INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION

国际创新药学院

Influence of Physical Form on Tablet Behaviour

Course BSc (Pharm) or BSc (ATT)

Year 2024-2025 II

Module Medicines: Pharmaceutics 2 (MP2)

Lecturer Dr. Shi Du

Learning Outcomes

1. Revise the essential concepts of solid state properties, including crystals, amorphous solids, polymorphism and solvates/hydrates

2. Describe the commonly used methods to analyse polymorphic crystals: differential scanning calorimetry and powder X-ray diffraction

3. List the critical processes in tabletting where solid state properties of a drug can be altered

4. Review case studies that emphasise the influence of physical form on tablet behaviour

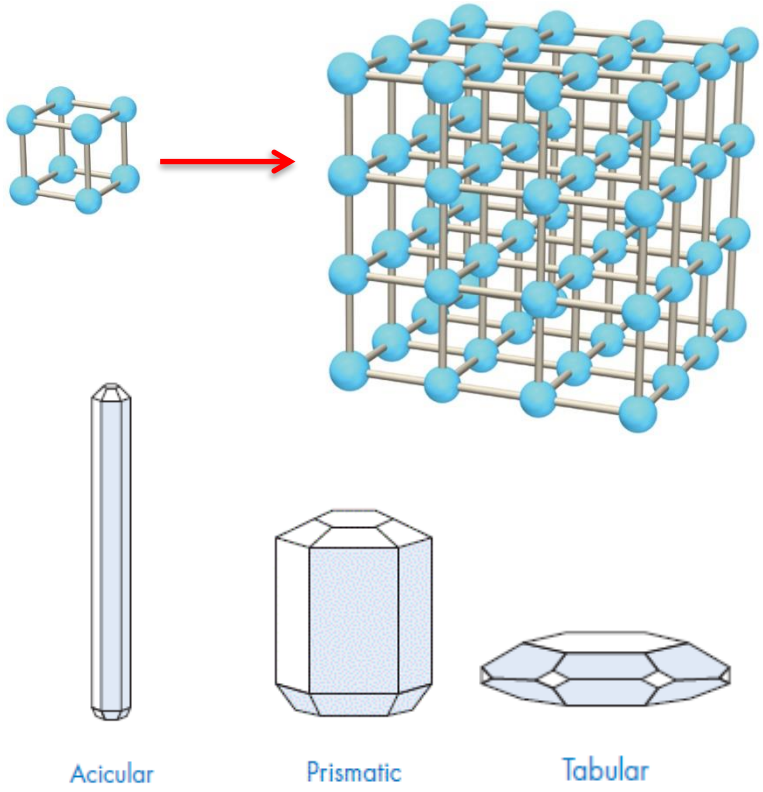
5. Outline the process of screening drug salts to identify lead candidates for tabletting

Background Theory:
Physical Behaviour of Drug Solids I & II

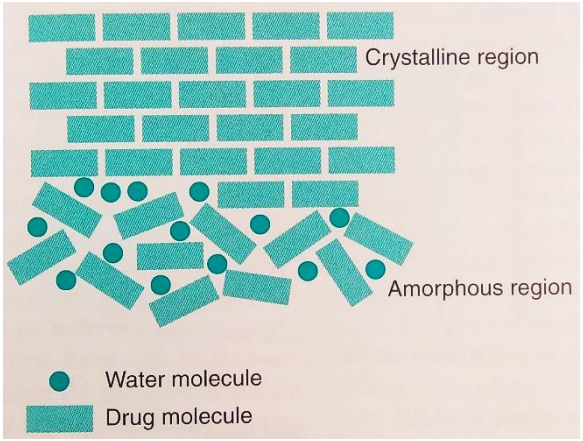
RCSI

Revision: Solid State Properties

- Crystalline solid
  - Possess a regular repetitive internal arrangement of atoms, molecules or ions in a structure called a crystal lattice
  - Crystal lattice-> Is an orderly three dimensional arrangement of molecules (unit cells) that permits optimal attractive interactions between adjacent molecules within a solid
  - Unit cell-> A unit cell is the simplest repeat unit in a crystal
  - Crystal habit-> a term used to describe the shape of the drug crystal that can be appreciated by visual inspection



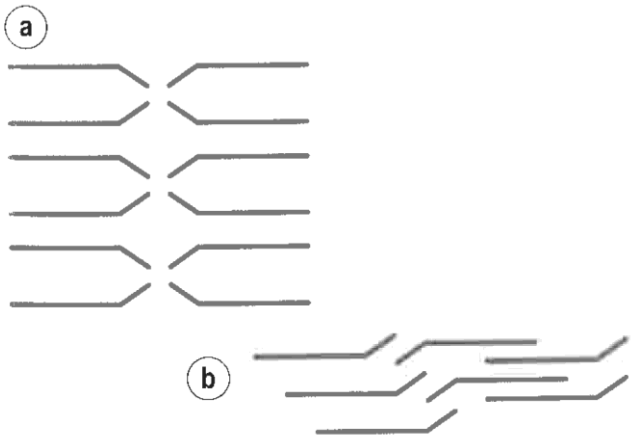
- Amorphous solid
  - Consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice
  - In simple terms, amorphous materials are a pile of molecules
  - Amorphous materials have improved solubility over crystalline materials, but are more unstable



RCSI

Revision: Polymorphism

- Crystal polymorphism
  - The phenomenon whereby molecules arrange themselves in more than one pattern within a crystal
  - Polymorphic behaviour Is a major concern of the pharmaceutical industry because it has considerable formulation, therapeutic, legal, and commercial implications



Box 1 | **Polymorph property differences**

Packing properties
- Molar volume and density
- Refractive index, optical properties
- Conductivity, electrical and thermal
- Hygroscopicity

Thermodynamic properties
- Melting and sublimation temperatures
- Internal energy
- Enthalpy
- Heat capacity
- Entropy
- Free energy and chemical potential
- Thermodynamic activity
- Vapour pressure
- Solubility

Spectroscopic properties
- Electronic transitions, ultraviolet-visible spectra
- Vibrational transitions, infrared and Raman spectra
- Rotational transitions
- Nuclear magnetic resonance chemical shifts

Kinetic properties
- Dissolution rate
- Rates of solid state reactions
- Stability

Surface properties
- Surface free energy
- Interfacial tensions
- Habit

Mechanical properties
- Hardness
- Tensile strength
- Compactibility, tabletability
- Handling, flow and blending

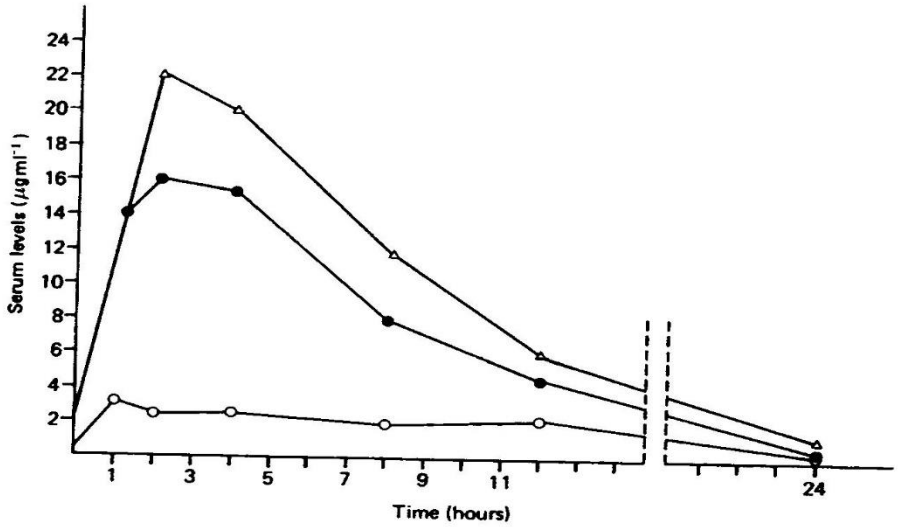


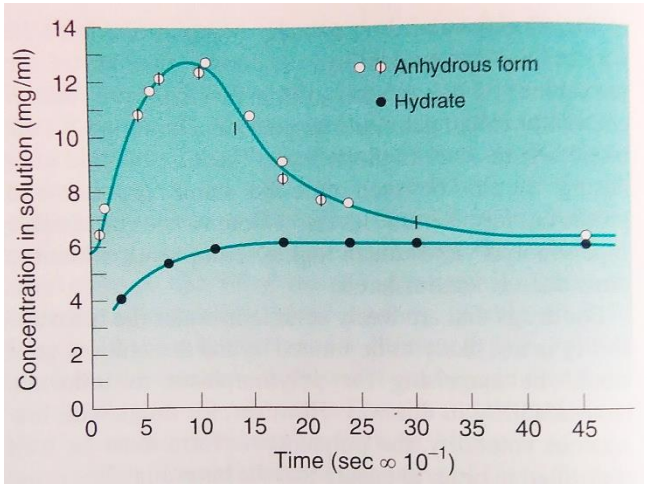
Figure 1.10 Comparison of serum levels obtained with suspensions of chloramphenicol palmitate after oral administration of a dose equivalent to 1.5 g of chloramphenicol: Δ, 100% form B; ● 50% form A and 50% form B; ○, 100% form A

RCSI

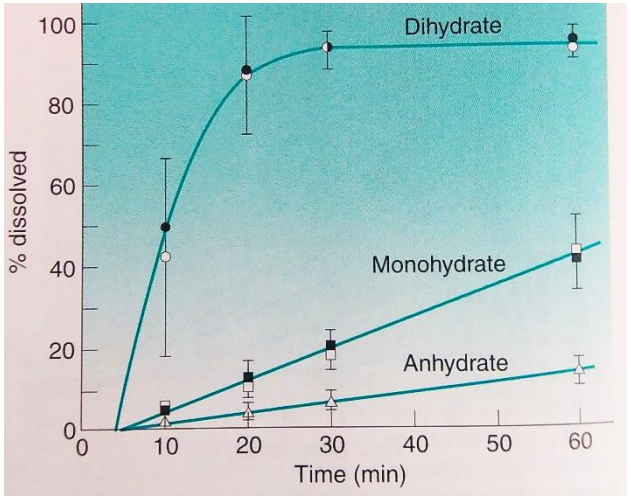
Revision: Solvates/Hydrates

- Solvent molecules can potentially become trapped in a crystal lattice structure
  - Anhydrous salt-> Crystal devoid of water in its solid structure
  - Solvate-> Crystal with a solvent incorporated into its structure
  - Hydrate-> A solvate where the trapped solvent is water
  - Usually trapped in an exact molar ratio-> One molecule of solvent for one molecule of drug etc.
    - Monohydrate?
    - Pentahydrate?
    - Heptahydrate?

- Hydrates often have very different properties to the anhydrous form
  - Usually due to different dissolution rates



Theophylline



Erythromycin

RCSI

Analytical Techniques in Solid State Characterisation

- Broadly, two categories of techniques exist: (a) Bulk techniques and (b) Molecular techniques:

1. Bulk techniques
   - Provide information on the state of the material
   1. Microscopy
   2. Differential scanning calorimetry (DSC)
   3. Thermogravimetric analysis (TGA)

   Thermal analysis

2. Molecular techniques
   - Provide information on the molecular interactions taking place
   1. IR spectroscopy
   2. Nuclear magnetic resonance (NMR)
   3. Powder X-ray diffraction (PXRD)

- Note: Bulk techniques can still provide information on the molecular level and vice-versa

RCSI

Differential Scanning Calorimetry (DSC)

- Calorimetry
  - Definition-> Study of heat transfer during physical or chemical processes
  - The calorimeter measures physicochemical changes of a material as a function of temperature change

- DSC
  - Concept-> A sample and a reference are heated simultaneously at a constant rate
  - The instrument monitors the amount of energy needed to heat both the sample and reference
  - Thermal events recorded as endothermic or exothermic
  - Thermal events include melting, re-crystallisation, glass transitions
  - DSC and polymorphs-> Different polymorphs exhibit different thermal events

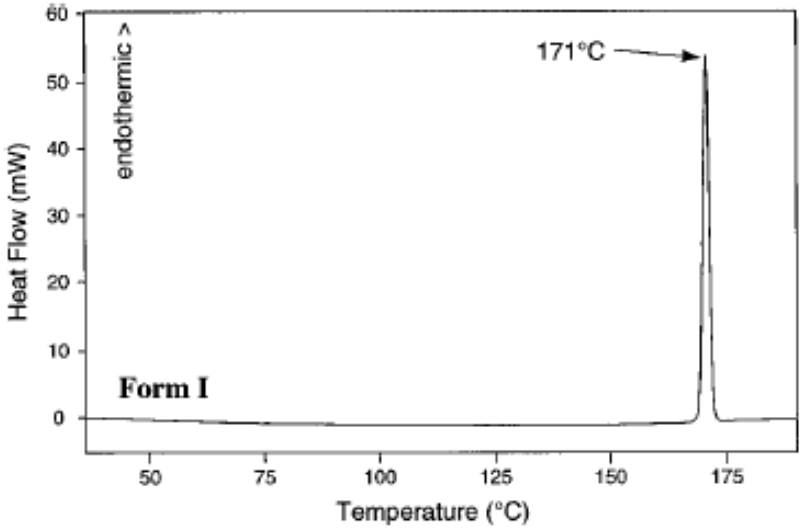


Figure 5—DSC thermogram for monoclinic paracetamol (form I).

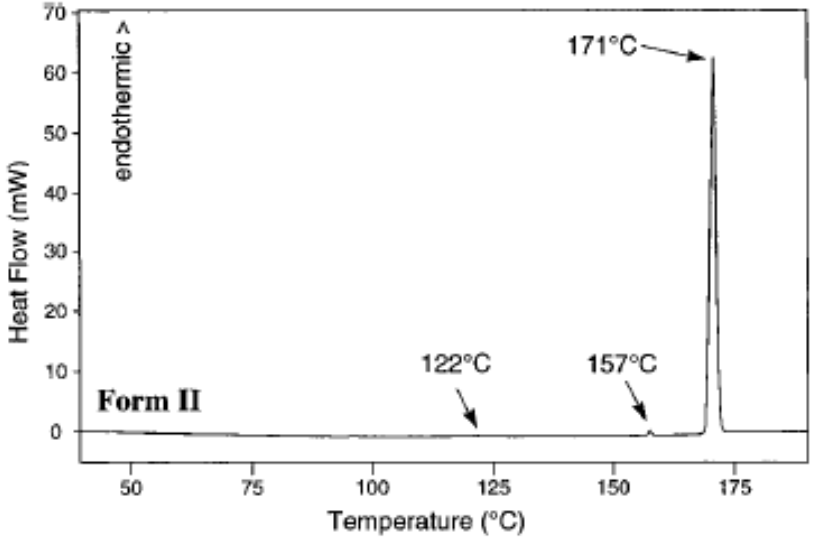
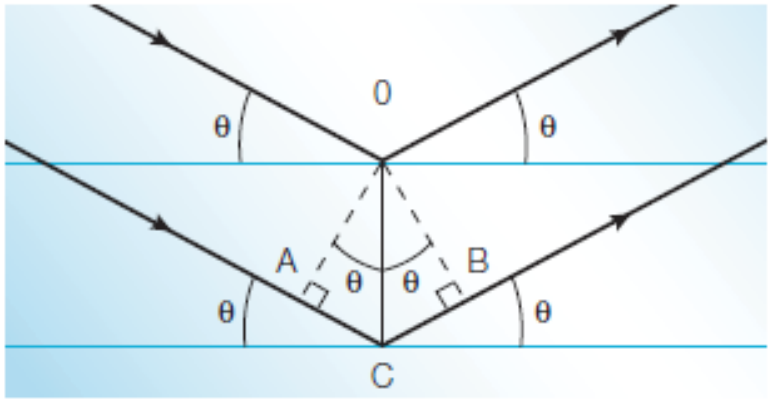


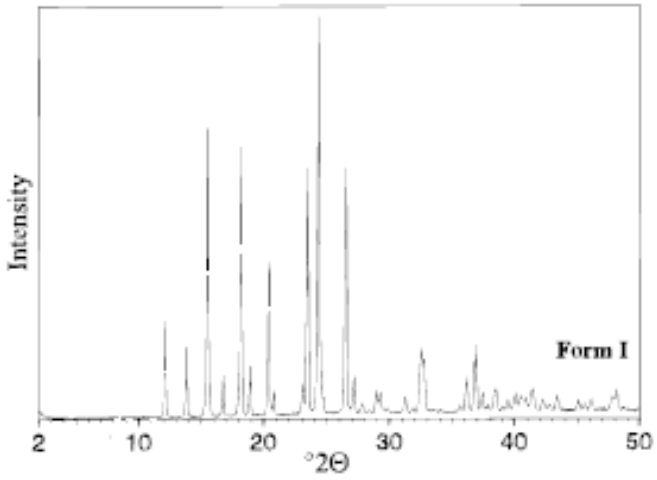
Figure 6—DSC thermogram for orthorhombic paracetamol (form II).

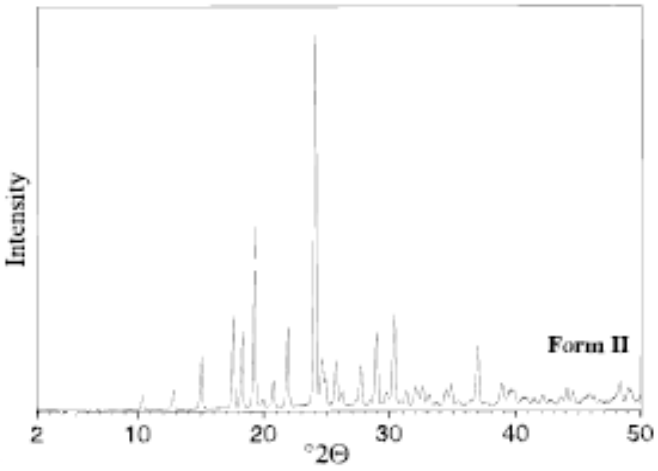
RCSI

Powder X-Ray Diffraction (PXRD)



$$n\lambda = 2dSin\theta$$



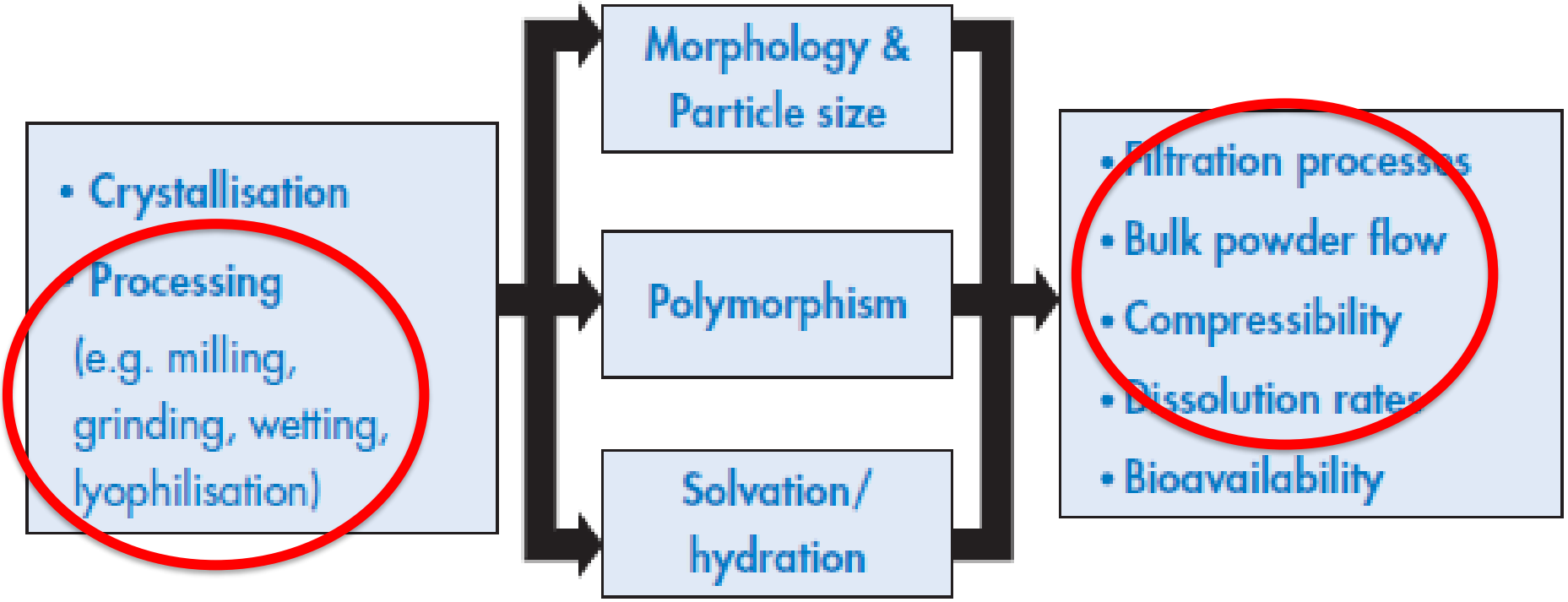


- X-Ray Diffraction
  - X-Rays-> Electromagnetic radiation of a characteristic wavelength
  - Diffraction-> The process by which a beam of light or other system of waves is spread out as a result of passing through a narrow aperture
  - This aperture is typically in the order of length similar to the wavelength of the electromagnetic beam
  - The wavelength of X-rays is in the order of distance between molecules in a crystal structure
  - Bragg's Law

- PXRD- "Gold standard" for polymorph identification
  - Very sensitive to unit cell differences
  - Different peaks a form of "fingerprint" for polymorph
  - Amorphous forms lack sharp peaks- Why??

RCSI

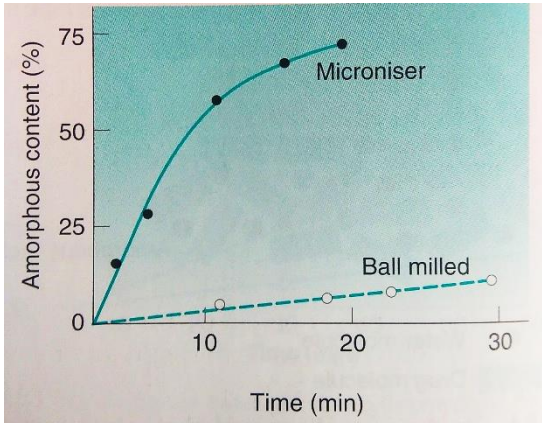
The Physical Form and Tablet Behaviour: Where do these properties fit in?

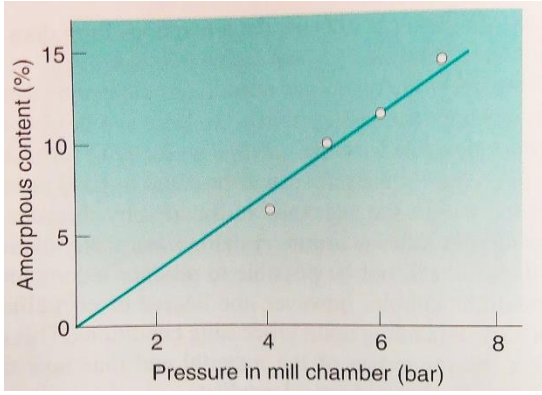


RCSI

Processes in Tablet Manufacture where Solid State Properties can be altered

- General considerations
  - Processes involved in tabletting that input a large amount of energy can disrupt crystal structure and as a result, increase the formation of amorphous forms or formation of polymorphs
  - Because amorphous solids form when the solidification process is too rapid for molecules to align in a regular (crystalline) order, processes that involve rapid heat transfer can increase amorphous solid formation





- Examples of processes
  - Particle size reduction-> Milling
  - Drying-> Spray drying, freeze drying
  - Granulation-> Wetting, grinding

(Processes outlined in later lectures-> Keep in mind!)

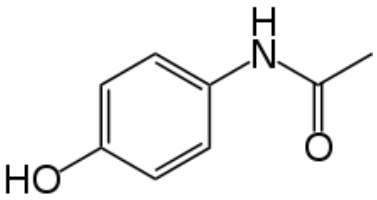
Table 8.1 The chemical stability of cephalothin sodium related to the amorphous content of the sample (data derived from Pikal et al 1978)

Sample	% amorphous	% stable drug after storage at 31% RH 50°C
Crystalline	0	100
Freeze dried	12	100
Freeze dried	46	85
Spray dried	53	44

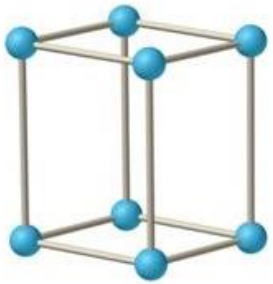
RCSI

The Influence of Physical Form on Tablet Behaviour: Example of Paracetamol Polymorphism & Tabletting

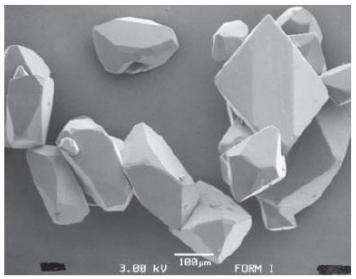
- 1998: Nichols et al., J. Pharm Sci.
  - Investigation of properties of two polymorphs of paracetamol
  - One form was less stable at room temperature but could be directly compressed without any binders



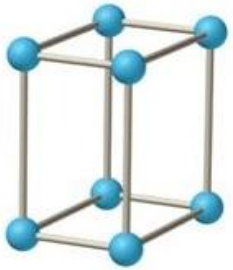
FORM I



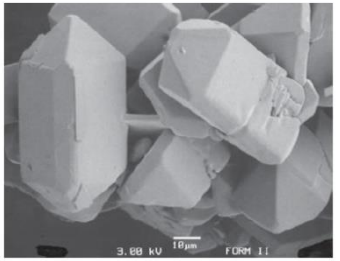
Monoclinic



FORM II



Orthorhombic



More stable form at room temperature

Commercially used form

Not suitable for direct compression into tablets

Binders required in tabletting

Costly processing

Easily crystallised from solvents

Less stable form at room temperature

Not used commercially

Form suitable for direct compression into tablets

No binders necessary in tabletting

Processing advantage

Nucleation from FORM II Seed

RCSI

The Influence of Physical Form on Tablet Behaviour: Example of Paracetamol Polymorphism & Tabletting

- 1998: Nichols et al., J. Pharm Sci.
  - Investigation of properties of two polymorphs of paracetamol
  - One form was less stable at room temperature but could be directly compressed without any binders

Table 4—Results from the Compaction Simulator Experiments Conducted on Paracetamol Forms I and II with Punch Velocities of 2 and 220 mm s^{-1}

sample	1st run (MPa)	2nd run (MPa)	3rd run (MPa)	mean (MPa)	standard deviation	strain rate sensitivity (%)
2 mm s^{-1}						
form I	70.06	72.30	72.92	71.76	1.23	
form II	48.42	43.67	42.52	44.87	2.55	
220 mm s^{-1}						
form I	76.59	79.28	79.88	78.58	1.43	9.5
form II	53.87	56.53	56.87	55.76	1.34	24.3

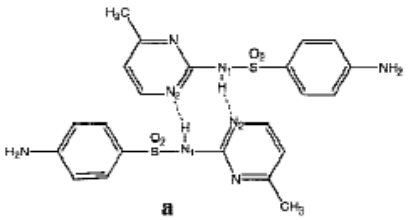
Table 5—Summary of the Microscopical Observations during the Solution-Phase Polymorphic Conversion of Paracetamol Form II to Form I in a Seeded, Supersaturated IMS Solution at 0 °C over a Period of 6 h

time from seeding	observations
10 min	well-formed prismatic crystals of form II; form I not found
1 h	well-formed prismatic crystals of form II, but showing signs of dissolution
2 h	form II crystals undergoing extensive dissolution; a few, small, well-formed form I crystals observed
3 h	form II crystals are extensively eroded; form I crystals growing larger
4 h	well-formed platy form I crystals are dominant; a few ragged form II crystals remain
6 h	all crystals are form I

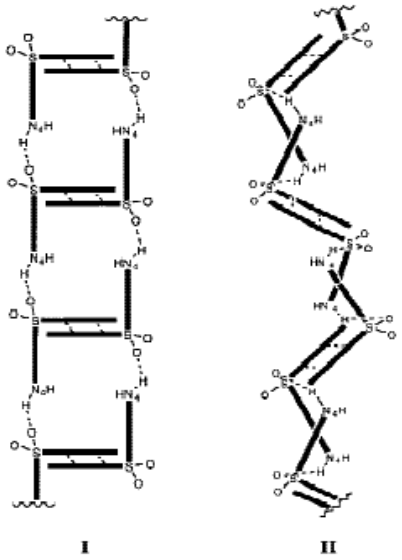
RCSI

The Influence of Physical Form on Tablet Behaviour: Example of Sulphamerazine Polymorphism & Tabletting

- 2001: Sun et al., Pharm. Res.
  - Investigation of properties of two polymorphs of sulphamerazine



a



I II

b

Scheme 1. (a) Structure of the dimer in crystals of sulfamerazine. (b) Infinite hydrogen-bond structure within sulfamerazine polymorphs: **I** and **II**. Hydrogen-bonds are indicated by broken lines. Even though the hydrogen bond connectivity patterns are the same for both polymorphs, the secondary structures are different. For clarity, only atoms directly involved in the formation of infinite chains of hydrogen bonds are shown.

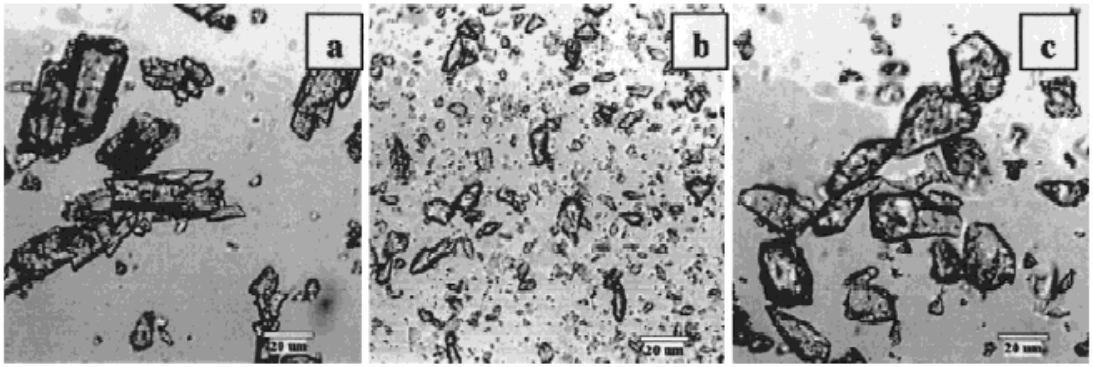


Fig. 1. Photomicrographs of three sulfamerazine powders: (a) **I**; (b) **II(A)**; (c) **II(B)**.

Table I. Densities and Mechanical Properties of Three Sulfamerazine Powders (Standard Deviations in Parentheses)

Powder form	Particle size (μm)	True density[a] (g/cm^3) (n = 3)	Tapped density (g/cm^3) (n = 3)	σ_0 (MPa)[b] (n = 3)	P_y (MPa)[c] (n = 3)
I	10–40	1.335 (0.004)	0.633 (0.004)	5.10	68.4 (1.5)
II(A)	1–15	1.415 (0.005)	0.683 (0.008)	5.77	77.5 (4.5)
II(B)	10–40	1.414 (0.003)	0.751 (0.003)	3.93	86.2 (5.6)

[a] True density is measured using helium pycnometry.
[b] σ_0 is tensile strength extrapolated to zero porosity in Eq. (3).
[c] P_y is the mean yield pressure, which is derived from Heckel analysis, Eq. (2).

RCSI

The Influence of Physical Form on Tablet Behaviour: Example of Sulphamerazine Polymorphism & Tabletting

- 2001: Sun et al., Pharm. Res.
  - Investigation of properties of two polymorphs of sulphamerazine

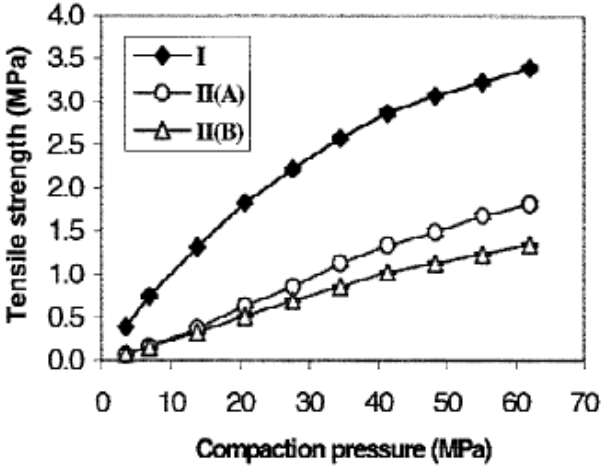


Fig. 3. Plots of tensile strength against compaction pressure, showing the tabletability of three powders of sulfamerazine, **I**, **II(A)**, and **II(B)**. The tabletability follows the order: **I** >> **II(A)** > **II(B)**.

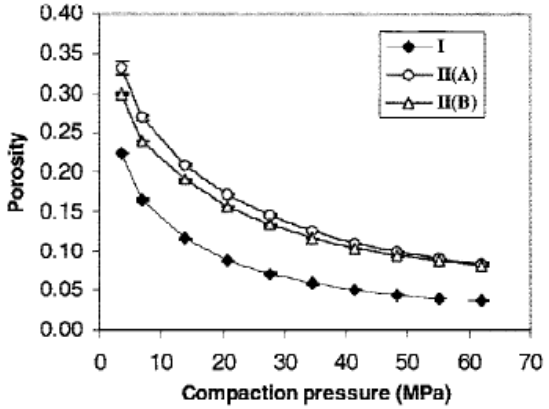


Fig. 4. Plots of tablet porosity against compaction pressure, showing the compressibility of three powders of sulfamerazine, **I**, **II(A)**, and **II(B)**. The compressibility follows the order: **I** >> **II(B)** > **II(A)**.

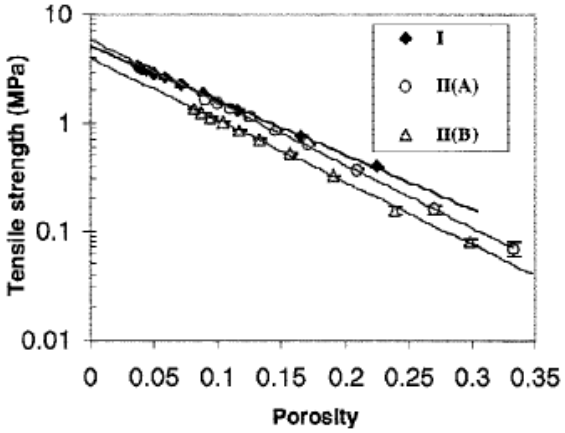


Fig. 5. Plots of tensile strength against tablet porosity, showing the compactibility of three powders of sulfamerazine, **I**, **II(A)**, and **II(B)**. The compactibility follows the order: **II(B)** <**II(A)** ≈ **I**.

RCSI

The Influence of Physical Form on Tablet Behaviour: Example of Ibuprofen Crystal Habit & Flow

- 2002: Rasenack et al., Drug Dev. Ind. Pharm.
  - Investigation of properties of crystallisation methods and flow properties

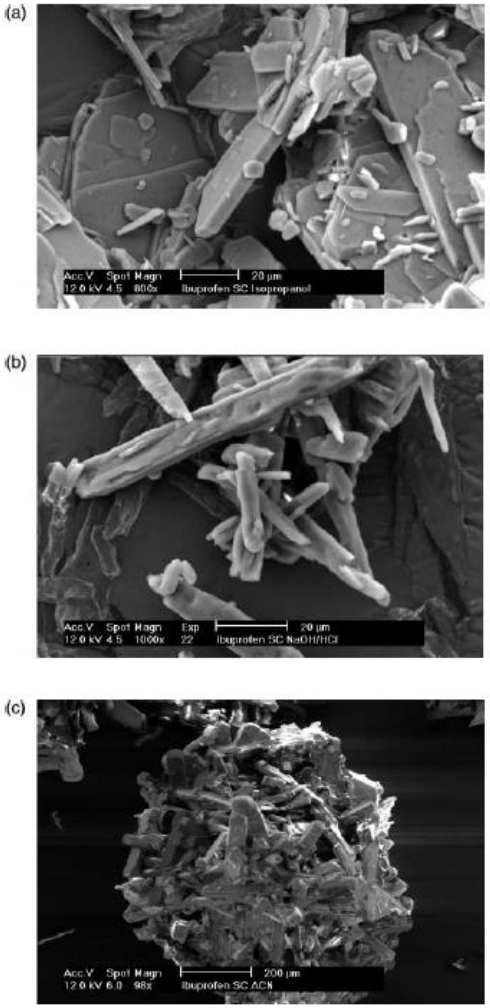


Figure 3. SEM photographs of ibuprofen crystals prepared by solvent change method: (a) isopropyl alcohol, (b) NaOH, (c) acetonitrile.

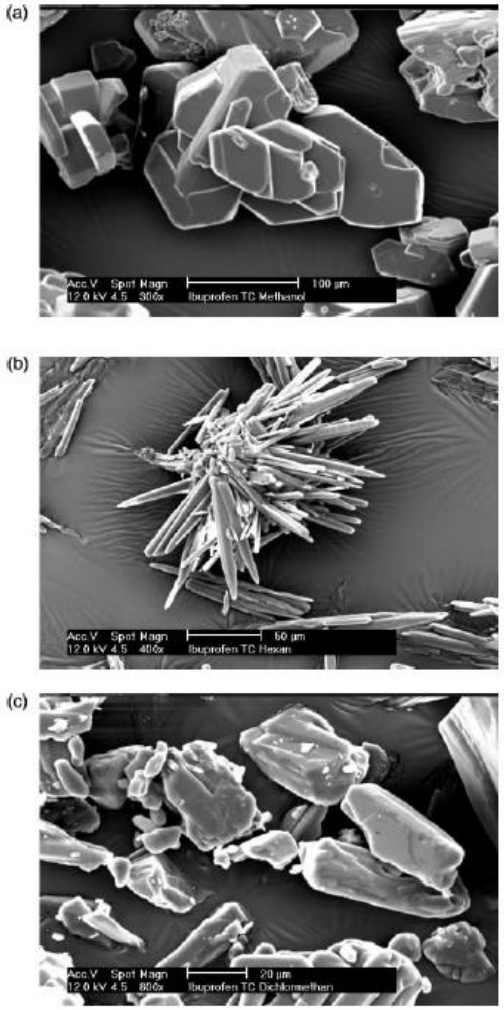


Figure 4. SEM photographs of ibuprofen crystals prepared by temperature change method: (a) methanol, (b) hexane, (c) dichloromethane.

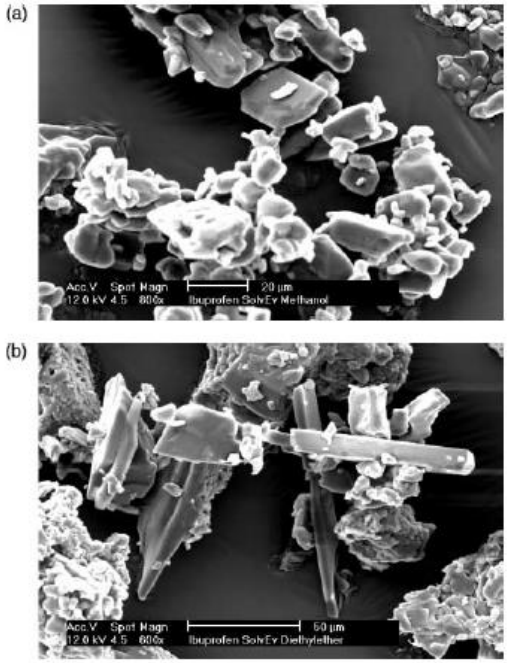


Figure 5. SEM photographs of ibuprofen crystals prepared by solvent evaporation method: (a) methanol, (b) diethyl ether.

RCSI

The Influence of Physical Form on Tablet Behaviour: Example of Ibuprofen Crystal Habit & Flow

- 2002: Rasenack et al., Drug Dev. Ind. Pharm.
  - Investigation of properties of crystallisation methods and flow properties

Angle of Response of Ibuprofen

	Control	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Propylen Glycol	NaOH/HCl
				Ibuprofen crystallized by solvent change method				
Angle of response (°) (± SD)	*60.5 ± 0.86*	40.5 ± 0.72	44.3 ± 0.91	37.7 ± 0.95	28.8 ± 0.51	41.0 ± 1.03	57.7 ± 1.43	58.0 ± 1.28
				Ibuprofen crystallized by temperature change method				
	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Diethyl Ether	Dichloromethane	Hexane
Angle of response (°) (± SD)	40.7 ± 1.14	49.7 ± 0.93	55.0 ± 0.87	29.0 ± 0.76	55.3 ± 0.91	58.5 ± 1.21	51.3 ± 0.99	58.7 ± 1.28
				Ibuprofen crystallized by solvent evaporation method				
	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Diethyl Ether	Dichloromethane	Hexane
Angle of response (°) (± SD)	42.5 ± 1.05	47.3 ± 0.91	44.5 ± 1.21	43.5 ± 0.82	44.5 ± 0.87	48.3 ± 0.012	52.5 ± 1.01	50.0 ± 0.95

Results: mean of three measurements: SD = standard deviation.

RCSI

The Influence of Physical Form on Tablet Behaviour: Example of Hydrates & Flow Properties

- 2009: Sun et al., J. Pharm. Sci.
  - Investigation of influence of hydration on powder flow and mechanical properties

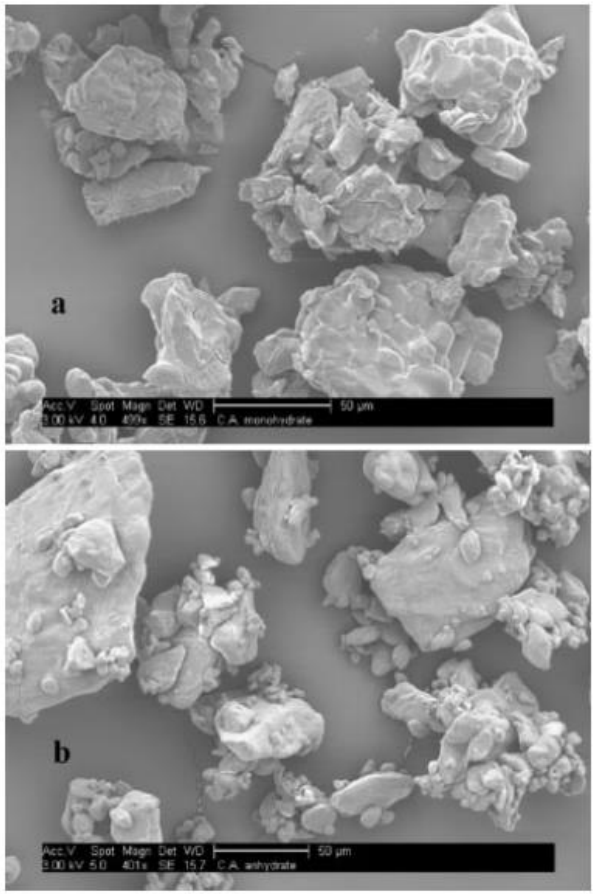


Figure 2. Scanning electron microphotographs of (a) citric acid monohydrate and (b) citric acid anhydrate.

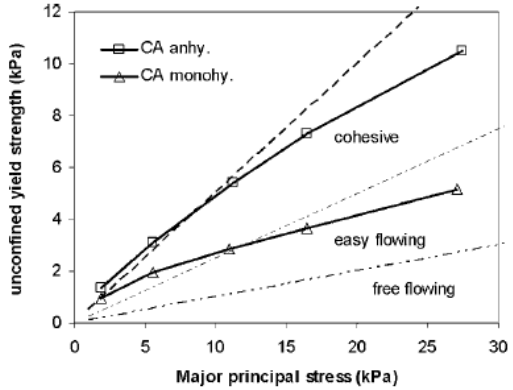


Figure 4. Flow functions of citric acid anhydrate and monohydrate. Flow properties of the monohydrate are significantly better. The Jenike flow classification criteria are shown as broken lines.

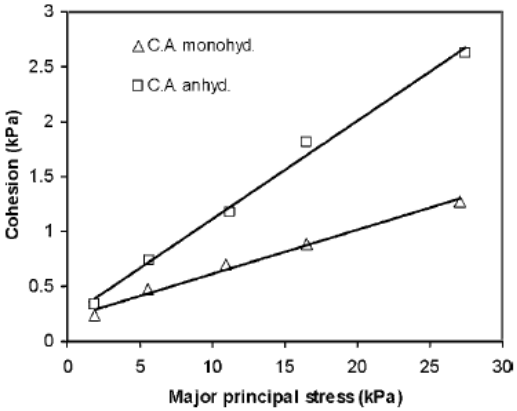


Figure 7. Dependence of powder cohesion on major principal stress for the citric acid monohydrate and anhydrate.

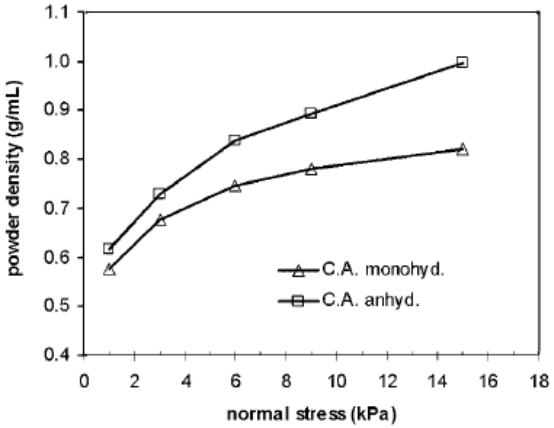
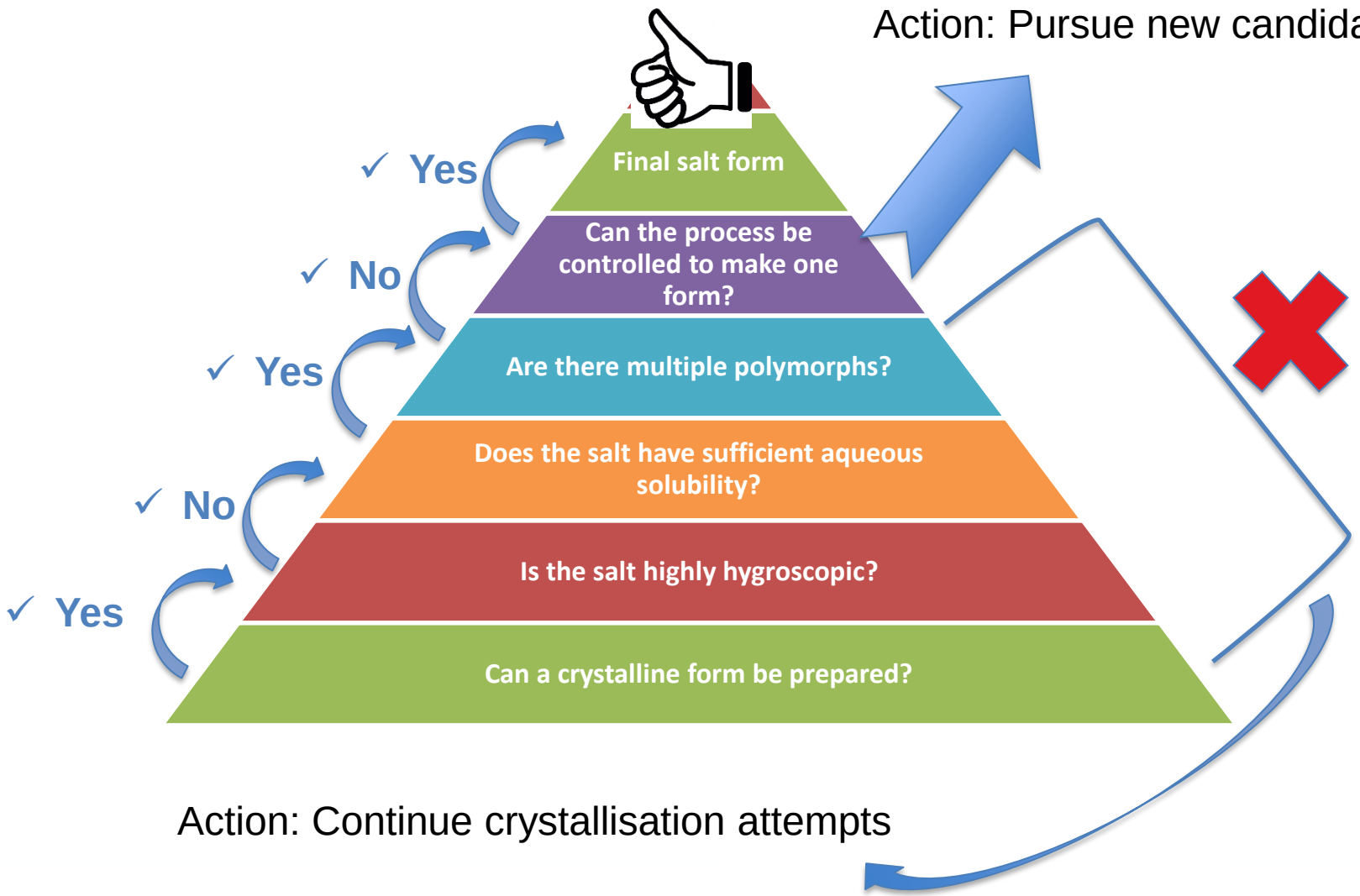


Figure 8. Dependence of powder density on normal stress for the citric acid monohydrate and anhydrate.

RCSI

Selection of Salt for Tablet Form: Minimising Polymorphism in Selection of Candidates for Tablet Manufacture



RCSI

Contact information

Shi Du

Associate Professor

International College of Pharmaceutical Innovation

Soochow University

Room 707, International Innovation Center

Jiuyong East Rd #1, Wujiang District, Suzhou, China

T: +86-15952400997

E: dushi@suda.edu.cn

RCSI