Investigating the optimal ratio between drug and co-former in co-amorphous systems

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Crystalline Drug
Solid with orientational and positional long-range order in three dimensions.

- Low solubility
- Stable

Amorphous Drug
Solid with no orientational or positional long-range order.

- High solubility
- Unstable
- High solubility
- Unstable
Marketed Products
Amorphous APIs

- Accolate® (zafirlukast)
- Ceftin® (cefuroxime axetil)
- Accupril® (quinapril hydrochlorid)
- Viracept® (nelfinavir mesylate)
Amorphous solid dispersions

A polymeric amorphous solid dispersion is (ideally) a homogenous molecular dispersion of drug molecules in an amorphous polymeric matrix.
Drug in polymer solubility

Phase diagram of a drug-polymer mixture including the solubility curve (solid line), miscibility curve (dashed line) and the Tg curve (dotted line). **Area I** represents the thermodynamically stable amorphous solid dispersion (glass solution), **area II** represents a metastable amorphous solid dispersion where the mixture is kinetically stabilized due to low molecular mobility, **area III** represents a unstable amorphous solid dispersion in which phase separation occurs spontaneously.
• Amorphous solid dispersions
  
  A polymeric amorphous solid dispersion is (ideally) a homogenous molecular dispersion of drug molecules in an amorphous polymeric matrix.

• Co-amorphous systems
  
  Co-amorphous systems consist of two low molecular weight, initially crystalline, materials that upon co-amorphization are mixed at the molecular level to form a single amorphous phase.
Drug-Drug Combination

Naproxen

- BCS class II
- Non-steroidal anti-inflammatory drug (NSAID)
- Side effect: Gastro-intestinal disorders

\[ M = 230.26 \text{ g mol}^{-1} \]

Cimetidine

- BCS class III
- Used in the treatment of gastro-intestinal disorders
- similar dosing range for NAP&CIM

\[ M = 254.34 \text{ g mol}^{-1} \]
Individual APIs before and after ball milling

$T_g = 36.1 \pm 2.0 \, ^\circ C$

$T_g$ of quench-cooled NAP $= 6.2 \pm 0.6 \, ^\circ C$
Co-milled APIs at different ratios

- All drug-drug molar ratios resulted in X-ray amorphous mixtures
- No trace of crystallinity in DSC

**DSC**

\[ T_g = 40.2 \pm 1.1 \, ^\circ\text{C} \quad T_g = 34.5 \pm 0.3 \, ^\circ\text{C} \quad T_g = 31.5 \pm 0.7 \, ^\circ\text{C} \]**
Physical stability - 60-day storage at dry conditions

Most stable

Not the highest $T_g$ after preparation

Still stable after 6 months
Eutectic behaviour of co-amorphous drug-drug systems

Thermograms for Indometacin/Naproxen systems

Thermograms for Paracetamol/Celecoxib systems

Kissi et al, Pharmaceutics 2019, 11, 628
Naproxen/Indomethacin systems

Celecoxib/Paracetamol systems

Kissi et al, Pharmaceutics 2019, 11, 628
Solid-state characterisation using XRPD

Naproxen/Indomethacin systems

Celecoxib/Paracetamol systems

Samples that show crystalline peaks immediately after melting and cooling can be ruled out

Kissi et al, Pharmaceutics 2019, 11, 628
Tgs for co-amorphous drug-drug systems

There is general decrease or increase in Tg with increasing or decreasing drug concentration.

*Kissi et al, Pharmaceutics 2019, 11, 628*
Physical stability test

After preparation

After storage

Test under dry conditions at room temperature

Kissi et al, Pharmaceutics 2019, 11, 628
Days these systems stayed amorphous

Kissi et al, Pharmaceutics 2019, 11, 628
Superimposing eutectic behaviour and physical stability

Kissi et al, Pharmaceutics 2019, 11, 628
Carvedilol-organic acids co-amorphous systems

*Molar ratios: from 4:1 to 1:4 (CAR-OAs)*
*Samples preparation: Spray drying*

Glass transition temperatures of CAR-OAs systems (mDSC results)

- Highest $T_g$ values: CAR-BA 1.5:1, CAR-MA 2:1 and CAR-CA 2:1.
- In the case of CAR-BA and CAR-CA, the highest $T_g$ was not found at the hypothesized ideal salt forming stoichiometric conditions (CAR-BA 1:1 and CAR-CA 3:1), but at molar ratios of CAR-BA 1.5:1 and CAR-CA 2:1.

Physical stability of CAR-OAs systems (40°C, dry condition)

Carvedilol-amino acid co-amorphous systems with strong interaction

**CAR to ASP molar ratios:**
From 2:1 to 1:4

**Sample preparation:**
Spray drying

**Strong interaction (Salt formation)**

![Carvedilol (CAR)]

**Non-strong interaction**

![L-Aspartic acid (ASP)]

![L-Tryptophan (TRP)]
Comparison of experimental $T_g$s and theoretical $T_g$s

Gordon-Taylor equation:

\[ T_{g12} = \frac{w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2}}{w_1 + K \cdot w_2} \]

\[ K = \frac{T_{g1} \cdot \rho_1}{T_{g2} \cdot \rho_2} \]

Component 1: Amorphous CAR

Component 2: Amorphous ASP

- All experimental values had a positive deviation from the theoretical $T_g$s
- Strong molecular interactions between CAR and ASP in co-amorphous systems
- The highest deviation was observed at the CAR-ASP 1:1.5 molar ratio (rather than at the 1:1 molar ratio)

PCA on FTIR data

- PC-1: Varying molar ratios
- PC-2: Molecular interactions

- $1717 \text{ cm}^{-1}$: -COOH group of ASP
- $1571 \text{ cm}^{-1}$: Aromatic ring stretching of CAR

Physical stability (under dry condition)

- The presence of an excess compound, relative to the sample at the optimal molar ratio (CAR-amino acids 1:1.5), resulted in re-crystallization of the excess component.

Carvedilol-amino acid co-amorphous systems with non-strong interaction

**Carvedilol-amino acids co-amorphous systems**

**Strong interaction (Salt formation)**

**Non-strong interaction**

**CAR to TRP molar ratios:**
From 10% to 90%

**Sample preparation:**
Ball milling

**L-Aspartic acid (ASP)**

**L-Tryptophan (TRP)**
Transition temperatures in co-amorphous CAR-TRP
Transition temperatures in CAR-TRP co-amorphous systems

The experimental $T_g$s were consistent with the theoretical $T_g$s.

Transition temperatures in co-amorphous CAR-TRP

![Graph showing transition temperatures with Tgα and Tgβ markers](image)
Transition temperatures in CAR-TRP co-amorphous systems

Similar $T_{gb}$ values over large concentration ranges of the drug (and amino acid) imply that these transitions originate from an excess component.

Physical stability and $T_{g\beta}$ of co-amorphous CAR-TRP

Diffractogram of the CAR–TRP samples after 62 weeks of storage under dry conditions at 40 °C.

Conclusions

• In systems that can form eutectic mixtures the eutectic ratio is a good starting point for finding the most stable co-amorphous systems.

• In systems with strong interactions, it is not necessarily the stoichiometric molar ratio of the strong interaction that leads to the most stable system.

• In systems with weak interactions the beta relaxation values can be a good guide to find the most stable system.

• Current work looks at other methods to determine the ideal ratio of drug to co-former for systems with weak interactions...

• Current work looks at other methods to determine the ideal ratio of drug to co-former for systems at non-day storage conditions...

• …to be continued…
References:

Thank you for listening!