# Fed and Fasted Conditions Dissolution Studies

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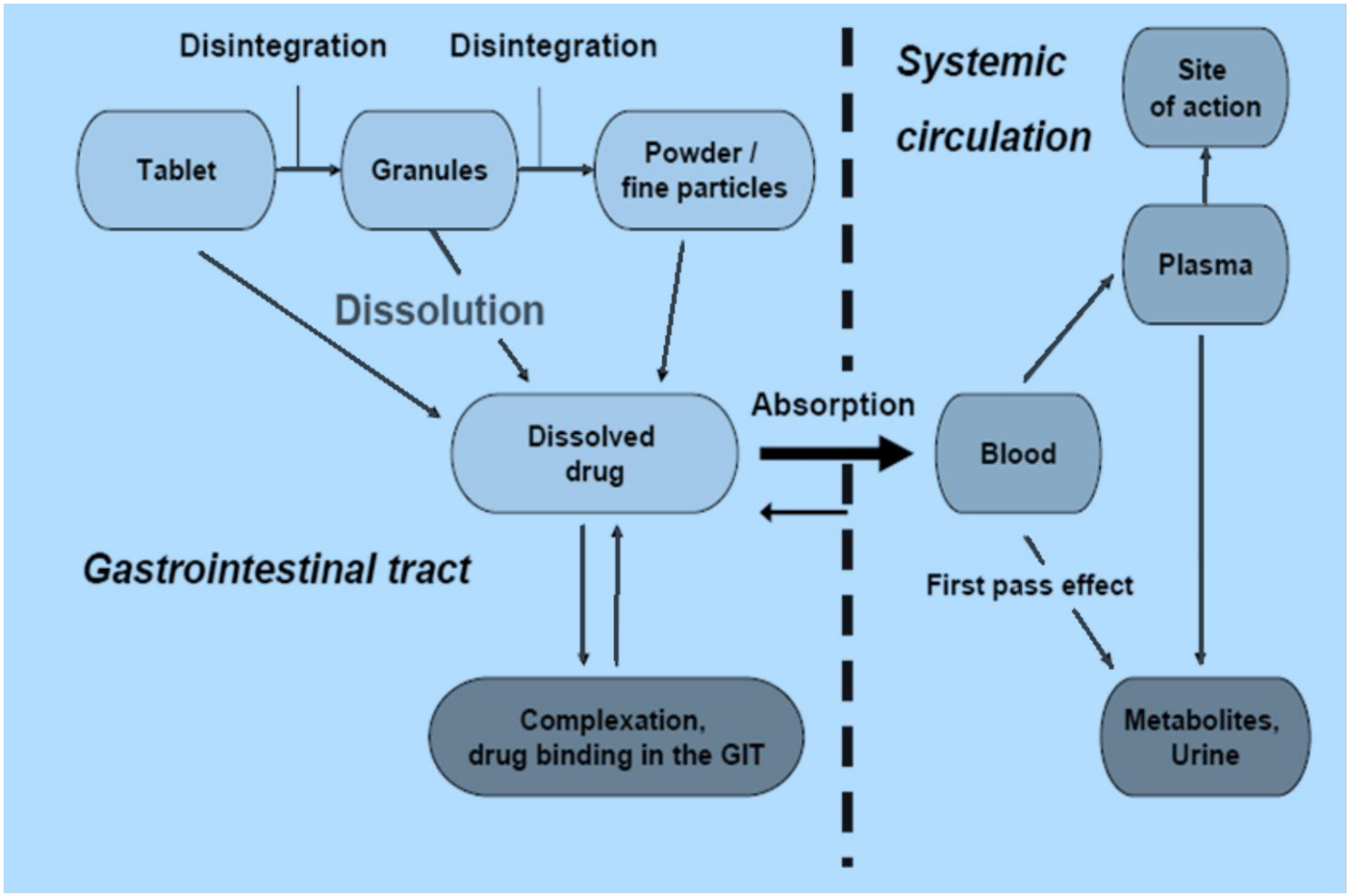
## OUTLINE

- Factors effecting solubility and dissolution
- Selection of dissolution medium
- Fasted and Fed State
- Physiological dissolution methodologies
- Biorelevant dissolution media, *FaSSIF/FeSSIF*
- Case Examples
- New generation dissolution media *(FaSSIF-V2 and FaSSIF- V3*

**Pharmaceutical solid oral dosage forms must undergo dissolution in intestinal fluids of the gastrointestinal tract before they can be absorbed and reach the systemic circulation.**

***Dissolution is a critical part of the drug delivery process.***




**Dissolution and oral drug delivery**

# Factors effecting solubility and dissolution of drug in GI system

| Parameter | Physicochemical Characteristic | Physiological Variable |
|---|---|---|
| Surface area (A) | Particle size, wettability | Surfactants and bile salts in gastric fluid |
| Diffusion (D) | Molecular size | Viscosity of GI fluid |
| Thickness of diffusion layer (h) | | GI motility |
| Saturation concentration ($C_s$) | Hydrophilicity, crystalline structure, solubility | pH, surfactants, buffering capacity, bile salts, food content |
| Concentration of dissolved drug (C) | | Permeability |
| Volume of solvent (V) | | Volume of GI fluids and secretions |

# In vitro and in vivo dissolution parameters

| Parameter | In Vitro Dissolution | In Vivo Dissolution |
|---|---|---|
| Media | Compendial media<br>USP media<br>Biorelevant media | Gastrointestinal fluids |
| Volume | Variable according to apparatus used and simulated condition (fasted or fed state) | Variable according to condition (fased or fed state) |
| Duration | Variable according to apparatus used, dosage form and simulated condition (fasted or fed state) | Variable according to dosage form and condition (fasted or fed state) |
| Hydrodynamics | USP Apparatus 1,2,3,4 | Gastrointestinal motility |
| Location | Constat (unless media change occurs, i.e., USP App 3 and 4) | Variation with time |
| Amount of drug | Constant in closed systems<br>Decrease in open system | Decreases as drug is absorbed |

*Wang et al. Dissolution Technology, 2009,* *Klein S. AAPSJ, 12 (3): 397-406, 2010.*

# Dissolution/In vitro Release Testing-Important Tool

- Assess batch to batch quality of the product
- Determine product stability/shelf life
- Guide in the development and/or process control of formulations

# Dissolution/In vitro Release Testing-Important Tool

- Ensure quality and performance after changes in the formulation,the manufacturing process, the site of manufacture and the scale-up of manufacturing (SUPAC) process
- Bioequivalency Test: Biowaivers
- Predict the in vivo release in terms of IVIVC

# Important points to find the right dissolution test

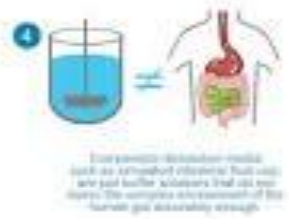
- Where in the GI tract is drug released from the dosage form
- How long does the dosage form have to release the drug
- Composition of the fluids into which drug is released

# Selection of dissolution medium

- pH of the dissolution medium
- Surface tension of dissolution medium
- Viscosity of dissolution medium and sink conditions
- Presence of unreactive and reactive additives in dissolution medium
- Temperature of dissolution medium

# Selection of dissolution medium

- **Selection of the proper medium for dissolution testing depends largely on the physicochemical properties of the drug as well as more economics and practical reason.**



# Selection of dissolution medium

- **The choice of medium will depend on the purpose of the dissolution test.**

- **For batch-to batch quality testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of the drug product to ensure that sink conditions are met.**

# Fasted and Fed State

- Food ingestion is known to induce various physiological changes in the GI envirronment.
- Poorly soluble compounds are especially pyrone to higher systemic exposure when given in the fed state, with the main effect being faster and more extensive dissolution under fed conditions,
- due to higher levels of native surfactant, presence of lipophilic meal components and the products of fat digestion, larger volumes of fluids available to dissolve the drug and the longer upper GI residence time.

- **The in vivo dissolution behavior of weak bases is additionally influenced by variations in upper GI pH, making these drugs especially prone to food effects.**

# Fasted and Fed State

- Since the rate-determining step to the intestinal absorption of poorly soluble drugs is the dissolution in the gastrointestinal (GI) tract, postprandial changes in GI physiology,

- in addition to any specific interactions between drug and food, are expected to affect the pharmacokinetics and bioavailability of such drugs.

# Fasted and Fed State

**In fed state, the environment in the small intestine also changes considerably after a meal compared with the fasting conditions.**

# Fasted and Fed State

- In the fed state lipid digestion products may also contribute to the solubilization of lipophilic compounds, so inclusion of lipid digestion products in the medial would no prediction of fed v.s fasted state dissolution in vivo.

- Another continuing area of focus will be the refirement of efforts to predict food effects for MR formulations (osmotic pumps, coated pellets etc.) and to model drug-absorption processes.

# Fasted and Fed State

- As food intake triggers many of the secretions in the small intestine, the composition of fed state intestinal fluid can vary greatly from fasted state intestinal fluid.
- This difference in composition can be partially responsible for differences in bioavailability seen when drug is administered in the fed versus the fasted state.
- For some lipophilic drugs, co-administration with a meal has been shown to increase bioavailability compared to fasted state.

# Physiological Dissolution Methodologies

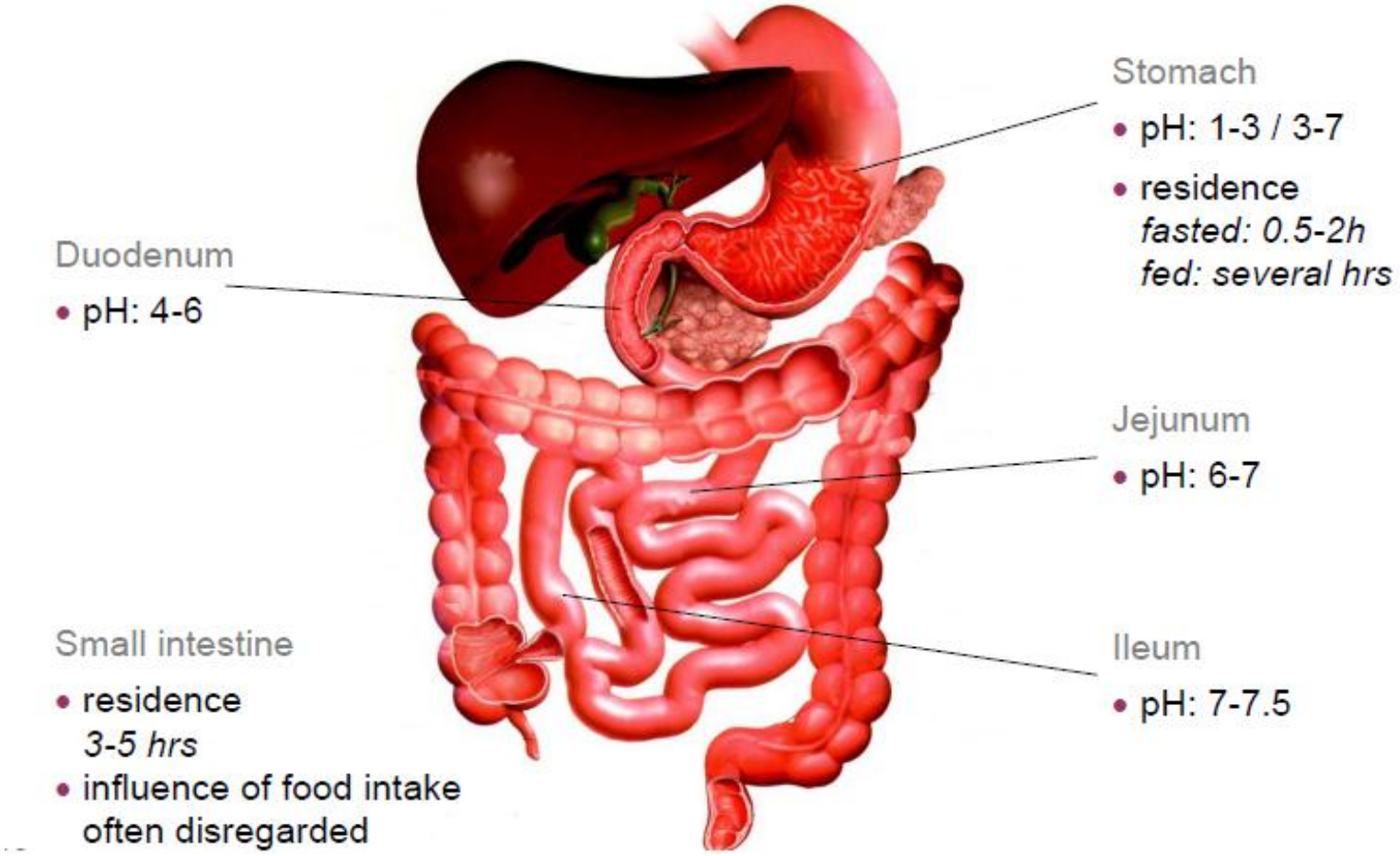
- **Simulated gastric and intestinal fluids are media designed to mimic the major characteristics of *in vivo* fluids.**

- **A frequently used medium for the simulation of small intestinal (SI) conditions in the fasted state is simulated intestinal fluid (SIF), a medium that was first described as a standard test solution in the USP more than 50 years ago.**

- **The only parameter that has been changed is the pH of the medium.**
- **As it was assumed that the pH in the small intestine is very close to blood plasma, the pH of SIF was initially set at 7.5 .**
- **However, subsequent examinations of the pH in the intestinal tract revealed that a pH gradient exists within the small intestine, that the pH becomes less acidic at more distal locations, and that pH values close to 7.5 can only be measured in the terminal ileum.**

# Human GI tract

| | pH |
|---|---|
| Stomach | 1-3 (fasted)<br>3-7 (fed) |
| Duodenum | 4-6 |
| Jejunum | 6-7 |
| Ileum | 7-7.5 |
| Colon | 5-7 |




# Gastrointestinal passage

- **The passage of the dosage form through the stomach depens on unit size and prandial state.**
- **In the fasted state, motility in the upper GI tract is cyclical and passage is size independent.**
- **In the fed state, passage of bigger units may be considerebly delayed.**

- As drug absorption during SI passage is most efficient when drug release from the dosage form occurs at proximal SI sites, the more relevant pH values are those in the duodenum and the proximal jejunum.

- The use of an in vitro medium with an unsuitably high pH in contrast would most probably lead to false positive results, especially for poorly soluble, weakly acidic drugs and enteric coated dosage forms.

**Simulation of GI conditions is essential to adequately predict the *in vivo* behavior of drug formulations.**

**To reduce the size and number of human studies required to identify a drug product with appropriate performance in both the fed and fasted states,it is advantageous to be able to pre-screen formulations *in vitro.***

- **More physiologically relevant media have been designed in order to simulate the composition of the stomach contents in both fasted and fed states.**

# Biorelevant Dissolution Media

- Recently, the use of biorelevant testing conditions has become standard in the characterization of new compounds and development of formulations.

- They can also be used as the basis for developing appropriate quality control test, under consideration of appropriate pH and buffer capacity, by substituting appropriate synthetic surfactants for the natural one.

# Biorelevant Dissolution Media

- **Simulated small intestinal biorelevant media are increasingly seen as a helpful tool to assess the dissolution and solubility of drugs.**

- **Biorelevant media are commonly used to simulate the physiological composition of human intestinal fluids (HIF) in *in vitro* solubility and dissolution investigations.**

# Biorelevant Media

**To reflect the entire human gastrointestinal tract, media have been introduced to**

- ✓ **simulate gastric juice (FaSSG) and (FeSSGF)**
- ✓ **small intestinal(FaSSIF) and (FeSSIF)**
- ✓ **colonic fluids (FaSSCoF and FeSSCoF)**

**under pre- and postprandial conditions.**

# Gastric Media

**Fasted conditions in the stomach**

- **Simulated gastric fluid (SGF) , which has a pH 1.2 and contains pepsin is described in the USP.**

- **A fasted state simulated gastric fluid (FaSSGF) which contains pepsin and very low (micromolar) amounts of bile salt and lecithin , was subsequently developed by *Vertzoni et al.***

# Biorelevant conditions in the fasted stomach

| FaSSGF | |
|---|---|
| Sodium taurocholate | 80 mmol/L |
| Lecithin | 20 mmol/L |
| Pepsin | 0.1 mg/mL |
| NaCl | 34.2 mmol/L |
| HCl conc. | ad pH 1.6 |
| Deionized water | ad 1000 mL |
| *pH* | *1.6* |
| *Surface tension* | *42.6 mN/m* |
| *Osmolality* | *121 mOsm/kg* |

*Vertzoni et al. Eur J Pharm Biopharm. 60 : 413-417, 2005*

# *Composition of the Medium to Simulate the Fasted-State Stomach: Fasted-State Simulated Gastric Fluid (FaSSGF)*

| Composition | |
|---|---|
| Sodium taurocholate (µM) | 80 |
| Lecithin (µM) | 20 |
| Pepsin (mg/mL) | 0.1 |
| Sodium chloride (mM) | 34.2 |
| Hydrochloric acid q.s. | pH 1.6 |

| Properties | |
|---|---|
| pH | 1.6 |
| Osmolality (mOsm/kg) | 120.7 ± 2.5 |
| Buffer capacity (mmol/L/pH) | – |
| Surface tension (mN/m) | 42.6 |

# Biorelevant Media Content

| | SGF | FaSSIF | FeSSIF |
|---|---|---|---|
| pH | 1.2 (1.6) | 6.5 | 5.0 |
| Lecithin Conc., mM | 0 | 0.75 | 3.75 |
| NaTau, mM | 0 | 3 | 15 |
| Ionic Strength, M | 0.26 | 0.16 | 0.32 |

*Galia E. et al.,1998,*

# FaSSIF and FeSSIF

- **Fasted-state simulated intestinal fluids (FaSSIF) and Fed-state simulated intestinal fluids (FeSSIF) were introduced *by Prof. J.Dressman in 1998.***

# FaSSIF and FeSSIF

- **Conventional dissolution media for poorly soluble drugs contain synthetic surfactants, such as sodium dodecyl sulphate,which form micelles.**

- **In contrast, FeSSIF and FaSSIF contain natural surfactants that form more complex lipid aggregates.**

# FaSSIF and FeSSIF

- **The use biorelevant media such as Fed state simulated intestinal fluid- *FeSSIF* and Fasted state simulated intestinal fluid-*FaSSIF* is particulary important for poorly water-soluble compounds because they simulate the solubilizing environment of mixed micelles.**

# Biorelevant dissolution media

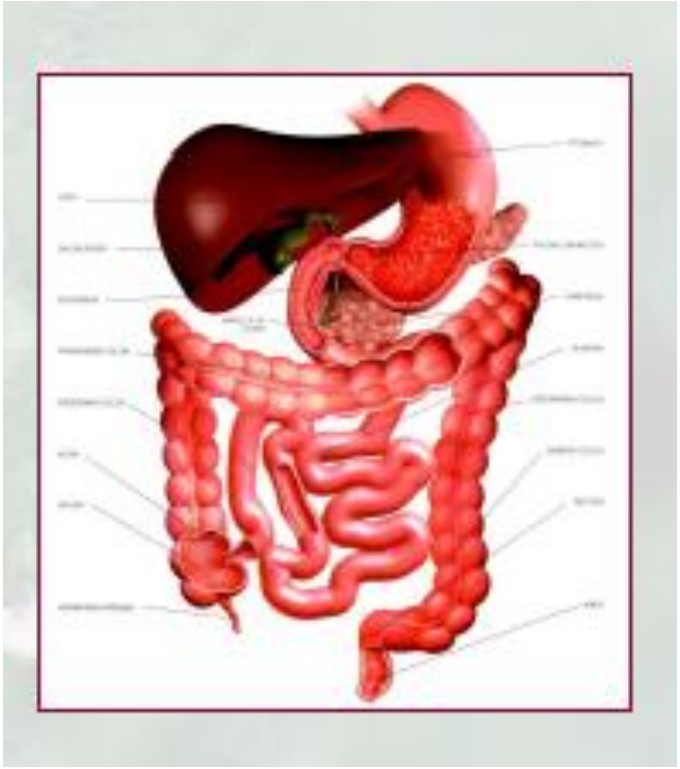
## Fasted Stated

**Stomach**

- **FaSSGF: Simulates reduced surface tension in the stomach**

**Small intestine**

- **FaSSIF to simulate basal bile secretion in upper SI**



*Vertzoni et al. EJPB 2005,*
*Dressman et al. Pharm.Res. 1998*

# Biorelevant dissolution media

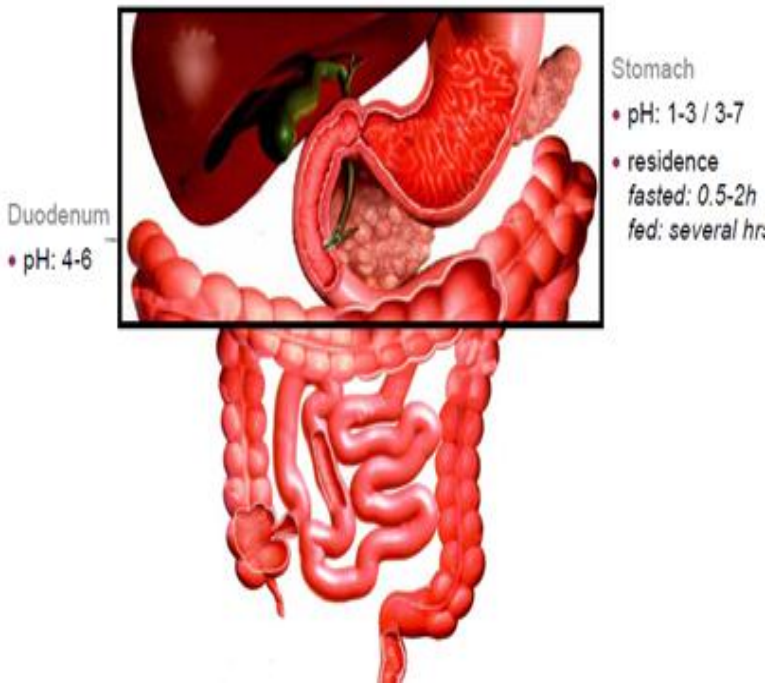
## Fed State

### Stomach

- **FessGF:** Milk/buffer pH 5 combination simulate gastric conditions after a standard breakfast

### Small intestine

- **FeSSIF-V2** to simulate postprandial bile secretion, lipolysis products, increased buffer capacity and osmolality in upper SI after food intake




*Jantratid, 2008*

# Simulation of The Physiological Gı Contents

# Biorelevant Dissolution Media Biorelevant pH Gradient

| | Preprandial | Postprandial |
|---|---|---|
| Stomach | FaSSGF | Milk, Ensure$^{R}$ Plus |
| Small intestine | FaSSIF | FeSSIF |

*Klein S. AAPSJ, 12 (3): 397-406, 2010.*

**FeSSIF and FaSSIF  comprice a bile salt and lecithin, which are responsible for the emulsification of dieatary fats in humans and animals.**

## *Composition of the Media to Simulate the Fed-State Stomach, Including Fed-State Simulated Gastric Fluid (FeSSGF)*

| Composition | Early | Middle (FeSSGF) | Late |
|---|---|---|---|
| Sodium chloride (mM) | 148 | 237.02 | 122.6 |
| Acetic acid (mM) | – | 17.12 | – |
| Sodium acetate (mM) | – | 29.75 | – |
| Ortho-phosphoric acid (mM) | – | – | 5.5 |
| Sodium dihydrogen phosphate (mM) | – | – | 32 |
| Milk/buffer | 1:0 | 1:1 | 1:3 |
| Hydrochloric acid/ sodium hydroxide q.s. | pH 6.4 | pH 5 | pH 3 |
| **Properties** | | | |
| pH | 6.4 | 5 | 3 |
| Osmolality (mOsm/kg) | 559 | 400 | 300 |
| Buffer capacity (mmol/L/pH) | 21.33 | 25 | 25 |
| Surface tension (mN/m) | 49.7 ± 0.3 | 52.3 ± 0.3 | 58.1 ± 0.2 |

# *Composition of the Media to Simulate the Fed-State Upper Small Intestine, Including Fed-State Simulated Intestinal Fluid,Updated Version (FeSSIF-V2)*

| Composition (mM) | Early FeSSIF | Middle FeSSIF | Late FeSSIF | FeSSIF-V2 |
|---|---|---|---|---|
| Sodium taurocholate | 10 | 7.5 | 4.5 | 10 |
| Lecithin | 3 | 2 | 0.5 | 2 |
| Glyceryl monooleate | 6.5 | 5 | 1 | 5 |
| Sodium oleate | 40 | 30 | 0.8 | 0.8 |
| Maleic acid | 28.6 | 44 | 58.09 | 55.02 |
| Sodium hydroxide | 52.5 | 65.3 | 72 | 81.65 |
| Sodium chloride | 145.2 | 122.8 | 51 | 125.5 |
| **Properties** | | | | |
| pH | 6.5 | 5.8 | 5.4 | 5.8 |
| Osmolality (mOsm/kg) | 400 ± 10 | 390 ± 10 | 240 ± 10 | 390 ± 10 |
| Buffer capacity (mmol/L/pH) | 25 | 25 | 15 | 25 |
| Surface tension (mN/m) | 30.1 ± 0.2 | 32.7 ± 0.5 | 46.0 ± 0.2 | 40.5 ± 0.2 |

# Media to simulate upper GI Contents

## Biorelevant dissolution media

| Location | pre-/postprandial | Medium |
|---|---|---|
| Stomach | preprandial | FaSSGF |
| Stomach | postprandial | Ensure® Plus, Milk, FeSSGF |
| Small intestine | preprandial | FaSSIF, FaSSIF V-2 |
| Small intestine | postprandial | FeSSIF, FeSSIF V-2 |

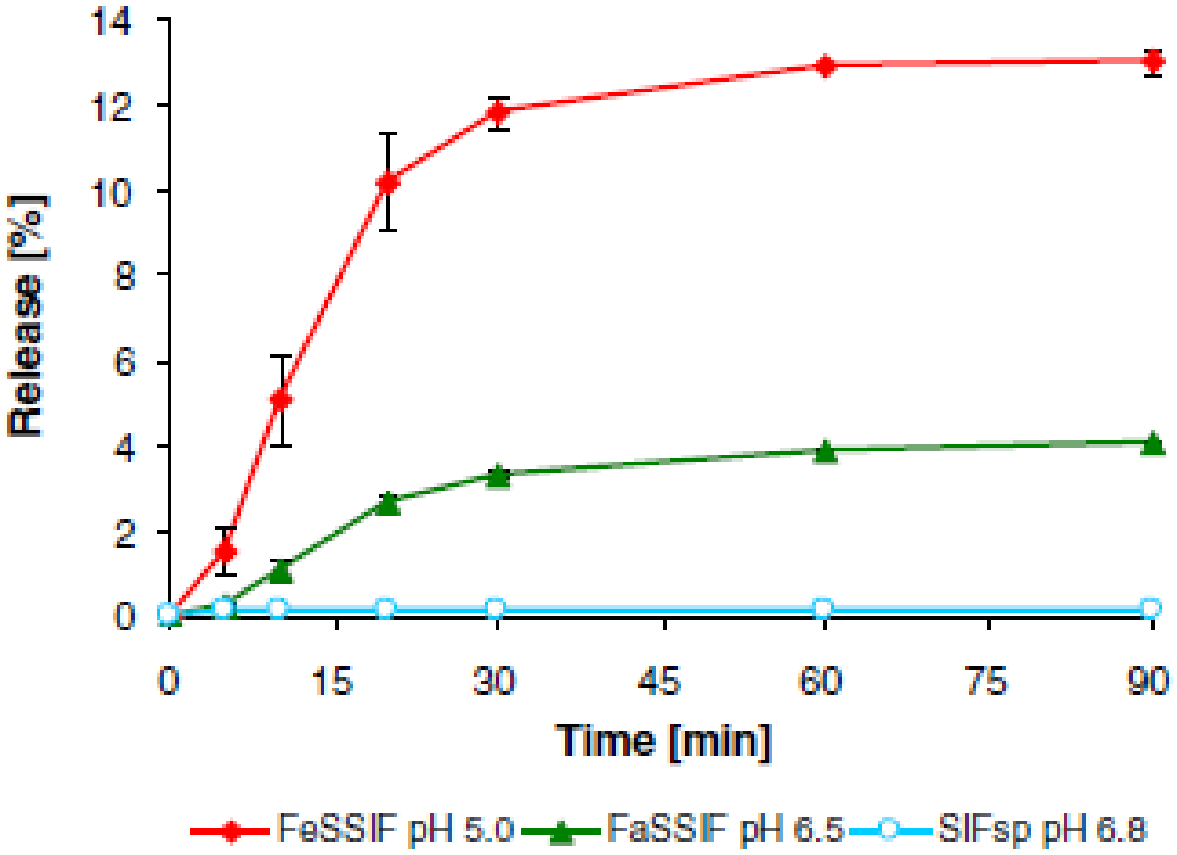
*S Klein The AAPS Journal, 2010*

# CASE -EXAMPLES

**DANAZOL** → **BCS ClassII (Neutral Compound)**

- **Solubility: 0.42 µg/ml**
- **LogP: 4.53 Strongly lipophilic**
- **good permeability across GI membranes**

- ***in vitro* performance of tablets (200mg)**
- **Using the paddle apparatus (100 rpm)**
- **500 ml, SIF sp,FaSSIF, FeSSIF**




- Clearly reflect the poor aqueos solubility of the drug since in SIFsp, no drug was released
- The total amount of drug released in FeSSIF was three to four times higher than in FASSIF

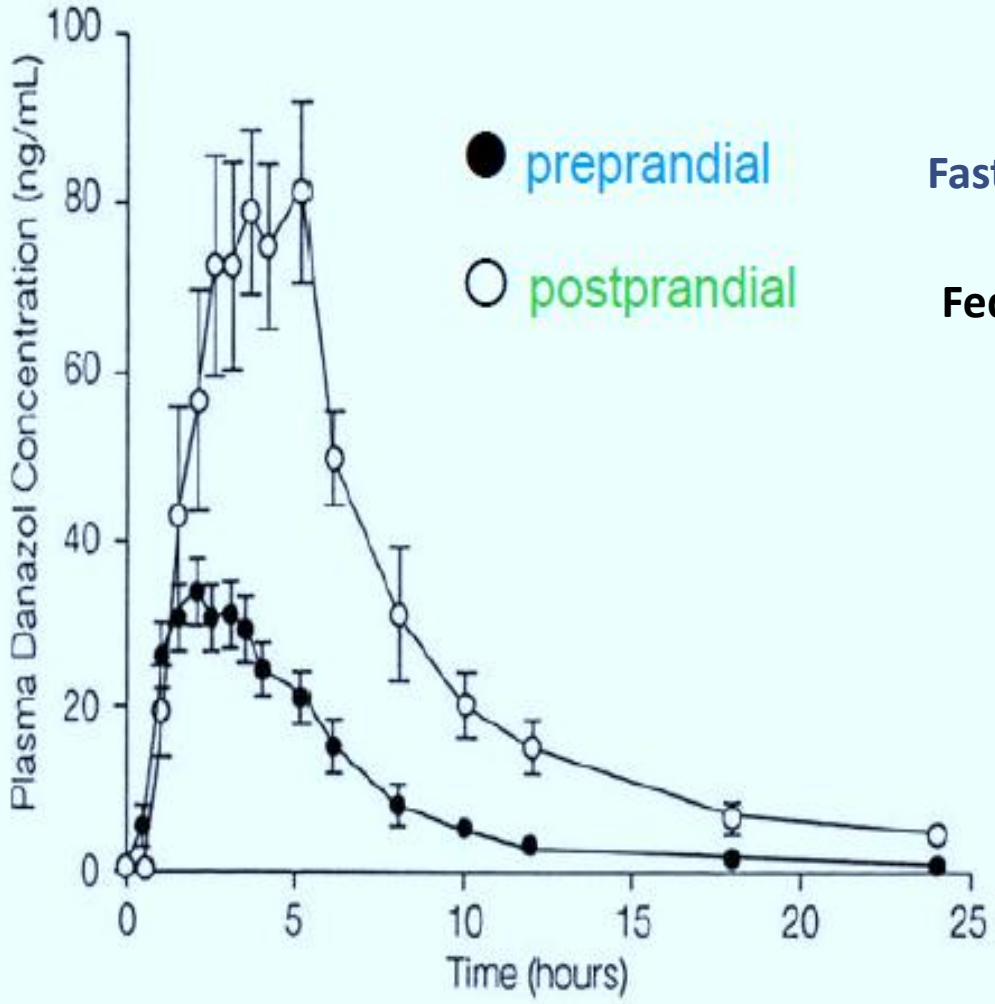
**Dissolution profiles of Danatrol tablet obtained in media simulating the intraluminal composition of the small intestine before and after a meal (n=3±SD)**

*S Klein,2010, adapted from Galia, 1999*

- **Dissolution results indicate that the BA of danazol would be better when the drug is administered in the fed state.**

- **These results are in good agreement with pharmacokinetic data available in literature (Chairman et al. 1993)**

**Danazol**




Charman et al., *J. Clin. Pharm.* 33: 1207-1213 (1993)

**It can be concluded that two biorelevant media,FaSSIF and FeSSIF, are a useful tool to to predict the BA of the neutral BCS class II compound danazol.**

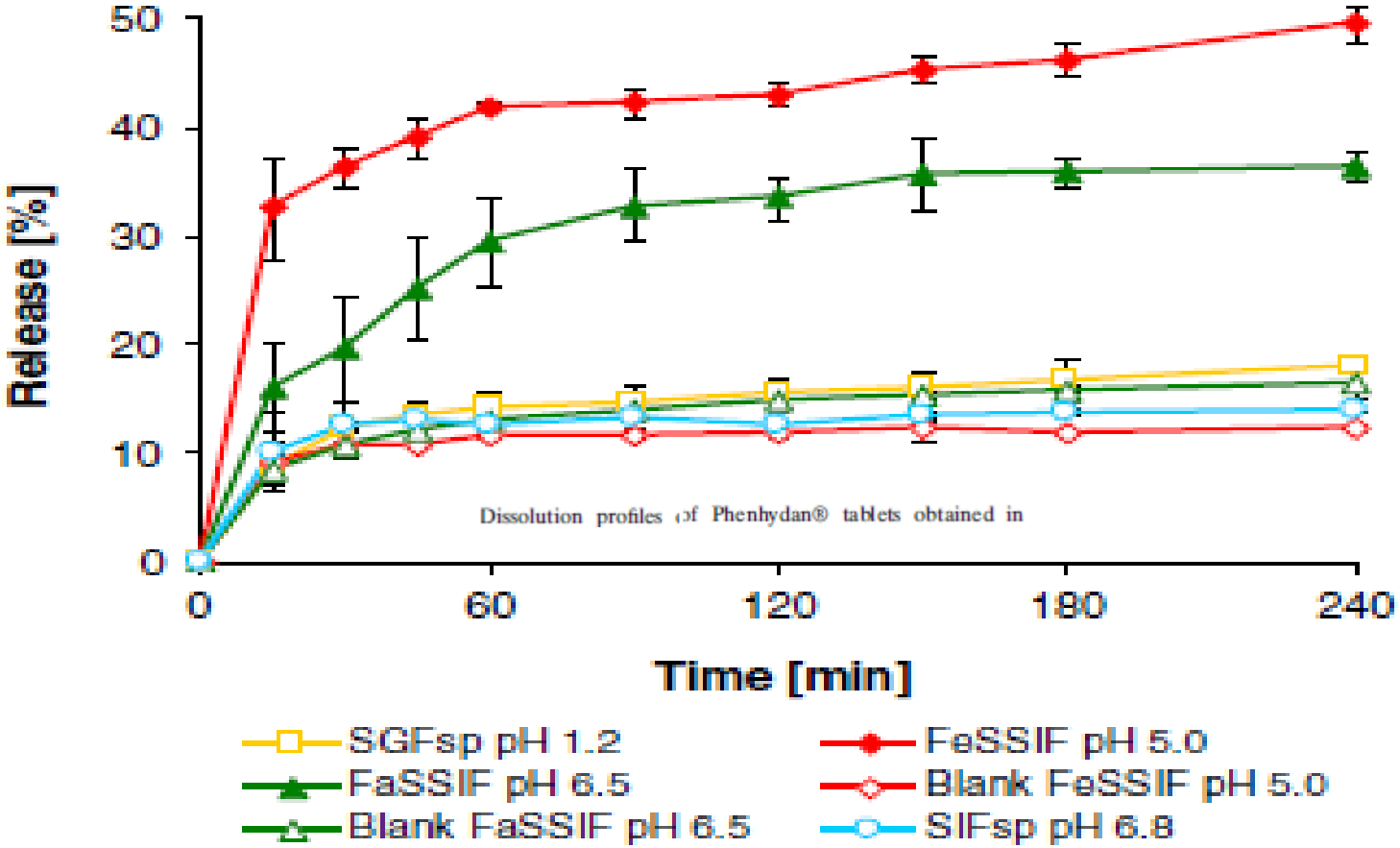
**PHENYTOIN** → **BCS Class II ( poorly soluble weak acid drug)**

-LogP: 2.47

-pKa : 8.3

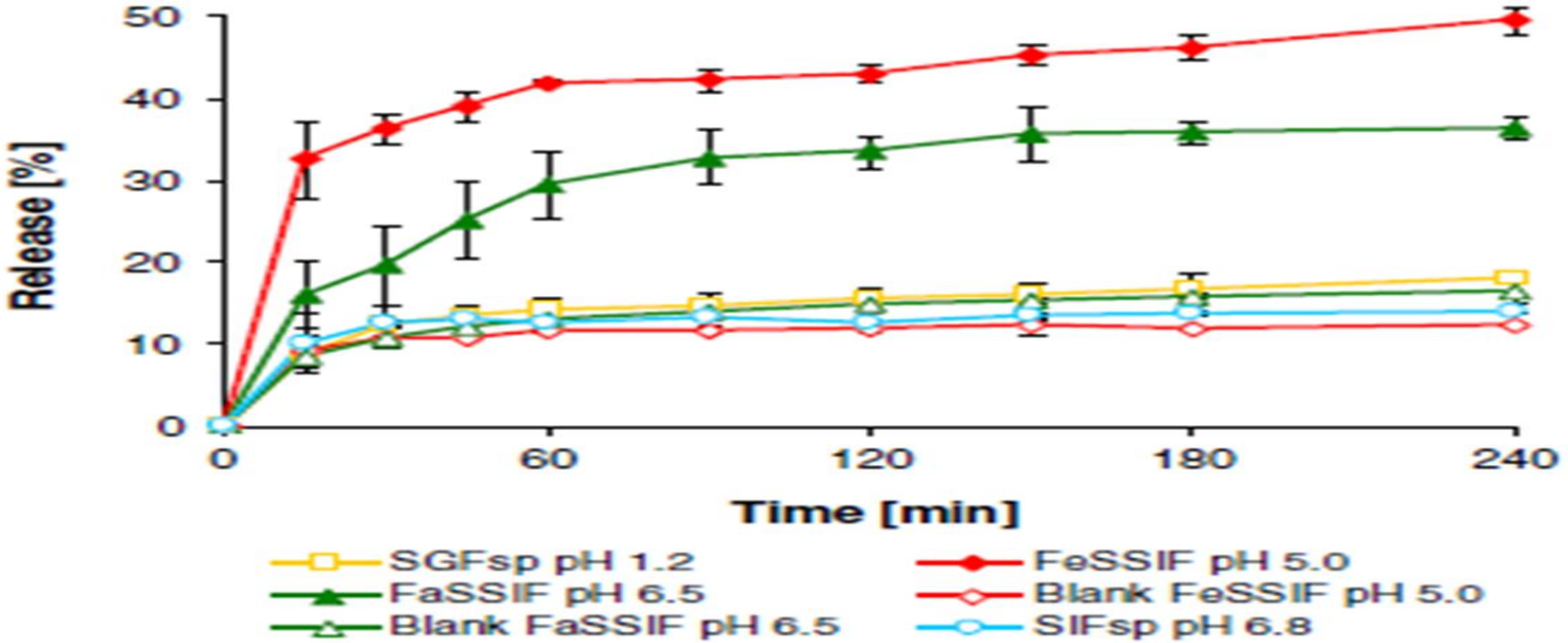
-solubility: 0.032 g/L

**IR formulation, Phenhydan tablets were examined for in vitro dissolution behavior in compendial and biorelevant media.**

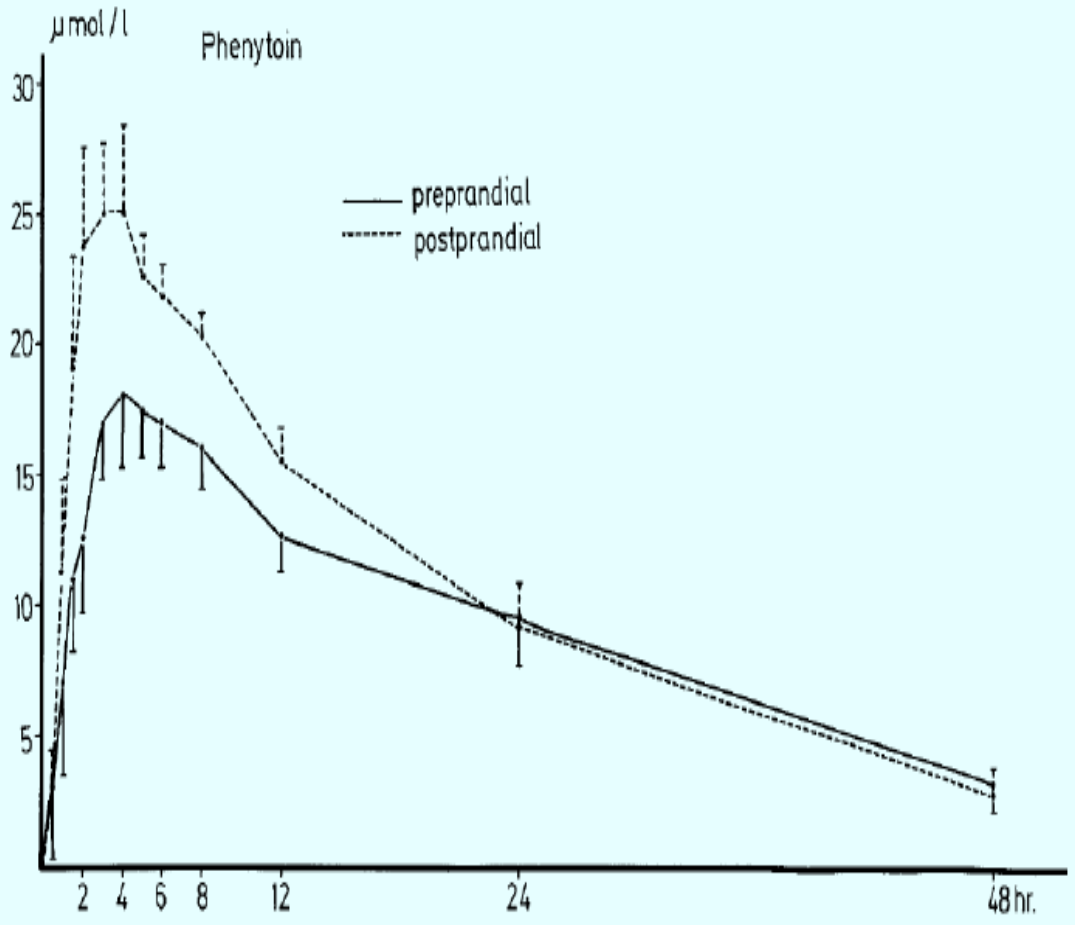



**Dissolution profiles of Phenhydran tablet obtained in media simulating the intraluminal composition of the small intestine before and after a meal (n=3±SD)**

*S Klein , 2010*




**Comparison of dissolution profiles obtained in blank FaSSIF ad FaSSIF and blank FeSSIF and FeSSIF indicates that bile components play an important role in the solubilization of phenytion (~ 36% of drug released in FaSSIF and ~ 50% in FeSSIF over 4h).**

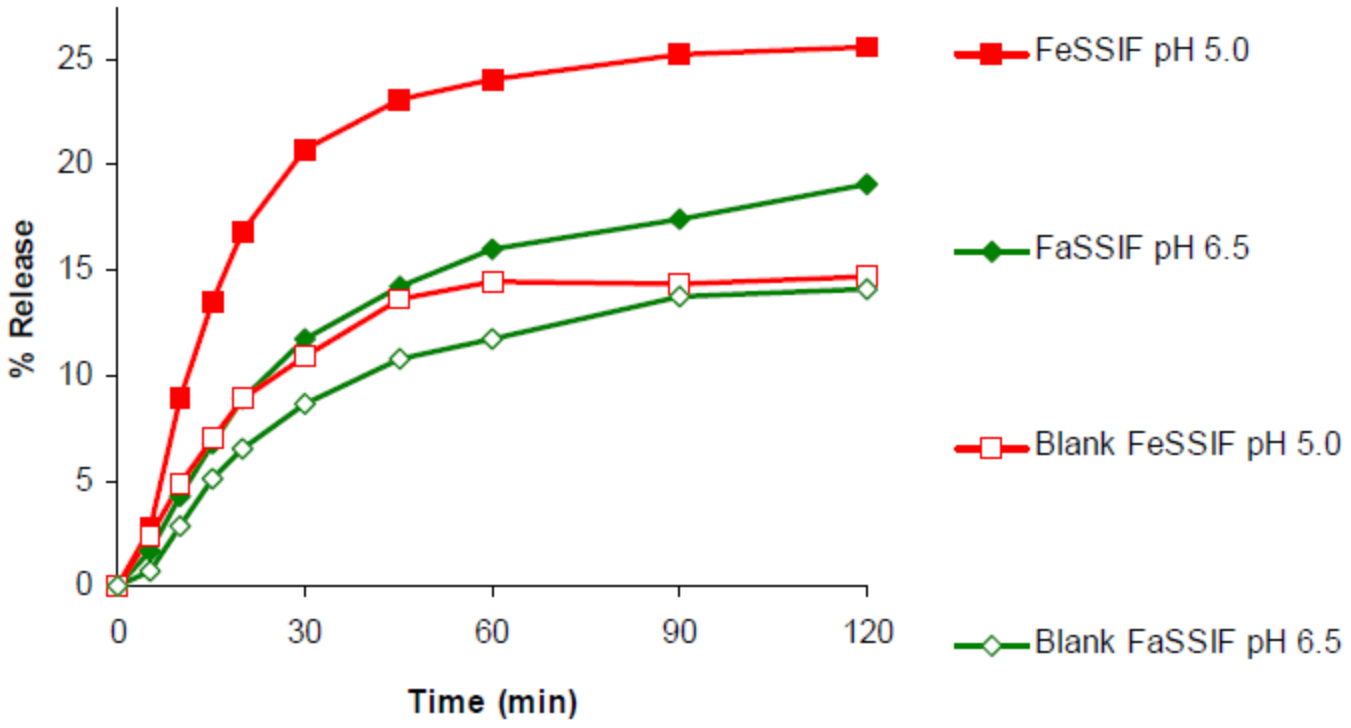



A Melander et al. Europ. J. Clinical Pharmacol. 15 269-274 (1979)

**The results are in good agreement with study performed in human volunteers where an enhanced absorption of phenytoin was observed when a phenytoin formulation was administered with food.**

**It can be concluded that for predicting the *in vivo* performance of weakly acidic lipophilic drugs, it can  is essential to not only focus on the  changing pH conditions in the human GI tract but also to consider the impact on bile components on drug solubilization in the small intestine.**

## Phenytoin AWD 100 mg tablets

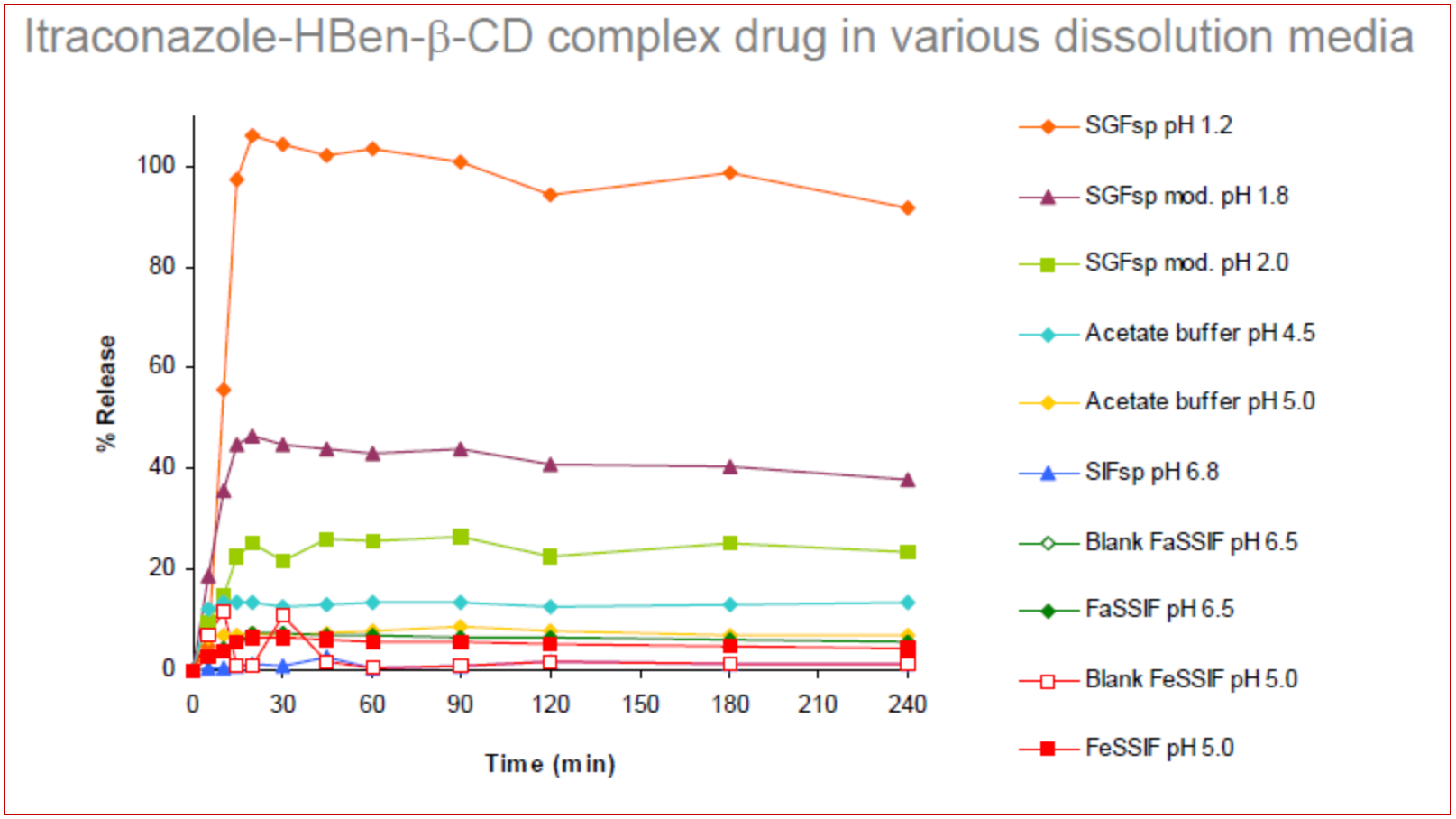


**ITRACONAZOLE** → **Weak bases**

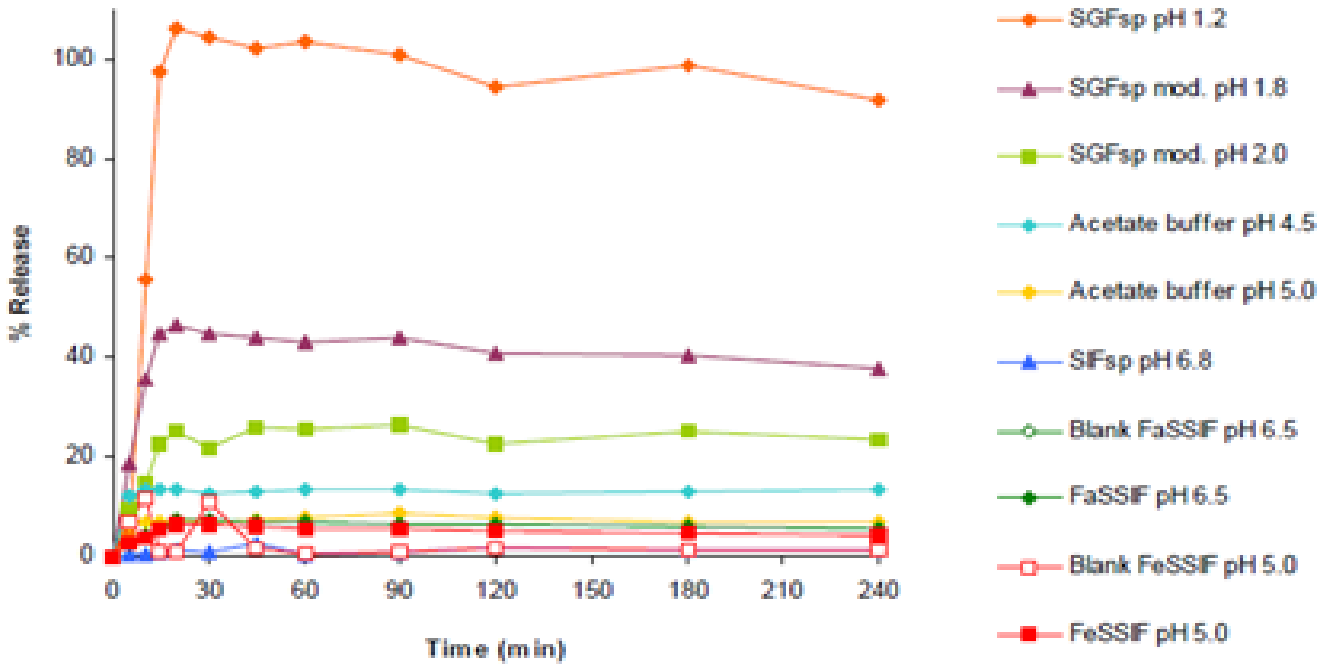
- pKa: approx. 3.7
- log P: 5.66
- very poor water solubility
- can only be ionized and solubilized in aqueous media of very low pH.

**The solubility and dissolution rate of itraconazole could be tremendously improved by formulation with HBenβCD.**

**Dissolution profiles of itraconazole in compendial and biorelevant test media**




*CM Buchanan et al, 2007*



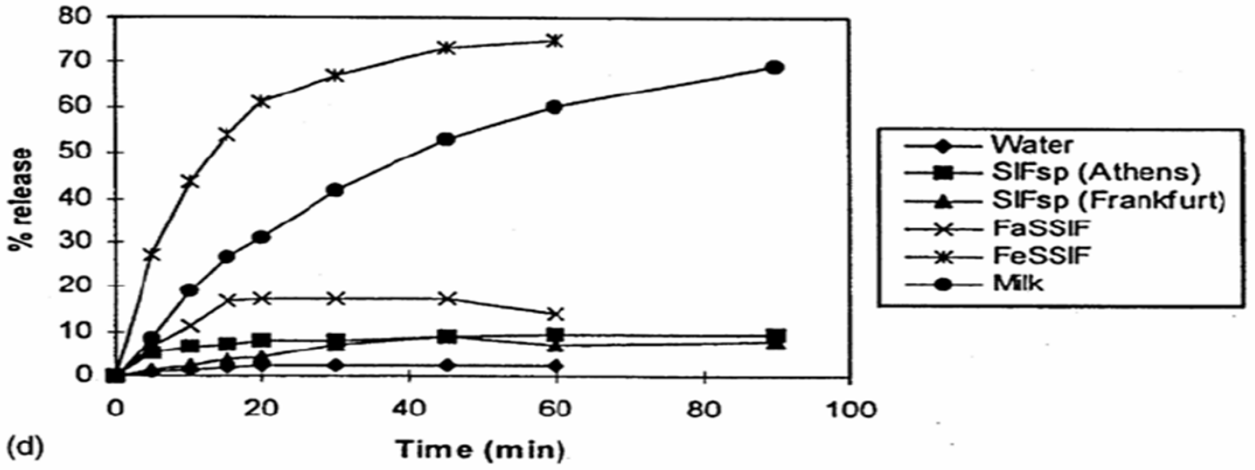

**As seen in Figure, it was possible to completely dissolve a 100 mg dose of itraconozole under conditions of the fasted stomach at pH 1.2. Dissolution experiments also revealed the strong pH dependence of the drug's solubility and dissolution rate.**

**The results indicated that very similar amounts of the drug can be dissolved in FaSSIF and FeSSIF when itraconazole is formulated with HBenβCD are no food effects should be observed after oral administration of an itraconazole/ HBenβCD complex.**

# TROGLITAZONE → BCS Class II

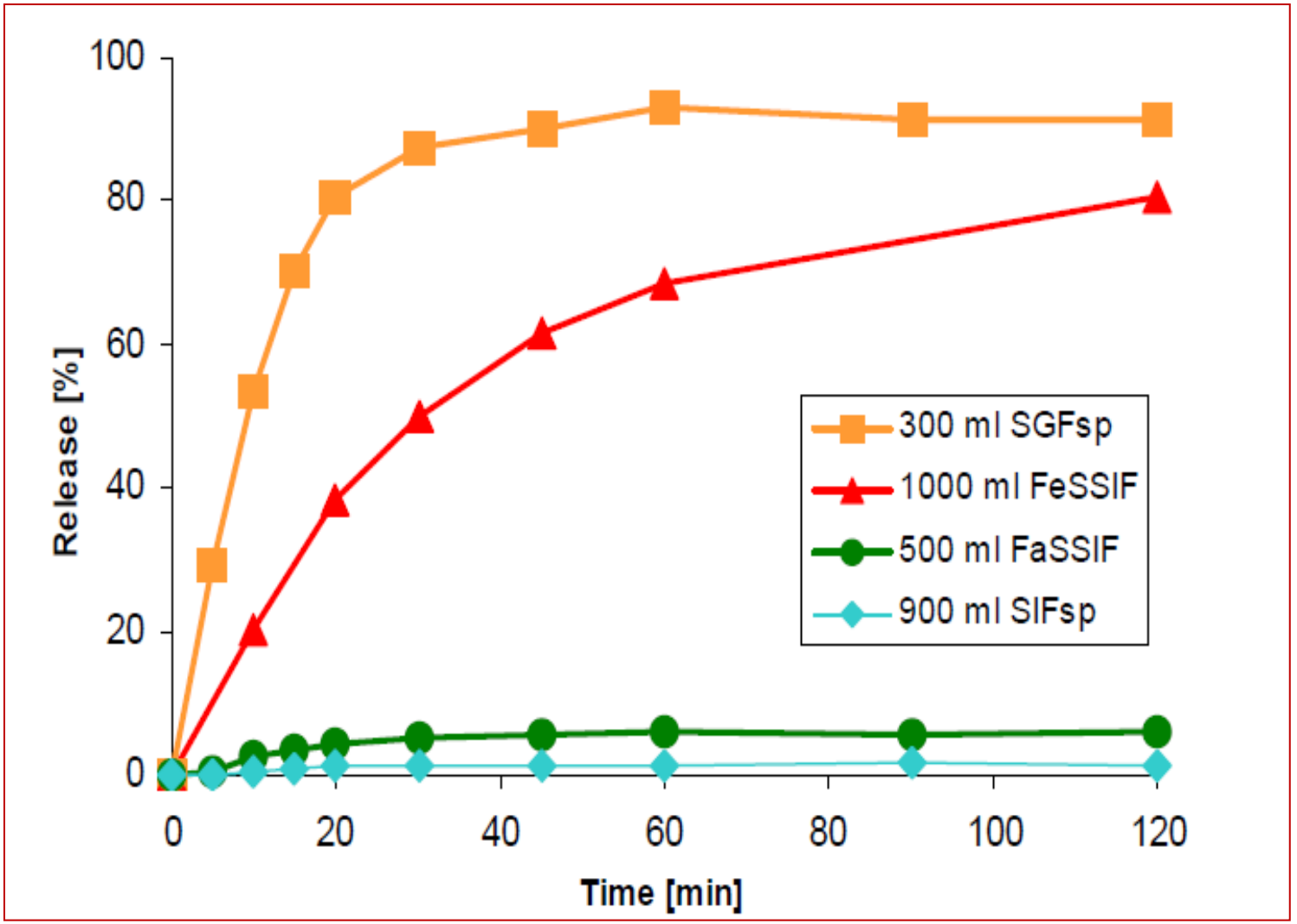
| | |
|---|---|
| Aqueous solubility: | 2 µg/ml |
| Dose: | 200-400 mg |
| pKa: | 6.1; 12 |

Romozin® tablets

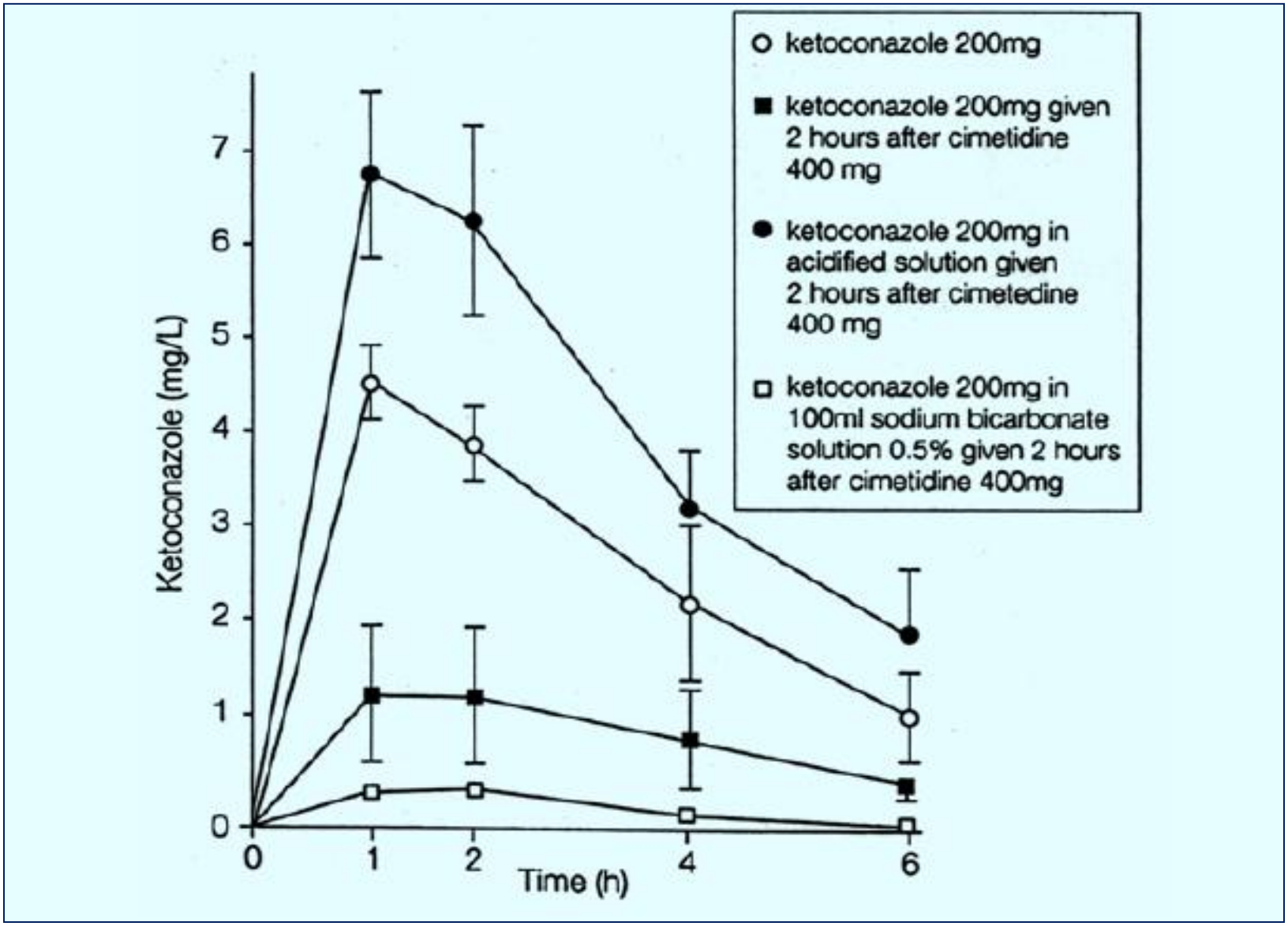



Nicolaides et al. *Pharm. Res.* 16: 1876-1882 (1999)

**KETOCONAZOLE** → **BCS Class II**



# Ketocanozole



# Dissolution media for Class II and Class IV Substances

| Location | pre-/postprandial | Medium |
|---|---|---|
| Stomach | preprandial | SGFsp (USP)<br>***plus surfactant***<br>***z.B. Triton X 100, SDS***<br>FaSSGF |
| Stomach | postprandial | Ensure® Plus,<br>Milk |
| Small intestine | preprandial | **FaSSIF** |
| Small intestine | postprandial | **FeSSIF** |

Dr. Sandra Klein, 04/2008

# FaSSIF-V2

In 2008 *Jantraid et al.* introduced **FaSSIF-V2** and **FeSSIF-V2**

## FaSSIF-V2

**The composition of the uptated FaSSIF, so-called FaSSIF-V2, was changed slightly to more closely reflect the *in vivo* data, while the buffer has been changed from phosphate to maleate for practical reason.**

# *Composition of the Medium to Simulate the FastedState Upper Small Intestine: Fasted-State Simulated Intestinal Fluid, Updated Version (FaSSIF-V2)*

| Composition (mM) | |
|---|---|
| Sodium taurocholate | 3 |
| Lecithin | 0.2 |
| Maleic acid | 19.12 |
| Sodium hydroxide | 34.8 |
| Sodium chloride | 68.62 |

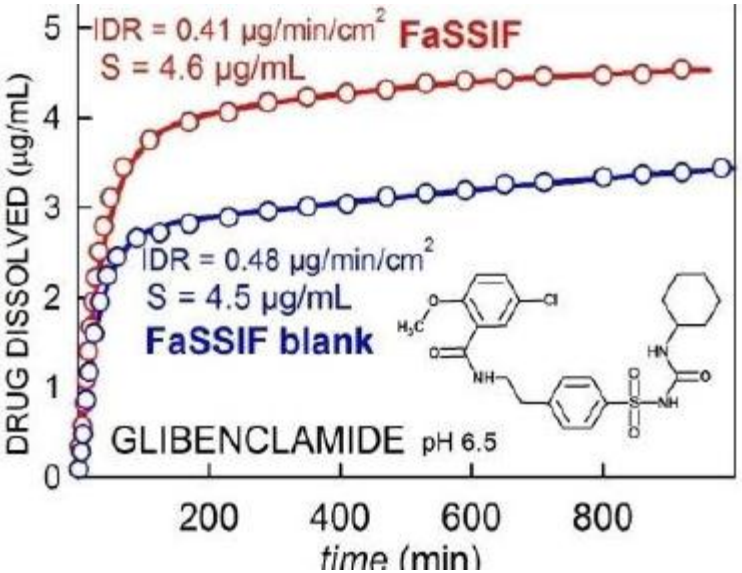
| Properties | |
|---|---|
| pH | 6.5 |
| Osmolality (mOsm/kg) | 180 ± 10 |
| Buffer capacity (mmol/L/pH) | 10 |
| Surface tension (mN/m) | 54.3 |

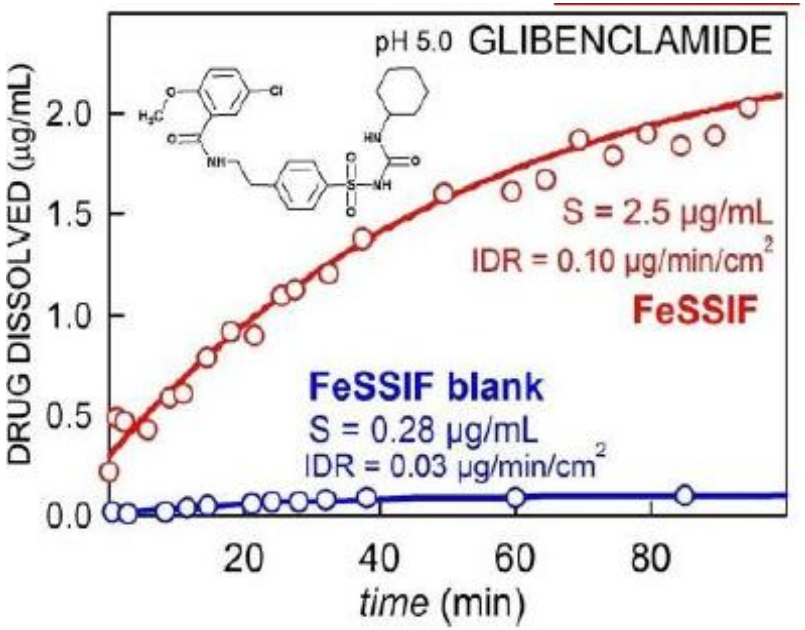
**A new medium reprenting the conditions in the proximal small intestine after meal ingestion has been designed.**

**This uptated FeSSIF medium is called FeSSIF V2.**

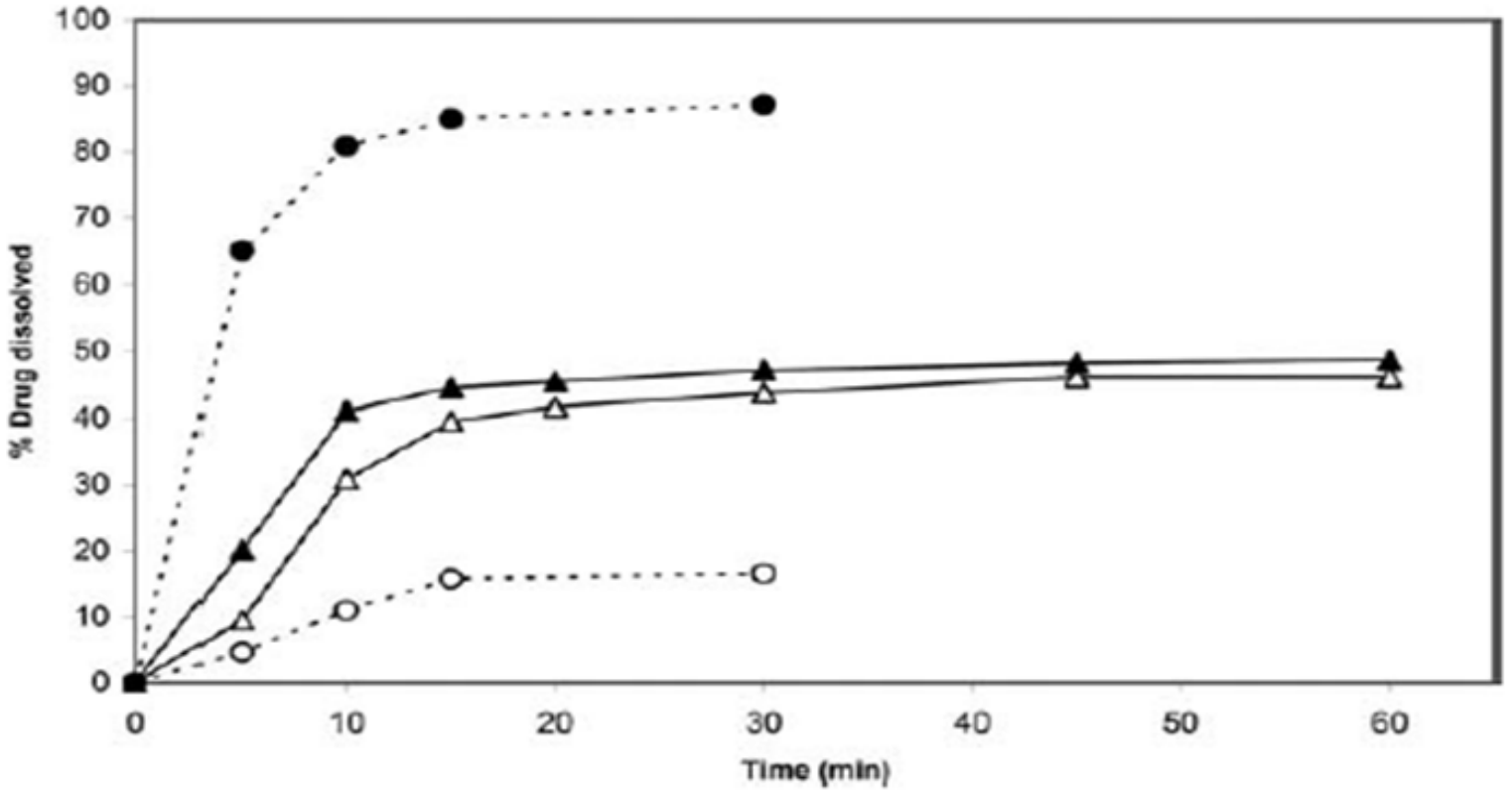
**It has been shown recently that the updated versions of small intestinal media, FaSSIF-V2 and FeSSIF –V2 demonstrate better *in vivo* predictiveness than their predecessor.**

# Glibenclamide



# Glibenclamide




*Dissolution profile comparison of glibenclamide tablets (Euglucon N) in FaSSIF (●) and FeSSIF (○) (dotted lines), and in FaSSIF-V2 (▲) and FeSSIF-V2 (△) (continuous lines).*

*Jantratid, Dressman, 2009*

## Fasted State Simulating Intestinal Fluids:FaSSIF-V3

**Various prototypes of FasSSIF-V3 were prepared with each of the following five bile salts.**

- **Taurocholate (TC)**
- **Glycocholate (GC)**
- **Tauroursodexycholate (TUDC)**
- **Taurochenodeoxycholate (TCDC)**
- **Glycochenodeoxycholate (GCDS)**

*As well as replacing lecithin with its hydrolysis products, lysolecithin and sodium oleate.*

**Recently, *Fuchs et al* (2014) published a commentary in which relevant literature data about the composition and physicochemical properties of fasted state human intestinal fluid were summarized and evaluated.**

**Final version of FaSSIF-V3 was evaluated and compared with the FaSSIF and FaSSIF-V2.**

**Several protypes of FaSSIF-V3 were constructed according to;**

- **Osmolarity**
- **pH**
- **phospholipid content of fasted state human intestinal fluids**

*Fuchs et al.,2015*

## *Composition of maleate and phosphate buffers used to prepare prototypes of FaSSIFV3*

| | Maleate Buffer | Phosphate Buffer |
|---|---|---|
| **pH** | **6.7 ± 0.05** | |
| **Buffer capacity** | **5.6 mmol/L/ΔpH** | |
| **Osmolarity** | **215 ± 10 mOsmol/L** | |
| **Maleic acid** | **10.26 mM** | **-** |
| **Sodium dihydrogen phosphate** | **-** | **13.51 mM** |
| **NaOH** | **16.56 mM** | **3.19 mM** |
| **NaCl** | **93.3 mM** | **91.62 mM** |

# Composition of various media which have been proposed to simulate fluids in the fasted state small intestine

| Medium | | FaSSIF | FaSSIF-V2 | FaSSIF-V2plus | Copenhagen fasted | SEIF |
|---|---|---|---|---|---|---|
| BS (mM) | GC | | | | | 1 |
| | GDC | | | | | 0.7 |
| | GCDC | | | | | 1 |
| | TC | 3 | 3 | 3 | | 0.5 |
| | TDC | | | | | 0.3 |
| | TCDC | | | | | 0.5 |
| | Crudea | | | | 2.5 | |
| PL (mM) | PC | 0.75 | 0.2 | 0.2 | 0.625 | |
| | LPC | | | | | 1 |
| Ratio | BS/PL | 4/1 | 15/1 | 15/1 | 4/1 | 4/1 |
| SO | | | | 0.5 | | |
| Chol | | | | 0.2 | | 0.25 |
| pH | | 6.5 | 6.5 | | 6.5 | 6.5 |
| Buffer | | Phosphate | Maleate | Maleate | Trizma maleate | Phosphate |
| Osmolarity | | 270 | 180 | 181.2 | 270 | 289.25 |
| Stabilizer | | NaN3 | | | | 6 |

**FaSSIF** = Fasted State Simulated Intestinal Fluid; **FaSSIF-V2** = Fasted State Simulated Intestinal Fluid Version 2; **FaSSIF-V2plus** = Fasted State Simulated Intestinal Fluid Version 2plus; **SEIF** = Simulated Endogenous Intestinal Fluid; Copenhagen fasted. **BS** = bile salts; **PL** = phospholipids; **SO** = sodium oleate; **Chol** = cholesterol; **GC** = glycocholate; **GDC** = glycodeoxycholate; **GCDC** = glycochenodeoxycholate; **TC** = taurocholate; **TDC** = taurodeoxycholate; **TCDC** = taurochenodeoxycholate.

## *Composition of various FaSSIF-V3 prototypes used for solubility studies.*

| FaSSIF-V3-prototype | Bile Salt(s) | mM | Phospholipids | mM | NaOleate mM | Chol mM |
|---|---|---|---|---|---|---|
| FaSSIF-V3-TC | TC | 2.8 | PC/LPC | 0.035/0.315 | 0.315 | - |
| FaSSIF-V3-GC/TC | GC/TC | 1.4/1.4 | PC/LPC | 0.035/0.315 | 0.315 | - |
| FaSSIF-V3-GC | GC | 2.8 | PC/LPC | 0.035/0.315 | 0.315 | - |
| FaSSIF-V3-TC-½PL | TC | 2.8 | PC/LPC | 0.0175/0.1575 | 0.1575 | - |
| FaSSIF-V3-TUDC | TUDC | 2.8 | PC/LPC | 0.035/0.315 | 0.315 | - |
| FaSSIF-V3-TCDC | TCDC | 2.8 | PC/LPC | 0.035/0.315 | 0.315 | - |
| FaSSIF-V3-GC/TC_CHOL | TC/GC | 1.4/1.4 | PC/LPC | 0.035/0.315 | 0.315 | 0.2 |
| FaSSIF-V3-GCDC | GCDC | 2.8 | PC/LPC | 0.035/0.315 | 0.315 | - |

Ratio bile salt/phospholipid= 9/1
Osmolarity= 220 ± 10 mOsmol/kg

pH = 6.7 ± 0.05
Buffer capacity = 5.6 mmol/L/DpH

TC = taurocholate; GC = glycocholate; TUDC = tauroursodeoxycholate; TCDC = taurochenodeoxycholate; GCDC = glycochenodeoxycholate; PC = phosphatidylcholine (lecithin); LPC = lysophosphatidylcholine (lysolecithin); NaOleate = sodium oleate; Chol = cholesterol.

- **All biorelevant media showed a significantly lower surface tension than the blank buffer solution.**

- **Furthermore, all prototypes of FaSSIF-V3 that contain the lipolysis products of lecithins have signifacantly lower surface tensions than those measured in FaSSIF and FaSSIF-V2 or in FaSSIF-V3-GC/TC-Lecithin.**

# CONCLUSIONS

- Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF) are extremely similar to juices present in the human intestine before and after a meal respectively.

- These biorelevant dissolution media reflect GI conditions in both the fasted and fed states, they can be used to predicts food effects.

# CONCLUSIONS

- For poorly soluble drugs, prediction of in vivo performance would not have been possible without biorelevant dissolution media.

- **Biorelevant dissolution tests have not been accepted by regulatory agencies yet, so the further investigations are needed.**


# *T H A N K YOU……*

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