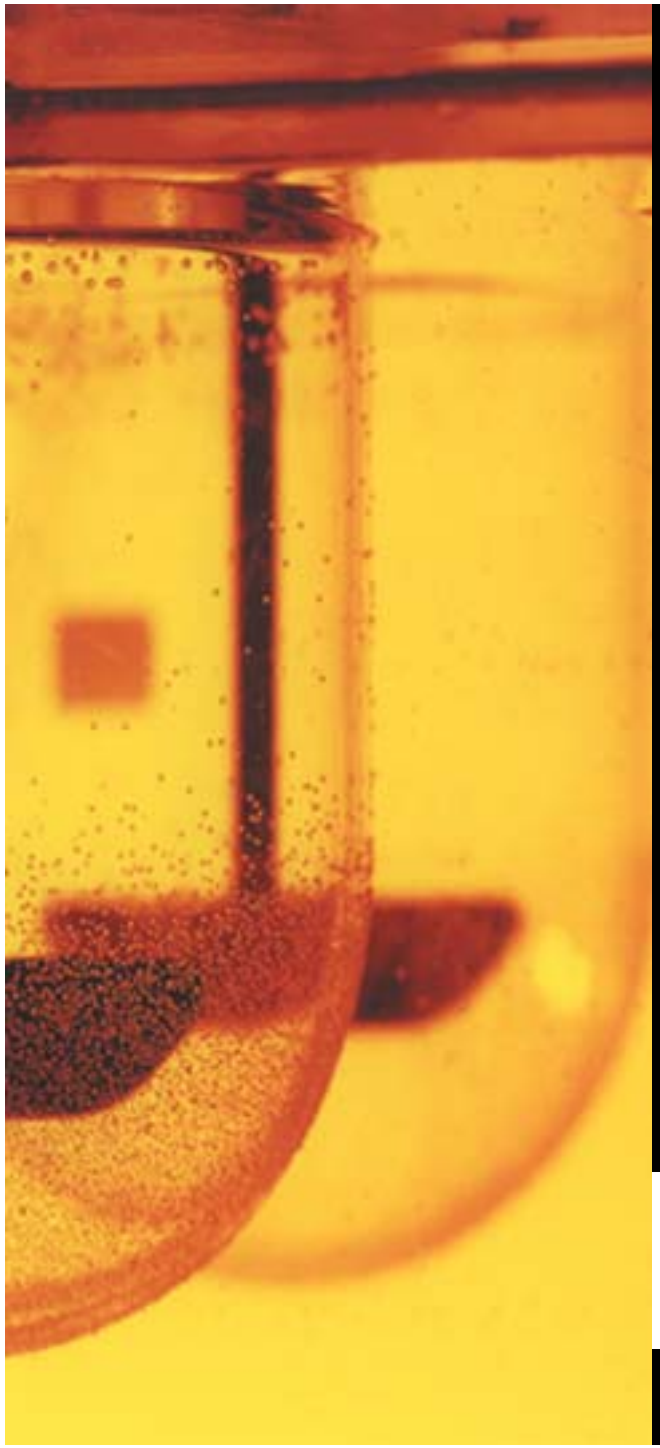


Bioavailability and Bioequivalence

IKEV / APV Conference Istanbul April 15-16, 2004

Physiological Meaningful Dissolution Testing?

Dr. Johannes Krämer

PHAST

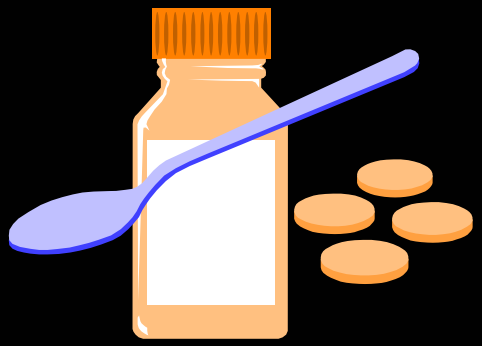
Pharmazeutische Qualitätsstandards

Objectives

Gives answers to the following questions:

- **What do I need to know about the in vivo physicochemical and mechanical conditions?**
- **What are the physiological variables that have to be modelled by in vitro dissolution and how do they change?**
- **What is certainly known from physiology and anatomy?**
- **What is not yet clearly known and needs a broader approach by in vitro modelling?**
- **What do we need to know about combination of factors to develop dissolution methods?**

In Vivo Drug Release May Depend on

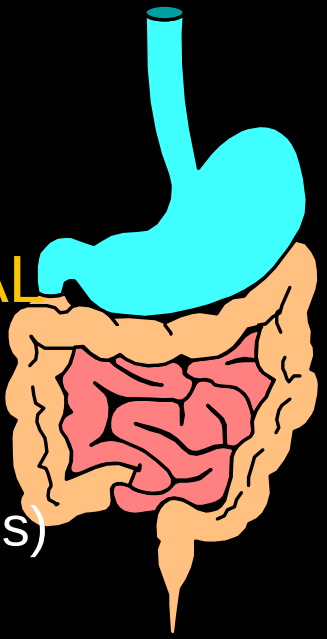


TECHNOLOGY OF DOSAGE FORM

dissolution rate

- robustness of rate controlling mechanism
- .....

ANATOMY & **PHYSIOLOGY** OF THE GASTROINTESTINAL TRACT



- geometry (pylorus)
- mechanics (peristalsis)
- chemistry (pH)
- biochemistry (enzymes)
- .....

Activity of GI-tract

Food

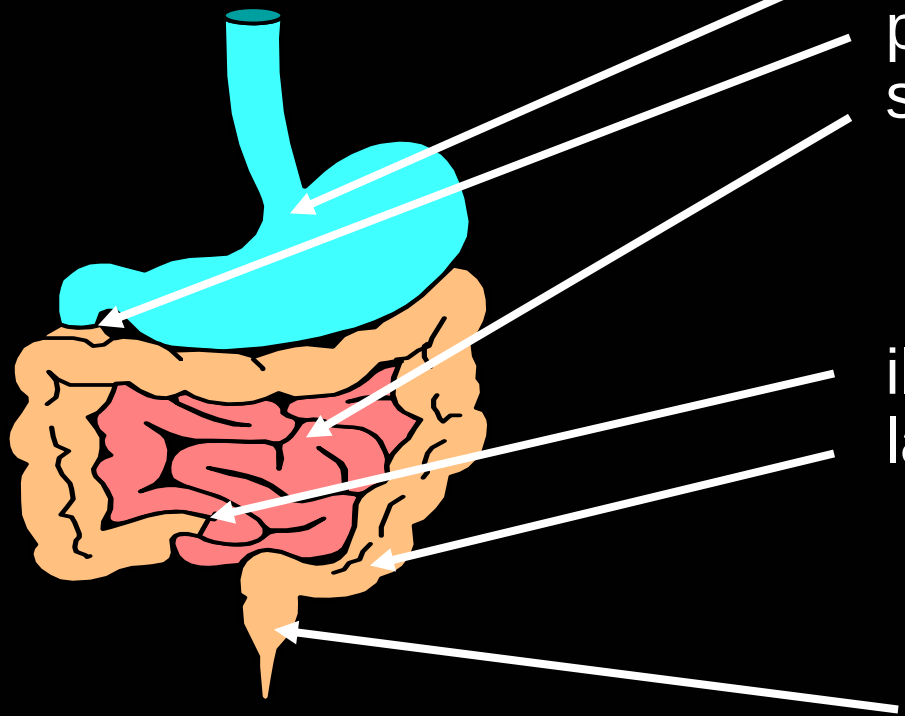
- Storage
- Separation
- Transport
- Processing = Digestion
  - mechanical
  - biochemical
- Absorption
  - all essential food components are absorbed by active processes (amino acids, fat components > 12C, carbohydrates)

Activity of GI-tract

Dosage Forms

- Storage
- Separation – depending on technological type
- Transport
- Processing
  - disintegration
  - dissolution
  - decomposition
- Absorption of drugs
  - many xenobiotics are absorbed by passive diffusion (lipophilicity, molecular weight)
- Resecretion of drugs to GI-Tract

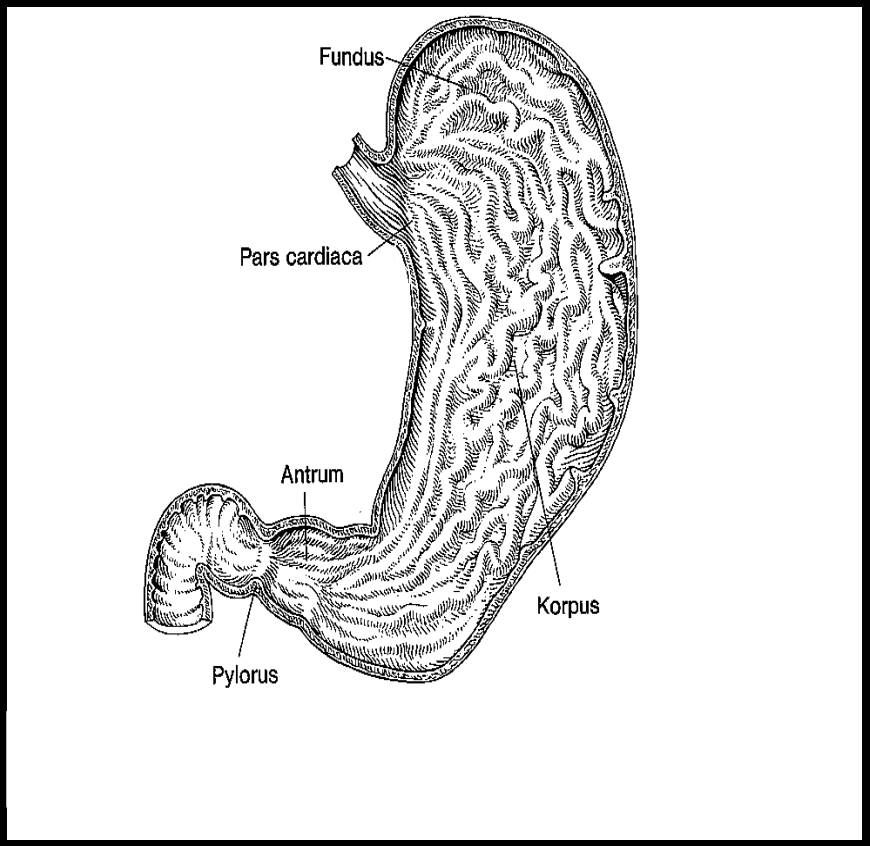
Gastrointestinal Transit: Anatomy I



From proximal to distal

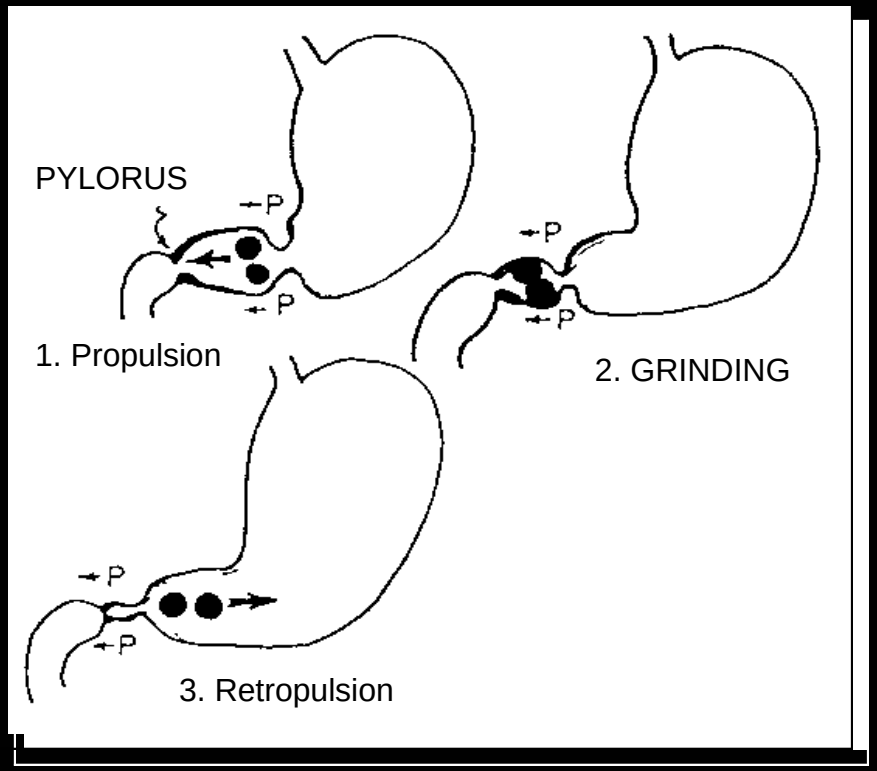
- stomach
- pylorus
- small bowel:
  - duodenum
  - jejunum
  - ileum
- ileocecal valve
- large bowel:
  - colon ascendens
  - colon transversum
  - colon descendens
  - sigmoideum and rectum

Gastrointestinal Transit: Anatomy II



- The stomach
  - storage “room”
  - regulates transport
  - continues grinding of food:
    - antral mill
  - emptying controlled by pylorus
    - exlcusion size
    - different kinetics for solids and liquids
    - emptying of isocaloric masses vs. time
  - motoric activity different:
    - fasted state
    - fed state

Gastrointestinal Transit: Anatomy III



The stomach cont'd
- continues grinding of food:
  - antral mill
- emptying controlled by pylorus
  - exlcusion size 5-7 mm
  - large particles only with housekeeper wave
  - small particles (2mm) together with grinded chyme

Gastrointestinal Transit: Emptying from Proximal Section

Stomach

MMC in the fasted state (interdigestive)
phase I: 40 - 60 min, no to small activity
phase II: 30 - 45 min some occasional activity
phase III: 5 - 15 strong contractions, housekeeper wave
phase IV: leads to next cycle

MMC in the fed state (postprandial)
one phase with constant peristaltic activity
strong antral activities
pylorus is generally closed but opens to release chyme

Gastrointestinal Transit: Emptying of Solids

- strong influence of various factors
  - body posture
  - physic activity
  - psychic activity
    - *stress increases emptying rate*
    - *pain decreases emptying rate*
  - age
  - health
  - daytime (morning faster than night)
  - gender
- mean gastric residence time 0.5 to 14.5 h

Gastrointestinal Transit: Emptying of Solid Dosage Forms from Stomach

- **Variability of multiparticulate smaller than for monoparticulate dosage forms**

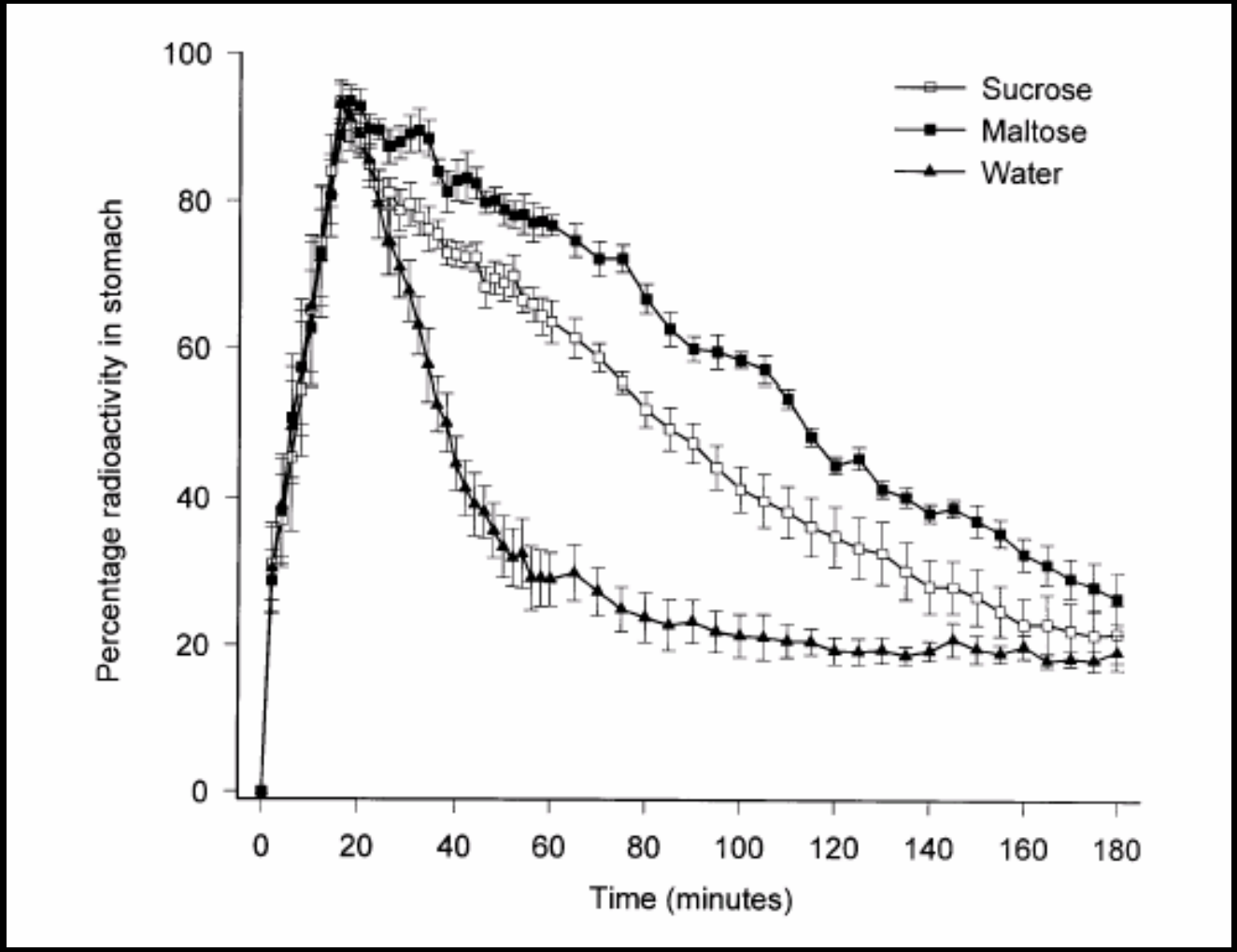
- **multiparticulate dosage forms**
  - fasted state:
    - like concomitantly ingested fluid
  - fed state
    - like concomitantly ingested food
  - influence of size (pylorus) no influence of density
- **monoparticulate dosage forms**
  - high variability, e.g. 0 - 24 h
  - fasted state: only at phase III of MMC
  - fed state: no emptying

Gastrointestinal Transit: Emptying of Liquids

- fasted state
  - according to first order kinetic
  - saline solutions faster than acidic soln. and lipoid soln.
  - volume dependent
  - temperature dependent
    - 4- 6 °C: approx. 15 min
    - 20 - 25 °C: approx. 50 min
    - 45 °C: approx. 70 min
  - ethanol containing beverages slower than control
- fed state
  - according to zero order kinetic (5ml/min)
  - independent from pylorus

Emptying of Liquids from Stomach

Fed state



Lavin et al.,
Int. J. Obesity 2002

Small Intestinal Transit

Liquids 1-2 h
Solids 3-4 h

- no pronounced differences between fasted and fed state
- velocity of propagation is not consistent

Small intestinal transit time measurements highly method dependant because of 2D- / 3D positioning, resolution, time grid

- gamma scintigraphy (Ian Wilding)
- MRI (Werner Weitschieß)
  magnetic resonance imaging
- breath test

Gastrointestinal Transit:
Emptying of Solid Dosage Forms from Small Intestine

Small Intestine

- according to circadian rhythms
- no difference between multiparticulate and monoparticulate dosage forms
- no difference between fasted and fed state
- mechanical stress at ileocecal valve
- mean intestinal residence time 3.5 h

Large Intestinal Transit

- Duration extremely variable: 4-72 h
- Propagation not consistent rate and direction usually vary
  - dependant on many factors
    - day time (circadian rhythm)
    - sleep
    - nutritional status
    - composition of meals
    - body posture
    - emotional status
    - health status
    - gender

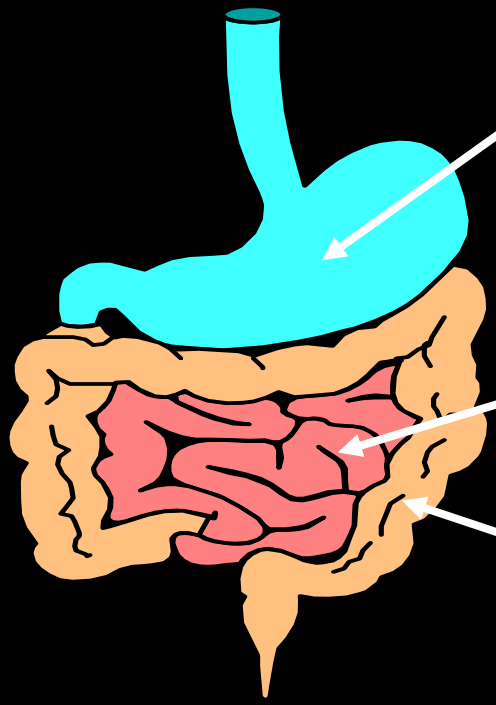
Gastrointestinal Transit: Emptying from Distal Section

small intestine
- propulsive and retropulsive contractions
- fasted: phase III of MMC in stomach is continued
- fed: segmental circular contractions at irregular pattern

ileocecal valve
- prevents reflux from microbiologically active large bowel
- regulates transit (regrouping of particles)

large intestine
- small and weak peristaltic activity
- no to small differences between fasted and fed state
- large bowel never empty at regular nutritional behavior

Gastrointestinal Transit: Physiology I



From proximal to distal

- stomach
  - fasted pH 1.5
  - fed pH 5
  - contains
    - acids
    - salts
    - enzymes
    - surface active ingredients
- small bowel:
  - proximal pH 6.5 - 7.6
  - distal pH 6.9 - 7.9
  - contains
    - salts
    - enzymes
    - surface active ingredients
- large bowel:
  - pH 6 - 8
  - contains
    - ....microorganisms

Biochemistry of Stomachial Content

Interdigestive = fasted

- Liquid volume: 50-100 ml, filling capacity: 0.5 L

		Ventricle (n = 36)	
		Average	±S.D.
Osmolality	mOsm/kg	191	36
Ionic Strength		0.100	0.025
pH		2.9	1.97
Na+	mM	68	29
K+	mM	13.4	3.0
Cl−	mM	102	28
Ca2+	mM	0.6	0.2
Bile Acids	mM	0.2	0.5
Proteins	g/l	1.8	0.7

Lindahl et al., Pharm. Res. 1997

Biochemistry of Stomachial Content

Postprandial = fed

- Liquid volume: 1-2 L
- Enzymes
  - proteases
    - pepsin
    - chymosin
    - human gastric lipase (HGL)
    - surfactants
      - » non-steroids
      - » steroids

Biochemistry of Intestinal Content

- Volume: about 9L of water are recirculated within 24 h
- Composition

		Jejunum (n = 37)	
		Average	±S.D.
Osmolality	mOsm/kg	271	15
Ionic Strength		0.139	0.014
pH		7.1	0.60
Na−	mM	142	13
K+	mM	5.4	2.1
Cl−	mM	126	19
Ca2÷	mM	0.5	0.3
Bile Acids	mM	2.9	2.9
Proteins	g/l	2.1	1.2

Lindahl et al., Pharm. Res. 1997

Conclusions: IR Dosage Forms

- depending on their galenical properties dosage forms may disintegrate (mechanical property) site-independently
- if disintegration happens instantaneously dissolution is expected to depend from
  - drug in vivo-medium interaction
    - wettability
    - solubility
      - pH-effect
      - saline concentration
      - ional composition
      - surfactant concentration
    - stability
- the simulation of a certain combination of fixed physical, physicochemical, chemical, and biochemical conditions may work with conventional dissolution instruments!

Promising Results with FaSSIF / FeSSIF

	FaSSIF	FeSSIF
Sodium taurocholate	3 mM	15 mM
Lecithin	0.75 mM	3.75 mM
pH	6.5	5.0
Osmolality	270 ± 10	635 ± 10 mOsm
Buffer Capacity	10 ± 2	76 ± 2 mEq/L/pH unit

- Developed at Frankfurt University by JB Dressman
- Mainly limited to Research Projects
- No use in routine QC / GMP
  - highly variable ingredient quality
  - time consuming and variable preparation
  - high costs

actual research project: synthetic subsitute for use in the GMP-environment

Conclusions MR Dosage Forms

- depending on their geometry dosage forms may have different transit behavior
- dosage form and drug dissolved may have different transit kinetics
- anatomy and physiology cause an additional variability

the nutritional status may add further variability

- the simulation of a combination of changing, physical, physicochemical, chemical, biochemical, and microbiological conditions that are met by a dosage form along it's GI passage, is not possible with conventional dissolution instruments!

Drug / Dosage Form in the Presence of Food

Food Interaction with IR and MR Dosage Forms

concomitant food intake may effect the bioavailability of a formulation

this may be drug related at the site of

- absorption (tetracyclines and milk)
- distribution
- metabolism (nifedipine and grapefruit)
- excretion (phenylbutazone and vegetables)

this may also be dosage form related

worst case: “dose dumping” phenomenon

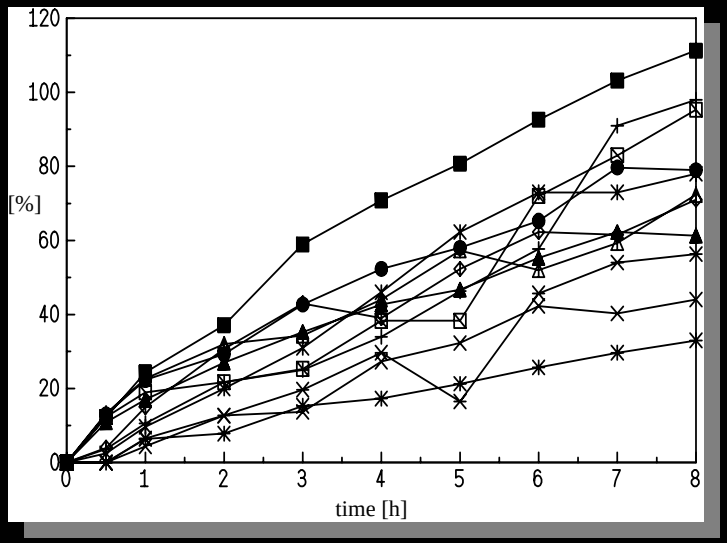
Dosage Form Related Food / Drug Interactions

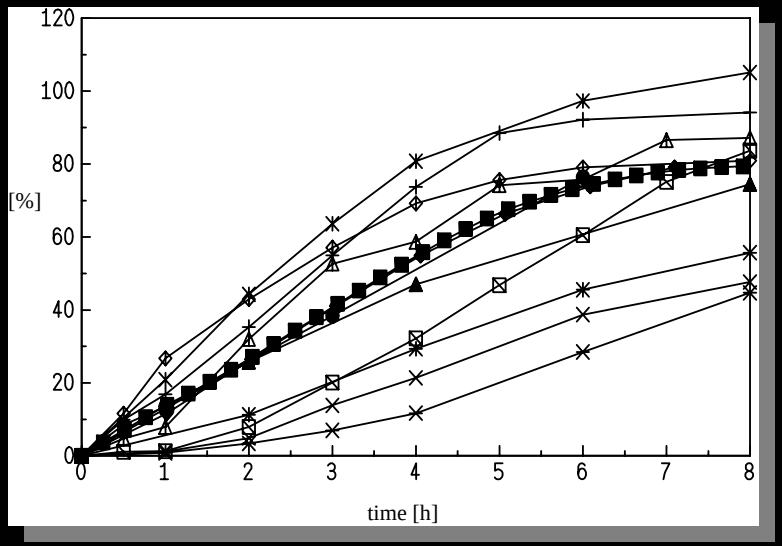
brant name	technolog. type	manufacturer / lot	effect on bioavailability	
			extent	rate
Armophylline	multiparticulate	Rorer, F	±0	±0
Cronasma 350	multiparticulate	Thiemann, D	↓	↓
Dilatrane AP	multiparticulate	Fisons, F	±0	±0
		Fisons, UK	±0	±0
Euphylong	multiparticulate	Byk Gulden, D	±0	±0
Slo-Phyllin Gyrocaps	multiparticulate	Dooner, USA	±0	±0
		Rorer, USA	±0	±0
Somophyllin-CRT	multiparticulate	Fisons, UK	±0	±0
		Fisons, USA	↑	±0
Theo-24	multiparticulate	Searle, USA, lot 1283-873	↑	↑
		Searle, USA, lot 983-810	↑	↑
Theo-Dur	monoparticulate	Key Pharmaceuticals, USA	±0	±0
		Key Pharmaceuticals, USA	±0	↓
Theo-Dur Sprinkle	multiparticulate	Key Pharmaceuticals, USA	↓	↓
		lot 304501,265201	↓	↓
Theodur-G Retard	multiparticulate	Mitsubishi, J	↓	↓
		lot TG-035AS		
Theograd	monoparticulate	Abbott, NL	↑	↓
Theolair-SR	monoparticulate	Riker, USA	no information	↓
Nuelin Retard	monoparticulate	Riker, UK	±0	↓
Nuelin S.A.	monoparticulate	Riker, UK	↓	↓
Nuelin Retard		Riker, UK	no information	↓
Theolin Retard	monoparticulate	Draco, S, lot PG 317	±0	±0
Theolong Retard	multiparticulate	Esai, J, lot 7101	↓	↓
Theostat	monoparticulate	Sinbio, F	±0	±0
		Fabre, F, lot 160	±0	±0
Unilair	multiparticulate	3M Medica, USA	±0	±0
Uniphyl	monoparticulate	Purdue Frederick, USA	↑	↓
		lot 1P5, 1L6	↑	↓
		lot O9W	↑	↓
Uniphyllin	monoparticulate	Napp, UK	±0	±0

±0: no effect
↑: extent of bioavailability and/or rate **higher**
↓: extent of bioavailability and/or rate lower than in fasted state

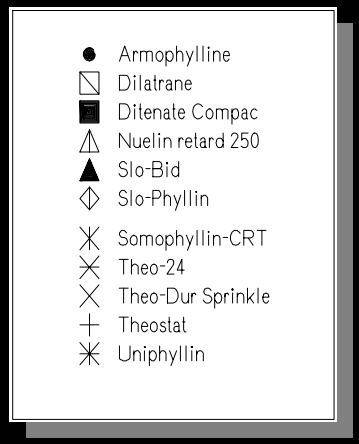
Example Theophylline ER Products

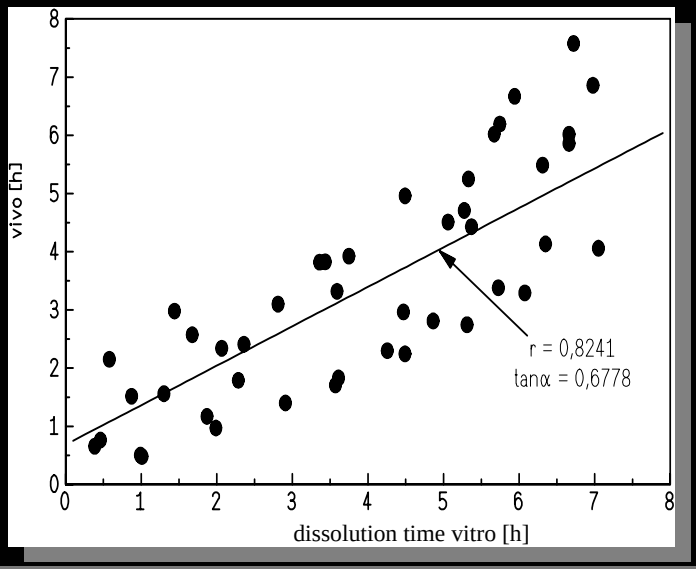
In Vitro- / In Vivo-Correlation of Theophylline Extended-Release Dosage Forms: Fed





paddle, homo-genized food

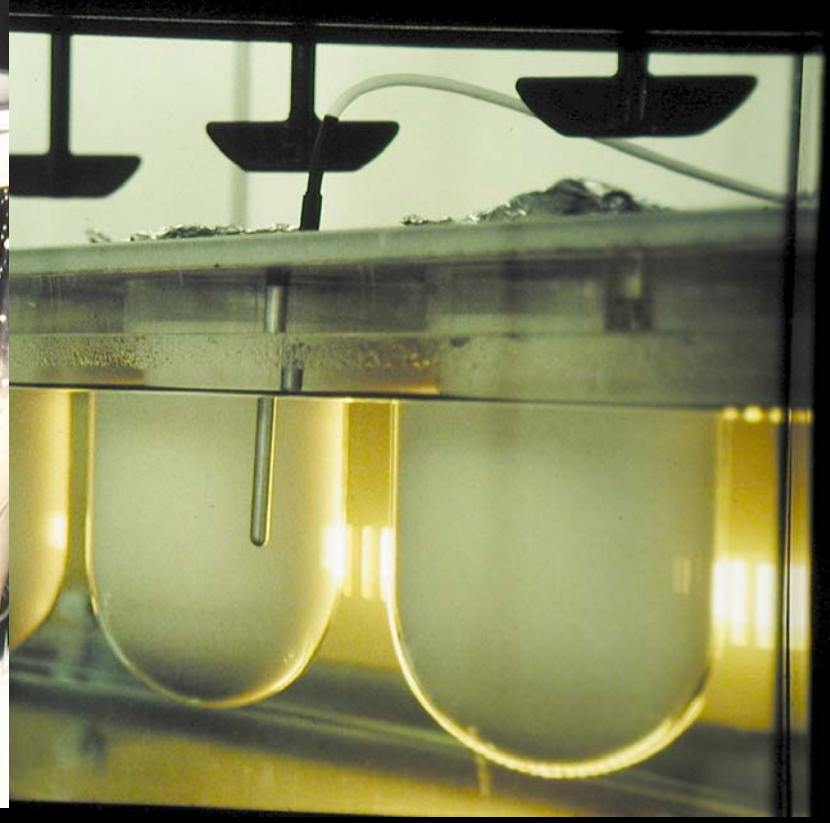




in vivo-dissolution bio-studies

in vitro modeling of food effects

standard breakfast - mixer - dissolution test



Robustness: e.g. In Vitro "Modeling" of Food-Interactions

influences on rate-controlling mechanism by:...

...a strong initial contact

- Maturu: presoak with lipids / rotating bottle
- Wearly: presoak with lipids / basket
- Esbelin: presoak with lipids / recip. cyl.

...weak, but continuing interference

- Junginger: high caloric beverage / paddle
- Macheras: milk / basket
- Krämer / Blume / Stricker / Siewert:
  - » neutral oil emulsion / paddle
  - » neutral oil emulsion with lipase / paddle
  - » homogenized breakfast

...strong and continuing interference

- El-Arini: lipids / paddle

In vitro-Modeling of Dosage Form-Related Factors on Bioavailability of Modified-Release Pharmaceuticals

Progress

in vitro-modeling possible

- **of in vivo-dissolution under *fasted* conditions by topographical characterization**
- **of in vivo-dissolution under *fed* conditions (only direct interactions)**

non-resolved issues

in vitro-modeling impossible

- **of gastrointestinal transit**
- **of site of absorption**

prediction of food effects bioavailability by in vitro-means is barely feasible

In Vitro Dissolution Testing of Oral Dosage Forms

- great use as surrogate according to the BCS
- mandatory in pharmaceutical quality testing
  - during product development
  - during the scale-up procedure
  - in QC

    intra-lot homogeneity
    lot-to-lot conformity
  - in stability testing
  - after changes of recipe
  - after changes of manufacturing site of ...

    ....one product

but not useful as surrogate for food studies

Conclusions cont'd

- .....
- the simulation of a combination of changing, physical, physicochemical, chemical, biochemical, and microbiological conditions that are met by a dosage form along it's GI passage, is not possible!
- .....special investigations concerning the robustness of ER dosage forms ... also towards food required!
- .....even if already done for IR form