[1], Sandra Suarez-Sharp[5], Melanie Dumarey[6], Sara Manteiga[7], Sarah Nielsen[8], Stan Altan[9], Adriene Malsbury[10], Beverly Nickerson[11], and Yanmei Lan[12]

[1]*Synthetic Molecule Design and Development, Eli Lilly and Company, Indianapolis, IN, USA.*
[2]*Analytical Commercialization Technology, Merck & Co., Inc., Rahway, NJ, USA.*
[3]*Laboratory of Pharmaceutical Process Analytical Technology, Department of Pharmaceutical Analysis, Ghent University, Ghent, Belgium.*
[4]*Division of Biopharmaceutics, Office of New Drug Products, Office of Pharmaceutical Quality (OPQ), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), Silver Spring, MD, USA.*
[5]*Regulatory Affairs, Simulations Plus Inc., Lancaster, CA, USA.*
[6]*Oral Product Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Gothenburg, Sweden.*
[7]*Analytical Development, Vertex, Boston, MA, USA.*
[8]*Janssen Supply Chain, Johnson & Johnson, New Brunswick, NJ, USA.*
[9]*Statistics and Decision Sciences, Manufacturing and Applied Statistics, Janssen Pharmaceutical R&D LLD, Raritan, NJ, USA.*
[10]*Drug Product Development, Bristol Myers Squibb, New Brunswick, NJ, USA.*
[11]*Global Regulatory Affairs CMC, Pfizer Inc., Groton, CT, USA.*
[12]*Analytical Development, Pharmaceutical Sciences, Takeda, Lexington, MA, USA.*

e-mail: zaborenko_nikolay@lilly.com

ABSTRACT

To date, few examples of dissolution models for real-time release testing (RTRT) have been approved for commercial drug products or published in literature. Thus, a structured approach has not been established by which a novice to the field could design, develop, validate, and implement an RTRT dissolution model. Moreover, with scant examples available, there has not been a body of work by which to learn of general regulatory expectations for such models. To address these gaps and to encourage conversation between regulatory and industrial experts on these topics, a virtual (web-based) workshop entitled "Predictive Dissolution Models for Real-Time Release Testing: Development and Implementation" was held November 11–12, 2021. This article summarizes key points from the podium presentations, panel discussions, and breakout sessions focusing on (1) the current best practices to establish predictive model specifications; (2) designing models to predict the "safe space" of a release test and creating models utilizing process analytical technology (PAT); and (3) exploring the strategy of compliant regulatory submissions, including model validation and post-approval lifecycle management. Industrial case studies were presented showcasing attempted approaches to and successful implementations of RTRT of dissolution for drug product manufacturing.

KEYWORDS: Drug dissolution, in vitro dissolution, real-time release testing (RTRT), modeling and simulation (M&S), process control, process analytical technology (PAT)

BACKGROUND

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Workshop on Predictive Dissolution Models for Real-Time Release Testing: Development and Implementation was held on November 11–12, 2021, virtually using the WebEx video conferencing platform (*1*). Recordings of all podium talks and panel discussions have been made available by the IQ Consortium (*2*).

The workshop was attended by 256 scientists representing 85 organizations from the pharmaceutical industry and academia as well as regulatory and standards agencies. Figure 1 shows the distribution of workshop registrants by organization type and by experience with dissolution real-time release testing (RTRT), based on their answers to the questionnaire provided electronically during registration. Of the registrants, 86% represented the pharmaceutical industry; additionally, of the 8% who identified as "other," most represented vendors to the pharmaceutical industry (e.g., equipment or software manufacturers, pharmaceutical testing laboratories). Less

*Corresponding author

than a quarter of registrants self-identified as having had prior experience with dissolution RTRT.

The goal of this workshop was threefold. First, teaching sessions were intended to educate the attendees about the principles of dissolution RTRT, the selection and development of models, and their lifecycle and management. Second, industrial examples and regulatory perspectives were provided to demonstrate the application of the theory into practice. Third, panel discussions and Q&A sessions enabled communication with regulatory attendees and speakers, beginning the process of harmonizing the expectations around the regulatory requirements for dissolution models for RTRT. Overall, the event was designed to enable the industrial attendees to return to their respective companies with the ability to develop and implement predictive dissolution models (PDMs) for RTRT, with the expectation that regulatory authorities are beginning to follow the same consistent set of principles. Table 1 summarizes the key points of talks presented at the workshop.

OVERVIEW OF IN VITRO PDM DEVELOPMENT FOR DRUG PRODUCT RELEASE

The first speaker of the symposium was Tessa M. Carducci, PhD (Merck & Co., Inc., Rahway, NJ, USA) (*3*). Her talk was entitled "Development of an In vitro Predictive Dissolution Model for Drug Product Release – Overview and Impact," which provided a fitting kickoff to the 2-day symposium. She began by providing definitions from relevant regulations and a previous white paper on the topic, drivers for use of modeling and surrogate testing in the pharmaceutical industry, and a map to level set on the present topic in the broader realm of predictive technologies (Fig. 2) (*4–11*). PDM is one aspect of a larger RTRT control strategy that has benefits including lead time gains, inventory reduction, which equates to financial savings, and enhanced safety and compliance. Specifically, the addition of a predictive dissolution model to an RTRT strategy can extend business drivers of RTRT to low solubility products (Biopharmaceutics Classification System [BCS] class II/IV), avoidance of traditional dissolution testing, and lead to enhanced mechanistic understanding of the product's dissolution.

Dr. Carducci presented an end-to-end strategy for development of a PDM of a drug product. Understanding the dissolution mechanism is important for identifying the factors that influence the dissolution performance. A design of experiments (DoE) is performed to vary dissolution predictors, and the resulting dissolution data are collected. An empirical or hybrid model can be constructed in two steps: 1) curve fitting the dissolution profiles, followed by 2) regression of the curve fit parameters in step one against the predictors and/or near-infrared (NIR) data. The model predictions vs. measured dissolution results are then assessed. Routine and periodic verification will trigger future model updates and revalidation if needed.

The next part of her talk focused on a case study for development of a PDM. Through early stage DoEs, tablet disintegration was found to be the rate limiting step for dissolution, so parameters like hardness are impactful on the dissolution process. Dr. Carducci noted that first-principles modeling can aid in determination of the dissolution mechanism and identification of key inputs to model; although, there can be secondary effects from process parameters that are only able to be included in a multivariate model. She also emphasized that understanding the dissolution process is critical to the modeling strategy as well as method selection and specification strategy. The quality control (QC) method must be justified (i.e., discriminating) and robust because the model is built using data as generated by this method. Potential factors that affect dissolution were identified using a fishbone framework and investigated through

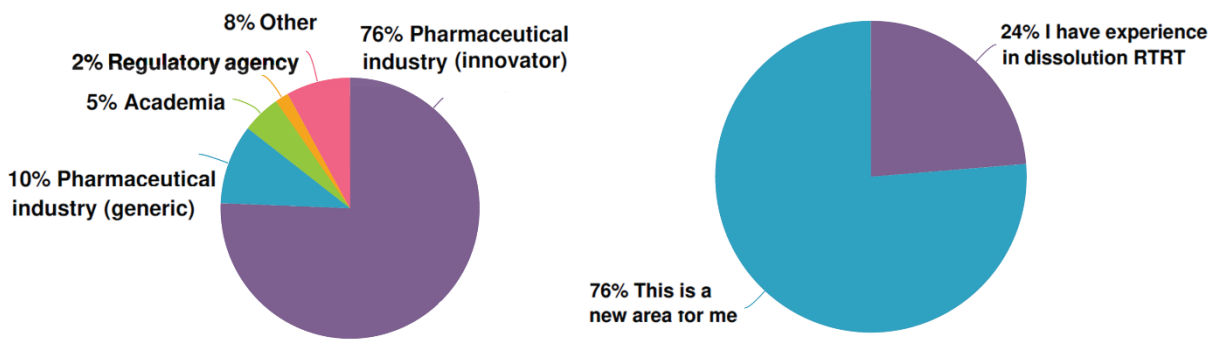


Figure 1. Distribution of workshop registrants based on self-identification on a registration questionnaire, by organization type (left) and by previous experience with dissolution real-time release testing (RTRT) (right).

Table 1. Overview of workshop presentations and key teaching points.

Presenter (Company)	Title of Presentation	Key Teaching Points
Tessa Carducci (Merck & Co., Inc., Rahway, NJ, USA)	Development of an In vitro Predictive Dissolution Model for Drug Product Release – Overview and Impact	PDM is one aspect of a larger RTRT strategy with benefits to cost, assurance of safety, and compliance. Understanding the dissolution mechanism is important for identifying the factors that influence the dissolution performance, and first-principles modeling can guide that understanding, but some process parameters can only be included in a multivariate model. In CM, a continuous-study DoE for model calibration can save time and reduce material use.
Nikolay Zaborenko (Eli Lilly & Co.)	RTRT PDM Model Selection and Development	Development of PDMs for RTRT is very flexible, based on first principles, empirical models, or a hybrid, incorporating or excluding spectroscopic PAT, or predicting adherence to a dissolution safe space based on RTRT of other CQAs. A PLS model of dissolution vs. process and material variables can elucidate CPPs/CMAs, leading to a PDM. This should be validated by a DoE around critical variables to demonstrate the model's predictive capability and the ability to detect outliers.
James Drennen (Duquesne University)	Prediction of Dissolution Profiles from Process Parameters, Formulation, and Spectroscopic Measurements	Individual drug characteristics will determine which parameters are critical to guide DoE building, which must provide adequate dissolution variability for model training. A hierarchical modeling approach for PDM development can provide understanding of how certain variables affect dissolution through linkage between their variation and the effect on different parameters of the PDM. Spectroscopic PAT can capture individual tablet differences and incorporate it into prediction of dissolution behavior.
Alexander Ryckaert (Ghent University)	Fast and Non-destructive PAT-based Dissolution Assay for Immediate Release Tablets	A BCS class II (poorly soluble) drug product dissolution performance can be rate-limited by disintegration in certain cases. Therefore, it is possible to establish disintegration as a surrogate for dissolution performance of a poorly soluble drug. A NIR spectroscopic model can predict disintegration (and by extension dissolution) of such a drug product across a range of API particle sizes and tablet compression profiles.
Haritha Mandula (FDA)	Dissolution RTRT: Summary of Regulatory Requirements and Expectations	A PDM for RTRT is a high-impact model on the condition that it can predict outliers in behavior across variation of all parameters that could possibly vary in drug product manufacturing. Thus, model development should consider variations in all such parameters through a dedicated DoE to demonstrate understanding of CPPs/CMAs and model validation. It is expected that a discriminating, in vivo relevant dissolution method would be established as early as possible in development, and the PDM would be capable of predicting performance against this method across all time points. It is recommended that sampling is equally spaced, statistically justified for dissolution prediction and sufficient to detect the dissolution variability of the batch for the production duration.
Matthew Walworth (Eli Lilly and Co.)	Data Selection and Generation for PDM and RTRT Development	The initial stage of model training is establishing technical feasibility, which should be completed as soon as possible in process development. Once PDM technical feasibility has been established, a more robust data set should be acquired. Samples should be representative of the commercial manufacturing process. The entire design space should be represented in the samples using a statistically relevant sampling method (such as factorial sampling); the training data set should have designed sources of variability and statistical probability. Samples specifically designed to fail should be created to confirm that the model can identify a failing sample. In production, data should be continually collected to support continued use or justify the need for a model update.
Sandra Suarez-Sharp (Simulations Plus)	From QC Dissolution Method to RTRT Dissolution Model	A dissolution method must be fit for purpose, with PBPK modeling used to establish its in vivo relevance. A successful model is built upon identification and inclusion of all relevant failure modes in the dissolution method and their interactions. A clinically relevant dissolution method should be established as early as possible in drug product development to enable determining which variables are critical to meaningful dissolution performance.
Melanie Dumarey (AstraZeneca)	Predictive Modeling for RTRT of Dissolution: Quality Considerations	PDMs for RTRT require detailed description in the CTD, including justification for the selected model parameters based on dedicated DoE and/or first principles analysis. Models must be validated with a data set not included in model calibration, including non-compliant batches. The validity range of the model should be defined, as well as diagnostics implemented to prevent invalid model predictions. Long-term validity of a model is ensured by the implementation of a lifecycle management plan, monitoring common and special cause variation over time, and triggering model updates as needed.
Sara Manteiga (Vertex)	Putting it All Together: PDM RTRT in Action – Case Study 1	PDM was accepted for RTRT of a CM product. Segmented sampling (12 segments per batch) is used for dissolution prediction, consistent with USP <711> stage 2 testing. Each PAT input method was validated per ICH Q2(R1). The model was challenged against 25 CM batches with variations spanning the manufacturing range of process parameters and material attributes. Model maintenance includes assessing model performance through routine parallel testing, after changes to materials/ instruments/ process, and observation of trends (including model diagnostics). PDM was demonstrated to detect non-conforming batches.
Stan Altan and Sarah Nielsen (Janssen)	Putting it All Together: PDM RTRT in Action – Case Study 2	A PDM was used for batch RTRT of a fluid-bed granulated BCS class IV product. CPPs had been identified from prior manufacturing designs, and PDM was developed via a comprehensive DoE, using process parameters and tablet content measured by NIR as inputs. Model provided "health check" of current batches against historical standard.

BCS: Biopharmaceutics Classification System; CM: continuous manufacturing; CMA: critical material attribute; CPP: critical process parameter; CQA: critical quality attribute; CTD: common technical document; DoE: Design of Experiments; IV: intravenous; NIR: near infrared; PAT: process analytical technology; PBPK: physiologically based pharmacokinetics; PDM: predictive dissolution modeling; PLS: partial least squares; QC: quality control; RTRT: real-time release testing.

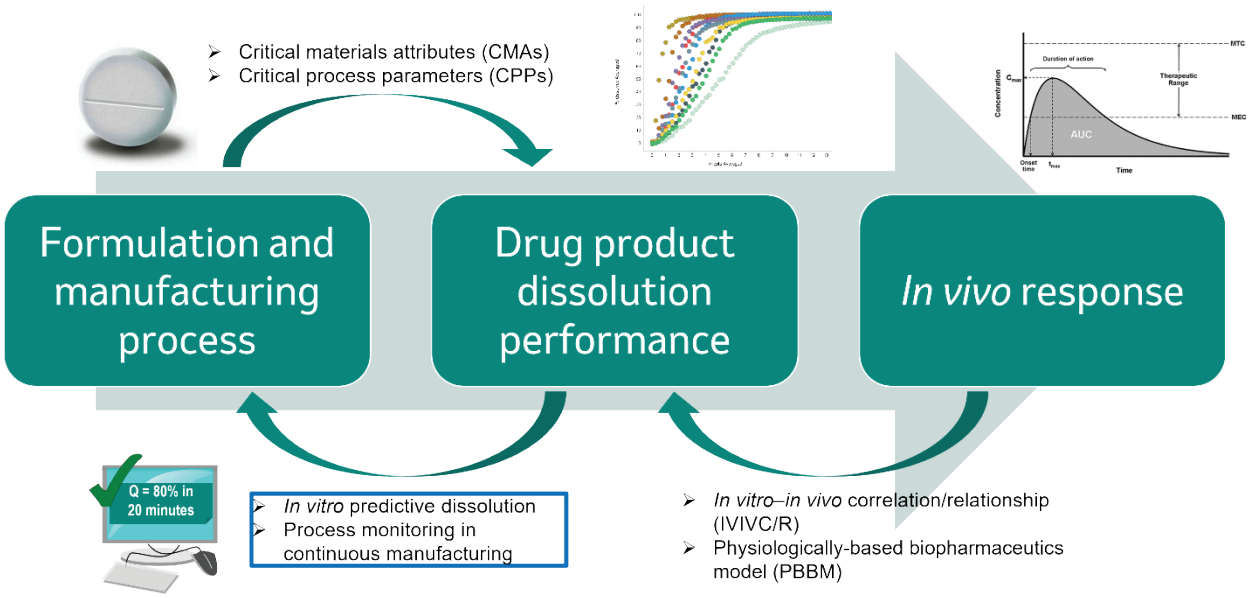


Figure 2. Types of dissolution modeling in the realm of predictive technology.

DoE or one-factor-at-a-time experiments. She stressed the importance of performing a raw materials risk assessment to ensure either that material attributes are not critical to the dissolution performance of the product or that they are captured in the model if they are critical. After building mechanistic dissolution understanding, the dissolution-critical parameters/attributes should be confirmed and model training set finalized. Spotfire was used to aggregate the large amount of dissolution and process parameter data to facilitate modeling iterations.

The strategy for selecting the model was performed in two stages: 1) exploratory analysis involving regression of dissolution predictors (X-block) and a variety of individual dissolution time points (Y-block) to better understand the X-Y relationship; and 2) iterative development towards the final model using dissolution profile fit coefficient regression as the Y-block (*12*). At this stage, parameters that do not significantly impact dissolution performance or those that are encompassed by other parameters were excluded from the X-block with appropriate justification. Model rank and condition number were evaluated for empirical models and mechanistic/hybrid models based on a Noyes-Whitney framework. The Gompertz model explained the dissolution profiles best, especially at the approach of the plateau region (*13*, *14*). Also, no advantage was identified to using "high resolution" dissolution data using fiber optic versus "low resolution" or traditional discrete time point dissolution sampling. Furthermore, traditional sampling is seen as preferable for model maintenance in supply. Future steps include model validation and implementation.

Alternate modeling approaches including spectrum-based (or process analytical technology [PAT]) modeling were also discussed, and a case study of a first-principles modeling approach to support a particle size distribution (PSD) specification was presented. Then, the topic shifted to how PDM can play a role in continuous manufacturing (CM). If executed as a continuous study, the main DoE used for the model calibration set would use significantly less material and require a much shorter manufacturing duration. To realize the full benefits of CM of low-solubility drug products, Dr. Carducci opined that development of a PDM to enable a full RTRT strategy is imperative. In closing, Dr. Carducci summarized lessons learned for PDM through her work and through external networks and mentioned some interesting topics for future research and development.

MODEL SELECTION AND DEVELOPMENT

Nikolay Zaborenko, PhD (Eli Lilly & Co., USA; Chair of the organizing committee) presented his perspective on the selection and development of PDMs for RTRT (*15*). An overview of first-principles and empirical approaches to predicting in vitro dissolution for product release testing, as previously presented and published in an industry white paper and reviews, described the difference between mechanistic and empirical modeling approaches, including chemometric modeling (*9*, *16*, *17*). The aim of PDM for RTRT was stated as predicting a quantitative value of the level of drug released at a specific time point, as is done traditionally with a physical dissolution test. A PDM can achieve this either by predicting the entire dissolution profile (mathematically describing the profile

curve) or by directly predicting release at one or more time points (typically via statistical modeling). Both the speaker and subsequent discussions established that regulatory reviews do not find it sufficient to only predict qualitatively whether the unit or batch passes or fails its dissolution specification, even when operating in a process safe space. Indeed, the regulatory expectation for a PDM is that it predicts a full dissolution profile, either as a mathematical function or as a series of time points, and not just a single time point value. However, it is acceptable for validation to be performed only on the specification time point.

Dr. Zaborenko provided a framework for building models based solely on critical material attributes and critical process parameters (CMAs/CPPs), as well as for building models that incorporate PAT, e.g., spectroscopic measurements, providing literature examples of both methodologies (*18*–*21*). It was emphasized, both through the talk and in subsequent panel discussions including the FDA speaker Dr. Haritha Mandula, that spectroscopic PAT is not a requirement for successful implementation of dissolution RTRT. A sufficiently robust PDM can be developed and validated using only CMAs/CPPs and inline or at-line measurements of certain critical quality attributes (CQAs), such as, e.g., tablet weight, hardness, or solid fraction. Either methodology requires demonstrated understanding of dissolution dependence on process and material variables including which variables are critical to dissolution performance and examples of significant variation of process and material parameters, including variations performed at final production scale.

One type of PDM for RTRT presented was partial least squares (PLS) regression, which uses singular value decomposition to extract predictive component variables through covariance of independent (X block) and dependent (Y block) variables (*22*). An advancement of the method, O2-PLS, which separates correlated variation in X and Y variables from structured noise in X and in Y, has been used previously for PDM (*16*, *23*). Another approach discussed was the use of artificial neural networks (ANN), an error-minimizing technique that adjusts weights of variables based on a learning set to generate a black-box predictive algorithm, with literature examples of their use in pharmaceutical PDM (*24*–*26*). The strength of ANN lies in its ability to solve nonlinear or multi-response systems and to use historical data generated without reliance on a rules-based DoE; however, it requires very large amounts of data to train.

To incorporate spectroscopic PAT, principal component analysis (PCA) was briefly described. PCA is the statistical approach to processing large amounts of correlated data (e.g., dissolution vs. time, absorption vs. wavelength). It allows for predictive modeling that maximizes the variance of projected data with fewer dimensions by producing latent variables (principal components) that combine aspects of individual X variables. Its use in pharmaceutical development has been well documented (*22*, *23*, *27*). The use of PAT generally requires preprocessing of spectral data, with various approaches commonly used (*28*). For PDM application, PCA typically delivers one or several summary values of a spectrum for use as input into the PDM.

The need to quantitatively evaluate model performance was discussed. In general, for prediction of any single value (e.g., dissolution at a given time point), this includes absolute and relative standard errors of prediction (SEP) and the R^2 value (goodness of fit, or level of correlation between predicted and actual values). For PCA models, one should evaluate Hotelling's T^2 (the model's ability to detect outliers) and the residuals Q^2(Y) and R^2(Y), or the "scores" of the model's abilities to predict novel samples and account for variation in the model inputs, respectively. For prediction of an overall profile, one can also evaluate f_1 and f_2, the difference and similarity factors, although there is a great deal of debate and discussion as to the applicability of these factors and the situations in which they are relevant, as well as alternative methods of comparing dissolution profiles (*29*–*31*).

Finally, a series of case studies were presented, highlighting the different approaches to establishing a PDM for RTRT. An example was presented of establishing a PDM using only spectroscopic data to correlate with dissolution, in this case using an ANN for the analysis and prediction (*26*). Subsequently, a converse example was shown of a PDM for an immediate-release (IR) tablet made via continuous direct compression (CDC). The model was based on process parameters and material attributes (without the use of spectroscopic data), as illustrated in Figure 3. Dissolution profiles were measured for coated and uncoated tablets across multiple tablet strengths with variations in formula (composition), active pharmaceutical ingredient (API), filler excipient particle sizes, and in CDC and coating process parameters. A PCA analysis established a 4-PC model to predict dissolution at the investigated time points (addition of a fifth PC did not show improvement in R^2 or Q^2 over the 4-PC model). The 45-minute time point had been selected as the specification (Q) time point, and the model showed reasonable correlation between predicted and

measured values (in this case, R^2 of 0.55) with adequate absolute and relative SEP. A PLS analysis showed that the biggest contribution to variation in dissolution stemmed from variations in filler and disintegrant levels in the composition (as well as from differences in performance across tablet strengths). To validate the model, tablets were made with large changes to filler and disintegrant levels from the target formula. The 4-PC PDM was able to predict the release (%LC of API) of these tablet batches at the proposed specification point with sufficient accuracy (with the exception of one outlier, the predicted value for any individual test was within 6% of observed value).

Another example of a dissolution surrogate model without the use of spectroscopic data was presented. In this example, a PDM was built to predict performance within an established clinical safe space (i.e., performance ensuring bioequivalent [BE] maximum plasma concentration, C_{max}) (*19*). An in vivo-in vitro correlation (IVIVC) was established between C_{max} and dissolution. Additionally, CQAs of tablet hardness and thickness were able to predict the %LC dissolved at the specification time point. Thus, the IVIVC enabled rapid at-line measurement of non-destructive CQAs to establish if the tablets were within the clinical safe space.

Lastly, a case study was presented exemplifying a process safe space, with assay and content uniformity (CU) RTRT and control that ensured operation within a safe space for those CQAs (*17*). The example demonstrated the use of final blend NIR in a CDC tablet process for RTRT of assay and CU, rejecting nonconforming drug product. Dissolution measurement at specification time point was shown to consistently reproduce the drug product assay across wide variation of process parameters and material attributes, behavior typical of (but not exclusive to) BCS class I drug products. An argument was made that the assay model can be extended to use for PDM against this dissolution specification. The overall ability to reject nonconforming drug product thus ensures RTRT and safe-space operation for CU, assay, and dissolution.

PDM DEVELOPMENT VIA PAT AND CPPS/CMAS

In the first of two academic talks, Professor James K. Drennen, III, PhD (Duquesne University, USA) presented "Prediction of Dissolution Profiles from Process Parameters, Formulation, and Spectroscopic Measurements" (*32*). He discussed the academic state of the art based on his and his colleagues' work as well as that of other researchers in the field (*21*, *33–35*).

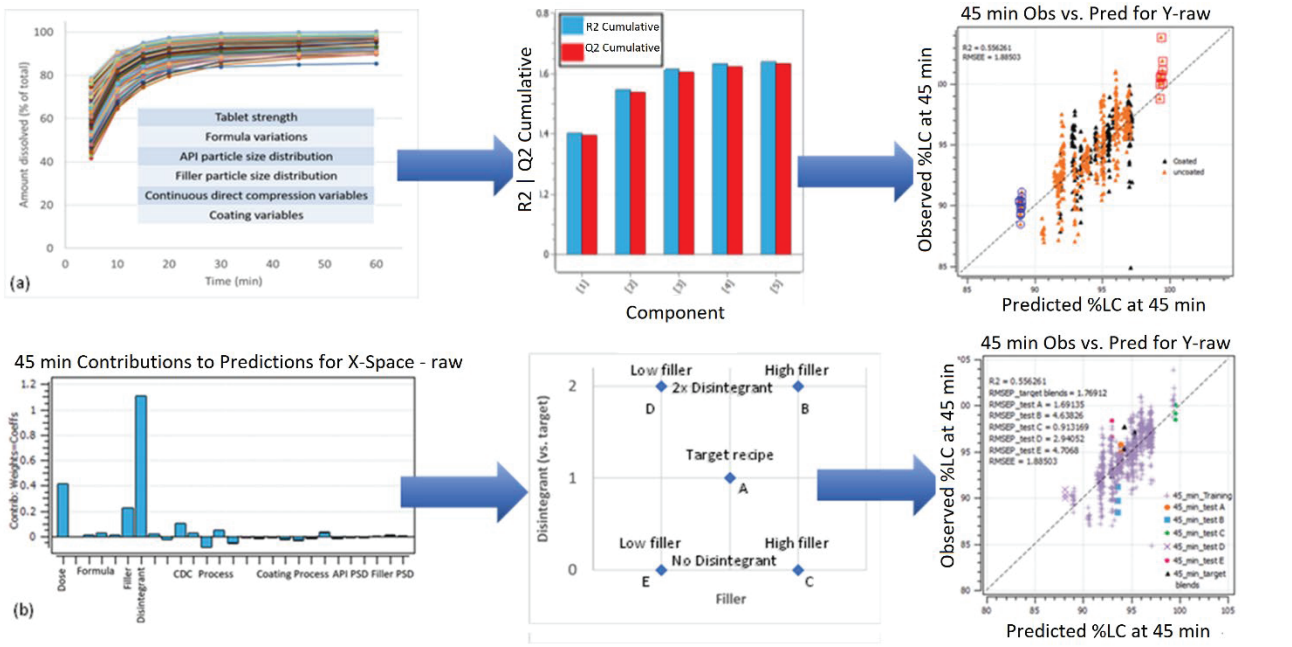


Figure 3. PDM for RTRT based on process parameters and material attributes.
(a) Model development (left to right): Measurement of dissolution of drug products with variations in process and material variables, PC analysis to establish a 5-PC PDM for release levels at specified time points, predicted vs. observed API %LC dissolved at 45-minute time point for training set (including coated and uncoated tablets).
(b) Model validation (left to right): Partial least squares analysis to establish CPP/CMAs for release at 45 minutes, creation of a validation set DoE of tablets with large declination in CMAs, predicted vs. observed API %LC dissolved at 45-minute time point for validation set (plotted against the training set data).
API: active pharmaceutical ingredient; CPP: critical process parameter; CMA: critical material attribute; DoE: Design of Experiments; PC: principal component; PDM: predictive dissolution modeling; RTRT: real-time release testing; %LC, percent label claim.

The talk focused on a series of components necessary for overall model building, including: 1) building a DoE based on individual drug characteristics for acceptable dissolution variability; 2) selecting between global models vs. a hierarchical modeling approach for PDM; 3) training PLS models based on formulation, material, process, and spectroscopic data; and 4) using the models to predict dissolution profiles as direct time points vs. as mathematical functions (e.g., a Weibull curve).

DEVELOPMENT OF PDM USING ONLY PAT

In the second academic session, Alexander Ryckaert, PhD (Ghent University, Belgium) presented a case study where in vitro PDMs were developed for an IR tablet using solely spectroscopic measurement (*36*). The tablets consisted of a hydrophobic API of BCS class II, lactose, microcrystalline cellulose (MCC), a disintegrant, and a lubricant. The predictive models were built using offline collected NIR data, offline collected Raman data, or process/material information with the ultimate goal to enable RTRT in tablet manufacturing. As the API particle size was identified as the CMA and the tablet compression force as the CPP, these variables were used for the experimental design. Compression force was varied at 7 levels (i.e., 2, 4, 6, 8, 10, 12, and 16 kN), resulting in tablets with varying porosity. Although the applied range for compression force was probably beyond the meaningful variation that would be expected during manufacturing, it provided more dissolution variability, which enhances the discriminative power of the predictive models. In addition, four different API batches, each having a different API particle size (i.e., d50 values of 30, 40, 43, and 51 µm), were used for the production of the tablets.

Dissolution profiles were obtained for all tablets using USP apparatus 2. Figure 4 shows the dissolution profiles at the two most extreme compression forces (i.e., 2 and 16 kN) for the four different API batches. It was observed that tablets compressed at lower compression force resulted in a faster release because the higher porosity promoted liquid penetration through the pores in the tablets more easily. According to Maclean et al., this is due to the combination of the poorly soluble MCC and the slowly dissolving lactose, making the effect of porosity dominant (*37*). The fastest dissolution rate was observed for tablets made with the smallest API particle size, whereas the slowest dissolution rate was observed for those with the largest API particle size. Although this is a logical finding due to the surface area-to-volume ratio, it does show that API batch-to-batch variability can clearly influence the dissolution rate.

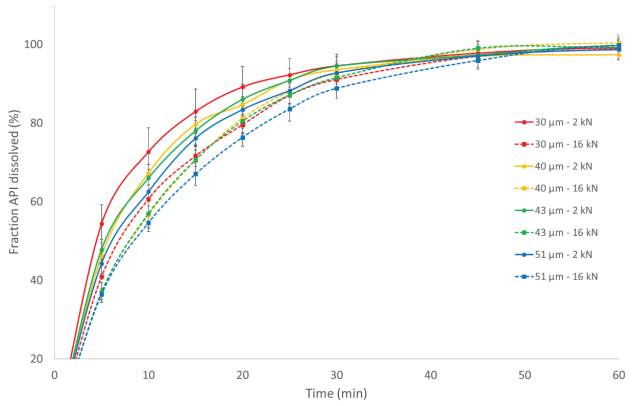


Figure 4. Dissolution profiles of tablets compressed with the lowest (solid line) and the highest (dotted line) compression force for the API batches with differing particle size. API: active pharmaceutical ingredient.

The Weibull model was fitted to all dissolution profiles; and Weibull scale and shape parameters were determined (see the "Data Selection and Generation" summary below for detailed review of the Weibull function). Furthermore, traditional linear PLS regression and non-linear kernel ridge regression (kRR) modelling techniques were applied to predict these parameters from the NIR spectra, Raman spectra, or the process/material information (i.e., compression force and API particle size) of the tablets. The models were evaluated by cross-validation where a test set consisting of 10% of the data was left out of the model. Weibull scale and shape parameters were subsequently predicted and used to reconstruct the dissolution profiles. Figure 5 shows a representative example where the dissolution profiles predicted with kRR for Raman, NIR, process/material information with PLS for Raman (as results were similar for NIR), and their corresponding measured profile are plotted. KRR outperformed PLS when spectroscopic data were used as the reconstructed profiles, with kRR for both NIR and Raman being very similar to the measured profile. This is probably due to kRR being able to model the non-linearity between compression force/API particle size and the dissolution profile. Using only information of the applied process parameters and material attributes resulted in a poor fit with an R^2 value for both the Weibull a and b parameter below 0.4, indicating that the limited amount of information was not sufficient to build a good model. Two concerns about kRR modelling were mentioned during the workshop. The first concern was kRR sensitivity to the scale of the input; however, this was avoided by applying standard-scaling of the features beforehand. The second concern was the risk of overfitting. The study was not yet completed at the time of writing, so this still has to be evaluated by using an independent validation set that falls within the operation space of the calibration

model. In addition, similarity between the measured and predicted profiles has also to be tested, and a more in-depth statistical analysis has to be performed to evaluate the model performances.

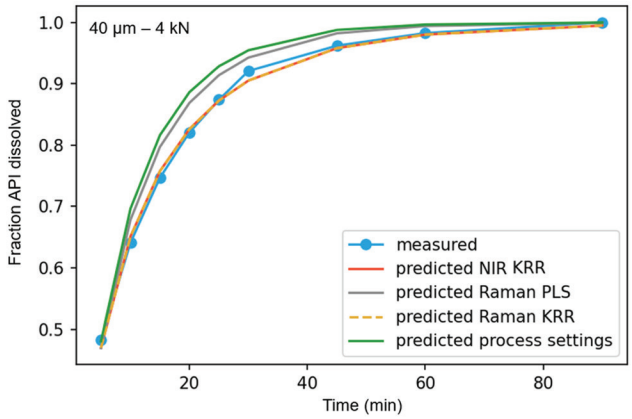


Figure 5. Representative example of the predicted and measured dissolution profiles for a tablet with an API particle size of 40 µm compressed with 4 kN. API: active pharmaceutical ingredient; KRR: kernel ridge regression; NIR: near infrared; PLS; partial least squares.

REGULATORY REQUIREMENTS AND EXPECTATIONS

In the final podium presentation of the first day of the workshop, Haritha Mandula, PhD (United States Food and Drug Administration [FDA]) presented her views on the regulatory requirements and expectations for dissolution RTRT (*38*). In her presentation, Dr. Mandula provided detailed definitions of RTRT and its components, lifecycle, considerations, and requirements for implementation and regulatory submission, and two case studies of regulatory approval of dissolution RTRT as a surrogate for traditional testing.

Dr. Mandula began her talk with an overarching definition of RTRT as the ability to evaluate and ensure the quality of in-process and/or final product based on a valid combination of measured material attributes and process data (*4*). Figure 6 shows an example of RTRT within a continuous process, wherein input materials are continuously received into the system with continuous blending, continuous granulation, continuous compression, and continuous film coating followed by parallel at-line and inline assays. The measurements generated from these assays are input into the dissolution model to generate a dissolution rate, which could be further used for real-time dissolution testing. Examples of RTRT approaches involving dissolution include fast at-line measurements like disintegration in lieu of dissolution. Dissolution models serve as a surrogate for traditional time-consuming measurements like release tests are usually multivariate high-impact models and typically relate process parameters and/or material attributes to dissolution.

Methodology

A dissolution method for traditional QC dissolution testing is typically developed in a lab based on critical material, process, and manufacturing variables, as well as design space (Fig. 7). Sometimes, these methods incorporate clinical relevance and such a method is highly desirable. During CM, product quality is also monitored by NIR measurements. These measurements are incorporated into PCA, and a final dissolution model based on multiple linear regression is developed. The observed and predicted data are compared to verify the model. Once the model is developed, model validation is performed using a different independent set of validation batches that were not included as part of the model development.

Model Development Regulatory Considerations

Several recommendations for dissolution model development were made. 1) An RTRT model should be developed based on a dedicated DoE study. For DoE studies, detailed formulation and process parameters for each studied development run/batch, as well as dissolution profile data (including the mean, individual vessel data, and CV% for each test), should be provided. 2) A detailed description of the dissolution RTRT model and justification for the selection of the model and its inputs should be provided. 3) All model calibration and validation activities and results should be provided. The RTRT model should be able to predict the entire dissolution-time profile instead of dissolution at one time point and predict non-conforming batches (batches that fail dissolution). 4) Dissolution profile data for model calibration and validation including individual vessel data as well as the mean and CV% should be provided. 5) A detailed sampling plan of RTRT for batch release should be provided. The sampling locations should be equally spaced and statistically justified for dissolution prediction. The sampling plan should be sufficient to detect the dissolution variability of the batch for the production duration. 6) If physiologically based pharmacokinetics (PBPK) modeling and simulation is used to support the proposed manufacturing design space, then the complete study report is to be submitted.

Model Validation Regulatory Considerations

Consideration for models serving as surrogates for release tests involve development of a robust calibration model. This can be accomplished by use of an appropriate reference method that would include variations in raw materials and would cover the entire design space.

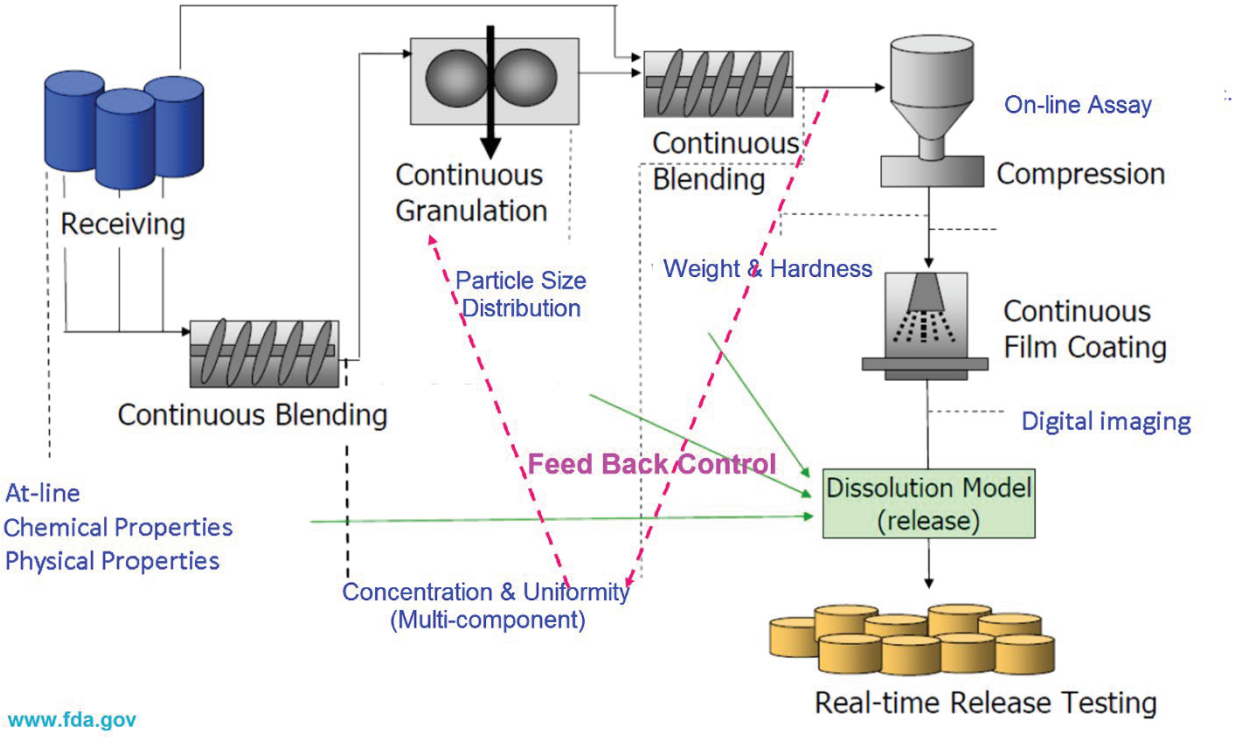


Figure 6. Example of real-time release testing within a continuous process, wherein input materials are continuously received into the system with continuous blending, granulation, compression, and film coating followed by parallel at-line and inline assays.

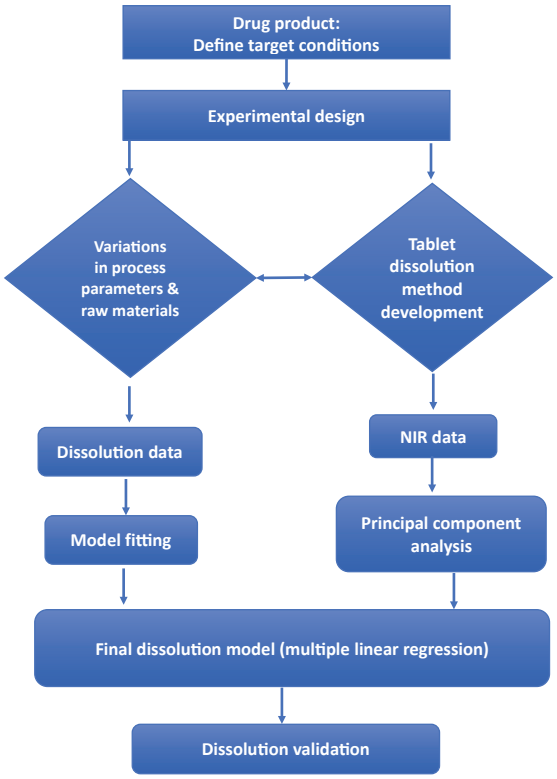


Figure 7. Methodology for traditional quality control dissolution testing based on critical material, process, and manufacturing variables and design space. NIR: near infrared.

Typically, an independent dataset is recommended for validation. The model performance should be demonstrated at a commercial scale. To accomplish this, it is important to understand and work within the model limitations and model assumptions and compare the model results to a reference method for a statistically acceptable number of batches. Some of the general considerations for dissolution models involving RTRT include justification/appropriateness of sample size; approach for data pretreatment; statistical analysis of data showing fit and prediction ability and rationale for selection of model diagnostic criteria; robustness of the model outside the ranges used for calibration/validation; strategy for model suitability throughout drug product life cycle as part of applicant's quality system; and in the case of CM process, and strategy for verification of state of control and potential trending due to random variability; as well as sampling strategy for dissolution testing.

Case Study 1

The first case study was an original new drug application (NDA) wherein a PDM was included as part of an RTRT model. This NDA consisted of two APIs, one belonging to BCS class II (low solubility and high permeability) and the other being BCS class IV (low solubility and low permeability). Owing to the low solubility, both drug substances were provided as amorphous spray dried dispersion (SDD) intermediates for drug product formulation. Biopharmaceutics review focused on dissolution method, acceptance criterion, and alternative approach of dissolution testing as RTRT. Dissolution testing was also used in establishment of manufacturing design space for the fixed dose combination tablet. Acceptance criterion was based on pivotal clinical batches, stability data, tablet to tablet variability from individual pharmacokinetics (PK) of clinical batches, and risk-based assessment of critical parameters to dissolution such as crystalline content and granule particle size. RTRT dissolution testing was based on a PLS model. The in-process material attributes and process parameters measured by PAT in CM were used to calculate a dissolution rate (Z). The dissolution rate is then used to predict the dissolution profile based on a modified Noyes-Whitney equation. The measured final blend API content, average granule particle size, API SDD bulk density, hardness, tablet weight, and thickness were used as input factors in the PLS dissolution rate model. Calibration of the PLS dissolution rate model was performed using reference dissolution methods for core tablets from manufacturing runs spanning design space and manufacturing range with various drug substance, SDD, and excipient lots. Predicted vs. reference sets with R of 0.95 were included for calibration (the absolute differences for percent dissolved between the two methods are < 5%). In addition, root mean square error (RMSE) and root mean square error cross validation (RMSECV) vs. factors plot and factor loadings plot were used to justify latent variables. RTRT dissolution results were consistent with those obtained from regulatory dissolution methods with no more than 5% difference across the 19 continuous Quality by Design (QbD) runs during development and launch setup and three QbD confirmation runs. To further verify if results fall within the calibrated space of the model, non-confirming batches were detected using Hotelling T^2 with not more than (NMT) 23.6 and Q-residual with NMT 35.4 as the criteria. Stratified sampling of 12 segments for each batch was considered. An out-of-specification investigation would be initiated if an RTRT dissolution result does not conform to the specification.

Case study 2

The second case study was a post-approval NDA. At the time of approval of the original NDA, a regular QC dissolution method was approved. Eventually, the applicant chose to include PDM as part of RTRT as a post-approval supplement. The agency reviewed the RTRT dissolution model that was submitted as surrogate of dissolution testing to replace the in vitro analytical dissolution method and as additional in-process control under CM. The dissolution model was not found to be acceptable initially due to the following reasons. The developed model was bivariate that predicts dissolution at 30 min. The proposed model was based on PLS analysis of DoE data based on API concentration and tablet weight and thickness. The study did not include API particle size and their interactions with other critical parameters. During initial dissolution method development, release was thought not to be affected by particle size in the ranges tested. Hence, API particle size was excluded from DoE studies. However, based on previous supplements it was found that particle size (coarse vs. fine API) affects the bioavailability (based on a relative bioavailability [RBA] study), although QC release was not able to capture the differences at Q = 80% of the labelled amount dissolved in 30 minutes. Further, PLS analysis and DoE study were thought to be confounded as approvability ranges were wider than ranges tested. Variable ranges evaluated in the DoE study were narrower than the approved ranges, resulting in dissolution profiles that are likely to fail dissolution comparison, which in turn would lead to variation in in vivo product performance and lack of BE. In addition, approved ranges in PSD would result in drug product batches that are not BE when

comparing the upper/lower bounds. Mitigation strategies involved exploring the model with a dedicated design space including API particle size or revision of dissolution acceptance criterion to Q = 80% of the labelled amount dissolved in 20 minutes along with tightening of three-tier API PSD based on clinical experience. Recommended sampling strategy was to include 10 tablets randomly selected within each of the 16 Quarantine Hoppers (QH) tested. The applicant counter-proposed a sampling plan to align with sampling for at-line NIR testing (for assay and uniformity analysis – collection of ten tablets from each QH prior to each QH being released). The applicant's proposed final plan was acceptable as it aligned with current CM line sampling and analysis workflow along with risk mitigation by tightening of API PSD specification.

Dr. Mandula's presentation spurred quite a few questions from the audience, leading to further discussion and clarification of the above points in the subsequent interactive question/answer session. The discussion centered on the acceptance of PDM models and the components of successful justification packages that gain regulatory acceptance. In general, Dr. Mandula's perspective was that it is advisable to have a discriminating method early in the development process. She suggested that filing a dissolution method at the IND stage, as an amendment, if necessary, may be helpful because dissolution methods can be approved ahead of the NDA. This presents an opportunity to engage in face-to-face meetings with the health authority ahead of submission, which allows both parties to gain insight into the applicant's dissolution strategy and for the applicant to receive input from the agency.

In response to a query regarding discriminating capability of a PDM method as compared to an in vitro one, Dr. Mandula indicated that they both should serve to address the same risks. Both QC and PDM methods should ensure safety and efficacy, be discriminating and clinically relevant when possible, and if not possible, to ensure adherence to a safe operating space. The PDM method will be subject to scrutiny due to the inherent risks involved with a predictive method. When preparing packages for submission, a risk-based approach should drive experimentation and data set decisions. Sample sets should represent the entirety of a run and be subject to rigorous statistical analysis to inform risk. In terms of sampling strategy, applicants should propose sample plans that adequately capture risk. It is advisable to test the PDM with batches that differ from those used for the model building process. The preferred approach is data from real batches, conforming and non-conforming, as non-conforming batches help to define the operating space of the model. Data based on simulated batches should be avoided for defining process operating space, although simulated batches could be used to supplement model evaluation. Applicants are encouraged to consider the PDM approach for all types of manufacturing processes (e.g., wet granulation, modified-release formulations, etc.).

DATA SELECTION AND GENERATION

The first presentation of the second day of the workshop was given by Matthew J. Walworth, PhD (Eli Lilly & Co., USA), providing the basis and rationale for data selection and generation in service of a PDM for RTRT, exemplified by a case study (*39*). A PDM in support of RTRT of pharmaceutical tablets can enable cost and time savings over standard dissolution methods such as USP <711> (*8*). A PDM must reliably produce accurate predictions to be accepted by regulatory agencies. To successfully build a PDM, high-quality dissolution data (i.e., data obtained using a well-developed reference method) is essential to model training and validation.

Model Training

The initial stage of model training is establishing technical feasibility, which should be completed as soon as possible in process development. Because dissolution is evaluated in early-stage control strategy development, nondestructive analytical techniques such as NIR or Raman could be performed before destructive dissolution in order to establish whether RTRT is feasible. Once PDM technical feasibility has been established, a more robust data set should be acquired. The following factors should be considered: 1) samples are representative of the commercial manufacturing process; 2) the entire design space should be represented in the samples using a statistically relevant sampling method (such as factorial sampling); 3) the training data set should have designed sources of variability and statistical probability; 4) and samples specifically designed to fail should be created to confirm that the model can identify a failing sample.

An SDD-based roller-compacted IR tablet formulation with two commercial dosage strengths and an accelerated commercialization plan was presented as a case study. To create a PDM, a Weibull function (see equation below) can be used to accurately model the dissolution profile.

$$\textit{Fraction of drug released (t)} = A\left(1 - e^{-\left(\frac{t}{\lambda}\right)^{k}}\right)$$

The Weibull function describes the fraction of drug released as a function of time, *t*, where *A* is the potency

factor, λ is a scale factor, and *k* is a shape factor.

Figure 8 shows how varying the *k* and λ factors affects the dissolution profile. In this case study, a PLS model based on NIR predicts *A*. Another PLS model based on NIR, roll force, roll gap, and compression force predicts λ. Finally, a linear relationship was established between the compression force and *k*.

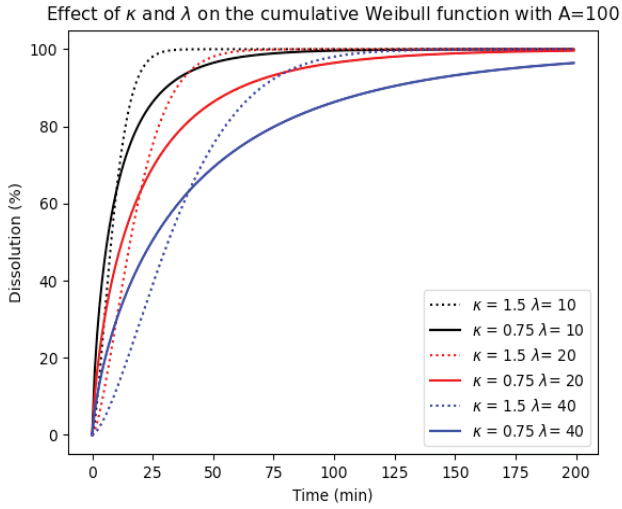


Figure 8. Weibull function profiles.

Model Validation

Training data is critical to model development and model validation. A best-case scenario for model validation involves collecting data from a serial experiment/production of drug product. This data set should include data outside of the operating space (non-conforming material), as well as data that is representative of the entire design space. Special care should be taken to include data that samples the extreme ranges of critical process parameters and common failure modes.

Model Lifecycle

Following model validation and deployment, data should be continually collected to support continued use or justify the need for a model update. After initial deployment for use in supporting GMP activities, a period of heightened monitoring against the reference method (per USP <711>) should be considered (*8*). Additionally, non-conforming material should be prepared to support the continued use of the model. The most common reason for a model update might be an ingredient (API or excipient) supplier change or a change in excipients.

QC METHOD DEVELOPMENT FOR PDM APPLICATION

Sandra Suarez-Sharp, PhD (Simulations Plus, USA) presented her perspective on developing a dissolution release method with the aim of serving as the basis for a PDM (*40*). Dr. Suarez-Sharp's perspective as an expert in the field and previous experience in the FDA afforded a unique opportunity for detailed discussion of this topic.

The implementation of RTRT to drug product development offers the possibility of reduced timelines and inventory and, therefore, reduction of end product testing and manufacturing costs. RTRT dissolution models are key in completing the system, especially for extended-release (ER) formulations and drug products containing BCS class II/IV compounds. Without an RTRT dissolution model, companies are not truly releasing the drug product in the regulatory sense. The successful implementation of these models relies heavily on having exhaustive drug product understanding, which involves several steps, including identification of all relevant failure modes and their potential interactions; implementation of dissolution testing; inclusion of all relevant failure modes within the RTRT model; and adequate internal and external validation of the model showing its ability to accurately predict batches that are considered to be out of specification. Dr. Suarez-Sharp's presentation focused on describing a strategy that relies on modeling and simulation (i.e., physiologically based biopharmaceutics modeling [PBBM]) for developing a biopredictive dissolution method to ensure regulatory approval of RTRT dissolution models.

Among all steps that go into developing RTRT dissolution models, the application of a fit-for-purpose dissolution method (FPDM) as an endpoint in the DoE studies constitutes one of the key measures to ensure a successful RTRT strategy. In many cases, whether an attribute, parameter or in-process control is considered critical to the performance of the drug product will depend on whether the dissolution specification (i.e., the method and acceptance criterion) was met following variations of that specific attribute or parameter being evaluated. In addition, which attribute(s) and/or parameter(s) are considered for building the RTRT model is dependent on the sensitivity of the dissolution method used to identify the specific failure modes. Given the criticality of this step, efforts should be made early in drug product development to utilize a FPDM. In other words, a method for which its discerning ability/scrutiny has been established based on biopharmaceutics risk assessment (Fig. 9). The successful implementation of a FPDM will then facilitate the selection of the true CMAs and CPPs (*41*, *42*). To this end, FPDM testing then serves as both a sensor of potential interactions among parameters and

an indicator representing the impact of implemented CMC changes on in vivo performance. By varying one parameter at a time to determine its in vivo impact, or relying on quality attributes other than dissolution to define the performance of the drug product, the true net effect on product quality and in vivo impact may not be properly represented due to 1) the potential interaction among the CMAs/CPPs that could result in synergism or neutral effect and 2) dissolution being considered as the only quality attribute that proves both the rate and extent of in vivo drug release.

Figure 10 depicts a proposed path from QC method to an RTRT dissolution model that takes into consideration biopharmaceutics risk assessment. In other words, it is applicable to drug products other than IR products containing high-solubility drug substances. This strategy is centered around the development of a FPDM that is biopredictive/clinically relevant via the construction of an in vitro/in vivo relationship (IVIVR) and a safe space utilizing PBBM. Efforts for developing and selecting such a dissolution method should start early in drug product development by relying on the construction of a baseline PBPK model utilizing data inputs from preclinical PK studies and dissolution data generated from several methods (including biorelevant media) (*43*). A preliminary biopredictive method can then be used in DoE studies to make an informed decision on the selection of the CMAs and CPPs. The data collected from the DoE studies is valuable because one can continue making educated decisions on the relevant formulation variants to be considered in RBA/BE studies, which in turn will be utilized to build an IVIVR/safe space. The information gathered in this last step is critical to confirm the predictive ability of the dissolution method and criticality of the variables selected (which will be part of the RTRT model), based on clinical PK data.

In conclusion, robust and successful RTRT dissolution models necessitate the integration of FPDM (e.g., biopredictive methods) as part of DoE studies. RTRT dissolution models developed based on a dissolution method and acceptance criterion that do not meet expectations are the most common cause of revisions to the design space(s) and/or removal of RTRT dissolution models from regulatory submissions.

The broad applicability of Dr. Suarez-Sharp's presentation to all oral drug product submissions that are considering PDM development generated a robust discussion with the audience in the interactive question/answer session. Generally, audience questions fell into two broad categories: (1) how to ensure that a dissolution method

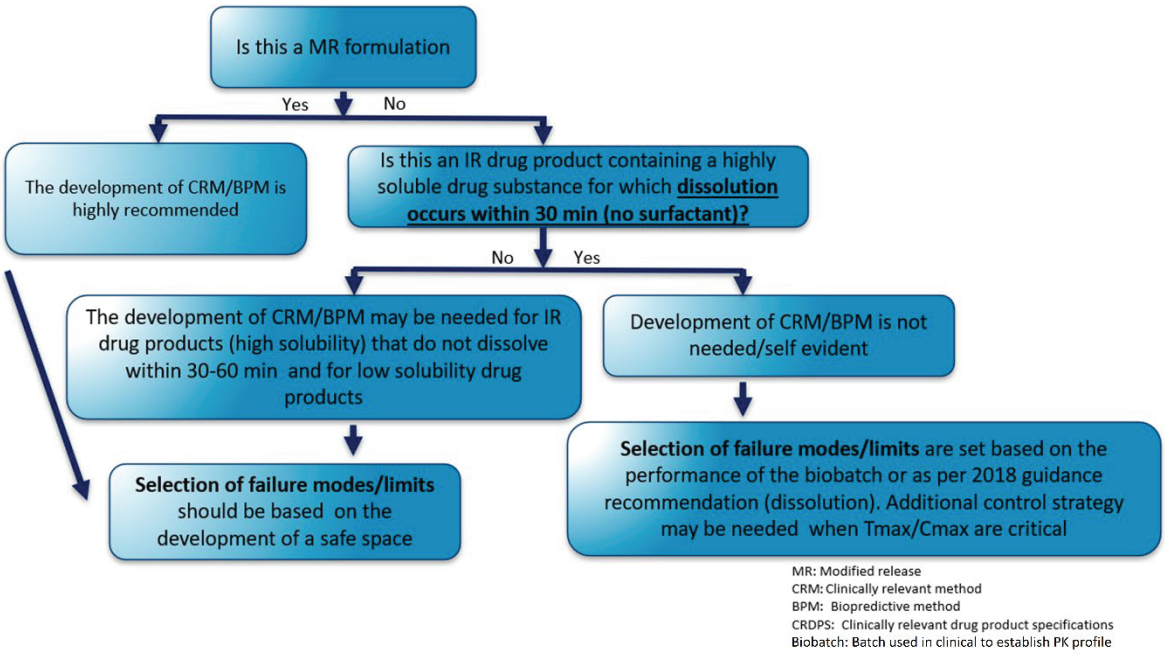


Figure 9. Biopharmaceutics risk assessment decision tree for determining the criticality of developing a biopredictive/clinically relevant dissolution method, with reference to the 2018 FDA guidance for dissolution of highly soluble drug substances.
Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evalution and Research (CDER), August 2018.

is discriminating at different stages of development, and (2) how many and what variations to the drug product need to be made to demonstrate dissolution method discriminability.

Early in development, prior to availability of clinical data, dissolution should be understood across the physiological pH range and in biorelevant media (e.g., fasted/fed-state simulated intestinal fluids). If no such media provide full release of the drug product at those stages, addition of surfactants should be explored. This work will elucidate the potential for a physiologically relevant dissolution method, as well as providing the basis for early-phase modeling of in vivo performance. A method that provides a dissolution profile with full but not instant release, ideally with physiological relevance, should be selected for early formulation discrimination and dissolution model building. Subsequently, as clinical data become available, they should inform whether or which dissolution method provides discrimination for variations that result in in vivo performance differences. Such a clinically relevant dissolution method is ideal for selecting CPPs and CMAs.

Selecting variations in drug product to determine the discriminability of the dissolution method is also dependent on the phase of drug development. Early understanding of dissolution behavior, combined with modeling and simulation, can help select meaningful variations for formulation development. To justify a proposed QC method, it is necessary to demonstrate sufficient variation in clinically tested drug product. The predictive ability of the method is best justified through verification against actual in vivo performance. Additionally, selecting variations that lead to non-BE performance is highly beneficial because it can inform the borders of a process or attribute safe space and help in setting specifications that offer the greatest flexibility for the applicant.

QUALITY CONSIDERATIONS

Next, Melanie Dumarey, PhD (AstraZeneca, Sweden) presented the quality considerations of implementation of PDM for RTRT (*44*). Predictive models are a critical part of RTRT for dissolution as they enable linking measured PAT signals and/or process parameters to the dissolution profile of a formulation. Following the ICH-endorsed guide for ICH Q8/Q9/Q10, these models are classified as high-impact because they are a significant (and sole) indicator of product quality (*7*). Similar models could be used solely to support product development, in which case they are classified as low-impact. A current gray area is the use of predictive dissolution models to define a safe space, i.e., a multivariate design space where observed variability in dissolution has no clinical relevance (*9*). Further detailed studies are needed to demonstrate to regulators that the latter approach does not compromise patient safety.

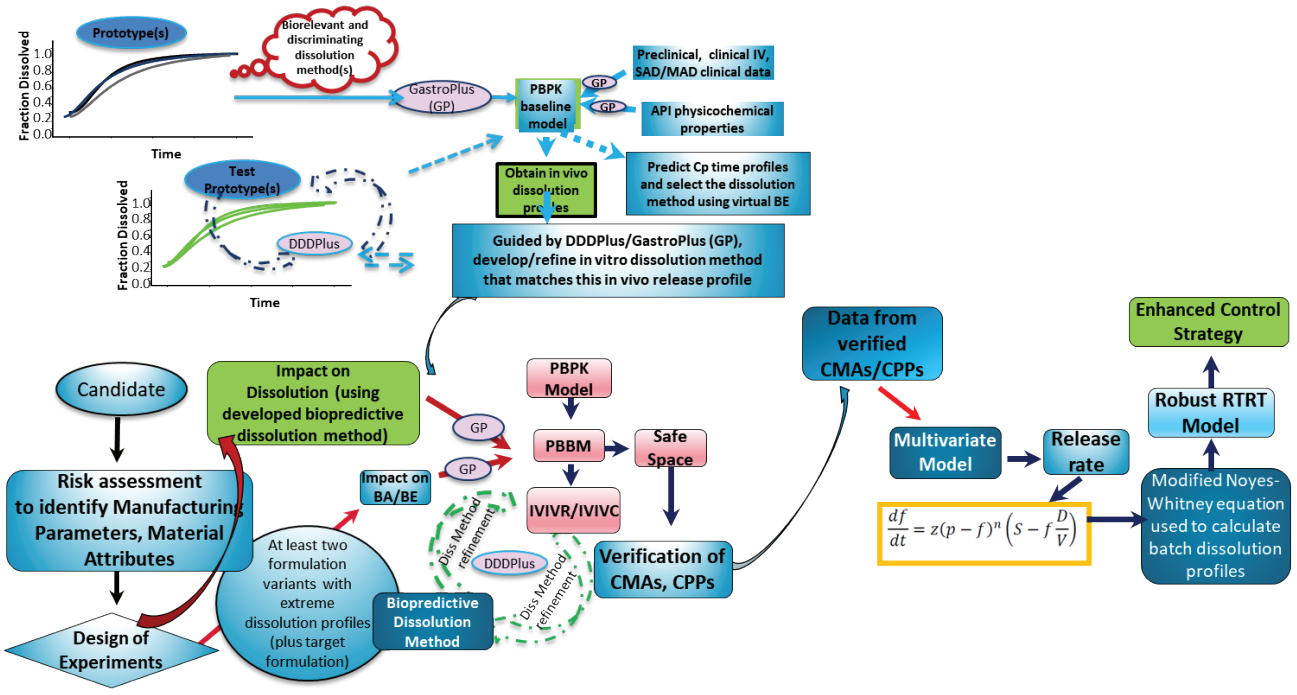


Figure 10. Proposed strategy for developing a biopredictive dissolution method and building clinical relevance into RTRT.
PBPK: physiology-based pharmacokinetics; SAD/MAD: single/multiple ascending dose; API: active pharmaceutical ingredient; Cp: concentration in plasma; BA: bioavailability; BE: bioequivalence; PBBM: physiologically-based biological model; IVIVR/IVIVC: in vivo-in vitro relationship/correlation; CMA: critical material attribute; CPP: critical process parameter; RTRT: real-time release testing.

High-impact models, such as models supporting RTRT for dissolution, require a detailed description in the common technical document (CTD), including a justification for the selected model parameters. In the prior section, current and former regulators stressed that the relationship between process variability and the complete dissolution profile should be fully understood to ensure all relevant CPPs and CQAs are included in the predictive model. This can be achieved by performing a dedicated DoE and/or by applying first principles (*45*). Regulators strongly recommended to model the entire dissolution profile rather than dissolution at a selected time point. Model robustness should be maximized by accounting for all process variability as expected during routine manufacture, e.g., excipient variability (*45*). The model description in the CTD should also contain model assumptions, sampling plan (number and justification), data pre-treatment, and a statistical evaluation of the model (*7, 45*).

High-impact models also require a high level of validation implementing an external validation set, which consists of samples not included in model calibration (*7*). Hereby, the predicted model values should be compared to the values measured with a validated reference method. Moreover, it should be demonstrated that non-compliant tablets are detected by the RTRT. During the workshop, it was clarified that validation can be based on dissolution prediction at one single time point but should be based on commercial scale data. Additionally, simulations can be used to complement the experimental validation, e.g., simulation of a batch failure. The validity range of the model should be defined, as well as diagnostics implemented to prevent invalid model predictions. NIR guidance issued by the European Medicines Agency (EMA) and FDA both provide detailed information on regulatory submission requirements for multivariate models (*46*, *47*).

The long-term validity of a model is ensured by the implementation of a lifecycle management plan monitoring common and special cause variation over time and triggering model updates as needed (e.g., change of a PAT instrument) (*7*). When implementing model changes with a major impact on product quality and/or model performance as part of the life cycle management, regulatory actions are required. Regulators recommended to capture anticipated model changes and associated actions in a post-approval change management protocol (PACMP), enabling to decrease the reporting category and helping to ensure business continuity.

INDUSTRIAL CASE STUDIES

Finally, the podium speaker presentations concluded with a series of industrial case studies (*48*). Sara Manteiga, PhD (Vertex, USA) presented a case study of implementation of PDM for RTRT as an alternative release method in an original NDA of a CM process. Stan Altan, PhD and Sarah Nielsen, PhD (Janssen Pharmaceuticals, USA) presented a PDM for RTRT developed as a post-approval process change, implemented on a batch manufacturing process, using multivariate statistical process control (MSPC) to enhance batch release.

Case Study 1

Dr. Manteiga presented a case study of a Vertex drug product manufacturing process for which RTRT was accepted as an alternative dissolution method to the regulatory release method. The drug product in the case study is an IR tablet manufactured continuously. The CM process train is equipped with multiple PAT stations to assess in-process material attributes. Together with an automated control strategy, these PAT measurements enable real-time process monitoring, control, and RTRT. The automated control strategy consists of four levels of control, from the lowest level to highest level, including: control of unit operations to set point through feedback loops, process design space monitoring, in-process controls (IPC), and RTRT. The IPCs have been set to ensure the process stays within the design space and that product variability within a batch is acceptable. Non-conforming IPC results lead to the removal of material from the process.

The RTRT dissolution methodology employs a hybrid modeling approach that links inline measured attributes to the dissolution results through a dissolution rate model, based on a modified Noyes-Whitney equation:

$$\frac{df}{dt} = z\,(p - f)^n\,(S - f\,\frac{Dose}{V})$$

The rate equation describes the fraction of API (f) dissolved over time (t) expressed as percent label claim (%LC), z is the rate factor, p is the extent of dissolution, n is a fitted particle shape factor, S is the API solubility representing the surface concentration from the dissolving material, and the dose/volume correspond to the tablet strength and volume of dissolution media in the USP apparatus 2 vessel.

Implementation of the modified Noyes-Whitney equation allows prediction of the full dissolution profile from measured in-process material attributes. A segmented

sampling approach is employed in which each batch is divided into 12 segments of nearly equal size, and results are calculated on each segment. This segmentation strategy ensures results are reported consistent with USP <711> stage 2 testing criteria and affords increased assurance of product quality through comprehensive representation of the batch. To determine the batch dissolution result, first *z* is calculated using the measured material attributes results and a PLS model. For prediction of the dissolution curve's plateau, API content in the final blend, measured directly by in-line NIR, is utilized. The predicted *z* and extent of release are then used to calculate the full dissolution profile and obtain the %LC at the specification timepoint using the modified Noyes-Whitney equation.

The PLS model for rate factor *z* is calibrated by fitting the reference method USP apparatus 2 dissolution profiles curves to the modified Noyes-Whitney equation and determining *z* for each profile in the calibration set. The samples used in the model calibration span the process design space and desired manufacturing range. To generate the calibration data set, key raw material attributes and process parameters (such as granulation and compression parameters) were intentionally varied using a multivariate DOE to achieve a range of dissolution performance to ensure robustness was built into the PLS model. The PLS model inputs were selected from known measured in-process material attributes based on a risk assessment using knowledge of the process and factors influencing dissolution performance at the time of batch release. This approach enabled a direct link to be made from raw material and process attributes to measured physical and chemical in-process material attributes, and finally, to tablet dissolution.

The PLS model for determining dissolution rate was rigorously assessed during development to ensure accurate prediction without overfitting. Samples used for model development were collected throughout development and analyzed by the PAT methods and the reference dissolution method. Selection of the calibration samples and appropriate number of latent variables for the PLS model was achieved through evaluation of calibration and cross validation statistics. An independent test set, including clinical batches and a parallel testing batch continuously manufactured at full-scale, was evaluated to ensure suitability of the model for its intended use.

For validation of the RTRT dissolution method, each PAT input method was validated in accordance with ICH Q2 (R1) (*49*). Additionally, direct comparison between the RTRT dissolution method and the reference dissolution method was made for a batch and shown to meet the established acceptance criteria. To further demonstrate the capability of the RTRT dissolution method to properly characterize the dissolution performance of a batch, comparison of results obtained using the reference dissolution method and the RTRT dissolution method was carried out for 25 continuously manufactured batches intentionally designed to span the desired manufacturing range, producing a range of dissolution performance. The RTRT results were consistent with those obtained from the reference dissolution method indicating good prediction accuracy, including the ability to detect non-conforming material.

A model lifecycle management strategy was also described for the RTRT dissolution method, to ensure performance of the RTRT method throughout its lifecycle. The PLS model maintenance practice requires assessing the performance of the model on a periodic or event driven basis, including routine parallel testing, changes to materials/instruments/process, observation of trends (including model diagnostics), and investigations. Based on the outcome of the assessment, a model update may be warranted. This may entail but is not limited to adding or subtracting calibration samples, changing the model prediction range, changing variable preprocessing, or changing the number of latent variables in the model. An updated model is ready for routine use upon successful completion of supplemental validation. Model updates are governed by a change management process.

Last, some of the key elements for successful implementation of the RTRT method in this case study were summarized:

- Knowledge-based justification for selection of input parameters to the RTRT PLS model, based on significance of impact of input parameter on drug release.
- Calibration and verification of RTRT method showed similar prediction outcomes with those obtained from the regulatory dissolution methods.
- For batch release using the RTRT method, the sampling approach ensures compliance with USP <711>.
- Demonstration that the RTRT model can detect non-conforming batches.

Case Study 2

Drs. Altan and Nielsen presented a case study of a real-time release strategy of a fluid bed granulated BCS class IV batch manufactured drug product, showcasing Janssen's unified approach to RTRT in the context of traditional batch manufacture. The approach involves monitoring CPPs at the dispensing and granulation steps, identified from earlier experimental manufacturing designs, that allowed the creation of a "health check" model to evaluate current batches against a historical standard (Fig. 11). The importance of comprehensive and adaptive experimental designs to provide the basis for de-risking was emphasized, as well as to set the stage for the development of a surrogate dissolution model. A comparison of the current release methods with the RTRT methods indicated greater assurance of quality due to larger sample sizes.

The surrogate dissolution model developed by Janssen relied on a comprehensive DoE (*50*). The designs provided a clear identification of the CPPs used to develop a "process" model in the first step. The process model related dissolution variables as the response variables to the CPPs. Dissolution variables, for example, could be specific selected time points on the dissolution profile, e.g., release at 20 and 30 minutes, or they could be the parameters of the Weibull function describing the full profile. In the former, it is a specific time point(s) model, whereas in the latter, it is a full dissolution profile prediction model. Once the response variables are defined as a multivariate vector, augmented by the content of the tablet measured by NIR, a conditional regression method was applied to the process model. The second step was to develop a predictive surrogate model of the dissolution response vector, relying on a population average approach, with process parameters and NIR content as inputs. The use of this statistical approach, in a Bayesian context, permits simulations that can characterize future manufacturing performance with respect to USP <711> testing, as well as estimates of the surrogate model's accuracy and precision in relation to the standard in vitro release test, on a batch average basis. It was also emphasized that the experimental manufacturing protocols be coupled with in vitro dissolution testing that orthogonalizes dissolution/high-performance liquid chromatography (HPLC) run effects with vessel and experimental batch effects.

DISCUSSIONS

Each of the 2 days of the workshop was capped by a panel discussion, allowing for interaction among the speakers and with the audience. The speakers participating in the first day's panel were Nikolay Zaborenko, Tessa Carducci, Alexander Ryckaert, James Drennen, Haritha Mandula, and Sandra Suarez-Sharp, moderated by Carrie Coutant (Eli Lilly & Co., USA) and James Mann (AstraZeneca, Sweden) (*51*). Discussion included the following topics:

- The skills necessary for developing PDMs for RTRT
- Global regulatory climate for accepting PDMs for RTRT
- Acceptance criteria for PDMs in relation to USP <711>
- Resources required to develop a PDM for RTRT as

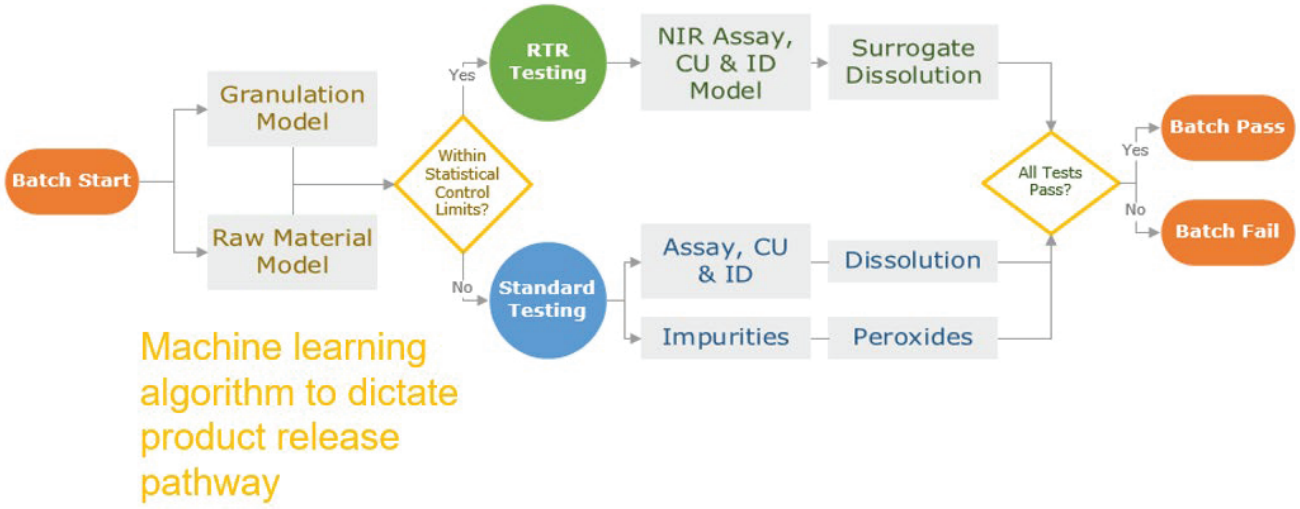


Figure 11. Real-time release using a "health check" model to evaluate current batches against a historical standard. RTR: real-time release; NIR: near infrared; CU: content uniformity; ID: identity.

compared to traditional dissolution

- Future direction of PDM

The first question was around what skills are important for developing PDMs for release. The importance of knowing and understanding regulations, the business case, having a good understanding of the manufacturing process and product dissolution including the method, specification time point, and failure modes, and multivariate modeling skills were all mentioned. The panel was asked a follow-up question on how to approach modeling if the dissolution is very fast or if the product is highly soluble (BCS class I or III). The risk for dissolution failure is seen as low for these products, and Dr. Mandula mentioned that there have been models of disintegration for release testing of products previously approved by the FDA.

The panel was then asked about the regulatory climate for PDMs for release and the importance of global acceptance. The business case is magnified when approved globally, and conversely, the benefits to a company could be questionable if routine traditional dissolution testing is still required for some markets. Approvals have been realized in the US and EU, and South Korea has just approved a new RTRT guideline that mentioned PDM.

There was robust discussion around assessment of acceptance criteria and whether PDM for release should follow USP <711> criteria. The panelists generally agreed that a larger number of replicates should be used to compute confidence intervals but that there may be additional approaches that would be successful, and applicants should make a proposal with justification of sampling plan as addressing the risk of failing to capture out-of-specification results. A related question asked was about how to handle error introduced through model inputs. This was seen by the panel as being analogous to any other type of analytical measurement where there are multiple contributing sources of error, and it is important to define the appropriate statistical sample size and confidence interval considering variability of model inputs. It is important to understand and minimize error in the traditional dissolution method because a PDM model will be based upon the reference method like other PAT-based models.

The next question was if the panelists have any advice for managing the increased resources required for development of a PDM as compared to traditional dissolution including those required for the model validation and maintenance efforts. In reply, it was suggested to convince the manufacturing teams of the benefits of eliminating dissolution testing, especially for high-volume products. Additionally, integrating model development with product development and starting early during development seems to help so that it is not seen as a separate or additional effort. Finally, implementing PDM for multiple products is more valuable than for only one product, and subsequent efforts should be easier since the experience and infrastructure can be leveraged.

The panel was concluded with a question on future directions in the field of predictive dissolution modeling. Research into models beyond simple PLS to improve quality of predictions, terahertz spectroscopy as an alternative method for dissolution, and sensor performance advancements to enable use of PDM as a process performance algorithm were mentioned as valuable future novel advancements.

The speakers participating in the second day's panel discussion were Nikolay Zaborenko, Melanie Dumarey, Sandra Suarez-Sharp, James Drennen, Matthew Walworth, Sarah Nielsen, and Stan Altan. The panel was moderated by Andre Hermans (Merck & Co., Inc., USA) and Siddhi Santosh Hate (Eli Lilly & Co., USA) (*52*).

The day 2 panel discussion included the following topics/questions:

- Panel experience of implementing apex vessels and global regulatory outreach
- How to build a PDM as an alternative QC method related to in vivo performance
- How many different formulation variants are needed for PDM model validation
- How the framework of RTRT models can be extended to non-oral drug delivery systems that require dissolution testing
- How a model fitting function and its parameters are selected for a dissolution profile prediction model
- Circumstances where a disintegration test may replace dissolution methods that only reproduce assay results

The first question was about the initiative by the IQ Consortium's Dissolution working group and AAPS In Vitro Release and Dissolution Testing community to implement apex vessels into USP testing. Apex vessels

were introduced to improve the hydrodynamic situation in the USP apparatus 2, the most commonly used apparatus for oral solid dosage forms (*53*). Several efforts have been made for global outreach to both the scientific dissolution community and the regulatory community worldwide. The topic was brought up to stimulate discussion and conversation with a diverse audience, especially for those people from countries that are newer to RTRT modelling and can share new global perspectives.

Then there was a follow-up question to the panel about PDM, which can be used as a surrogate to QC methods related to in vivo performance. Dissolution models used as a surrogate for QC release tests are high-impact models. These predictive models are typically built based on CMAs and CPPs, with a good understanding on how the QC method reflects in vivo performance. The panel shared their futuristic view of how a direct linkage can be made to model in vivo performance directly based on variations in CMAs/CPPs. It is also possible to simulate the process to link the multivariate models to drug safety and efficacy. It can be achieved by leveraging the available PK data that were already collected during development to train the models.

The panel was also asked if there is an ideal number of different formulation variants that need to be generated for validation of in silico modeling, such as the software DDDPlus, which could potentially link to PBBM. The panel commented that a minimum of two formulation variants are typically needed. The panel also discussed if validation should include batches with expected out-of-specification performance. The failing batches are often generated in early development when they are not fully representative of the final process or at scale and often use parameter values that are outside of the working model that eventually ends up being built. Using them to build the model will be challenging, and generating them at scale expends materials and time. Therefore, simulation tools such as DDDPlus might be used to do multicolumn analysis of variations and show that the deviation can be picked up by the model. It is appealing to generate the simulated data to support the dissolution model.

The examples presented in the workshop were focused on RTRT models for IR dosage forms. The panel was asked for opinions on expanding the framework to other drug delivery systems, such as extended-release dosage forms. RTRT modeling for other dosage form might be found acceptable, but it is handled on a case-by-case basis when advancing to complex dosage forms. The panel also mentioned that when using the framework for prediction of performance, replicates of 6 or 12 are recommended during model building and model validation. Sufficiently reproducible data is needed to build a PDM confidently. It is important to consider this so that DoE studies performed in early development can be designed in such a way as to provide useful data for PDM building.

The panelists were asked for their advice on the selection of fitting function and parameters for dissolution profile prediction models. The Noyes-Whitney function and Weibull function (with two parameters and a plateau multiplier) are the most commonly used functions in literature for fitting dissolution performance. Some experts commented that generally there is no dictating factor for selecting a function, as long as it provides adequate and consistent description of the dissolution profile. In addition, the calibration approach used should be robust over time to reduce errors in the long term.

Finally, it was asked when the dissolution method is very robust and a disintegration test can be used instead, is a PDM still needed? Some participants commented that it should not be necessary, as a process/material safe space for dissolution performance can be established and maintained to provide confidence of acceptable dissolution for every batch. However, the regulatory position on this has not been established. The panelists shared an experience where disintegration had been used as surrogate for dissolution and approved by FDA, but this was for a very low-risk product, where disintegration was more discriminating than dissolution. The group all agreed that this is a regulatory question, so in such cases, discussion should be had with the health agencies well in advance of submission.

CONCLUSIONS AND FUTURE DIRECTIONS

RTRT of dissolution based on PDM has been shown to enable QC release of drug products with equivalent or better quality assurance compared to traditional dissolution testing. In fact, the development of a PDM for RTRT necessitates a high degree of understanding of the drug product, including the interactions of its CPPs/CMAs and the sensitivity of its in vivo performance to the potential variations in the drug substance and drug product. Thus, the development of PDM for RTRT can be an integral part of a QbD approach, providing confidence in the consistent and satisfactory performance of released drug product.

The development of a PDM for RTRT requires a great deal of understanding and effort. However, it is not an insurmountable challenge. In fact, much of the work

required to develop an appropriate dissolution method for release is foundational and applicable to PDM development. Beyond dissolution method development, many approaches are available to build a PDM, with a high level of flexibility based on the needs of the drug product. A PDM can be applied to CM or to batch processes, with different PAT needs and opportunities presented by each. It can incorporate spectroscopic measurements, whether in-line, at line, or offline, or a PDM based only on process parameters and material attributes can be developed. However, in all cases, the PDM development submission must demonstrate the applicant's understanding of all factors that can influence dissolution behavior and show that those that are critical to dissolution performance are discriminated for by the PDM. CPPs/CMAs should be demonstrated through a DoE specifically designed to ascertain dissolution behavior across changes in these variables. Although a single DoE can be designed to serve multiple CQAs, including dissolution or dissolution surrogate release, it is important that it be designed explicitly with dissolution as one of its purposes. Attempts to repurpose post-hoc prior DoEs for PDM development have generally been met with skepticism from health authorities; however, it should be theoretically possible to demonstrate the applicability of a previously executed DoE to a new CQA (e.g., dissolution) as being equivalent to one designed solely for that purpose.

In developing a PDM for RTRT, it is critical to select an appropriately discriminating dissolution method for which the PDM is predicting release. Ideally, the dissolution method should be clinically relevant (differences in dissolution release behavior correlate with differences in in vivo performance) and able to detect non-bioequivalent product (preferably demonstrated clinically). If no clinical relevance can be established, then the method must be shown to ensure adherence to a safe space within which drug product quality has been ascertained. A PDM for QC must be able to detect non-conforming material by demonstration on physical non-conforming batches. Although simulating batch failure is a potential alternative approach, regulatory authorities express preference for and higher confidence in physical demonstration of the ability to detect non-conformance.

Development of a PDM for RTRT should be done in partnership with health authorities throughout the development process. The FDA and EMA encourage and welcome communications regarding dissolution method development as early as the IND stage, with opportunities for applicants to ask questions and solicit feedback at various stages of the process. Discussions of dissolution method appropriateness for quality control, the development of a PDM based on said method, the discriminating ability of both, and the level of support and justification for the method and model are all topics that should be discussed with regulatory agencies during drug product development prior to the final regulatory submission for the process utilizing the PDM (whether for a new drug product or a post-approval change).

Currently, the primary barriers for drug product applicants to consider developing RTRT for dissolution are the lack of concrete (published) guidances and expectations around PDMs for RTRT and the uncertainty around acceptability of this approach to global regulatory agencies. The uncertainty of successful acceptance of an RTRT approach in all intended markets results in applicants questioning whether or not the investment of developing a PDM will lead to realization of the benefits associated with reducing/eliminating destructive in vitro testing of the drug product. As such, it is imperative for industry members to continue collaborating with global health authorities to establish a common framework of expectations for regulatory submissions containing PDMs for RTRT. As more guidances are published or adopted in global markets, these can serve as the foundation for eventual harmonization. Original NDAs and post-approval changes introducing PDMs for RTRT as alternatives to traditional dissolution testing submitted to regulatory agencies around the world will provide evidence of assurance of drug product quality and generate confidence in acceptability and, eventually, desirability of this approach to drug product release.

ACKNOWLEDGEMENTS

This article was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators, and the broader research and development community. The meeting organizers are infinitely grateful to Maja Leah Marshall for her tremendous efforts in organizing and facilitating this workshop; and to all speakers, moderators, and scribes whose participation was key to having a very informative workshop.

CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

DISCLAIMER

This article reflects the views of the authors and should not be construed to represent their organizations' views or policies.

REFERENCES

1. 2021 Real-time Release Testing Predictive Dissolution Models: Development and Implementation Workshop. International Consortium for Innovation and Quality in Pharmaceutical Development website. Accessed February 11, 2022. https://iqconsortium.org/initiatives/working-groups/dissolution/2021-real-time-release-testing-predictive-dissolution-models-development-implementation-workshop.
2. International Consortium for Innovation and Quality in Pharmaceutical Development Recordings. November 11, 2021. AccessedFebruary 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/browse/null/title-az/null/0/null.
3. Carducci, T. RTRT Workshop-Development of an In vitro Predictive Dissolution Model for Drug Product Release – Overview and Impact. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 11, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/b1abb55c0dbb4272ab67425cdaf9377c1d
4. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. P*harmaceutical Development, Q8(R2)*; ICH Harmonized Tripartite Guideline: Geneva, Switzerland, November 2009.
5. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Quality Risk Management, Q9*; ICH Harmonized Tripartite Guidelines: Geneva, Switzerland, June 2006.
6. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Pharmaceutical Quality System, Q10*; ICH Harmonized Tripartite Guidelines: Geneva, Switzerland, April 2009.
7. *ICH Quality IWG Points to consider for ICH Q8/Q9/Q10 guidelines*; EMA/CHMP/ICH/902964/2011; Committee for Human Medicinal Products (CHMP), European Medicines Agency: London, February 2012.
8. <711> Dissolution. In USP-NF. The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2022. DOI: 10.31003/USPNF_M99470_02_01.
9. Zaborenko, N.; Shi, Z.; Corredor, C. C.; Smith-Goettler, B. M.; Zhang, L.; Hermans, A.; Neu, C. M.; Alam, M. A.; Cohen, M. J.; Lu, X.; Xiong, L.; Zacour, B. M. First-principles and empirical approaches to predicting in vitro dissolution for pharmaceutical formulation and process development and for product release testing. *AAPS J.* **2019**, *21* (3), 32. DOI: 10.1208/s12248-019-0297-y.
10. Kuehn, S. Pharmaceutical manufacturing: Current trends and what's next." American Institute of Chemical Engineers website. December 2018. https://www.aiche.org/resources/publications/cep/2018/december/pharmaceutical-manufacturing-current-trends-and-whats-next
11. Top 10 Trends in Pharmaceutical Industry in 2021. Global Industry Reports website. June 5, 2021. Accessed July 17, 2022. https://www.globalindustryreports.com/blog/top-trends-in-pharmaceutical-industry.
12. Siepmann, J.; Siepmann, F. Mathematical modeling of drug dissolution. *Int. J. Pharm.* **2013**, *453* (1), 12–24. DOI: 10.1016/j.ijpharm.2013.04.044.
13. Noyes, A. A.; Whitney, W. R. The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.* **1897**, *19* (12), 930–934. DOI: 10.1021/ja02086a003.
14. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philos. Trans. R. Soc. Lond.* **1825**, *115*, 513–583. DOI: 10.1098/rstl.1825.0026.
15. Zaborenko, N. RTRT PDM model selection and development. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 11, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/9d515870593244f9bf7b216c891eea1d1d
16. Zaborenko, N. IQ Analytical LG Dissolution Working Group Webinar Series: Predictive Dissolution Modeling - When and How? Presented June 7, 2019. Webinar recording. https://register.gotowebinar.com/recording/2632594075073280771
17. Markl, D.; Warman, M.; Dumarey, M.; Bergman, E.-L.; Folestad, S.; Shi, Z.; Manley, L. F.; Goodwin, D. J.; Zeitler, J. A. Review of real-time release testing of pharmaceutical tablets: State-of-the art, challenges and future perspective. *Int. J. Pharm.* **2020**, *582*, 119353. DOI: 10.1016/j.ijpharm.2020.119353.
18. Dumarey, M.; Goodwin, D. J.; Davison, C. Multivariate modelling to study the effect of the manufacturing process on the complete tablet dissolution profile. *Int. J. Pharm.* **2015**, *486* (1-2), 112–120. DOI: 10.1016/j.ijpharm.2015.03.040 https://www.ncbi.nlm.nih.gov/pubmed/25797055
19. Kesisoglou, F.; Hermans, A.; Neu, C.; Yee, K. L.; Palcza, J.; Miller, J. Development of in vitro-in vivo correlation for amorphous solid dispersion immediate-release suvorexant tablets and application to clinically relevant dissolution specifications and in-process controls. *J. Pharm. Sci.* **2015**, *104* (9), 2913–2922. DOI: 10.1002/jps.24362.
20. Vargas, J. M.; Nielsen, S.; Cárdenas, V.; Gonzalez, A.; Aymat, E. Y.; Almodovar, E.; Classe, G.; Colón, Y.; Sanchez, E.; Romañach, R. J. Process analytical technology in continuous manufacturing of a commercial pharmaceutical product. *Int. J. Pharm.* **2018**, *538* (1-2), 167–178. DOI: 10.1016/j.ijpharm.2018.01.003.
21. Pawar, P.; Wang, Y.; Keyvan, G.; Callegari, G.; Cuitino, A.; Muzzio, F. Enabling real time release testing by NIR prediction of dissolution of tablets made by continuous direct compression

(CDC). *Int. J. Pharm.* **2016**, *512* (1), 96–107. DOI: 10.1016/j.ijpharm.2016.08.033.

22. Principal components. In *Handbook of Chemometrics and Qualimetrics: Part A*; Massart, D. L.; Vandeginste, B. G. M.; Buydens, L. M. C.; De Jong, S.; Lewi, P. J.; Smeyers-Verbeke, J., Eds; Volume 20, Elsevier, 1998; pp 519-556.
23. Trygg, J.; Wold, S. O2-PLS, a two-block (X–Y) latent variable regression (LVR) method with an integral OSC filter. *J. Chemometr.* **2003**, *17* (1), 53–64. DOI: 10.1002/cem.775.
24. Shi, G.; Lin, L.; Liu, Y.; Chen, G.; Luo, Y.; Wu, Y.; Li, H. Pharmaceutical application of multivariate modelling techniques: a review on the manufacturing of tablets. *RSC Advances* **2021**, *11* (14), 8323–8345. DOI: 10.1039/D0RA08030F.
25. Ibrić, S.; Djuriš, J.; Parojčić, J.; Djurić, Z. Artificial neural networks in evaluation and optimization of modified release solid dosage forms. *Pharmaceutics* **2012**, *4* (4), 531–550. DOI: 10.3390/pharmaceutics4040531.
26. Nagy, B.; Petra, D.; Galata, D. L.; Démuth, B.; Borbás, E.; Marosi, G.; Nagy, Z. K.; Farkas, A. Application of artificial neural networks for Process Analytical Technology-based dissolution testing. *Int. J. Pharm.* **2019**, *567*, 118464. DOI: 10.1016/j.ijpharm.2019.118464.
27. Tomba, E.; Facco, P.; Bezzo, F.; Barolo, M. Latent variable modeling to assist the implementation of Quality-by-Design paradigms in pharmaceutical development and manufacturing: a review. *Int. J. Pharm.* **2013**, *457* (1), 283–297. DOI: 10.1016/j.ijpharm.2013.08.074.
28. Rinnan, Å.; Berg, F.; Engelsen, S. Review of the most common pre-processing techniques for near-infrared spectra. *Trends Analyt. Chem.* **2009**, *28* (10), 1201–1222. DOI: 10.1016/j.trac.2009.07.007.
29. Costa, P.; Sousa Lobo, J. M. Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci.* **2001**, *13* (2), 123–133. DOI: 10.1016/S0928-0987(01)00095-1.
30. Xie, F.; Ji, S.; Cheng, Z. In vitro dissolution similarity factor (f2) and in vivo bioequivalence criteria, how and when do they match? Using a BCS class II drug as a simulation example. *Eur. J. Pharm. Sci.* **2015**, *66*, 163–172. DOI: 10.1016/j.ejps.2014.10.002.
31. Suarez-Sharp, S.; Abend, A.; Hoffelder, T.; Leblond, D.; Delvadia, P.; Kovacs, E.; Diaz, D. A. In vitro dissolution profiles similarity assessment in support of drug product quality: what, how, when-workshops summary report. *AAPS J.* **2020**, *22* (4), 74. DOI: 10.1208/s12248-020-00458-9.
32. Drennen, J. K.; III. Prediction of Dissolution Profiles from Process Parameters, Formulation, and Spectroscopic Measurements. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 11, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/c9749e3241344bb3afba504ede0db40b1d
33. Zhao, Y.; Li, W.; Shi, Z.; Drennen, J. K., III; Anderson, C. A. Prediction of dissolution profiles from process parameters, formulation, and spectroscopic measurements. *J. Pharm. Sci.* **2019**, *108* (6), 2119–2127. DOI: 10.1016/j.xphs.2019.01.023.
34. Singhvi, G.; Shah, A.; Yadav, N.; Saha, R. N. Prediction of in vivo plasma concentration-time profile from in vitro release data of designed formulations of milnacipran using numerical convolution method. *Drug Dev. Ind. Pharm.* **2015**, *41* (1), 105–108. DOI: 10.3109/03639045.2013.850706.
35. Hernandez, E.; Pawar, P.; Keyvan, G.; Wang, Y.; Velez, N.; Callegari, G.; Cuitiño, A.; Michniak-Kohn, B.; Muzzio, F. J.; Romañach, R. J. Prediction of dissolution profiles by non-destructive near infrared spectroscopy in tablets subjected to different levels of strain. *J. Pharm. Biomed. Anal.* **2016**, *117*, 568–576. DOI: 10.1016/j.jpba.2015.10.012.
36. Ryckaert, A. Fast and Non-destructive PAT-based Dissolution Assay for Immediate Release Tablets. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 11, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/0a456db39f784d8ba808f24fa508ba6b1d
37. Maclean, N.; Walsh, E.; Soundaranathan, M.; Khadra, I.; Mann, J.; Williams, H.; Markl, D. Exploring the performance-controlling tablet disintegration mechanisms for direct compression formulations. *Int. J. Pharm.* **2021**, *599*, 120221. DOI: 10.1016/j.ijpharm.2021.120221.
38. Mandula, H. Dissolution RTRT: Summary of Regulatory Requirements and Expectations. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 11, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/688fed22d0f349c0a0a4367b460791081d
39. Walworth, M. J. Data Selection and Generation for Predictive Dissolution Model and Real Time Release Testing Development. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 12, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/e937913c1cd44e71b8e515e255a0d42d1d
40. Suarez-Sharp, S. From QC dissolution method to RTRT dissolution model. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 12, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/732d43fc19214592b5108a23b690a9f71d
41. Suarez, S.; Marroum, P. J.; Hughes, M. Chapter 15: Biopharmaceutic considerations in drug product design and in vitro drug product performance. In: *Applied Biopharmaceutics and Pharmacokinetics*, 7th ed., Shargel, L.; Yu, A. C.; Eds; McGraw Hill, 2016; pp 415-476.
42. Lee, J.; Gong, Y.; Bhoopathy, S.; DiLiberti, C. E.; Hooker, A. C.; Rostami-Hodjegan, A.; Schmidt, S.; Suarez-Sharp, S.; Lukacova, V.; Fang, L.; Zhao, L. Public workshop summary report on Fiscal Year 2021 generic drug regulatory science initiatives: data analysis and model-based bioequivalence. *Clin. Pharmacol. Ther.* **2021**, *110* (5), 1190–1195. DOI: 10.1002/cpt.2120.

43. *The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls*, Draft Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evalution and Research (CDER), October 2020. https://www.fda.gov/media/142500/download
44. Dumarey, M. Predictive modeling for RTRT of dissolution: quality considerations. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 12, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/81c5f536931a41efb877f30e362353c11d
45. Kourti, T.; Lepore, J.; Liesum, L.; Nasr, M.; Chatterjee, S.; Moore, C. M. V.; Korakianiti, E. Scientific and regulatory considerations for implementing mathematical models in the quality by design (QbD) framework. *Pharm. Eng.* **2014**, *34* (6), 1–21.
46. *Guideline on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations*; EMEA/CHMP/CVMP/QWP/17760/2009 Rev2, Committee for Medicinal Products for Human Use (CHMP), Committee for Veterinary Medicinal Products (CVMP), European Medicines Agency: London, January 27, 2014.
47. *Development and Submission of Near Infrared Analytical Procedures*; Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2021.
48. Manteiga, S.; Altan, S.; Nielsen, S. Putting it All Together: PDM RTRT in Action. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 12, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/cb7faefb33bf47beb2a0084e103e2e7c1d
49. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Validation of Analytical Procedures: Text and Methodology, Q2(R1)*; ICH Harmonized Tripartite Guidelines: Geneva, November 2005.
50. Graybill, F. A. *Theory and Application of the Linear Model*; Wadsworth Publishing Company: Belmont, CA, 1976; p 94002.
51. Mann, J.; Coutant, C. Panel Discussion, Day 1. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 11, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/4e42114b427043dbbfcd92232a7843391d
52. Hermans A.; Hate, S. S. Panel Discussion, Day 2. IQ Consortium Workshop for Predictive Dissolution Models For RTRT, Presented November 12, 2021. Accessed February 11, 2022. https://faegredrinker.mediasite.com/mediasite/Channel/iqrecordings/watch/675b3bc1ee824cad8c26740cc9d473951d
53. Mann, J.; Cohen, M.; Abend, A.; Coutant, C.; Ashworth, L.; Shaw, R.; Reynolds, G.; Nir, I.; Shah, V.; Shaw, S.; Patel, A.; Lu, X.; Cicale, V.; Mccallum, M.; Patel, S.; Topolski, J.; Prüfer, S.; Tomaszewska, I.; Kourentas, A.; Mueller-Zsigmondy, M.; Williams, J.; Ainge, M; Berben, P.; Bouquelle, A.; Abrahamsson, B.; Karlsson, A.; Varghese, R.; Li, F.; Orce, A.; Nickerson, B.; Shao, X. The case for apex vessels. *Pharmacop. Forum* **2021**, *47* (6). https://online.usppf.com/usppf/latest-draft/GUID-AE7ED747-2E41-478C-9F1D-23AC1F001FA7_10101_en-US

Tergus

Think Topicals, Think Tergus

Getting a promising new topical product from lab to patient is challenging. That's why it makes sense to **think ahead** and **partner with the topical experts** that can give pharma companies like yours more opportunities for **success, every step of the way.**

If you are developing a topical product, let's discuss how Tergus' **IVRT** and **IVPT** service can help you meet BA/BE waivers, SUPAC-SS requirements, and in vitro skin permeation Proof-of-Concept (PoC) studies. Whether through our **unrivaled expertise** in R&D, providing clinical trial materials, and now the addition of full-scale commercial manufacturing, we are **eager to support** every aspect of your topical drug pipeline.

- **Formulation Development**
- **Analytical R&D**
- **Skin Biology Services**
- **IVPT/ IVRT**
- **Clinical Trial Materials**
- **Scale-Up & Registration Batches**
- **Full-Scale Commercial Manufacturing**

Let's work together. **Because getting there starts here.**

Tergus Pharma
4018 Stirrup Creek Drive, Durham, NC 27703, USA
Toll Free: 888-4-TERGUS International: +1 919-549-9700
busdev@tergusphar ma.com www.tergusphar ma.com

dx.doi.org/10.14227/DT290322P174

Q+A Question & Answer Section

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

Q If the acceptance criteria in the *USP* individual monograph is not less than (NLT) 80% (*Q*), what is the meaning of *Q*?

A *Q* is defined in the USP general chapter <711> Dissolution as the amount of dissolved active ingredient specified in the individual monograph, expressed as percentage of the labeled content of the dosage unit.

Q Is it possible to have dissolution results greater than the assay results obtained from the same product batch? For example, the mean assay result is 99.0% and dissolution results of about 108%.

A The amount of dissolved drug should not exceed the assay results obtained for the product. When this occurs, you should investigate the possible reasons for high dissolution results. Typically, possible causes for the dissolution value exceeding the assay value include: difference in solubility of the active ingredient in the assay media versus the dissolution media – both methods should be validated; improper selection of the type and pore size of filter material used in the assay and/or dissolution procedure; inadequate evaluation of possible interference of the placebo; inadequate sampling procedure; and/or high variability in the manufacturing process. With this in mind, it is also helpful to check the uniformity of dosage units for the particular batch being evaluated.

Q Regarding the dissolution test for delayed-release dosage forms, where the drug substance is unstable in acidic medium, how can the amount of drug released in the acid stage can be quantified?

A Determine the amount of drug that is remaining in the dosage form after the acid stage. To do this, remove the dosage form from the vessel and determine the amount of drug in the dosage form using the procedure for uniformity of dosage units or an adaptation to the assay procedure. Then, perform the acid stage with 6 new units, and transfer them directly to the buffer stage to determine the amount released in the buffer stage.

Q We are a dissolution instrument supplier and sometimes our customers would like our engineer to provide the service of performance verification test (PVT) test for them. We would like to know if we can provide them with this service.

A Yes, a contractor/third party can verify/qualify any dissolution equipment. Keep in mind that an additional objective of the PVT is to verify the analyst technique and to ensure that the analyst is following the entire procedure and using proper technique.

Q In the *USP* monograph for Cimetidine Tablets, under Apparatus 1, it is stated "100 rpm, a 20-mesh basket may be used for 800-mg strength tablets." What is the mesh size for the other label claims, e.g., 200 mg or 400 mg?

A The default basket mesh size in USP is 40 mesh. The monograph will state the mesh size only in cases where the mesh size is different from 40 mesh. If the monograph does not mention the mesh size, 40 mesh should be used.

Q In the USP general chapter <711> Dissolution, under *Procedure, Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms*, it states: "Note—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh Dissolution medium at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test and verify

the temperature of the mixture under test at suitable times."

If it is not stated in a particular monograph to replace the dissolution medium, is the default to replace the aliquot drawn with fresh dissolution medium?

A Yes.

Q In that case, if the medium is not replaced, is this volume change considered a big enough change to the method to require validation?

A This needs to be evaluated in a case-by-case approach. There is no standard rule. Checking this at validation is too late. This question should be evaluated during method development. Typically, two issues may arise:

1) Depending on the sample volume withdrawn at each time point, the volume of medium remaining in the vessel may make it difficult to to sample at the appropriate sampling point.

2) If the samples are withdrawn and the medium is not replaced, you may approach the active ingredient solubility limit and the dissolution rate may be reduced.

Therefore, generally the recommendation is to always to replace the medium to ensure that the volume remains constant throughout the test.

Q We are verifying the dissolution test for calcium in the *USP* monograph for calcium with vitamin D Tablets. When evaluating accuracy, due to the characteristics of the raw material calcium carbonate, it is difficult to add it to the vessel, as it floats and sticks to the vessel wall. Do you have any suggestions to minimize this problem?

A In situations like the one you are describing, the best approach is to have the formulation or placebo mixed/granulated/prepared by the appropriate group, e.g., research and development or the formulation group, in your organization. Then transfer the prepared amount of material equivalent to the amount in the dosage form to the dissolution vessel.

Q The dissolution test in the *USP* monograph for Cabergoline Tablets states that the medium is degassed with helium. We performed the dissolution test with and without degassing and we did not observe any significant variation in the dissolution profile. Can we perform the test without degassing?

A It is not mandatory to degas all dissolution media. In some instances it is necessary to to verify whether degassing the media has an appreciable effect on the dissolution results for the specific formulation, especially considering that helium is expensive and there may be issues with supply. When degassing is necessary, the recommendation is to use the procedure described in the *USP* general chapter <711> Dissolution. Other deaeration/degassing procedures may be used with appropriate validation.

Q We are evaluating dissolution results using the Acceptance Table 1 from the USP general chapter <711> Dissolution and noticed that S1 stage results are outliers that may not comply with S3 stage criteria. We started an investigation and before finalizing it, shall we continue to S2 stage analysis in parallel to the investigation?

A The results you obtained are not outliers. They are just results not meeting the acceptance criteria. It is up to your organization to decide if you are stopping at S1 or if you are going to continue to the other two stages. Because the investigation of out-of-specification results in dissolution should also include the manufacturing and any other groups associated with the production of the batch, you may need to generate additional results to better evaluate the issue.

USEFUL RESOURCES FOR DISSOLUTION, DISINTEGRATION, AND DRUG RELEASE TESTING (all are free of charge)

USP Dissolution Methods Database

https://www.usp.org/resources/dissolution-methods-database

It lists the test conditions as stated in USP monographs for finished products.

The database allows you to search by (via drop-down lists):

- Monograph name
- Dissolution medium: composition, surfactant (if used), pH, volume, and deaeration (if used)
- Apparatus: type and rotation speed, dip rate, or flow rate
- Duration of the test
- Analytical finish

- Exceptions: any additional information not covered by the previous items such as type of sinker, use of special software, use of a wavelength other than the one for maximum absorbance, etc.

Acceptance criteria can be found in the USP monographs.

FDA-Recommended Dissolution Methods

https://www.accessdata.fda.gov/scripts/cder/dissolution/

It lists the test conditions recommended by the US FDA. It allows search only by drug substance name. It does not contain acceptance criteria. The printable version may facilitate the searches.

USP Performance Verification Test

https://www.usp.org/small-molecules/pvt

For additional information regarding the performance verification test and instrument qualification procedures.

Dissolution Toolkit Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and Apparatus 2

https://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/dissolution-toolkit-version2.pdf

This toolkit provides procedures that help manufacturers and others to evaluate the correct set-up, operation, and performance of the basket and paddle apparatuses and the test assembly.

Calculation Tool for the Performance Verification Test (PVT) of Dissolution Assemblies

https://apps.usp.org/app/USPNF/pvtCalculationTool/

This calculation tool allows the evaluation of the performance of a dissolution assembly by comparing the results obtained from the PVT to limits given in the Acceptance Criteria for PVT Tablets.

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:
Attn: Q&A
9 Yorkridge Trail, Hockessin, DE 19707
Email: vagray@rcn.com
Submit via our website:
www.dissolutiontech.com

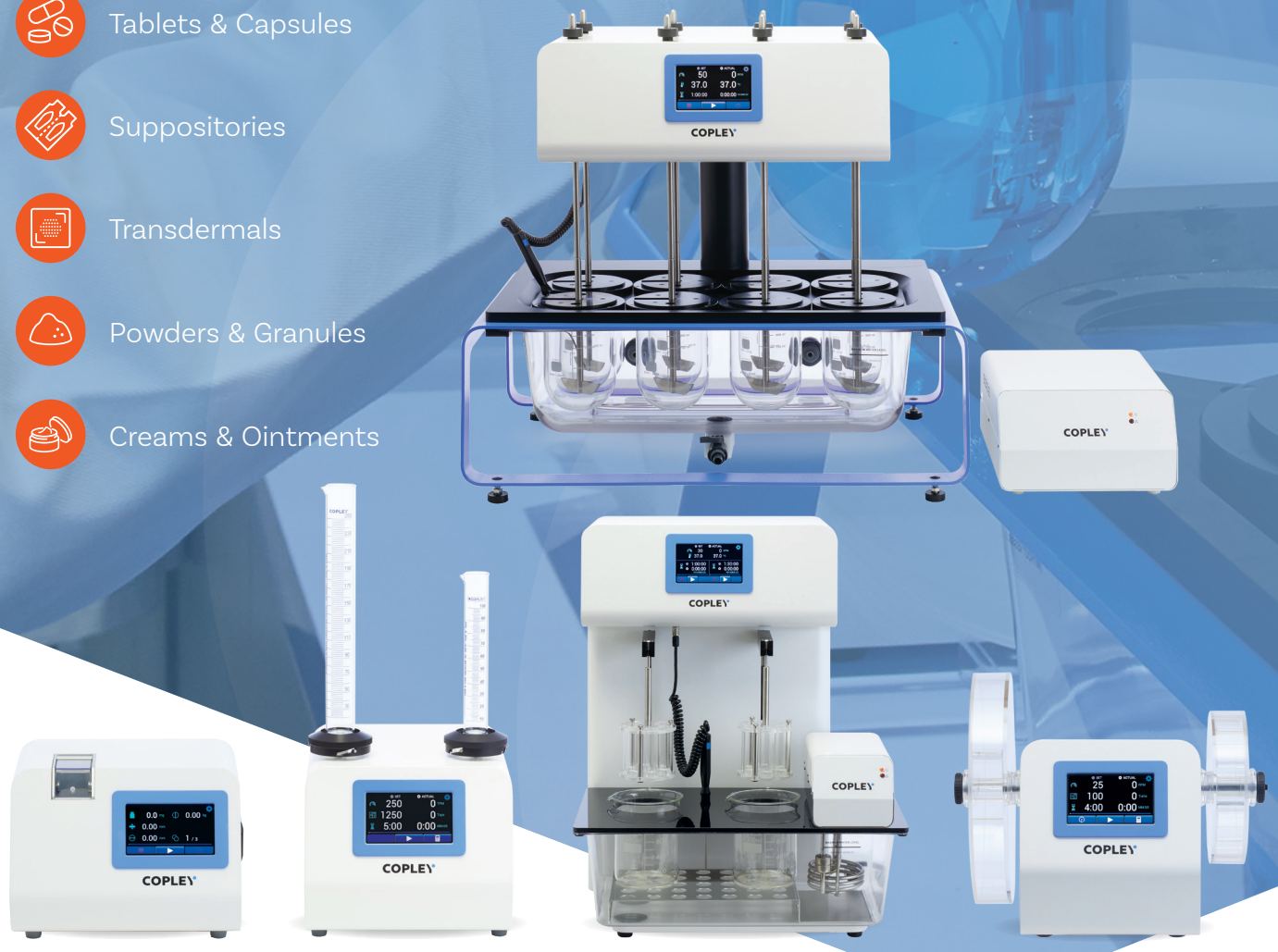
COPLEY

INNOVATIVE
COMPLIANT
TRUSTED

Precision Engineered Systems for Everyday Pharmaceutical Testing

Trusted equipment for routine testing that consistently delivers results

- Tablets & Capsules
- Suppositories
- Transdermals
- Powders & Granules
- Creams & Ointments



+44 (0)115 961 6229 copleyscientific.com sales@copleyscientific.co.uk

Calendar of Events

August 16, 2022
AAPS workshop: Dissolution Best Practices and International Harmonization
Location: Online
For information, visit https://www.aaps.org/education-and-research/workshops/dissolution

August 22–23, 2022
GastroPlus® PBPK Modeling and Simulations Workshop
Location: PharminoGen in Yongin-si, South Korea
For information, visit https://www.simulations-plus.com/calendar-event/introductory-gastroplus-pbpk-modeling-simulation-workshop/

September 19–21, 2022
Dissolution Science: Principles and Applications
Sponsored by the Society for Dissolution Scientists, US Chapter (SPDS US)
Location: Double Tree by Hilton Boston, Westborough, MA, USA
For information, visit https://www.spds.us

September 28–29, 2022
EUFEPS/AAPS Global Bioequivalence Harmonisation Initiative 5th International Workshop – GBHI 2022
Location: Amsterdam, The Netherlands
For information, visit https://gbhi.eufeps.org/

October 16–19, 2022
PharmSci 360 AAPS Meeting
Location: Boston Convention and Exhibition Center, Boston, MA, USA
For information, visit https://www.aaps.org/pharmsci/annual-meeting

November 10, 2022
Dissolution Discussion Group Quarterly Online Meeting— A Trip to the Vet: Expert Advice about Dissolution Testing of Veterinary Products
Location: DDG Online Meeting at 10:30 am ET
Registration: http://www.dissolution.com/ddg/content.php?30-Free-DDG-Online-Meetings

November 13–16, 2022
Eastern Analytical Symposium and Exhibition
Location: Crowne Plaza Princeton-Conference Center, Plainsboro, NJ, USA
For information, visit eas.org

November 16–17, 2022
A Quest for Biowaivers, Including Next Generation Dissolution Characterization and Modeling Workshop
Sponsored by AAPS IVRDT Community and Jagiellonian University
Location: Online
For information, email: aleksandermendyk@uj.edu.pl

Industry News

RIGGTEK Dissolution Tester "Dissilio"

Martinsried/Munich, Germany – RIGGTEK is is proud to introduce the new **Dissolution Tester "Dissilio"**.

We have designed our dissolution tester "Dissilio" for you under the following premise:

SIMPLY SMART - MAKE YOUR EVERDAY WORK EASIER

This means that the Dissilio is aiming towards simplifying your everyday work through clever solutions.

One of the SIMPLY SMART features is the standard "Browser Interface", which allows for comfortable operation of your Dissilio simply via your web browser without any additional software installation (in addition to using the intuitive touchscreen). This enables you to supervise the current status of a running test or to manage methods, reports, and more conveniently from your computer.

Additional SIMPLY SMART features like the centering rings or the integrated drawers for paddles, baskets, and other accessories make the use of the Dissilio easy and functional.

Many users are afraid of time consuming cross-validations when they change to a new brand of dissolution tester, but the possibility to use vessels from various manufacturers is another SIMPLY SMART feature that makes cross-validation only a formality when switching to the Dissilio.

With all kind of accessories, 6-16 vessel positions, and optional firmware packages, you can configure your Dissilio individually and flexibly according to your needs.

SIMPLY SMART features are complemented with the robust design **made in Germany** and Quality standards according to ISO 9001: 2015. Of course, the current specifications of the European, United States, and associated Pharmacopoeias are complied with as well.

To learn more about the new Dissolution Tester Dissilio, explore RIGGTEK at www.riggtek.com or contact us at sales@riggtek.de.

ABOUT RIGGTEK GmbH

RIGGTEK is in the dissolution business for more than 25 years and is known for its Dissolution Media Preparation System "DissoPrep". With precison, passion, and ISO-certified quality **made in Germany**, we provide innovative and smart dissolution instruments to our international customers.

RIGGTEK Dissolution Test Systems

Simulations Plus Enters New Collaboration to Advance DDDPlus™ Software

Funded partnership with large pharmaceutical company will enhance mechanistic dissolution models for injectable formulations

LANCASTER, CA - *April 21, 2022* – Simulations Plus, Inc. (Nasdaq: SLP), a leading provider of modeling and simulation solutions for the pharmaceutical, biotechnology, chemical, and consumer goods industries, today announced a new funded collaboration with a large pharmaceutical company to expand and validate the mechanistic in vitro dissolution models for intravitreal injectable formulations within the DDDPlus™ software.

James Mullin, Senior Principal Scientist and lead programmer on DDDPlus, said: "The DDDPlus software is being utilized by numerous companies and regulatory agencies around the globe to support oral drug product development. Recent enhancements to the tool have focused on improvements to the *in vitro* analysis of precipitation kinetics and functionality to help establish drug product specification limits. Through this new collaboration, we will expand into the injectable product space and apply our novel approaches to capture dissolution kinetics within in vitro systems designed by our industry partner. We look forward to the fruitful interactions."

"Our team of scientists and programmers have designed unique workflows between DDDPlus and GastroPlus® to advance innovative *in vitro-in vivo* extrapolation (IVIVE) methods for dissolution and precipitation modeling," added Haiying Zhou, Director of Simulation Technologies. "Turning our attention to injectable products, and the special *in vitro* systems used to measure formulation performance, opens new market opportunities for our IVIVE workflows. Like other collaborations, Simulations Plus will own all improvements made to our software programs, and we look forward to sharing these exciting developments with all users to advance model-informed drug development."

Logan PERMETRO System - Revolutionizing the World of Bioequivalence Studies

PERMETRO introduces a new way for drug development, such as IVIVC, BE, and the interferences of food or during drug absorption. The system collects samples incrementally and cumulatively at the same time. For the first time, the Logan Permetro system uses a bionic intestinal membrane to simulate the release and absorption of drugs in the gastrointestinal tract in the human body, providing a dynamic absorption profile for permeation through the dissolution cycle, and vividly mimicking the in-vivo drug absorption in the intestine. PERMETRO is fully automated and works seamlessly with all USP dissolution apparatuses e.g., 1, 2, 3, or 4.

PERMETRO 1200 is designed for simultaneous USP apparatus 1&2 dissolution and permeation tests; a special program is included to study the bioequivalence (BE).

PERMETRO 3700 is designed for simultaneous USP apparatus 3 dissolution and permeation tests to study drug permeation under different pH conditions.

LOGAN INSTRUMENTS CORP.

PERMETRO 4000 is designed for USP apparatus 4, which can perform open/close loop experiments. The flow-rate change makes it possible to adjust sink conditions in the flowthrough apparatus for a longer period.

Logan is excited to announce our exhibition at **AAPS 2022 PHARMSCI 360**. Please visit us at **booth 431** to see all the new products!

Products:

- 15-Position Automated Dissolution System
- PERMETRO 3700
- USP Apparatus 4 with Flow Cell
- Automated Diffusion Cell System
- Inhaler Tester

Event information:

- Date: October 16-19, 2022
- Location: Booth 431, Boston Convention & Exhibition Center, Boston, MA

For more information please contact info@loganinstruments.com
19-C Schoolhouse Road, Somerset, NJ Phone: 732.302.9888 www.loganinstruments.com

LOGAN INSTRUMENTS CORP.

BATHLESS DISSOLUTION

- Patented bathless heating
- Ambient to 37°C in less than 15 minutes
- In-shaft continuous temperature sensors
- USP compliant
- Reduced energy usage and operating costs

DISSOLUTION
FIBER OPTIC
MEDIA PREP
AUTOSAMPLER

DiSTEK

distekinc.com • info@distekinc.com

Agilent

Trusted Answers

Elevating the Dissolution Environment

The Agilent 280-DS Mechanical Qualification System (MQS) enables the physical qualification of USP dissolution Apparatus 1 (Rotating Basket) and 2 (Rotating Paddles) using Enhanced Mechanical Qualification (EMQ) guidelines. The system's sensing technology allows hands-free measurements to be performed in seconds, while recording critical physical parameters.

A proactive approach. Easily shorten your qualification interval for more frequent insight into instrument performance, reducing the chance of failures.

Save time. Instant feedback helps the user investigate aberrant results or abnormalities at an early stage and reduce errors.

For more information about the Agilent 280-DS, visit:
www.agilent.com/chem/280-DS

DE32237991