Solid dispersions as a formulation strategy for poorly soluble compounds

G. Van den Mooter
University of Leuven, Belgium
Outline

- Introduction: 1. General view on the solubility problem
  2. Formulation strategies for class II compounds

- Rationale for using solid dispersions
- Physical structure of solid dispersions
- Carriers in the formulation of solid dispersions
- Analysis of the physical structure
- Preparation of solid dispersions
- Advantages and disadvantages of solid dispersions
Introduction: general view on the solubility problem

Oral delivery is preferred route for drug administration

Candidates for oral drug delivery:
- adequate solubility / dissolution properties
- adequate absorption through the gut
- metabolic stability and no efflux

High number of all development candidates fail due to biopharmaceutical reasons

Poor physicochemical properties (solubility/dissolution) account for the majority of these failures (ca. 40%)

BCS classification: (Amidon et al., 1995)
- Class I: high permeability and solubility
- Class II: high permeability but low solubility
- Class III: low permeability but high solubility
- Class IV: low permeability and low solubility
The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine

**Formulation independent**

The bioavailability of class II compounds is limited by drug solubility/dissolution

**Formulation dependent**

The bioavailability of class III compounds is limited by intestinal permeability

**Dependent on barrier properties**

The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability

**Formulation and barrier properties dependent**
<table>
<thead>
<tr>
<th>Liquid systems</th>
<th>(semi)solid systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronisation, nano-sizing (nanosuspensions)</td>
<td>Micronisation, nano-sizing</td>
</tr>
<tr>
<td>Complexation</td>
<td>Complexation</td>
</tr>
<tr>
<td>Co-solvent approach</td>
<td>Surfactant based strategies (S(M)(N)EDDS, wetting agents)</td>
</tr>
<tr>
<td>Surfactant based strategies (micelles, emulsions, S(M)EDDS, liposomes)</td>
<td>Salts</td>
</tr>
<tr>
<td>pH adjustment</td>
<td>Adsorption forms</td>
</tr>
<tr>
<td></td>
<td>Solid dispersions (e.g. <em>amorphous</em> systems)</td>
</tr>
</tbody>
</table>
Solid dispersions

Introduction:
Formulation strategies for class II compounds

In vitro dissolution of itraconazole in SGF

Dissolution properties ↑↑
Different carriers: different dissolution behavior

Six et al, J. Pharm. Sci, 2004
Introduction: Formulation strategies for class II compounds

Solid dispersions

**Itraconazole in vitro dissolution (SGF)**

- Eudragit E100 (ME)
- HPMC (ME)
- Sporanox

40% drug loading

In vitro ≠ in vivo

**Itraconazole in 8 human volunteers**

- Eudragit E100
- HPMC
- Sporanox

Rationale for using solid dispersions

- **Lattice energy**: Poor solvatation → Reaggregation
- **Solvatation/hydration**

**Solubility process**

- Crystalline material
  - High lattice energy → Amorphous materials
  - Poor solvatation → Protective materials

Diagram:
- Crystalline material
- Lattice energy
- Solvatation/hydration
Rationale for using solid dispersions

Amorphous materials: structural relaxation

Amorphous (glass) → Supercooled liquid → Liquid

Thermodynamically metastable
relaxation, nucleation, crystallization

PURE DRUGS ??
Pure amorphous drugs can be used rarely (stability)

Formulation of amorphous drugs in protective environment/matrix

Solid state physical stability ↑↑
No precipitation following dissolution

Solid dispersion:
“A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method” (Chiou & Riegelman, 1971)
“An product formed by converting a fluid drug-carrier combination to the solid state” (Corrigan, 1985)

No physical mixtures
Mechano-chemical processing?
Drug particle size?
Solid state?

Physical structure
Physical structure of solid dispersions

Eutectic systems

Two phases in the solid state
Particle size reduction
Solubilizing effect of carrier
Crystalline material

\[ T_{\text{drug}} \]

\[ T_{\text{carrier}} \]

L; 1P
L+S
E
S; 2P

% carrier

\[ \text{L} + \text{S} \]
Physical structure of solid dispersions

**Molecular dispersion:** crystalline carrier

**Substitutional solid solution:** carrier molecules are replaced with drug molecules → one phase systems

**Molecular isomorphism!!**
Physical structure of solid dispersions

Molecular dispersion: crystalline carrier

Interstital solid solution: interstitial positioning of drug molecules in the carrier lattice → one phase systems

Size of guest molecules !!
Physical structure of solid dispersions

Molecular dispersion: crystalline carrier

Solid state solubility:
- continuous
- discontinuous

Two phases in the solid state:
\( \alpha + \beta \) (\textit{b in a and a in b})

Particle size reduction at molecular level: \textit{solid solution}
Physical structure of solid dispersions

Molecular dispersion: amorphous (glassy) carrier >> glass solutions

Hydrophilic polymers

carrier + drug → Amorphous solid solution (1P; “interstitial”)
Physical structure of solid dispersions

Partial molecular dispersion

Phase separation (P>1)

Clusters:
amorphous or crystalline

Molecular dispersion

Complex phases:
nanocrystalline domains

carrier

+ drug
Selection criteria for polymeric carriers

- high Tg
- supersaturation potential
  - screening studies from DMSO, DMF,…in aqueous carrier solutions
- possibility of interactions with drug
- solid state solubility (miscibility) of drug in the carrier (molecular dispersion)
  - phase behavior studies ("one Tg")
    - films
  - theoretical models (e.g. Flory-Huggins)
  - solubility in monomers (e.g. NMP)
  - ternary phase diagrams
- solubility in water (organic solvents depending on manufacturing process)
- manufacturing process
Carriers for solid dispersions

Type of carriers

Neutral cellulose derivatives (HPMC, HPC,…)
Acidic cellulose derivatives (HPMC-phtalate, HPMC-acetate-succinate,…)
PVP (K25, K30)
PVPVA64
PEG’s
p-(meth)acrylates (e.g. Eudragit E100)
Kollicoat IR

Gelucire 44/14
TPGS

Mannitol, urea, citric acid

Combination of carriers (polymer-polymer; polymer-surfactant)

“SE-solid dispersion”
Solid dispersions on the market

Sporanox® (itraconazole)
Intelope® (etravirine)
Prograf® (tacrolimus)
Crestor® (rosuvastatin)
Gris-PEG® (griseofulvin)
Cesamet® (nabilone)
Solufen® (ibuprofen)

NOT SO MANY !!!
“Unknown = unloved”

Physical stability ??
Solid dispersions on the market

Drug: molecular dispersion → solid state solubility
- crystalline / amorphous suspension
- agglomerates / aggregates
- polymorphic modifications
- mixed / combined systems (P>1)
- chemical / physical interaction with carrier

Manufacturing Processing Materials

In vitro In vivo dissolution

Physical structure

Stability
Analysis of the physical structure of solid dispersions

Thermal analysis (DSC):
- mixing/phase behaviour
- characteristics of “pure” solid
  - amorphous: Tg
  - crystalline: melting transition

XRD:
- crystallinity, unit cell parameters

IR/Raman/ss-NMR:
- interactions

Mobility in amorphous systems:
- thermal analysis (DSC); ss-NMR; rheology

More recently:
- Imaging techniques
  - (µTA, nano-TA; (E)SEM; TEM; AFM)
  - Inverse GC

- surface properties
- complex phases

Thermal analysis (DSC):
- characteristics of “pure” polymer
  - amorphous: Tg
  - crystalline: melting transition

XRD:
- crystallinity, unit cell parameters
Mixing and phase behavior

Gordon-Taylor equation:

Binary:

$$T_g = \frac{w_1 T_{g1} + Kw_2 T_{g2}}{w_1 + Kw_2}$$

Ternary:

$$T_g = \frac{w_1 T_{g1} + K_1 w_2 T_{g2} + K_2 w_3 T_{g3}}{w_1 + Kw_2 + K_2 w_3}$$

Volume additivity
Total miscibility
Interactions =

Not:
Water, solvents,
Interactions (H, dipolar,...)

Itraconazole/Eudragit E100
Hot melt extrudates

Six et al, Pharm. Res. 2003
Analysis of the physical structure of solid dispersions

Intermolecular interactions


COOH → COO⁻
# Preparation of solid dispersions

<table>
<thead>
<tr>
<th>Solvent based methods</th>
<th>Heat based methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Spray drying</td>
<td>- Hot melt extrusion</td>
</tr>
<tr>
<td>- Bead coating</td>
<td>- Melt compression</td>
</tr>
<tr>
<td>- (Film casting, rotavapor)</td>
<td>- Melt compounding</td>
</tr>
<tr>
<td></td>
<td>- Melt granulation</td>
</tr>
</tbody>
</table>

**Mechanical methods**

- Dry mixing (pressure)
Preparation of solid dispersions

Solvent based manufacturing methods

“Dissolve the drug and the carrier in a common solvent and remove the solvent”

Rate of solvent removal largely determines the physical structure ("maintenance of chaos" – entropic contribution)
(film casting ≠ spray drying !!)

Thermally instable drugs and carriers

Environmental and toxicological issues

Residual solvents

Down stream processing: capsules, tablets,…
Preparation of solid dispersions

- Solution
- Atomisation of solution
- Mixing of spray with gas
- Evaporation of solvent
- Separation of particles from gas
- Collection of particles

Buchi Mini Spray Dryer
Preparation of solid dispersions

Spray drying

Pro-C-epT Micro Spray Dryer
Preparation of solid dispersions

Spray drying

Nozzle
Atomisation pressure

Drying (air, nitrogen) rate
Inlet temperature

Outlet temperature
Condenser outlet temperature

Feed rate
Preparation of solid dispersions

Bead coating, layering

Core (bead, pellet)
Coating (solid dispersion)
Protective coating

e.g.: Sporanox® capsules: HPMC/Itraconazole/PEG 20000
Preparation of solid dispersions

Heat based manufacturing methods

“Apply heat and/or shear forces to a physical mixture of drug and carrier, followed by cooling”

Physical structure is mainly determined by the intrinsic miscibility, the amount of heat applied (processing temperature), shear forces (mixing) and rate of cooling

No or less environmental and toxicological issues

Thermally stable drugs and carriers

Down stream processing: capsules, tablets,…

Preparation of solid dispersions

Hot melt extrusion
Preparation of solid dispersions

Hot melt extrusion
Preparation of solid dispersions

Hot melt extrusion

- Twin screw extruders: Micro-scale equipment
  - Approximately 5g of product
  - Batch mode
  - Vendor: Haake, DSM
Preparation of solid dispersions

Hot melt extrusion combined with super- or subcritical CO$_2$

Temporary plasticizer

“Foaming agent” $\rightarrow$ increased surface area

Processing of thermolabile drugs
Preparation of solid dispersions

Hot melt extrusion combined with super- or subcritical CO₂

Ethylcellulose with CO₂ injection in Leistritz twin screw extruder
(Verreck et al., J. Supercritical Fluids, 2006)

130°C/40bar 130°C/60bar 100°C/100bar
Preparation of solid dispersions

Hot melt extrusion combined with super- or subcritical CO₂

Processing of thermolabile drugs: p-ASA in ethylcellulose matrix
(Verreck et al, Int. J. Pharm. 2006)

| Minimum temperature settings for hot stage extrusion of p-ASA/EC 20 cps 10% (w/w) with and without CO₂ injection |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Without CO₂ injection** | | | | | | | | | | | |
| $T_{1-2}$ (°C) | $T_3$ (°C) | $T_4$ (°C) | $T_5$ (°C) | $T_6$ (°C) | $T_7$ (°C) | $T_{\text{die}}$ (°C) | $T_{\text{flange}}$ (°C) | Torque (%) | $P_{\text{pump}}$ (bar) | % p-ASA (n = 3 ± R.S.D.) |
| 180 | 115 | 115 | 115 | 115 | 115 | 115 | 115 | 87–100 | – | 36.4 ± 0.6 |
| 130 | 130 | 130 | 130 | 130 | 130 | 130 | 130 | 78–93 | – | 83.7 ± 0.2 |
| 130 | 130 | 130 | 130 | 130 | 130 | 130 | 130 | 75–91 | – | 83.3 ± 0.3 |
| **With CO₂ injection** | | | | | | | | | | | |
| 130 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80–100 | 90 | 87.9 ± 0.2 |
| 130 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 86–100 | 90 | 86.4 ± 1.1 |
| 125 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 86–100 | 75 | 89.6 ± 1.1 |
| 110 | 110 | 110 | 105 | 105 | 100 | 100 | 100 | 95 | 85–100 | 75 | 96.3 ± 0.8 |

The screw speed and feed rate were maintained at 100 rpm and 1 kg/h, respectively.

*a* Temperature settings of barrel segments 1 and 2.

*b* Temperature settings of the die (see Fig. 2).

*c* Temperature settings of the flange (see Fig. 3).

*d* % of p-ASA which is not degraded.
Advantages and disadvantages of solid dispersions

**Advantages**

- Processing equipment available at small and large scale
- Thermolabile products
- Relatively high drug doses are possible
- Most carriers can act as “solid” solvent
- Carriers (mainly surface active agents) can maintain supersaturation in GI tract
- Down stream processing is possible

**Disadvantages**

- Understanding the physics of amorphous materials
- Understanding the physical structure of solid dispersions
- Understanding the relationship between physical structure and drug release
- Stability issues; residual solvents
- Prediction of shelf life of amorphous materials?
- Increasing number of drugs with low solubility in organic solvents
- Few new carriers (>> combination!!)

………