8TH ANNUAL PTI TRAINING PROGRAM

FORMULATION AND PROCESS DEVELOPMENT FOR ORAL DOSAGE FORMS

A 5-Day Modular and Case Study Oriented Training Program

AUGUST 27-31, 2012 - NASSAU INN - PRINCETON - NJ - USA

Historical Location, Reputable Speakers & Innovative Program

Module 1: Crystal Forms of API

Part Ia.

STRUCTURES OF CRYSTALLINE SOLIDS

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Crystal Lattice Structure (1)

- An ideal crystal is constructed by the infinite regular repetition in space of identical structural units.
  - For crystals of monatomic elements, the basic structural elements are the individual atoms.
  - For crystals of organic molecules, the basic structural unit will contain one or molecules.

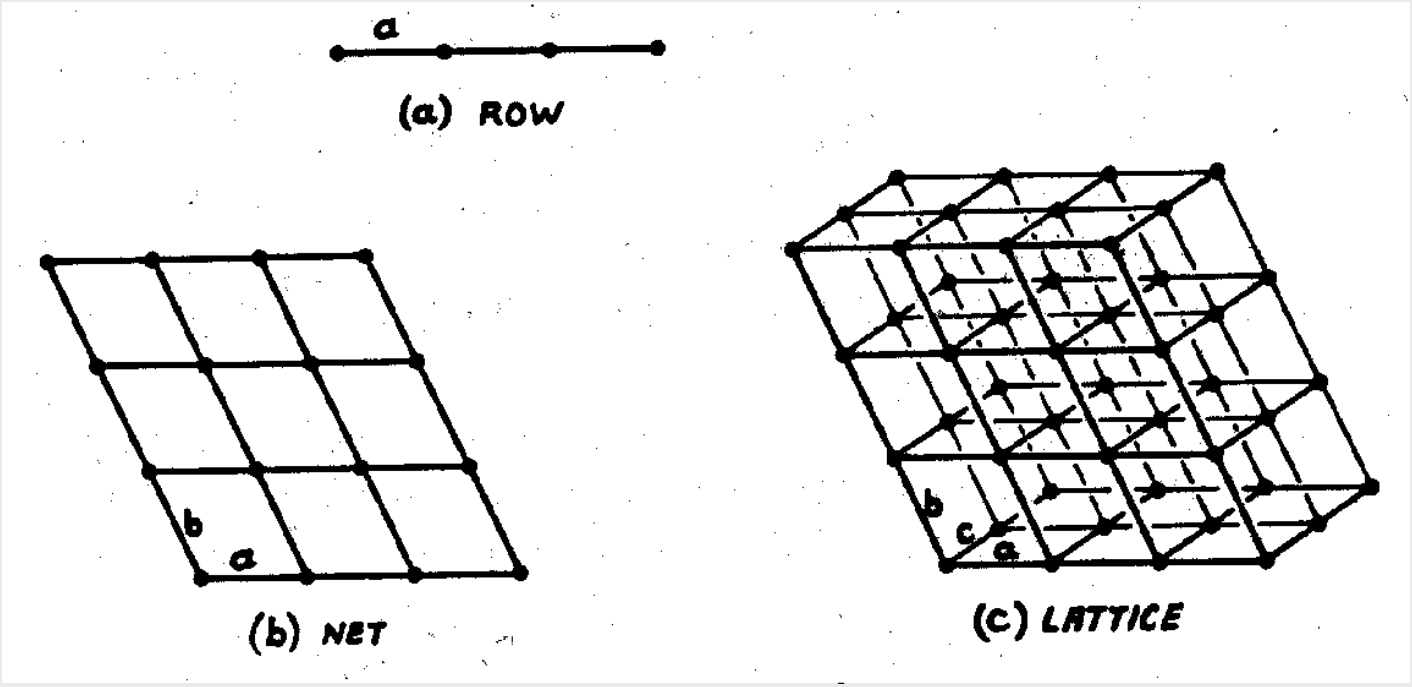
Crystal Lattice Structure (2)

A lattice is defined as a regular periodic arrangement of points in space, and contains all of the translational repetitions that define a given pattern.

The crystal structure is formed when a fundamental unit is attached identically to each lattice point, and extended along each crystal direction through translation.

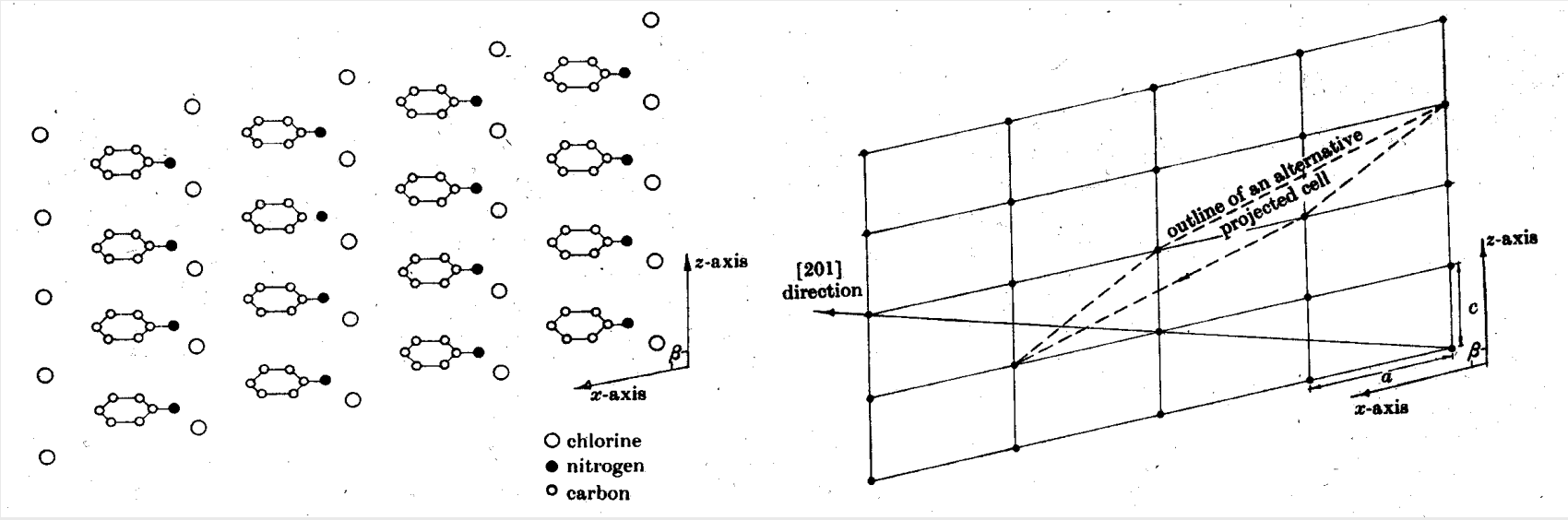
Crystal Lattice Structure (3)

Rows, nets, and lattices:



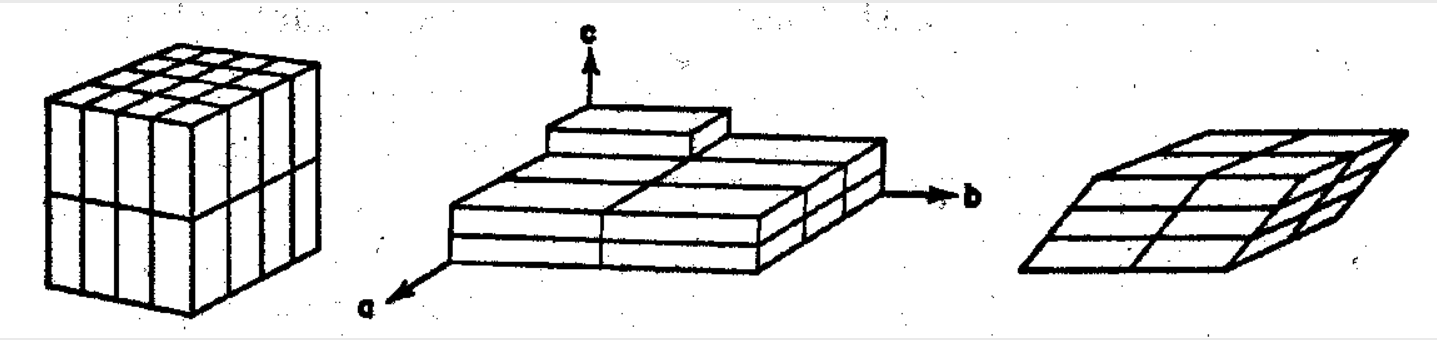
Crystal Lattice Structure (4)

y-axis projection of aniline hydrochloride



Crystal Lattice Structure (5)

- The crystal structure is generated through the periodic repetition (by the three unit translations) of matter contained within the volume of the unit cell.

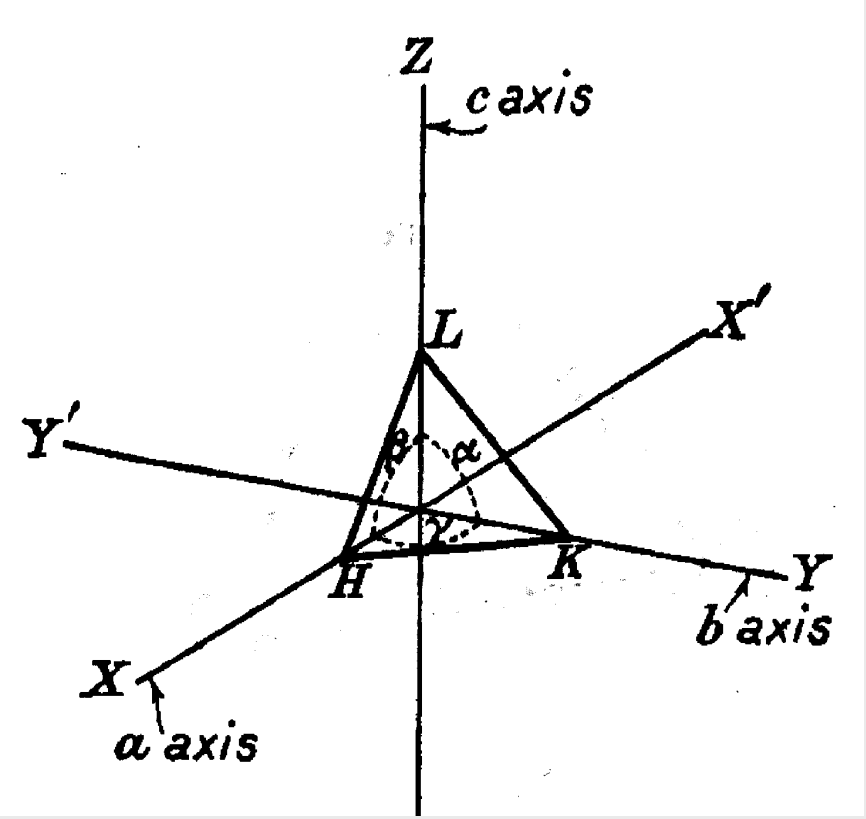


Crystal Lattice Structure (6)

- The unit cell is defined by the lengths (*a*, *b*, and *c*) of the crystal axes, and by the angles (α, β, and γ) between these.
- The position of any face on the crystal is fixed by its intercepts on the axes as (HKL), also known as the Miller index of that face.

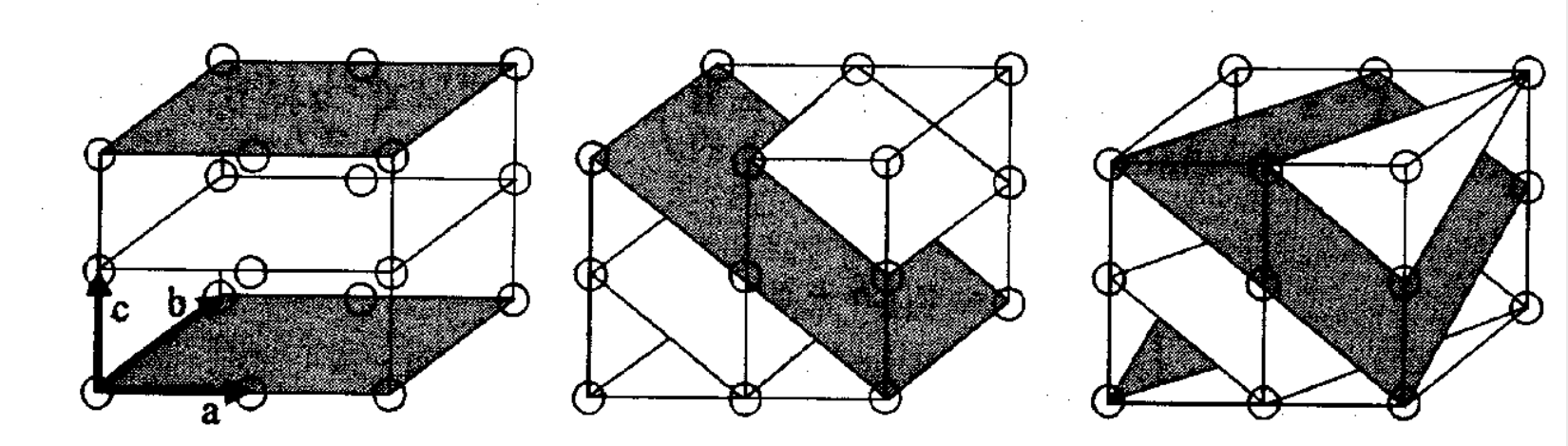
Crystal Lattice Structure (7)

- α = angle between the *b*- and *c*-axes.
- β = angle between the *a*- and *c*-axes.
- γ = angle between the *a*- and *b*-axes.
- H = *a*-axis intercept.
- K = *b*-axis intercept.
- L = *c*-axis intercept.



Crystal Lattice Structure (8)

Families of planes in a given lattice:



Crystal Lattice Structure (9)

- While there are seven types of primitive unit cells that represent unique combinations of axis lengths and angles (these unit cell characteristics define the seven crystal classes), only three classes are of importance to drug substances having pharmaceutical importance.

Crystal Lattice Structure (14)

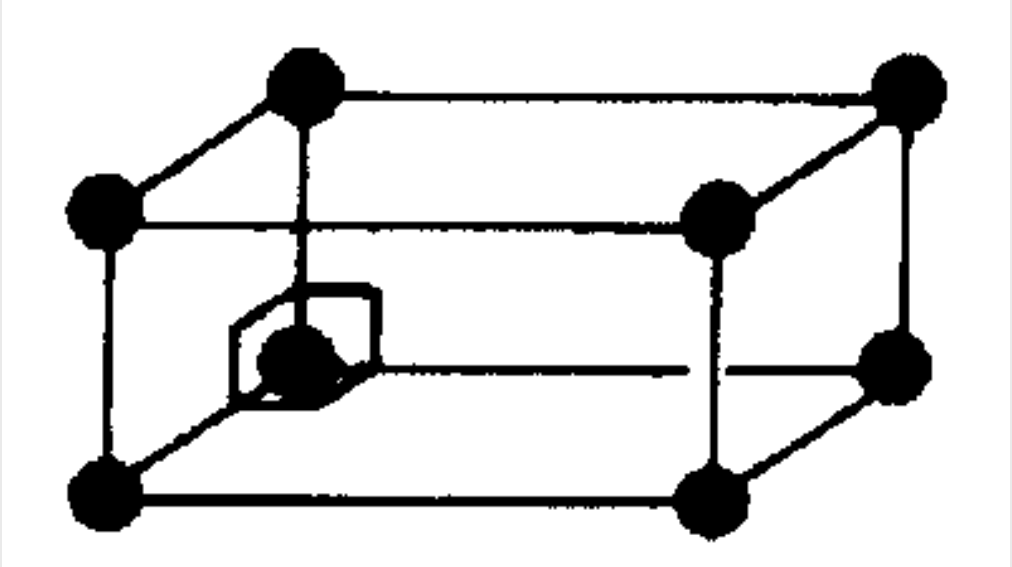
Orthorhombic system

$$a \neq b \neq c$$

$$\alpha = 90^\circ$$

$$\beta = 90^\circ$$

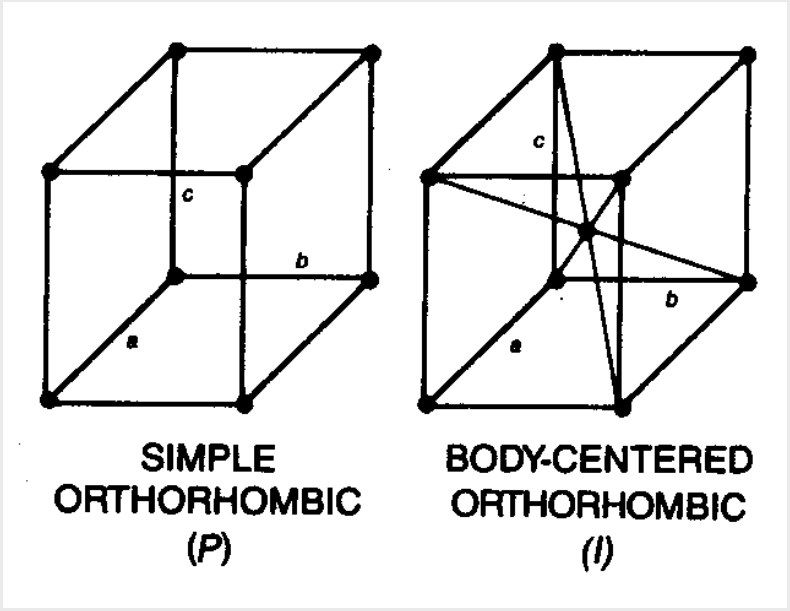
$$\gamma = 90^\circ$$



4 lattice types possible

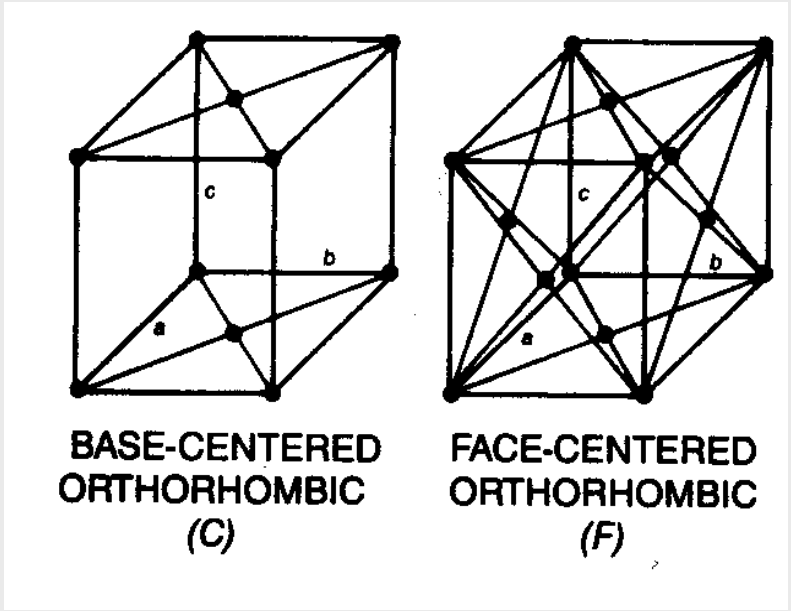
Crystal Lattice Structure (15)

Orthorhombic system lattice types:



SIMPLE ORTHORHOMBIC (*P*)

BODY-CENTERED ORTHORHOMBIC (*I*)



BASE-CENTERED ORTHORHOMBIC (*C*)

FACE-CENTERED ORTHORHOMBIC (*F*)

Crystal Lattice Structure (16)

Monoclinic system

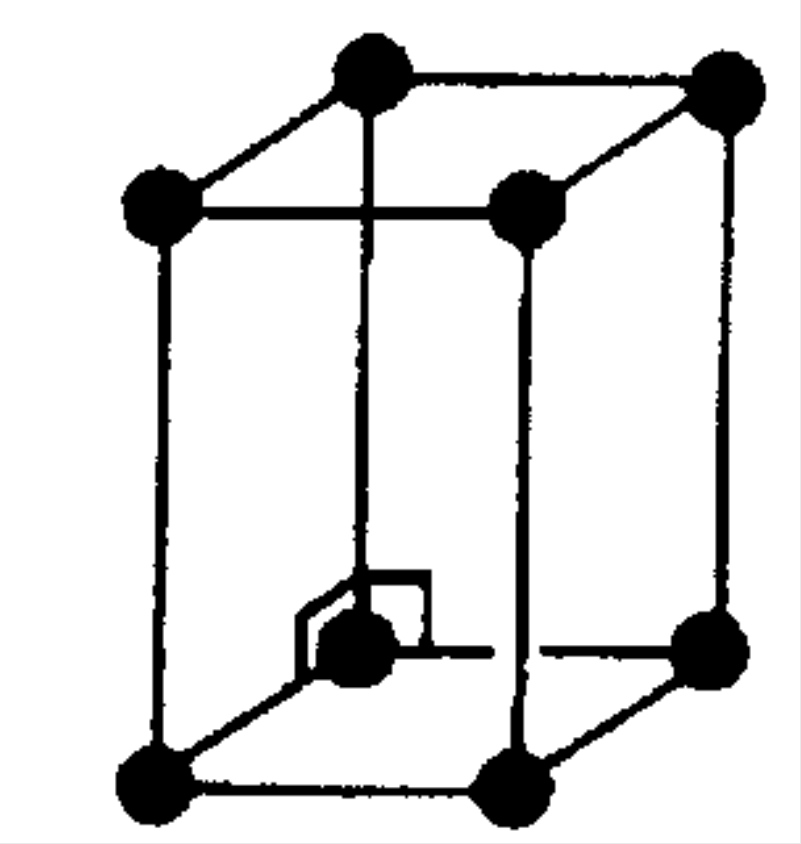
$$a \neq b \neq c$$

$$\alpha = 90^\circ$$

$$\beta \neq 90^\circ$$

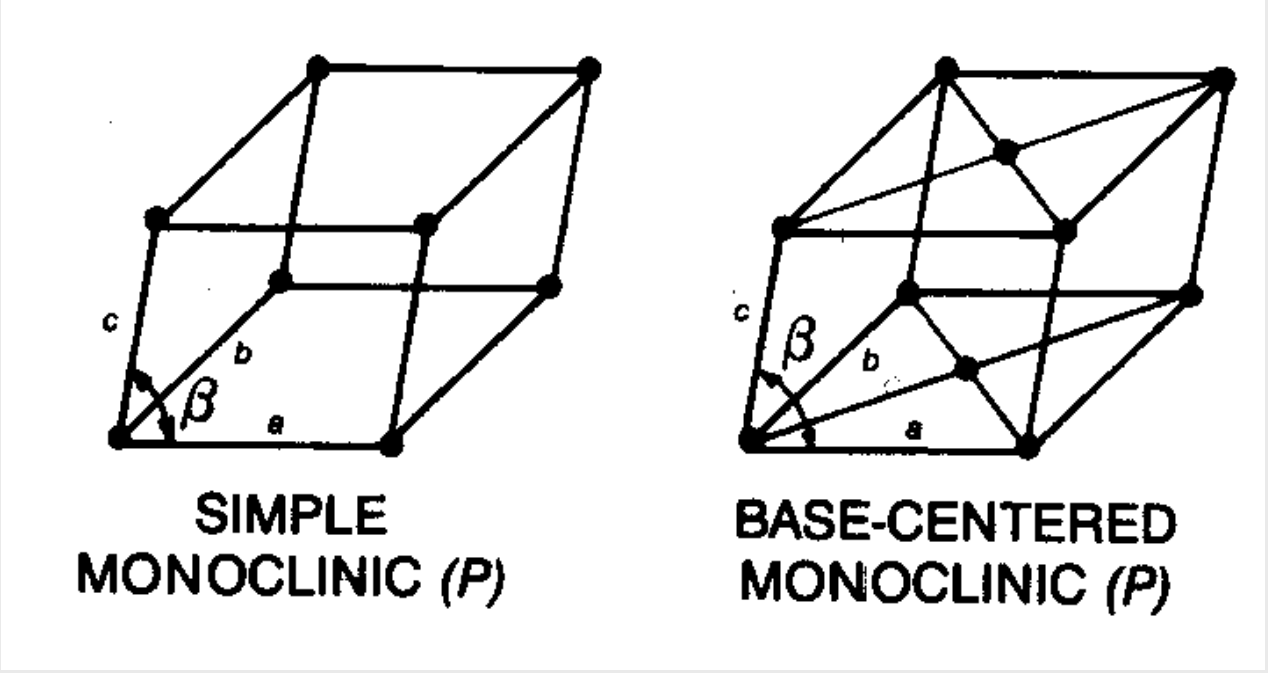
$$\gamma = 90^\circ$$

2 lattice types possible



Crystal Lattice Structure (17)

Monoclinic system lattice types:



SIMPLE MONOCLINIC *(P)*

BASE-CENTERED MONOCLINIC *(P)*

Crystal Lattice Structure (18)

Triclinic system

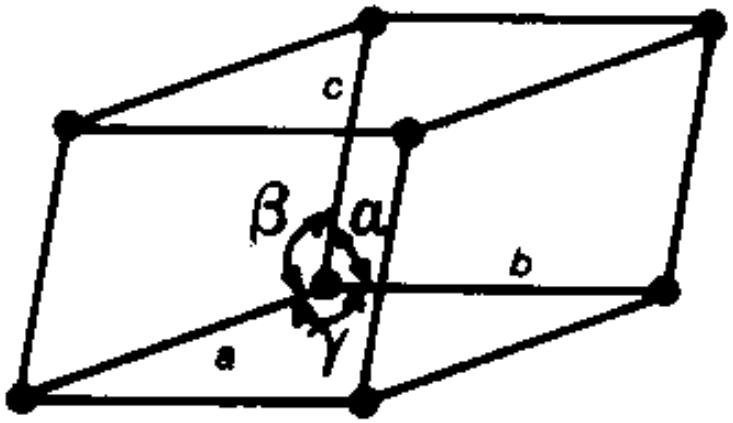
$$a \neq b \neq c$$

$$\alpha \neq 90^\circ$$

$$\beta \neq 90^\circ$$

$$\gamma \neq 90^\circ$$

1 lattice type possible



TRICLINIC *(P)*

Molecular Crystals (1)

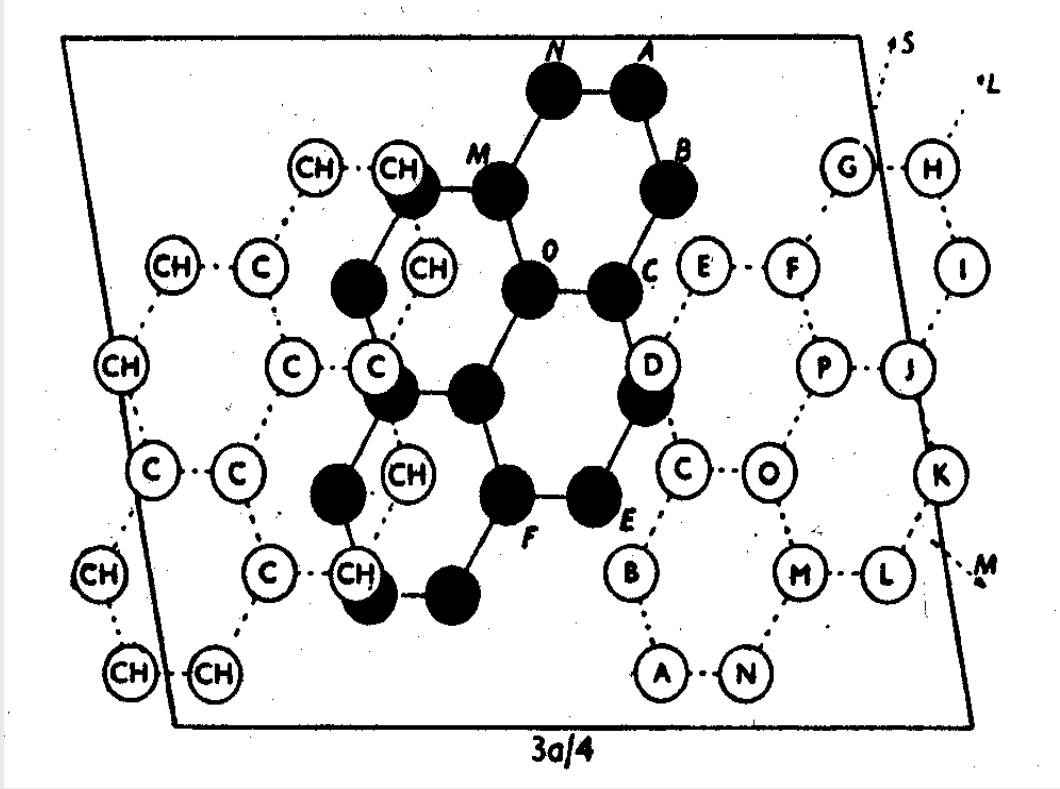
- Ordinary packing mechanisms dominate, with the structures being defined by the most favorable close-packing possible.
- The only forces of attraction between molecules are the van der Waals forces.
- The weak nature of these attractive forces leads to existence of only modest degrees of lattice energy.

Pyrene (1)

- Pyrene crystallizes in the $P2_1/a$ space group and contains four molecules per unit cell.

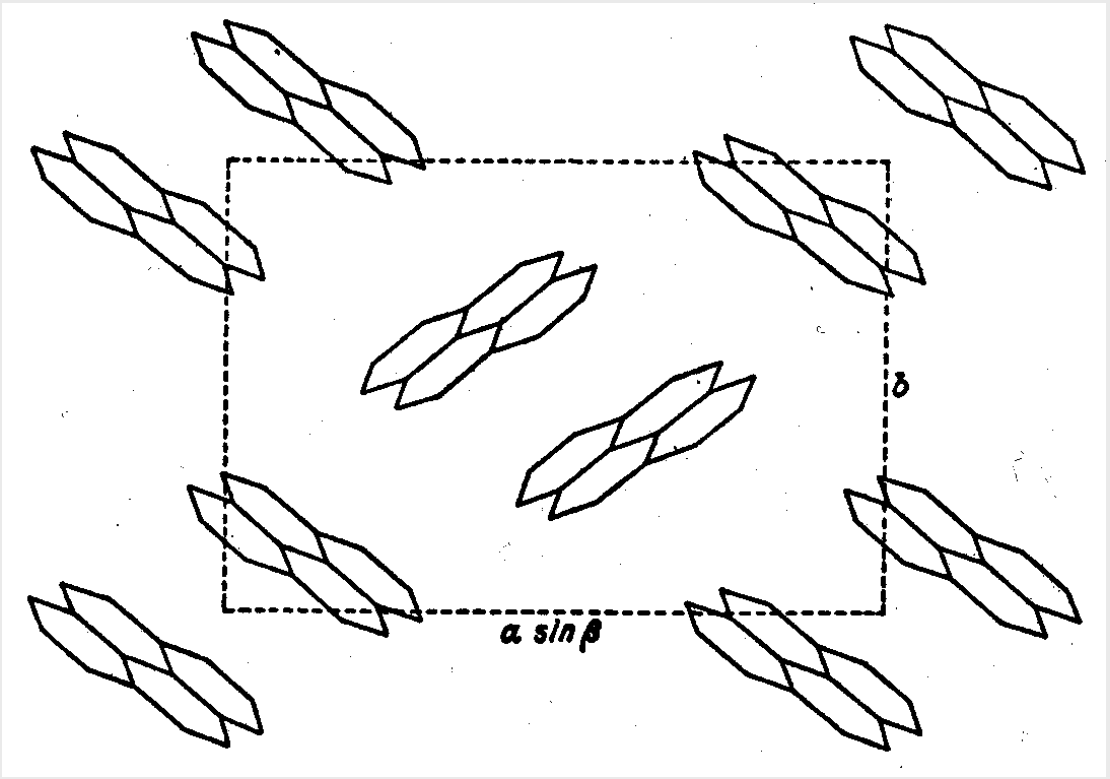
a = 13.60 Å	α = 90°
b = 9.24 Å	β = 100.2°
c = 8.37 Å	γ = 90°

Pyrene (2)



Location of atoms projected on the (010) plane of pyrene.

Pyrene (3)



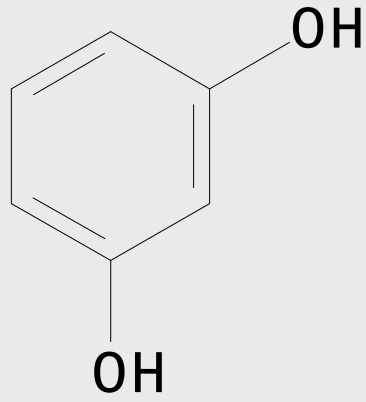
The pyrene crystal structure, viewed along the *c*-axis.

Hydrogen-Bonded Structures

- For compounds containing electronegative groups with replaceable hydrogen atoms, a more compact type of molecular grouping is observed.
- Such crystals are generally more brittle, and have higher melting points than molecular crystals.
- These properties signify the existence of higher degrees of lattice energy.

Resorcinol (1)

- Resorcinol is characterized by the existence of two polymorphic forms that can be interconverted about a transition temperature of 75°C. The form that is more stable at the higher temperature has the larger crystal density.
  - *Proc. Royal Soc.*,
  - A157, 79 (1936);
  - A167, 122 (1938)



Resorcinol (2)

α-Form

Orthorhombic

P*na*

Z = 4

a =10.53 Å

b = 9.53 Å

c = 5.66 Å

α = 90°

β = 90°

γ = 90°

β- Form

Orthorhombic

P*na*

Z = 4

a = 7.91 Å

b = 12.57 Å

c = 5.50 Å

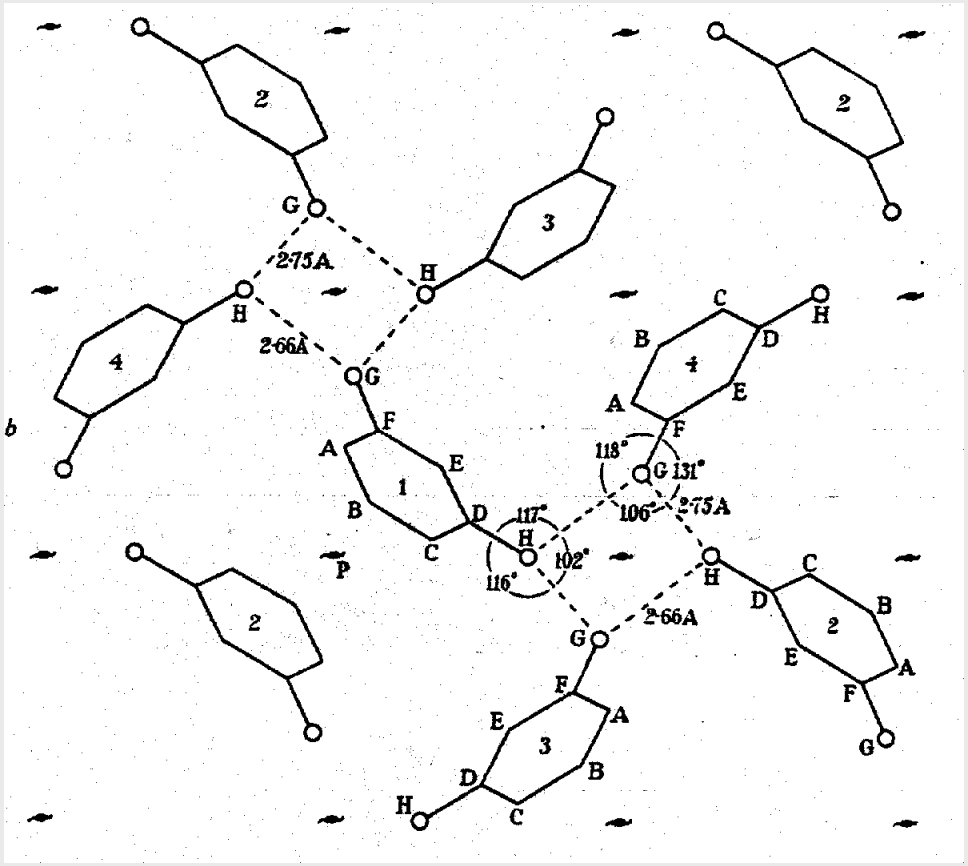
α = 90°

β = 90°

γ = 90°

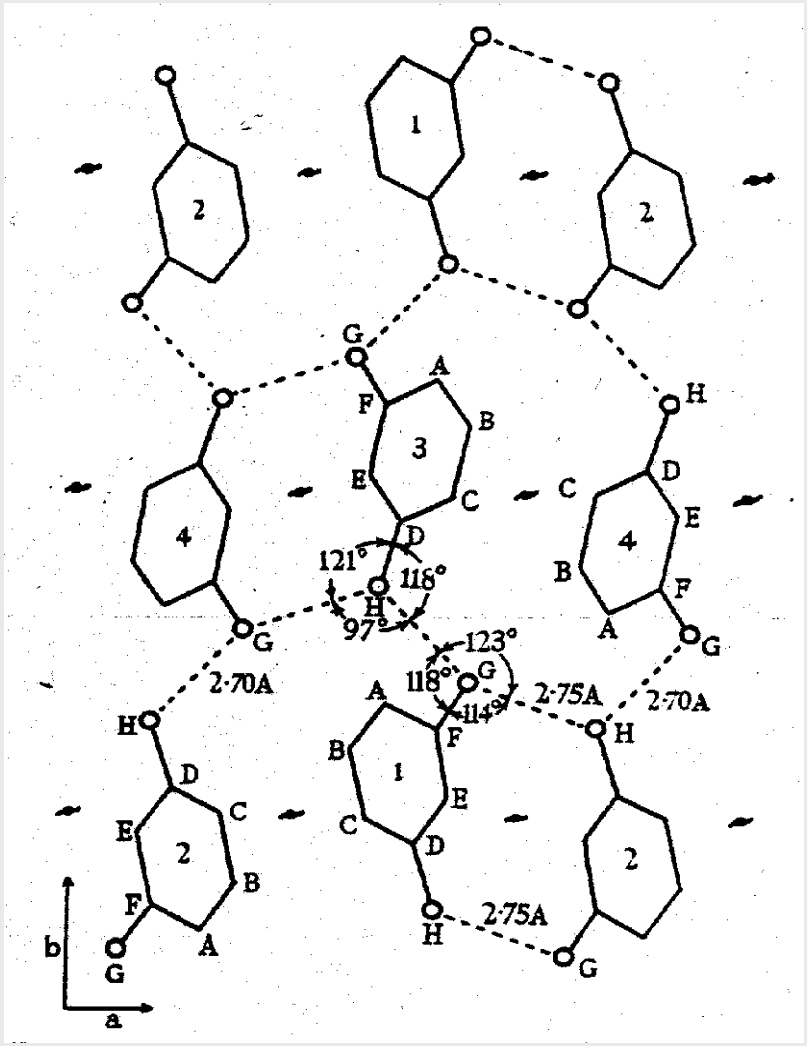
Resorcinol (3)

- Crystal structure of the α-phase as deduced from the electron density contour diagram.
- The hydrogen bonding pattern promotes the open structure.



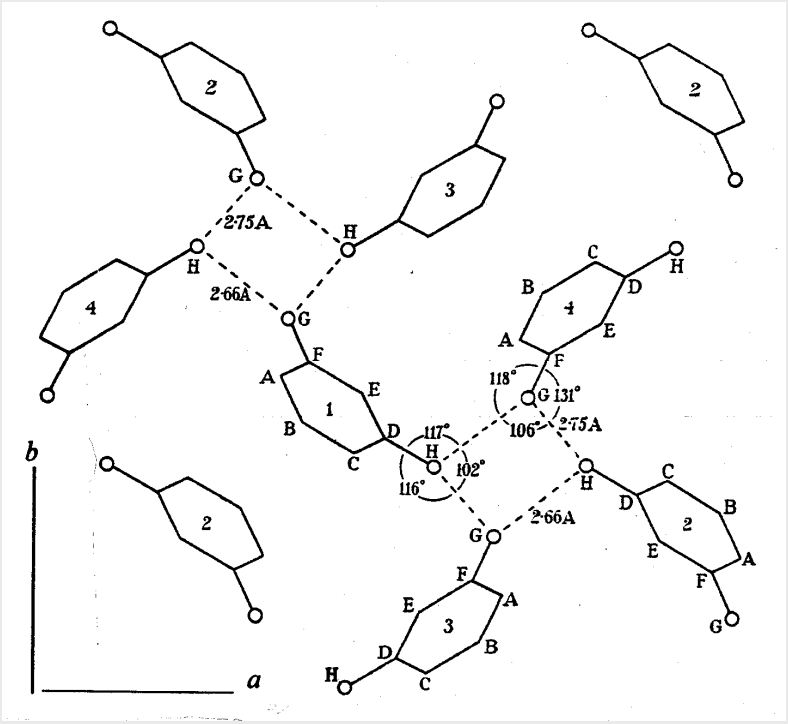
Resorcinol (4)

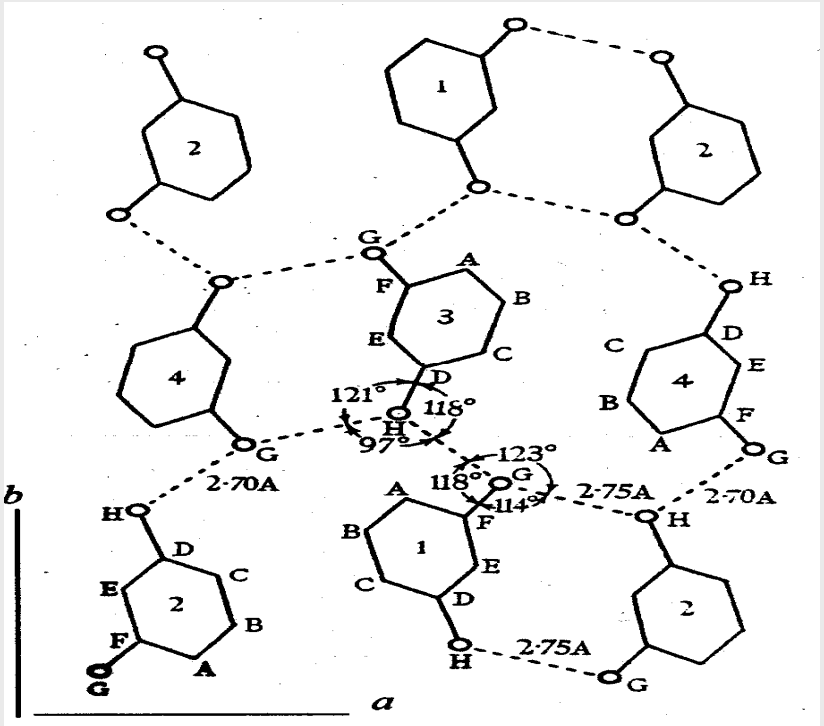
- Crystal structure of the β-phase as deduced from the electron density contour diagram.
- The weaker hydrogen bonds of the high temperature form cause the open structure to collapse.



Resorcinol (5)

α-phase (001) plane β-phase





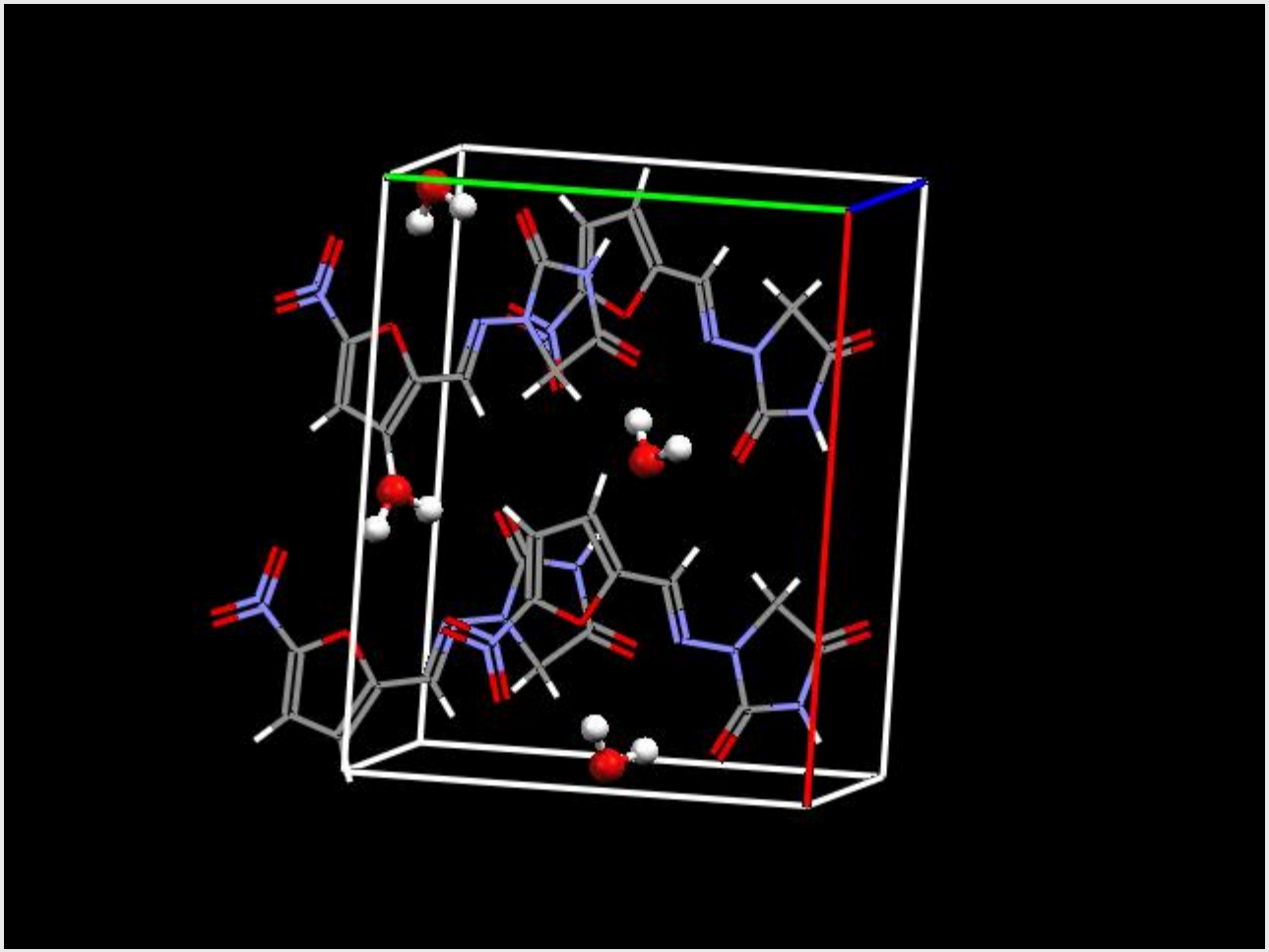
Solvatomorphs (1)

- In most crystalline solvatomorphic structures, the included hydrate/solvate molecule(s) occupy regular positions within the lattice with respect to the chemical entity.
- The hydrate/solvate molecule(s) included in the structure facilitate crystal growth by supplying additional intermolecular bridging that enhances the lattice energy.

Solvatomorphs (2)

- For regular crystalline hydrates or solvates, there will be a specific stoichiometry existing between the hydrate/solvate molecules and the chemical entity.
- For certain solids whose structures contain tunnels lined by hydrophilic sites, the existence of less site-specific channel solvent is possible.

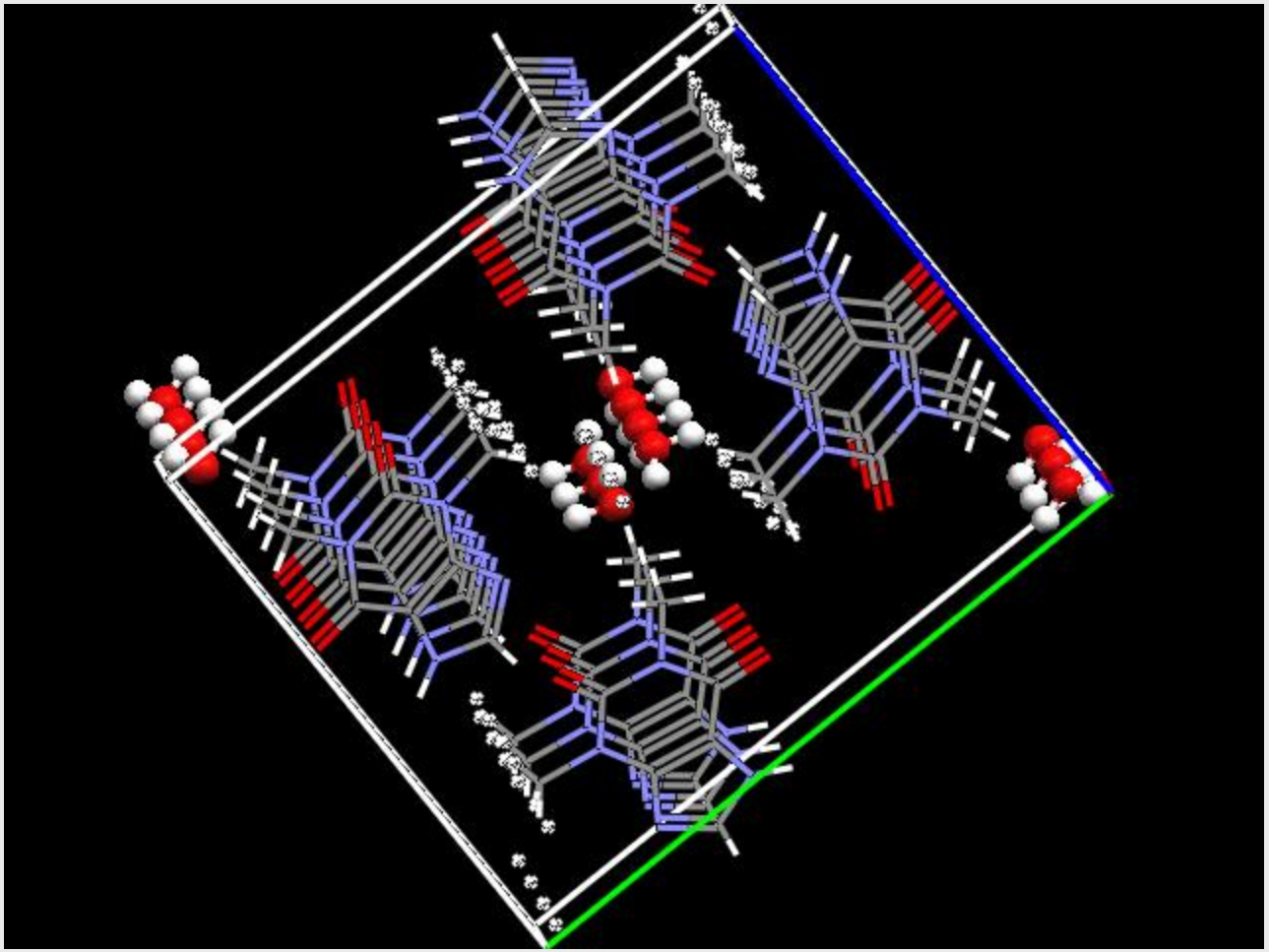
Isolated Site Hydrate



Packing Diagram for Nitrofurantoin monohydrate

[1] Cambridge Structural Database (Nov. 2003)

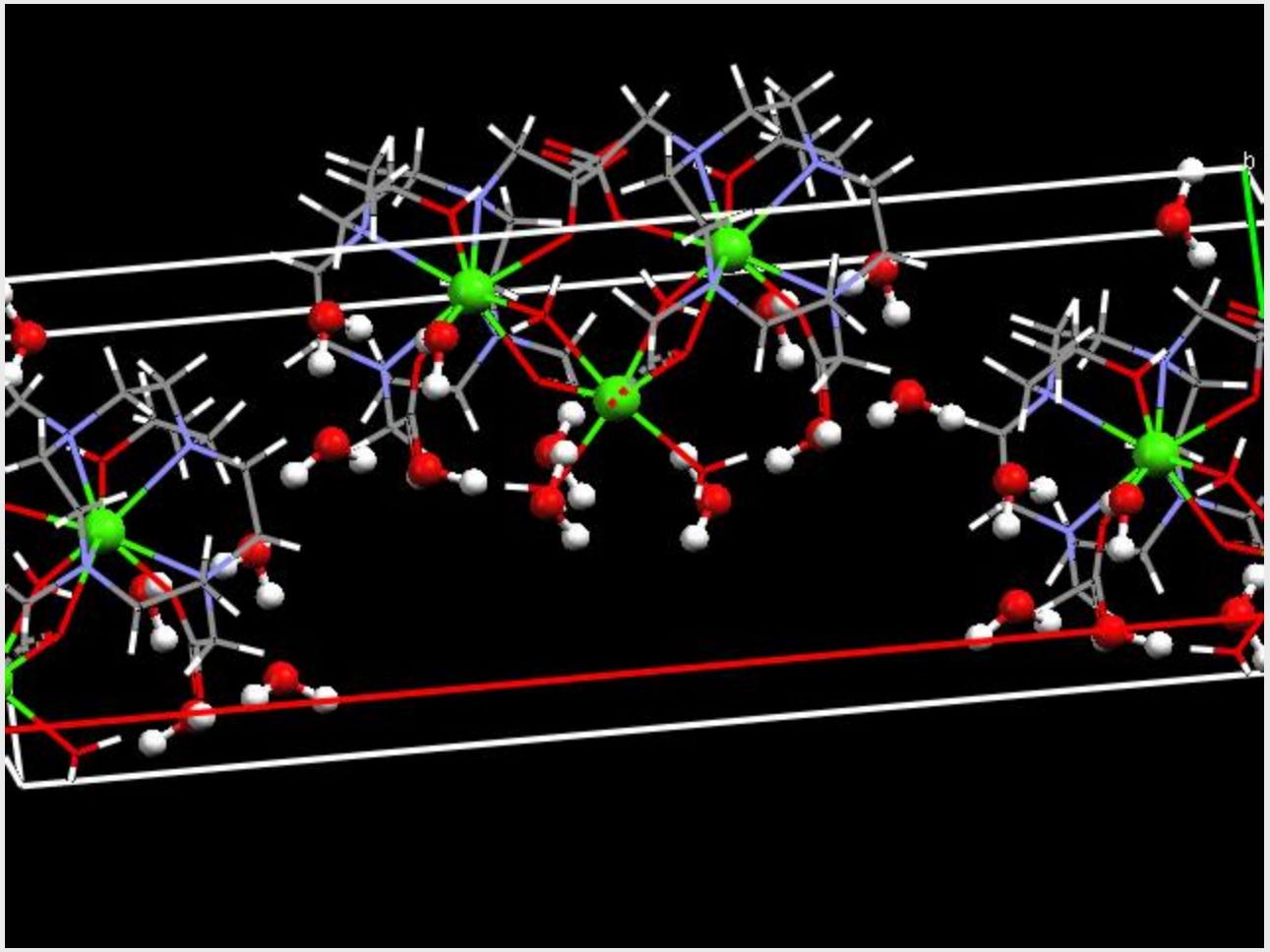
Channel Hydrate



Packing Diagram for Theophylline monohydrate

[1] Cambridge Structural Database (Nov. 2003)

Ion Coordinated Hydrate



Packing Diagram for Calteridol tetra-decahydrate

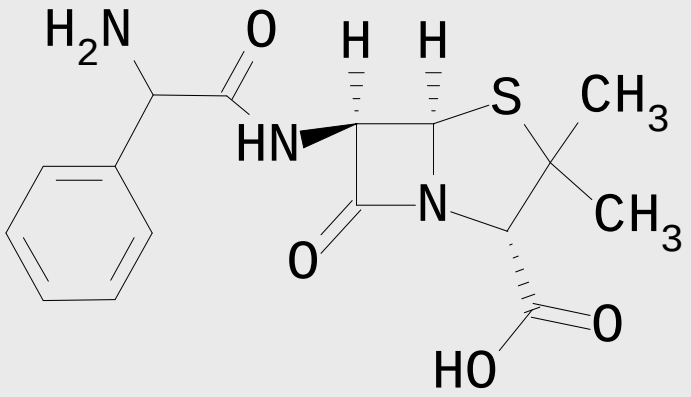
[1] Cambridge Structural Database (Nov. 2003)

Ampicillin (1)

- Ampicillin is known to exist both as an anhydrate phase and as a trihydrate.
  - Trihydrate:

    Nature, 220, 168 (1968)
  - Anhydrate:

    Acta Cryst., B32, 2279 (1976)



Ampicillin (2)

Anhydrate

Monoclinic

$P2_1$

$Z = 2$

$a = 12.32$ Å

$b = 6.18$ Å

$c = 11.90$ Å

$\alpha = 90°$

$\beta = 114.3°$

$\gamma = 90°$

Trihydrate

Orthorhombic

$P2_12_12_1$

$Z = 4$

$a = 15.490$ Å

$b = 18.891$ Å

$c = 6.662$ Å

$\alpha = 90°$

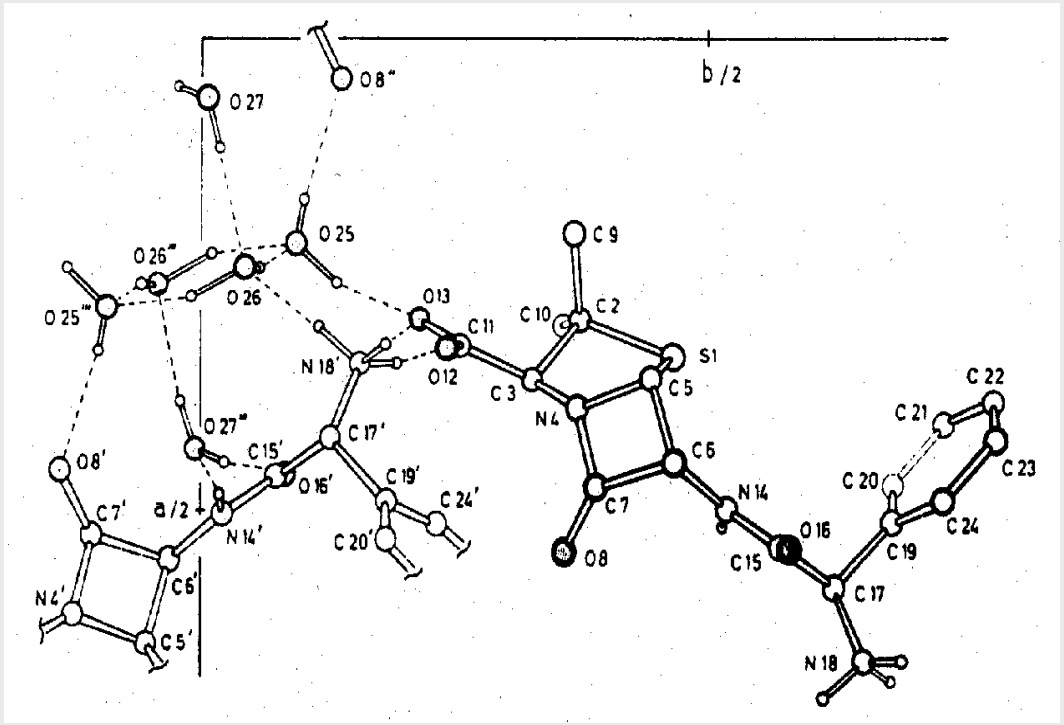
$\beta = 90°$

$\gamma = 90°$

Ampicillin (3)

Trihydrate phase

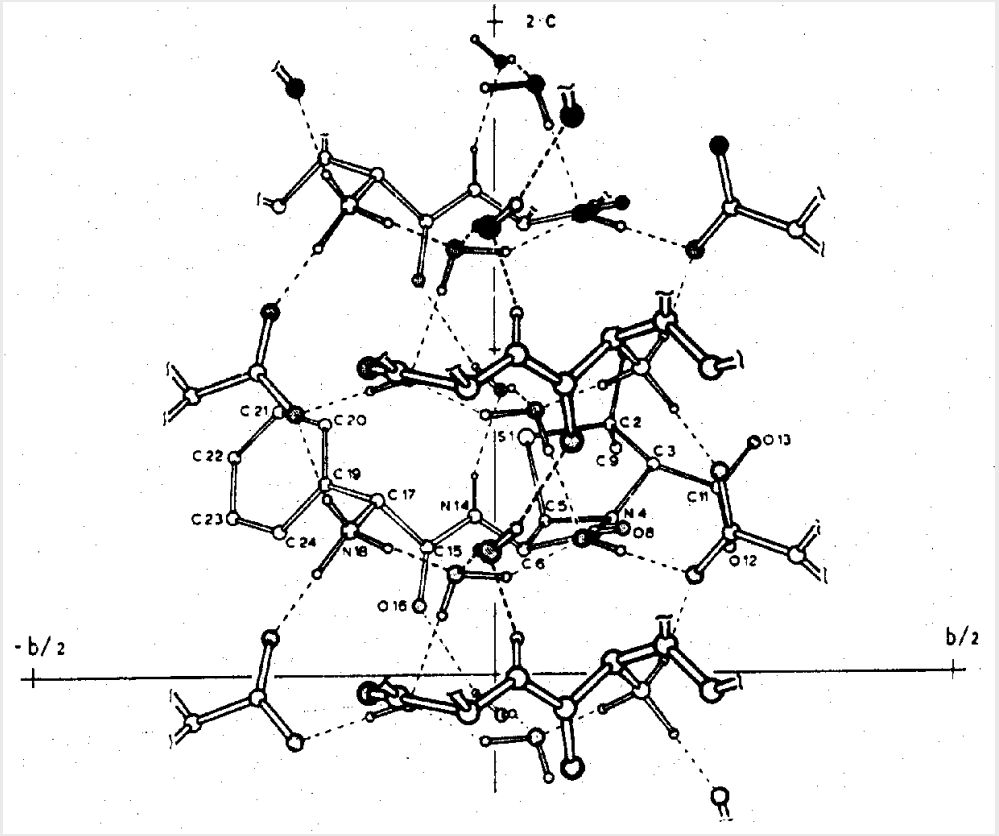
Projection of the structure down the *c*-axis.



Ampicillin (4)

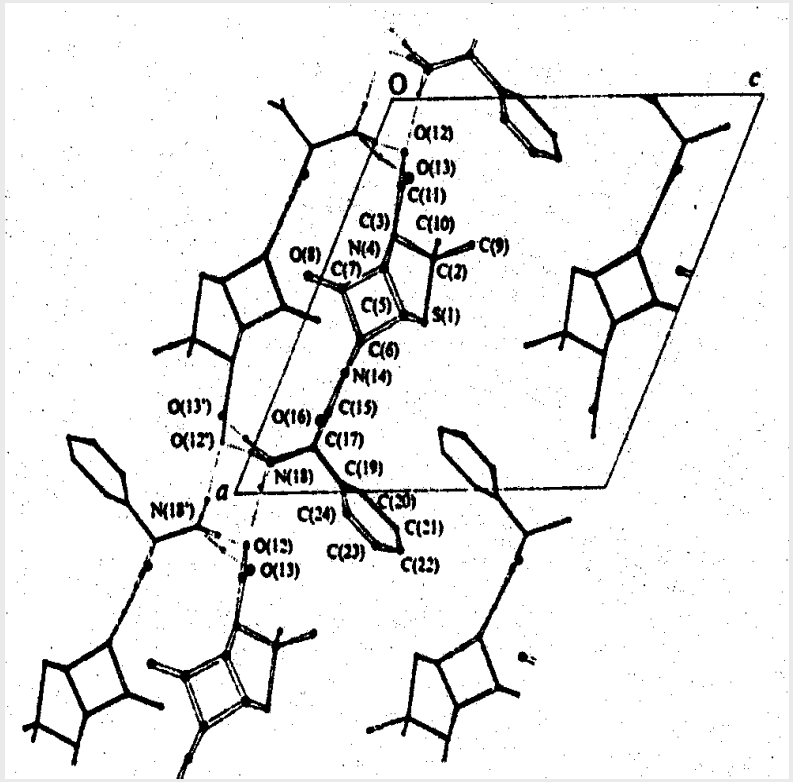
Trihydrate phase

Projection of the structure down the *a*-axis.



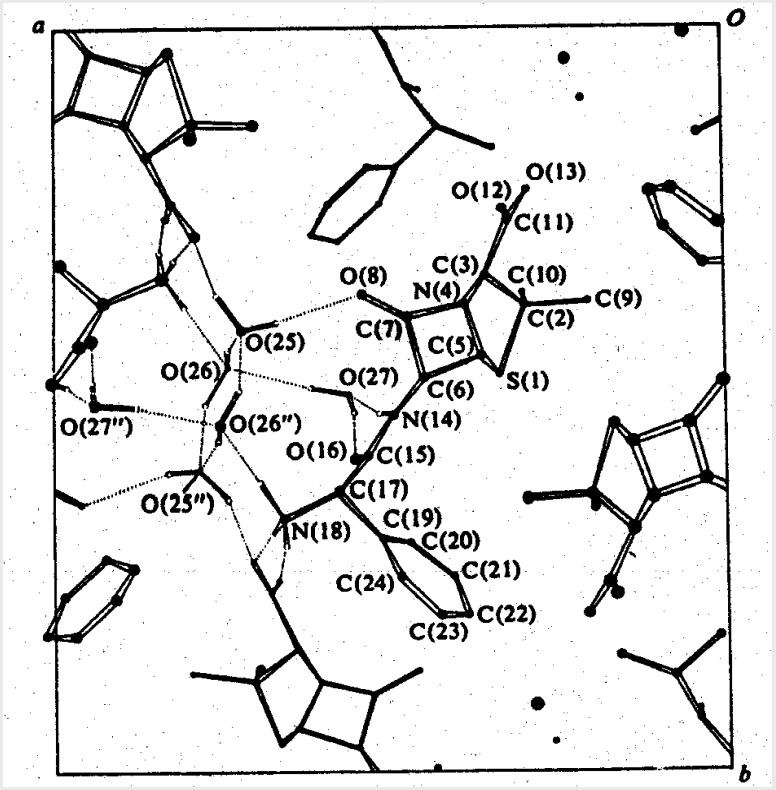
Ampicillin (5)

Anhydrate



(along *b*-axis)

Trihydrate



(along *c*-axis)

Module 1: Crystal Forms of API

Part Ib.

X-RAY POWDER DIFFRACTION

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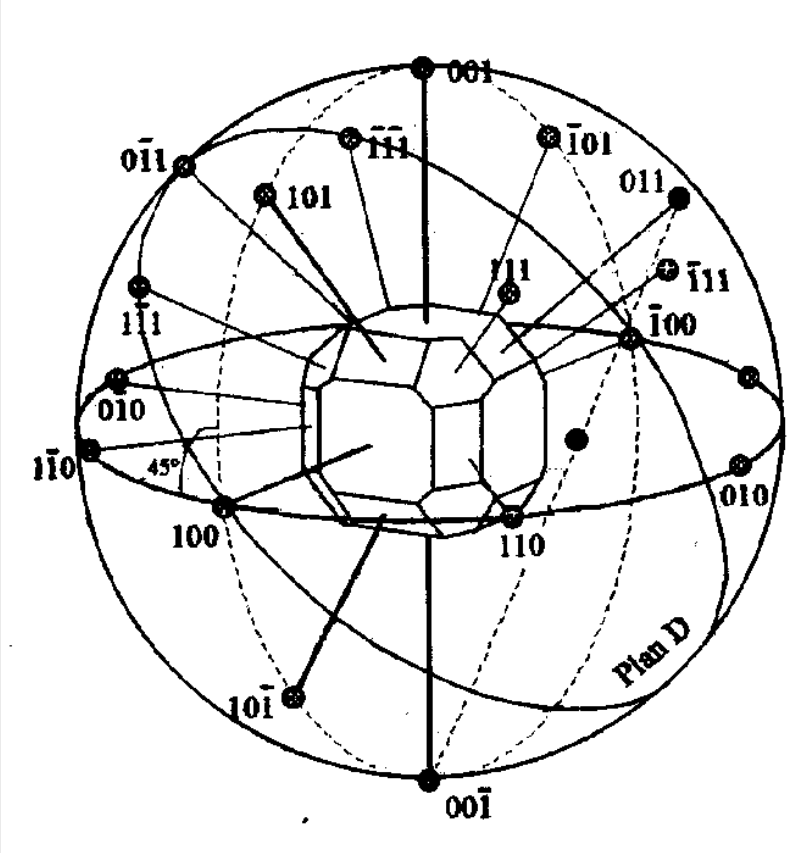
X-Ray Powder Diffraction (1)

- Although the full determination of a crystal structure provides the greatest degree of solid-state comprehension, this technique is not suitable for routine analysis.
- Since most bulk drug substances are obtained as crystalline powders, the technique of x-ray powder diffraction (XRPD) is a much more useful method for the study of these materials.

X-Ray Powder Diffraction (2)

- A correctly prepared sample will present an entirely random selection of all possible crystal faces at the powder interface.



X-Ray Powder Diffraction (3)

- Orthorhombic class:

$$1 / d^2 = [h^2 / a^2] + [k^2 / b^2] + [l^2 / c^2]$$

$$V = a\,b\,c$$

- Monoclinic class:

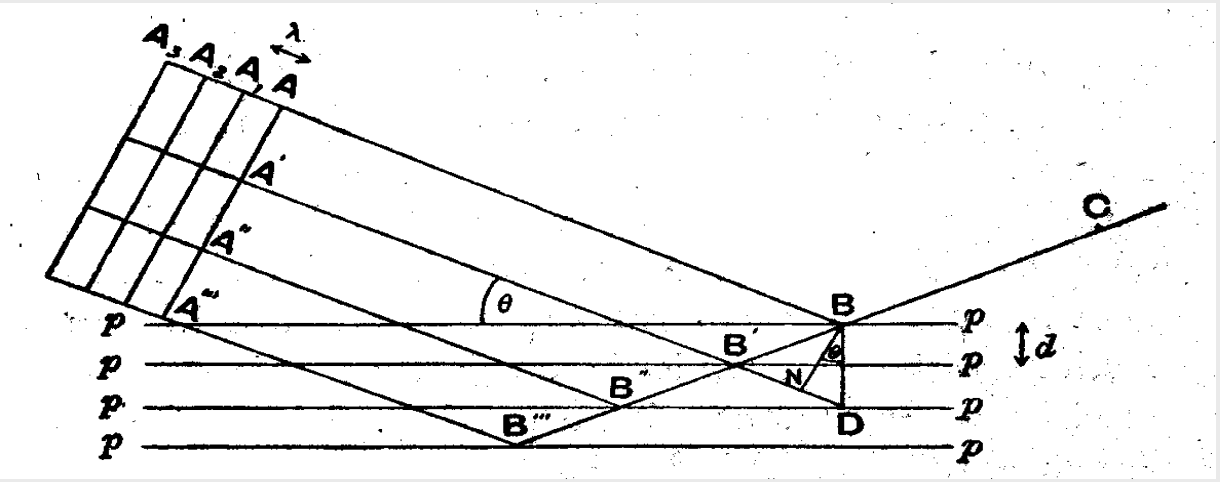
$$1 / d^2 = [h^2 / a^2 \sin^2 \beta] + [k^2 / b^2] + [l^2 / c^2 \sin^2 \beta] - [(2hl \cos \beta) / ac \sin^2 \beta]$$

$$V = a\,b\,c \sin \beta$$

X-Ray Powder Diffraction (4)

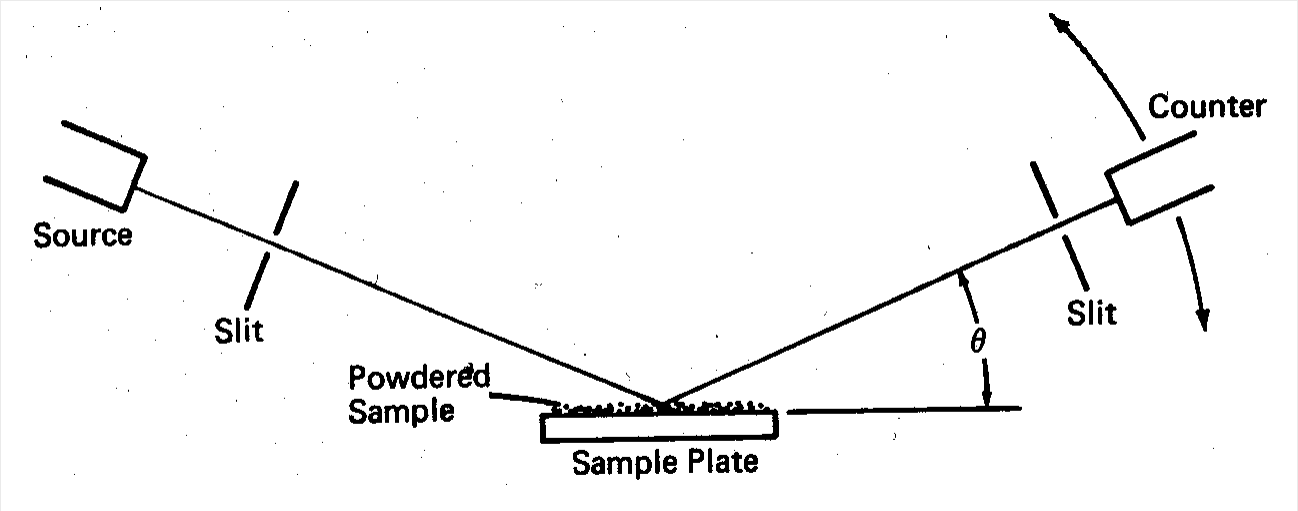
- Diffraction off the ensemble of surfaces yields information on all possible atomic spacings in the crystal lattice.
- Bragg's Law is used to interpret the data:

$$n\,\lambda \;=\; 2\,d\,\sin\theta$$



Automatic Diffractometer Method

- Automatic diffractometers obtain the XRPD of a sample through measurement of the scattering off the surface of a powder slab.



Preferential Orientation (1)

- Since almost all organic crystals are anisotropic in nature, their morphology can influence the relative intensities measured for various diffractions.
- If the powder slab of a given sample is processed in such a way that a statistically random sampling of crystal planes is not obtained, the observed powder pattern will over-emphasize the selected planes.

Preferential Orientation (2)

- If the microscopic examination of a sample indicates a plate-like morphology, the XRPD of the sample should be obtained a second time after performance of mild grinding or milling.
- The degree of particle size reduction must not lead to a reduction in the degree of crystallinity.

Powder Diffraction: Applications

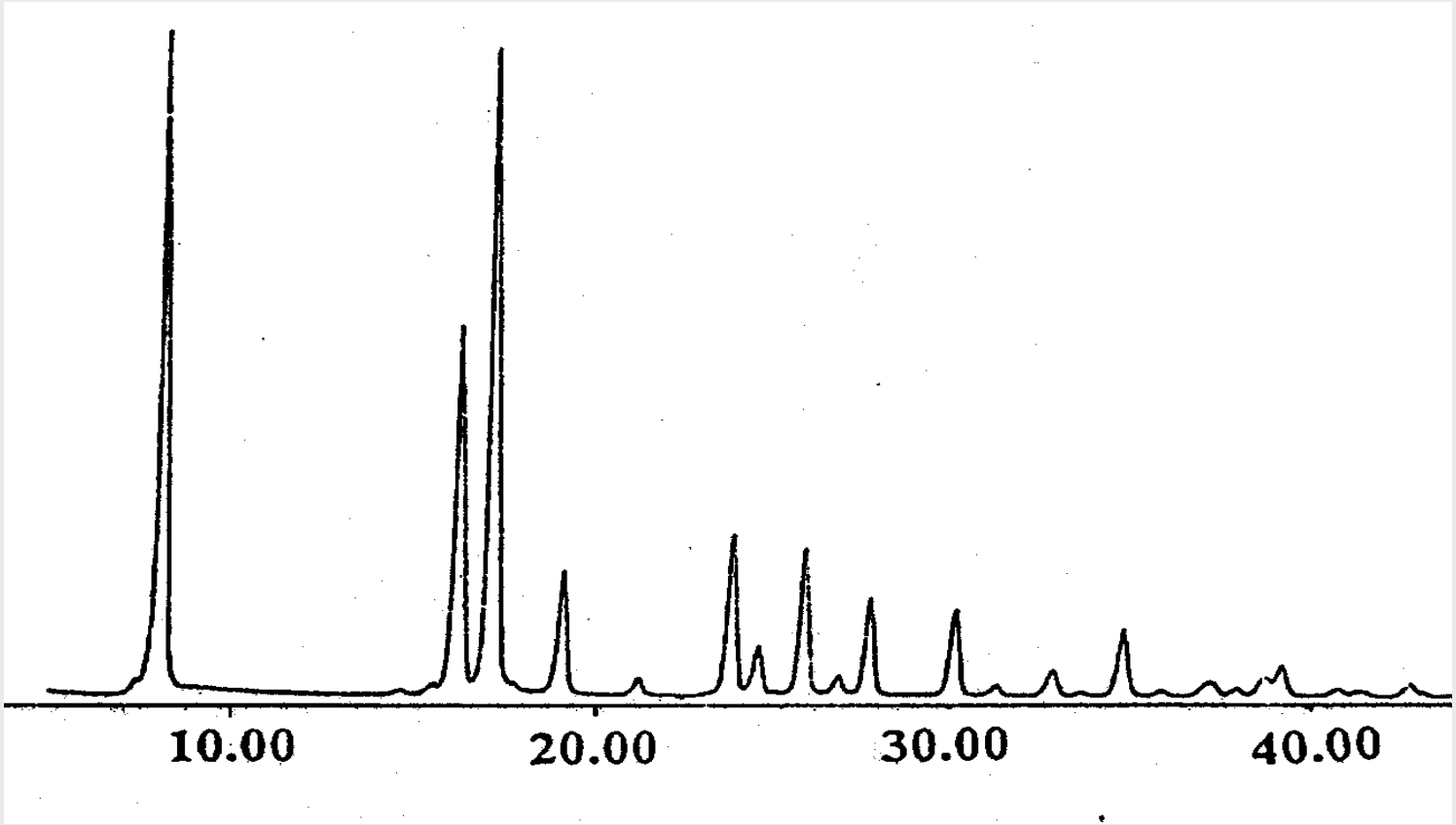
- **Conventional XRPD**
  - Phase identity of materials
  - Crystallographic properties (class, *a*, *b*, *c*)
  - Degree of crystallinity
  - Primary determinant of polymorphism
  - Phase composition of mixtures
- **Variable Temperature XRPD**
  - Structural interpretation for thermal events
  - Accelerated stability studies

Phase Identification (1)

- The USP general chapter on x-ray diffraction (<941>) states that identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree to within $\pm 0.20°$ 2-θ with that of the reference material, and that the relative intensities of these reflections do not vary by more than 20%.

Phase Identification (2)

- XRPD of benzoic acid:



Phase Identification (3)

- Data obtained for benzoic acid:

Scattering Angle (degrees 2-θ)	d-spacing (Å)	Relative Intensity (I/I_o)
17.2	5.1482	100
8.13	10.8662	95
16.29	5.4368	56
23.81	3.7334	27
25.85	3.4437	25
19.09	4.6452	21
27.77	3.2099	17
30.13	2.9636	16
34.85	2.5723	12
24.53	3.626	9

Phase Identification (4)

- Acceptability criteria for benzoic acid:

d-spacing (Å)	Lower Limit of Scattering Angle (deg. 2-θ)	Reference Scattering Angle (deg. 2-θ)	Upper Limit of Scattering Angle (deg. 2-θ)	Lower Limit of Relative Intensity (I/I_o)	Reference Relative Intensity (I/I_o)	Upper Limit of Relative Intensity (I/I_o)
5.1482	17.00	17.20	17.40	100	100	100
10.8662	7.93	8.13	8.33	76	95	114
5.4368	16.09	16.29	16.49	44.8	56	67.2
3.7334	23.61	23.81	24.01	21.6	27	32.4
3.4437	25.65	25.85	26.05	20.0	25	30.0
4.6452	18.89	19.09	19.29	16.8	21	25.2
3.2099	27.57	27.77	27.97	13.6	17	20.4
2.9636	29.93	30.13	30.33	12.8	16	19.2
2.5723	34.65	34.85	35.05	9.6	12	14.4
3.6260	24.33	24.53	24.73	7.2	9	10.8

Crystallographic Properties (8)

- The crystal structure of brinzolamide has been determined, and the derived cell parameters used to index its powder pattern.
  - *Anal. Prof. Drug. Sub. Excip.*, 26, 47 (1999)

Monoclinic ($P2_1$), Z = 4

a = 9.686 Å	α = 90°
b = 8.792 Å	β = 92.33°
c = 10.085 Å	γ = 90°

Crystallographic Properties (9)

- Indexed XRPD data for brinzolamide

Scatter Angle 2θ (deg.)	D Spacing (Å)	Relative Intensity (%)	Miller Indices		
			h	k	l
8.771	10.073	7.0	0	0	1
9.112	9.6971	4.5	1	0	0
12.422	7.1198	100.0	-1	0	1
13.371	6.6166	6.3	0	1	1
16.020	5.5279	7.2	-1	1	1
16.412	5.3965	16.8	1	1	1
18.329	4.8364	18.5	2	0	0
19.541	4.5391	6.8	-1	0	2
20.168	4.425	27.7	-2 1 0 0	0 0 2 1	1 2 0 2

Crystallographic Properties (10)

- When the cell constants are now previously known from the single crystal structure, the powder pattern can be indexed using:
  - Trial and error
  - Graphical techniques
- The accuracy of the indexing is directly dependent on the quality of the XRPD data.

Evaluation of Polymorphism (1)

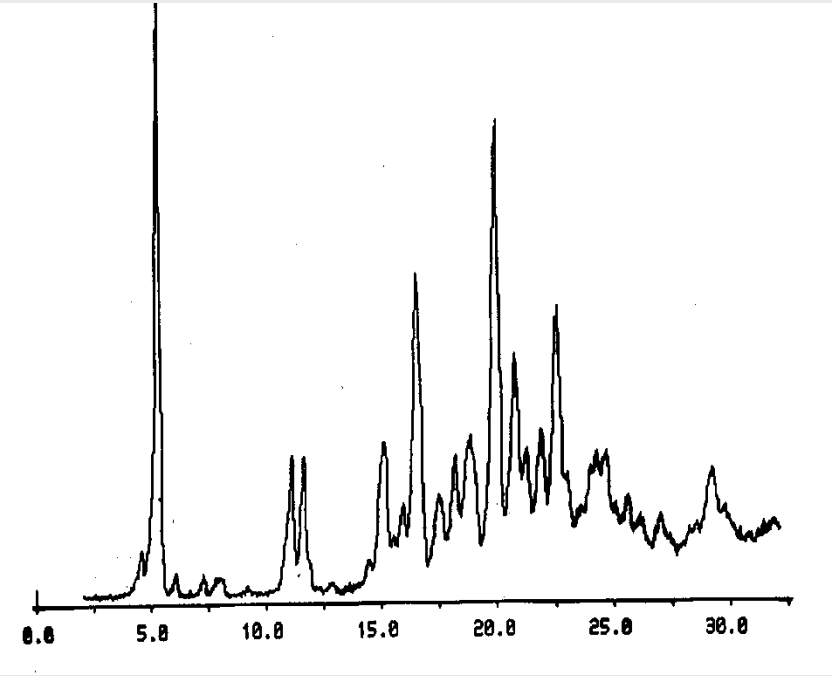
- Since the existence of polymorphism (or of solvatomorphism) is a crystallographic phenomenon, XRD techniques are the primary methods for determination.
- Owing to its ease of data acquisition, XRPD is particularly useful as a screening technique for batch characterization.

Evaluation of Polymorphism (2)

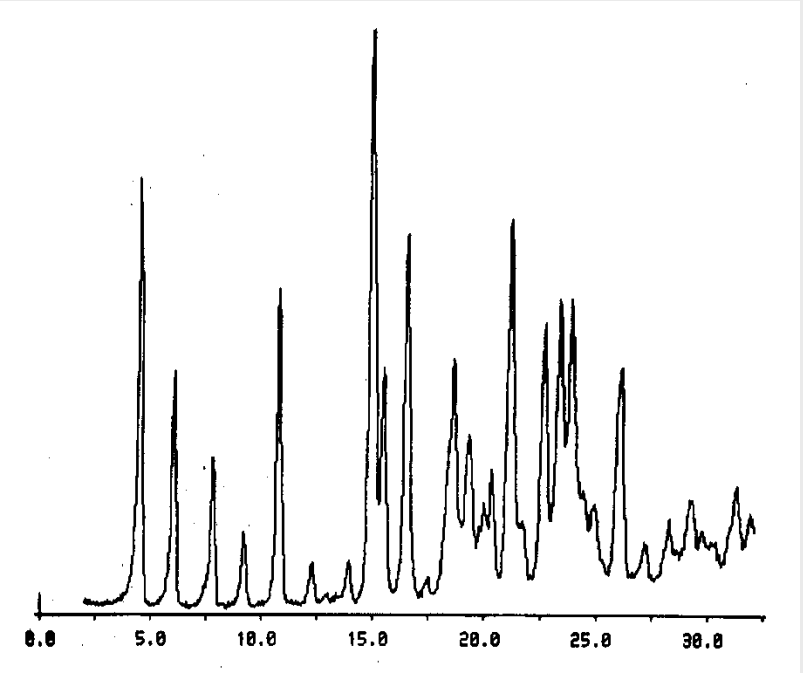
- Form-A of fosinopril sodium is obtained through slow crystallization, and the identity of the solvent does not affect the crystal type.
- Form-B can only obtained by flash evaporation from alcoholic solutions. Large surface areas within the crystallizing vessel are required to obtain phase pure Form-B material.
  - *J. Pharm. Biomed. Anal.*, 11, 1063 (1993).

Evaluation of Polymorphism (3)

Fosinopril Na, Form A

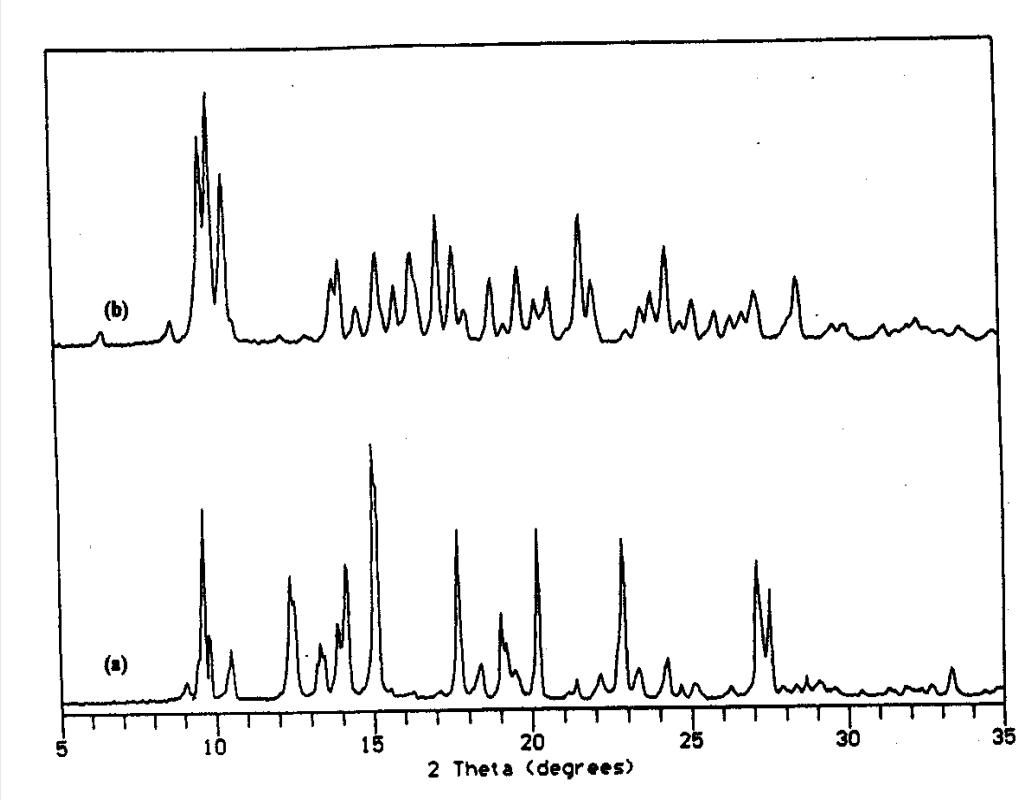


Fosinopril Na, Form B



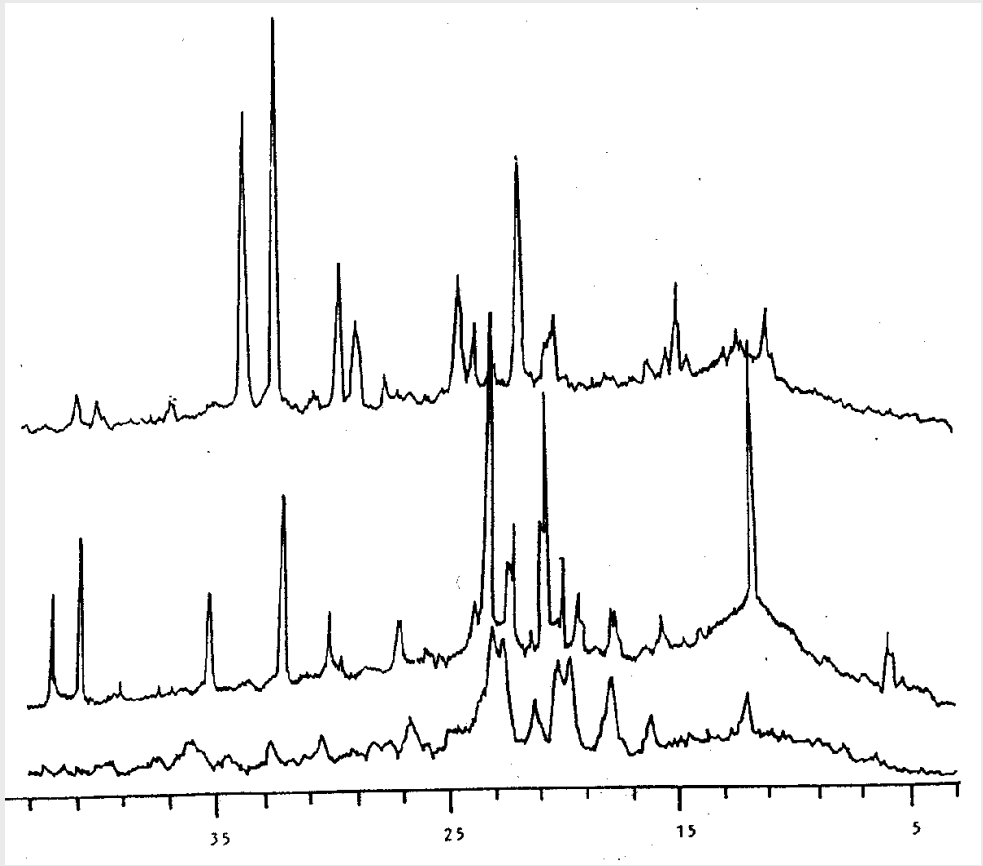
Evaluation of Polymorphism (4)

- XRPD of the two forms of piroxicam pivalate.
  - *J. Pharm. Sci.*, 87, 333 (1998)



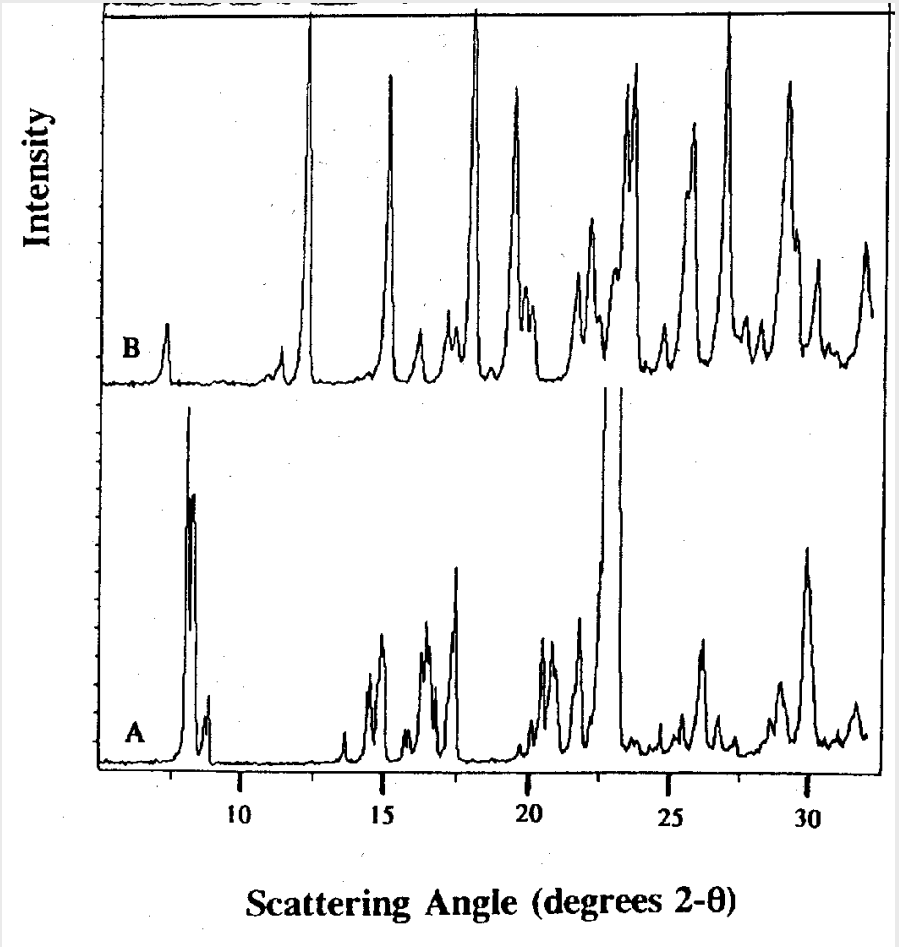
Evaluation of Polymorphism (5)

- XRPD of the three forms of famotidine.
  - *Int. J. Pharm.*, **149**, 227 (1997)



Evaluation of Polymorphism (6)

XRPD of the (A) anhydrate and (B) trihydrate phases of ampicillin.

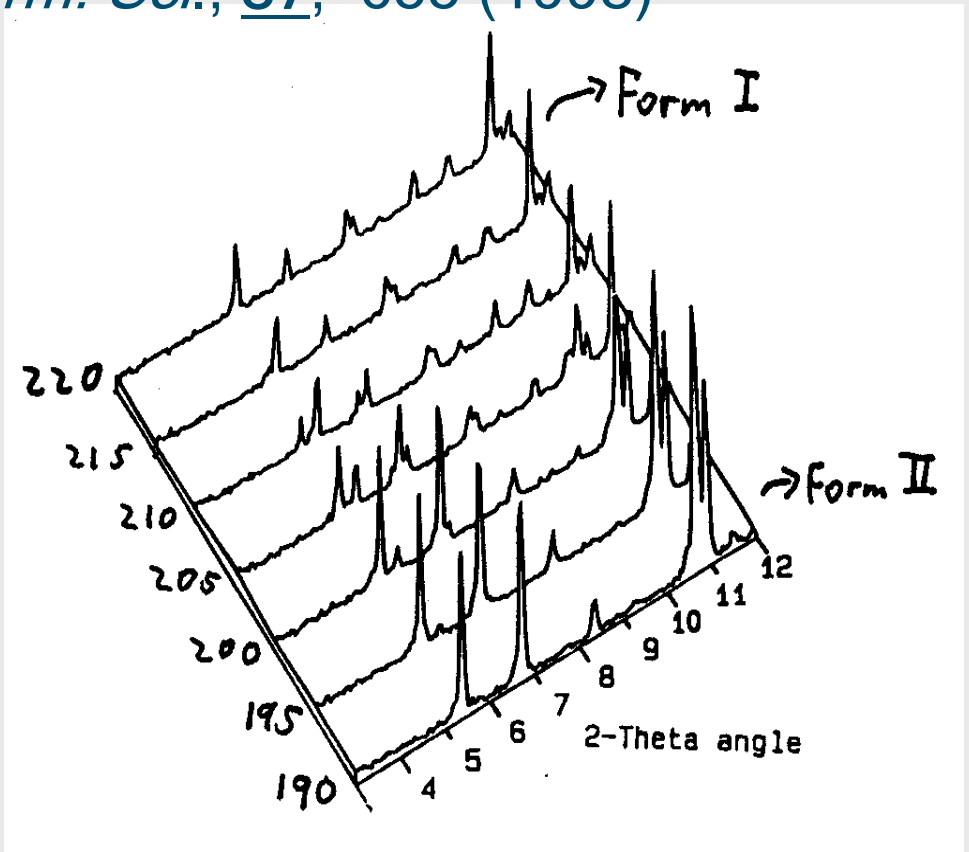


Thermal XRPD (1)

- When XRPD is conducted on a heatable stage, the nature of thermally induced transitions noted in a DSC or TG thermogram can be studied.
- The technique is most appropriately applied to the study of:
  - Phase transitions
  - Desolvations

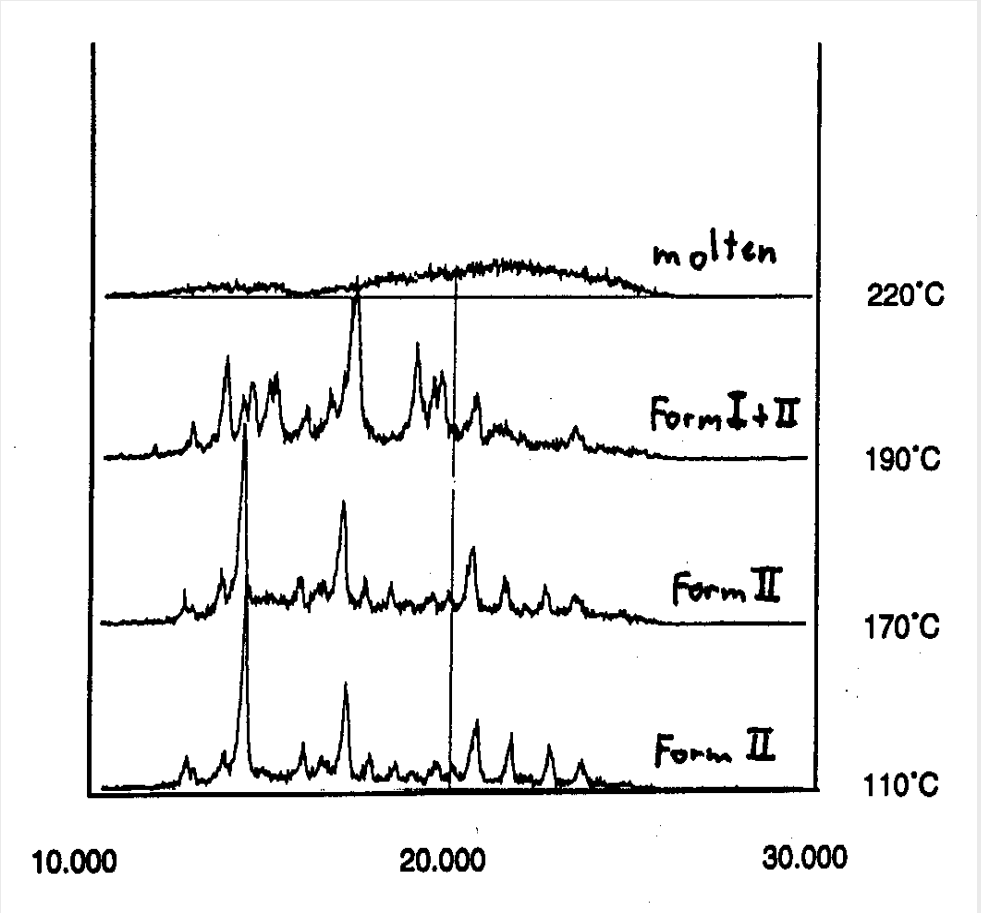
Thermal XRPD (2)

- XRPD of chlordiazepoxide showing the phase change from Form-II to Form I.
  - *J. Pharm. Sci.*, 87, 655 (1998)



Thermal XRPD (3)

- XRPD of Iomeridine HCl, showing the partial Form-II to Form I phase change prior to melting.
  - *J. Pharm. Sci.*, **85**, 761 (1996)



Summary (1)

- XRPD represents the methodology of choice for the crystallographic characterization of drug substances produced on a routine, batch-type basis.
- Properly prepared samples yield powder patterns that contain a scattering peak for each crystal plane / face, and therefore constitute an identification test for a given crystalline phase.

Summary (2)

- When the data are of suitable quality, XRPD can be used to deduce details of the unit cell and the crystal structure.
- With the generation of appropriate calibration data, XRPD can be used as a means to deduce the:
  - Degree of crystallinity in a given sample.
  - Composition of a physically heterogeneous mixture.

Summary (3)

- Since polymorphism and solvatomorphism are crystallographic occurrences, XRPD will always be the primary determinant of the existence of such phenomena.
- Variable temperature XRPD is a valuable tool to understand thermally induced reactions, and to characterize materials during the conduct of stability studies.

Module 1: Crystal Forms of API

Part Ic.

THERMAL METHODS OF ANALYSIS

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Defining Characteristics of Thermal Analysis Methods

- The physical property and the sample temperature are measured continuously.
- Both the property and the temperature are recorded automatically.
- The temperature of the sample is altered at a predetermined rate.

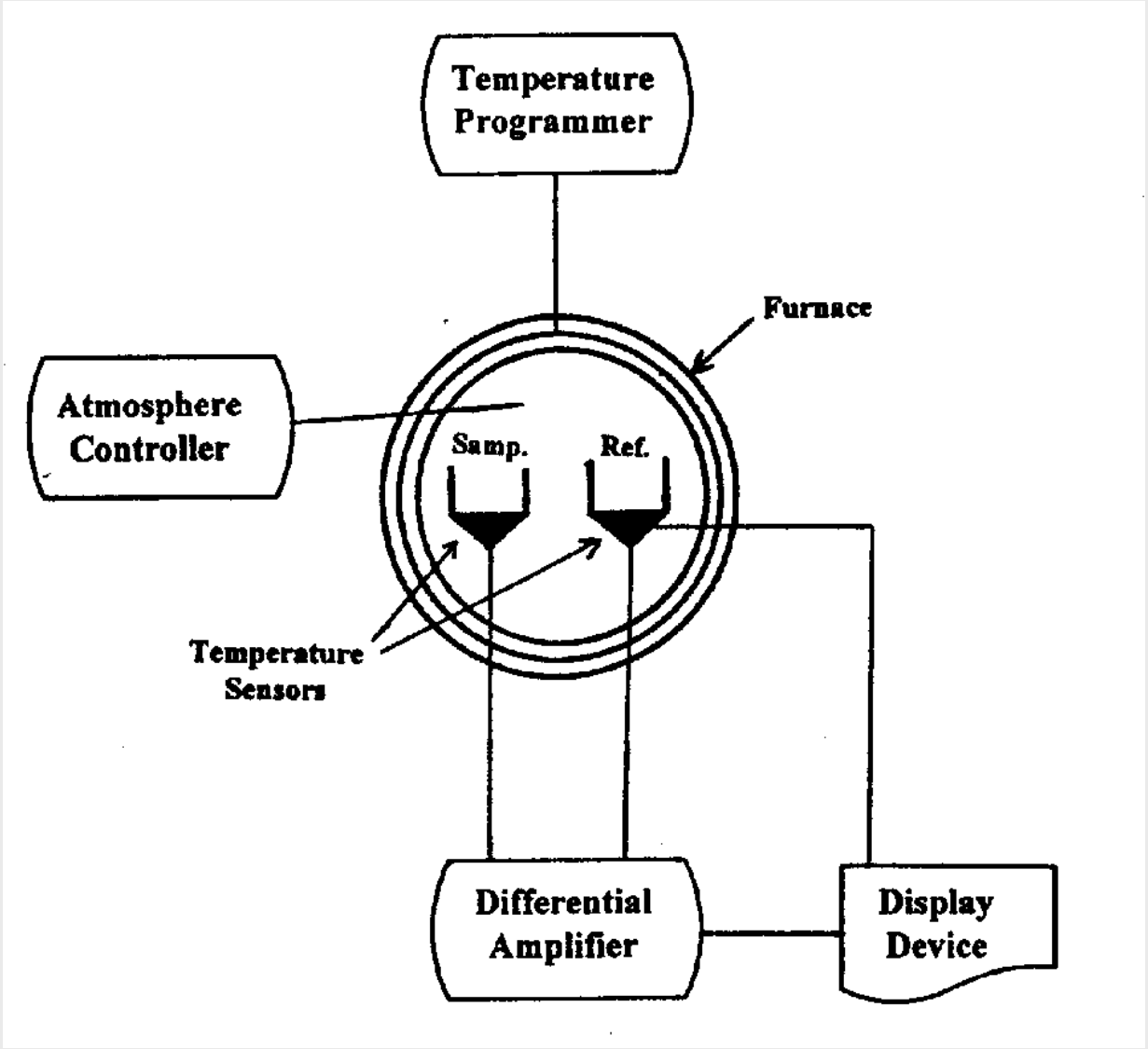
Reaction Types

- Endothermic
  - Melting, boiling, sublimation, vaporization, desolvation, phase transitions, chemical degradation.
- Exothermic
  - Crystallization, oxidative decomposition.

Differential Thermal Analysis (1)

- The technique is mostly used for the qualitative identification of thermally induced chemical and physical reactions, and for the determination of the temperatures associated with these processes.
- Typical reactions studies include phase transformations, structural conversions, desolvation reactions, and decomposition reactions.

Differential Thermal Analysis (2)



Differential Scanning Calorimetry (1)

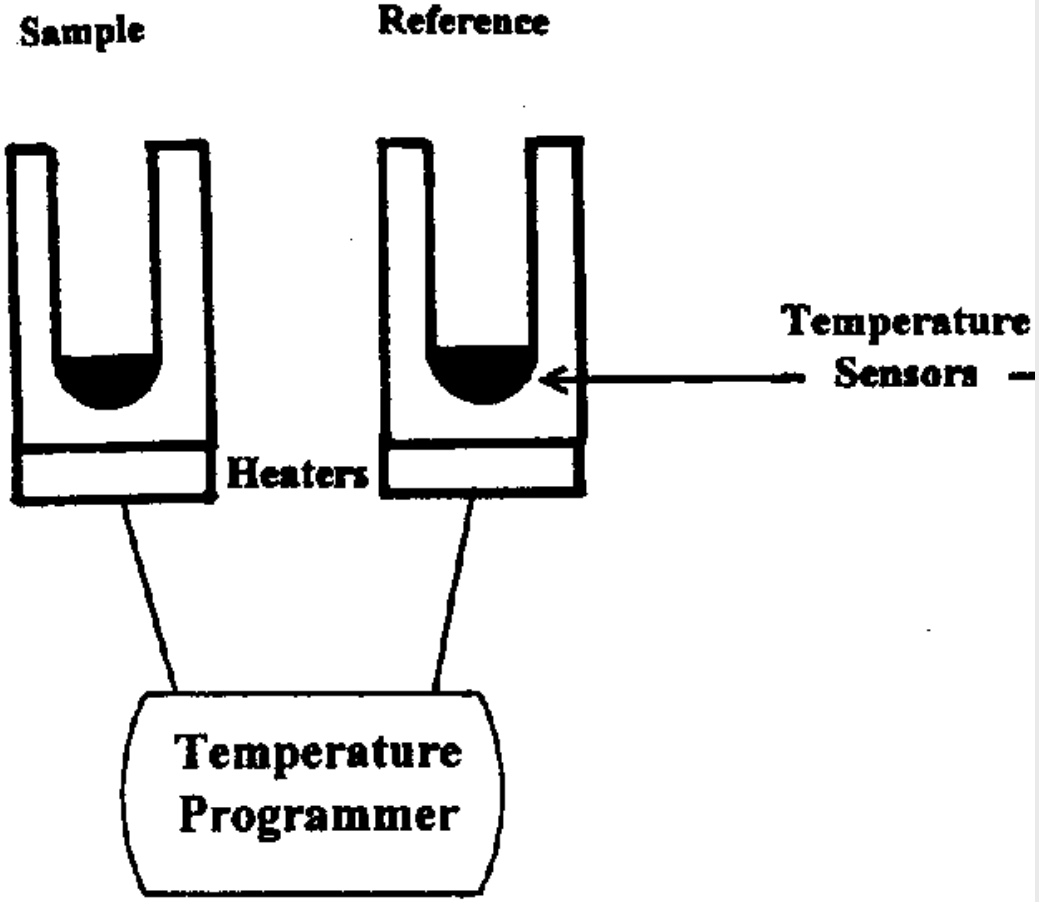
- DSC analysis entails a measurement of the differential heat capacity of the sample.
- The sample and reference are maintained at the same temperature, and the heat flow required to keep the equality in temperature is measured.
- Consequently, DSC thermograms are plotted as the differential rate of heating (*e.g.*, J/sec) against temperature.

Differential Scanning Calorimetry (2)

- As with DTA, DSC is used for the identification of thermally induced chemical and physical reactions, and for the determination of the temperatures associated with these processes.
- The area under a DSC peak is directly proportional to the heat absorbed or evolved by the thermal event, and integration of the peak area yields the heat of that reaction.
- When a compound is found to melt without decomposition, DSC analysis can be used to determine the absolute purity.

Differential Scanning Calorimetry (3)

- Power-compensation DSC:

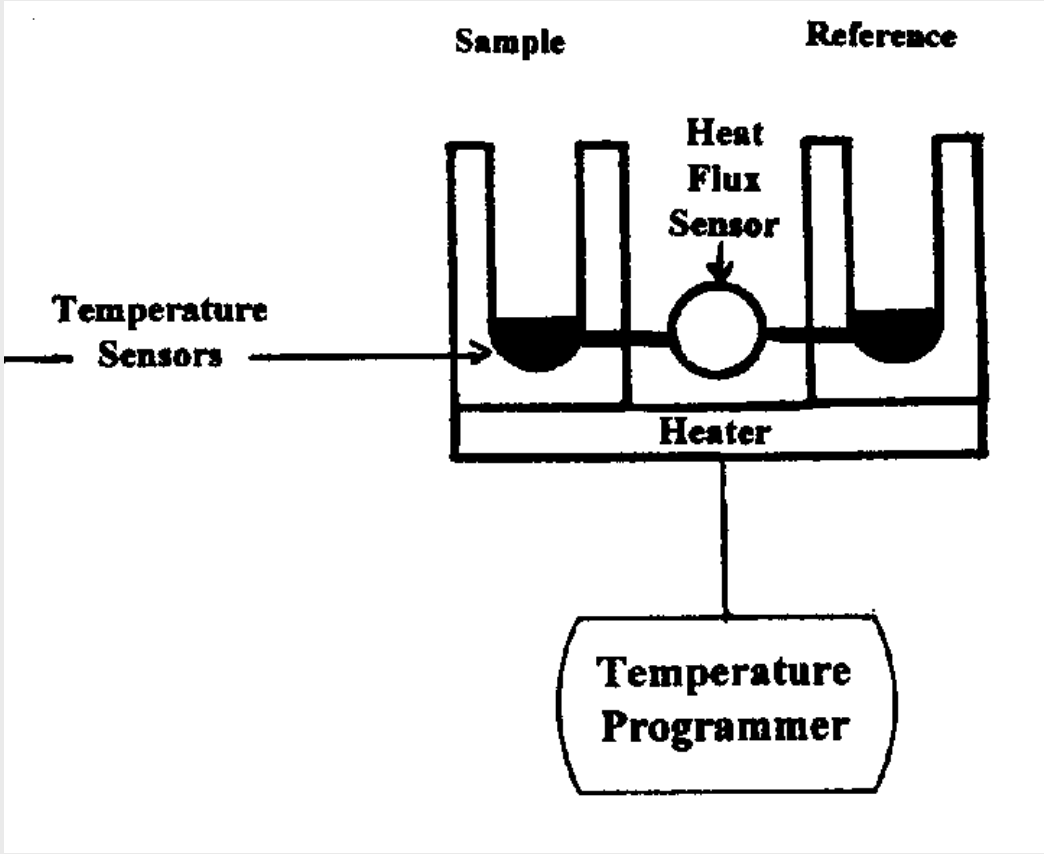


Differential Scanning Calorimetry (4)

- In power-compensated DSC, the sample and reference materials are kept at the same temperature by the use of individualized heating elements.
- The observable parameter recorded is the difference in power inputs to the two heaters.

Differential Scanning Calorimetry (5)

- Heat-flux DSC:

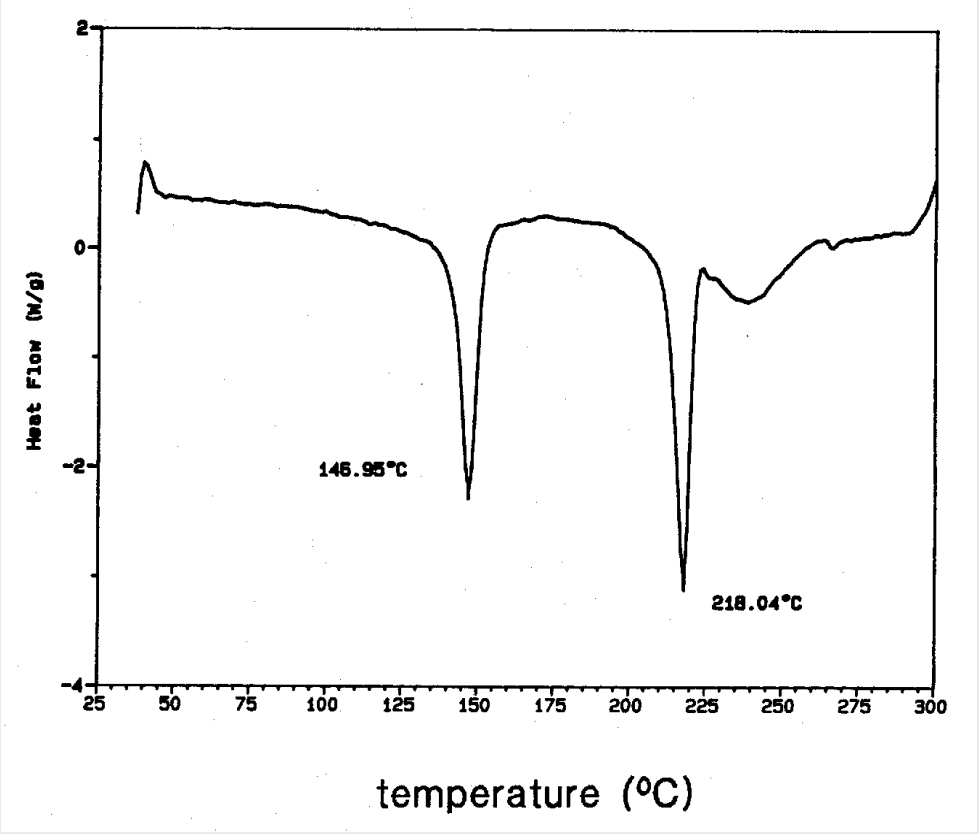


Differential Scanning Calorimetry (6)

- In heat-flux DSC, one monitors the heat differential between the sample and reference materials through the use of a heat flux sensor.
- The heat-flux methodology is quite similar to that used to obtain DTA thermograms.

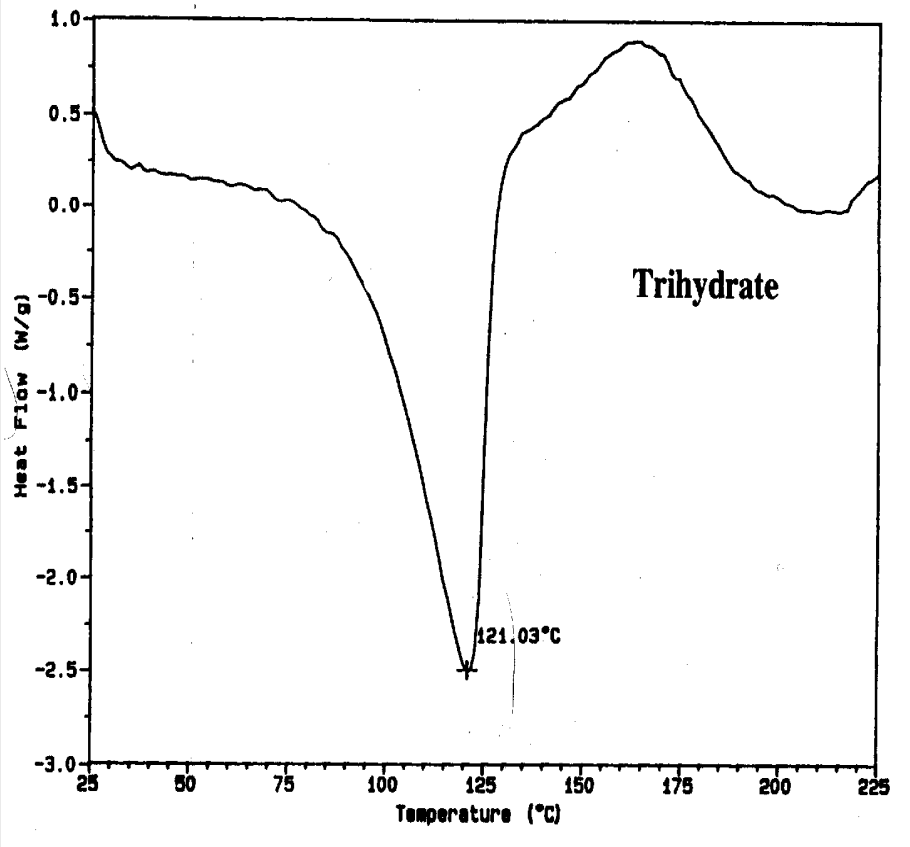
Differential Scanning Calorimetry (8)

- DSC thermogram of lactose monohydrate.
- The dehydration of lattice water from a strong crystal structure yields sharp thermal features.



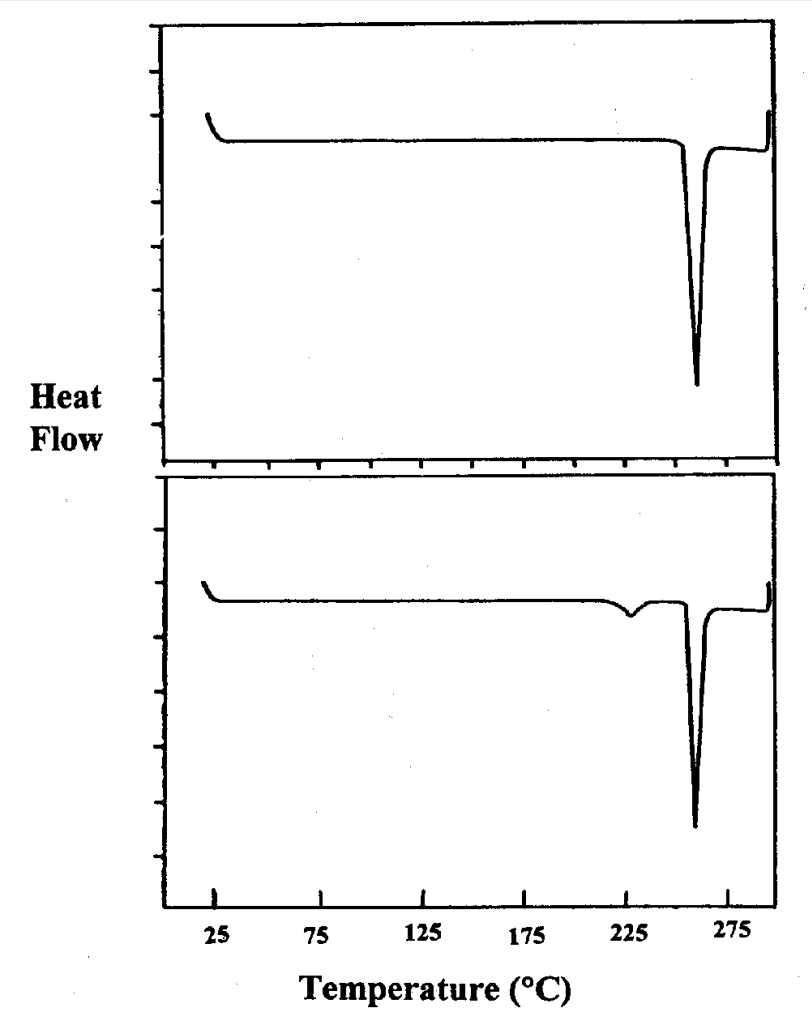
Differential Scanning Calorimetry (9)

- DSC thermogram of ampicillin trihydrate.
- The dehydration of lattice water from a weak crystal structure yields broad thermal features.



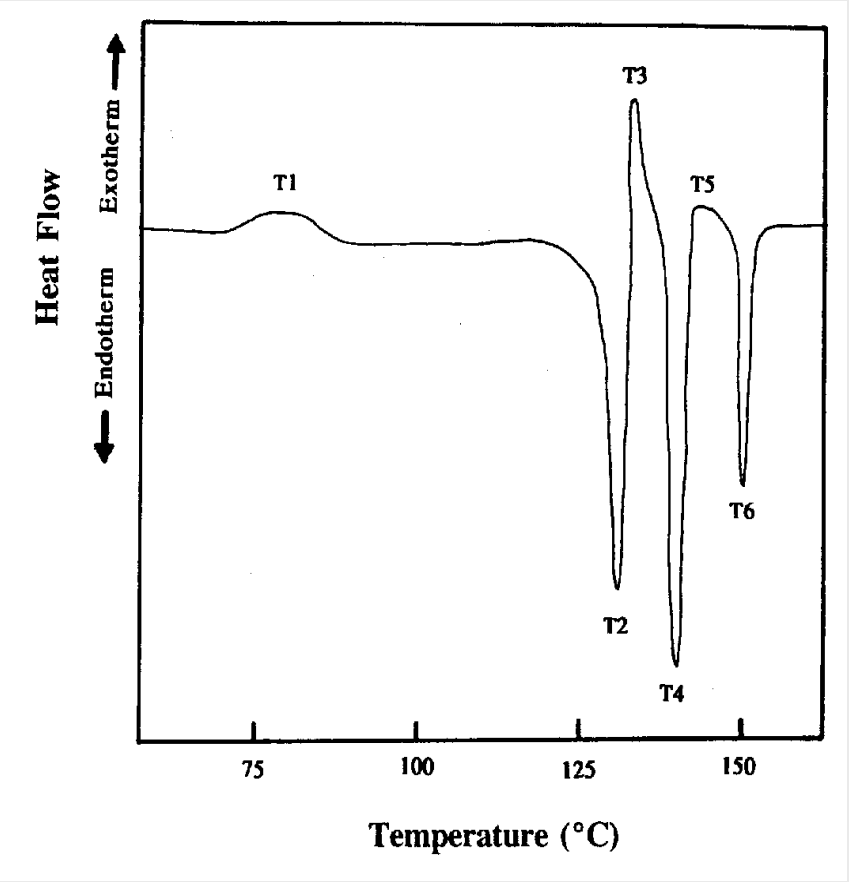
Differential Scanning Calorimetry (10)

- DSC thermograms of proscar, form II (upper trace) and form I (lower trace). The latter thermogram shows the I⌧II phase transformation prior to the melting transition.
  - J.A. McCauley, unpublished results.



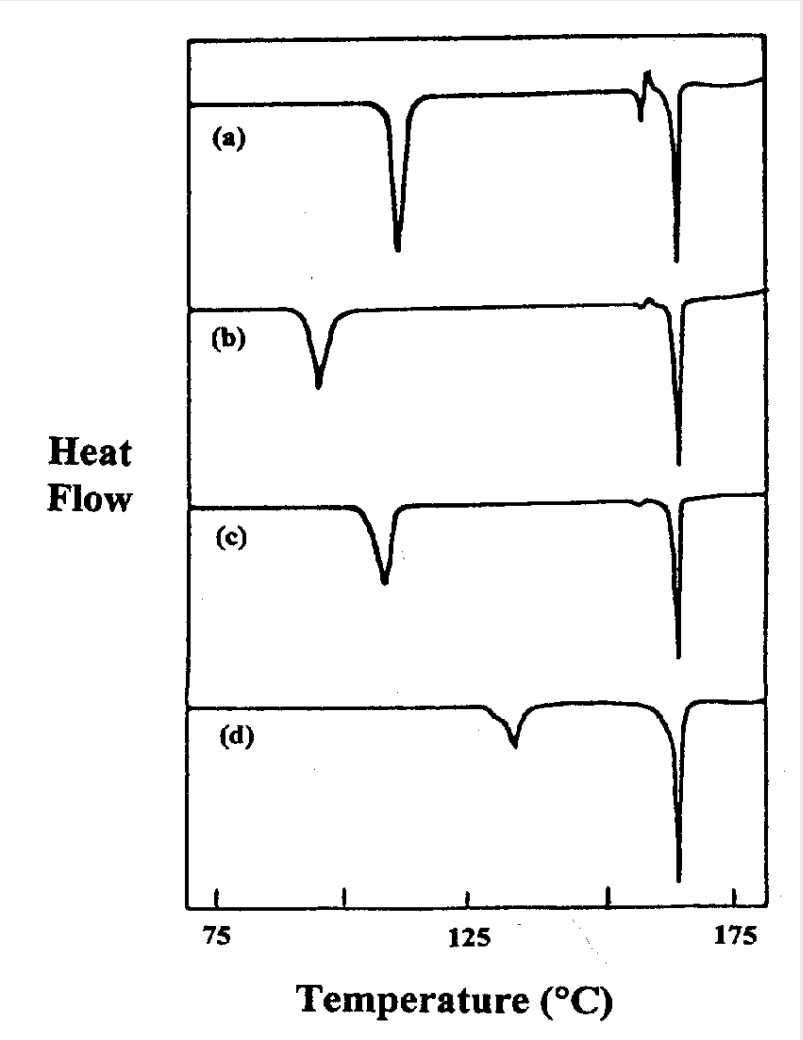
Differential Scanning Calorimetry (11)

- DSC thermogram of 2,4-dinitrophenyl-2,4-dinitrobenzoate, showing recrystallization of form IV to form III (T1), melting of forms III and II (T2 and T4), solidification of the melts produced by T2 and T4 (t3 and T5), and melting of form I (T6).
  - *Microchim. Acta*, II, 107 (1987).



Differential Scanning Calorimetry (12)

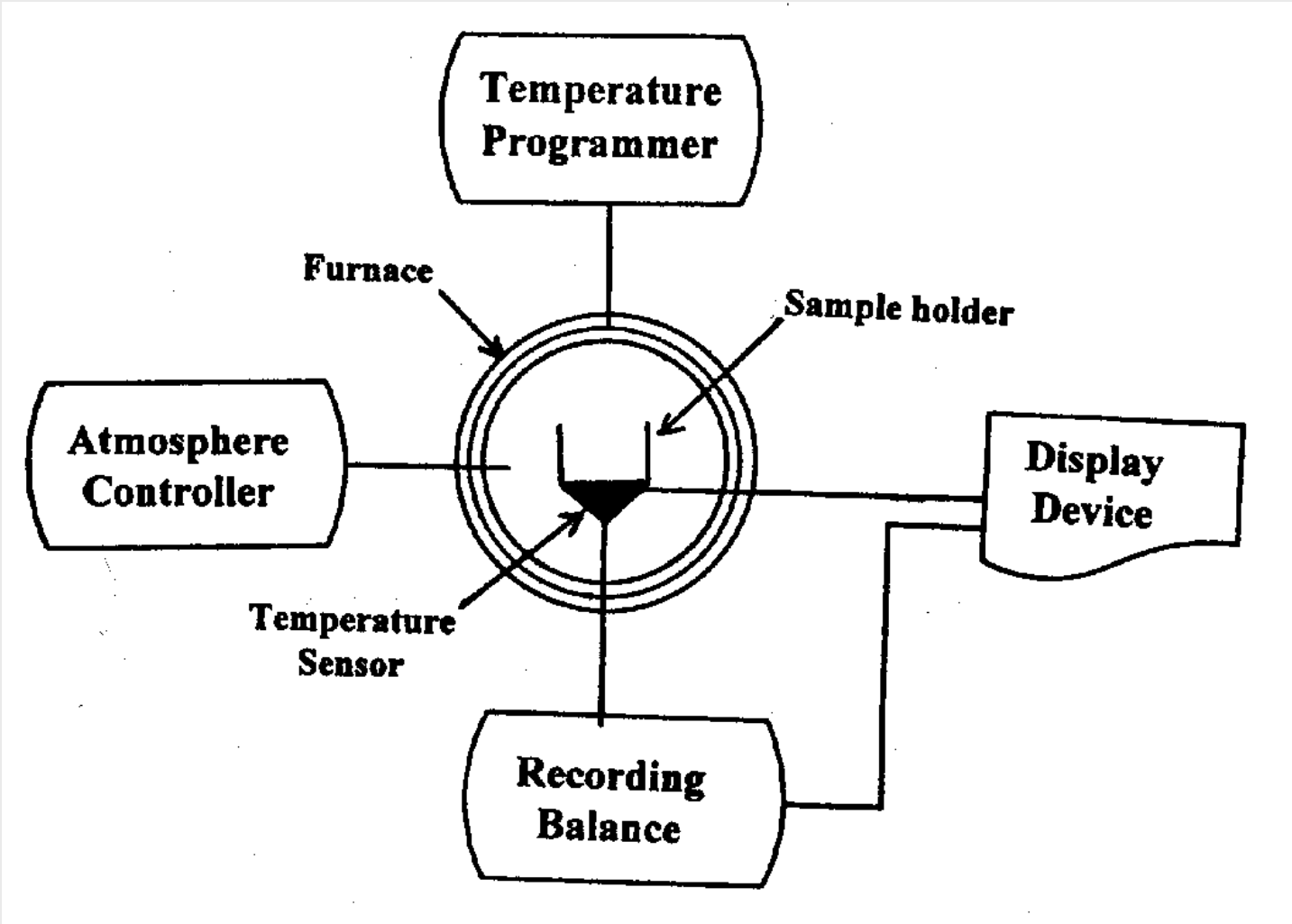
- DSC thermograms of piretanide, as recrystallized from (a) *t*-butanol, (b) *n*-butanol, (c) *i*-propanol, and (d) *N,N*-dimethyl formamide.
  - *Chem. Pharm. Bull*., **42**, 1123 (1994).



Thermogravimetry (1)

- TG is a measurement of the thermally induced weight loss of a material as a function of the applied temperature.
- Consequently, TG analysis is restricted to studies involving either a gain or loss in sample mass, such as desolvation decomposition reactions.
- TG is a highly useful adjunct to either DTA or DSC in that it permits an easy differentiation between endotherms that involve loss of mass and those that do not.

Thermogravimetry (2)

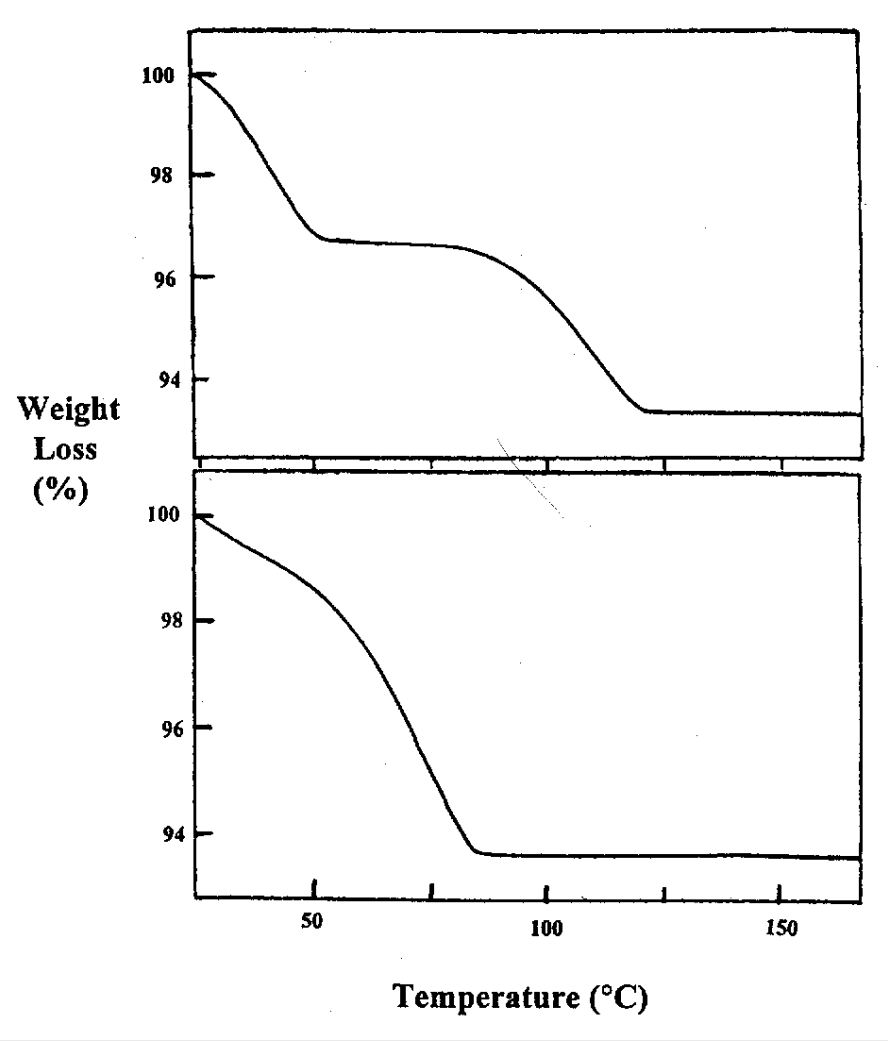


Thermogravimetry (3)

- When a solid is capable of decomposing by means of discrete sequential reactions, the magnitude of each step can be separately determined.

Thermogravimetry (4)

- TG thermograms associated with the dehydration of two dihydrate polymorphs of an experimental compound.

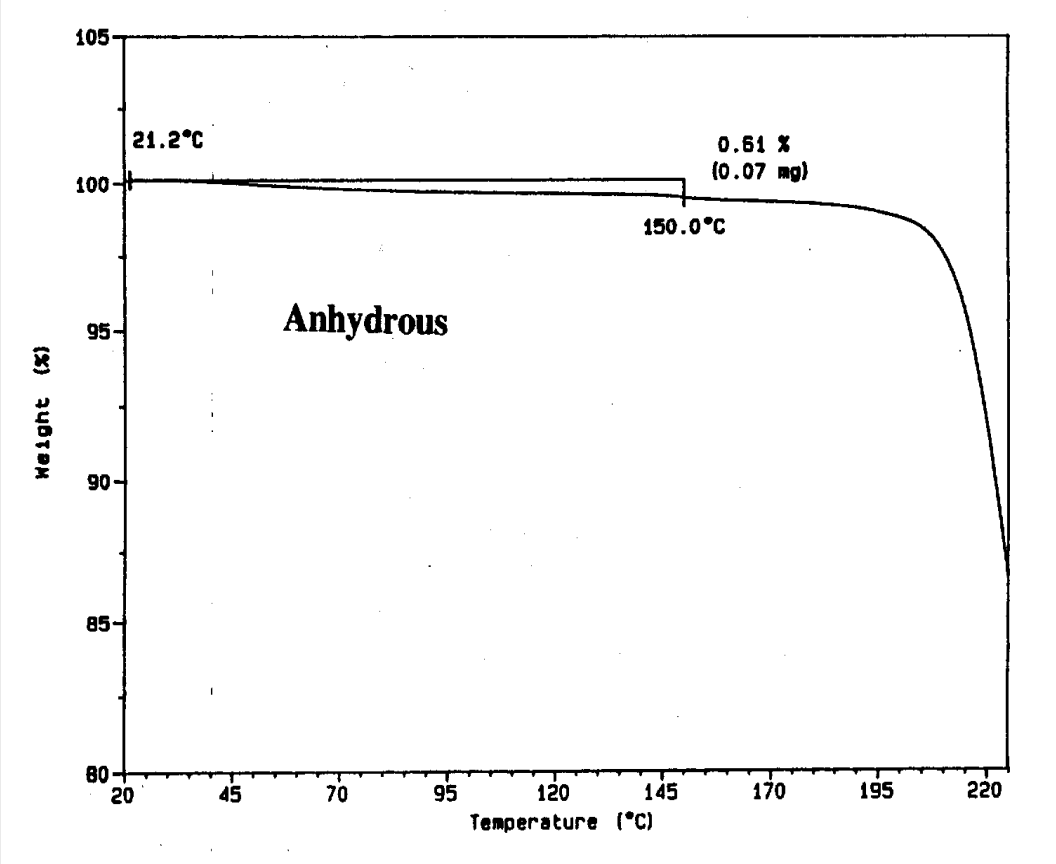


Thermogravimetry (5)

- When considering a series of related compounds, the higher the decomposition temperature the more stable a compound is considered to be.

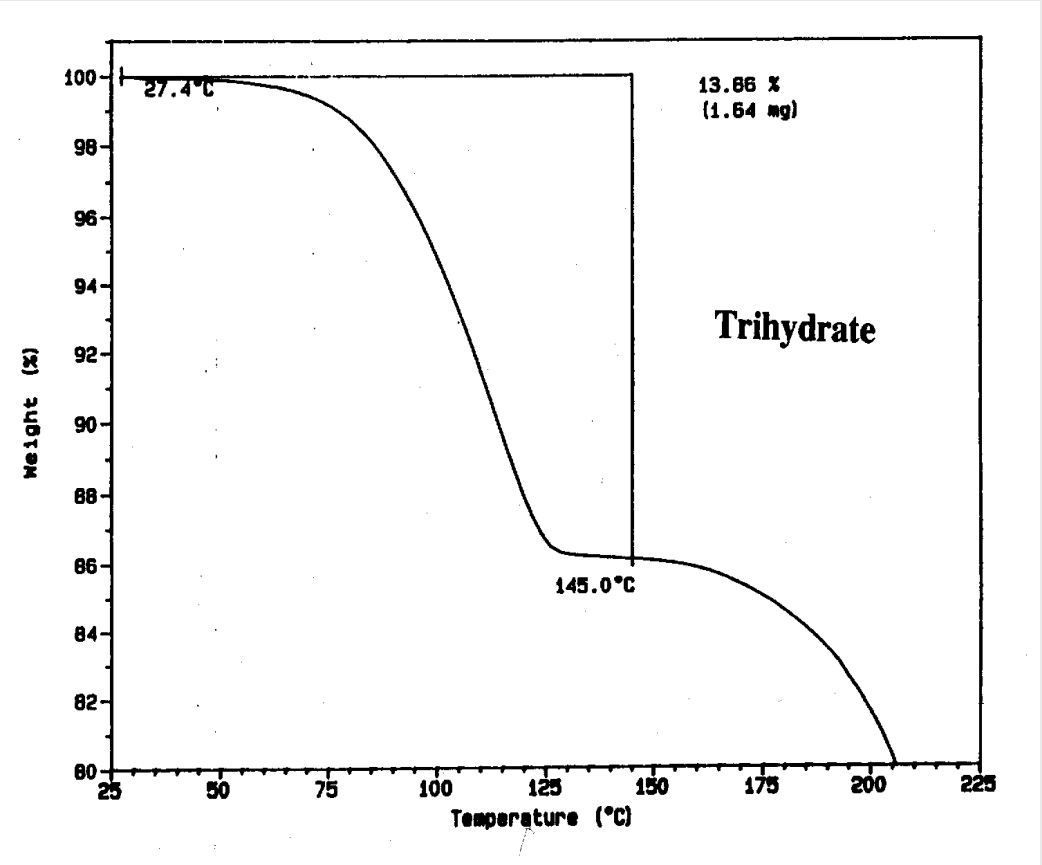
Thermogravimetry (6)

- TG of ampicillin anhydrate: the onset of oxidative degradation is approximately 215°C.



Thermogravimetry (7)

- TG of ampicillin trihydrate: the onset of oxidative degradation is approximately 190°C.



Module 1: Crystal Forms of API

Part Id.
USE OF SOLID-STATE SPECTROSCOPY FOR THE CHARACTERIZATION OF POLYMORPHS AND SOLVATOMORPHS

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Spectroscopic Properties of Polymorphs (1)

- When the differing crystal structures of polymorphs or solvatomorphs translates into a perturbation of the pattern of molecular vibrations, then the techniques of vibrational spectroscopy (*i.e.*, infrared absorption or Raman scattering) can be used to study the solids.

Spectroscopic Properties of Polymorphs (2)

- When the differing crystal structures of polymorphs or solvatomorphs translates into a perturbation of the chemical environments of the component nuclei, then the technique of nuclear magnetic resonance (usually ^{13}C-NMR) can be used to study the solids.

Spectroscopic Properties of Polymorphs (3)

- When the differing crystal structures of polymorphs or solvatomorphs translates into an alteration of molecular orbital energies, then technique associated with ultraviolet or visible spectroscopy (*i.e.*, UV/VIS reflectance or fluorescence spectroscopy) can be used to study the solids.

Overview

Solid-State Vibrational Spectroscopy (fundamental transitions)

a. Infrared Absorption Spectroscopy

b. Raman Spectroscopy

Spectroscopy of overtone vibrational transitions (Near-Infrared Spectroscopy).

Solid-State Nuclear Magnetic Resonance Spectrometry

Vibrational Spectroscopy

Spectroscopic transitions among states whose wave functions are independent of electronic character, but are defined as having predominantly nuclear motion properties (states of molecular vibration).

- IR absorption spectroscopy (EMR = IR or NIR)
- Raman spectroscopy (a scattering technique using EMR = UV, VIS, or NIR)

- Since the energy levels of vibrational states are strongly affected by details of chemical bonding, these spectroscopic transitions are also very useful for the study of molecular properties.

Infrared Absorption Spectroscopy (1)

- Measurement of IR spectra in the solid state requires the simultaneous use of Fourier Transform detection methodology and special sample measurement techniques (DRIFTS or ATR).

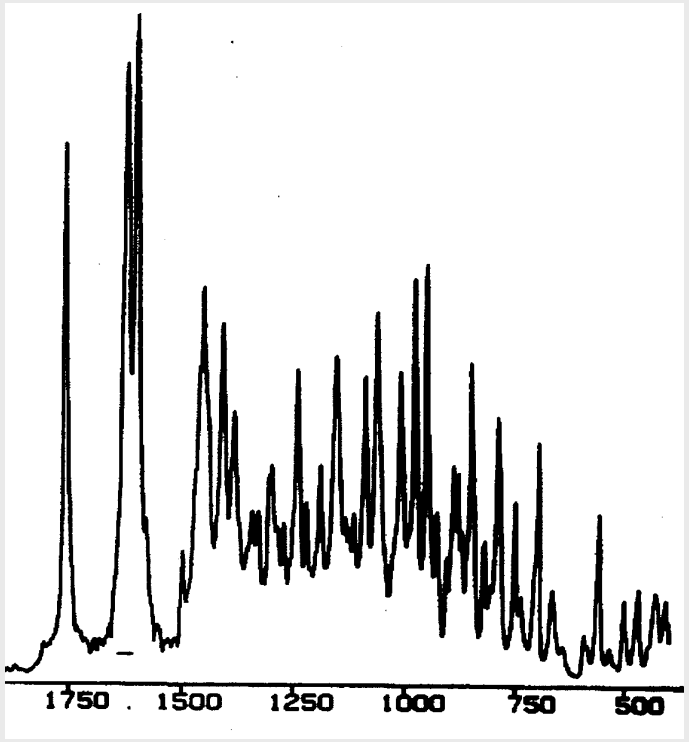
  Far IR = 10 to 400 cm^{-1}

  Mid IR = 400 to 4000 cm^{-1}

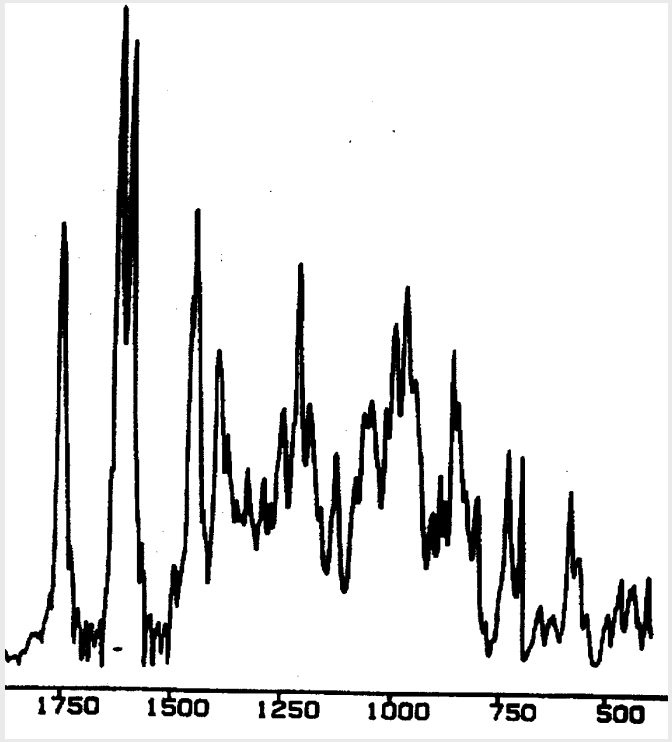
  Near IR = 4000 to 20,000 cm^{-1}

Infrared Absorption Spectroscopy (2)

Form A



Form B



Fosinopril Sodium: *J. Pharm. Biomed. Anal.*, 11, 1063 (1993)

Infrared Absorption Spectroscopy (3)

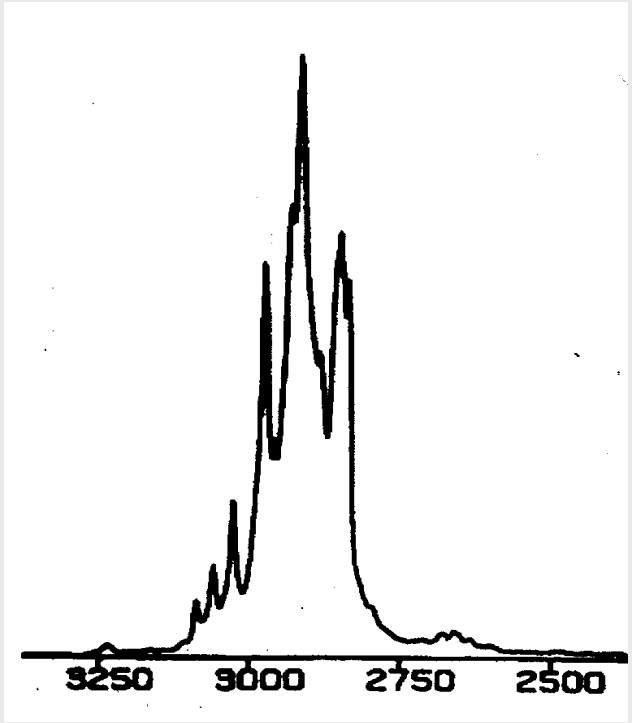
Comparison of carbonyl stretching frequencies in the mid-IR region

Assignment	Form-A	Form-B
C-15	1759 cm^{-1}	1753 cm^{-1}
C-6	1622 cm^{-1}	1621 cm^{-1}
C-1	1600 cm^{-1}	1598 cm^{-1}

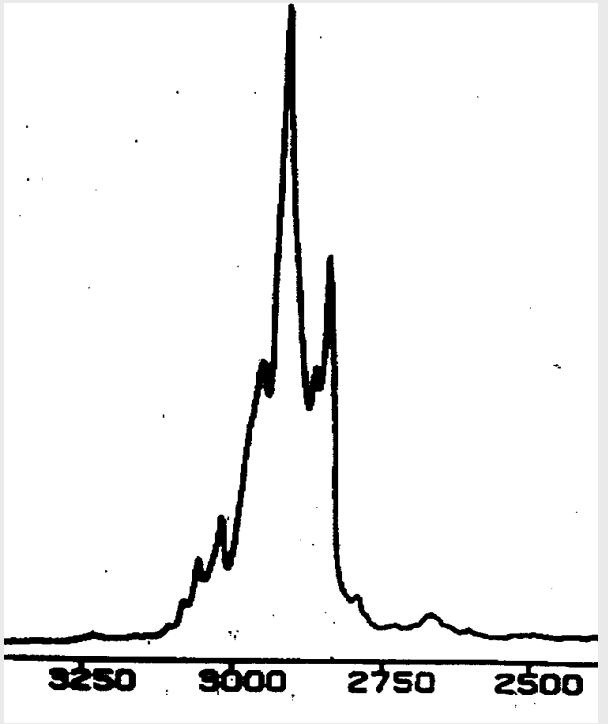
Fosinopril Sodium: *J. Pharm. Biomed. Anal.*, 11, 1063 (1993)

Infrared Absorption Spectroscopy (4)

Form A



Form B



Fosinopril Sodium: *J. Pharm. Biomed. Anal.*, 11, 1063 (1993)

Raman Spectroscopy (1)

- In Raman spectroscopy, one measures the inelastic scattering of radiation by a non-absorbing medium.
- The scattered light can be detected at lower (Stokes lines) and higher (anti-Stokes lines) frequencies relative to that of the incident (or elastically scattered) light.
- The energy displacements relative to the energy of the incident beam correspond to the vibrational transition frequencies of the scattering molecule.

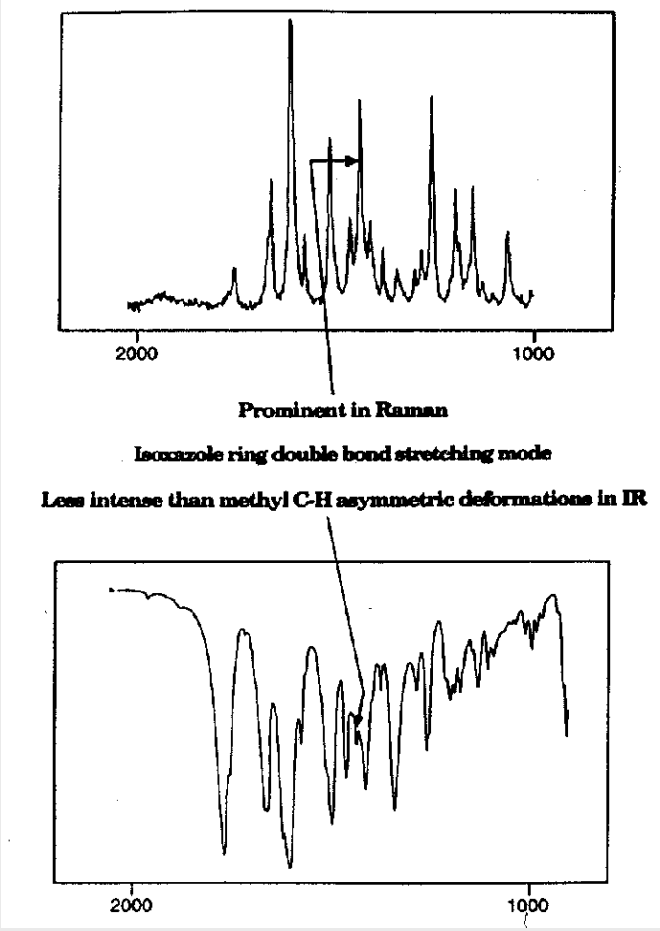
Raman Spectroscopy (2)

- The Raman effect originates from the interaction of the oscillating induced polarization or dipole moment of the molecule with the electric field vector of the incident radiation.
- Although both infrared absorption and Raman scattering both yield information on the energies of the same vibrational motion, different selection rules govern the band intensities for each type of spectroscopy.

Raman Spectroscopy (3)

- Symmetric vibrations and nonpolar groups yield the most intense Raman scattering bands, while anti-symmetric vibrations and polar groups yield the most intense infrared absorption bands.
- Raman scattering bands are usually sharp, and consequently Raman spectra often contain significantly less spectral overlap relative to infrared absorption spectra.

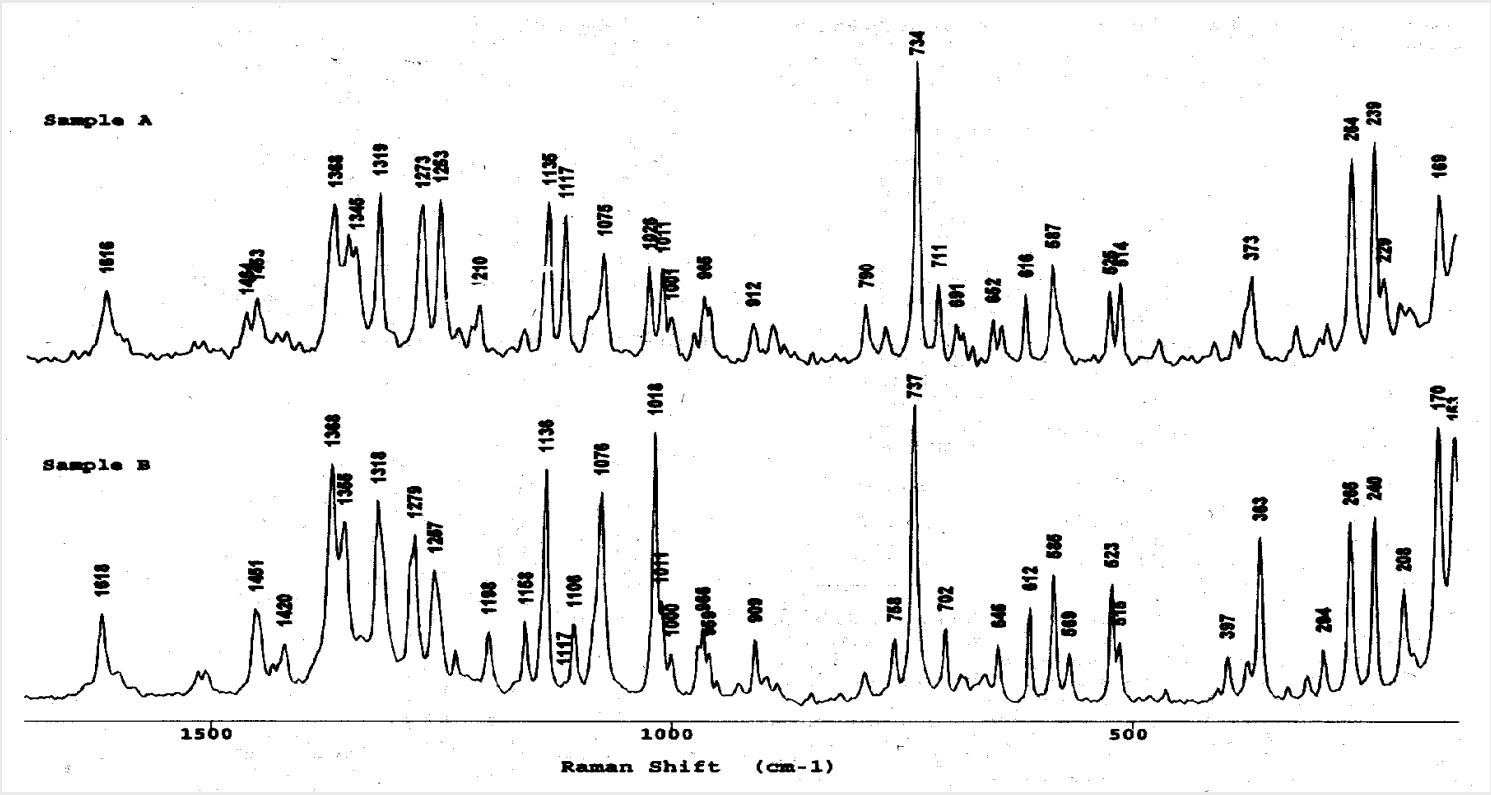
Raman Spectroscopy (4)



Raman (upper trace) and IR absorption (lower trace) spectra of flucloxacillin.

Spectrochim. Acta, 49A, 809 (1993)

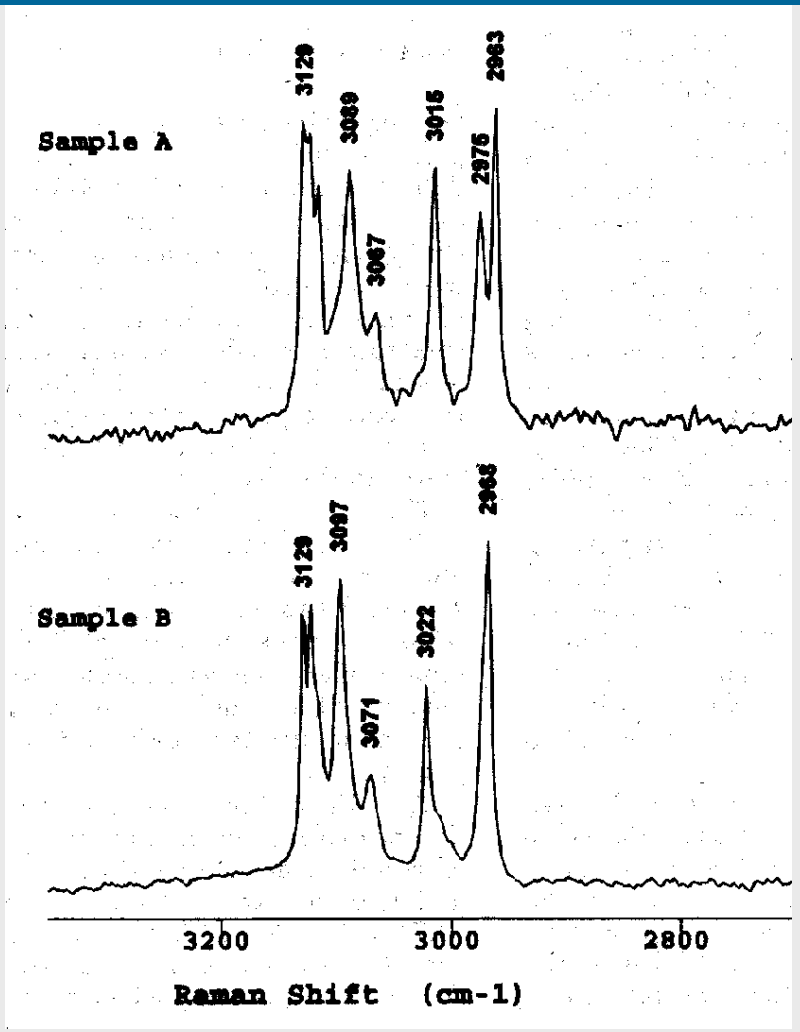
Raman Spectroscopy (5)



Raman spectra for fluconazole, Forms A and B.

J. Pharm. Sci., 84, 1438 (1995)

Raman Spectroscopy (6)



Raman spectra for fluconazole, Forms A and B.

J. Pharm. Sci., 84, 1438 (1995)

Solid-State NMR (1)

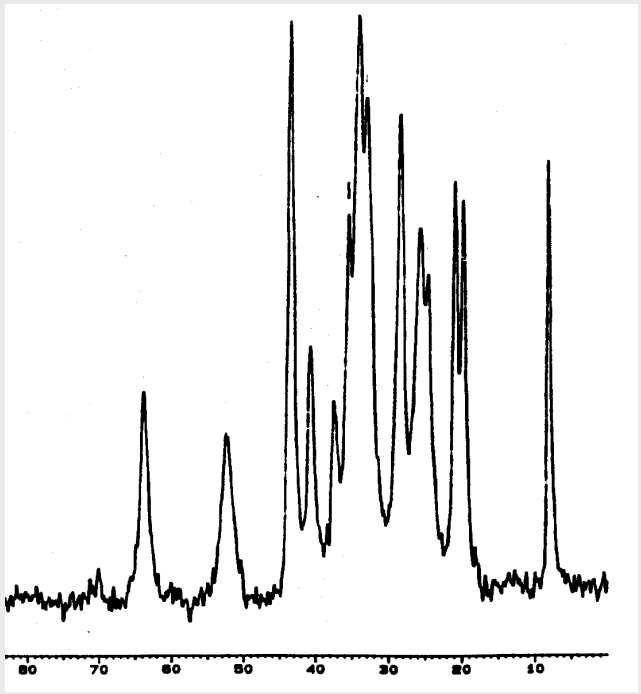
- The use of conventional solution-phase NMR data acquisition techniques on solid samples yields only featureless spectra.
- The broadening of resonance lines is due to dipolar interactions and chemical shift anisotropies which cannot be averaged out in the solid state.

Solid-State NMR (5)

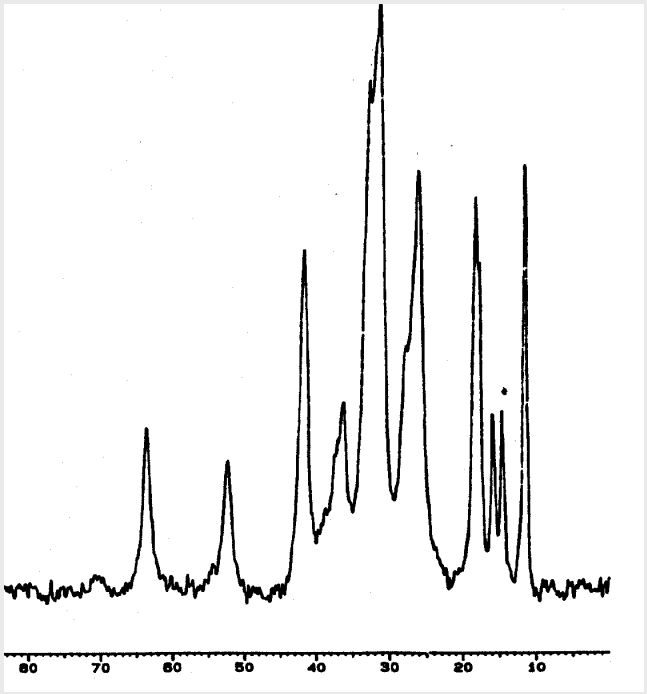
- **Cross-Polarization / Magic-Angle Spinning**:
  - The simultaneous use of magic-angle spinning and cross-polarization (CP/MAS) permits the recording of high-resolution NMR spectra for solid samples.
  - The spectrum of any NMR active nucleus can be obtained through suitably designed CP/MAS experiments.

Solid-State NMR (6)

Form A



Form B

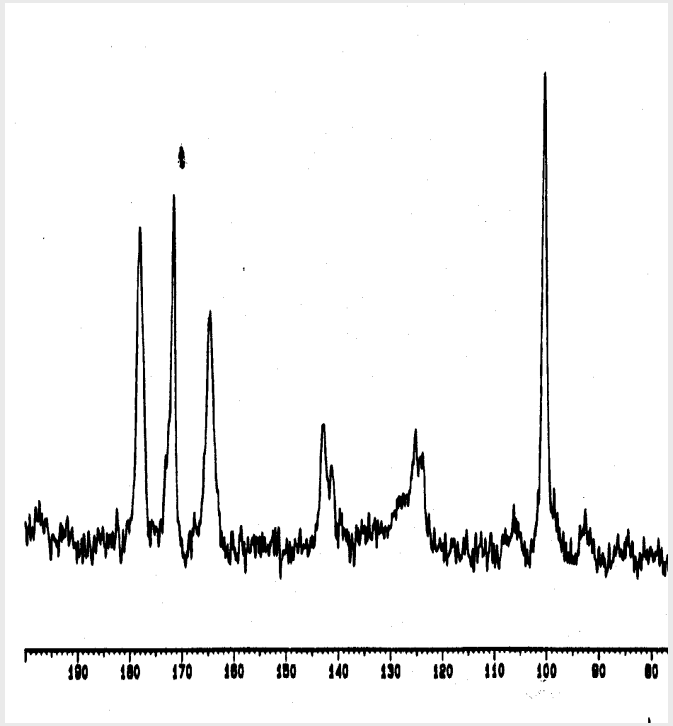


Fosinopril Sodium:

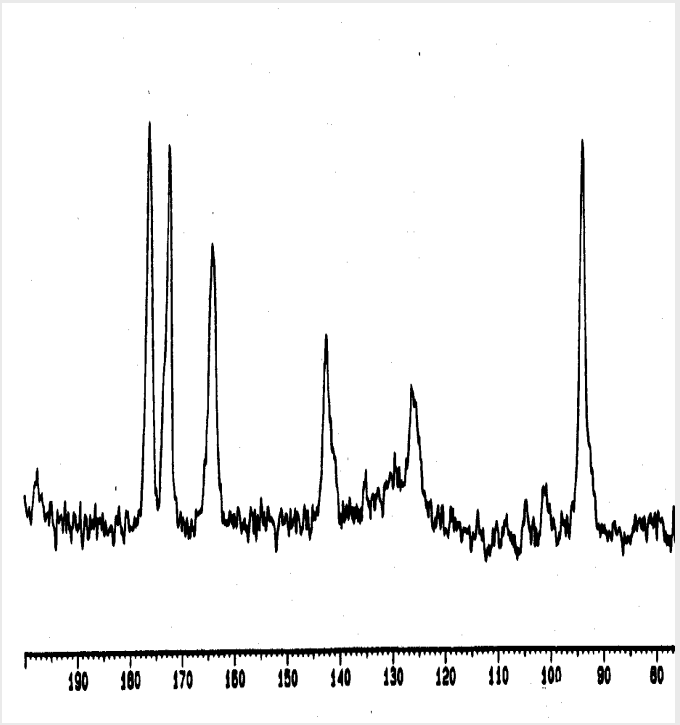
J. Pharm. Biomed. Anal., 11, 1063 (1993)

Solid-State NMR (7)

Form A



Form B



Fosinopril Sodium:

J. Pharm. Biomed. Anal., 11, 1063 (1993)

Solid-State NMR (8)

C - H Aliphatic Region:

C-17

Form-A = 7.9 ppm

Form-B = 11.8 ppm

C-14, C-14’

Form-A = 19.6, 20.7 ppm

Form-B = 14.9, 16.2 ppm

Fosinopril Sodium: *J. Pharm. Biomed. Anal.*, **11**, 1063 (1993)

Solid-State NMR (9)

C - C Aliphatic Region:

- C-5: Form-A = 52.2 ppm
- Form-B = 52.4 ppm
- C-2: Form-A = 63.4 ppm
- Form-B = 63.8 ppm
- C-21, C-19, C-19', C20, C20':
- Form-A = 125.2 ppm
- Form-B = 126.6 ppm
- C-18: Form-A = 142.8 ppm
- Form-B = 142.7 ppm

Fosinopril Sodium: *J. Pharm. Biomed. Anal.*, 11, 1063 (1993)

Solid-State NMR (10)

Carbonyl Region:

- C-6: Form-A = 164.5 ppm
- Form-B = 164.3 ppm
- C-15: Form-A = 171.5 ppm
- Form-B = 172.6 ppm
- C-1: Form-A = 178.0 ppm
- Form-B = 176.4 ppm

Fosinopril Sodium: ***J. Pharm. Biomed. Anal.***, 11, 1063 (1993)

Module 1: Crystal Forms of API

Part Ie.

ISSUES ASSOCIATED WITH SCIENTIFIC PHARMACEUTICAL DEVELOPMENT

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Polymorphism

- Defined as the ability as the ability of a substance to exist in two or more crystalline phases that differ in the arrangement and/or conformation of the molecules in the crystal lattice.
- The elemental analyses of a polymorphic pair are identical.

Solvatomorphism

- Defined as the ability as the ability of a substance to exist in two or more crystalline phases that may differ in the arrangement and/or conformation of the molecules in the crystal lattice, and which contain differing numbers of solvate molecules.
- The elemental analyses of a solvatomorphic pair cannot be identical.

Crystal Forms

- It appears that FDA does not differentiate between polymorphs and solvatomorphs.
- FDA considers these to be differing crystal forms of the same compound, and treats them equally as requiring characterization methodology.

Importance of Crystal Forms to the Pharmaceutical Industry

- Polymorphs or solvatomorphs can have different:
  - solubility
  - stability
  - processing characteristics
- Different crystal forms are most likely to be uncovered during the latter stages of development.

Why care about the crystal form of a new chemical entity?

Only one crystal form can have the lowest free energy at a given temperature and pressure.

- The most stable crystal form has the lowest:
  - vapor pressure
  - solubility
  - intrinsic dissolution
  - bioavailability

Relative Stability of the Unique Forms (1)

- When the existence of more than one crystalline form is demonstrated, the ensemble of information available after the performance of the work described in the previous sections usually permits a determination of the relative stability order of the polymorphs and solvatomorphs.
- This is especially true if vapor pressure and/or solubility studies have been performed.

Relative Stability of the Unique Forms (2)

- Enantiotropy
  - One polymorph is stable within a defined temperature/pressure region, while the other is stable within a different temperature/pressure region.
  - Enantiotropic pairs will undergo a reversible interconversion at the transition point.

Relative Stability of the Unique Forms (3)

- Monotropy
  - Only one polymorph is stable over all temperatures and pressures below the melting point. The other form is always metastable with respect to the stable form.
  - The metastable phase will undergo an irreversible interconversion to the stable phase at the transition point.

Relative Stability of the Unique Forms (4)

- Gay-Lussac's Observation
  - During crystallization, metastable forms are ordinarily obtained first. If possible, these will transform into a stable form.
- Ostwald's Step Rule
  - In all processes, it is not the most stable state with the lowest amount of free energy that is initially formed, but the state lying nearest in free energy to the original state.

Relative Stability of the Unique Forms (5)

- Solubility
  - The more stable is a crystalline form at some temperature, the less soluble it will be in a given solvent with respect to the other forms.
  - The equilibrium solubility evaluation must be performed in at least two solvents.
  - Whenever possible, the solubility of each form should be obtained as a function of temperature and fit to the Clausius-Claperon equation.

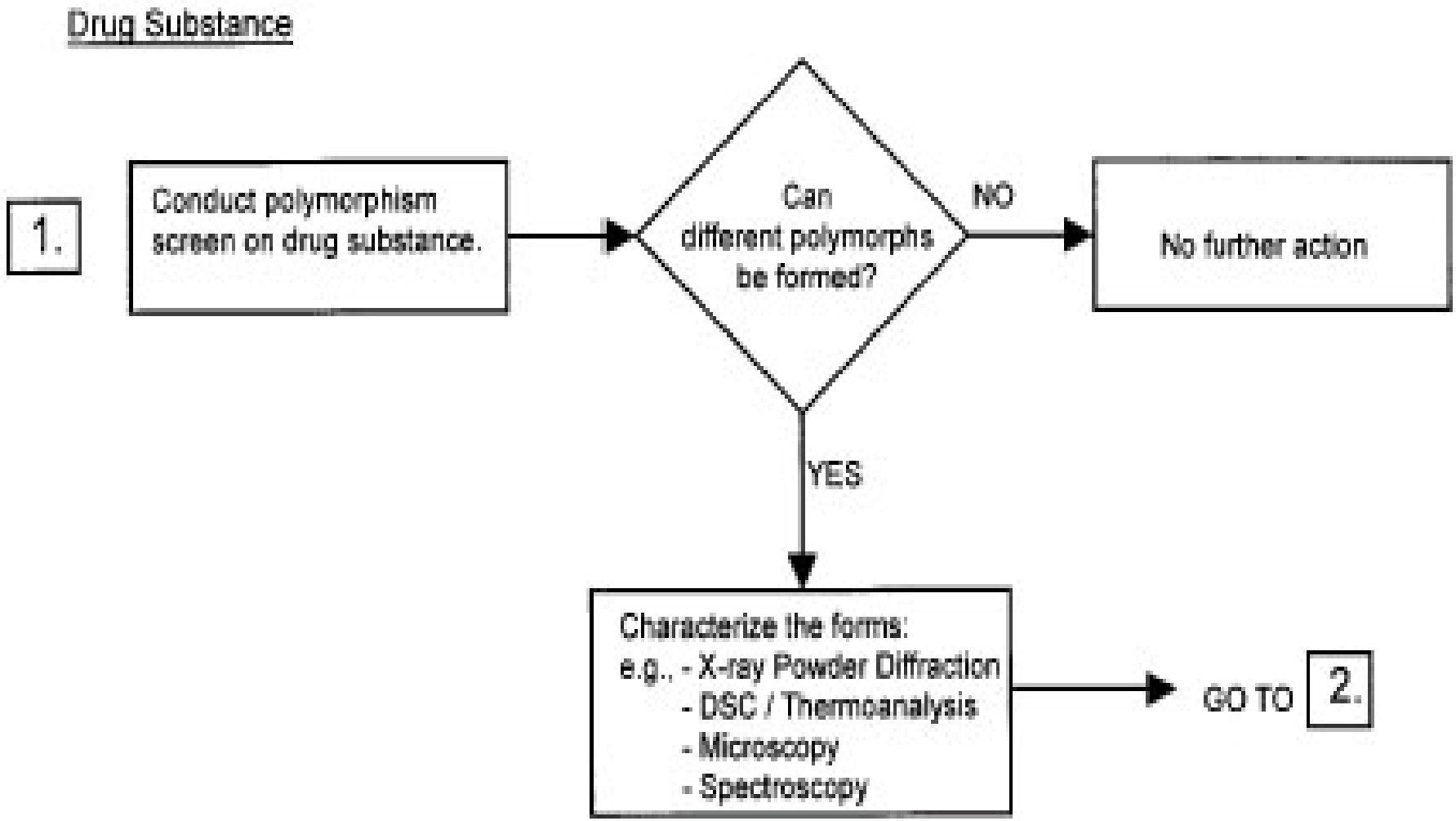
Relative Stability of the Unique Forms (6)

- **Ostwald Ripening Experiments**
  - Solids of two unique forms of the DS are suspended in a saturated solution of the DS. This can be performed either in a bulk solution or in the well of a microscope slide.
  - After equilibrium is attained, only one form will be left as a suspended solid in the dispersion.
  - The form that remains will be the more stable of the two forms originally suspended.

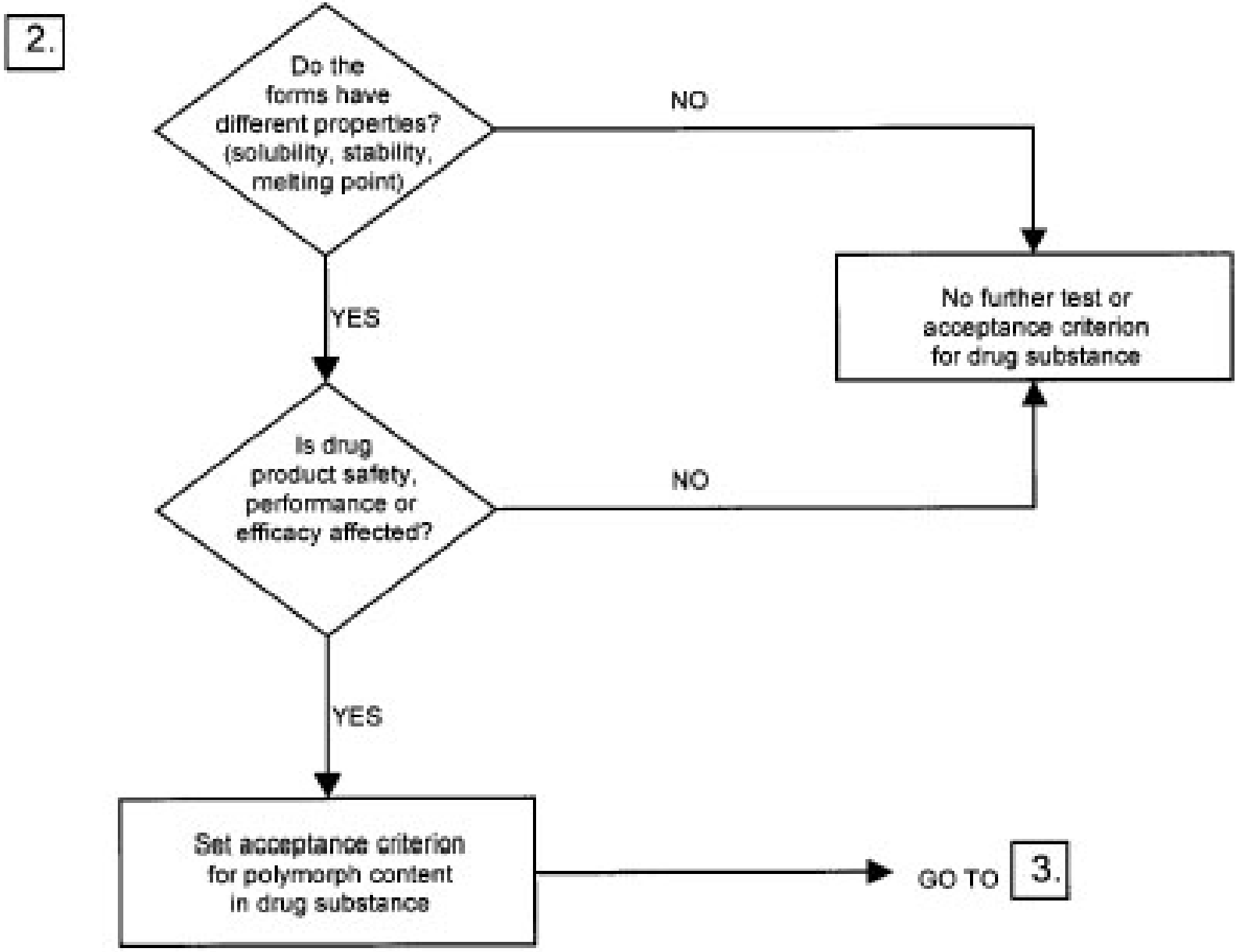
Decision Tree Development on Polymorphism in ANDA's

- A process should be developed for evaluating when and how polymorphs of drug substances in ANDA's should be monitored and controlled
  - ICH Guidance Q6A decision trees on polymorphism
  - The Biopharmaceutics Classification System (BCS)

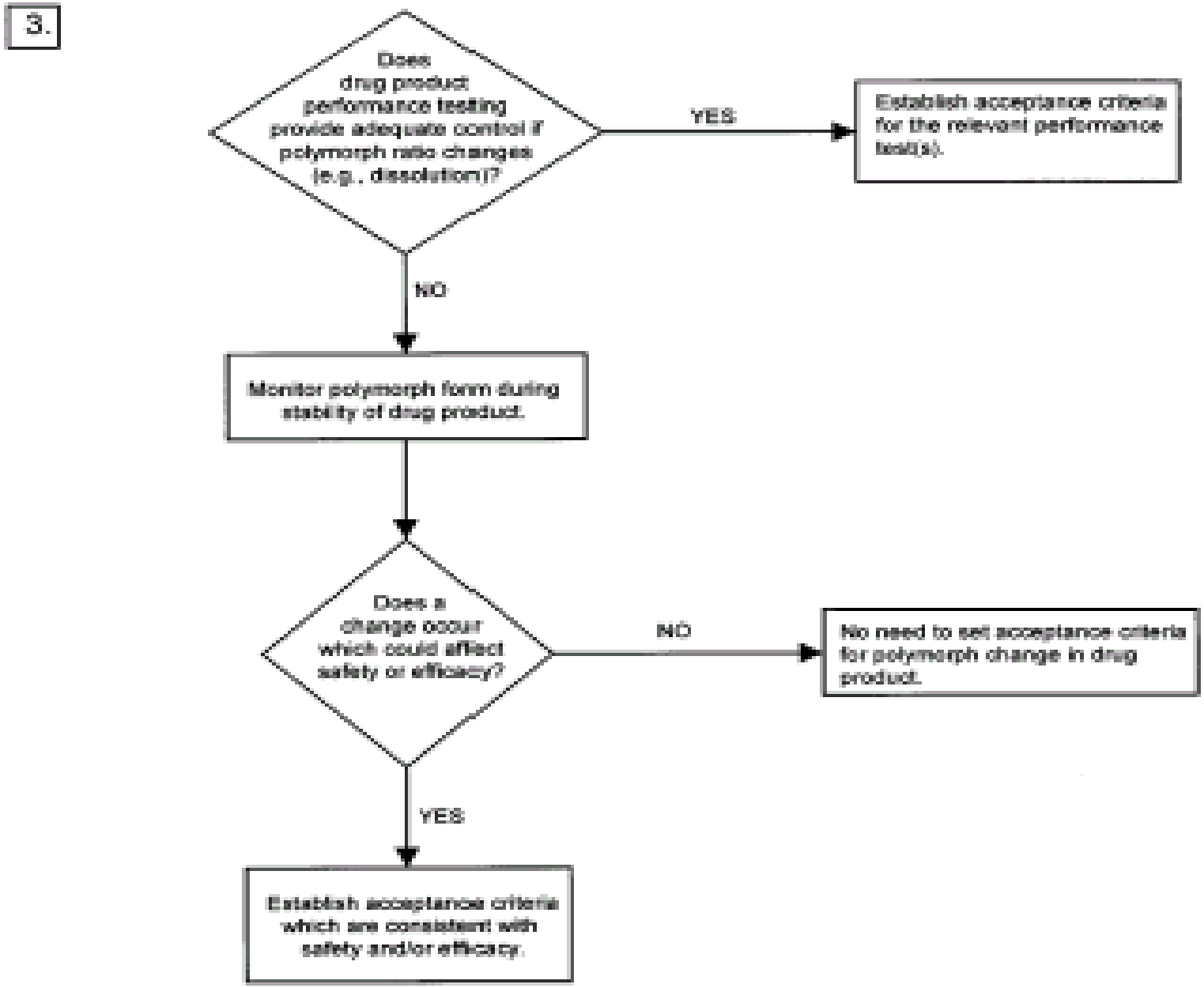
Decision Trees (1)



Decision Trees (2)



Decision Trees (3)



Guidance

- Whenever possible, it is recommended that the most stable crystalline phase of the drug substance be chosen as the commercial form.
- This choice should lead to the most robust primary process for manufacture of the drug substance.

Any Questions?

Module 1: Crystal Forms of API

Part 2.

ROLE OF WATER IN SOLID-STATE STABILITY

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Outline

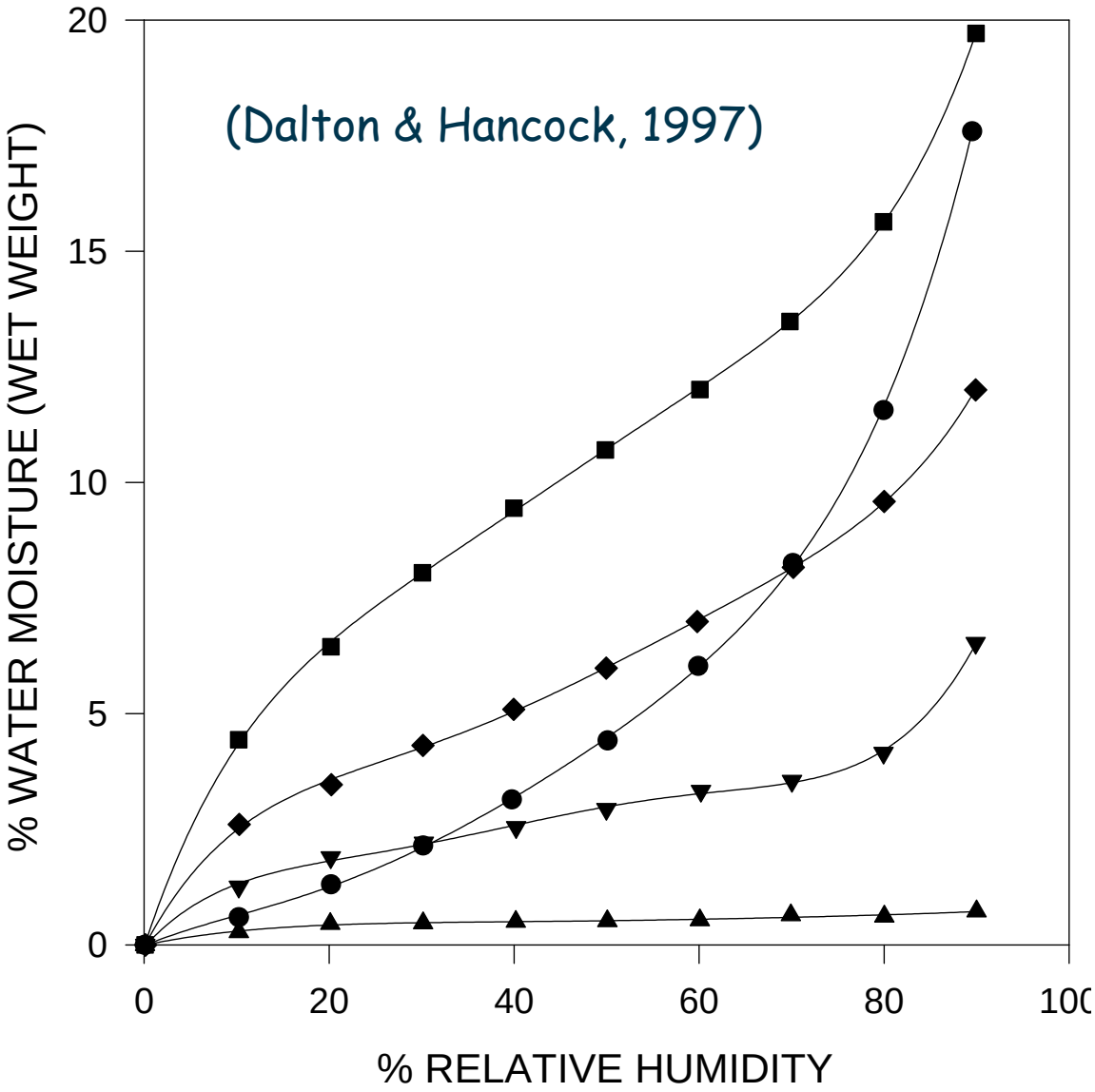
- Mechanisms of water-solid interaction
- Sources of water during processing and storage
- Impact of water on chemical and physical stability
- Processing and water-solid interactions
- Conclusions

Introduction

- Residual water is commonly associated with pharmaceutical systems
- The amount of water (weight percent) ranges from fractions of a percent to up to 25%
- Solids interact with water by different mechanisms.

  e.g. Sodium Chloride vs. Starch

Water vapor sorption isotherms



Starch

HPC

Microcrystalline cellulose

Magnesium stearate

Lactose monohydrate (crystalline)

Properties of Water

Special characteristics make water capable of interacting with many pharmaceutical solids in different modes:

- Its small size (29.92 $Å^3$)
- Its capability of forming hydrogen bonds and hydrogen bond networks
  - Ubiquitous hydrogen bonding is a result of hydrogen bond donor and acceptor capabilities
  - Hydrogen bonding can occur with other water molecules, with functional groups of drug molecule, or to anions

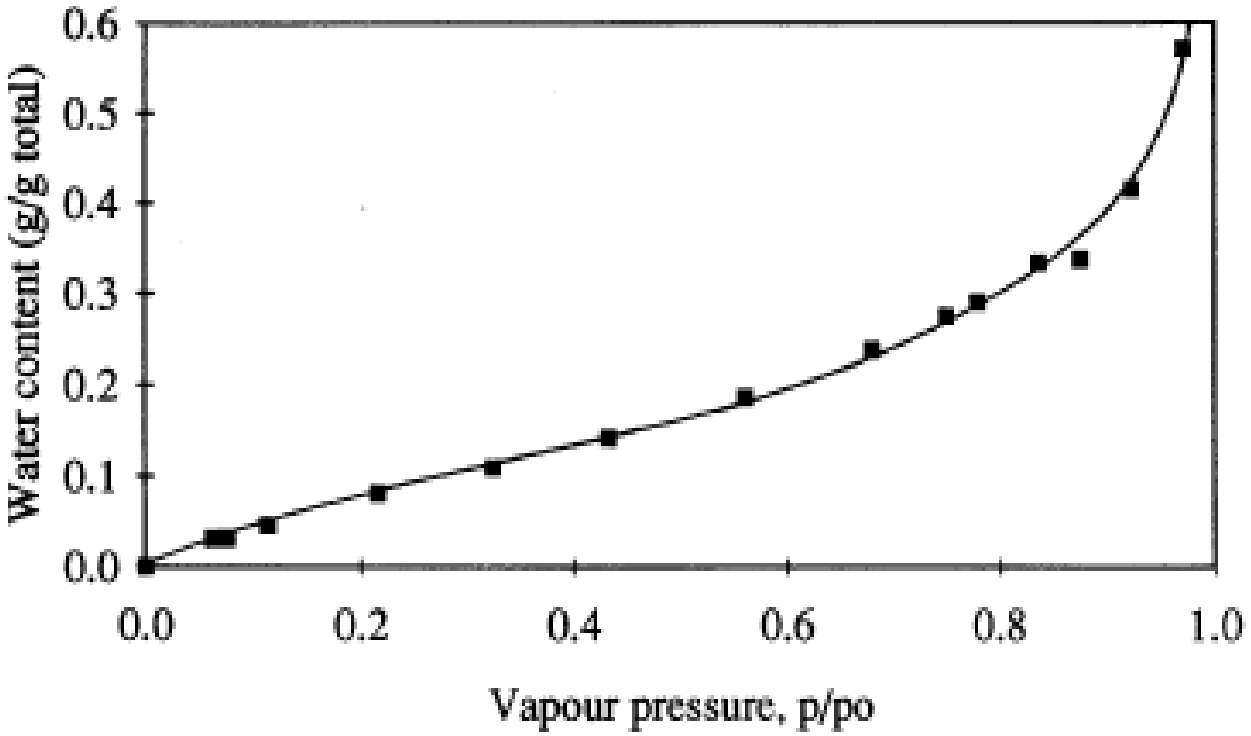
Water and Pharmaceutical Solids

- To understand different water-solid interactions and their potential impact on chemical and physical stability, we need to answer the following questions:

  - How much water is associated with solid?
  - Where is the water located?
  - What is the physical chemical state of the water and the solid?
  - How does the presence of such amount of water affect physicochemical properties of the solid?

Vapor Sorption Isotherms

- The most fundamental manner of demonstrating water-solid interaction is using “Vapor Sorption Isotherms”



Typical vapor sorption isotherm: PVP [1]

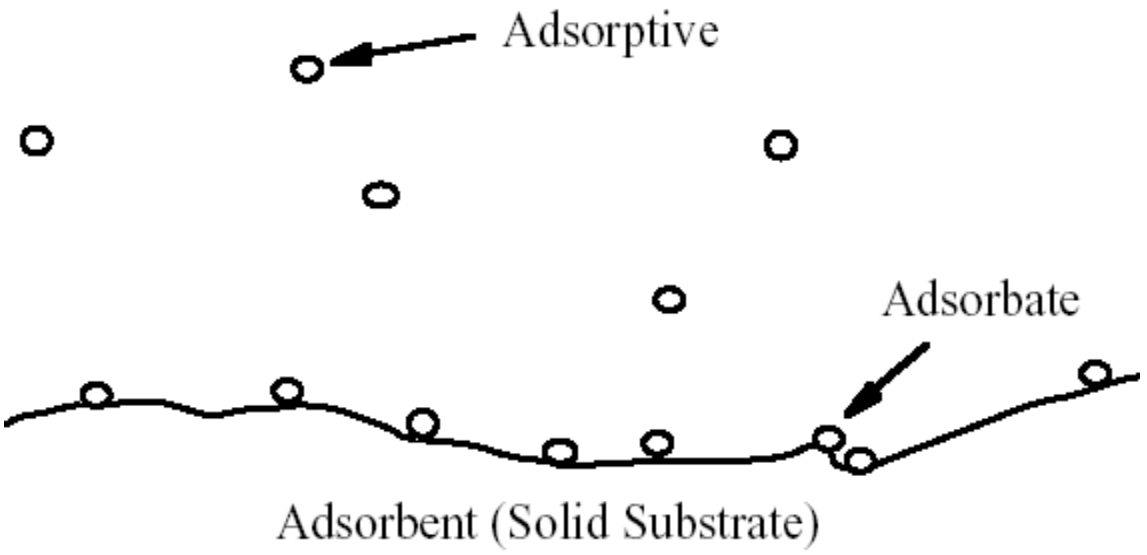
[1] Oksanen, C.A., PhD. Thesis 1992)

Mechanisms of water-solid interaction

- Adsorption
- Capillary condensation
- Deliquescence
- Absorption:
  - Disordered phases (Amorphous)
  - Crystal hydrate formation

Adsorption

- Process where molecules of a gas contact and adhere to a solid surface
- Crystalline solids with hydrophilic surfaces
- It is a dynamic surface phenomenon
  - Physisorption – non-covalent interactions, reversible
  - Chemisorption – covalent or ionic interactions, irreversible



Adsorption

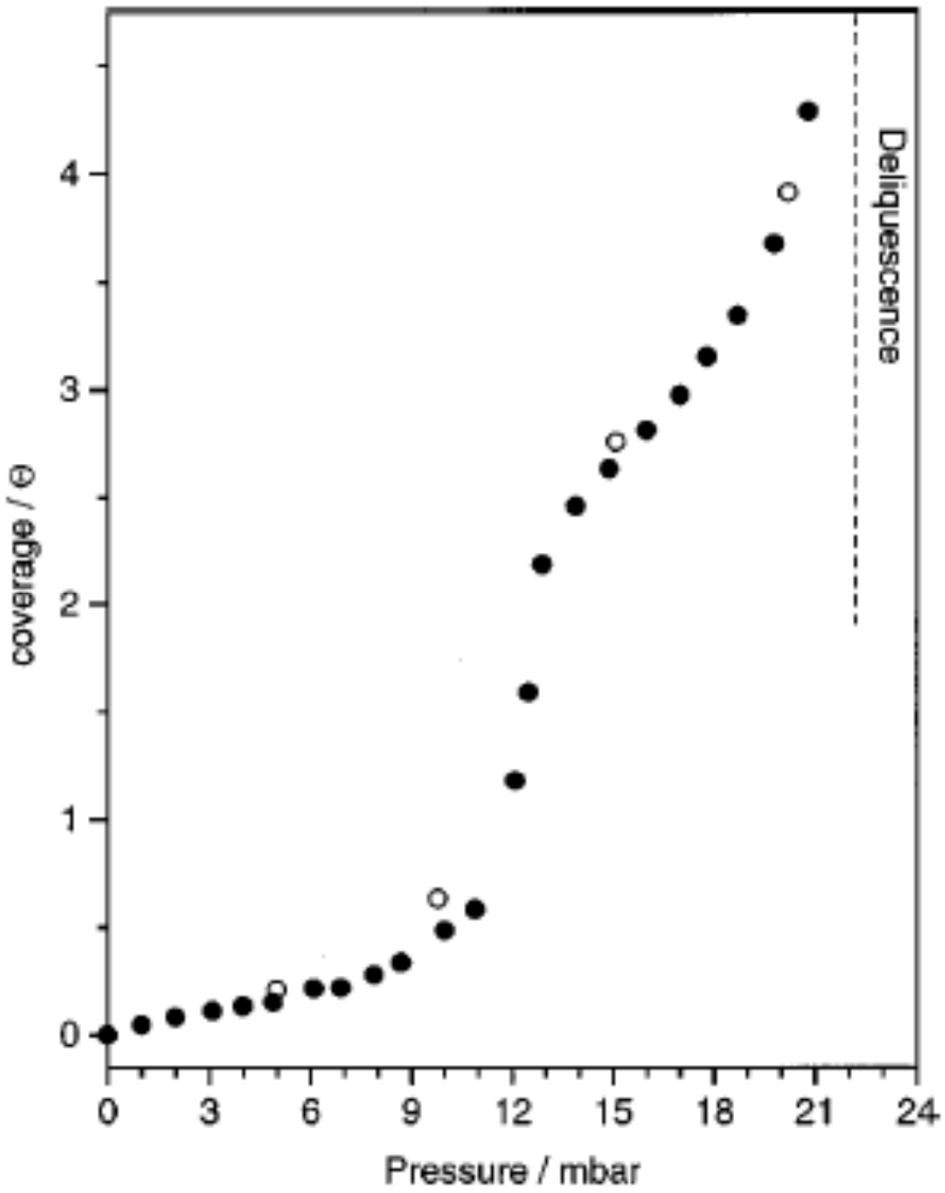
- Mass of water adsorbed depends on:
  - Affinity between water and surface
  - Temperature
  - Water vapor pressure
  - Area of exposed surface

Effective molecular layers adsorbed as function of water content and specific S.A. [1]

Water content (%)	Specific Surface Area (m^2/g)		
	0.1	1.0	10
0.1	41.8	4.2	0.4
1.0	418	41.8	4.2
10.0	41,800	418	41.8

[1] Zografi and Hancock. Proceedings of 53rd International Congress of Pharmaceutical Sciences(1994)

Water Vapor Adsorption of Crystalline NaCl



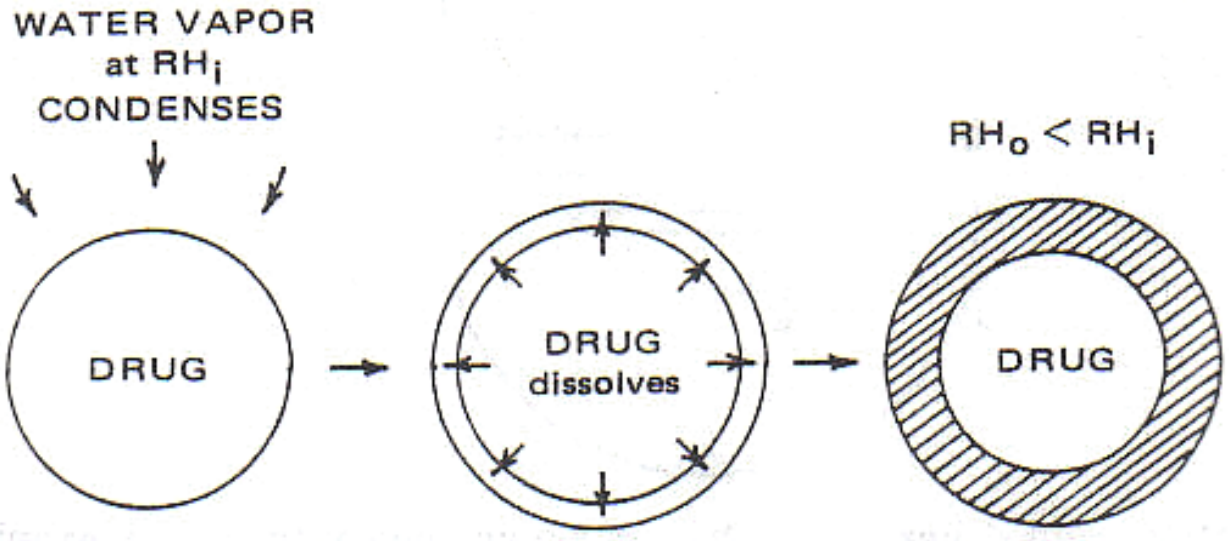
← Equivalent of 3 molecular layers of water

NOTE :
The lack of adsorption/desorption hysteresis

Foster and Ewing J. Chem. Phys. 2000

Deliquescence

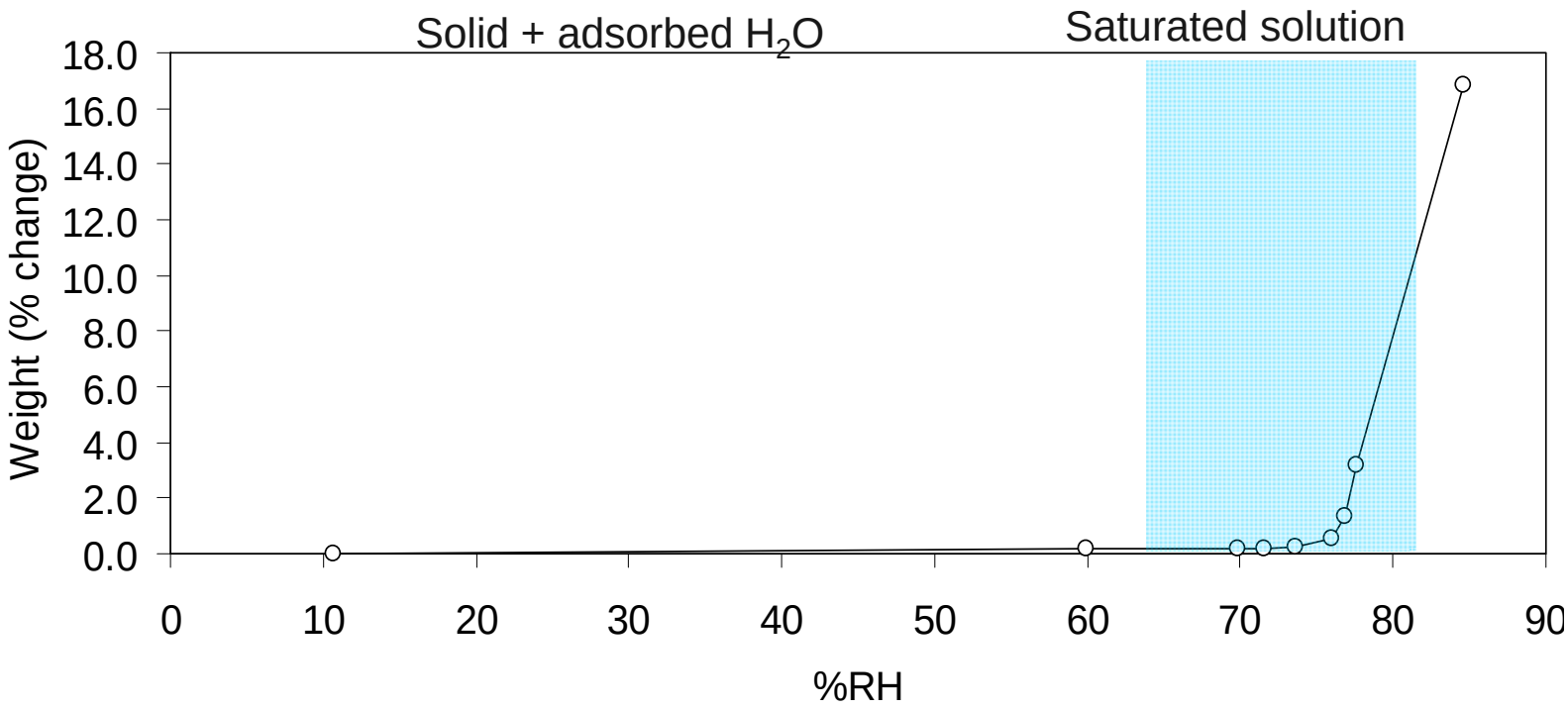
- It results in liquid water production in solids at relative humidities less than 100%
- Usually occurs with crystalline and highly water soluble solids
- It is triggered when ambient relative humidity surpasses the critical relative humidity (RH_0) of the solid



[1] Van Campen et al., Journal of Pharmaceutical Sciences (1983)

Deliquescence

- Adsorption below RH_0
- Rapid increase in mass at RH_0



RH_0 – Properties

- RH_0 is an inherent property of the substance
- $RH_0 \approx a_w$ of saturated solution in equilibrium with solid phase
- Deliquescence RH can be reduced by presence of a second deliquescent solid – API's and excipients are deliquescent

Compound	***RH_0 (%), 25°C***	***a_w*100, 25°C***	***Literature RH_0(%) values***
Ranitidine HCl	76	76	76, 25°C (19), 67, 40°C (20)
Diphenhydramine HCl	82	82	77, 37°C (21)
Thiamine HCl	89	90	88, 37°C (21)
Sucrose	85	85	84, 25°C (22)
Lactose anhydrous	95	97	95, 40°C (23)

Deliquescent Excipients

Compound	RH_0 (25°C)
Sucrose	85
Lactose anhydrous	95
Maltose monohydrate	95
Mannitol	95
Citric acid monohydrate	78
Sorbitol	69
Sodium citrate dihydrate	86
Sodium Chloride	75
Potassium chloride	84

Absorption

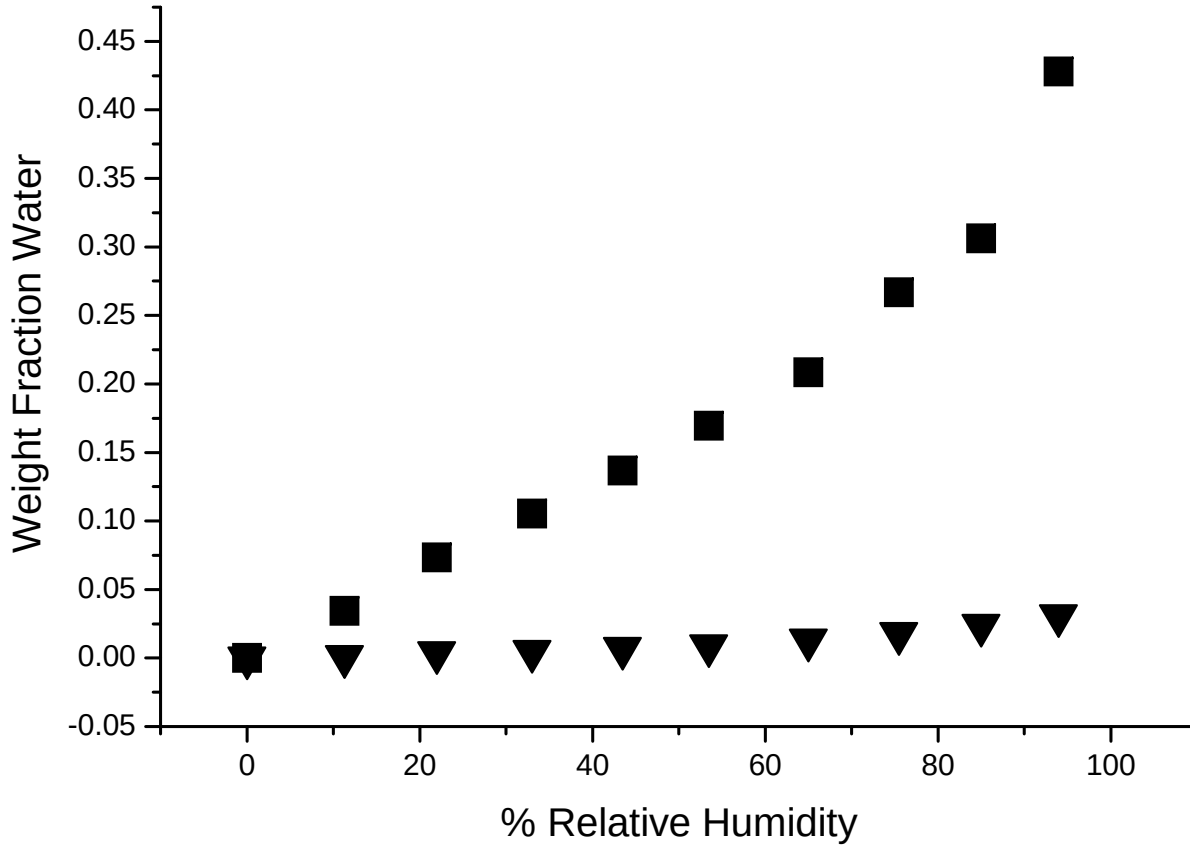
- Refers to the accumulation of water within the solid (not on the surface)

- Two situations where absorption occurs:
  - Into the amorphous (disordered) solids/regions
  - into the crystal structure of a solid to form a crystalline hydrate

Absorption into Amorphous Solids

- Amorphous solids adsorb and absorb water vapor
- Partially amorphous (disordered) solids absorb water (microcrystalline cellulose)
- Absorption can be viewed as dissolution of H_2O vapor into the solid with a consequent effect on material properties
- Evidence for absorption into amorphous solids:
  - Amount of H_2O taken up depends on mass not surface area
  - Substantially more than 2-3 monolayers of H_2O are taken up

Example – Chemical Structure

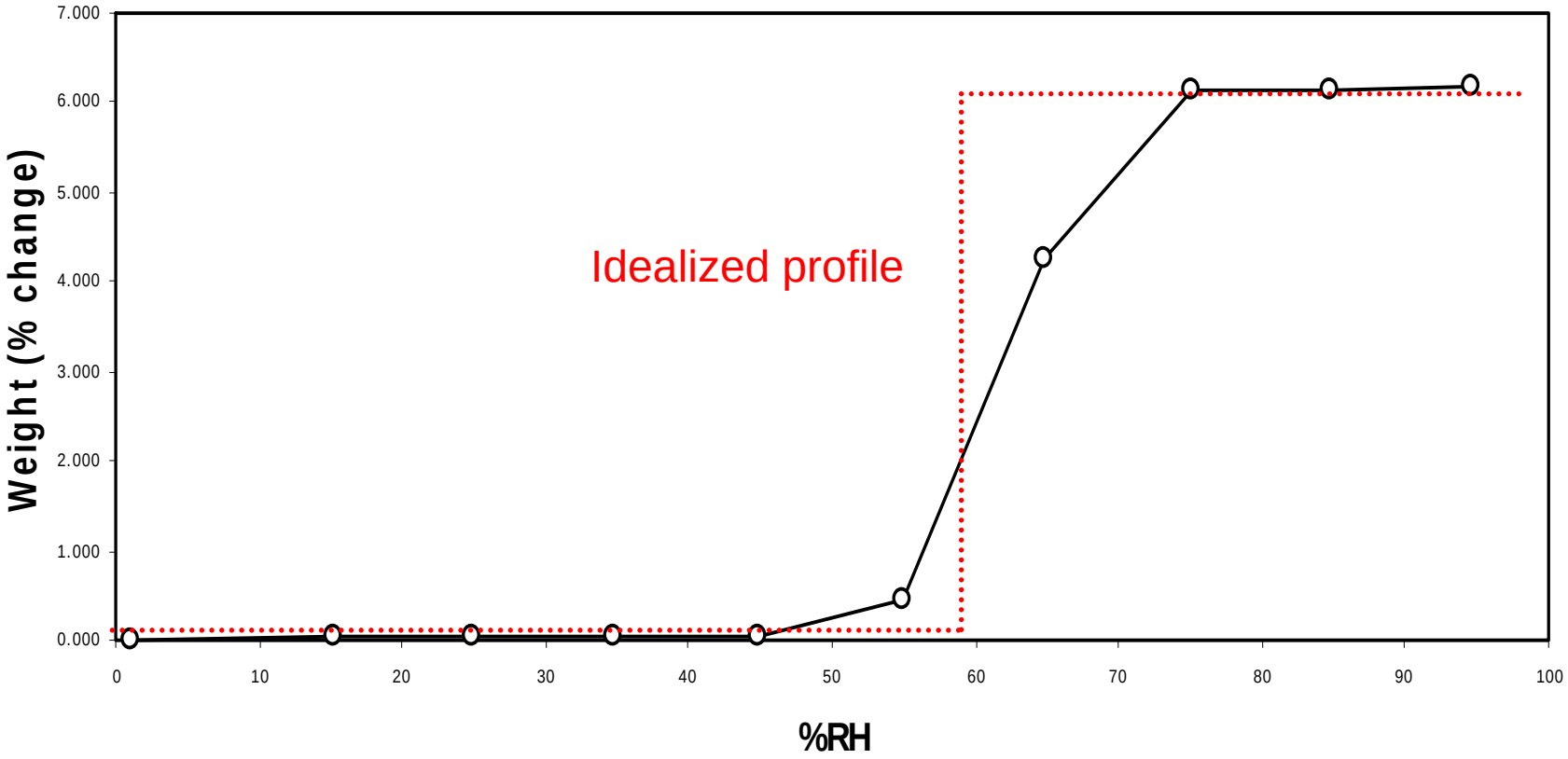


Water vapor sorption profile for a hydrophilic vs hydrophobic amorphous polymer

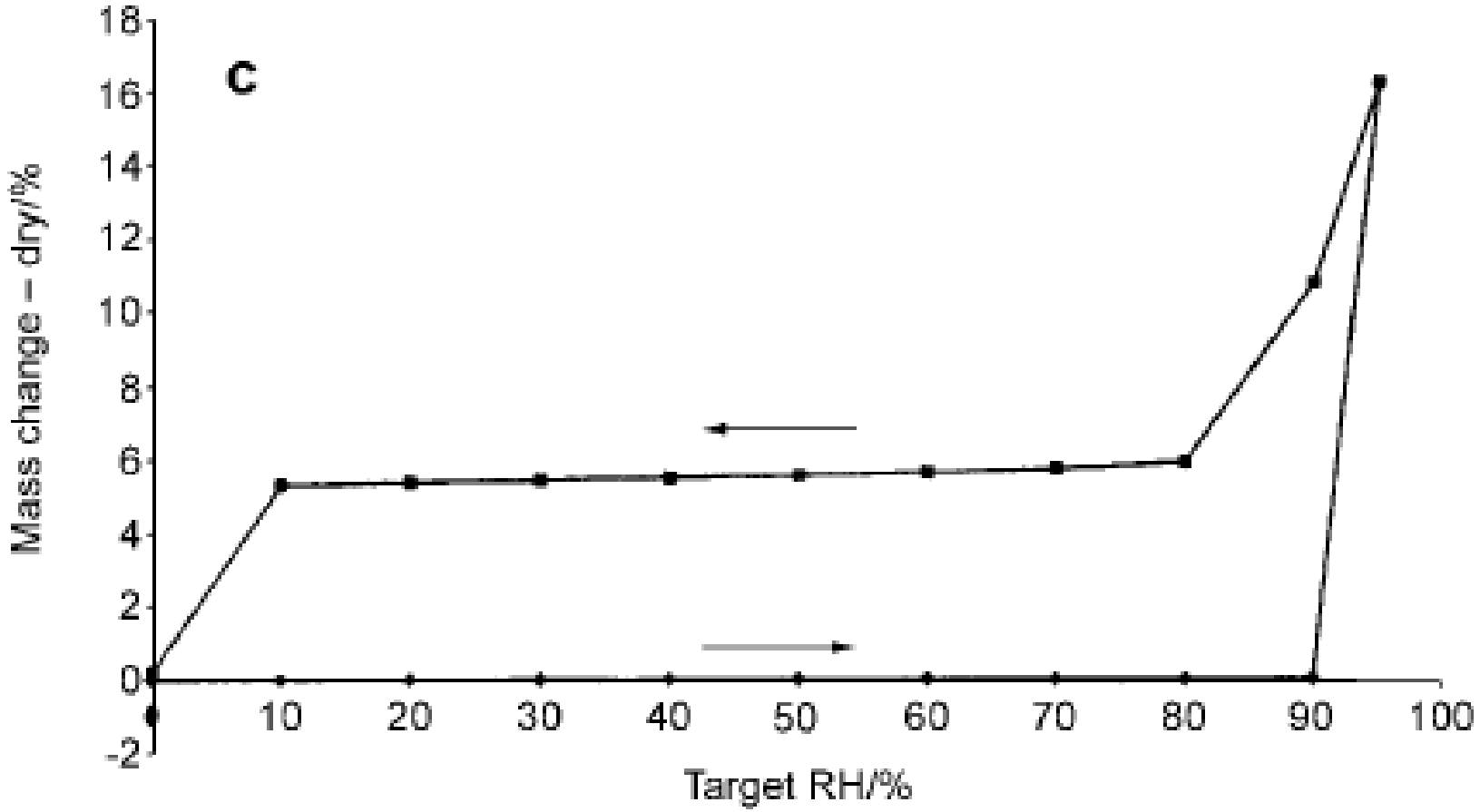
Crystalline Hydrates

- Approximately 1/3 of APIs are capable of forming crystalline hydrates
- In crystalline hydrates water forms an integral part of the crystal lattice
- Based on structural considerations hydrates can be classified:
  - Isolated site hydrates
  - Channel hydrates
  - Metal or ion coordinated hydrate
- Hydrates can be stoichiometric or non- stoichiometric (water content can vary with vapor pressure)

Formation of a Stoichiometric Hydrate – Dynamic Water Vapor Sorption Experiment



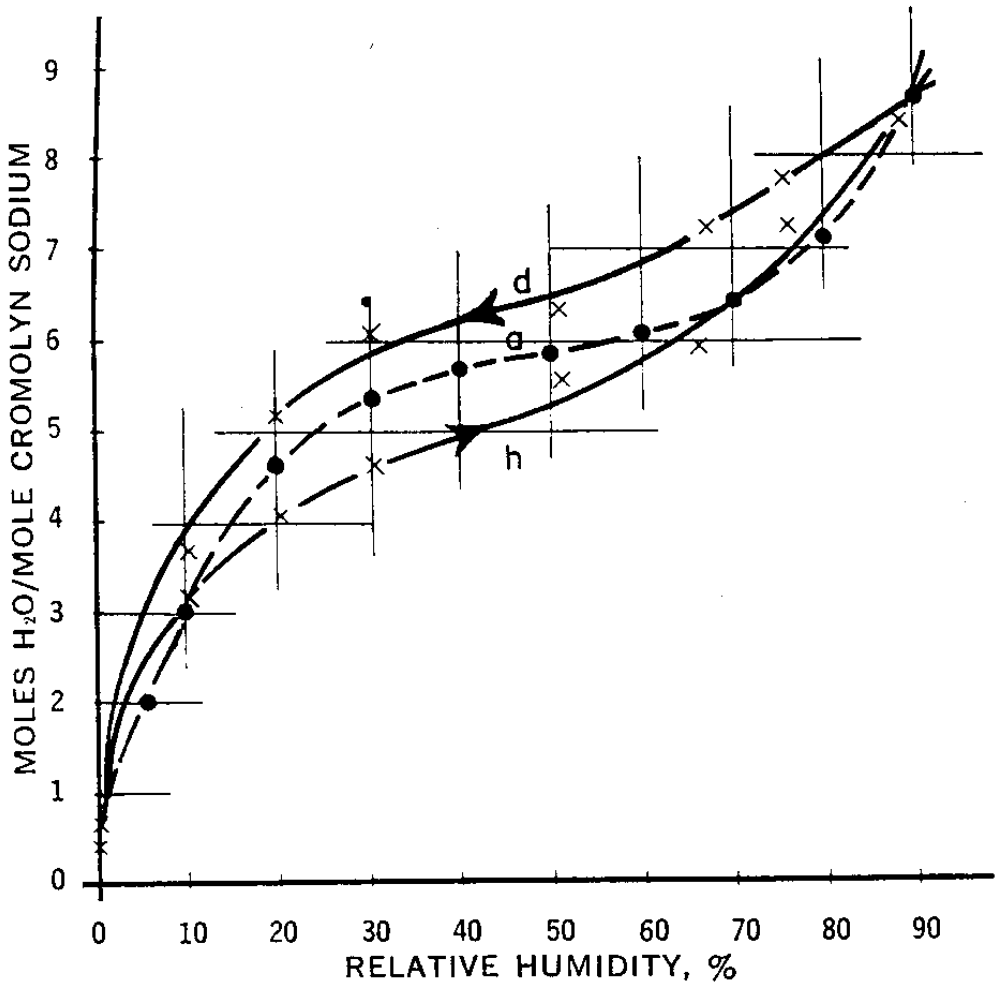
Formation of a Stoichiometric Hydrate



Formation of monohydrate from anhydrate form (note the stability of the monohydrate form)

[1] Giron et al., Journal of Thermal Analysis and Calorimetry (2002)

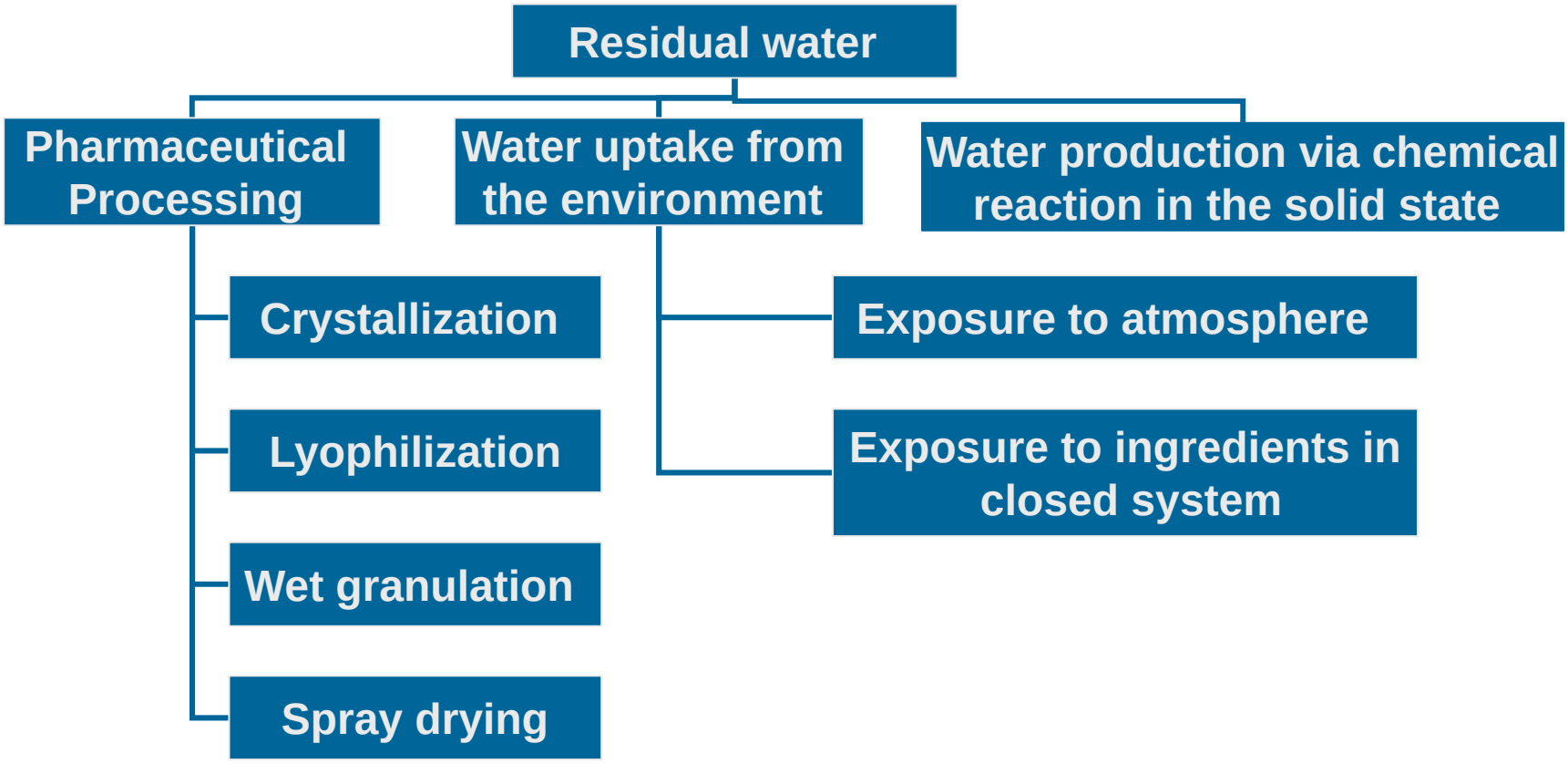
Formation of a Non-stoichiometric Hydrate



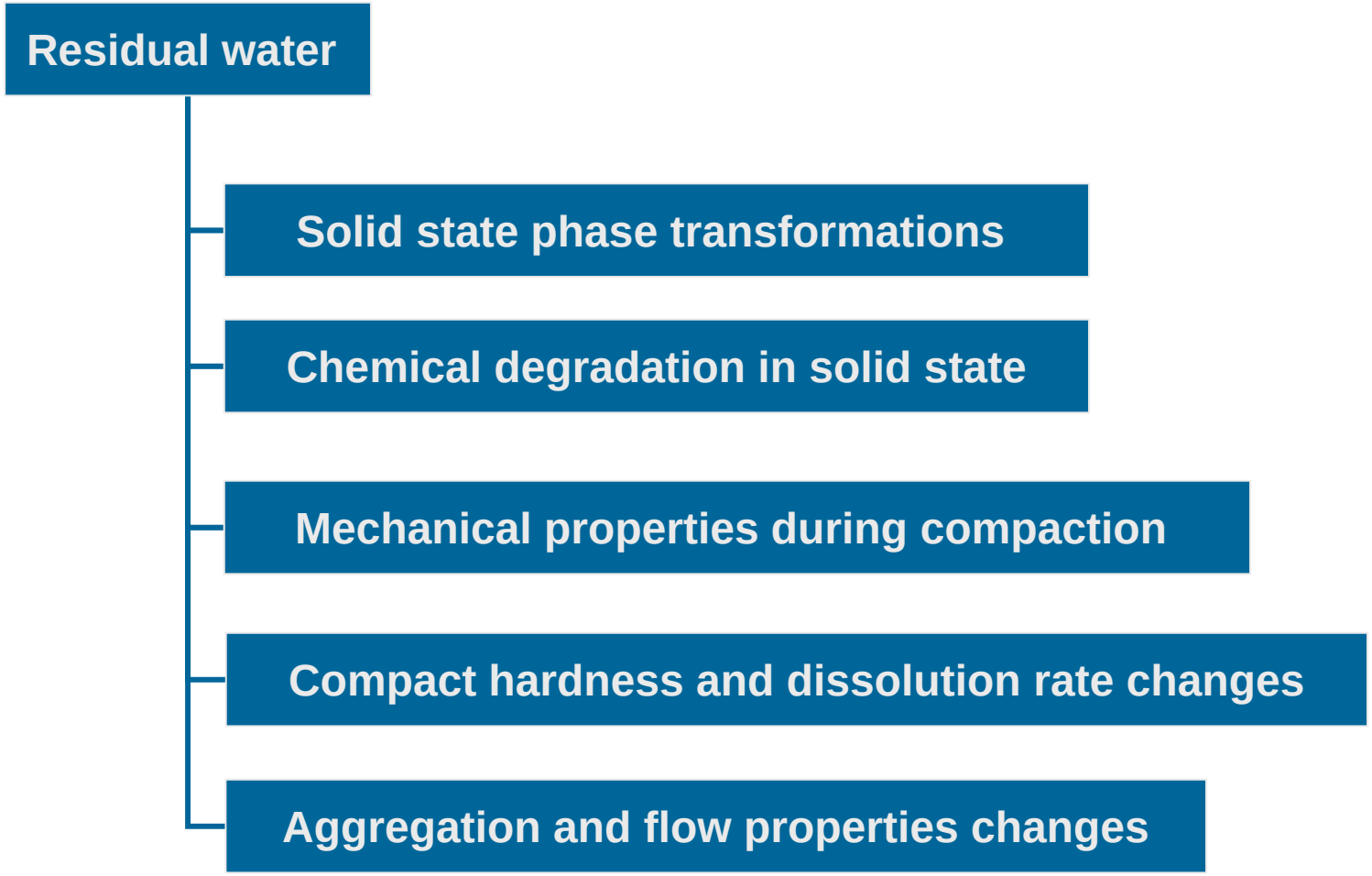
Cromolyn Na forms an infinite number of non-stoichiometric hydrates

[1] Cox et al. Journal of Pharmaceutical Sciences (1971)

Sources of Residual Water



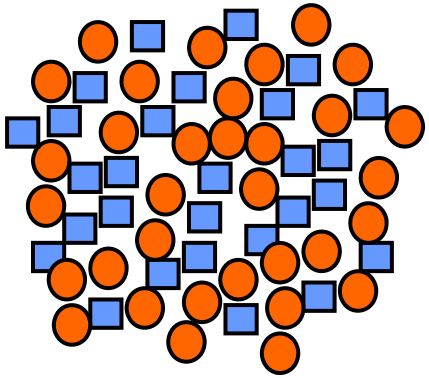
Influence of Residual Water



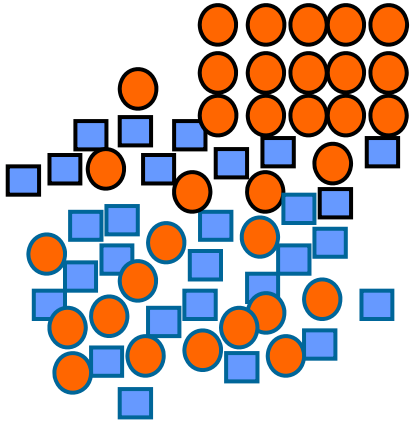
Water and Solid State Stability

- Water affects both chemical and physical stability of solids
- Both are important to achieve optimum product performance
- Physical Stability:
  - Solid-solid phase transformation:
    - Polymorphism
    - Anhydrous-hydrate
    - Amorphous-crystalline
    - Solvate-anhydrate/solvate-hydrate
    - Hydrate-amorphous
  - Solid-solution phase transformation
    - Deliquescence

Sequence of Events During Crystallization



Amorphous matrix with H_2O



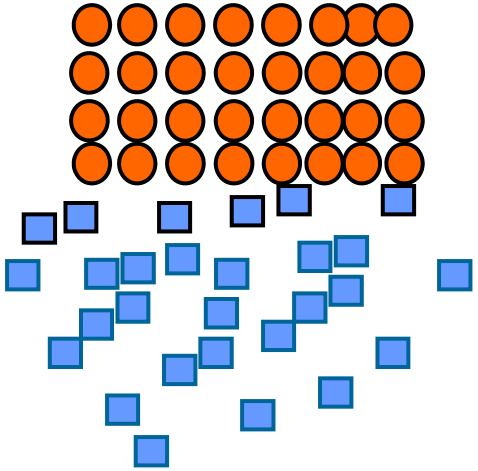
Partial crystallization

↓

H_2O amplification

↓

T_g decrease



Complete crystallization

↓

H_2O expulsion

↓

Increase in a_w

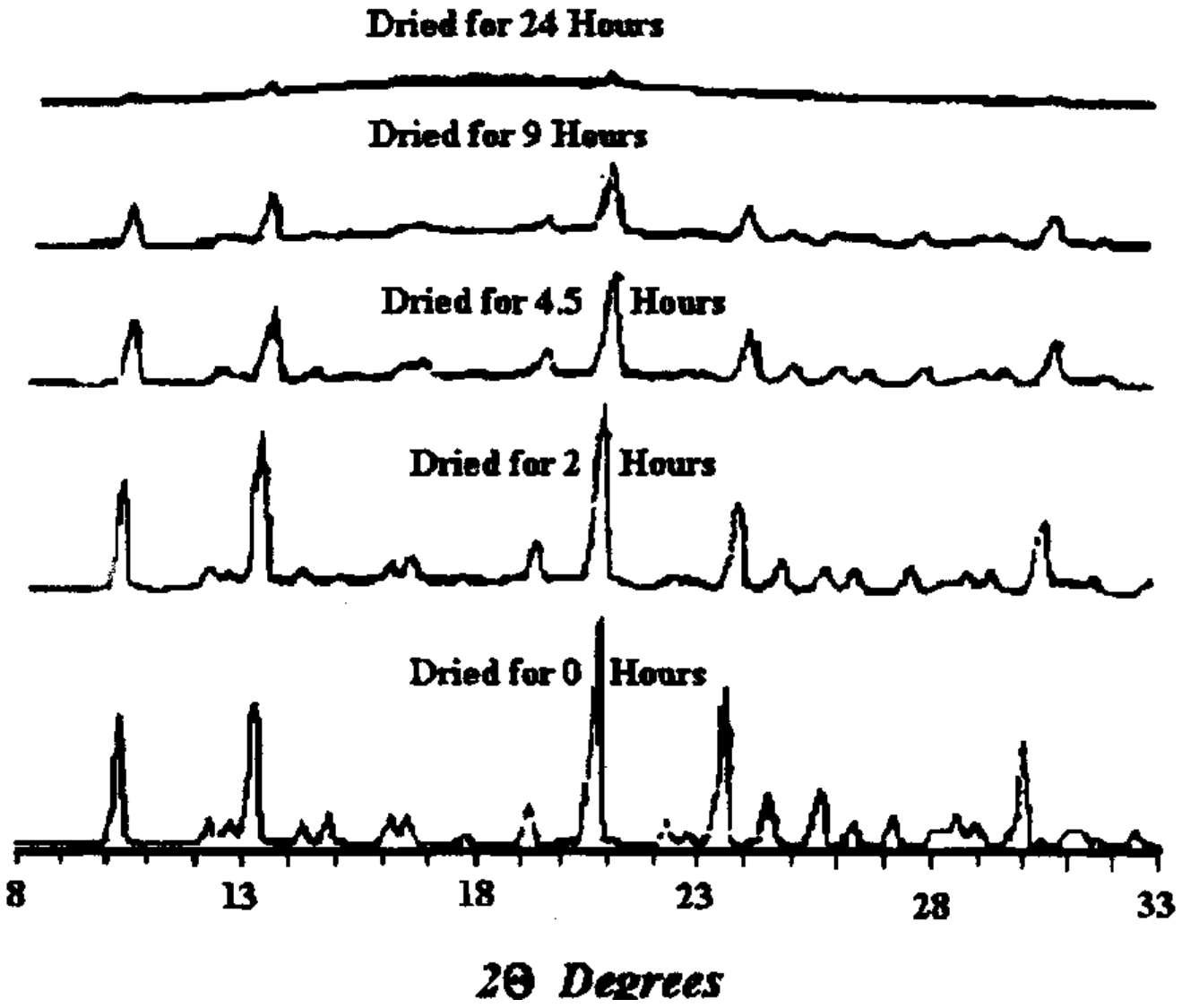
Chemical Stability

- Mechanisms:
  - "Structural"- association of H_2O with solid results in some type of structural change that influences chemical reactivity- this would include changing molecular mobility
  - "Chemical"
    - H_2O is a solvent (deliquescence)
    - H_2O is a reactant e.g. hydrolysis
    - H_2O is a product (condensation reactions) e.g. Maillard reaction
    - H_2O changes medium polarity
  - Water activity is likely to be a critical parameter for "chemical" category

Mechanisms – Structural

- Loss of H_2O from crystal can result in:
  - Empty channels that can convey O_2 into crystal structure
  - Structural collapse to disordered amorphous phase (amorphous phase will have enhanced reactivity)

Dehydration of Raffinose Pentahydrate to Amorphous Phase

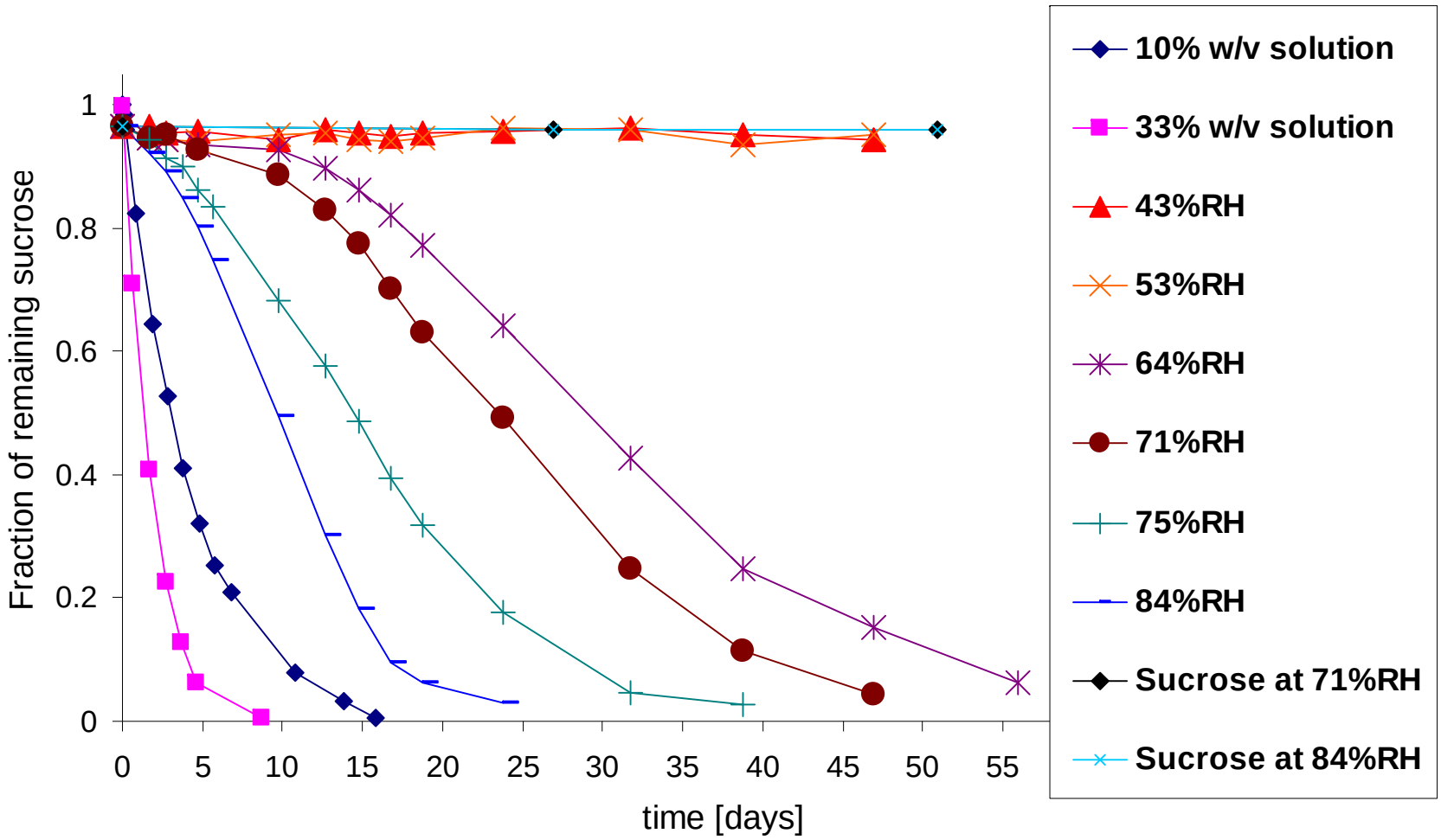


[1] Saleki-Gerhardt et al., Journal of Pharmaceutical Sciences (1995)

Chemical – Sucrose Hydrolysis

- Sucrose undergoes acid catalyzed hydrolysis
- Sucrose is deliquescent and forms a solution at high RH
- If formulated with acidic component, protons are provided and hydrolysis can occur
- Moisture provides the reaction medium and affects degradation kinetics

Sucrose Inversion Kinetics

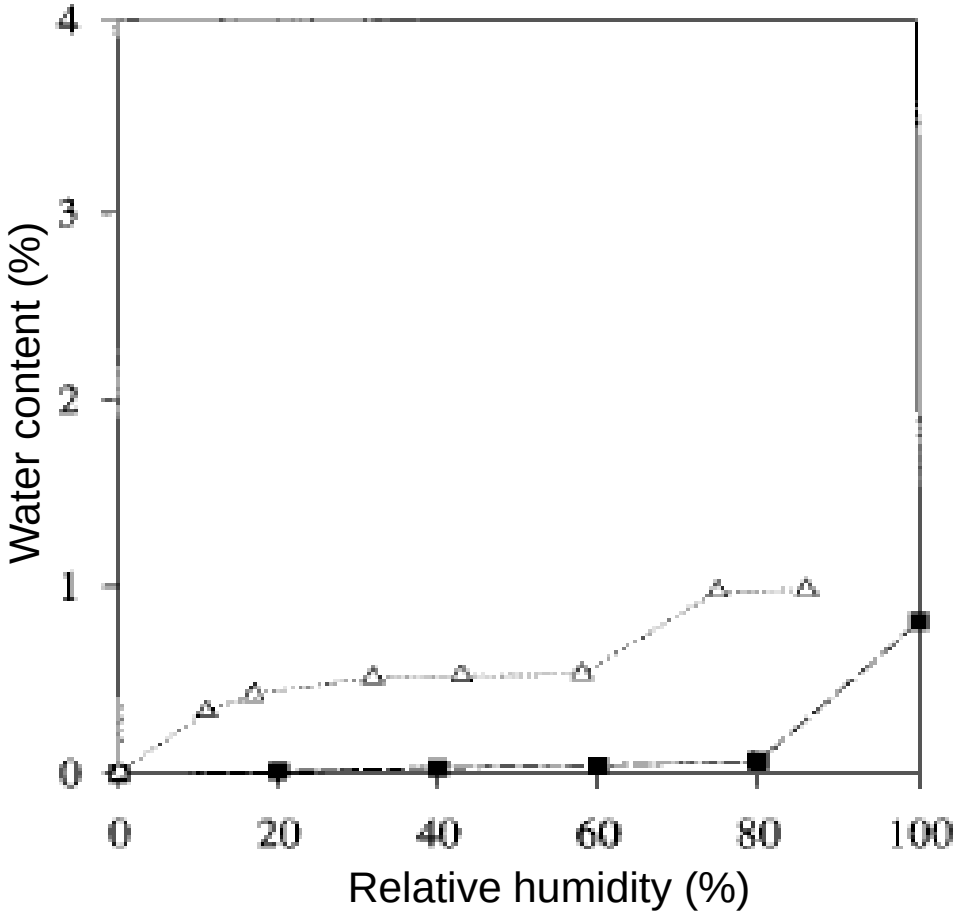


Salameh and Taylor, J. Phys. Chem. B. 2006

Water-Solid Interactions and Processing

- Processing can:
  - Bring water (liquid/vapor) into contact with API and excipients, e.g. wet granulation
    - Moisture labile substances (chemical degradation)
    - Moisture induced phase transformations
  - Change solid state properties so water interaction is altered, e.g. milling

Effect of Processing on Vapor Sorption



Unprocessed vs rollar compacted aspirin Roller compacted sample estimated to have 10% amorphous content

[1] Hancock and Zografi, Journal of Pharmaceutical Sciences (1996)

Conclusions

- Residual water is capable of producing significant changes in physicochemical properties
- Water-solid interactions are complex
- Both chemical and physical stability can be affected
- Moisture induced phase transformation are of greatest concern:
  - Solid-solid: Hydrates and amorphous phases
  - Solid-solution: Deliquescence

Conclusions

- In amorphous systems, T_g considerations and water activity affect chemical reactivity
- Processing can leave pharmaceutical systems susceptible to phase transformations and increased chemical reactivity
- Important to consider that nominally crystalline material may have disordered regions

Any Questions?

Module 2: Preformulation

PHYSICO-CHEMICAL PROPERTIES OF API

Impact on Formulation Development

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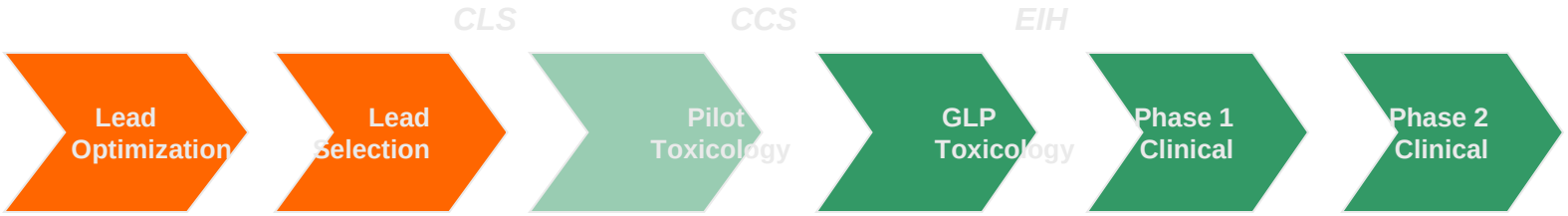
Pharmaceutical & Analytical R&D
Hoffmann-La Roche Inc.
Nutley, NJ

Overview

- Preformulation in Drug Discovery Perspective
- Preformulation in Drug Development Perspective
- Preformulation in Dosage Form Design Perspective
  - Case Studies

Tiered Preformulation Activities



High Throughput

- Kinetic Solubility
- cpKa
- cLogP
- PAMPA
- Melting Point

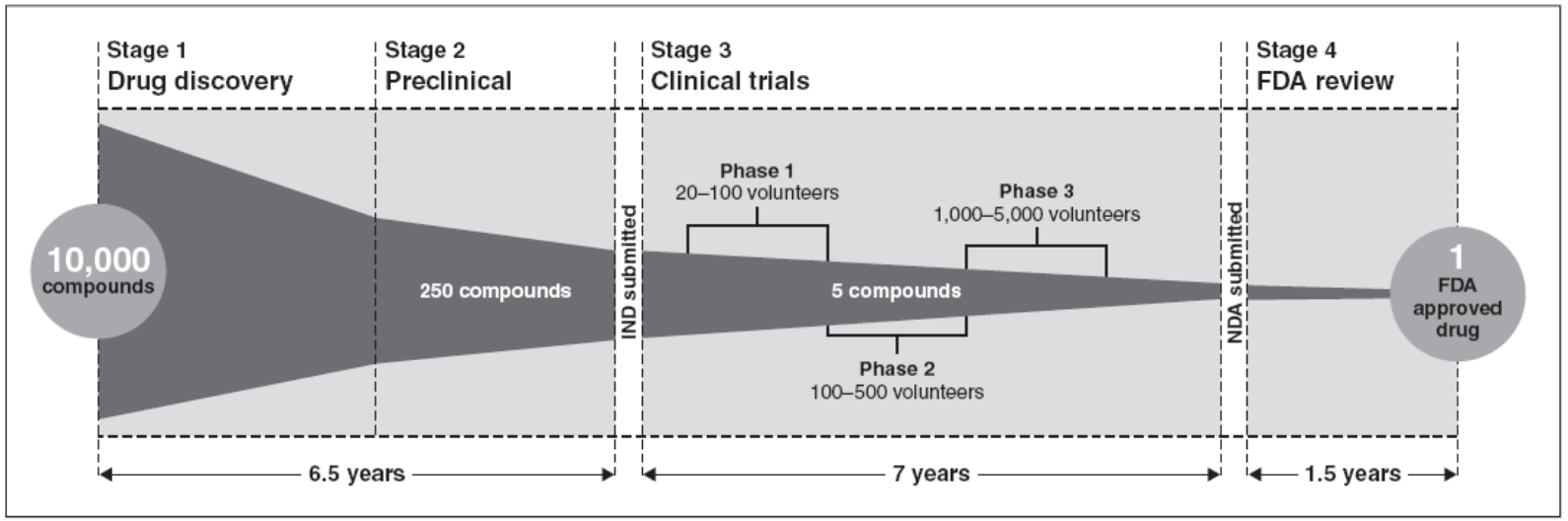
Preliminary Preformulation

- Thermodynamic Solubility
- pH Stability
- pH Solubility
- pKa
- Log P/D
- Caco-2, P-gp liability
- Salt selection
- Polymorph Screening
- Purity/Impurity Profile of API
- Preliminary stability
- Hygroscopicity
- Crystallinity
- Particle size distribution
- Forced degradation of API

Comprehensive Preformulation

- Polymorph screening
  - Single crystallography
- Micromeritics
- Particles characterization
  - Particle size
  - Surface area & surface energy
  - Flowability, bulk density
- Solubility in pharmaceutical vehicles
  - Binary mixture, complexation
- Solubility characteristics
- Thermal properties
- Excipient compatibility
- Degradation mechanism
- Structure elucidation

Landscape in Drug Development; Attrition Rate



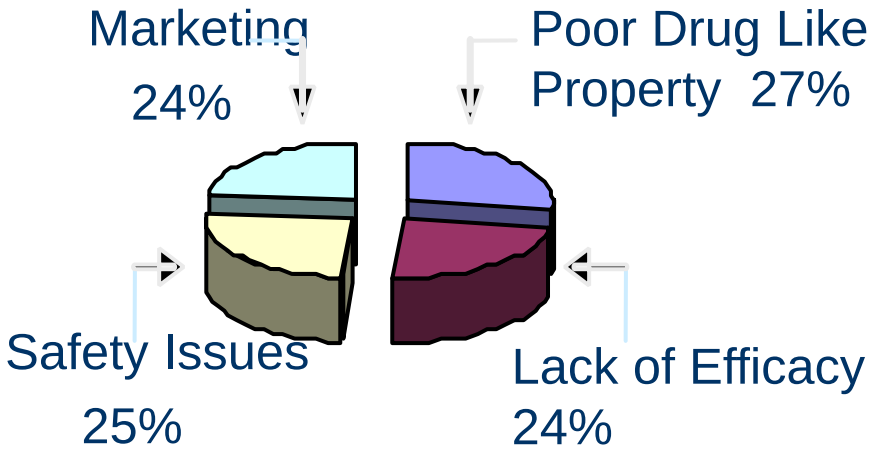
Source: Pharmaceutical Research and Manufacturers of America.

Figure 1 shows the amount of time, on average, for a successful new drug to move through and complete the four stages. It also illustrates that for every 10,000 compounds initially identified, only one, on average, will be found safe and effective, and be approved by FDA.

* New Drug Development, GAO-07-49, Nov 2006

Why compounds fail and slow down in development?

- Reasons for failure
  - Safety issues
  - Lack of efficacy
  - Business cases
  - Poor drug like properties



- Reasons for slowdown
  - Synthetic complexity
  - Low potency
  - Ambiguous toxicity findings
  - Complex target indication
  - Manufacturability – stability and consistency
  - Poor drug like properties

*Robert Lipper, Modern Drug Discovery, 1999, 2(1), p 55

“Drug Like Properties” impact on absorption

Melting Point

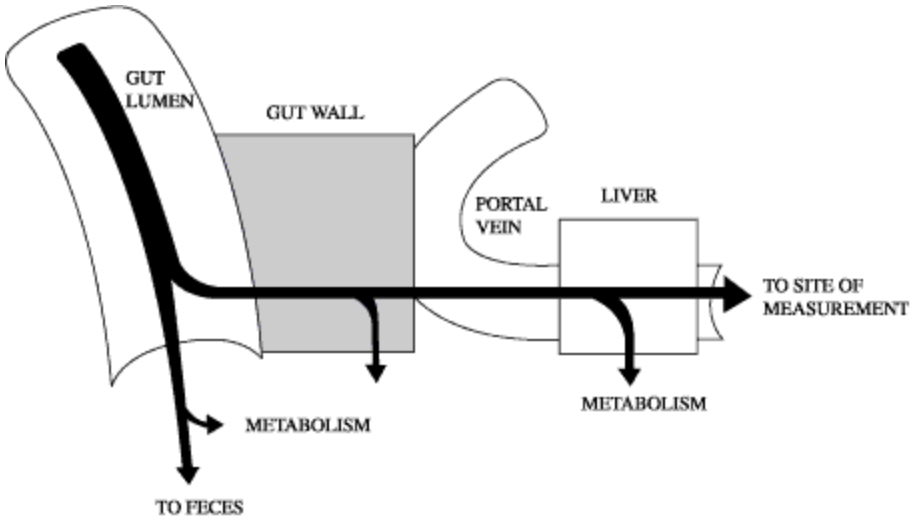
Molecular Wt

H Bonding

Solubility

Polar Surface Area

Stability



pKa

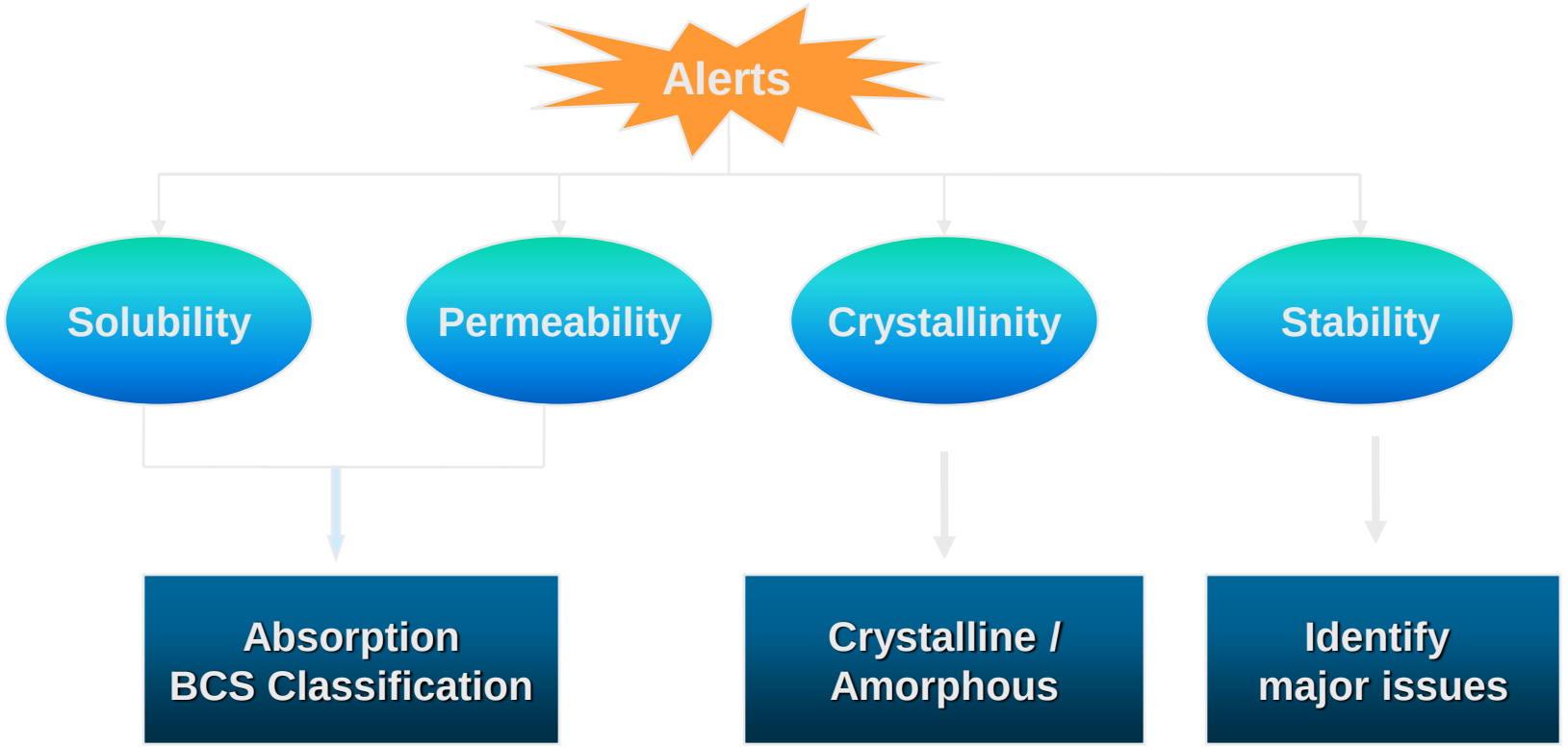
Lipophilicity (Log P / D)

P-gp Efflux

Permeability

Gut Wall Metabolism CYP3A4

“Point-to-Consider” for Clinical Candidate
Develop-ability Criteria in Pharmaceutics



These properties have potential impact on absorption, synthesis, manufacturability and shelf life

BCS Classification

Class	Solubility	Permeability	Example
1	High	High	Enalapril L-dopa
2	Low	High	Naproxen Phenytoin
3	High	Low	Cimetidine Ranitidine
4	Low	Low	Cyclosporine Furosemide

- A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in $\leq$ 250 ml water over a pH range of 1 to 7.5.
- A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be $\geq$ 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose

Permeability Consideration for BCS

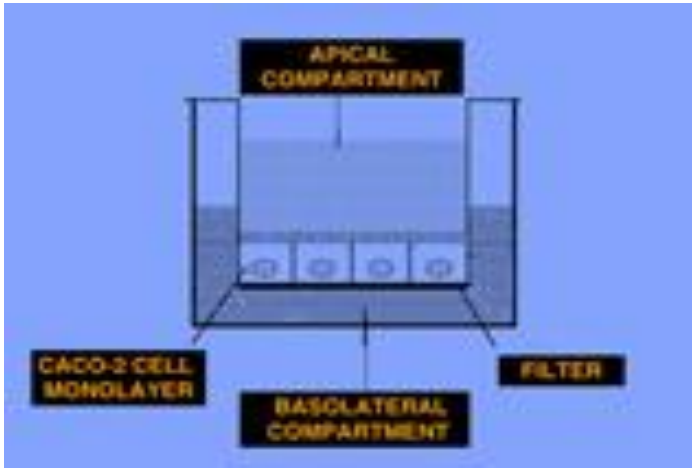
- Extent of absorption in humans:
  - Mass-balance pharmacokinetic studies.
  - Absolute bioavailability studies.

- Intestinal permeability methods:
  - *In vivo* intestinal perfusions studies in humans.
  - *In vivo* or *in situ* intestinal perfusion studies in animals.
  - *In vitro* permeation experiments with excised human or animal intestinal tissue.
  - *In vitro* permeation experiments across epithelial cell monolayers.

The Biopharmaceutics Classification System (BCS) Guidance, CDER

Permeability Estimation

- Partitioning: Log P / D
  - cLog P
  - Partitioning in n-octanol
    - Shake Flask Method
    - Potentiometric Titration
    - HPLC-IAM
- Permeability
  - PAMPA
  - Caco-2
  - Other transporters



(Human bioavailability data overrides *in-vitro* permeability data)

Solubility Consideration for BCS

- The pH-solubility profile of test article in aqueous media with a pH range of 1 to 7.5.
- Shake-flask or titration method for thermodynamic solubility.
- Analysis by a validated stability-indicating assay.

- Factors to consider:
  - Dose
  - Dose number (Do)
  - Dissolution medium

The Biopharmaceutics Classification System (BCS) Guidance, CDER

Dose Number

- Do = Dose / Cs / 250
  - Dose = Maximum dose strength
  - Cs = Minimum aqueous solubility in pH 1 - 8
  - 250 = FDA glass of water (8 oz)

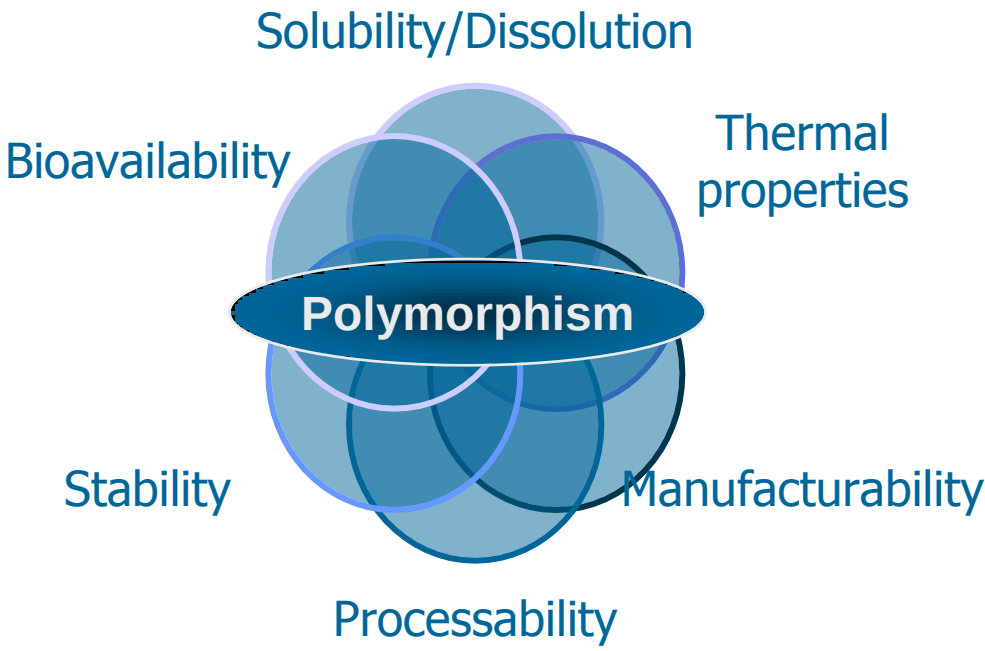
- Example
  - Ranitidine
    - Dose = 300 mg
    - Cs = 100 mg/mL
    - Do = 300 mg / 100 mg/mL / 250 mL = 0.006 : high solubility
  - Acetaminophen
    - Dose = 750 mg
    - Cs = 0.1 mg/mL
    - Do = 750 mg / 0.1 mg/mL / 250 mL = 30 : low solubility
  - Digoxin
    - Dose = 0.25 mg
    - Cs = 0.01 mg/mL
    - Do = 0.25 mg / 0.01 mg/mL / 250 mL = 0.1 : high solubility

What is polymorphism?

- Polymorphism is a phenomenon that involves different packing arrangements of the same molecule in the solid state
- Type of Polymorphism
  - Packing polymorphism: e.g. acetaminophen
    - Packing and bonding arrangement of the structure is different
  - Conformational polymorphism: e.g. spiperone
    - Different conformers of the same molecule in different crystalline modification
  - Pseudo polymorphism: e.g. paroxetine hydrochloride
    - Molecular adducts with solvent

Why Polymorphism is important?

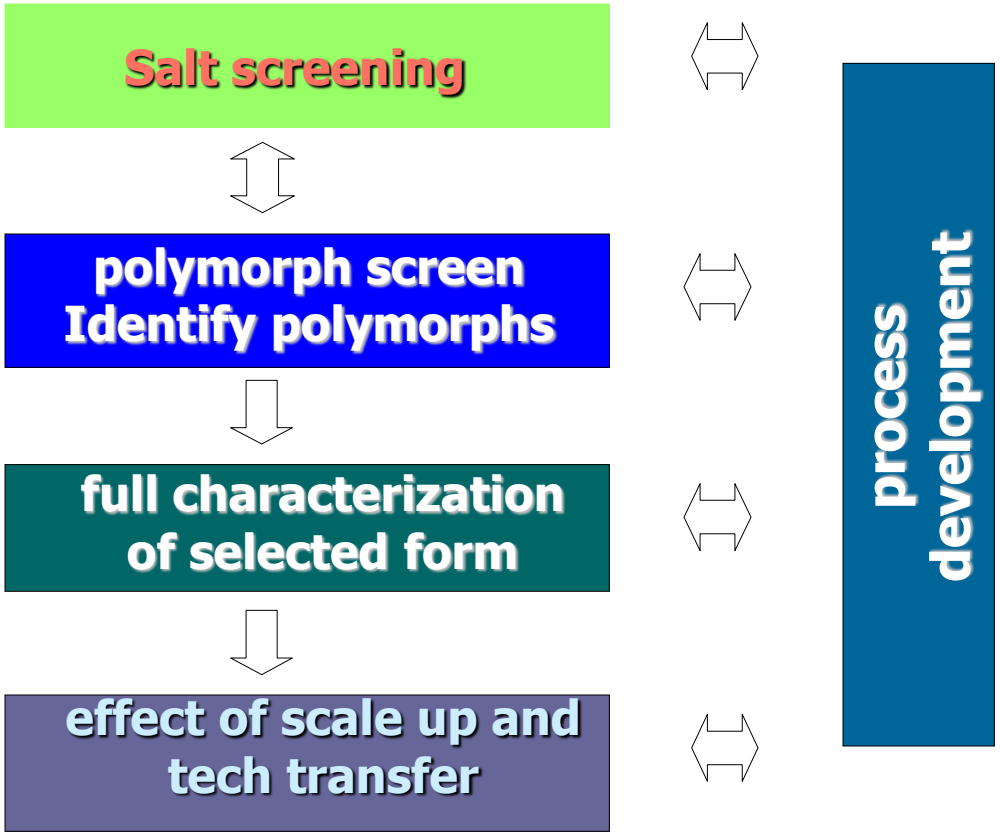
- It is regulatory requirement
- It provides strong IP position
- Polymorphs have different mechanical property impacting on manufacturability of drug
- Polymorphs have different solubility and dissolution rates, potentially leading to lower or higher biological activity than desired.
- Polymorphs can have profound effect on drug safety, efficacy, and quality



Chloramphenicol-3-palmitate has 3 crystalline forms and amorphous form. The most stable form A is marketed. Form B has an eight fold higher bioactivity than Form A, creating potential fatal dosage.*

*Haleblian, J. Pharm Sci, 1975, 64, p1269

API Form Selection Strategy / Timing



It is a balance between resources and completeness of studies

Salt Form Selection

- Once candidate molecule is identified, the feasibility of salt form should be considered
- Salt form may provide benefits of stability, solubility, dissolution rate, crystallinity, and manufacturability.
- The optimal salt form should be selected based on combination of physicochemical properties, manufacturability, processability and PK result.
- Changing salt form during development may require repeating most of studies. On the other hand, continuing with suboptimal form can lead to increased development time and/or product failure.
- Selection of optimal salt form is crucial at the initial stage of drug development

Factors to Consider in Selection of Salt Forms

- Feasibility and necessity of salt form
- Crystallinity
- Solubility and dissolution rate
- Stability – chemical and physical
- Hygroscopicity
- Manufacturability and processability
- Toxicity of counter ions
- Bioavailability

Commonly Used Counter Ions	
Anions	Cations
Acetate	Calcium
Bromide	Magnesium
Citrate	Potassium
Hydrochloride	Sodium
Maleate	
Mesylate	
Nitrate	
Phosphate	
Sulfate	
Tartrate	

Polymorph Screening

- Screen different solvents for crystallization
- Screen different kinetic conditions for crystallization
- Conduct stress studies under high humidity and heat to evaluate polymorphic conversion
- Study effect of pharmaceutical processing early in process development to evaluate polymorphic conversion
- Check water mediated transformation
- Select the most stable form as early as possible in the development to avoid late stage problems

Polymorph Screening – First Step Crystallization Experiment

- Crystallization of API
  - For crystallization to occur, solution must be supersaturated.
  - Methods to create supersaturation
    - Temperature
    - Evaporation of solvent
    - Reaction
    - Addition of anti-solvent
    - Alteration of pH
  - Attempts should be made to recrystallize the drug from various solvents.

McCrone's Law
Every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research of that compound

McCrone, Polymorphism in Physics and Chemistry of the Organic Solid State, Ed by Fox Labes, pg726-767

Factors Influencing Crystallization

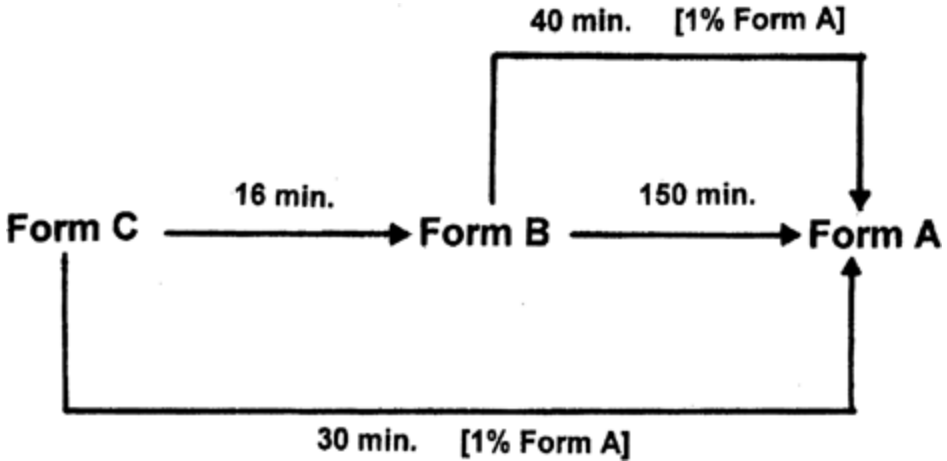
- Solvent composition and polarity
- Drug concentration and degree of supersaturation
- Temperature and cooling rate
- Presence of seed crystals and nucleation sites
- Additives to modify crystalline lattice
- Agitation rate, pH, salt
- Processing time
- Presence of impurities

Polymorph Screening – Second Step
Effect of Pharmaceutical Processing

- API can be subjected to various pharmaceutical processing conditions for final blend and dosage form. The conditions can be harsh for API (e.g. 80 °C and 100% RH with high shear)
- Unintentional phase transformation can (does) occur during pharmaceutical processing
- Thorough evaluation of polymorphism should be performed to ensure consistency, stability, and safety of drug product.

Effect of Pharmaceutical Processing on Polymorphism

- Milling
  - Milling can be used to produce homogeneity of the particle sizes (low energy) or to reduce the primary particle size (high energy)
  - High energy milling produces fresh surfaces with local increase in pressure and temperature on solids, which can cause polymorphic conversion or amorphization of drug.
  - Amorphous can revert back to crystalline over time, impacting bioavailability
  - Co grinding with excipient is an excellent way to produce co-crystal



Effect of grinding on polymorphic conversion of chloramphenicol-3-palmitate
M. Otsuka, 1983, J. Pharm Sci, 75, p 506

Effect of Pharmaceutical Processing on Polymorphism (continue)

- Wet granulation
  - Solvent (water) mediated transformation (hydration) can occur
- Drying
  - Removal of water (solvent) can incur dehydration of hydrate or amorphization. Spray drying and freeze drying typically produce amorphous form.
- Compaction
  - Energy applied in general is insufficient to exert polymorphic conversion. In the case of amorphous form, the selection of key excipients is crucial to absorb compression energy.

Case Study: Project A

Background

- After exhaustive search for an ideal compound, discovery team came up with two candidates that showed excellent selectivity, potency, and high affinity to receptor.

- Both compounds, however, exhibited less than desirable PK profile and bioavailability in animals.

Physicochemical Properties of Two Leads

Property	Compound A	Compound B
MW	457	470
∑ (N + O)	6	8
Melting point	220 ºC	251 ºC
cpKa (acidic)	3.5	3.4
cLog P	4.1	2.5
Caco-2 (10^{-7} cm/sec)	7.7	29
Solubility (SGF)	0.008 mg/mL	0.005 mg/mL
Solubility (SIF)	5.9 mg/mL	4.3 mg/mL
Bioavailability (Rat)	3 - 10%	3 - 10%

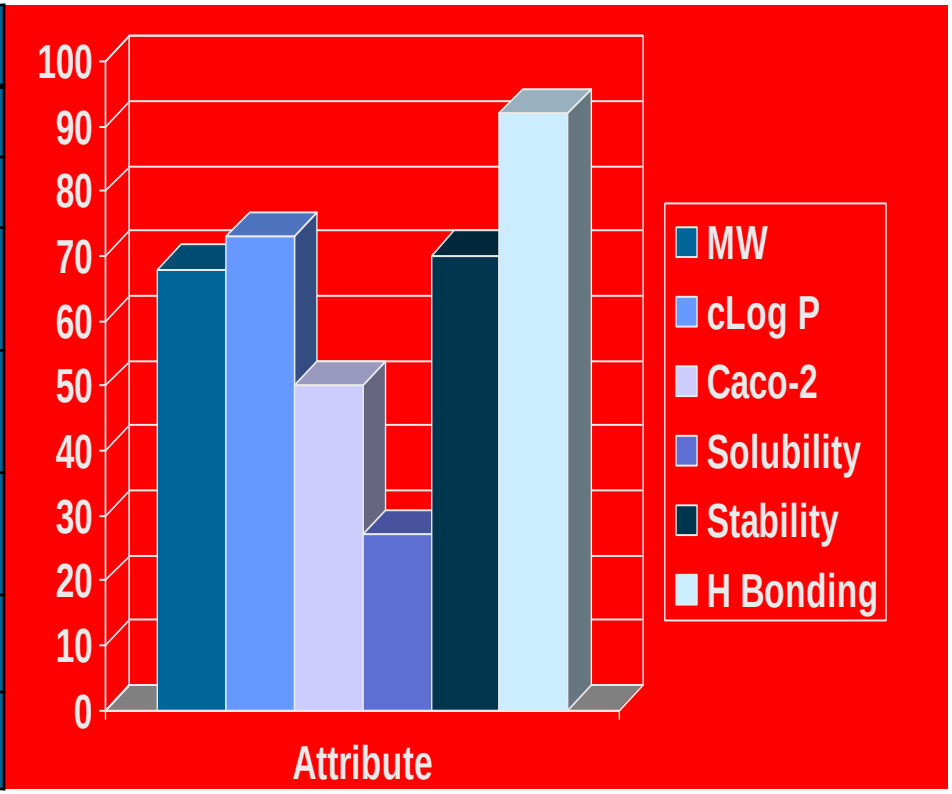
Pro-Drug Design

- The pro-drug moiety contained
  - Basic functional group (4)
  - Polarized functional group (5)
  - Hydrophobic functional group (3)

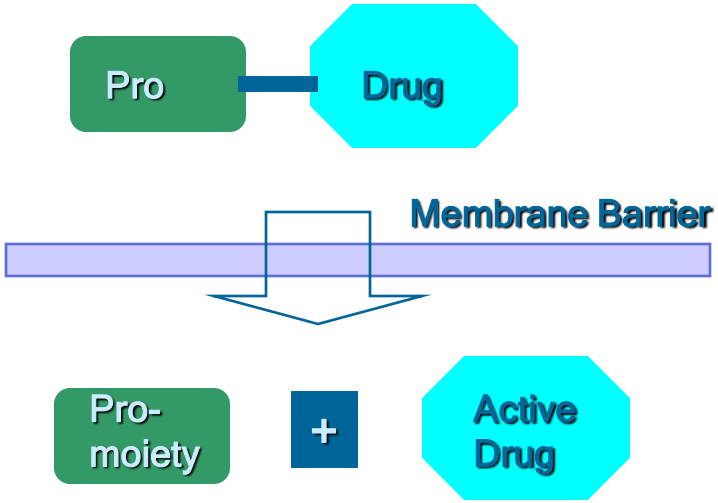
- Total 25 pro-drugs were synthesized and evaluated for drug like properties
  - Biological properties
    - Plasma stability, TDI, Caco-2, etc.
  - Physicochemical properties
    - Solubility, melting point, stability, etc.

How we have fared

Attributes	Target	% Target
MW	< 600	68%
cLog P	< 5	73%
H Bonding Potential	∑(N+O) = < 10	91%
Caco-2	> 100 x 10^{-7} cm/sec	50%
Aq. Solubility (in pH 2 – 8)	> 0.1 mg/mL	27%
Aq. Stability, $t_{0.9}$	> 0.5 Hr	70%
Crystallinity	Crystalline	100%



Property of Selected Pro-drug
(Out of 25 Candidates)



No pro-drug was found in plasma

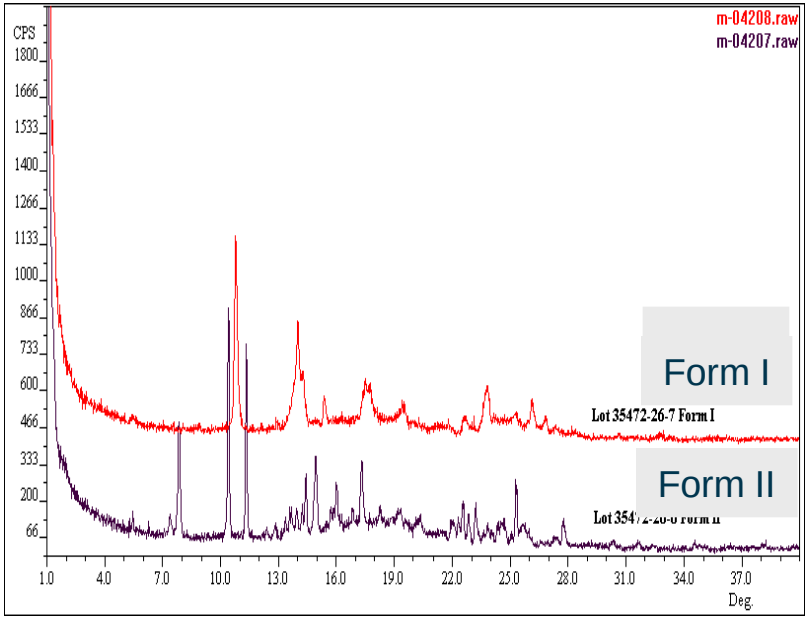
Property	Value
MW (FB)	570
Melting Point	248 °C
pKa (basic)	8.3
Caco-2	87 x10^{-7} cm/sec
Intrinsic Solubility	3 mg/mL
Bio in Rats	33%
Bio in Dogs	41%

Salt and Polymorph Selection

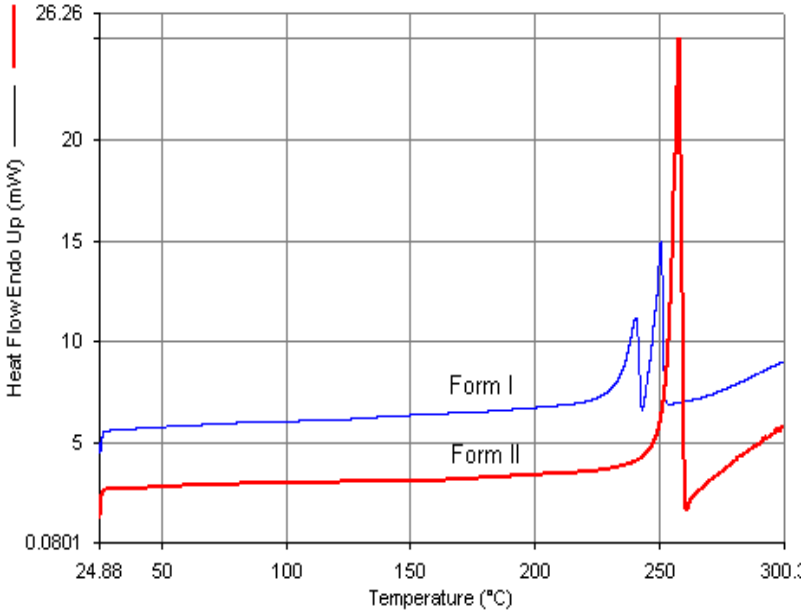
- Following selection of a drug candidate with good pharmacological and physicochemical properties, salt screening was performed
  - HCl salt was selected as final salt form
  - Good solubility and acceptable solid state stability
  - Non hygroscopic
  - Pharmaceutically process-able
- Preliminary polymorph screening found two polymorphs

Result of Polymorph Screening

Powder XRD showed two distinctive patterns



DSC showed two distinctive thermal transitions



Polymorph Characterization

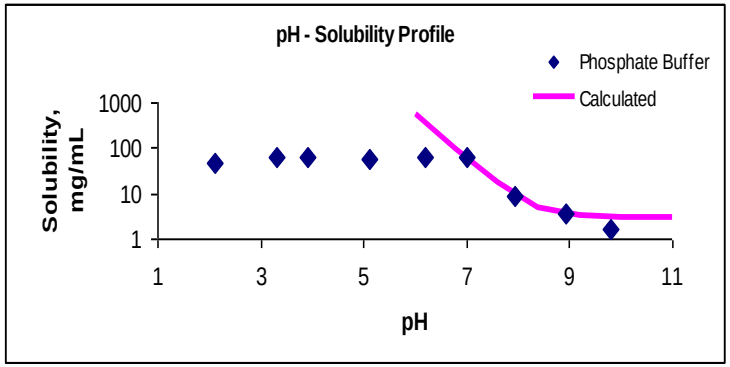
- Solvent mediated transformation study
  - At room temperature, Form I + Form II slurry mixture converted to Form II
  - Form I + II mixture converted to Form II at reflux

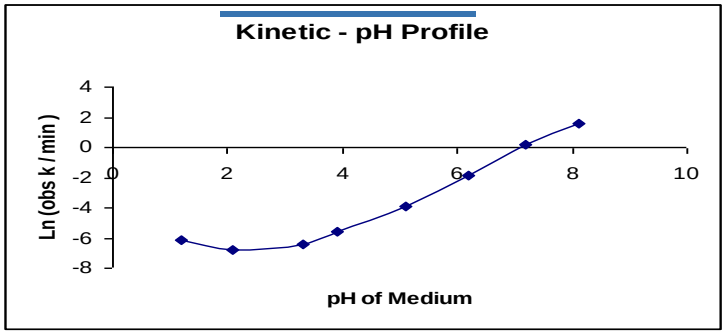
- Aqueous solubility at 25 ºC

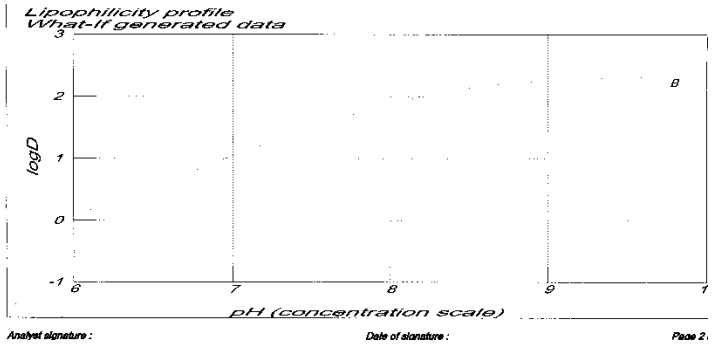
	SGF	SIF	Water
Form I	45 mg/mL	78 mg/mL	86 mg/mL
Form II	28 mg/mL	63 mg/mL	72 mg/mL

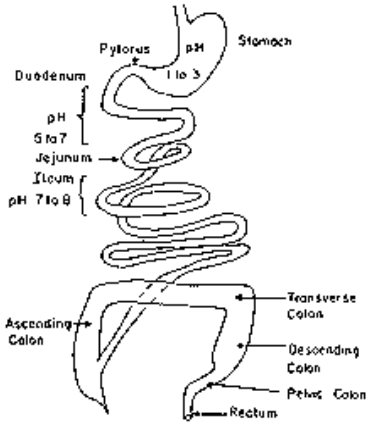
Form II is more stable form (monotropically related)

Physicochemical Property (Form II)



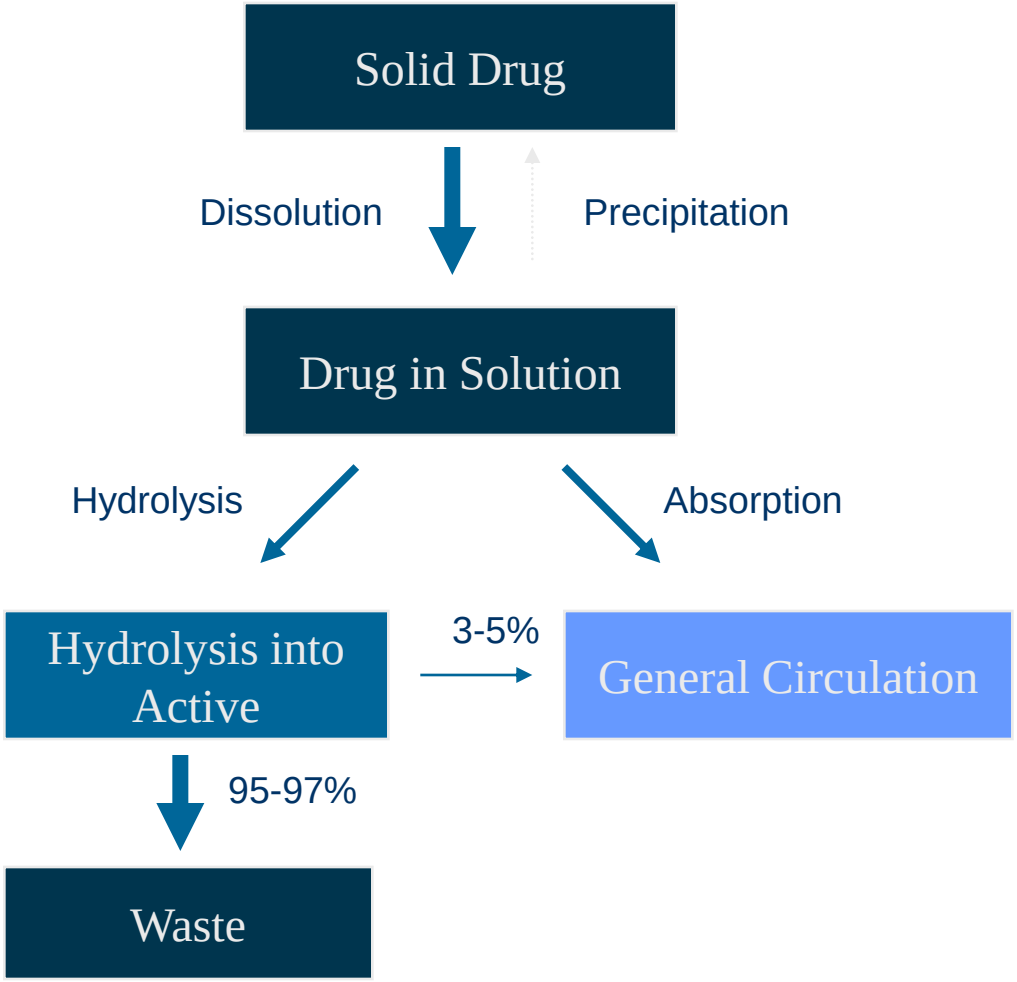


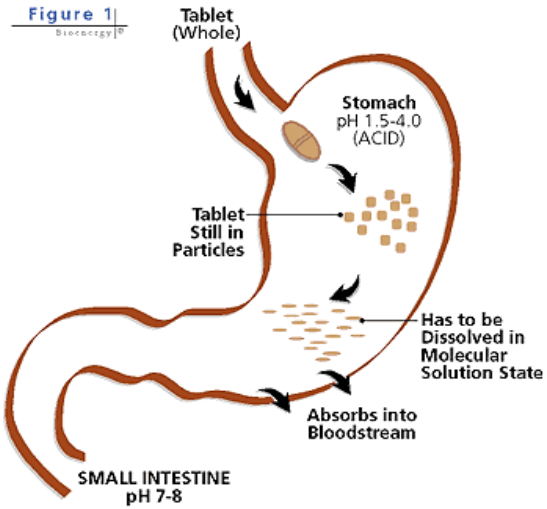




- Good solubility in physiological pH (So = 3 mg/mL)
- Hydrolyzes rapidly at pH > 7, but reasonably stable in pH 2 – 7
- Good partition coefficient, Log D at pH 7.4 = 1.4

Preformulation Perspective





Dosage Form Design?

Summary of Project A

- Preformulation characterization facilitated selection of clinical candidate
  - Selection of pro-drug with good “drug like properties”
  - Selection of HCl salt prior to GLP
  - Identification of stable polymorph prior to GLP
  - Acceptable bioavailability (> 40% in Dog)
- Preformulation characterization enabled design of toxicological and clinical dosage form design
  - Dosage form and release characteristics were defined

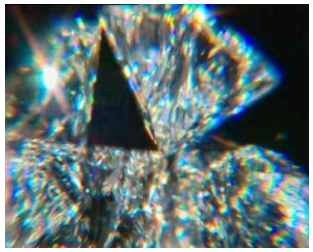
Excellent Team Work
Good Clinical Candidate

Case Study - Project B

Background of Project B

- After countless sleepless nights, discovery team brought three compounds onto table as clinical leads
  - Acceptable selectivity & potency

- Project team decided to do pilot tox study, PK study and physicochemical characterization on three molecules for ranking



Physicochemical Properties of Clinical Leads

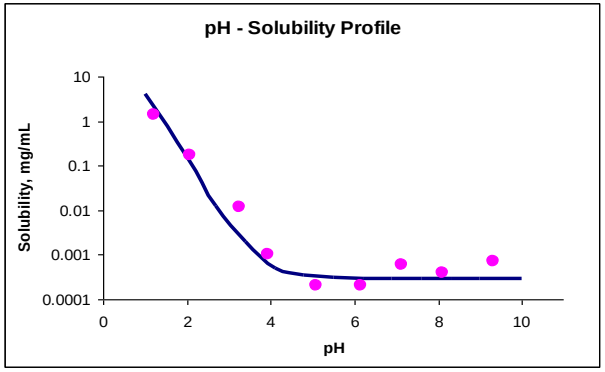
	B-1	B-2	B-3
pK (basic)	4.3	3.9	3.8
Solubility in SGF (pH 1.2)	2.0 mg/mL	> 5 mg/mL	1.4 mg/mL
Solubility in SIF (pH 7.4)	0.0052 mg/mL	0.010 mg/mL	0.0005 mg/mL
Stability in SGF & SIF	Stable	Stable	Stable
cLog P	2.2	2.1	2.3
Caco-2 (10^{-7} cm/sec)	249	51	84
Melting Point	201 °C	185 °C	218 °C
Crystallinity	Crystalline	Crystalline	Crystalline
MW	424	456	442
Solid State Stability	Stable	Stable	Stable

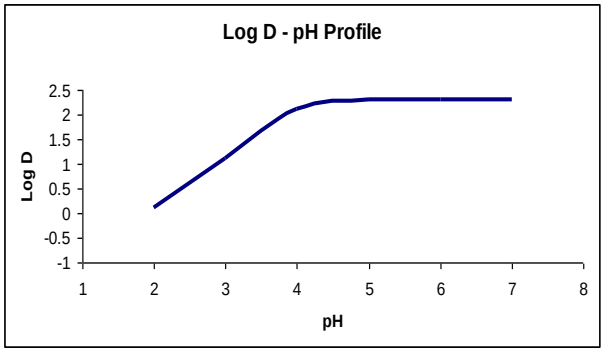
After careful evaluation of all data presented, project team endorsed B-3 as clinical candidate

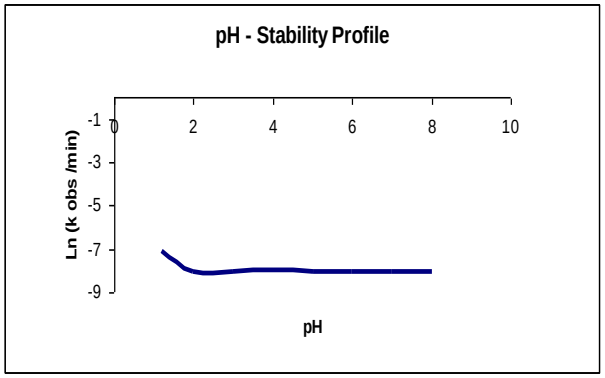
Selection Criteria

1. Potency
2. Selectivity
3. Animal safety
4. PK property (clearance, $t_{0.5}$, etc.)
5. Physicochemical property

Physicochemical Property





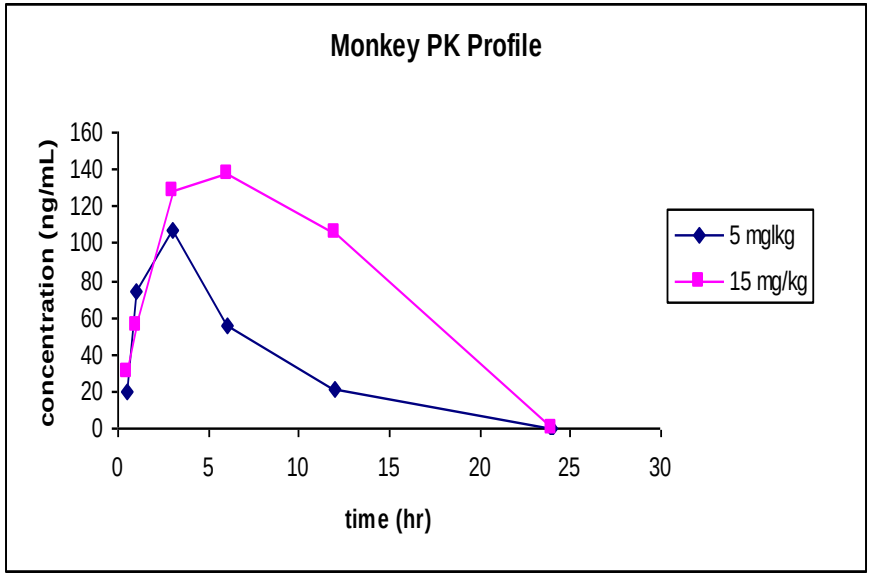


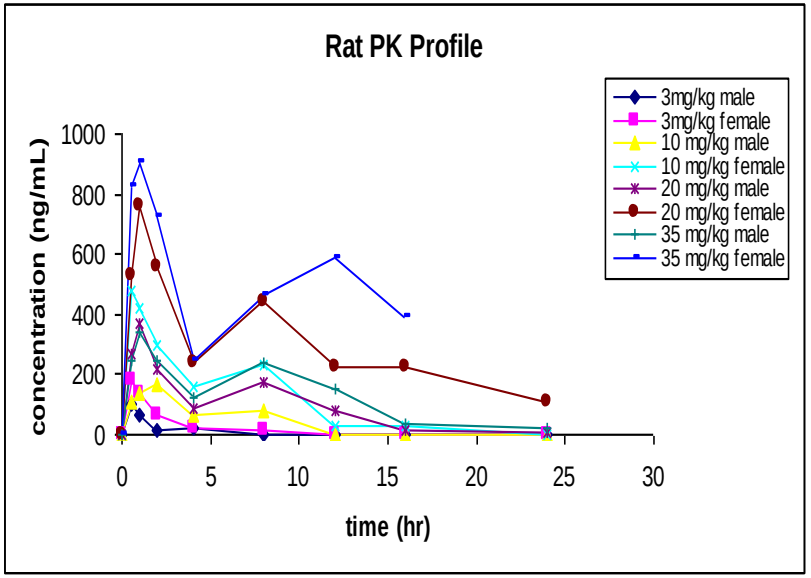
- Reasonable solubility in acidic media but poor solubility in pH greater than 4 (So = 0.0005 mg/mL)
- Good partition coefficient in intestinal pHs (Log D = 2.3 at pH 7.4)
- Chemically stable in gastro intestinal pH range

Dissolution limited absorption is expected

Absorption may vary depending on tox species (Gastric pH + emptying time + volume)

Monkey & Rat SD PK Profile

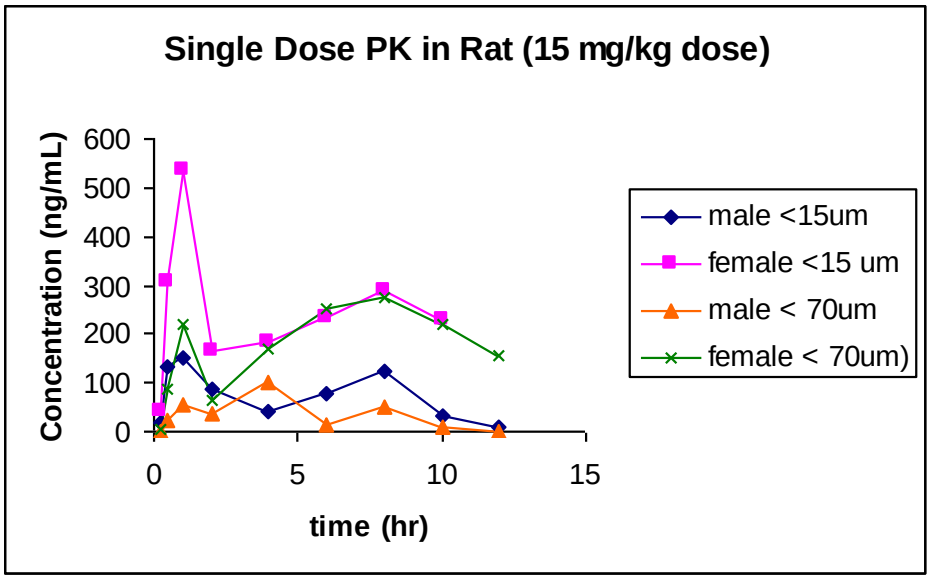




- Bioavailability in rat = 20%
- Bioavailability in monkey = 6% - 10%

Poor “drug like properties” resulted in poor bioavailability

Substantial Particle Size Effect on Exposure



Particle size of poorly water soluble compound has substantial impact on bioavailability

Particle size needs to be controlled.

	AUC (ng*hr/mL)		Cmax (ng/mL)	
	Male	Female	Male	Female
Un-milled (d_{90} <70)	446	2280	100	273
Micronized (d_{90} <15)	852	2960	152	537

Back to Drawing Board

- Team is content with selectivity, potency, and tox profile of lead compound
- Need to improve bioavailability
  - Caco-2 is classified as “medium”
  - Solubility at intestinal pH is poor (So = 0.0005 mg/mL)
  - Dissolution rate limited absorption
- Improve process-ability (minimize particle size effect)
- Pro-drug is not an option

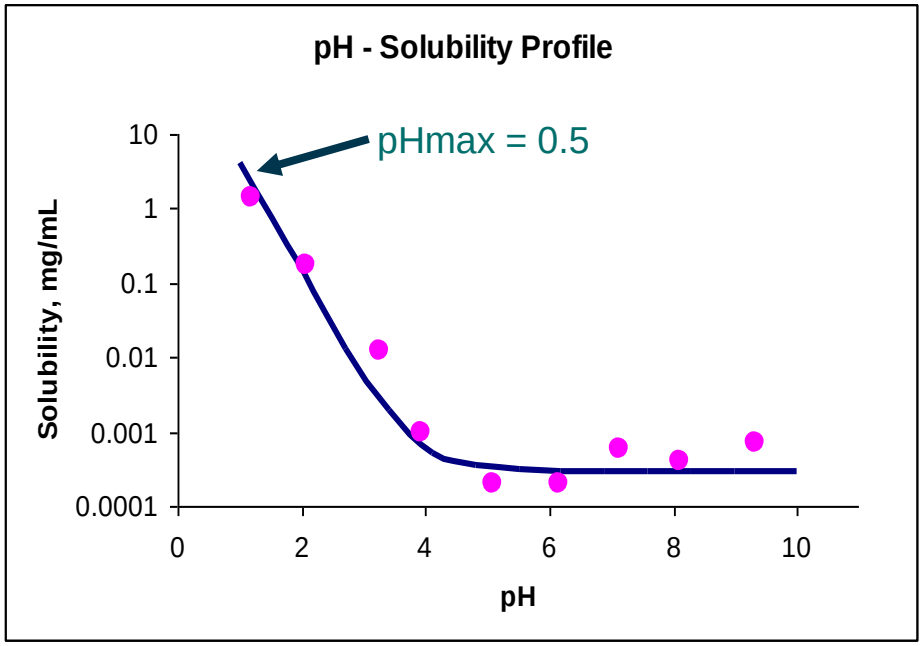
Can salt form provide desired properties?

Factors to Consider in Selection of Salt Forms

- Feasibility and necessity of salt form
- Crystallinity
- Solubility and dissolution rate
- Stability – chemical and physical
- Hygroscopicity
- Manufacturability and processability
- Toxicity of counter ions
- Bioavailability

Commonly Used Counter Ions	
Anions	Cations
Acetate	Calcium
Bromide	Magnesium
Citrate	Potassium
Hydrochloride	Sodium
Maleate	
Mesylate	
Nitrate	
Phosphate	
Sulfate	
Tartrate	

Is it feasible to form salt?



- Weak base with pKa of 3.8
- pH $_{max}$ is estimated to be ~ 0.5

$$S = So\ (\ 1 + 10^{\ pKa - pH}\ )$$

To form salt:
difference between drug and acid
pK > 2

Yes, it is likely to form salt, but
only with strong acid.

Summary of Salt Screening

Type of Salt	Crystallinity	Melting (DSC)	[S] in H_2O mg/mL	Hygroscopicity	SS Stability
Free Base	Crystal	218 ºC	0.0005	1%	Stable
Esylate	Crystal	232 ºC	0.27	2%	Stable
Mesylate	Crystal	231 ºC	0.08	1%	Stable
Tosylate	Crystal	254 ºC	0.07	2%	Stable
Bromide	Crystal	214 ºC	0.12	1%	Stable
Nitrate	Crystal	decompose	0.30	3%	Unstable
Chloride	Poor	decompose	0.35	5%	Unstable
Sulfate	Poor	decompose	0.30	3%	Stable

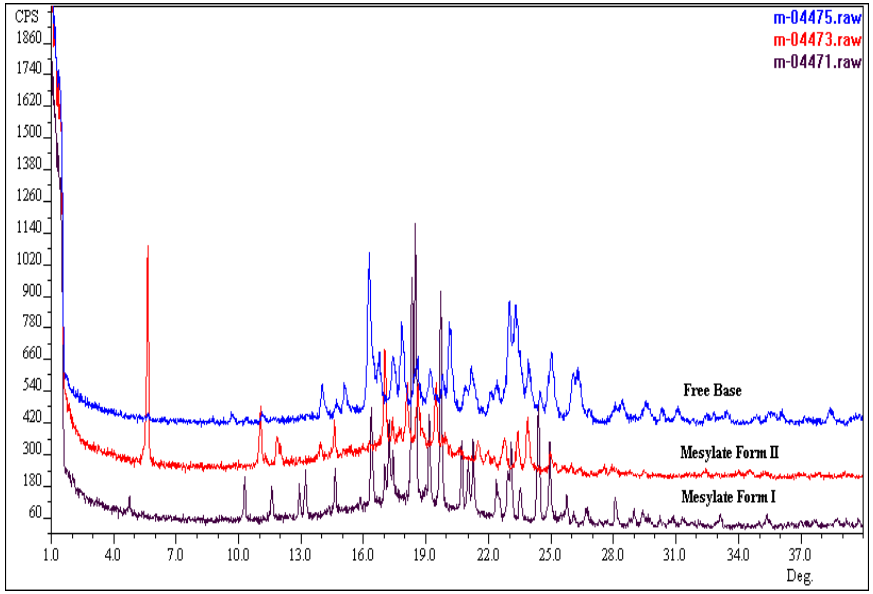
When we put all physicochemical data together

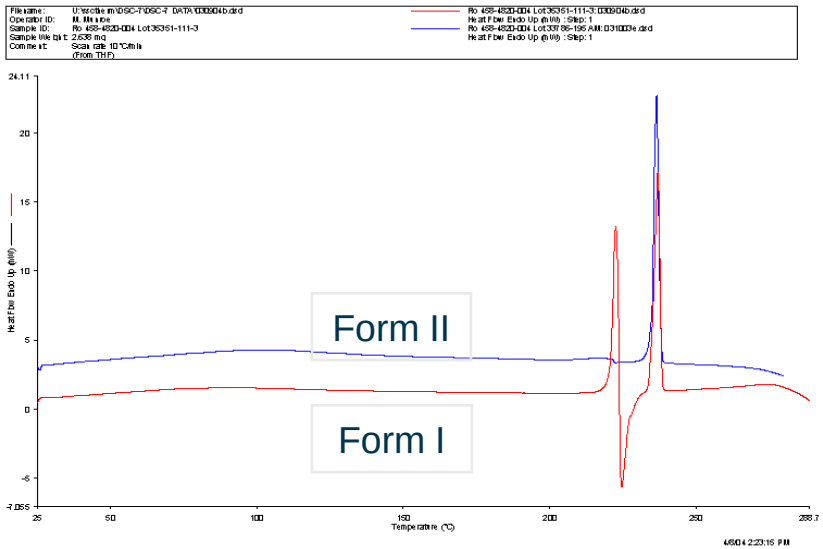
Mesylate Salt

was the winner

Polymorph screening of mesylate salt found two polymorphs

Polymorph Characterization of Mesylate Salt





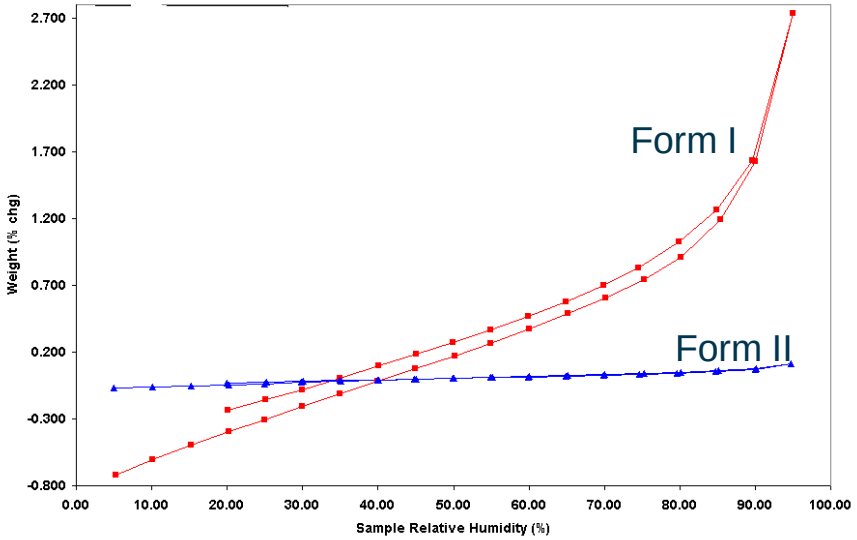
Polymorphs have different PXRD Patterns.

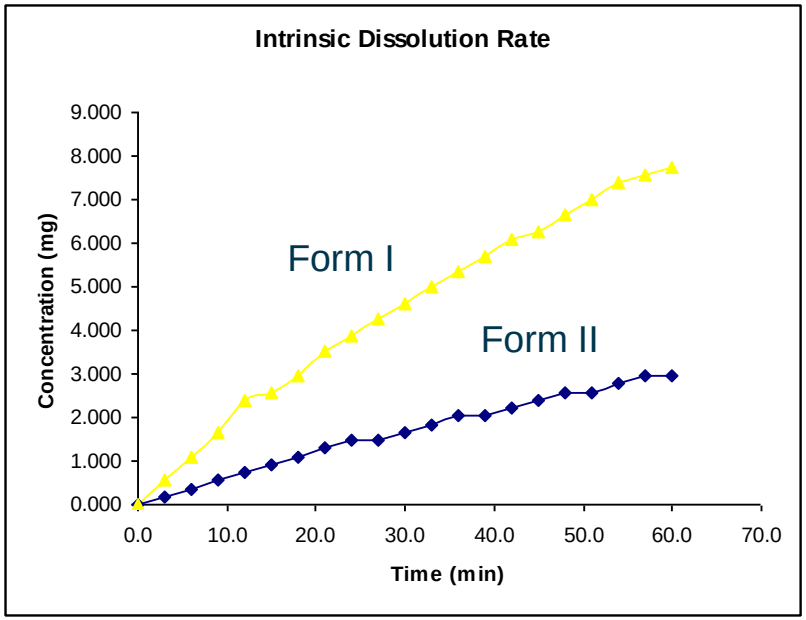
Two XPRD patterns of mesylate salt are shown against free base

Polymorphs have different melting points.

Form I melts at 218 ºC, re-crystallizes and melts at 231 ºC.

Polymorph Characterization of Mesylate Salt





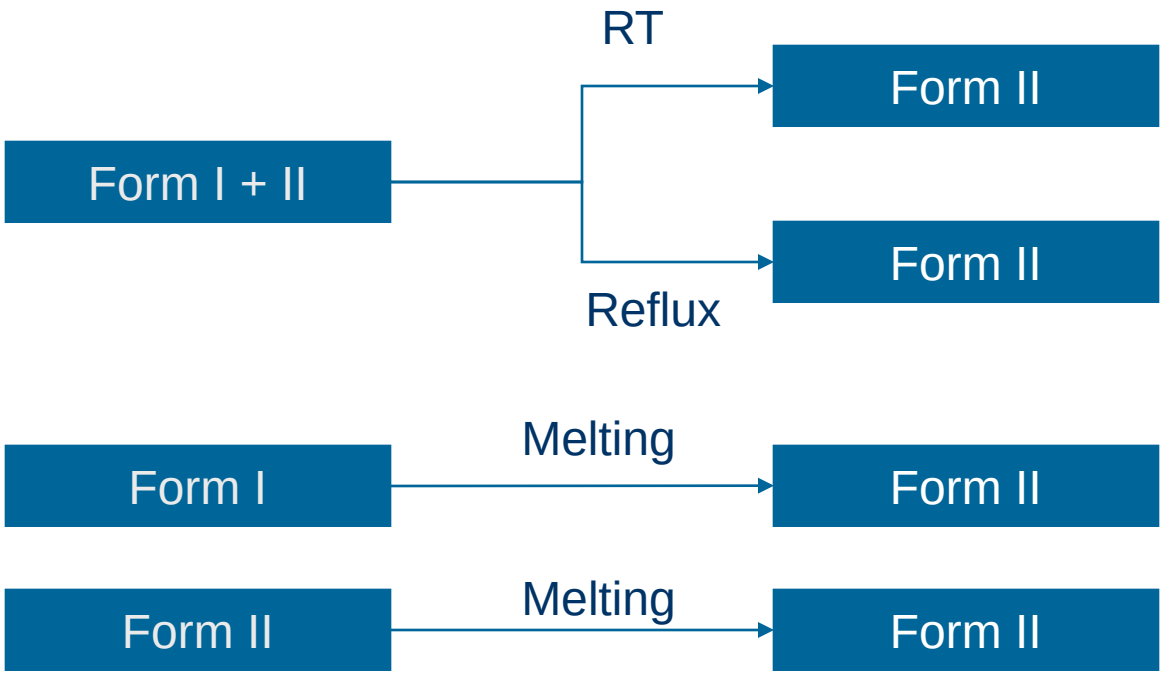
Polymorphs may have different hygroscopicity.

Form I is more hygroscopic than Form II.

Polymorphs may have different dissolution rates.

Intrinsic dissolution rate of Form I is faster than Form II.

Polymorphs Relationship

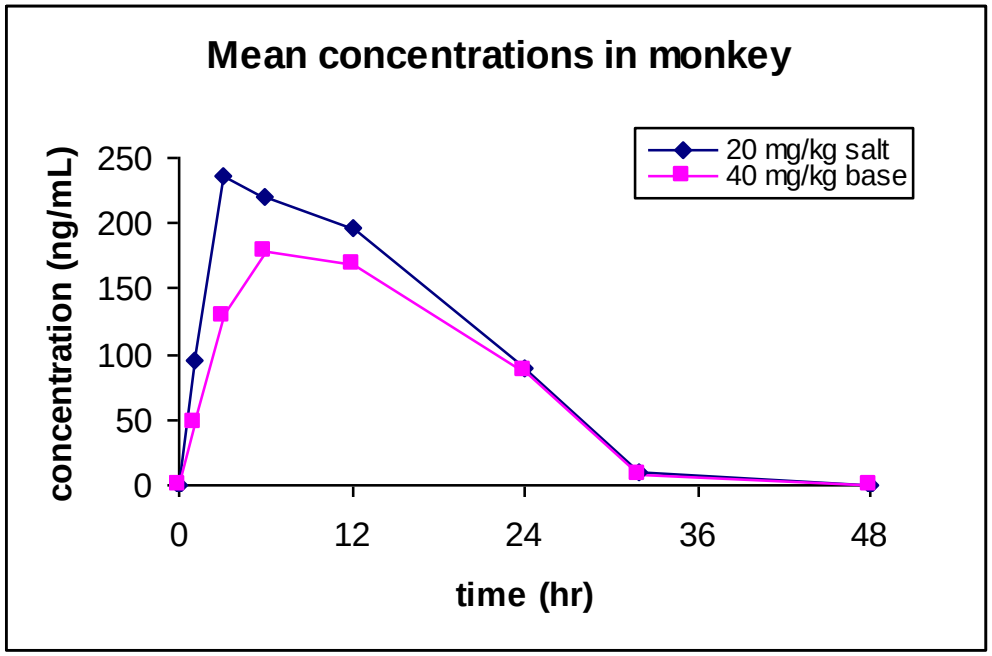


- Form I and II are monotropically related
- Form II is more stable form

Monkey PK Study Result

- Mesylate salt was selected
- Stable polymorph Form II was identified
- Outcome of Monkey PK Study

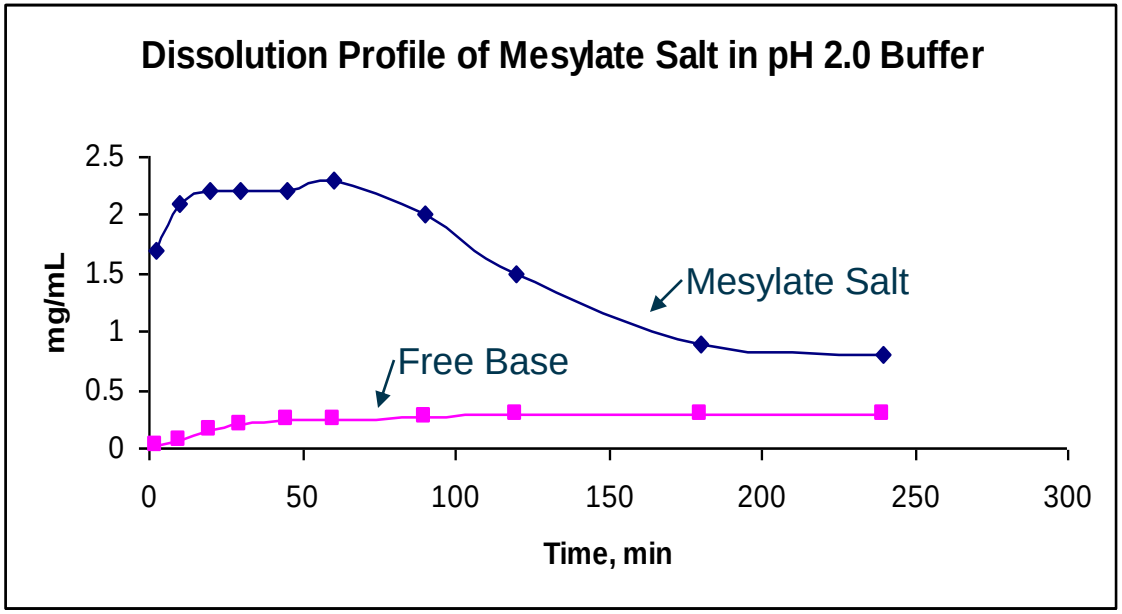
Single Dose PK Study in Monkey
(Mesylate vs. Free Base)



Mesylate salt improved bio about 2.5 fold. (20% in monkey)

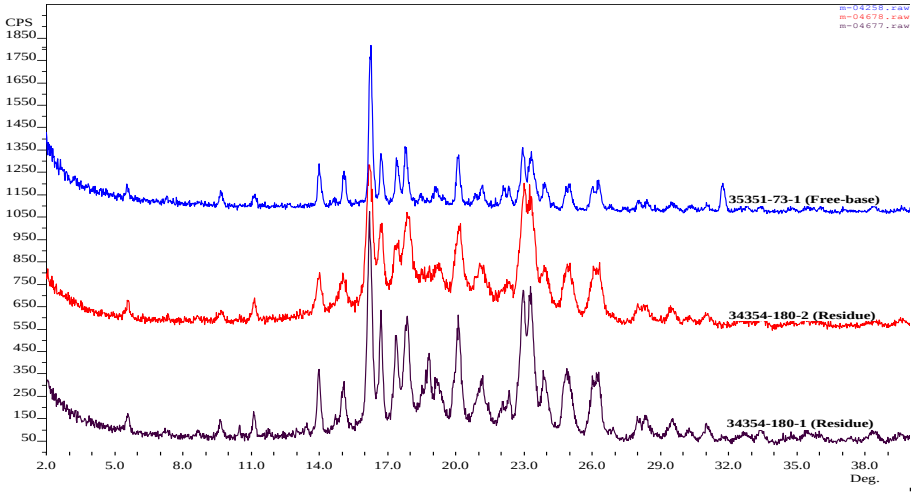
	AUC (ng*hr/mL)	CV (%)	Cmax (ng/mL)
40 mg/kg free base	3502	27	190
20 mg/kg mesylate	4310	32	250

Dissolution Profile of Mesylate Salt



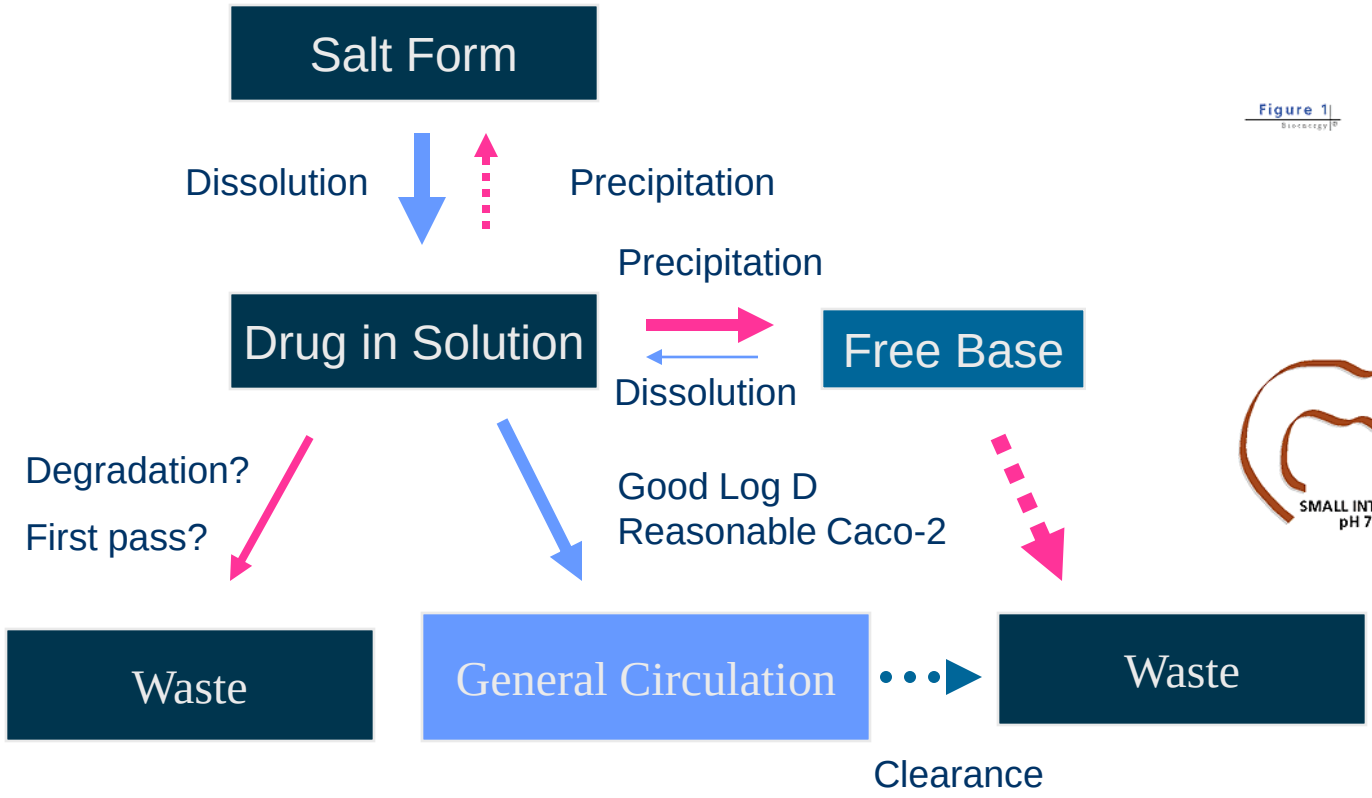
- Mesylate salt dissolves rapidly into a transient equilibrium state in 20 min, and begins to precipitate after 2 hours.
- Free base dissolves gradually into an equilibrium state in an hour.

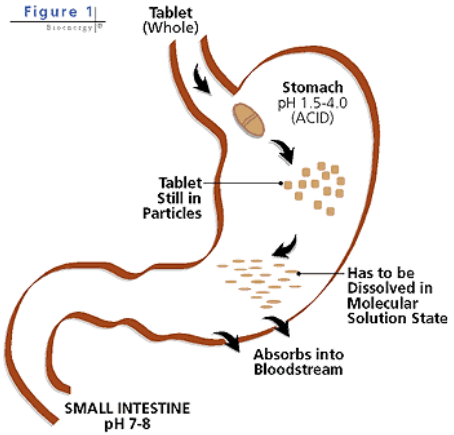
Mesylate Residue in Aqueous Media



- Mesylate salt converted to free base within 4 hours in simulated gastric fluid (SGF: pH 2)
- Conversion of mesylate salt to free base can cause variability in absorption

Preformulation Perspective
Absorption





- ❑ Deliver salt to absorption site before precipitation?
- ❑ Will salt in capsule increase bioavailability? With stabilizer?

Preformulation Summary

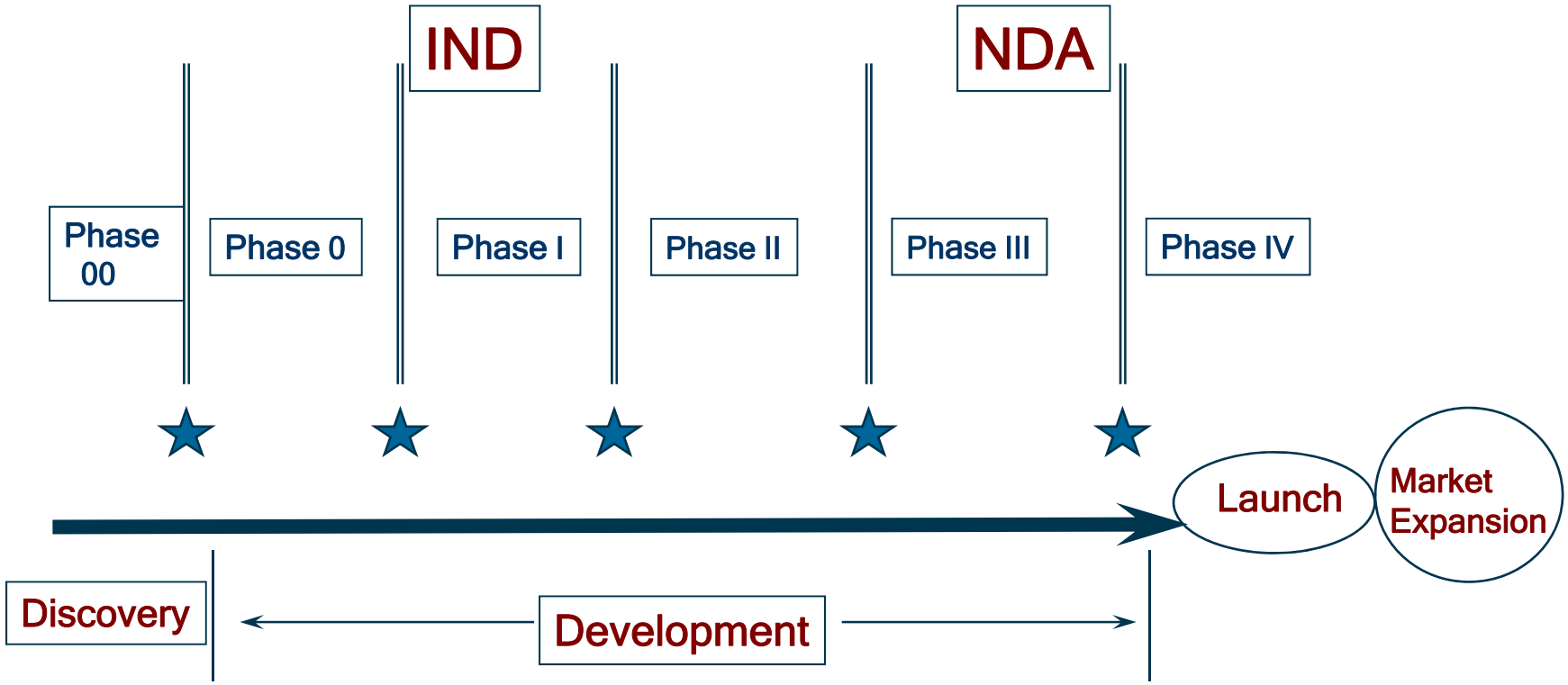
- Mesylate salt form has increased oral bioavailability via increased solubility and dissolution rate
  - From 10% (micronized free base) to 20% (micronized mesylate salt) in monkey
- Micronization had minimal impact on oral bioavailability of mesylate salt in monkey
  - Both un-milled and micronized API: F = 20%

Any Questions?

PHYSICO-CHEMICAL PRPPERTIES OF API AND EXCIPIENTS: IMPACT ON FORMULATION DEVELOPMENT

Navnit Shah, Ph.D.
Distinguished Research Leader
Pharmaceutical R&D
Hoffmann-La Roche Inc.
Nutley, NJ

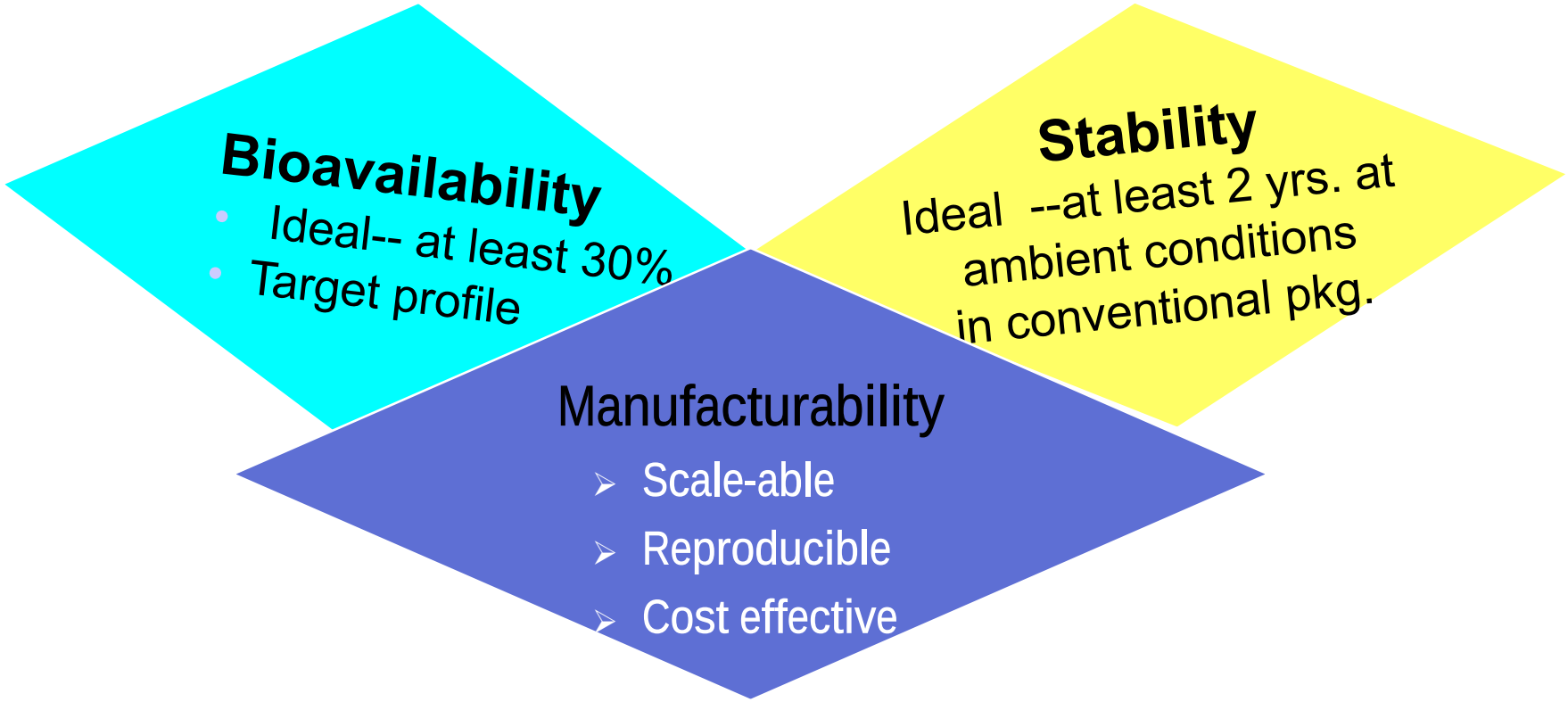
The Drug Development Process



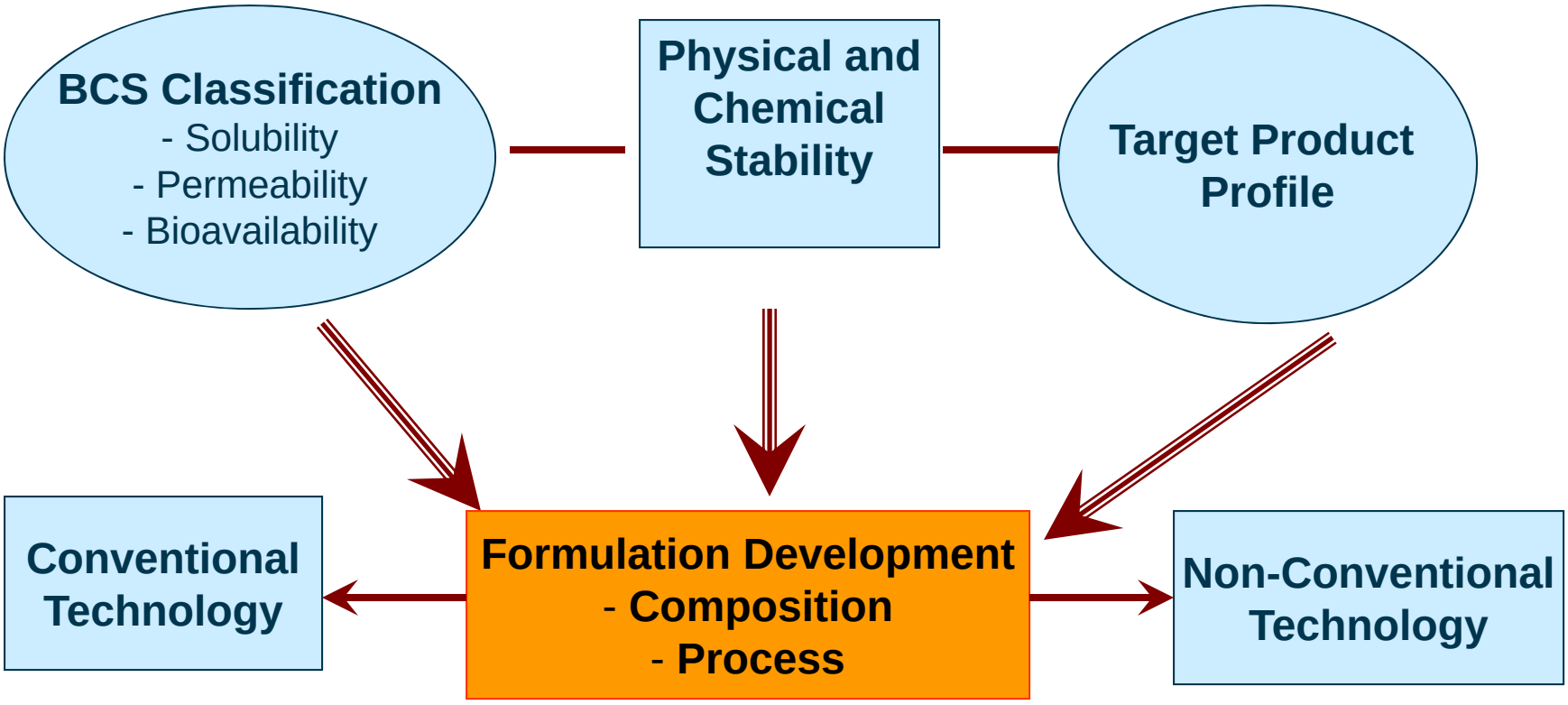
Physico-chemical Properties of API Impacting Formulation Development

- Molecular weight
- Stability
- Solubility in physiological fluids
- Crystal form
- Particle Size
- pKa
- Salt Form
- Log D (Partition coefficient)
- Permeability

Physico-chemical Properties of API Impacting Formulation Development



Drivers for Formulation Development



PHYSICO-CHEMICAL PROPERTIES IMPACTING BIOAVAILABILITY

- Molecular Weight
- Chemical Structure
- Solubility
  - Salt
  - Particle Size (rate)
  - Crystal Form
  - Melting Point
- Permeability

Drug Molecular Properties Impacting Bioavailability

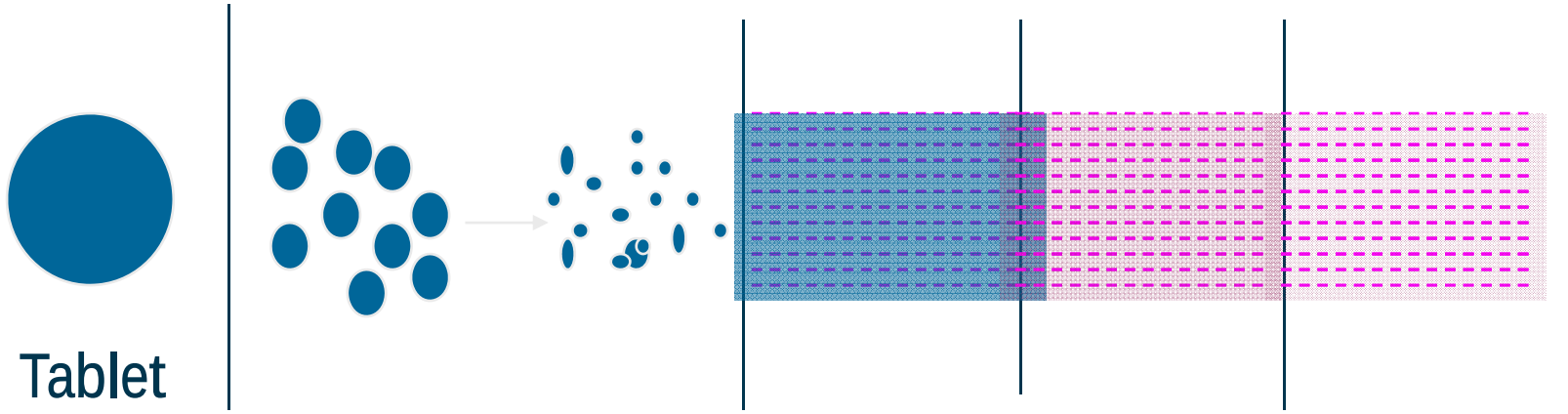
- Log P > 5 (poor aqueous solubility)
- Mol. Wt. > 500 (limited diffusivity)
- H-bond donors > 5 and H-bond acceptors >10 (impaired permeability)
- High melting point
- High dose of poorly soluble drugs

IDEAL PROPERTIES OF DRUG MOLECULE FOR ORAL DELIVERY

- Molecular weight < 500 g/mol
- Solubility > 1 mg/mL
- Permeability > $100 * 10^{-7}$ (Caco2 permeability*)
- Melting point 100 - 200 °C

* ***Human colonic cells used for permeability assessment***

JOURNEY OF MOLECULES FROM TABLET TO THE TARGET TISSUES



- Drug has to dissolve in the gastro-intestinal tract to be absorbed
- Drug has to be absorbed (via active or passive transport mechanism)
- Drug has to survive gastro-intestinal environment and first pass effect to reach target tissue

Oral Absorption and Bioavailability

Principle of Drug Absorption (Passive Transport)

$$J_w = P_w * C_w$$

J_w = Absorption Rate

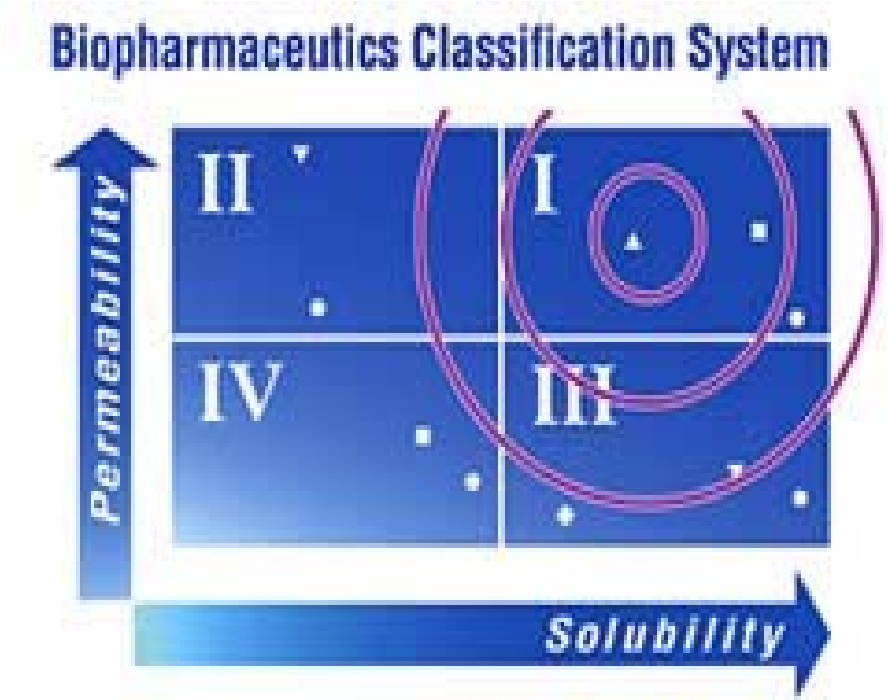
P_w = Intestinal Wall Permeability

C_w = Drug Concentration at Intestinal Wall

Maximal Absorption Rate:

$$J_{w,(max)} = P_w * Solubility$$

Biopharmaceutical Classification System: Solubility and Permeability



Class	Solubility	Permeability
1	High	High
2	Low	High
3	High	Low
4	Low	Low

Biopharmaceutical aspects (solubility and permeability) impact on bioavailability and as a result on formulation design

FORMULATION APPROACHES FOR IMPROVING THE ORAL ABSORPTION OF POORLY ABSORBED DRUGS

- Salt formation
- Particle size reduction
  - Micronization
  - Nano-particulate
- Lipid based delivery systems
  - Self emulsifying drug delivery systems- SEDDS,
  - Microemulsion
- Micro-precipitation
  - Solid dispersion and/or solid solution

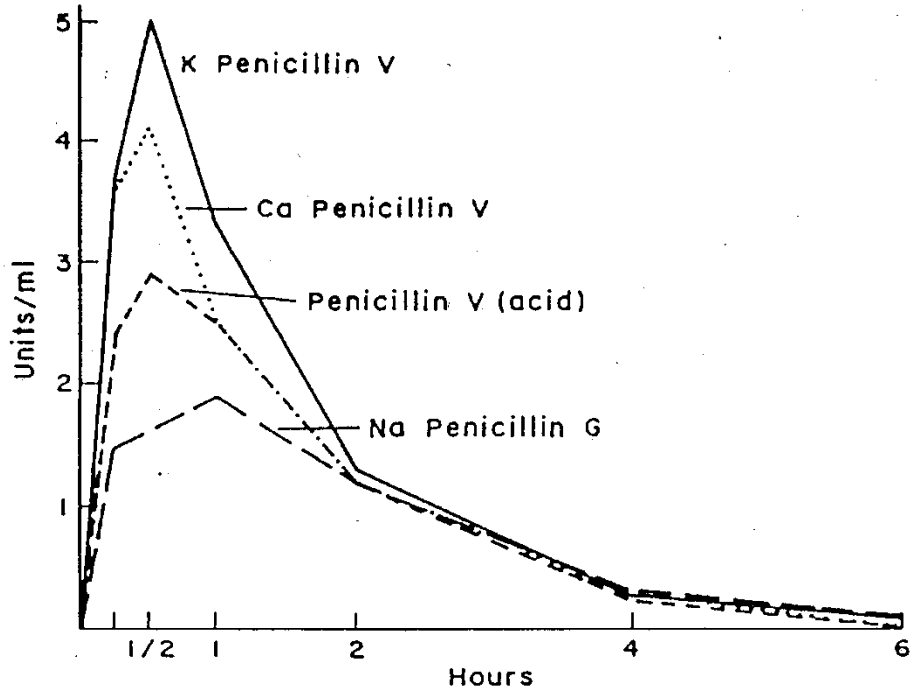
SALT FORMATION

Examples: Penicillin

- Salts improve solubility
- Provide rapid rate of dissolution and absorption
- Result in improved bioavailability

SALT FORMATION (PENICILLIN)

USE OF SALT FORMS TO IMPROVE BIOAVAILABILITY



Average penicillin levels in the plasma of ten fasting subjects following oral administration of 400,000 units of penicillin in the different forms. (From "The Solubility of Oral Preparations of Penicillin V" by H. Juncher and F. Raaschou, *Antibiotic Medicine and Clinical Therapy*, 4, 497 (1957).)

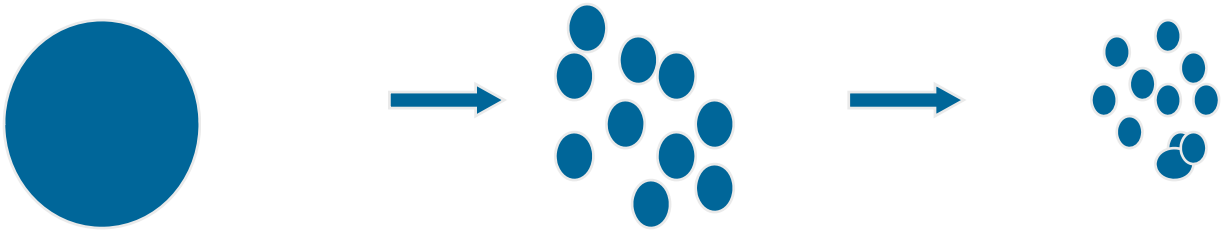
Appropriate salt form enhances aqueous solubility thereby increasing absorption

PARTICLE SIZE REDUCTION

- Increases surface area
- Improves dissolution rate and bioavailability

PARTICLE SIZE REDUCTION

Particle size reduction significantly increases drug surface area resulting in increased rate of dissolution and potentially absorption



Particle size: radius 1 cm

Surface area: 12.56 cm^2

Radius 0.1 cm

Surface area 126.6 cm^2

10 fold increase

Radius 0.001 cm

Surface area 1126.6 cm^2

1000 fold increase

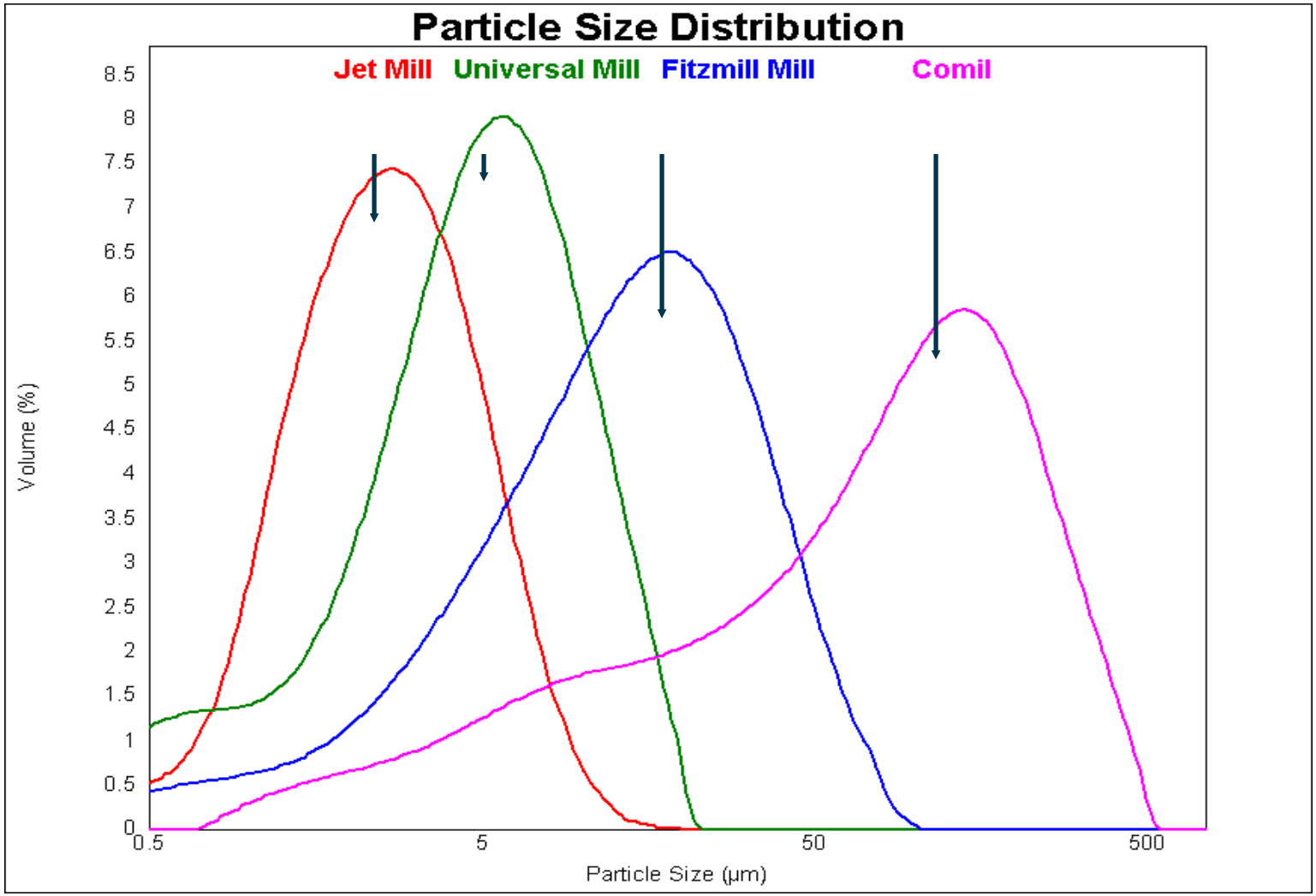
Effect of Particle Size Reduction on Dissolution Rate (Noyes and Whitney, 1897)

$dM/dt = D S (Cs - C)/h$

PARTICLE SIZE REDUCTION METHODS

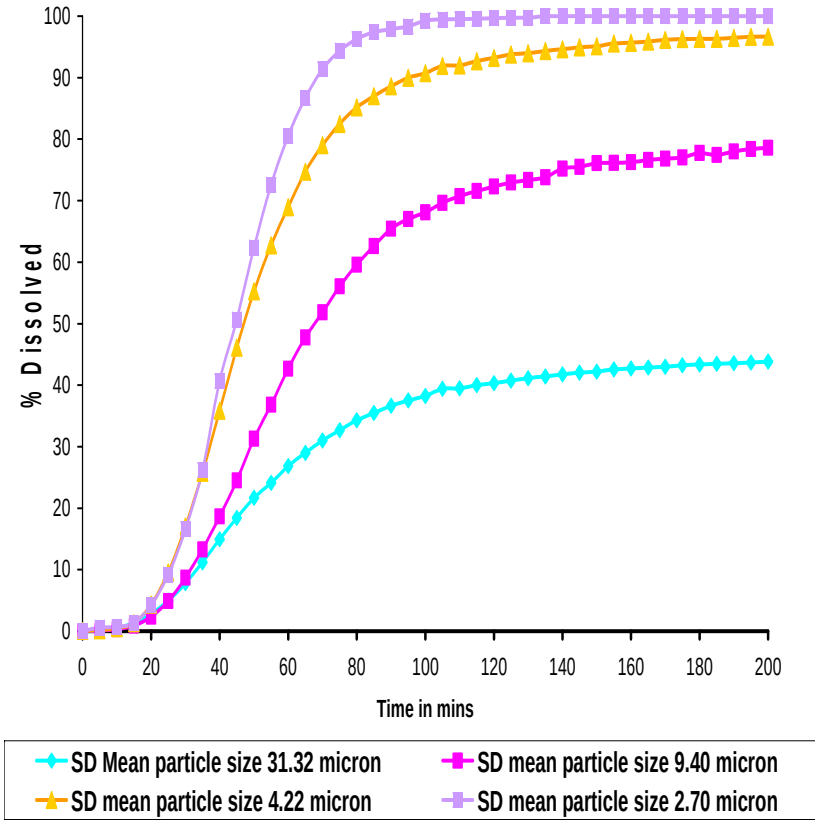
- **Low Energy Hammer Mill**
  Median Particle Size Range: 30 - 50 microns
- **High Energy Hammer Mill**
  Median Particle Size Range: 20 – 100 microns
- **Air-Jet Mill (Micronizer)**
  Median Particle Size Range: 2 – 10 microns
- **Wet Mill**
  Median Particle Size Range: 0.5 – 5 microns

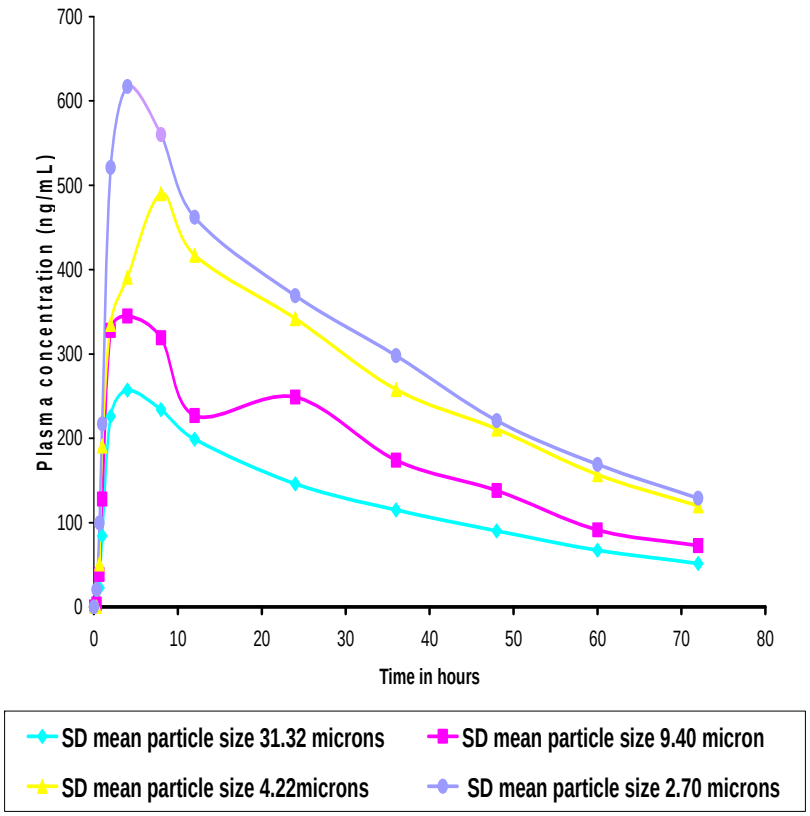
Mill Comparison



Finer → **Coarser**

Effect Of Particle Size On Dissolution Rate And Bioavailability





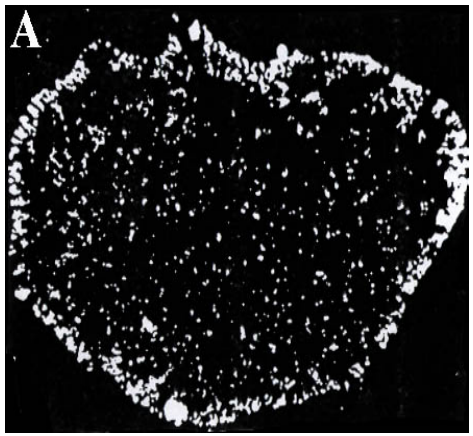
- Significant improvement in rate of dissolution with increase in surface area (smaller particle size)
- Higher bioavailability achieved in dogs

Effect of Drug Agglomeration

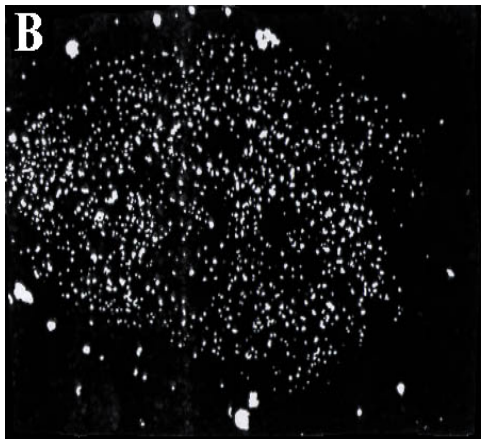
- Reduces effective surface area
  - surface area of agglomerates vs. surface area of primary particles
- Resist wetting: poor dissolution
- Poor content uniformity, especially for potent drugs

Pictorial View Demonstrating the Improvement of Wetting Behavior of a Poorly Soluble Drug by Forming a High Energy Ordered Mixture

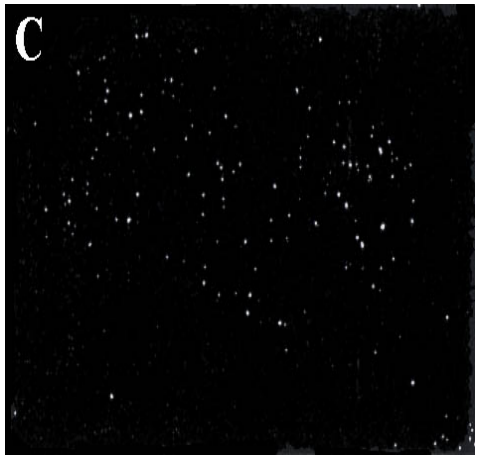
After Dispersed in Water



Micronized Drug



Simple Ordered Mixture
(Drug blended with
Hydrous Lactose)



High Energy Ordered
Mixture
(Drug blended with
Hydrous Lactose
and milled using
Micropulverizer)

Particle Size and Surface Area Impacting on Dissolution Rate

The mean contact surface area taking part in the dissolution was calculated as:

$$S_c = W/t\ G$$

S_c: the mean contact surface area taking part during dissolution

W: the amount of drug dissolved in time t

t: dissolution time

G: the intrinsic dissolution rate

LIPID FORMULATIONS
Self-Emulsifying Drug Delivery Systems (SEDDS)

Self-Emulsifying Drug Delivery Systems (SEDDS) are isotropic mixtures of a drug, lipophilic vehicle and one or more emulsifiers which forms fine emulsion with aqueous fluids on mild agitation

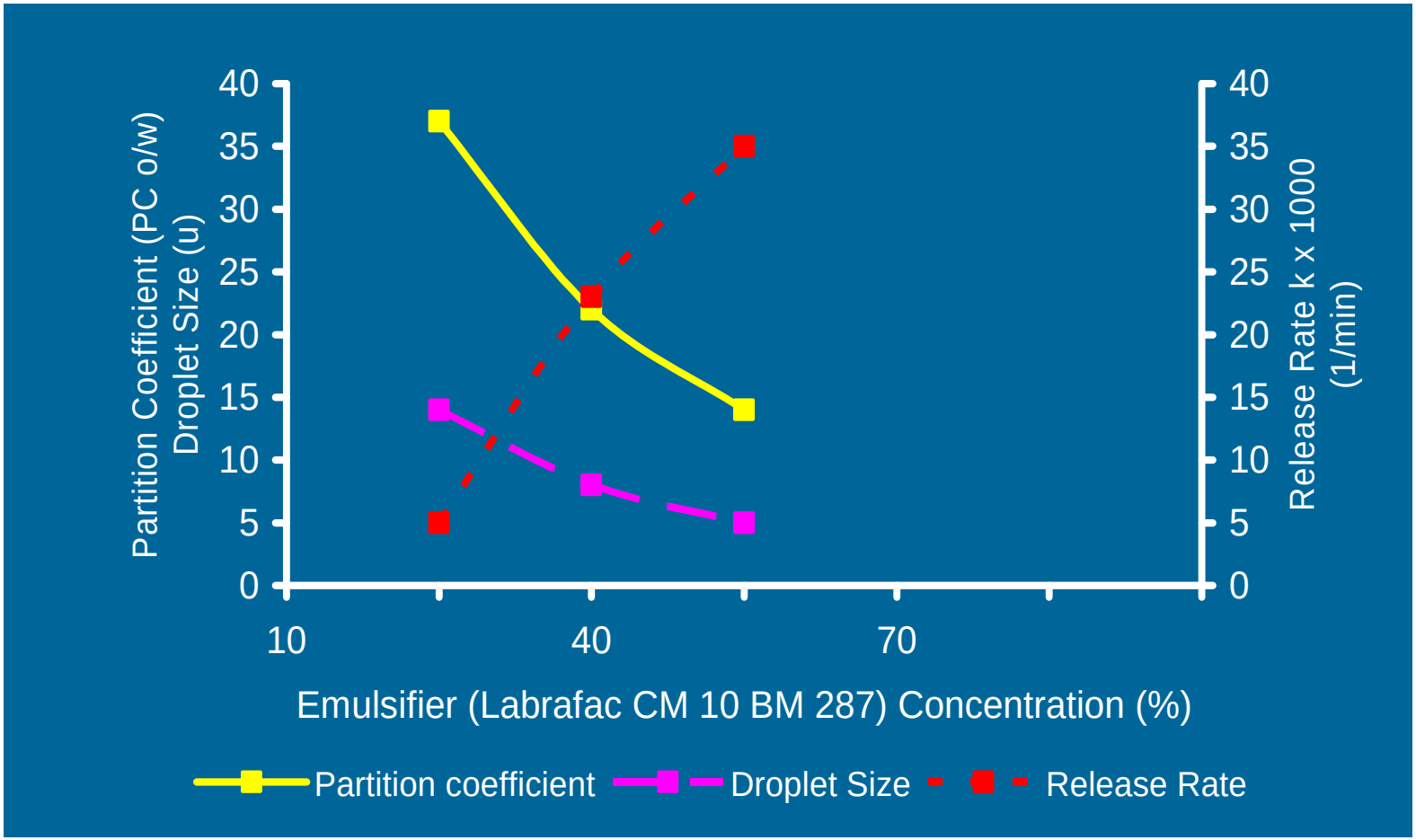
Attributes:

- **Drug in solution for maximum absorption**
- **Type of lipid plays a significant role in drug absorption**
- **Lipid digestion impacts bioavailability**
- **Particle size of emulsion affects rate and extent of absorption**

Lipid Effect on Solubility

- Choice of oil
- Choice of emulsifier
- Chain-length of fatty acids
- HLB values
- Degree of saturation

EFFECT OF EMULSIFIER CONCENTRATION ON PARTITION COEFFICIENT, DROPLET SIZE AND THE RELEASE RATE OF Ro 15-0778



Correlation between Particle Size of the Emulsion and In Vivo Performance of Cyclosporin Based Formulations

Dose: 300 mg

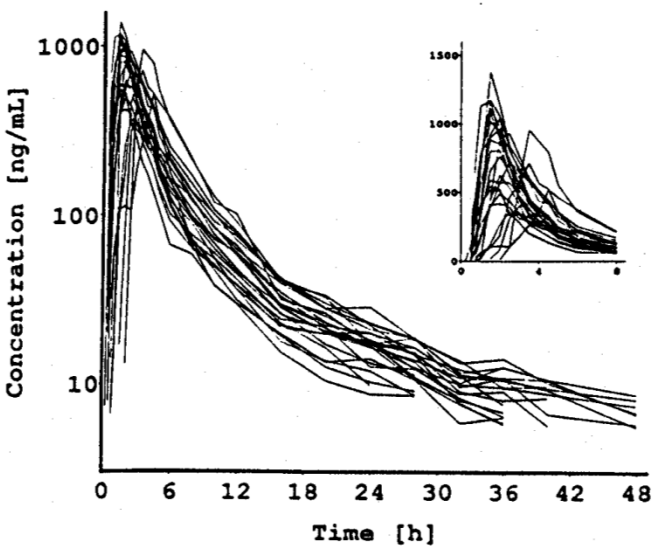


Figure 1—Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 300-mg reference formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

Formed a crude emulsion with D50 - 2 to 5 microns determined by a Dynamic Light Scattering

Dose: 180 mg

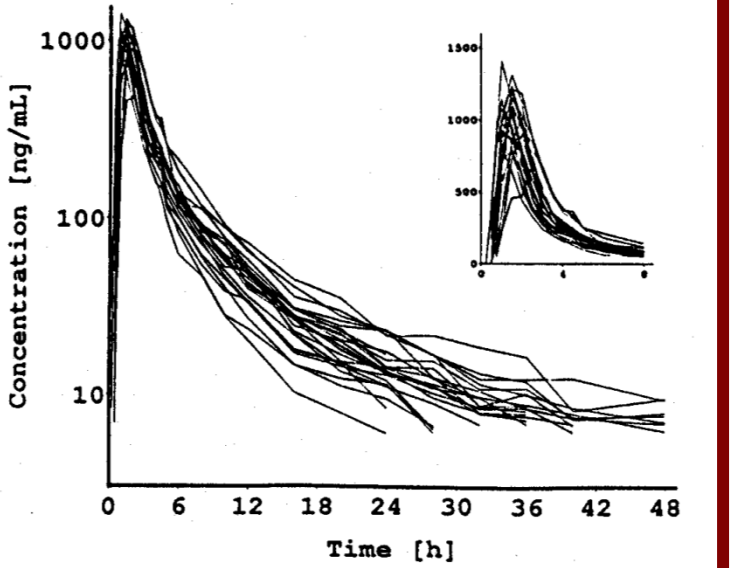
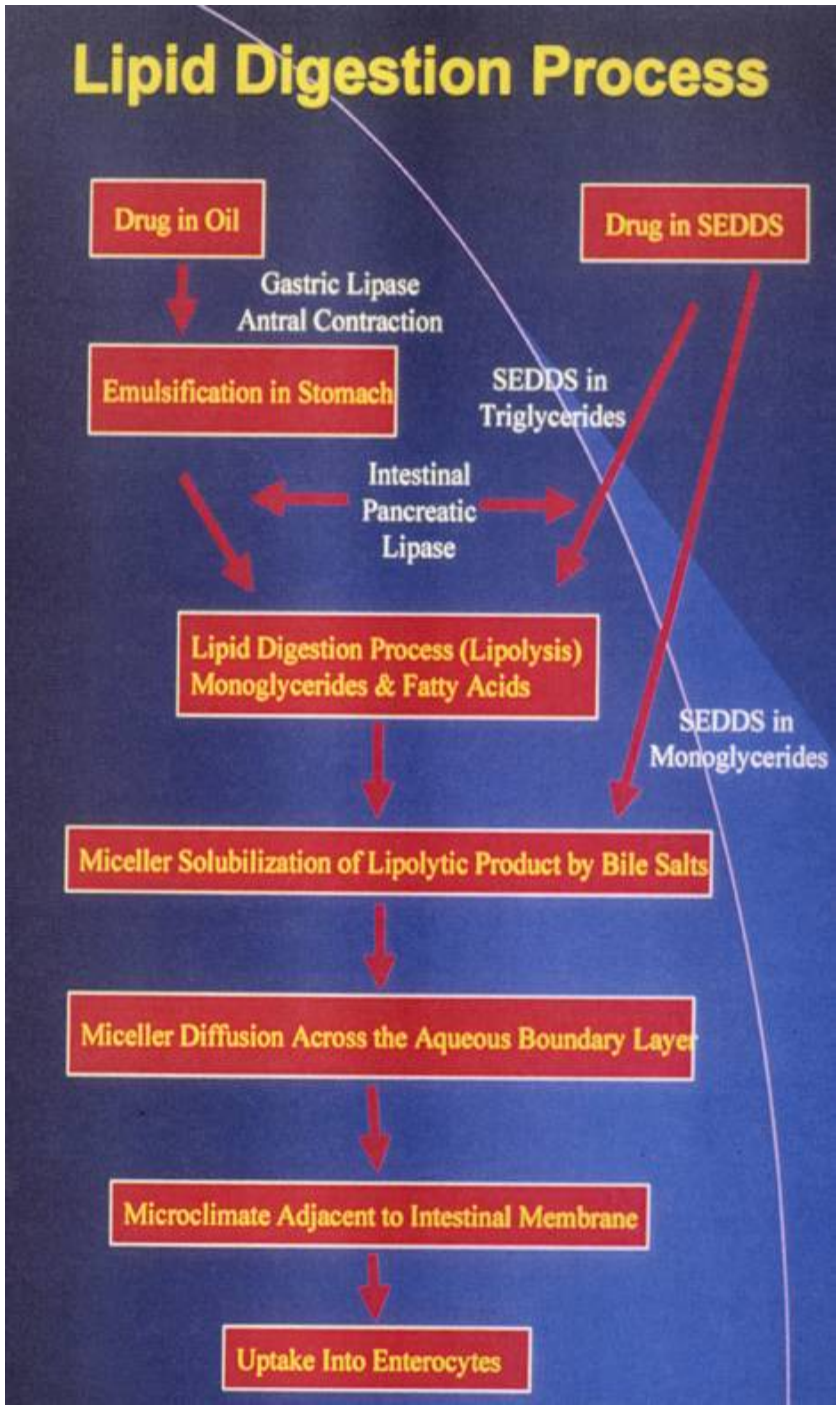


Figure 2—Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 180-mg test formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

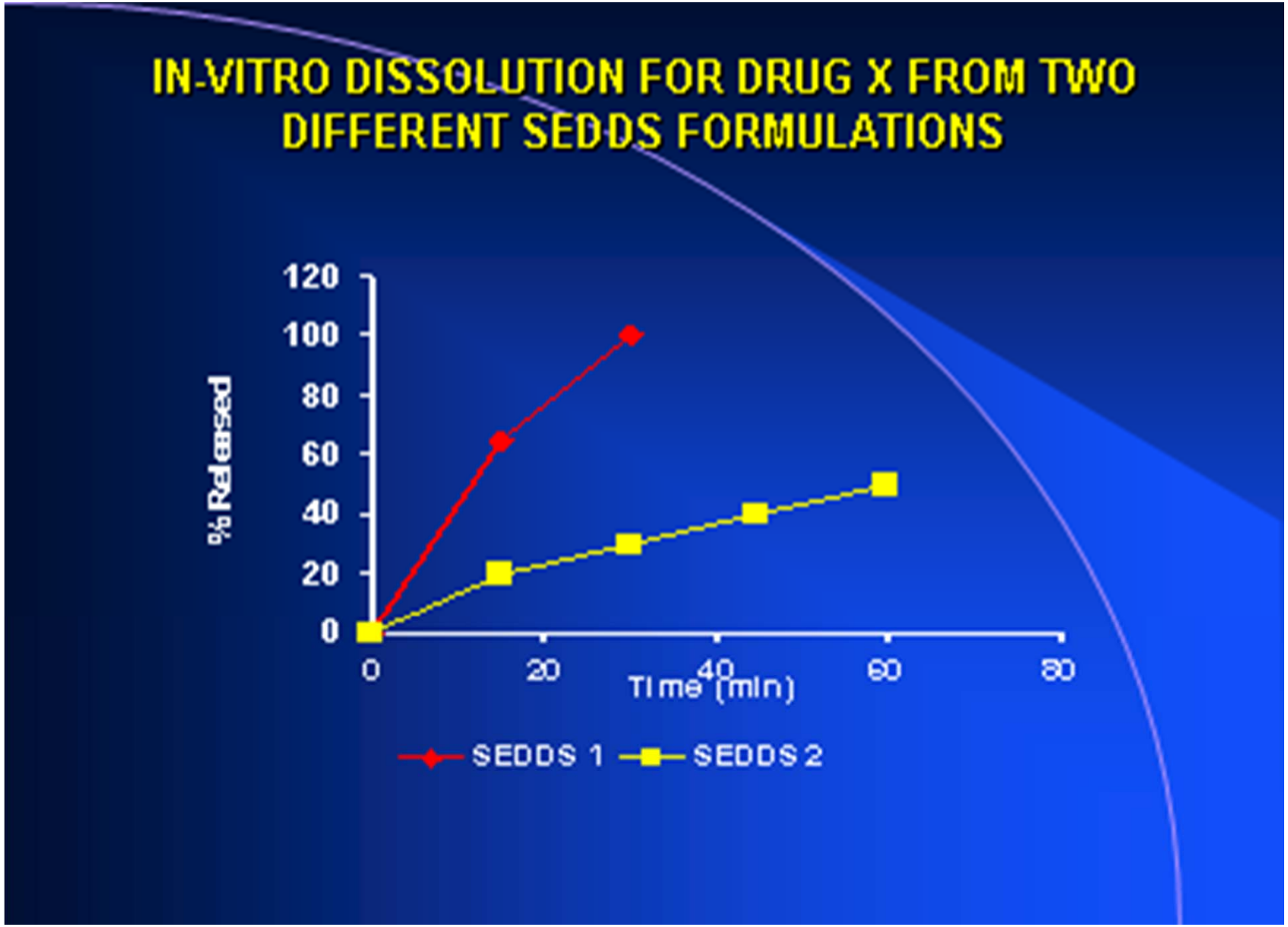
Formed a micro-emulsion with D50 - 30 nm determined by a Dynamic Light Scattering

Kovarik et al., J. Pharm. Sciences, Vol. 83, No. 3 March 1994

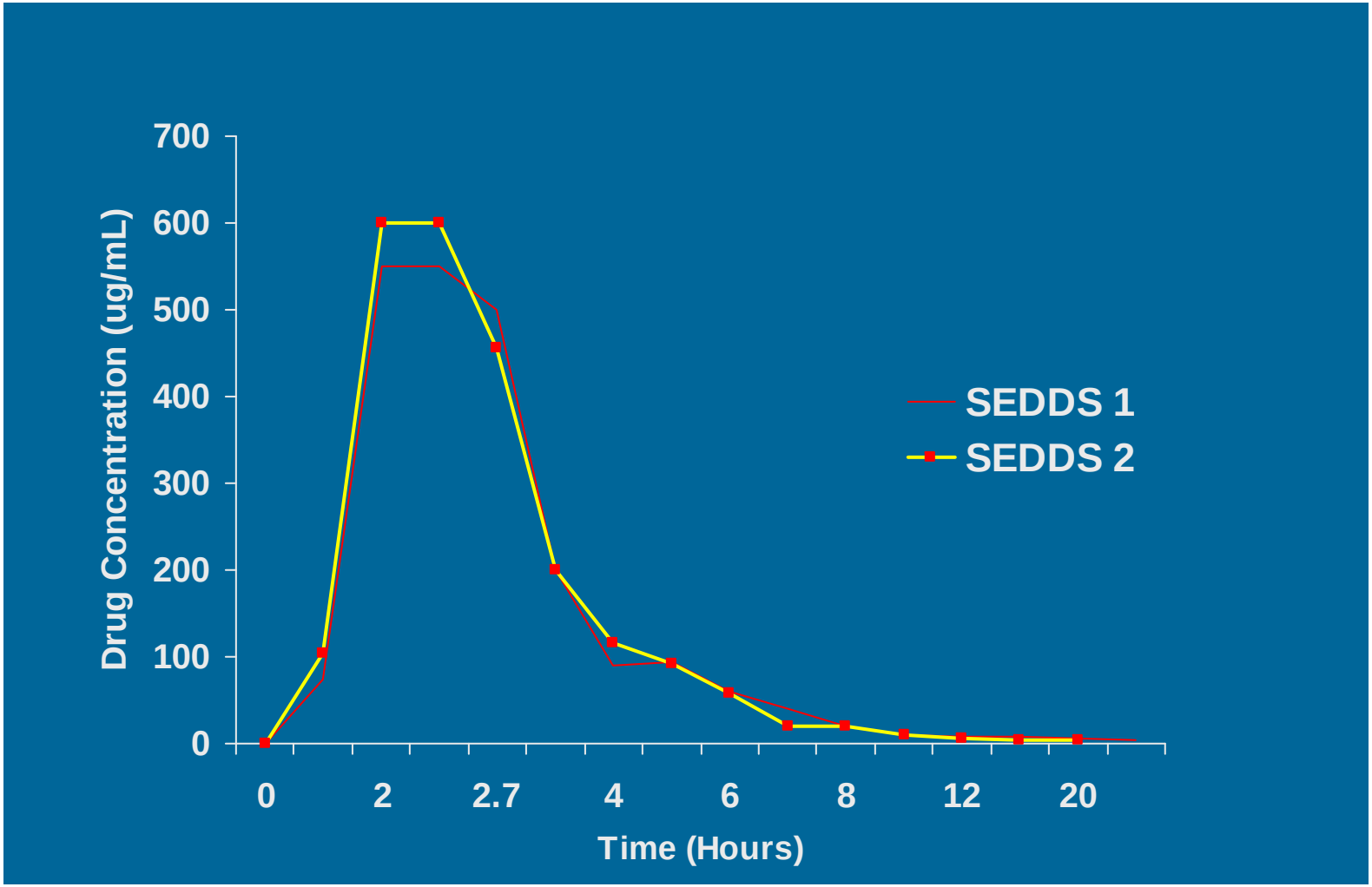
LIPID DIGESTION PROCESS



BIOAVAILABILITY OF DRUG X FOR SEDDS



BIOAVAILABILITY OF DRUG X FOR SEDDS

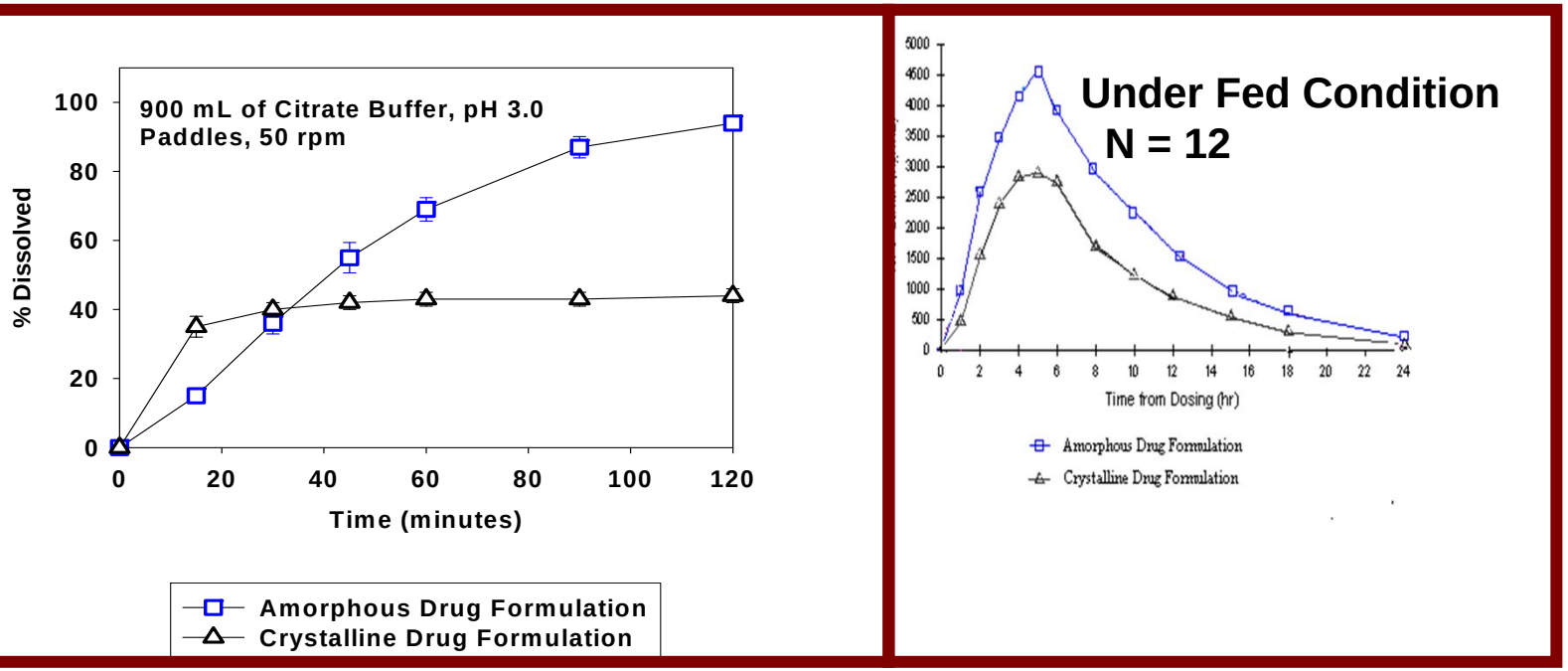


IMPACT OF CRYSTAL FORM ON BIOAVAILABILITY

Definitions of Crystal Forms

- Crystal - An orderly, infinite arrangement of molecules or atoms in a solid
- Polymorphs - Different crystalline arrangements possible for the same chemical entity
- Solvate - Crystal form in which solvent molecules are contained as part of the crystalline structure
- Hydrate - The special case of a solvate where the solvent in the crystal is water
- Amorphous form - A non crystalline material with random arrangement of molecules

In Vitro Dissolution and PK Profiles in Human of Amorphous Vs. Crystalline Form Tablet Formulations



In vitro dissolution in citrate buffer, pH 3 does provide good prediction for in vivo absorption.

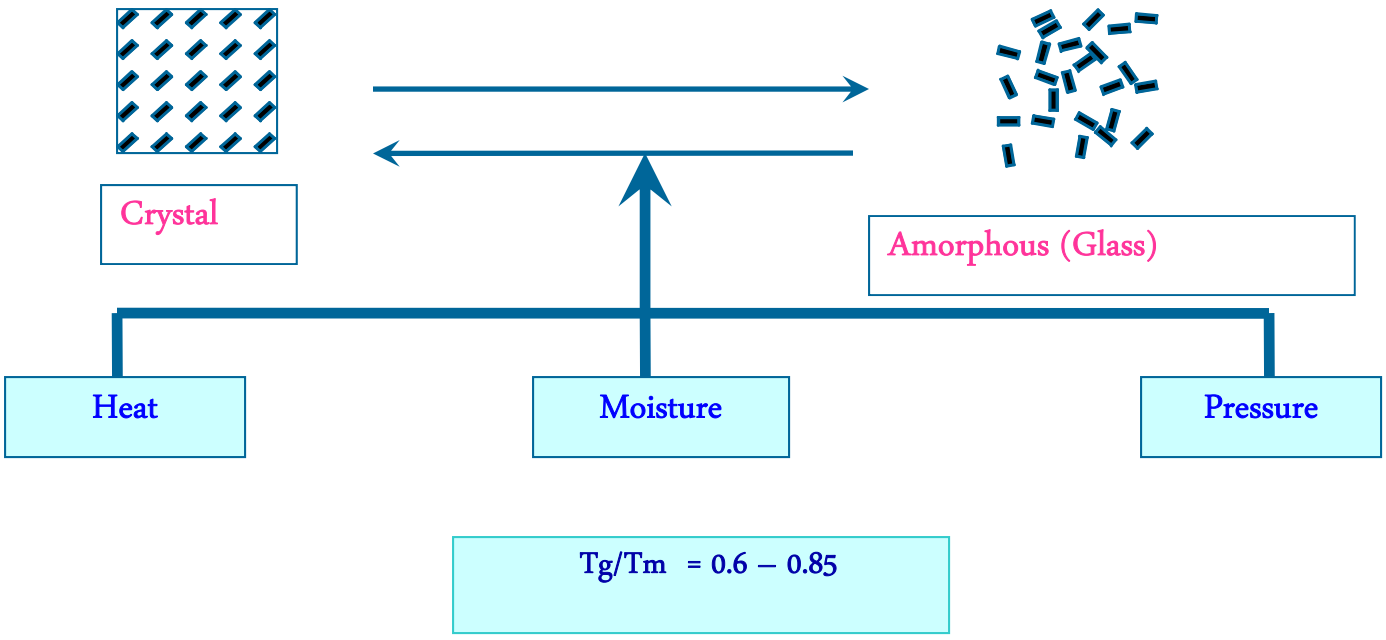
Impact of Crystal Forms of Drug X on Bioavailability in Dogs

Formulation	Cmax/Dose (ng/ml)(mg/kg)	AUC/Dose (ng.hours/ml)	Tmax (hours)
Suspension (Anhydrous Form)	174	1594	3.5
Suspension (Hydrate Form)	107	604	1.8

Anhydrous Form provided higher AUC approximately 2.6 times than Hydrate Form.

Amorphous Solids

- Thermodynamically unstable (metastable) configuration of the molecules
- Macroscopic properties of a solid with the microscopic structure of a liquid
- Improved solubility/dissolution rate and bioavailability

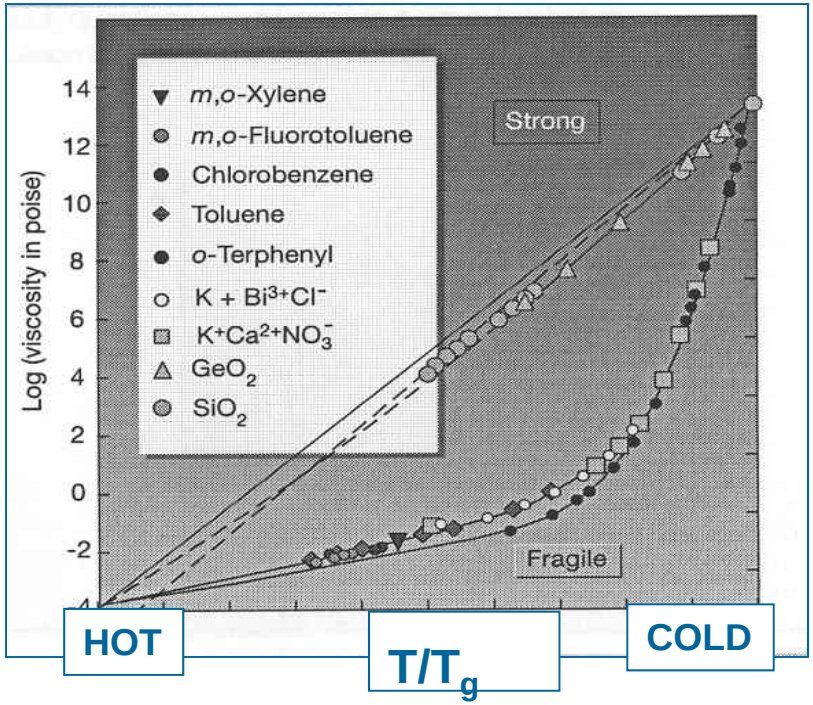


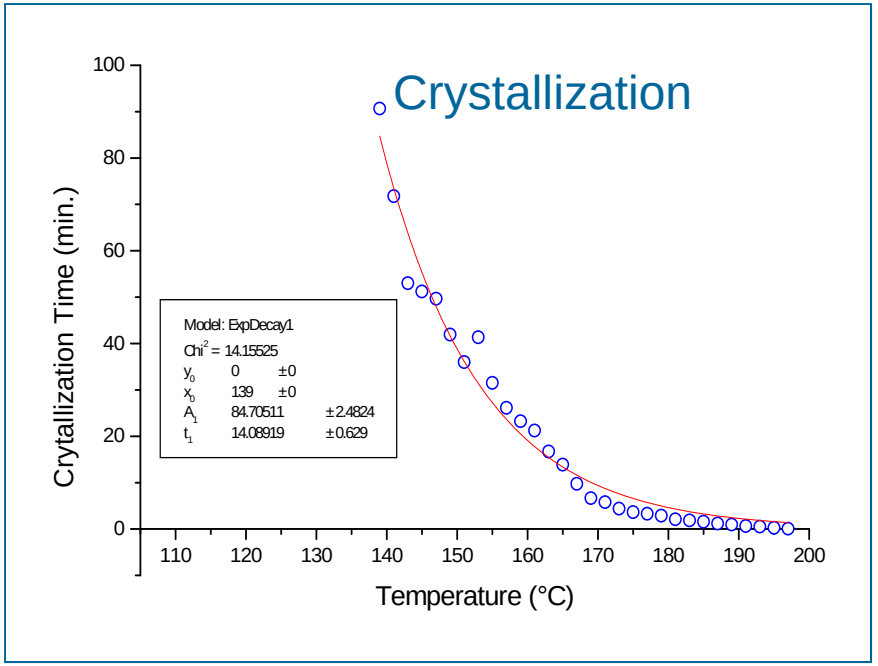
Amorphous Materials

- The ideal glass is a liquid with virtually “infinite” viscosity, *i.e.*, very low molecular mobility or (“frozen in”)
- The glass transition temperature (Tg) is a measure of molecular mobility in a glass
- At Tg the material passes from a glass to a rubbery liquid
- A high glass transition is desirable in order to avoid unwanted physical changes over time (*e.g.*, crystallization)
- A good rule of thumb is to have a Tg that is 50°C higher than that of the processing, stability or storage conditions

Temperature Enhances Crystallization of Amorphous Solids

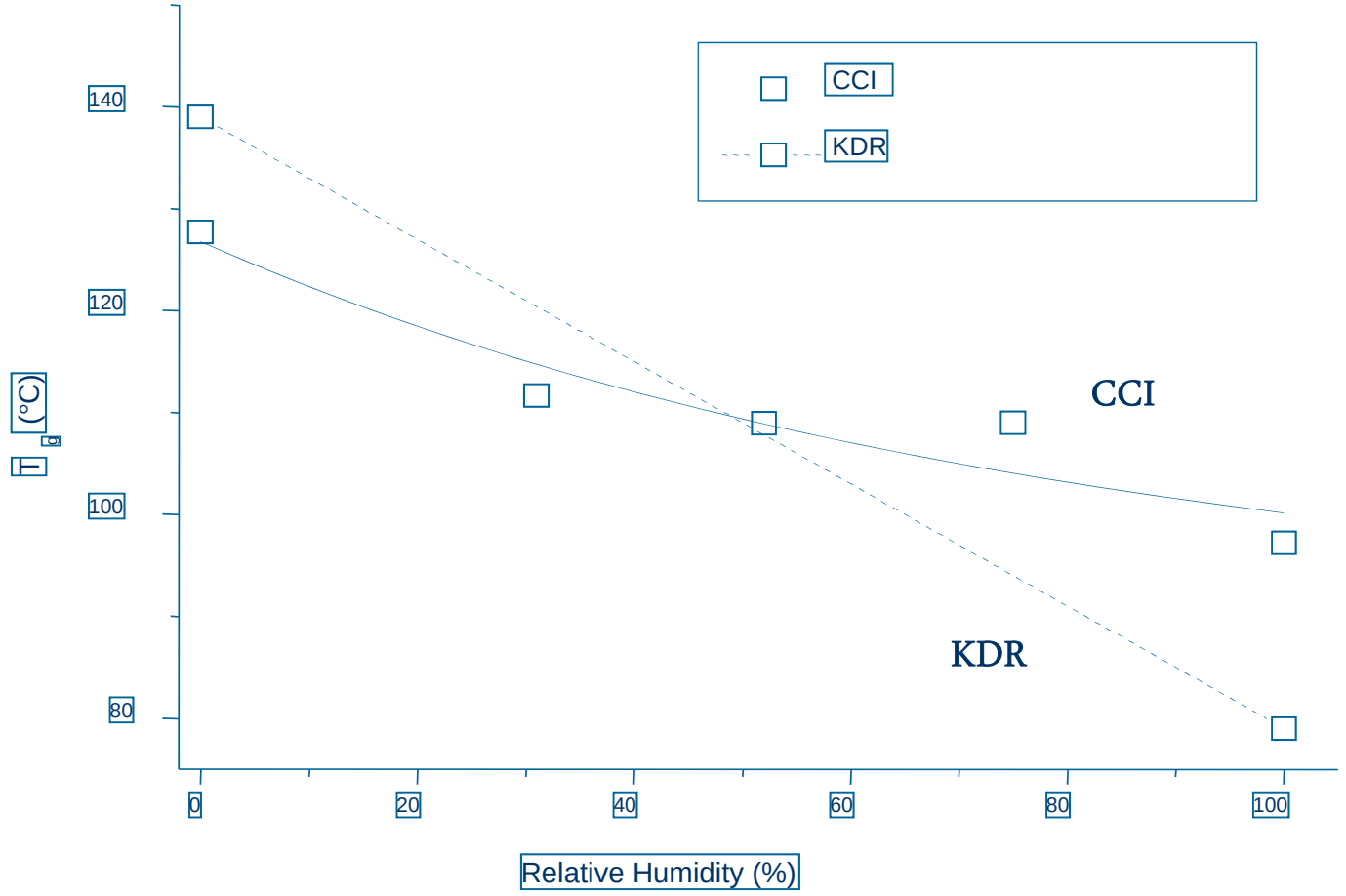
- The glass is 10^{10} to 10^{12} times more viscous than the liquid





Moisture Enhances Crystallization of Amorphous Solids

- Sorbed moisture plasticizes glasses, *i.e.*, reduces the glass transition thus increasing molecular mobility

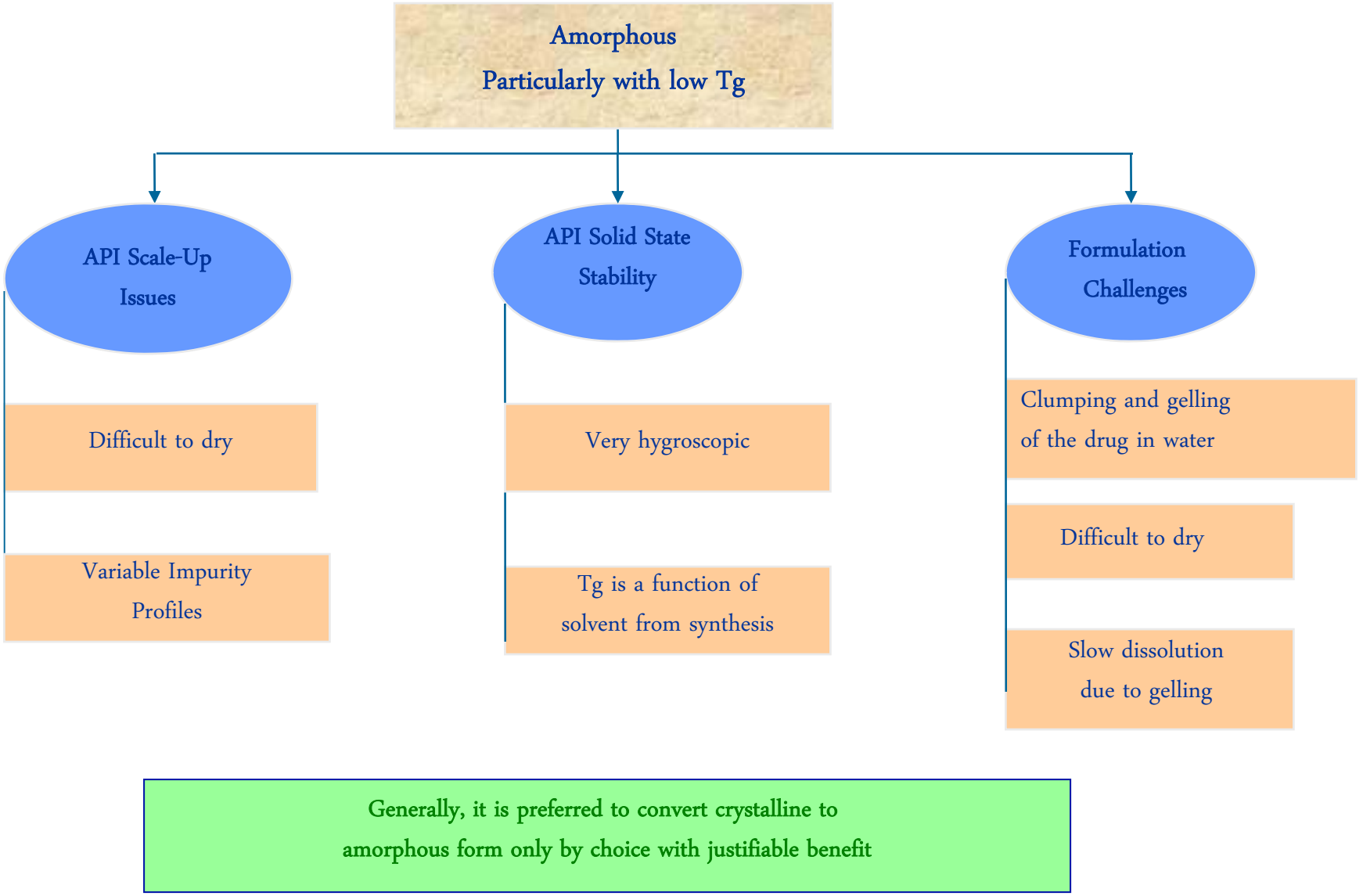


Amorphous API Handling Considerations

- The mechanical properties and hygroscopicity are markedly different from the corresponding crystalline API
- Water is known to have a profound effect on the Tg of amorphous API, acting as a plasticizer by increasing the free volume of the material, enhancing structural mobility and decreasing the Tg
- Manufacturing processing, packaging configuration and storage conditions are the most important factors influencing stability of the amorphous API
- In many instances, amorphous API itself can not withstand the manufacturing processing conditions and maintain its stability throughout the shelf-life

Therefore, stabilization of amorphous API by excipients (polymers) is very important

Amorphous API Technical Challenges



Generally, it is preferred to convert crystalline to amorphous form only by choice with justifiable benefit

Desirable Attributes of the Polymer for Amorphous Stabilizer

- High Tg
- Ideally, solubility parameter close to that of the API
- Maintains supersaturation solution of the drug in the GI fluids, maximizing drug exposure
- High molecular weight
- Acts a moisture scavenger protecting the drug from moisture
- Prevents fusion/nucleation of amorphous API particles under compaction

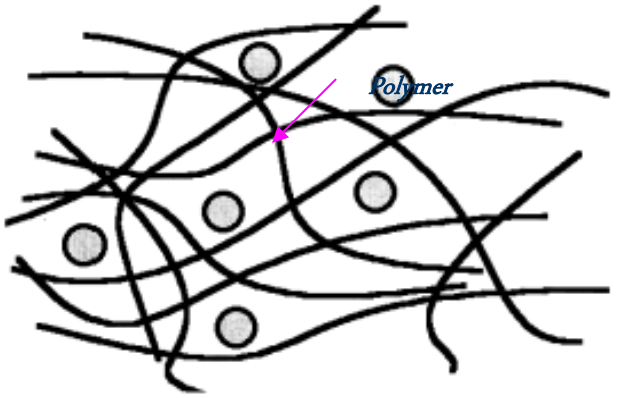


Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

C. Leuner and J. Dressman, Eur. J. of Pharmaceutics and Biopharmaceutics,

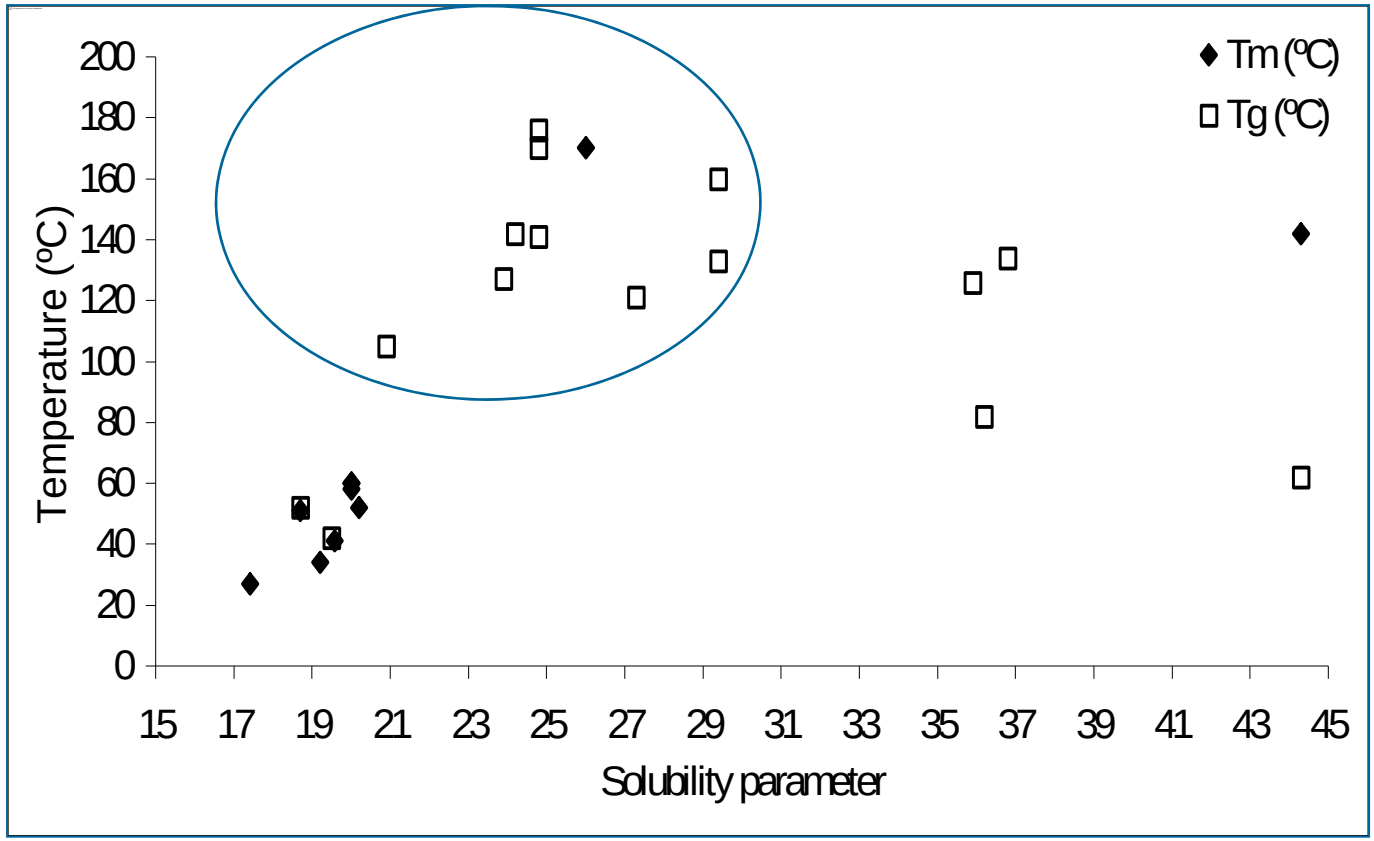
50: 47-60 (2000).

Stabilization of Amorphous API by Formulation Intervention

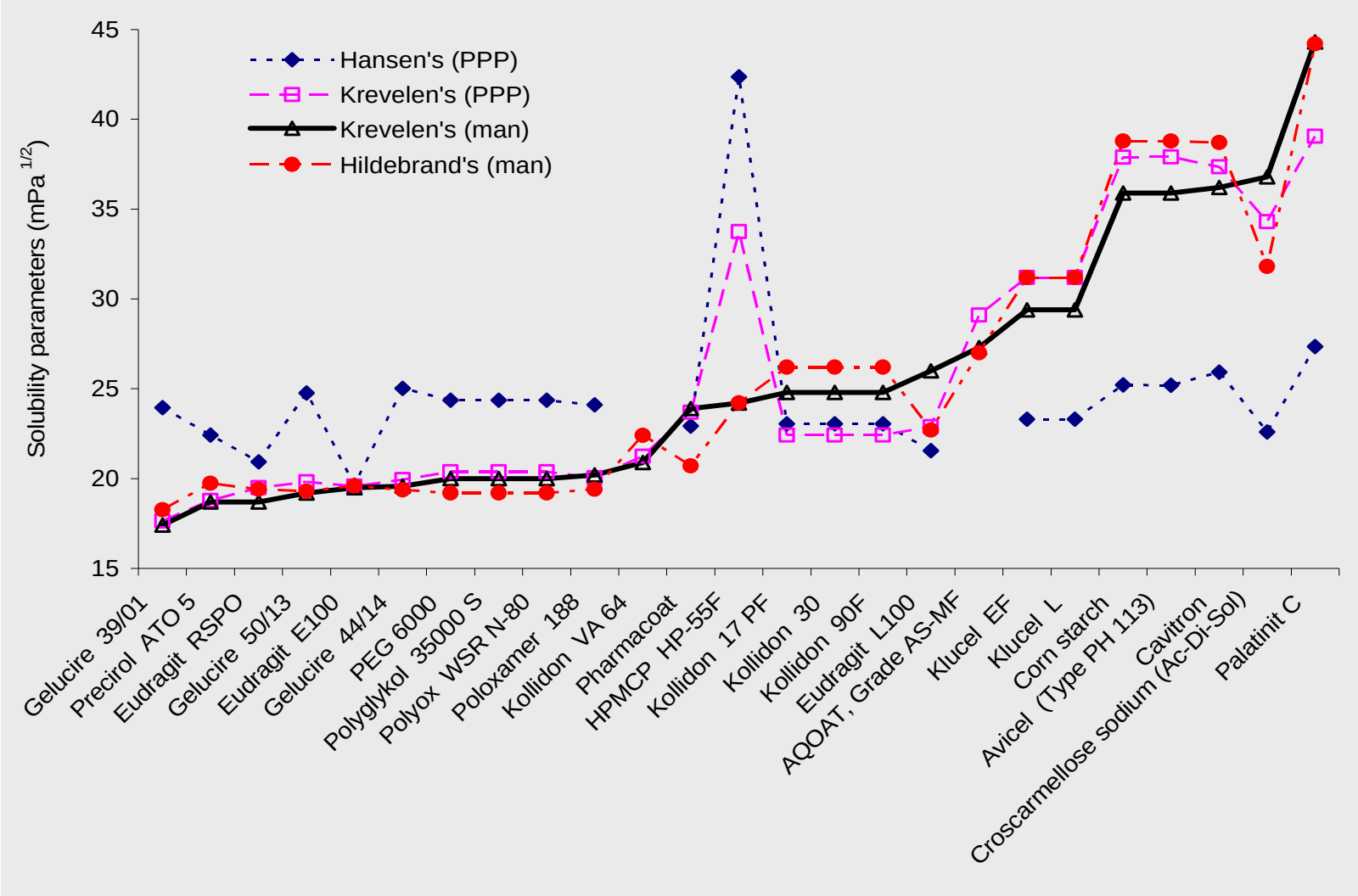
Selection of polymers and processes is critical for amorphous stabilization to achieve:

- Immobilization
- Prevents nucleation
- Protects from moisture
- Maintains supersaturation
- Maintains Tg
- H-bonding formation ability

Comparison of the T_g and T_m of the Excipients Vs. the Corresponding Solubility Parameter



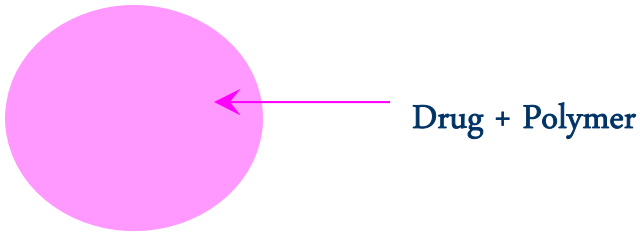
Excipients Solubility Parameters (δ)



Stabilization of Amorphous API by Polymer Additive

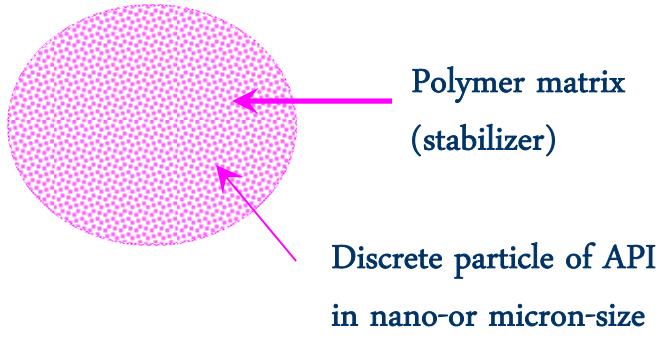
ONE PHASE

- Amorphous API and polymer are miscible
- One composite glass transition
- Physical stability is expected to be concentration-dependent
  - ❖ Relies on the molecular dispersion of the API in the polymer matrix



TWO PHASES

- Amorphous API and polymer are immiscible
- Two glass transitions, one for each component
- Physical stability is expected not to be concentration-dependent
  - ❖ Relies on the immobilization and isolation of the labile amorphous API in rigid glasses of inert polymer matrix



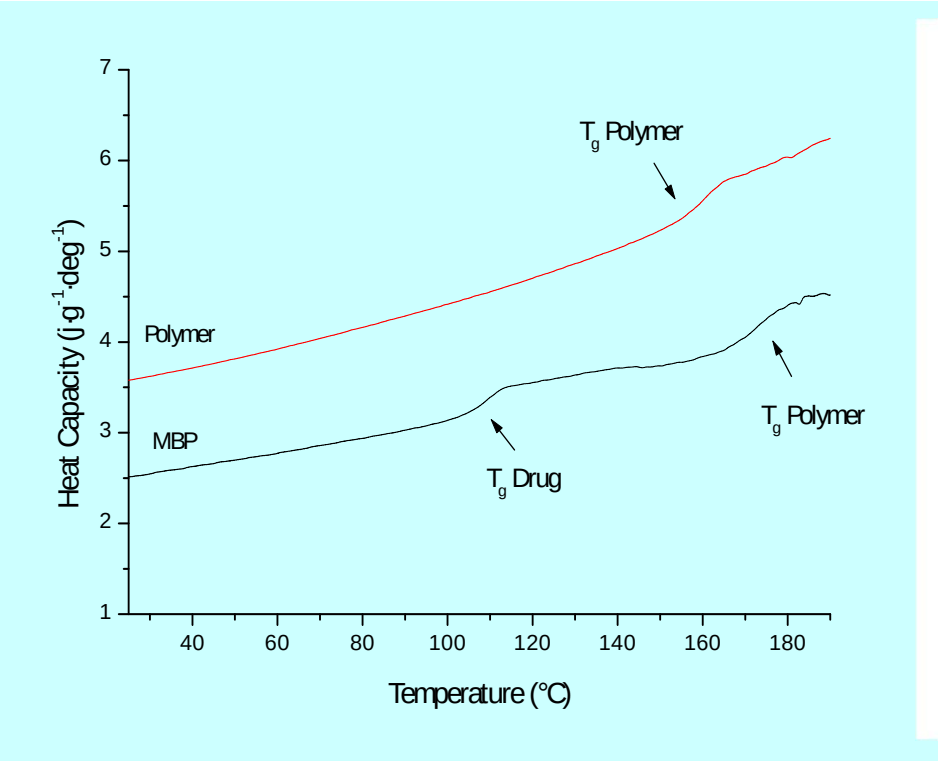
Miscibility Definition

The miscibility was determined by the Tg and Tm of the mixtures.

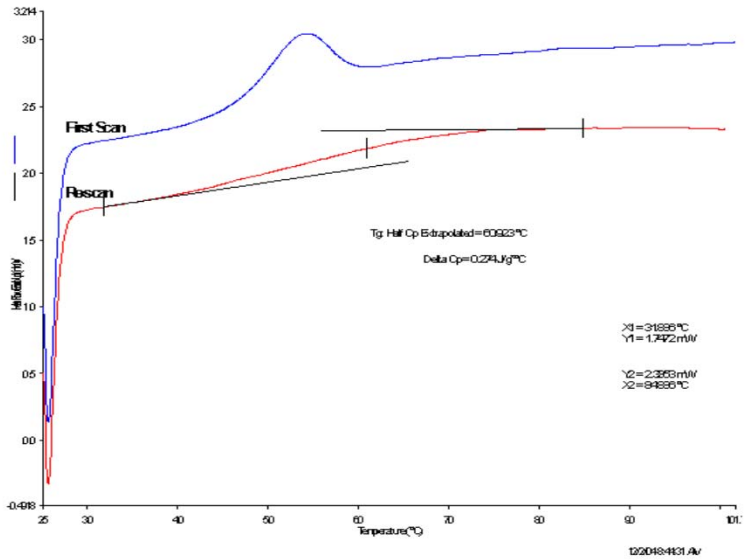
- Miscible: One Tg in the temperature range between the Tg of the pure components.
- Partially miscible: Two Tg observed in the temperature range between the Tg of the pure components. Depression of Tm.
- Not miscible: Tg or Tm of the pure components unchanged.

Gordon-Taylor or Couchman-Karasz equations may be used to predict Tg of amorphous solid solutions

DDSC Profile of Amorphous Formulation



Two Phases



One Phase

Amorphous Methods of Preparation

- Solvent-controlled microprecipitation
- Hot melt extrusion
- Solvent-evaporation (i.e., spray dryer, fluid bed coater)

Factors Impacting Amorphous Processing Selection

- Glass transition temperatures (Tg) and melting points for both API and polymer
- Degree of plasticizing effect by water or residual solvent(s)
- MW and viscosity of the polymers
- Solubility of the API and the polymer in solvents

Amorphous Formulations
Microprecipitation Technology

- Development of a stable amorphous formulation can be an effective approach to increasing dissolution and solubility
- A novel patented technology was developed at Roche and applied to Experimental Drug A having poor solubility of <10 mcg/ml
- Formulations provided higher bioavailability and a sustained release profile

AMORPHOUS FORMULATIONS MICRO-PRECIPITATION (CCI)

Challenges:

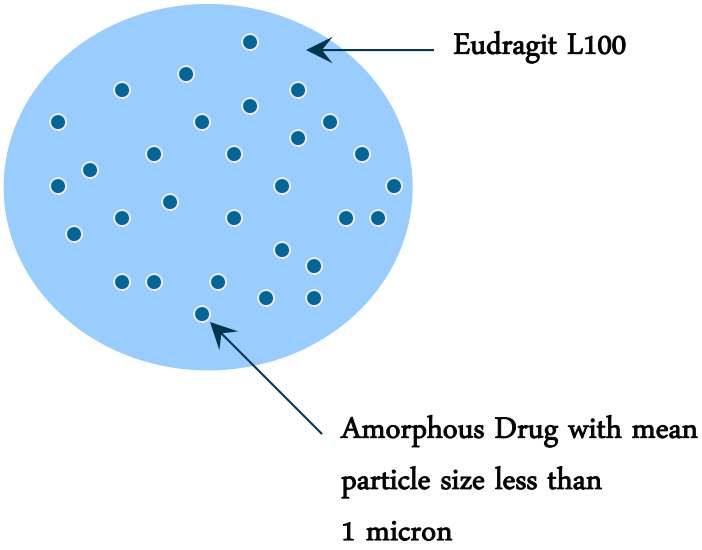
The poorly soluble Drug A initially existed in a crystalline form having very low aqueous solubility (<10 mcg/mL), resulting in poor bioavailability

Ro 31-7453 in addition has very low solubility in lipids and oils (<10 mcg/ml)

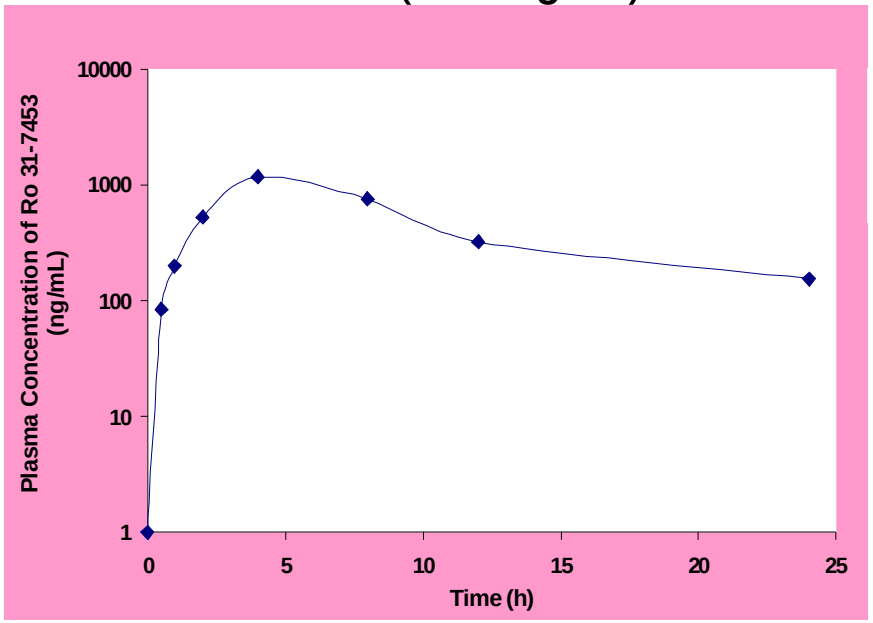
Formulation Intervention:

Convert the crystalline form to amorphous form while maintaining its stability

QUALITY ATTRIBUTES OF THE MICROPRECIPITATED POWDER



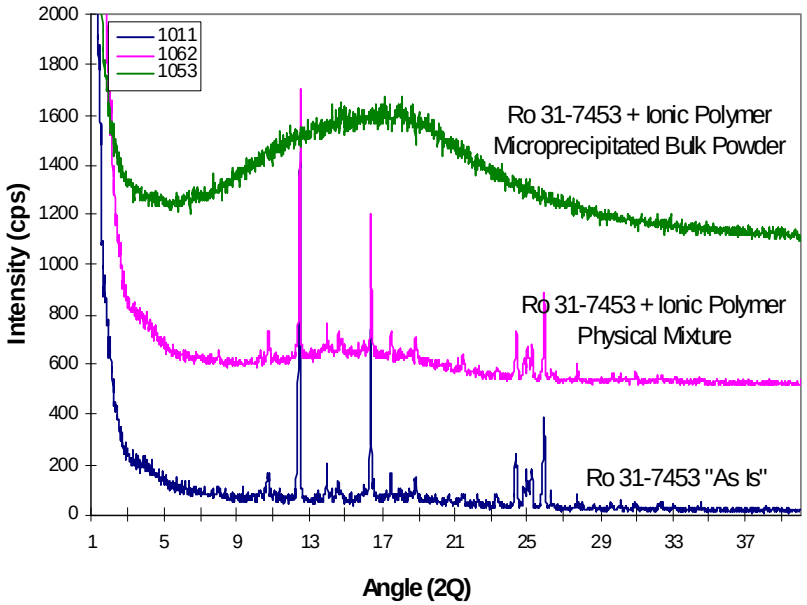
PK profiles in human after a single dose oral administration (560 mg/m^2)



Amorphous drug incorporated in the ionic polymer matrix improved bioavailability, stability and provided a prolonged plasma profile in man.

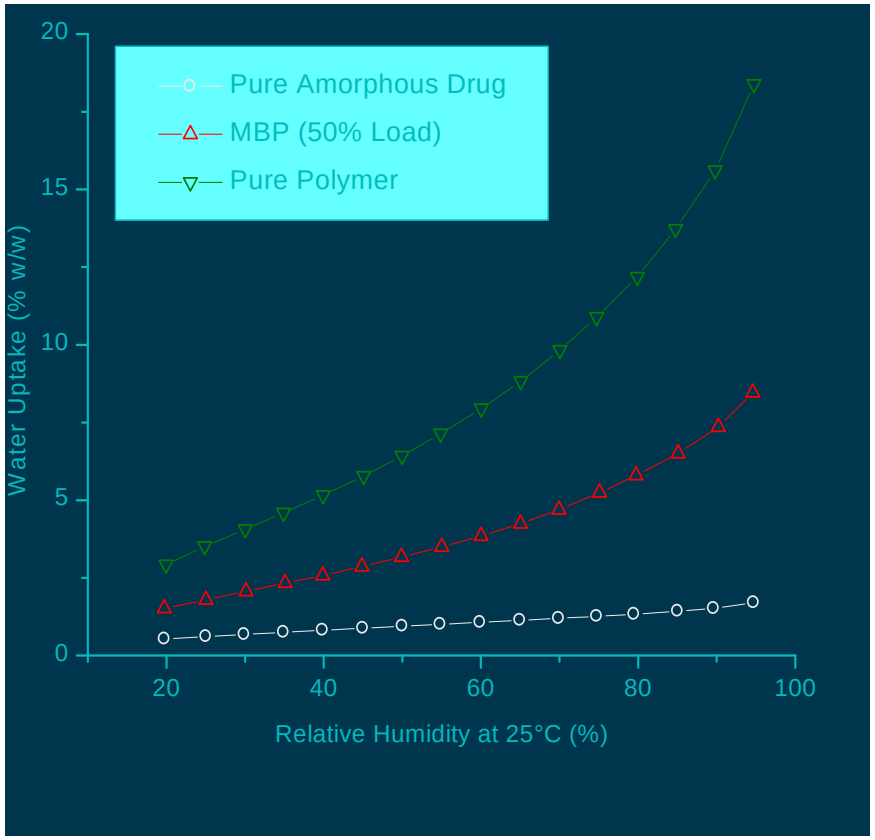
"ROCHE PATENTED TECHNOLOGY"

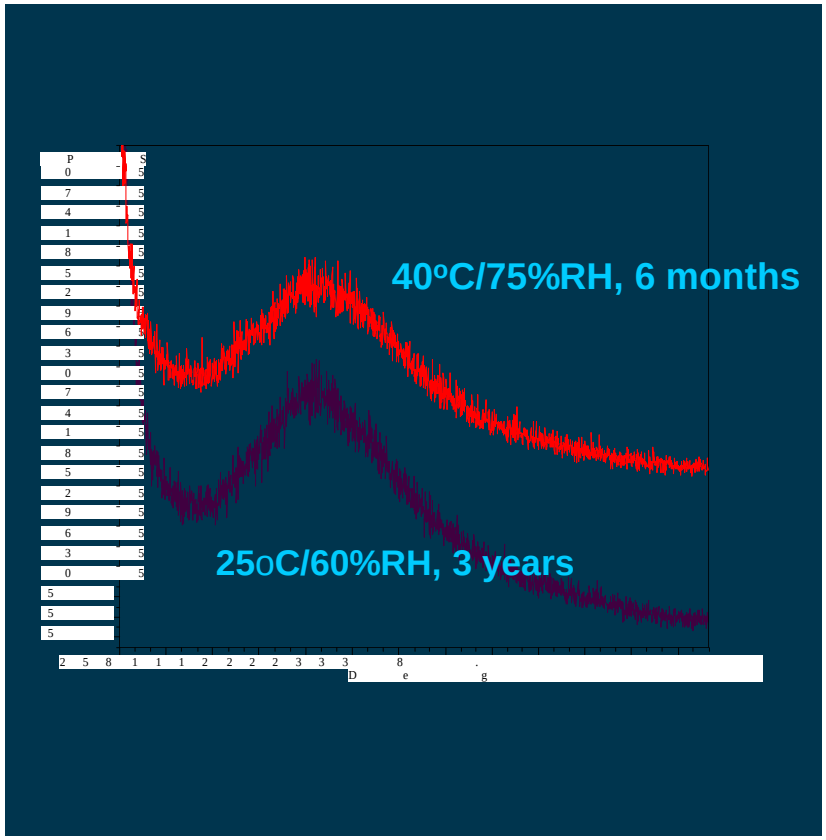
Powder X-Ray Diffraction of Ro 31-7453 Showing the Amorphous Nature of the MBP



- The MBP technology converts the drug to be in the amorphous form.

Moisture Sorption and Physical Stability of Microprecipitated Powder





Due to the high molecular weight and high glass transition temperature of the polymer, as well as its relative insolubility in water, the polymer acts as a desiccant and stabilizes the amorphous drug

FORMULATION SCREENING IN DOGS

Parallel design, N = 4

Formulation	AUC/Dose (N.h/mL)(mg/kg)	Tmax (hr)	Cmax (ng/mL)	% Bioavailability
Micronized Drug Suspension	29.5 ± 8.3	1.0	55 ± 17	3.9
Nanosized Drug Suspension	86.1 ± 13.7	1.5 ± 0.6	142 ± 53	11.2
50% microprecipitated powder	868 ± 237	2.5 ± 0.9	1212 ± 358	89.0

* Microprecipitated Bulk Powder contains 50% amorphous drug in ionic polymer

•All conventional technologies, such as particle size reduction, failed to achieve satisfactory bioavailability.

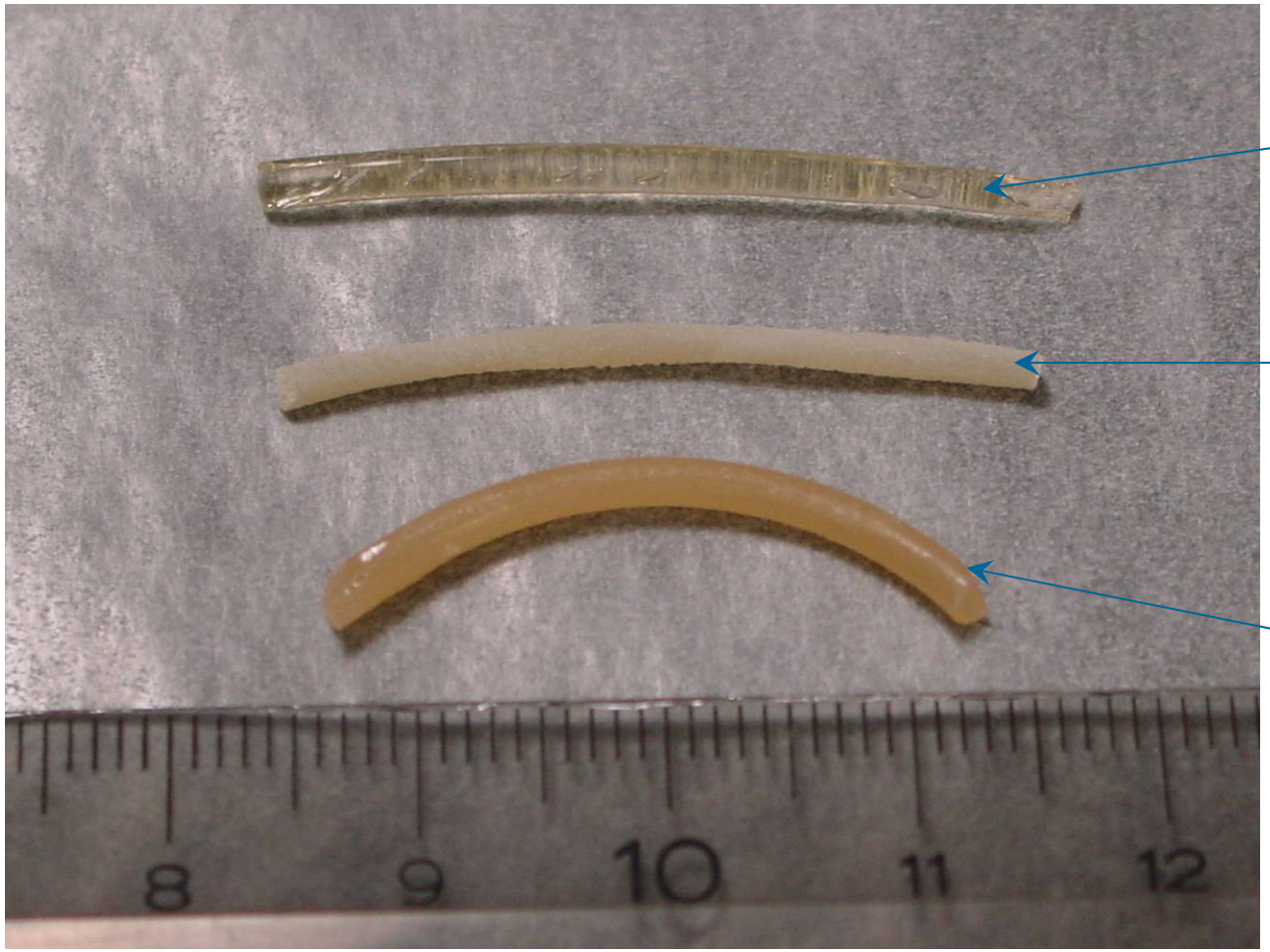
•Significant bioavailability enhancement and prolonged exposure achieved with Micro precipitation technology.

Hot Melt Extrusion

Hot Melt Extrusion

- With high energy of mixing applied in a molten mass of the drug and the polymer during the process, the drug can be uniformly embedded into the polymer matrix
- Typical co-extrudate is dense, minimizing moisture uptake and improving both physical and chemical stability of the product
- Downstream densification process is typically not required
- Processing temperature should not cause any degradation of the API and the polymer

Hot Melt Extrusion



One Phase
(Glass)

Two Phases
or Drug
Crystallized out

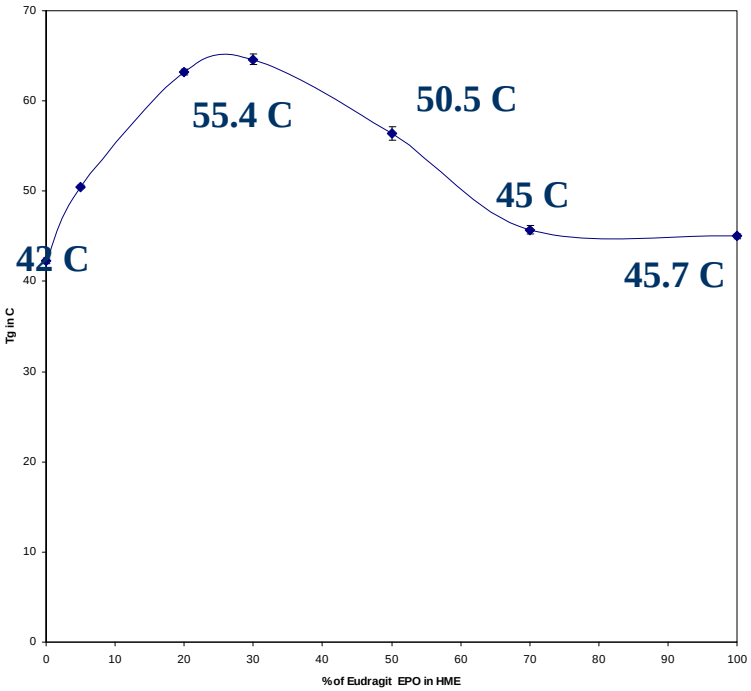
Degradation
(Discoloration)

MATERIALS
Physico-Chemical Properties

Physico-chemical properties	Starting Indomethacin	Eudragit EPO	PVP K30
Aqueous Solubility	Very poorly soluble (~0.004 mg/ml)	Soluble at pH <5	Water soluble
Molecular Weight	357.81 gm/mol	150,000 gm/mol	50,000 gm/mol
Tm and Tg	165° C and Tg 42 ° C	45 ° C	161 ° C
XRD Pattern	Crystalline	Amorphous	Amorphous

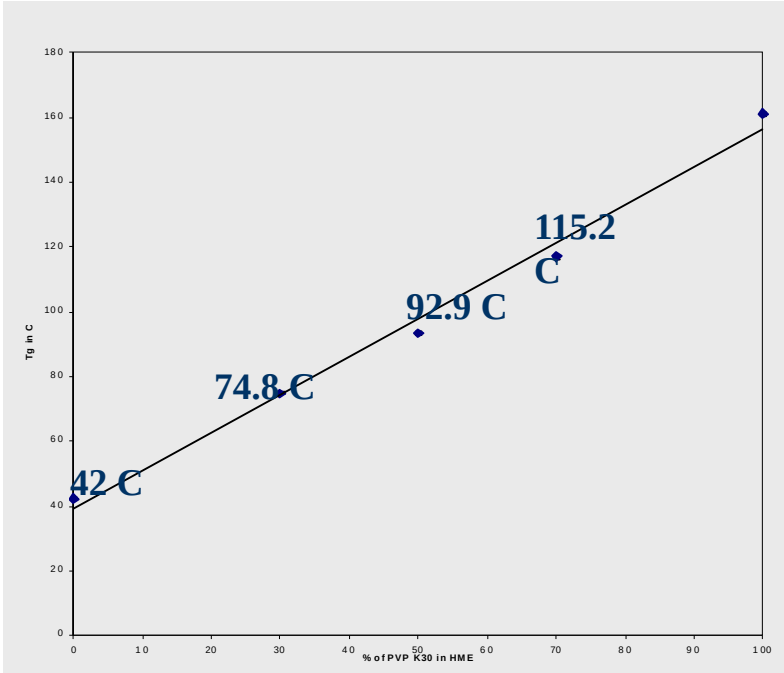
Effect of Indomethacin : Polymer Ratios on Tg of the Extrudates

With Eudragit EPO



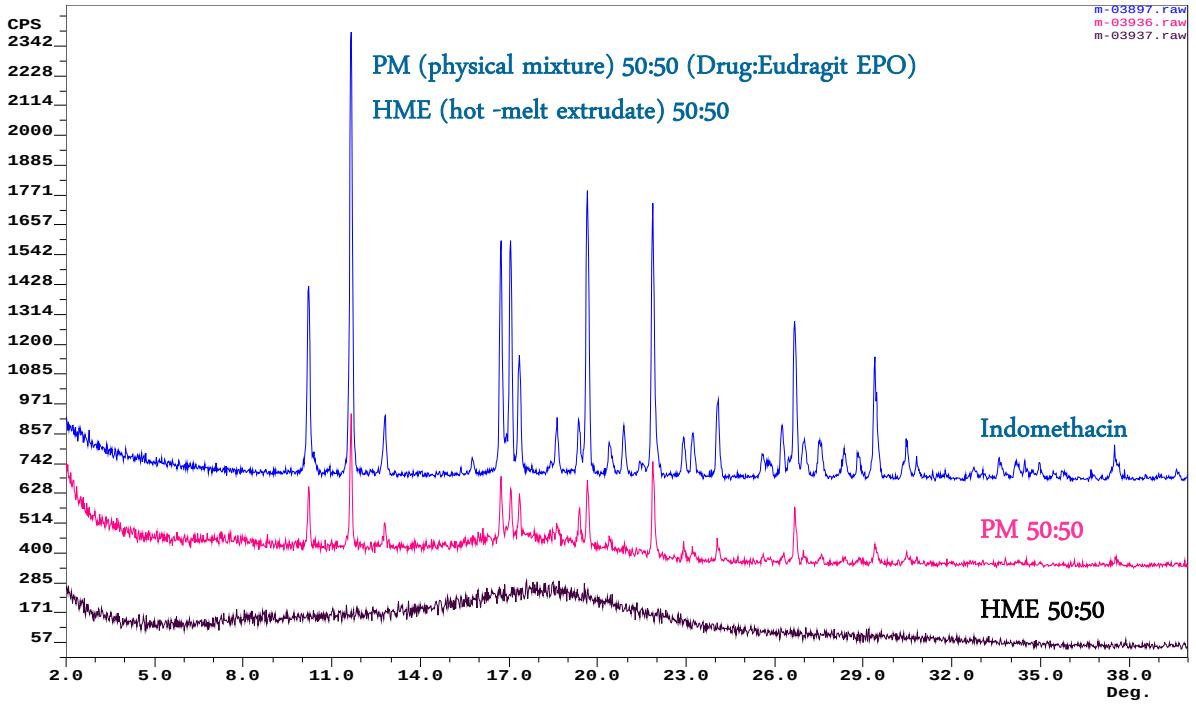
Non- ideal phase behavior

With PVP K30



Ideal phase behavior

POWDER X-RAY DIFFRACTION



Indomethacin converts to amorphous form in hot-melt extrudate and retains its crystalline form in physical mixture with Eudragit EPO

Improved Aqueous Solubility

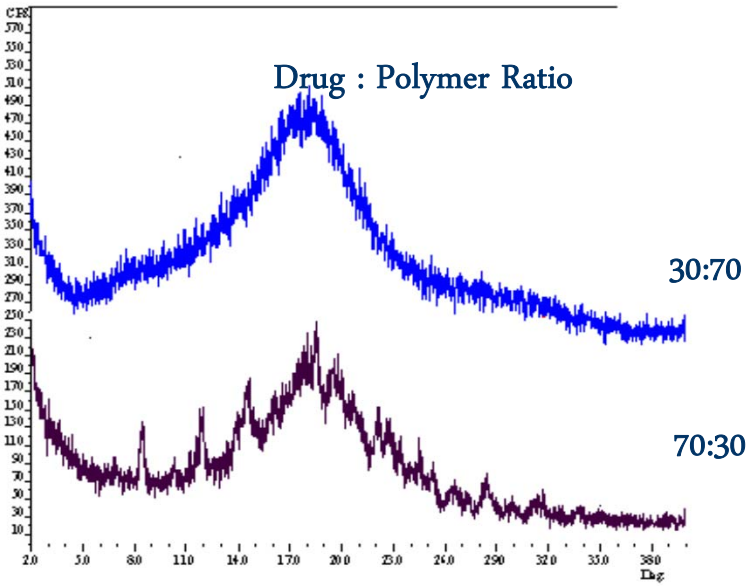
Formulation	Solubility in SGF in mg/ml	
	24 hrs.	72 hrs.
Indomethacin	Can not be detected	0.051
Hot melt extrudate with Eudragit EPO		
HME 70:30	0.20	0.15
HME 50:50	6.52	0.14
HME 30:70	41.42	38.31
Hot melt extrudate with PVP K30		
HME 70:30	0.002	0.02
HME 50:50	0.04	0.05
HME 30:70	0.09	0.12

Improved Intrinsic Dissolution Rates

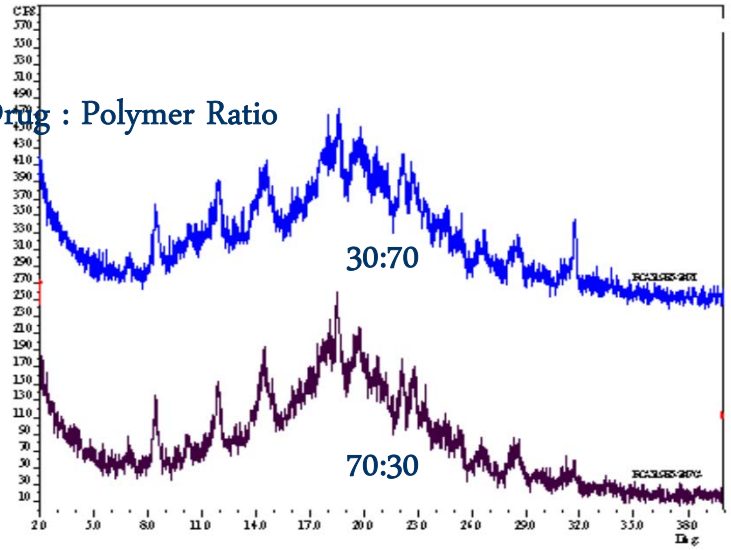
Formulations	Intrinsic Dissolution Rates ($\mu g/cm^2/min$) in SGF		Formulations
Indomethacin	0.0008	0.0009	Amorphous Indomethacin
Hot melt extrudate with Eudragit EPO			Hot melt extrudate with PVP K30
HME 70:30	1.51	0.0058	HME 70:30
HME 50:50	2.68	0.0076	HME 50:50
HME 30:70	1.80	0.012	HME 30:70

Powder X-Ray Diffraction of Indomethacin Extrudates After Exposed to the SGF

With Eudragit EPO



With PVP K30



- Eudragit EPO stabilized Indomethacin better than PVP K30
- The higher level of Eudragit EPO, the better stabilization effect

Solvent-Evaporation Method

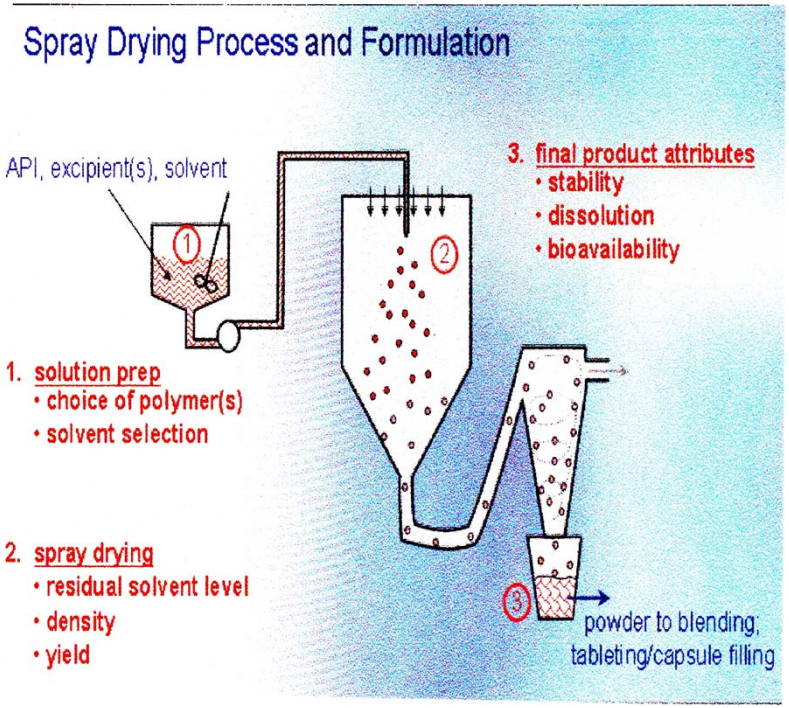
Spray Drying

Fluid Bed Drying

Spray Drying Process

- A single solvent is highly recommended to avoid potential drug segregation
- Difference in the precipitation rate between drug and polymer may result into drug segregation
- Applicable for low boiling point solvents (i.e. acetone, ethanol)
- Downstream densification process is typically required to improve flowability and bulk density of the co-precipitate
- The co-precipitate typically exhibits poor bonding under compaction due to its spherical particle shape

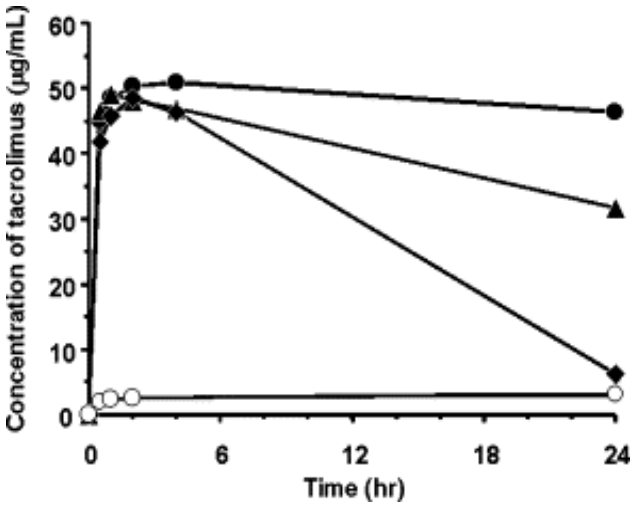
ISP Courtesy



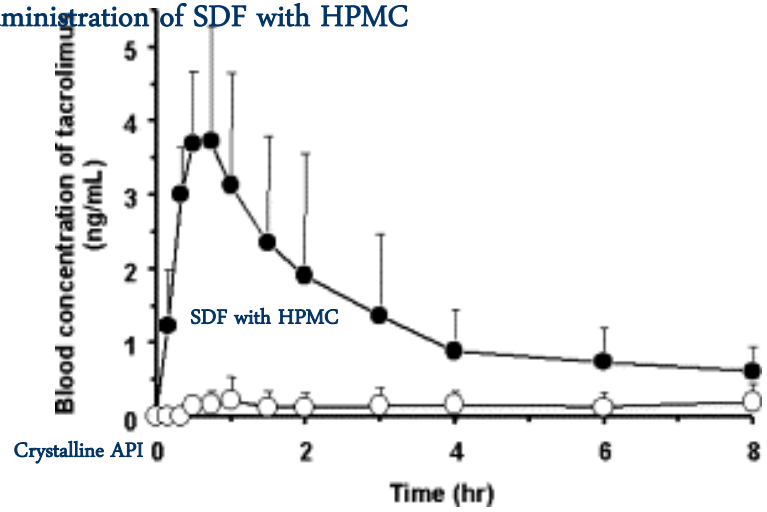
- To prevent drug recystallization, product temperature must be well below Tg of the amorphousAPI

Effect of Polymers on Maintaining Supersaturation of Tacrolimus

Dissolution Profiles of Tacrolimus from SDF by Solvent Evaporation Method



Plasma Profiles of Tacrolimus in Beagle Dogs after Oral Administration of SDF with HPMC



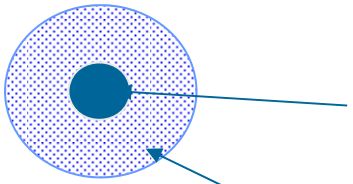
K. Yamashita et al., Int. J. of Pharmaceutics, 267: 79-91 (2003)

HPMC polymer was found to be effective in maintaining supersaturation of Tacrlimus when exposed to GI fluids, maximizing drug exposure

Stabilized Amorphous Formulation Via Particle Design Engineering

Microcrystalline Cellulose Sphere

Depositing of drug : polymer in ethanol solution onto a microcrystalline cellulose sphere using a Fluid Bed Coater

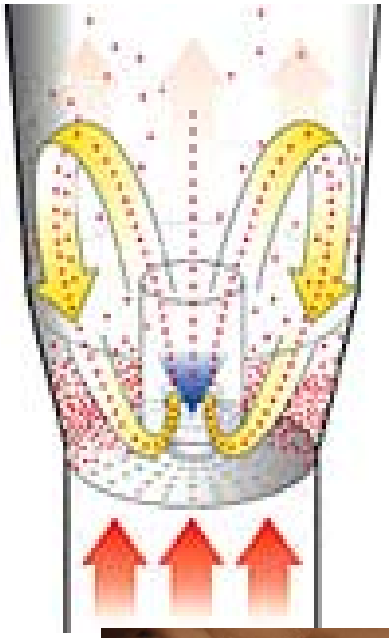


Microcrystalline Cellulose Sphere

Amorphous drug embedded in the polymer matrix

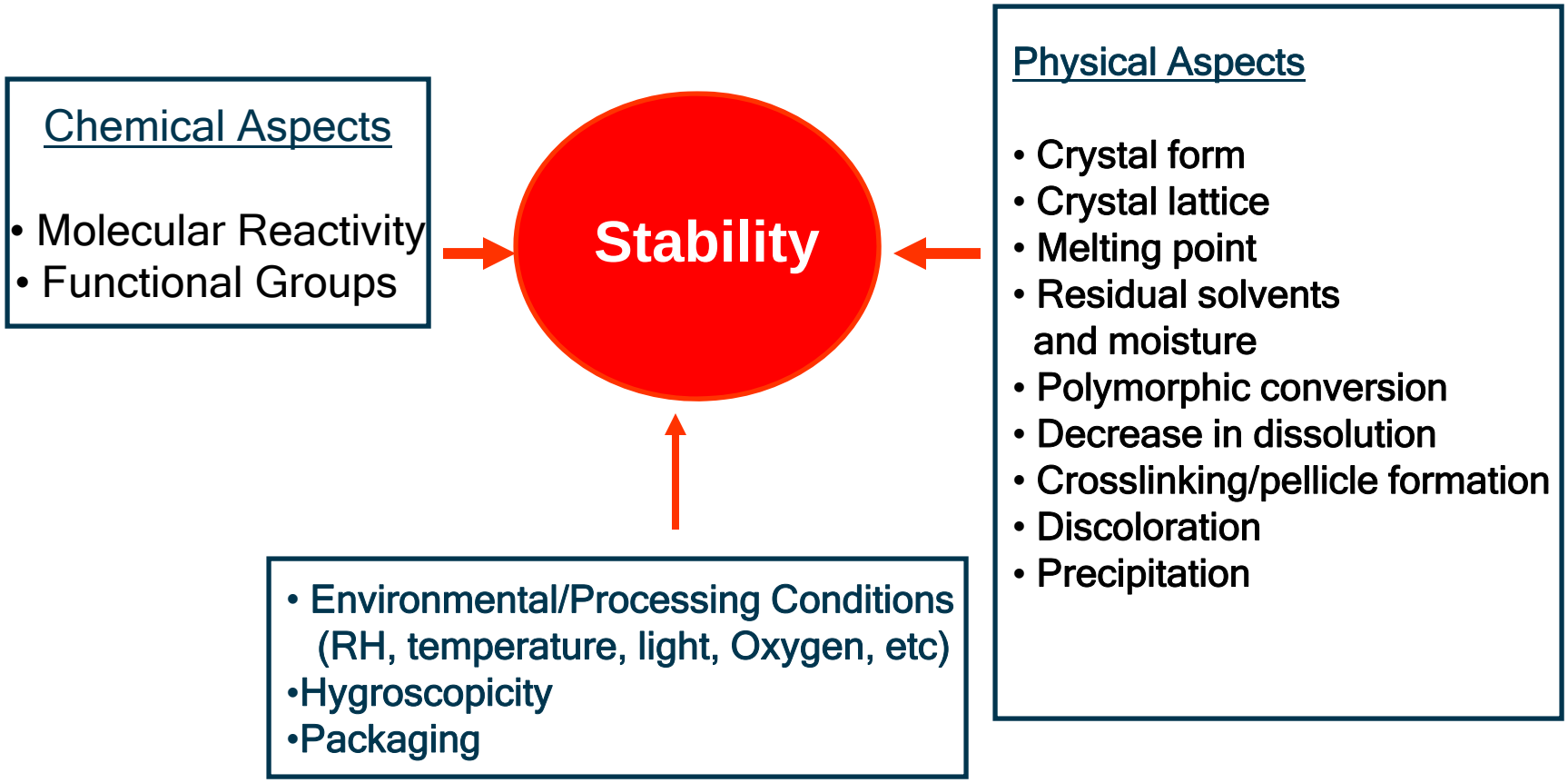
Dosage Form: Beadlets filled in HGC

Fluid Bed Coater

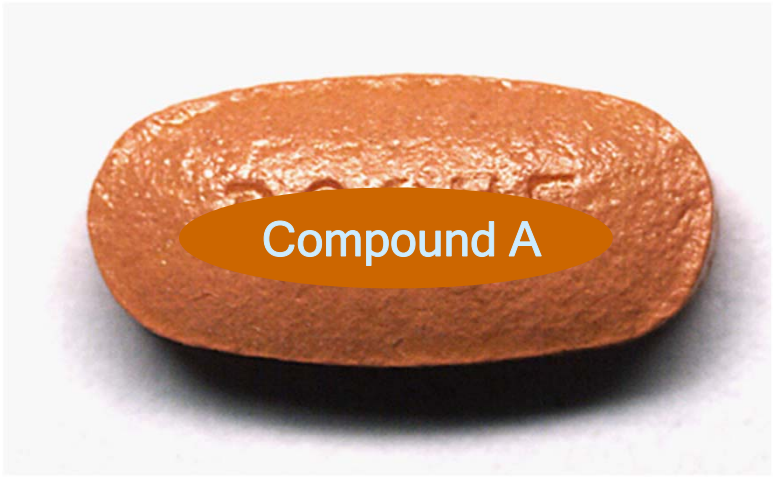


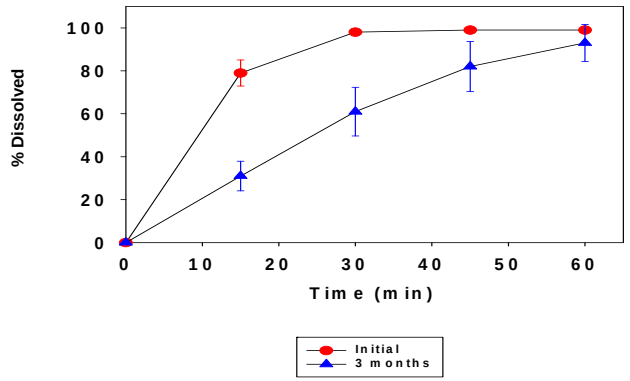
PHYSICO-CHEMICAL PROPERTIES IMPACTING STABILITY

Stability


Chemical Aspects
• Molecular Reactivity
• Functional Groups
Stability
Physical Aspects
• Crystal form
• Crystal lattice
• Melting point
• Residual solvents and moisture
• Polymorphic conversion
• Decrease in dissolution
• Crosslinking/pellicle formation
• Discoloration
• Precipitation
• Environmental/Processing Conditions (RH, temperature, light, Oxygen, etc)
•Hygroscopicity
•Packaging

Physical Instability of a Tablet Formulation

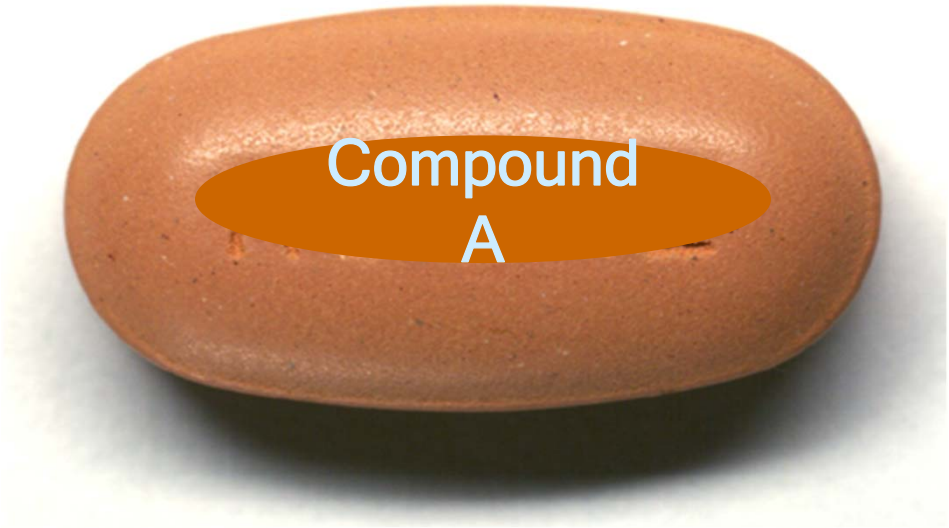


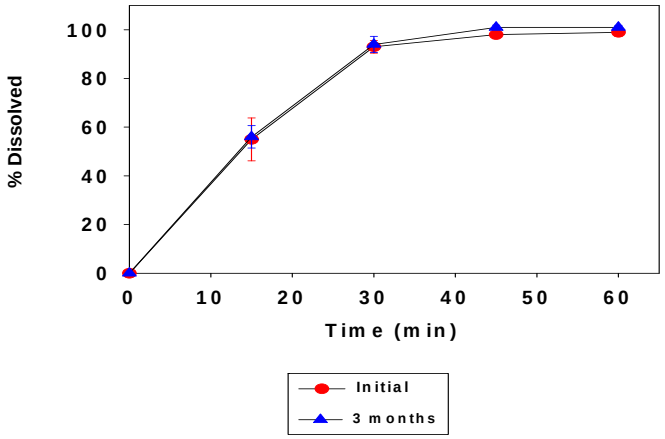


Example demonstrating sintering phenomena of a porous tablet containing high drug loading of a water-soluble drug when exposed to high humidity and temperature

- Wrinkle of the film coat
- Decrease in dissolution of tablet

Means to Overcome Physical Instability of Tablet Formulation





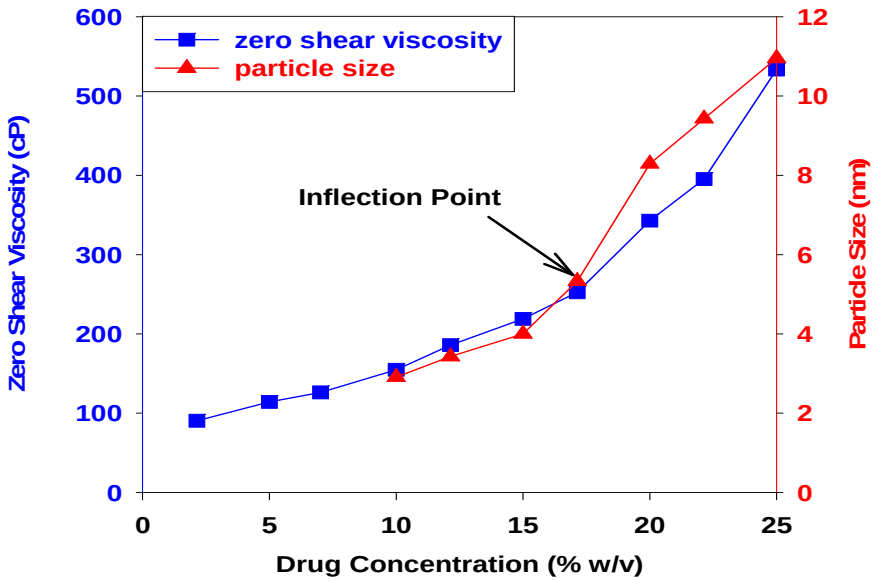
Wrinkling of the film coat and decrease in dissolution of the tablet can be resolved by:

- Use a high shear granulator (instead of a low shear) to produce granulator denser granulation, minimizing moisture uptake
- Optimize the film coat composition to minimize moisture uptake

Stability Considerations for Lipid Delivery System

- Solubility and super-saturation of the drug in the formulation
- Effect of shear and cooling rate on crystallization, thereby affecting the resultant viscosity and release rate of the drug
- Hygroscopicity of the formulation on the physical stability of capsule shell
- Effect of peroxide, acid value, and degree of unsaturation
- Change in crystallinity during storage
- Kinetics of degradation

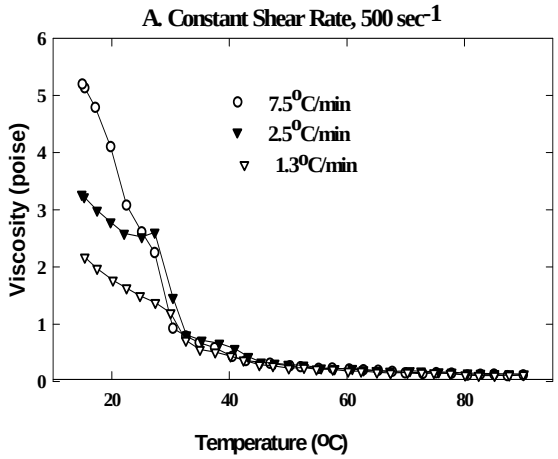
Establishment of Drug Loading to Avoid Potential Crystallization or Gelling of the Lipid Formulation



Supersaturated solutions beyond the inflection point exhibit high viscosity, increasing molecular interaction and subsequent aggregation, crystallization or gelling of the lipid formulation

Effect of Cooling Rate on the Resultant Viscosity of the Wax-Based Formulation

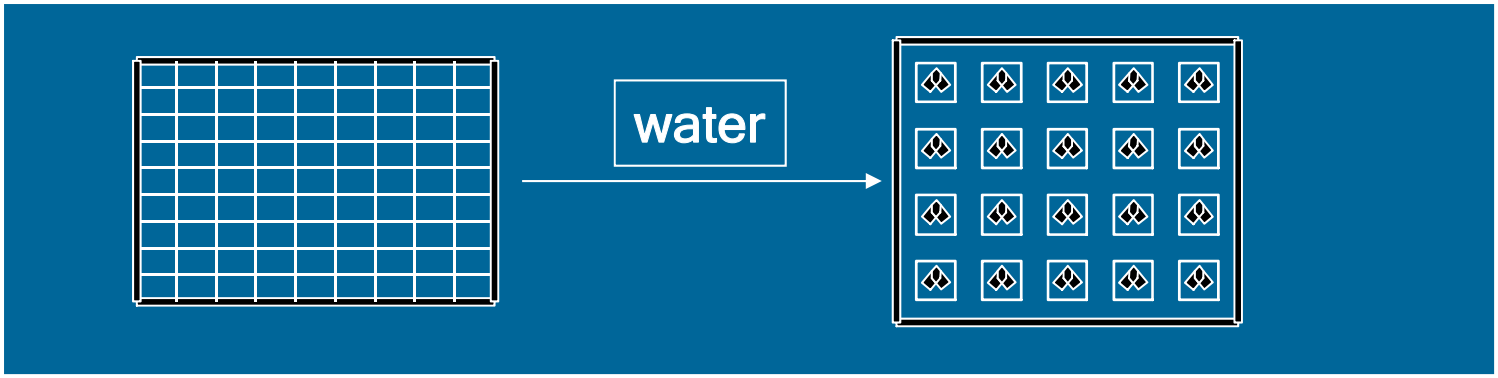
Effect of Cooling Rate on the Viscosity vs. Temperature Profiles of the Wax Based Vehicle



Cooling Condition	Cooling Time (min)	Viscosity (cps)
Fast	21	1000
Slow	103	415

HYDRATES TRANSFORMATION

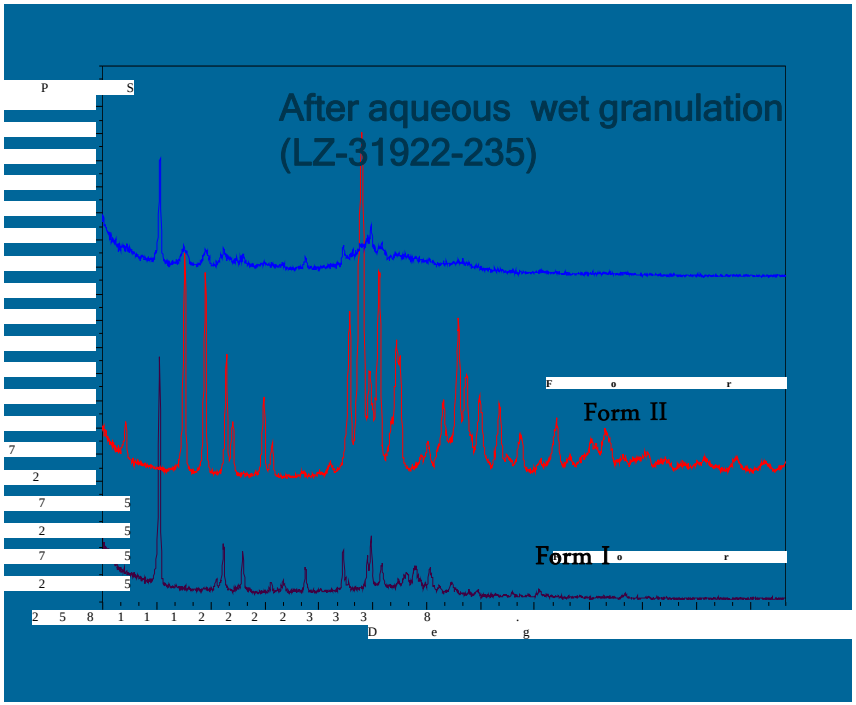
- Thermodynamic stability set by pressure, temperature and water activity (P-T, a_w)



Anhydrous Hydrate

- Hydrates have lower aqueous solubility and slower dissolution than non-hydrates
- Hydrates can form by exposure of the drug to water during processing or storage

XRD Patterns Indicating Hydrate Transformation During Manufacturing Process



Form I - Anhydrous

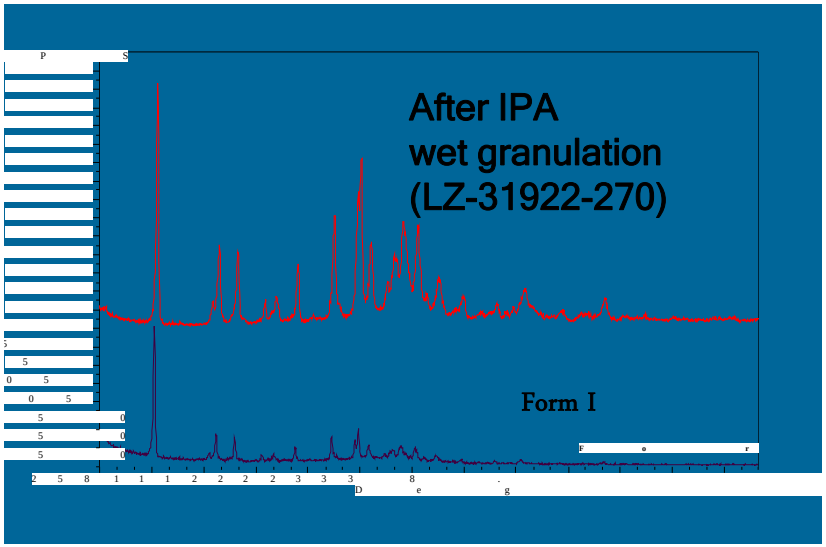
Form II - Hydrate

- The result indicates potential conversion of the drug from Form I to Form II (hydrate form) when granulated with water.

Means to Overcome the Polymorphic Transformation Mediated by Water

- **Choice of Manufacturing Processes**
  - Solvent granulation (i.e, ethanol, isopropyl alcohol)
  - Non-solvent granulation processes (i.e, hot melt granulation, roller compactor)
  - Direct compression which may have some limitations for high drug loading with poor compressibility and sticking nature of the drug
- **Selection of excipients**
  - Excipients with low moisture adsorption properties were selected
- **Selection of package**
  - Desiccant was included in the package

Appropriate Selection of Manufacturing Process to Overcome Polymorphic Conversion



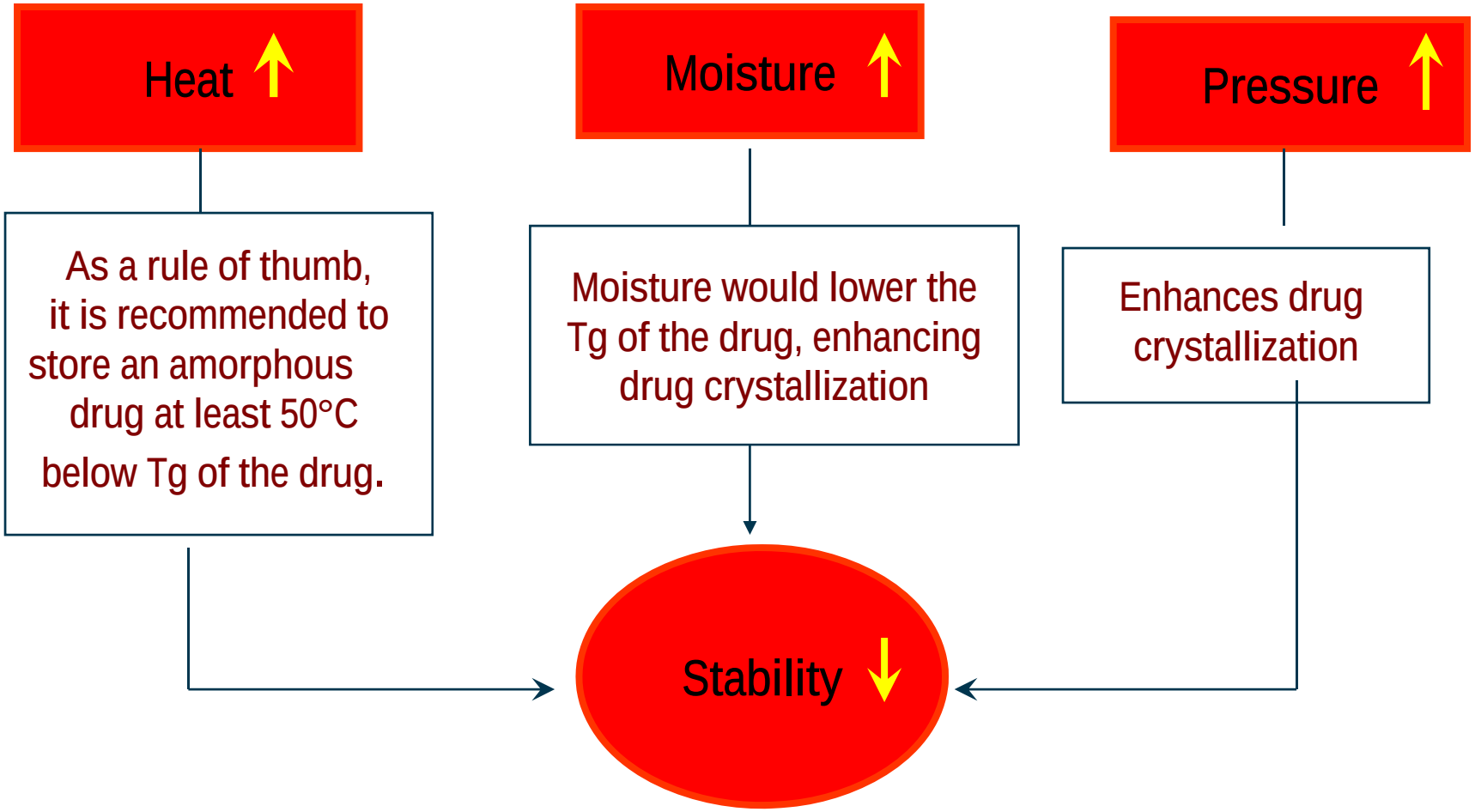
- There is no evidence of conversion to the crystal form of the drug when granulated with “Isopropyl Alcohol (IPA)”.

AMORPHOUS FORM

- High energy form (higher solubility and bioavailability)
  - Stability depends on
  - Tg (glass transition temperature)
  - Hygroscopicity
  - Purity may be variable from lot- to-lot, which may also impact solubility
  - Storage conditions (heat and humidity)
  - Clumping and gelling of the drug when exposed to aqueous solution

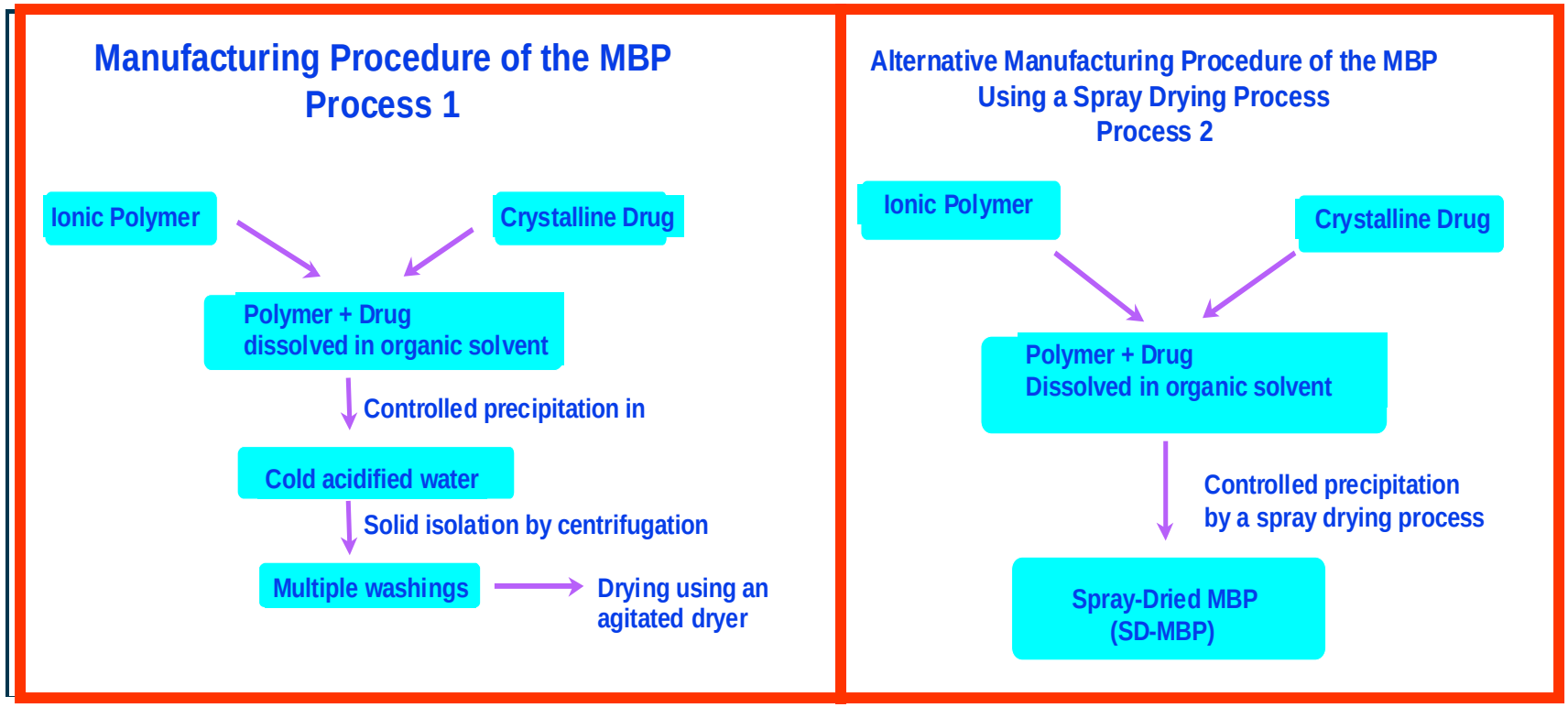
- Unpredictable shelf life if storage condition results into lowering of Tg
- Non-hygroscopicity and high Tg (50oC above the storage conditions) are
- the pre-requisites for stable solid dosage form
- If low Tg, solution in non-aqueous vehicle below the saturation solubility is the only possibility. However, change in purity could change the solubility.

Processing Considerations for Amorphous Compound



These reality checks are the most importance at the early stage of development.

Impact of Two Different Manufacturing Procedures of the Amorphous Formulation (MBP) on Bioavailability

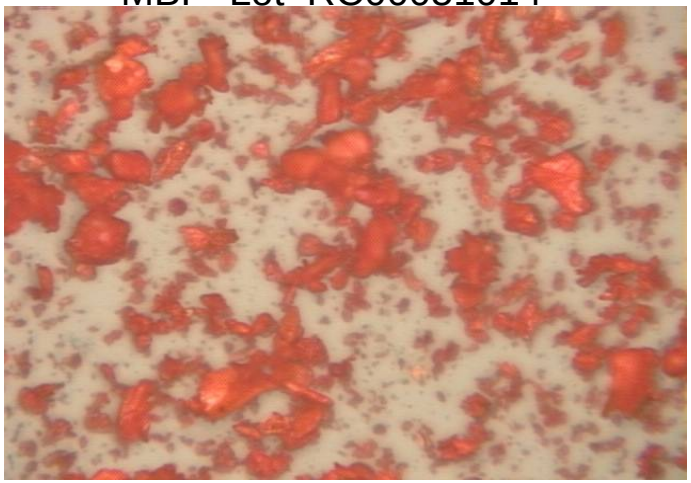


PK Profiles in Dogs After Administration of Drug A Capsules (90 mg) Prepared Using MBP Vs. SD-MBP (Randomized Crossover Study, N = 12)

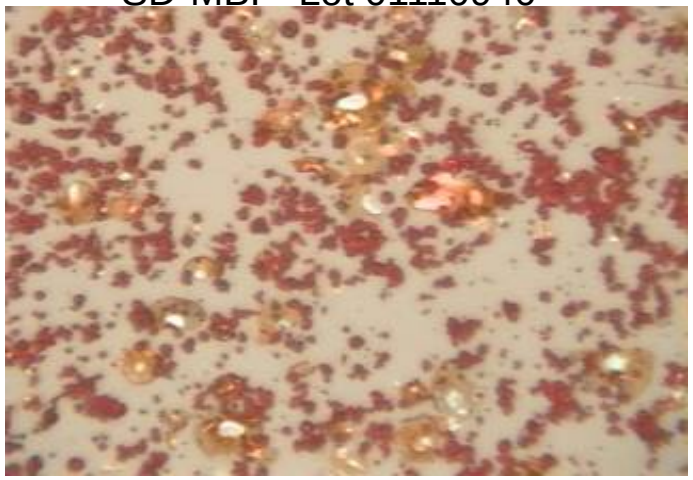
Drug Product	Cmax/Dose (ng/mL)(mg/kg)	Tmax (hr)	AUC/Dose (ng.h/mL)(mg/kg)	% Relative Bioavailability
MBP **(by Co-Precipitation Process)**	121 ± 34	2.50 ± 0.90	686 ± 237	100
SD-MBP (by Spary Drying Process)	61 ± 24	2.08 ± 0.67	329 ± 162	48

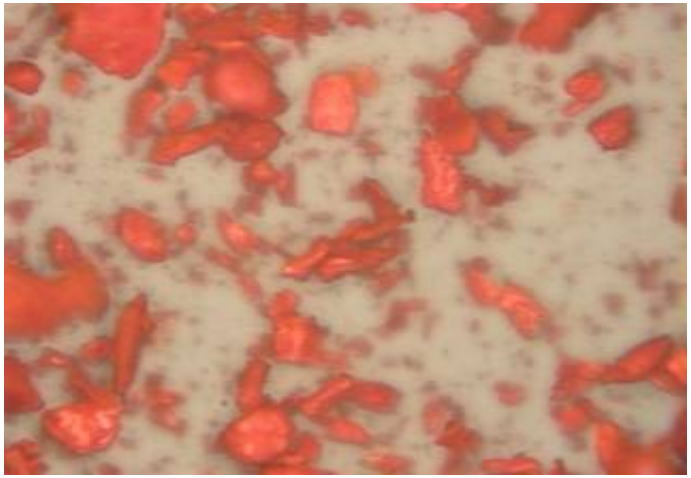
Comparison Between MBP and SD-MBP Photo-Microscopy

MBP Lot RC00051014

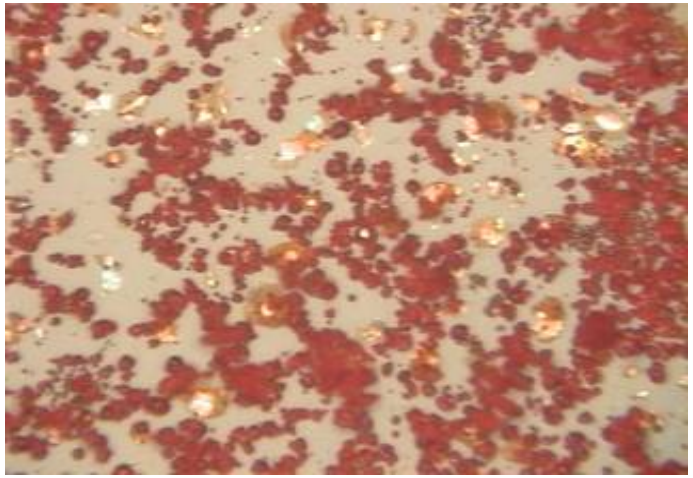


SD-MBP Lot 01110940





MBP Lot RC00051015



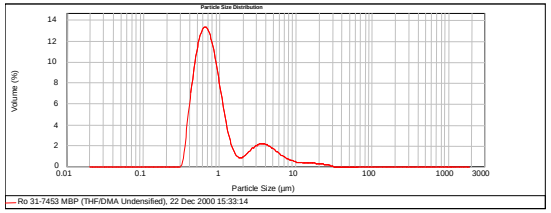
SD-MBP Lot GSR0003/50

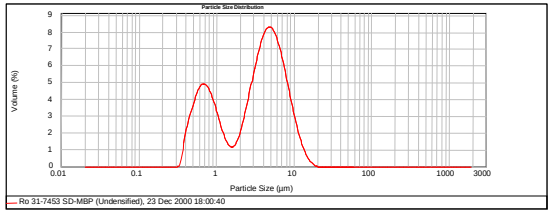
Intrinsic Particle Size of MBP vs SD-MBP

MBP RC00051015

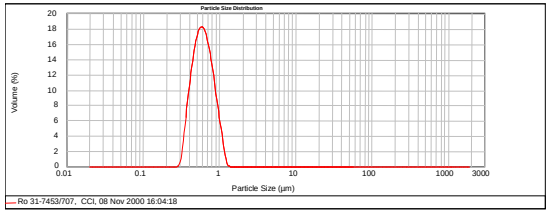
SD-MBP GSR0003/50

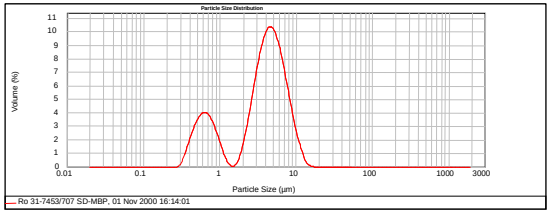
No sonication





With sonication

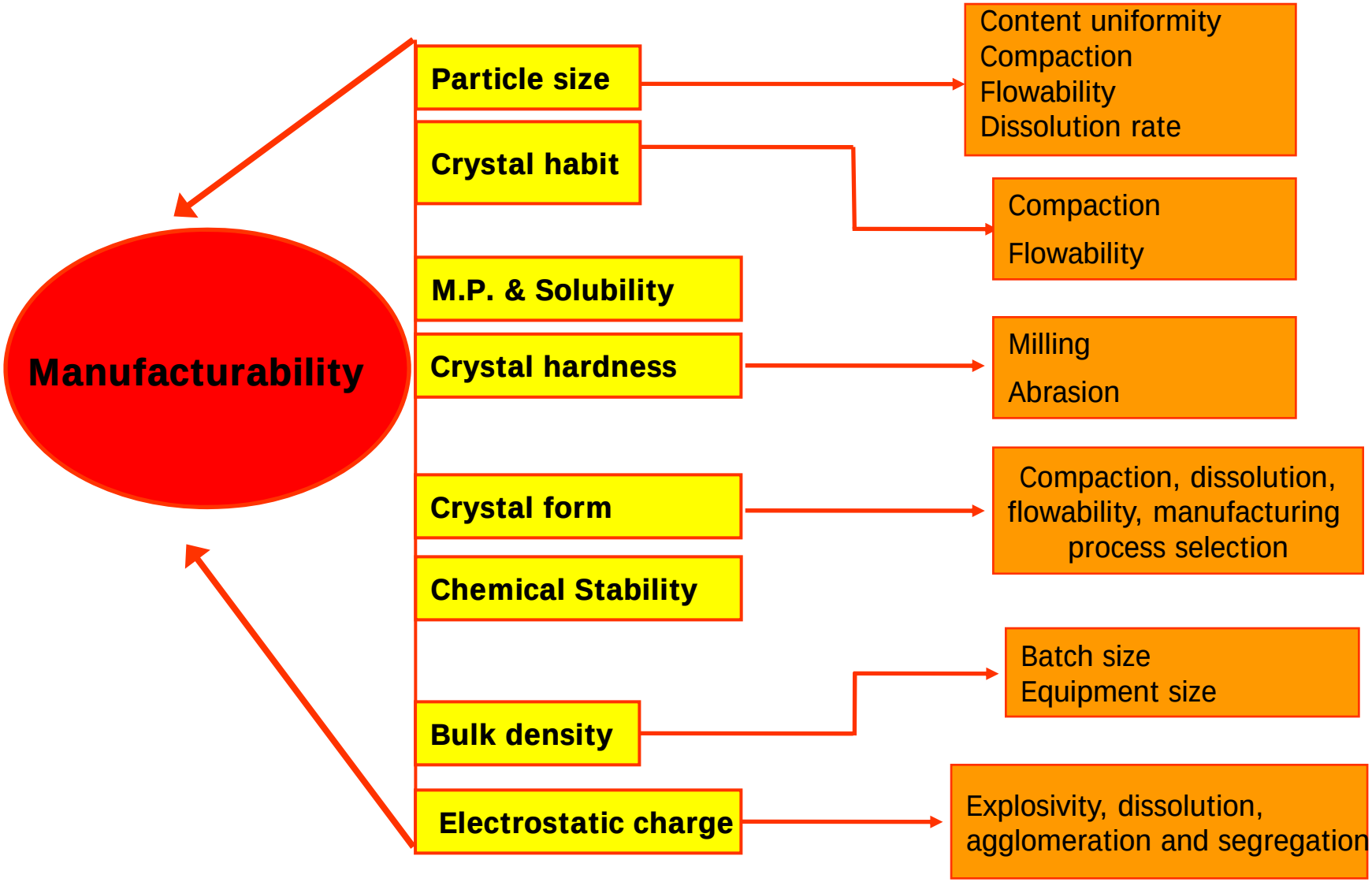




	MBP RC00051015			SD-MBP GSR0003/50		
Intrinsic Particle Size (micron)	D10	D50	D90	D10	D50	D90
No sonic	0.46	0.76	3.81	0.6	3.63	8.31
W/sonic	0.41	0.60	0.91	0.6	3.96	7.77

PHYSICO-CHEMICAL PROPERTIES AFFECTING MANUFACTURING

PHYSICO-CHEMICAL PROPERTIES OF API IMPACTING MANUFACTURABILITY



Physico-chemical Properties of API Impacting Manufacturability Aspect

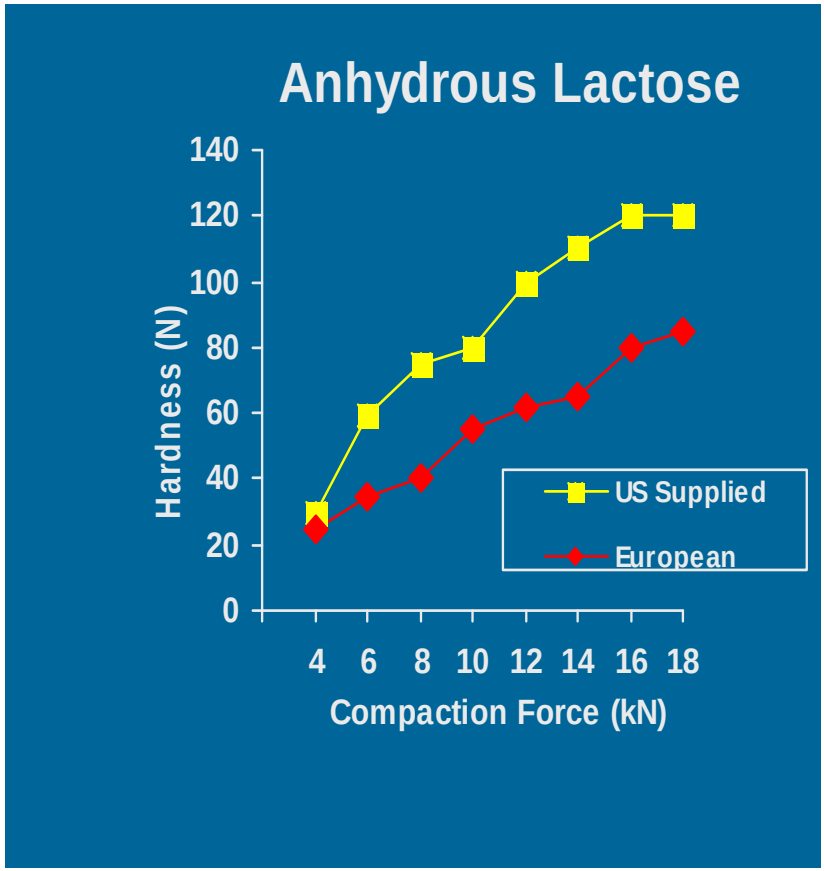
API Properties	Impact	Solutions
Particle Size/Shape Bulk Density Crystal Habit Surface Morphology	Compaction Tablet Ejection Flowability	❑ Wet granulation to improve flowability and compactability
Melting Point	Low melting point contributed to picking and sticking during tabletting or encapsulating.	❑ Utilize pelletization technology
Solubility	Aqueous wet granulation may not be robust for API having aqueous solubility (> 200 mg/mL).	❑ Select appropriate granulating liquid in which the API is less soluble
Chemical Stability	Oxygen-sensitive compounds (i.e., Vitamin D3 analog)	❑ Keep the API in lipid vehicle to prevent oxidation

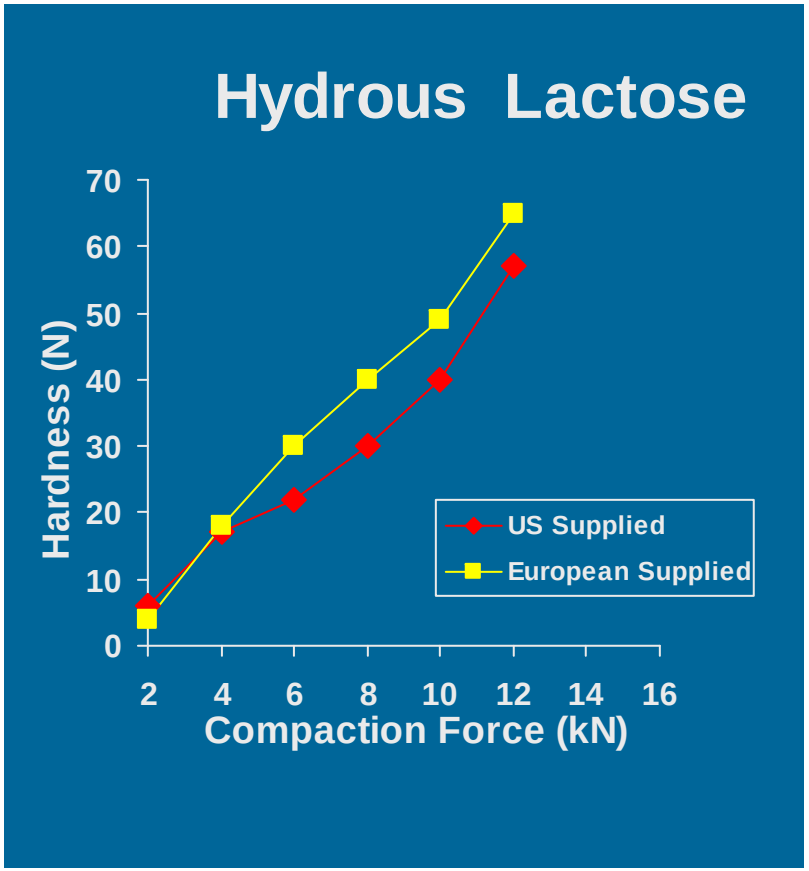
Physico-chemical Properties of API Impacting Manufacturability Aspect

API Properties	Impact	Solutions
Amorphous vs. Crystalline Form	➢ Crystalline is the most stable form and desirable for development ➢ Amorphous cpd. is typically hygroscopic and tacky in nature.	❑ Residual solvent(s) and impurities may have impact on Tg and must be well controlled ❑ Low Tg – Liquid or semi-solid filled in capsules ❑ High Tg - Possible conventional tablet/capsule dosage form or hot melt granulation process
Hydrate	➢ Potential loss of bound water during storage and processing	❑ Packaging becomes critical
Polymorphs	➢ Potential polymorphic conversion	❑ Select the most stable form ❑ Appropriate solvent selection for granulation to avoid polymorphic conversion

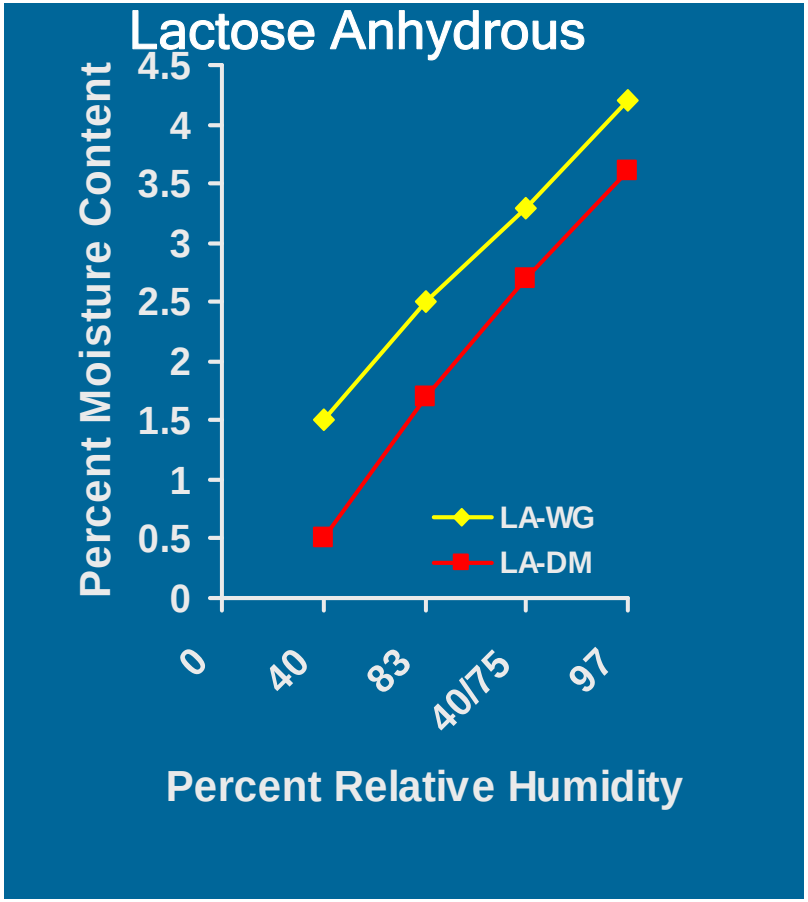
IMPACT OF EXCIPIENTS

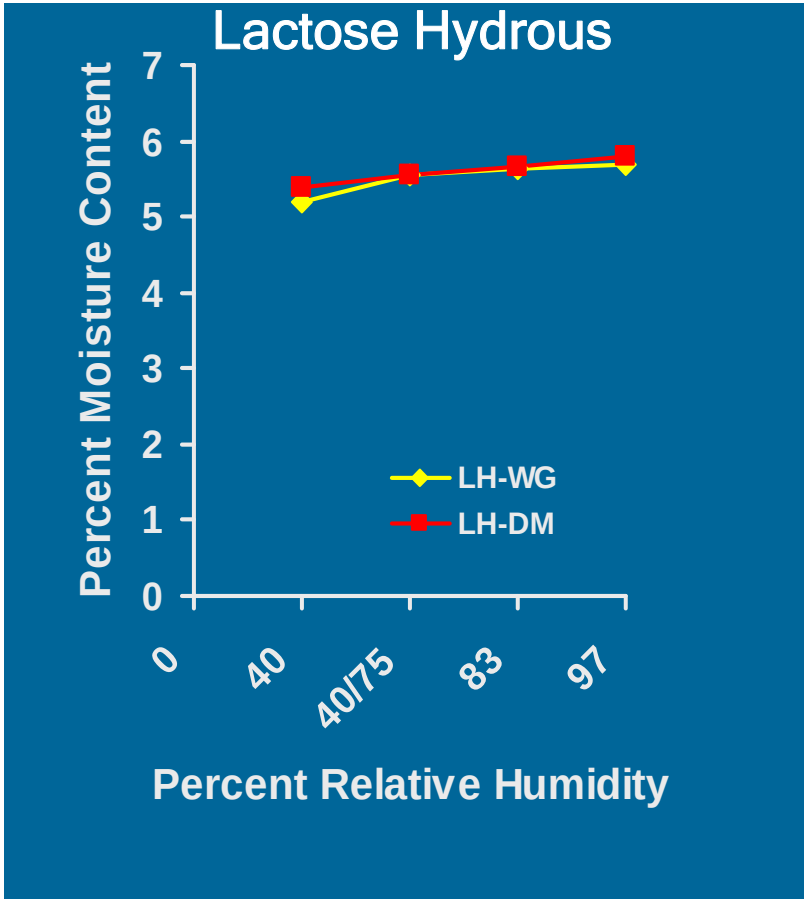
COMPACTION FORCE AND HARDNESS PROFILE OF LACTOSE





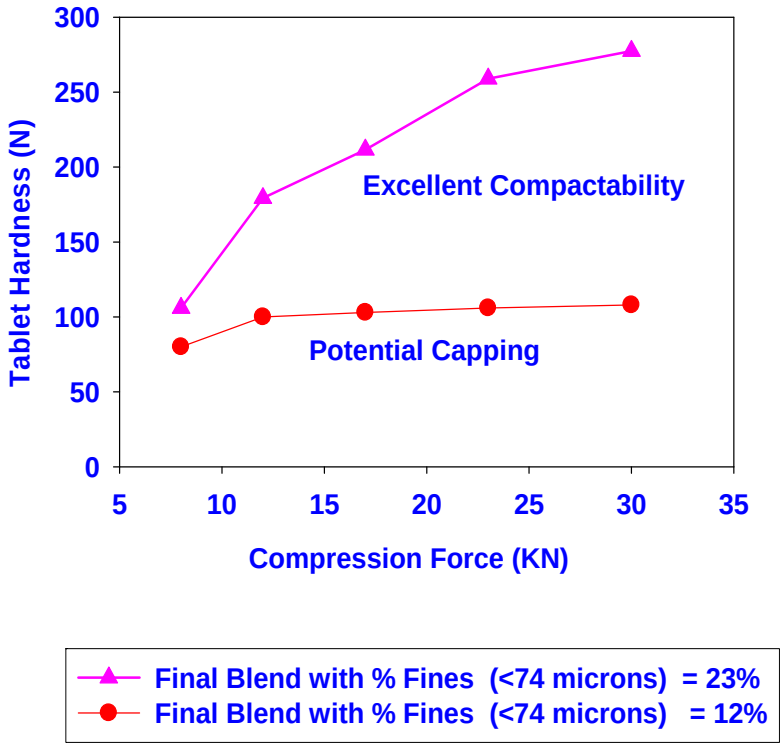
Impact of Hygroscopicity of Excipients





Lactose hydrous is less hygroscopic compared to Lactose Anhydrous, therefore it is a preferred diluent for a moisture-sensitive compound.

Effect of Magnesium Stearate Level



- Lubricant properties of magnesium stearate
  - Plates unfold ("Deck of Cards")
  - Coat powder surfaces
  - Reduce friction at tablet-die wall interface
  - Impede compaction at high levels
- Magnesium stearate level needs to be established based on percentage of fines of the granulation.
- Over-lubrication of magnesium stearate may result into poor compaction.

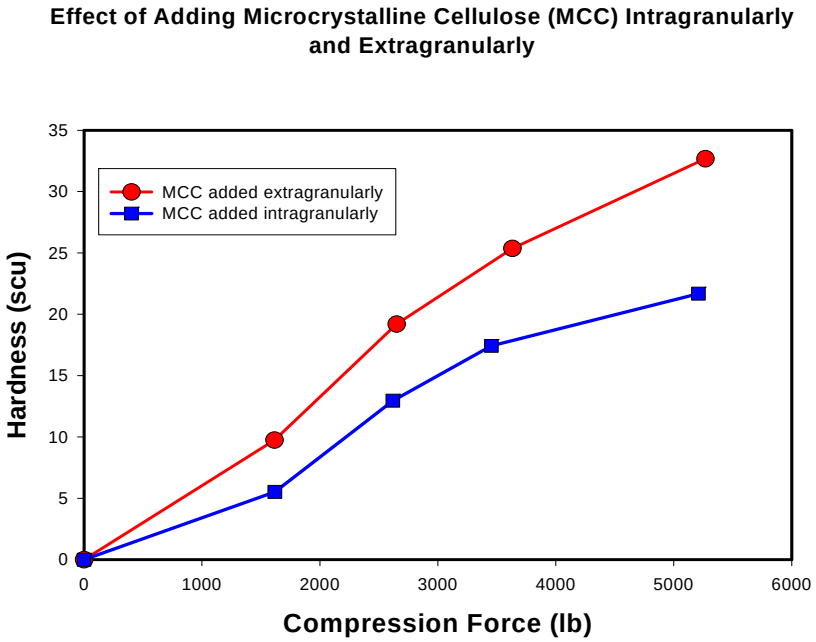
THE EFFECT OF ORDER OF ADDITION OF EXCIPIENTS ON TABLET PROPERTIES

- Microcrystalline Cellulose (MCC) and its effect on tablet hardness

  - MCC is a purified de-polymerized ∝-cellulose. Compaction results from plastic deformation of the powder particles. Hydrogen bonds play a significant role in compaction of MCC.

  - Addition of MCC internally (during granulation) contributes to significant loss of plastic deformation and thereby compactibility and tablet hardness. The compressibility of the formed granules is far less than the original primary particles.

  - Addition of MCC externally results in a significant improvement in compressibility of MCC and thereby, stronger tablets.



Summary

- Physico-chemical properties of drug substance and excipients play a significant role on dosage form selection and development.
  - Thorough knowledge on their implications on bioavailability, stability and manufacturability is vital in developing dosage form.

- Formulation technologies, namely salt selection, particle size reduction, lipid delivery, amorphous formulation will help improve bioavailability of poorly soluble drugs.

- Dosage form design and characterization, including careful selection of excipients are critical to effectively address potential stability issues of solid, lipid and amorphous formulations.

- Thorough knowledge of API physico-chemical properties and unit operations would result in a robust formulation which would enable manufacturing on large scale commercial production without compromising stability and bioavailability.

Practical Uses of Amorphous Materials; Features and Stability

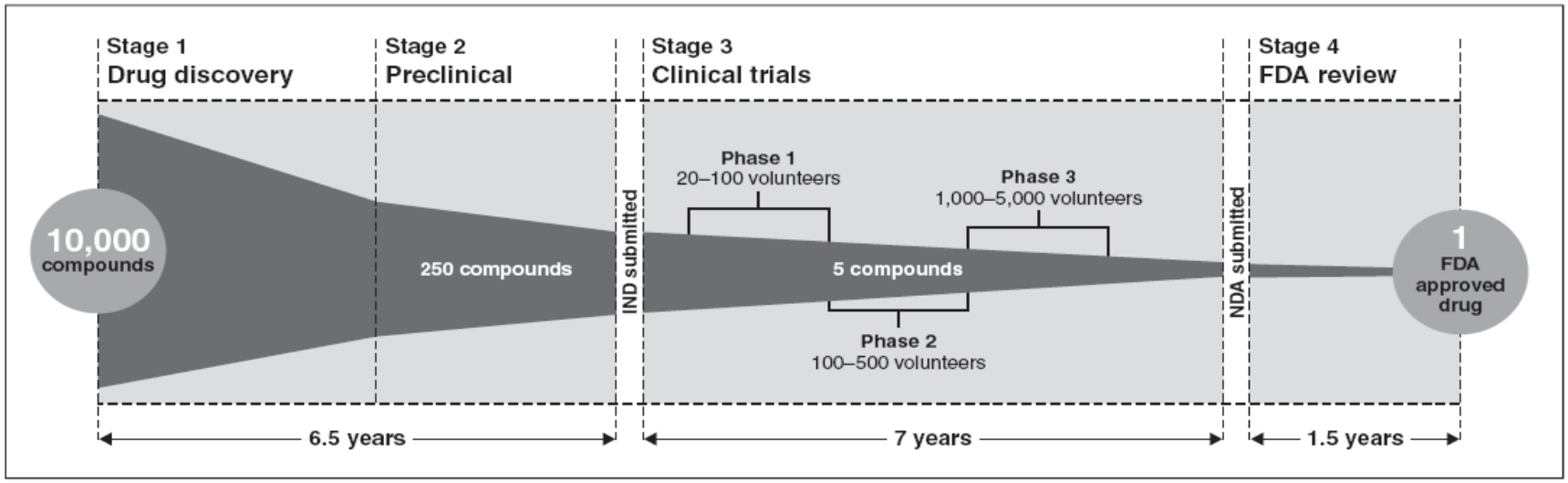
Duk Soon Choi, Ph.D.

Hoffmann La Roche, Nutley

Outline

- Where amorphous material fits in drug development
  - Landscape in drug development
  - Approaches to address BCS 2/4 molecules
- Definition of amorphous material and properties
  - Pros and cons of amorphous material
- Preparation of amorphous formulation
  - Stabilization of amorphous solids in solid dispersion
  - Selection of polymer
  - Selection of process
- Case studies
- Remarks on solid state stability

Landscape in Drug Development; Attrition Rate



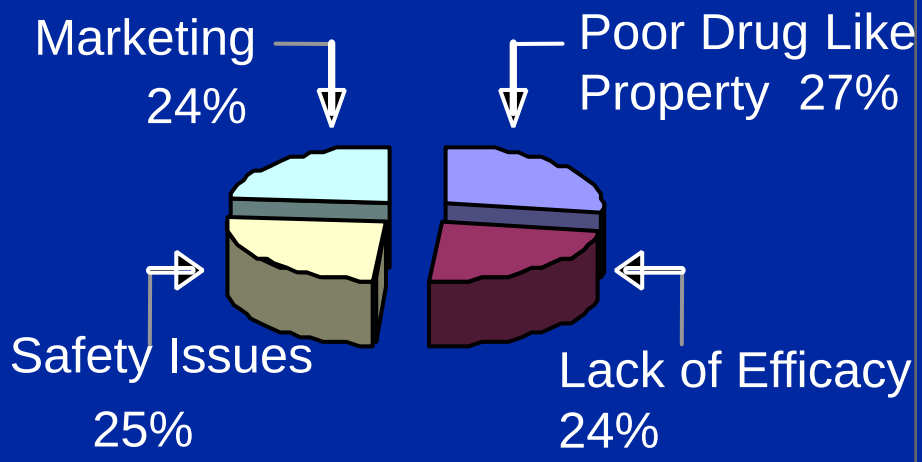
Source: Pharmaceutical Research and Manufacturers of America.

Figure 1 shows the amount of time, on average, for a successful new drug to move through and complete the four stages. It also illustrates that for every 10,000 compounds initially identified, only one, on average, will be found safe and effective, and be approved by FDA.

* New Drug Development, GAO-07-49, Nov 2006

Failure Analysis

- **Reasons for failure***
  - Safety issues
  - Lack of efficacy
  - Business cases
  - **Poor drug like properties**

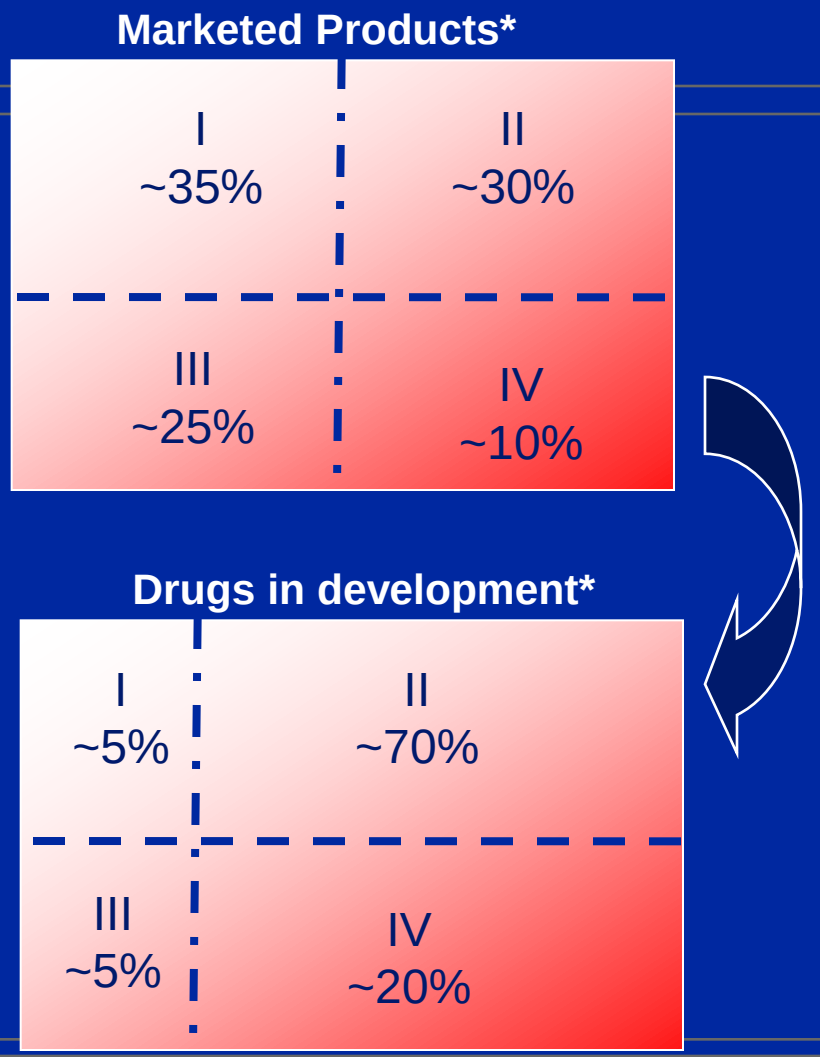


- **Reasons for slowdown**
  - Synthetic complexity
  - Low potency
  - Ambiguous toxicity findings
  - Complex target indication
  - Manufacturability – stability and consistency
  - **Poor drug like properties**

*Robert Lipper, Modern Drug Discovery, 1999, 2(1), p 55

Poorly Water Soluble Compounds; A growing challenge

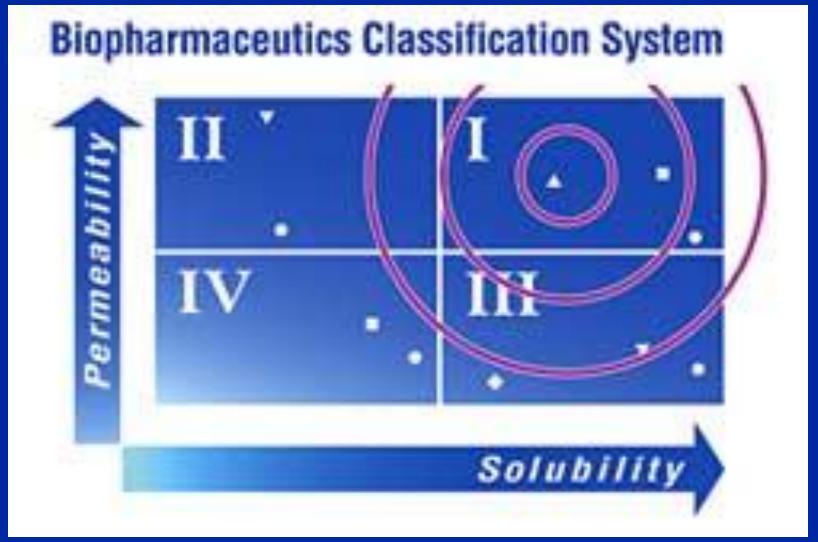
- About 40% of drug in market is poorly water soluble (BCS 2/4)
- Percentage of poorly water soluble APIs in development is further increasing owing to HT screening, combinatorial chemistry, and paradigm shift!
- Numerous APIs don't even enter development due to extremely low solubility
- BCS 2/4 compounds, if not addressed properly,
  - Lack of dose proportional absorption
  - High inter- and intra-subject variability
  - Substantial food effect
  - Potential side effects for narrow TI drugs



* Sigrid Stokbroekx (2008). 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Baro

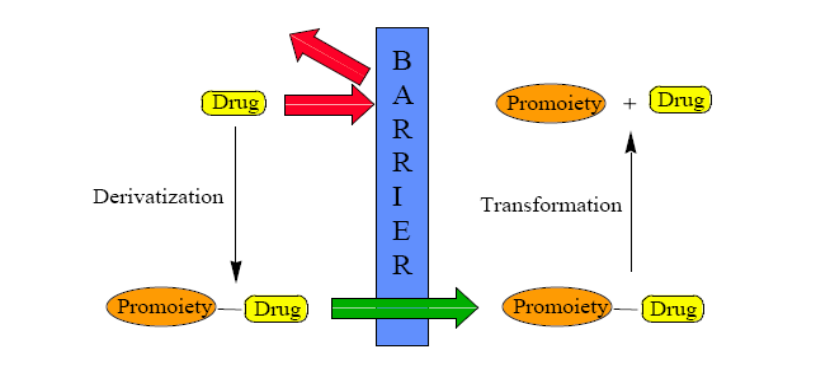
Approaches to Address BCS 2/4 Drugs

- Chemical Modifications
  - Pro-drugs
  - Salts / Co-crystals
- Physical Form Modifications
  - Particle size reduction
  - Amorphous forms
- Formulation Intervention
  - Cosolvents
  - Complexation (cyclodextrins, dendrimers)
  - Lipid drug delivery: SEDDS/SMEDDS

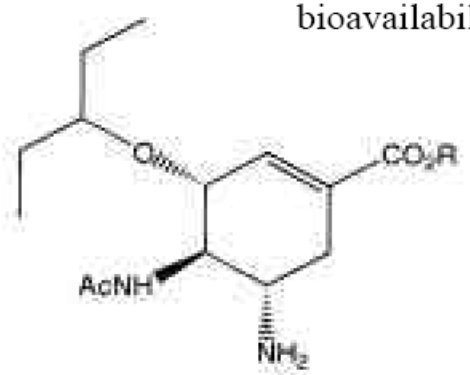


Approaches to Address BCS 2/4 Drugs

Chemical Form Modification - Pro-drug



TAMIFLU® (oseltamivir ethyl ester) is a prodrug of the antiviral drug oseltamivir carboxylate which was designed to improve its intestinal mucosal permeation; thus, its oral bioavailability.



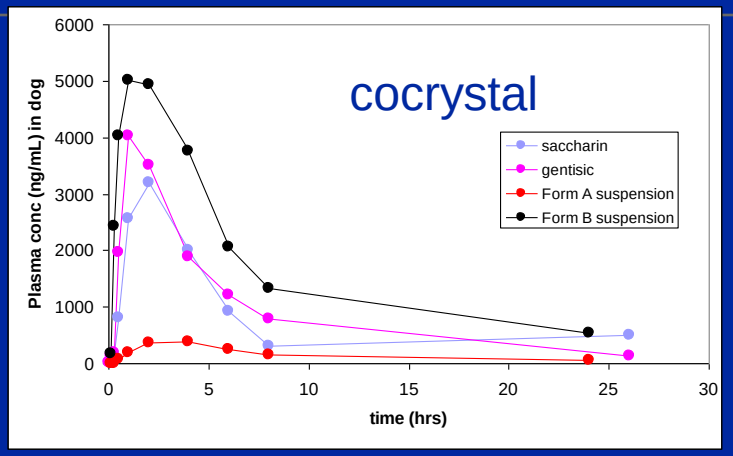
	Bioavailability
Oseltamivir carboxylate, R = H	**4.3% ± 1.6**
Oseltamivir ethyl ester, R = CH_2CH_3	**35% ± 11**

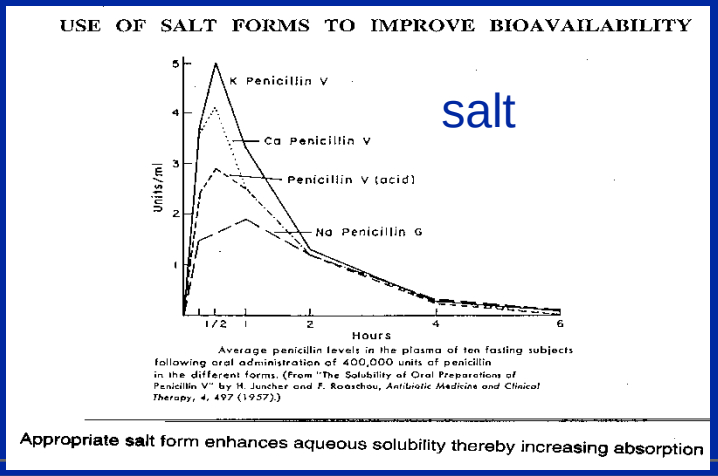
Prodrug can improve solubility and permeability; thus bioavailability

Approaches to Address BCS 2/4 Drugs

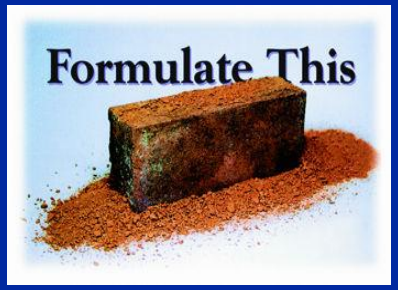
Chemical Form Modification - Salt / Cocrystal

- Advantages of salt / cocrystal formation
  - Improves solubility
  - Provides rapid rate of dissolution and absorption
  - Results in improved bioavailability
- Saccharin and gentisic cocrystal of compound X provided > 7 fold increase in AUC in dog over crystalline API Form A





Amorphous Forms



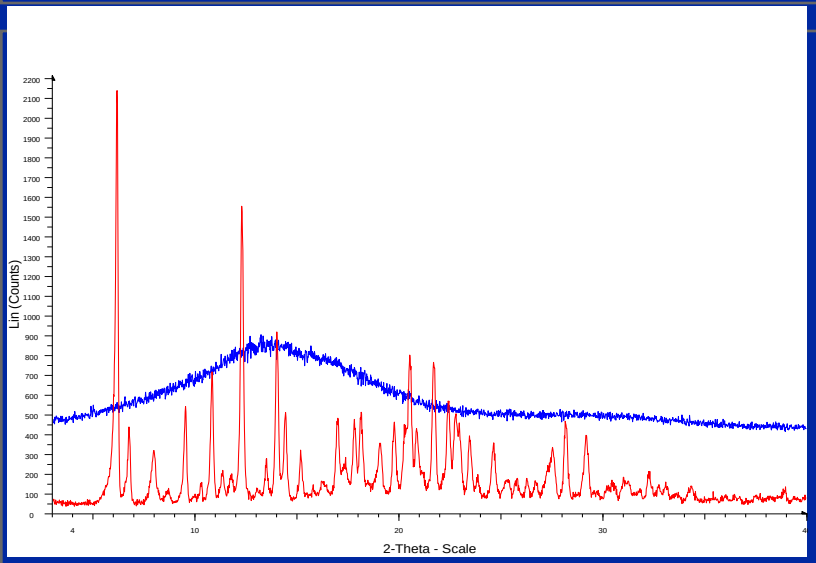
Examples of Amorphous Products

Product	Polymer	Process	Comments
Certican®	HPMC	Amorphous API	Stabilized by anti-oxidant
Rezulin®	PVP	Melt Extrusion	Solubility
Palladone®	Eudragit RL/RS	Melt Extrusion	Solubility and CR
Kaletra®	PVP VA	Melt Extrusion	Solubility (safety/efficacy)
Isoptin®	HPC/HPMC	Melt Extrusion	Solubility and CR
Sporanox®	HPMC	Fluid bed coating and HME	Solubility
Cesamet®	PVP	Solvent Granulation	Solubility, viscous liquid
Intelence®	HPMC and MCC	Spray Drying	Solubility
Nivadil®	HPMC	Emulsion-precipitation	Nanoparticle (solubility)
Prograf®	HPMC	Rapid freezing	Solubility
Depot Profact ®	PLGA		Implant
Zoladex ®	PLGA		Implant
Torcetrapib	HPMC-AS	Spray Drying	Solubility (Phase 2)

Although concept of amorphous product has been around for more than half a century (1961 by Sekiguchi and Obi), yet very few commercial products are available

What is amorphous material?

Crystalline vs. Amorphous



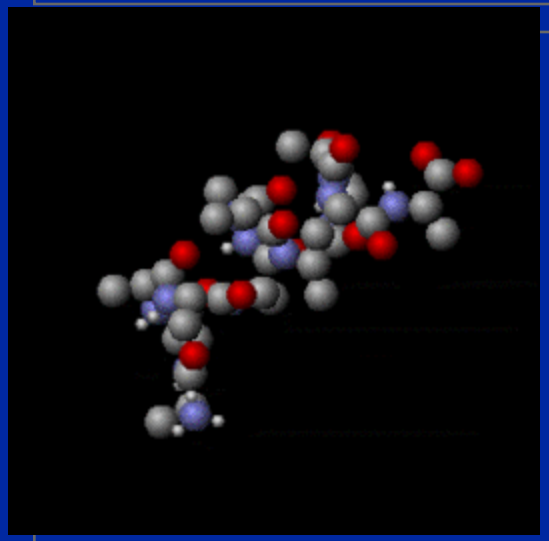
In most pharmaceutical application, a material is called amorphous if it exhibits XRPD profile that devoid sharp peaks

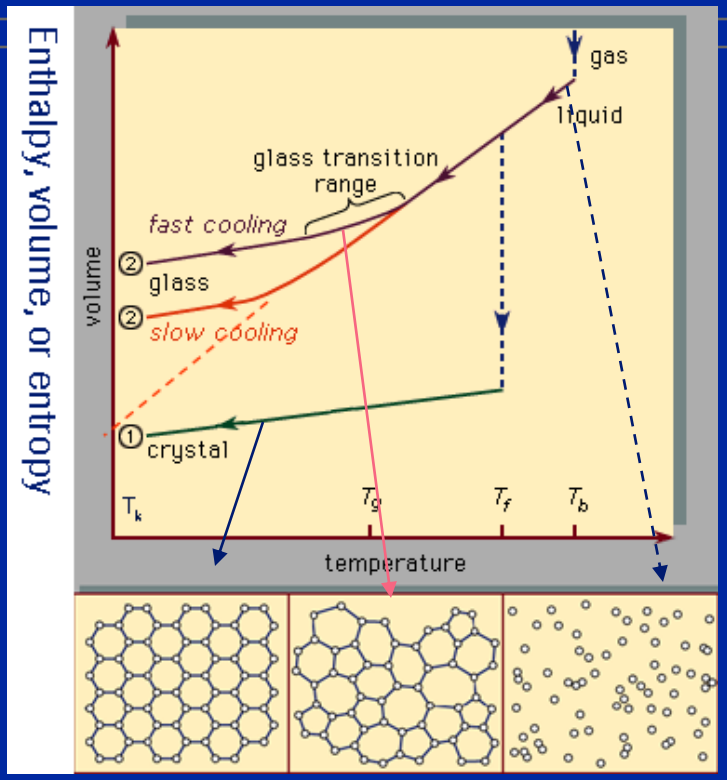
Attributes	Crystalline State	Amorphous State
Melting	Has defined melting	Has **no** melting; usually has glass transition temperature
Birefringence	Except cubic, crystal is anisotropic and exhibits birefringence	Amorphous is isotropic and exhibits **no** birefringence
X-Ray Diffraction	Reflect X-ray radiation, exhibiting characteristic diffraction pattern	Does **not** reflect X-ray beam, exhibiting characteristic amorphous defused halo
Energy level	Lower in E state, exhibits lower solubility, slower dissolution, more stable	Higher in E state, and exhibits higher solubility, faster dissolution and less stable.
Mechanical Properties	Lower specific molecular volume, leading to denser & harder material	Randomness causes higher molecular volume and less dense material
Spectroscopic	Interaction to NN	Interaction to NN

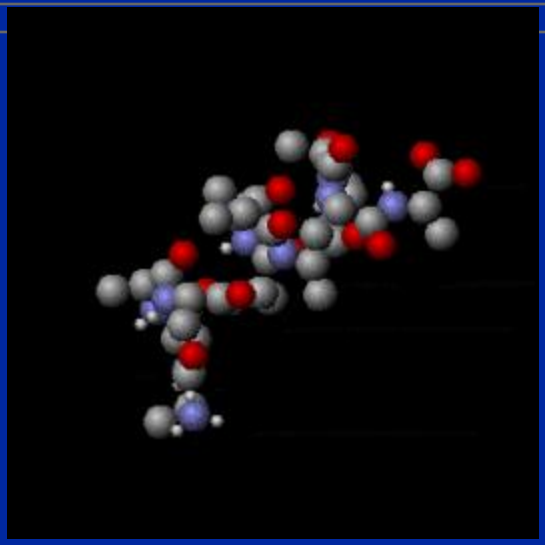
Amorphousness is **NOT** measured directly; only implied/derived from absence of

Characteristics of Amorphous State

The glass is 10^{10} to 10^{12} times more viscous than the liquid







Minimum mobility temperature: Kauzmann Temp

Projected temperature at which thermodynamic properties of amorphous solid reach to those of crystalline solid

Properties of Amorphous Material

- Amorphous material is a disordered system with random molecular conformation/packing. Individual molecules are randomly oriented to one another and exist in a variety of conformational states, and experience different inter and intra molecular interactions.
- Amorphous material has higher chemical potential than crystalline counter part
  - Good
    - More soluble
    - Faster dissolution
    - More bioavailable
  - Bad
    - Chemically unstable
    - Physically unstable
    - Regulatory complex

Solubility Enhancement / Comparison

Compound	API Form	Theoretical*	Experimental
Compound A	A / Form III	60 - 480	>10
Compound B	A / Form I	77 - 114	> 6
Compound C	A / Form I	100 – 600	> 5
Indomethacin	A / Crystal	25 – 104	> 4
Griseofulvin	A / Crystal	38 - 441	> 2

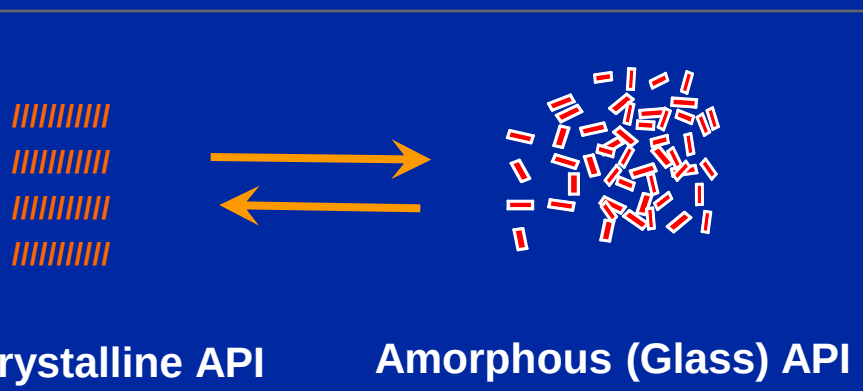
* Hancok and Parks, Rham Res 17, 2000

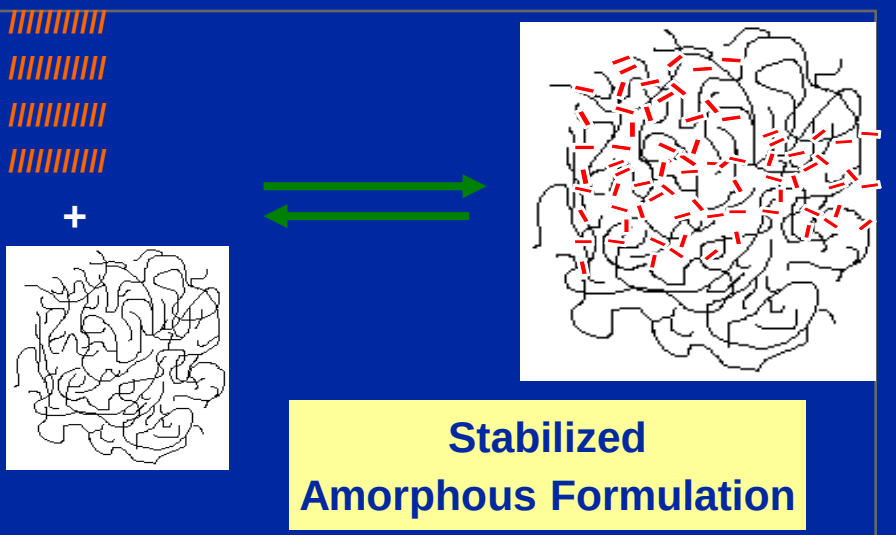
Concerns with Amorphous API

- The mechanical properties and hygroscopicity are markedly different from the corresponding crystalline API
- Water is known to have a profound effect on the Tg of amorphous API, acting as a plasticizer by increasing the free volume of the material, enhancing structural mobility and decreasing the Tg
- Manufacturing processing, packaging configuration and storage conditions are the most important factors influencing stability of the amorphous API
- In many instances, amorphous API itself can not withstand the manufacturing processing conditions and maintain its stability throughout the shelf-life

Therefore, stabilization of amorphous API by excipients (polymers) is very important.

Design of Amorphous Formulations (Solid Dispersion)



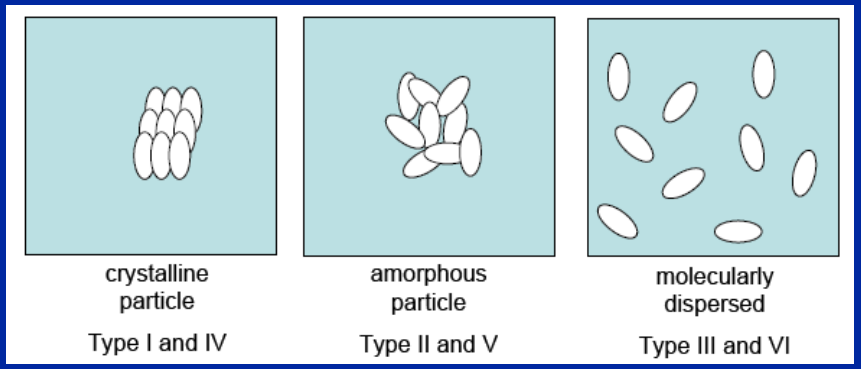


- Higher chemical potential results in higher dissolution rate and solubility but also makes them thermodynamically unstable
- API, without protection from matrix, may revert back to crystalline state
- Selection of polymer and process are crucial in designing amorphous formulations

Solid Dispersions Classification

Solid dispersions is defined as the system in which drug is dispersed in an inert carrier (polymer) or matrix at solid state

	Eutectic	Amorphous Precipitation	Solid Solution	Glass Suspension		Glass Solution
Type	I	II	III	IV	V	VI
Phase	2	2	1 or 2	2	2	1
Drug	Crystalline	Amorphous	Molecular Dispersion	Crystalline	Amorphous	Molecular Dispersion
Matrix	Crystalline	Crystalline	Crystalline	Amorphous	Amorphous	Amorphous



- Maegerlein M. Solid dispersions of poorly water soluble substances – a challenge for analytical development. Innovative Drug Delivery
- Chiou & Riegleman, Pharmacutical applications of solid dispersion systems, J. Pharm Sci, 1971, 60(9), 1281
- Combining the incompatible, Dissertation (2006) by Drooge, Dirk Jan van

Role of Polymer in Amorphous Formulation

- Selection of polymers and processes is critical for amorphous stabilization to achieve
  - Delay the onset of crystallization
    - Reduction in molecular mobility
    - Reduction in driving force for crystallizatio
    - Increase in energy barrier for crystallizatio
    - Disruption of molecular recognition
  - Maintains supersaturation
- Desired properties of polymers
  - Thermoplastic behavior deformability
  - Suitable Range of Tg 75 °C –180 °C
  - Low hygroscopicity
  - No toxicity – GRAS status
  - Chemical and physical compatibility with drug
  - Ability to prevent crystallization and maintain super-saturation of the drug

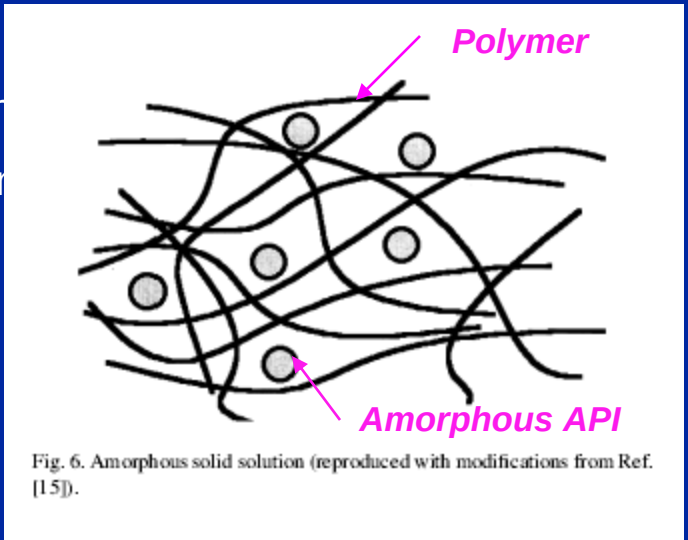


Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

C. Leuner and J. Dressman, Eur. J. of Pharmaceutics and Biopharmaceutics,

50: 47-60 (2000).

Factors in Selection of Polymer

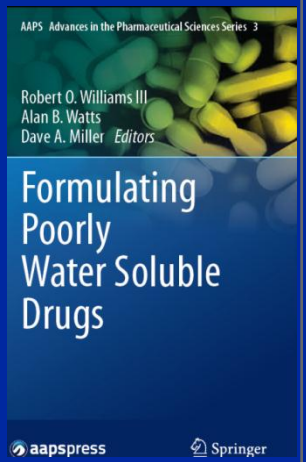
What to look for?

- Solubility Parameter
- Miscibility by Thermal Analysis: DSC
- Hot Stage Microscopy
- Spectroscopic Investigation (FTIR, Raman, NIR, ssNMR)
- Solubility Assessment of Drug in Polymer
  - Flory Huggins interaction parameter
  - Solubility determination in monomer unit
- Others
  - Matching hydrophobicity and partition coefficient
  - Ionic interaction potential
  - H-bonding potential / interaction

Structured Development Approach for Amorphous Systems

Navnit Shah, Harpreet Sandhu, Duk Choi, Oskar Kalb, Susanne Page, Nicole Wyttenbach

A structured development approach is presented to guide the development of stable and commercially viable amorphous formulations. The proposed approach should not only enable the delivery of poorly soluble drugs but also help reduce the API needs, reduce in-vivo screening, minimize risks for late stage development and ensure consistent quality. During initial assessment, a guided evaluation of the physicochemical properties of API help to assess the degree of difficulty for the development. A range of tests including the in-silico evaluation, high-throughput screening assays, and miniaturized screening tools provide the road map for selecting the appropriate polymer, drug loading and suitable manufacturing process.



Selection of Polymer
Solubility Parameter

- Intrinsic physicochemical property
- Predictors of miscibility/solubility in solid dispersions
- Provides an easy and fast prediction tool for interaction between drug and polymer
- Matching solubility parameters for miscibility prediction of drug and polymer
  - Two components are assumed to be
    - miscible if $\Delta\delta < 7$ $MPa^{0.5}$
    - immiscible if $\Delta\delta > 10$ $MPa^{0.5}$

Polymer	Solubility Parameter (δ)*			
	Hansen	Hoftyzer/van Krevelan	Hoy	Mean
Drug A	25.5	29.9	–	27.7
HPMC	21.7	26.0	24.6	24.1
PVA	25.6	30.3	29.5	28.5
MC	24.2	28.7	24.7	25.9

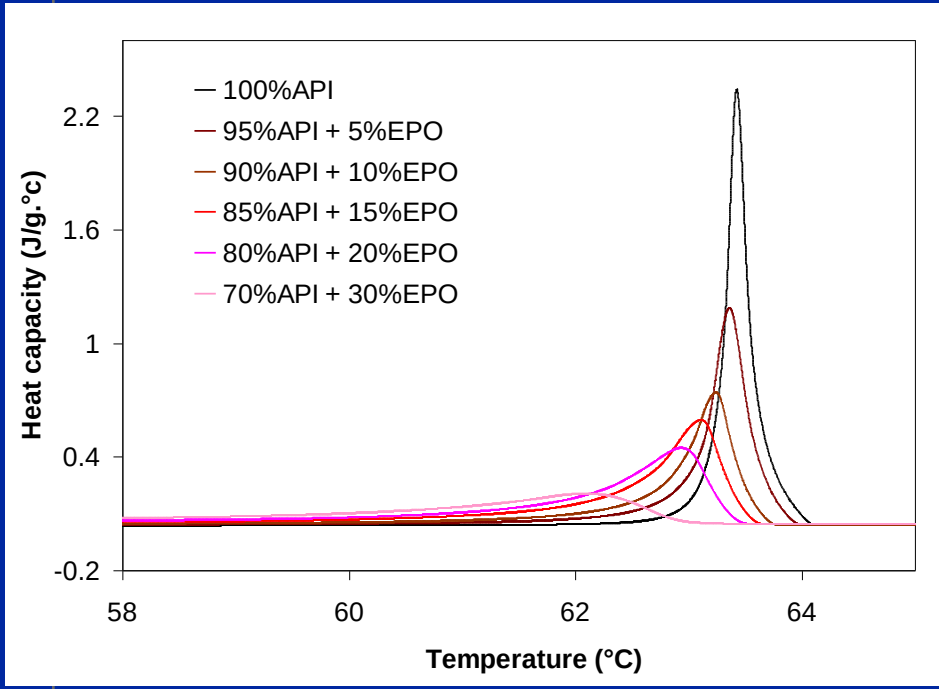
- Hildebrand Parameter
- Hansen Parameter
- Hoftyzer / van Krevelen Parameter
- Hoy Parameter

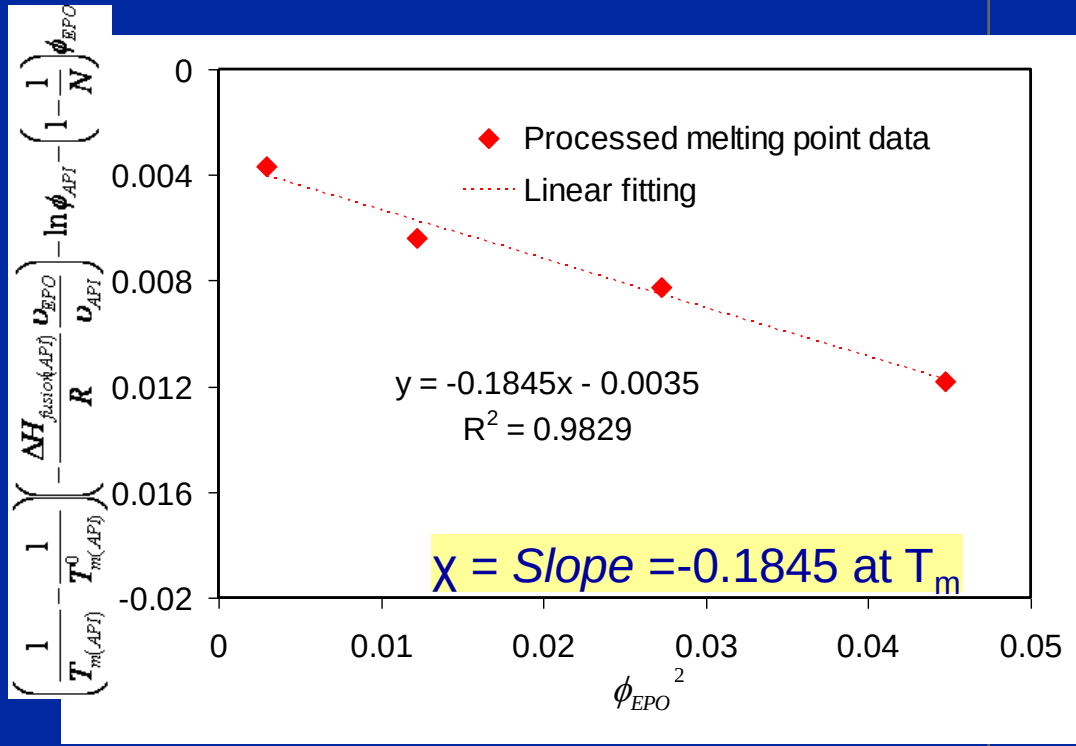
* Calculated using Molecular Modeling Pro

Selection of Polymer and Drug Loading

Melting Point Depression at T_2*

$$\left(\frac{1}{T_{m(API)}}-\frac{1}{T^0_{m(API)}}\right)\left(-\frac{\Delta H_{fusion(API)}}{R}\cdot\frac{\upsilon_{EPO}}{\upsilon_{API}}\right)-\ln\phi_{API}-(1-\frac{1}{N})\phi_{EPO}=\chi\phi_{EPO}^{\ 2}$$





* Zhao et. al. J. Pharm Sci. vol 100 (2011), pg 3196-3207

Selection of Polymer and Drug Loading

One Approach for Predicting Drug Solubility in Polymer*

Determine interaction parameter

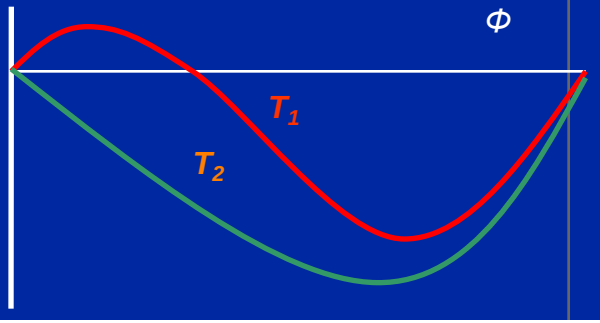
(χ_1 at T_1) and (χ_2 at T_2)

$$\chi = \alpha + \frac{\beta}{T}$$

Flory – Huggins

$$\frac{\Delta G_m}{RT} = \phi \ln \phi + \frac{(1-\phi)}{N} \ln(1-\phi) + \phi(1-\phi)\chi$$

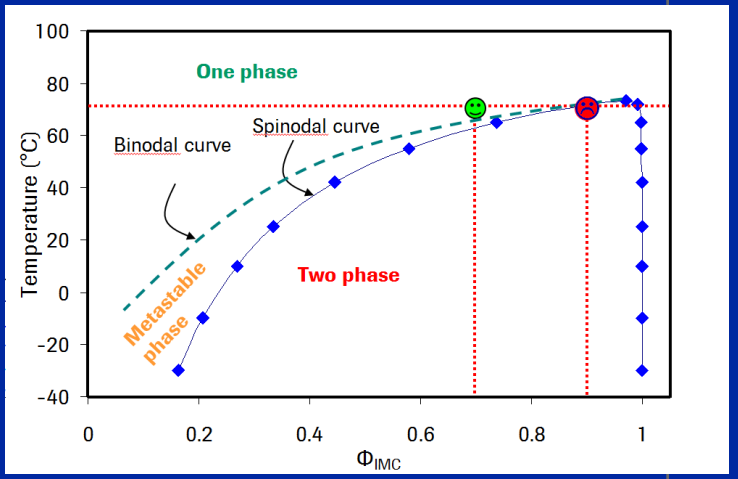
$$\frac{\Delta G_m}{RT}$$



Convert Flory-Huggins phase diagram to *T*-Φ diagram

$$\frac{\partial \Delta G_m}{\partial \phi} = \ln \phi + 1 - \frac{1}{N} - \frac{1}{N} \ln(1-\phi) + (1-2\phi)\chi = 0$$

$$\frac{\partial^2 \Delta G_m}{\partial \phi^2} = \frac{1}{\phi} + \frac{1}{N} \frac{1}{(1-\phi)} - 2\chi = 0$$



Do not exceed drug loading above binodal zone at T g

* Zhao et. al. J. Pharm Sci. vol 100 (2011), pg 3196-3207

Miniaturized Screening Approach

SPADS (Screening of Polymer for Amorphous Drug Stabilization)

- Preparation of solid dispersion
  - Dissolve preset drug and polymer mixtures in volatile organic solvent
  - Cast solid dispersion film by evaporating solvent leaving residue on glass slides, 96 well plate or aluminum pans
- Screening
  1. SPADS dissolution in 96 well plate format
     - Take two time points at 60 min and 180 min in FaSSIF of 37 C
  2. SPADS imaging in glass plate
     - Examine under PLM and/or AFM
  3. SPADS interaction assay in Al pan on 96 well plate format
     - Examine FTIR
- Stability assessment
  - Reanalyze the samples after storage at accelerated conditions

* Wyttenbach et. al. AAPS (2009, 2011)

Amorphous Process Technology

- **Solvent-Based Methods**
  - ✓ Solvent evaporation (Spray Drying)
  - ✓ Freeze-drying
  - ✓ Solvent-emulsion evaporation
  - ✓ Desolvation
  - ✓ Co-precipitation
  - ✓ Supercritical fluid
  - ✓ Solvent-based coating/granulation
  - ✓ Electrospinning
- **Melting Methods**
  - ✓ Co-grinding
  - ✓ Vapor deposition
  - ✓ Melt granulation
  - ✓ Melt extrusion
  - ✓ Ultrasonic

Pros and Cons of Common Technologies

Process	Pros	Cons
Spray Drying	- Rapid removal of solvent and fast solidification - Equipment available from lab to full-scale commercial production - Relatively low temperature processing feasible for highly volatile solvents (reducing thermal stress and degradation of the API) - Continuous processing	- Use of organic solvents (environmental safety) - Difficulty to identify a common volatile solvent for API and polymer - Difficulty to remove solvent completely requiring secondary drying process - High manufacturing cost - Generally results in very fine particles with low bulk density and poor flow properties
Melt Extrusion	- Short exposure to processing temperature (residence time less than a minute) - Non-solvent processing (eliminate the need for solution preparation and removal steps) - Customizable process (screw/die design, temperature profile, and solvent addition) - Effect of humidity and oxygen can be almost completely eliminated - Robust process control and easy scale-up - Continuous process - Broad selection of excipients with different molecular weight and physico-chemical properties	- High energy mainly related to shear forces and temperature (high thermal stress in case of high melting compounds) - High melt viscosity causing torque limitations - High density and low porosity of the thermoplastic extrudates reduces the compaction of the material

Pros and Cons of Common Technologies

Process	Pros	Cons
Co-precipitation (MBP)	- Suitable for compounds that cannot be processed by spray drying (due to low solubility in volatile organic solvents) or melt extrusion (due to high melting point with thermal degradation). - Provides high degree of super-saturation due to use of ionic polymers - High exposure and prolonged plasma profile due to pH-dependent solubility - Amenable for continuous processing	- Currently limited to ionic polymers - Weak bases (and acid drugs) exhibit significant solubility in acidic (and basic) solvents - Adequate solubility in water miscible solvents (for ease of extraction); may require multiple washings to remove solvents - Downstream processing to be considered carefully

Point to Consider in Selecting Processing Technology

Solvent Based Methods

- Solubility of the API and the polymer in solvents
- Ease of removal of solvent (boiling point)
- Residual solvents
- Degree of plasticizing effect by water or residual solvent (s)

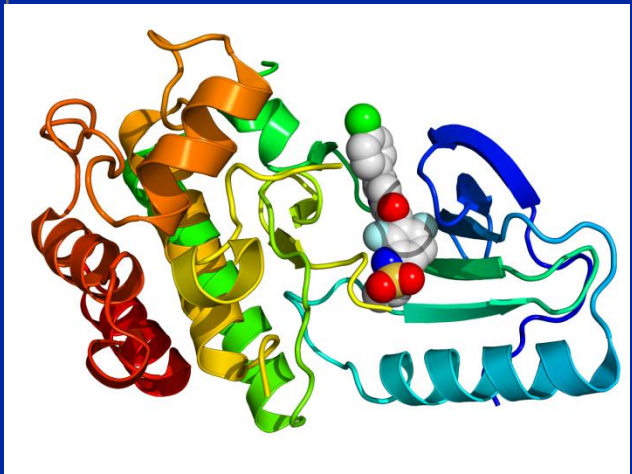
Melt Methods

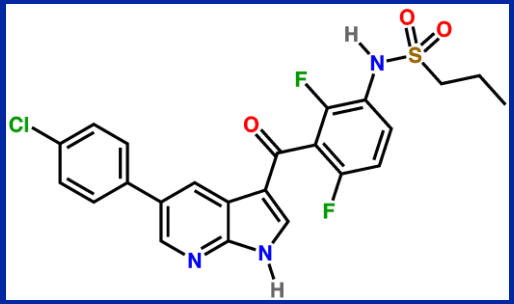
- Glass transition temperature (Tg) and melting point of both API and polymer
- Molecular weight and viscosity of the polymer
- Thermal stability
- Interaction of API and polymer (plasticizing or antiplasticizing)

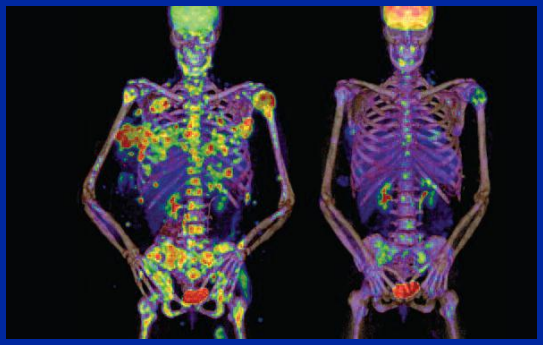
Characterization Techniques

- **Examination of physical state**
  - XRD
  - PLM
  - DVS
  - DSC
  - Calorimeter
  - IR/Raman
  - SAXS
- **Examination of molecular arrangement**
  - Confocal Raman
  - IR
  - mDSC
  - AFM
  - TEM
  - Chemical imaging system
  - Limited by spatial resolution
- **Dissolution method**
  - Need adequate discriminating power for quality and prediction of in vivo performance
  - Dissolution condition (does, volume, surfactant) target to100% saturation based on kinetic solubility at 60 min
- **Stability Prediction**
  - Molecular mobility as predictive tools
  - Empirically
    - ICH condition
    - Excessive stress condition

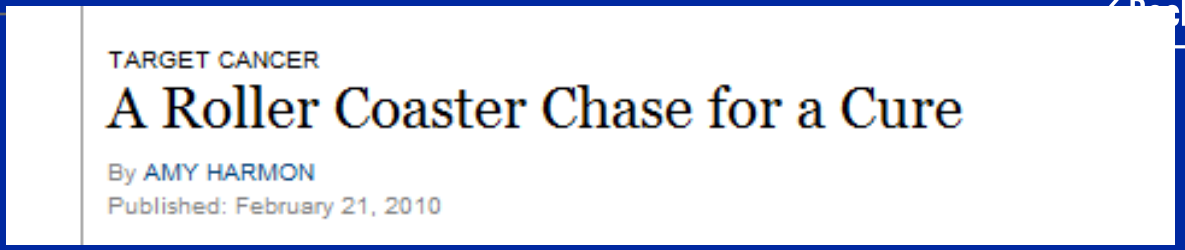
Case Studies (Vemurafenib)







The Need



TARGET CANCER

A Roller Coaster Chase for a Cure

By AMY HARMON

Published: February 21, 2010

- From “A Roller Coaster Chase for a Cure” published on February 21, 2010 in New York Times by Amy Harmon
- *“The woman known in the trial as Patient 18 was one of the three who took 1,600 milligrams — 32 pills a day, she complained mildly, was a lot of pills.”*
- *“The higher doses, Dr. Flaherty and Dr. Chapman realized, were not getting from the digestive tract into their patients’ bloodstreams.” ,,”the doctors instructed patients to take the drug with high-fat foods in hopes that would help it dissolve more readily, but to no avail.”*
- *“In December 2007, the companies halted the trial. They would wait while Roche chemists tried to reformulate the drug.”*

Initial Assessment

Vemurafenib API Properties

- MW: 489.9
- Log P: 3.0
- Weak acid with 7.6(A) 10.9(A)
- Tm: 270 C; Tg: 105 C

Polymer	T_g (or Tm) (°C)	Mol. Wt. (g/mol)	δ $(MPa)^{0.5}$	pH Solubility	Hygroscopicity (Moisture @ 75%RH/RT)	Comments
Cellulose Based						
Hyperomellose 2910	170-180	10,000-50,000	23.8	1-10	~10%	Used in Sporanox™
Hydroxypropylcellulose EF[3]	100-150	80,000	31.5	1-0	12% (@ 84% RH)	Thermo-reverisble gel
Hydroxyethylcellulose LF[3]		95,000	31.0			
Hydroxyethylcellulose HF[3]		115,0000				
Hyperomellose acetate succinate, (HPMC AS) LF[1,4]	113 ± 2	55,000-93,000	40.5	>5.5	7-8%	Can stabilize due to hydrophobicity and possibility of forming colloidal structures in aqueous solutions.
HPMC AS , MF[1,4]	113 ± 2	55,000-93,000	31.2	>6.0	6-7%	
HPMC AS , HF[1,4]	113 ± 2	55,000-93,000	-	>6.5	5-6%	
Cellulose acetate phthalate[1]	160-170 (192)	N/A	27	>6.0	7-8%	
Cellulose acetate butyrate[6,7]	130 (155-165)	30,000	28.7	negligible	N/A	
Cellulose acetate[1]	170-190 (230-300)	30,000-60,000	25.8-26.2	N/A	N/A	
Hyperomellose phthalate[1,5]	133-137 (150)	20,000-200,000	28	>5.0	7-8%	
Ethyl cellulose[1]	129-133	-	-	insoluble	~3%	Controlled release

Polymer Selection

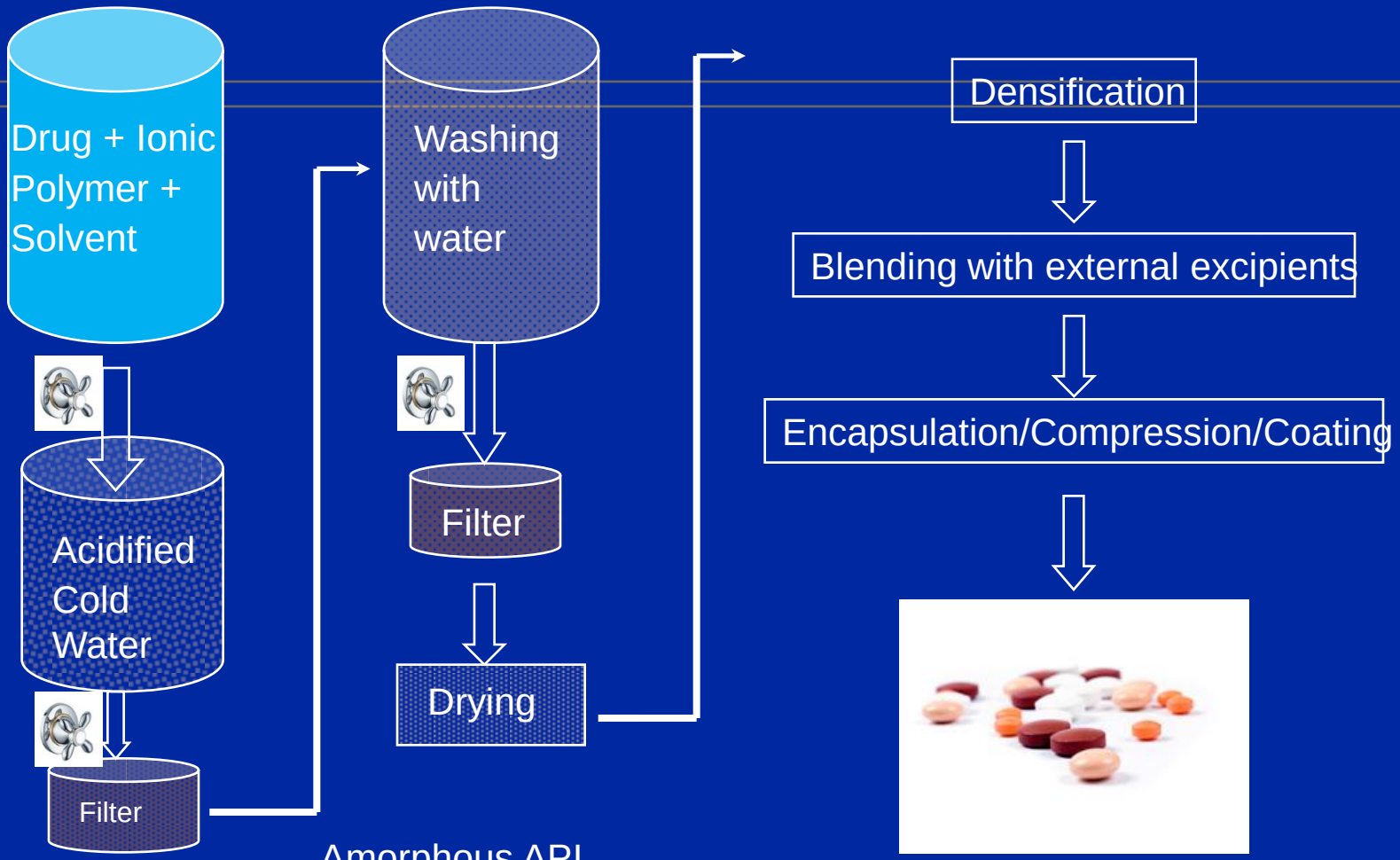
- *In-silico* prediction and modeling suggested HPMC-AS as candidate

Manufacturing Technology

- Evaluation of physicochemical properties suggested MBP as viable process

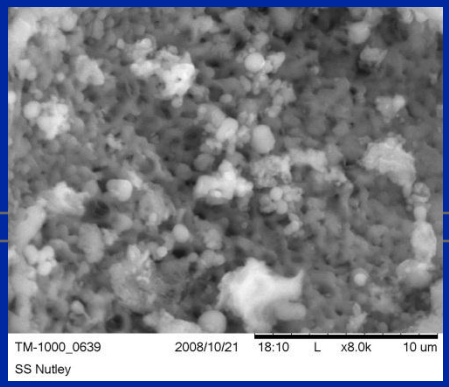
Overall Assessment

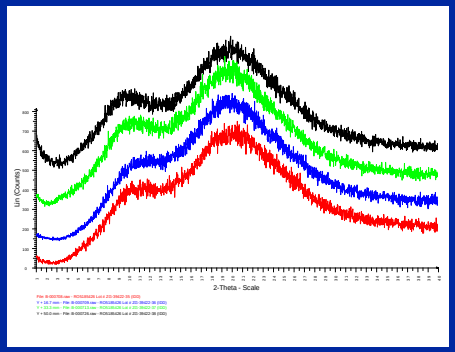
MBP Manufacturing Scheme

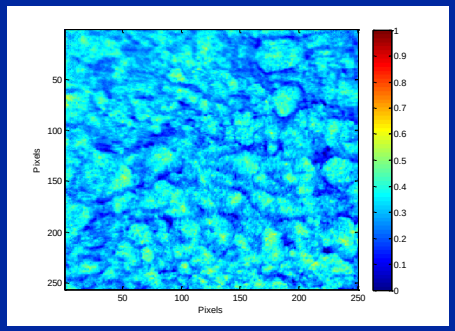


Characterization

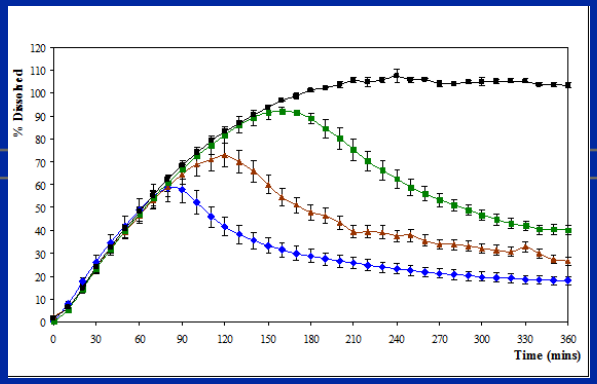
- XRPD indicates MBP is amorphous and stays amorphous
- Spectroscopy (IR, Raman and ssNMR) suggests disruption of drug – drug interaction and existence of drug – polymer interaction.
- TEM, EDAX, AFM and NIR CI indicate molecular distribution of drug molecules within polymer matrix without sign of heterogeneity
- Long term stability (> 36 months) show satisfactory physical stability when stored at ambient storage condition.

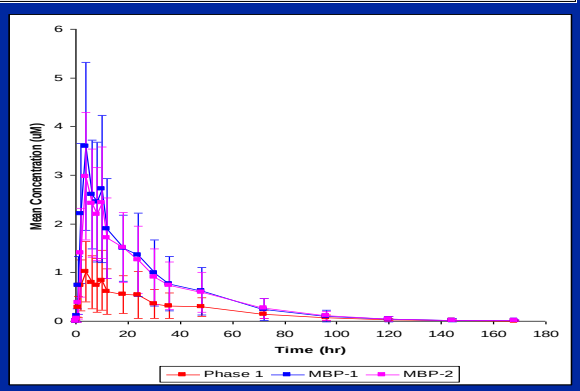






Performance

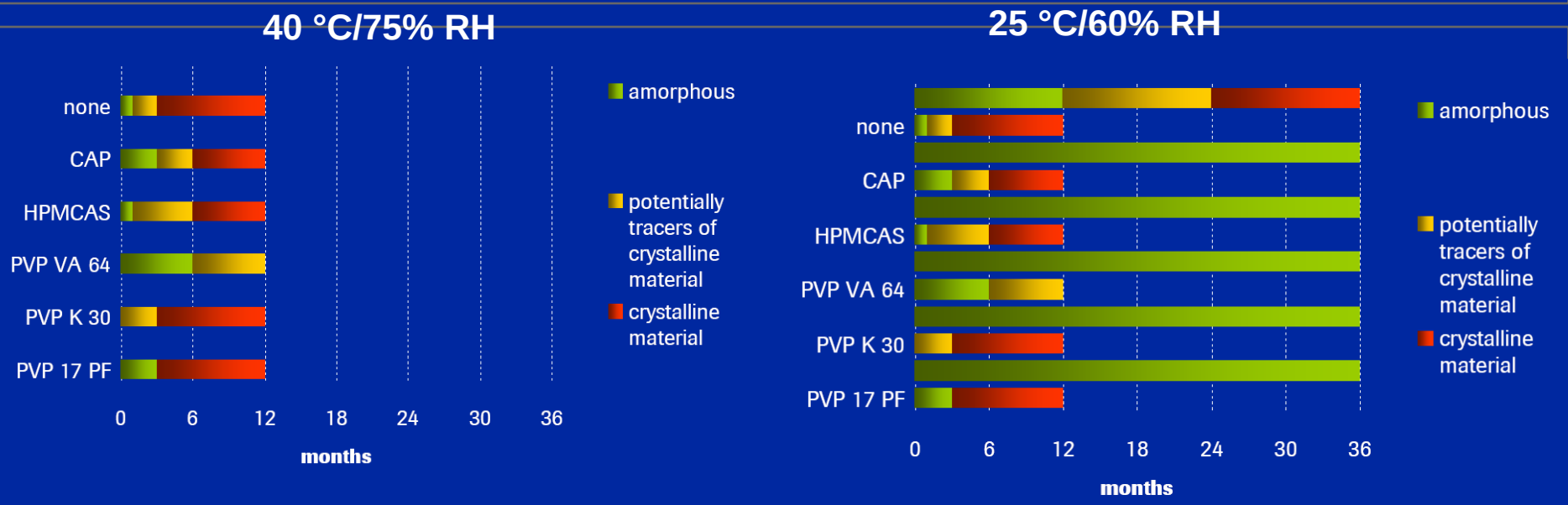




- MBP formulation maintained supersaturation during dissolution for up to 4 hours
- MBP formulation provided satisfactory PK profile
- MBP formulation demonstrated satisfactory physical stability
- MBP formulation successfully scaled up to commercial scale

Stability Prediction

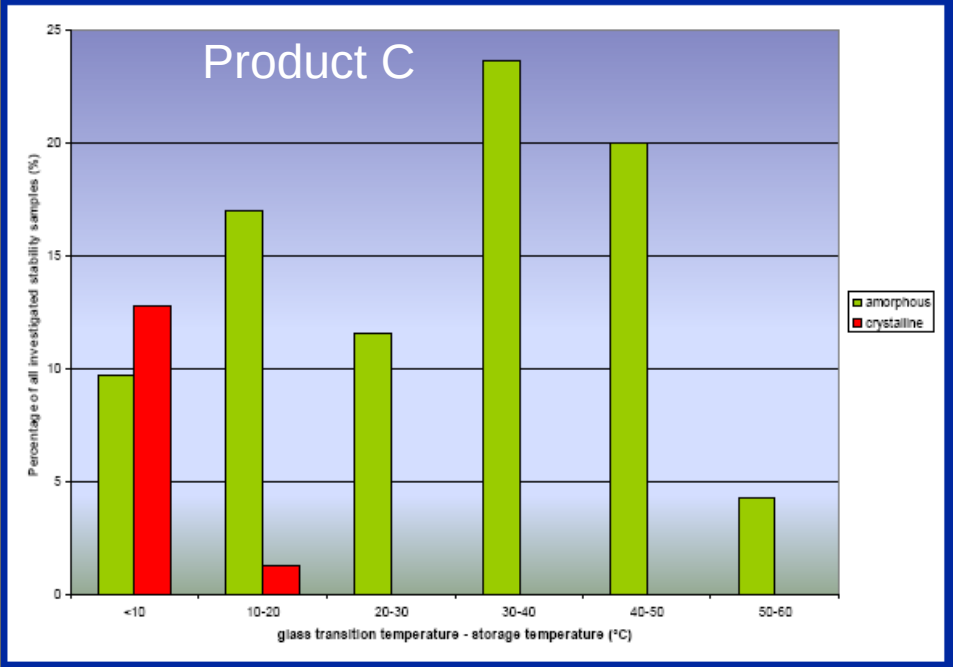
Storage Condition - 40 °C/75% RH vs 25 °C/60% RH Open

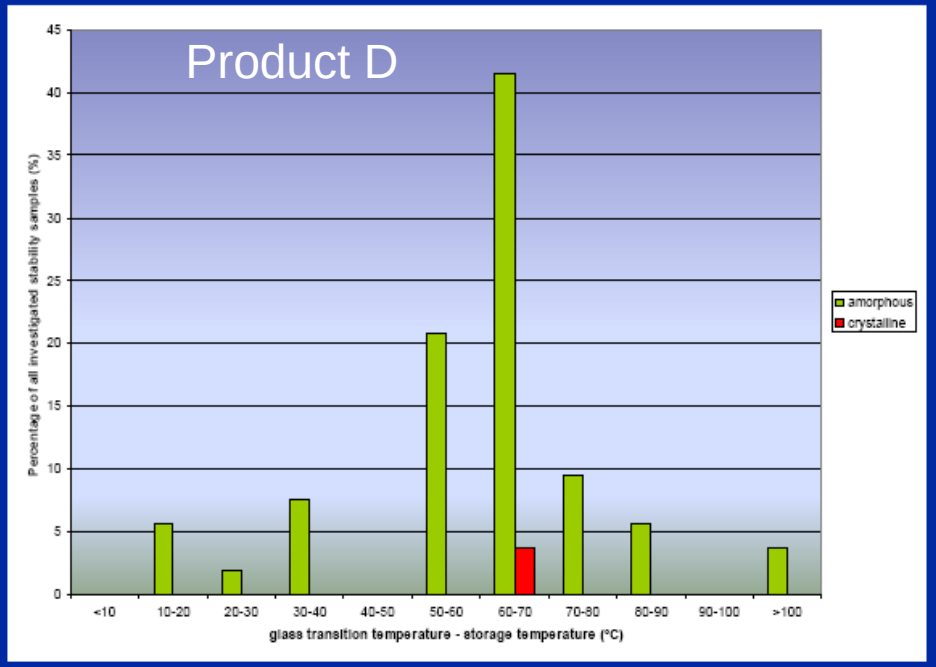


- Amorphous formulations showed instability at an accelerated stability condition (40°C/75% RH, 12 months); but good stability at room temperature (25°C/60% RH, 36 months)
- Accelerated stability condition is not predictive for long term stability

Solid State Stability Prediction

Glass transition temperature vs and storage temperature

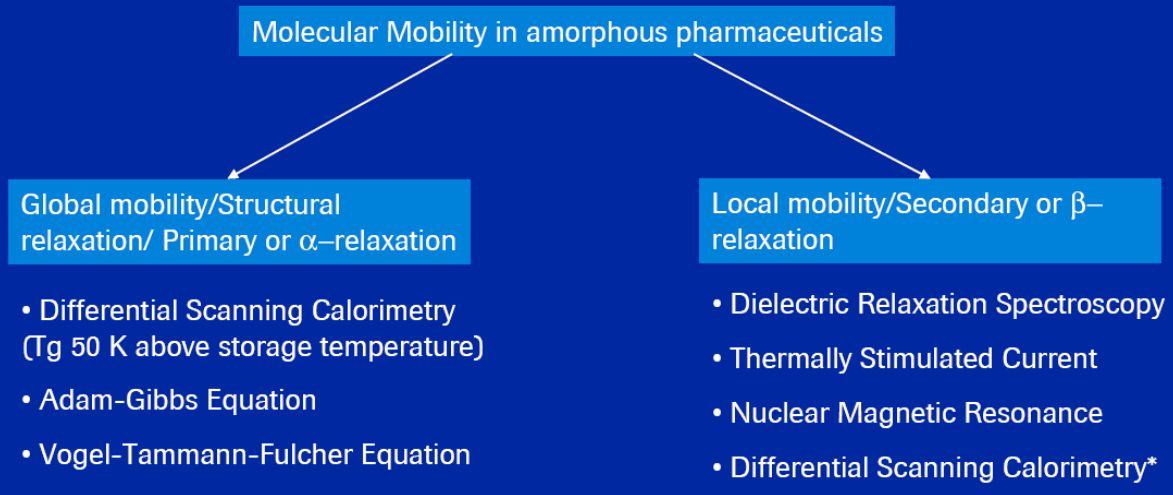




- The rule of thumb that a stable solid dispersion is obtained when the glass transition temperature is 50 K above the storage temperature worked nicely for one compound, but not for the other one.

Summary

- Amorphous formulation, if properly manufactured, does provide superior bioavailability over crystalline form
- Selection of right polymer and process is critical for stable amorphous formulation
- Stability Prediction
  - As of today, there is still a lack of a predictive stability model
  - Molecular mobility estimation as predictive tools



Acknowledgement

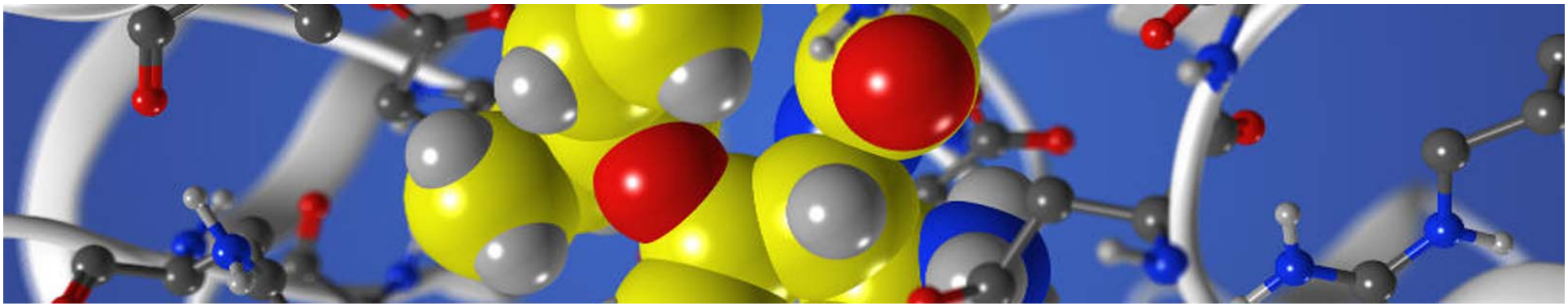
- Dr. Hitesh Chokshi
- Dr. Navnit Shah
- Dr. Harpreet Sandhu
- Dr. Susanne Page
- PF Group Members

Challenges and Opportunities for Oral Delivery of Poorly Soluble Drugs

Dr. Navnit Shah

Distinguished Scientist

Hoffmann-La Roche, Inc.



Outline

- Overview of Industry Today
  - Sources of Oral Bioavailability Limitations
  - Market Trends
- Challenges & Opportunities for Poorly Soluble APIs
  - Impact of low solubility in development
  - Case studies of successful development
- Technologies and Limitations for Handling Poorly Soluble Compounds
  - Emerging Opportunities to Improve Amorphous Development
- Future Direction and Concluding Comments

Sources of Bioavailability Limitations

Technological Intervention to improve solubility and dissolution rate

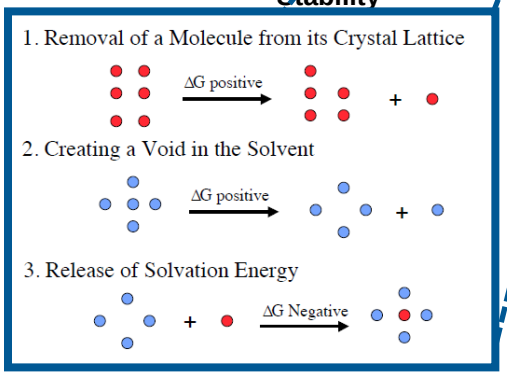
Tablet

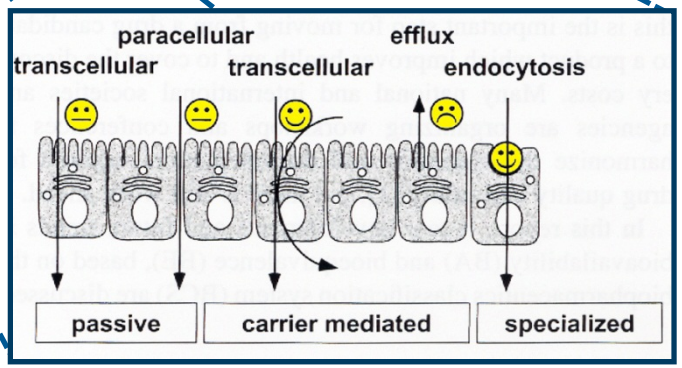
G. I. Tract
-Solubility/ dissolution
-Stability

Intestinal wall
- **Permeability**
- **Stability**

Systemic Circulation
- **First-pass**
- **Metabolism/clearance**

Target tissue





$$\frac{dW}{dt} = \frac{D \cdot A \cdot (C_s - C(t))}{L}$$

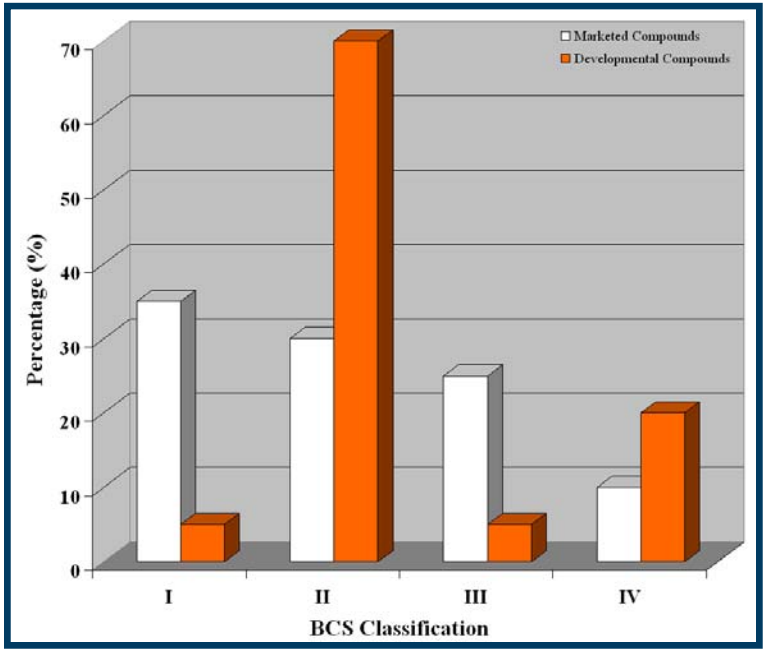
Noyes-Whitney Equation

$$MAD = K_a \cdot C(t) \cdot V_{SI} \cdot t$$

Maximum Absorbable Dose

Solubility Trends & Developmental Pipelines

Compound Trends



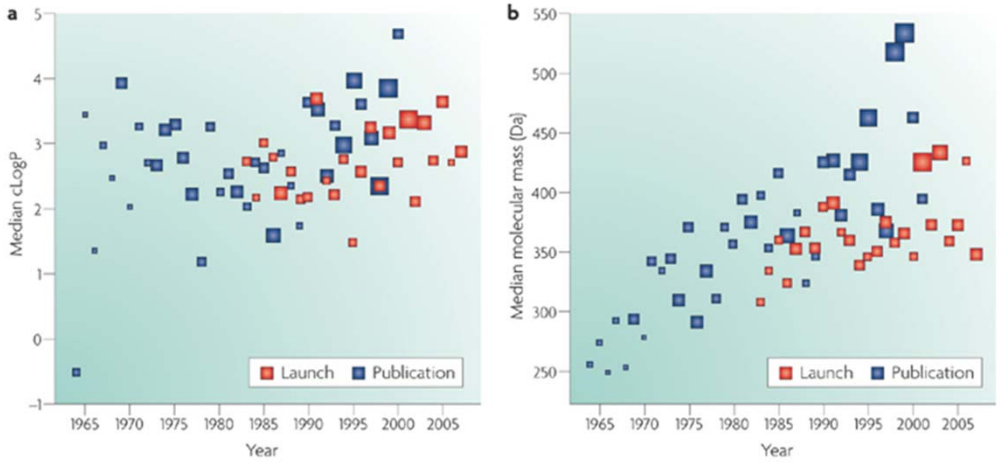
Lipinski's Rule of 5

- Predictor of Limited Oral Bioavailability
  - Molecular Weight > 500
  - Log P > 5
  - H-Bond Donors > 5
  - H-Bond Acceptors > 10

- Examples Meeting The Rule of 5
  - Cyclosporine
  - Itraconazole
  - Ritonavir
  - Lopinavir

592 oral drugs approved worldwide between 1983 and 2007

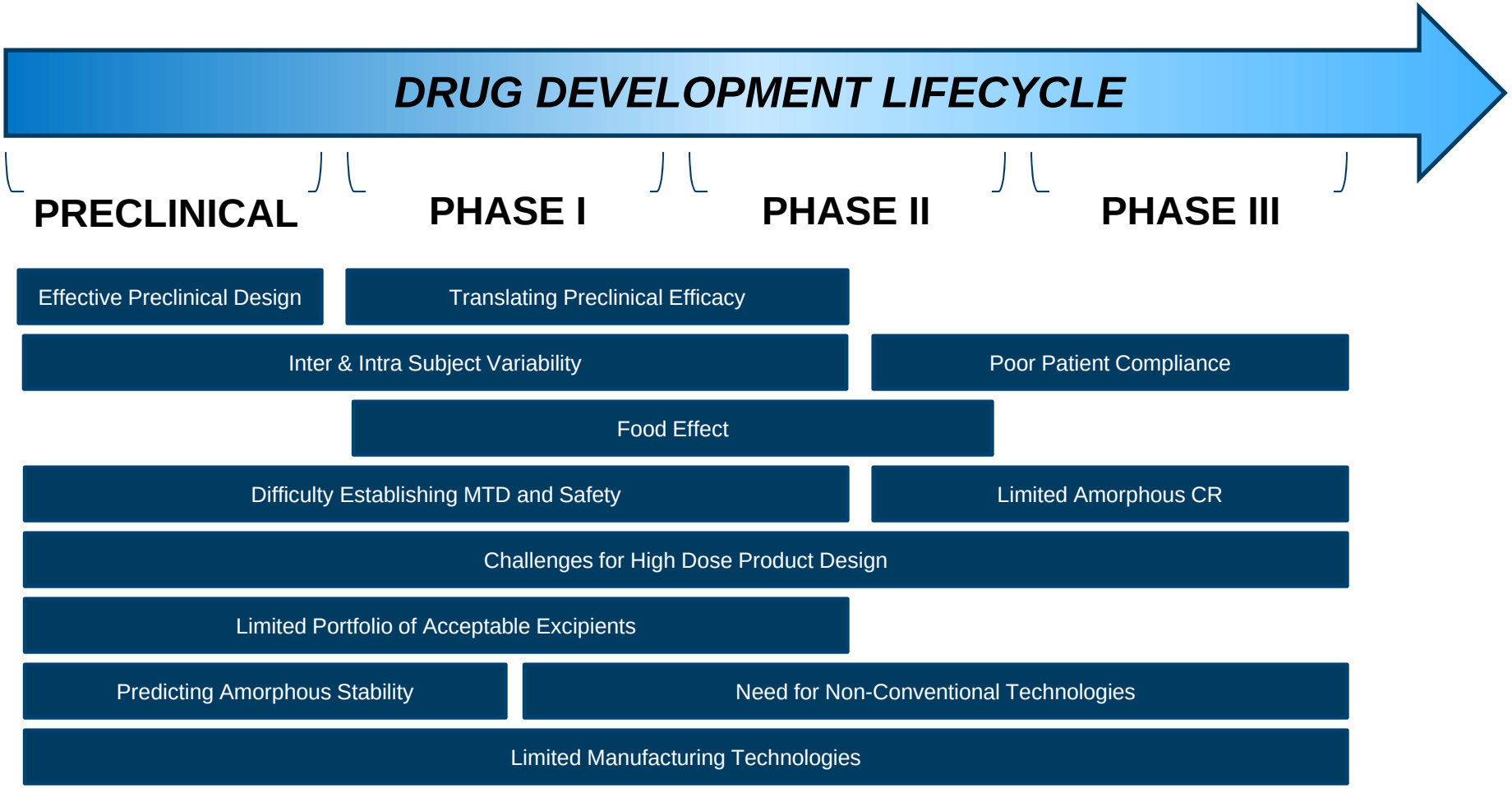
The size of the squares represents the mean Lipinski score



Nature Reviews | Drug Discovery

BLUE SHEET RELEASED FOR PRESENTATION

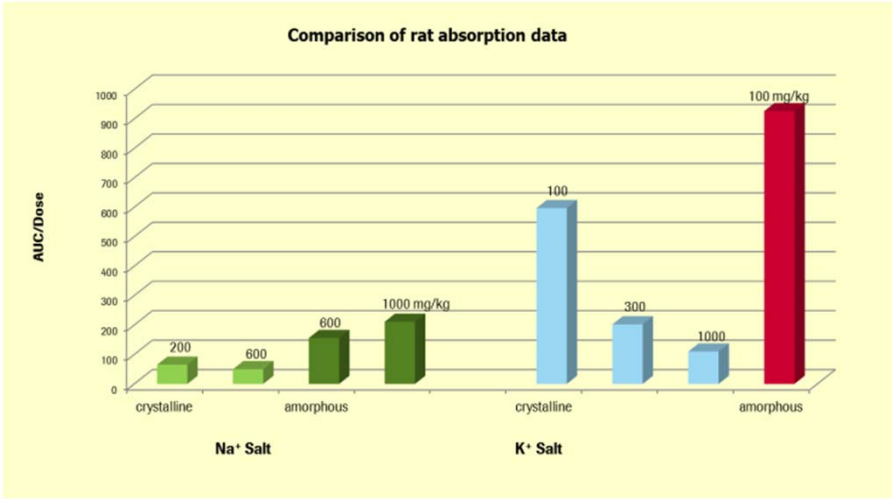
Low Solubility Drug Development Challenges



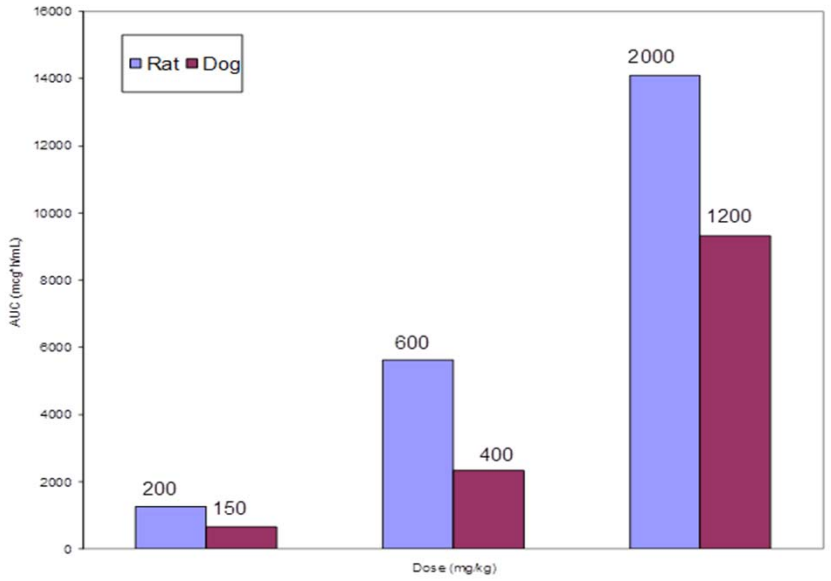
- Low solubility can present major challenges to the successful development of NCEs
- The nature of the challenges change as the program progresses through clinical development

Solubility Driven Challenges in Preclinical Development

- Adequate solubility needed for potency and safety assays and must be considered during design and execution of *in vitro* assays
  - Compounds with poor solubility have the potential to precipitate in assay media/buffer.
  - DMSO stock solutions of poorly soluble compounds have the potential to precipitate during freeze thaw cycles.
  - Assay media greatly impacts solubility



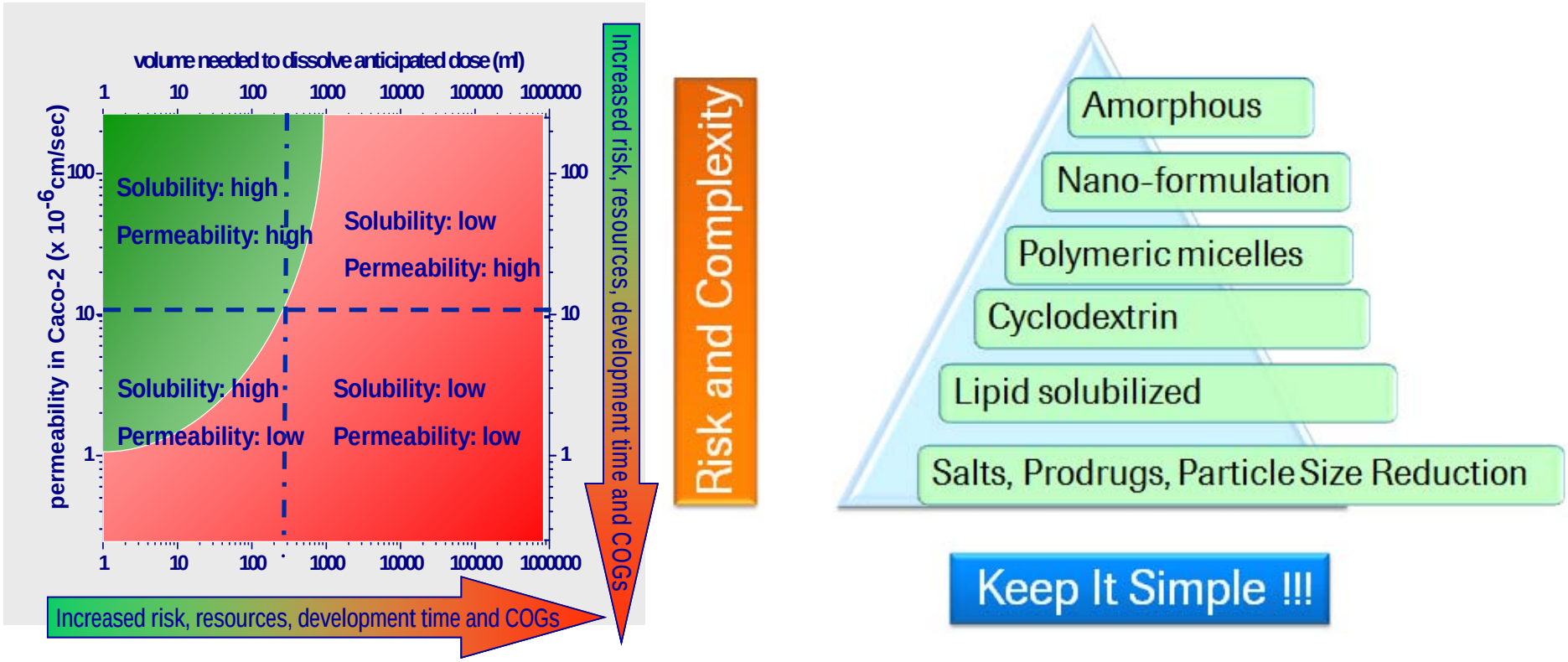
- Adequate solubility is needed for *in vivo* studies at all stages leading to EIH
  - To achieve optimal exposure in PK/PD studies to get proof of concept (POC) in appropriate animal models for project to move to the next stage
  - Multiple fold exposure is required for safety studies in preclinical tox species
  - Salt forms or special formulation are needed to achieve the desired exposure
  - To achieve the exposure in human studies



- Future Challenges
  - Design and development of technologies and compositions to support early development work with limited API supply
  - Optimization of in silico methods to improve computer based design
  - New materials for achieving maximum exposure (multiples over anticipated dose)

Options for Improving Solubility

Compound & Technology Risk Mapping



- Low solubility compounds are inherently more challenging to develop, raising the risk of failure
- Many technologies can address low solubility but also present trade-offs

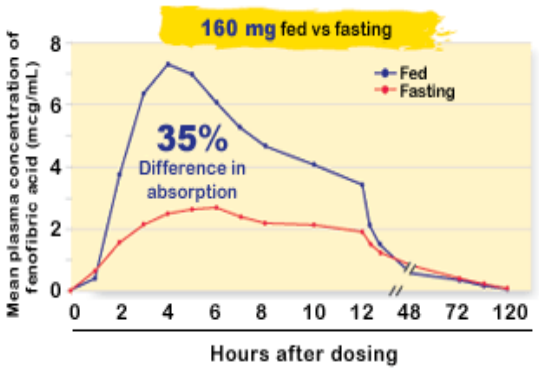
Current Success Stories

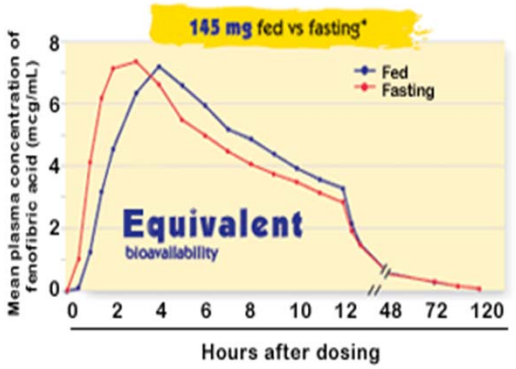
Tricor® - Formulation Intervention to Improve Delivery

200 mg Capsule
- Milled fenofibrate

160 mg Tablet
- Micronized fenofibrate

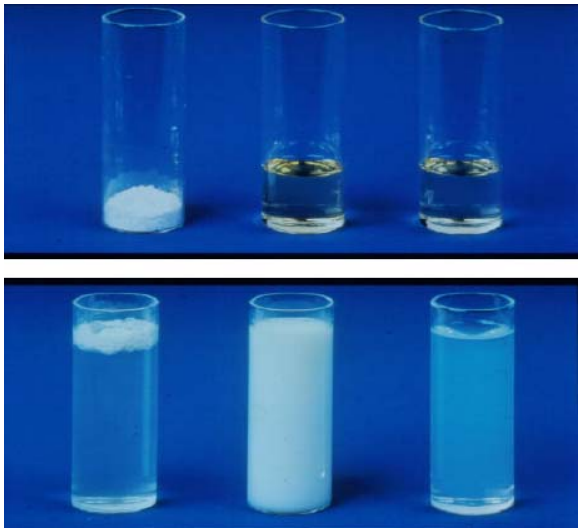
145 mg Tablet
- NanoCrystal fenofibrate



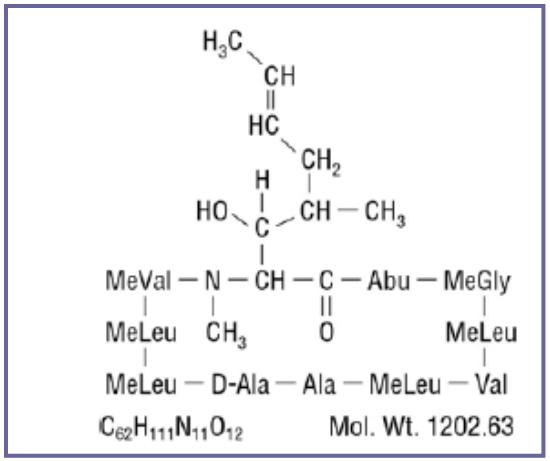


Current Success Stories

Neoral® - Formulation Intervention to Improve Delivery and Extend Market Protection



API | Sandimmune™ | Neoral™



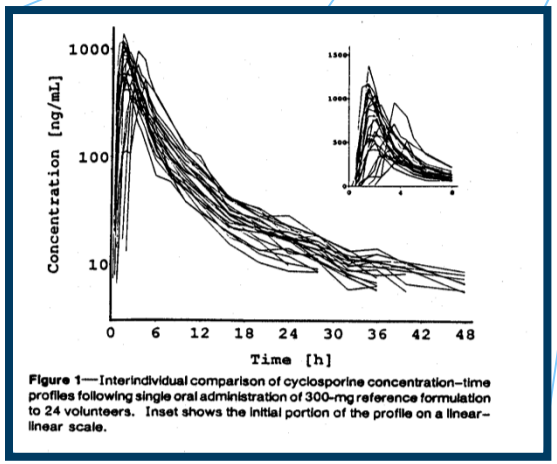


Figure 1—Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 300-mg reference formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

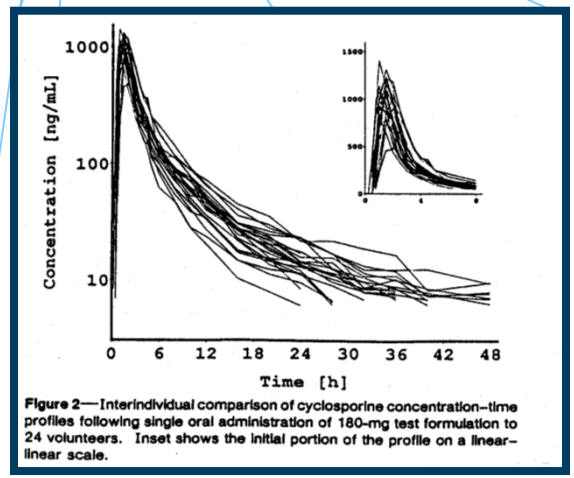
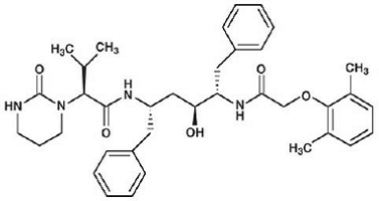
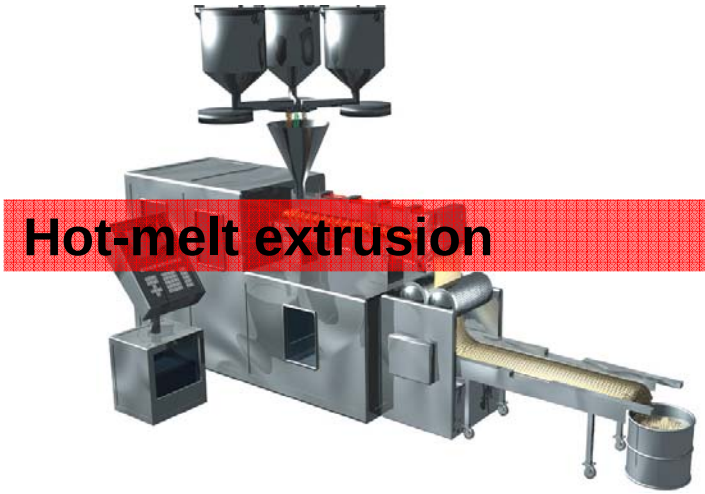


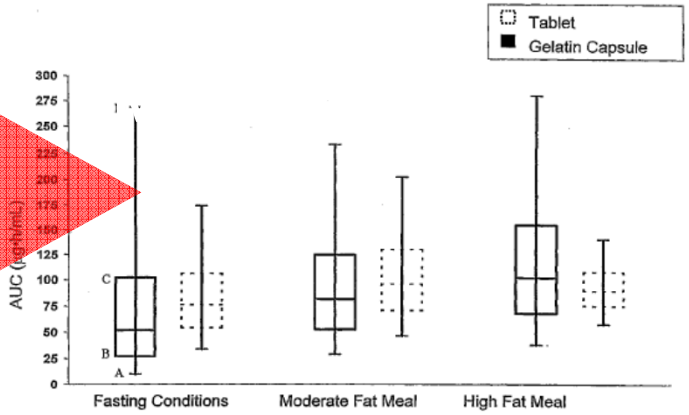
Figure 2—Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 180-mg test formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

Current Success Stories

Kaletra® - Amorphous Dispersion for Improve Delivery



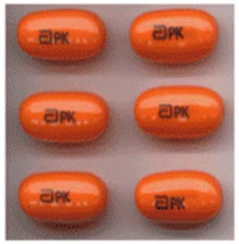




Rosenberg et al. Patent # WO 2006/091529 A2

Kaletra Soft Gelatin Capsule

- Dose per unit:
  - 133 mg lopinavir/33 mg ritonavir
- Dose administration:
  - t.i.d. with food
- Refrigerated storage required

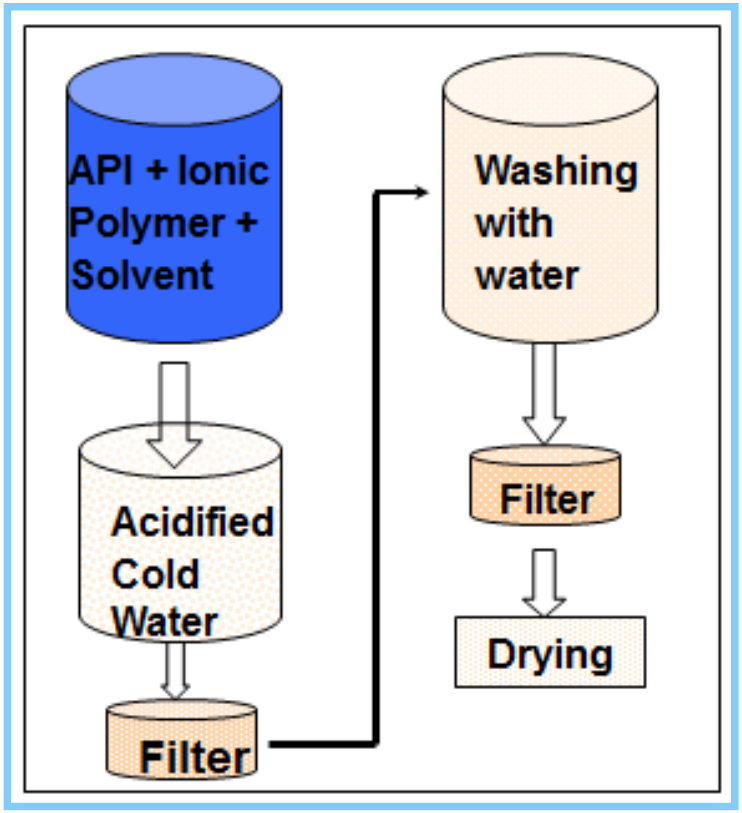


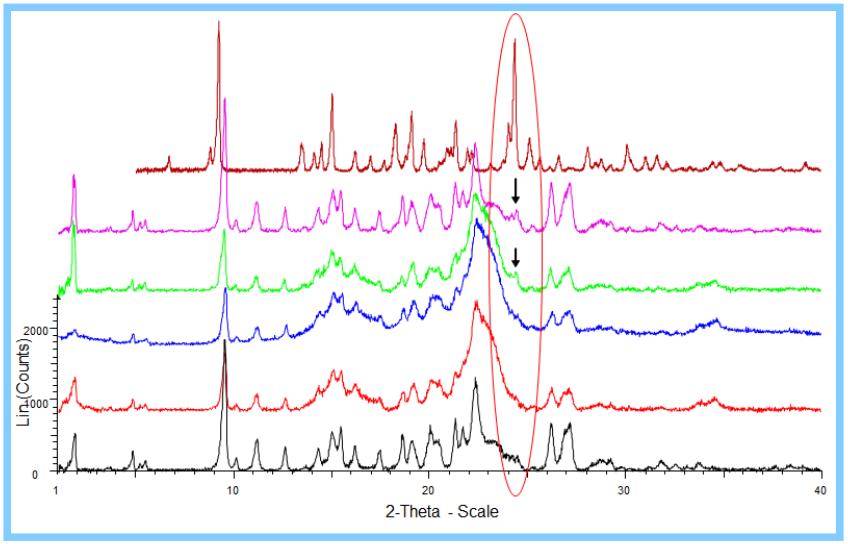
Kaletra Tablet

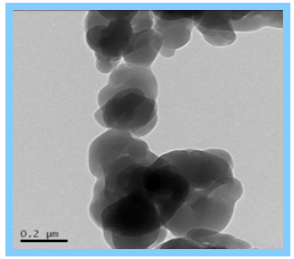
- Dose per unit:
  - 200 mg lopinavir/50 mg ritonavir
- Dose administration:
  - b.i.d. independent of food
- Store at ambient conditions

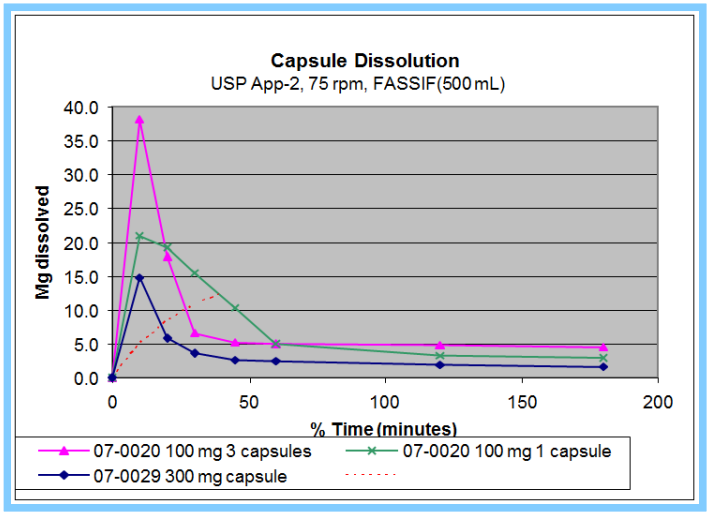
Current Success Stories

Zelboraf® - Molecule to Medicine with Novel Technology







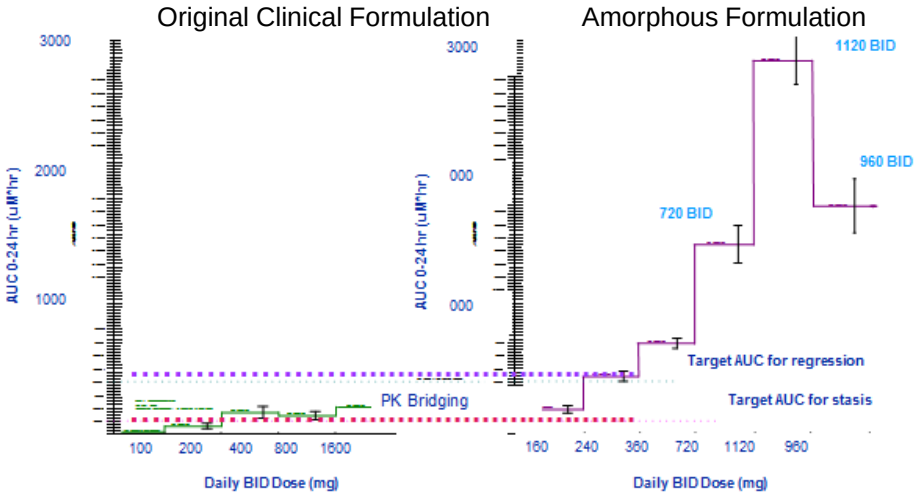


- **Poor Solubility >>>>> Poor Bioavailability**
- Polymorphic Transformation (metastable Form I to stable Form II) **>>>>** Clinical Supply Stock-out Situation
- High Dose **>>>>** Patient Dosing Convenience

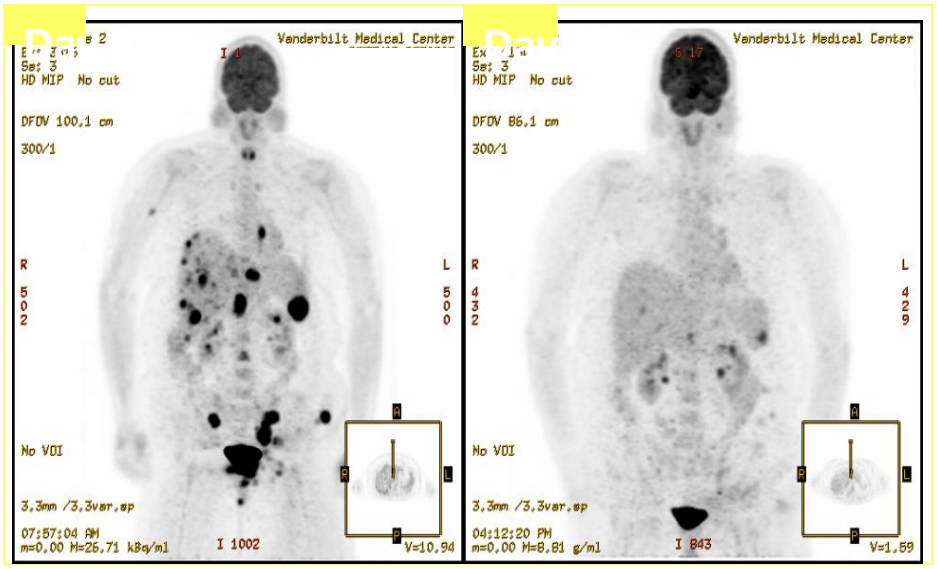
Current Success Stories

Zelboraf® - Making a Difference in Therapy

Bioavailability Comparison



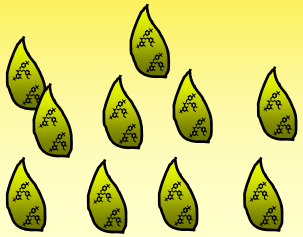
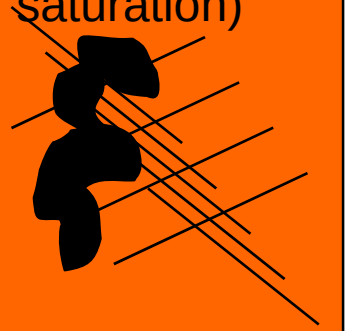
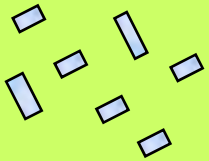
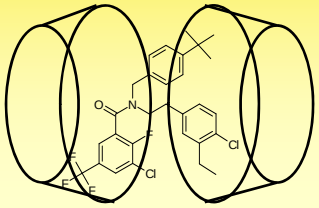
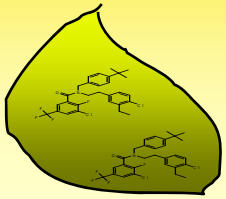
Treatment Results in Tumor Regression



- Development of an amorphous formulation enabled a molecule which could otherwise not be delivered → Life saving benefit to patients in need
- Successful implementation of new technology led to commercial product

Oral Formulations Approaches for Poorly Water Soluble Compounds (BCS 2/4 compounds)

Conventional → No-Conventional: Risk and complexity

Salts Pro-drug 	SEDDS/SMEDDS 	Nanoparticles Polymeric micelles Dendrimers	Amorphous (high dissolution rate and super saturation) 
Particle size reduction 	Complexes Co-crystals 	Crystalline Solid Dispersion 	

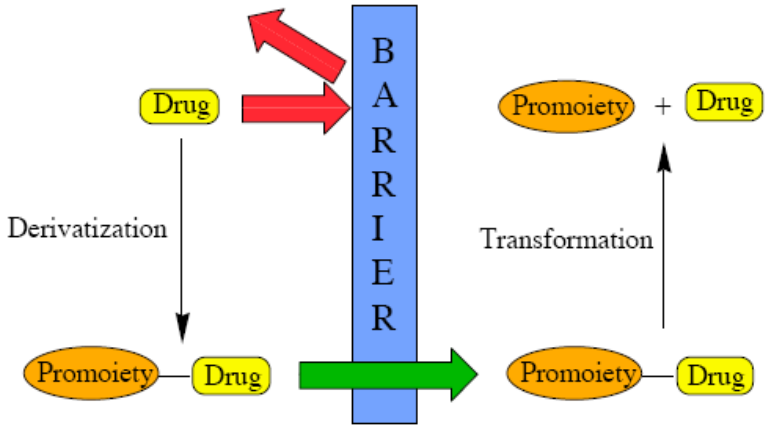
Need for amorphous formulation has significantly increased

Technologies to Improve Solubility

PRODRUGS

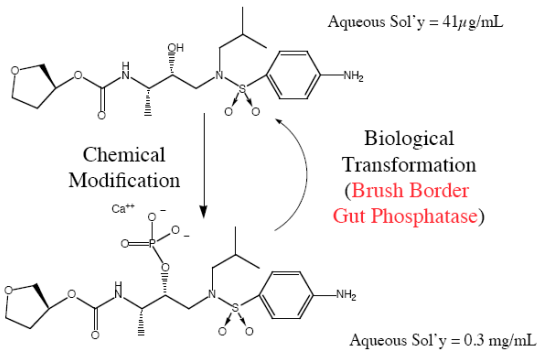
Chemical approach using reversible derivatives that is pharmacologically inert

Successfully applied to a number of commercially marketed products



Prodrugs represents a Chemical/Biochemical approach to the Optimization of Drug Delivery

VX-175/GW 908
(A Phosphate Prodrug of Amprenavir)



7 fold increase in solubility

Advantages

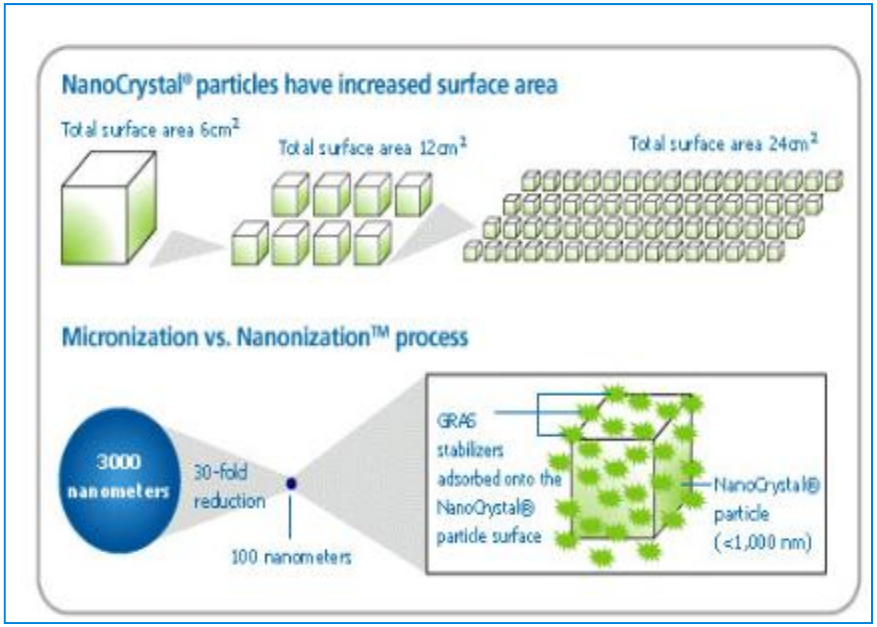
- NCE, Patentable
- Enhanced biopharmaceutical performance

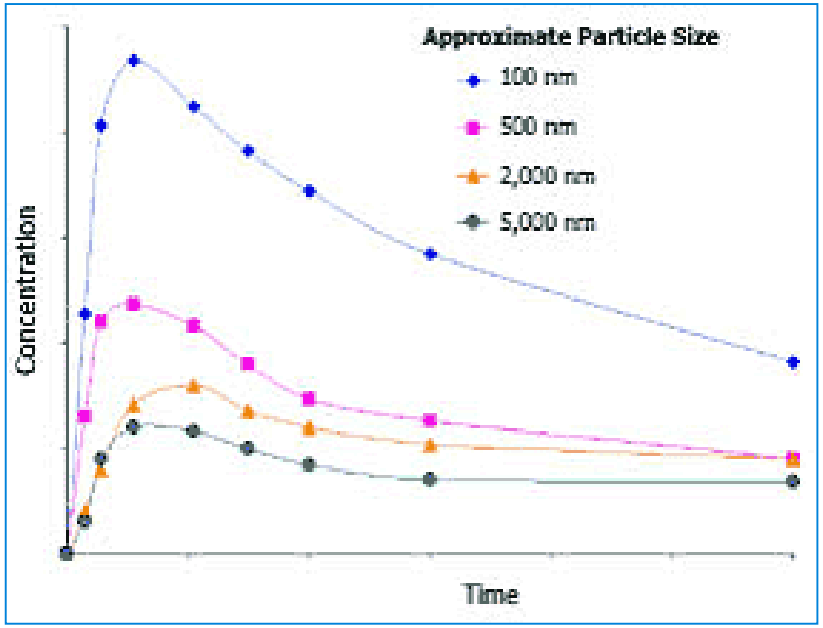
Opportunities

- Reducing development cost
- Site targeted prodrug design
- Expanding chemistries

Technologies to Improve Solubility

PARTICLE SIZE REDUCTION





Advantages

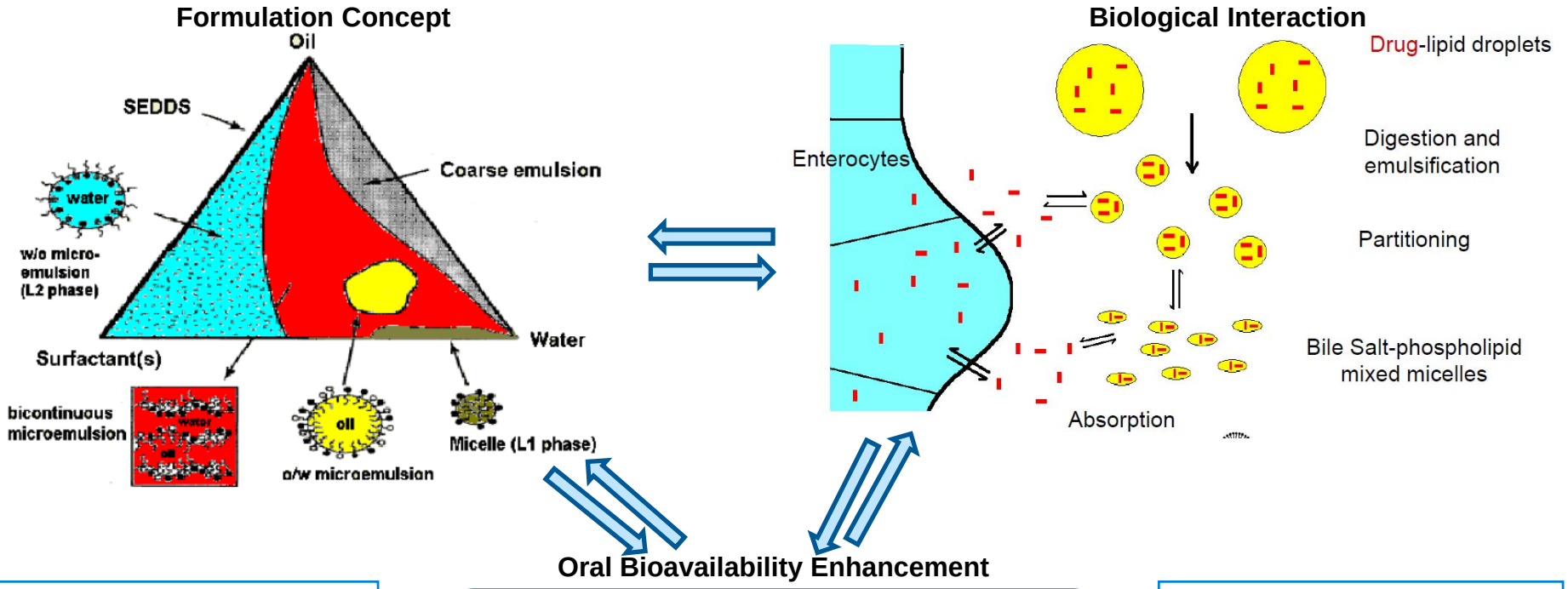
- **Improve exposure –** reduce dose
- **Faster onset of action –** improve efficacy
- **Minimize variability –** improve efficacy and decrease toxicity
- **Reduce/eliminate food effect –** improve convenience and compliance

Opportunities

- **Need for more advanced MFG technologies –** Imprinting, Templating, etc…
- **Expansion of nanotechnology into drug-device hybrid products –** MEMs technology
- **Lower cost of goods for manufacturing –** Current technologies are expensive, proprietary and time consuming

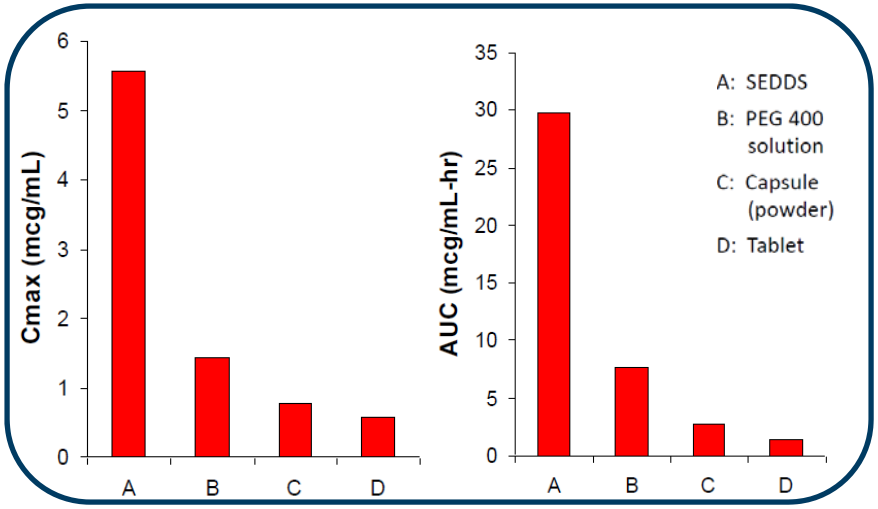
Technologies to Improve Solubility

LIPID FORMULATIONS



Advantages

- Reduced food effect
- Permeability enhancement
- Liquid nature provides for ease of scale-up



Opportunities

- Expansion of materials to support formulation development
- New technologies to improve manufacturability

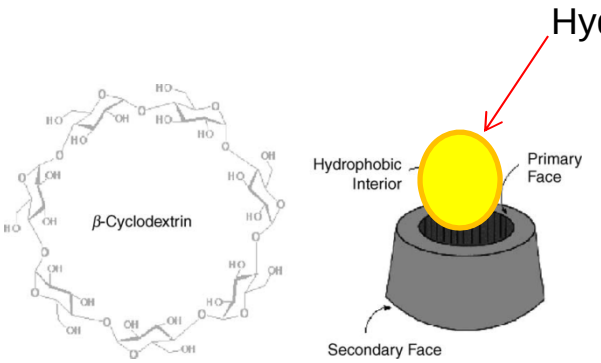
BLUE SHEET RELEASED FOR PRESENTATION

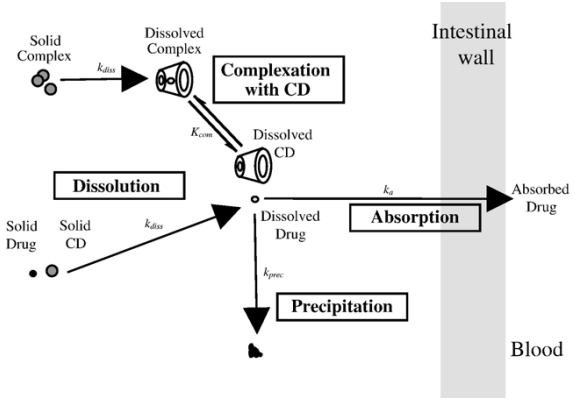
Technologies to Improve Solubility
CYCLODEXTRINS

Cyclodextrins

Oligosaccharides (6 or

more glucopyranose units)



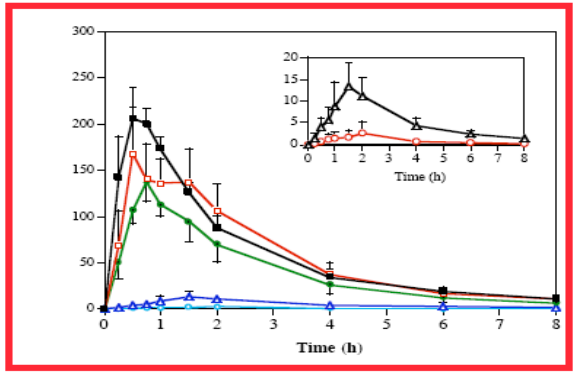


Forms inclusion complexes with drugs

- Steric
- Thermodynamic interactions

Advantages

- Enhanced drug delivery through biological membranes
- Increased stability



Plasma Concentration (±S.E.) Versus Time Profile of Cinnarizine After a 25 mg Dose to Male Beagle Dogs (n=4), SBE4-β-CD, pH 4.5 Solution (❑); HP-β-CD, pH 4.5 Solution (■)); SBE4-β-CD, Capsule (●); pH 4.5 Aqueous Suspension (Δ); Plain Capsule - No SBE4-β-CD (O)

Opportunities

- Improve stability of cyclodextrin in the intestinal environment

From: Javinen et al. *J. Pharm. Sci*., 84, 295-299 (1995)
Del Valle et al., *Process Biochem*,. (2003) Carrier et al. *J. Control. Release.* 123, 78-99. (2007)

Technologies to Improve Solubility

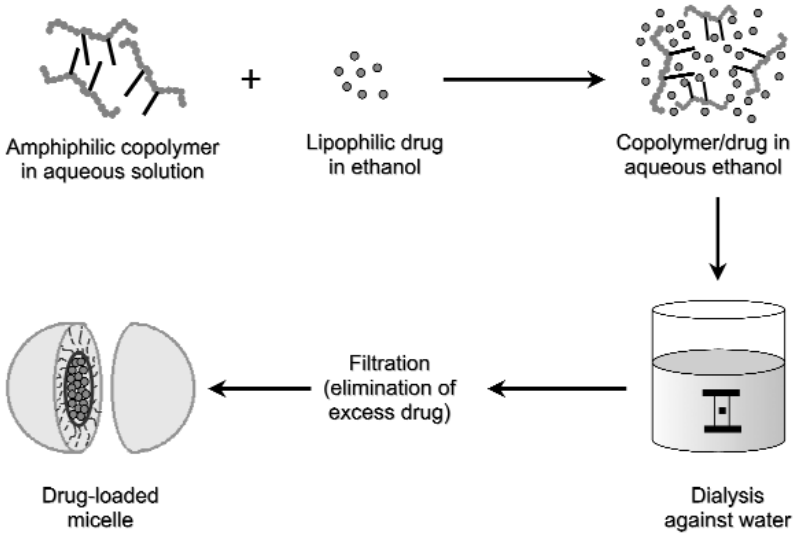
POLYMERIC MICELLES

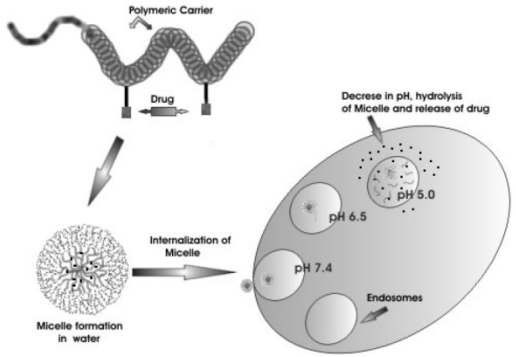
Self-assembling amphiphilic polymer

(i.g. poly(ethylene oxide)-*b*-poly(L-amino acid)

(PEO-*b*-PLAA)) forms micelles (< 100 nm)

- Provides sites for attachment of drugs
- Better kinetic and thermodynamic stability than surfactant based micelles





Advantages

- Stays unrecognized during blood circulations
- Extended circulation time
- Lower toxicity

Opportunities

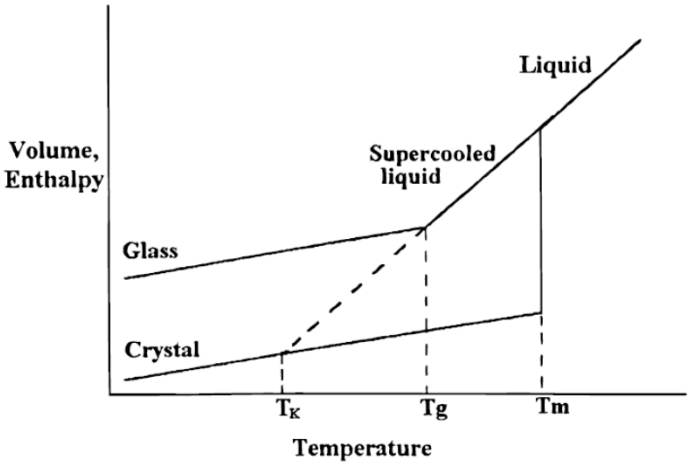
- Loading efficiency

Lavasanifar et al. *Adv. Drug Deliv. Rev.* 54, 169-190 (2002)
Francis, et al. *Pure Appl. Chem*. 76, 1321-1335, (2004).

Technologies to Improve Solubility

AMORPHOUS TECHNOLOGIES

THERMODYNAMIC PROPERTIES



SOLUBILITY ADVANTAGE

ACHIEVING SUPERSATURATION

PARTICLE SIZE REDUCTION

$S = S_\infty e^{\left(\frac{2\gamma M}{rpRT}\right)}$

THERMODYNAMIC CONTROL

$\Delta G = \Delta H - T\Delta S$

STABILIZING SUPERSATURATION

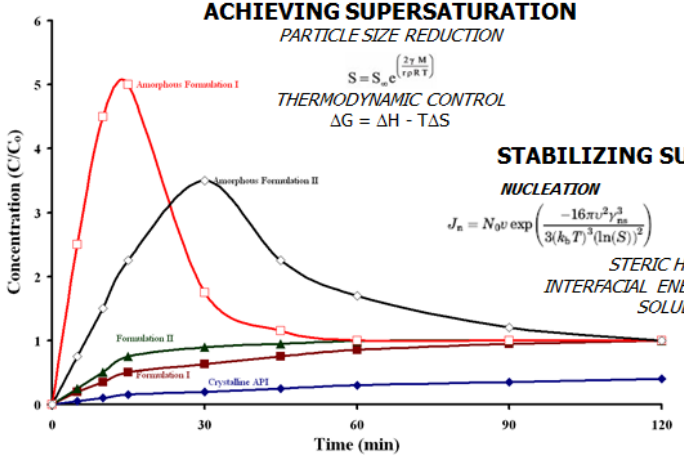
NUCLEATION

$J_n = N_0 \upsilon \exp\left(\frac{-16\pi\upsilon^2\gamma_{ns}^3}{3(k_bT)^3(\ln(S))^2}\right)$

GROWTH

$\frac{dr}{dt} = \frac{D\upsilon N_A}{r + D/k_+}(C - C_{eq})$

STERIC HINDERANCE
INTERFACIAL ENERGY MODIFICATION
SOLUBILIZERS

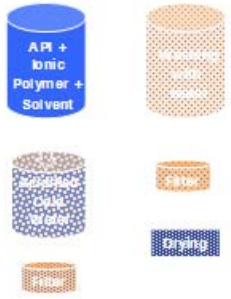


Advantages

- Supports solid dosage form
- Continuous manufacturing
- Potential for greater exposure than other technologies

AMORPHOUS MANUFACTURING

Spray Drying (SDD)
- Solvent evaporation
- Low boiling solvent



Microprecipitation (MBP)
- Solvent/Antisolvent
- Enables high BP solvent

Hot Melt Extrusion (HME)
- Temp. and shear
- Non-solvent

Fluid-bed layering (FBL)
- Drug/polymer layering
- Solvent evaporation
- Low boiling solvent

Opportunities

- Develop predictive tools for dispersions
- New materials to improve exposure and drug loading
- New technologies to improve manufacturing

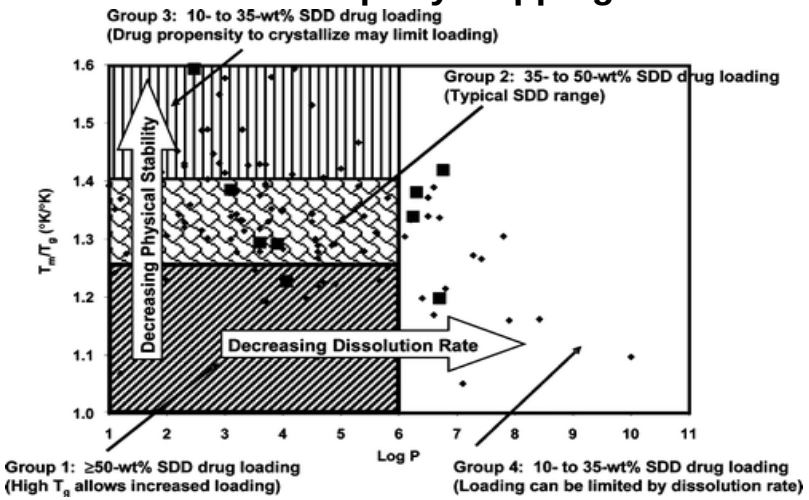
Examples of Commercial Products Using Amorphous API or ASD

Product	Form	Mol.Wt	Tm	Tg	Tm/Tg (C/C)	Tm/Tg (K/K)	Log P	Marketed Name
Zafiralukast	Amo. API	575.7	139	98	1.4	1.1	4.8	Accolate (GSK)
Rosuvastatin Ca	Amo. API	481.5	135	102	1.3	1.1	1.5	Crestor (AZ)
Quniapril HCl	Amo. API	474.9	125	91	1.4	1.1	0.9	Accupril (Pfizer)
Nelfinavir Mes.	Amo. API	663.9	133	105	1.3	1.1	4.1	Viracept (Pfizer)
Itraconazole	ASD	705.6	166	59	2.8	1.3	5.6	Sporanox (Jansen)
Ritonavir	ASD	720.3	123	87	1.4	1.1	4.9	Norvir (Abbott)
Lopinavir	ASD	628.8	125	101	1.2	1.1	~4.3	Kaletra* (Abbott)
Telaprevir	ASD	679.9	246	105	2.3	1.4	3.5	Incivek (Vertex)
Vemurafenib	ASD	489.9	270	109	2.5	1.4	3.8	Zelboraf (Roche)

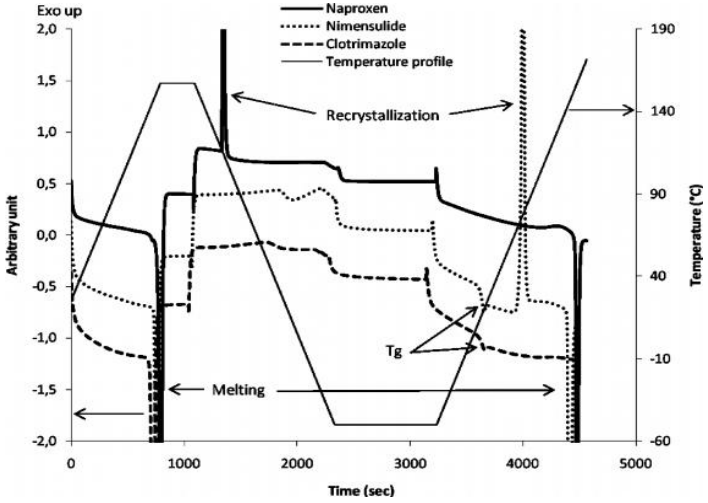
- Pure amorphous API poses much higher risk compared to ASD
- Development of stabilized ASD is preferred
- Successful commercialization of ASDs has been achieved with multiple technologies

Challenges for Predicting Suitability & Stability of Amorphous Dispersions

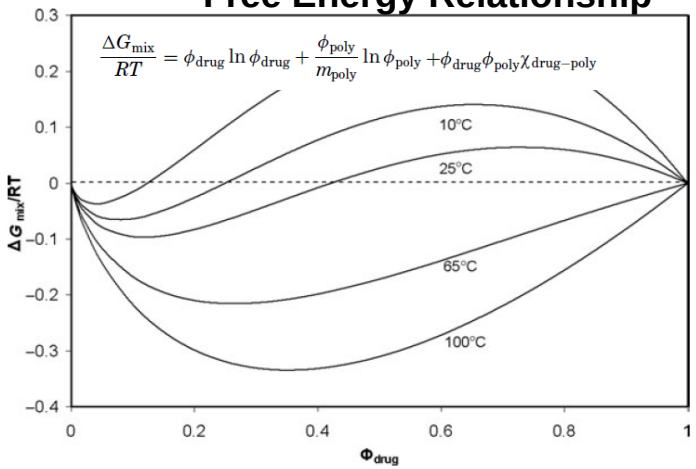
API Property Mapping



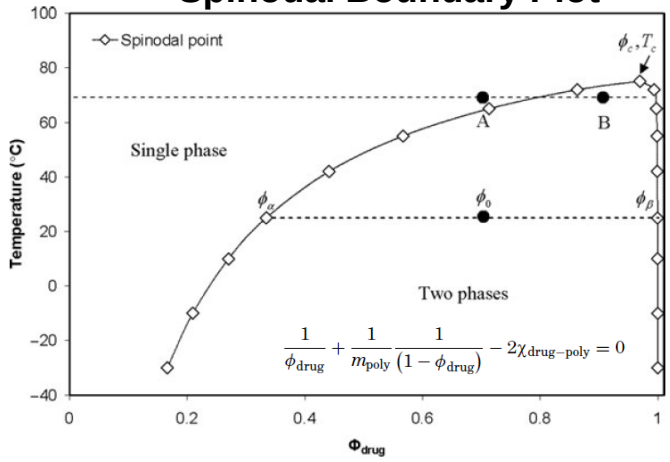
Thermal Characterization



Free Energy Relationship



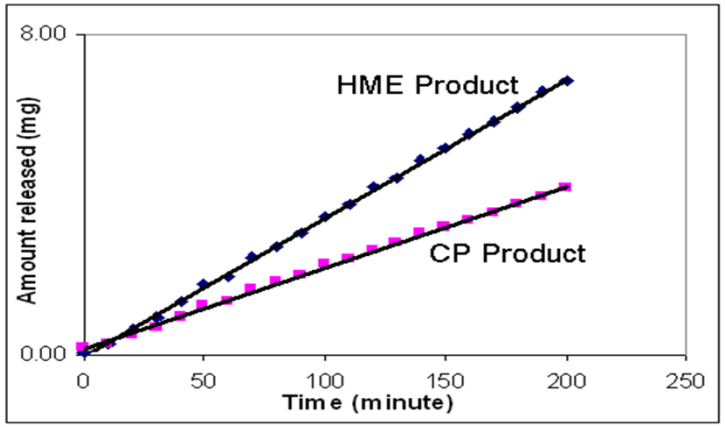
Spinodal Boundary Plot

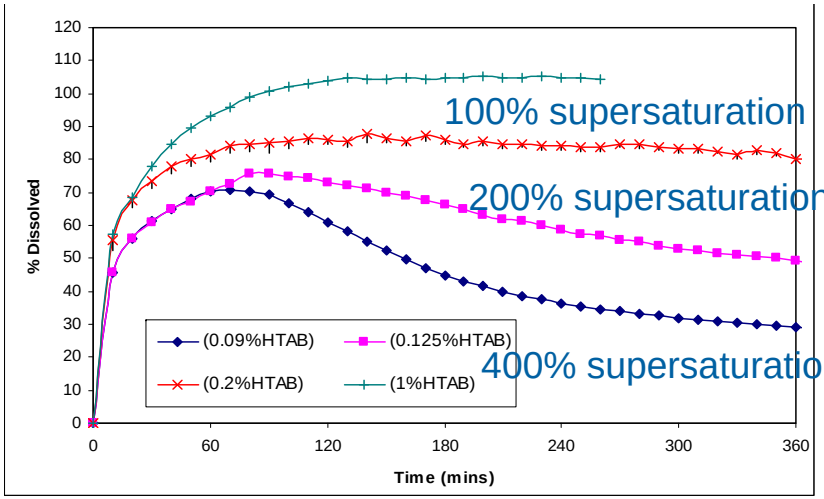


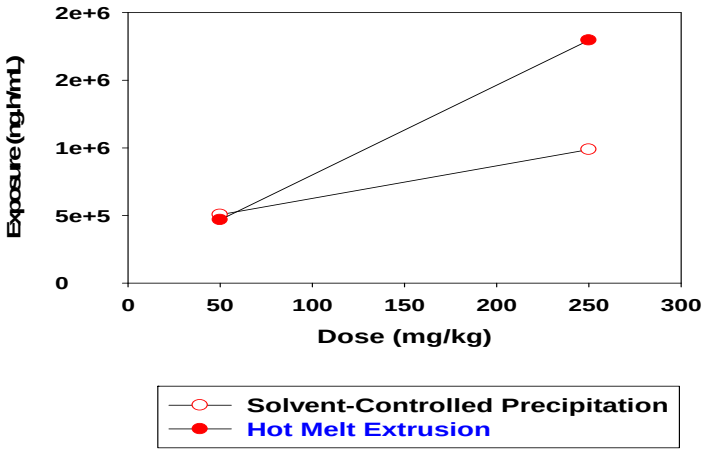
- Heating & Cooling method has an issue of decomposition of the compound with high melting point
- The compound of "easy amorphous" can be categorized into non-crystallizing compounds and has low Tm/Tg ratio
- Even if a compound has low Tm/Tg ratio and categorized as "easy amorphous", the compound can still be difficult to make amorphous

Dissolution Methods and Challenges

- High energy systems prone to crystallize during dissolution
- Crystallization kinetics depend on Temperature, Sink Condition and Media Composition
- Drug may be associated with polymer (free drug vs. bound drug)
- Higher supersaturation generally causes faster precipitation (lower recovery)

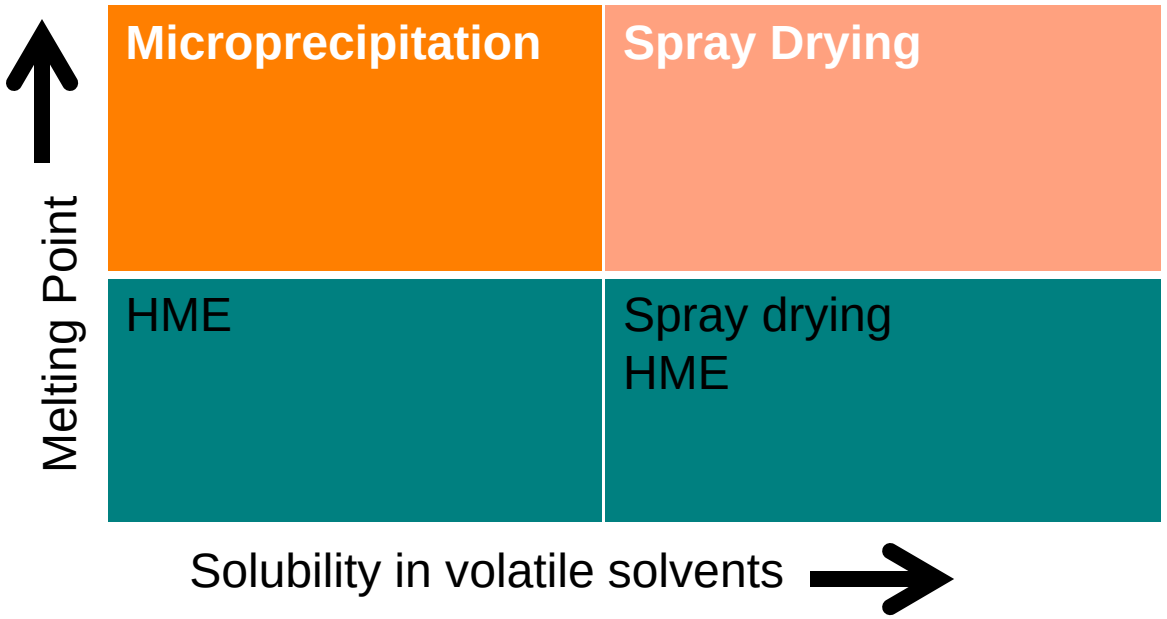






Judicious selection of dissolution condition is critical for " meaningful" interpretation of data

Amorphous Processing Technology Selection Guide



Compounds with melting point < 200°C could be suitable for HME and compounds with solubility > 50 mg/mL in low boiling point volatile solvent are suitable for SD

Pros & Cons of Amorphous Technologies

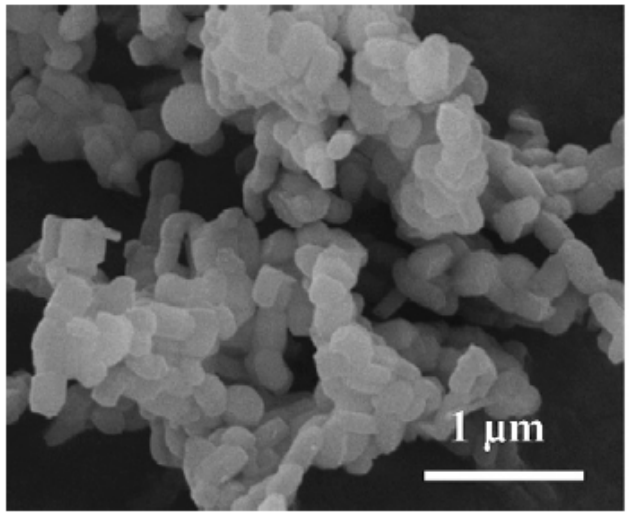
Technology	Pros	Cons
Melt Extrusion	Non-solvent based Short exposure to high temperature Modular design provides flexibility Extrudate density helps improve stability Continuous process Established scale-up and commercial feasibility	Thermal degradation Limited application for high T_m compounds Dissolution (erosion) Reduced compactability
Spray Drying	Rapid removal of solvent Established scale-up and commercial feasibility Processing occurs below Tg Applicable for low boiling point, low toxicity solvents (i.e. ethanol, acetone)	Requires adequate solubility in volatile solvent Residual solvent levels must be tested Phase separation may occur based on solubilities Low bulk density requires densification
Microprecipitation	Useful for compounds not amenable to HME or SD Provides high degree of super-saturation (ionic interaction) Modulated plasma profile due to enteric polymer Semi-continuous processing	Require ionic polymers Not suitable for weakly basic drugs Solvent extraction may require multiple washings Downstream processing required Scale-up challenges exist

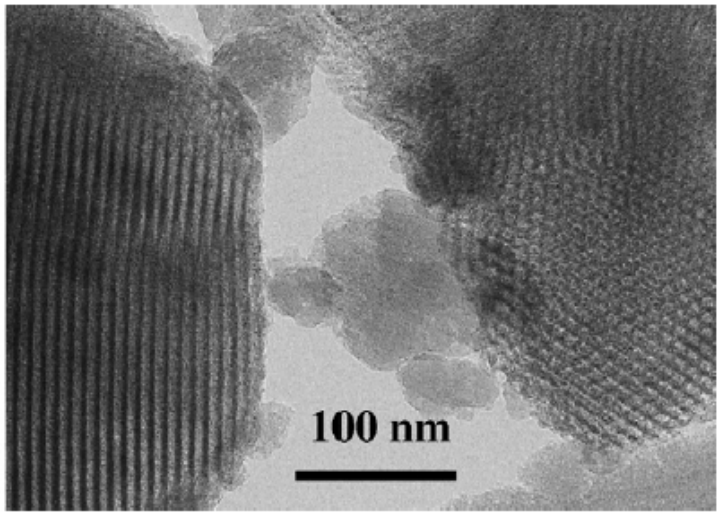
t is important to select the right process for the molecule, not force a process onto the compound

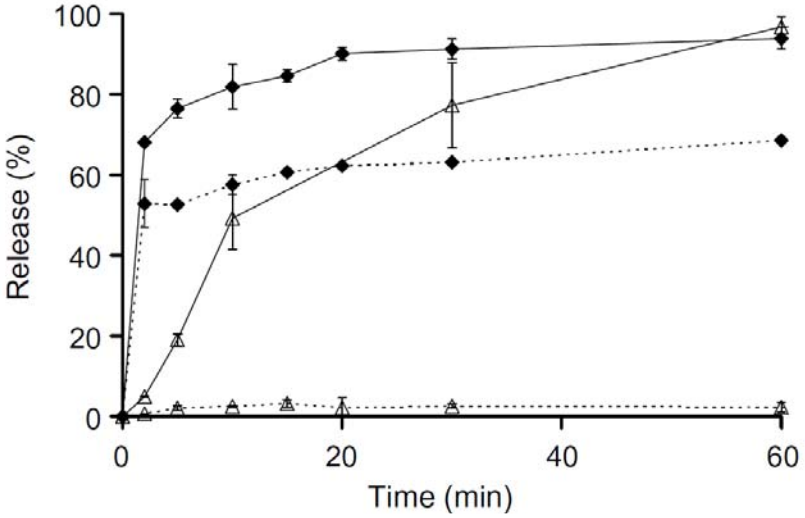
If necessary consider other novel technologies (i.e. mesoporous silica, KinetiSol)

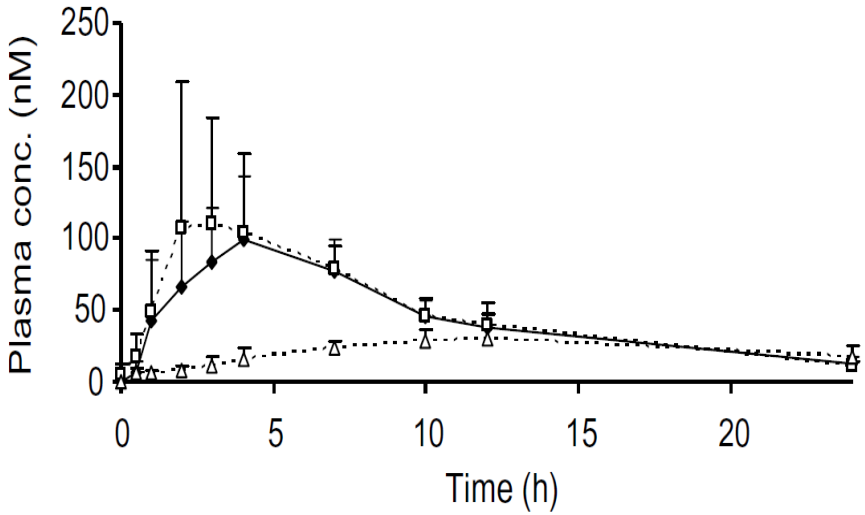
Opportunities for New Technologies

Case Study with Mesoporous Silica









- Mesoporous silica can improve dissolution rates and exposure of poorly soluble compounds

Mellaerts et al., EJPB. 69 2008, p. 223

Opportunities for New Technologies

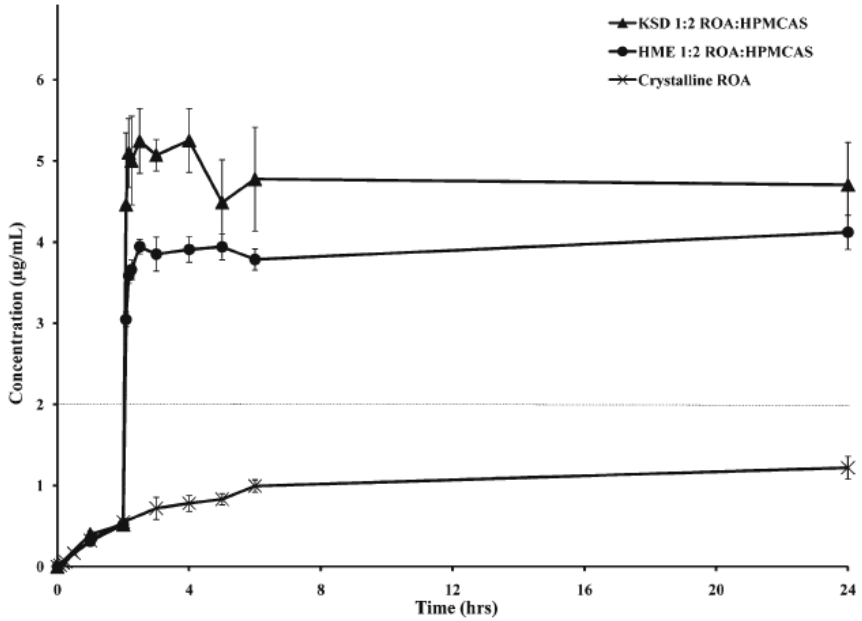
Case Study with KinetiSol

Melt Extrusion

Polymer	Particle size	Temperature (°C)	Screw speed (rpm)	Recirculation time (min)	Recovery (%)	Impurities (%)
Eudragit® L100-55	Unmicronized	140	300	2	22.7±0.5	55.9
Eudragit® L100-55	Micronized	140	300	0	69.1±0.5	17.3
HPMCAS	Unmicronized	170	300	2	70.9±0.3	10.2
HPMCAS	Micronized	170	300	0	78.4±0.1	8.9

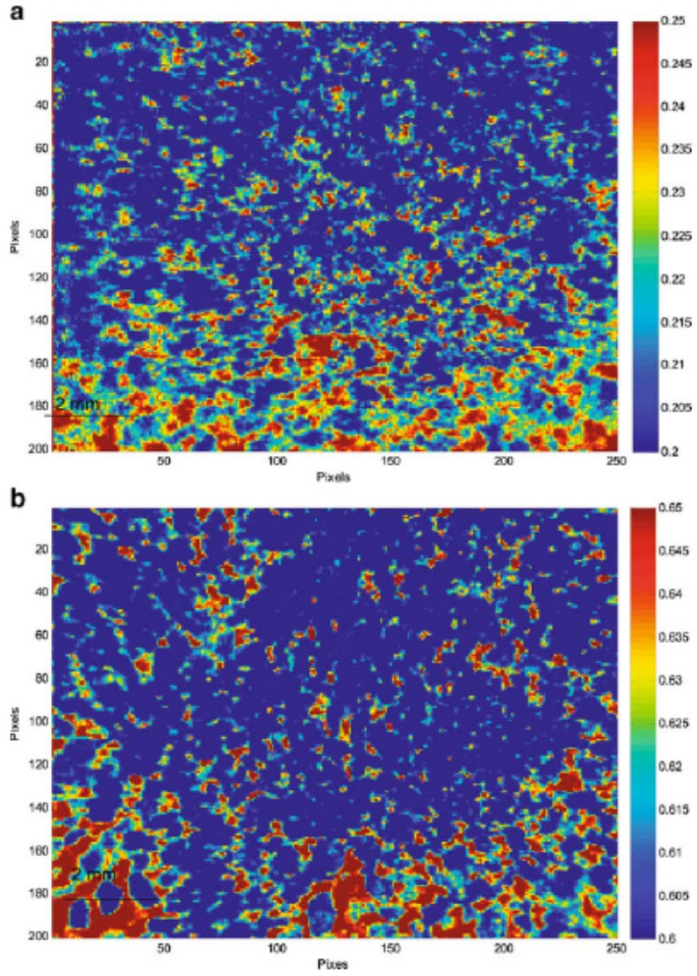
KinetiSol

Polymer	Particle size	Speed (rpm)	Temp. (°C)	Recovery (%)	Impurities (%)
Eudragit® L100-55	Unmicronized	1,450	100	70.9±0.8	12.9
HPMCAS	Unmicronized	2,400	112	99.4±1.2	1.6



Melt Extrusion

KinetiSol®



- Application of new technologies offers the possibility to significantly expand manufacturing window

Hughey et al., AAPS Pharm. Sci. Tech. 11 (2) June 2010

Future Directions

TODAY		TOMORROW
Many industrial pipelines have solubility limitations	ACTIVES	Chemistry of compounds becomes highly engineered to reduce solubility liabilities
Limited number of approved excipients for solubility enhancement	EXCIPIENTS	Pharma companies and excipient manufacturers work jointly to develop excipients with unique advantages
Simple models and descriptors predict stability and performance of advanced systems	MODELING	*In silico* methods advance to provide computer aided design and a priori prediction
Batch manufacturing processes with a limited portfolio of techniques to prepare advanced systems	MANUFACTURING	Continuous manufacturing and new technologies provide advantages to poorly soluble compounds

Summary Remarks

- Even today, poorly soluble compounds present major development challenges that may limit or even prevent a life saving medication from reaching the market
    - *Drives substantial investments in new technologies and products*

- Limitations of materials and technologies present unique opportunities for partnerships and collaborations to develop these areas
    - *Will generate new models for conducting business and developing therapies*

- True innovation allows a molecule to become a medicine

Acknowledgements

We Innovate Healthcare

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- Dr. Raman Iyer
  Hoffmann-La Roche, Inc.
- Ms. Kaoru Tominaga
  Hoffmann-La Roche, Inc.

Questions