Oral Formulations for Poorly Water Soluble Compounds

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Oral Delivery of Poorly Water Soluble Compounds

- For systemic activity of an API molecule after oral administration it must be absorbed from the intestine and reach the bloodstream / the site of action.

- Passive diffusion is the most dominant mechanism of drug absorption from the intestinal lumen (GIT).

Oral Delivery of Poorly Water Soluble Compounds

With a few exceptions, molecular dispersion of a drug is a prerequisite for its absorption across biological membranes.

This dictates that after oral administration the drug has to dissolve in the gastrointestinal fluid before partitioning into and across the enterocyte.

This implies that the dissolution of a poorly water soluble drug can become the rate limiting step for the onset of drug levels in the blood (if absorption is reasonable fast) → Negative impact on Oral Bioavailability.
Drug Dissolution – Noyes Whitney

\[
\frac{dX}{dt} = \frac{A \cdot D}{h} \left( C_s - \frac{X_d}{V} \right)
\]

- **dx/dt** Dissolution rate
- **A** Interfacial surface area
- **D** Diffusion coefficient
- **h** Thickness of diffusion layer
- **X_d** Amount of drug dissolved
- **C_s** Saturation solubility
- **V** Volume of dissolution medium

- **Key parameter that influence dissolution rate**
  - **Solubility of the API**
    - Polymorph, pKa, Gastro-intestinal pH, Buffer Capacity of the GIT
  - **Surface area (A)**
    - Particle size, wetting properties

- **Physico-chemical properties of the API AND the physiological state of the GIT** can have a significant impact on the in-vivo dissolution of the drug
Dose and Dose number ($D_0$)

- **Solubility and Dose always have to be considered together**

\[
D_0 = \frac{M_0}{V_0} C_s
\]

- $M_0$ = dose administered (mg)
- $V_0$ = 250 ml (reference volume of *human* stomach, FDA-approach)
- $C_s$ = solubility (mg/ml)

**Remarks:**
- $D_0 > 20$ at pharmacological doses -> already critical
- In practice, $D_0$ values often between 20 and 100 for pharmacological and human doses.
- For TOX doses, $D_0$ up to 1000 and more are frequent ...!
Absolute bioavailability vs. variability

Inverse relationship between the absolute bioavailability (F) of an oral dosage form and its total intersubject variability (CV).

To lower the variability means for a formulation scientist in most cases to improve the bioavailability in the fasted state.
Solubility and Permeability are key determinant of oral bioavailability → Biopharmaceutical Classification System

- **Class II**
  - Low solub
  - High perm

- **Class I**
  - High solub
  - High perm

- **Class III**
  - High solub
  - Low perm

- **Class IV**
  - Low solub
  - Low perm

**Formulation**

- **Class II**
- **Class I**

- **Class IV**
- **Class III**

Limited formulation influence
Use of Drug Delivery Systems in Major Pharmaceutical Companies

Source: Kermani, F., et.al., Drug Delivery Technology, Oct. 2001

Distribution with regard to route of administration

- Oral: 47%
- Parenteral: 18%
- Inhalation: 16%
- Transdermal: 11%
- Other: 8%
Approaches to improve Solubility, Dissolution of poorly water soluble APIs and decrease Variability

1. Physical modifications
   • Particle size reduction *(Nanosuspensions, micronization)*
   • Dispersion of drug in a polymer matrix *(Solid Dispersions, solid solutions)*
   • Polymorphs / Pseudopolymorphs
   • Complexation / Solubilization

2. Lipid-based systems
   • e.g. *Microemulsions* (SMEDDS)
Examples

Impact of a particle size reduction on dissolution and oral bioavailability of a poorly water soluble drug

Nanosuspenions
I. Nanosuspensions

- **Working principle**
  Increased dissolution rate by reducing particle size to the nanometer range (and thereby increasing the surface area)

\[
\frac{dX}{dt} = \frac{A}{h} \cdot D \left( C_s - \frac{X_d}{V} \right)
\]

Noyes Whitney (modified)

- **Technology**
  - Downstream Process (e.g. Milling)
  - Up-stream Process (e.g. Precipitation)
  - Drying of nanosuspension → Solid Dosage Form
I. Nanosuspensions

- Nanosizing
  - Most prominent manufacturing technology (e.g. NanoCrystal® wet milling technology by Elan)
  - Addition of stabilizers (polymers, surfactants) to prevent agglomeration of nanosized particles

Ref. E. Merisko-Liversidge et.al.  
Eur. J. Pharm. Sci. 18 (2003), 113-120

Particle size distribution of Naproxen crystals before milling (triangle, mean 24.2 um) and after milling (circle 0.147 um)
I. Nanosuspensions

Impact of particle size reduction on dissolution rate

- Example: Cilostazol (BCS II)

- Particle size (median)
  - Hammer-milled (□) 13 μm
  - Jet-milled (◊) 2.4 μm
  - NanoCrystal (△) 0.2 μm

- Dissolution rate testing
  - water 37°C, 900ml
  - 50rpm, USP apparatus 2
  - 5 mg cilostazol

Dissolution rate of Cilostazol from a suspension is clearly increased by a reduction of the drug substance particle size

I. Nanosuspensions

Pharmacokinetic of Cilostazol suspensions in fasted and fed beagle dogs


Serum concentration vs. time after oral administration of cilostazol suspensions (100mg/body) in fasted (open) and fed (closed) beagle dogs (n=4) (mean; SD)

Major increase in bioavailability with minimal food effect observed for the Cilostazol nanosuspension (NanoCrystal®)
Examples

Impact of a formulation parameter on oral bioavailability of a poorly soluble compound

Solid dispersion
II. Solid Dispersions

- **Definition**
  A poorly water soluble drug that is highly dispersed and stabilized in a hydrophilic carrier

- **Working principle**
  - "Ultimate" particle size reduction
  - No crystal structure
  - Hydrophilic carrier
    - improved wetting of the drug
    - inhibits recrystalization/precipitation of supersaturated solution
  - Surfactant (optional)
    - increase solubilization of the drug
II. Solid Dispersions
Oral Absorption of Poorly Water Soluble Drugs

Solvent evaporation

Melt-extrusion

Solid Dispersions

NOT bioavailable

Organic Solution

Solvent evaporation

Bioavailable

Melting
II. Solid Dispersions

*In-vitro dissolution rate and in-vivo pharmacokinetic data of NVS02 (BCSII)*

- Crystaline drug
- Amorphous drug
- Solid Dispersion
- Solid Dispersion with 10% SDS

Same rank order of tested formulations in in-vitro dissolution rate and in-vivo plasma level curves
II. Solid Dispersions

*Impact of surfactant on pharmacokinetic of NVS02 (BCSII)*

Arithmetic mean ± SD whole blood concentration of NVS02 following administration of 30 mg tablets in healthy volunteers (n=18)

<table>
<thead>
<tr>
<th>Solid Dispersion</th>
<th>AUC$_{0-\infty}$ [ng h/ml]</th>
<th>CV %</th>
<th>C$_{max}$ [ng]</th>
<th>CV %</th>
<th>t$_{max}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Polox.</td>
<td>214 (97)</td>
<td>51</td>
<td>28 (9)</td>
<td>36</td>
<td>1.5</td>
</tr>
<tr>
<td>+10% Polox.</td>
<td>296 (130)</td>
<td>47</td>
<td>72 (16)</td>
<td>23</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The formulation containing a surfactant showed a higher and less variable absorption of the drug from the GIT.
II. Solid Dispersions

Physical and chemical stability

RISK: Recrystallization of amorphous drug during storage
II. Solid Dispersions

Pharmacokinetics of NVS02 solid dispersions (with diff. % of crystalline DS)

- Data indicate that exposure is significantly reduced when drug crystalizes out during storage of the solid dispersion
- Physical stability can cause significant variability in pharmacokinetics of solid dispersions

Single dose, 3-arms, crossover study in fasted dogs (n=9)
Example

Formulation approach for a lipophilic, poorly water soluble drug

Microemulsion
III. Lipid based formulations
Enhancement of oral absorption of poorly water soluble drugs (PWSD)

1. Increasing solubilization and drug disposition in the intestinal lumen
2. Affecting absorption pathway of drug transport to the systemic circulation
3. Interacting with enterocyte-based transport and metabolic processes

*Fig from Porter CJH et al., Nature Reviews | Drug Discovery, Vol. 6, March 2007, 231-248*
III. Lipid based formulations
Increasing solubilization and drug disposition in the intestinal lumen

- Digestion of **exogenous** lipids by pancreatic enzymes (lipase, co-lipase) \(TG \rightarrow DG \rightarrow MG + FA\)
- Formation of colloidal structures with **endogenous** biliary lipids
- Increase solubilization capacity for lipid digestion products and drugs in the small intestine

*Fig from Porter CJH et al., Nature Reviews | Drug Discovery, Vol. 6, March 2007, 231-248*
III. Lipid based formulations

In-vivo performance

Lipid-based formulations must maintain drug in solution in the GIT to enhance oral bioavailability.

Risk: Precipitation on Dispersion of the formulation
Risk: Precipitation on Digestion of the formulation

Fig from Porter CJH et al., Nature Reviews | Drug Discovery, Vol. 6, March 2007, 231-248

III. Lipid based systems  
Micellar systems, Microemulsions, Emulsions

- **Micelle (o/w)**
- **Microemulsion (o/w):**
  - Thermodynamically stable
  - Translucent, isotropic
- **Emulsion (o/w):**
  - Thermodynamically unstable
  - Milky appearance

Size:
- 20 – 150 nm (< 200 nm)
- Up to a few µm
III. Lipid based systems:
Microemulsions: Phase diagram screening – Potential formulations

**Undiluted Preconcentrate**
- Clear, homogenous formulation
- No precipitation with a reasonable drug loading

**Diluted**
- Self-dispersing
- Stable and no precipitation in physiological relevant time frame

![Phase diagram of microemulsions showing the composition of surfactant, hydrophilic phase, and lipophilic phase.](image)
III. Lipid based Systems
Oral Absorption of Poorly Water Soluble Drugs

Solubilisation → Organic or lipid-based solutions

Encapsulation → Bioavailable

Filling → Microemulsion

NOT bioavailable
III. Lipid based formulations

*From Preconcentrate to the Microemulsion*

- Soft gel capsule filled with microemulsion preconcentrate
- Water
- In-situ formation of the microemulsion
III. Lipid-based formulations
Cyclosporine A

- Cyclic peptide (containing 11 amino acids)
- Lipophilic, low aqueous solubility (< 0.004% w/v)
- Higher solubility in lipids (olive oil >4%) and ethanol (~10%)
III. Lipid based formulations

*Cyclosporine vs. Sandimmun ® vs. Sandimmun Neoral ®*

- Prior to dilution with water
- Diluted with water
III. Lipid based formulations

*Sandimmun® vs. Sandimmune Neoral®* - Pharmacokinetic data

- **Sandimmun®**: Adsorption is dependent on digestion of the lipid-formulation → solubilization depends on individual physiological state in the GIT (e.g. food intake, bile flow) → high inter- and intra-subject variability

- **Sandimmun Neoral®**: Spontaneous formation of the microemulsion in the GIT without the need of endogenous compounds like bile salts / phospholipids → significant reduction of dose as well as inter-, and intra-subject variability

Concentration-time profiles following single oral administration of **300 mg** Sandimmun® to 24 volunteers

Concentration-time profiles following single oral administration of **180 mg** Sandimmun Neoral® to 24 volunteers

J.M. Kovarik et al., Journal of Pharmaceutical Sciences, 83 (3), 1994
III. Lipid based formulations

*Lipid digestion models* for in-vitro assessment lipid-based formulations

Undispersed **oil phase** containing drug (D)

**Aqueous phase** containing drug solubilized in micellar and vesicular structures,

**Pellet phase** containing precipitated drug and insoluble (calcium) soaps of FA

Porter CJH et al., Nature Reviews Drug Discovery, 2007, 6:231-248*
III. Lipid based formulations

*In vitro* digestion test to evaluate solubilization pattern after digestion

Digestion needed to release and maintain drug in the aqueous solution

Similar solubilization pattern in fasted and fed state

Examples

Improved oral bioavailability of a weakly basic drug

pH-modified Formulations
IV. pH-modified Formulations

Improved bioavailability of weakly basic drugs by modulating the micro-pH

- Gastrointestinal pH is influenced by several factors (e.g. food, age) → intra-, intersubject variability

- pH-modified Formulation: Incorporation of acids to improve dissolution of weakly basic drugs

Stomach (fasted): pH 1-2

Intestine (fasted): pH 5-6

Dipyridamole: Solubility pH=2.72 36.64 mg/ml
pH=6.80 0.0031 mg/ml
IV. pH-modified Formulations
Effect of different pH-modifier (20%) on release rate of Dipyridamol tablets

Dissolution in phosphate buffer pH 6.8, SDS 0.1%

- Acidic strength and solubility of the acids have an impact on drug release
- Fumaric acid selected due to most favourable phys.-chem. properties

<table>
<thead>
<tr>
<th>Acid type</th>
<th>pK&lt;sub&gt;a1&lt;/sub&gt;</th>
<th>pK&lt;sub&gt;a2&lt;/sub&gt;</th>
<th>pK&lt;sub&gt;a3&lt;/sub&gt;</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumaric acid</td>
<td>3.0</td>
<td>4.4</td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Citric acid</td>
<td>3.1</td>
<td>4.8</td>
<td>6.4</td>
<td>59.2</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>4.2</td>
<td>5.6</td>
<td></td>
<td>7.7</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>4.2</td>
<td>11.6</td>
<td></td>
<td>28.6</td>
</tr>
</tbody>
</table>

IV. pH-modified Formulations

Dissolution rate of NVS05 (20%) pH-modified tablets (monolytic-, mini-tablets)

- Optimal drug to pH-modifier ratio (1:1)
IV. pH modified Formulations

In-vivo study in fasted, gastric-acidity controlled beagle dogs (n=6)

- The incorporation of an acidic pH-modifier improved oral bioavailability of a weakly basic drug (exposure, variability)
- Intersubject variability of multiparticulates < monolytic tablet

Summary

- Several formulation approaches are available to improve the dissolution rate of poorly water soluble compounds.

- To identify the most appropriate formulation principles the drug substance properties, the pharmacological dose (range) and physiological state have to be considered.

- *In-vitro* and *in-silico* tools should be fully utilized to select the most appropriate technology / formulation variant.

- Today *in-vivo* studies for a final proof of concept are still needed.
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