Advances and applications in Dissolution Science
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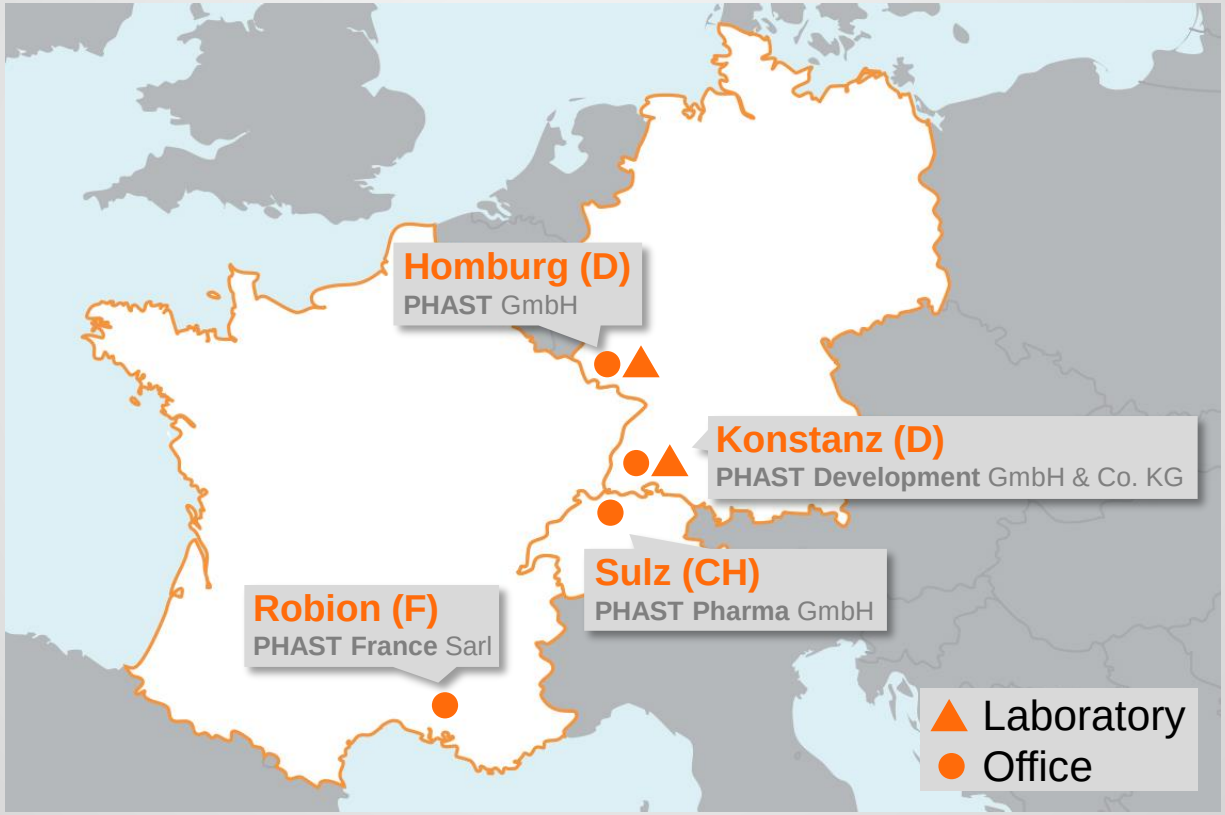
Strategies in development of dissolution tests

Dr. Johannes Krämer

PHAST (Pharmaceutical Quality Standards)

Facilities



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- Science
  - Compendial Science: USP General Chapter <1088, 1092>
    - In Vitro Evaluation
    - Currently recognized IVIVC Levels and Techniques as described in USP Chapter <1088>
- Alternative Strategies
  - Case report in Dissolution Method Development

Dissolution Testing

Pharmaceutical product lifecycle

dissolution method development

Product development

quality control testing clinical trial supply

Quality control testing market supply

Variations / SUPAC

Biorelevant Dissolution Testing of Oral Drug Products

PHAST quality standards

- Predict changes of bioavailability – surrogate of the therapeutic efficacy
  - Pre-clinical phase (discriminatory power required)
    - Sensitive to dosage form / drug substance solubility – differences
  - Development phase (discriminatory power required)
    - Sensitive to formulations – differences
    - Sensitive to variations in the manufacturing process with critical influence on the dosage form in vivo performance
  - Market supply phase (discriminatory power required)
    - Quality control - similarity
      - To prove similarity to lot used for BA in dossier (link to therapy)
        - Intra-lot homogeneity
        - Lot-to-lot conformity

Plus: indicate the robustness of dosage form – drug product related safety

Selected Strategies for Dissolution Method Development

- Apply a Compendial Product Monograph (e.g. USP)
- Apply a Method Taken from Regulatory Databases (e.g. FDA Database)
- Apply a Method Taken from Literature (e.g. Dissolution Technologies)
- QbD Risk Based Aproach

- Apply Science (e.g. compendial science; USP Chapters <1088, 1092>
- Alternative Strategies

Selected Strategies for Dissolution Method Development

- Apply a Compendial Product Monograph (e.g. USP) www.USP.org

Verapamil Hydrochloride Extended-Release Tablets

DEFINITION
Verapamil Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$).

IDENTIFICATION
• **A. Infrared Absorption ⟨197F⟩**
Standard: 1.92 mg/mL of USP Verapamil Hydrochloride RS in water. Transfer 25 mL of this solution to a 125-mL separatory funnel. Add 2 mL of 1 N sodium hydroxide, and extract with 25 mL of chloroform, shaking for 2 min. Pass the chloroform extract through a filter containing anhydrous sodium sulfate, and collect the filtrate in a porcelain dish. Rinse with an additional 10 mL of chloroform, collecting the rinsing in the same porcelain dish. Evaporate on a steam bath with the aid of a current of air to dryness, and dry the oily residue at 105° for 30 min.
Sample: Nominally 1.2 mg/mL of verapamil hydrochloride in 50 mM hydrochloric acid prepared as follows. Crush 1 Tablet, and transfer the powder to a volumetric flask of suitable size. Add 50 mM hydrochloric acid to about 75% of the final volume, and dissolve by heating, with stirring, for 40 min. Cool, and dilute with 50 mM hydrochloric acid to volume. Filter, and transfer 40 mL of the filtrate to a 125-mL separatory funnel. Add 4 mL of 1 N sodium hydroxide, and extract with 20 mL of chloroform, shaking for 2 min. Pass the chloroform extract through a filter containing anhydrous sodium sulfate, and collect the filtrate in a porcelain dish. Rinse with an additional 10 mL of chloroform, collecting the rinsing in the same porcelain dish. Evaporate on a steam bath with the aid of a current of air to dryness, and dry the oily residue at 105° for 30 min.
Acceptance criteria: Meet the requirements

ASSAY
• **Procedure**
Buffer: To 0.82 g of sodium acetate add 33 mL of glacial acetic acid, and dilute with water to 1 L.
Mobile phase: Acetonitrile, 2-aminoheptane and *Buffer* (60:1:140)
System suitability solution: 2.5 mg/mL of USP Verapamil Hydrochloride RS and 2.0 mg/mL of USP Verapamil Related Compound B RS in *Mobile phase*
Standard solution: 1.2 mg/mL of USP Verapamil Hydrochloride RS in *Mobile phase*
Sample solution: Transfer an amount equivalent to 240 mg of verapamil hydrochloride, from NLT 20 powdered Tablets, to a 200-mL volumetric flask, and add about 160 mL of *Mobile phase*. Sonicate for 15 min, stir for 15 min, dilute with *Mobile phase* to volume, and mix. Centrifuge a portion for 20 min, and use the supernatant as the *Sample solution*.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 278 nm
Column: 4.6-mm × 15-cm; packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.5 between verapamil and verapamil related compound B, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of verapamil from the *Sample solution*
r_S = peak response of verapamil from the *Standard solution*
C_S = concentration of USP Verapamil Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of verapamil hydrochloride in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution ⟨711⟩**
Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*. Proceed as directed for *Apparatus 1* and *Apparatus 2, Delayed-Release Dosage Forms, Method B, Procedure.*
Acid stage: Using 900 mL of simulated gastric fluid TS (without enzyme), conduct this stage of the test for 1 h.
Buffer stage: Using 900 mL of simulated intestinal fluid TS (without enzyme), conduct this stage of the test for 7 h.
Apparatus 2: 50 rpm
Times
Acid stage: 1 h
Buffer stage: 2, 3.5, 5, and 8 h
Standard solution: USP Verapamil Hydrochloride RS in 0.01 N hydrochloric acid
Sample solution: Pass portions of the solution under test through a suitable filter. Dilute with *Medium* as necessary.
Blank solution: 0.01 N hydrochloric acid
Analysis: Wrap each Tablet in a wire helix to prevent the Tablets from floating. After 1 h in the *Acid stage*, withdraw a specimen for analysis, and carefully transfer the dosage form, including the wire helix, to a vessel containing the *Buffer stage* medium, which has been previously warmed to 37 ± 0.5°. At each time interval, pass a portion of the solution under test through a suitable glass microfiber filter paper. Dilute, if necessary, the filtered portions of the solutions under test with water at the 1-h interval and with 0.1 N hydrochloric acid at the 2-, 3.5-, 5-, and 8-h intervals. Determine the percentage of the labeled amount of verapamil hydrochloride dissolved.
[NOTE—Use only filters that have been shown not to absorb verapamil.]
Detector: UV 278 nm
Tolerances: See *Table 1* and *Table 2*.

Table 1. For Products Labeled to Contain 180 or 240 mg

Time (h)	Amount Dissolved
1	7%–15%
2	16%–30%
3.5	31%–50%
5	51%–75%
8	NLT 85%

USP Monographs

Selected Strategies for Dissolution Method Development

- Apply a Method Taken from Regulatory Databases (e.g. FDA Database)
  www.accessdata.fda.gov/scripts/cder/dissolution

Federal

Food and Drug Administration

Dissolution Methods Database

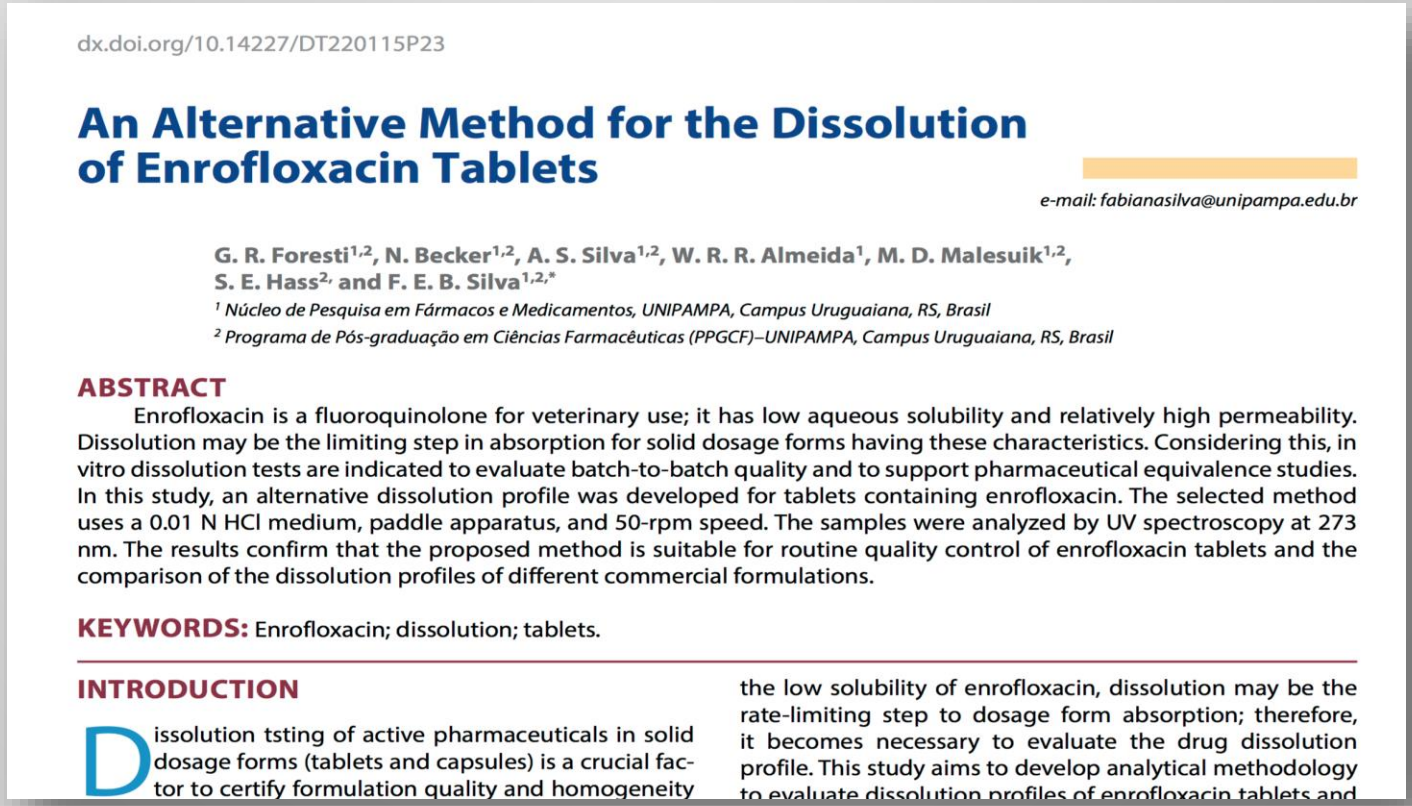
Metadata Updated: Apr 06, 2016

For a drug product that does not have a dissolution test method in the United States Pharmacopeia (USP), the FDA Dissolution Methods Database provides information on dissolution methods presently recommended by the Division of Bioequivalence, Office of Generic Drugs.

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Acetaminophen/Aspirin/Caffeine	Tablet			Refer to USP			06/25/2015
Aspirin	Capsule			Refer to USP			05/28/2015
Aspirin/Butalbital/Caffeine	Capsule			Refer to USP			06/24/2010
Aspirin/Butalbital/Caffeine	Tablet			Refer to USP			06/24/2010
Aspirin/Butalbital/Caffeine/Codeine Phosphate	Capsule			Refer to USP			08/27/2009
Aspirin/Caffeine/Orphenadrine Citrate	Tablet	I (Basket)	75	Water (deaerated)	900	10, 20, 30, 45 and 60	01/15/2004

Selected Strategies for Dissolution Method Development

- Apply a Method Taken from Literature (e.g. Dissolution Technologies) www.dissolutiontech.com



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An Alternative Method for the Dissolution of Enrofloxacin Tablets

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ABSTRACT

Enrofloxacin is a fluoroquinolone for veterinary use; it has low aqueous solubility and relatively high permeability. Dissolution may be the limiting step in absorption for solid dosage forms having these characteristics. Considering this, in vitro dissolution tests are indicated to evaluate batch-to-batch quality and to support pharmaceutical equivalence studies. In this study, an alternative dissolution profile was developed for tablets containing enrofloxacin. The selected method uses a 0.01 N HCl medium, paddle apparatus, and 50-rpm speed. The samples were analyzed by UV spectroscopy at 273 nm. The results confirm that the proposed method is suitable for routine quality control of enrofloxacin tablets and the comparison of the dissolution profiles of different commercial formulations.

KEYWORDS: Enrofloxacin; dissolution; tablets.

INTRODUCTION

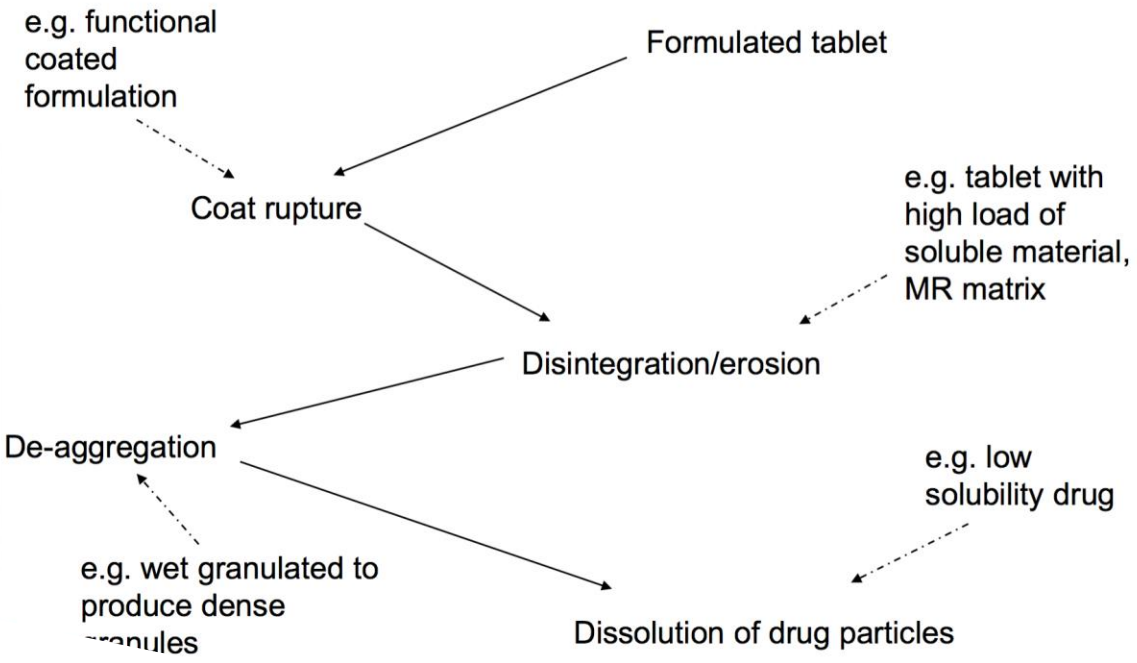
Dissolution tsting of active pharmaceuticals in solid dosage forms (tablets and capsules) is a crucial factor to certify formulation quality and homogeneity

the low solubility of enrofloxacin, dissolution may be the rate-limiting step to dosage form absorption; therefore, it becomes necessary to evaluate the drug dissolution profile. This study aims to develop analytical methodology to evaluate dissolution profiles of enrofloxacin tablets and

Selected Strategies for Dissolution Method Development

- QbD Risk Based Aproach (e.g.

Breaking down the dissolution process – for a specific product, what is/are the rate-limiting/critical quality attribute(s)?



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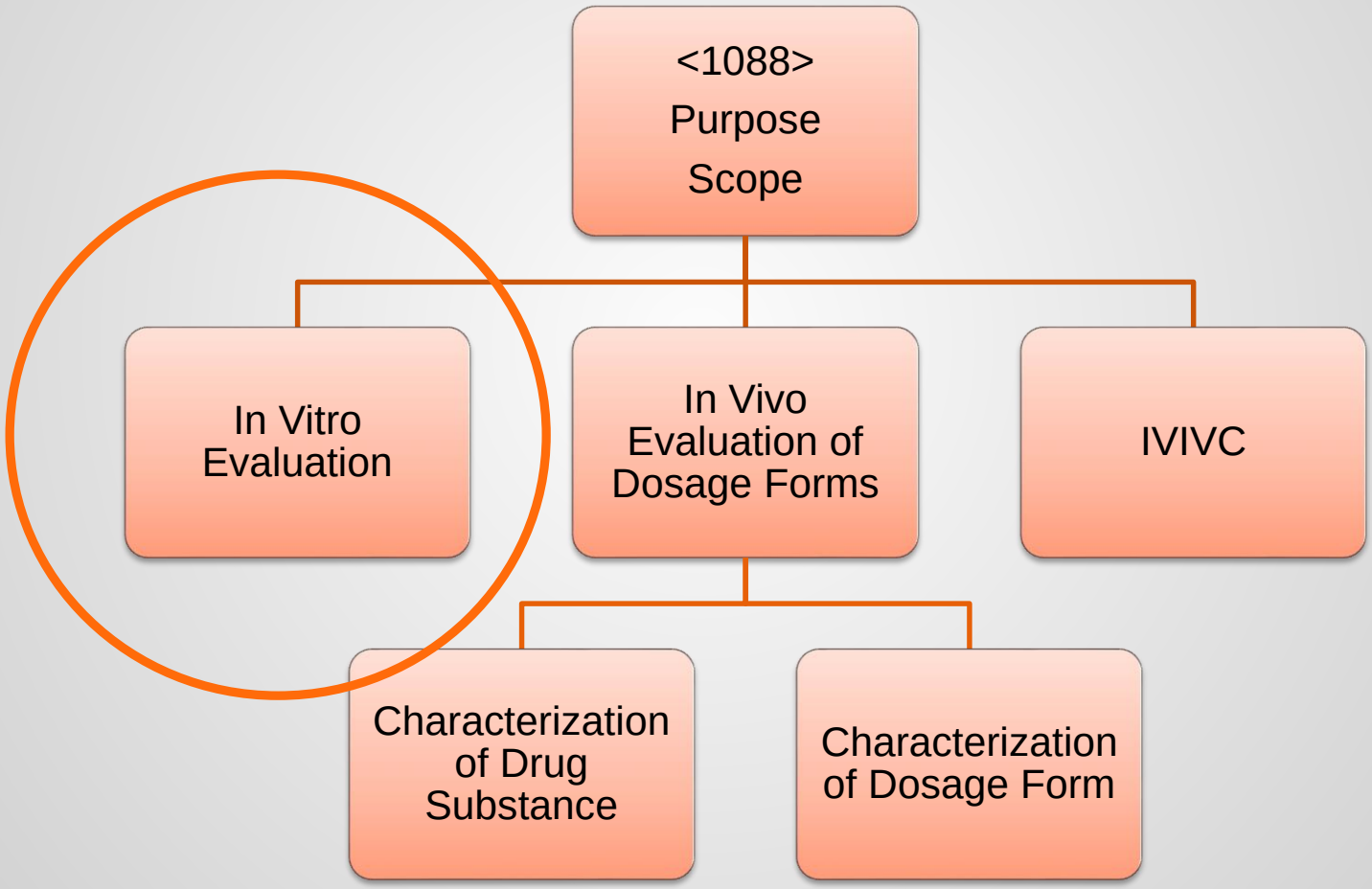
USP Chapter <1088>

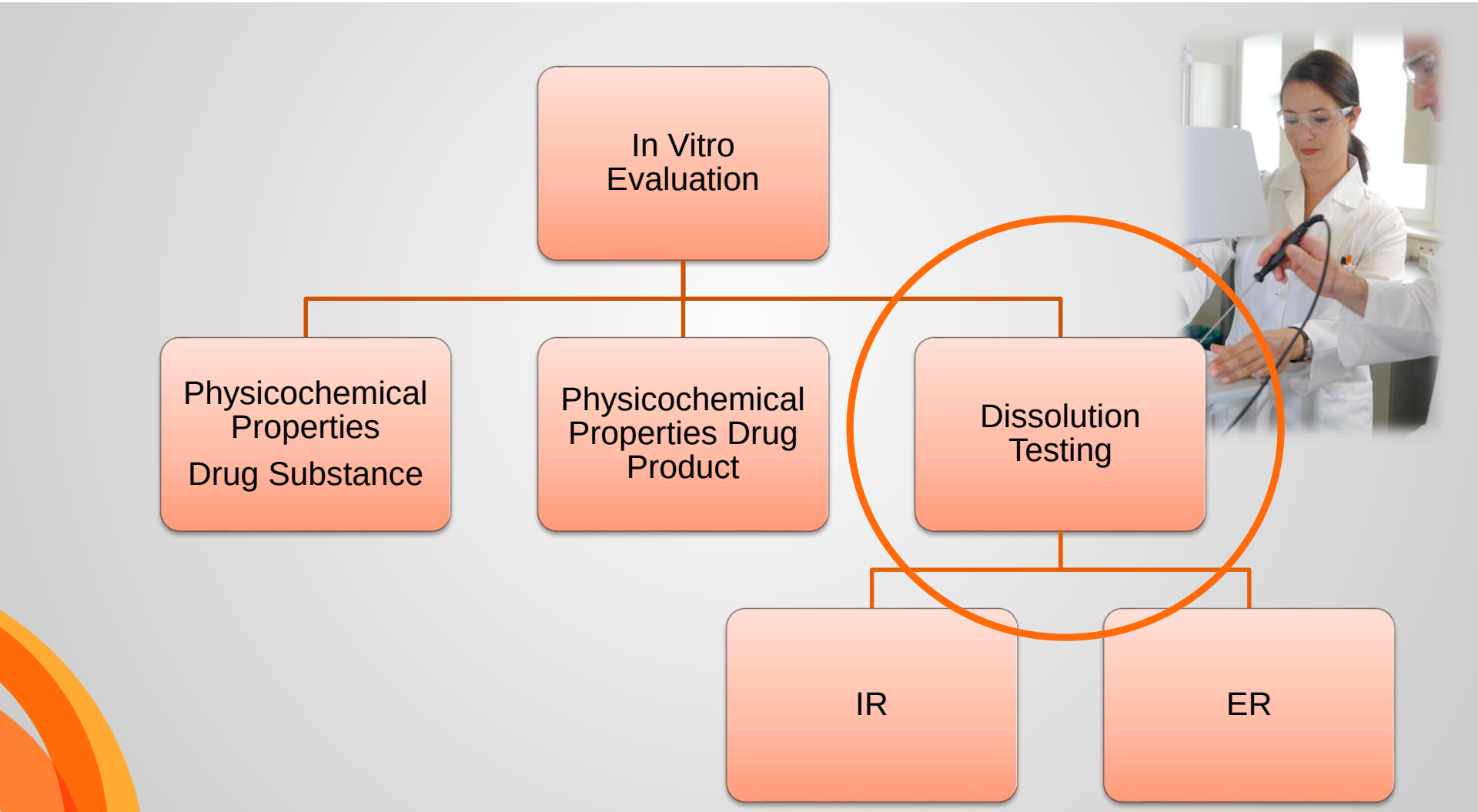
- Purpose of <1088>

  "Provides an overview for the methodology for characterizing the physicochemical properties of a drug substance as well as its associated drug product and discusses the relationship...of these properties to the pharmacokinetic and pharmacodynamic properties of the drug product. Results are linked with information from in vivo evaluations through an in vitro-in vivo correlation (IVIVC)."

<1088> Subdivided in 5 Sections



Section 1: In Vitro Evaluation



In Vitro Evaluation
Dissolution Testing

- Dissolution Testing
  - For all non-solution oral dosage forms required
  - Equipment according to Chapter <711>
  - Equipment performance proven according to USP
  - In vitro conditions should mimic in vivo dissolution
  - No reliable default condition available, therefore; range of conditions to be applied (see <1092>)
    - pH
    - Surfactant
    - Agitation
  - Knowledge required for
    - Drug substance
    - Formulation
    - GI physiology
    - Pharmacokinetics

If product contains more than one active ingredient, dissolution required for each active

For multisource products multiple dissolution tests are allowed – labeling required to indicate appropriate dissolution test for the specific product

In Vitro Evaluation cont'd

- Dissolution Testing IR
  - In vitro Testing ≤ 60 min
  - Single time-point specification mostly adequate
  - Disintegration < 30 min

For IVIVC purpose profiles mandatory

- Dissolution Testing ER
  - Multiple sampling time points
  - Apparatus choice based on dosage form
  - USP Apparatus <1> and <2> useful at higher rpm (100 rpm for paddle)
  - USP Apparatus <3> for beads
  - USP Apparatus <4> for poorly soluble API
  - Spec's for ≥ 3 timepoints

USP General Chapter <1092> Purpose and Scope

Purpose

General information chapter *The Dissolution Procedure: Development and Validation* 1092 provides approach for:

- Developing and validating dissolution methods
- And the accompanying analytical procedures
  - Including the use of automation and its validation
  - Addressing the treatment of the data

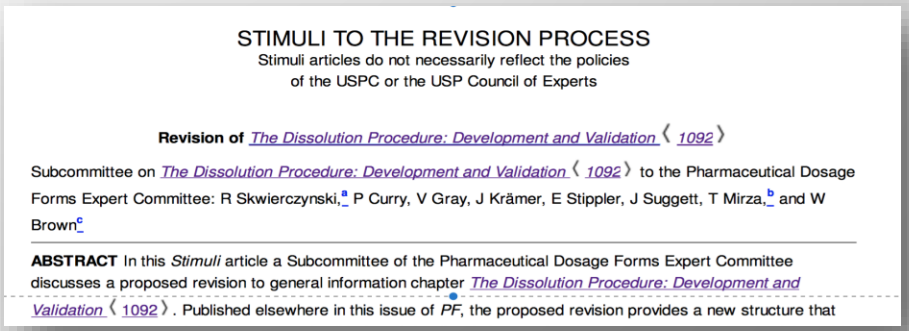
for immediate- and modified-release oral solid dosage forms

Scope

- Chapter 1092 for solid oral dosage forms.
- Many of the concepts presented, however, may be applicable to other dosage forms and routes of administration.
- The organization of 1092 follows the sequence of actions of dissolution testing.

Outline of Chapter <1092>
The Dissolution Procedure

General Chapter <1092>	
1. Introduction	5. Automation
2. Preliminary method development	6. Validation
3. Method development	7. Acceptance criteria
4. Analytical finish	8. References



STIMULI TO THE REVISION PROCESS

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

Revision of *The Dissolution Procedure: Development and Validation* ⟨ *1092* ⟩

Subcommittee on *The Dissolution Procedure: Development and Validation* ⟨ *1092* ⟩ to the Pharmaceutical Dosage Forms Expert Committee: R Skwierczynski,[a] P Curry, V Gray, J Krämer, E Stippler, J Suggett, T Mirza,[b] and W Brown[c]

ABSTRACT In this *Stimuli* article a Subcommittee of the Pharmaceutical Dosage Forms Expert Committee discusses a proposed revision to general information chapter *The Dissolution Procedure: Development and Validation* ⟨ 1092 ⟩. Published elsewhere in this issue of *PF*, the proposed revision provides a new structure that

2. Preliminary Method Development

- **Performing filter compatibility**
  - Selection of the proper filter material and pore size
  - Filter material compatible with the dissolution media
  - Drug substance should not adsorb on the filter
  - Leachables from the filter should not interfere with the analytical determination
  - Filters used for the automated systems

- **Determining the solubility and stability of drug substance in various media at 37° C**
  - Investigate the influence on the drug solubility
  - Type of buffer used for dissolution medium
  - pH value
  - Surface active agents
  - Investigation of the stability of the drug in selected dissolution medium

Preliminary Method Development cont'd

- **Choosing the appropriate dissolution medium and volume**
  - The goal is to achieve sink conditions
  - The appropriate dissolution medium is defined by the drug solubility
  - The use of surfactants and the concentration level needs to be justified

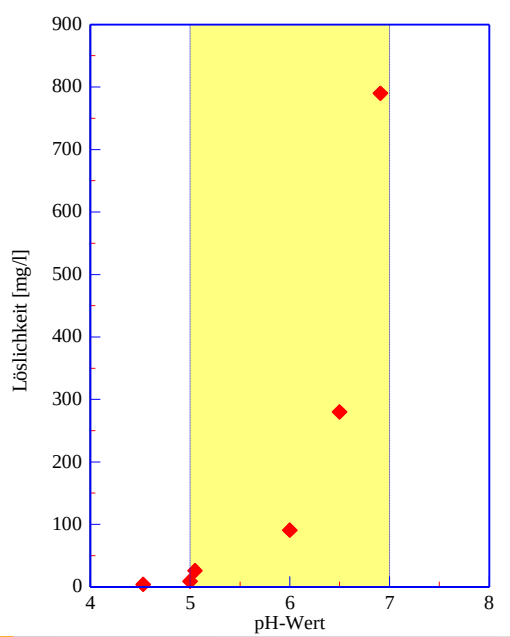
- **Choosing dissolution apparatus based on**
  - Formulation design
  - Practical aspects of dosage form properties and performance
  - Generally compendial apparatus should be selected
  - Changes to the compendial apparatus need justification
  - Non-compendial apparatus need justification

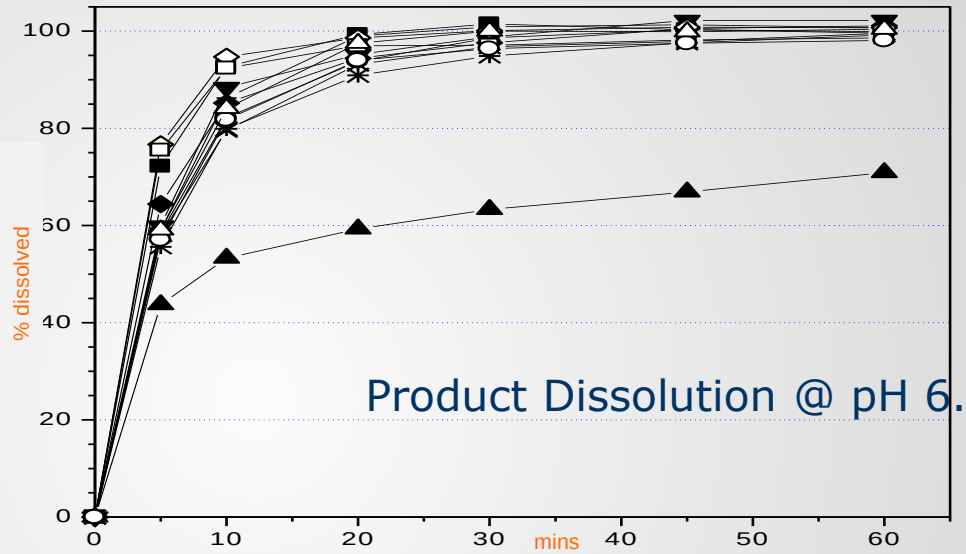
Example:
Buffer vs. Purified Water

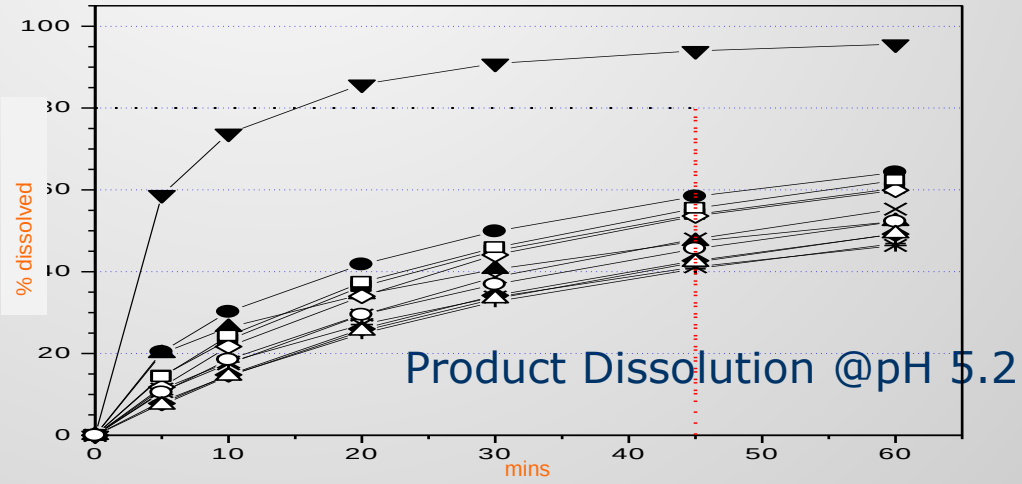
PHAST quality standards

Appropriate Medium

Phenprocoumon API
pKa 5.12
Solubility in Water







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Suggested Reading

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Questions?

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