U.S. FOOD & DRUG ADMINISTRATION

Toward Biorelevant *In Vitro* Testing

- Dissolution Method Development beyond Compendial Approaches

Zongming Gao, Ph.D.
Division of Complex Drug Analysis
FDA/CDER/OPQ/OTR

***Disclaimer:** This presentation represents the personal opinions of the speaker and does not necessarily represent the views or policies of US FDA.

Overview

Regulatory perspectives

- FDA missions
- Pharmaceutical quality of drug products

Current status of *in vitro* dissolution testing

- Compendial approaches
- Non-compendial approaches

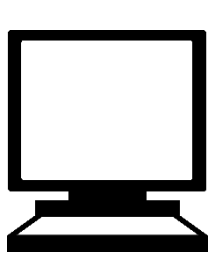
FDA's efforts

- Development of biorelevant *in vitro* methods
- PBPK modeling

Conclusions

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Regulatory Perspectives

FDA's Mission: to assure that quality medicines are available for the American public.

- Safe and Effective
- Deliver the same performance (stated in the label) over time
- Are not contaminated and made in a manner that ensures quality
- Will be available when needed

The federal role in regulating pharmaceutical quality

- The customers are not able to independently assess the quality of the drugs they use.
- FDA must determine, on behalf of the public, what constitutes acceptable quality of pharmaceutical products.

J. Woodcock. The concept of pharmaceutical quality. Am. Pharm. Rev. Nov/Dec 2004:pp. 1–3.

Application of Dissolution Testing

- Dissolution methods evolve during the product development life cycle.
- Product Development Aspects
  - Guide formulation development
  - Guide manufacturing process
- Regulatory Aspects
  - Provide quality assurance
    - A link to batches used in clinical studies
    - Information on batch to batch consistency
  - Assist in bridging differences in products, and in some cases, can reduce the need for bioequivalence studies
    - Assess impact of post-approval changes
    - Compare products from different sources and with different dosages

Current USP Dissolution Apparatuses

Apparatus from Different Vendors

- **Apparatus 1 - Basket** (37º)
- **Apparatus 2 - Paddle** (37º)
- **Apparatus 3 - Reciprocating Cylinder** (37º)
- **Apparatus 4 - Flow-Through Cell** (37º)
- **Apparatus 5 - Paddle over Disk** (32º)

  Transdermal Delivery System, use paddle and vessel from Apparatus 2 with a stainless steel disk assembly to hold the transdermal on the bottom of vessel.
- **Apparatus 6 - Cylinder** (32º)

  Transdermal Delivery System, use Apparatus 1 except replace the basket shaft with a stainless steel cylinder element.
- **Apparatus 7 - Reciprocating Holder**

  for transdermal delivery systems and also a variety of dosage forms

Challenges in Dissolution Testing

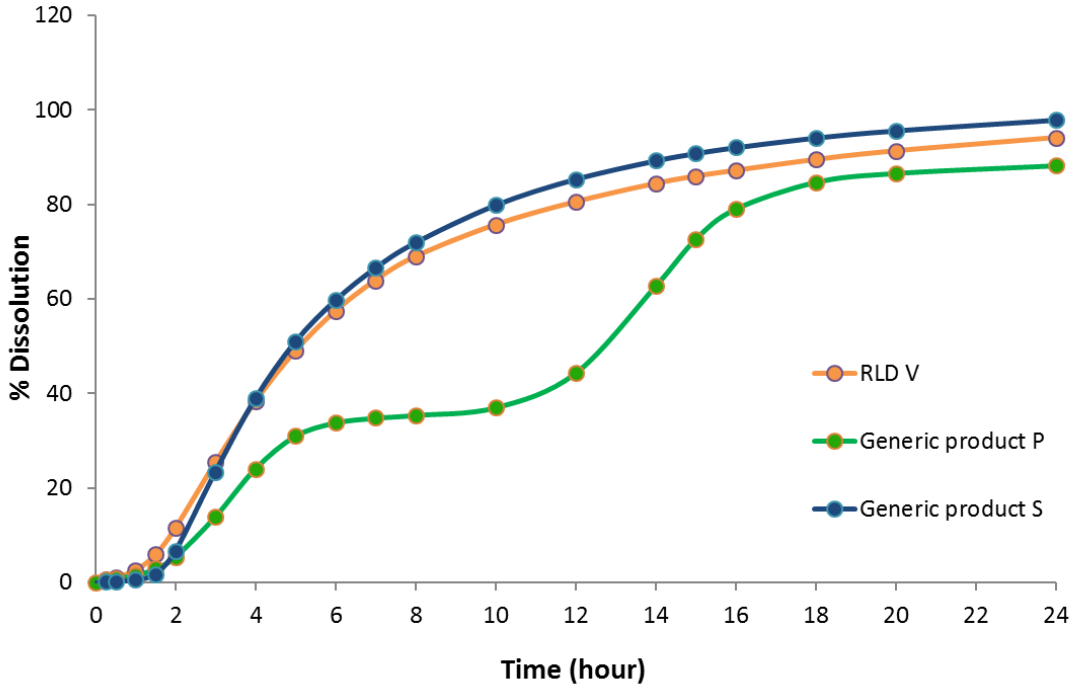
Issues as QC tool:

- Variability associated with dissolution testing
- Method validation and transfer

Issues on physiological relevance:

- Dissolution (80% in 45 minutes) may have no clinically relevance
- Dissolution testing is not sufficient to assure product bioavailability
- Demonstration of IVIVC is necessary
- IVIVCs are “Product Specific”

Comparison of Dissolution Profiles for ER Formulation



Medium	pH6.8 Buffer (Degassed)
Volume	900 mL
Apparatus	II (Paddle)
RPM	100
Temperature	37±0.5 C

Data from FDA labs.

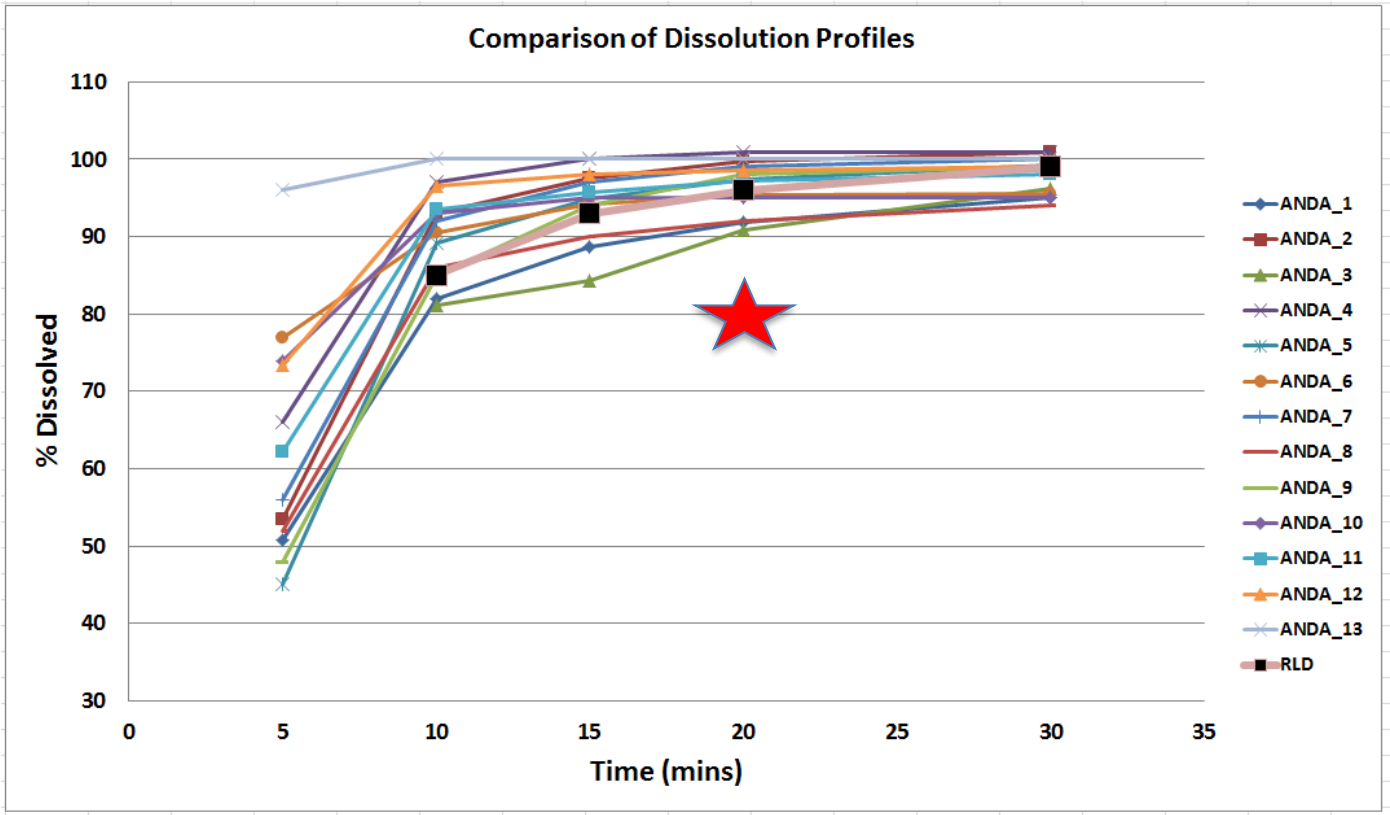
USP Specifications for RLD

Time (h)	Amount Dissolved (%)
2	NMT 25
4	25–50
8	60–85
12	NLT 70
16	NLT 80

USP Specifications for generic product P

Time (h)	Amount Dissolved (%)
1	NMT 10
6	30–40
12	36–58
18	NLT 85

Comparison of Dissolution Profiles for IR Formulation



Medium	Buffer (Degassed)
Volume	900 mL
Apparatus	II (Paddle)
RPM	50
Temperature	37±0.5 C

NDA Specification:
Not less than 80% (Q) of the labeled amount of LC is dissolved in 20 minutes

Data from FDA review.

When Dissolution Testing Has No Link to Clinical Performance

- Can be "over discriminating" if dissolution flags differences in products that are clinically bioequivalent (Type I error)
  - Unnecessary use of resources to resolve issue or reject batch
  - Potential for unnecessary clinical testing
- Can be "non-discriminating" if dissolution is not capable of rejecting non-bioequivalent products (Type II error)
  - Lack of meaningful product quality assurance
  - Potential for product failure in patient

Dissolution testing may not be a reliable tool to assure pharmaceutical quality if it is not representative of clinical performance

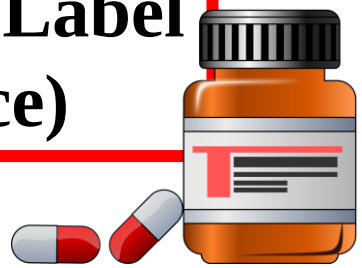
Product Development

- Identify characteristics (Quality target product profile -QTPP) that are critical to quality from the patient's perspective (Target product profile -TPP).
- Translate QTPP into the drug product critical quality attributes (CQAs).
- Establish the relationship between formulation/manufacturing variables and CQAs.
- Design and understand process including identification of critical process parameters (CPPs), linking CPPs to CQAs.
- Set up a control strategy and specification acceptance criteria to consistently deliver a drug product with such CQAs to the patient.

Lawrence X. Yu, Gregory Amidon, Mansoor A. Khan, Stephen W. Hoag, James Polli, G. K. Raju, and Janet Woodcock, Understanding Pharmaceutical Quality by Design, The AAPS Journal, Vol. 16, No.4, 2014

Quality by Design - TPP to QTPP?

TPP
Described in Label
(user interface)



QTPP – CQAs – CMAs/CPPs
Quantitative Performance

- **Quality Target Product Profile** (QTPP) is used by formulators and process engineers as a quantitative surrogate for aspects of **Target Product Profile** (TPP, clinical safety and efficacy) during product development.
- QTPP can be used to design and optimize a formulation and manufacturing process.

Biorelevant Condition - pH

Enteric coated ER tablet samples using USP paddle method

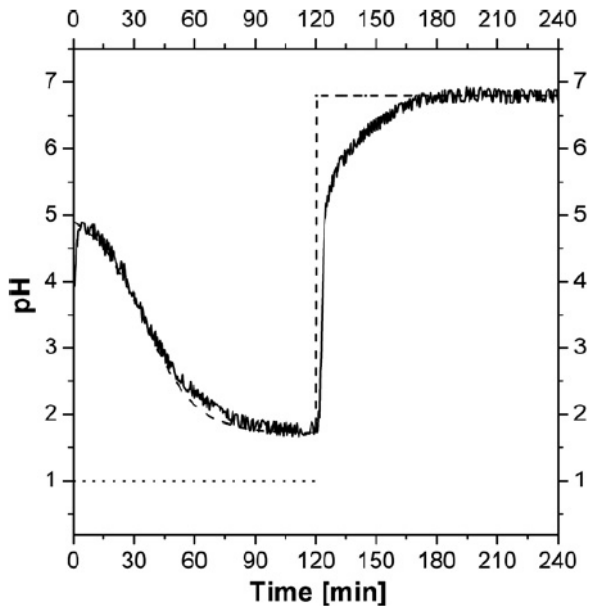


Fig. 1. The pH histories in the conventional method, dotted line (USP method 1.0 for the first two hours, then pH 6.8); a real pH evolution [28], dashed lir decreasing from 4.8 to 2.0 in the first two hours, then pH 6.8); and the pH evo realized in the modified apparatus, continuous line (as obtained by the c system programmed to follow the real pH evolution).

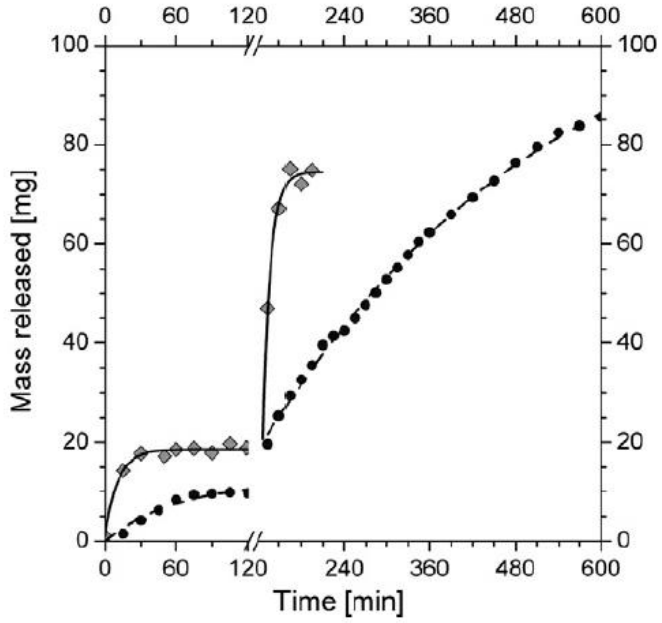


Fig. 2. The release kinetics obtained by the conventional method (USP Method full circles and dashed line) and by the novel technique (diamonds and continuo line). Symbols are experimental data, and lines are fitting equation to be used pharmacokinetic simulations.

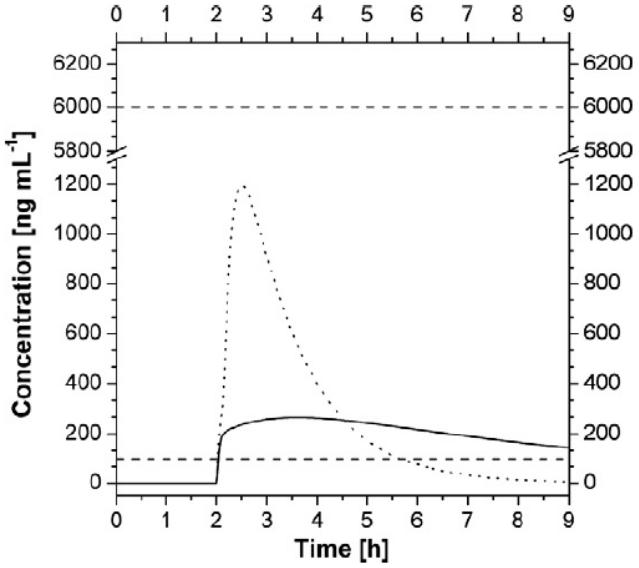
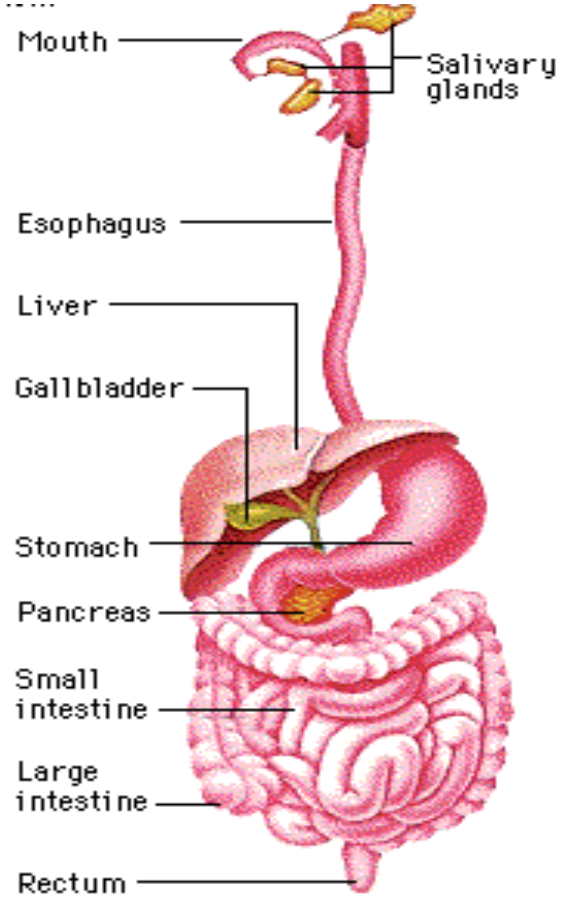


Fig. 5. The plasma profiles obtainable: (a) if the real *in vitro* release kinetics would be the one observed using the conventional USP method A (the continuous line), (b) if the real *in vitro* release kinetics would be the one observed using the novel apparatus (the dotted line). The horizontal dashed lines represent the minimum effective concentration (the lower one, [31]) and the minimum toxic concentration (the higher one, [32]); therefore, they identify the therapeutic window.

Sara Cascone, Felice De Santis, Gaetano Lamberti, Giuseppe Titomanlio, The influence of dissolution conditions on the drug ADME phenomena, European Journal of Pharmaceutics and Biopharmaceutics 79 (2011) 382–391

Does Current USP Dissolution Method Have Any Physiological Relevance?



- Disintegration
- Solids transfer
- Dissolution
- Changing pH
- Food and drink
- Sample GI transit time
- Stomach Contraction
- Absorption
- Clearance

Possible Solutions

- Beyond USP apparatus – noncompendial dissolution models
- Use of new technologies for product development and understanding IVIVC
  - Artificial stomach duodenal model (ASD)
  - FloVitro (DOW)
  - Gastro-Intestinal Model (TIM/TNO)
  - Dynamic gastric model (DGM/IFR)
  - Combined dissolution-absorption models
  - Dissolution models which simulate GI physical stress forces
  - Computational tools/models

Mark McAllister, Dynamic Dissolution: A Step Closer to Predictive Dissolution Testing? MOLECULAR PHARMACEUTICS, VOL. 7, NO. 5, 1374–1387, 2010

Desired Dissolution Testing

FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

August 8, 2012 and September 20, 2018

- Sensitive enough to detect relevant product changes so as to ensure the quality and consistent performance of products
- Predictive of *in-vivo* performance of drug products and thus reduce unnecessary human studies, accelerate drug development, as well as evaluation of post-approval changes

Regulatory Perspectives

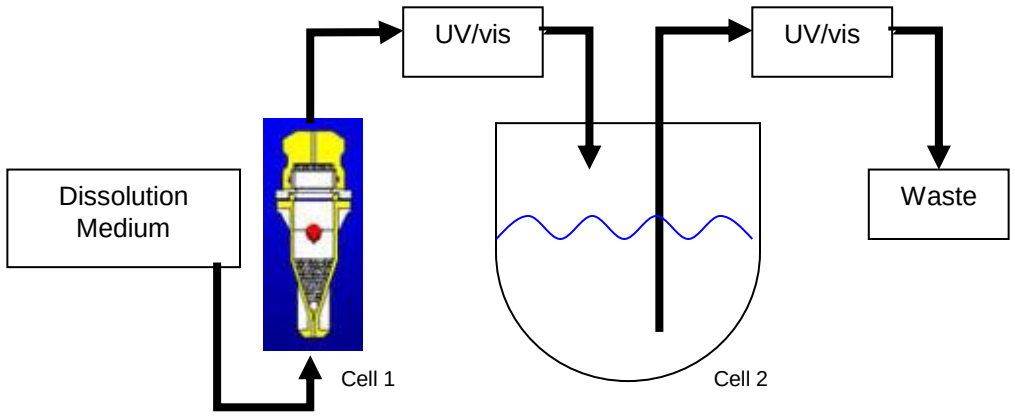
- **Biopredictive dissolution method**: A set of testing conditions for which *in vitro* dissolution profiles are capable of predicting PK profiles.
- **Biorelevant dissolution tests** are believed to increase the chance to be biopredictive because the test conditions are intended to mimic the environment for the *in vivo* dissolution.

Food and Drug Administration Guidance for Industry, The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls https//www.fda.gov/media/142500/download. 2023.

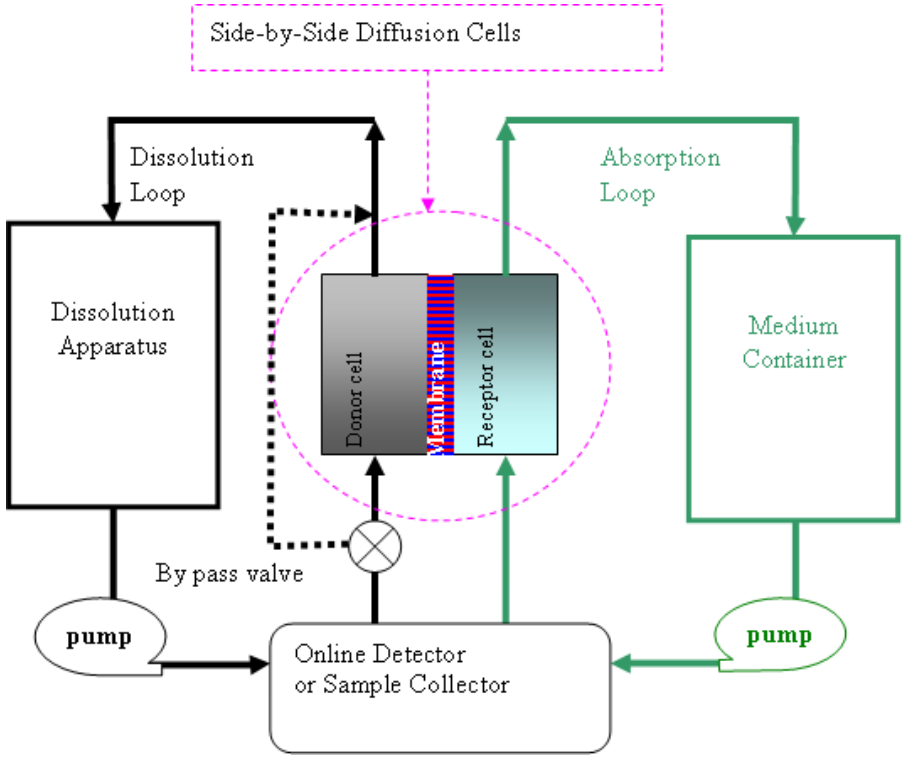
- The use of biorelevant dissolution methodology is encouraged as a starting point in the development of a biopredictive dissolution method.
- A biopredictive dissolution profile can be used to assess the *in vivo* effect of the quality attributes and process parameters that cannot be directly input into the model.

FDA Draft Guidance for Industry, The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls, 2020

Biorelevant Dissolution Methods Based on USP Methods



Modified USP 4 Method



Z Gao, AAPS PharmSciTech, 10(4), 1401-1405, 2009.

Z Gao, AAPS PharmSciTech, Vol 13, 1287-1292, 2012.

Stomach Motility and Contraction

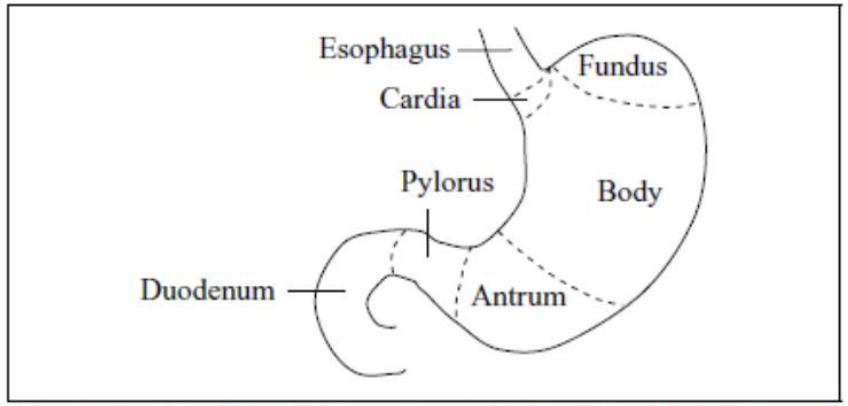
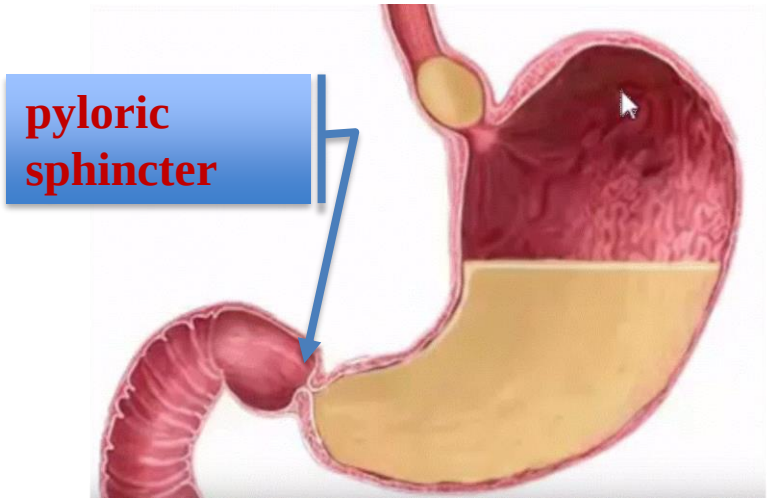


Figure 1 – Diagram of the stomach showing the different regions.

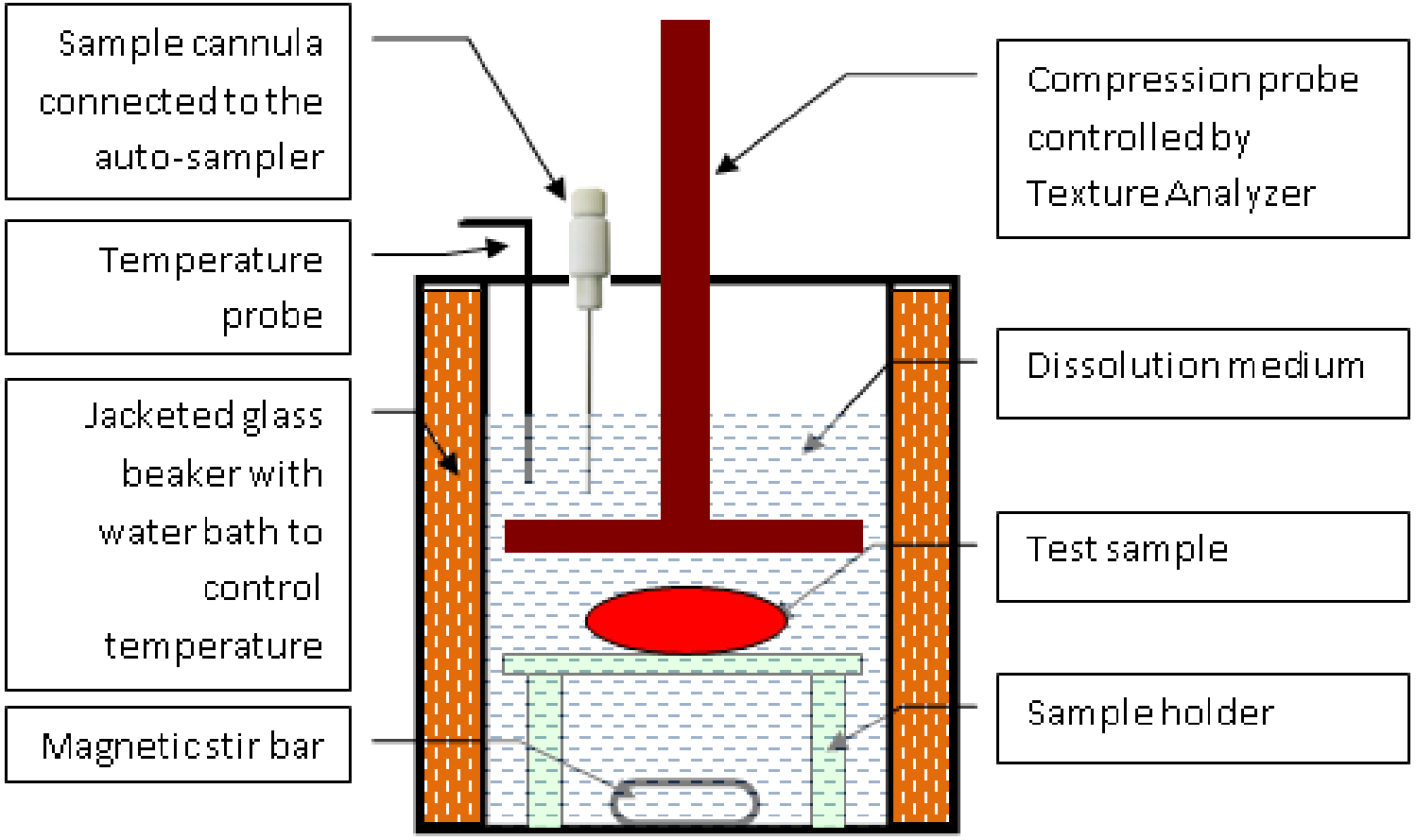


- The pattern of stomach motility is distinct in the fasting and fed states
- There is a 3-phase movement in the fasting state and continuous movement in the fed state
- Volume
- Fluid composition, pH, viscosity, surface tension…
- Compression/pressure

Mirko Koziolek, Michael Grimm, Felix Schneider, Philipp Jedamzik, Maximilian Sager, Jens-Peter Kühn, Werner Siegmund, Werner Weitschies, Navigating the human gastrointestinal tract for oral drug delivery: Uncharted waters and new frontiers, Advanced Drug Delivery Reviews 101 (2016) 75–88

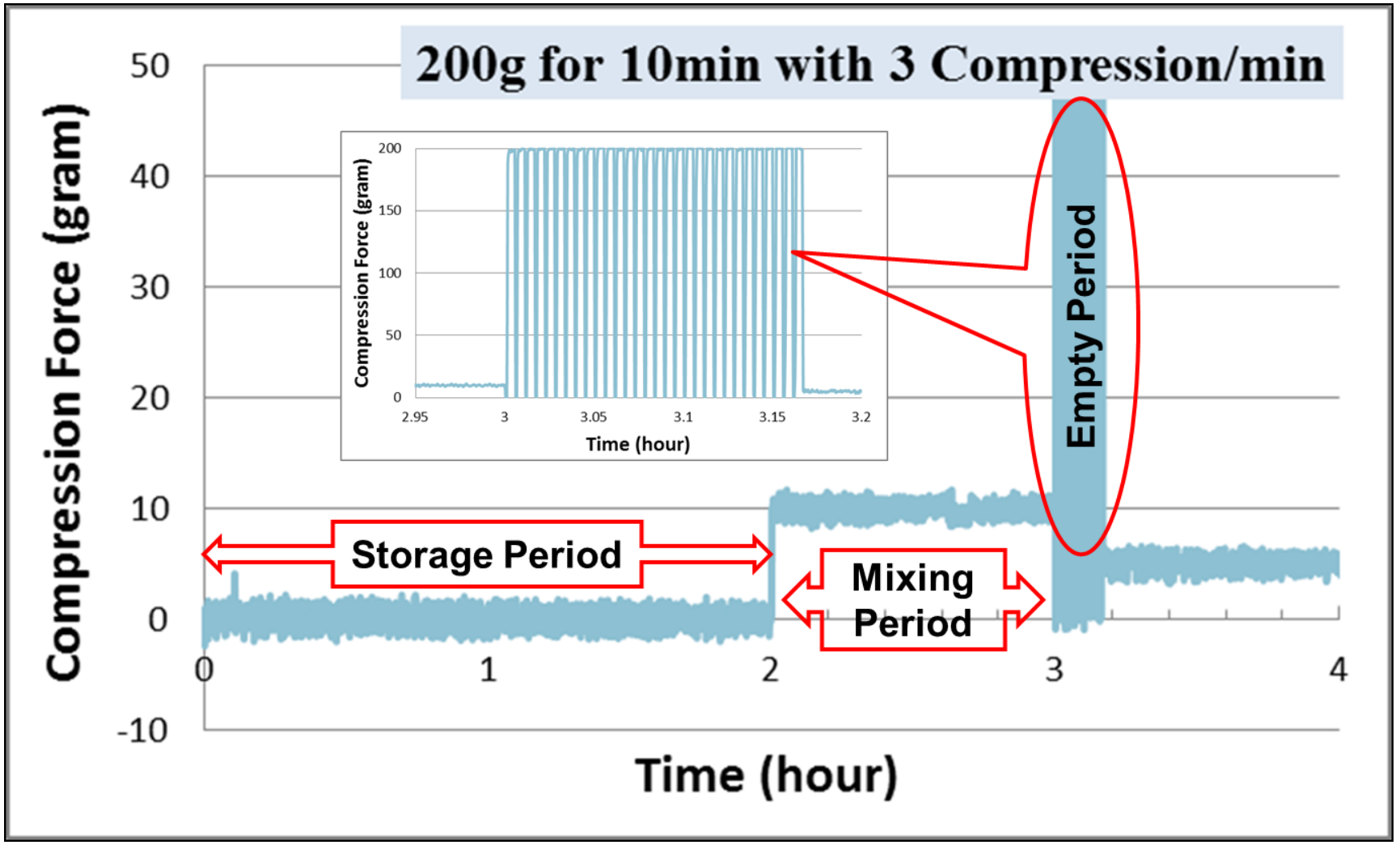
F. KONG AND R.P. SINGH, Disintegration of Solid Foods in Human Stomach, JOURNAL OF FOOD SCIENCE, Vol. 73, Nr. 5, 2008.

Dissolution Apparatus with Applied Compression – Non Flow-through Design

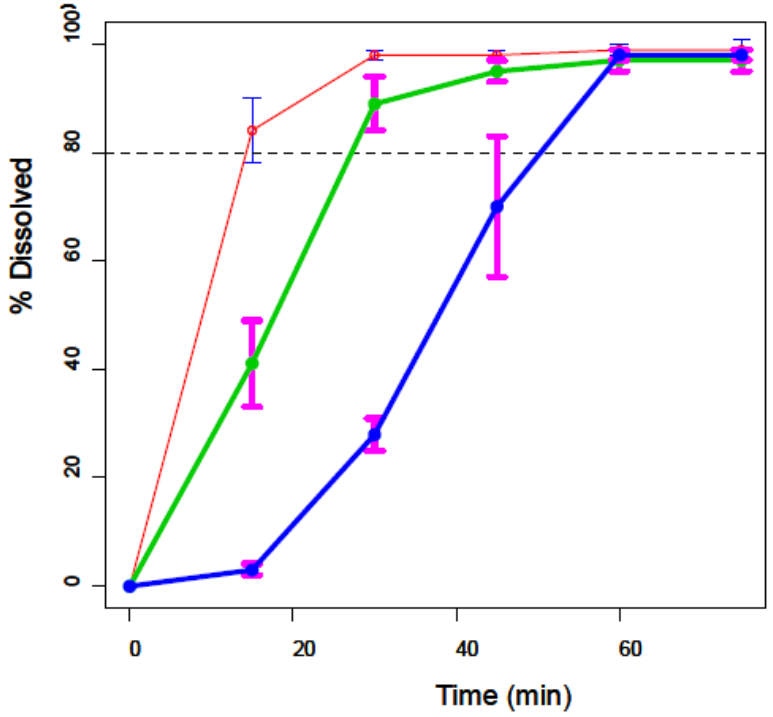


Z Gao, AAPS PharmSciTech, Vol 18, 231, 2017.

Simulate Fasted Stomach Contraction During Dissolution Testing



Clinical Study with Crosslinked Capsule Samples



Q = 80% at 30 min can differentiate between BE and non-BE batches

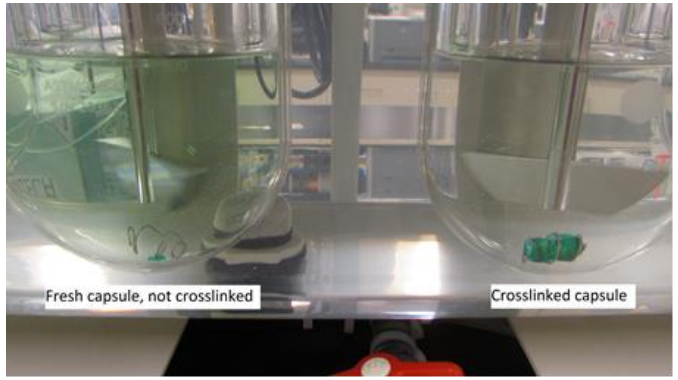
BE study: 24-subject

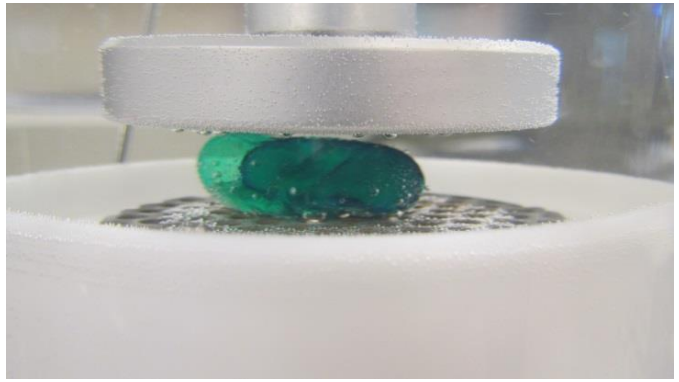
Crosslink	Par	Mean	CV%
No	Cmax	3.85	30
No	AUC	12.91	25
No	Tmax	0.93	45
No	Tlag	0.08	145
Moderate	Cmax	4.29	35
Moderate	AUC	13.5	26
Moderate	Tmax	0.99	67
Moderate	Tlag	0.16	71
Severe	Cmax	4.4	31
Severe	AUC	12.87	22
Severe	Tmax	0.85	57
Severe	Tlag	0.55	67

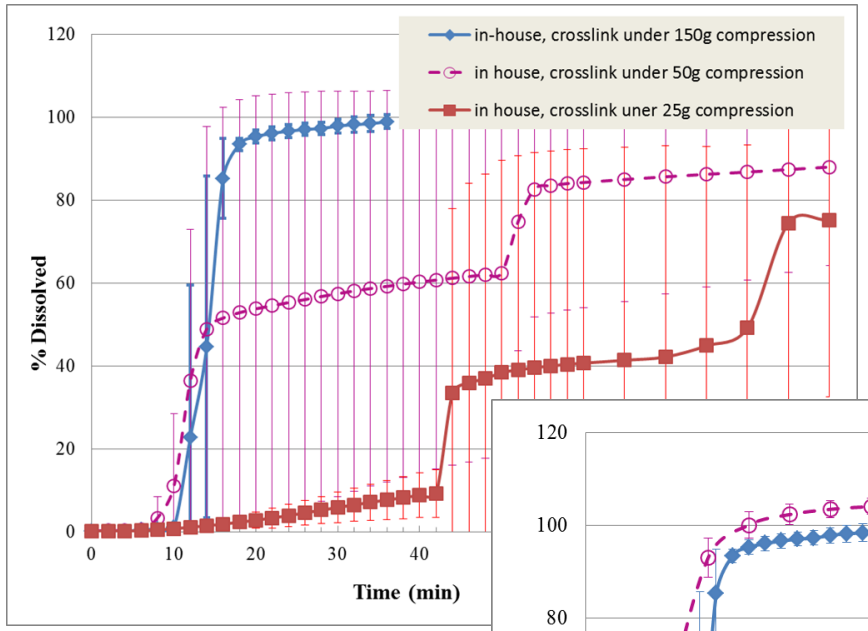
Data from FDA/OPQ Biopharmaceutics team

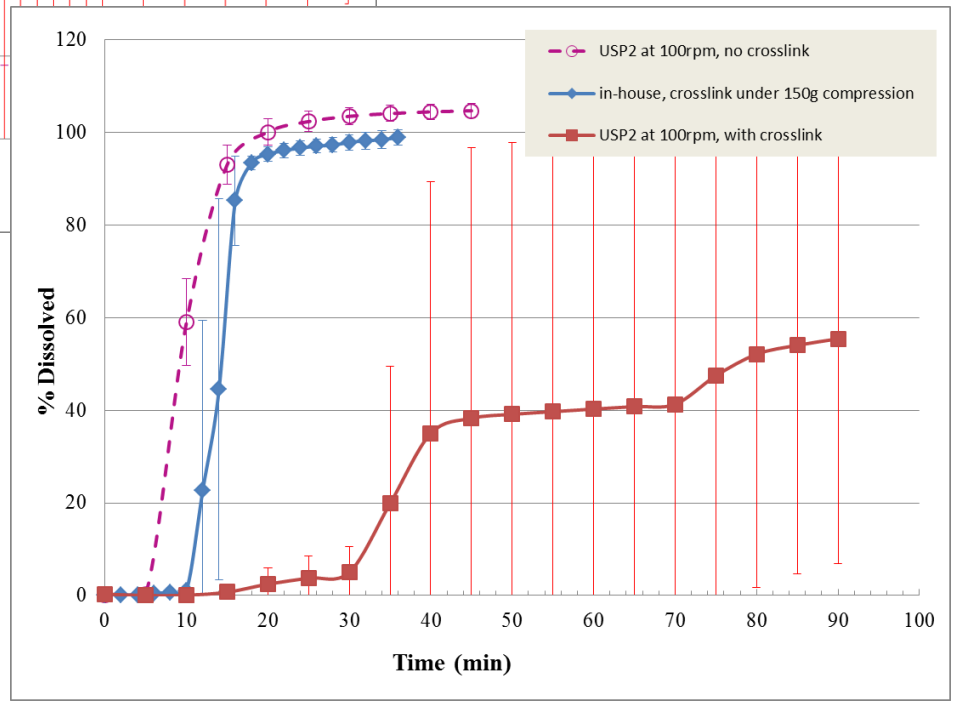
Case Study:

Dissolution Testing of Crosslinked Capsules Under Compressions



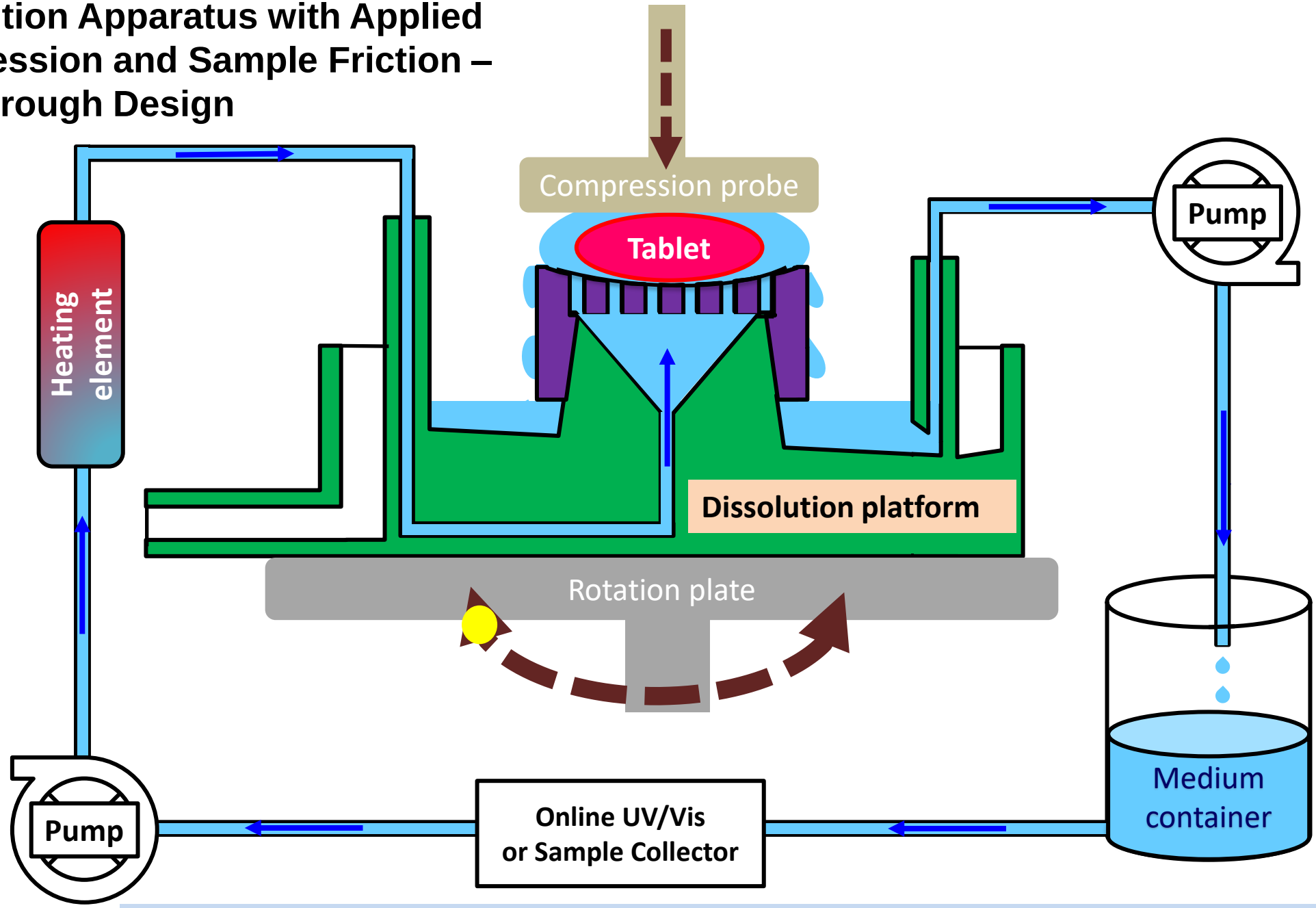






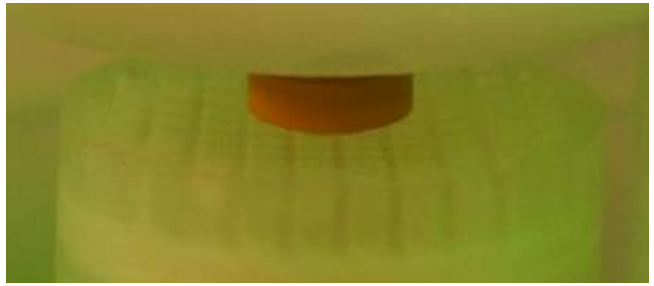
Z Gao, AAPS PharmSciTech, Vol 18, 231, 2017.

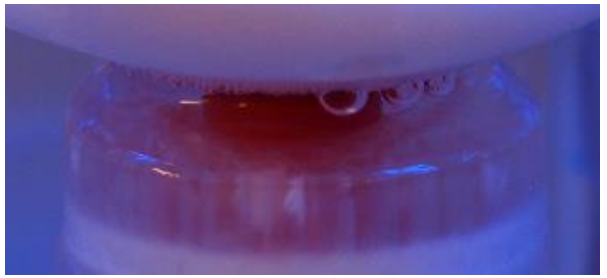
Dissolution Apparatus with Applied Compression and Sample Friction – Flow-through Design

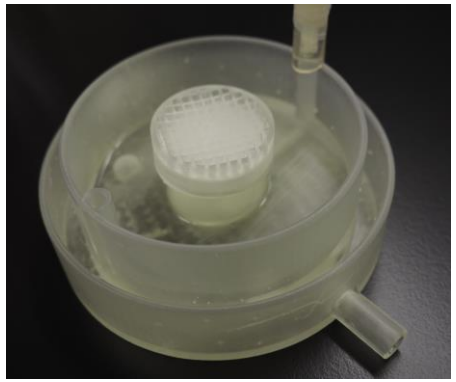


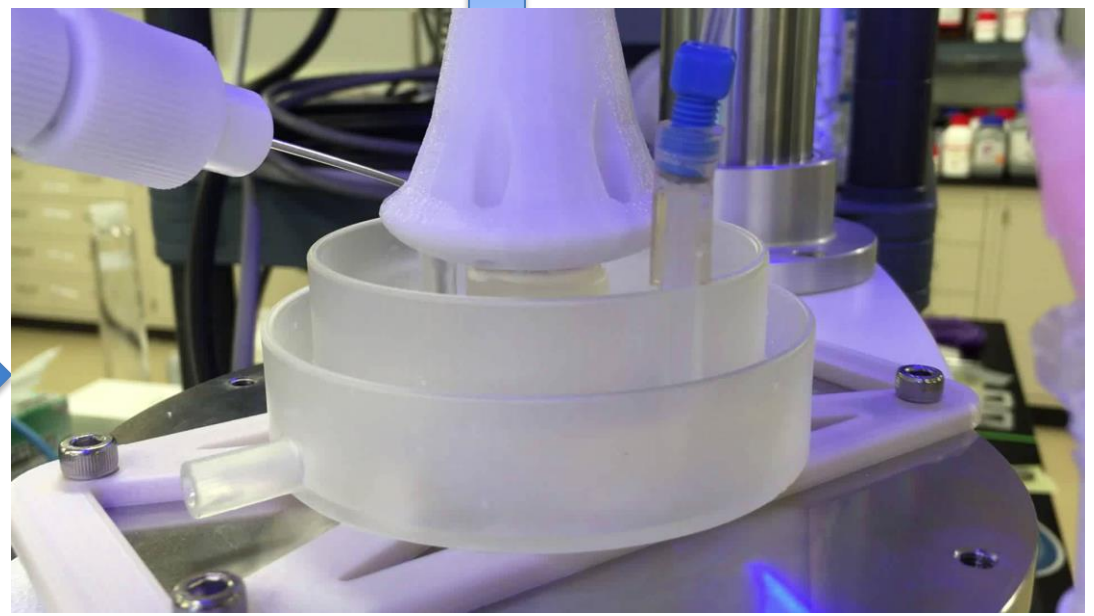
Z Gao, LN.Y. Cao, X Liu, L Tian and J Rodriguez,, J Pharm Sci, Vol.111, 1652-1658, 2022; DOI: https://doi.org/10.1016/j.xphs.2021.10.036.

3D Printed Flow-through Dissolution Platform



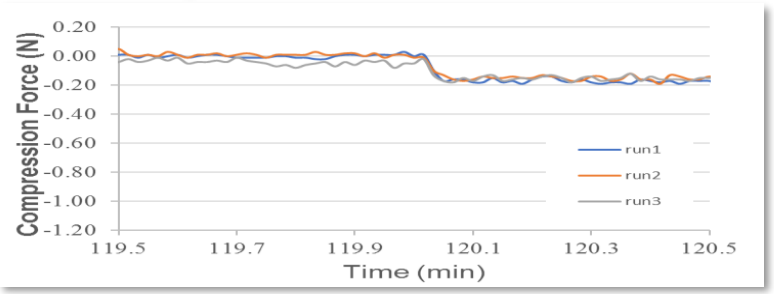


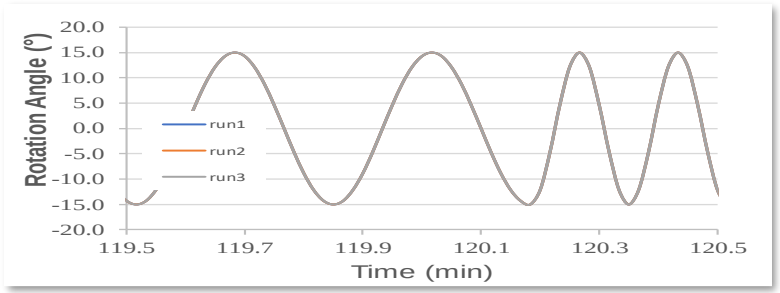




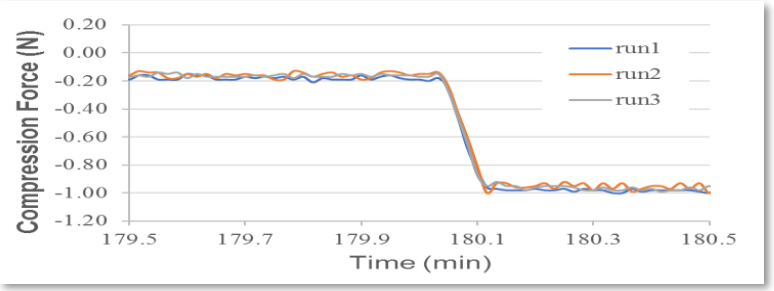
Simulate Stomach Contraction Through Staged Sample Compression and Rotation

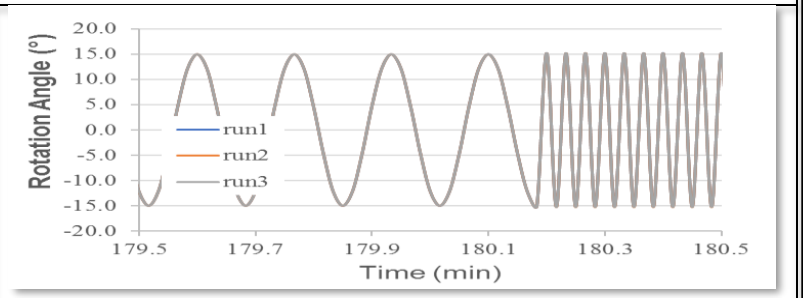
A: Stage 1 to Stage 2, transition from 0.05N compression with ±15° rotation at 0.05 Hz to 0.2 N compression with ±15° rotation at 0.1 Hz



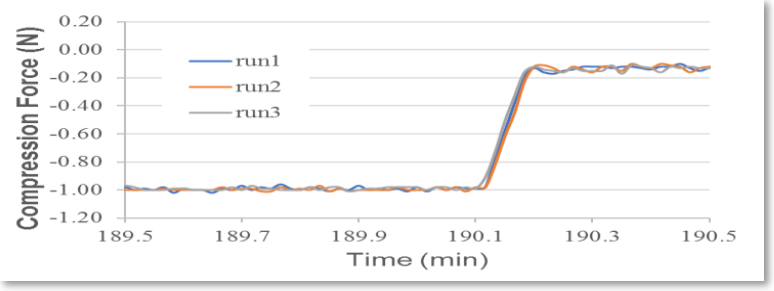


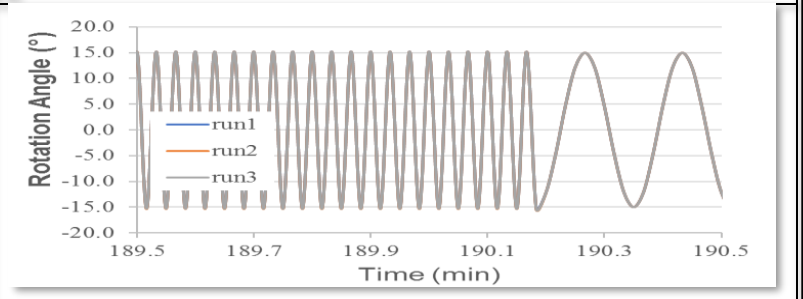
B: Stage 2 to Stage 3, transition from 0.2N compression with ±15° rotation at 0.1 Hz to 1 N compression with ±15° rotation at 0.5 Hz



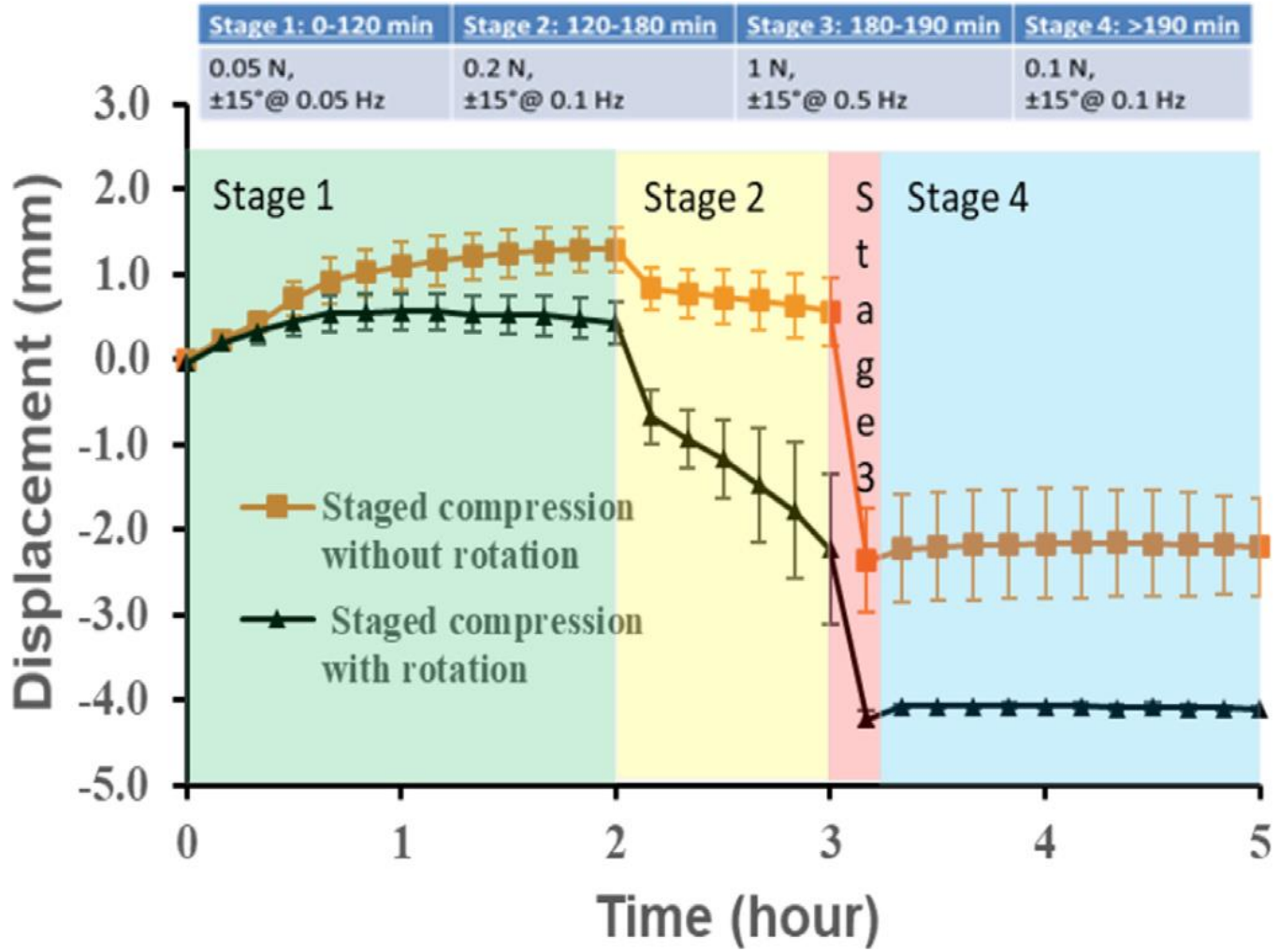


C: Stage 3 to Stage 4, transition from 1N compression with ±15° rotation at 0.5 Hz to 0.1N compression with ±15° rotation at 0.1 Hz





Displacement Profiles of Nifedipine ER Tablet Under Staged Sample Compressions and Rotation



Stage 1:

0.05 N,
±15°@ 0.05 Hz

Stage 2:

0.2 N,
±15°@ 0.1 Hz

Stage 3:

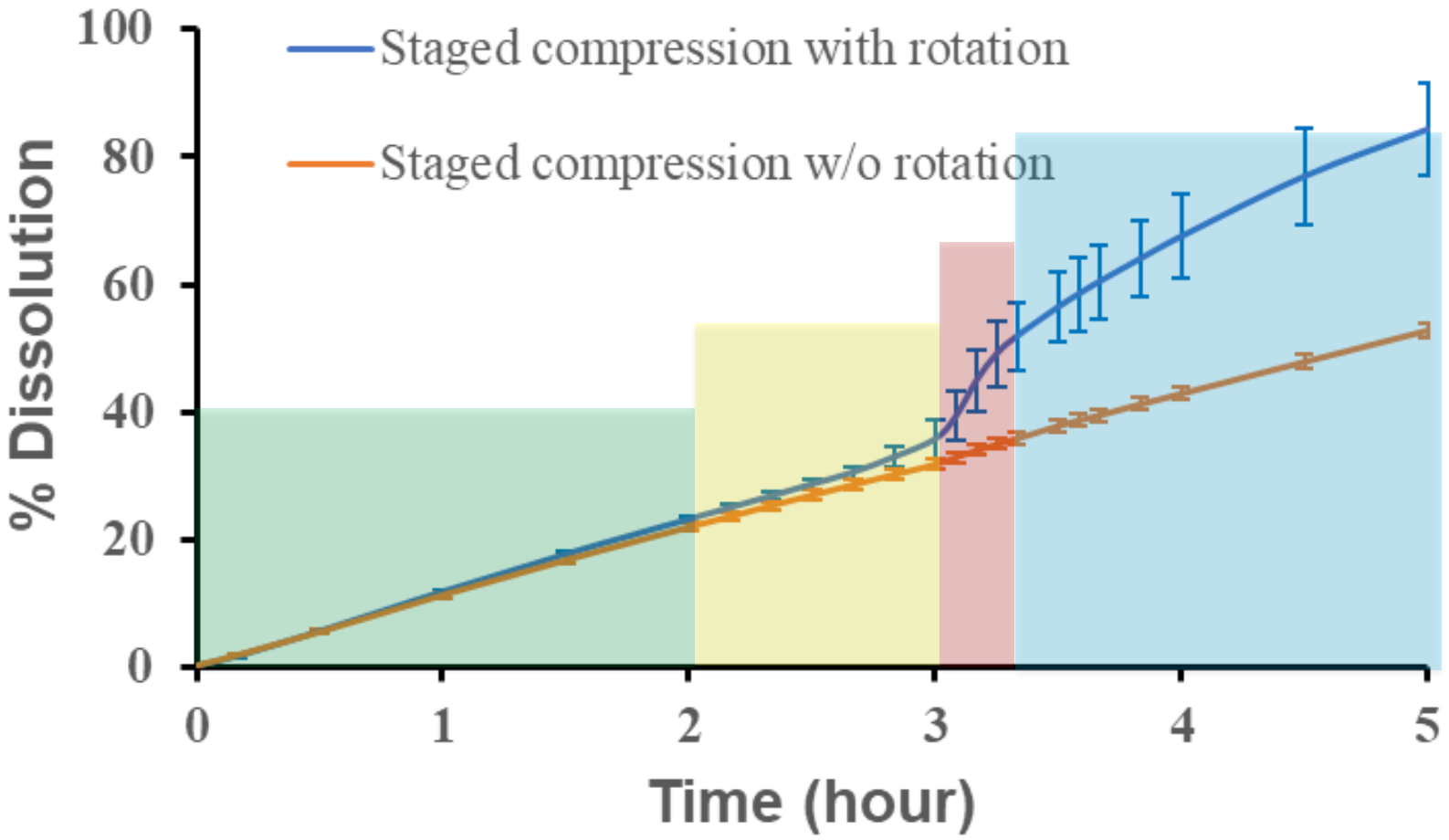
1 N,
±15°@ 0.5 Hz

Stage 4:

0.1 N,
±15°@ 0.1 Hz

Zongming Gao, Leo N.Y. Cao, Xiaofei Liu, Li Tian and Jason D. Rodriguez, An In Vitro Dissolution Method for Testing Extended-Release Tablets Under Mechanical Compression and Sample Friction, J Pharm Sci, Vol.111, 1652-1658, 2022; DOI: https://doi.org/10.1016/j.xphs.2021.10.036.

Dissolution Profiles of Nifedipine ER Tablet Under Staged Sample Compressions and Rotation



Stage 1:
0.05 N,
±15°@ 0.05 Hz

Stage 2:
0.2 N,
±15°@ 0.1 Hz

Stage 3:
1 N,
±15°@ 0.5 Hz

Stage 4:
0.1 N,
±15°@ 0.1 Hz

Zongming Gao, Leo N.Y. Cao, Xiaofei Liu, Li Tian and Jason D. Rodriguez, An In Vitro Dissolution Method for Testing Extended-Release Tablets Under Mechanical Compression and Sample Friction, J Pharm Sci, Vol.111, 1652-1658, 2022; DOI: https://doi.org/10.1016/j.xphs.2021.10.036.

FDA Guidance on Modeling

Physiologically based pharmacokinetic (PBPK) analyses use models and simulations that combine physiology, population, and drug substance and product characteristics to mechanistically describe the pharmacokinetic (PK) and/or pharmacodynamic behaviors of a drug product.

Food and Drug Administration Guidance for Industry, The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls https//www.fda.gov/media/142500/download. 2023.

Modeling

- Physiologically based biopharmaceutics modeling (PBBM) emphasizes the integration of physicochemical properties of drug substance and formulation characteristics with system physiological parameters to predict the absorption and pharmacokinetics (PK) of a drug product.
- The use of PBBM facilitates drug development and can reduce the number of preclinical and clinical studies.
  - formulation selection and development,
  - biopredictive dissolution method development,
  - biopharmaceutics risk assessment,
  - clinically relevant specification settings,
  - food effect evaluation
  - pH-dependent drug-drug-interaction risk assessment.

(PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives.

August 29-31, 2023

https://www.pharmacy.umaryland.edu/centers/cersievents/PBBM2023/

Di Wu, Min Li, Current State and Challenges of Physiologically Based Biopharmaceutics Modeling (PBBM) in Oral Drug Product Development, Pharmaceutical Research (2023) 40:321–336

Conclusions

- Dissolution testing is an important technique that can guide formulation selection, set up manufacturing parameters and ensure product consistency.
- Drug dissolving process in human GI tract is very complicated, dissolution testing may not be a reliable tool to assure pharmaceutical quality if it is not representative of clinical performance.
- FDA recognizes this challenge and encourages the development and use of new tools and approaches for linking pharmaceutical quality to clinical performance.
- Dissolution Testing may better bridge TPP with QTPP when physiological relevance is considered.
- FDA will continue working with stakeholders to assure that quality medicines are available for the public.

Acknowledgements

UM-CERSI/FDA Workshop– Planning/Organizing Committee

FDA/CDER/OPQ

Lucinda Buhse, Ph.D.

FDA/CDER/OPQ/ONDP/DB

Bhagwant Rege, Ph.D.

Kimberly Raines, Ph.D.

FDA/CDER/OTR/DPA Chemists

Anjanette Smith

Cindy Ngo

Wei Ye

FDA/CDER/OTR/DCDA Chemists

Li Tian, Ph.D.

FDA/CDER/OTR management and support

Thank You !

Contact Email : Zongming.Gao@fda.hhs.gov

ORISE Fellows

One year position (renewable depends on funding) in FDA St Louis laboratory.

Candidates:

- MS or PhD with extensive training in analytical chemistry, pharmaceutical science, and biopharmaceutics
- Experience with dissolution testing is highly desirable
- Salary is commensurate with education and experience.
- US citizenship, green card, EAD, OPT or CPT is required.
- An H1 visa cannot be sponsored for this position.

Contact Email : Zongming.Gao@fda.hhs.gov