# Importance de l'étude expérimentale des équilibres solide-vapeur lors du développement d'un solide actif pharmaceutique (mais pas que….)

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# Laboratoire Sciences et Méthodes Séparatives

UR 3233 - Direction Pr. Pascal CARDINAEL

## RESEARCH/EXPERTISE FIELDS

→ **CRYSTALLIZATION OF ORGANIC SOLIDS**

→ Nucleation and growth of molecular species
→ Separation and Chirality
→ Purification by Crystallization

→**Thermodynamics of heterogeneous equilibria.**

- **Experimental building of phase diagram**
- **Rationalization of crystallization processes**

➢ Fundamental and applied research (pharmaceutical industry)

## Thermodynamic of crystallized solids.

| | |
|---|---|
| **Solid-Solid** | Polymorphism,<br>Order-disorder transitions<br>Interactions between two solids<br>→ **Formation of new solid forms** |
| **Solid-liquid** | **Cristallization** (from molten state of from solution) , formation of solvates (**hydrates**).. |
| **Solid-vapor** | Interactions between solid and surrounding vapor (in particular water vapor or crystallization solvent) |

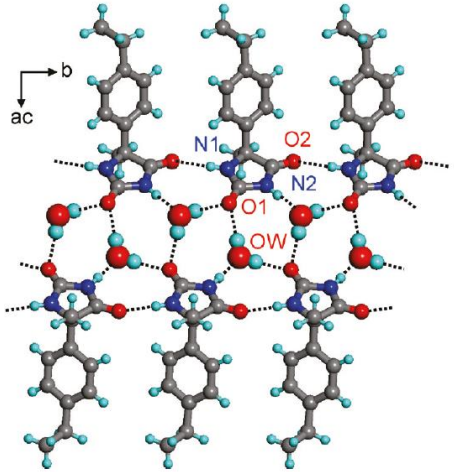
**EXPERIMENTAL STUDIES DEDICATED to HYDRATES and SOLVATES**
→ **ORGANIC and INORGANIC solids**

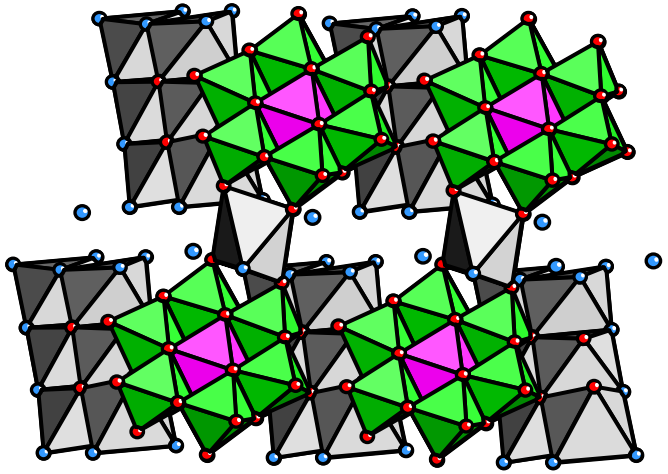
## Why studying hydrated solids?

- Change of physico chemical properties during the **storage**, annealing, heating, the drying process, filtration,….
- Variable quantity of water in a solid after its crystallization
- Appearance of new solid phases after a change of solvent in the crystallization process (green chemistry)

## What is the role of water molecule in solids

- Space filler of the crystalline structure(located or in channels)
- Link between molecules via hydrogen bonds
- Coordination spheres of cations



**→ OUR WORK : Characterize experimentally the behaviour of hydrated phases from molecular to macroscopic scale**

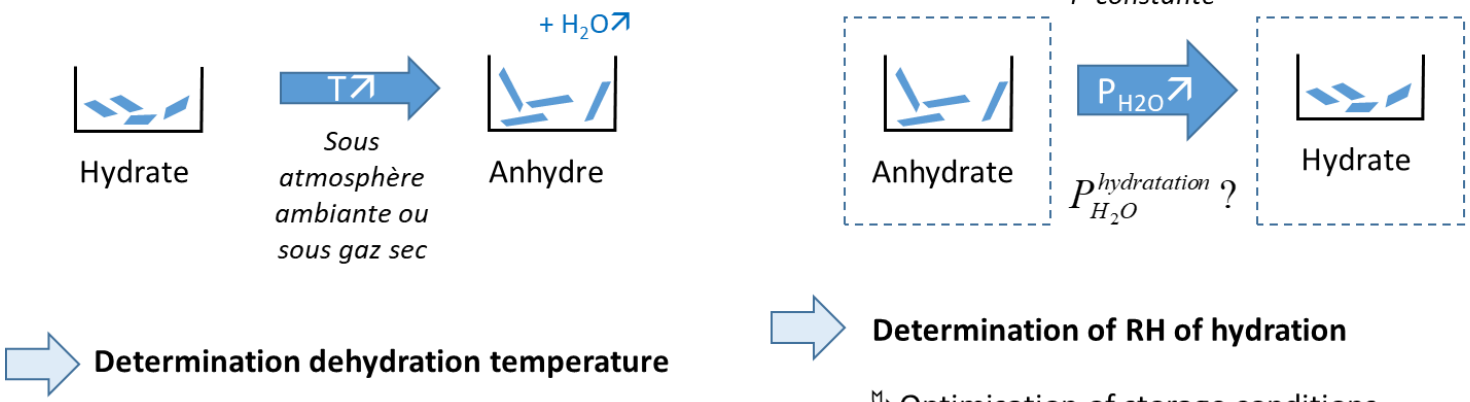
# « Phase diagram » approach

An HYDRATE = Defined compound in the binary system between Compound A/Water

**Solid-vapor** At fixed temperature, anhydrate/hydrate transformation

**A (solid) + p $H_2O$ (vapeur) ⇆ A,p $H_2O$ (solid)**

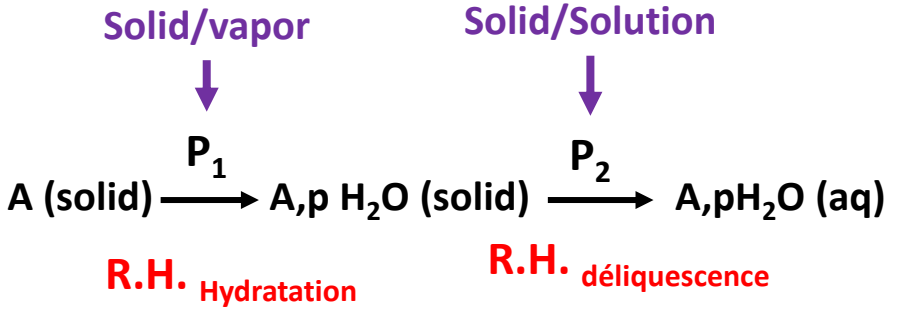
$$R.H.(\%) = \left(\frac{P_{H_2O}}{P^{sat}_{H_2O}}\right)_{T=const}$$

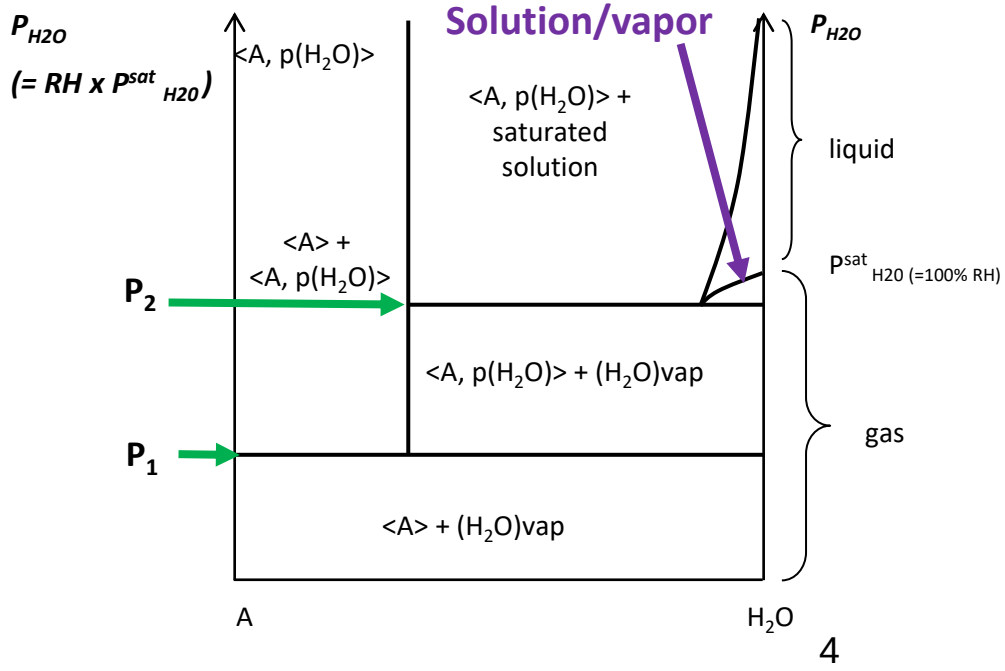



**Determination dehydration temperature**

**Determination of RH of hydration**

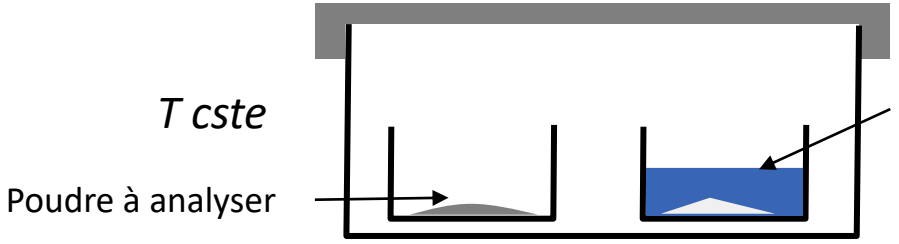
↳Optimisation of storage conditions



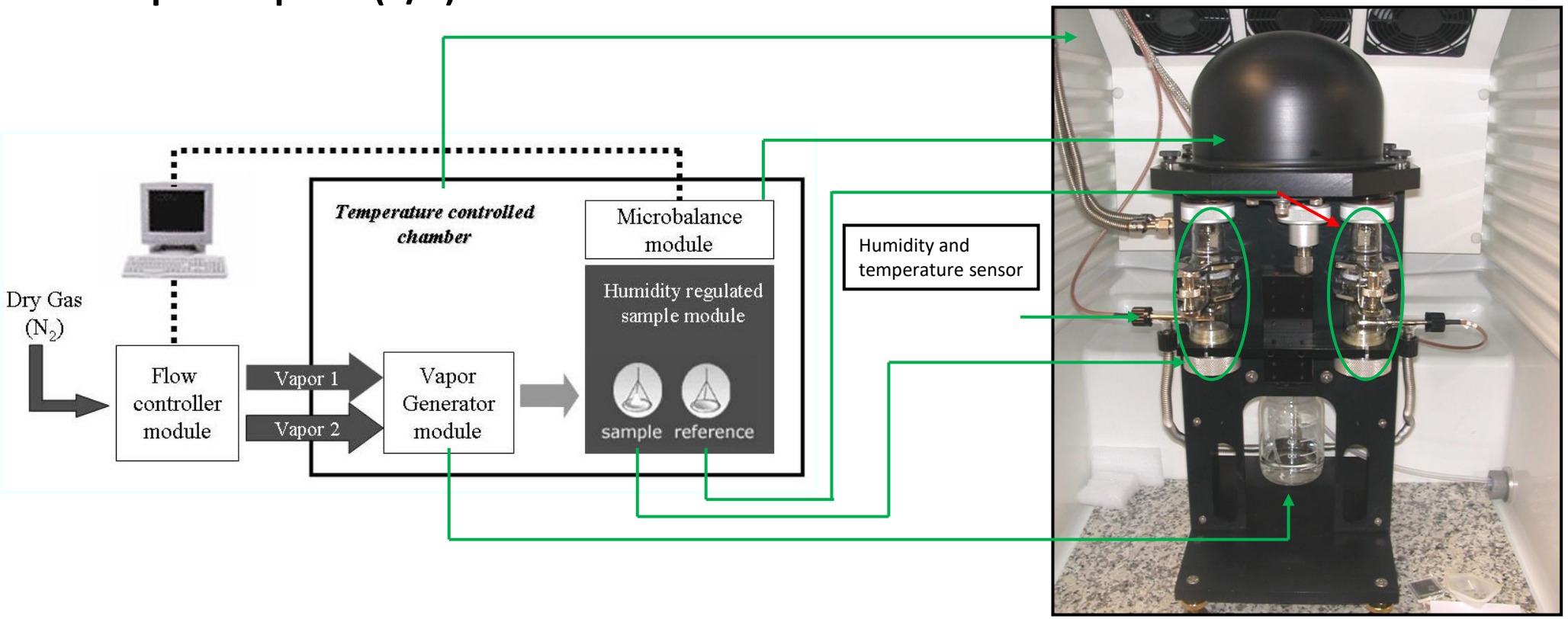
## Gravimetric analyses *vs* R.H. = HYGROSCOPICITY

- **Static Gravimetric Vapor Sorption**



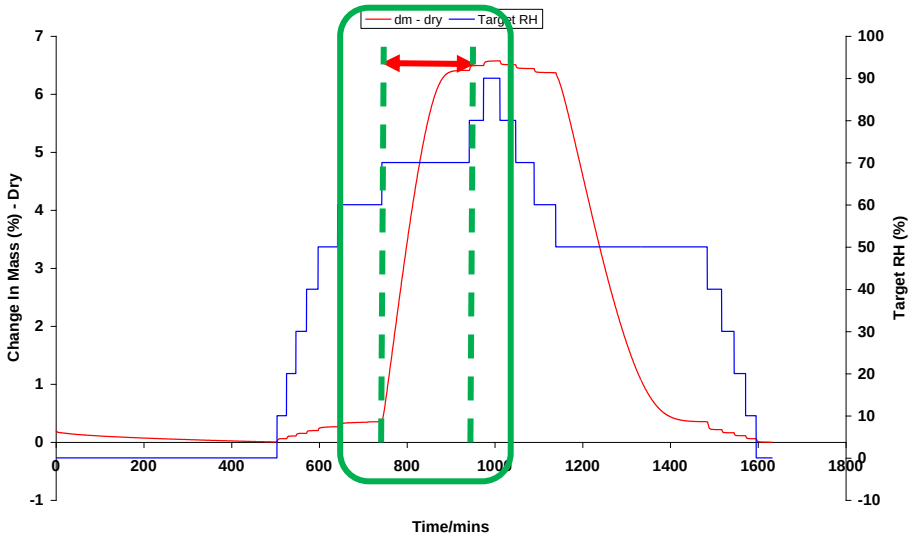

- **Humidity generator**

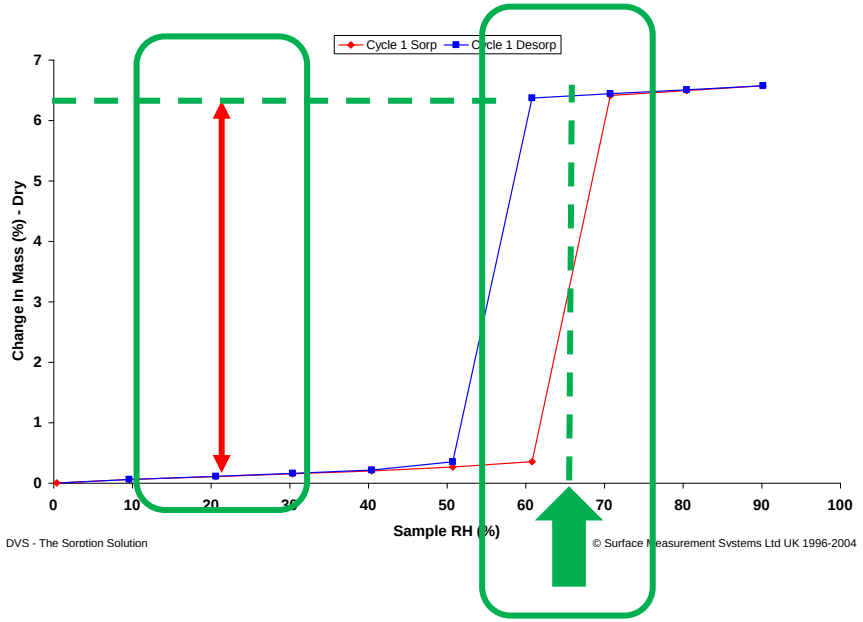
- **Dynamic Vapor Sorption (1/3)**




*DVS one – Systems Measurements Systems - UK*

# ➢ Dynamic Vapor Sorption (2/3)




- Determination of $RH_{hydratation}$
- Stoichiometry of the hydrate(s)
- Information of kinetic of hydration
- Thermodynamic nature of the hydrate :
  - stoichiometric (fixed quantity of water molecule inside the structure)
  - Non-stoichiometric (variable quantity of water molecules in the solid = solid solutions

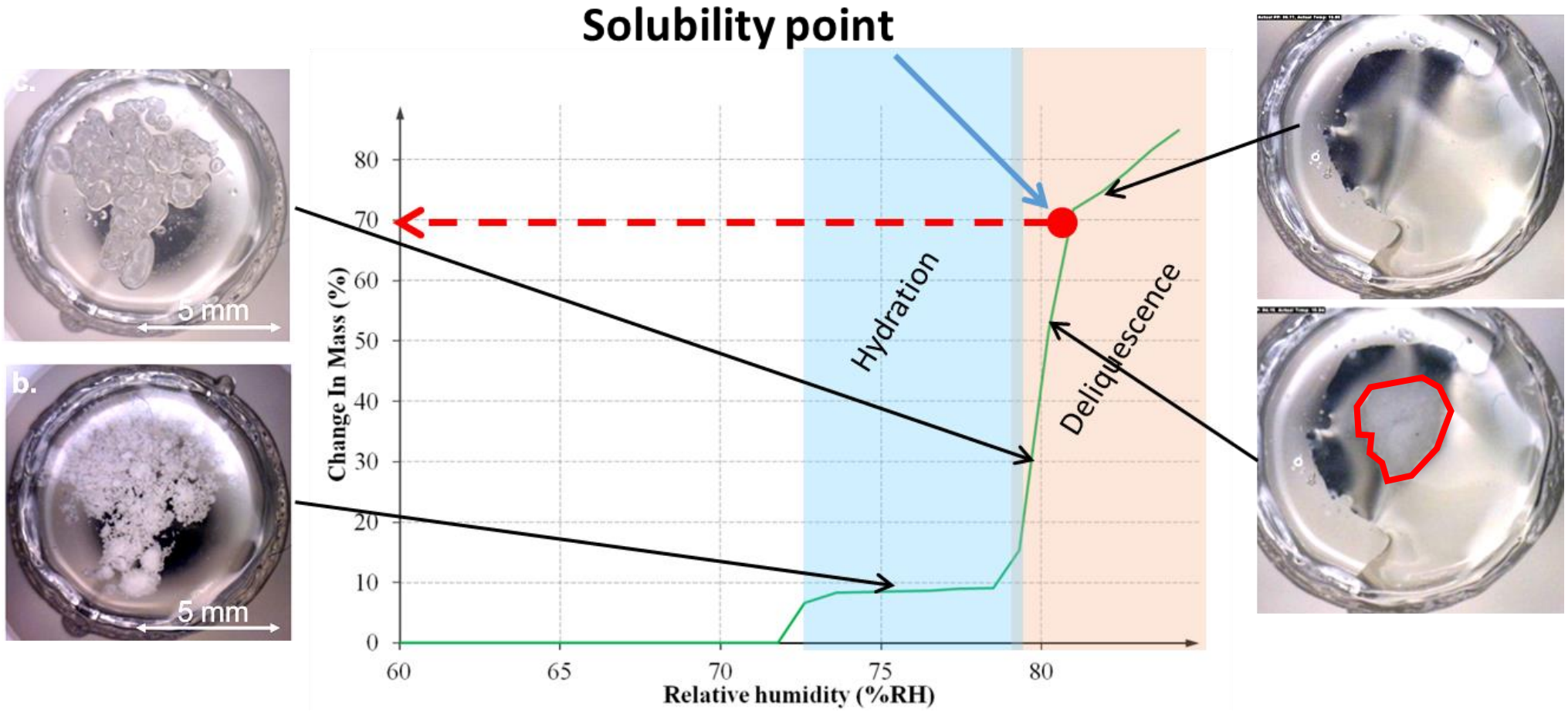
## ➢ Dynamic Gravimetric vapor sorption (3/3)

Determination of $RH_{deliquesence}$

Solid-Vapor equilibria

Solid-solution equilibria

Solution-vapor equilibria

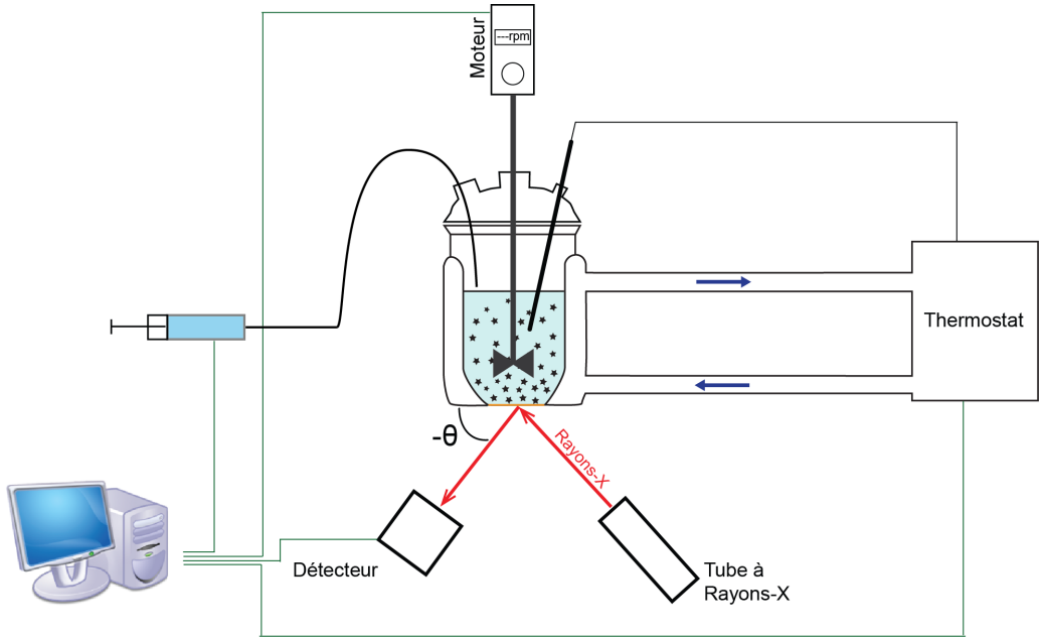


## Equilibres solide - liquide

Reproduction des procédés de cristallisation:

⇨ Réacteur avec fond transparent aux rayons X:

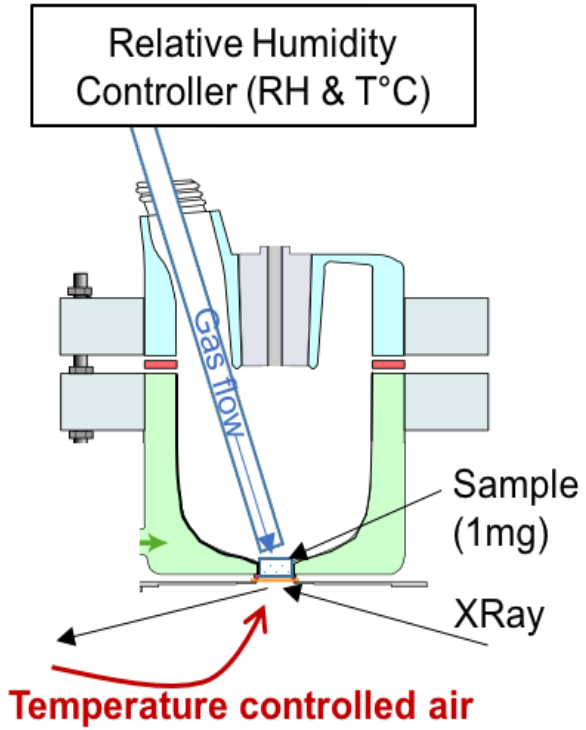
- Thermostaté: via un thermostat
- Système d'agitation: moteur + mobile
- Ajout de liquide
- ...




## Equilibres solide - gaz

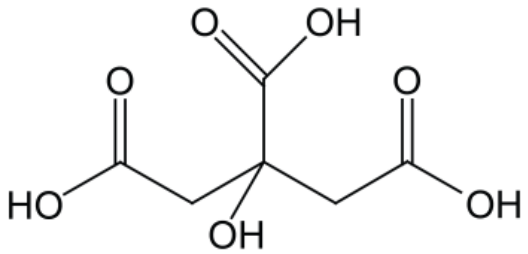
Etude des solides sous pression de vapeur variable

⇨ Similaire à une analyse DVS (Dynamic Vapor Sorption) avec suivi structural

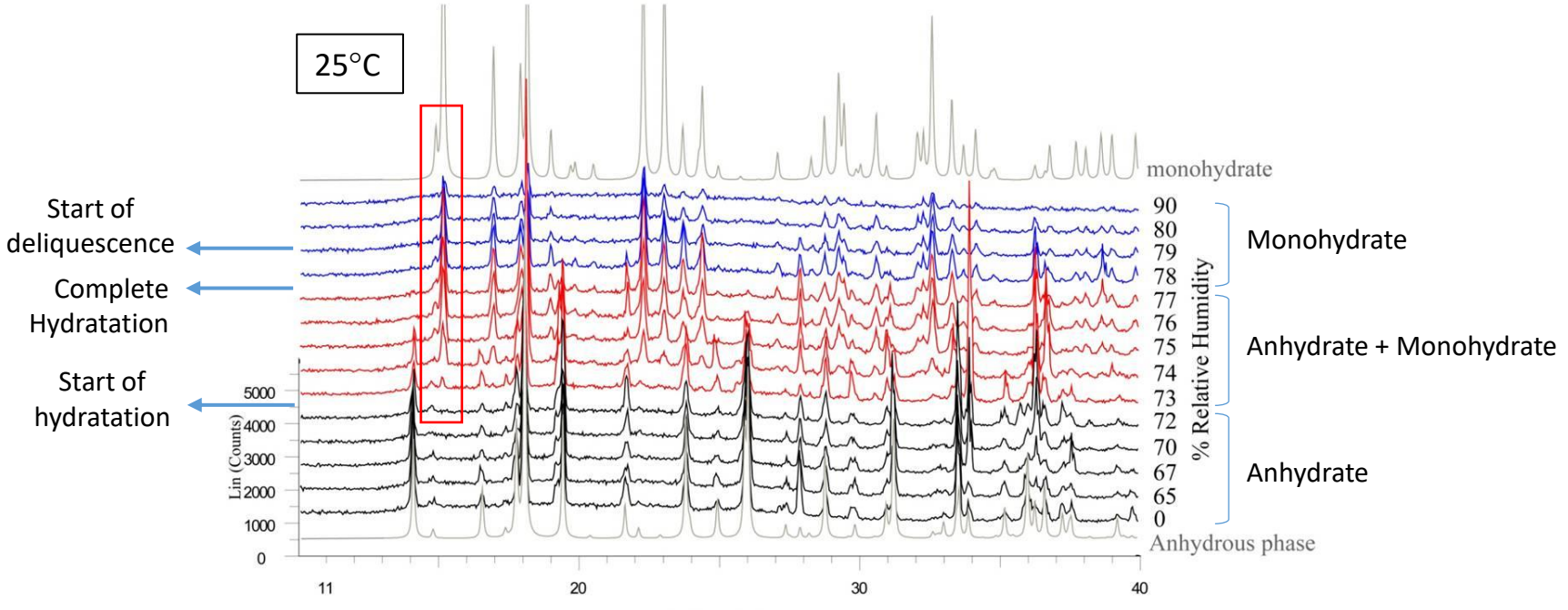


## ➢ XRPD *vs* R.H.

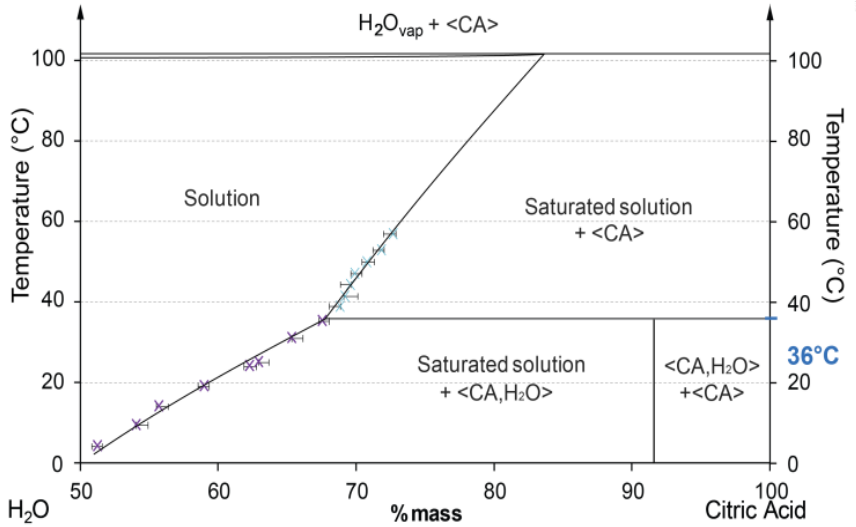
↳ Hydration ⇨ 72%RH< $RH_{min}$ < 73%RH
↳ Deliquescence ⇨ 79%RH




**Acide citrique**




## ➢ XRPD *vs* Temperature




## ➢ TG-DSC-MS

## ➢ SC X-Ray Diffraction

## ➢ Discontinuous Isoperibolic Thermal Analyses (DITA – prototype)

➢ Les méthodes testées sont cohérentes entre elles et avec la littérature :

**36°C < $T_{péritectique}$ < 37.5°C**

## $CoSO_4/H_2O$ – Solid/vapor equilibria

Thèse THERMOSALT (2022-2025)

RÉGION NORMANDIE

Géosciences pour une Terre durable
brgm

**Thermodynamic model for $CoSO_4$(aq) and the related solid hydrates in the temperature range from 270 to 374 K and at atmospheric pressure.**

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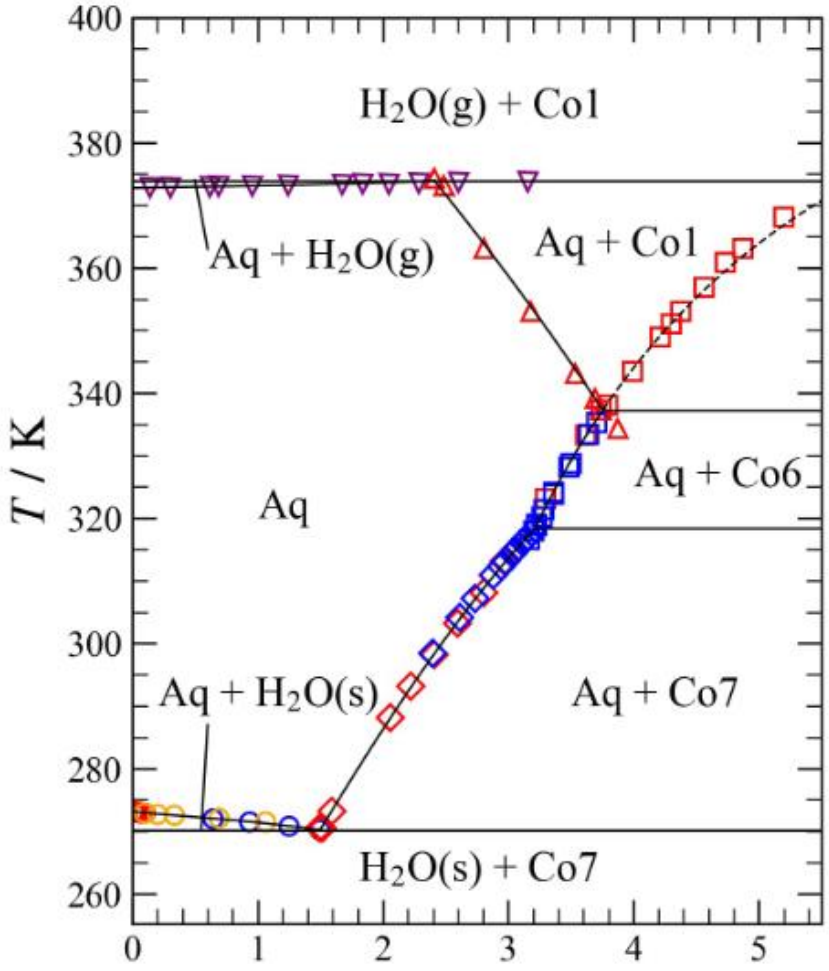



$H_2O$ $CoSO_4$ →

$CoSO_4$

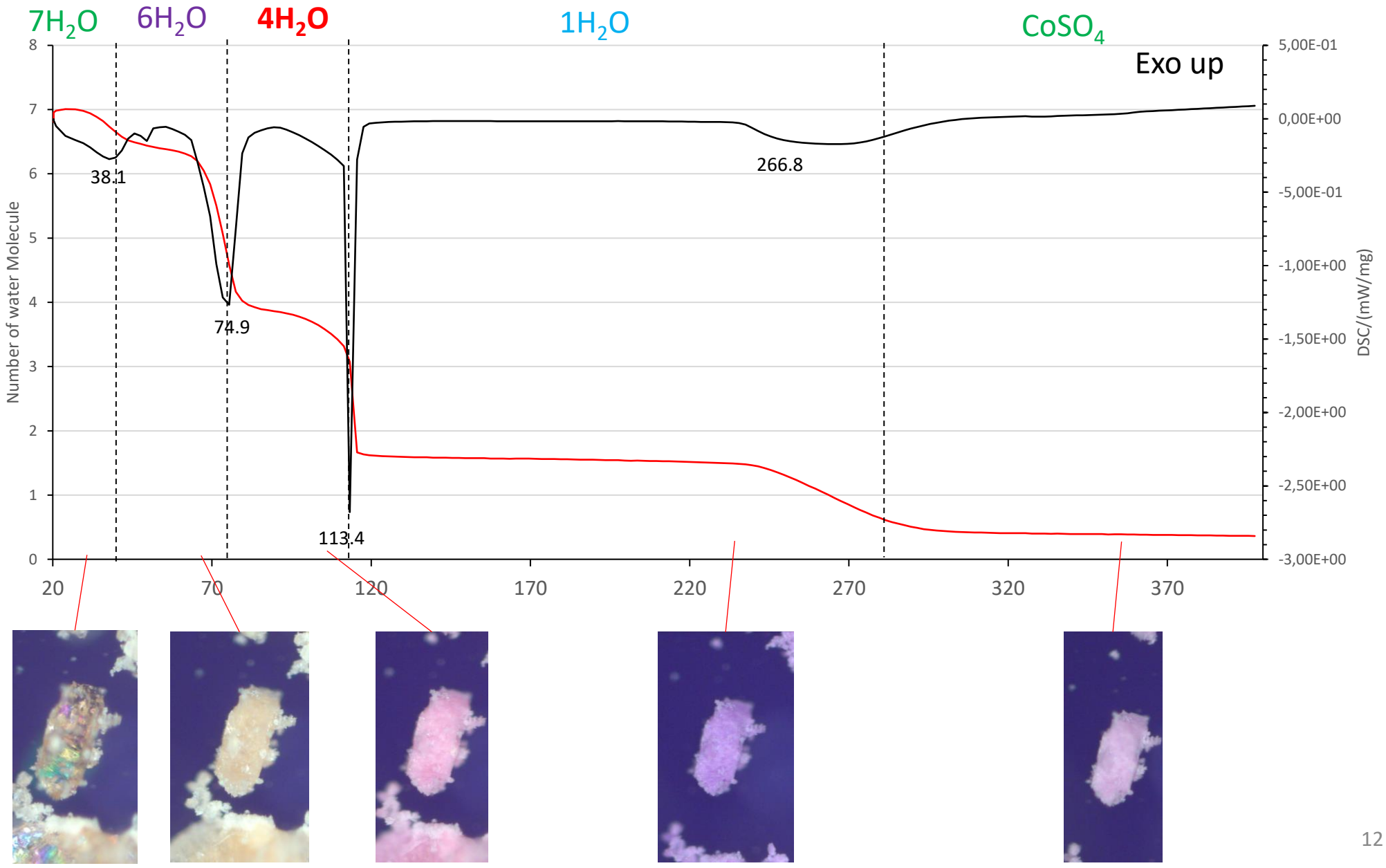
$CoSO_4$, $1H_2O$

$CoSO_4$, $6H_2O$

$CoSO_4$, $7H_2O$

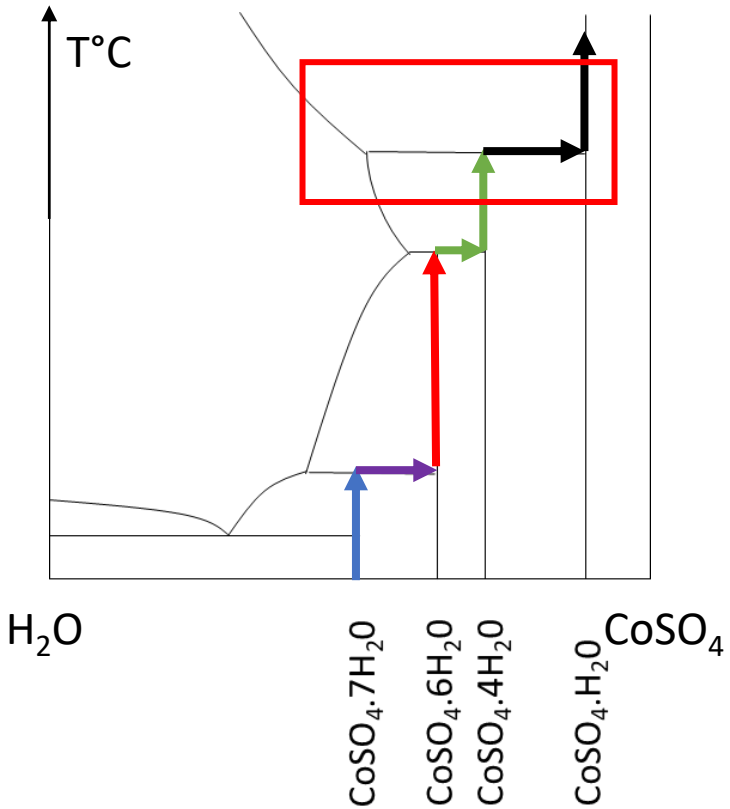
**$CoSO_4/H_2O$ – Solid/vapor equilibria**

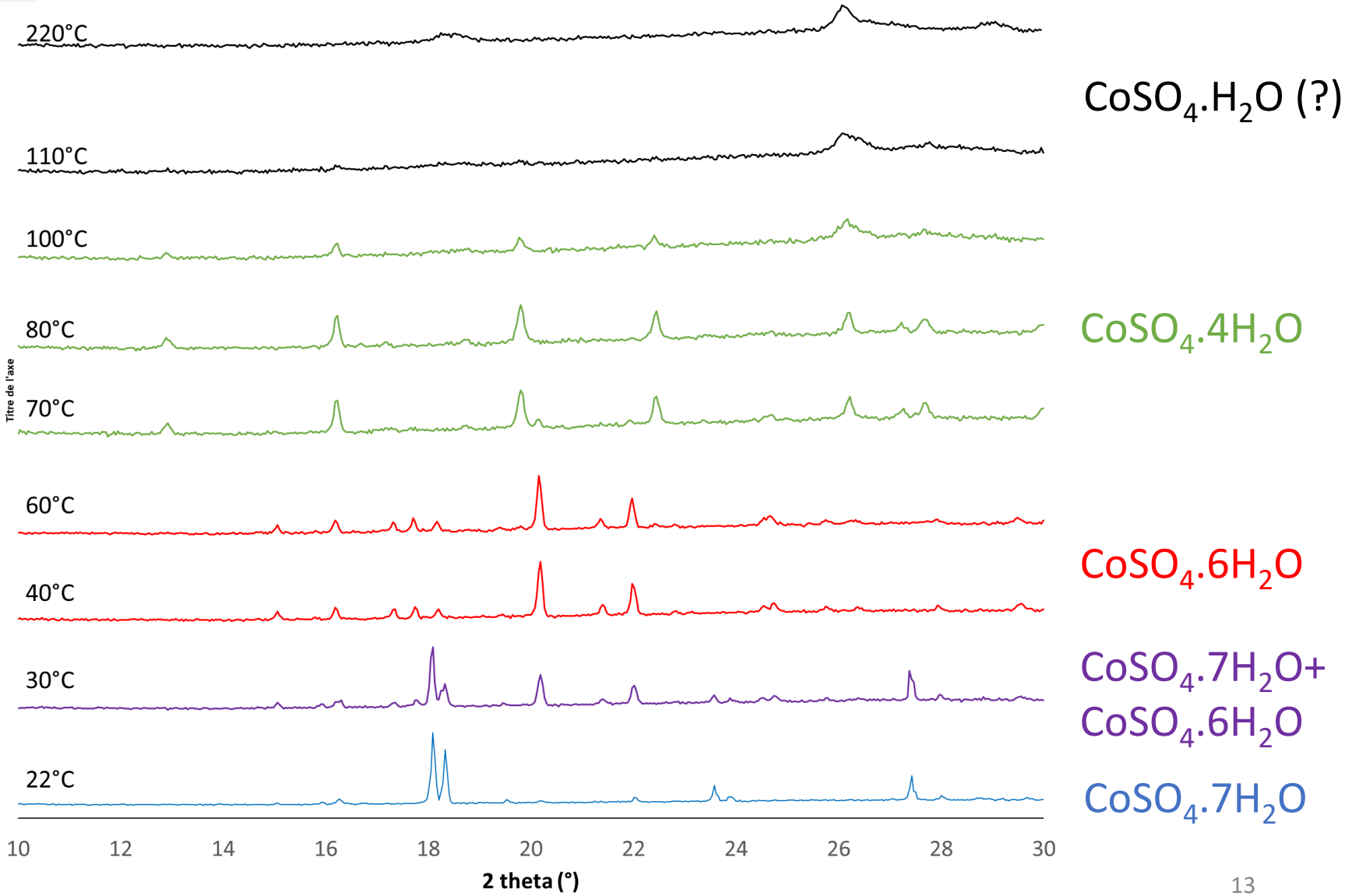
- TGA-DSC and hot-stage microscopy performed on $CoSO_4.7H_2O$ at 2K°/min
- $CoSO_4.4H_2O$.



## $CoSO_4/H_2O$ – Solid/vapor equilibria

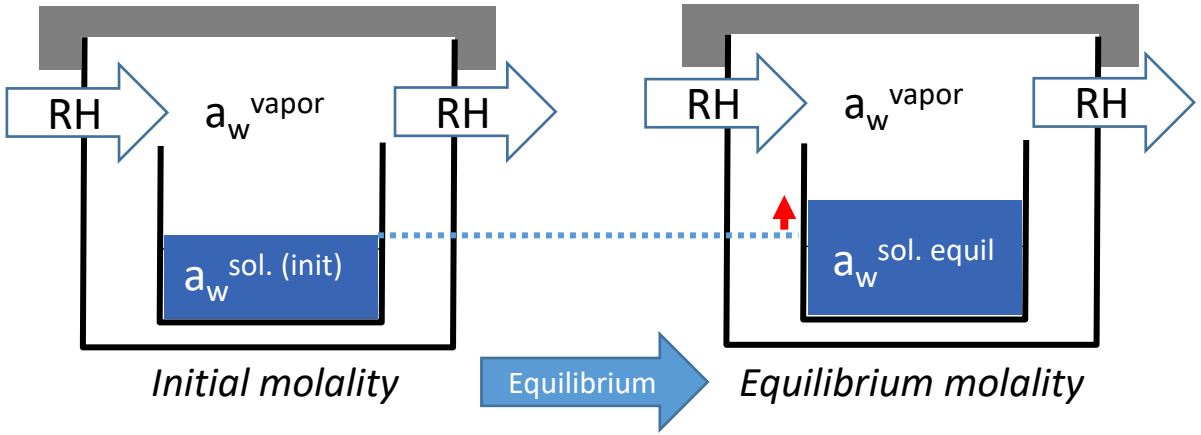
- Temperature resolved XRD on $CoSO_4.7H_2O$.
- Dehydrations consistent with TGA-DSC.
- Appearance of $CoSO_4.4H_2O$.

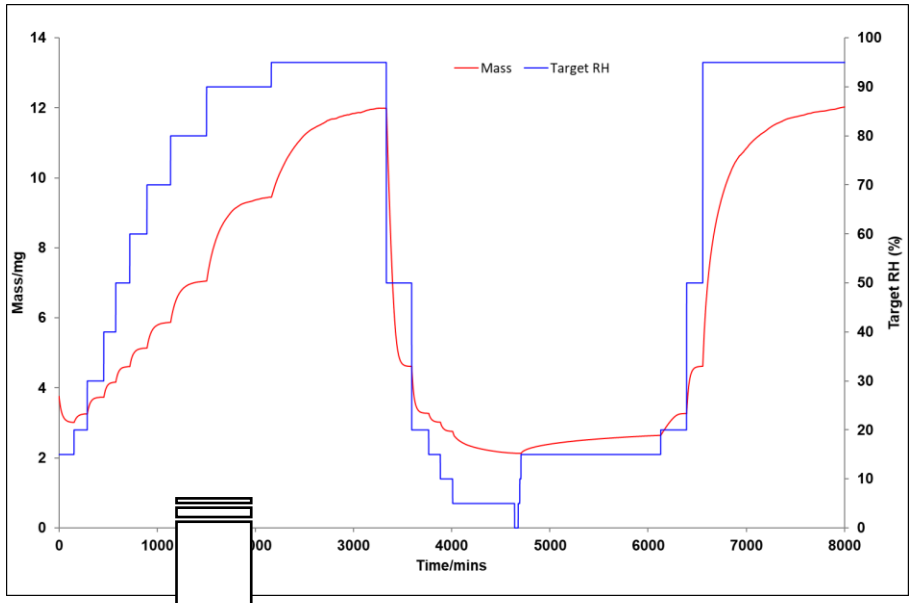


# $CaCl_2/H_2O$ – Solution/vapor equilibria

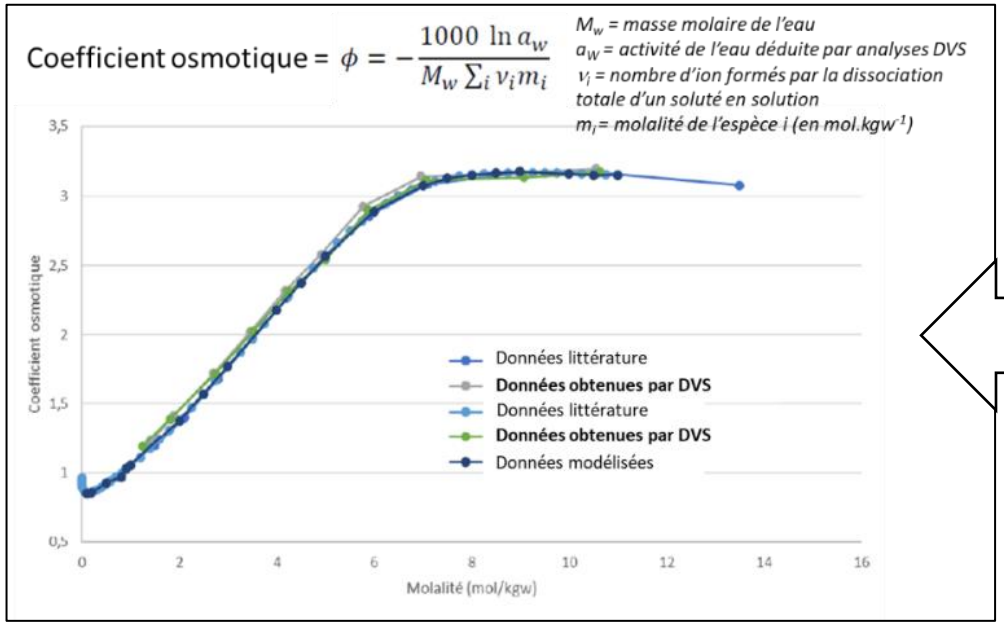
## Isopiestic method (by DVS)

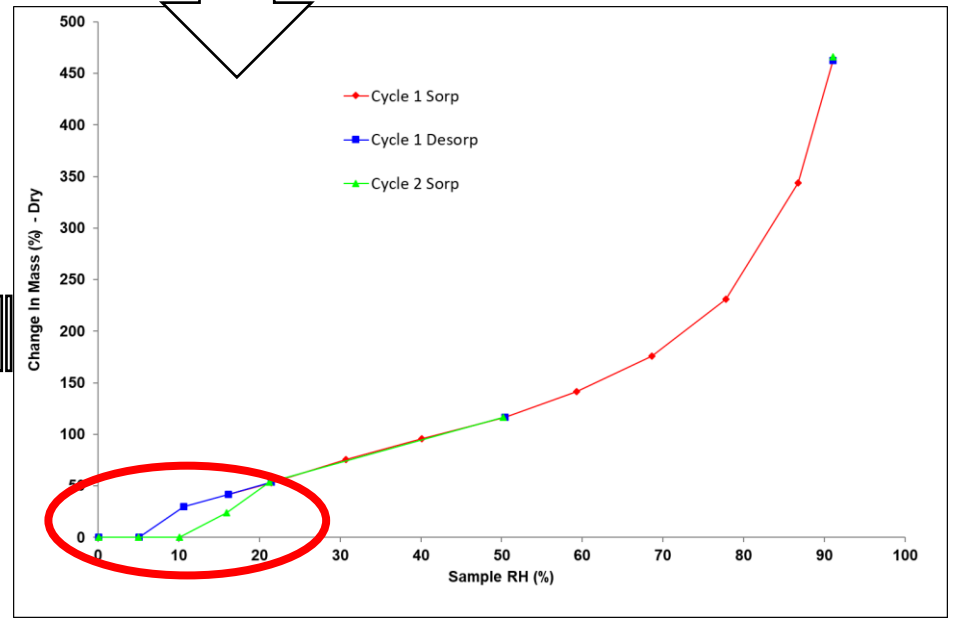



Coefficient osmotique = $\phi = -\frac{1000 \ln a_w}{M_w \sum_i \nu_i m_i}$

$M_w$ = masse molaire de l'eau
$a_w$ = activité de l'eau déduite par analyses DVS
$\nu_i$ = nombre d'ion formés par la dissociation totale d'un soluté en solution
$m_i$ = molalité de l'espèce i (en mol.kgw$^{-1}$)



**Importance de l'étude expérimentale des équilibres solide-vapeur lors du développement d'un solide actif pharmaceutique (mais pas que….)**

**Approche TRANS MATERIAUX**

↳ caractérisation de la nature thermodynamique des hydrates/solvates.

↳ solvatation à l'état solide pour mettre en place des procédés de discrimination à l'état solide (contexte d'énantioséparation)

↳ accès à de nouvelles phases originales hydratées ou anhydres,

↳ proposition de mécanismes d'hydratation/déshydratation à l'échelle moléculaire pour comprendre l'évolution des solides au cours de leur stockage.

↳ corrélation entre le niveau d'hydratation/solvatation d'un solide et ses propriétés physiques (capteur d'humidité, polymorphisme,…)

# Merci pour votre attention!!

https://labsms.univ-rouen.fr

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# Conclusions