Bioavailability and Bioequivalence
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Physiological Meaningful Dissolution Testing?

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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
The stomach storage “room” regulates transport continues grinding of food:
- antral mill
- emptying controlled by pylorus
- exclusion size
- different kinetics for solids and liquids
- emptying of isocaloric masses vs. time
- motoric activity different:
  - fasted state
  - fed state
The stomach cont’d continues grinding of food:
- antral mill
- emptying controlled by pylorus
- exclusion size 5-7 mm
- large particles only with housekeeper wave
- small particles (2mm) together with grinded chyme
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
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
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

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>± S.D.</th>
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<tbody>
<tr>
<td>Osmolality</td>
<td>mOsm/kg</td>
<td>191</td>
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<tr>
<td>Ionic Strength</td>
<td></td>
<td>0.100</td>
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<tr>
<td>Na+</td>
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<tr>
<td>K+</td>
<td>mM</td>
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<tr>
<td>Cl−</td>
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<td>Ca2+</td>
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<tr>
<td>Bile Acids</td>
<td>mM</td>
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<tr>
<td>Proteins</td>
<td>g/l</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Jejunum (n = 37)</th>
<th>Average</th>
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<td>Osmolality</td>
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<td>0.139</td>
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<td>pH</td>
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<tr>
<td>Na−</td>
<td>mM</td>
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<tr>
<td>K+</td>
<td>mM</td>
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<tr>
<td>Cl−</td>
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<td>Ca2+</td>
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<td>0.3</td>
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<tr>
<td>Bile Acids</td>
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<td>2.9</td>
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<tr>
<td>Proteins</td>
<td>g/l</td>
<td>2.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>FaSSIF</th>
<th>FeSSIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium taurocholate</td>
<td>3 mM</td>
<td>15 mM</td>
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<tr>
<td>Lecithin</td>
<td>0.75 mM</td>
<td>3.75 mM</td>
</tr>
<tr>
<td>pH</td>
<td>6.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Osmolality</td>
<td>270 ± 10</td>
<td>635 ± 10 mOsm</td>
</tr>
<tr>
<td>Buffer Capacity</td>
<td>10 ± 2</td>
<td>76 ± 2 mEq/L/pH unit</td>
</tr>
</tbody>
</table>

- 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 substitute 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 its GI passage, is not possible with conventional dissolution instruments!
Drug / Dosage Form in the Presence of Food
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

<table>
<thead>
<tr>
<th>brand name</th>
<th>technolog. type</th>
<th>manufacturer / lot</th>
<th>effect on bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armophylline ER</td>
<td>multiparticulate</td>
<td>Rorer, F</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Cronasina 350</td>
<td>multiparticulate</td>
<td>Thiemann, D</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Dilatrace AP</td>
<td>multiparticulate</td>
<td>Fisons, F</td>
<td>±0 ±0</td>
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<tr>
<td>Euphyllone</td>
<td>multiparticulate</td>
<td>Byk Gulden, D</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Slo-Phyllin GyrOCUS</td>
<td>multiparticulate</td>
<td>Dooner, USA</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Somophyllin-CRT</td>
<td>multiparticulate</td>
<td>Fisons, UK</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Theo-24</td>
<td>multiparticulate</td>
<td>Searle, USA, lot 1283-873</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Theo-Dur</td>
<td>monoparticulate</td>
<td>Key Pharmaceuticals, USA</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Theo-Dur Sprinkle</td>
<td>multiparticulate</td>
<td>Key Pharmaceuticals, USA</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Theodur-G Retard</td>
<td>multiparticulate</td>
<td>Mitsubishi, J</td>
<td>±0 ±0</td>
</tr>
<tr>
<td>Theograd</td>
<td>monoparticulate</td>
<td>Abbott, NL</td>
<td>↑↑</td>
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<tr>
<td>Theolair-SR</td>
<td>monoparticulate</td>
<td>Riker, USA</td>
<td>no information</td>
</tr>
<tr>
<td>Nuelin Retard</td>
<td>monoparticulate</td>
<td>Riker, UK</td>
<td>±0 ↓</td>
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<tr>
<td>Nuelin S.A.</td>
<td>monoparticulate</td>
<td>Riker, UK</td>
<td>±0 ↑</td>
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<tr>
<td>Nuelin Retard</td>
<td>monoparticulate</td>
<td>Riker, UK</td>
<td>no information</td>
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<td>Theolin Retard</td>
<td>monoparticulate</td>
<td>Draco, S, lot PG 317</td>
<td>±0 ±0</td>
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<tr>
<td>Theolong Retard</td>
<td>multiparticulate</td>
<td>Estai, J, lot 7101</td>
<td>±0 ↑</td>
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<td>Theostat</td>
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<td>Stabillo, F</td>
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<td>Unilair</td>
<td>multiparticulate</td>
<td>3M Medica, USA</td>
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<td>Uniphyll</td>
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<td>Purdue Frederick, USA</td>
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<tr>
<td>Uniphyllin</td>
<td>monoparticulate</td>
<td>Napp, UK</td>
<td>±0 ±0</td>
</tr>
</tbody>
</table>

±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, homogenized food

in vivo-dissolution bio-studies

Levy-Plots

http://www.phast.de
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
## Progress vs. non-resolved issues

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

### 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
• the simulation of a combination of changing, physical, physicochemical, chemical, biochemical, and microbiological conditions that are met by a dosage form along its 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