CHALLENGES OF PHYSICO – CHEMICAL CHARACTERIZATION OF API

9th Sci & Tech Forum | Markus von Raumer

ACTELION

TABLE OF CONTENTS

- Drug substance – Physical State, Solid Form
- Analytical characterization – general thoughts and cases

PHYSICO-CHEMICAL CHARACTERIZATION

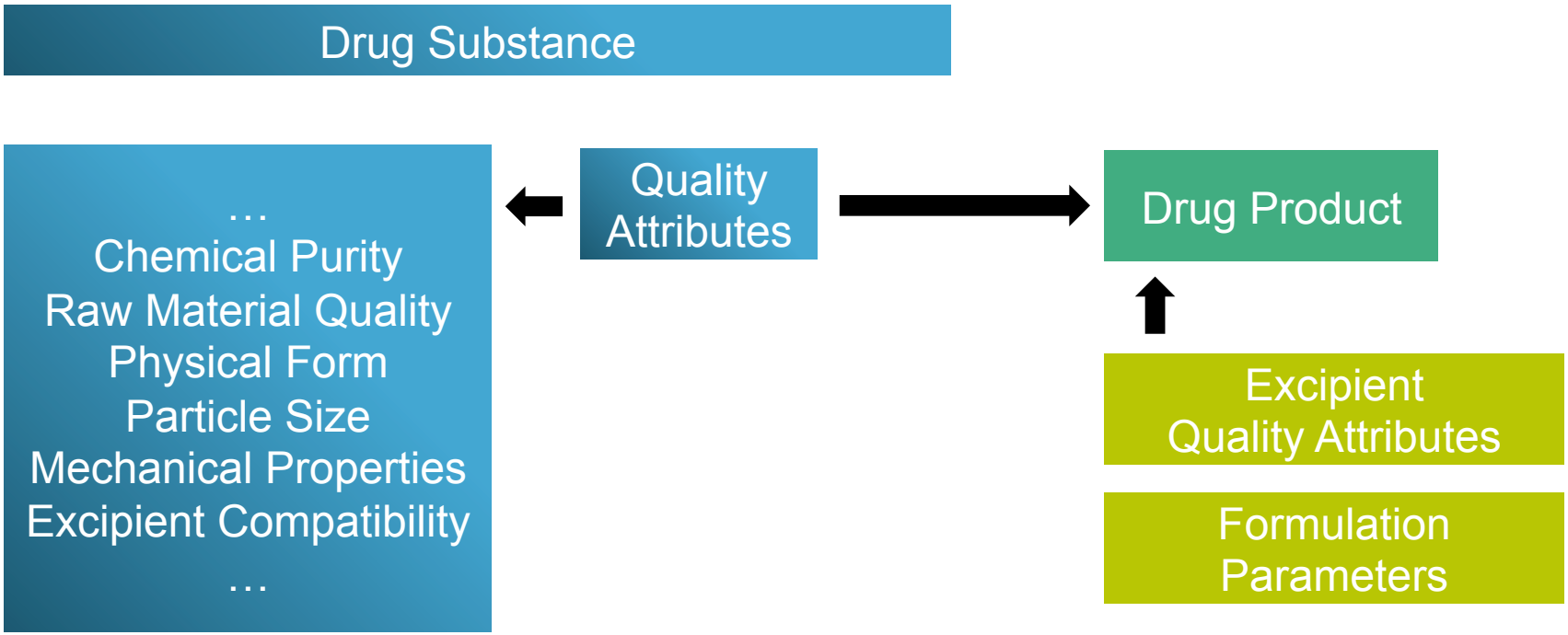
WHAT IS THE SCALE: MOLECULE *VS* ENSEMBLE OF MOLECULES

- Examples for molecular properties
  - e.g., pKa, logD

- Examples for ensemble properties
  - e.g., melting point, crystal form

During this presentation physico-chemical characterization will refer to ensemble properties at mostly **room temperature**

FROM DRUG SUBSTANCE TO DRUG PRODUCT



Not all attributes are necessarily formulation process related

FROM DRUG SUBSTANCE TO DRUG PRODUCT

- Influence of the Drug Substance on the Drug Product processing depends on
  - The type of drug product (tablet, capsule, solution, etc.)
  - The concentration of the API (drug load)

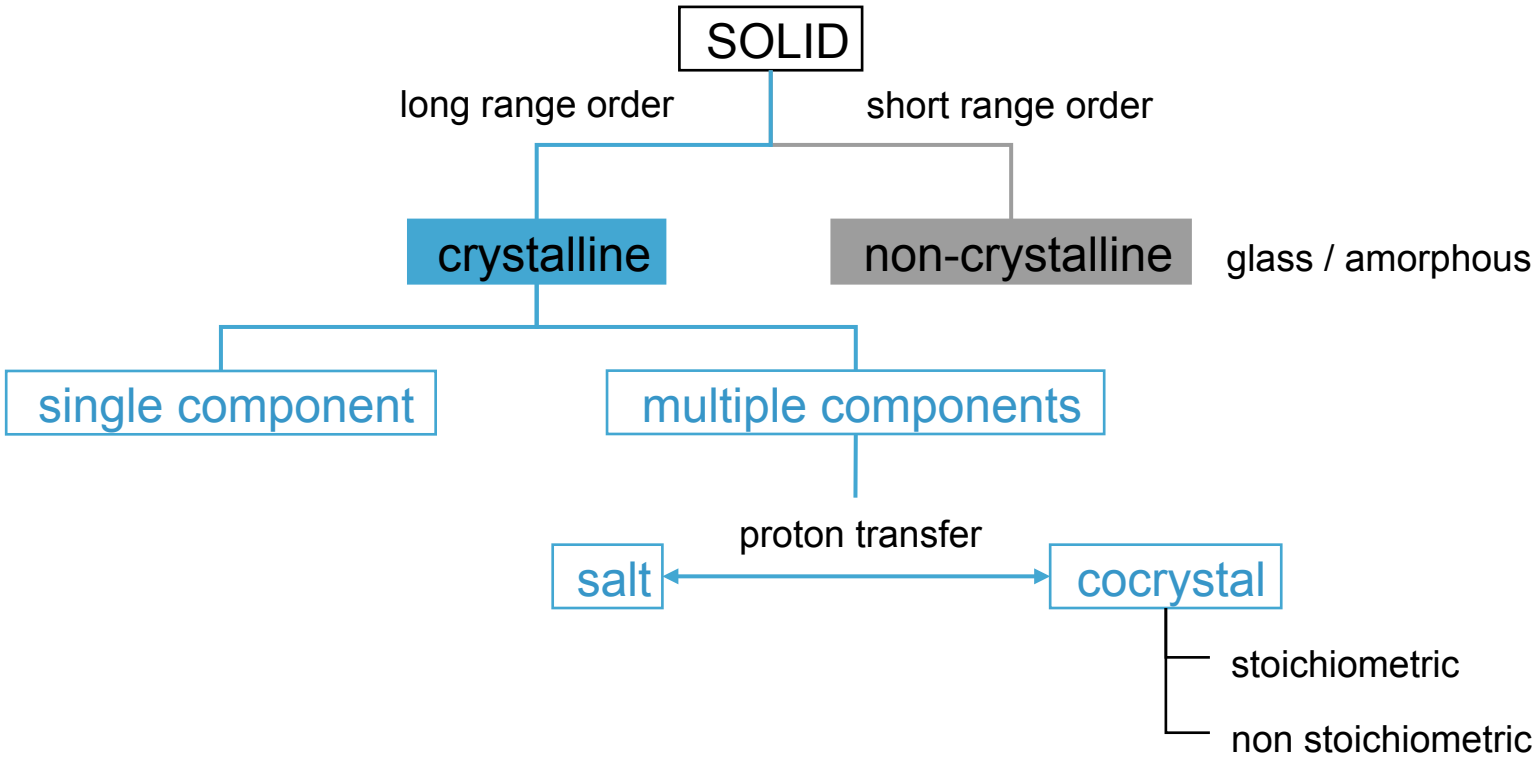
DRUG SUBSTANCE - PHYSICAL STATE

BROWN RESINS ... **OR** **…WHITE POWDERS**

PHYSICAL STATE – HOW TO CLASSIFY SOLIDS

CLASSIFICATION SCHEME OF ORGANIC SOLIDS

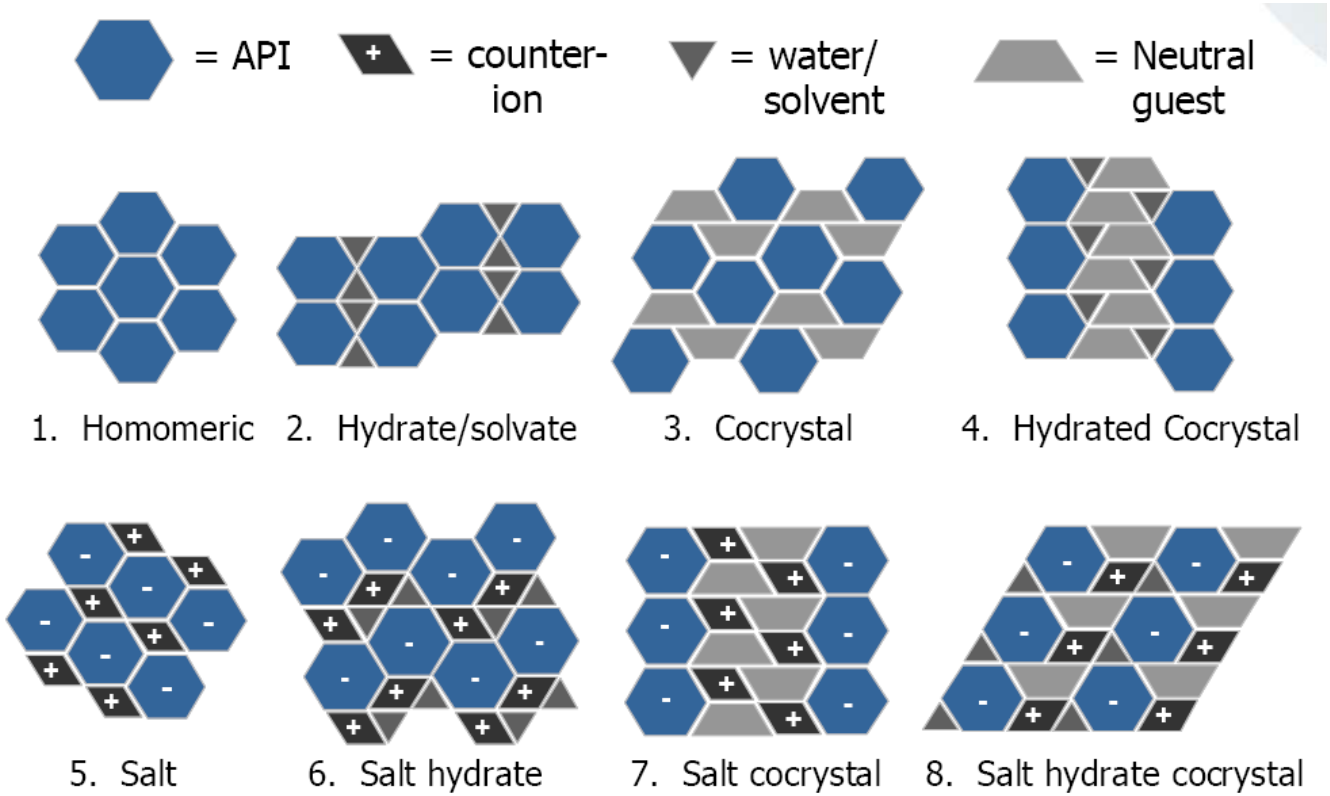
Adapted from: G. P. Stahly, Cryst. Growth Des., 7 (2007) 1007-1026



THE SEARCH FOR THE BEST SOLID FORM

SOLID FORMS: POSSIBILITIES FOR MULTI-COMPONENT CRYSTALS

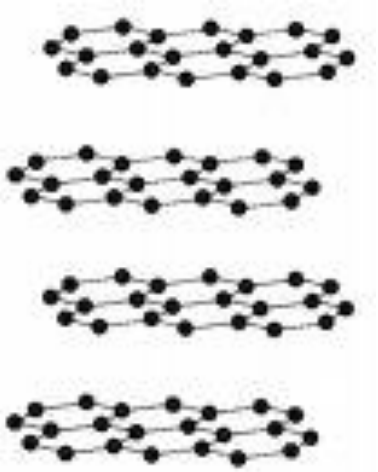
S. Childs, Cocrystallizing pharmaceuticals, presentation at PCL-meeting Bologna 2008



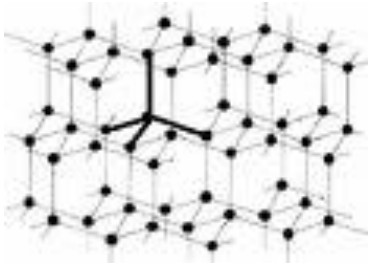
THE SEARCH FOR THE BEST SOLID FORM

WHAT WOULD YOU LIKE TO HAVE ?

Same composition



or



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THE SEARCH FOR THE BEST SOLID FORM

WHAT WOULD YOU LIKE TO HAVE ?

Same composition

graphite

or

diamond

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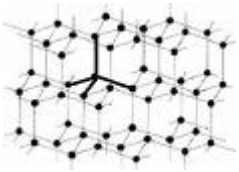
THE SEARCH FOR THE BEST SOLID FORM

POLYMORPHISM

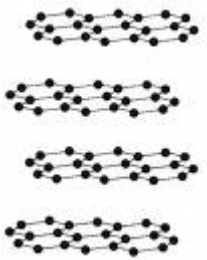
Called allotropism when exhibited by elements.

- Example: carbon

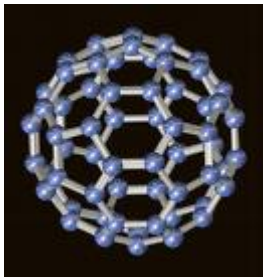
Same composition, different spatial arrangement, ...



diamond



graphite



buckminsterfullerene

... different properties and ... ... value

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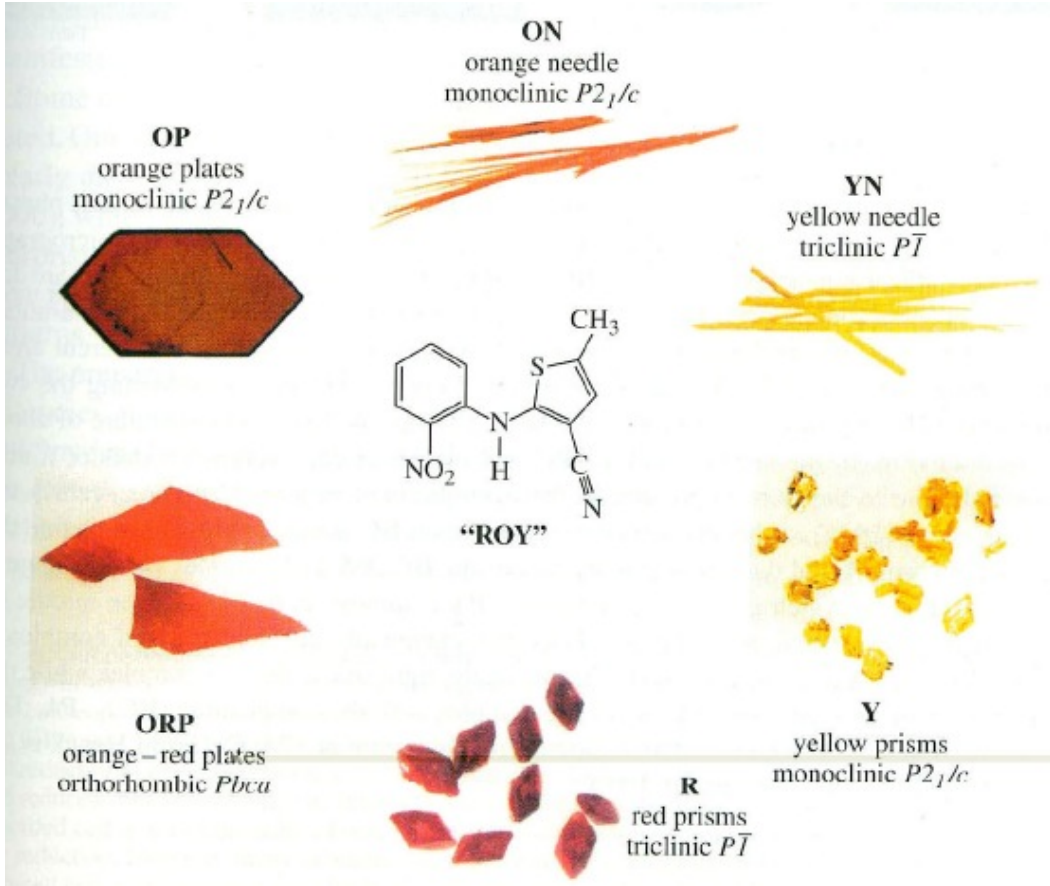
POLYMORPHISM

EXAMPLE FOR SMALL ORGANIC MOLECULE

Yu et al.
J. Am. Chem. Soc. 122, 585-591 (2000)
J. Phys. Chem. A106, 544-550 (2002)

ROY (**R**ed **O**range **Y**ellow)

- Visual differences in
  - color
  - shape
- Phys.chem properties also change
  - melting, stability, hygroscopicity
  - …



WHY BOTHER ?

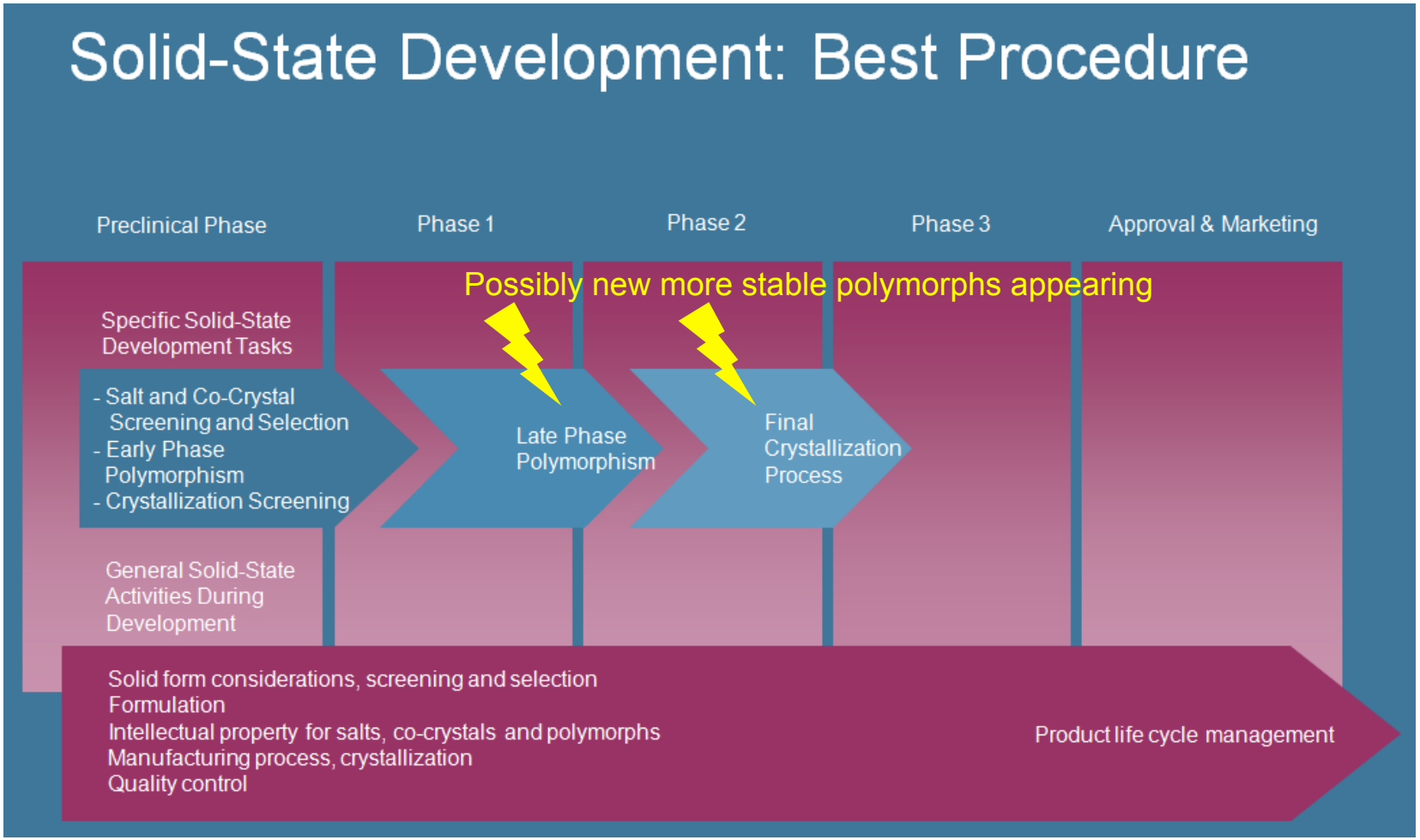
PHYSICO-CHEMICAL PROPERTIES !

- The properties of different solids are different, e.g.:
  - Melting point
  - Chemical stability
  - Moisture sorption
  - Mechanical properties (e.g., plasticity, …)
  - Habit, flow
  - …

- In turn, by screening you can tune and possibly optimize selected properties

DRUG SUBSTANCE

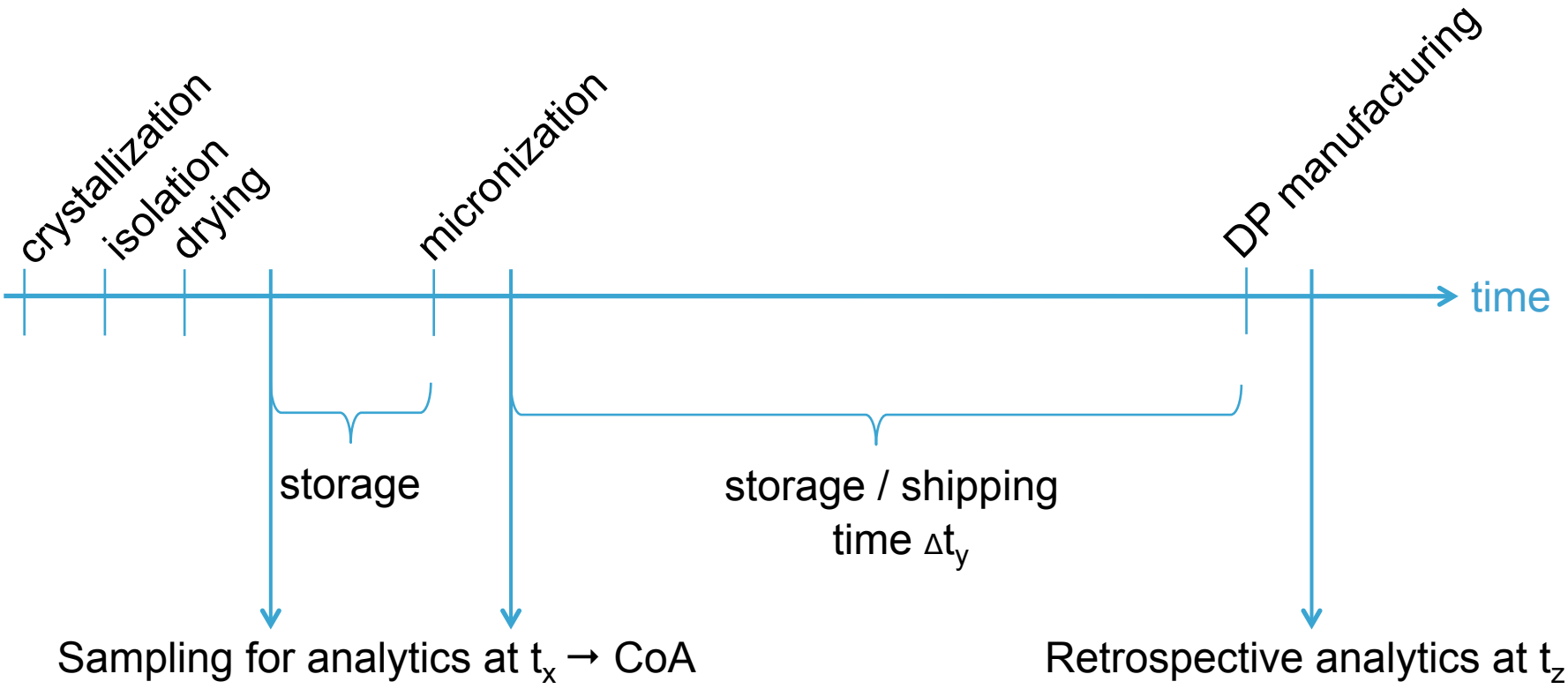
TYPICAL PROCEDURE IN VIEW OF PHARM. DEV. - TIME



Solvias AG

DRUG SUBSTANCE

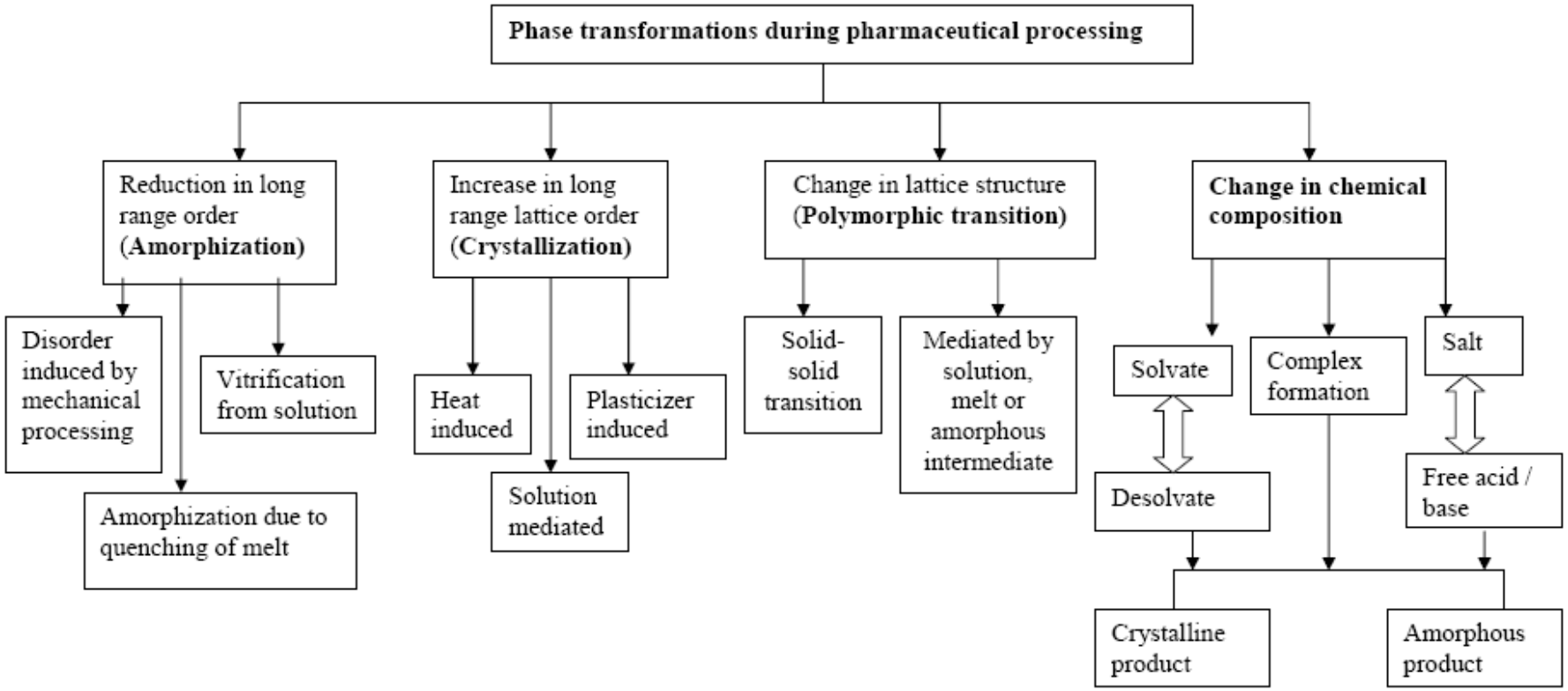
TYPICAL PROCEDURE: TIME AS A VARIABLE



PROCESS INDUCED PHASE TRANSFORMATION

WATCH AND UNDERSTAND YOUR PROCESS !

R. Govindarajan and R. Suryanarayanan 'Processing-induced phase transformations' in: Polymorphism in the Pharmaceutical Industry (R. Hilfiker ed.), 2006, Wiley-VCH



PROCESS INDUCED PHASE TRANSFORMATION

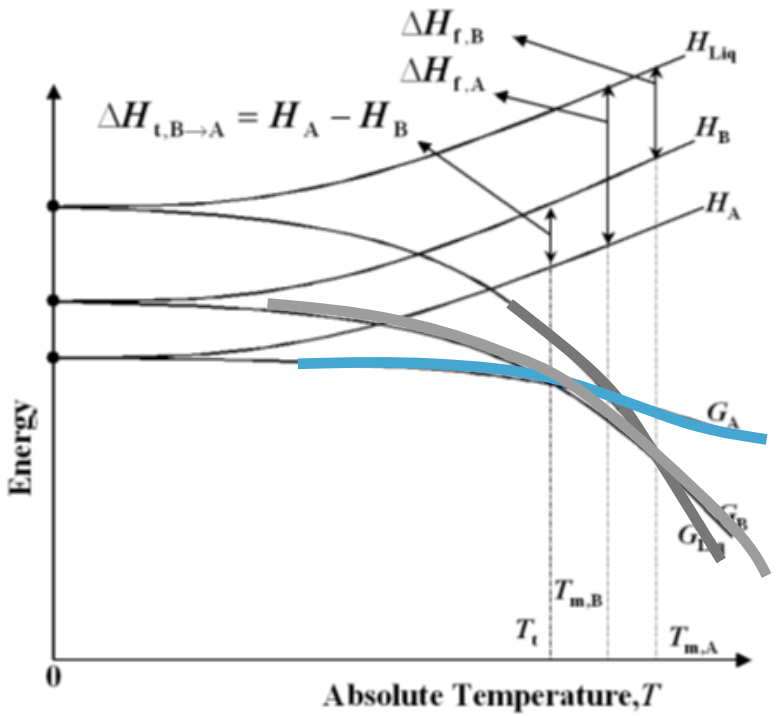
CRITICAL ?

- Is the attribute that you measure at defined conditions relevant of the process conditions?
- Drug substance solid characteristics must be understood !
  - E.g., polymorphism monotropism / enantiotropism
  - Multicomponent systems
    - Salts: disproportion as function of microenvironmental pH

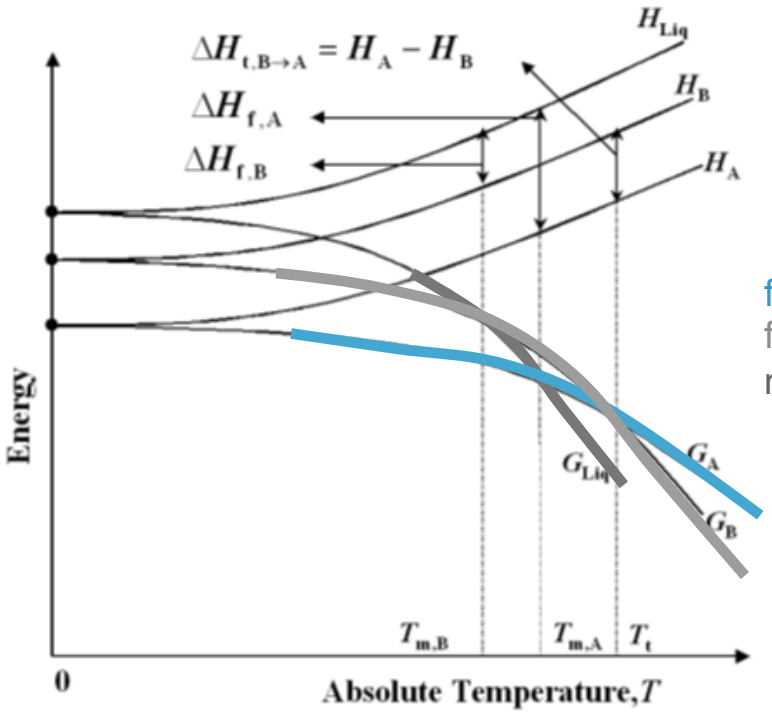
      Merritt et al., 'Implementing QbD in Pharmaceutical Salt Selection: A modeling approach to understanding disproportionation', Pharm Res 30, 2013, 203-217
    - Hydrates
      - Behaviour as function of r.h at constant temperature
      - Behaviour as function of temperature
      - Behaviour in function of excipients

POLYMORPHISM: ENANTIOTROPISM & MONOTROPISM

KNOW YOUR SYSTEM



Enantiotropic system

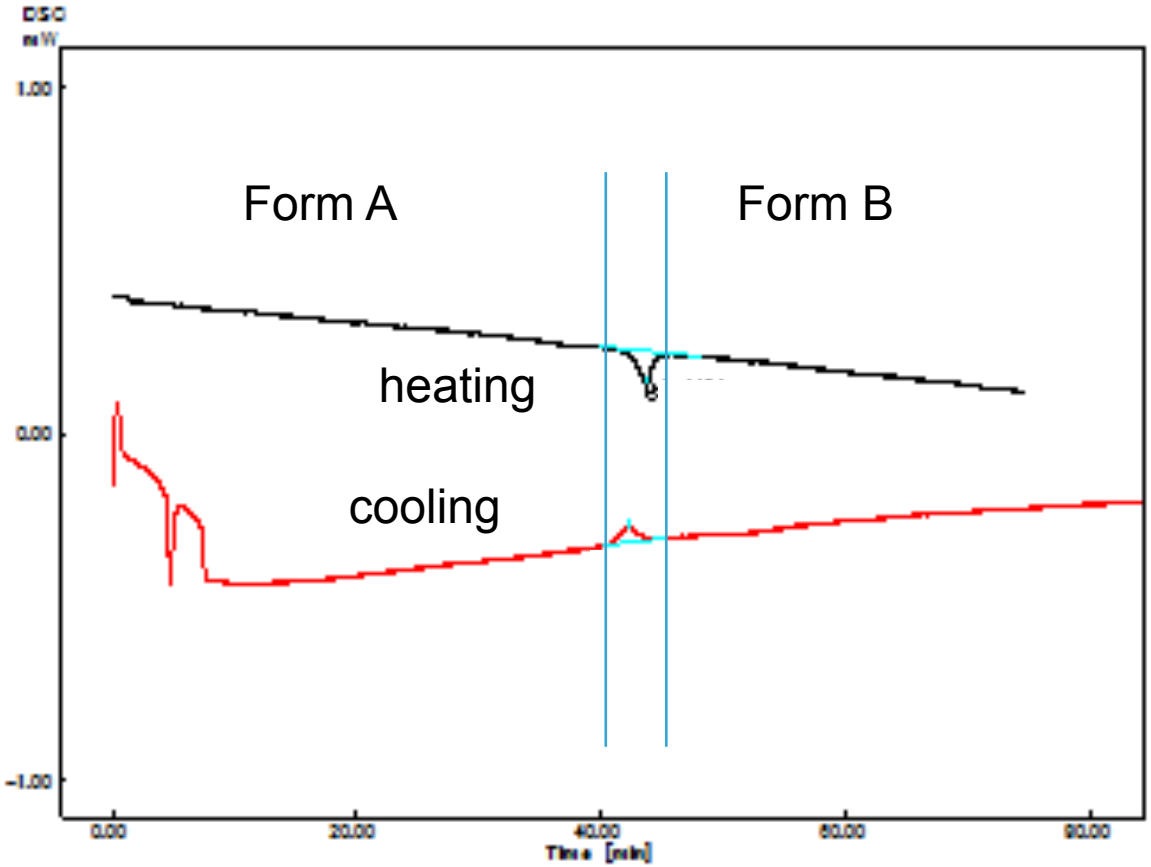


Monotropic system

form A
form B
melt

POLYMORPHISM: ENANTIOTROPISM

EXAMPLE: RAPID REVERSIBLE SOLID-SOLID TRANSFORMATION



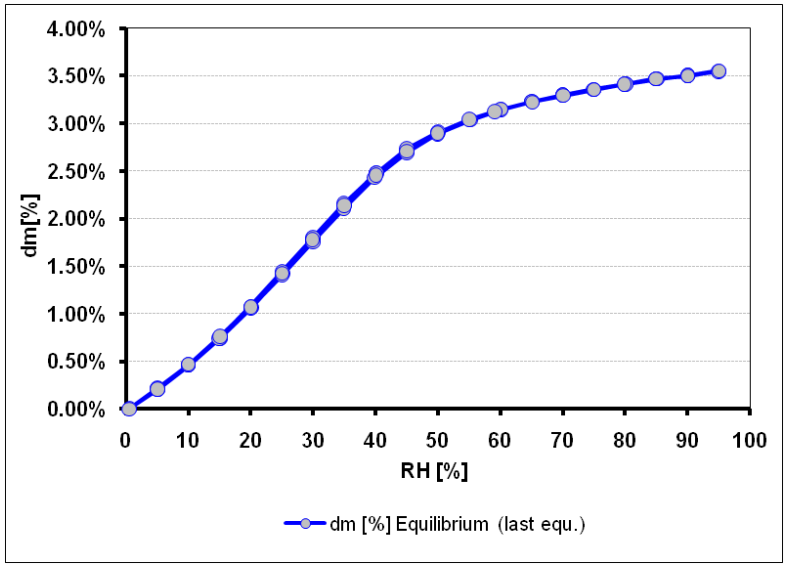
PROCESS INDUCED PHASE TRANSFORMATION

DRUG SUBSTANCE CHARACTERISTICS: HYDRATE

- Widely described in literature

  S.M. Reutzel-Edens & A.W. Newman, 'Physical Characterization of Hygroscopicity in Pharmaceutical Solids' in: Polymorphism in the Pharmaceutical Industry (R. Hilfiker ed.), 2006, Wiley-VCH

- Example of DS: Probing by gravimetric vapor soprtion (GVS)

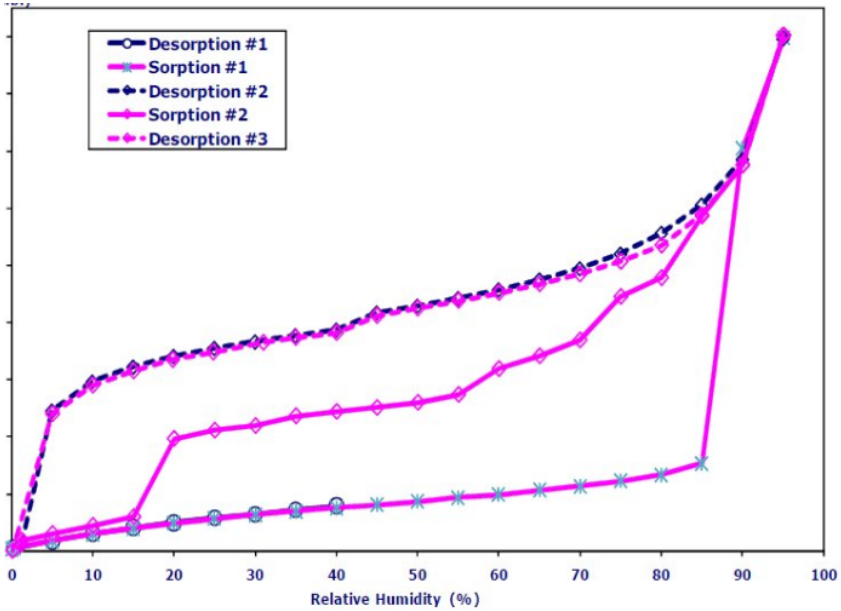


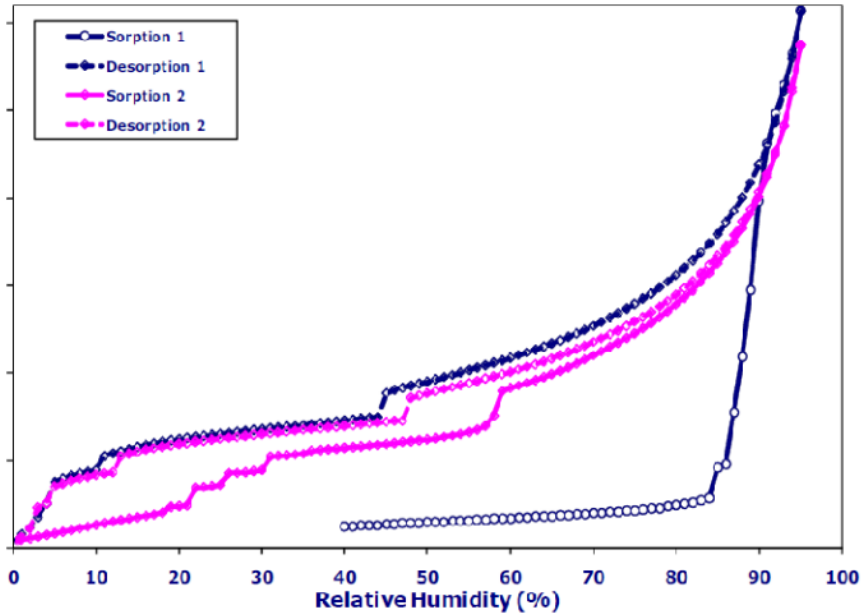
PROCESS INDUCED PHASE TRANSFORMATION

DRUG SUBSTANCE CHARACTERISTICS: HYDRATE

- Constant temperature

Time and step size matter !





Standard procedure: 5% step size

Refined procedure: 1% step size

PROCESS INDUCED PHASE TRANSFORMATION

DRUG SUBSTANCE CHARACTERISTICS: HYDRATE

- Peritecticum

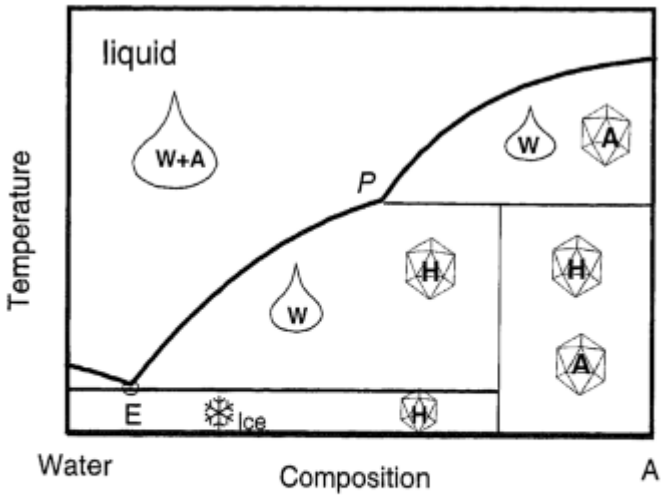
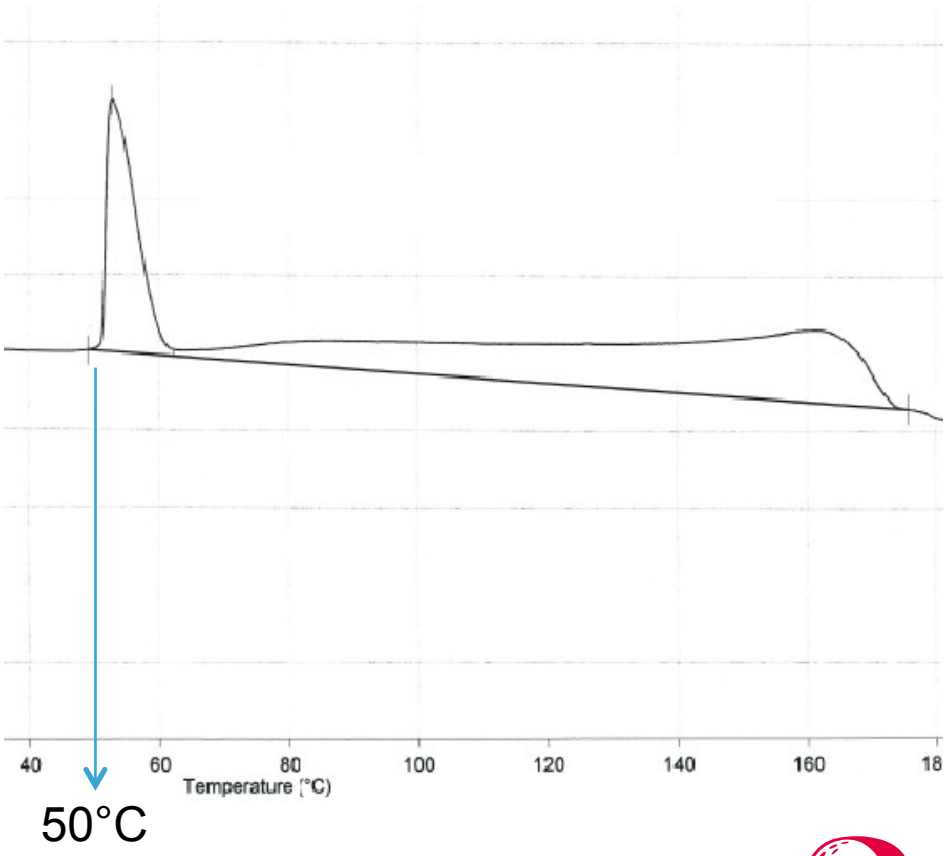


Fig. 5. A composition versus temperature (x–T) phase diagram of ater and compound (A) showing an incongruently melting 'rate (H) form. The hydrate form is stable between the eutectic nd the peritectic (P) points below the liquidus curve.

K. Morris, Adv. Drug. Del. Rev., 48, 91-114 (2001)



DRUG SUBSTANCE CHARACTERIZATION

TYPICAL PROCEDURE

- Certificate of analysis (CoA)
  - primary focus on purity and aspect criteria
  - Some physico-chemical information (for information and case dependent), e.g.:
    - Melting
    - XRPD
    - Particle size distribution
- Methods evolve with time of development
  - Generic vs specific methods
  - Validation status

DRUG SUBSTANCE CHARACTERIZATION

DILEMMA

- In early phase critical quality attributes are not yet known
- It makes sense to broadly characterize early drug substance batches beyond methods that are then put on the CoA
  - Implement a batch tracking strategy until the DS → DP link is understood (or thought to be understood)
    - How to sample? When to sample?
    - Aging?
    - What techniques, what method, what granularity?
- Collect data

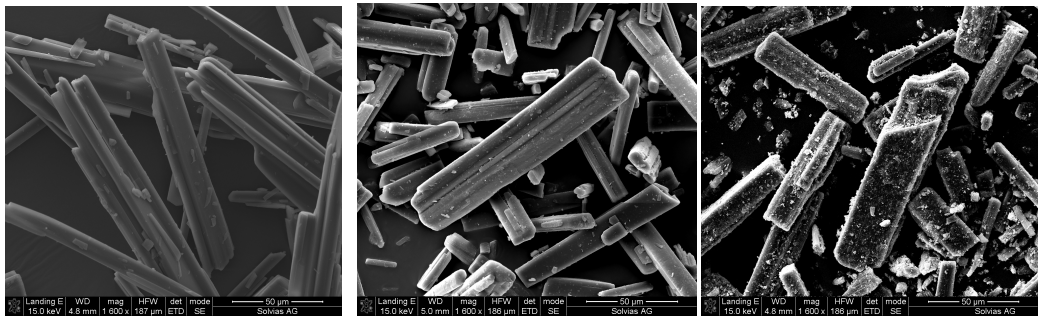
DRUG SUBSTANCE CHARACTERIZATION

EXAMPLE (1-1)

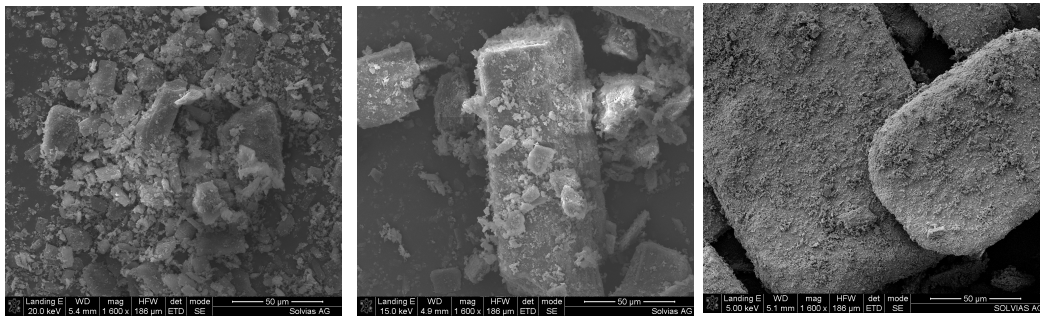
- Upon scale-up of DS poor flow of mixture for secondary processing was observed.
  - No difference in purity, XRPD, DSC melting, … of drug substance
  - Difference in appearance by scanning electron microscopy

DRUG SUBSTANCE CHARACTERIZATION

EXAMPLE (1-2): SEM – QUALITATIVE DESCRIPTION



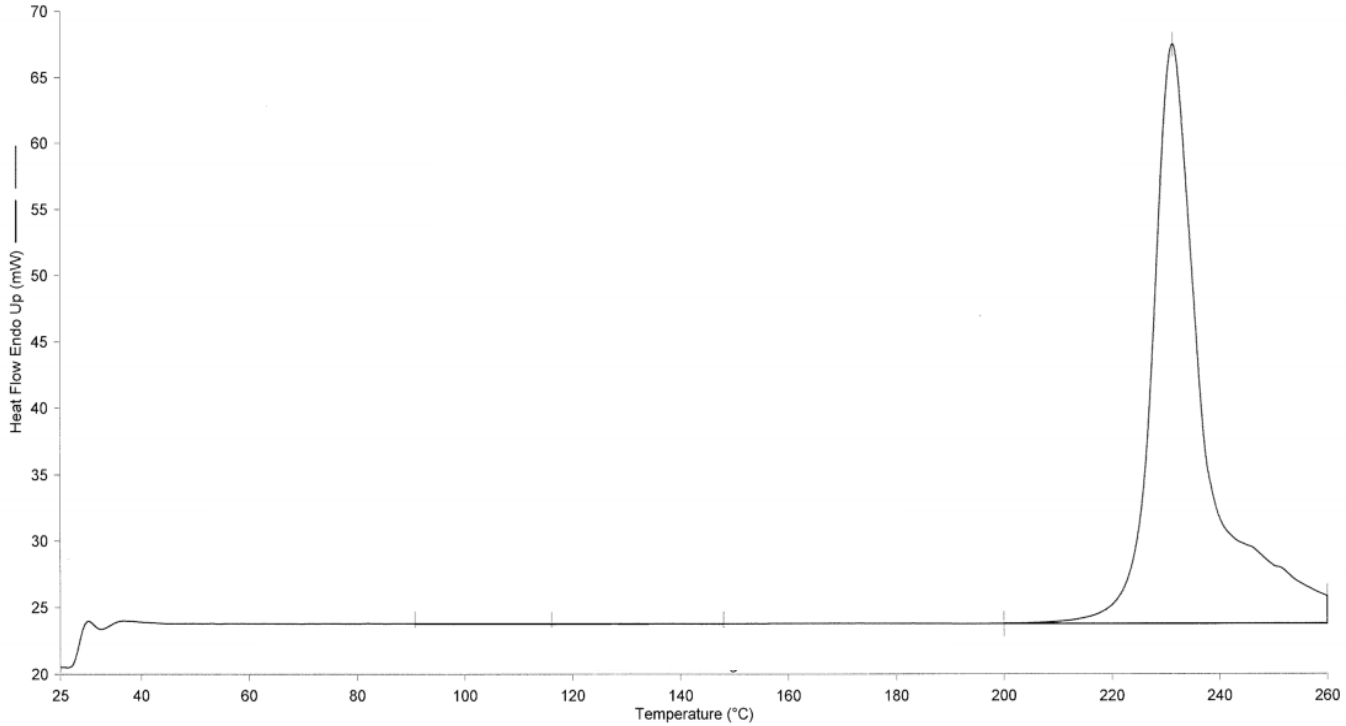
Various batches smaller scale
Used for DP process development



Various batches large scale
Not processable – poor flow

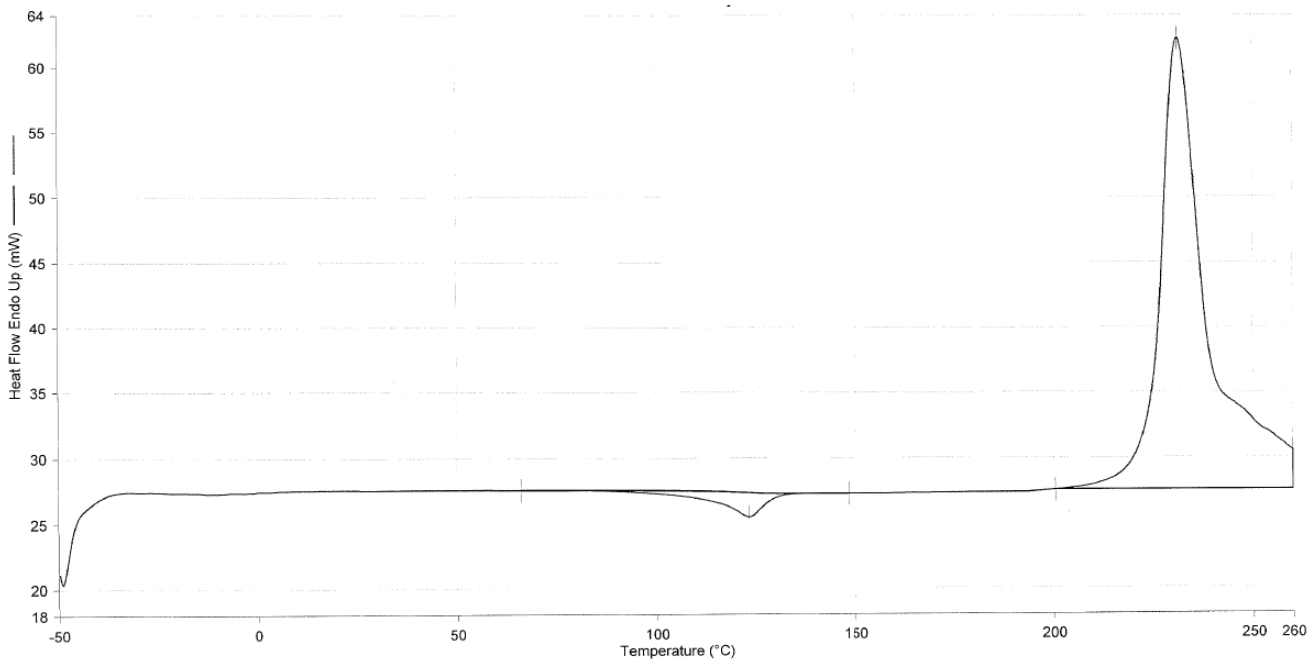
DRUG SUBSTANCE CHARACTERIZATION

EXAMPLE (1-3): DSC OF REAL SAMPLE



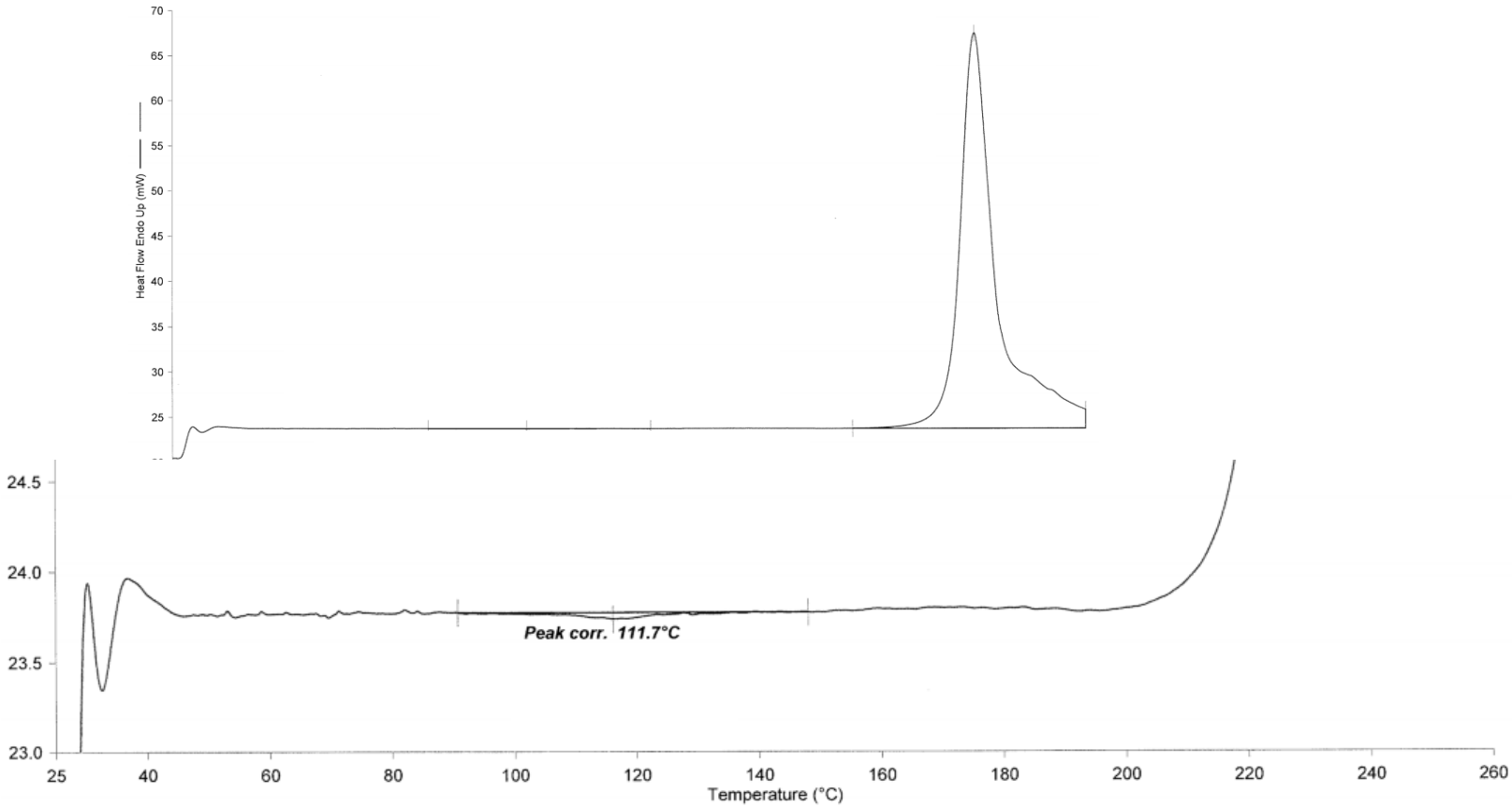
DRUG SUBSTANCE CHARACTERIZATION

EXAMPLE (1-4): DSC OF SAMPLE GROUND IN MORTAR



DRUG SUBSTANCE CHARACTERIZATION

EXAMPLE (1-5): DSC OF REAL SAMPLE - REVISITED



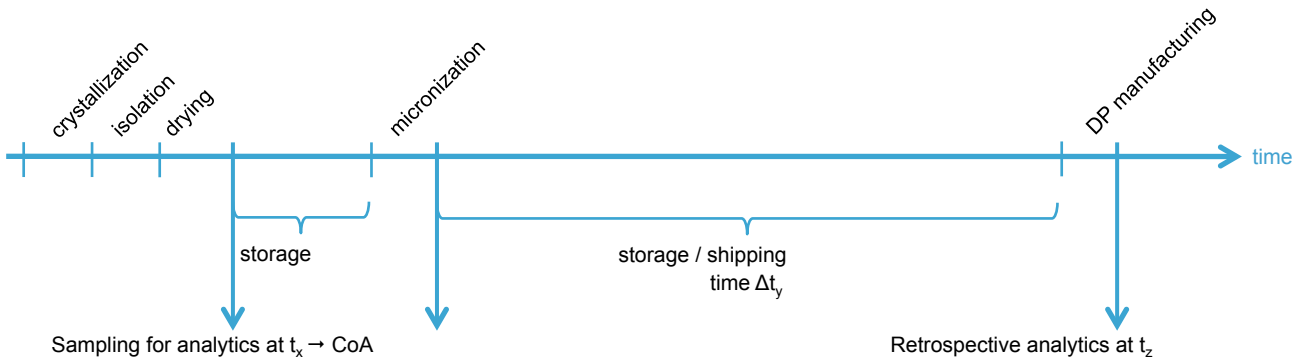
DRUG SUBSTANCE CHARACTERIZATION

EXAMPLE (1-6): DSC – AGING OF A SAMPLE

- DSC results – tracing of exothermic event

t0m	**-1.5 J/g**	→	**poor flow**
t3m	**-0.5 J/g**	→	**flow ok**
t8m	**< LOD**		

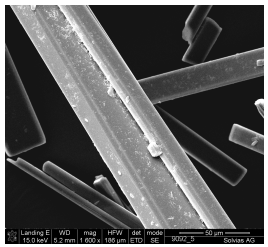
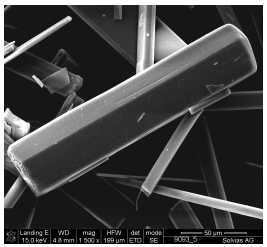
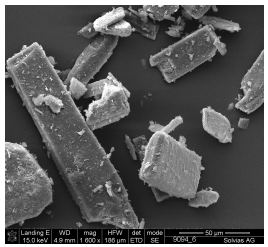
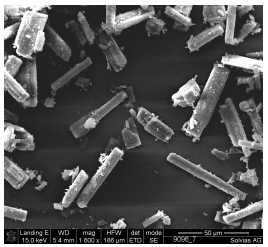
Remember DS as function of time !

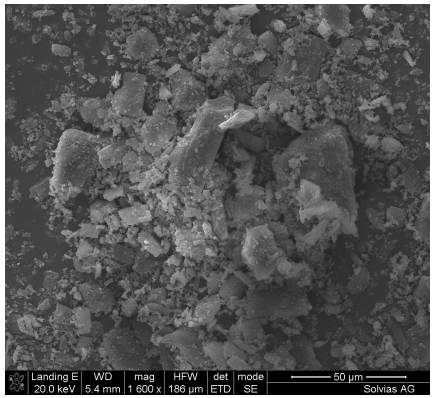


DRUG SUBSTANCE CHARACTERIZATION

EXAMPLE (1-7): ROOT CAUSE ANALYSIS:

- Check critical unit operations – crystallization, isolation, drying, etc.

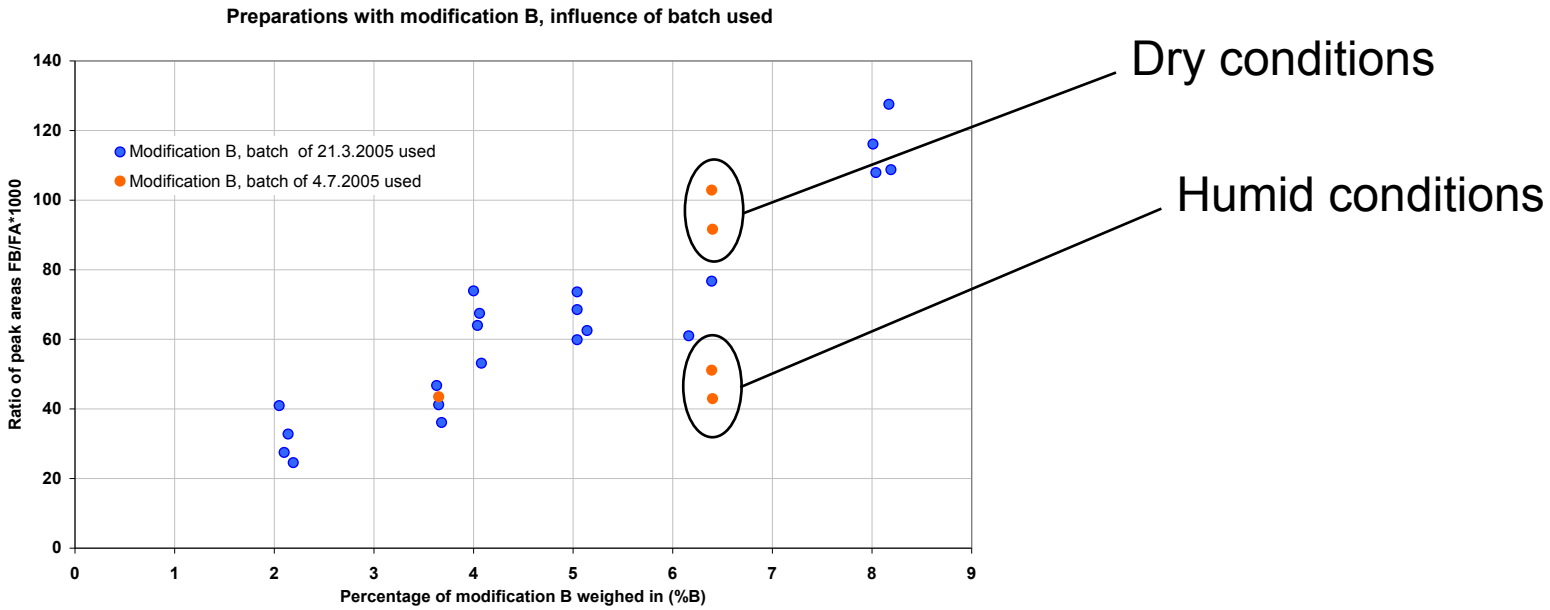


Delumping before filling drums was critical unit operation !

DRUG SUBSTANCE CHARACTERIZATION

METHOD DEVELOPMENT: POSSIBLE PITFALLS

- Polymorphic purity in DS: Case study by XRPD



➔ Form B to form A conversion under moist conditions is accelerated

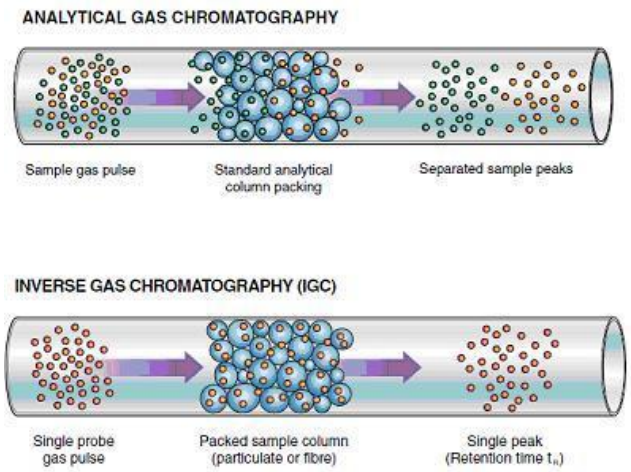
➔ Consider kinetic stability upon all steps (mixture preparation, etc.)

(courtesy Solvias AG)

DRUG SUBSTANCE CHARACTERIZATION

SOPHISTICATED TECHNIQUES: IGC

- iGC: Inverse Gas Chromatography
  - Drug substance is packed to a column
  - Single probe gas is used for probing the surface
  - Probe gas is changed
- Two operation modes
  - At infinite dilution
  - At finite concentration
- Literature



Ho et al., 'Role of Surface Chemistry and Energetics in High Shear Wet Granulation'
Ind. Eng. Chem. Res. 50, 2011, 9642-9649

DRUG SUBSTANCE CHARACTERIZATION

SOPHISTICATED TECHNIQUES: IGC-ID (INFINITE DILUTION)

- During the travel through the column, the injected probes are interacting with the sample surface leading to numerous cycles of molecules adsorption-desorption.
- Several probes, having different properties, are injected separately at very low concentration (no interaction between the injected probes).
- The multiplicity of the collected ΔG_a allows the determination of the surface energy (γ_s^d), the surface nanoroughness and of the surface acid-base character.

DRUG SUBSTANCE CHARACTERIZATION

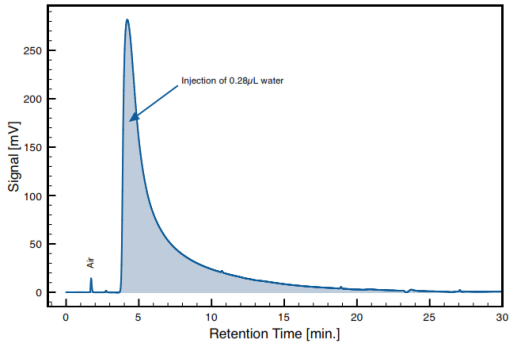
SOPHISTICATED TECHNIQUES: IGC-FC (FINITE CONCENTRATION)

- IGC at Finite Concentration (IGC-FC) measurements involve important amounts of probe, leading to a large surface coverage, close or above to the monolayer coverage.
- IGC-FC offers the convenient way to record the desorption isotherm of a multitude of solutes in a large range of measurement temperatures.
- The interpretation of the isotherms leads to information such as specific surface area and the evaluation of the surface energetic heterogeneity (Adsorption energy distribution function).

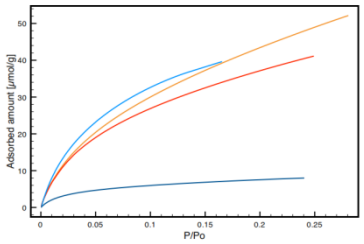
DRUG SUBSTANCE CHARACTERIZATION

SOPHISTICATED TECHNIQUES: IGC-FC (FINITE CONCENTRATION)

Chromatogram of a batch, e.g. with **water**

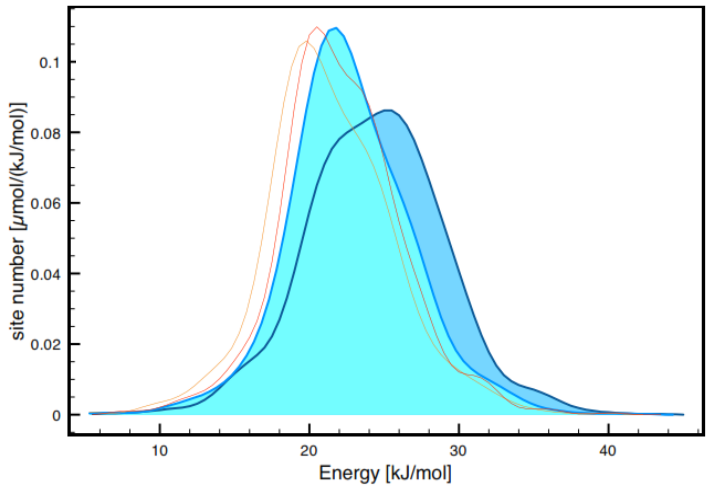


→ Desorption isotherm → BET algorithm on isotherm



Q_0 [µmol/g]	S_{BET} [m²/g]	C_{BET}
6.3 ± 0.6	0.45 ± 0.04	44.3 ± 3.7
41.0 ± 2.4	2.9 ± 0.2	25.4 ± 4.2
43.6 ± 1.6	3.1 ± 0.1	13.7 ± 0.8
36.0 ± 1.1	2.6 ± 0.1	19.4 ± 1.1

↓ AEDF algorithm on isotherm



- Differences made visible for different DS batches
- Significance ?
- No correlation with wet granulation performance observed

DRUG SUBSTANCE CHARACTERIZATION

CHALLENGES (I)

- What is to be tracked?
- What technique?
- What method?
- What sophistication?
- Significance?

DRUG SUBSTANCE CHARACTERIZATION

CHALLENGES (II) – PARTIAL ANSWER TO QUESTION

- Understand your drug substance solid state behavior, as function of:
  - Temperature
  - Relative humidity
- Know the unit operations in drug substance manufacturing, what changes if site/ scale is changed
- Understand the secondary processing, drug product manufacturing
- ➡ Each of this point is a challenge at early stages of projects and might change over time
- ➡ The more data is available and the more the rational of DP development is known the better potential problems can be anticipated

DRUG SUBSTANCE CHARACTERIZATION

CHALLENGES (III) – GENERAL

- Documentation and description is key
  - ‘It does not work’ or ‘it is different’ is not sufficient
- If various labs (and organizations) are involved, be sure about common understandings and methods (e.g., particularly true for laser diffraction)
- Particular attention to sampling and sample preparation!
- External conditions (what is ambient? r.h. / T)
- Time – development time axis as well as aging

THANK YOU.