Laboratoire de Dynamique et Structure des Matériaux Moléculaires
UMR 8024 – Université de Lille 1-France

SOLID STATE TRANSFORMATIONS OF PHARMACEUTICAL COMPOUNDS UPON MILLING: LACTOSE & MANNITOL

(authorized version)

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In the field of

MOLECULAR MATERIALS

(i.e. pharmaceutical compounds) :

NO

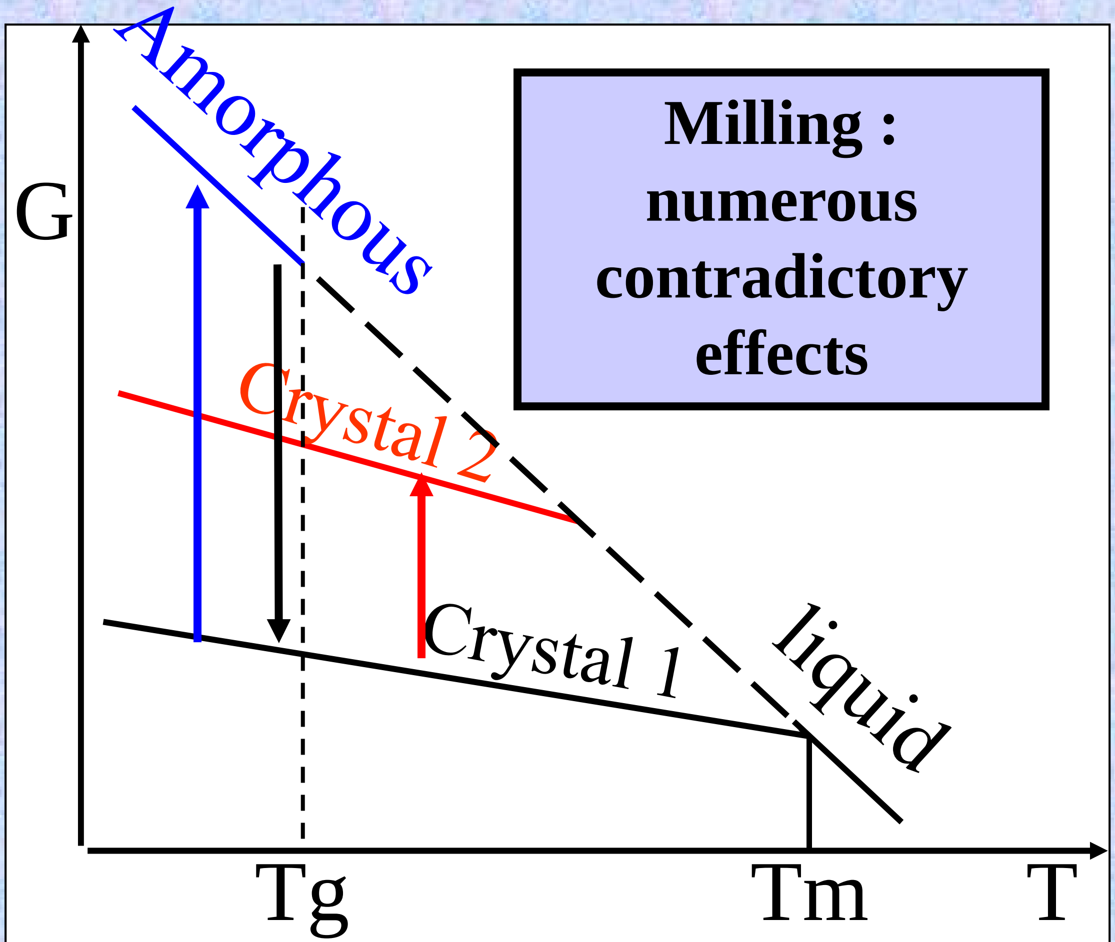
SYSTEMATIC

INVESTIGATIONS

(theoretical or experimental)

Milling of pharmaceutical compounds

Pharma field → **Milling** → Grain size ↓ ⟹ Solubility, bioavailability ↑



No systematic investigations

In spite of :

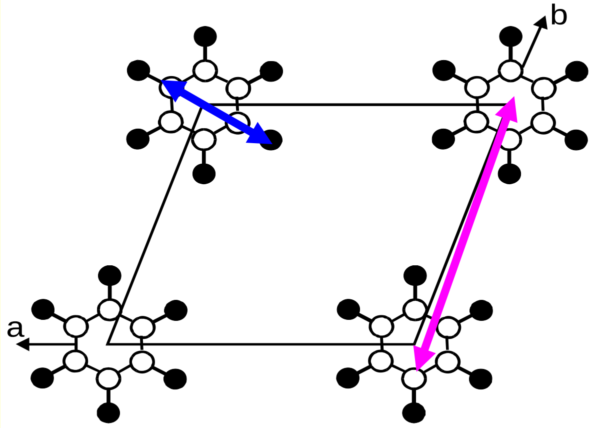
- **Importancy of applications**
- **Original aspects of molecular materials (Fundamental studies)**

Molecular compounds specificities

Contrast between :

Weak inter-molecular interactions

Strong intra-molecular interactions

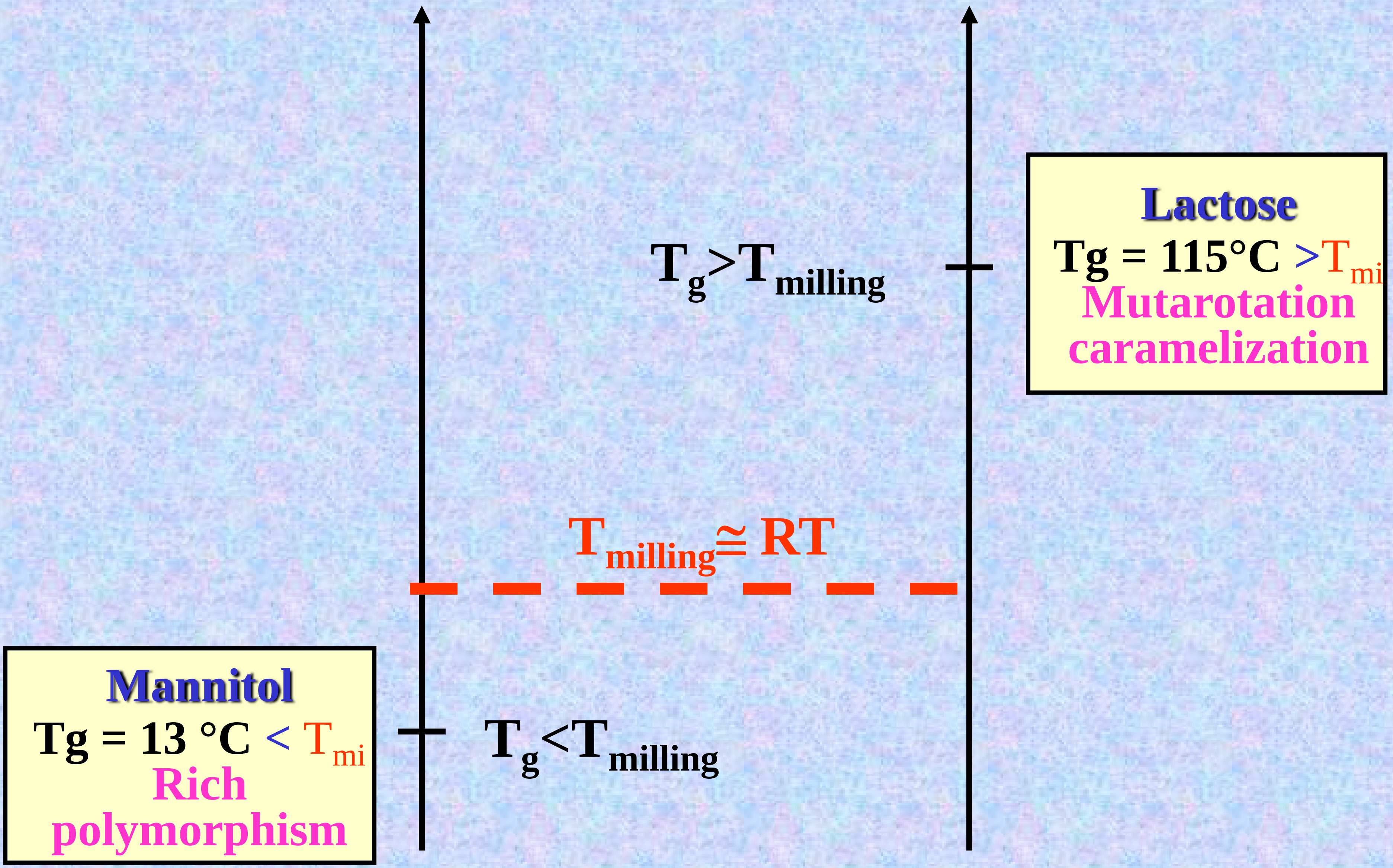


Low Symmetry / **Important size** { **Molecules** / **cells (often tricl., mono. or ortho.)**

- **Low melting temperatures**
- **Glass transition temperature close of RT ≅$T_{milling}$**
- **Low kinetics of cryst** ⟷ (Easy) **Quench-Vitrification**
- **Very sensitive to mechanical and thermal perturbations**

Transfo. on milling of pharmaceutical compounds

Materials selection



Plan of speech

I – Milling

Characteristics of milling experiments realized at the laboratory

II – Stable anhydrous α-lactose

- Solid-state amorphization of αL_S
- Mutarotation (^{13}C NMR)

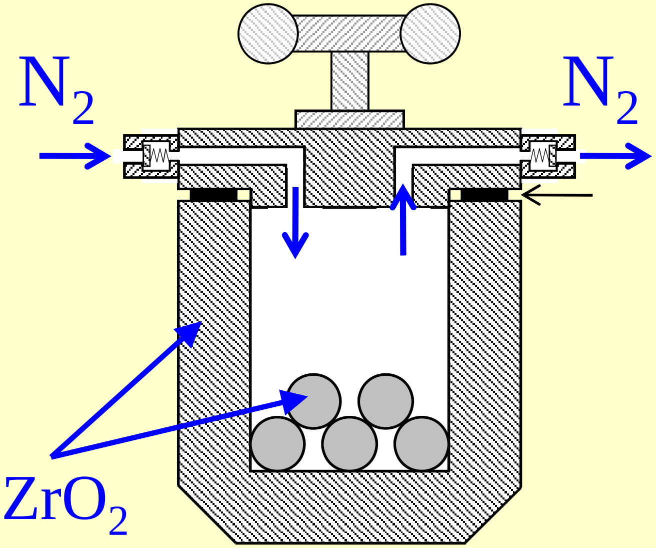
III – Mannitol

Mannitol δ
Mannitol β
} Polymorphic transformations

Characteristics of milling

Pulverisette 7
Fritsch

N x { milling (20min)
pause (10min) }

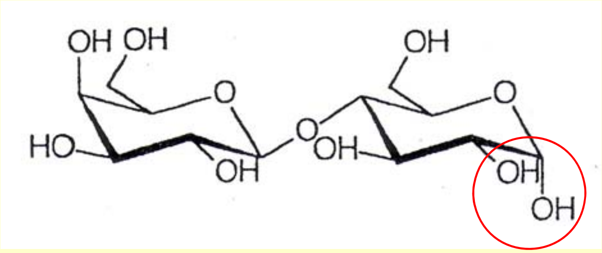


Prevention of hygroscopy

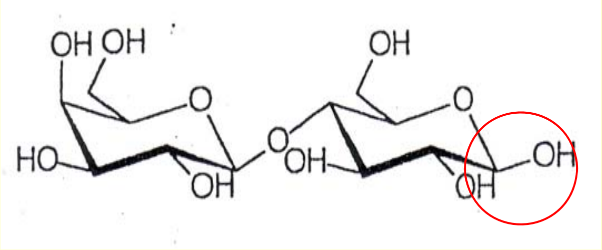
Lactose – possible solid-state forms

Disaccharid often used in Pharmaceutical and Food industries

2 types of molecules of lactose :



α-lactose



β-lactose

Various solid-state forms:

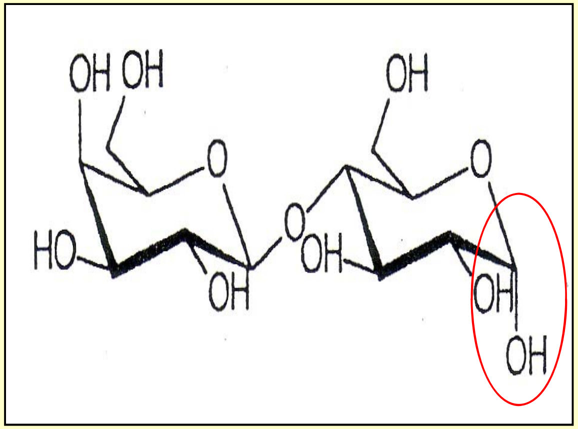
- Monohydrated α lactose (L_α-H_2O) (stable)
- Hygroscopic anhydrous α lactose
- **Stable anhydrous α lactose (αL_S)**
- Anhydrous β lactose
- Molecular compounds α/β with various stœchiometries

Problems encountered for producing amorphous lactose

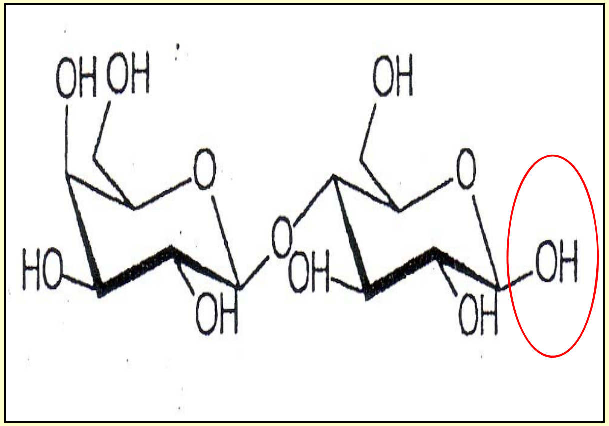
Thermal degradations and caramelization

Mutarotation

(in solution…)

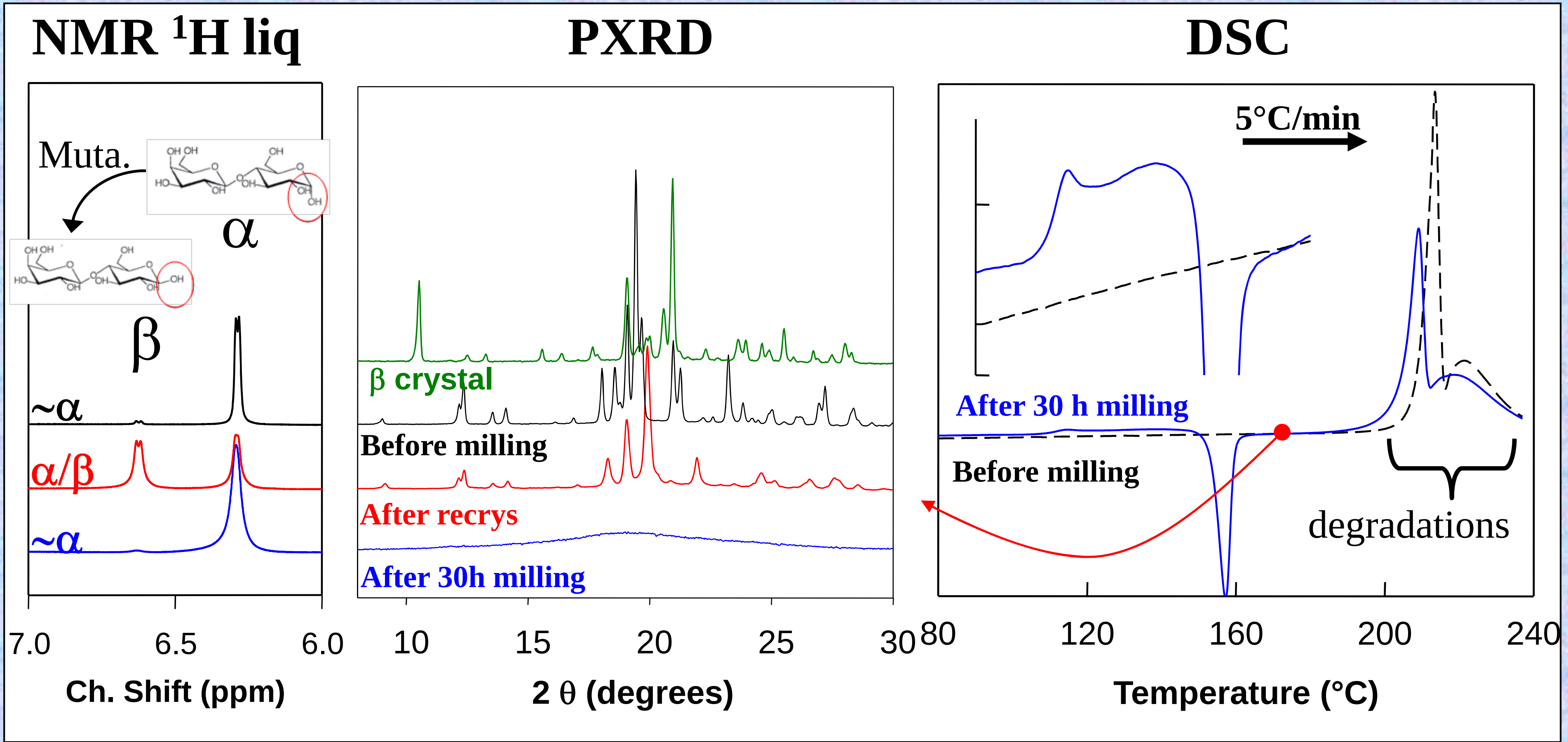


α-lactose



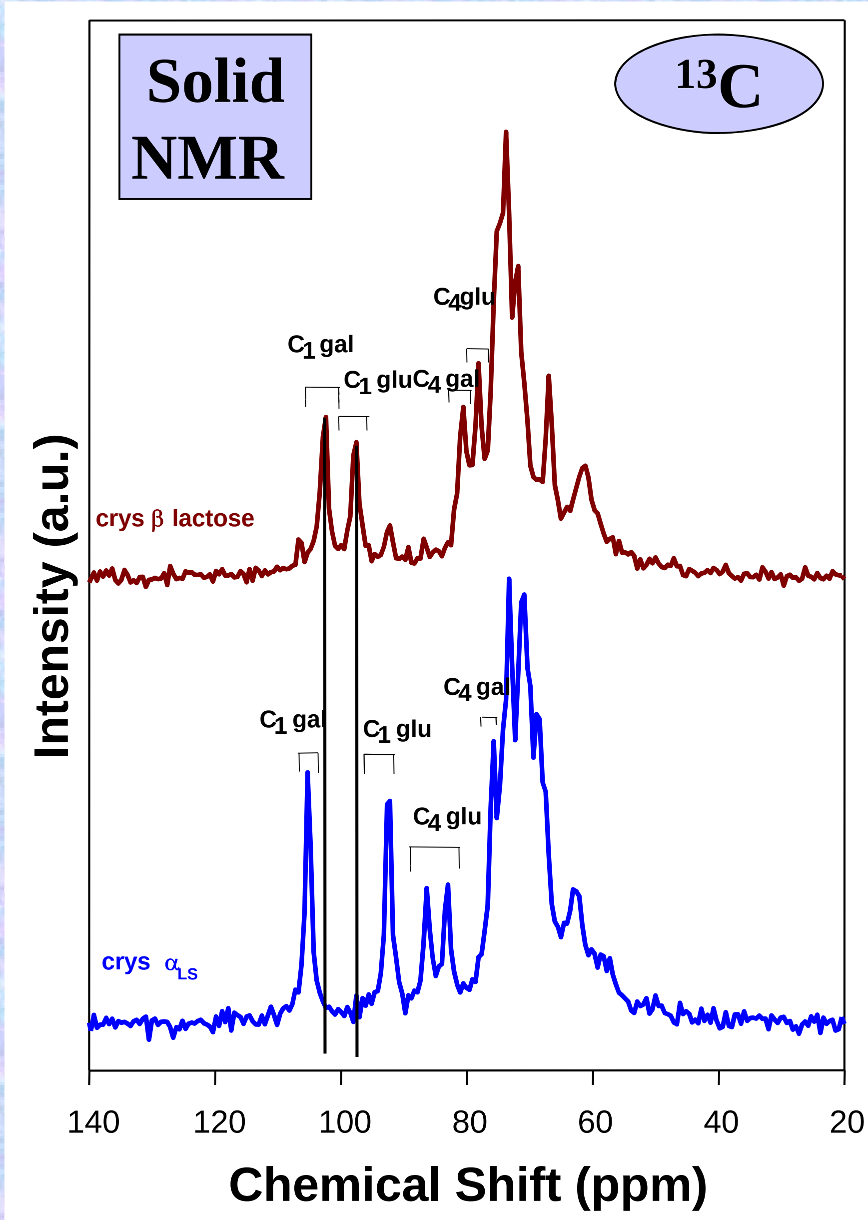
β-lactose

Amorphization of αL_S under milling



Crystalline α lactose —*milling*→ Glassy α lactose without degradations —*recrys*→ Crystalline α/β lactose

Solid-state NMR ^{13}C : characterization in situ % β

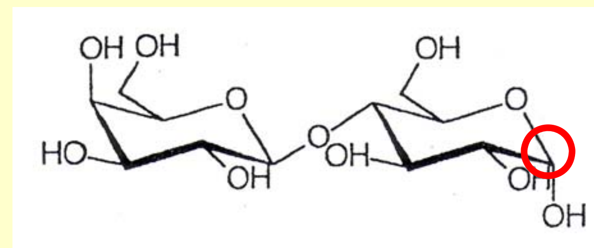


C_1 glu$_{\alpha lactose}$

≠

C_1 glu$_{\beta lactose}$

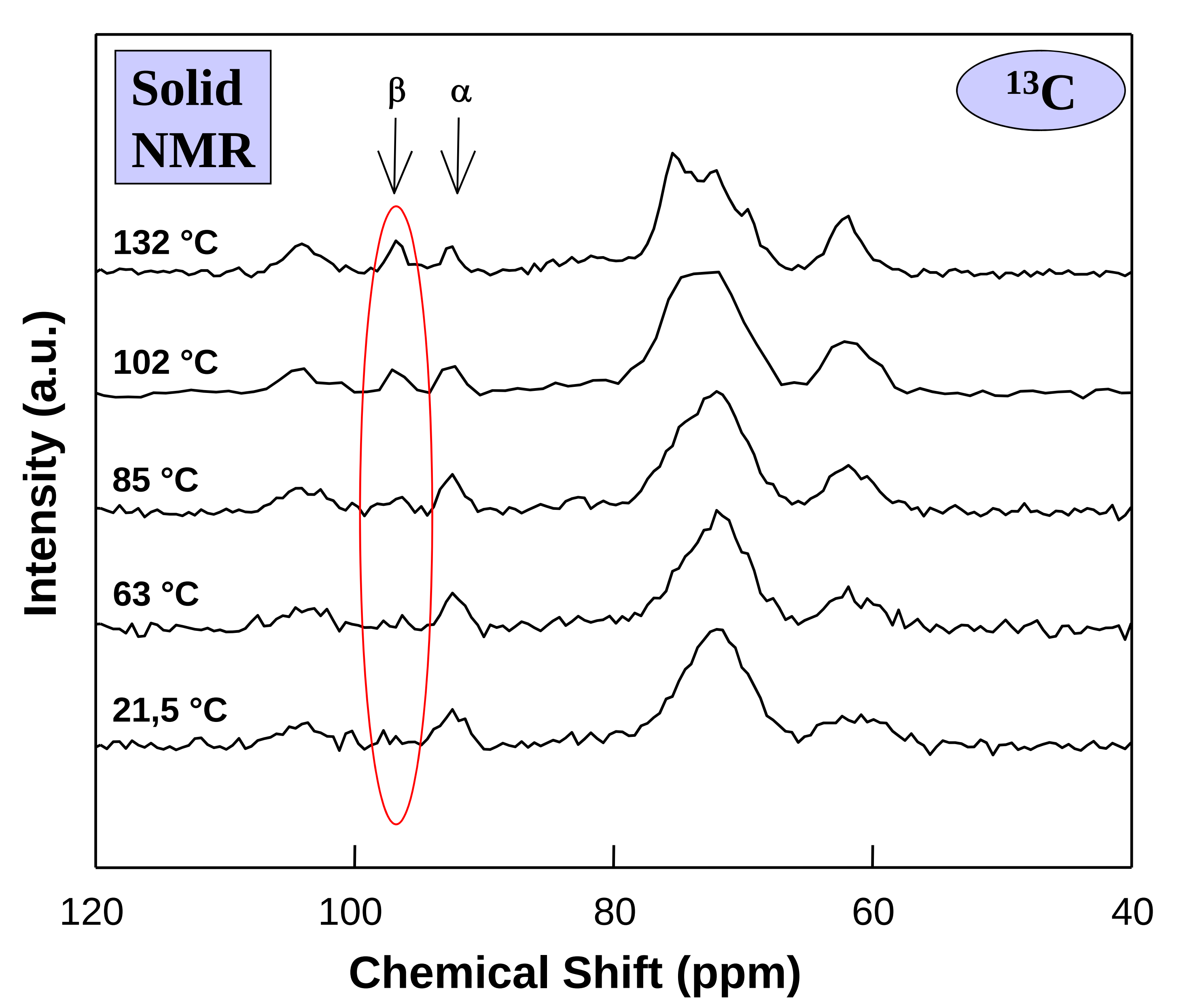
Crystalline or amorphous states



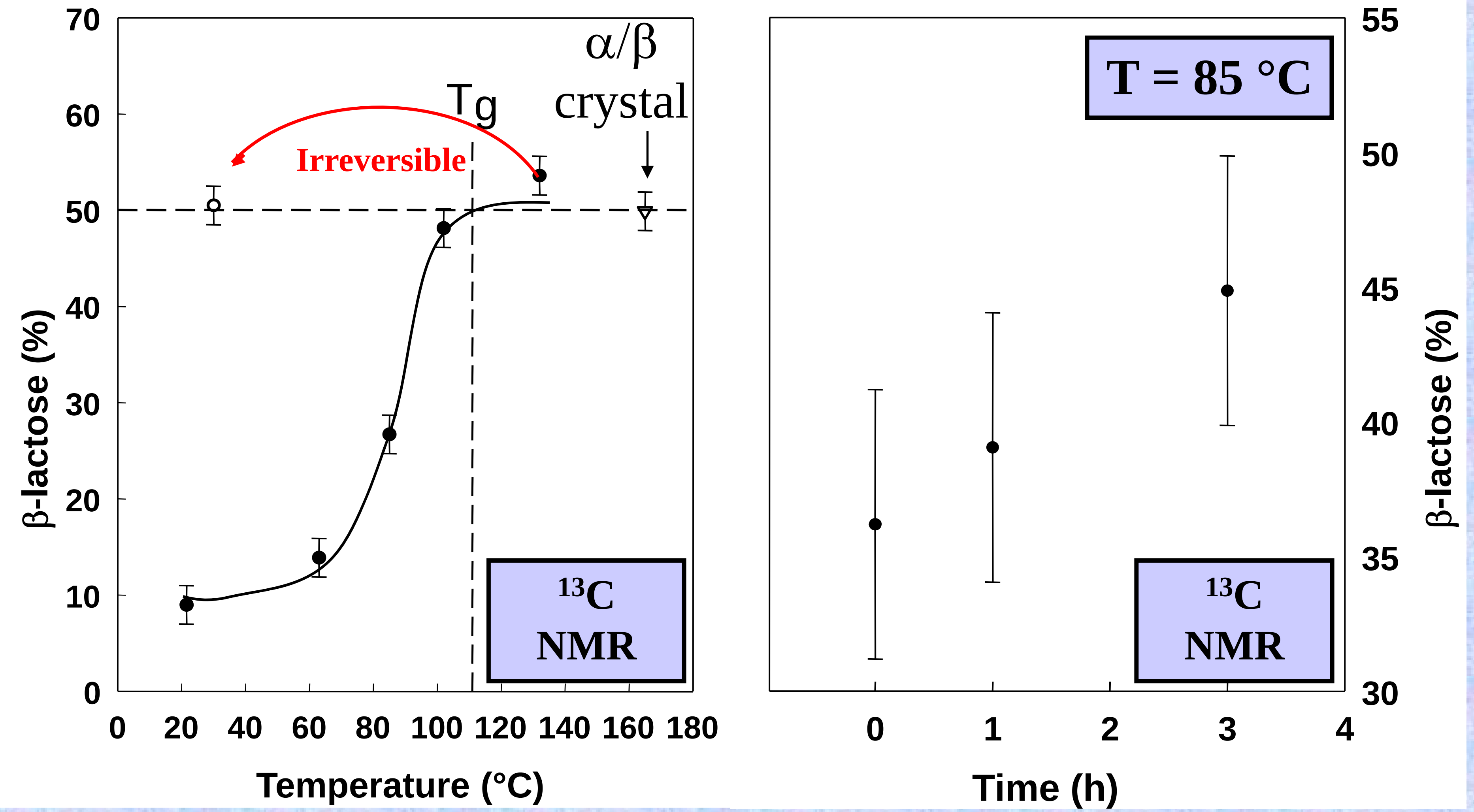
C_1 glu

- **Detection mutarotation**
- **Quantification % β in situ**
- **% β = f(T°C)**

Mutarotation during heating of amorphous αL



Milling amorphization ≠ local melting-quench



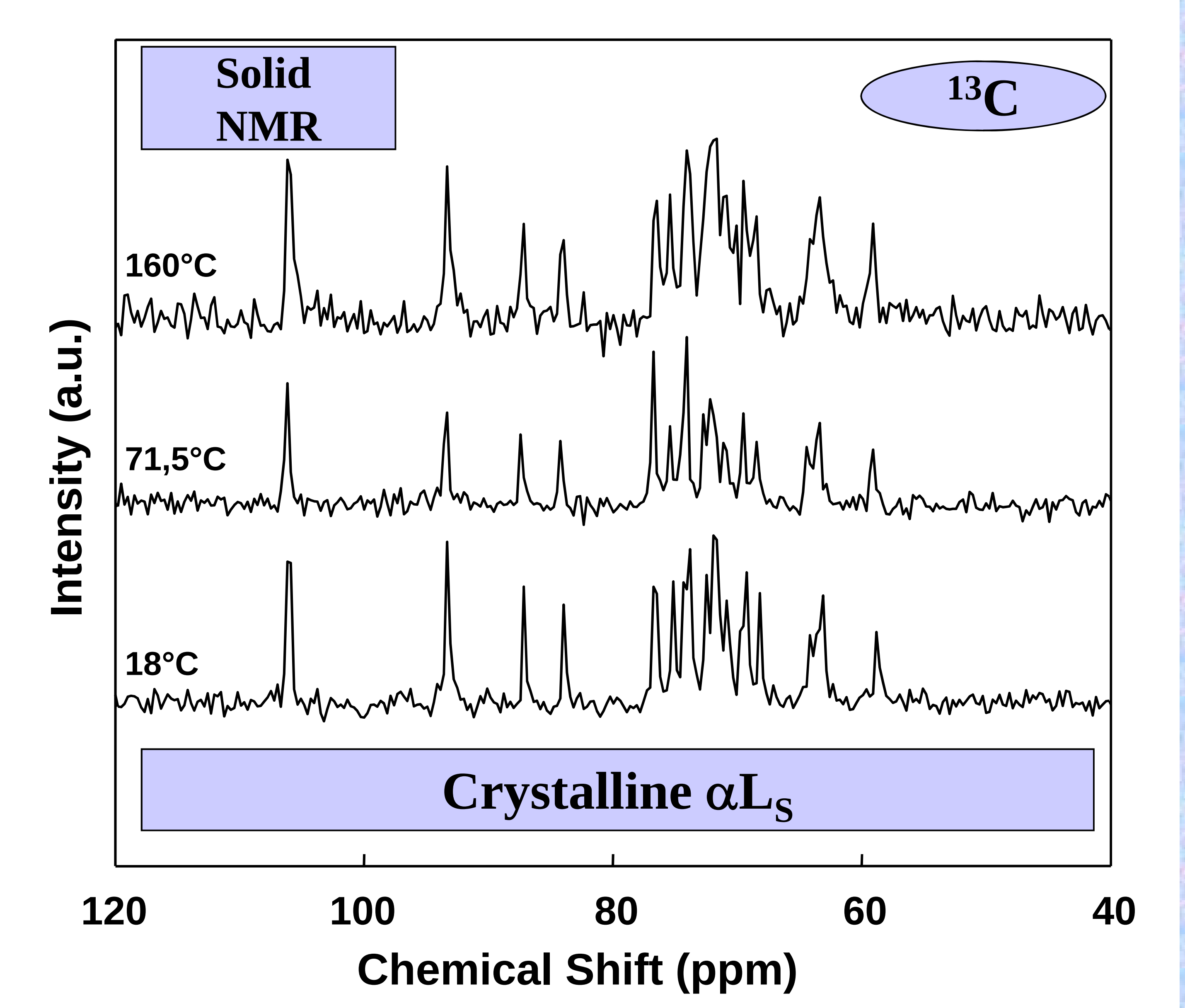
Glassy αL → Out of equilibrium

Mutarotation ↔ Structural relaxation below Tg

$T_{mil} < 85°C < T_m$

~~Local melting / quench~~

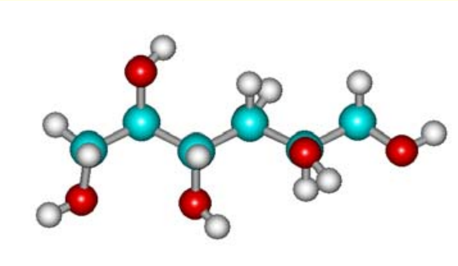
No mutarotation during heating of crystalline αL_S



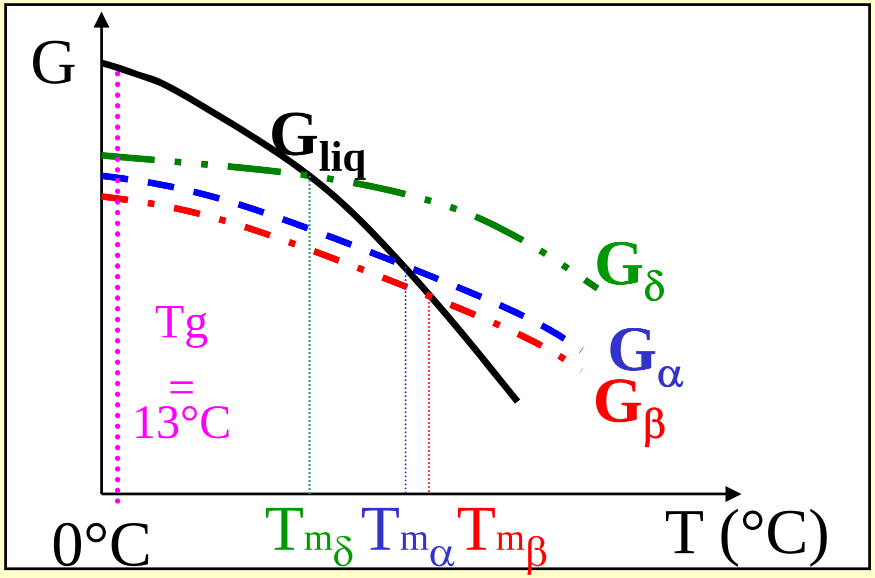
Mannitol

Characteristics of Mannitol :

• Acyclic polyol present in seafood, fruits, mushrooms…

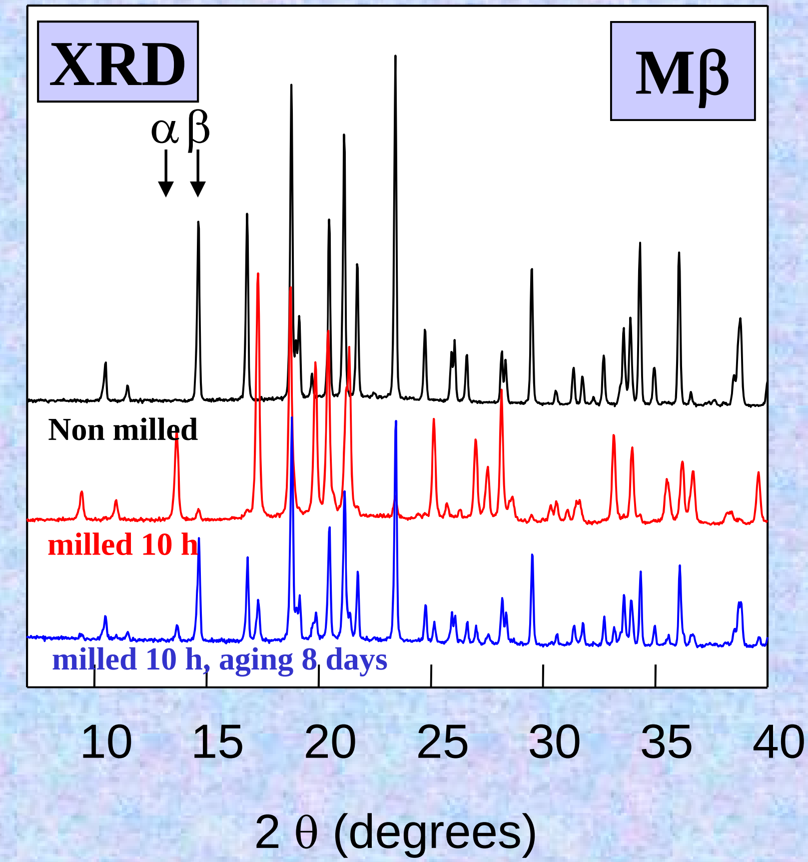


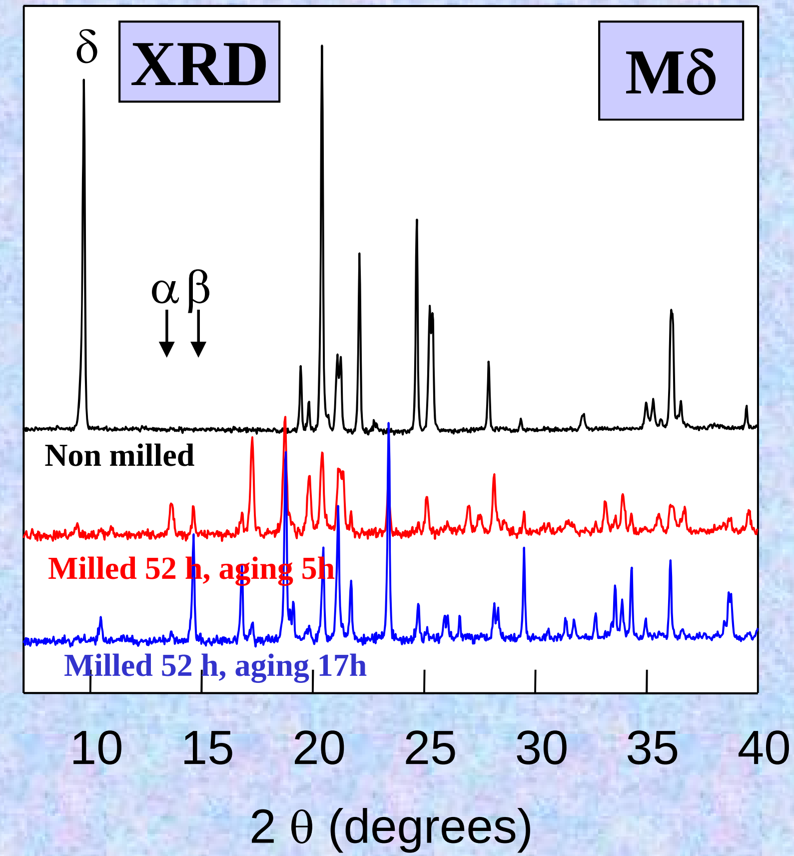
• Used as excipient, sweetener, API

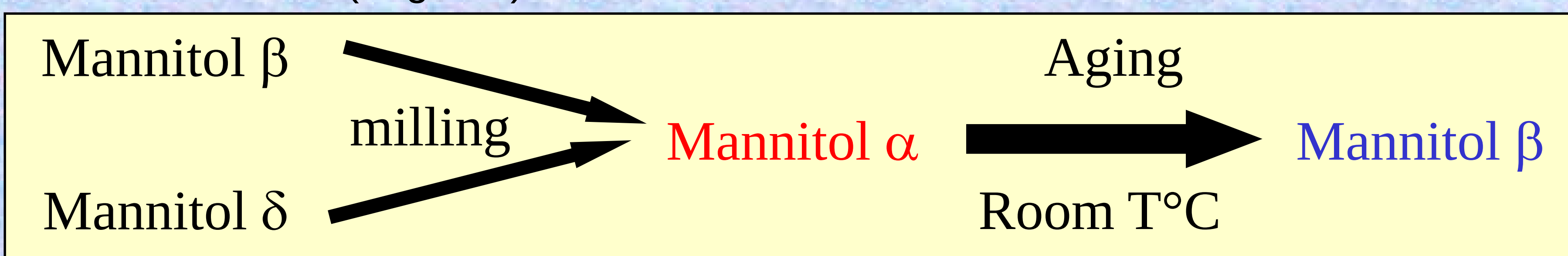


Adapted from Burger et al., *J. Pharm. Sciences*, 2000, 89, 457

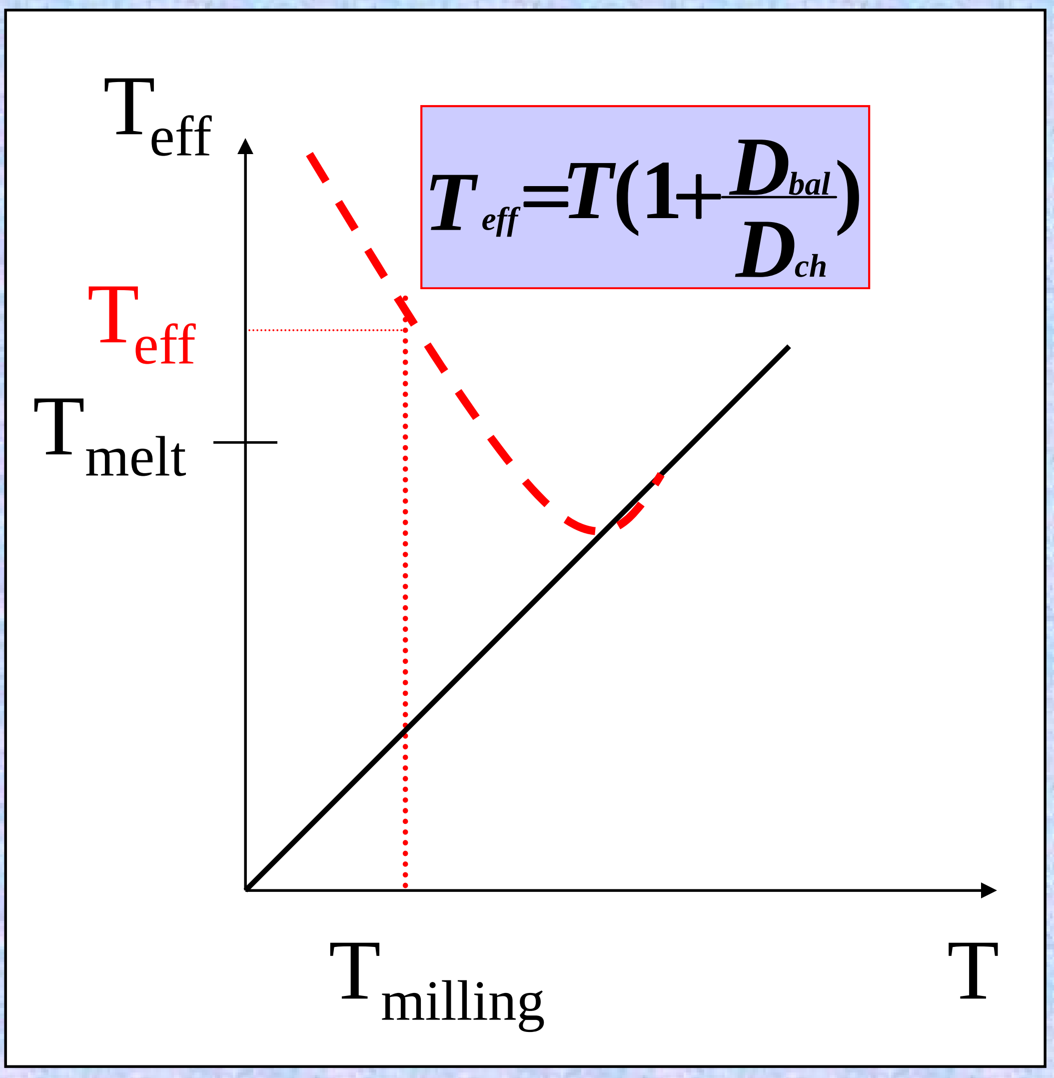
Polymorphic transformation under milling of Mβ and Mδ







Interpretation of amorphization αL_S under milling as a « Driven system* »



Milling αL_S

↓

$D_{bal} > D_{ch}$

↓

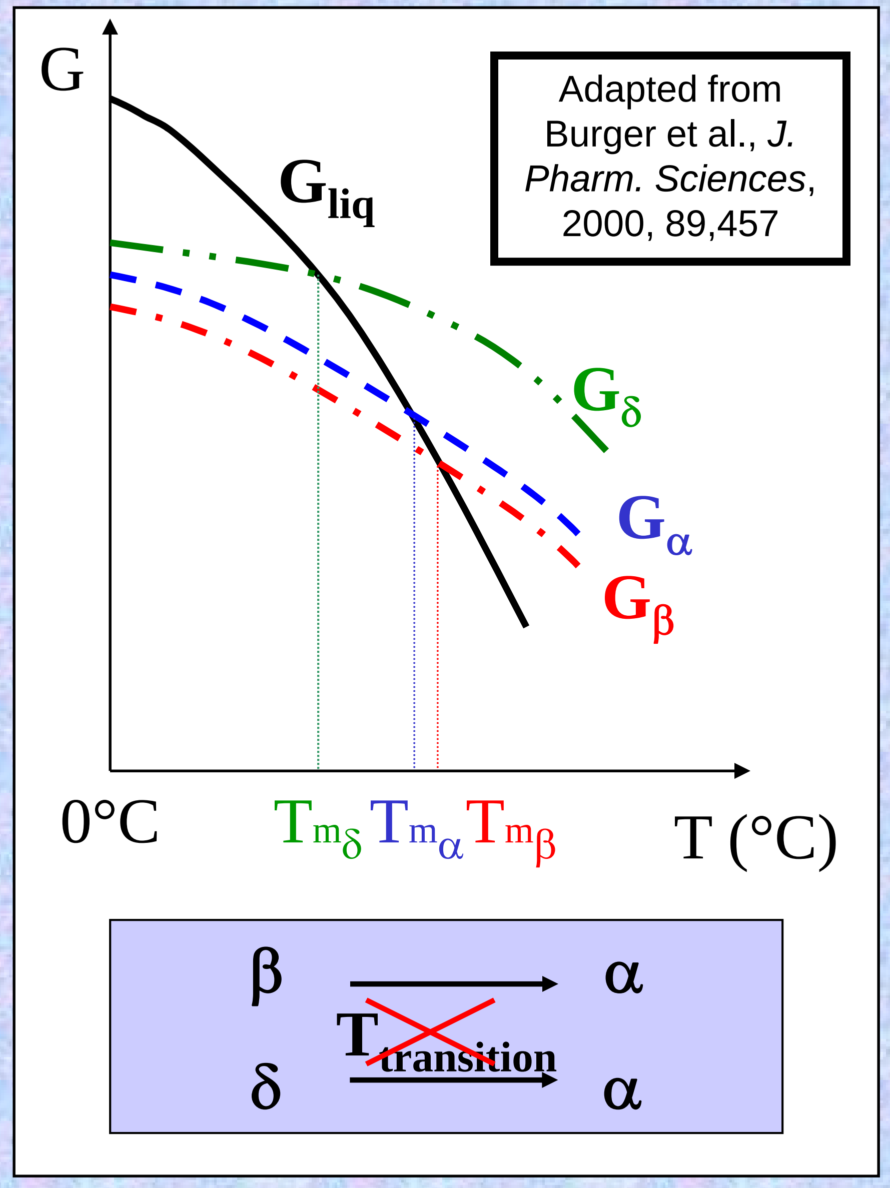
$T_{eff} > T_{fusion}$

↓

Amorphization

***Driven alloys, Martin et al, Solid State Physics, *50*, p189 (1997)**

Interpretations polymorphic transformations mannitol under milling as a Driven system



Single T_{eff} > T_{fusion}

Mβ, Mδ —milling→ **glass**

glass —stop milling→ **Mα**

2 T_{eff}

Mβ, Mδ —$T_{eff} > T_m$→ **glass**

glass —$T_{eff} < T_m$→ **Mα**

Conclusion

Crystalline α lactose —*milling*→ Glassy α lactose without degradations

Glassy αL —*heating*→ Mutarotation → Irreversible / at T < Tg

~~Local quench melting~~

Glassy αL **Out of equilibrium**

Mannitol β / Mannitol δ —Milling→ Mannitol α —Aging, Room T°C→ Mannitol β

States reached are stationary states rather than thermodynamic equilibrium states

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- Pr. Jacques Lefebvre
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- M. Dominique Prevost

Publications related to this presentation

- J.F. Willart, V. Caron, R. Lefort, F. Danède, D. Prévost and M. Descamps, "Athermal character of the solid state amorphization of lactose induced by ball milling", *Solid State Communications*, 2004, 132, pp. 693.
- J. Lefebvre, J.F. Willart, V. Caron, R. Lefort, F. Affouard and F. Danede, "Structure determination of the 1/1 α/β mixed lactose by X-ray powder diffraction", *Acta Cryst. B*, 2005, 61, pp. 455.
- R. Lefort, V. Caron, J.F. Willart and M. Descamps, "Mutarotational kinetics and glass transition of lactose", *Solid State Communications*, 2006, 140, pp. 329.
- P. Zhang, N. Klymachyov, S. Brown, J.C. Ellington and P.J. Grandinetti, "Solid state 13C NMR investigations of the glycosidic linkage in a-a' trehalose", *Solid state Nuclear Magentic Resonance*, 1998, 12, pp 221.

Publications related to this presentation

• R. Lefort, A. De Gusseme, J.F. Willart, F. Danede and M. Descamps, "Solid State NMR and DSC methods for quantifying the amorphous content in solid dosage forms: an application to ball-milling of trehalose", *International Journal of Pharmaceutics*, 2004, 280, pp. 209.

• M. Descamps, J.F. Willart, E. Dudognon and V. Caron, "Transformation of Pharmaceutical Compounds upon milling and comilling : The role of Tg", *Journal of Pharmaceutical Sciences*, 2007, 96, 00, pp. 1-10.

• J. Rodriguez-Carvajal, T. Roisnel, "Fullprof 98 and WinPLOTR: New Windows 95/NT Application for Diffraction", Newletter 20, 1998.

• H.M. Rietveld, "Line profiles of neutron powder diffraction peaks for structure refinement", *Acta Cryst*, 1967, 22, pp 151.

• H.M. Rietveld, "A profile refinement method for nuclear and magnetic structures", *J. Appl. Cryst.*, 1969, 2, pp 65.