

When Size matters



Well, Miss Jones, it seems our scale up procedure worked.
Question now, is, do we blister pack or bottle?

Performance Testing in Quality Control and Product Development, Where are We?

- Disintegration comparison 701 vs. 2040
- Beaker specifications and Harmonization
- Rupture test
- Disintegration vs. Dissolution
- BCS sub classification
- Buffer capacity and dissolution

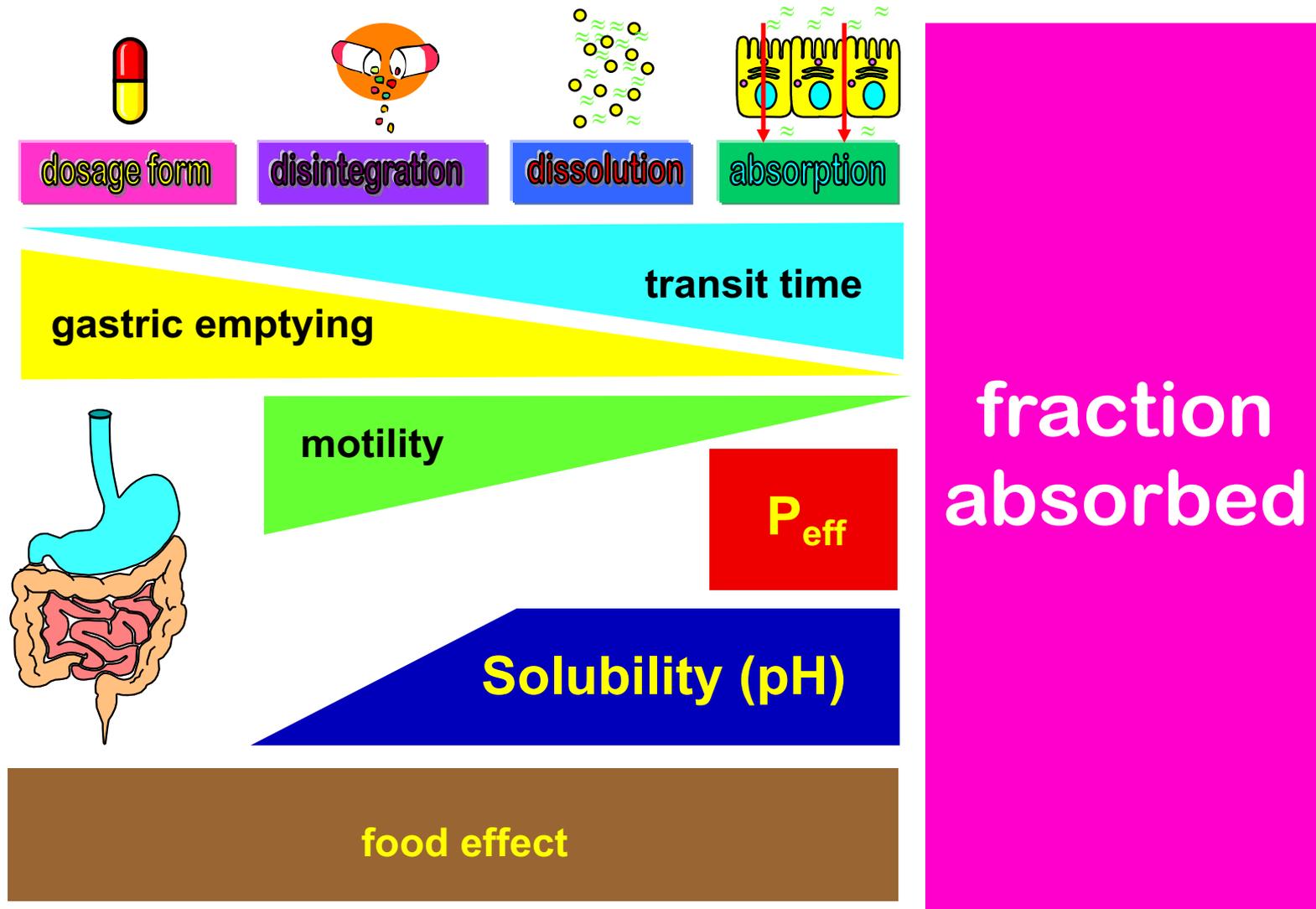


DDIC



UNIVERSITY OF
ALBERTA

Factor for oral drug absorption



Tablet disintegration <701/2040>

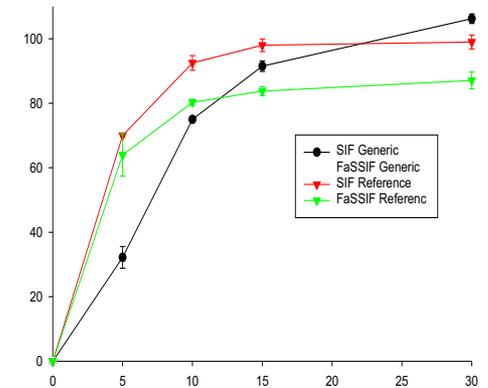
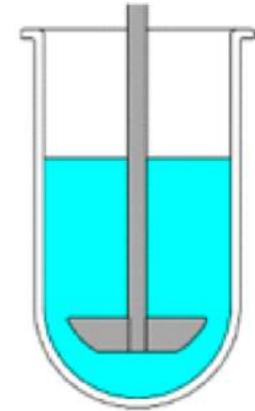
- **Disintegration**

- **USP specifies for drugs and Dietary Supplements in vitro disintegration test a dosage form must pass**



- 6 units are tested
- if one or two fail 12 additional units are tested...

Dissolution testing / Rapture test



Pharmaceutical vs. Dietary Supplement Chapters

2040
Disintegration



Disintegration

701
Disintegration

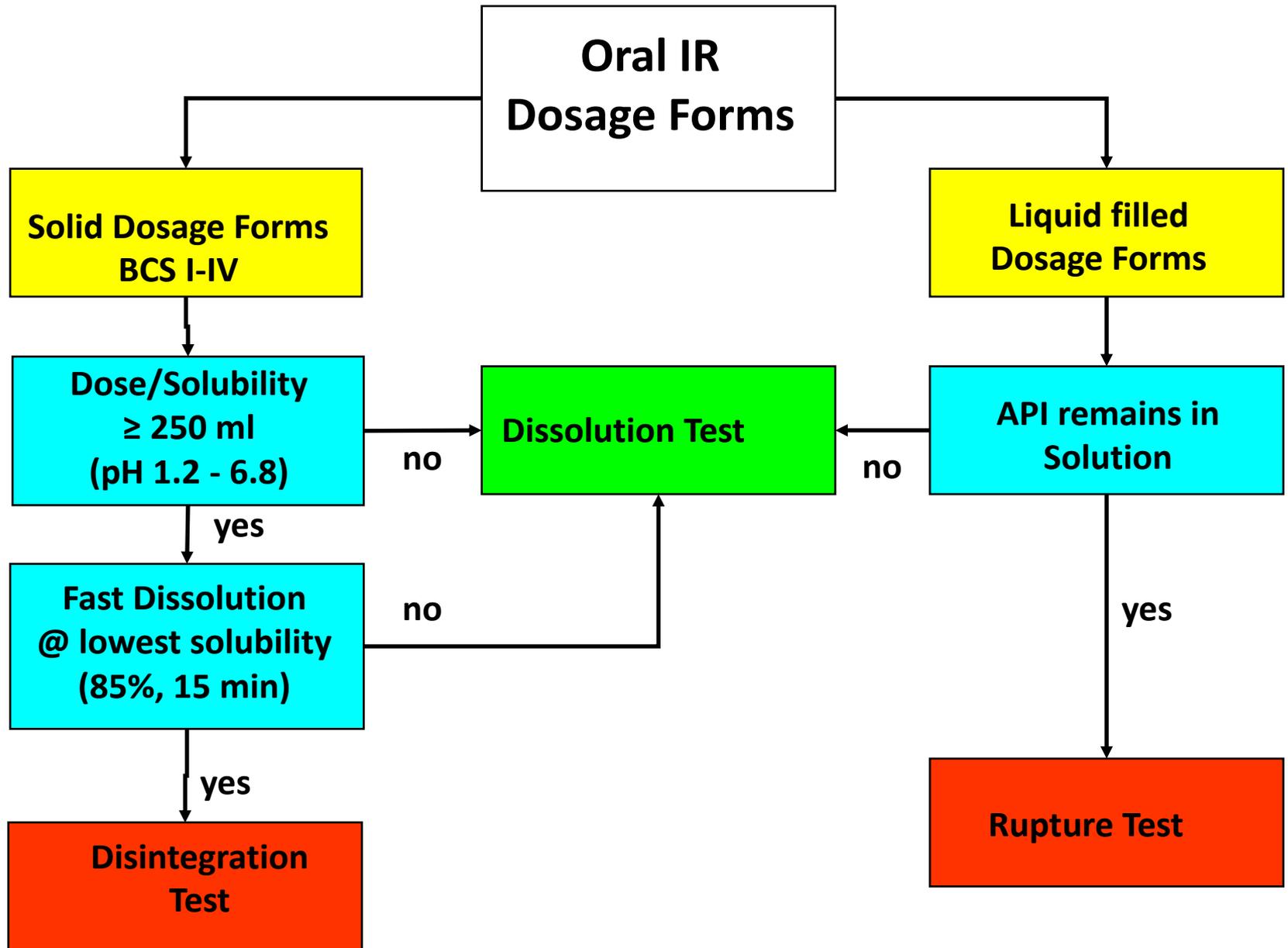


2040
Rupture App 2

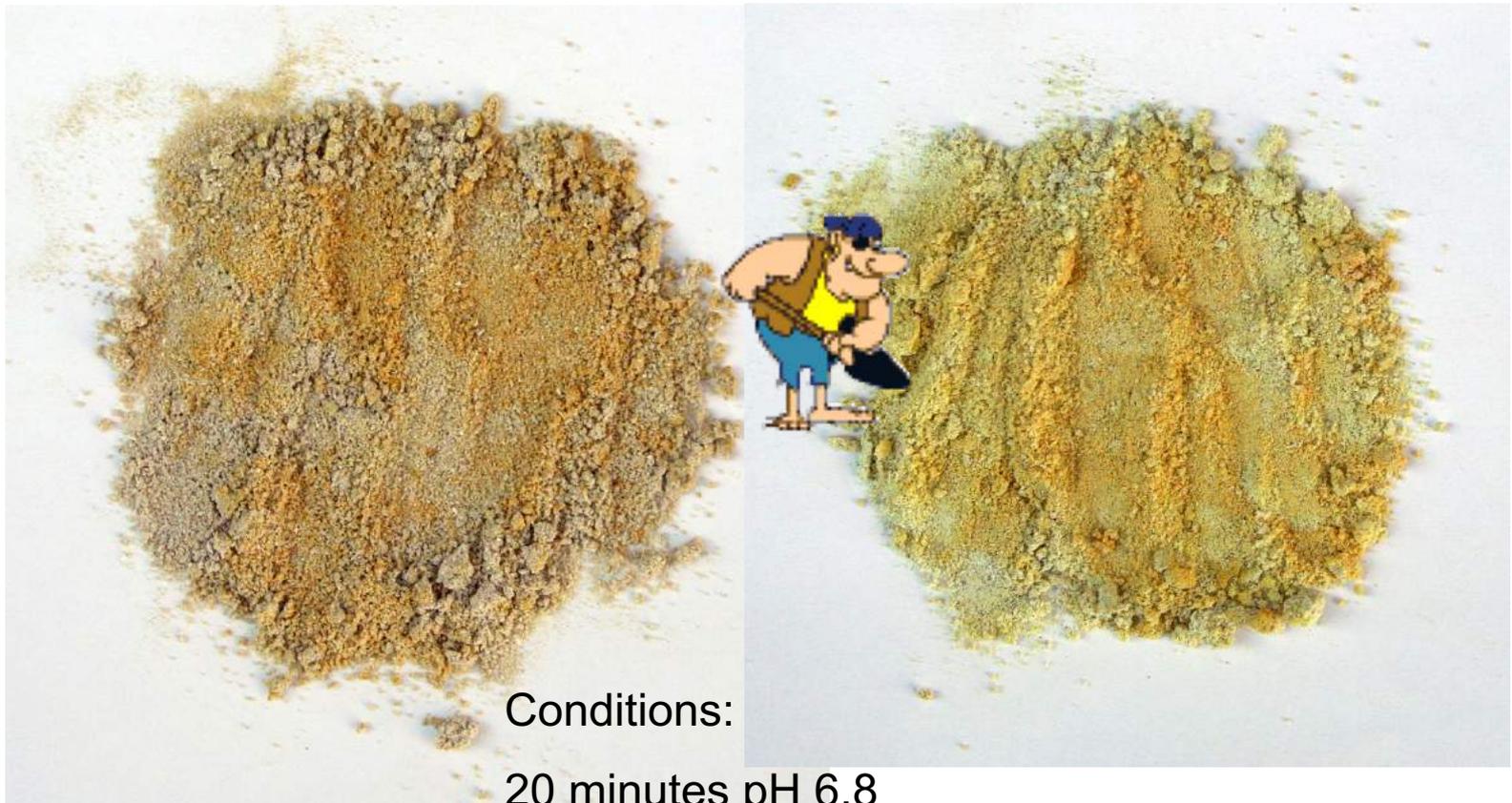


Disintegration, Dissolution and Rupture

- **Disintegration** = Dosage form is dispersed
- **Dissolution** = rate and extend of release
- **Rupture** = non-aqueous content is exposed



Disintegration study: Minerals and Vitamins on the Canadian Market



Conditions:

20 minutes pH 6.8

No disk

Disintegration



Available online at www.sciencedirect.com



International Journal of Pharmaceutics 345 (2007) 2–8

INTERNATIONAL JOURNAL OF
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Historical Perspective

A mini review of scientific and pharmacopeial requirements for the disintegration test

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Available online 1 September 2007

Disintegration in USP 28

| Dosage Form | <701> APP | <701> Medium | <2040> APP | <2040> Medium |
|--|---------------------|------------------|---------------------|-----------------------|
| Uncoated Tablets | DIS | Water | DIS | Water |
| Film Coated | | | DIS | Water |
| Plain Coated Tablets (other than Film Coated) | DIS | Water | PCT | Water |
| Sublingual Tablets | DIS | Water | ⊗ | - |
| Buccal Tablets | DIS | Water | ⊗ | - |
| Chewable Tablets | ☺ | ☺ | ☺ | - |
| Modified Release Tablets | - | - | - | - |
| Delayed Release Tablets | DRT | SGF / SIF | DRT | SGF / SIF |
| Hard Shell Capsules | DIS + WM | Water | DIS + WM | Buffer 4.5 |
| Soft Shell Capsules | DIS + WM | Water | RUP | Water |

DIS = Disintegration Test Apparatus A or B

PCT = Plain Coated Tablets Test

RUP = Rupture test

DRT = Delayed Release Tablets Test

WM = Wire Mesh to cover top of apparatus A

⊗ = not listed

☺ = scientifically justified to be considered for disintegration tests

Disintegration



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PHARMACEUTICS

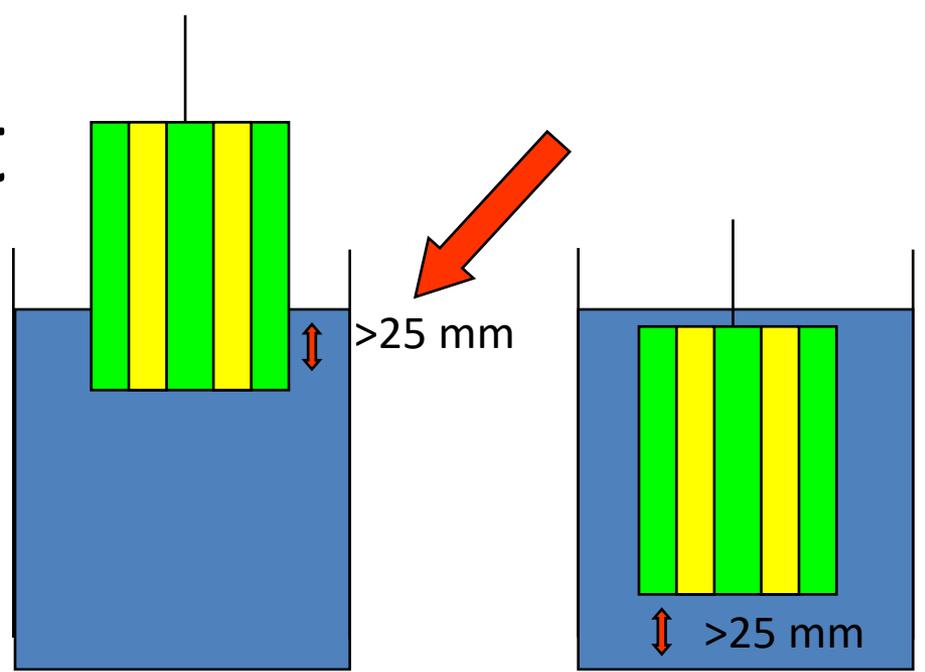
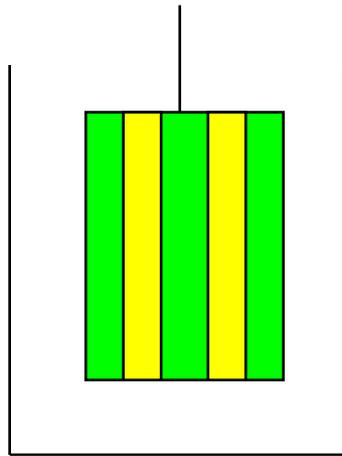
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A number of changes made to the disintegration test since the USP 23 need to be evaluated as to whether they will have any impact on the measured disintegration time of dosage forms.

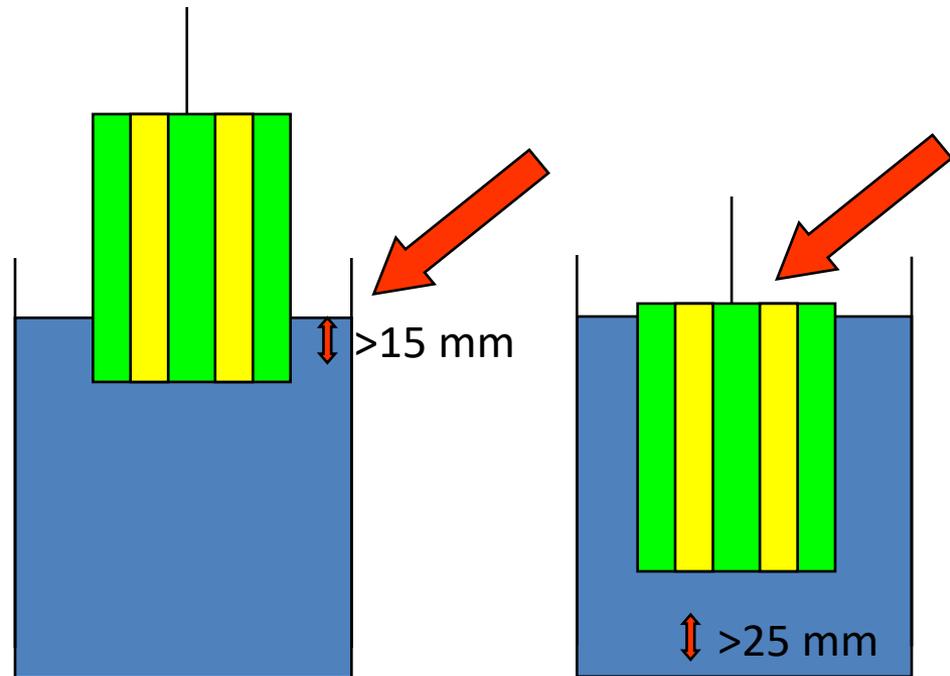
Disintegration will continue to be a valuable quality control procedure, but clearly further work is required to strengthen its place among the tools that assess the performance of dosage forms.

Disintegration test

USP 27 and earlier



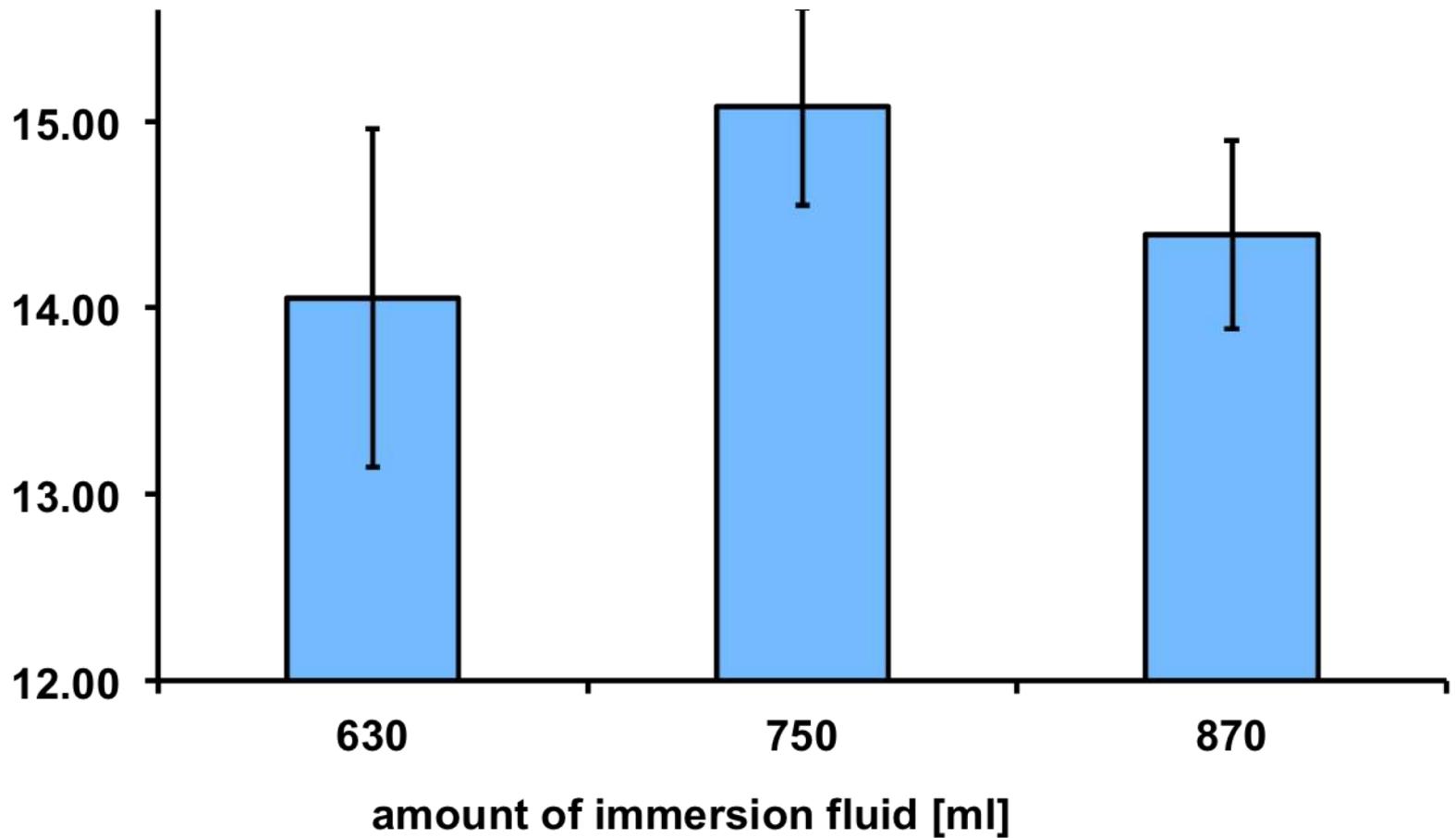
USP 28 and later



Problems with current Specifications

- **USP:** The moving range of the basket-rack assembly should be between 53 and 57 mm
- **USP:** the height of the basket from the bottom should be at least 25 mm and 15 mm from the top.
- **Math:** This is a total height of 93 to 97 mm.
 - Taking the current beaker diameter specifications into account this adds up to a **volume of between 687 and 1007 mL** depending on the beaker diameter.
- For 900 mL the medium height in a beaker with 115 mm diameter will only be 87 mm.
- 900 mL will be too much in a 97 mm diameter beaker if the basket assembly should not be submerged.

Disintegration Times



Influence of the Changed USP Specifications on the Disintegration Test Performance

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Ludwig-Maximilians-University Munich, 81377 Munich, Germany

²Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta,
Edmonton, AB, T6G 2N8, Canada

ABSTRACT

The aim of this study was to investigate if the changes made in the specifications of the disintegration procedure impact the performance of the disintegration test described in *USP* chapters <701> and <2040>. Different tablets and capsules were produced, and their disintegration times were determined. The following disintegration time parameters were analyzed: volume of the immersion fluid, type of apparatus (Apparatus A for method <701>; Apparatus B for method <2040>), and attachment of a wire cloth to the basket assembly. By adjusting the compaction force and lubricant level, the disintegration time of the tablets was standardized to 15 min. The disintegration time change was statistically significant when varying the volume of the immersion fluid. The type of apparatus and the attachment of a wire cloth resulted in no significant difference in the disintegration time of capsules. The *USP* requirements for immersion medium volume should be strictly followed to obtain correct and reproducible test results. The disintegration test is a suitable performance test for certain pharmaceutical and dietary dosage forms.

Influence of the Changed USP Specifications on the Disintegration Test Performance

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ABSTRACT

The USP requirements for immersion medium volume should be strictly followed to obtain correct and reproducible test results. The disintegration test is a suitable performance test for certain pharmaceutical and dietary dosage forms.

ICH Harmonization



European Medicines Agency

June 2008

EMEA/CHMP/ICH/308895/2008

**ICH Topic Q4B Annex 5
Disintegration Test General Chapter**

Step 3

**ANNEX 5 TO NOTE FOR EVALUATION AND RECOMMENDATION OF
PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS
ON
DISINTEGRATION TEST GENERAL CHAPTER
(EMEA/CHMP/ICH/308895/2008)**

ICH Q4B Annex 5

Apparatus

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 160 mm in height and having an inside diameter of 97 to 115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35 ° and 39 °, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become



Beaker specifications

and distance of the bottom wire mesh of Apparatus A in the USP, European

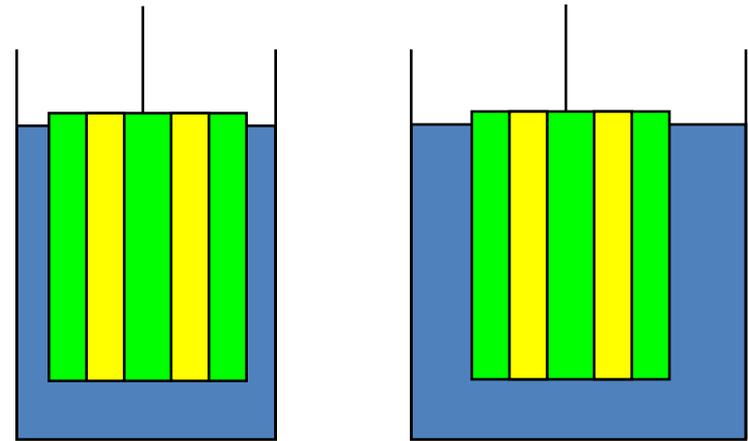
Pharmacopeia and Japanese Pharmacopeia.

| Apparatus A | USP 23 (701) | USP 26 (701/2040) | USP 30 (701/2040) | European Pharm. 2007 (5.8) | Japanese Ph. (14) |
|--|---------------------------|-------------------|-------------------|----------------------------|-------------------|
| Volume of beaker (mL) | 1000 | 1000 | 1000 | 1000 | - |
| Height of beaker (mm) | 142-148 (USP 23, suppl.9) | 138-155 | 138-160 | 149+/-11 | about 155 |
| Diameter (inside, mm) | 103-10 (USP 23, suppl. 9) | 97-110 | 97-115 | 106+/-9 | about 110 |
| Upward stroke: distance wire mesh/ surface (mm) | ≥25 | ≥25 | ≥15 | ≥15 | - |
| Downward stroke: distance wire mesh/ bottom (mm) | ≥25 | ≥25 | ≥25 | ≥25 | 25 |

Disintegration test Study Design

Two Beakers (diameter)

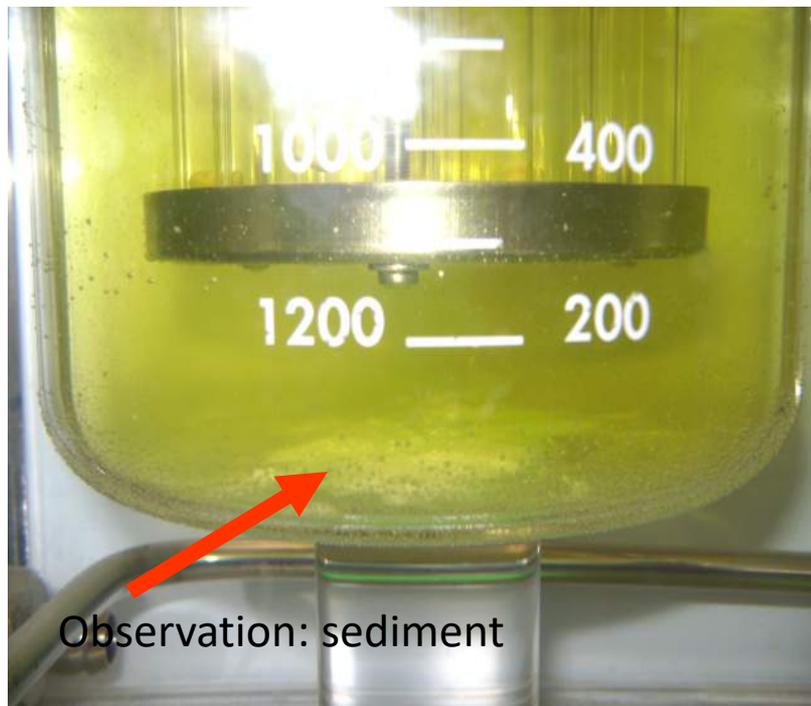
- 1) narrow USP specification
- 2) 1.5 L larger than new USP specification
- 3) With and without disk
- 4) Immersion medium
- 5) App A and B



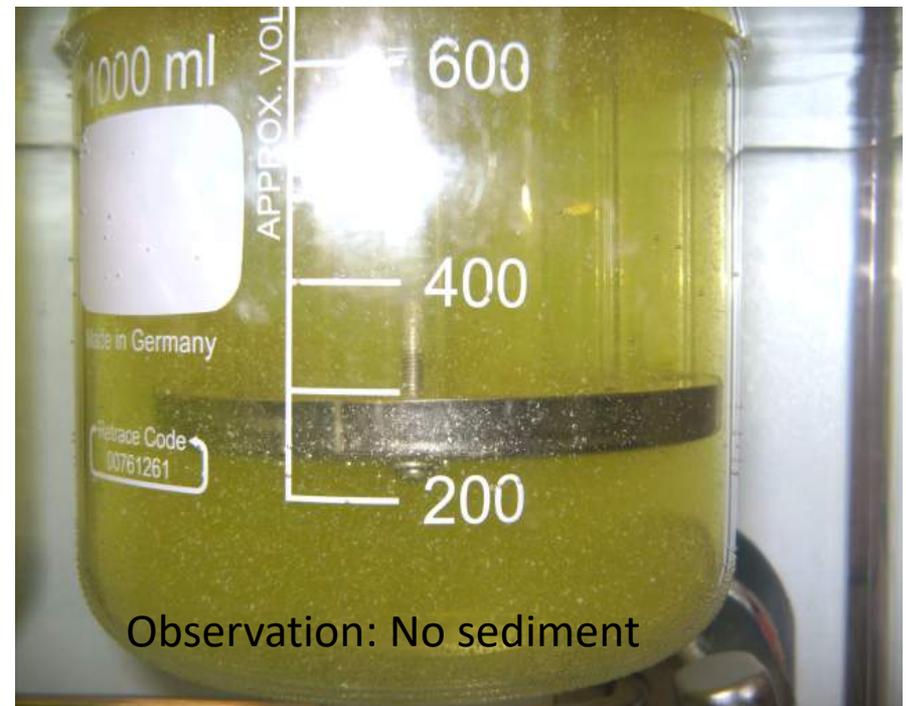
USP and ICH

1.5 L Beaker vs. Small Beaker

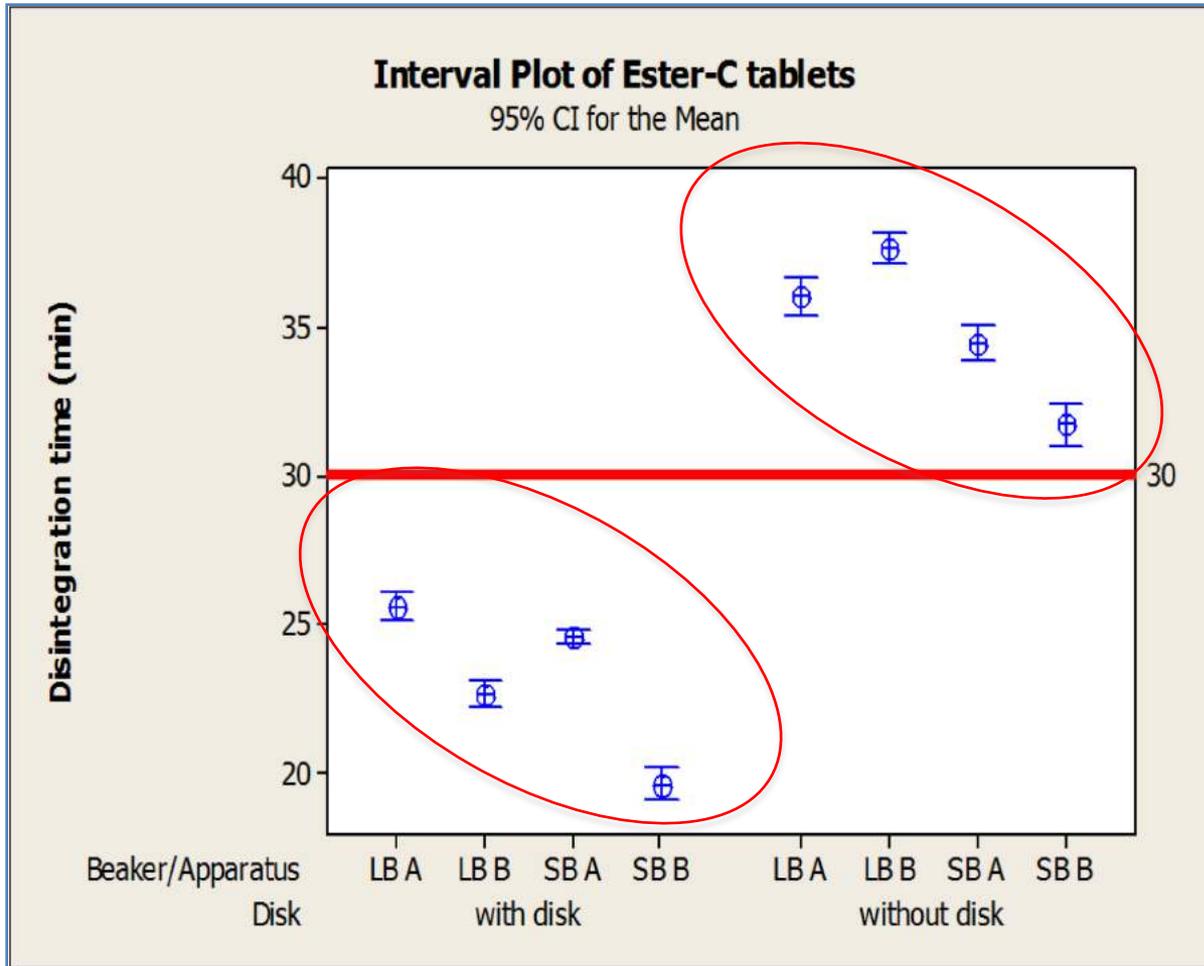
- 1.5 L Beaker



- Small Beaker



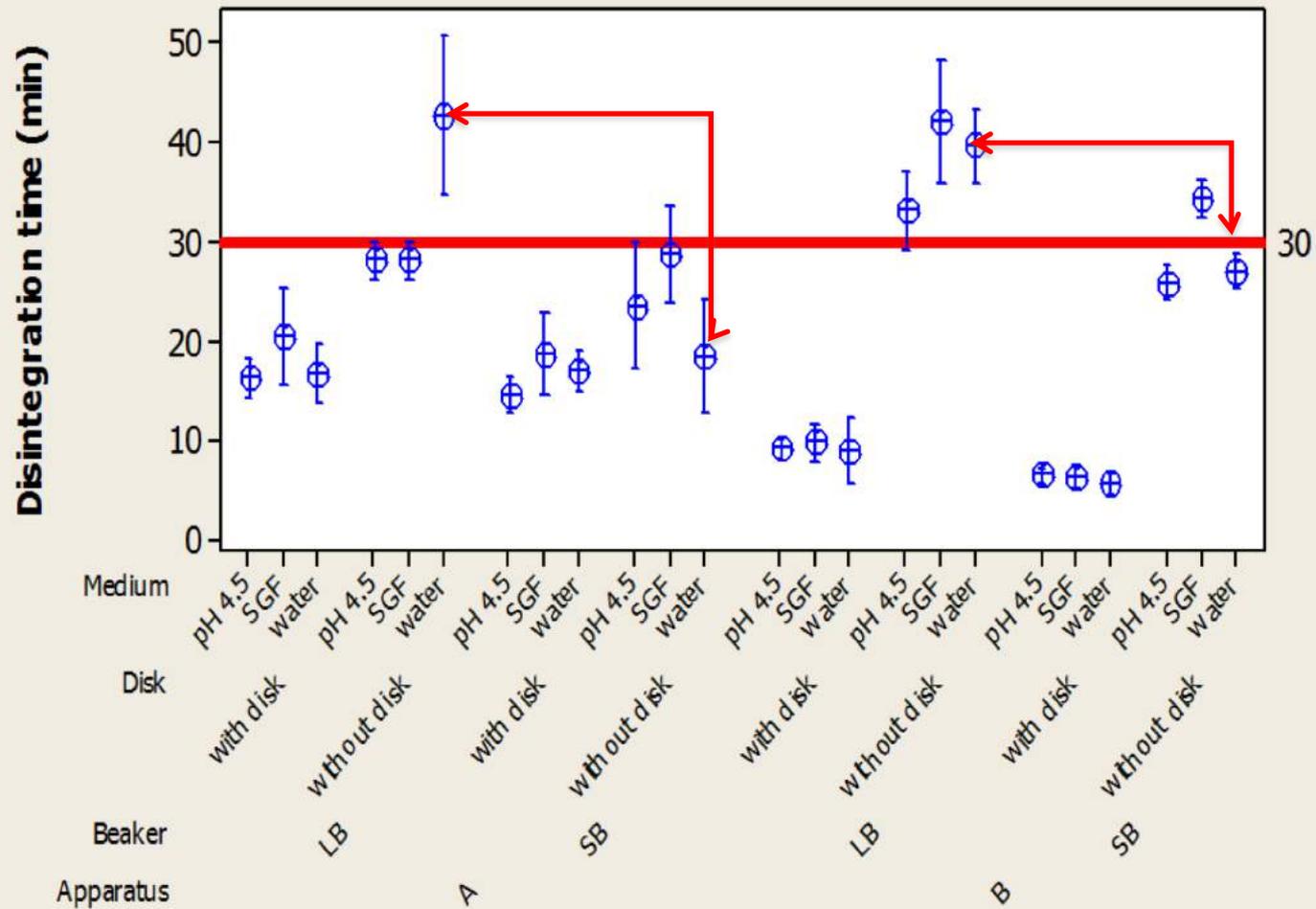
Result (Tables)



Result (Capsules)

Interval Plot of Chasteberry capsules

95% CI for the Mean



Investigation of the Performance of the Disintegration Test for Dietary Supplements

The AAPS Journal, Vol. 12, No. 4, December 2010 (© 2010)
DOI: 10.1208/s12248-010-9221-1

May Almukainzi,¹ Mahnor Salehi,¹ Nadia Araci Bou-Chacra,² and Raimar Löbenberg^{1,3}

Received 11 May 2010; accepted 28 June 2010; published online 24 July 2010

Abstract. The aim of this study was to investigate how beaker size, basket assembly, use of disk, and immersion medium impact the disintegration time of dietary supplements. The disintegration times were determined for five tablet and two capsule products. A two-station disintegration tester was used with Apparatus A or Apparatus B as described in the United States Pharmacopeia (USP) chapters, <701> and <2040>. Two beakers complying with the harmonized specifications were used, one with a volume of 1,000 mL and one with a 1,500-mL volume. The disintegration data were analyzed using ANOVA for the following factors: beaker size, equipment (App A and B) and condition (with/without disk). Two tablet products were not sensitive to any changes in the test conditions or equipment configurations. One product was only partially sensitive to the test conditions. The other products showed impact on the disintegration time for all test conditions. The results revealed that these tablet products might pass or fail current USP disintegration requirements depending on the equipment configuration. Similar results were obtained for the two investigated capsule formulations. One product might fail current USP disintegration requirements if the large beaker was used, but might pass the disintegration requirements when the small beaker was used. Hydroxy propyl methyl cellulose capsules were mostly influenced if sodium instead of a potassium buffer was used as the immersion medium. The results demonstrate that the current harmonized ICH specifications for the disintegration test are insufficient to make the disintegration test into reliable test for dietary supplements.

Investigation of the Performance of the Disintegration Test for Dietary Supplements

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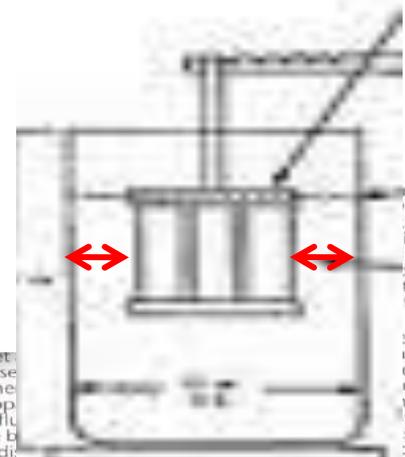
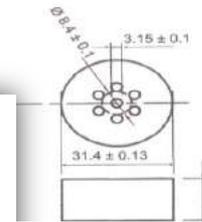
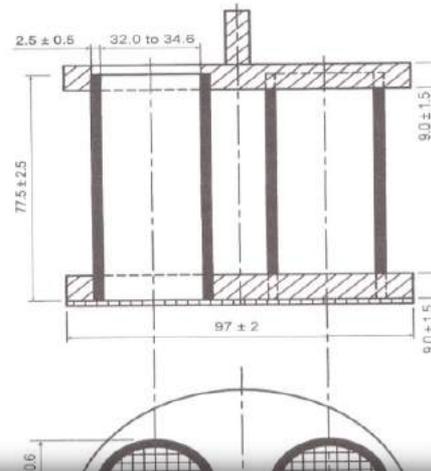
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Change in USP Standard



Beaker—Low form, 1000 mL; the difference between the diameter of the plastic plates, which hold the tubes in a vertical position, and the inside diameter of the beaker should not be more than 6 mm.² ■_{2S} (USP33)

² 1000-mL low-form beakers, designed in compliance with the current ASTM E 960 Type I or Type II or ISO 3819 specifications, are suitable. ■_{2S} (USP33)

³ The use of automatic detection employing modified disks is permitted where the use of disks is specified or allowed. Such disks must comply with the requirements for density and dimensions given in this chapter.

of the basket. For the basket, immerse the basket in the immersion fluid for 5 minutes. Then operate the apparatus for 10 minutes. Lift the basket and the tablets. If the tablets do not disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Soft Gelatine Capsules



http://www.sixthseal.com/archive/June2006/normison_capsules_gel.jpg



<http://www.jsppharma.com/Liquid-capsule-softgel.html>

Method

5 different products, in form of soft gelatine capsules, were Received:

1. Amantadine HCL → *Suspension*
 2. Pseudoephedrine HCl → *Solution*
 3. Flaxseed Oil
 4. Ginseng 100mg
 5. Soybean Oil
- } *Oil base*

Method



Each Product

12 Capsules
(Disintegration test)

12 Capsules
(Rupture test)

6 Capsules
(Coated)

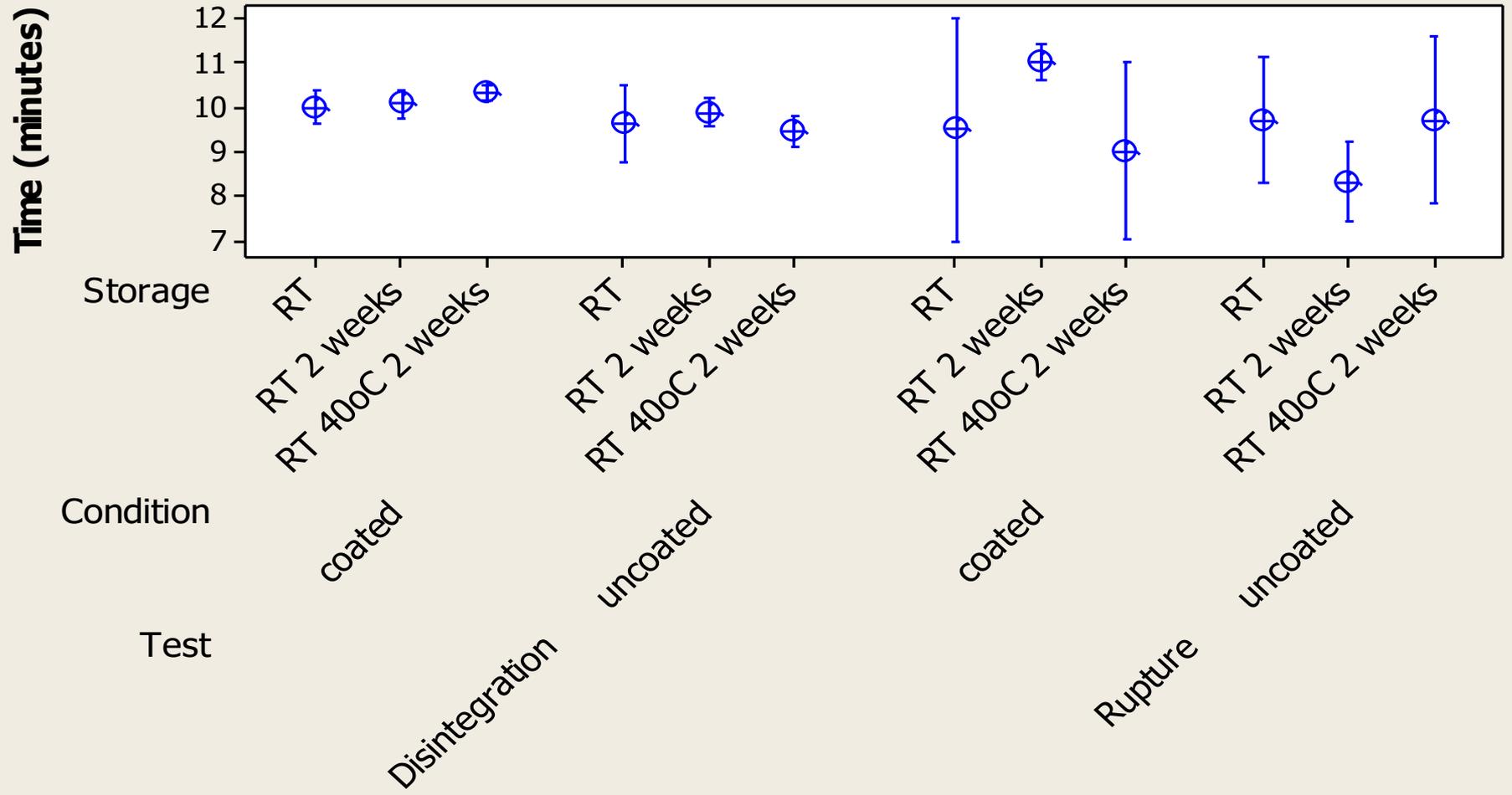
6 Capsules
(intact)

6 Capsules
(Coated)

6 Capsules
(intact)

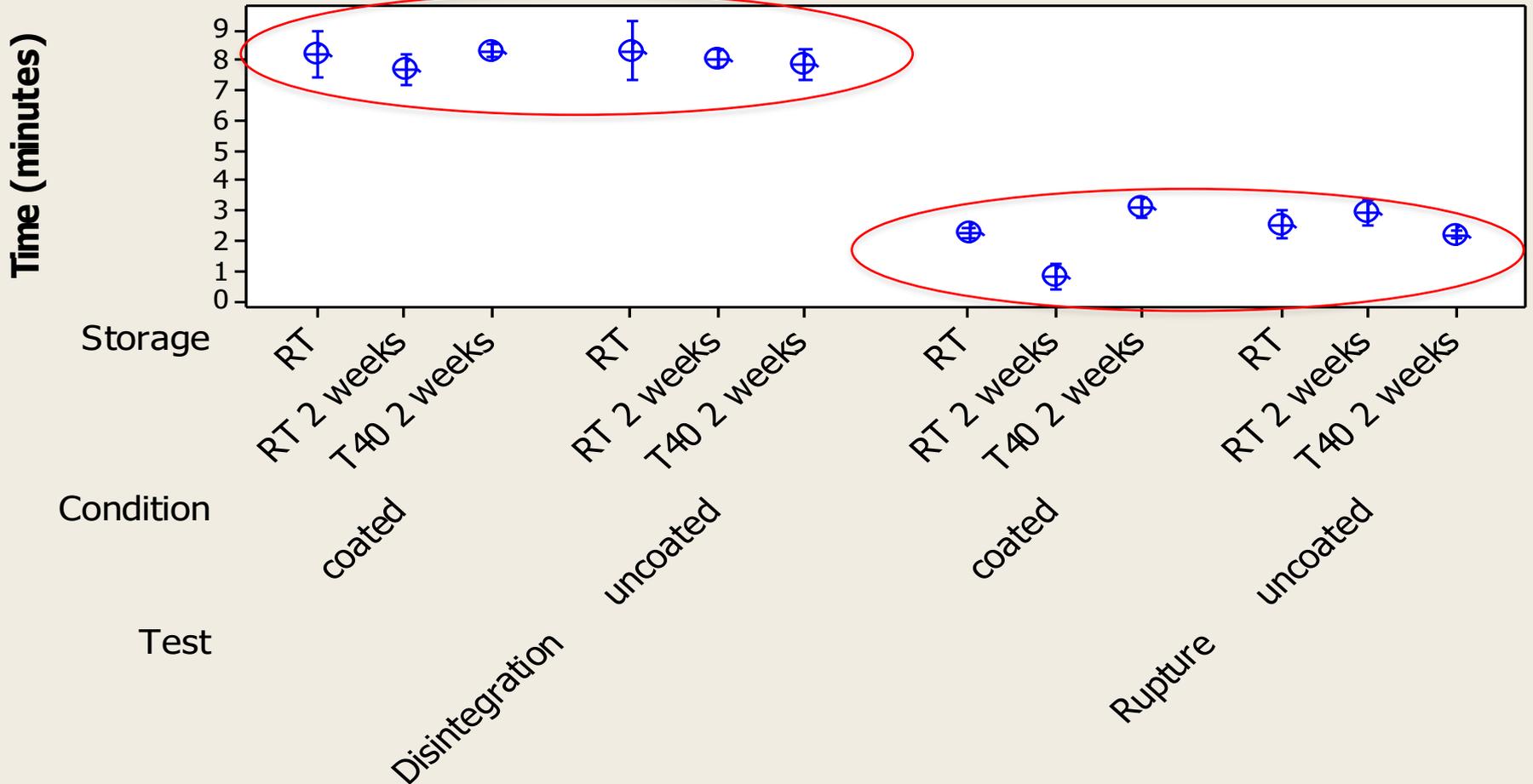
Result

Interval Plot of Time (minutes): test, condition and storage for Amadantine capsule
95% CI for the Mean



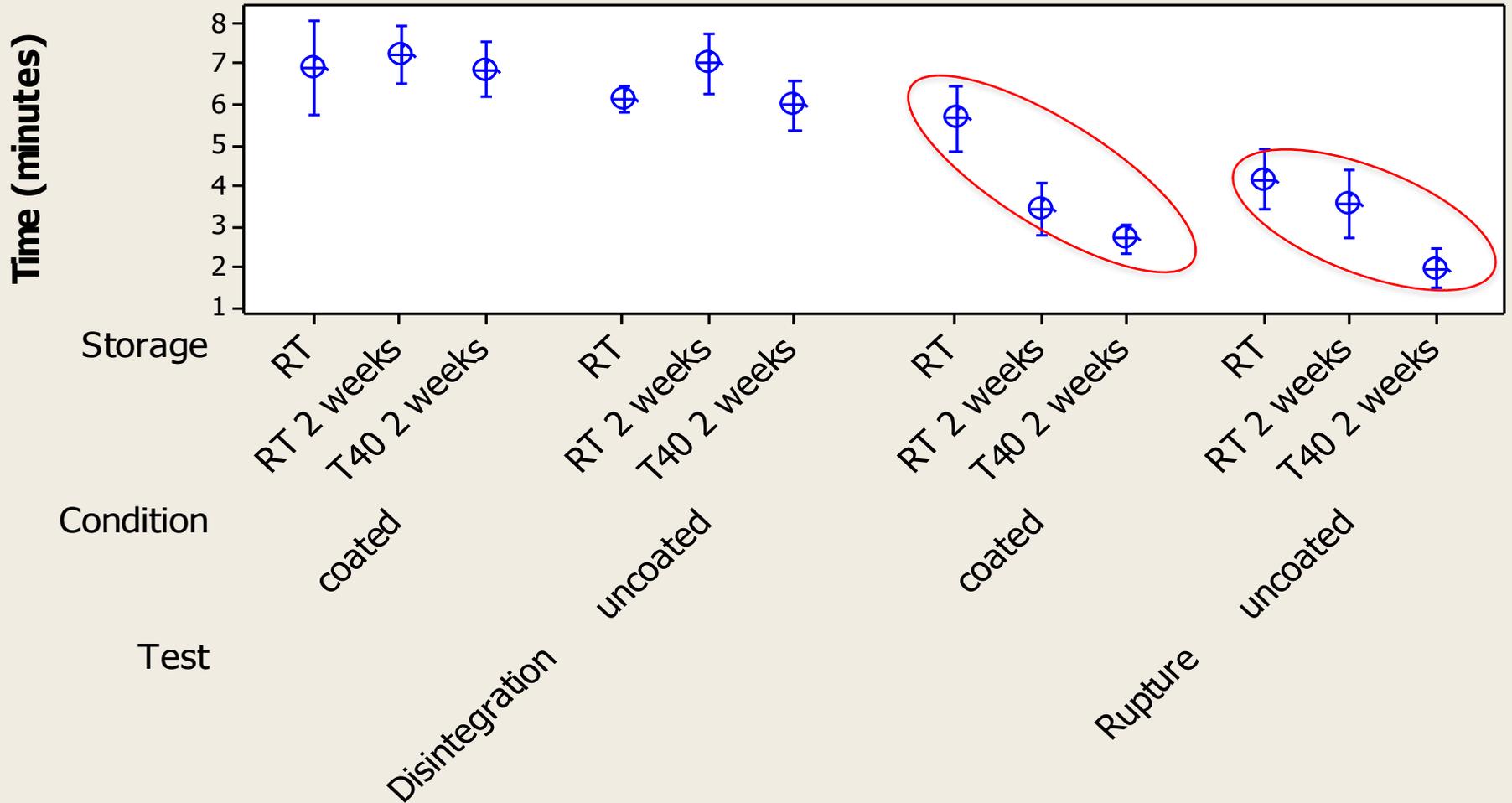
Result

Interval plot for Time (minutes): test; condition and storage for Flaxseed oil capsule
95% CI for the Mean



Result

Interval Plot for Time (minutes): test; condition; storage for Pseudoephedrine capsule
95% CI for the Mean



Comparison of the Rupture and Disintegration Tests for Soft-Shell Capsules

May Almukainzi¹, Mahnor Salehi¹, Nadia A. B. Chacra²,
and Raimar Löbenberg^{1,*}

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1123A Dentistry/Pharmacy Centre, Edmonton, Alberta, Canada*

²*Department of Pharmaceutical Science, University of Sao Paulo, Brazil*

ABSTRACT

The *USP* General Chapter <2040> Disintegration and Dissolution of Dietary Supplements introduced a rupture test as a performance test of soft-shell capsules. Traditionally, the disintegration test was used for determining the disintegration time of all solid oral dosage forms. The aim of this investigation was to investigate differences between the rupture test and the disintegration test using soft-shell capsules.

Five different soft-shell capsule products were chosen based on their filling contents and treated to simulate a production deficiency. The study design compared capsules as received with capsules that were treated by coating them with the liquid contents of another capsule. The capsules were incubated at room temperature and at 40 °C. The tests were repeated after two weeks, and at each time point, twelve capsules of each product were tested using the rupture and the disintegration tests. Six capsules were tested untreated, while the other six capsules were treated. Rupture and disintegration times were recorded as dependent variables in each experiment. The data were analyzed using ANOVA.

According to the *USP* definition for disintegration, the rupture of a soft-shell capsule can be seen as fulfilling the disintegration criterion if the capsule contents is a semisolid or liquid. Statistical analysis showed no advantage of the rupture test over the disintegration test. On a product-by-product basis, both tests were sensitive to certain investigated parameters. A noticeable difference between both tests was that in most cases, the rupture test reached the defined endpoint faster than the disintegration test.

Soft-shell capsules that are subject to a Quality by Design approach should be tested with both methods to determine which performance test is the most appropriate test for a specific product.

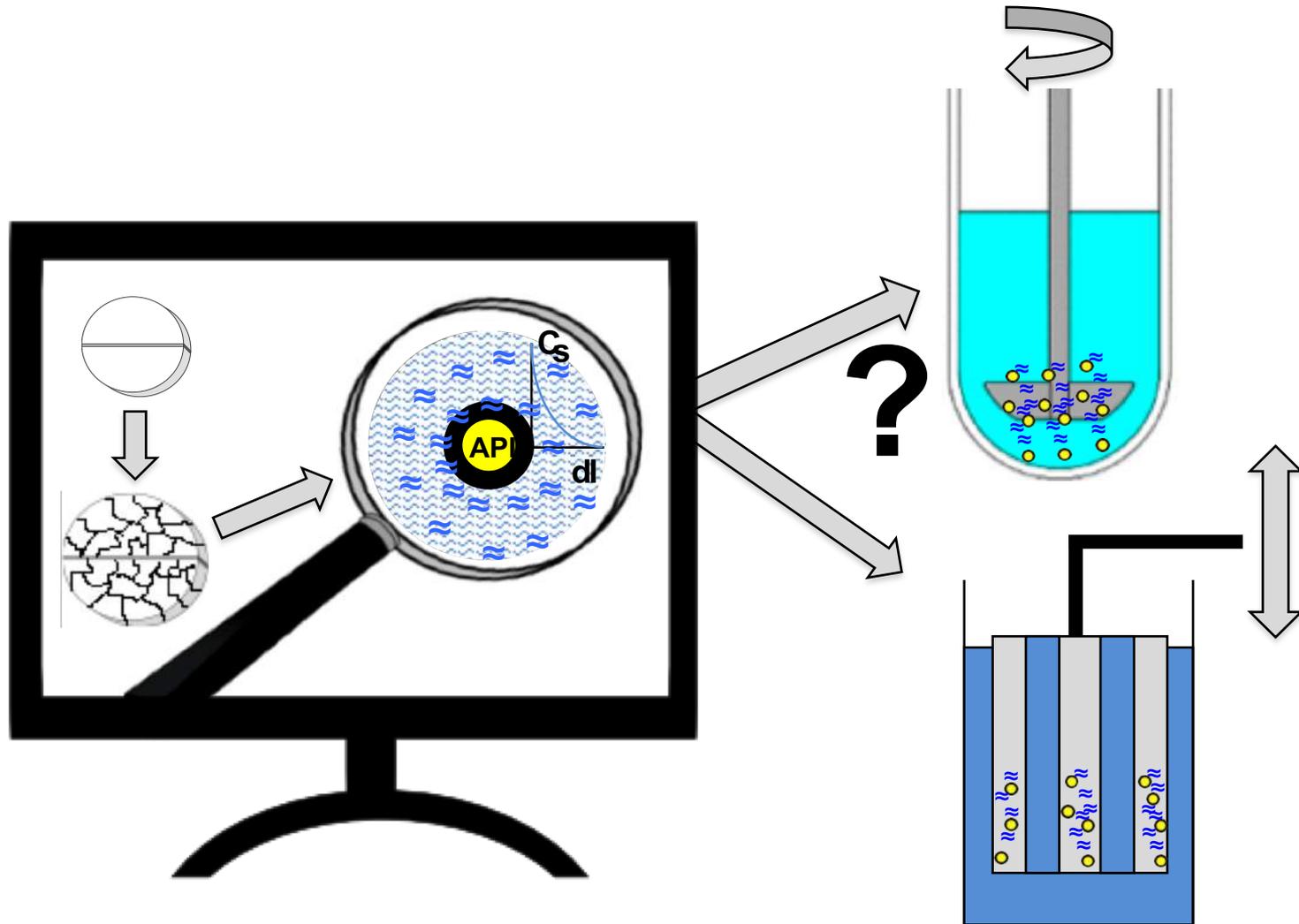
Comparison of the Rupture and Disintegration Tests for Soft-Shell Capsules

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Dissolution or Disintegration?

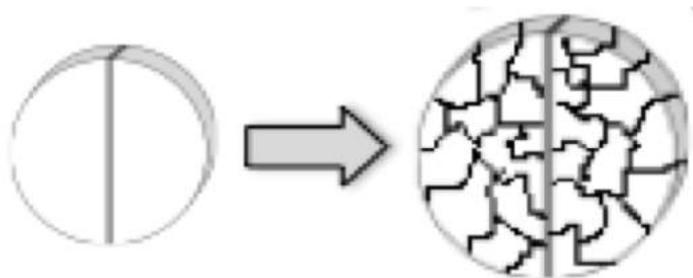


When to use which test?

The FDA draft guidance on “Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs” [U.S. Department of Health and Human Services, 2015](#) allows the use of disintegration testing as a surrogate for routine release and stability dissolution testing for certain BCS class 1 & 3 drug products. **The acceptance criteria is a 5 min disintegration time for drug products which passed a dissolution Q=80% within 15 min.**

Dissolution Controlled Dosage Forms

- **immediate release** oral drug products, such as **tablets** and capsules, are formulated to **release the active drug immediately after oral administration.**
- In the formulation **no deliberate effort is made to modify the drug release rate.**



Direct compression

Granulation:

Wet
Dry
Sinter

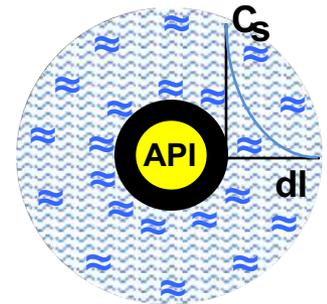
Q value

Immediate release a mechanistic view

Two cases:

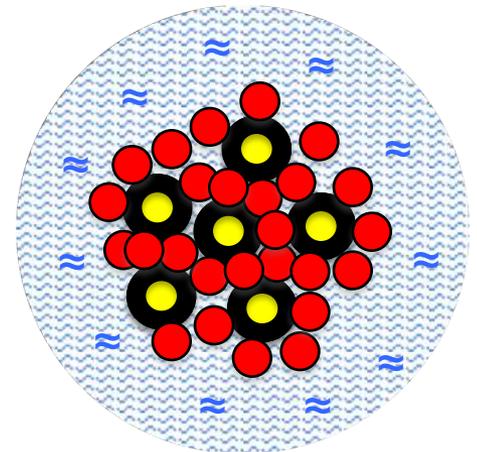
- 1) API driven Dissolution (drug particle properties)

- Example: direct compression

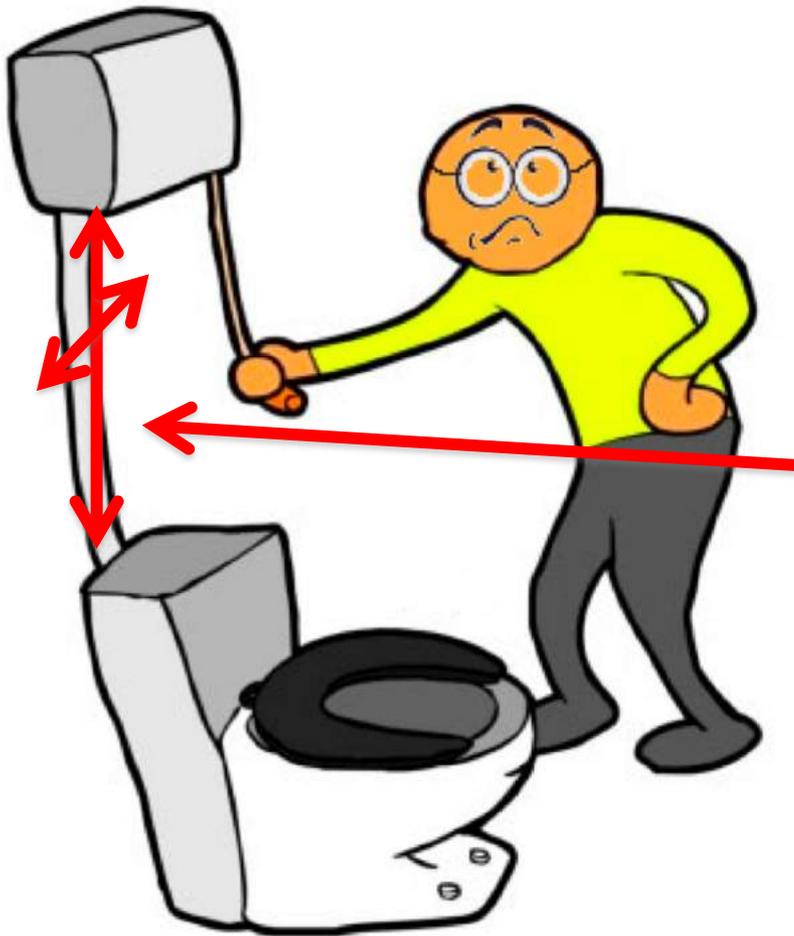


- 2) Formulation impacted or controlled dissolution (excipient API interaction – drug particles properties can not be linked to dissolution behavior)

- Example: wet granulation



Flushing a Toilet vs. opening a Faucet



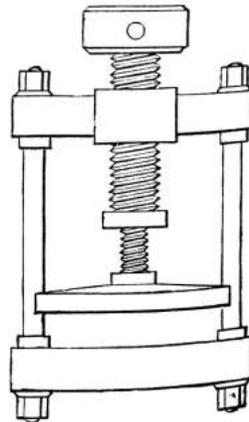
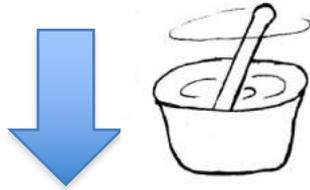
- The **rate** depends only on the **hydrostatic pressure** and **diameter of the pipe**
- Opening a faucet you can **control the amount and rate** of water



Two manufacturing methods

Direct compression

Drug
MCC
CaPO₄ X 2H₂O
Croscarmellose Na
Mg Stearate



FDT

Granulation

Drug
MCC
CaPO₄ X 2H₂O
Water
+
Croscarmellose Na
Mg Stearate



SET

Research Article

Evaluation of the DDSolver Software Applications

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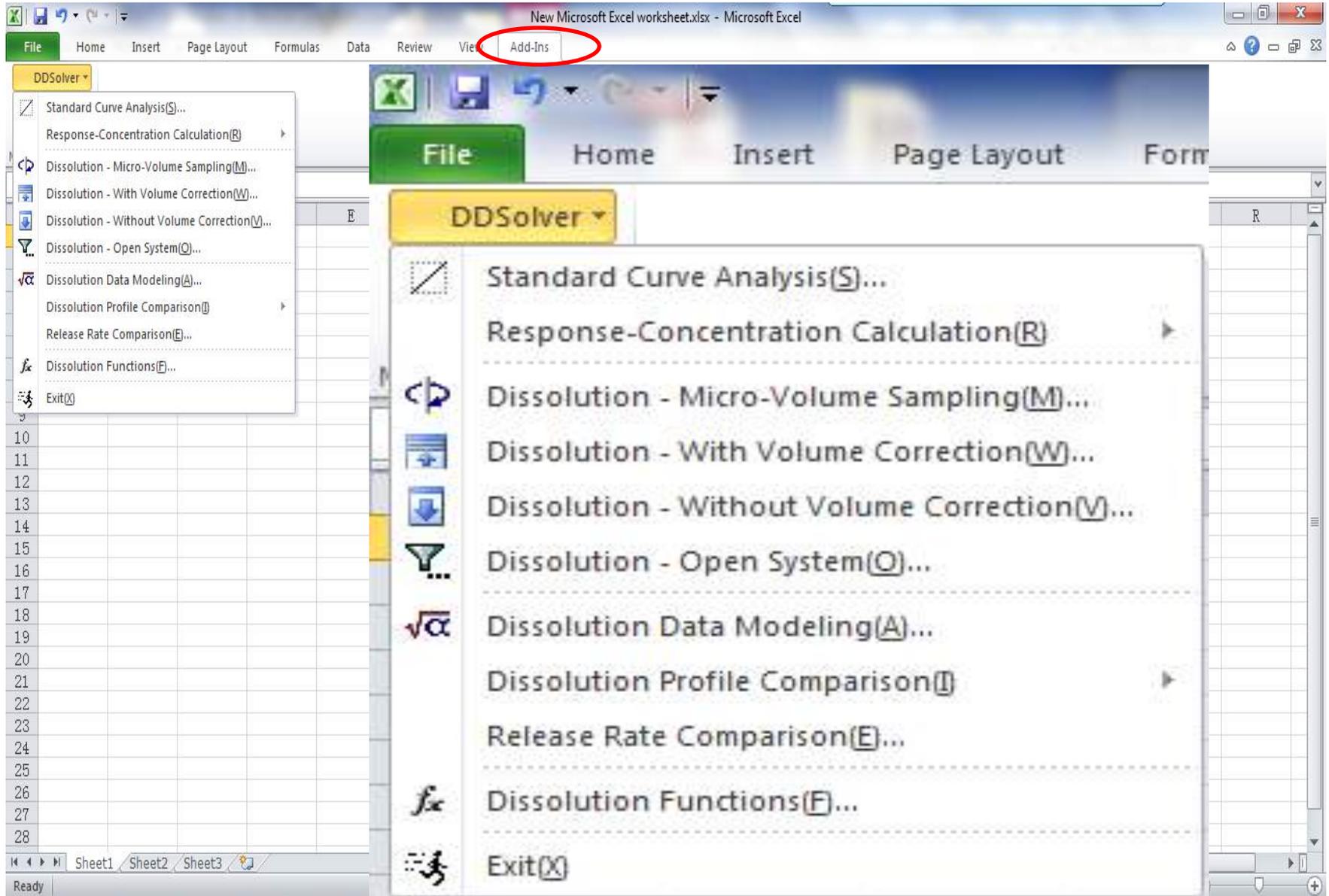
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When a new oral dosage form is developed, its dissolution behavior must be quantitatively analyzed. Dissolution analysis involves a comparison of the dissolution profiles and the application of mathematical models to describe the drug release pattern. This report aims to assess the application of the DDSolver, an Excel add-in software package, which is designed to analyze data obtained from dissolution experiments. The data used in this report were chosen from two dissolution studies. The results of the DDSolver analysis were compared with those obtained using an Excel worksheet. The comparisons among three different products obtained similarity factors (f_2) of 23.21, 46.66, and 17.91 using both DDSolver and the Excel worksheet. The results differed when DDSolver and Excel were used to calculate the release exponent “ n ” in the Korsmeyer-Peppas model. Performing routine quantitative analysis proved to be much easier using the DDSolver program than an Excel spreadsheet. The use of the DDSolver program reduced the calculation time and has the potential to omit calculation errors, thus making this software package a convenient tool for dissolution comparison.

Model Fitting using Excel-Add-In



Common release Models for IR and ER dosage forms

- Zero Order $F = k_0 \cdot t$
- First Order $F = 100 \cdot (1 - e^{-k_1 \cdot t})$
- Gompertz $F = 100 \cdot e^{-\alpha \cdot e^{-\beta \cdot \log(t)}}$
- Hixson Cromwel
$$F = 100 \cdot \left[1 - (1 - k_{\text{HC}} \cdot t)^3 \right]$$
- Hopfenberg $F = 100 \cdot [1 - (1 - k_{\text{HB}} \cdot t)^n]$
- Weibull $F = 100 \cdot \left[1 - e^{-\frac{(t-T_i)^\beta}{\alpha}} \right]$

Drug release mechanism

Korsmeyer

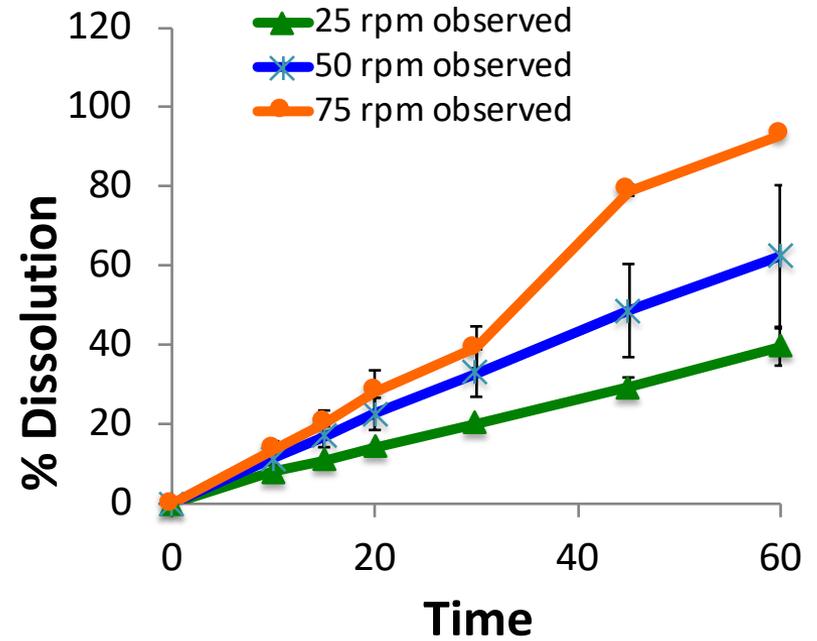
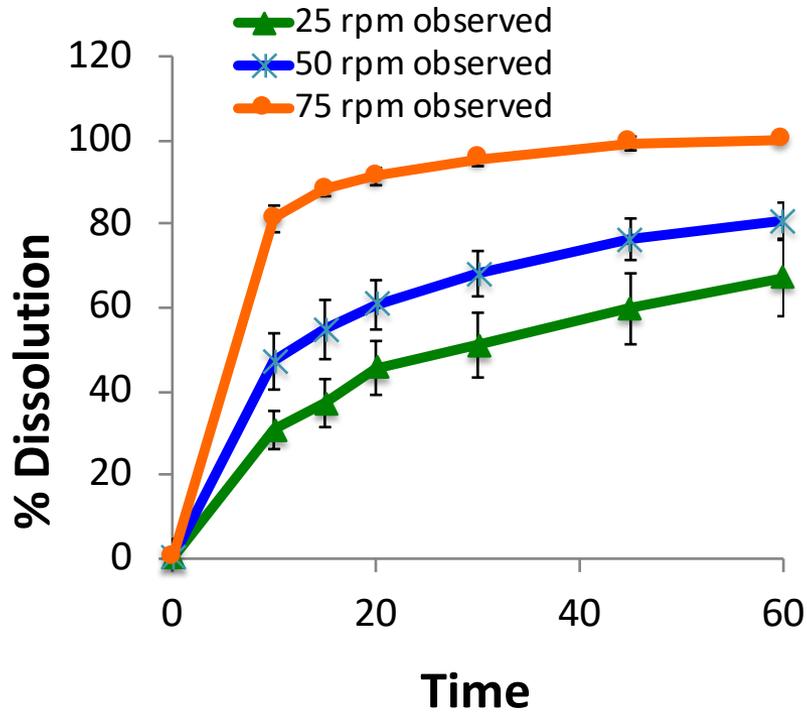
Peppas equation:

$$F = k_{KP} * t^n$$

Exponent n of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry

| n values | | | Drug release mechanism |
|-----------------|-------------------|---|--------------------------|
| Thin Film | Cylinder | Sphere | |
| 0.5 | 0.45 | 0.43 | Fickian Diffusion |
| $0.5 < n < 1.0$ | $0.45 < n < 0.89$ | $0.43 < n < 0.85$ | Anomalous Transport |
| 1 | 0.89 | 0.85 | Case-II Transport |

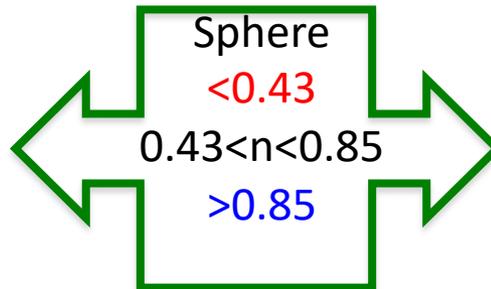
Fast Disintegrating Slow Eroding Tablet



Korsmeyer-Peppas n values

| | |
|----|-------|
| 75 | 0.111 |
| 50 | 0.293 |
| 25 | 0.413 |

Fickian Diffusion



Korsmeyer-Peppas n values

| | |
|----|-------|
| 75 | 1.11 |
| 50 | 0.938 |
| 25 | 0.924 |

Controlled Release

How to show that disintegration is the most important step?

ICH Guideline Q6A “Specifications: Test procedures and acceptance criteria for new drug substances and new drug products” outlines acceptance criteria for different dosage forms and routes of administration. The guidance document contains **decision tree #7.1, which allows disintegration testing to be used as a performance/quality control test if a relationship between dissolution and disintegration has been established**

U.S. Department of Health and Human Services, 1999

FDA Study 2009

Disintegration of Highly Soluble Immediate Release Tablets: A Surrogate for Dissolution

Abhay Gupta,¹ Robert L. Hunt,¹ Rakhi B. Shah,¹ Vilayat A. Sayeed,² and Mansoor A. Khan^{1,3}

Received 4 June 2008; accepted 1 March 2009; published online 23 April 2009

Abstract. The purpose of the work was to investigate correlation between disintegration and dissolution for immediate release tablets containing a high solubility drug and to identify formulations where disintegration test, instead of the dissolution test, may be used as the acceptance criteria based on International Conference on Harmonization Q6A guidelines. A statistical design of experiments was used to study the effect of filler, binder, disintegrating agent, and tablet hardness on the disintegration and dissolution of verapamil hydrochloride tablets. All formulation variables, i.e., filler, binder, and disintegrating agent, were found to influence tablet dissolution and disintegration, with the filler and disintegrating agent exerting the most significant influence. Slower dissolution was observed with increasing disintegration time when either the filler or the disintegrating agent was kept constant. However, no direct corelationship was observed between the disintegration and dissolution across all formulations due to the interactions between different formulation components. Although all tablets containing sodium carboxymethyl cellulose as the disintegrating agent, disintegrated in less than 3 min, half of them failed to meet the US Pharmacopeia 30 dissolution criteria for the verapamil hydrochloride tablets highlighting the dependence of dissolution process on the formulation components other than the disintegrating agent. The results identified only one formulation as suitable for using the disintegration test, instead of the dissolution test, as drug product acceptance criteria and highlight the need for systematic studies before using the disintegration test, instead of the dissolution test as the drug acceptance criteria.

FDA Study 2009

Disintegration of Highly Soluble Immediate Release Tablets: A Surrogate for Dissolution

Abhay Gupta,¹ Robert L. Hunt,¹ Rakhi B. Shah,¹ Vilayat A. Sayeed,² and Mansoor A. Khan^{1,3}

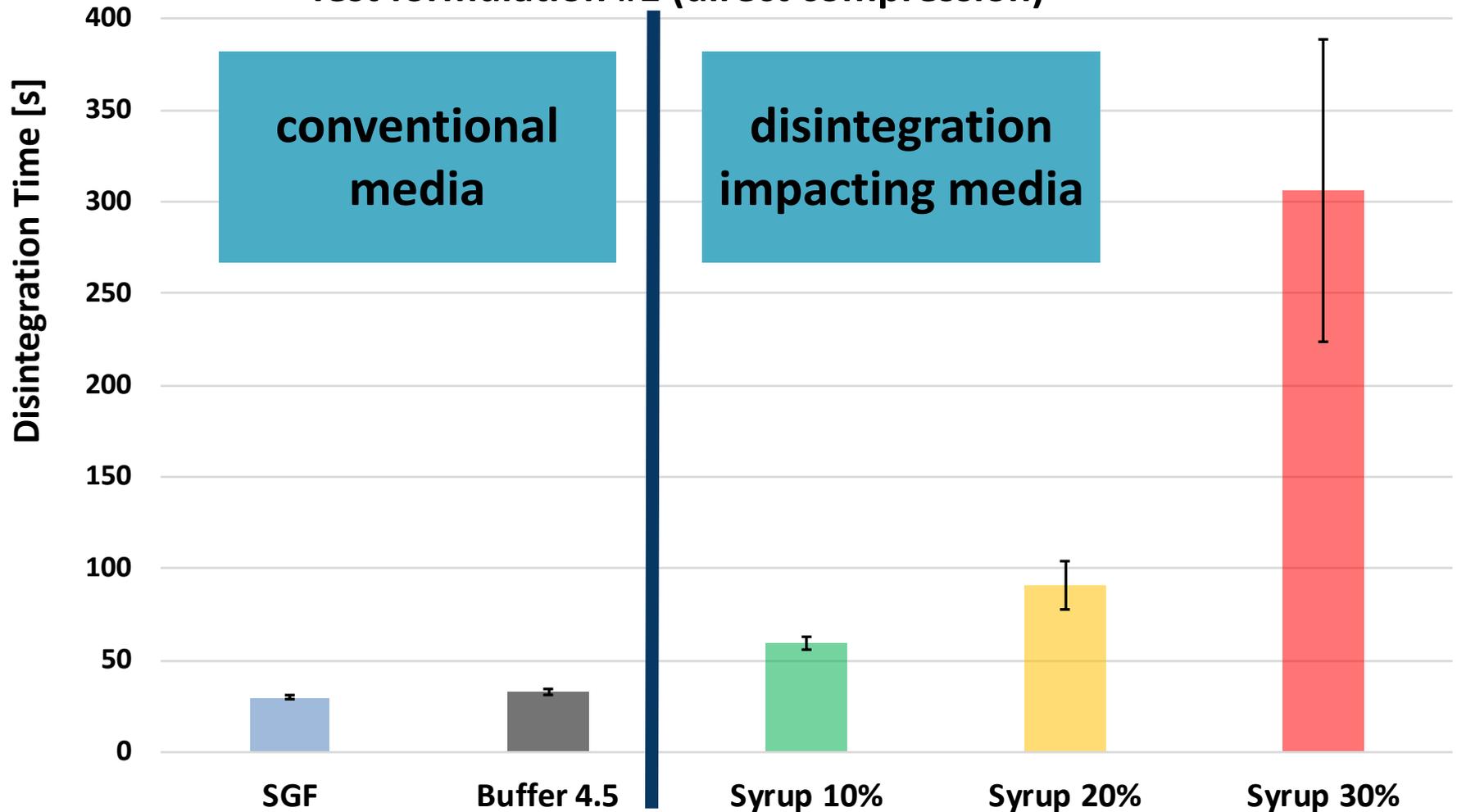
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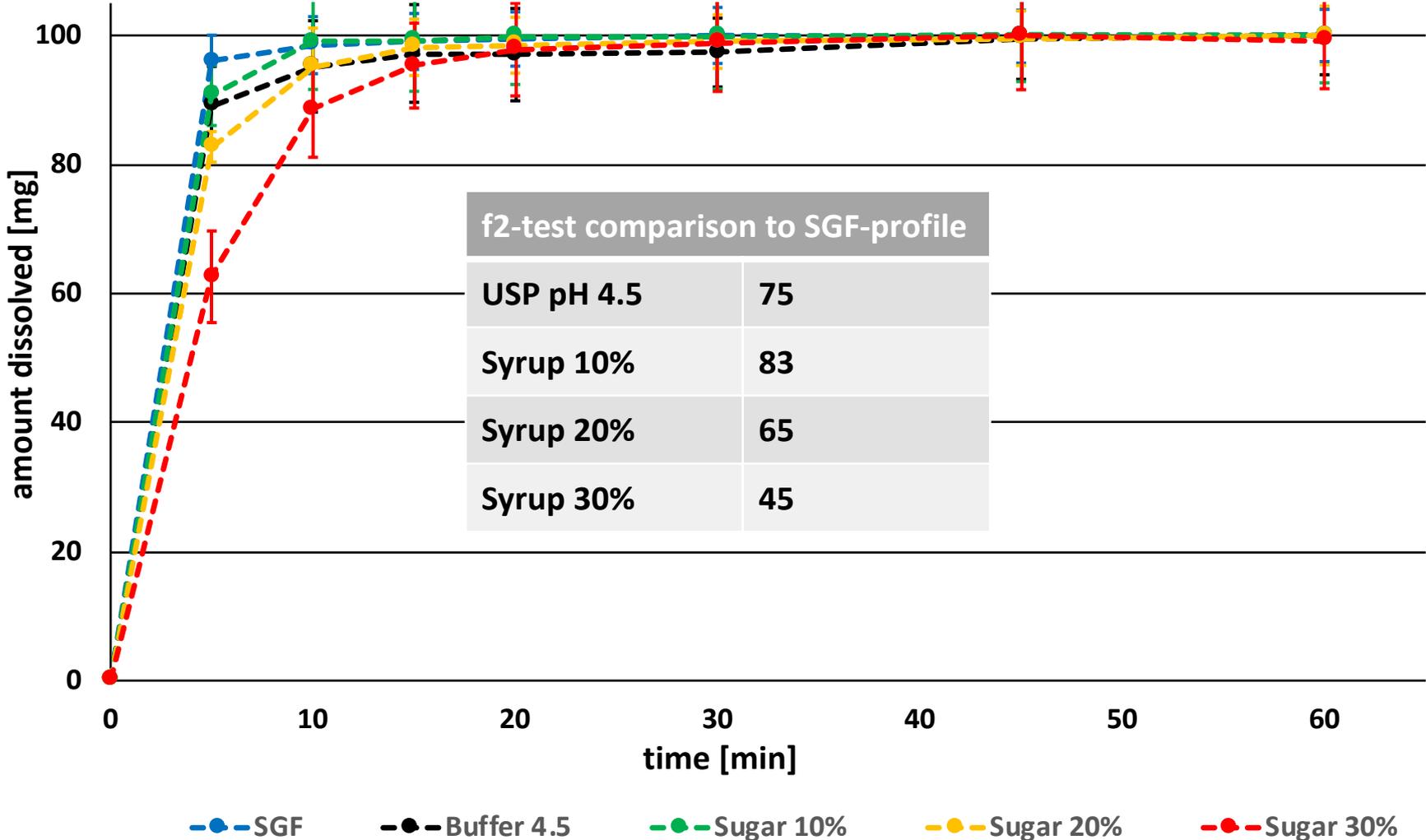
New method: Impact of immersion media on disintegration

Effect of dissolution medium on disintegration
Test formulation #1 (direct compression)



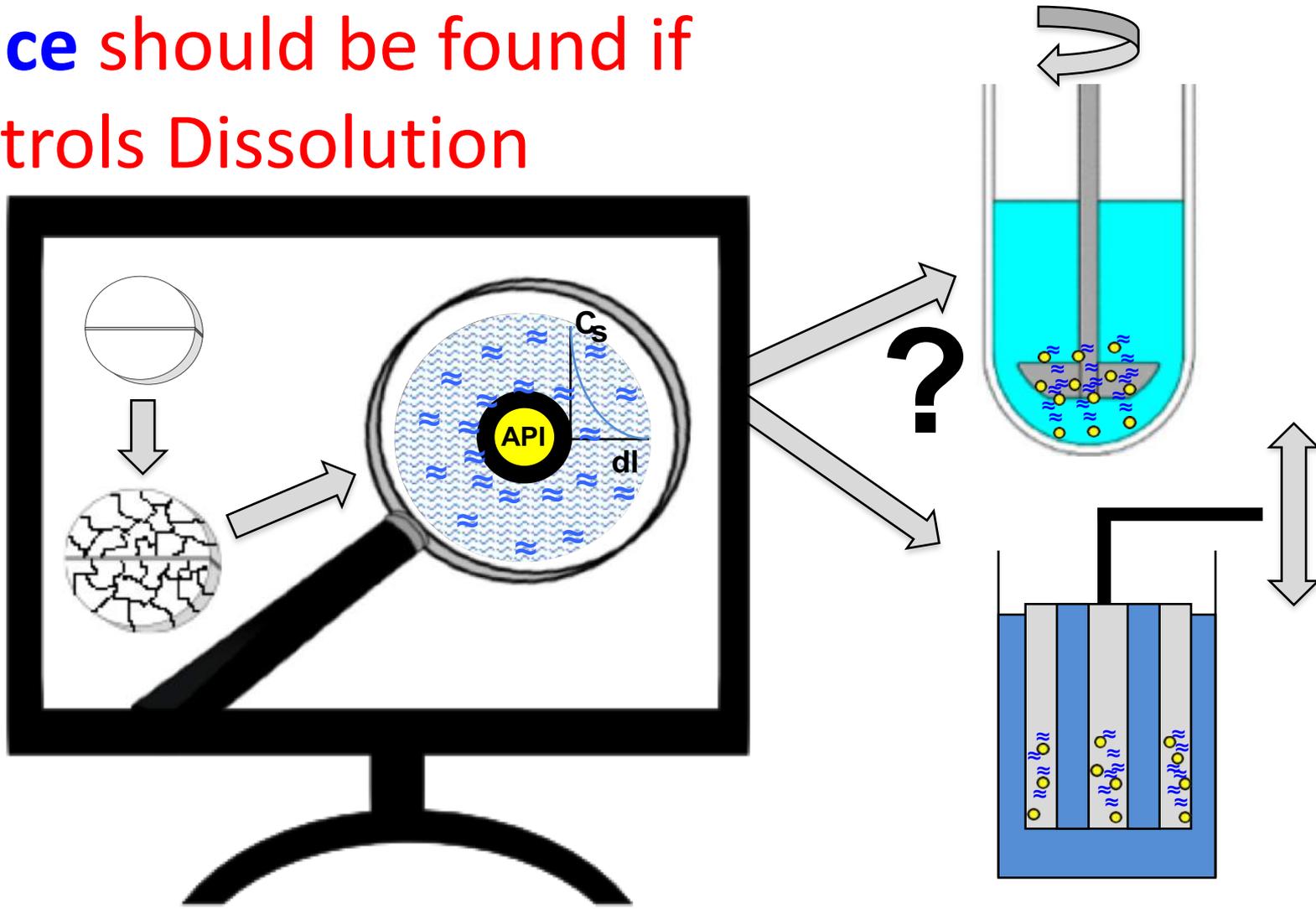
Dissolution test: media impact with formulation

Test formulation #1 (direct compression)



For certain Formulations Disintegration and Dissolution are Sequential Processes

No correlation other than the Sequence should be found if API controls Dissolution



Justification of disintegration testing beyond current FDA criteria using in vitro and in silico models

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11 April 2017

[Number of times this article has been viewed](#)

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Abstract: Drug product performance testing is an important part of quality-by-design approaches, but this process often lacks the underlying mechanistic understanding of the complex interactions between the disintegration and dissolution processes involved. Whereas a recent draft guideline by the US Food and Drug Administration (FDA) has allowed the replacement of dissolution testing with disintegration testing, the mentioned criteria are not globally accepted. This study provides scientific justification for using disintegration testing rather than dissolution testing as a quality control method for certain immediate release (IR) formulations. A mechanistic approach, which is beyond the current FDA criteria, is presented. Dissolution testing via United States Pharmacopeial Convention Apparatus II at various paddle speeds was performed for immediate and extended release formulations of metronidazole. Dissolution profile fitting via DDSolver and dissolution profile predictions via DDDPlus™ were performed. The results showed that Fickian diffusion and drug particle properties (DPP) were responsible for the dissolution of the IR tablets, and that formulation factors (eg, coning) impacted dissolution only at lower rotation speeds. Dissolution was completely formulation controlled if extended release tablets were tested and DPP were not important. To demonstrate that disintegration is the most important dosage form attribute when

a

CH

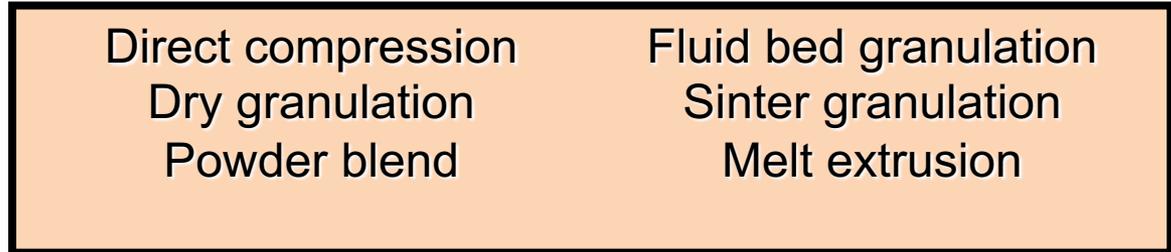
- It was found that disintegration and dissolution can be sequential or parallel processes, or both.
- If disintegration occurs first, API dependent dissolution can happen and disintegration can be used as performance test of rapidly disintegrating tablets beyond the current FDA criteria.
- The scientific data needed for this justification being, that dissolution is API dependent and formulation factors have to be negligible for the dissolution process.
- This approach will enable globally operating pharmaceutical companies to scientifically justify their product specifications for disintegration independent from national – sometimes contradicting – regulatory guidance documents.

PHASE 1/2 R&D DEVELOPMENT

**Capsule
Tablet or ODT/FDT**

Dosage form

Manufacturing
process



R&D
Development

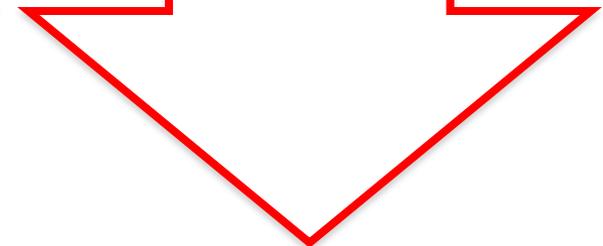
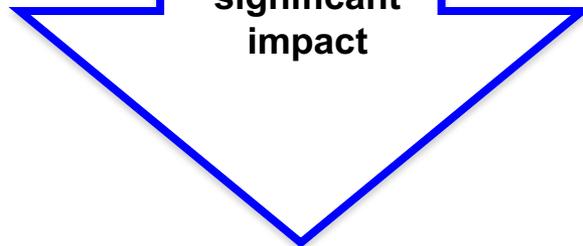


Proposed New
Formulation
Classification:

API vs.

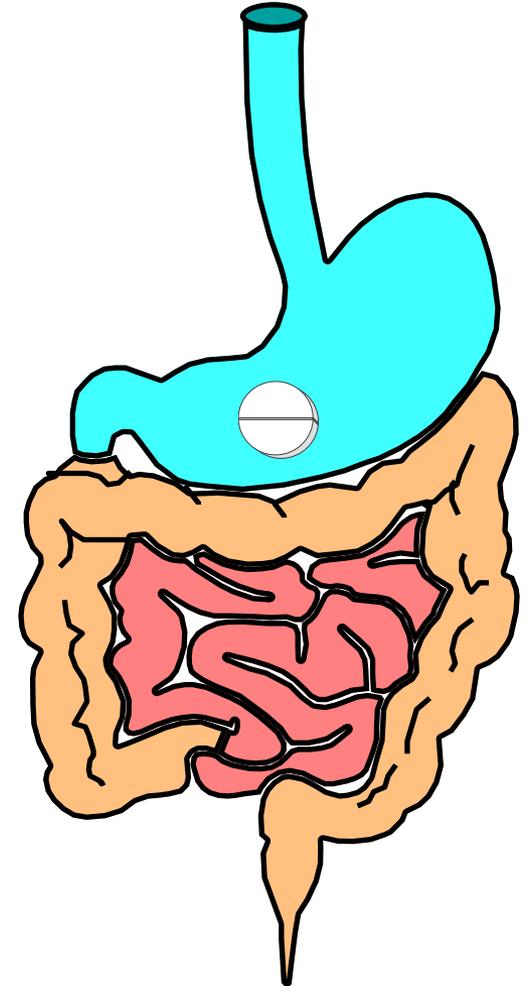
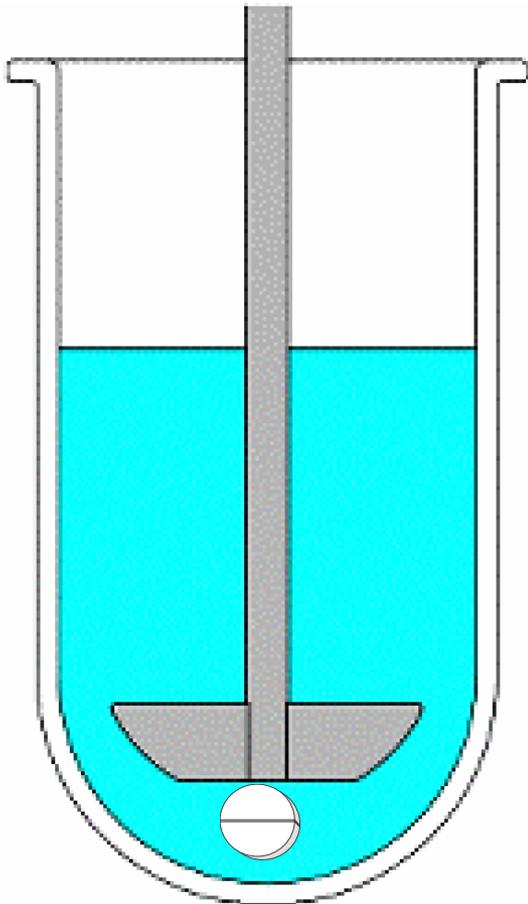
Formulation

Controlled Dissolution



QC Method

In Vitro vs. In Vivo Dissolution Mechanistic considerations



Review Article

Evolution of Choice of Solubility and Dissolution Media After Two Decades of Biopharmaceutical Classification System

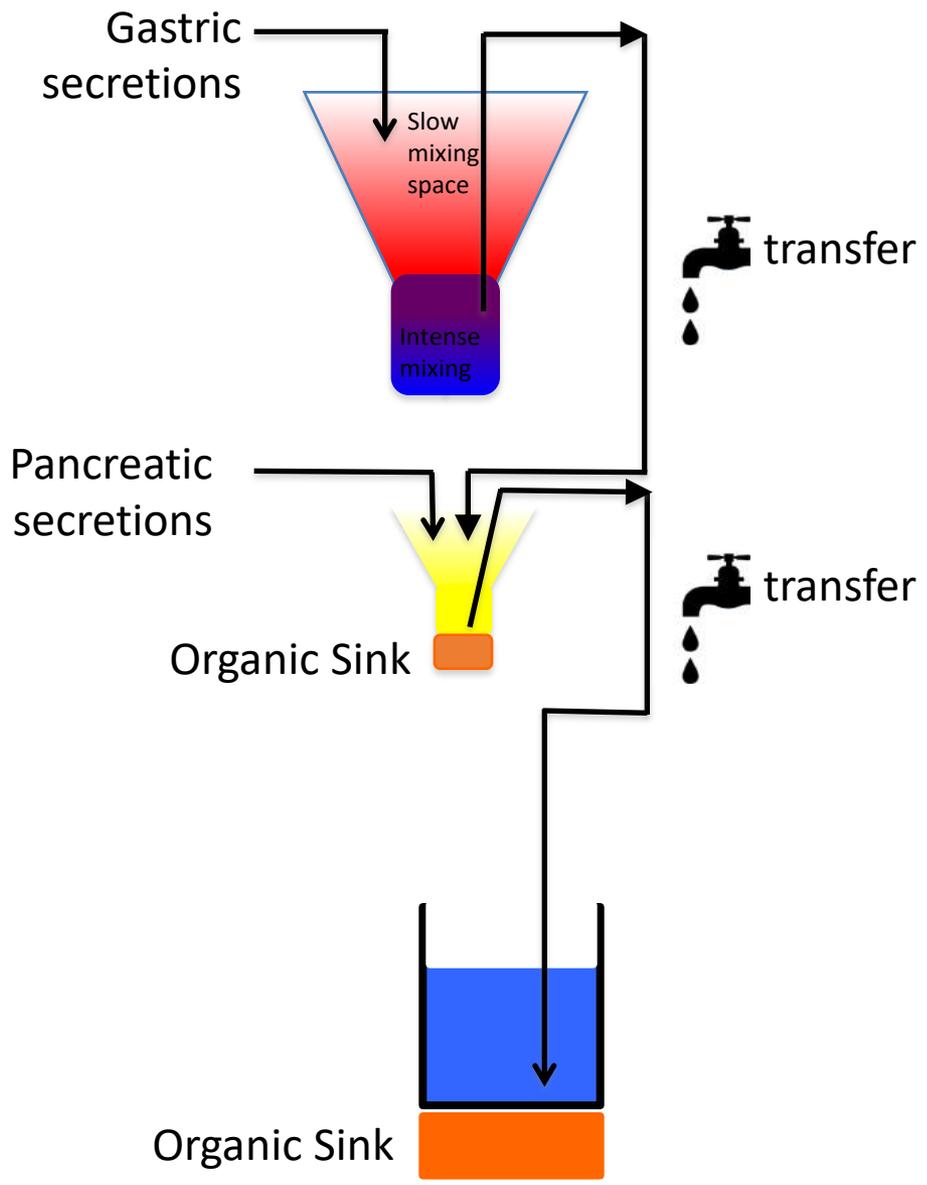
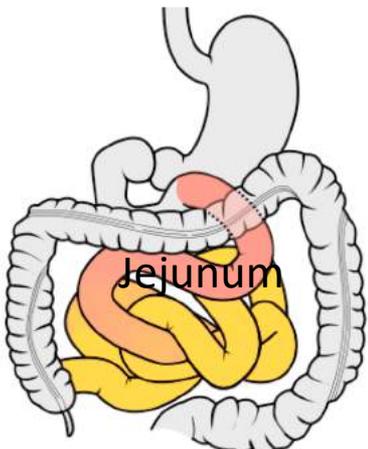
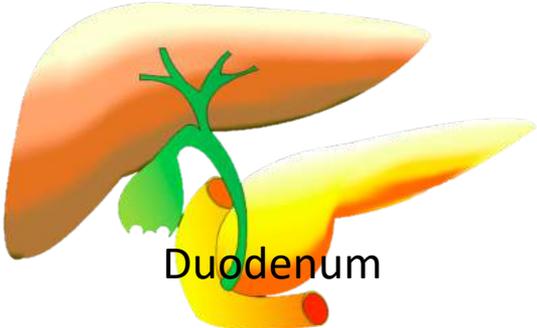
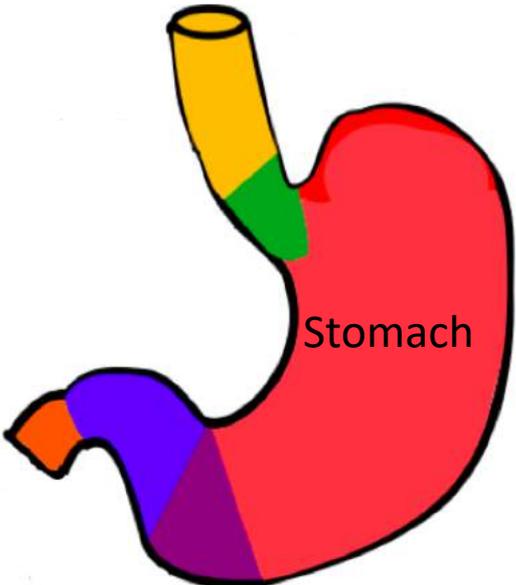
Nadia Bou-Chacra,¹ Katherine Jasmine Curo Melo,¹ Ivan Andrés Cordova Morales,¹ Erika S. Stippler,² Filippou Kesisoglou,³ Mehran Yazdanian,⁴ and Raimar Löbenberg^{5,6} 

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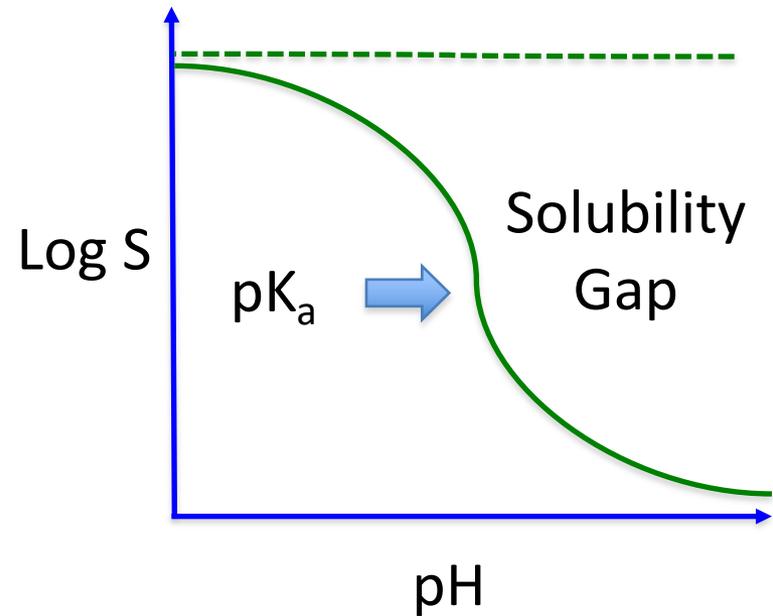
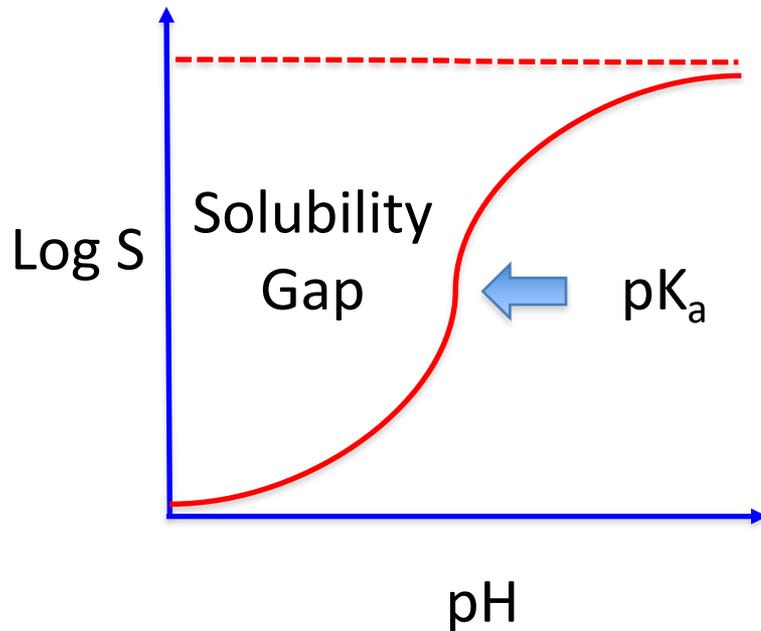
Abstract. The introduction of the biopharmaceutics drug classification system (Biopharmaceutics Classification System (BCS)), in 1995, provided a simple way to describe the biopharmaceutics behavior of a drug. Solubility and permeability are among the major parameters, which determine the fraction dose absorbed of a drug substance and consequently its oral bioavailability. The evolution of the dissolution media used in modern biopharmaceutics, such as buffers were introduced for the dissolution of drugs, solubilization media, and universal medium for a drug product's *in vitro* and additions made to the phosphate concentrations in buffers seem to be too high to correlate with the carbonate buffer concentrations *in vivo*. Biorelevant media were updated to correlate them better with the composition of human intestinal fluids. The BCS was introduced into regulatory sciences as a scientific risk management tool to waive bioequivalence studies under certain conditions. Today's different guidance documents define the dose-solubility ratio differently. As shown for amoxicillin, this can cause more confusion than certainty for globally operating companies. Harmonization of BCS guidelines is highly desirable.

At this time point, there is no universal medium available which can be used to predict every drug substance's solubility or a drug product's *in vivo* dissolution behavior.

anatomy & in vitro model



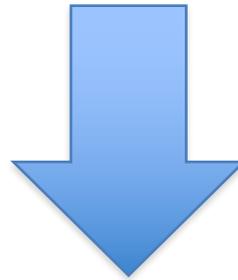
Solubility vs. pH Profile for **Acids** and **Bases** and their potential Solubility Gap



R&D Consideration for Dissolution Test Development BCS Sub-Classification

| | |
|---------|---------|
| BCS 1/3 | Acids |
| | Base |
| | Neutral |

| | |
|---------|---------|
| BCS 2/4 | Acids |
| | Base |
| | Neutral |



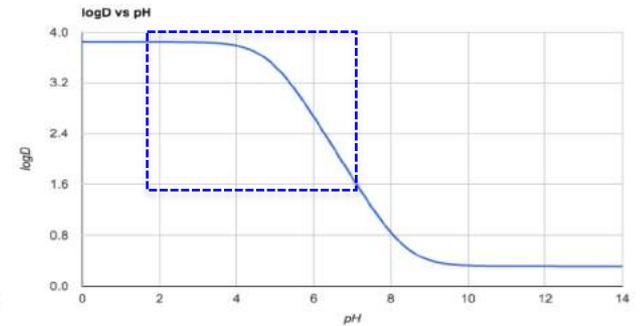
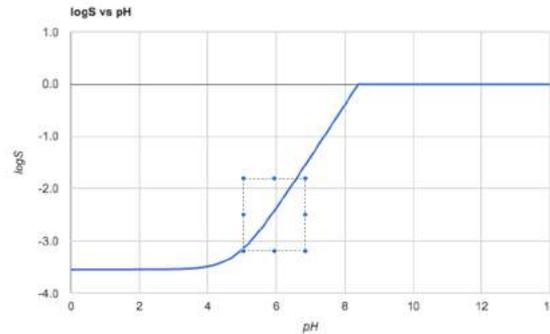
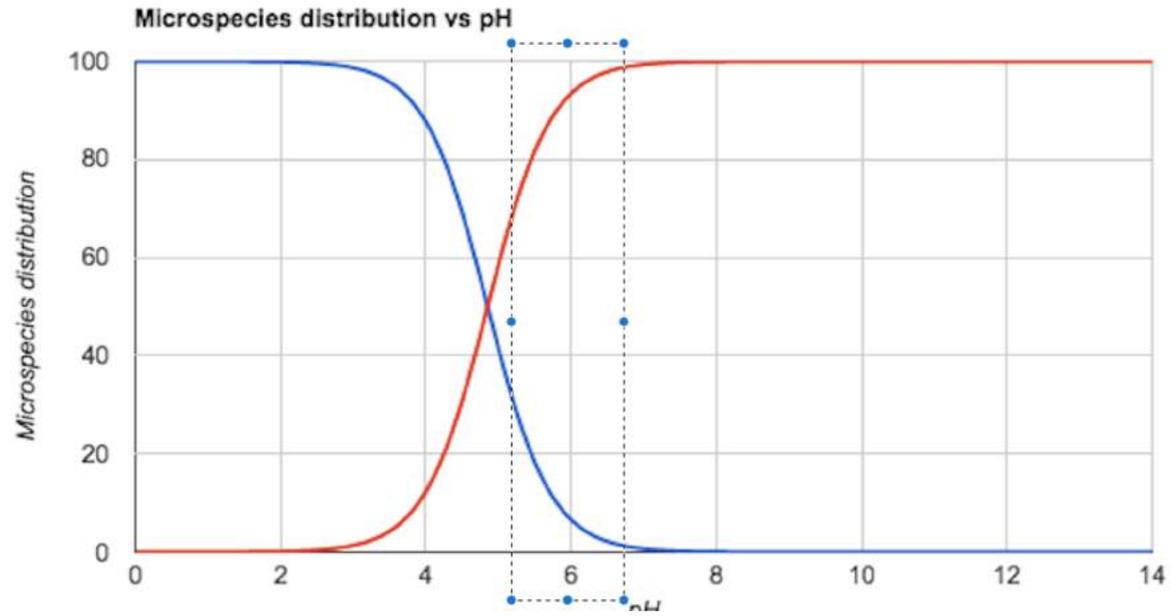
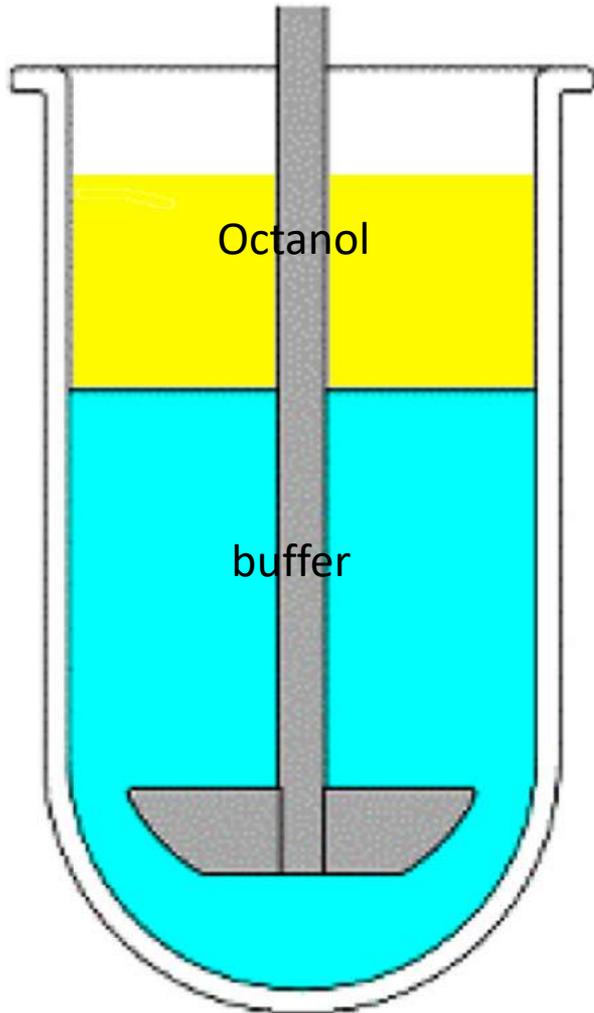
| | |
|----------------------|----------------------|
| Low dose / Fast Abs | Low dose / Slow Abs |
| High Dose / Fast Abs | High dose / Slow Abs |

High dose R&D investigations

Possible dissolution requirements

| | | | | |
|----------------------|-------|---------|---------------------------|-----------|
| High dose / Fast Abs | BCS 1 | Acids | transfer model | Biphasic |
| | | Base | transfer model | Biphasic |
| | | Neutral | Single vessel dissolution | Biphasic |
| High dose / Fast Abs | BCS 2 | Acids | transfer model | Biphasic |
| | | Base | transfer model | Biphasic |
| | | Neutral | Single vessel dissolution | Biphasic |
| High dose / Slow Abs | BCS 3 | Acids | Single vessel dissolution | Biphasic? |
| | | Base | transfer model | Biphasic? |
| | | Neutral | Single vessel dissolution | Biphasic? |
| High dose / Slow Abs | BCS 4 | Acids | transfer model | Biphasic? |
| | | Base | transfer model | Biphasic? |
| | | Neutral | Single vessel dissolution | Biphasic? |

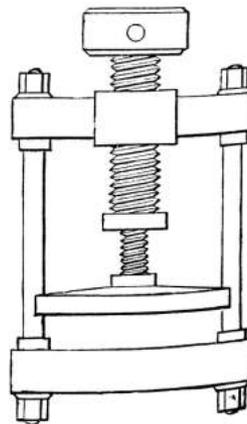
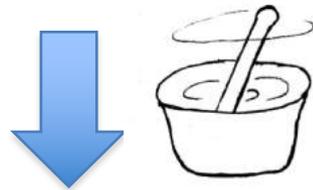
BIPHASIC – Dissolution Ibuprofen



Ibuprofen

Direct compression

Ibuprofen
MCC
CaPO₄ X 2H₂O
Croscarmellose Na
Mg Stearate



Granulation

Ibuprofen
MCC
CaPO₄ X 2H₂O
Water



Croscarmellose Na
Mg Stearate



Excipients characteristics

(Handbook of Pharmaceutical Excipients)

| | MCC (Avicel PH102) | Dextrose Monohydrate | CaHPO4 |
|------------|---|--|-------------------------------------|
| Solubility | -- | ++ | --- |
| pH | 5.0 - 7.0 | 3.5 – 5.5 | 7.4 |
| Uses | Adsorbent; suspending agent; tablet and capsule diluent (20-90%) ; tablet Disintegrant | Tablet and capsule diluent ; therapeutic agent; tonicity agent; sweetening agent. Binder as well | Tablet and capsule diluent . |

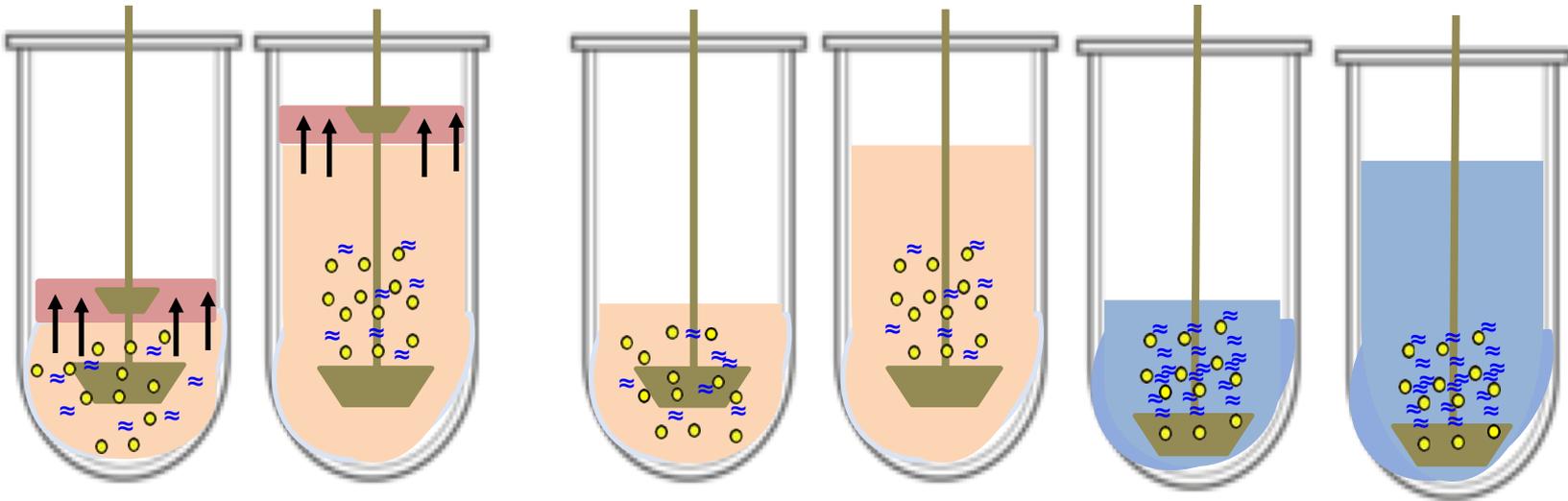


Wet granulation

Direct compression

Different excipient composition

Different excipient composition



200mL

900mL

200mL

900mL

200mL

900mL

BIPHASIC DISSOLUTION
Phosphate buffer 5mM
+ Octanol

Phosphate buffer 5mM

Phosphate buffer USP
strength

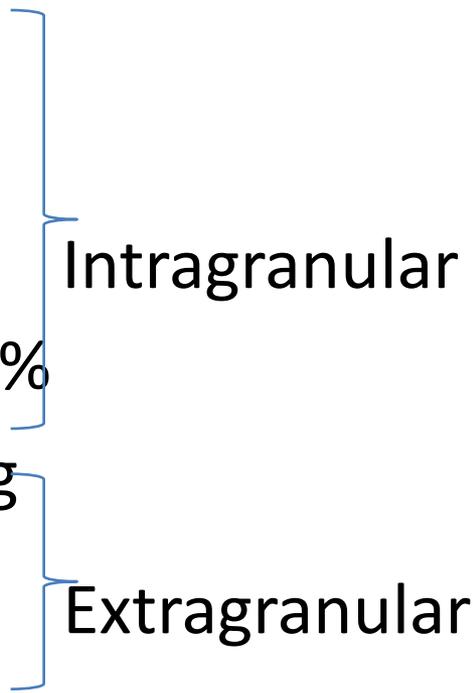
Microcrystalline Cellulose formulations

Direct Compression D formulation

Ibuprofen – 400mg
Avicel PH102 – 800mg
Croscarmellose Na – 3%
Mg Stearate – 1%

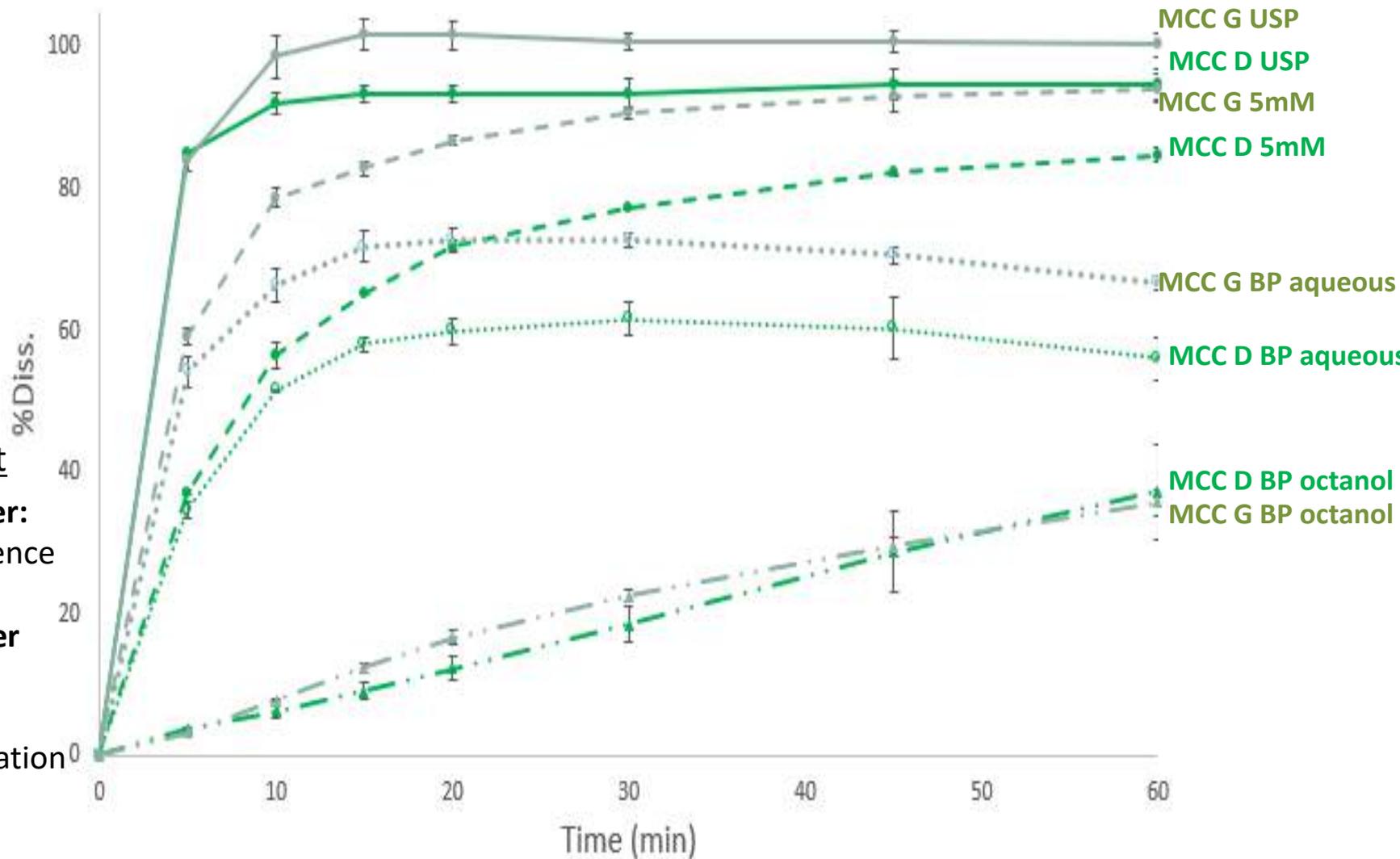
Wet Granulation G formulation

Ibuprofen – 400mg
Avicel PH102 – 800mg
Croscarmellose Na – 5%
Starch 1500* – 210mg
Mg Stearate – 1%

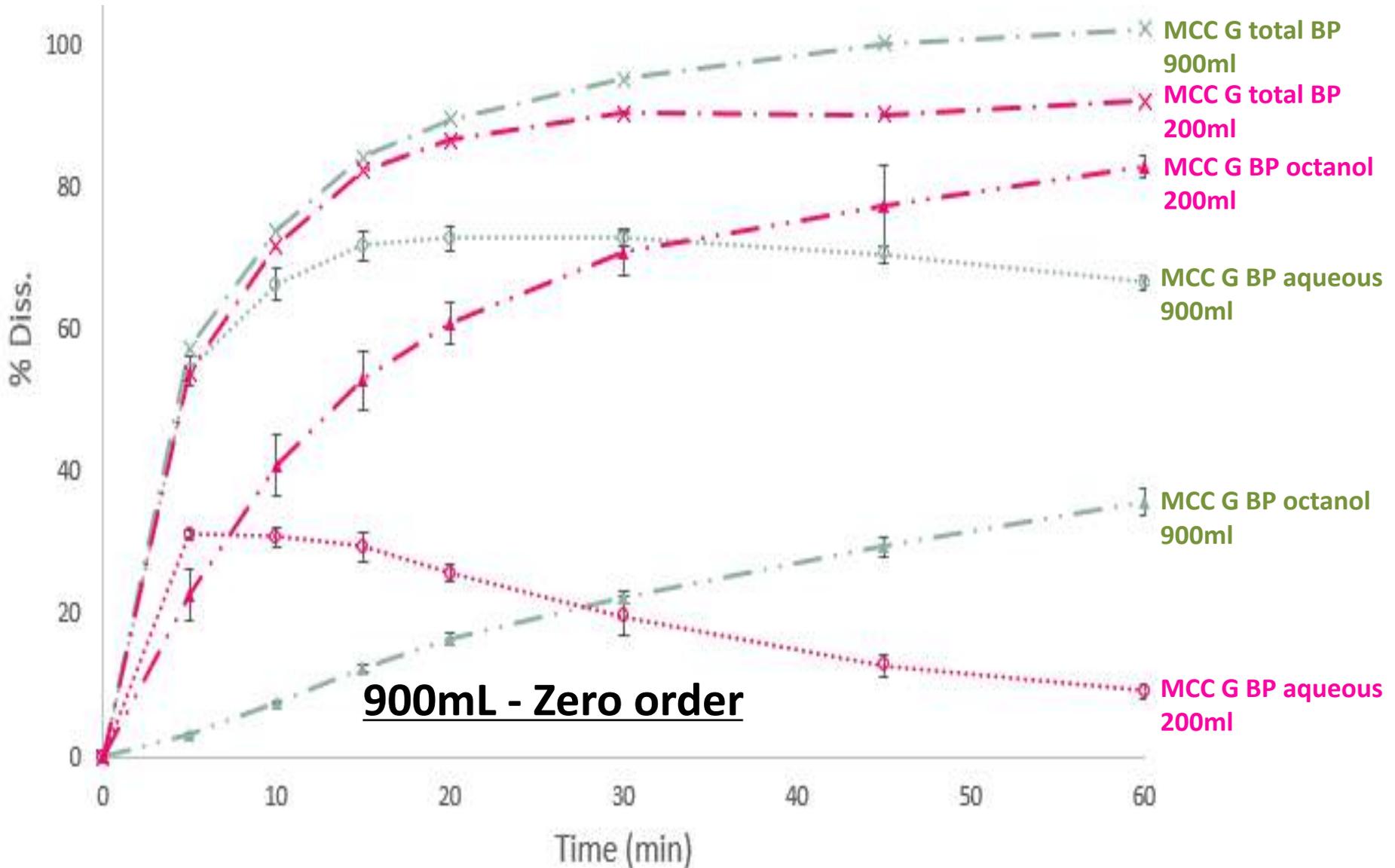


Granulation liquid: EtOH 70%
*Added as powder

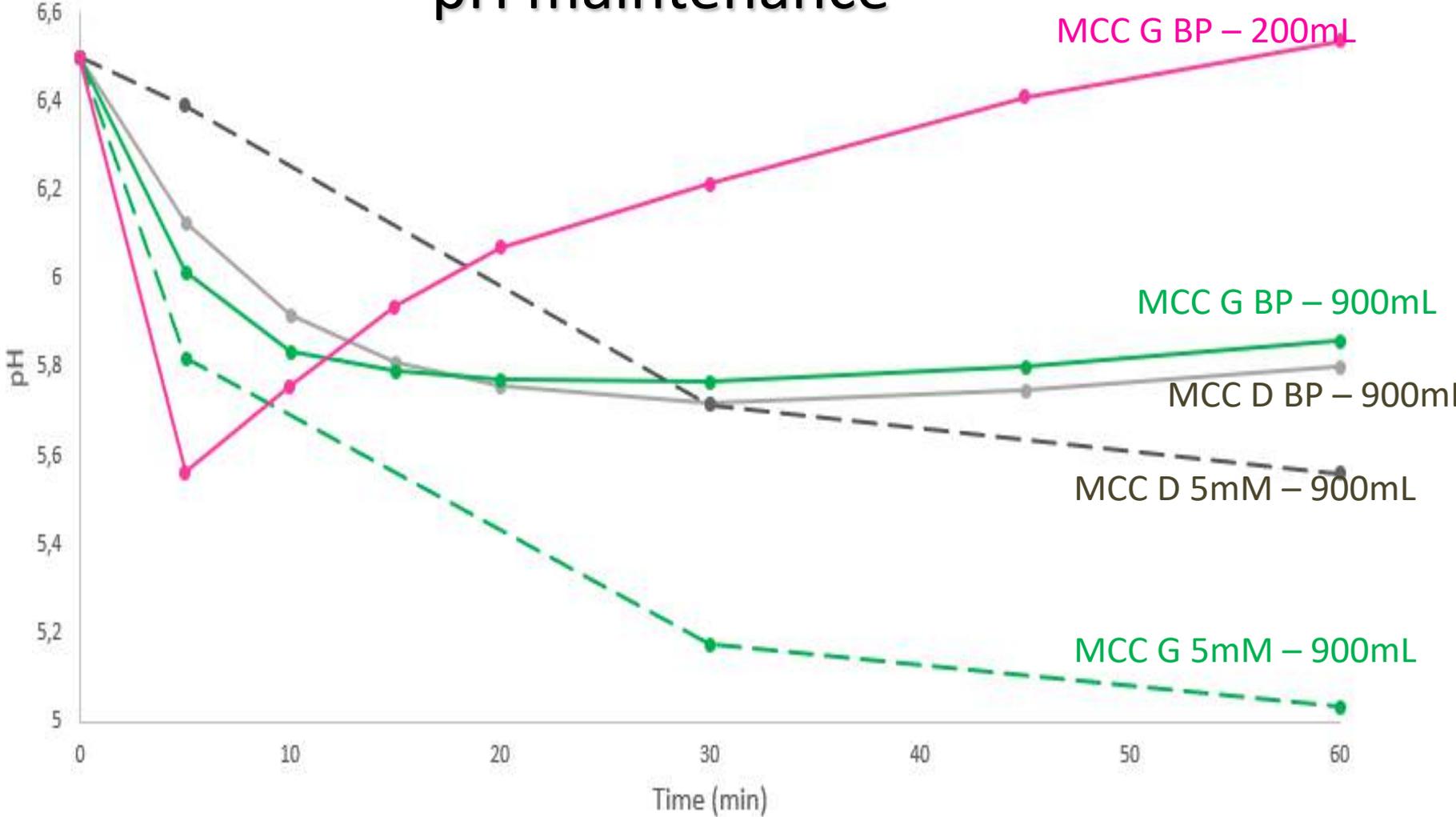
Overview G and D tablets in 900mL



MCC G tablets – 900ml vs 200ml



Additional sink assisted on medium pH maintenance



CaHPO₄ FORMULATIONS

Direct Compression

Ibuprofen – 400mg
Avicel PH102 – 400mg
CaHPO₄ - 400mg
Croscarmellose Na –
3%
Mg Stearate – 1%

Wet Granulation

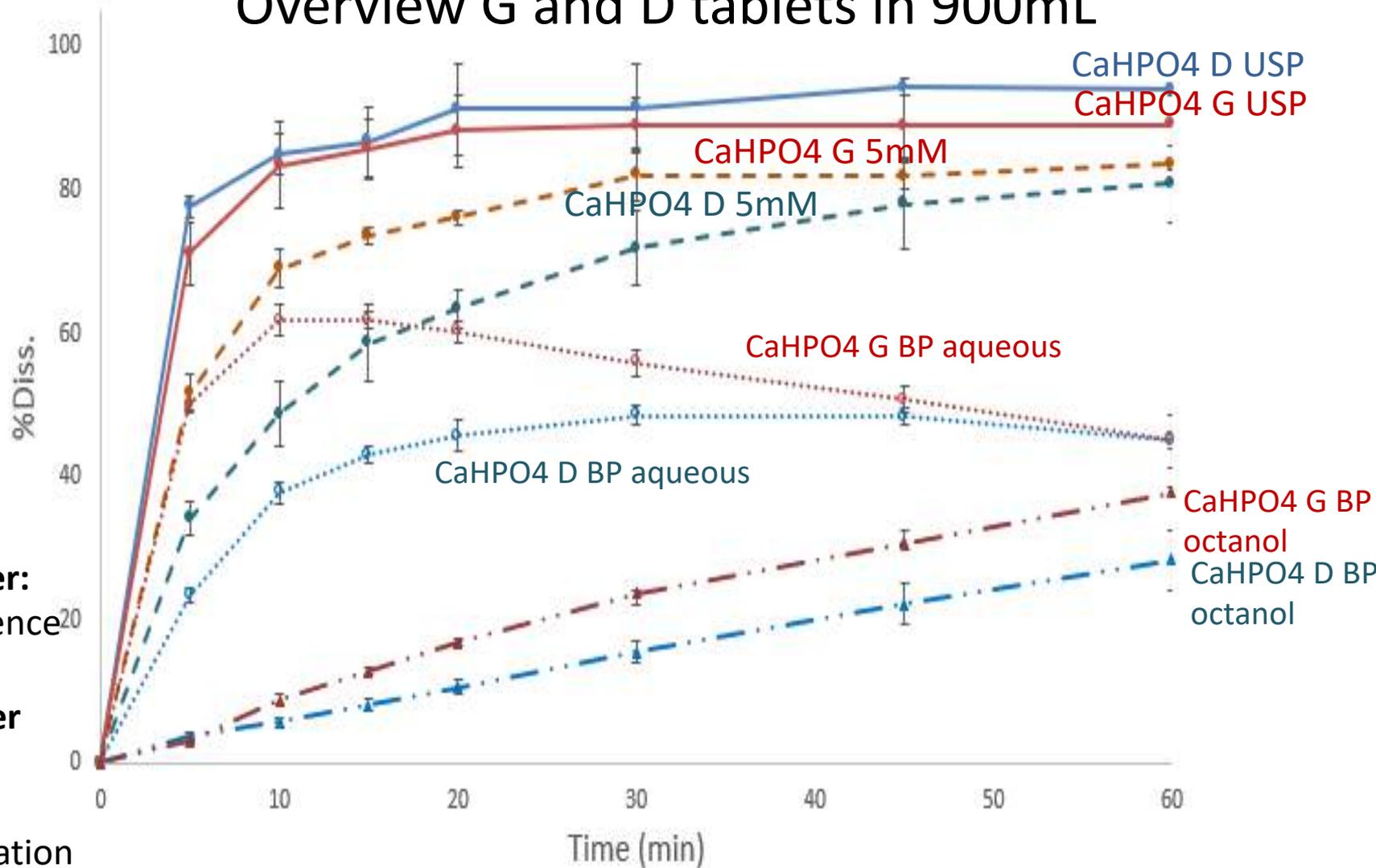
Ibuprofen – 400mg
Avicel PH102 – 400mg
CaHPO₄ – 400mg
Croscarmellose Na – 5%
Starch 1500* – 210mg

Mg Stearate – 1%

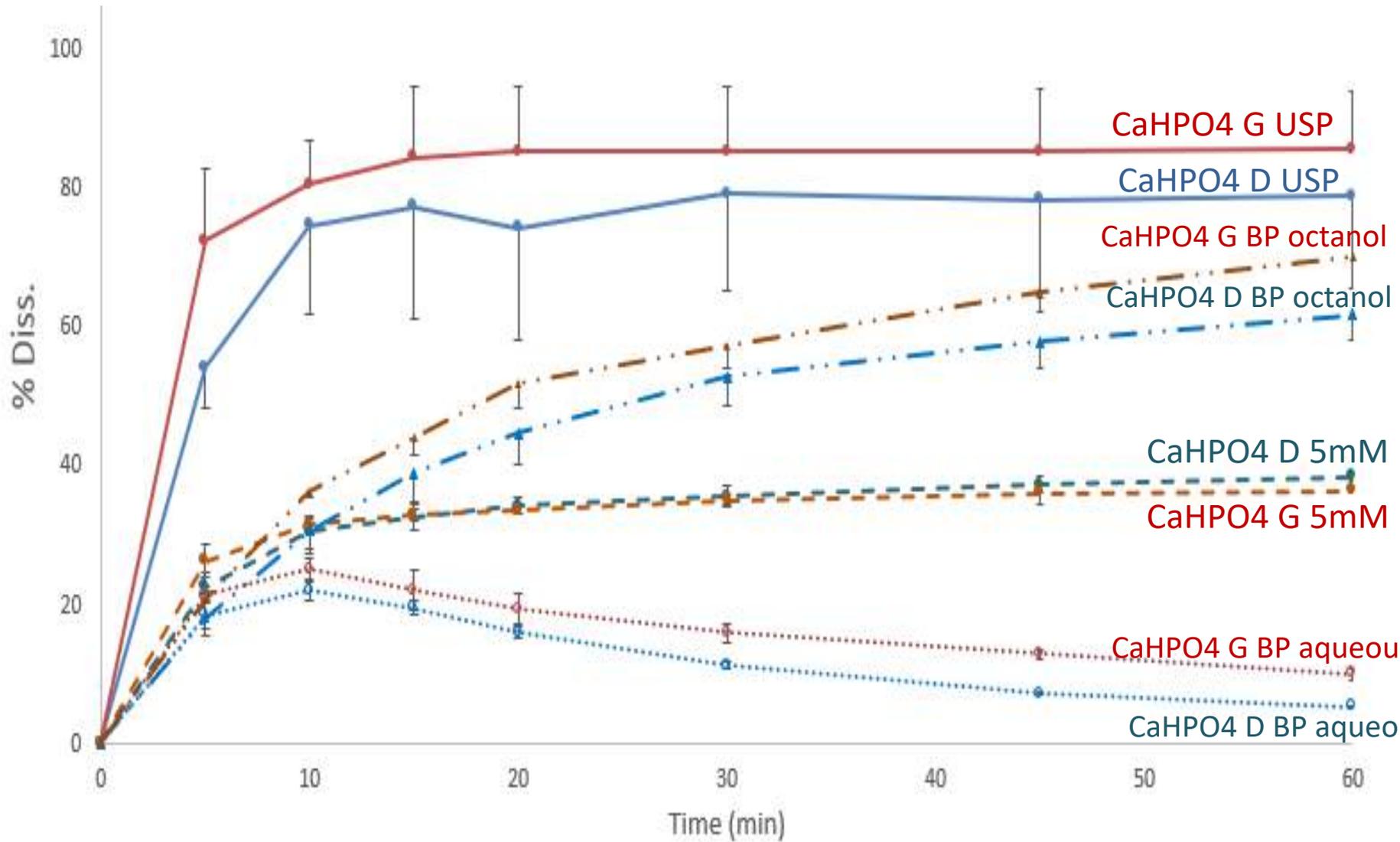
+ Granulation liquid: EtOH 70%

- Extragranular
- Intragranular

Overview G and D tablets in 900mL



Overview G and D tablets in 200mL



Dextrose monohydrate formulations

Direct Compression

Ibuprofen – 400mg
Avicel PH102 – 400mg
Dextrose - 400mg
Croscarmellose Na –
3%
Mg Stearate – 1%

Wet Granulation

Ibuprofen – 400mg
Avicel PH102 – 400mg
Dextrose – 400mg
Croscarmellose Na – 5%
Starch 1500* – 210mg

Mg Stearate – 1%

Granulation liquid: EtOH 70%

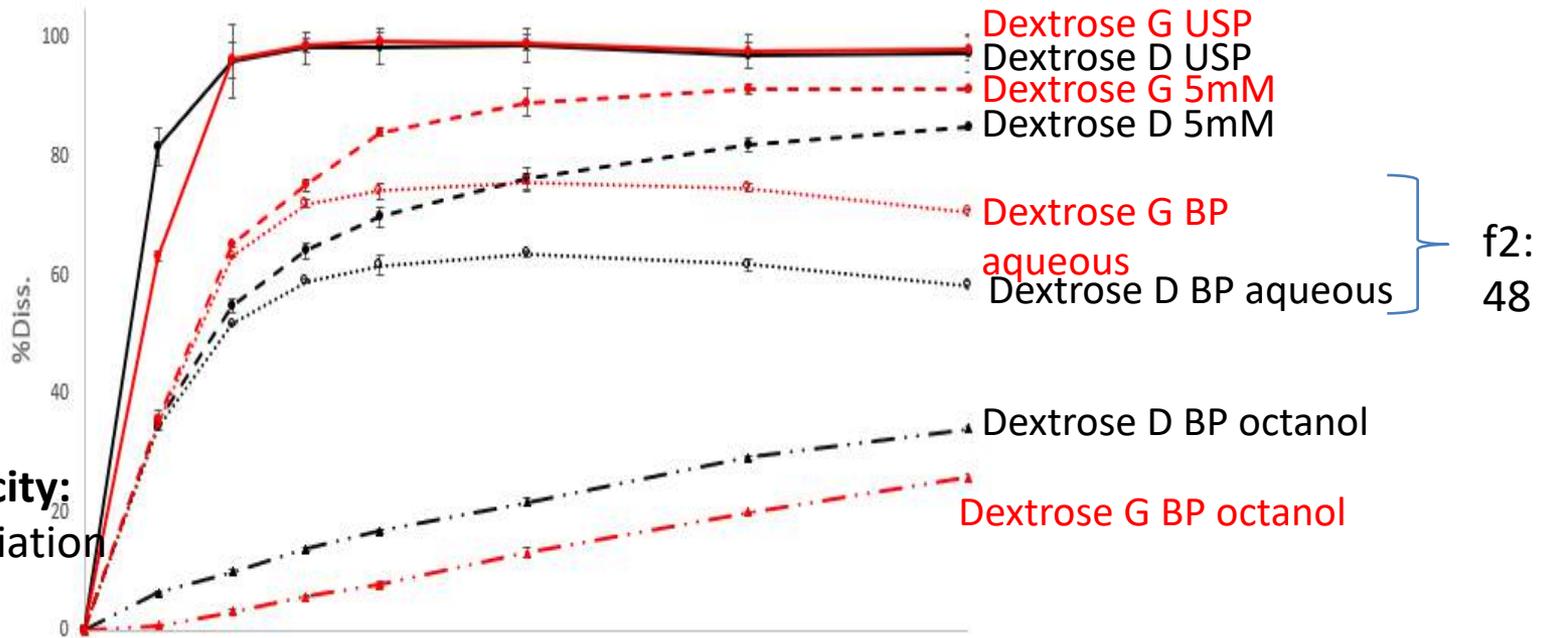
*Added as powder

- Intragranular
- Extragranular

900mL

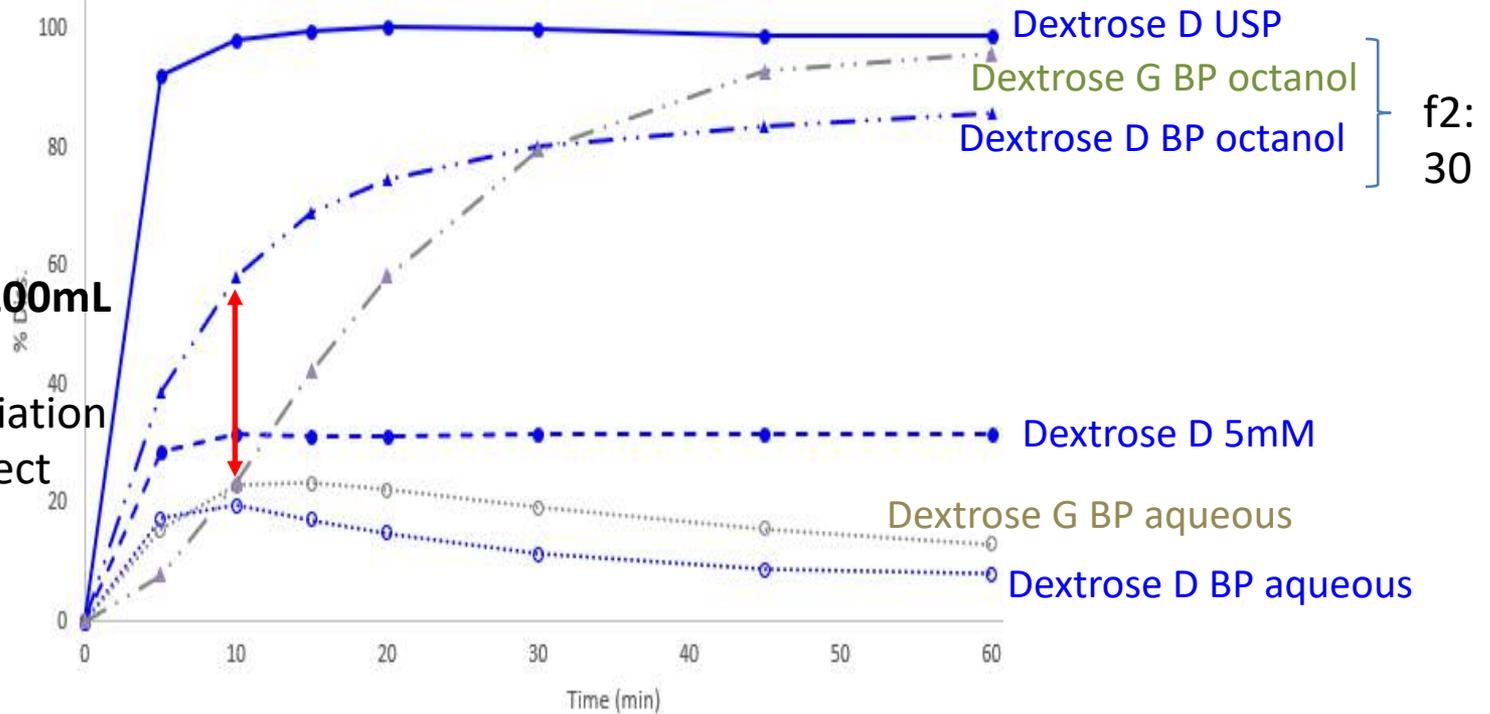
USP buffer:
No difference

Low buffer capacity:
Process differentiation



200mL

Octanol layer – 200mL
set up
Process differentiation
and excipient effect



Study summary

- USP buffer (50mM) did not differentiate between excipients nor manufacturing process.
- Low buffer capacity (monophasic) differentiated between processes in 900mL but not in 200mL due to medium saturation. (Also seen in the aqueous phase of biphasic dissolution – 900ml)
- For minor excipient changes within the same dosage form, biphasic dissolution (200mL) was much more discriminative in the octanol phase.
- More pronounced excipient effect on the G formulations was captured in the aqueous phase of the biphasic dissolution 900mL, whereas in the 200mL set up it was captured in the octanol phase.
- The additional sink helped maintaining the medium pH. In the 200mL set up the medium pH recovery was much faster.

Conclusions

- Pharmacopeial tests have their limitations
- More basic mechanistic questions need to be asked in drug development
- A BCS sub-classification helps to decide on the in vitro performance testing set-up
- Disintegration might be used for API driven dissolution
- Immediate release needs to be better defined.
- Biphasic dissolution needs to be more studied to find suitable conditions to differentiate between excipient and process variables.

Any Questions

