

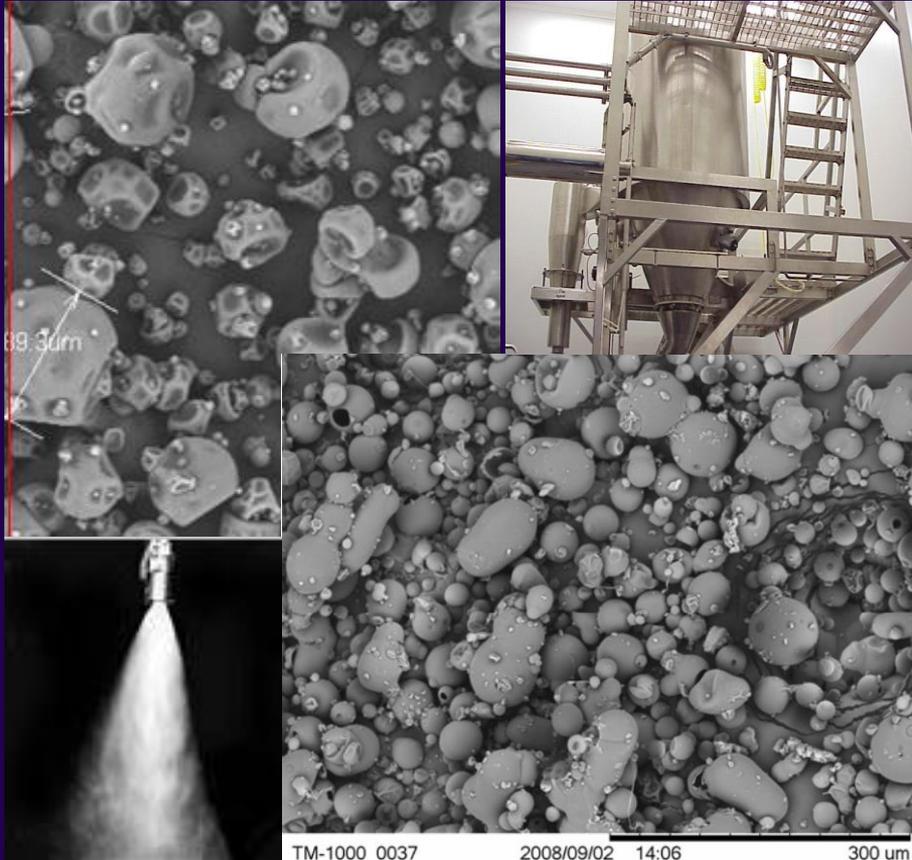
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# A Practical Method to Predict Physical Stability of Amorphous Solid Dispersion

*Jean René Authelin*

*SOS conference 2022 6  
Philadelphia*



09 . 19 . 20222

The content of this talk is mostly coming from a 2012 paper

## **A Practical Method to Predict Physical Stability of Amorphous Solid Dispersions**

Stéphanie Greco • Jean-René Authelin • Caroline Leveder • Audrey Segalini

Pharmaceutical research 2012 - 29 (10), 2792-2805

# Agenda :

- Amorphous spray dried dispersions a tool to mitigate low solubility of API's
- Physics of glassy (amorphous) state
- Predicting Crystallization kinetics from accelerated studies
- Conclusion

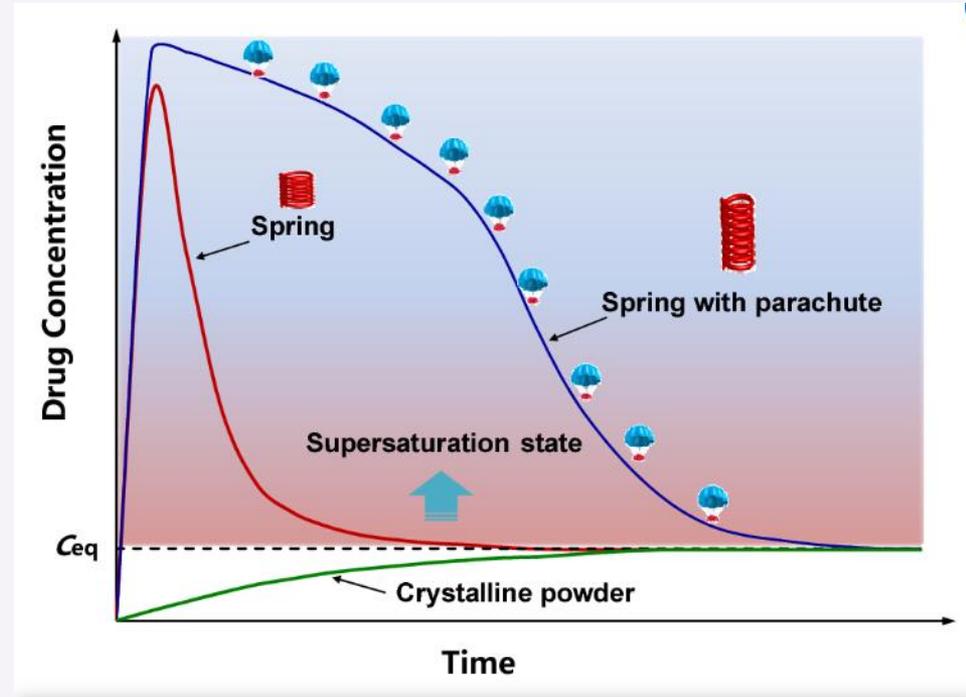
- 
- Amorphous Spray Dried Dispersions a tool to mitigate solubility issues
-

# The Spring and Parachute effect

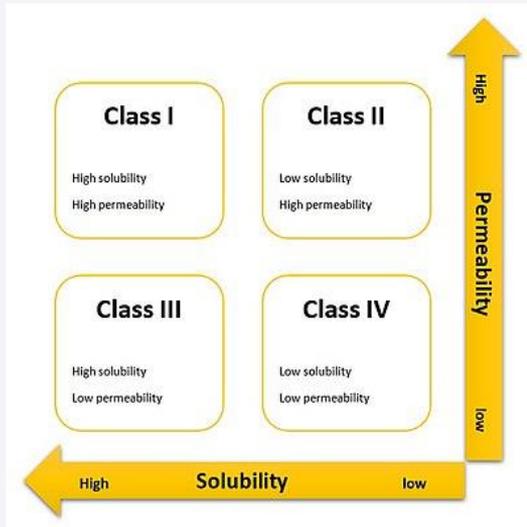
The amorphous dispersions solubilizes fast : "spring" effect. But it tends to recrystallize

The polymer inhibits the recrystallization: "parachute" effect

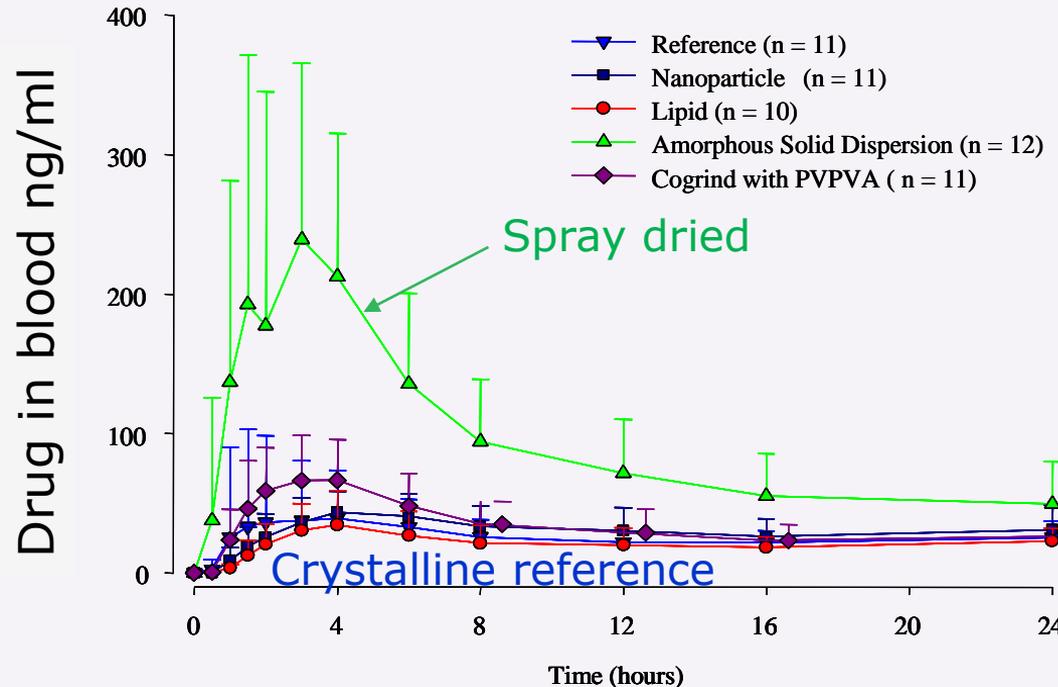
In vivo, the drug is absorbed by the GI tract before recrystallization take place



# Spray dried dispersions boost the BA of amorphous SDD's



Example : impact of formulation on a BCS II candidate BA (rat study). Former Sanofi product  
 Spray dried solid amorphous particles clearly exhibits the best profile

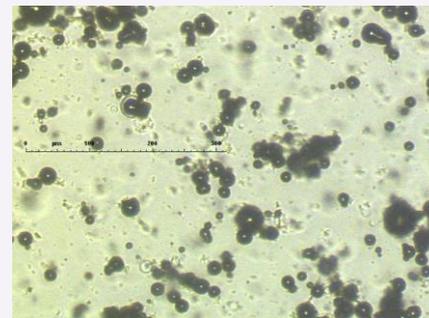


# Some data about SAR spray dried amorphous dispersion

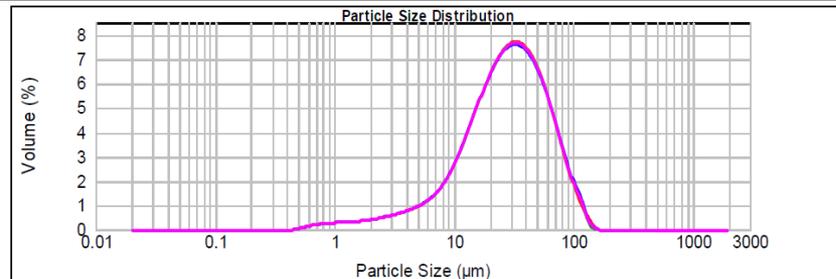


SDD composition:

- HPMCP HP55 80%
- SAR compound 20%



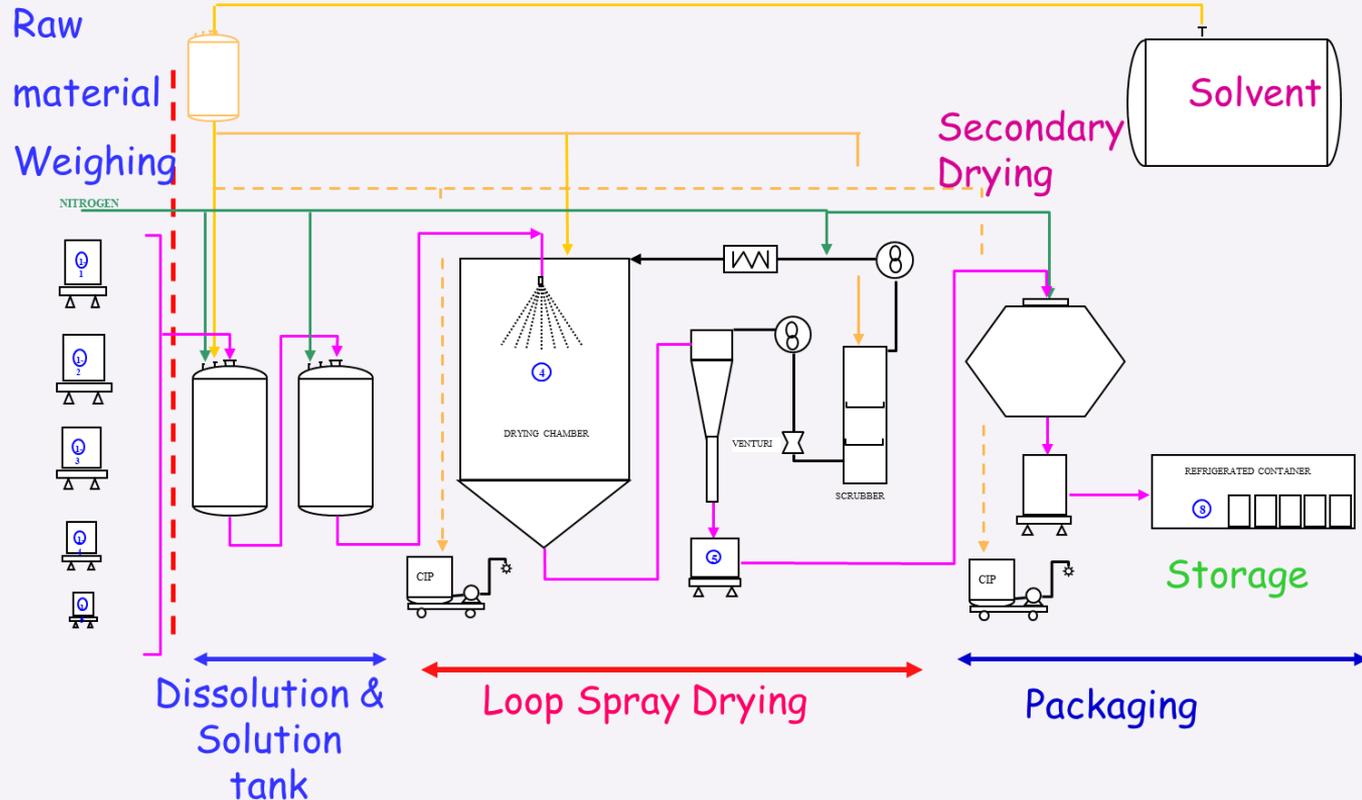
d(0.1): 7.751 um      d(0.5): 28.258 um      d(0.9): 69.424 um



FIN ATOMISATION LOT FTA181, jeudi 22 mars 2007 16:28:17  
FIN ATOMISATION LOT FTA181, jeudi 22 mars 2007 16:31:49  
FIN ATOMISATION LOT FTA181, jeudi 22 mars 2007 16:35:21  
FIN ATOMISATION LOT FTA181 - Average, jeudi 22 mars 2007 16:28:17

# Spray drying and secondary drying processes

SAR was dissolved with HPMCP HP55 in the solvent mixture CH<sub>2</sub>Cl<sub>2</sub>/EtOH 95%/5%. The ratio SAR/ HPMCP was 20%/80% and the total solid concentration was 6.2% (all percentages are given in weight ratios). The final solution was atomized with a large pilot-scale loop spray-drier supplied by the Drytec company (diameter: 1 m, length: 3 m, gas flow approx. 500 kg/h). Inlet and outlet temperatures were fixed at 95°C and 50°C. A bifluid nozzle was used. After spray drying, the residual solvents (about 3%) were fully removed to well below ICH specifications by drying under vacuum (P~50 mbar)



# Amorphous spray dried dispersions : the benefit / risk balance

Predicting API crystallization in amorphous spray dried formulations is a key challenge.



The goal of this work : predict long term physical stability (crystallization) from accelerated studies

•  
Just a little about physics of  
glassy (amorphous) state  
•

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Amorphous state is characterized by the absence of long-range order

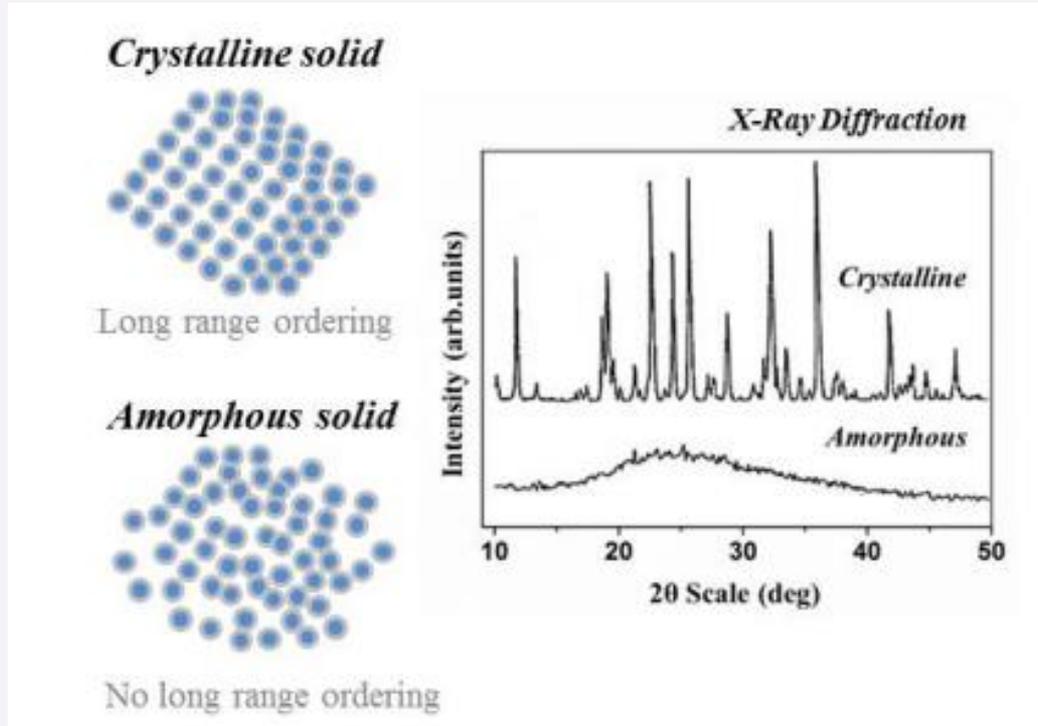
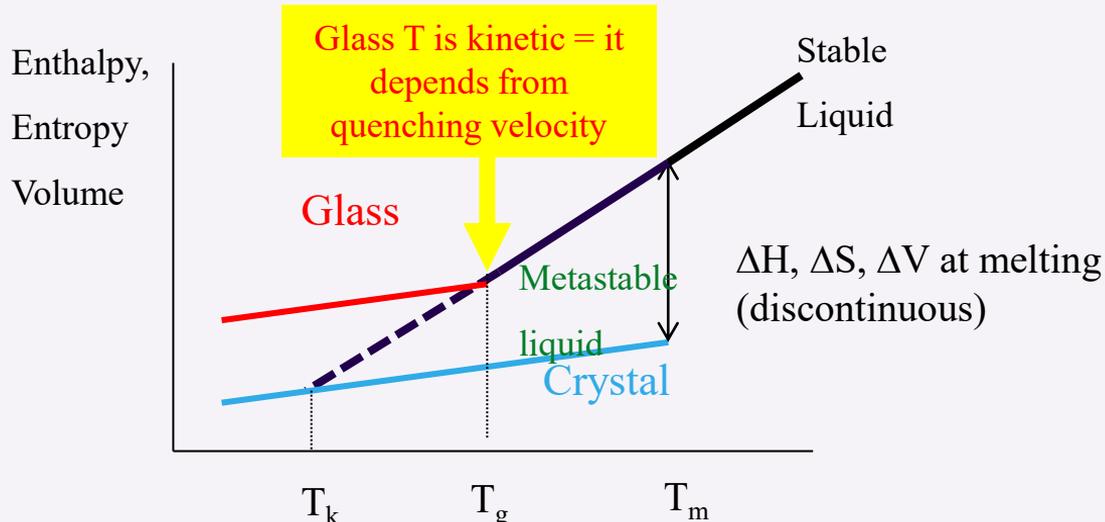


figure from "Glass-to-crystal transition in a chiral pharmaceutical system" PhD thesis Quentin Viel- available on research Gate

# Basic thermodynamics of amorphous systems



- At  $T_g$  there is no discontinuity in  $H, S, V$  (contrary to melting) but change in slope ( $C_p$  and dilatation coefficient)  $\rightarrow$  close to a « second order transition »
- Kauzmann pointed out that  $T_g$  cannot be lower than  $T_k$  (Kauzmann Temperature) elsewhere, glass entropy would be lower than crystal and therefore more ordered, which is absurd.
- Rule of thumb :  $T_k \sim T_g - 50 \text{ K}$  (often in organic glasses)

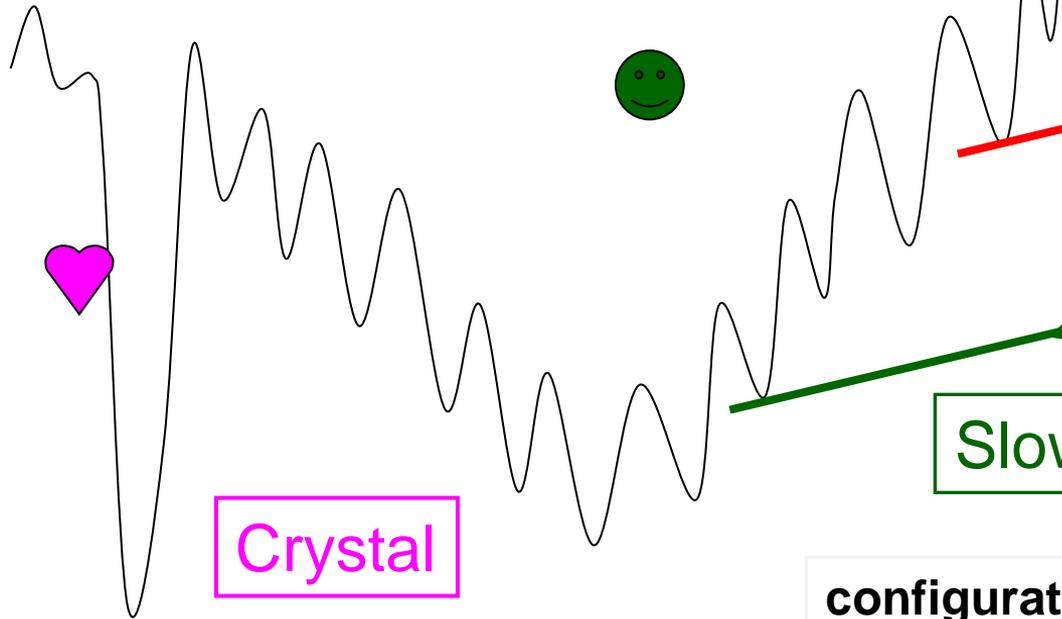
Walter Kauzmann, The Nature of the Glassy State and the Behavior of Liquids at Low Temperatures, Chemical Reviews (1948), Vol 43, pg. 219.

# Energy Landscape description

M. Descamps

Liquid fast, ergodic  
Defined physical parameters

Fast quenching



Crystal

Slow cooling

configurations



# Understanding relaxation processes in amorphous solids

(At least) 2 types of relaxation mechanisms are known in amorphous solids :

$\alpha$  relaxations : slow cooperative relaxations involving many molecules together, linked with the viscosity , and corresponding too deep energy minima. Non-Arrhenius behavior : the characteristic time tends to infinite when T approaches  $T_{\text{kauzman}}$  . However, below  $T_g$ , configuration is frozen and a relaxations have an apparent Arrhenius behavior, with an aging dependent activation energy.

$\beta$  relaxations : quick individual motions inside the molecule. Arrhenius behavior with T

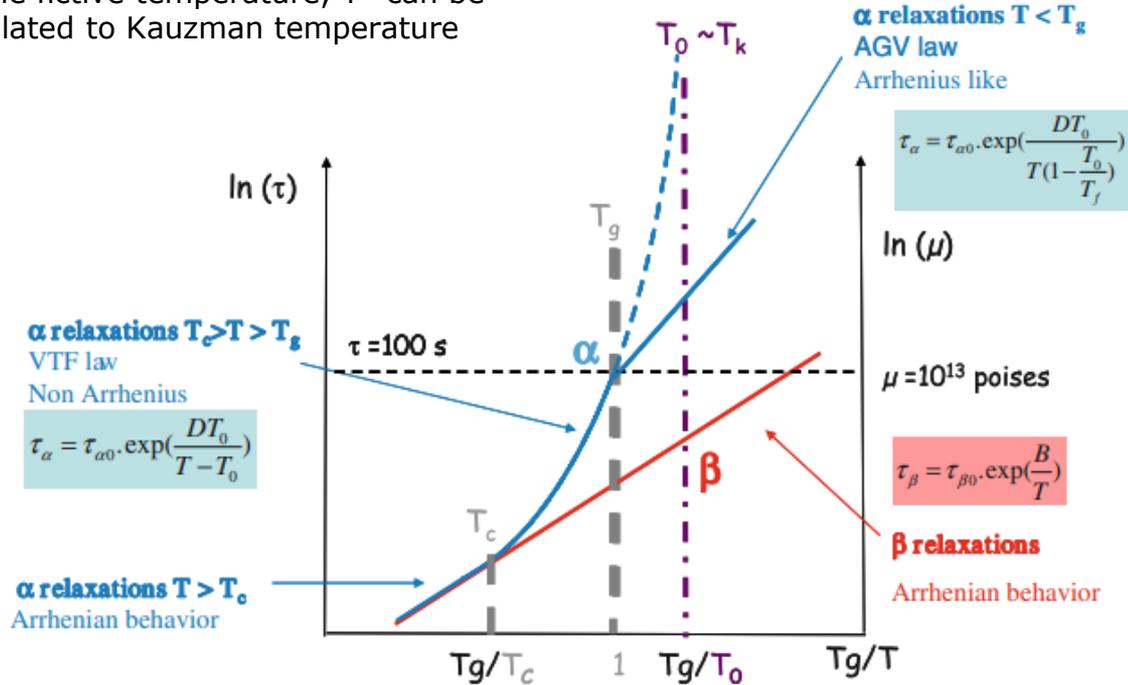
Alpha relaxation mode is often (may be not always ) the most important for recrystallization (diffusion limited)

At low enough T, mobility ( $\alpha$  and  $\beta$ ) decreases such a way that crystallization and even structural relaxations are very difficult

# Molecular Relaxations in amorphous solids

Arrhenius plot of relaxations : the relaxation time  $\tau$  is plotted against  $1/T$  (kelvin)

$T_f$  is the fictive temperature,  $T^0$  can be assimilated to Kauzmann temperature



# Predicting Crystallization kinetics from accelerated studies

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# Inspiration : chemical degradation kinetics

Chemical reactivity is linked to molecular mobility (alpha relaxations) and follows VFT law (above  $T_g$ )

$$R = R_g \cdot \exp\left(\frac{C_1 \cdot (T - T_g)}{C_2 + (T - T_g)}\right)$$

$$\ln(R / R_g) = \left(\frac{C_1 \cdot (T - T_g)}{C_2 + (T - T_g)}\right)$$

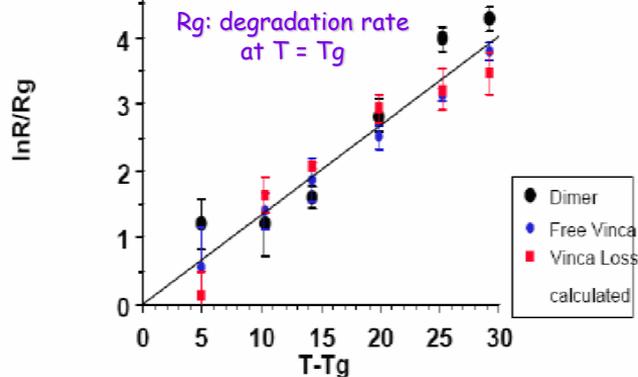
$C_2 \gg T - T_g \rightarrow \ln R/R_g$  linear variation with  $(T - T_g)$

## Stability and “ $T - T_g$ ” for KS1/4 MoAb:Vinca Conjugate

Roy, et al., Develop. Biol. Standard., 74, 323-340 (1991)

### KS1/4 HD Conjugate Decomposition

25°C and 40°C; 1.4%, 3%, and 4.7% Water



• Good Correlation of Stability with  $T - T_g$  (above  $T_g$ )

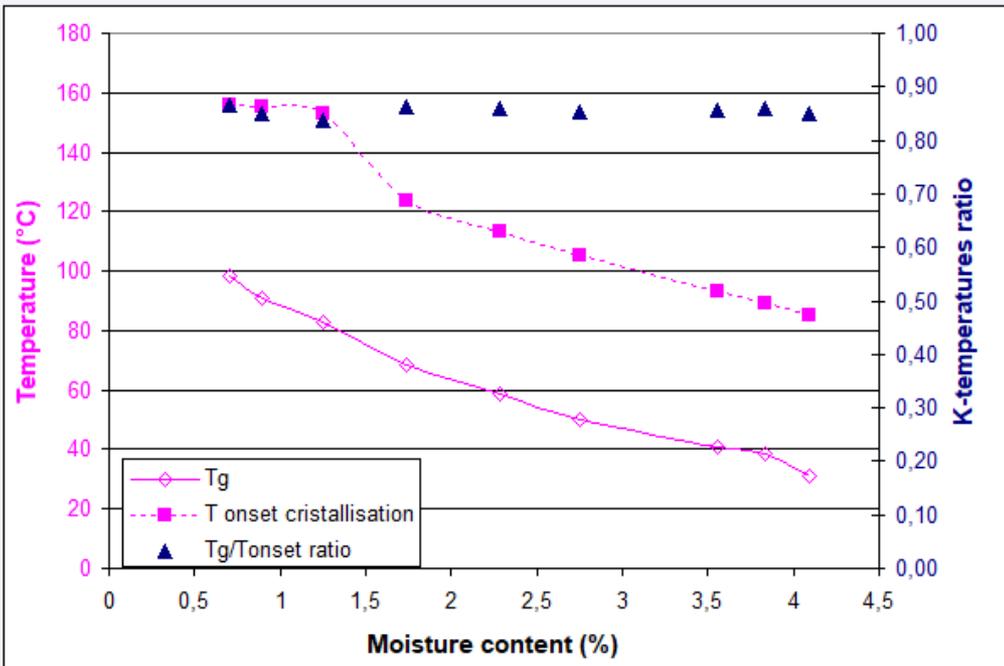
Roy, Pikal, Maloney Int Symp.

Dev. Biol. Standard, V 74, p 323 1991- degradation of a lyophilisate antibody

# Inspiration: crystallization onset follows Tg evolution with moisture

Schmitt et al. exposed spray dried amorphous lamotrigine mesylate to moisture.

A parallel decrease of Tg and crystallization onset was observed by DSC (hermetic pans). Based on their published data, we calculated that the ratio Tg/Tonset (in K) is approximately constant (0.84–0.87)



Adapted from Schmitt E, Davis CW, Long ST. Moisture-dependent crystallization of amorphous lamotrigine mesylate. J Pharm Sci. 1996;85 (11):1215–9

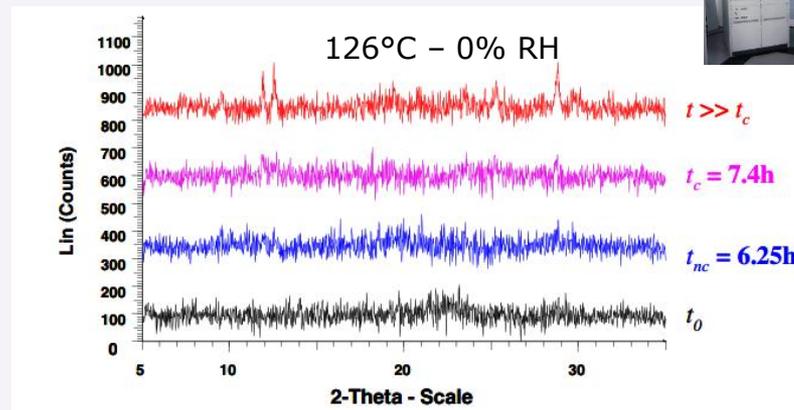
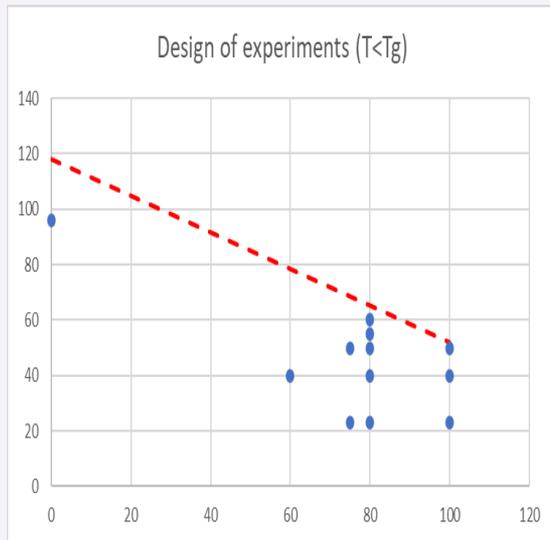
# Experimental protocol

$T < T_g$  : "slow crystallization" (days to weeks)

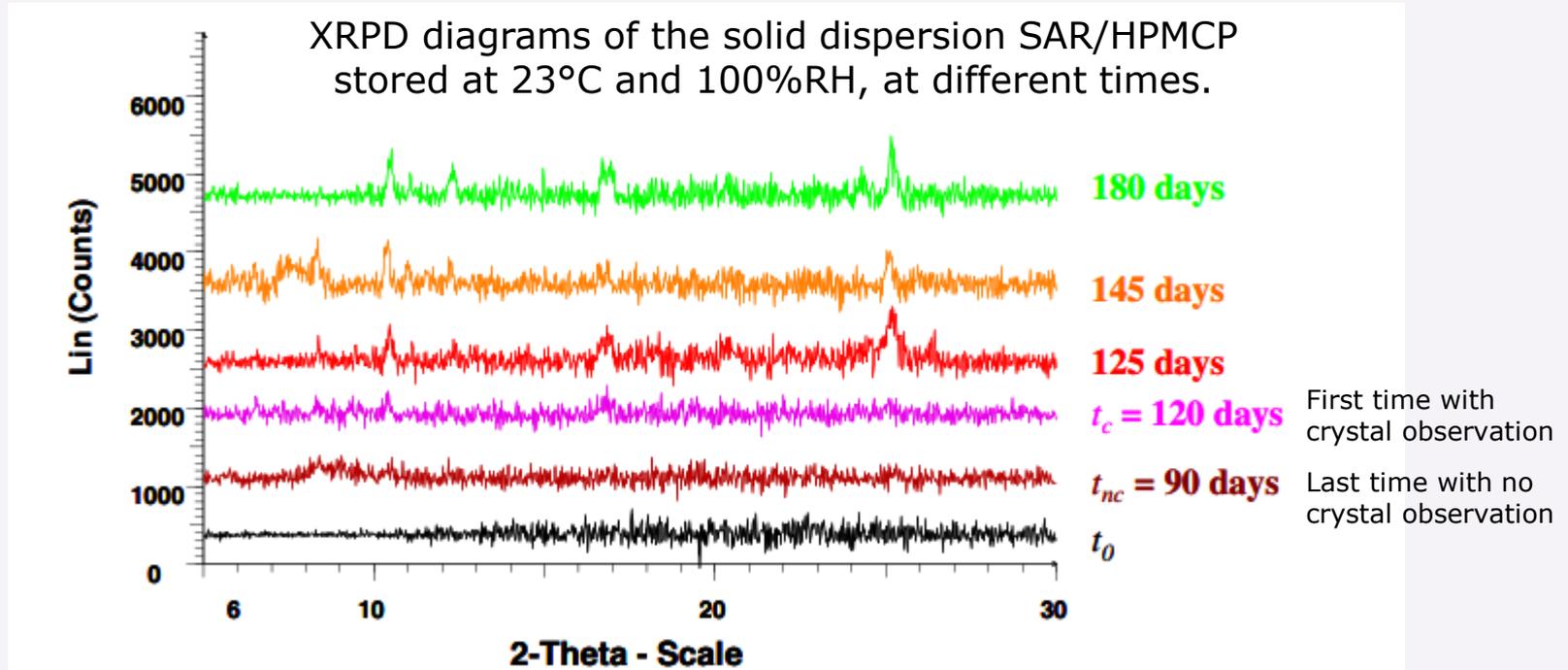
Samples were stored at various RH (salt solutions in desiccators). Periodic sampling for XRPD – sampling frequency depends on  $T_g/T$  ratio

$T > T_g$  : quick crystallization (hours)

Samples were kept monitored in situ in the CRPD (Brücker D5000 equipped with hot stage chamber) at  $T > T_g$ , dry N<sub>2</sub> sweep, until crystallization is observed

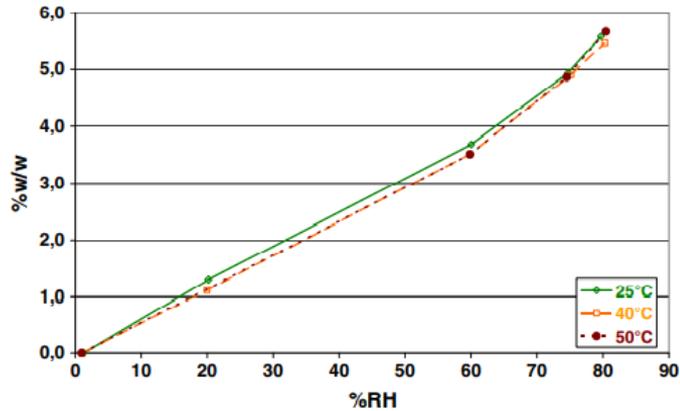


# Determination of the time of onset of crystallization



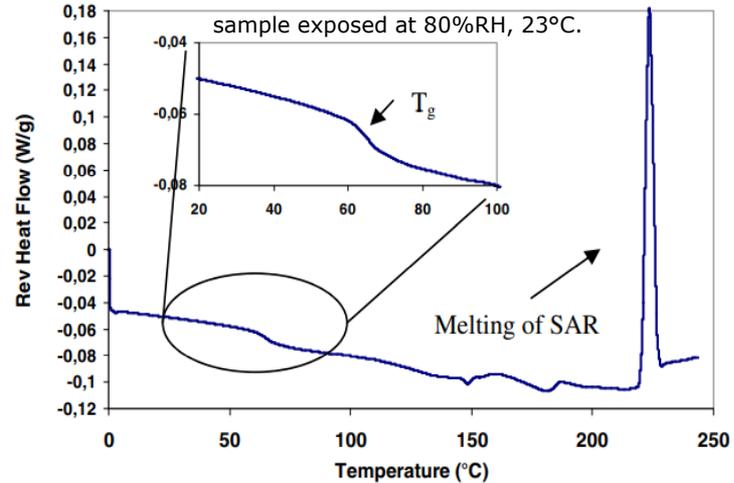
Crystallization time estimation  $\approx \frac{1}{2}(t_{nc} + t_c)$ ; incertitude  $\frac{1}{2}(t_c - t_{nc})$

# Water sorption isotherm and impact on $T_g$



**Fig. 3** Water sorption measured by VTI for the SAR/HPMCP sample as a function of RH% at the different storage temperatures: 25°C, 40°C and 50°C.

When expressed in function of RH (and not  $P_{H_2O}$ ) the isotherm is mostly temperature independent



Modulated DSC is measured in a sealed pan (to avoid water evaporation) .  $T_g$  is identified by a “ $C_p$  jump” on the reversible signal.

# Water Plasticizing effect

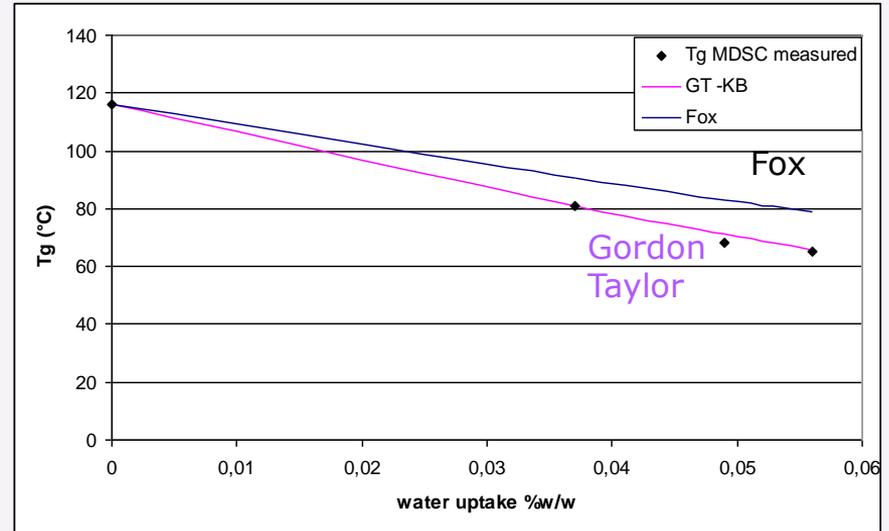
Gordon Taylor equation for T<sub>g</sub>

$$\text{Fox: } 1/T_{g \text{ mix}} = w_1/T_{g1} + w_2/T_{g2}$$

Gordon-Taylor/Kelley Bueche

$$T_g^{GT} = \frac{w_{dry} T_g^{dry} + K w_{H_2O} T_g^{H_2O}}{w_{dry} + K w_{H_2O}}$$

$$K = \left( \rho_{dry} T_g^{dry} \right) / \left( \rho_{H_2O} T_g^{H_2O} \right)$$

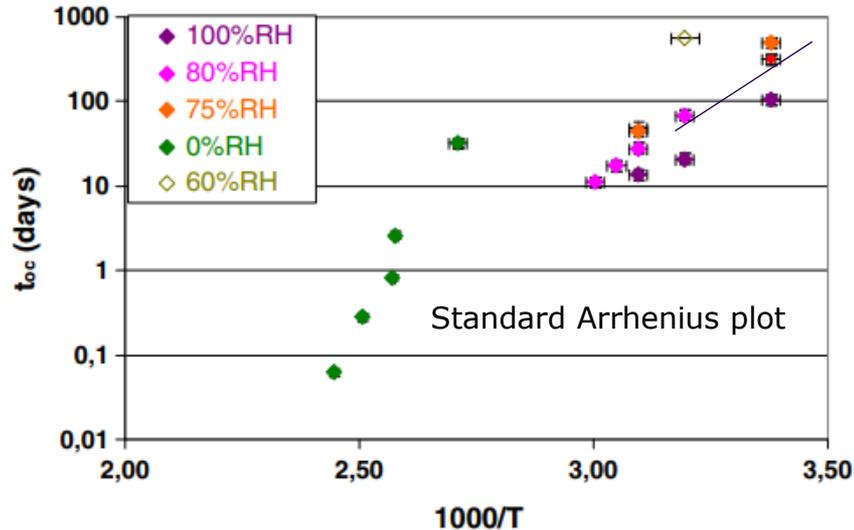


The water impact on T<sub>g</sub> is well described by the Gordon Taylor equation (better than Fox)

# Results: crystallization time

When the crystallization time results are expressed as a function on  $1/T$  the results appear scattered

When the data are expressed in  $T_g/T$ , taking into account the  $T_g$  depression by moisture, all data aligned with

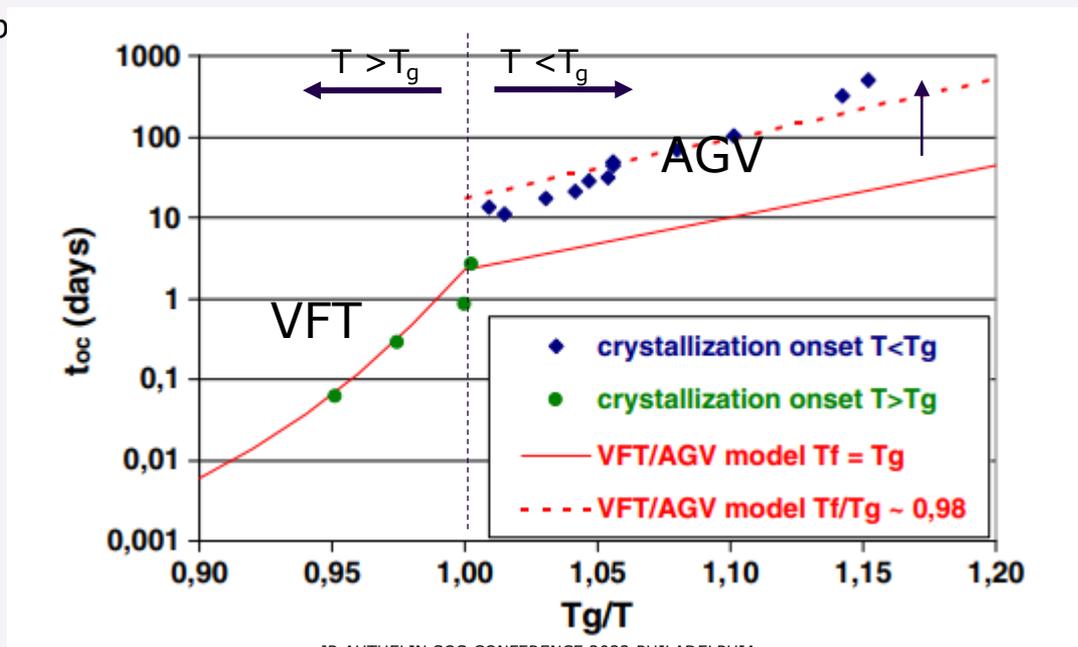


# Comparison with the $\alpha$ -relaxation theory

When the data are plotted in terms of  $T_g/T$  (including all RH data) all points align on a single graph, exhibiting 2 regimes

- For  $T > T_g$ , it is  $T_g/T < 1$ , the VFT equation is followed
- For  $T < T_g$ , it is  $T_g/T > 1$ , the AGV equation is followed with a fictive temperature  $T_f \sim 0.98 T_g$  (glass relaxation)

The crystallization kinetics follows the alpha relaxation general behavior, showing that molecular diffusion is probably the limiting step



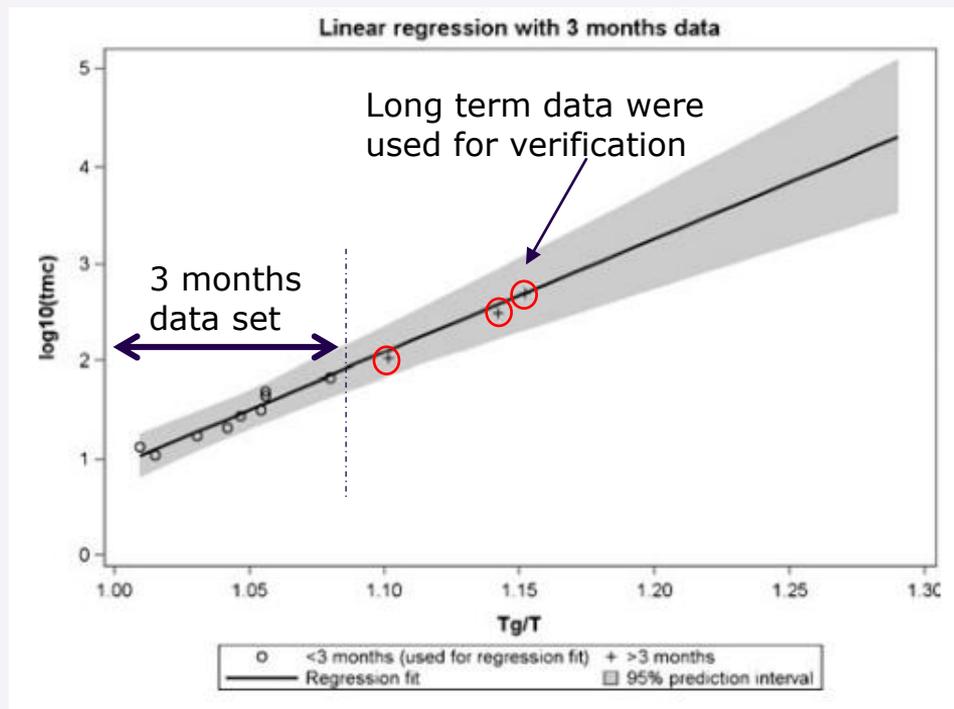
See theory in Back up slides

# Prediction of long-term stability

As the model is based on physics, it is possible to extrapolate the 3 months data ( $T_g/T < 1.1$ ). Long term data ( $T_g/T > 1.1$ ) were compared to the model established and fit very well the model except 40C/60% RH where no crystallization was observed at 570 d (predicted interval 287-555)

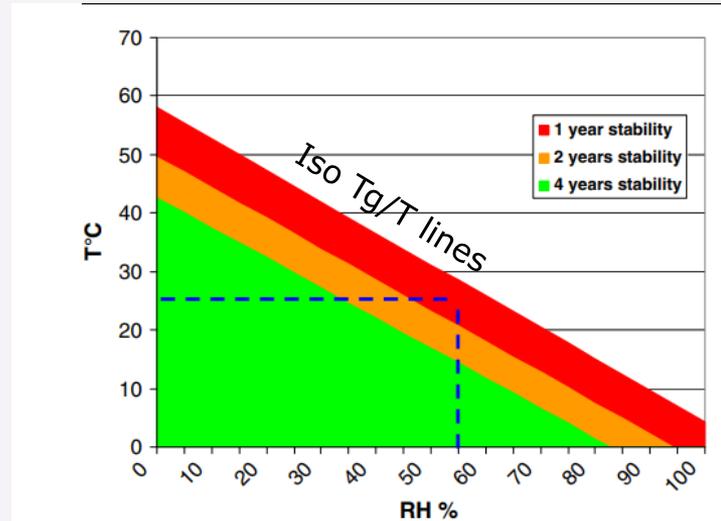
**Table VIII** Extrapolated mean crystallization time calculated from Eq. 14 and compared to experimental values

Storage T (°C)	Storage RH (%)	$T_g/T$	Experimental $t_{cc}$ (days)	Predicted $t_{cc}$ (days)	Calculated $t_m$ (days) 95% lower limit	Calculated $t_m$ (days) 95% upper limit	In the 95% prediction interval
23	100	1.101	105	130	83	199	Yes (-19%)
40	60	1.131	>570	287	150	555	No (> +100%)
23	80	1.142	315	385	185	814	Yes (-16%)
23	75	1.152	504	506	224	1151	Yes (-0.4%)



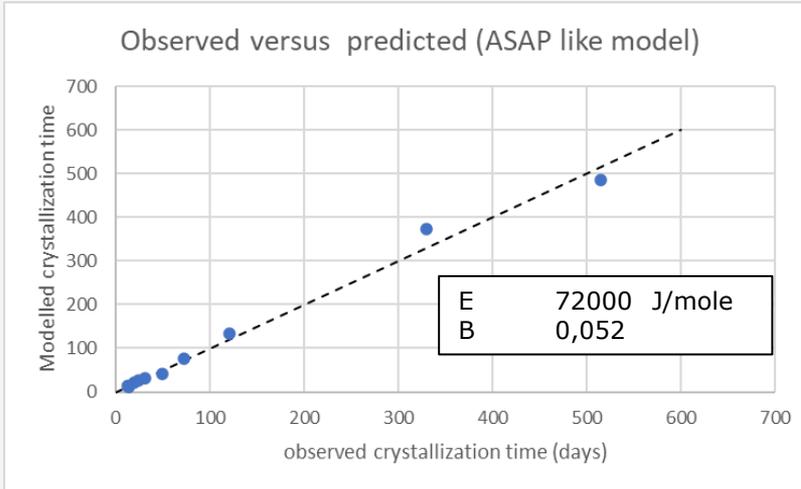
# Design space

A design space can be built: on iso Tg/T lines the crystallization time is constant . It allows to design packaging/storage conditions. To get 2 years stability at room temperature, the relative humidity should be < 40% (use of desiccants recommended)



# Would the ASAP model work ?

ASAP model : we assume  $t_{crys} = A. \exp\left(\frac{E}{RT} \cdot \left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right) \cdot \exp(-B \cdot (RH - RH_{ref}))$



Yes ! Although empirical ASAP model would have fit the data !  
Can be explained by maths : ASAP empirical expression may be considered as a first order approximation of the rigorous model

# Conclusion

- Kinetics of recrystallization of the API in a spray dried dispersions is governed by  $\alpha$ -relaxations and the  $T_g/T$  ratio, considering the plasticizing effect of moisture
- Long term predictions can be performed based on 3 months accelerated data
- A design space for packaging can be proposed
- Finally, ASAP like modelling would have worked as well ! ASAP empirically modified Arrhenius equation approximates well the complete model

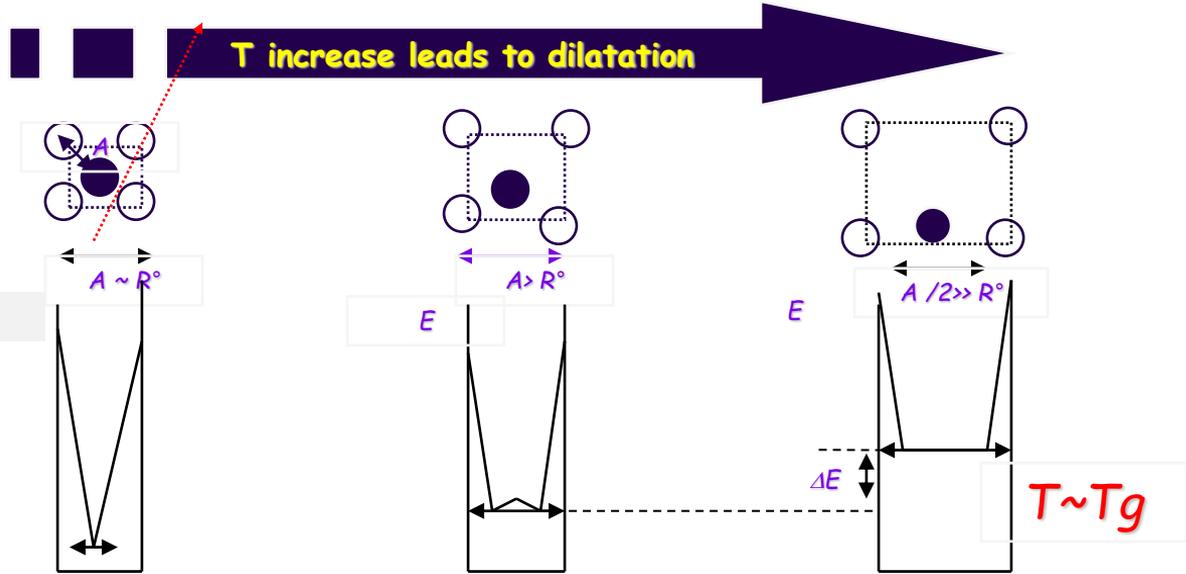
•  
Thank you : questions ?  
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•  
Back up slides : more  
scientific details  
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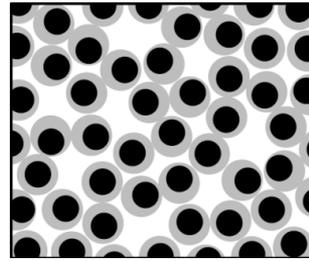
# Free volume theory of the glass transition (Flory)



The molecule cannot move in the cage

- The molecule becomes mobile  $\rightarrow C_p$  jump
- Expansion does not increase too much  $E$

# Free volume theory ctd

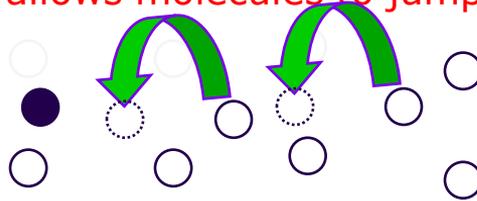


Above  $T_g$ , the free volume increases

$$V_{\text{free}} = \alpha \cdot v_m (T - T^\circ) \quad T > T^\circ \quad T^\circ \text{ close to } T \text{ Kauzman}$$

( $v_m$  : molecular volume,  $\alpha$  : dilatation cste)

The free volume allows molecules to jump from one cage to next cage



The diffusion coefficient increases with the free volume according

$$D = D^\circ \cdot \exp(-\gamma v^* / v_f) \longrightarrow D = D^\circ \cdot \exp\left(\frac{-\gamma v^*}{v_m \cdot \alpha \cdot (T - T^\circ)}\right)$$

The viscosity varies inversely to diffusion coefficient (Einstein law)

$$\frac{1}{\mu} = \frac{1}{\mu^\circ} \cdot \exp\left(\frac{-\gamma v^*}{\alpha \cdot v_m \cdot (T - T^\circ)}\right)$$

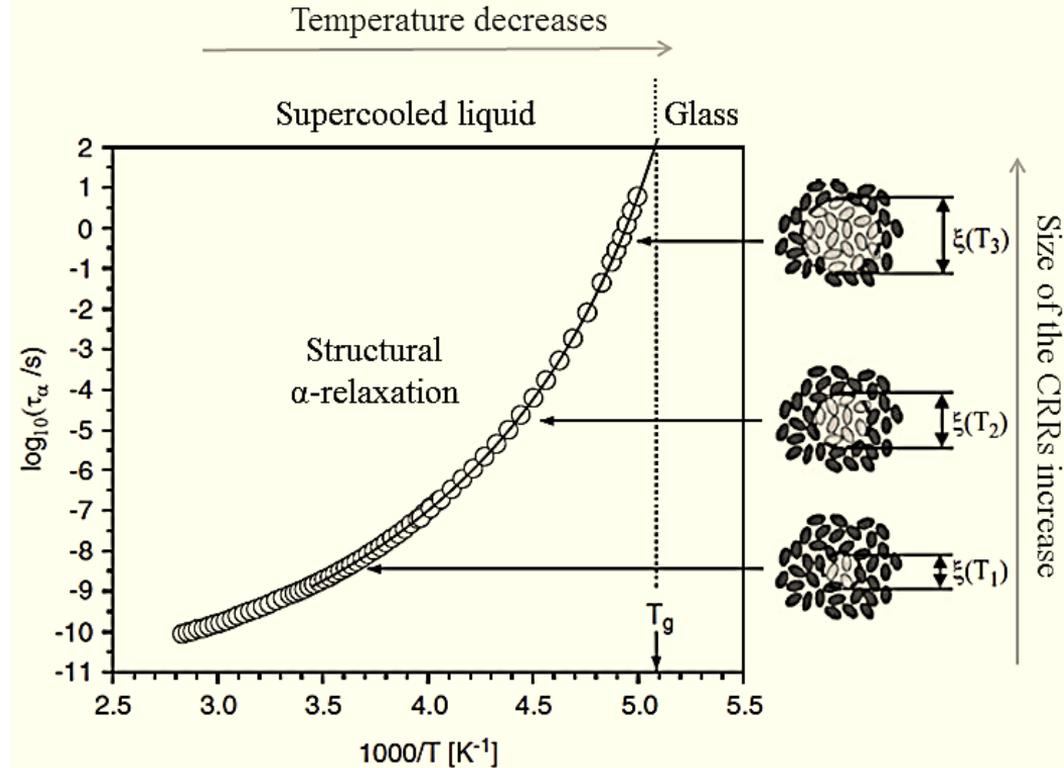
**Williams Landel Ferry law**  
**First experimentally observed**

# An alternative theory of Glass transition Adam Gibbs model

During cooling, molecular motions of a supercooled liquid decrease significantly. The structural relaxation time ( $\tau_\alpha$ ) increases non-linearly from values of the order of picoseconds up to hundreds of seconds in the vicinity of the glass transition.

According to the Adam-Gibbs model, this slowdown in the molecular dynamics is caused by the decrease in the number of possible system configurations ( $S_c$  decreases see Eq II, so the size of the Cooperative Rearranging Regions increases)

This theory as well results in the VFT equation



# Angell Strong/fragile glasses classification: distance from Arrhenius behavior

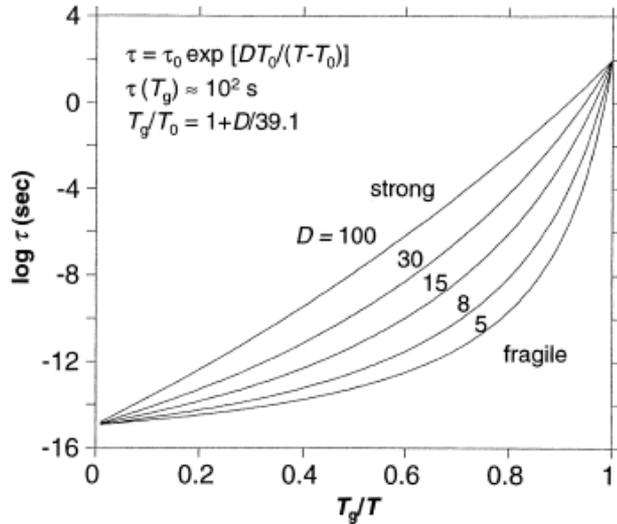


Fig. 5. The strong–fragile pattern that characterizes the temperature dependence of structural relaxation times of supercooled liquids. The series of curves are generated by Eq. (1) using different  $D$  values and give a good reproduction of the pattern that emerges from the “Angell plots” ( $\log \tau$  vs.  $T_g/T$ ) of many liquids. Strong liquids (e.g.,  $\text{SiO}_2$ ) are characterized by large  $D$  and quasi-Arrhenius behavior and fragile liquids (e.g., many small-molecule organics) by small  $D$  and non-Arrhenius behavior.

For  $T > T_g$ , VFT law can be rearranged :

$$\tau_\alpha = \tau_\alpha^0 \cdot \exp\left(\frac{E_\alpha^*}{T - T^0}\right) = \tau_\alpha^0 \cdot \exp\left(\frac{-D^* T^0}{T - T^0}\right)$$

• For large  $D \rightarrow T^0$  far from  $T_g$  and behavior is close to Arrhenius  $\rightarrow$  Strong glass

For small  $D \rightarrow T^0$  close to  $T_g$  and behavior is far from Arrhenius  $\rightarrow$  Fragile glass

## Fragility index

A fragility index  $m$  can be defined according Angell's classification :

At  $T = T_g$ , an apparent activation energy  $\Delta H^*$  can be measured

a dimension less parameter  $m = \Delta H^* / (2,303RT_g)$  is defined

$$T^\circ = T_g (1 - m_{\min} / m),$$

$$m_{\min} = 16, D = 2,303 (m_{\min})^2 / (m - m_{\min})$$

Small values of  $m$  correspond to strong glasses & large values correspond to fragile glasses

# Alpha relaxations above $T_g$

$T > T_g$

The molecular  $\alpha$ -relaxation time  $\tau_\alpha$  is related to the temperature by the Vogel-Tammann-Fulcher (VTF) equation:

$$\tau_\alpha = \tau_{\alpha 0} \exp\left(\frac{D T_0}{T - T_0}\right) \quad (3)$$

where  $\tau_{\alpha 0}$  is the limit for relaxation time at the high temperature limit, and  $T_0$  is the temperature where  $\tau$  becomes infinite.  $T_0$  is often taken as the Kauzmann temperature and  $D$  is a material specific parameter depending on the glass fragility.  $D$  is related to the fragility index  $m$  (defined in Eq. 4) by Eq. 5.

$$m = \left[ \frac{d \log(\tau_\alpha(T))}{d(T_g/T)} \right]_{T=T_g} \quad (4)$$

$$D = \frac{2.303 m_{\min}^2}{m - m_{\min}} \quad (2.303 \text{ is the conversion form } \log_{10} \text{ to } \ln) \quad (5)$$

$$\frac{T_0}{T_g} = \left( 1 - \frac{m_{\min}}{m} \right)$$

Screen shot from Greco et al. Pharm Res 2012 - 29 (10), 2792-2805

# Alpha relaxations below $T_g$

$$T < T_g$$

The glassy state below  $T_g$  is a non-equilibrium one (33), where the macroscopic configurational entropy remains constant and depends only on the fictive temperature  $T_f$ . As a consequence,  $\tau_\alpha$  has Arrhenius-like temperature dependence. The most common relation used to fit the temperature dependence to the relaxation times in this range is the so-called Adam-Gibbs-Vogel (AGV) equation (35):

$$\tau_\alpha = \tau_{\alpha 0} \exp\left(\frac{D T_0}{T(1 - T_0/T_f)}\right) \quad (8)$$

*Pikal and co-workers (21) have shown that it is possible to fit experimental measurements of  $\tau$  above and below  $T_g$  (measured by dielectric spectroscopy above  $T_g$  and by calorimetric method below  $T_g$ ) using the same set of values for  $D$  and  $T_0$ .*

Screen shot from Greco et al. Pharm Res 2012 - 29 (10), 2792-2805

# Link between alpha mobilities and crystallization

## Crystallization Onset: $\alpha$ -relaxations Relationship

As mentioned in the introduction, several studies (13,20) have related the chemical degradation or the crystallization rate in amorphous systems to the different relaxation times. In order to correlate the onset crystallization time ( $\tau_{oc}$ ) to the  $\alpha$  relaxation time we propose to use an equation very close to that already proposed by Bughra *et al.* (13):

$$\log(\tau_{oc}) = \xi \log(\tau_{\alpha}) + \log(\tau_{oc}^0) \quad (9)$$

where  $\xi \leq 1$  is a coupling parameter and  $\tau_{oc}^0$  is a constant.

When  $T > T_g$ , one expects therefore an apparent VTF law for crystallization time, as follows

By fitting experimental values of  $\tau_{oc}$  one may obtain  $\tau_{oc}^0$ ,  $D' = \xi D$  and  $T_0$ .

At  $T < T_g$ , the above equation may be modified according to AGV theory to:

$$\log(\tau_{oc}) = \log(\tau_{oc}^0) + \frac{1}{\ln(10)} \times \frac{\xi D T_0}{T(1 - T_0/T_f)} \quad (11)$$

Screen shot from Greco *et al.* Pharm Res 2012 - 29 (10), 2792-2805

# Moisture impact

## Humidity Effect

When a hygroscopic amorphous solid is exposed to humidity,  $T_g$  usually rapidly decreases. However it has been shown that  $D$  is mostly independent of the moisture (27,36).

Therefore one can assume that, while  $T_0$ ,  $T_g$ ,  $T_f$  change with moisture uptake, the ratios  $T_0/T_g$  will remain constant, according to Eq. 7, and so will do the  $T_0/T_f$  since  $T_f$  and  $T_g$  are very close. The Eq. 11 can be so rewritten:

$$\ln(\tau_{oc}) = \ln(\tau_{oc}^0) + \frac{\xi D T_0/T_g}{(T/T_g) \times (1 - T_0/T_f)} \quad (12)$$

$$\ln(\tau_{oc}(T, RH)) = \log(\tau_{oc}^0) + A \frac{T_g(RH)}{T} \quad (13)$$

where  $A$  is a constant:

$$A = \frac{\xi D T_0/T_g}{(1 - T_0/T_f)} \quad (14)$$

Therefore the plot of  $\tau_{oc}$  versus  $T_g/T$  is expected to be linear.

Screen shot from Greco et al. Pharm Res 2012 - 29 (10), 2792-2805

# ASAP model versus theory

The theoretical expression for crystallization time is :  $Ln(\tau_c) = Ln(\tau_{\circ c}) + A \frac{T_g}{T}$

Empirically  $T_g(RH) \sim T_g^{\circ} - C * RH$  , where C is a constant

Therefore  $Ln(\tau_c) = Ln(\tau_{\circ c}) + A \frac{T_g^{\circ} - C.RH}{T}$

As T varies much less than RH (From 60 to 96°C, it is 333 to 369 K) , T variation is only 36/360 ~10%)

$Ln(\tau_c) \approx Ln(\tau_{\circ c}) + A \frac{T_g^{\circ}}{T} - \frac{C.RH}{\langle T \rangle}$  where  $\langle T \rangle$  is the mean value of T ~351 K

This expression is the same as ASAP (with inverted signs as  $\tau=1/k$ ).  $E_a = A * T_g^{\circ}$ ;  $B = C / \langle T \rangle$