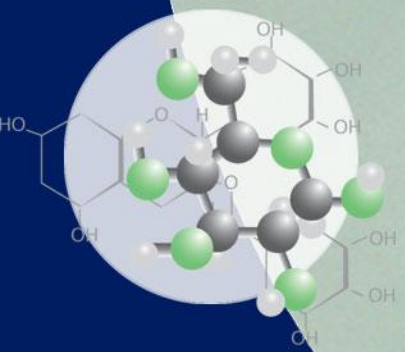
Review of GI physiology and use of biorelevant media

PQRI
Workshop
Bethesda 2012

Prof. Dr. Jennifer Dressman

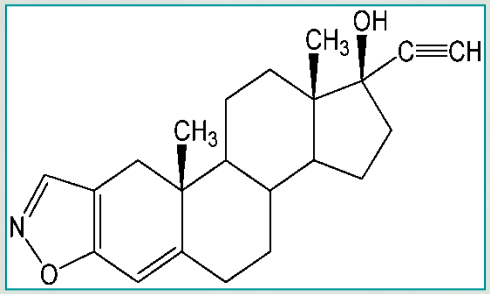


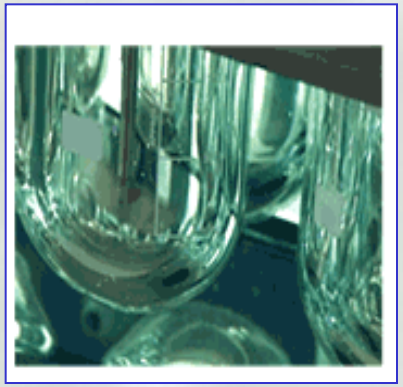
„An IVIVC can only be as good as the data used to produce it!“

With respect to the dissolution side, this means designing an appropriate dissolution test

Finding the right dissolution test…..

- **What factors influence release from drug products?**
  - **The properties of the drug**
  - **The quality and design of the drug product**
  - **The conditions under which the test is run**

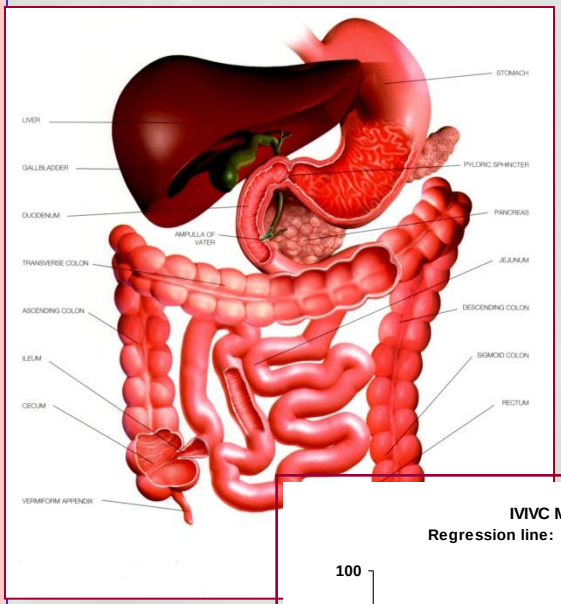


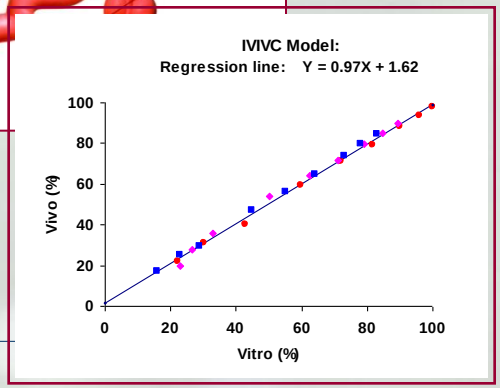


Finding the right dissolution test…..

Hypothesis:

the closer the dissolution test conditions to the physiology, the better the chances of predicting *in vivo* performance

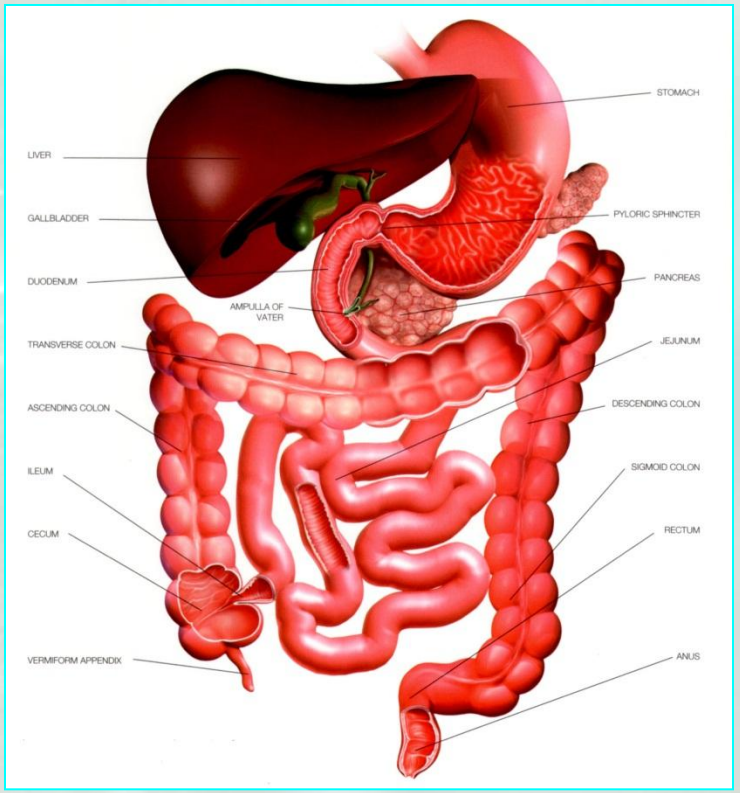




Finding the right dissolution test…..

THREE important considerations:

1) **WHERE** in the GI tract is drug released from the dosage form
2) **HOW LONG** does the dosage form have to release the drug
3) **COMPOSITION** of the fluids into which drug is released



Finding the right dissolution test…..

1) **WHERE** in the GI tract is drug released from the dosage form? This will vary with the drug product e.g.
   1) Immediate release dosage forms
   2) Enteric coated dosage forms
   3) Extended release dosage forms
   4) Pulsatile delivery….

The site(s) of release and/or % released at each site of release are often also dependent on whether the dosage form is given before or after a meal, so the dissolution test should reflect the dosing conditions

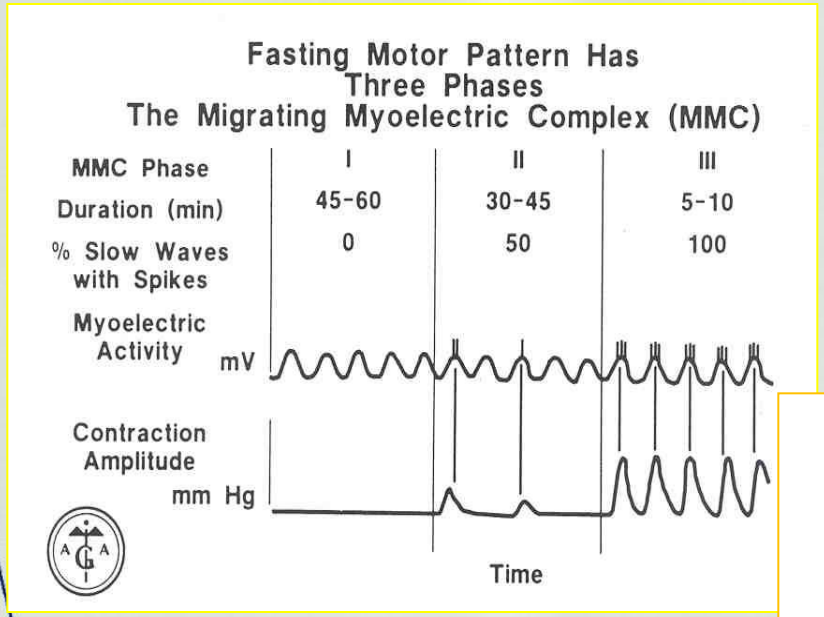
Finding the right dissolution test…..

1) **HOW LONG** does the dosage form have to release the drug?

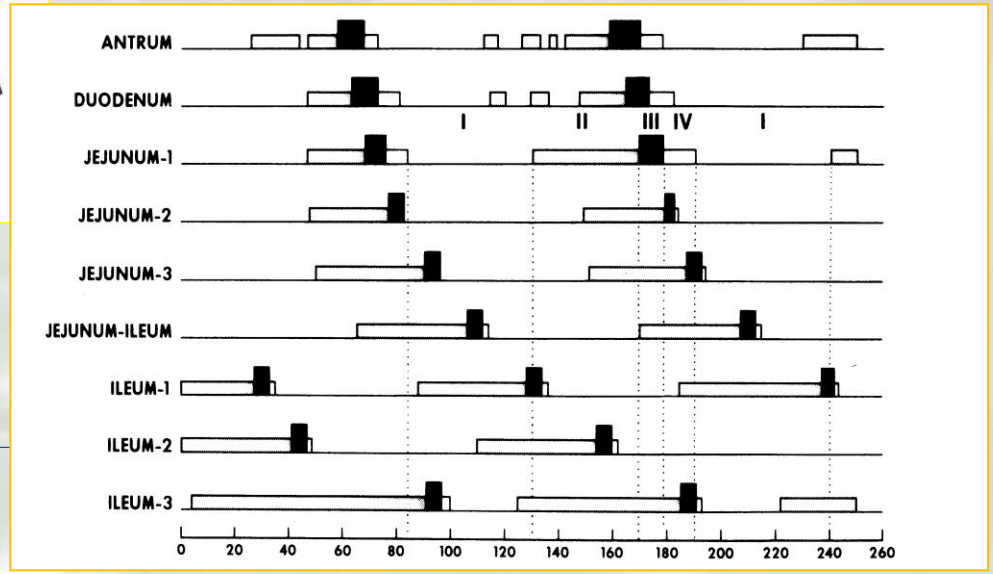
- The drug must be released before or at its site(s) of absorption, otherwise release will not result in absorption. So it is important to understand the permeability of the drug at various points in the gut.
- The passage of the dosage form through the stomach depends on **unit size** and **prandial state**.

Finding the right dissolution test…..

1) **HOW LONG** does the dosage form have to release the drug?



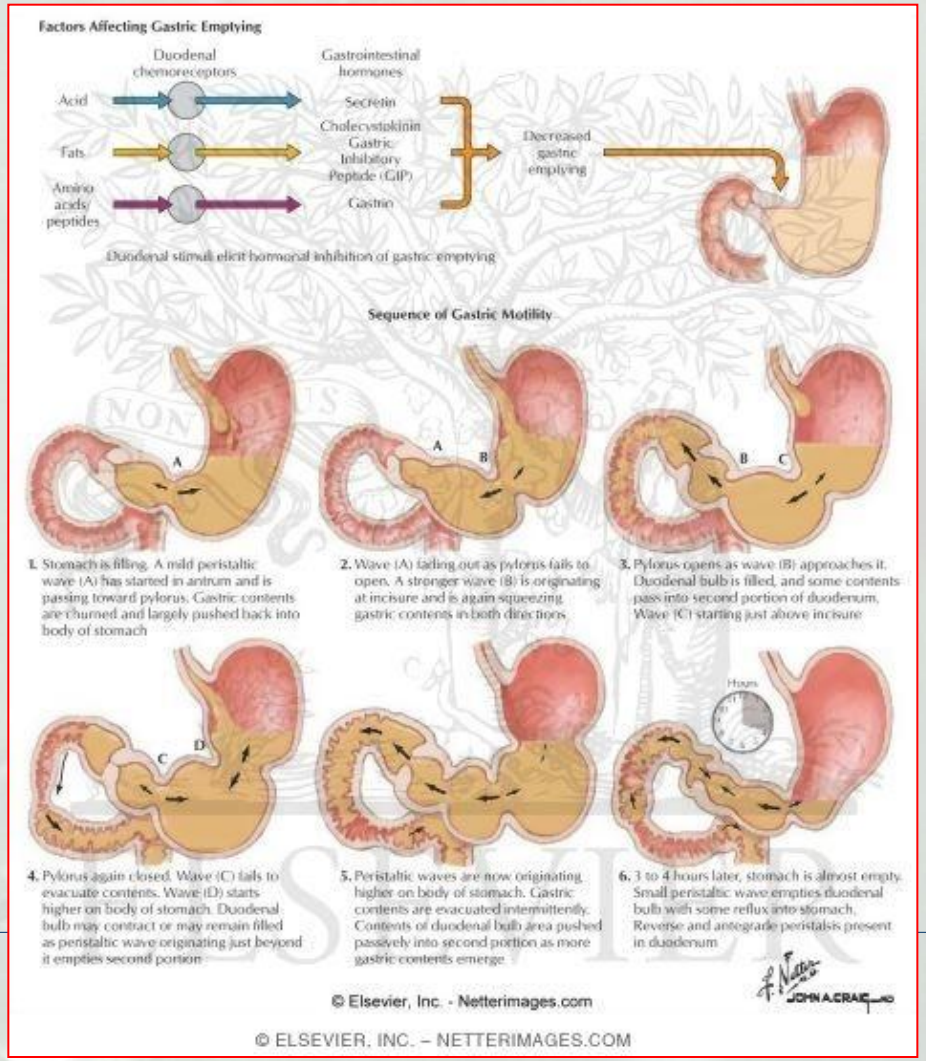
In the **fasted state**, motility in the upper GI tract is cyclical and passage is size-independent



Finding the right dissolution test…..

1) **HOW LONG** does the dosage form have to release the drug?

In the **fed state**, passage of bigger units may be considerably delayed



Finding the right dissolution test…..

1) **HOW LONG** does the dosage form have to release the drug?

These effects can lead to huge differences in the plasma profiles

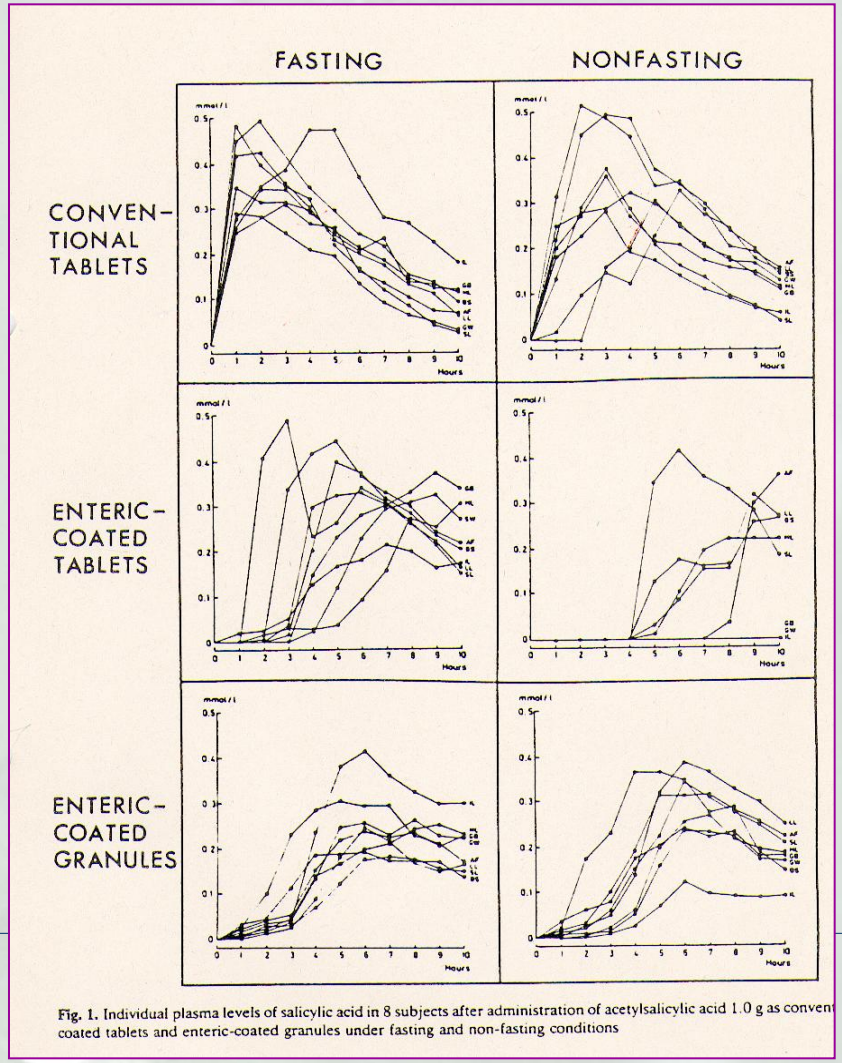
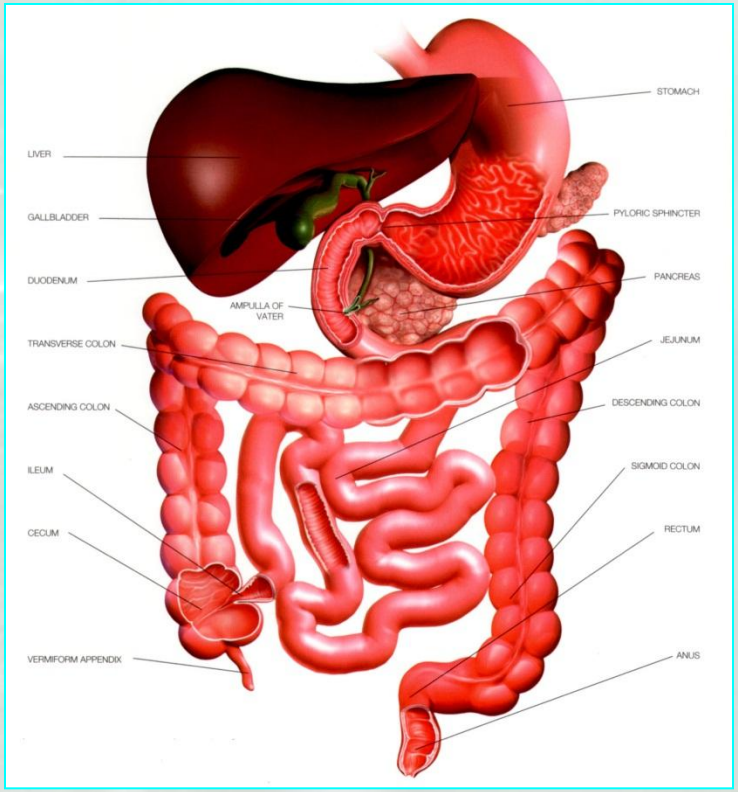


Fig. 1. Individual plasma levels of salicylic acid in 8 subjects after administration of acetylsalicylic acid 1.0 g as conven coated tablets and enteric-coated granules under fasting and non-fasting conditions

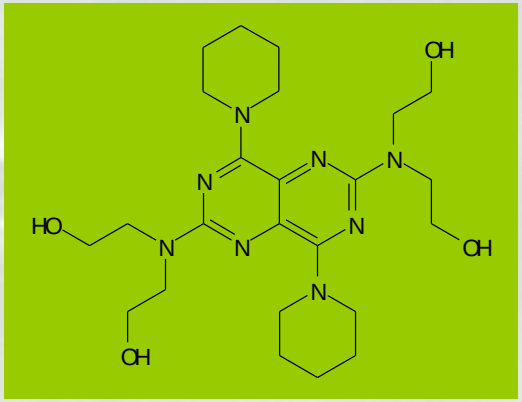
Finding the right dissolution test…..

COMPOSITION of the fluids into which drug is released

The foods and drinks we consume, gastric juices, bile, pancreatic juices, bacterial fermentation as well as water re-uptake all combine to influence the composition of the GI fluids at various points in the gut.



Solubility of Dipyridamole (µg/ml) in buffers and human aspirates



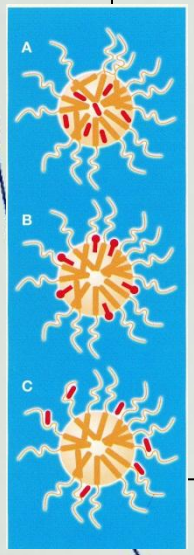
- pH 5 **60** (Kohri et al. IJP 1992)
- pH 6 **13** (Kohri et al. IJP 1992)
- pH 7 **5** (Kohri et al. IJP 1992)

HIF fasted (pH 6.7) **22.5**

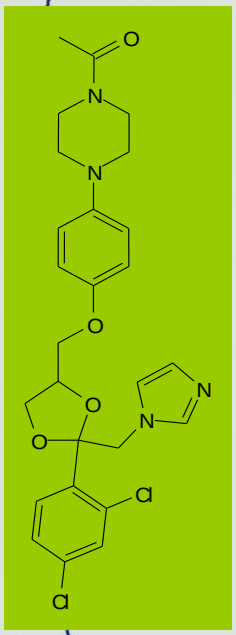
HIF fed 30 and HIF fed 60 (pH 6.5) **160**

HIF fed 120 (pH 5.8) **173**

HIF fed 180 (pH 4.9) **254**

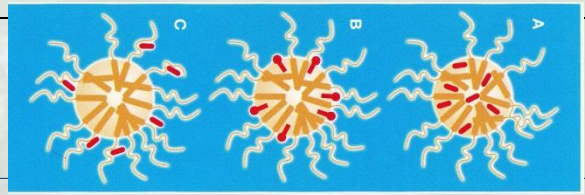


Solubility of Ketoconazole (µg/ml) in buffers and human aspirates



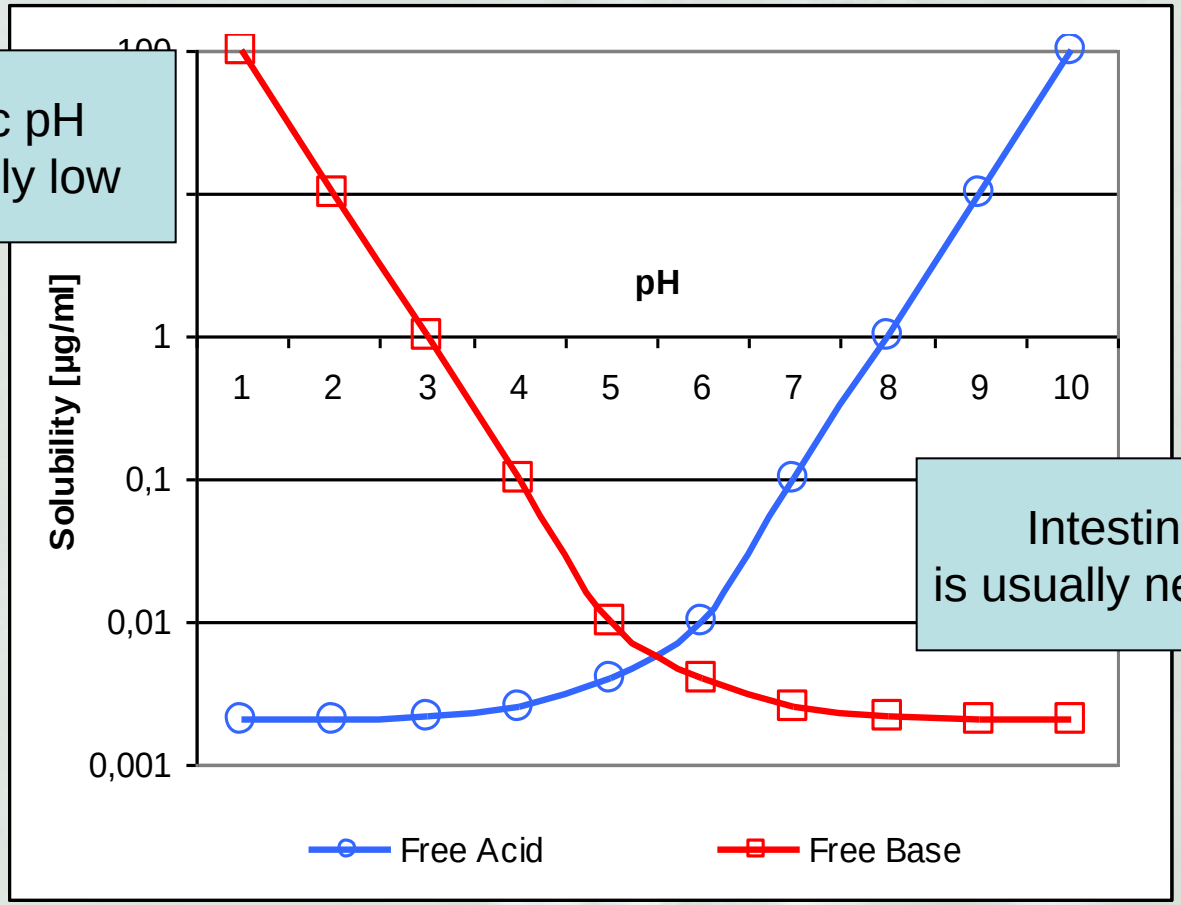
- pH 5 **~90** (Esclusa-Diaz et al. IJP 1996)
- pH 6 **~13** (Esclusa-Diaz et al. IJP 1996)
- pH 6.5 **6.9** (Poelma JPP 1991)

HIF fasted (pH 6.7)	**28.8**
HIF fed 30 and HIF fed 60 (pH 6.5)	**873**
HIF fed 120 (pH 5.8)	**989**
HIF fed 180 (pH 4.9)	**476**



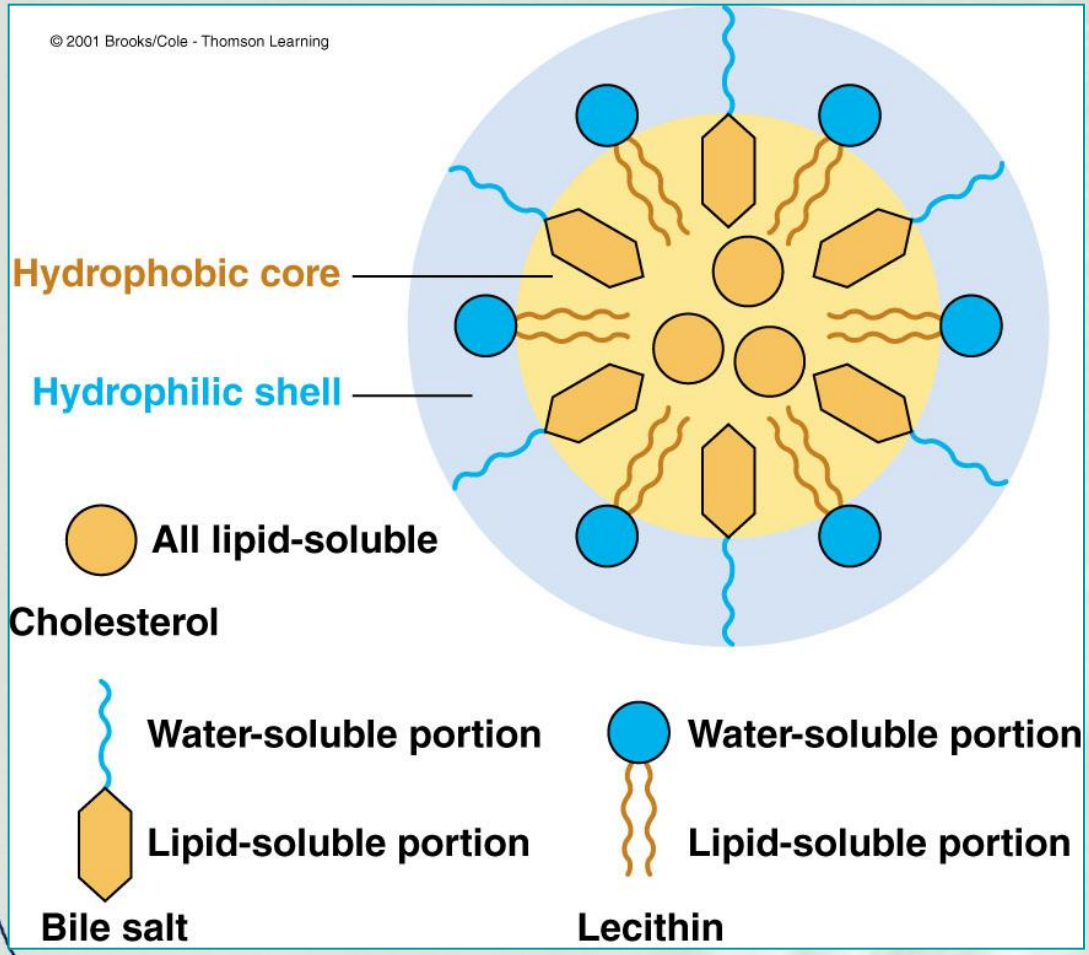
For weak bases and acids, solubility is highly dependent on pH

Gastric pH
is usually low



Intestinal pH
is usually near neutral

Solubilization by mixed micelles in the bile



Important for lipophilic drugs

Finding the right dissolution test…..

COMPOSITION of the fluids into which drug is released

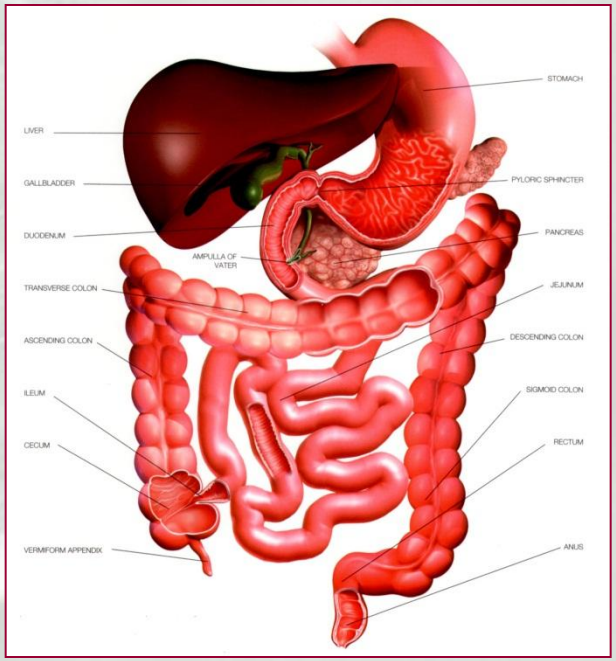
The foods and drinks we consume, gastric juices, bile, pancreatic juices, bacterial fermentation as well as water re-uptake all combine to influence the composition of the GI fluids at various points in the gut.

Not only the **drug**, but also the **excipients**, can have dissolution/release characteristics that are dependent on the composition.

GI-appropriate media composition and volume: „biorelevant“ dissolution media

1. Fasted state

- 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

In vitro simulation of the gastric contents: preprandial (FaSSGF)

HCl	*q.s. pH 1.6*
Pepsin	***0.1 g***
Sodium Taurocholate	***80 µM***
Lecithin	***20 µM***
Sodium chloride	*34.2 mM*
Distilled Water	*q.s 1,000 ml*

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

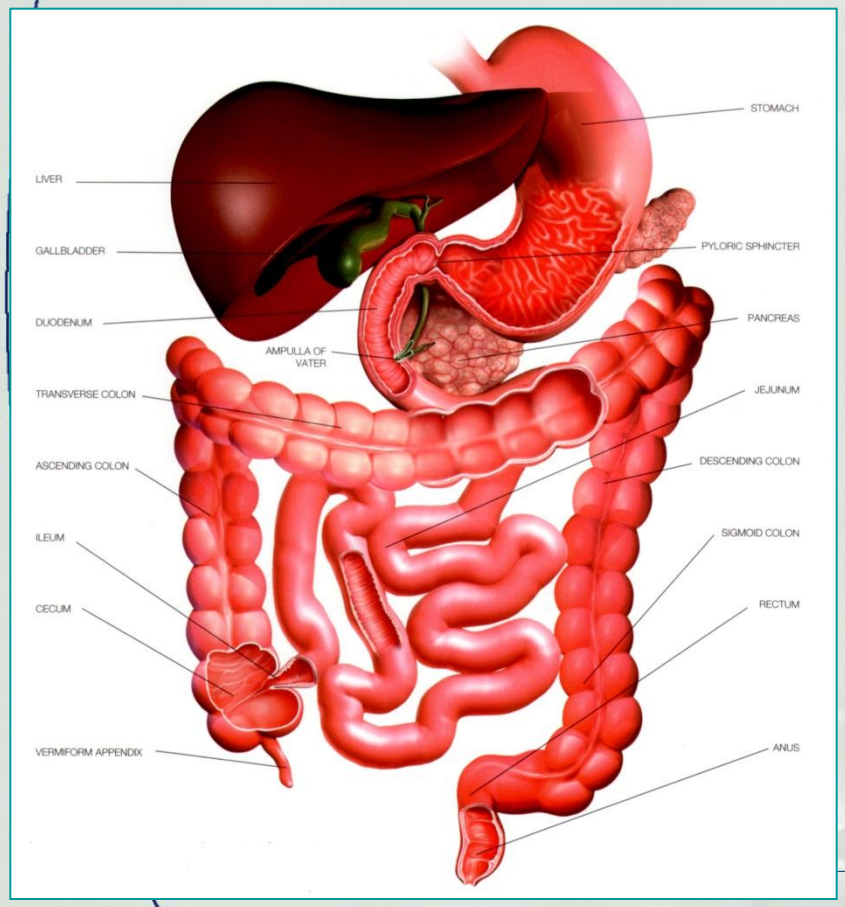
In vitro simulation of the small intestine contents: preprandial (FaSSIF-V2)

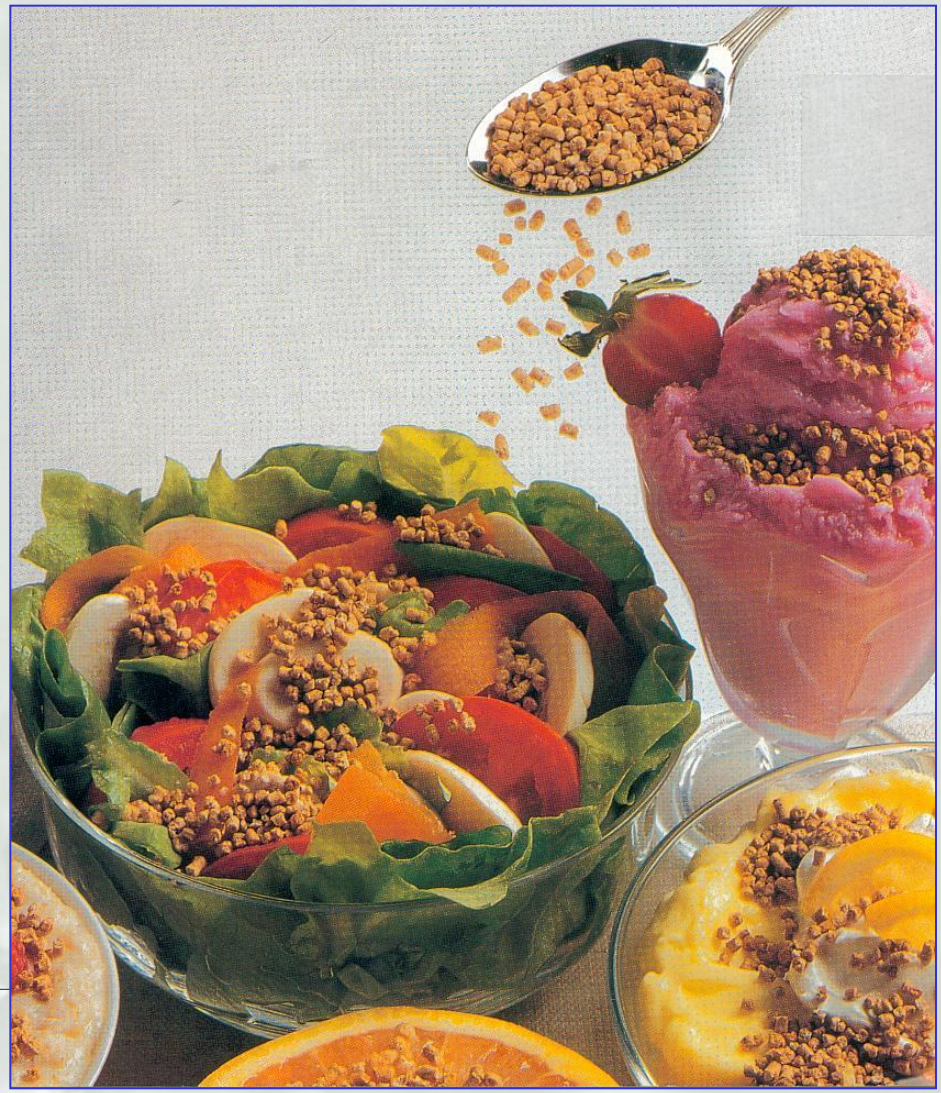
Maleic acid		19.12 mM
Sodium taurocholate		***3 mM***
Lecithin		***0.2 mM***
NaCl		68.62 mM
NaOH		34.80 mM
Distilled Water	qs	500 ml

pH	*6.5*
Osmolality	*180 ± 10 mOsm*
Buffer Capacity	*10 ± 2 mEq/L/pH unit*

E. Jantratid, Pharm Res 2008

Simulation of the fed state in the upper GI tract

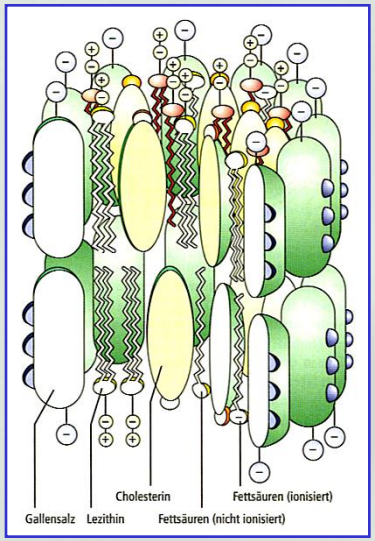




GI-appropriate media composition and volume: „biorelevant“ dissolution media

2. Fed State

- Stomach:
  - FeSSGF: Milk/buffer pH 5 combination to 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



E. Jantratid, Pharm Res 2008

in vitro simulation of the gastric contents: postprandial (FeSSGF)

Acetic acid	***17.12 mM***
Sodium acetate	***29.75 mM***
Sodium chloride	***237.02 mM***
Milk: Buffer	***1:1***
NaOH/HCl	***q.s. pH 5***

This medium has a pH of 5, Osmolality 400 mOsmol/kg, buffer capacity 25 mmolE/l/ΔpH

E. Jantratid, Pharm Res 2008

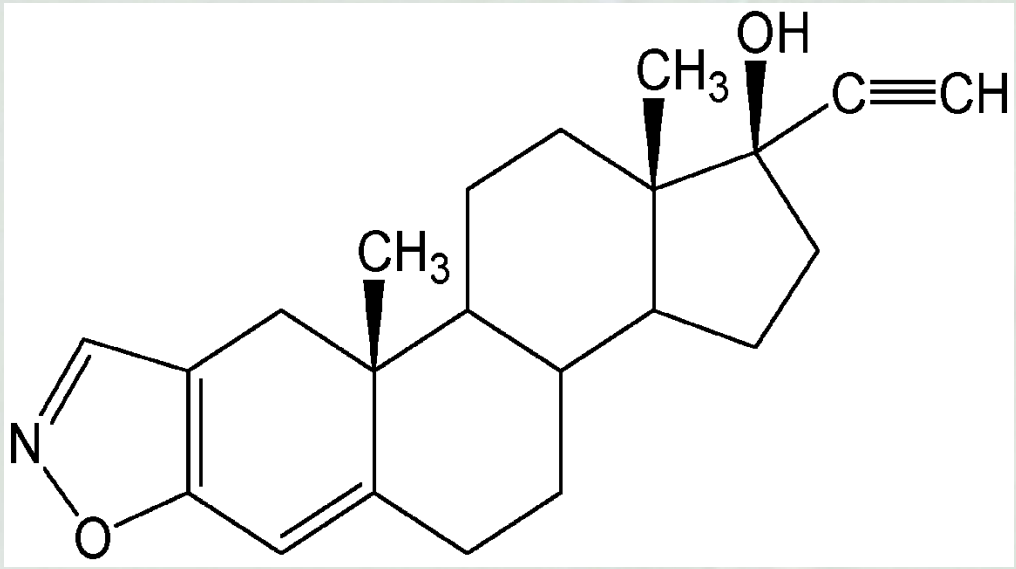
in vitro simulation of the small intestinal contents: postprandial (FeSSIF-V2)

Sodium taurocholate		***10 mM***
Lecithin		***2 mM***
Glycerol monooleate		***5 mM***
Sodium oleate		***0.8 mM***
Maleic acid		55 mM
Sodium hydroxide		81.65 mM
NaCl		125.5 mM
Distilled Water	qs	1 Liter

pH	5.8
Osmolality	*390 ± 10 mOsm*
Buffer Capacity	*25 mEq/L/pH unit*

E. Jantratid, Pharm Res 2008

Application of media to predicting food effects: Danazol



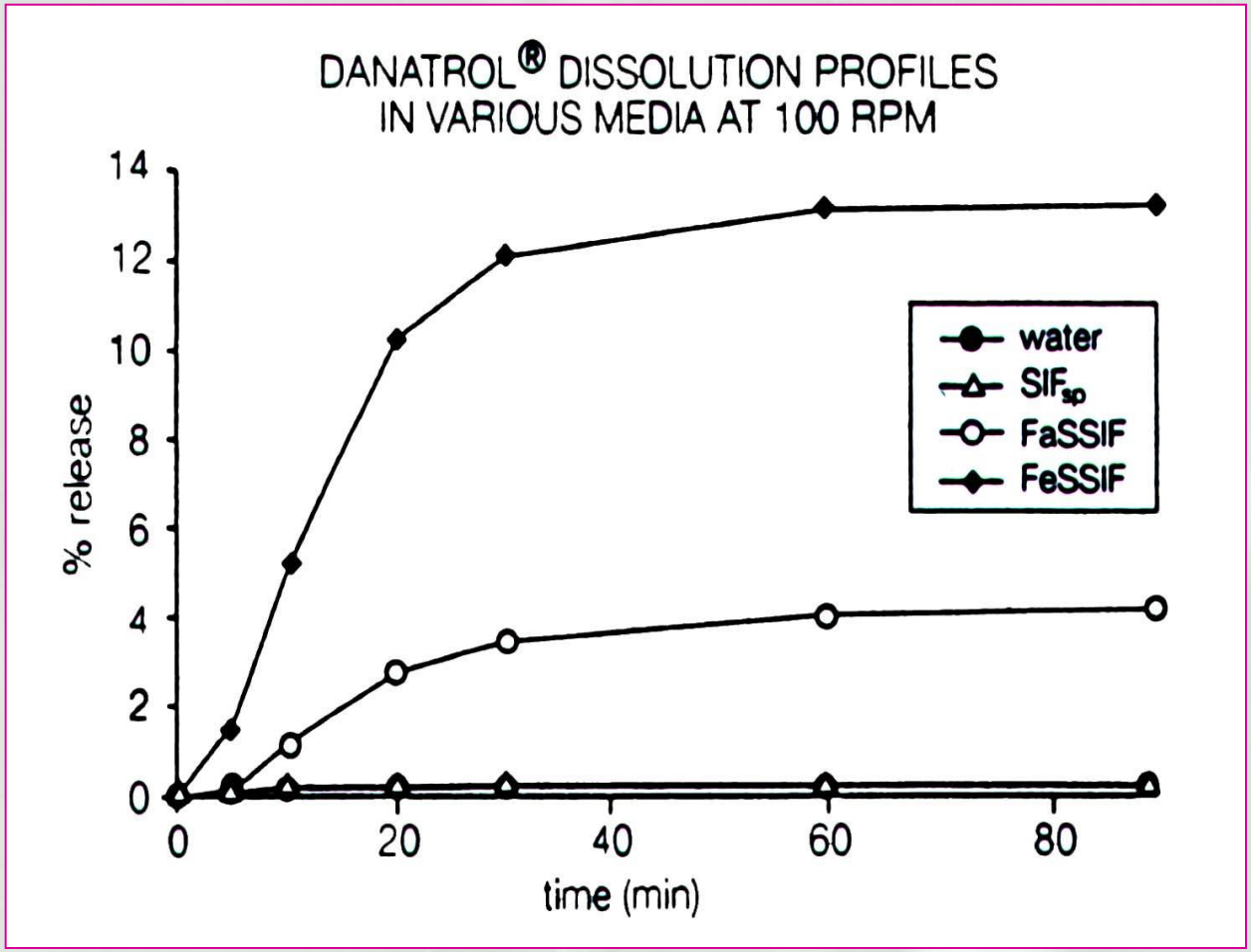
Aqueous solubility: 1µg/ml D:S 200 liters **H_2O**

Dose: 200 mg 20 liters **FaSSIF**

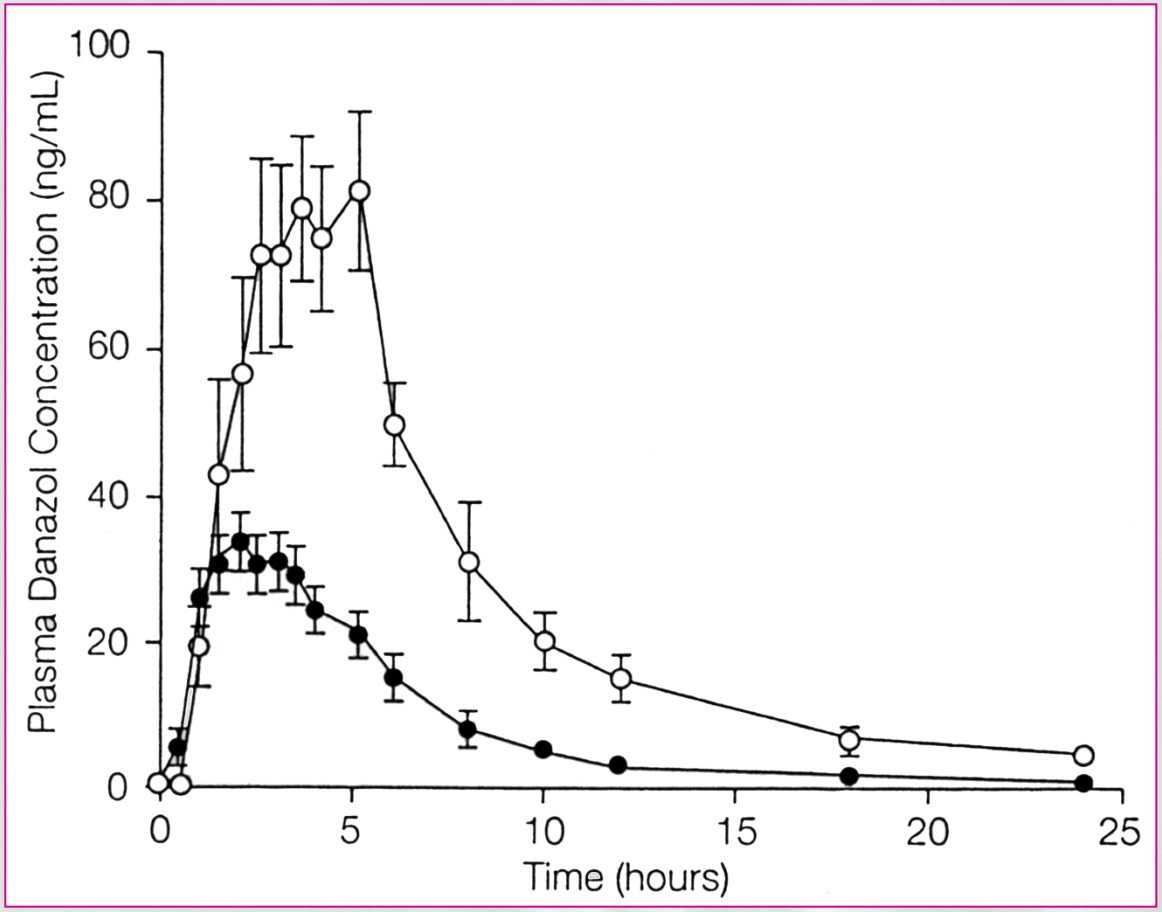
pKa: neutral 6 liters **FeSSIF**

log P: 4.53

Danatrol dissolution profiles in various media at 100 rpm



Danazol's food effect reflects ist dissolution characteristics

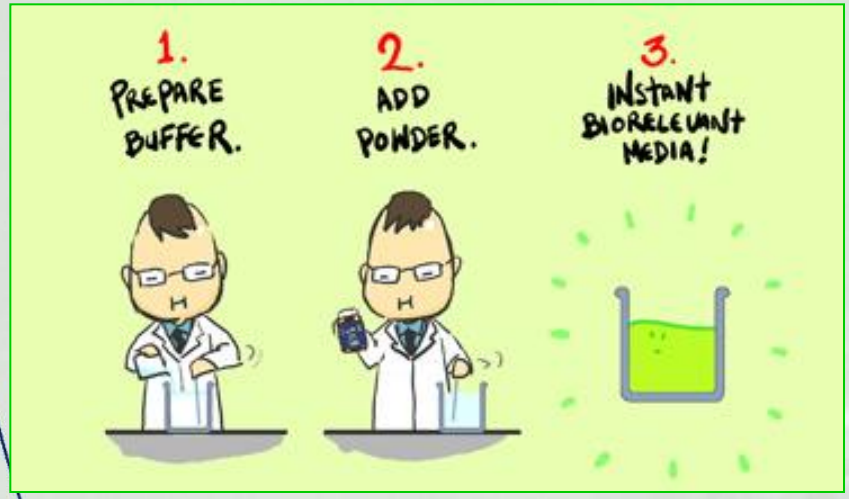


Plasma profiles of danazol after administration in the fasted ( ) and fed ( ) state
(from Charman et al.)

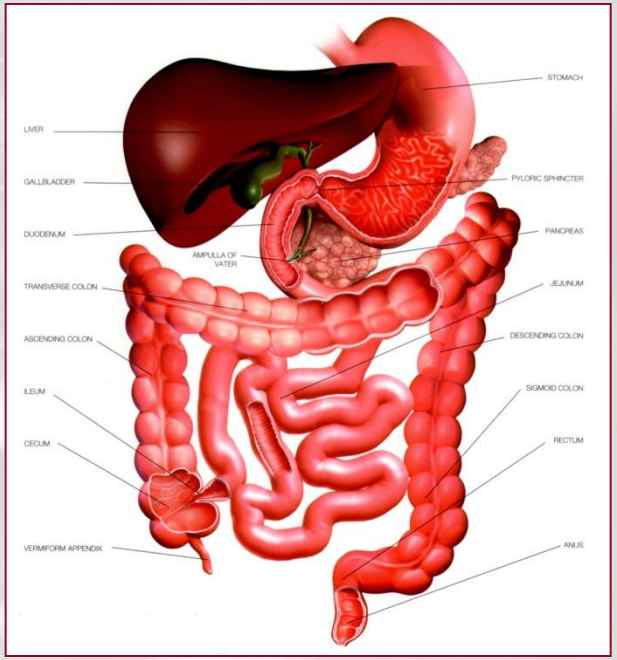
GI-appropriate media composition and volume: „biorelevant“ dissolution media

Making life easier:

Using „instant“ powders to make the biorelevant media

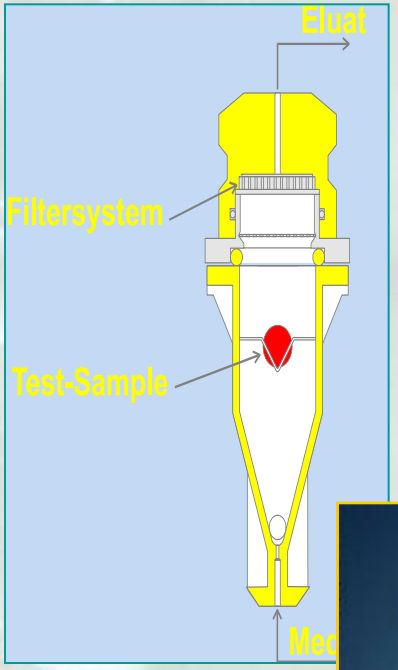


source: Biorelevant.com



Designing an appropriate Dissolution Test

- **Classify the drug substance according to BCS**
- **Choose appropriate media composition and volume**
- **Choose an appropriate apparatus**
- **Consider the hydrodynamics**
- **Determine whether de-aeration of the medium is necessary**
- **Choose an appropriate test duration**



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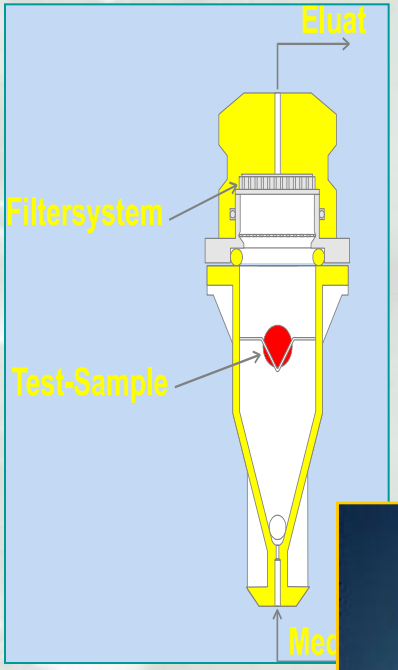


Designing an appropriate Dissolution Test

- Notes on Media composition and volume

1) for *highly soluble* drugs in IR dosage forms, media composition should be simple e.g. aqueous buffer

2) for *less soluble* drugs, consider biorelevant media

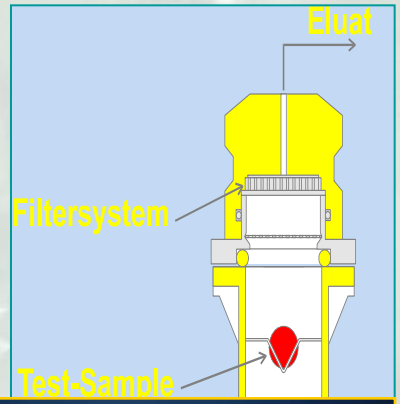
3) if the drug is poorly soluble but highly permeable, sink conditions may be generated in the GI tract and could be considered for dissolution

4) if the drug is poorly soluble and has low/moderate permeability, use of sink conditions for dissolution will likely lead to overprediction of absorption.

5) Some dosage forms are far more prone to composition effects than others e.g. *enteric coated dosage form* compared to *osmotic pump*.

Designing a Dissolution Test

- Classify the drug substance according to BCS
- Choose appropriate media composition and volume
- Choose an appropriate apparatus
- Consider the hydrodynamics
- Determine whether de-aeration of the medium is necessary
- Choose an appropriate test duration



Dissolution apparatus

- USP* Apparatus I/II
  - **one vessel/unit**
  - **basket/paddle**
  - **volume: 500-1000 ml**

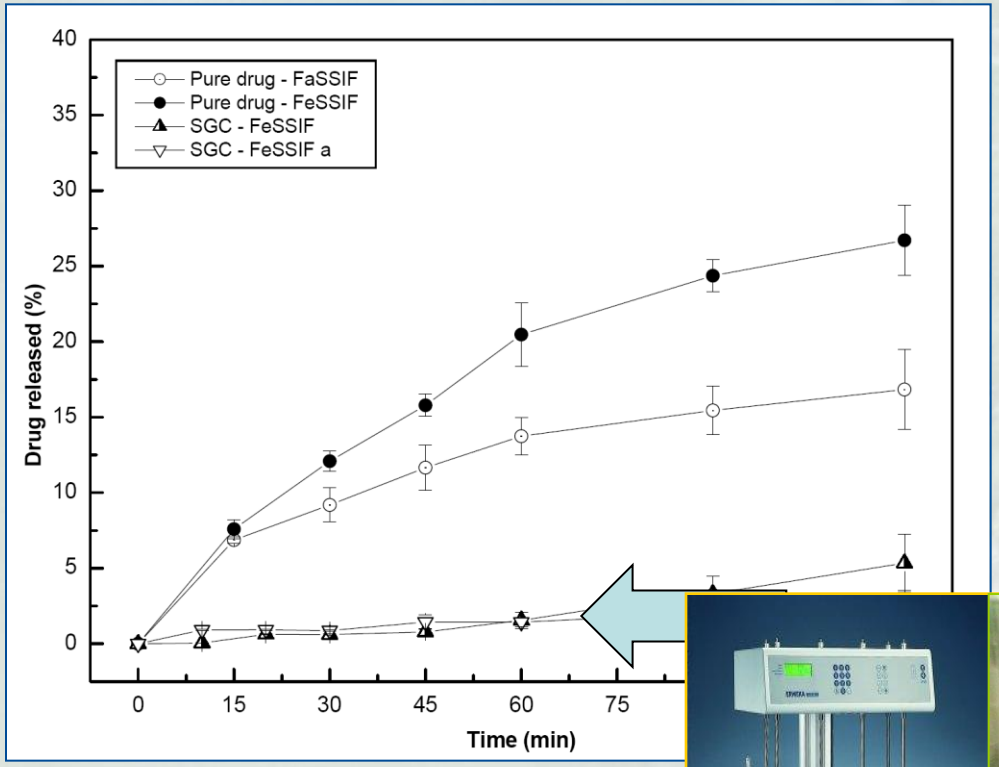
Useful when one or two media will be employed

- Less suitable for IVIVC with MR dosage forms, since IVIVC may not be possible if release testing is performed in a single medium

- Also unsuitable for lipid dosage forms due to poor dispersion of the lipid

*USP 26 United States Pharmacopoeia

Application of the fed state media to lipid-based formulations; paddle



Dissolution in the paddle method resulted in very poor release from the formulation due to inadequate dispersion.

Dissolution apparatus

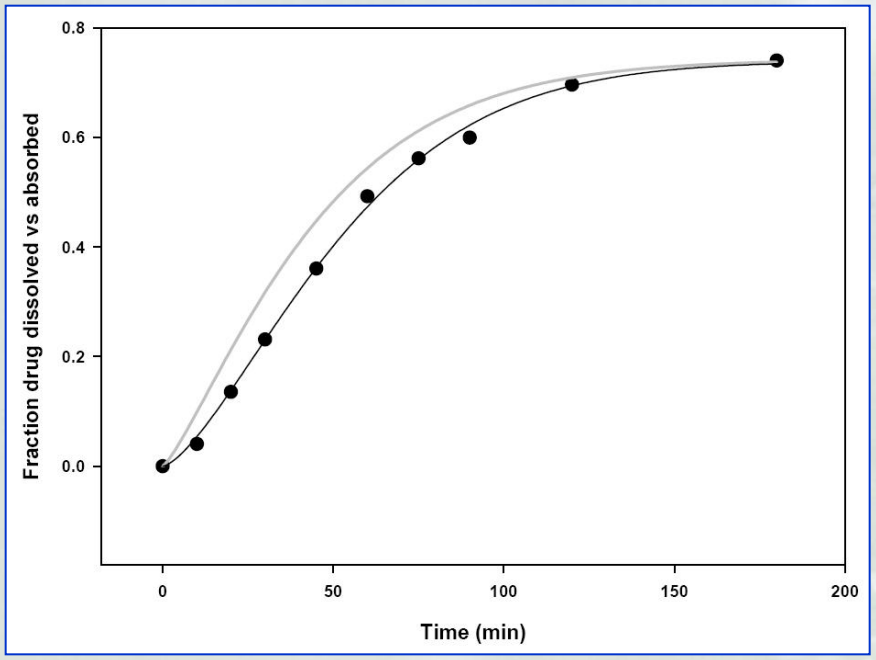
- USP Apparatus III (BioDis)

- **series of cylinders with sieves at each end**
- **volume per cylinder: 200-250 ml**

+ **Enables simulation of passage through the GI tract in one test**
+ **adjustment of dip-rate combined with sieve size can achieve emulsification of lipid dosage forms**

*USP United States Pharmacopoeia

Application of the biorelevant media to lipid-based formulations in the BioDis



In the BioDis, the formulation dissolved best in FeSSGF and the profile in this medium matched the absorption profile well

Jantratid et al., EJPB 2008

Application of biorelevant media in the BioDis to MR dosage form performance

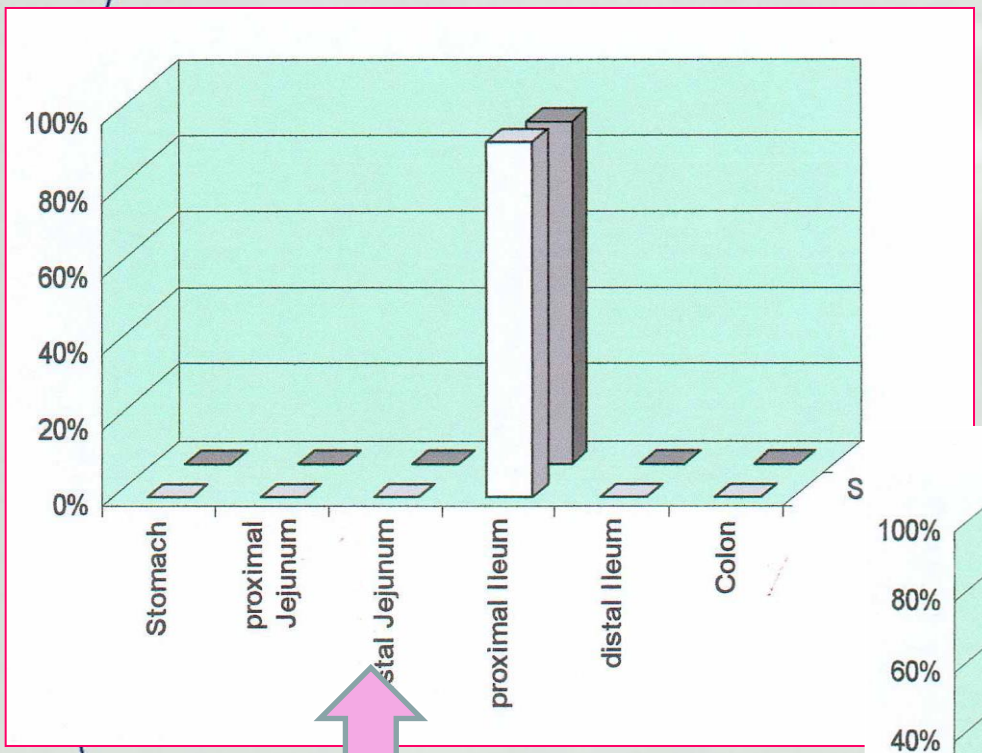
Segment of the GI tract	pH-gradient preprandial				Residence time (min)	
	blank medium	pH	biorelevant medium	pH	Tablets	Pellets
Stomach	Blank FaSSGF	1.6	FaSSGF	1.6	60	60
Duodenum/ Jejunum	Blank FaSSIF-V2	6.5	FaSSIF-V2	6.5	45	45
Jejunum/ Ileum	Blank Half-FaSSIF	7.0	Half-FaSSIF	7.0	45	45
Distal Ileum	FaSSIF-sans	7.5	FaSSIF-sans	7.5	120	120
Colon	SCoF	5.8	SCoF	5.8	480	480

Segment of the GI tract	pH-gradient postprandial				Residence time (min)	
	blank medium	pH	biorelevant medium	pH	Tablets	Pellets
Stomach	Blank FeSSGF	5.0	FeSSGF	5.0	240	120
Duodenum/ Jejunum	Blank FeSSIF-V2	5.8	FeSSIF-V2	5.8	30	45
Jejunum/ Ileum	Blank Half-FeSSIF	6.5	Half-FeSSIF	6.5	60	45
Distal Ileum	FaSSIF-sans	7.5	FaSSIF-sans	7.5	120	120
Colon	SCoF	5.8	SCoF	5.8	480	480

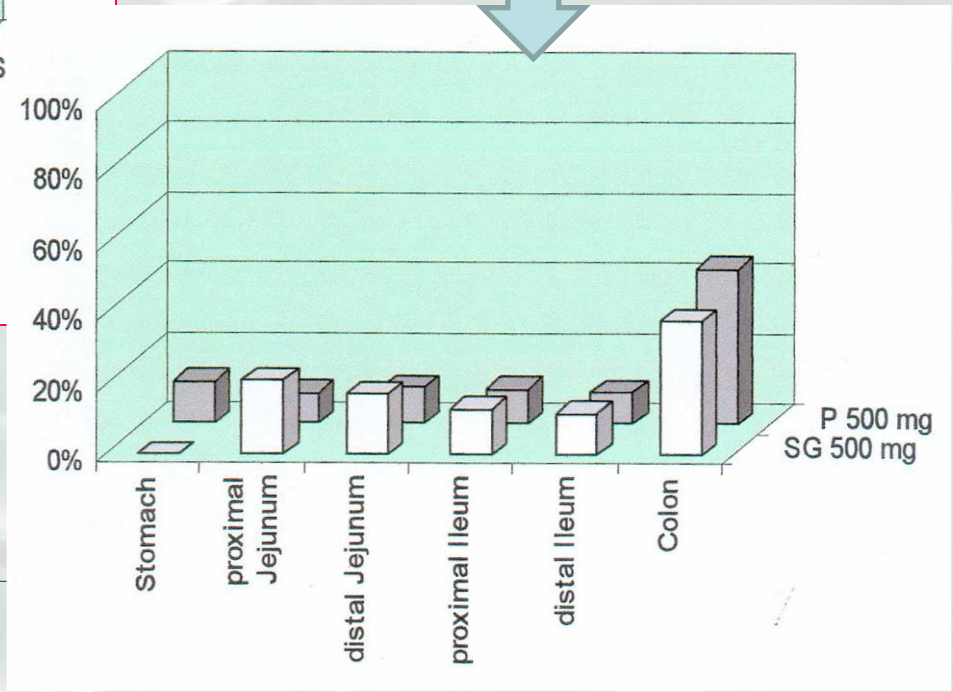
Case example: Mesalamine products

- These products are used for the therapy of Crohn‘s disease and ulcerative colitis in Europe
  - *Claversal®; Salofalk®*
    - Eudragit L coating (dissolves at pH > 6,0)
  - *Pentasa®*
    - Microgranulate with an Ethylcellulose coating
    - Release is diffusion driven
  - *Granustix®*
    - Eudragit L coating (dissolves at pH > 6,0) AND diffusion driven release

Case example: Mesalamine products



Pentasa and Granustix: Release sites in GI tract based on BioDis results



Salofalk and Claversal: Release sites in GI tract based on BioDis results

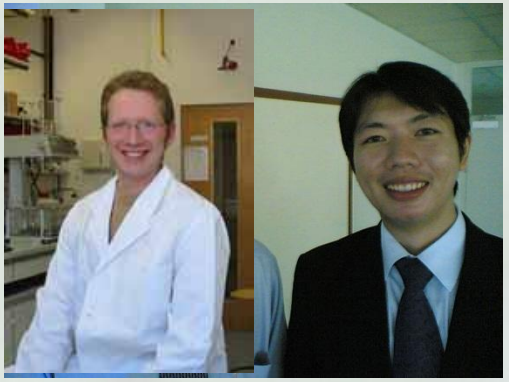
Summary

To come up with the „right“ dissolution test for generating an IVIVC, one needs to consider

- the drug‘s properties (solubility, permeability etc.)
- the mechanism of release of the dosage form
- dosage form dimensions
- the excipient properties
- dosing conditions in the *in vivo* study

With this information, it should be possible to generate an *in vitro* profile that closely reflects the *in vivo* release profile

Acknowledgements



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