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Development of Dissolution Methods for BCS Class 2/4 Drugs – A USP Perspective

Dr. Erika Stippler
Director
Dosage Form Performance

Dissolution Testing

- Dissolution assesses the performance of drug products
- To be effective, the test should be:
  - Predictive
    - relationship to in vivo response
  - Comparative
    - prediction only possible with comparative tests
  - Discriminatory
    - comparison only possible with discriminatory tests
  - Reproducible
    - discrimination only possible with reproducible tests
  - Precise
    - significant differences are based on the variability of the results

⟨1092⟩ THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

INTRODUCTION

Purpose

The Dissolution Procedure: Development and Validation ⟨1092⟩ provides a comprehensive approach covering items to consider for developing and validating dissolution procedures and the accompanying analytical procedures. It addresses the use of automation throughout the test and provides guidance and criteria for validation. It also addresses the treatment of the data generated and the interpretation of acceptance criteria for immediate- and modified-release solid oral dosage forms.

GC <1092> *The Dissolution Procedure: Development and Validation*

- Major revision of the chapter published in *PF 40(1)*
- Comments incorporated –
  - http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp_38-33_1s_commentary.pdf
- Official text *USP38–NF33* Supplement 1
  - Aug. 1, 2015

USP GC <*1092*> The Dissolution Procedure: Development and Validation

- Provides general information regarding development and validation of dissolution procedures
  - Preliminary assessment (for early stages of product development/ dissolution method development)
    - Performing filter compatibility
    - Determining solubility and stability of drug substance in various media
    - Choosing a dissolution medium and volume
    - Choosing an apparatus

USP GC <*1092*> The Dissolution Procedure: Development and Validation

- Method development
  - De-aeration
  - Sinkers
  - Agitation
  - Study design

- Analytical finish
  - Sample processing
  - Filter
  - Centrifugation
  - Analytical procedure
  - Spectrophotometric analysis
  - HPLC

USP GC <*1092*> The Dissolution Procedure: Development and Validation

- Automation
  - Medium preparation
  - Sample introduction and timing
  - Sampling and filtration
  - Cleaning
  - Operating software and computation of results
  - Common deviations from the compendial procedure that may require validation

USP GC <*1092*> The Dissolution Procedure: Development and Validation

- Validation
  - Specificity/ placebo interference
  - Linearity and range
  - Accuracy and recovery
  - Precision
  - Robustness
  - Stability of standard and sample solutions
  - Consideration for automation

- Acceptance criteria

Solubility of the Drug Substance

- Thermodynamic solubility – saturation concentration of the drug
  - In different aqueous media at 37°C
    - Shake-flask method (equilibrium solubility)
  - Alternative approaches

- Kinetic solubility - comparison of different forms/salts of the same compound
  - Intrinsic dissolution
  - Apparent dissolution

BCS Classification

FDA (2000)

High Solubility: **Highest strength** should be soluble in 250 mL or less of aqueous media over the **pH range of 1- 7.5** (at 37°C ± 1°C)

High Permeability: **90% or greater** absolute bio, or urinary recovery, or; permeability greater than the reference compound(s)

WHO (2015)

High solubility: **The highest single therapeutic dose** is soluble in 250 mL or less of aqueous media over the **pH range of 1.2 – 6.8** (at 37°C ± 1°C)

High permeability: **Extent of absorption** in humans is **85% or more** based on a mass balance determination or in comparison with an intravenous comparator dose

BCS Classification

EMA (2010)

High Solubility: highest single dose administered as immediate is completely dissolved in 250 mL of buffers within the range of **pH 1 – 6.8** (at 37°C ± 1°C)

High Permeability: extent of absorption is ≥ 85 % (data from absolute bioavailability studies or mass balance)

FDA Draft Guidance May 2015

Drug substance solubility class

- *highly soluble* - the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1-6.8

Drug substance permeability class

- *highly permeable* - the extent of absorption in humans is determined to be 85% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose

Instability in the gastrointestinal tract

- 1 hour in gastric fluid and 3 hours in intestinal fluid incubated at 37°C. Drug concentrations should be determined using a validated stability indicating assay method. Significant degradation (>5 %) of a drug in this study could suggest potential instability

Biopharmaceutics Classification System (BCS) *(1)*

High solubility class
D/S ≤ 250 mL
pH range 1 to 6.8

Low solubility class
D/S > 250 mL
pH range 1 to 6.8

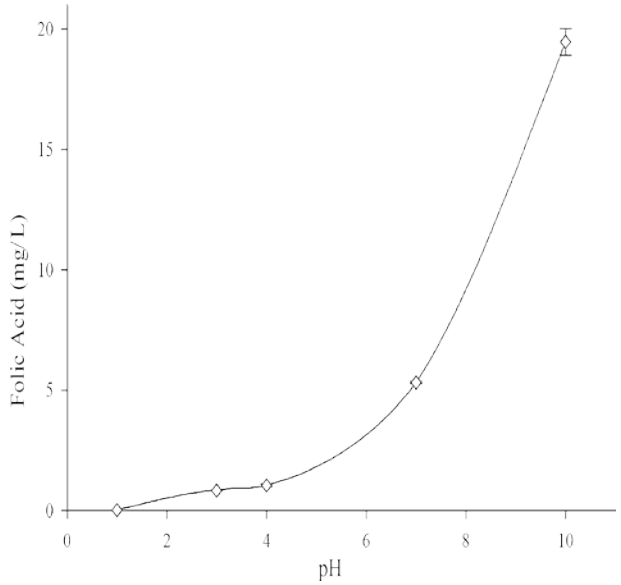
- **Class I** – high permeability
- **Class III** – low permeability
- **Class II** – high permeability
- **Class IV** – low permeability

Source: Pharm Res, 1995

Thermodynamic Solubility – Drug Substance

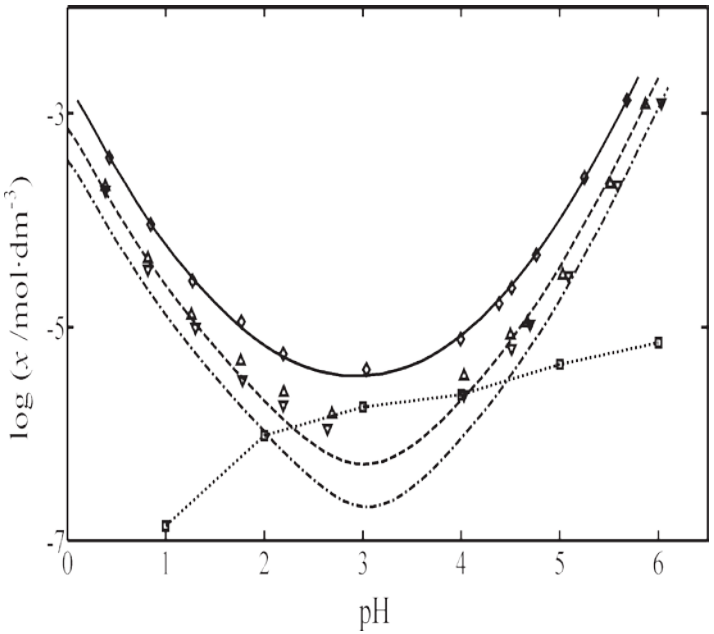
- pH dependent solubility
  - Buffer solutions with different pH values (e.g., pH 1 to pH 8)
  - Different buffer solutions may have different solubilizing properties
- Influence of salt composition
  - Different composition of buffer solution at the same pH value
- Use of solubilizing agents
  - To improve wettability
  - To improve solubility
- Effect of various surfactants (if applicable)
  - Different surfactant types (e.g., non-ionic, anionic, cationic)
  - Different concentrations of the same surfactant

pH Dependent Solubility – Folic Acid



Folic acid solubility-pH profile *(2)*

Source: International Journal of Pharmaceutics, 2009



Solubility of folic acid in water at different pH values and at different temperatures *(3)* (dash-dotted line model predicted data at 298.15K line, dash line model predicted data at 303.15K, real line model predicted data at 313.15K, symbols experimental data at 298.15K, 303.15K and 313.15K. Dotted line – data taken from literature)

Source: J. Chem. Eng. Data, 2010

Folic Acid Tablets Monograph *USP40-NF35*

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Medium: Water; 500 mL

Apparatus 2: 50 rpm

Time: 45 min

Standard solution: Solution having a known concentration of USP Folic Acid RS, corrected for water content, in *Medium*

Sample solution: Filtered portion of the solution under test, suitably diluted with the *Medium* if necessary

Low Solubility Drug: Weak Acid – Ibuprofen *(4)*

- Highest dose 800 mg

$$D/S = \frac{highest\ Dose \quad [mg]}{saturation\ concentration\ [mg/mL]} \leq 250mL$$

No	Medium	pH value of saturated solution	Concentration of saturated solution [mg/mL]	Dose/Solubility of the highest dose [mL]
1	Simulated Gastric Fluid, SGFsp, pH 1.2	1.2	0.0370	21609.9
2	Purified water, pH 5.8	5.6	0.0894	8944.5
3	Simulated Intestinal Fluid, SIFsp, pH 6.8	6.7	2.472	323.62
4	Phosphate buffer solution pH 7.2	7.0	4.524	176.83

Source: Ph.D Thesis, Shaker Verlag, 2006

Ibuprofen Tablets Monograph *USP40-NF35*

PERFORMANCE TESTS

- Dissolution ⟨711⟩

Medium: pH 7.2 phosphate buffer (see Reagents, Indicators, and Solutions—Buffers); 900 mL

Apparatus 2: 50 rpm

Time: 60 min

Standard solution: A known concentration of USP Ibuprofen RS in Medium

Sample solution: Filter a portion of the solution under test, and suitably dilute with Medium if necessary.

Instrumental conditions

Mode: UV

Analytical wavelength: Maximum absorbance at about 221 nm

Low Solubility Drug – Carbamazepine *(4)*

pH independent solubility

No	Medium	pH value of saturated solution	Concentration of saturated solution [µg/mL]	Dose/Solubility of the highest dose [mL]
1	Simulated Gastric Fluid, SGFsp, pH 1.2	1.2	191.9	2084.4
2	Purified water, pH 5.5	5.5	224.2	1784.1
3	FaSSIF-blank, pH 6.5	6.5	144.7	2764.3
4	Simulated Intestinal Fluid, SIFsp, pH 6.8	6.8	191.4	2089.9
5	Modified Simulated Intestinal Fluid, Na-SIFsp, pH 6.8	6.8	163.9	2440.5

$$D/S = \frac{highest\ Dose \quad [mg]}{saturation\ concentration\ [mg/mL]} \leq 250mL$$

Source: Ph.D Thesis, Shaker Verlag, 2006

Low Solubility Drug – Carbamazepine *(4)*

Selection of the suitable surfactant

No	Surface active agent	Concentration of surfactant at tenfold higher than CMC [%]	Concentration of saturated solution [µg/mL]	Dose/Solubility of the highest dose [mL]
1	FaSSIF-blank	0	144.7	2764.3
2	FaSSIF-blank + Pluronic F68	0.1	261.1	1532.0
3	FaSSIF-blank + Triton X100	0.2	524.2	763.1
4	FaSSIF-blank + Brij 35	0.1	274.2	1458.8
5	FaSSIF-blank + Tween 80	0.2	304.6	1313.2
6	FaSSIF-blank + Texapon N40	0.2	468.0	854.7
7	FaSSIF-blank + SLS	0.3	1092.7	366.1

$$D/S = \frac{highest\ Dose \quad [mg]}{saturation\ concentration\ [mg/mL]} \leq 250mL$$

Source: Ph.D Thesis, Shaker Verlag, 2006

Low Solubility Drug: Carbamazepine *(5)*

Evaluation of the appropriate surfactant concentration

No	Medium	Concentration of SLS [%]	Concentration of saturated solution [µg/mL]	Dose/Solubility of the highest dose [mL]
1	SGFsp, pH 1.2	0	191.9	2084.4
2	SGFsp + 0.3 % SLS	0.3	803.0	498.1
3	SGFsp + 0.5 % SLS	0.5	1255.3	318.6
4	SGFsp + 1.0 % SLS	1.0	2346.4	170.5
5	SGFsp + 2.0 % SLS	2.0	4722.0	84.7

Source: Ph.D Thesis, Shaker Verlag, 2006

Carbamazepin Tablets Monograph *USP40-NF35*

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

For products labeled as 100-mg chewable Tablets

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1.*

Medium: Water containing 1% *sodium lauryl sulfate*; 900 mL

Apparatus 2: 75 rpm

Time: 60 min

Standard solution: USP Carbamazepine RS in *Medium*. [NOTE—A volume of methanol NMT 1% of the final total volume of the *Standard solution* may be used to dissolve the carbamazepine.]

Sample solution: Filtered portion of the solution under test, diluted with *Medium* if necessary

Instrumental conditions Mode: UV

Analytical wavelength: Maximum absorbance at about 288 nm

Carbamazepin Tablets Monograph *USP40-NF35*

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

For products labeled as 200-mg Tablets

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium, Apparatus 2, Standard solution, Sample solution, and **Instrumental conditions:** Proceed as directed in *Test 1*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, Apparatus 2, Standard solution, Sample solution, and **Instrumental conditions:** Proceed as indicated in *Test 1*.

USP Dissolution Method Database

		USP Dissolution Methods Database Updated Feb 15, 2017, with the release of the First Suppl. of USP 40 – NF 35							abbreviations:		
									SGF = simulated gastric fluid		
									SIF = simulated intestinal fluid		
		TERMS OF USE: Copyright the United States Pharmacopeial Convention (USP). All rights reserved. The database content is not intended to and does not constitute legal advice and is not warranted or guaranteed by USP. Your use of database content is at your own risk. USP accepts no responsibility or legal liability for the use and/or accuracy of the database or for decisions made based on this data.							SLS = sodium lauryl sulfate (sodium dodecyl sulfate)		
									w/ = with		
									w/o = without		
		TIP: Search and sort by clicking on arrows in cells on top row. Drop down box with options will appear.									
MONOGRAPH	TEST	MEDIUM	SURFACTANT	pH	VOLUME (mL)	DEAERATION	APPARATUS	SPEED (rpm)/FLOW	TOTAL TEST TIME	QUANTITATIVE PROCEDURE	EXCEPTIONS
Acitretin Capsules	1	**3% SLS in water**	SLS	**9.6 - 10.0**	900		1	100	30	UV	correction w/ caps shell solution
Acitretin Capsules	2	**3% SLS in water**	SLS	**9.6 - 10.0**	900		1	100	30	HPLC	
Acitretin Capsules	2 Tier 2 Medium A	1750 USP units pancreatin in water		**8**	450	Y	1	100	10	HPLC	
Acitretin Capsules	2 Tier 2 Medium B	6**% SLS in water**	SLS	**10.5**	450	Y	1	100	20	HPLC	

Tier 1
Medium: 3% sodium lauryl sulfate in deaerated water, pH 9.6–10.0 (adjusted with 1 N sodium hydroxide); 900 mL
Apparatus 1: 100 rpm
Time: 30 min

Tier 2
Medium A: Prepare a solution containing pancreatin with NMT 1750 USP units of protease activity/L in deaerated water, pH 8.0 (adjusted with 1% sodium hydroxide); 450 mL, use immediately.
Medium B: 6% sodium lauryl sulfate in deaerated water, pH 10.5 (adjusted with 1% sodium hydroxide); 450 mL
Apparatus 1: 100 rpm
Time: 10 min *Medium A*; 20 min *Medium A* with the addition of *Medium B*

Dissolution Medium used in Monographs

- Addition of surface active agents
  - Synthetic surfactants
    - Sodium lauryl sulfate concentration varying between 0.02% and 6%
    - Polysorbate 80 concentration varying between 5ppm and 3%
    - Polysorbate 20: concentration varying between 0.35% and1.0%
    - Polysorbate 40: 2.0%
    - Polyoxyethylene(23)laurylether 0.6%
    - Polyoxyethylene(10)laurylether concentration varying 25mM - 60mM
    - Hexadecyltrimethylammonium bromide 0.0014M
    - Cetyltrimethylammonium bromide 0.01%
    - Hydroxypropylcellulose in water 1 in 2000
    - Lauryl dimethylamine oxide concentration varying 0.1% - 4.5%
  - Enzymes
    - pepsin
    - pancreatin
  - Alcohol
    - isopropanol 30% (e.g. Oxandrolone tablets)

Stability of Drug Substance in Dissolution Medium at 20°C ± 2°C *(*)*

- Chlorpheniramine: concentration 0.04 mg/mL

SGF blank

Stability	Area	%Diff.
4hr	249700	1.9
8hr	247122	0.9
12hr	240448	-1.8
24hr	242556	-1.0
48hr	240608	-1.8
Initial	244957	
%RSD	1.027	

SIF blank

Stability	Area	%Diff.
4hr	270641	1.2
8hr	270596	1.2
12hr	265321	-0.8
24hr	265672	-0.7
48hr	266863	-0.2
Initial	267484	
%RSD	1.240	

Stability of Drug Substance in Dissolution Medium at 20°C ± 2°C *(*)*

- Diphenhydramine HCl: concentration 0.05 mg/mL

SGF blank

Stability	Area	%Diff.
4hr	341698	**-3.2**
8hr	NA	**NA**
12hr	340231	**-3.6**
24hr	333093	**-5.6**
48hr	324312	**-8.1**
Initial	352929	
%RSD	0.112	

SIF blank

Stability	Area	%Diff.
4hr	380025	0.8
8hr	380875	1.0
12hr	381984	1.3
24hr	379027	0.5
48hr	379957	0.7
Initial	377163	
%RSD	0.193	

Selection of Apparatus

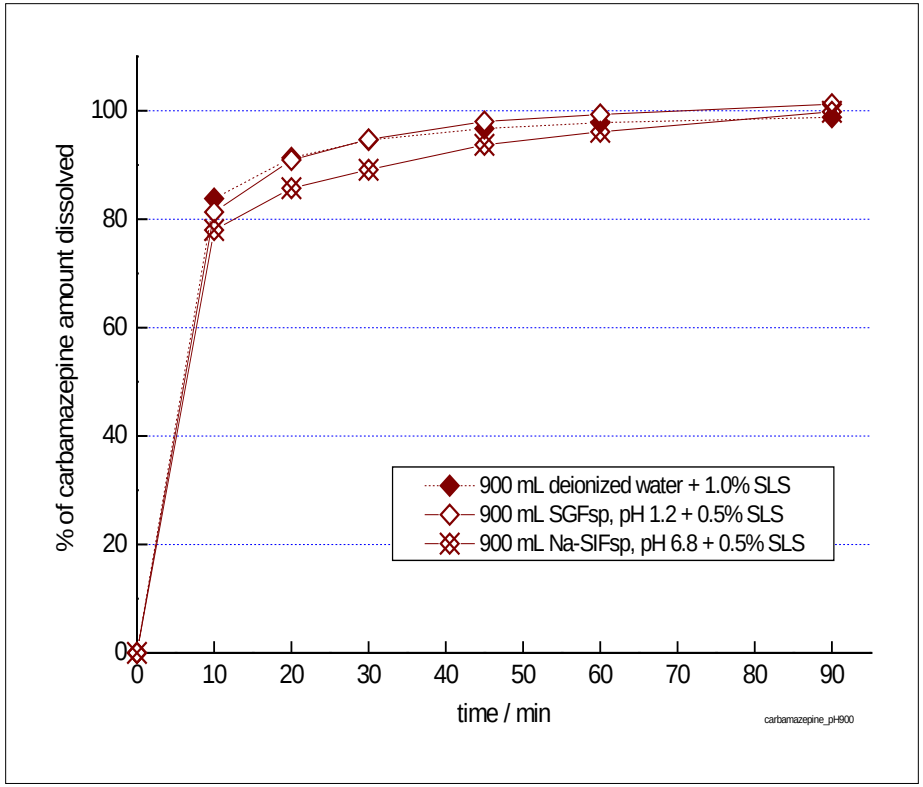
- Based on the knowledge of the design and the technical aspects of the dosage form performance
- For solid oral dosage forms
  - Apparatus 1 and Apparatus 2 are used most frequently
  - Apparatus 3: chewable tablets, delayed release dosage forms
  - Apparatus 4: various dosage forms
- Some changes can be made to the apparatus when the need is clearly documented by supporting data
  - Basket mesh size

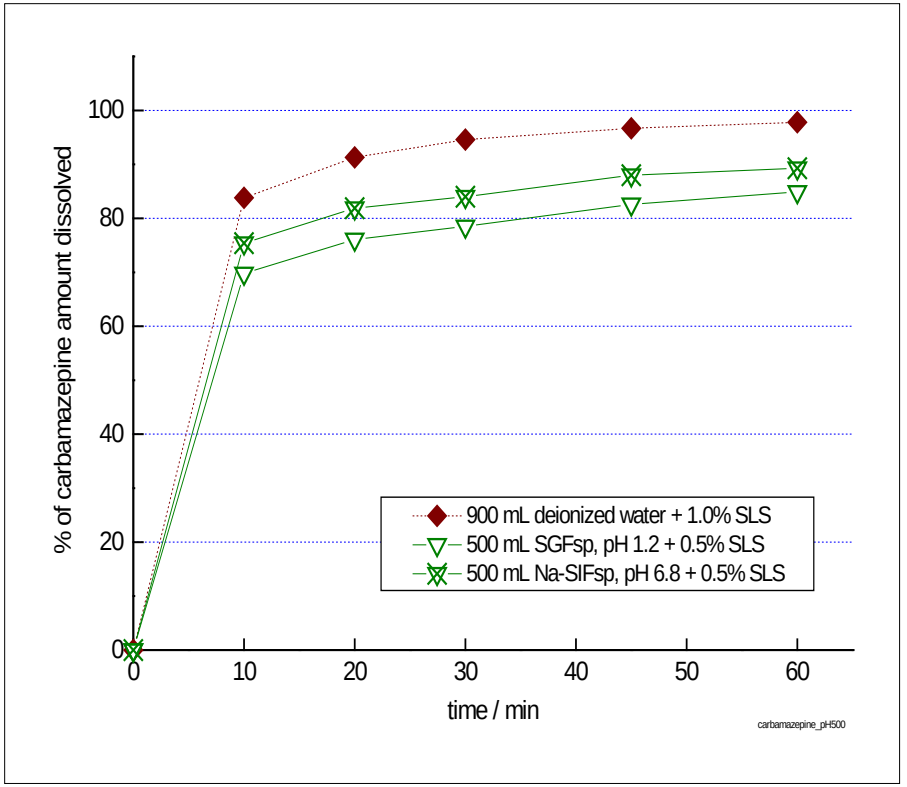
Selection of the Volume of Dissolution Medium

- Basket/ Paddle Apparatus
  - Generally: 500 mL – 1000 mL
  - Special cases: 2 or 4 liter
- Reciprocating Cylinder Apparatus
  - Up to 250 mL/vessel
  - Use of up to 6 rows for testing for a sample
- Flow-through Cell Apparatus
  - Generally: 4 mL/min – 16 mL/min
  - For implants: 1 mL/min – 2 mL/min, or less
  - Special cases: up to 50 mL/min
- Reciprocating holder

Selection of the Volume of Dissolution Medium

Dissolution of Carbamazepine drug substance *(4)*





Source: Ph.D Thesis, Shaker Verlag, 2006

Discriminating Dissolution Method for IR BCS Class II Soft Gelatin Capsule Formulation *(6)*

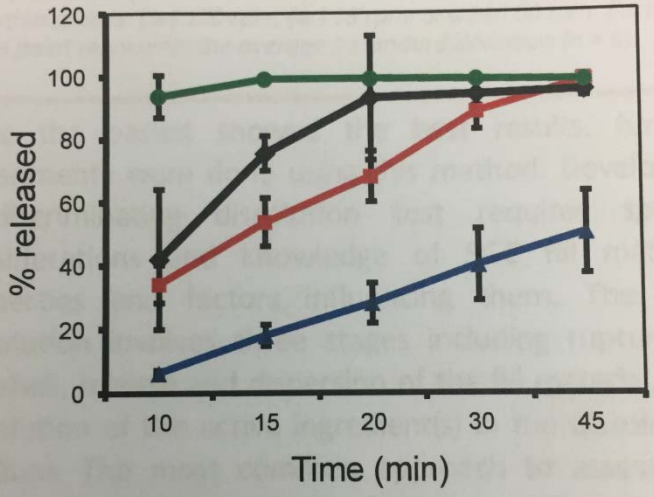


Figure 2. Dissolution profiles of loratadine SGCs using the basket and paddle methods, 0.1 N HCl in purified water as dissolution medium: (●) 100 rpm, paddle; (◆) 50 rpm, paddle; (■) 100 rpm, basket; and (▲) 50 rpm, basket. Each data point represents the average ± standard deviation (n = 6).

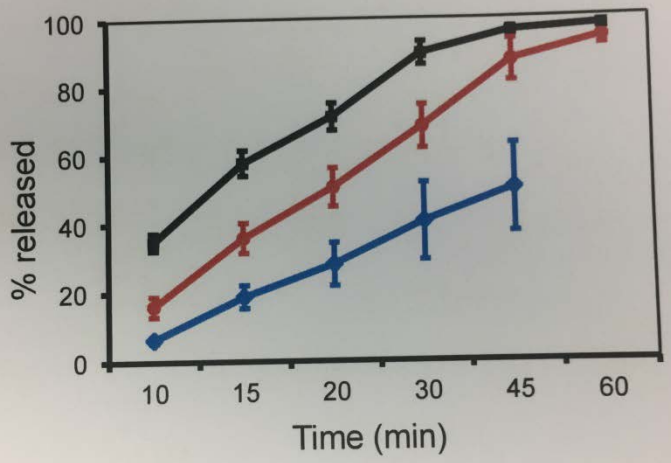


Figure 3. Dissolution profiles of loratadine SGCs using the basket, 0.1 N HCl in purified water as dissolution medium, and different rotation speeds: (■) 100 rpm; (●) 75 rpm; and (◆) 50 rpm. Each data point represents the average ± standard deviation (n = 6).

Medium	Solubility
pH 2 - 0.1 N HCl	484.27 µg/mL
pH 6.8 - phosphate buffer	4.32 µg/mL
pH 12.5 - buffer	3.16 µg/mL

Loratadine Tablets Monograph *USP40-NF35*

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 60 min

Standard solution: USP Loratadine RS at a known concentration in *Medium*

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*, if necessary

Instrumental conditions Mode: UV-Vis

Analytical wavelength: Maximum absorbance at about 280 nm

Dissolution Profiles of Gliclazide MR Tablets *(5)*

Gliclazide – weak acid (pKa 5.8)

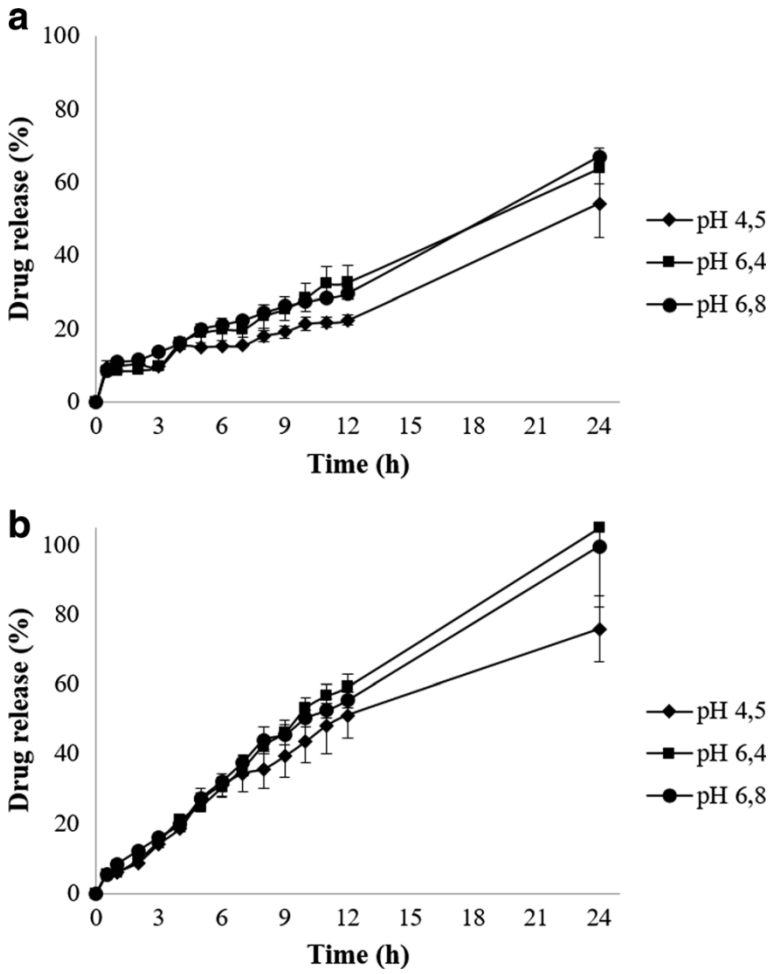


Fig. 1. Dissolution profiles of Azukon MR® 30 mg in apparatus 1, at different pH values and at a 50 and b 100 rpm

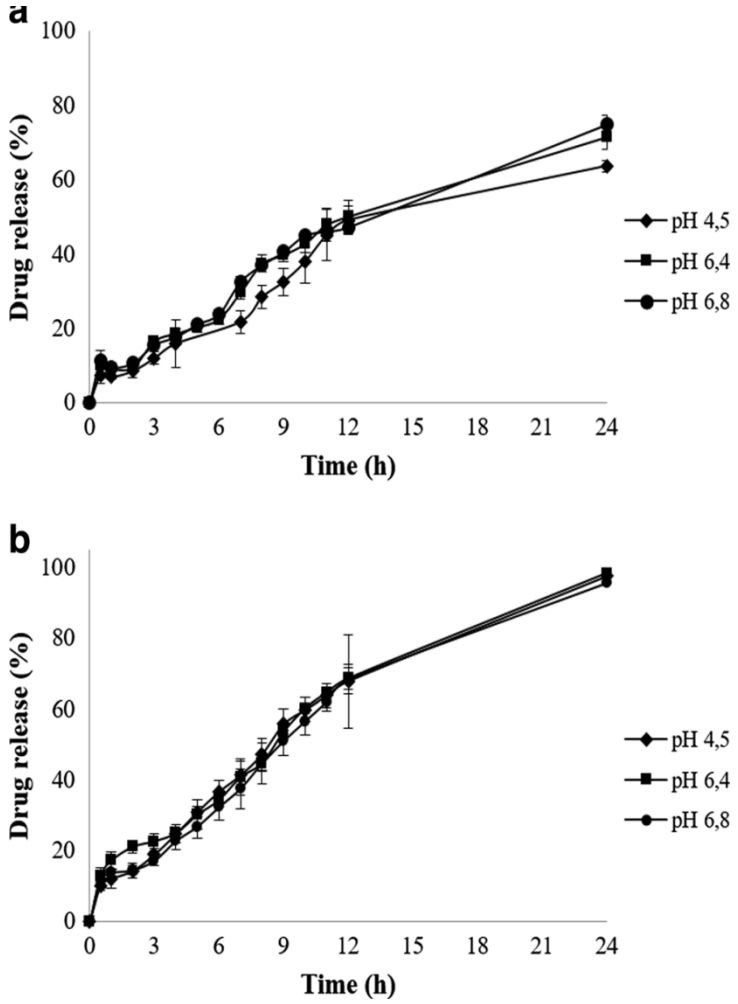


Fig. 2. Dissolution profiles of Azukon MR® 30 mg in apparatus 2, At different pH values and at a 50 and b 100 rpm

Source: AAPS PharmSciTech, 2016

Dissolution Profiles of Gliclazide MR Tablets

Selection of apparatus *(5)*

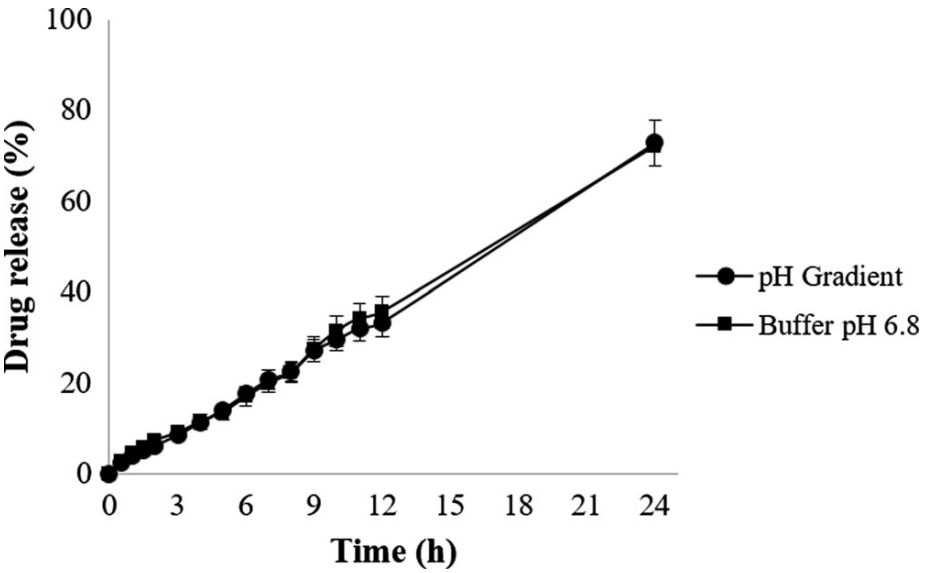


Fig. 3. Dissolution profiles of Azukon MR® 30 mg in apparatus 3, at pH 6.8 and pH gradient, mimicking the physiological conditions

Vessel row	pH	Residence time (min)
1	4.5	60
2	5.5	30
3	6.0	120
4	7.0	90
5	6.4	300
6	6.8	840

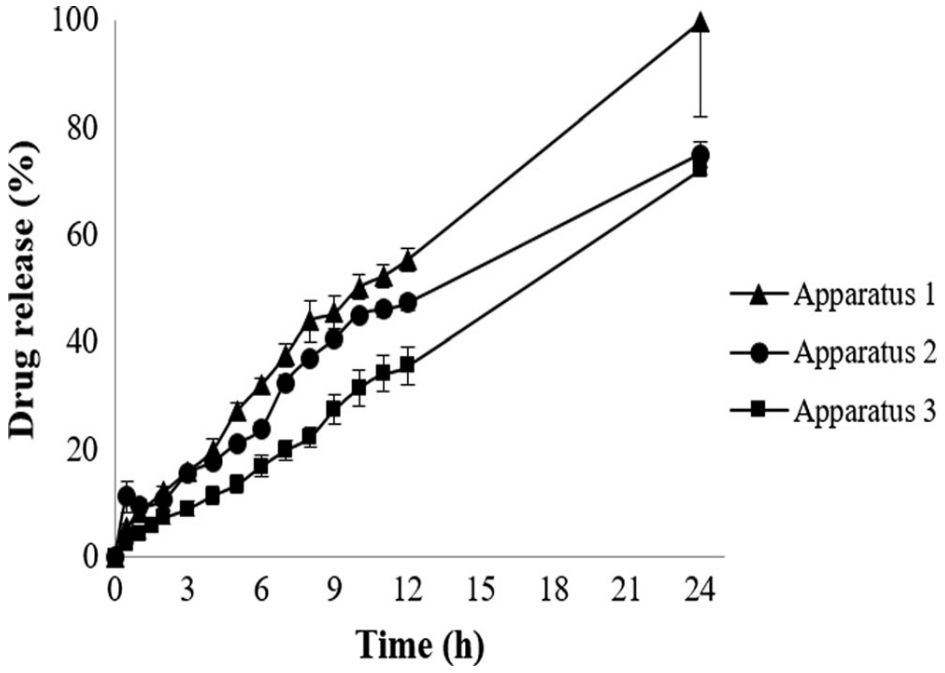


Fig. 5. Comparison of the dissolution profiles of Azukon MR® 30 mg in apparatuses 1, 2, and 3, at 100 rpm, 50 rpm, and 10 dpm, respectively

Source: AAPS PharmSciTech, 2016

Conclusions

- Evaluation of the solubility and stability of the drug in various aqueous media is critical in the dissolution method development
- Choice of dissolution testing conditions is based on
  - Solubility of the drug substance
    - Maintain sink-conditions
  - Stability of the drug substance
  - Properties of the dosage form
  - Release mechanism
  - Compendial dissolution apparatus
    - Preferred use
  - Non-compendial apparatus

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Relevant Guidelines

FDA

Guidance for Industry Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Oral Dosage Forms Based on a Biopharmaceutics Classification System, Aug. 2000

- *DRAFT* Revised version – May 2015

WHO

WHO Technical Report Series No. 937: WHO EXPERT COMMITTEE

ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS, Fortieth Report, Annex 7, 2006

- WHO Technical Report Series No. 992: ANNEX 7, 2015

EMA

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1, Jan. 2010

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Questions

U.S. Pharmacopeial Convention

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Thank You