ROLE OF WATER IN THE POLYMORPHIC TRANSITIONS OF SMALL CARBOHYDRATES

Mohamed MATHLOUTHI, Barbara ROGE, Ghazi BENMESSAOUD

Université de Reims Champagne Ardenne
UMR 614 – Laboratoire de Chimie
Physique Industrielle
SURVEY

INTRODUCTION
- Definition of polymorphism
- Small Carbohydrates Polymorphs
- Solubility and crystallization of polymorphs
- Examples of polymorph transitions investigated

EXPERIMENTAL RESULTS
- Dextrose Monohydrate – Anhydrous transition
- Dextrose Anhydrous – Monohydrate transition
- Sorbitol \( \beta \rightarrow \Gamma \) transition
- Comparison of Sorbitol and Mannitol transitions

DISCUSSION
- Hydrate transition
- Conformational transition
- Stability of sorbitol polymorphs
- Application aspects

CONCLUSION
What is polymorphism?

• Polymorphism = ability of a substance to crystallize into different crystalline forms, yet chemically identical

• Known since the 18th century: Calcium carbonates

• Particularly important in the pharmaceutical industry: characteristics of dissolution and diffusion of drugs (example: a stable polymorph of Ritonavir, a protease inhibitor in HIV treatment)

• Increased awareness of importance resulting in increased industrial and academic investment

• Cambridge Crystallographic data base:
  – 1987: 1500 polymorph structures
  – 2002: 250 000
## Small Carbohydrates Polymorphs

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Polymorph</th>
<th>Crystal structure</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Glucose</td>
<td>$\alpha$-D Glucose, monohydrate</td>
<td>Monoclinic</td>
<td>78°C</td>
</tr>
<tr>
<td></td>
<td>$\alpha$-D Glucose, anhydrous</td>
<td>Orthorombic</td>
<td>146°C</td>
</tr>
<tr>
<td></td>
<td>$\beta$-D Glucose, anhydrous</td>
<td>Orthorombic</td>
<td>150°C</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>Hydrate I</td>
<td>Triclinic</td>
<td>53°C</td>
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<tr>
<td></td>
<td>Hydrate II</td>
<td></td>
<td>57°C</td>
</tr>
<tr>
<td></td>
<td>$\Lambda$ anhydrous</td>
<td>Orthorombic</td>
<td>88.5°C</td>
</tr>
<tr>
<td></td>
<td>$\Gamma$ anhydrous</td>
<td>Monoclinic</td>
<td>95°C</td>
</tr>
<tr>
<td></td>
<td>$\Delta$ anhydrous</td>
<td>Orthorombic</td>
<td>75°C</td>
</tr>
<tr>
<td></td>
<td>$\Sigma$ anhydrous</td>
<td></td>
<td>88°C</td>
</tr>
<tr>
<td></td>
<td>$\Delta$ anhydrous</td>
<td></td>
<td>100°C</td>
</tr>
<tr>
<td>Mannitol</td>
<td>$\Lambda$ anhydrous</td>
<td>Orthorombic</td>
<td>165°C</td>
</tr>
<tr>
<td></td>
<td>$\beta$ anhydrous</td>
<td></td>
<td>166°C</td>
</tr>
<tr>
<td></td>
<td>$\Delta$ anhydrous</td>
<td>Monoclinic</td>
<td>155°C</td>
</tr>
</tbody>
</table>
Solubility and crystallization of polymorphs

Solubility curves of enantiotropic System ($T_r$: Transition temperature)
Polymorph II stable at $T < T_r$

Solubility curves of Polymorphs I and II related monotropically (b)
II more stable than I

Solubility and crystallization of polymorphs

Crystallization of polymorphs with different solubility curves

Monotropic system
Cooling from 1 to 2: nucleation of I
Growth from 2 to 3
Direct cooling 1 to 4: nucleation of II
Growth from 4 to 5

Kinetic factor prevails over thermodynamic: Metastable phase II nucleates

Crystallization of undersaturated solution (A) by Cooling ($\Delta T$) from solubility (B) to nucleation (C) limit and growth ($\Delta w$)
Examples of polymorphic transitions

α- D Glucose polymorphism:
  – Monohydrate – Anhydrous transition
    - Anhydrous – Hydrate transition

Sorbitol polymorphism:
  - Water adsorption mediated polymorphic transition
  - Conformational polymorphic transition
  - Comparison with Mannitol polymorphic transition
EXPERIMENTAL RESULTS

\( \alpha-D \) Glucose, monohydrate
\( \alpha-D \) Glucose, anhydrous
transition
Phase Diagram of D-Glucose

Solubility curves related enantiotropically
Hydrate-anhydrous transition $T^\circ = 50^\circ$C
α-D-Glucose Monohydrate – Anhydrous transition

Suivi par DRX de la déshydratation du dextrose monohydrate

XRPD Monitoring of Dextrose monohydrate dehydration at 60°C
α-D-Glucose Monohydrate – Anhydrous transition
DSC thermograms

No noticeable amorphous phase during transition
α-D-Glucose Monohydrate – Anhydrous transition kinetics

Anhydrous crystal formation

Monohydrate transformation
α-D-Glucose Anhydrous – Monohydrate transition

Hydratation du dextrose anhydre
granulométrie : 50 microns

XRPD Control of hydration by water vapor adsorption (ERH = 97%)
Anhydrous Dextrose - Monohydrate transition
DSC thermograms

Water vapor adsorption (ERH = 97%) mediated transition
Monohydrate occurrence after 90 min – No amorphous
Anhydrous $\alpha$-D-Glucose - Monohydrate transition kinetics

![Graph showing Anhydrous transformation and monohydrate crystal formation over time.](image)
Anhydrous $\alpha$-D-Glucose - Monohydrate transition pictures

Evolution of crystals during hydration at ERH = 75%

No dissolution or amorphization observed
EXPERIMENTAL RESULTS

B – Sorbitol – Γ – Sorbitol Transition
Crystallization of sorbitol

Molten sorbitol

High speed granulator

Seeding

Maturation

Grinding

Sifting

B-sorbitol seed fine particles

B-sorbitol conglomerates
XRD patterns of sorbitol polymorphs

Different XRD structures of $\beta$-sorbitol and $\Gamma$'-sorbitol
XRD pattern of B-Sorbitol at ERH = 58%

Comparable XR diffractograms for B-sorbitol at 0% RH and 58% RH
DSC thermograms of sorbitol polymorphs B (with E) and Γ

B-sorbitol \( (T_m = 97.8^\circ C) \); E-sorbitol \( (T_m = 86.3^\circ C) \) and Γ-sorbitol \( (T_m = 97.8^\circ C) \)
DSC thermograms of B sorbitol equilibrated with different RH

Nucleation yields unstable phases which might last few seconds or several years for kinetic reasons

Oswald (1897) rule: chemical systems don’t tend directly towards equilibrium but rather to the closest metastable crystalline phase
FTIR spectra of B-Sorbitol at 0% and 58% RH

At 58% RH:
- occurrence of $\delta$(HOH) at 1640 cm$^{-1}$
- change in CH and OH bands
Gaussian fitting of FTIR spectra of β-Sorbitol

58% RH

1 CH band    4 OH bands

0% RH

2 CH bands    3 OH bands

Moisture mediated Conformational change
Kinetics of water vapor adsorption

Water Content (%) vs. Time (h)

[1]: sorbitol beta
[2]: sorbitol gamma
Water vapor adsorption isotherms for sorbitol

Dynamic Vapor Sorption at 20°C

Critical ERH the higher the more stable the sample:
\[ \Gamma – \text{sorbitol } 600\mu \text{m} > \Gamma – \text{sorbitol } 300\mu \text{m} > \Gamma – \text{sorbitol } 20\text{-}60\mu \text{m} > \text{B–sorbitol} \]
Kinetics of water adsorption by mannitol polymorphs

Adsorption of water at 97% R.H. by Β - Mannitol (a) and Δ – Mannitol (b)
The less stable adsorbs more water more rapidly

Yoshinari et al., Int J. Pharmaceutics, 247(2002) 69_77
Adsorption of water vapor and mannitol polymorph stability

B- Mannitol before exposure to 97% R.H. (a) and after (b)
Almost no change

Yoshinari et al., Int J. Pharmaceutics, 247(2002) 69_77
Adsorption of water vapor and mannitol polymorph stability

△– Mannitol before exposure to 97% R.H. (a) and after (b)
Recrystallization of the more stable polymorph

Yoshinari et al., Int J. Pharmaceutics, 247(2002) 69_77
DISCUSSION
Dextrose Monohydrate – Anhydrous transition

- Hydrate/anhydrate transition mainly depends on T°
- Transition occurs at T > 50°C with no amorphization
- A zero order kinetics is observed

- Anhydrous/monohydrate transition seems to be water activity dependent at T < 50°C
- No dissolution or amorphization observed
- Zero order kinetics
Conformational Polymorphism

MD results: The most populated conformations of sorbitol in aqueous solution

<table>
<thead>
<tr>
<th>Conformation</th>
<th>Popularity</th>
</tr>
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<tbody>
<tr>
<td>gtttg+</td>
<td>5.7%</td>
</tr>
<tr>
<td>gtttt</td>
<td>13.8%</td>
</tr>
<tr>
<td>g+tttg+</td>
<td>3.4%</td>
</tr>
<tr>
<td>g+tttt</td>
<td>7.2%</td>
</tr>
<tr>
<td>ttttg+</td>
<td>15.1%</td>
</tr>
<tr>
<td>ttttt</td>
<td>46.2%</td>
</tr>
<tr>
<td>tg+ttg+</td>
<td>0.9%</td>
</tr>
<tr>
<td>tg+ttt</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Conformational Polymorphism

Sorbitol
Solution (left) and crystal (right) conformations

Mannitol
Solution (left) and crystal (right) conformations

Conformational Polymorphism

Sorbitol
H-Bonding in Sorbitol crystal compressed (left) and expanded (right)

Mannitol
H-Bonding in Mannitol crystal (same H-bond length)

Conformational polymorphism

Polymorphs differ only in the mode of packing of conformers

Crystallization of conformationally flexible molecules
Thermodynamic vs Kinetic stability of Sorbitol polymorphs

The more stable polymorph has the lowest free energy.

\[ G^*_\Gamma < G^*_B \]

\( \Gamma \)-Sorbitol the stable polymorph

Occurrence of the metastable form \( B \)-Sorbitol for nucleation kinetics reason

Thermodynamic parameters impose the final stability.
APPLIED ASPECTS: α-D-GLUCOSE MONOHYDRATE – ANHYDROUS Transition

- Anhydrous width of metastable zone:
  - $\sigma = 1.45$ (limit of spontaneous nucleation)

- Crystal growth of anhydrous dextrose very slow

<table>
<thead>
<tr>
<th></th>
<th>$T^\circ C$</th>
<th>$\sigma$</th>
<th>(g/m².min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose anhydrous</td>
<td>70</td>
<td>1.15</td>
<td>0.10</td>
</tr>
<tr>
<td>Sucrose</td>
<td>70</td>
<td>1.12</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Growth 70 times slower than sucrose

Crystallization of anhydrous dextrose by evapo-crystallization at temperature $> 80^\circ C$, duration $> 40h$ no traces of monohydrate

Applications of dextrose needing the absence of water:
- Food: Chocolate
- Pharmaceutical: Dry Formulations
Dextrose Monohydrate – Anhydrous transition

Dextrose Monohydrate needles

Dextrose Anhydrous prisms
APPLIED ASPECTS: Sorbitol polymorphs

Γ-Sorbitol needles

Properties
- Cooling effect
- Compression
- Rapid dissolution
- Apyrogenic
- Bulking Agent

Applications
- Refreshing tablets
- Tabletting
- Diluant for sachets
- Rehydratant in perfusion
- All medicines: syrups, ...
- Tablets

Γ-Sorbitol agglomerates after milling and sifting

Pharmaceutical applications

Food applications

Properties
- Cooling, acariogenic
- Compression
- Cryoprotection
- Microcrystallisation
- Surface Crystallisation
- Depression of Aw

Applications
- Chewing-gum tablets
- Surimi
- Confectionery losanges
- Baked goods
CONCLUSIONS

• Polymorphic transition plays an important role in determining the stability of small carbohydrates
• Enantiotropic systems (D-Glucose) have a transition temperature, frontier of stability between polymorphs
• Monotropic systems are subject to nucleation of unstable (kinetically stable polymorphs)
• They obey Oswald rule: nucleation of the closest unstable polymorph
• Sorbitol because of the numerous (8) possible conformers gives different crystalline polymorphs (7)
• Water plays a role of activator (lowering of activation energy) of polymorphic transitions
• Water as a plasticizer promotes sorbitol conformational polymorphism
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