Society for Pharmaceutical Dissolution Science (South Chapter)
JSS University Mysore, Karnataka

Winter Session on
Dissolution Science & Drug Testing

Scientific Principles and Advanced Concepts in Dissolution

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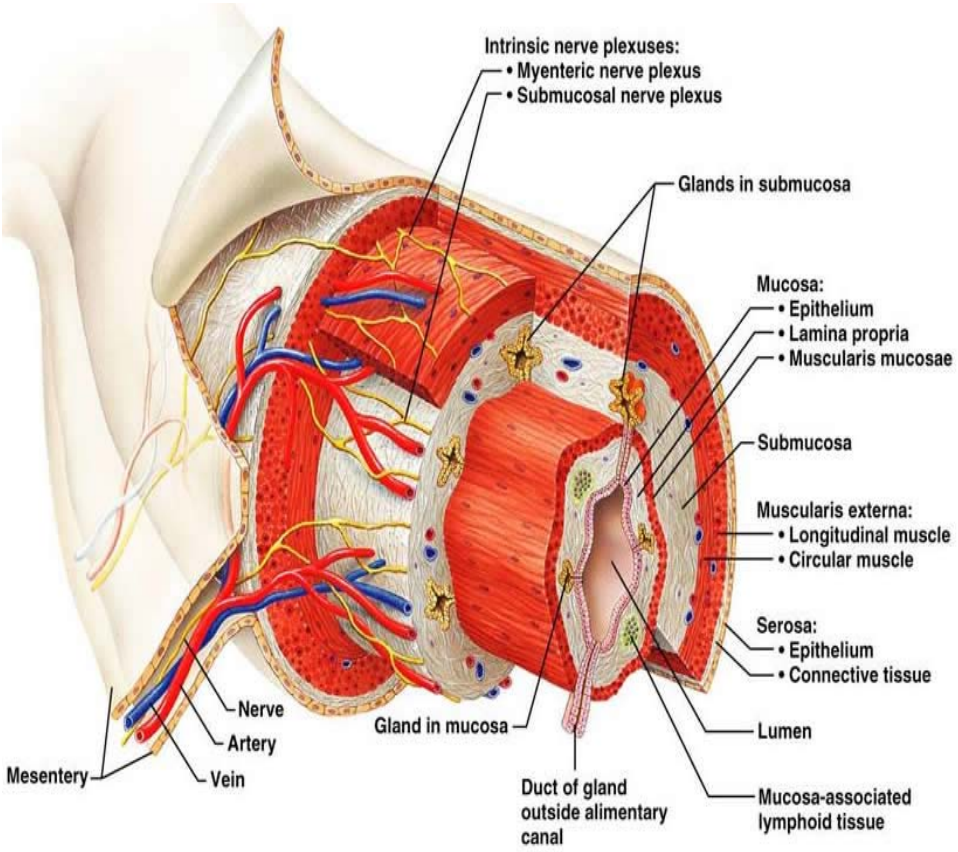
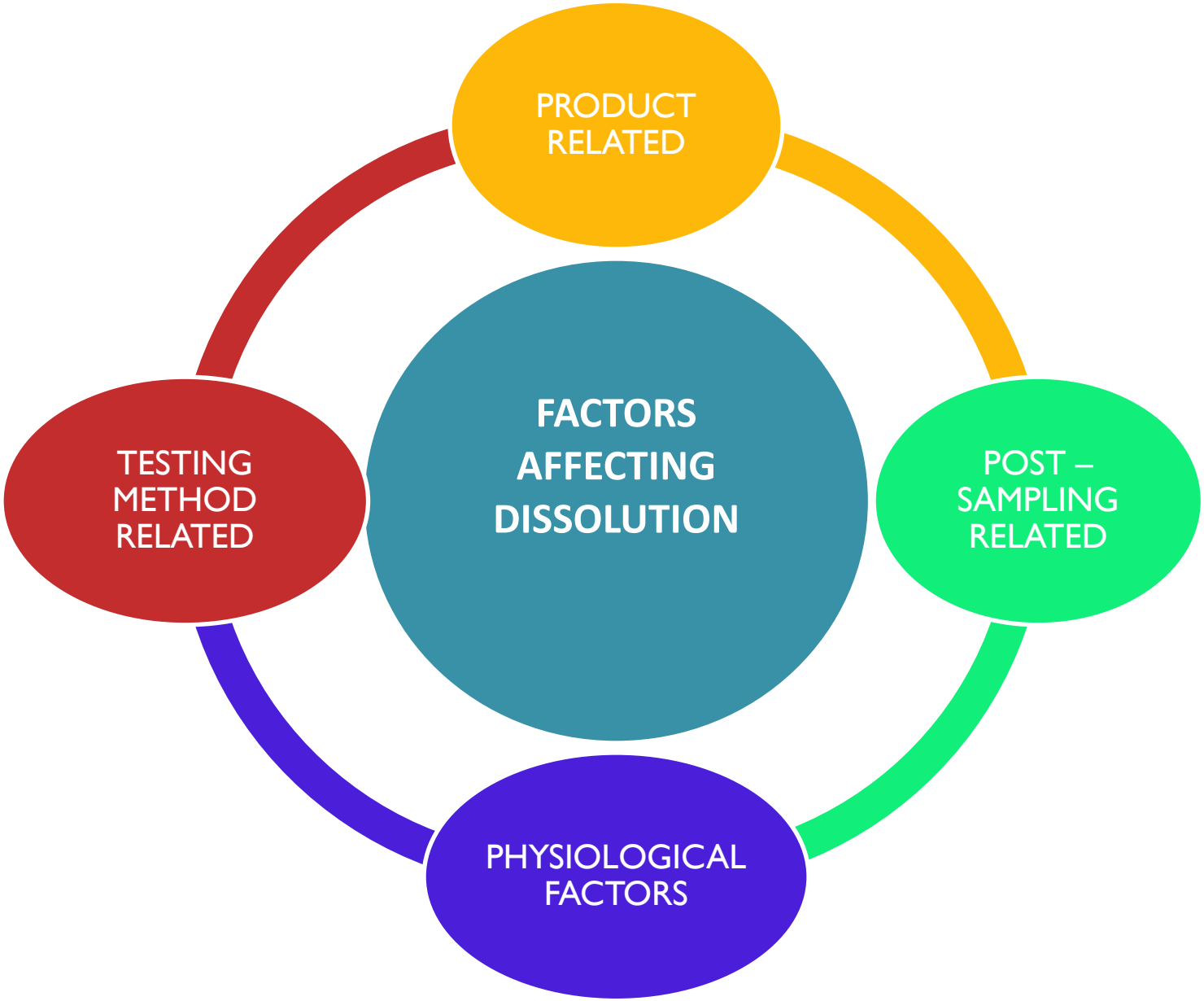
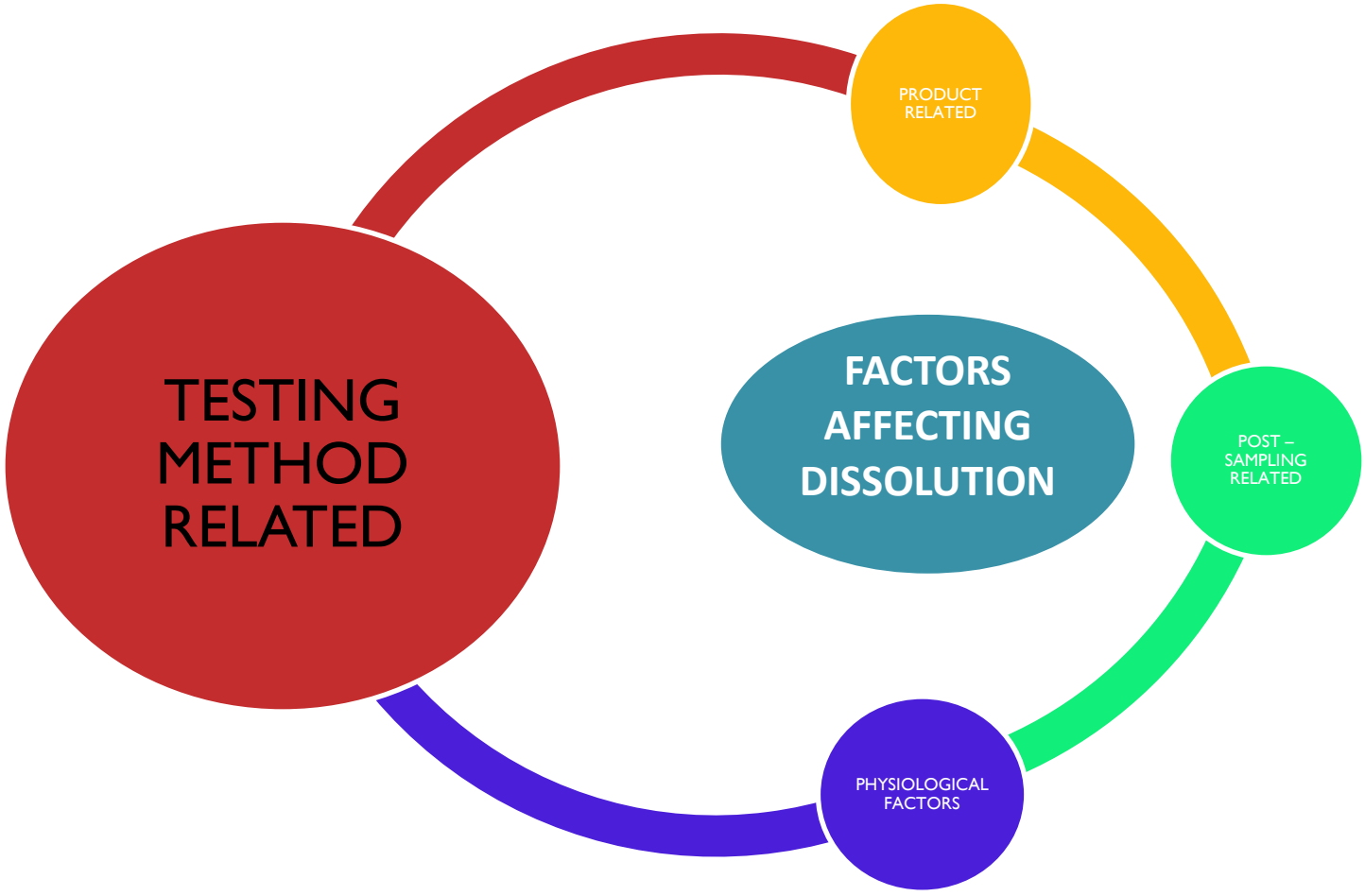
18th October 2013

Gastrointestinal Tract vs Dissolution Test




PRODUCT RELATED
TESTING METHOD RELATED
FACTORS AFFECTING DISSOLUTION
POST – SAMPLING RELATED
PHYSIOLOGICAL FACTORS


TESTING METHOD RELATED
FACTORS AFFECTING DISSOLUTION
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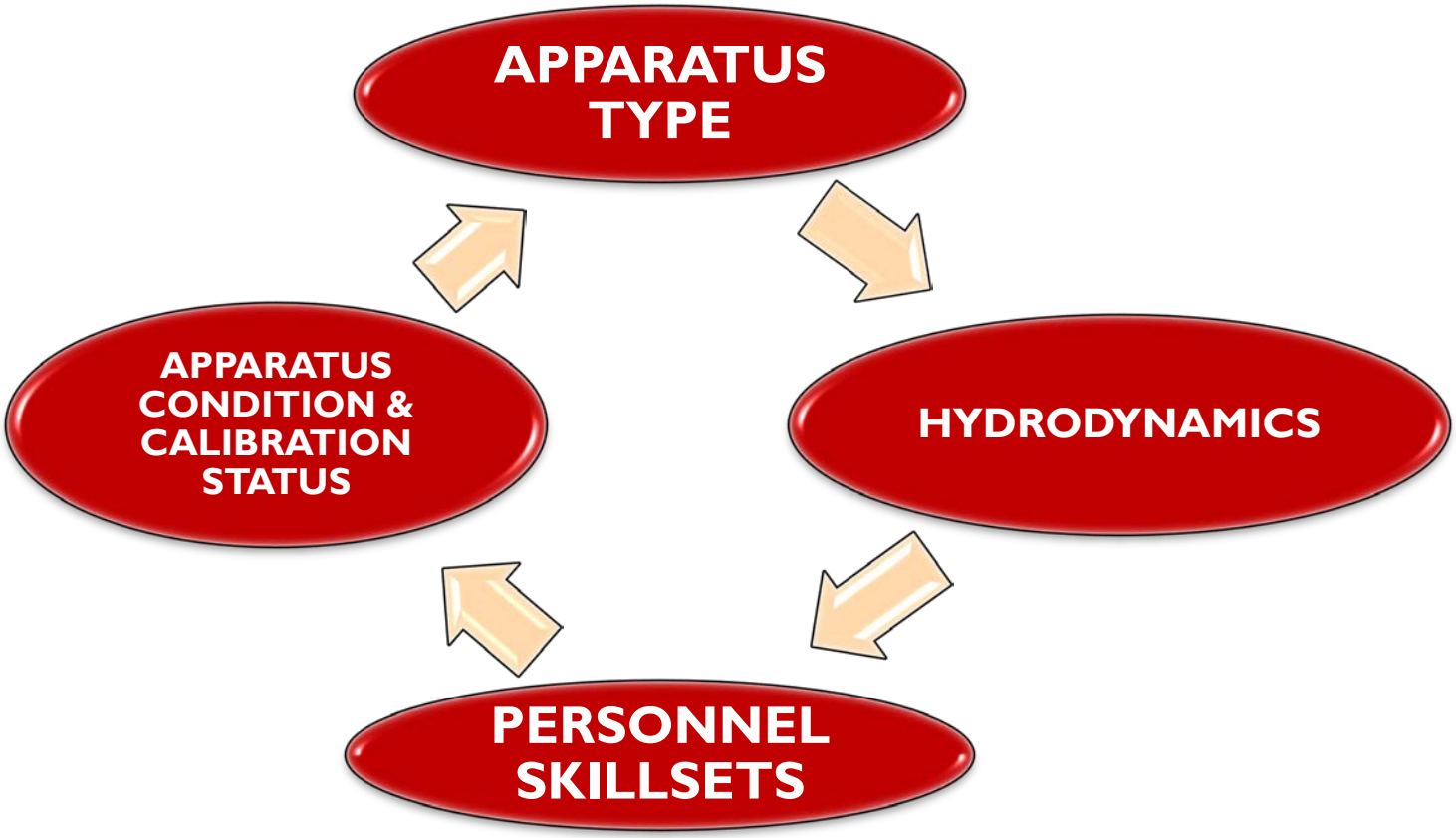
DISSOLUTION TESTING CONSIDERATIONS



General Principles of Developing a Dissolution Method

1. Appropriate medium for dissolution testing

    - Multimedia testing
    - Discriminatory media
    - Volume of media

2. Apparatus type

    - Dosage form dependent
    - RPM selection
    - Time points for sampling

3. Drug is sufficiently stable in the medium/media

4. Sink conditions

DISCRIMINATORY DISSOLUTION MEDIA

Dissolution medium or media that are able to pick out REAL differences between batches of a product.

- CAUTION: watch out for overly discriminating media

- WHAT IF DISSOLUTION IS TOO FAST - produces a profile that levels off too early to show discrimination between the formulations.

- WHAT IF DISSOLUTION IS TOO SLOW - the dissolution apparatus, rotational speed or dissolution medium may have to be changed to produce a discriminating dissolution profile.

- TYPICAL TARGET for IR products – aim for a profile that approaches 100% drug dissolved in 45 to 60 minutes.

DISCRIMINATORY DISSOLUTION MEDIA

Dissolution medium or media that are able to pick out REAL differences between batches of a product.

- CAUTION: watch out for overly discriminating media

- How do you find a discriminatory media?

1. From pH –solubility profile data, select least favourable medium
   - e.g medium with pH close to pKa of the molecule

2. Dissolution test conditions for e.g.,
   - Low RPM should be more discriminating
   - No surfactant to gradual increase in surfactant concentration

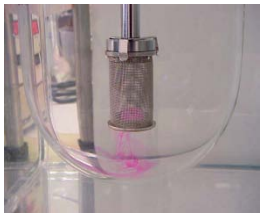
DISCRIMINATORY DISSOLUTION MEDIA..(contd)

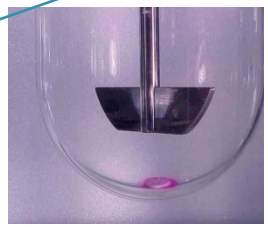
- How do you find a discriminatory media?

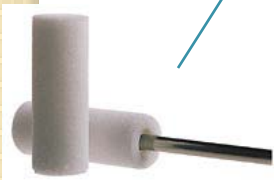
3. Make deliberate process changes that you anticipate in manufacturing, for e.g.
   - Hardness effects
   - Granulation kneading effects
   - Lubricant mixing time changes
   - API particle size changes
   - Excipient changes – fillers, binder concentration etc

DISSOLUTION METHODOLOGY

- Shaft centering
- Wobbling
- Vertical







- temperature
- agitation speed
- degassing
- sampling (position, timing,
- tubing compatibility
- filtration, dilution)
- Vibration

Importance of Inner Shape of Dissolution vessel

CONVENTIONAL VESSEL Vessel A (manufacturer A, Japan)

- exhibited distortion, and unevenness in various places.
- The vessel bottoms in particular deviated from the ideal hemispherical shape, and curvature among vessels differed widely.
- The inside of the cylinder of these two manufacturers' vessels also deviated from the ideal circular shape.

PRECISION VESSEL

(Takao, Japan) was manufactured by a new glass processing technology and displayed an almost ideal inner shape consisting of a cylinder and hemisphere.

Importance of Inner Shape of Dissolution vessel

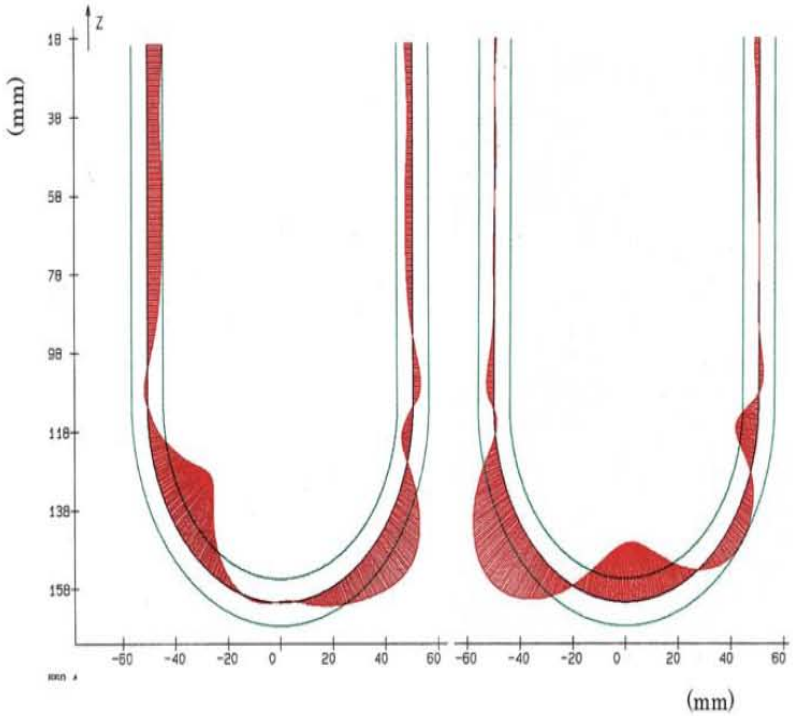


Figure 1. Inner Shape of Vessel A. The center of the three lines indicates the ideal shape of the cylinder and hemisphere. The two lines drawn on both sides represent ± 0.3 mm from the center line.

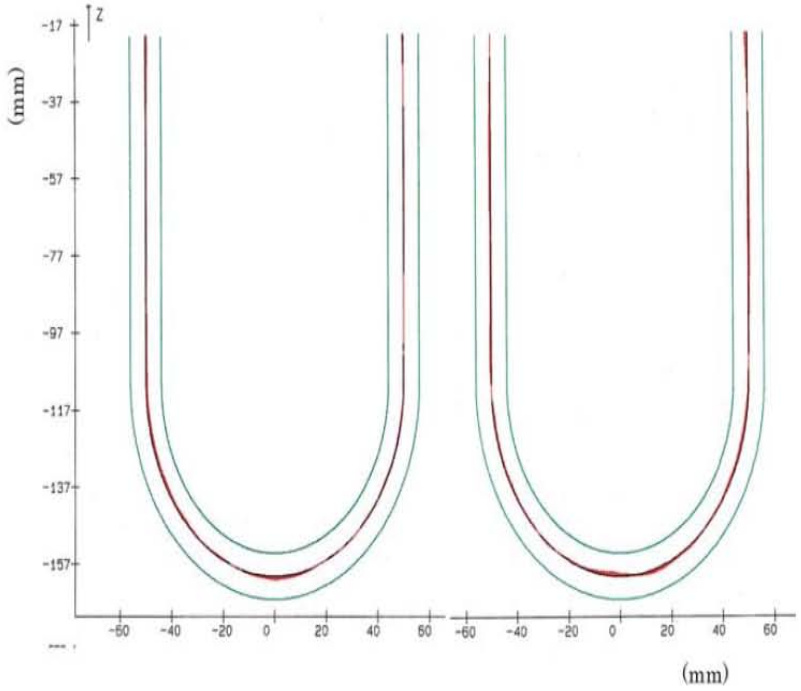


Figure 2. Inner Shape of the Precision Vessel. The center of the three lines indicates the ideal shape of the cylinder and hemisphere. The two lines drawn on both sides represent ±0.3 mm from the center line.

Importance of Inner Shape of Dissolution vessel

Calibrator Tablets renamed Performance Verification Standard

4 CONVENTIONAL Vessels were tested in all 6 positions

4 PRECISION Vessels were tested in all 6 positions

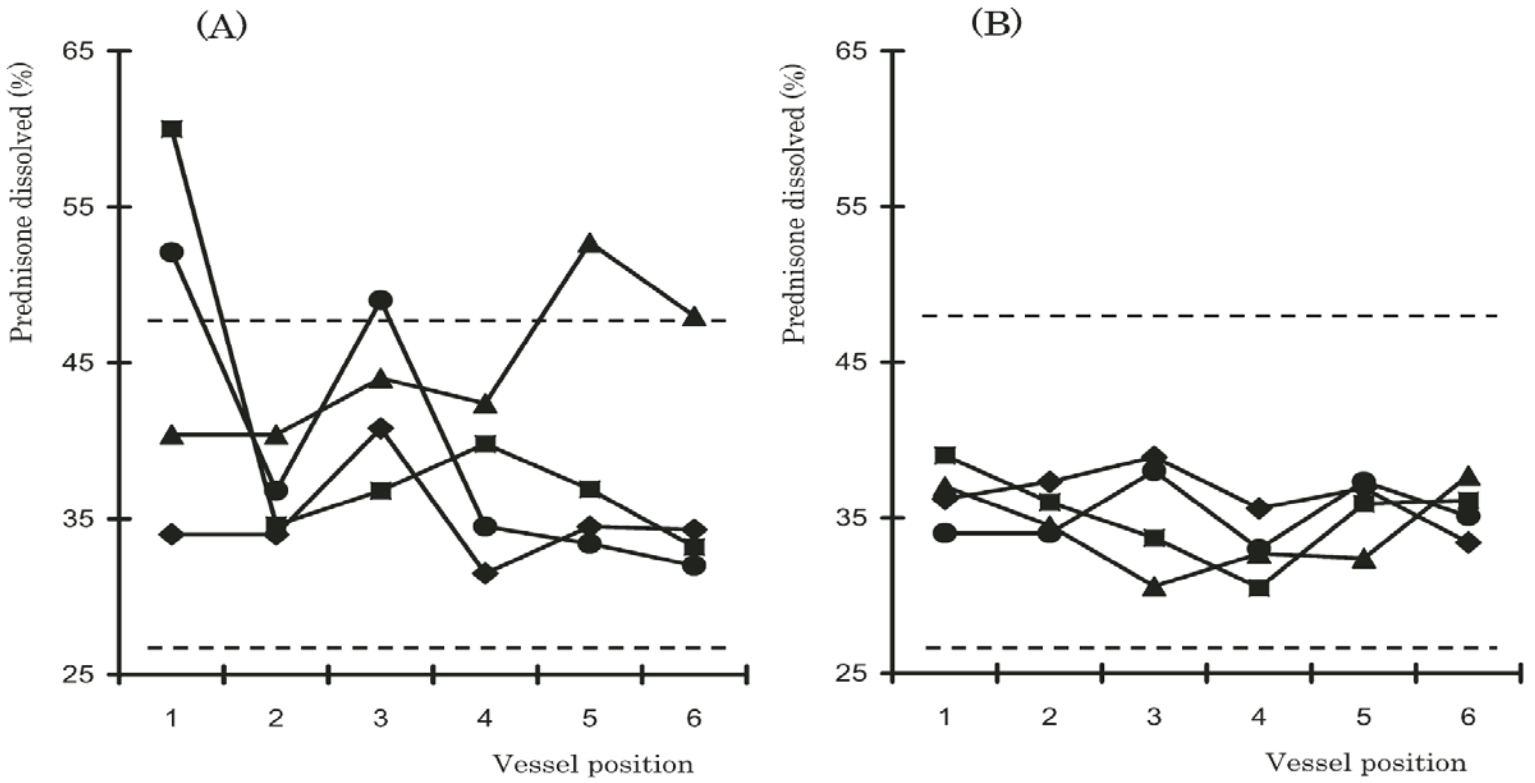


Figure 5. Dissolution Results for Prednisone Tablet Obtained from Vessel A and the Precision Vessel. (A) vessel A, (B) the precision vessel. Dotted lines represent the acceptable ranges (27–48%) for prednisone tablets (Lot O0C056) specified by USP.

Importance of Inner Shape of Dissolution vessel

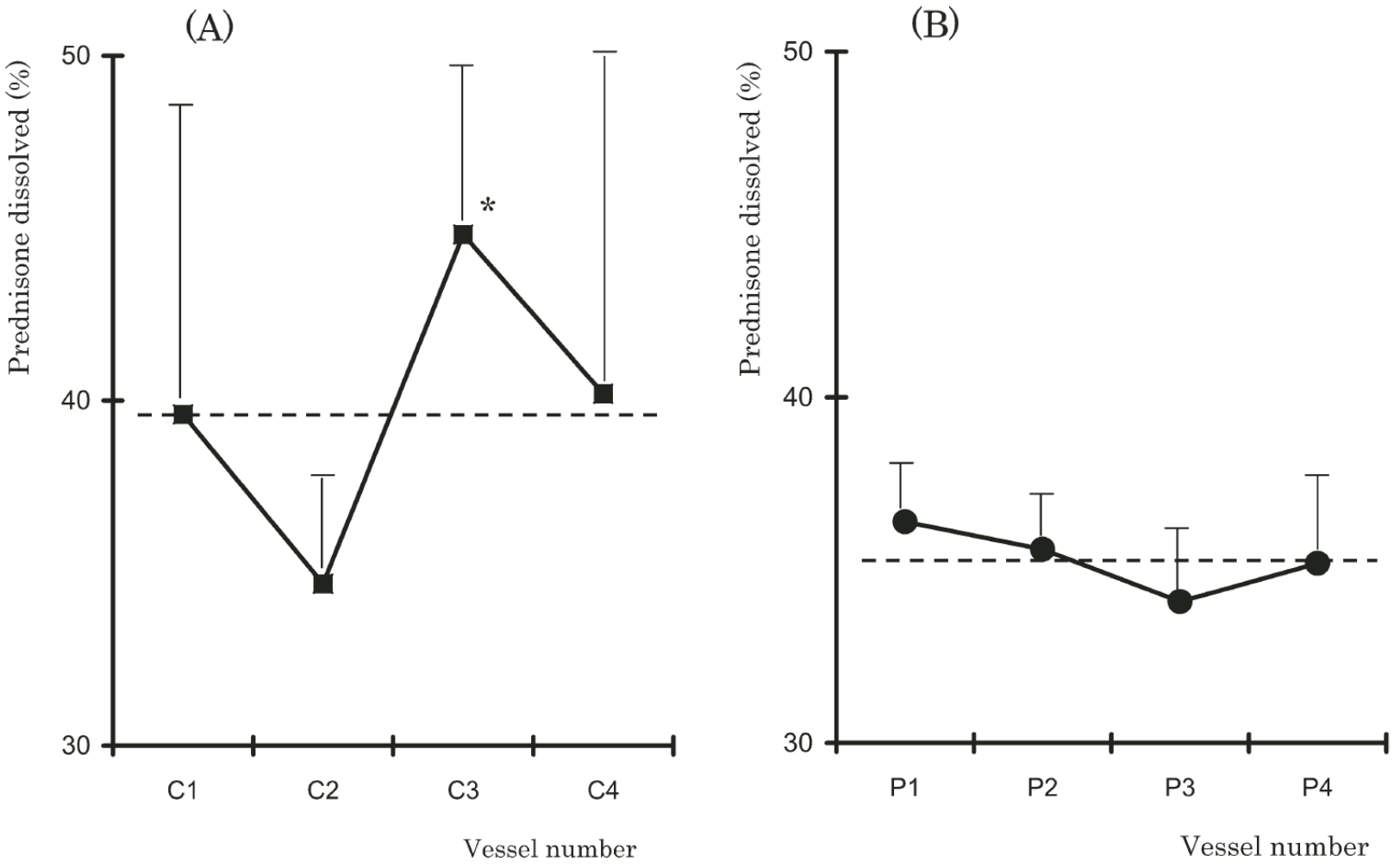
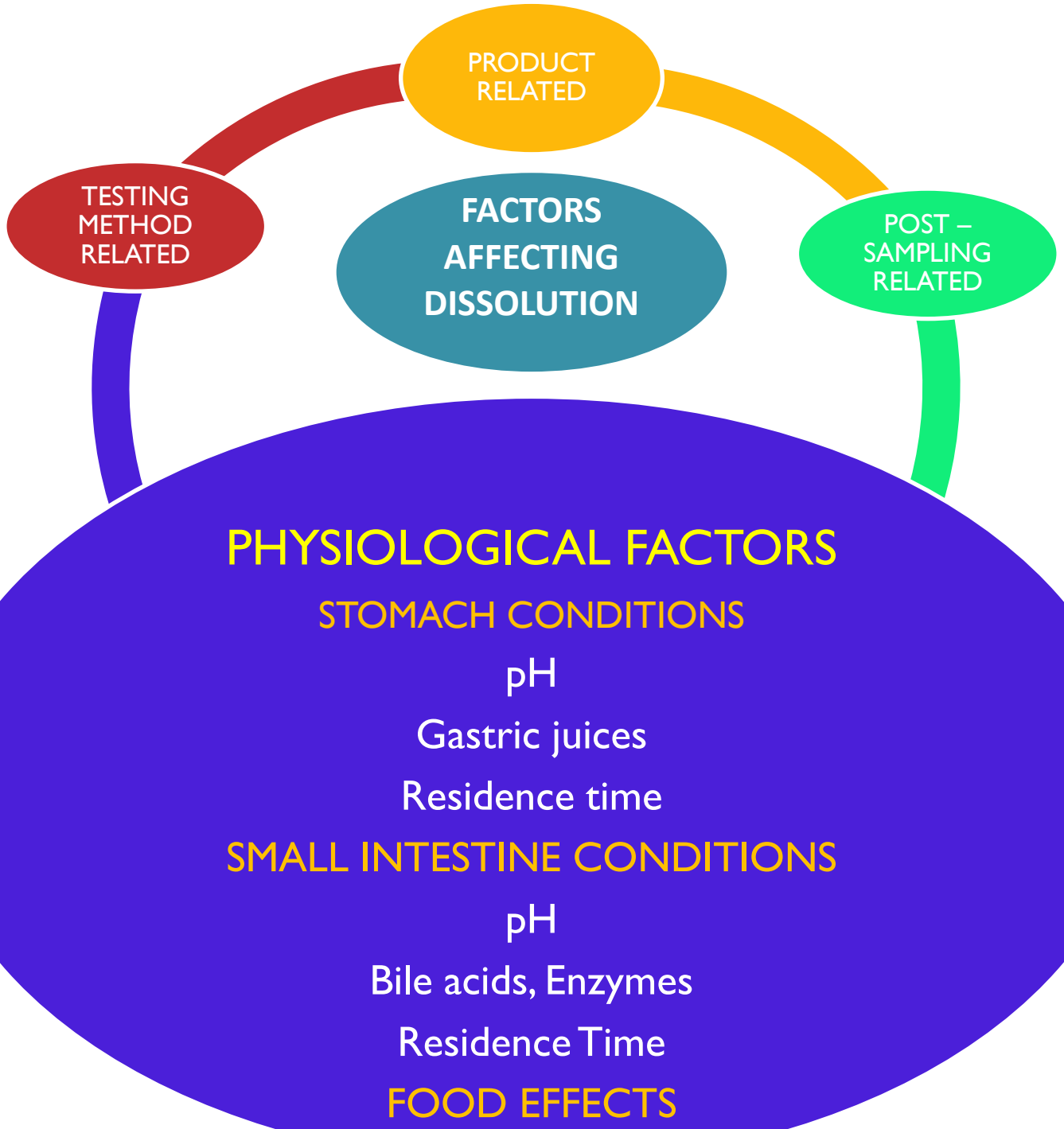


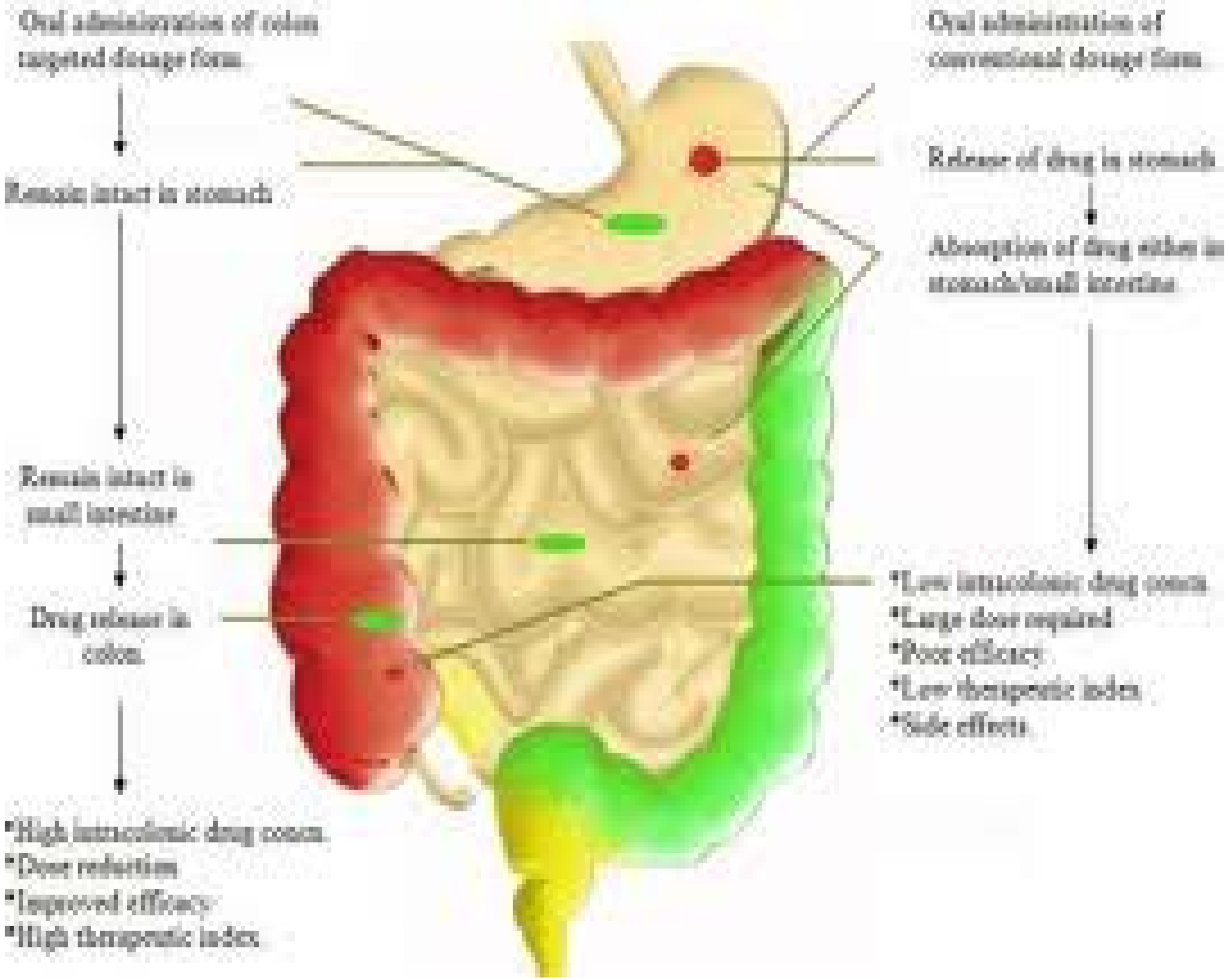
*Figure 6. Mean Dissolution Data for Prednisone Tablets Obtained from Six Vessel Positions. (A) vessel A, (B) the precision vessel. * $p<0.05$ vs. C2. Dotted line represents the mean value of 24 results. Each point represents the mean ± SD (vertical bar) of six determinations. ■, vessel A; ●, the precision vessel.*

Importance of Inner Shape of Dissolution vessel

- The dissolution results of USP Prednisone Calibrator tablets were compared for the precision vessel and vessel A.
- Variability in test results was markedly lower when the PRECISION VESSEL was used.
- For CONVENTIONAL VESSEL, however, test results varied widely between vessels used and between positions in the dissolution tester.
- In addition, the mean values of prednisone dissolution percentages obtained from six positions differed significantly ($p < 0.05$) among vessels.
- These results suggest that the shape of a glass vessel is critical to obtaining unvarying and reproducible dissolution test results.


PRODUCT RELATED
TESTING METHOD RELATED
FACTORS AFFECTING DISSOLUTION
POST – SAMPLING RELATED
PHYSIOLOGICAL FACTORS
STOMACH CONDITIONS
pH
Gastric juices
Residence time
SMALL INTESTINE CONDITIONS
pH
Bile acids, Enzymes
Residence Time
FOOD EFFECTS

Biorelevant Media



PHYSIOLOGICAL VARIABLES

STOMACH pH	**1 to 3 Fasting**	**3 to 7 fed**
Gastric Emptying	**0.5 to 2 h Fasting**	**Several hours Fed**
Duodenum: pH = 4-6 **• bile- and pancreatic secretion** **• short passage time (< 10 min)**	**Jejunum: pH = 6-7** **Ileum: pH = 7-7.5** **• quantitative absorption of bile salts (active transport)**	**Colon: pH = 5-7** **• great number and variety of bacteria** **• individual passage times differ largely**

Relationship - Ionization and Absorption

From Henderson Hasselbach equation,

weak acids = [$HA \leftrightarrow H^+ + A^-$] Acid is a proton donor

$pH = pKa + \log [A^-] / [HA]$

weak bases = [$B + H^+ \leftrightarrow BH^+$] Base is a proton acceptor

$pH = pKa + \log [B] / [BH+]$

- **Equation is used to calculate the percent ionization of a drug in cellular compartments of different pH.**

- **Understanding how changes in pH alter the ionization of drugs is very important since unionized drugs cross membranes.**

Percent Ionization of Drugs

pH	Weak Acids % ionization of aspirin		Weak Bases % ionization of codeine	
3 units > pKa	99.9%	log [A^-/HA = 1000/1]	0.1%	log [B/BH^+ = 1000/1]
2 units > pKa	99%	log [A^-/HA = 100/1]	1%	log [B/BH^+ = 100/1]
1 unit > pKa	90.9%	log [A^-/HA = 10/1]	9%	log [B/BH^+ = 10/1]
pH = pKa	50%	log [A^-/HA = 1/1]	50%	log [B/BH^+ = 1/1]
1 unit < pKa	9%	log [A^-/HA = 1/10]	90.9%	log [B/BH^+ = 1/10]
2 units < pKa	1%	log [A^-/HA = 1/100]	99%	log [B/BH^+ = 1/100]
3 units < pKa	0.1%	log [A^-/HA = 1/1000]	99.9%	log [B/BH^+ = 1/1000]

NEW DRUG DEVELOPMENT vs. GENERIC PRODUCT DEVELOPMENT

- Most Dissolution specifications are set based on brand product
- But in generics,
  - excipients could be different
  - Manufacturing processes may also differ significantly.
- Hence, dissolution methods and specifications that are appropriate for the brand product may not be suitable for the generic product
- tests and specifications have been unilaterally imposed in cases for which those tests and specifications are not appropriate.
- Therefore, moving to a regulatory process that encourages quality by design principles and dissolution methods and specifications that are based on product relevant characteristics

FDA DATABASE EXAMPLES of DISSOLUTION MEDIA

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Abacavir Sulfate	Tablet	II (Paddle)	75	0.1 N HCl	900	5, 10, 15, and 30	03/22/2006
Abacavir Sulfate/Lamivudine	Tablet	II (Paddle)	75	0.1 N HCl	900	10, 20, 30, and 45	01/03/2007
Abacavir Sulfate/Lamivudine/ Zidovudine	Tablet	II (Paddle)	75	0.1 N HCl	900	5, 10, 15, 30, and 45	01/03/2007
Acamprosate Calcium	Tablet (Delayed Release)	I (Basket)	180	Acid Stage: 0.1 N HCl Buffer Stage: "Citrate-sodium hydroxide" buffer pH 6.8 (150 ml of 2N NaOH, 21.014 gm of citric acid and ultra-pure water to 1000 ml) (Method B)	1000	120 (Acid) 30, 60, 90, 120, and 180 (buffer)	12/20/2005
Acarbose	Tablet	II (Paddle)	75	Water (deaerated)	900	10, 15, 20, 30 and 45	3/22/2006

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Triptorelin Pamoate	Injectable Suspension	II (Paddle)	200	Water-Methanol (95:5); Reconstitute vial in 2 mL Water for Injection, add to 500 mL medium at 37°C	500	1, 6, 12, 24, 48 and 72 hours	07/14/2008
Trospium Chloride	Tablet	II (Paddle)	50	0.1 N HCl	1000	10, 20, 30 and 45	12/03/2007
Trospium Chloride	Capsule (Extended Release)	II (Paddle) with sinker	50	0.1 N HCl, pH 1.1 for 2 hrs and then add 200 mL of 0.1 N NaOH in 200 mM Phosphate Buffer. Adjust pH to 7.5 using 2 N HCl and/or 2N NaOH	0-2 hrs: 750 ml, After 2 hrs: 950 ml.	2, 3, 4, 6, 8, 12 and 16 hours	07/15/2010
Vorinostat	Capsule	II (Paddle) with sinker	100	2% Tween 80 in Water	900	5, 15, 30, 45 and 60	09/03/2008
Theophylline (600 mg and 400 mg)	Tablet (Extended Release)	I (Basket)	100	SGF without enzyme, pH 1.2 during 1st hour. SIF without enzyme from end of hour 1 through the duration of the testing	900	1, 2, 4, 8, 12 and 24 hours	10/06/2008

◦ PHARMACOPOEIAL MEDIA

- Simulated Gastric Fluid EP
  - NaCl
  - HCl
  - Without Pepsin or with Pepsin
- Simulated Intestinal Fluid EP

  pH 6.8
  - NaOH
  - Pot dihydrogen phosphate
  - Pancreas powder
- Do they have physiological relevance?

• BIORELEVANT MEDIA

- Many media can be recognized based on
  - Fed state
  - Fasting state
  - Type of dosage form
  - Regional differences in GIT
  - Is this more appropriate for NDA rather than ANDA

DISSOLUTION MEDIA

1. Compendial buffers - Simulation of the pH conditions in the GI tract

2. Biorelevant media - Simulation of the physiological GI milieu

Fasted state

Stomach: FaSSGF
Small intestine: FaSSIF → FaSSIF–Gradient
Colon: SCoF

Fed State

Stomach: Milk / Ensure® Plus
Small intestine: FeSSIF → FeSSIF–Gradient
Colon: SCoF

Klein S. , *Dissolution Technologies, 16 (3): 28-40, 2009*

Simulated Gastric Fluid

Fasted: FaSSGF

"Biorelevant" conditions
in the fasted stomach

Na taurocholate	*80 µmol/L*
Lecithin	*20 µmol/L*
Pepsin	0.1 mg/mL
NaCl	34.2 mmol/L
HCl conc.	ad *pH 1.6*
Demineralized water	ad 1000 mL

pH 1.6
Surface tension 42.6 mN/m
Osmolality 121 mOsm/kg

M Vertzoni et al. *Eur J Pharm Biopharm. 60:413-417 (2005)*

Fed: FeSSGF

"Biorelevant" conditions in the
fed stomach some time after a meal

NaCl	237.02 mmol/L
Acetic acid	17.12 mmol/L
Sodium acetate	29.75 mmol/L
Demineralized water	ad 1000 mL

Milk:acetate buffer	1:1
HCl conc.	ad *pH 5.0*

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pH 5.0
Osmolality 400 mOsm/kg
Buffer capacity 25 mEq/L/pH

E Jantratid et al. *Pharm Res. 25 (7):1663–76 (2008)*

Simulated Intestinal Fluid

Fasted: FaSSIF

NaH2PO4	3.438 g
Na taurocholate	*3 mmol/L*
Lecithin	*0.75 mmol/L*
NaCl	6.186 g
NaOH	ad *pH 6.5*

Demineralized water ad 1 Liter

pH 6.5

Osmolality	*270 + 10 mOsm/kg*
Buffer capacity	*10 + 2 mEq/L/pH*

Fed: FeSSIF

Glacial acetic acid 8.65 g

Na taurocholate	*15 mmol/L*
Lecithin	*3.75 mmol/L*
NaCl	11.874 g
NaOH	ad *pH 5.0*

Demineralized water ad 1 Liter

pH 5.0

Osmolality 635 + 10 mOsm/kg

Buffer capacity 76 + 2 mEq/L/pH

SIMULATED COLONIC FLUID (SCoF)

Simulation of the pH-values and ions in the proximal colon

1 molar *acetic acid solution*	*170 mL*
1 molar NaOH solution	157 mL
Demineralized water	ad 1 Liter

pH 5.8
Osmolality 295 mOsm/kg
Buffer capacity 29 mEq/L/pH

Fotaki et al , *Eur. J. Pharm. Sci. 24 : 115-122, 2005*

CONCEPT OF GRADIENT DISSOLUTION MEDIA

Concentration of bile components: FaSSIF gradient

GI-section	pH	Biorelevant media	Sodium taurocholate	Lecithin
Proximal Jejunum	6.5	FaSSIF	3 mmol/l	0.75 mmol/l
Distal Jejunum	6.8	FaSSIF[a,b]	3 mmol/l	0.75 mmol/l
Proximal Ileum	7.2	FaSSIF[a,b]	1.5 mmol/l	0.375 mmol/l
Distal Ileum	7.5	Blank FaSSIF[a]	--------	--------

[a] pH modified, [b] Concentration of bile components modified

Concentration of bile components: FeSSIF gradient

GI-section	pH	Biorelevant media	Sodium taurocholate	Lecithin
Proximal Jejunum	5.0	FeSSIF	15 mmol/l	3.75 mmol/l
Distal Jejunum	6.5	FeSSIF[a,b]	15 mmol/l	3.75 mmol/l
Proximal Ileum	6.5	FeSSIF[a,b]	7.5 mmol/l	1.875 mmol/l
Distal Ileum	7.5	Blank FaSSIF[a]	--------	--------

[a] pH modified, [b] Concentration of bile components modified, [c] Phosphate buffer

DISSOLUTION PROFILE IN BIORELEVANT MEDIA

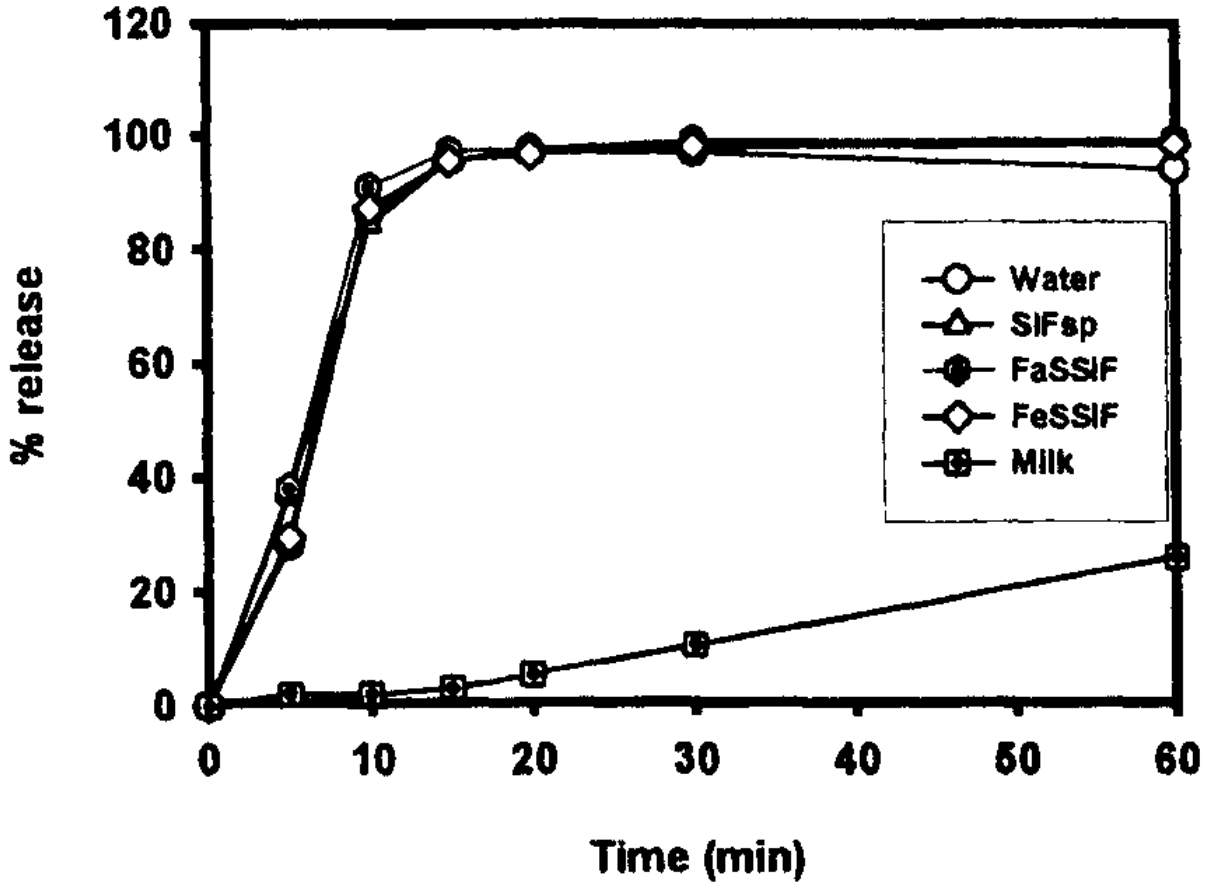

Fig. 1. Mean dissolution profiles of acetaminophen from Panadol® tablets in various media at 100 rpm.

Pharmaceutical Research, Vol. 15, No. 5, 1998

DISSOLUTION PROFILE IN BIORELEVANT MEDIA

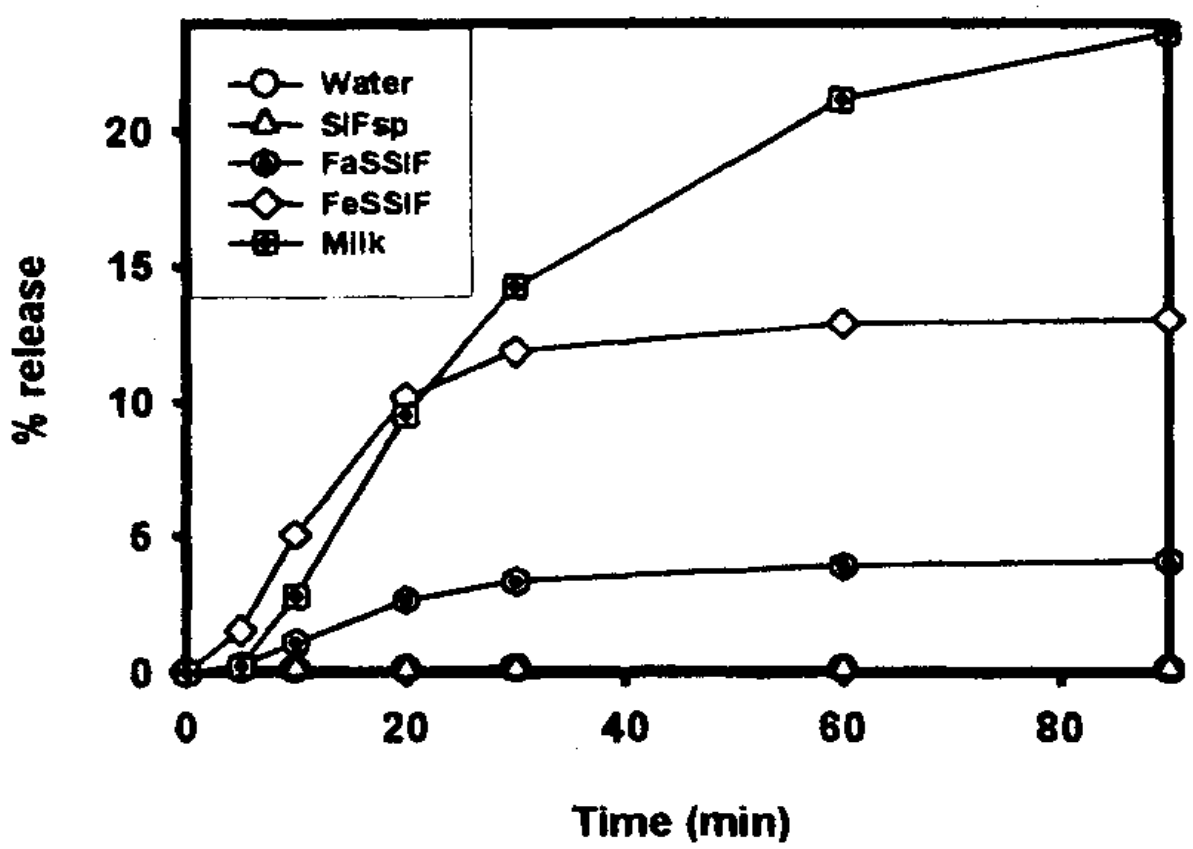

Fig. 3. Mean dissolution profiles of danazol from Danatrol® capsules in various media at 100 rpm.

DISSOLUTION PROFILE IN BIORELEVANT MEDIA

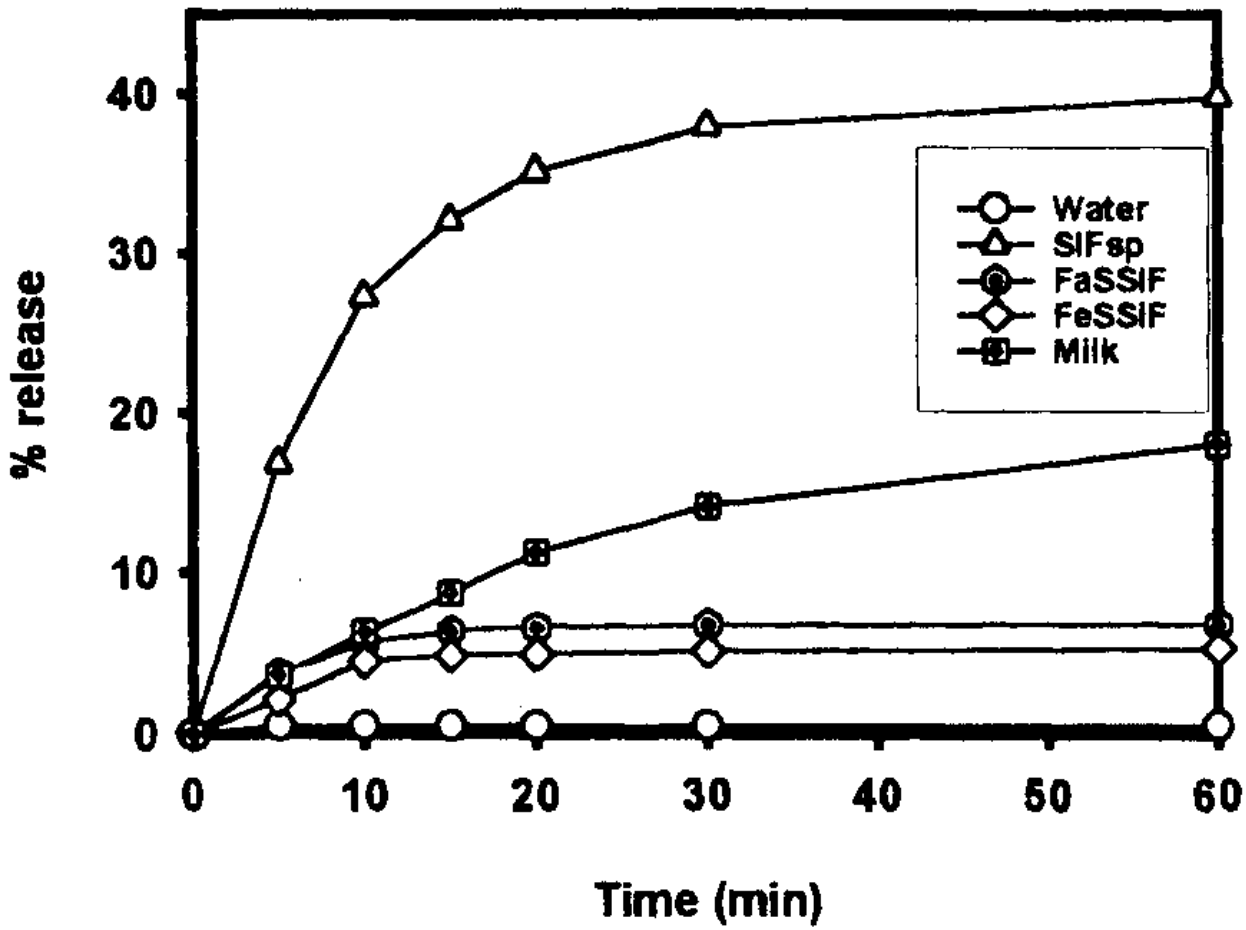

Fig. 4. Mean dissolution profiles of mefenamic acid from Parkemed® capsules in various media at 100 rpm.

DISSOLUTION PROFILE IN BIORELEVANT MEDIA

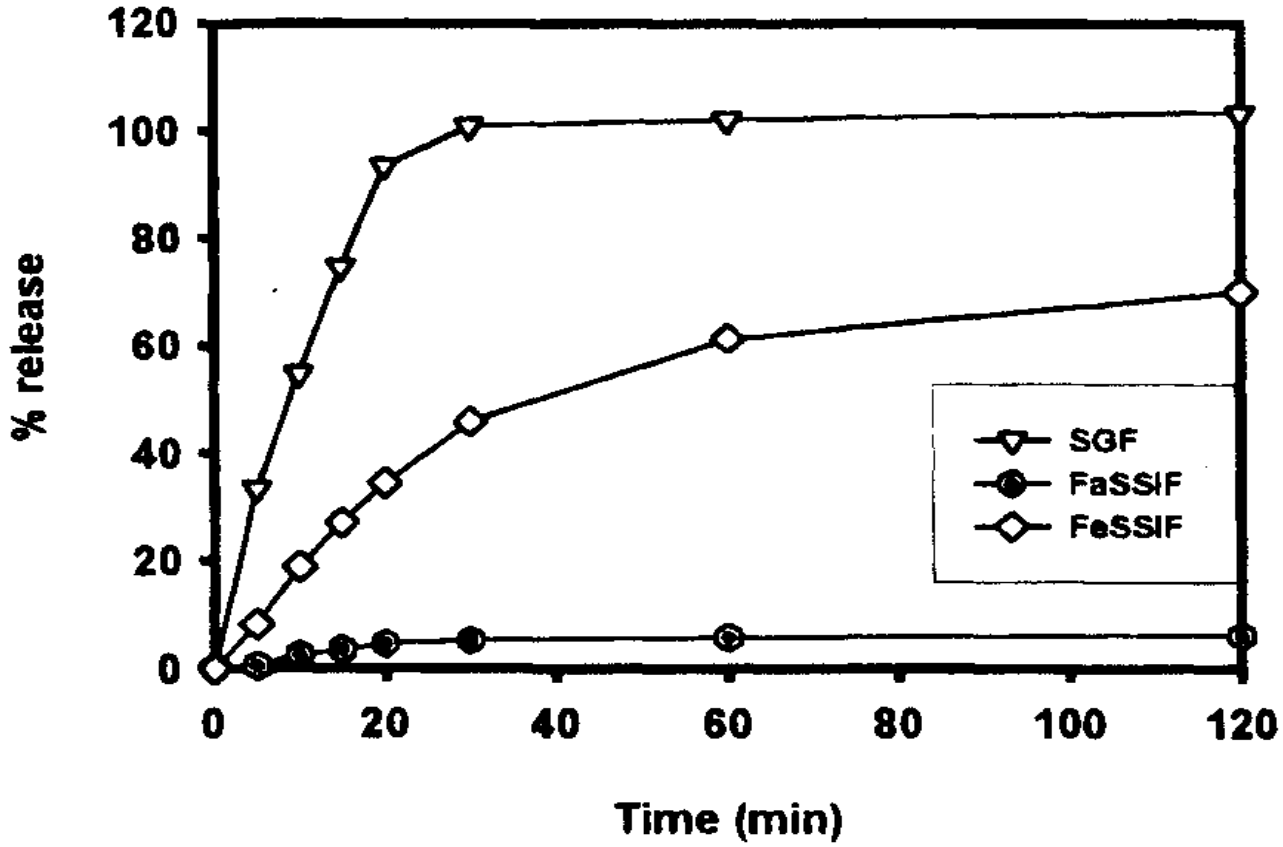

Fig. 5. Mean dissolution profiles of ketoconazole from Nizoral® tablets in various media at 100 rpm.

Thank You !!