Basics of Amorphous and Amorphous Solid Dispersions

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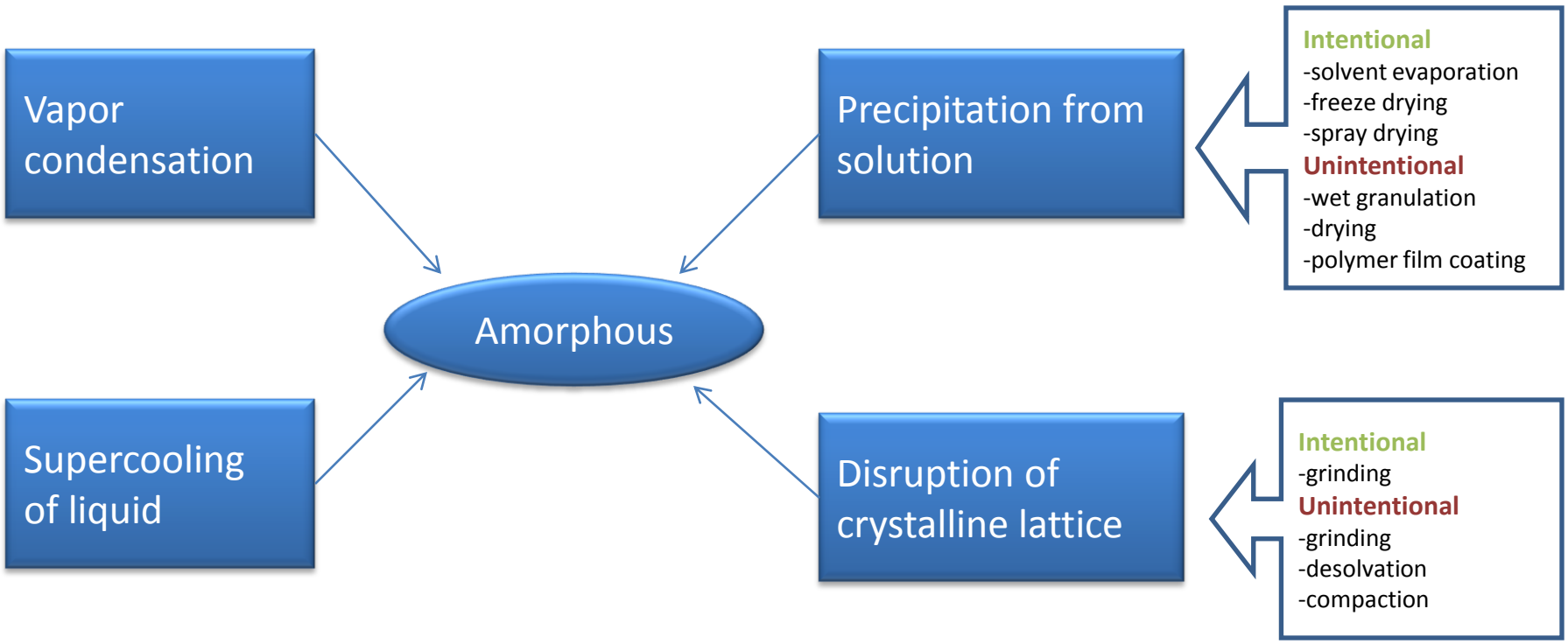
Amorphous Products

Amorphous active pharmaceutical ingredients (APIs) marketed as drug products:

- Accolate® (zafirlukast)
- Ceftin® (cefuroxime axetil)
- Accupril® (quinapril hydrochloride)
- Viracept® (nelfinavir mesylate)

Amorphous

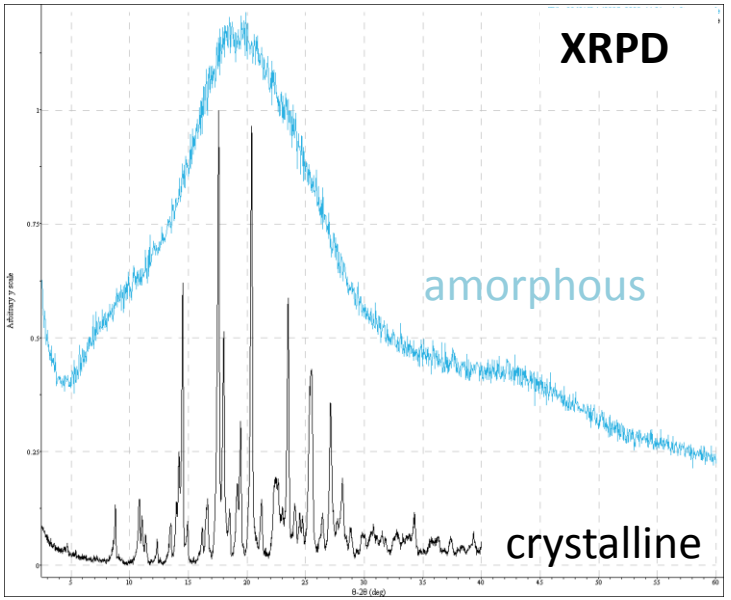
Amorphous can be produced in a variety of situations

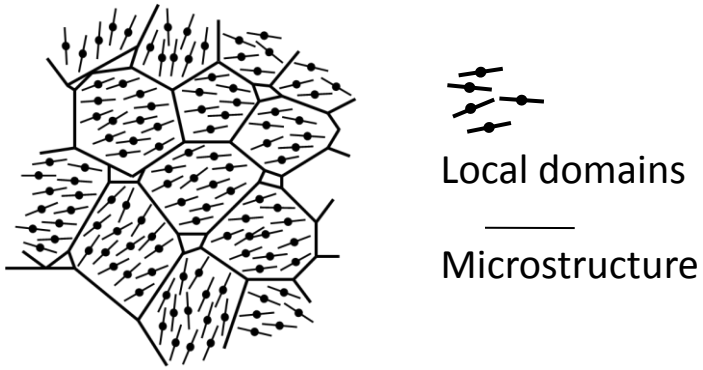


Hancock and Zografi. *J Pharm. Sci.* **1997**, *86,* 1-12

Amorphous

- Amorphous
  - No long range order
  - Exhibit a halo in XRPD patterns (vs crystalline peaks)
  - Do possess short range order
  - Less physically and chemically stable than crystalline materials
  - Higher apparent solubility and faster dissolution than crystalline materials

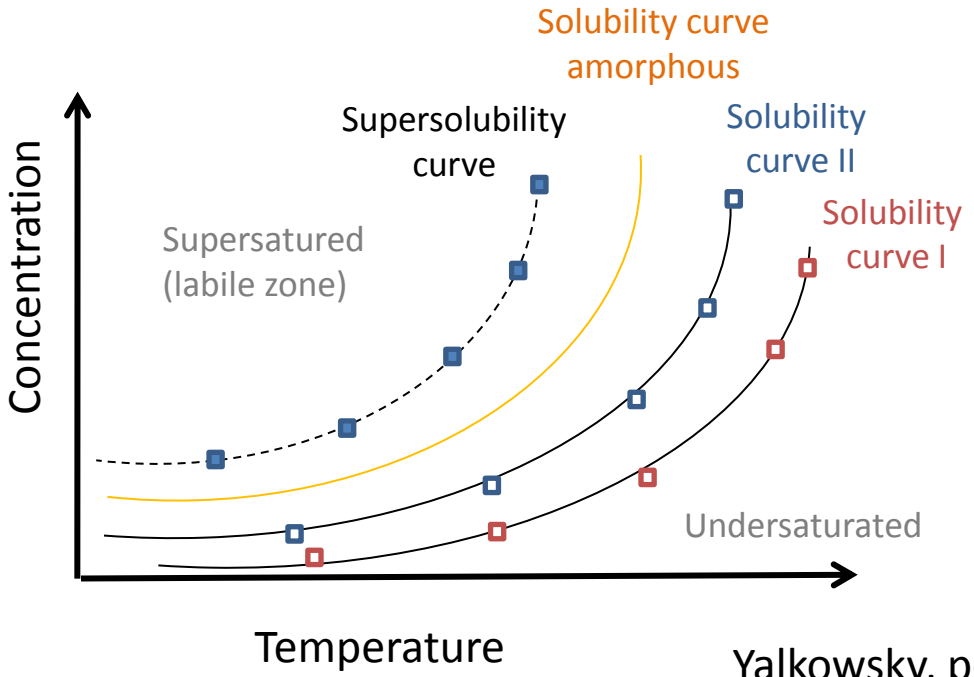




Bates et al. *Pharm. Res,* **2006**, *23*(*10*), 2333-2349

Solubility

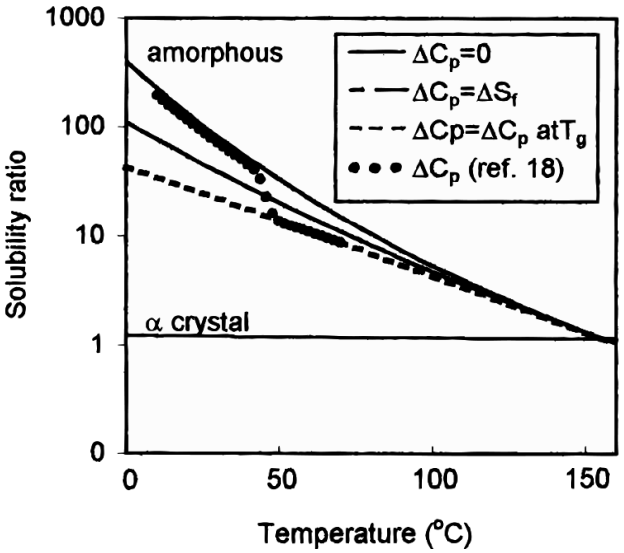
- The term "solubility" (unless otherwise specified) refers to the "equilibrium solubility" of the most stable crystal form in equilibrium with the solvent
- The solubility of anything other than the most stable form is reported as the "apparent solubility"



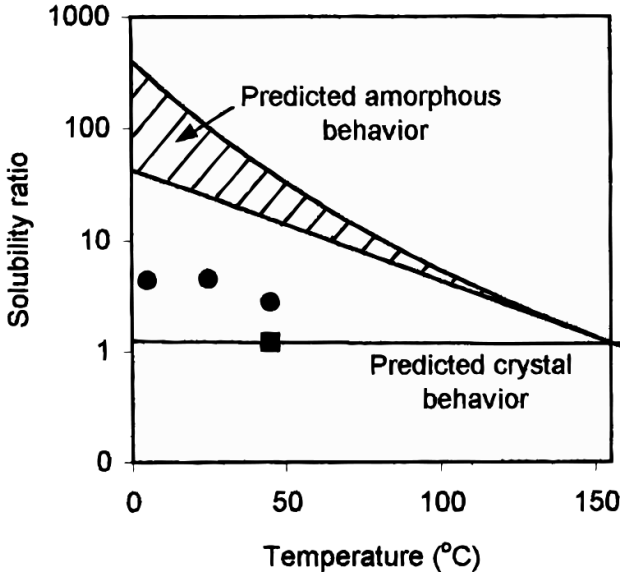
Yalkowsky, personal communication

Solubility

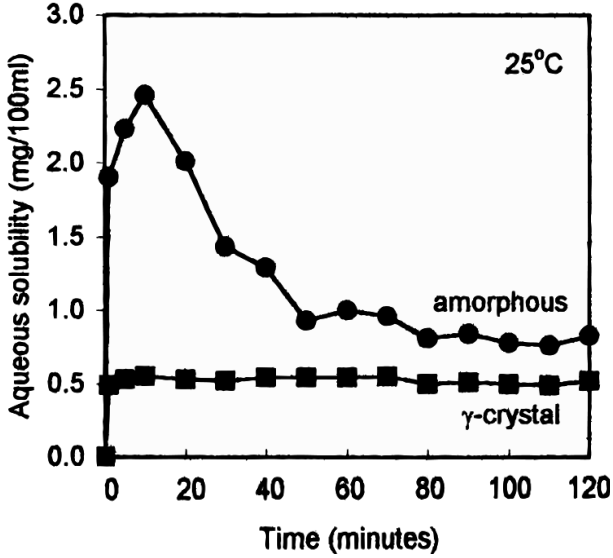
- Theoretical estimates of solubility ratios calculated from heat capacity measurements of crystalline and amorphous
- Theoretical estimates of solubility ratios higher than experimental values
- Solubililty profiles show conversion of amorphous to crystalline form



Solubility ratio calculated from the differences in heat capacities



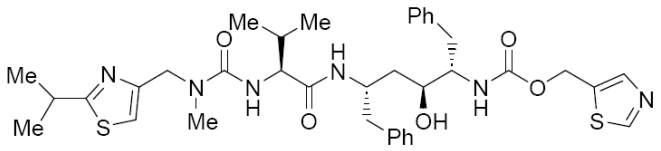
Measured solubility ratio for amorphous (●) and α-indomethacin crystal form (■)



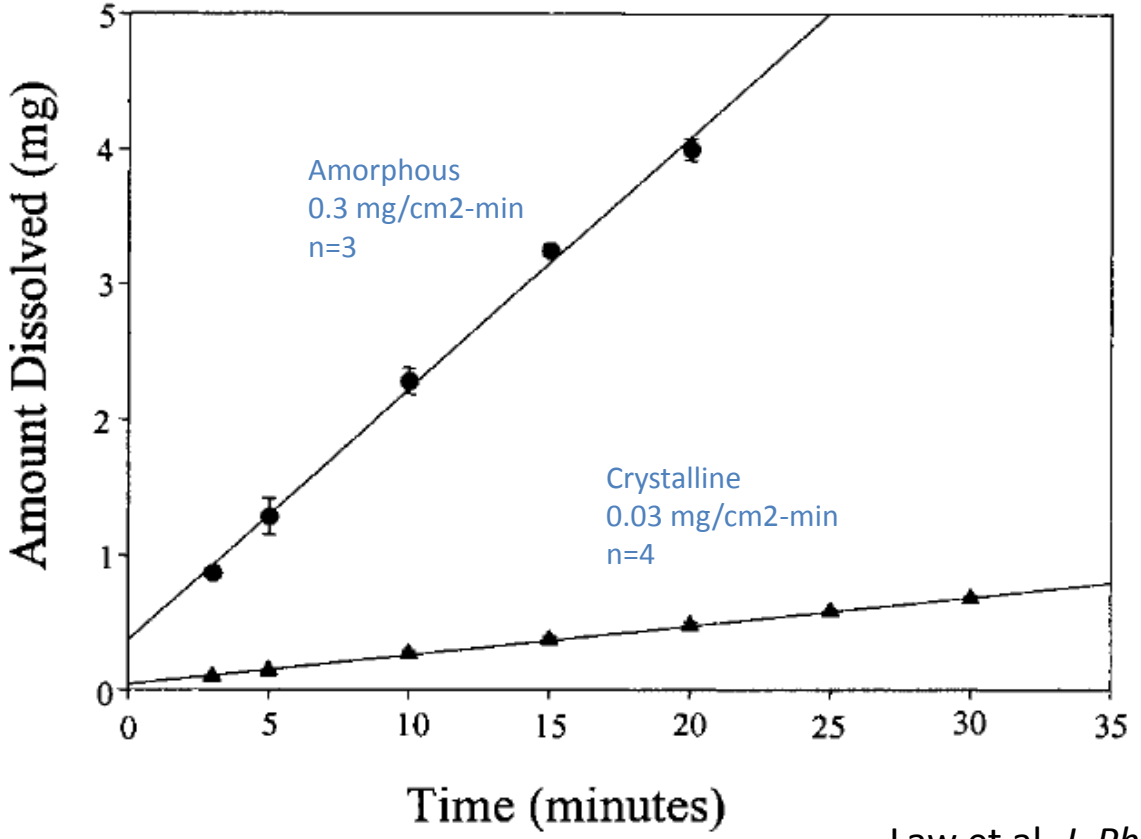
Aqueous solubility profiles for amorphous (●) and α-indomethacin crystal form (■)

Hancock and Parks. *Pharm Res* **2000**, *17*, 397-403.

Dissolution



- Amorphous materials will usually result in an increase in dissolution rate
- Remained amorphous over time frame of experiment



Ritanovir
0.1 N HCl at 37° C

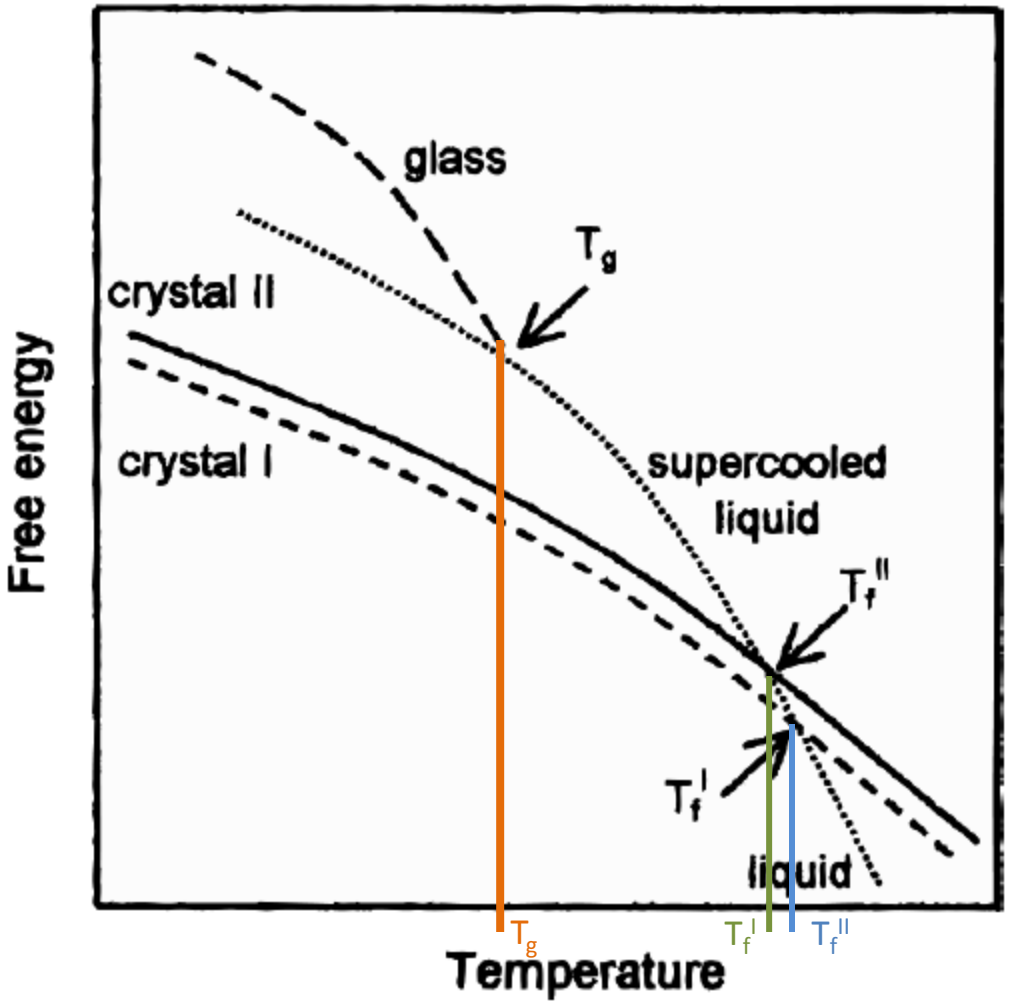
Law et al. *J. Pharm. Sci.* **2004**, *93*, 563-570

Glass Transition Temperature

- Amorphous solids can exist in two states
  - Super-cooled liquid (or rubbery state): a viscous equilibrium liquid form of the material
  - Glass: a solid non-equilibrium form of the same material
- The temperature at which one form converts to the other is the glass transition temperature, T_g
- Structural factors affecting T_g include
  - Molecular size and shape
  - Extent, strength, and direction of any hydrogen bonding
- These effect the strength of intermolecular interactions and packing (free volume)

Glass Transition Temperature

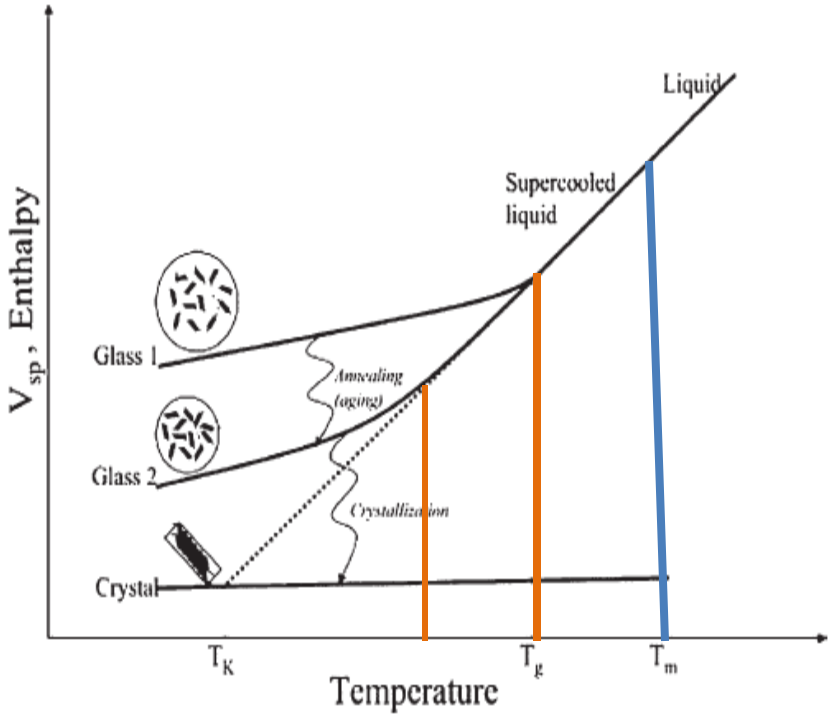
- Energy temperature (ET) diagram for amorphous and crystalline material
  - T_f^{II}: melting of crystal II
  - T_f^{I}: melting of crystal I
  - T_g: glass transition temperature where supercooled liquid changes to glass
- Upon cooling
  - Melt → supercooled liquid → glass



Hancock and Parks. *Pharm Res* **2000**, *17*, 397-403.

Glass Transition Temperature

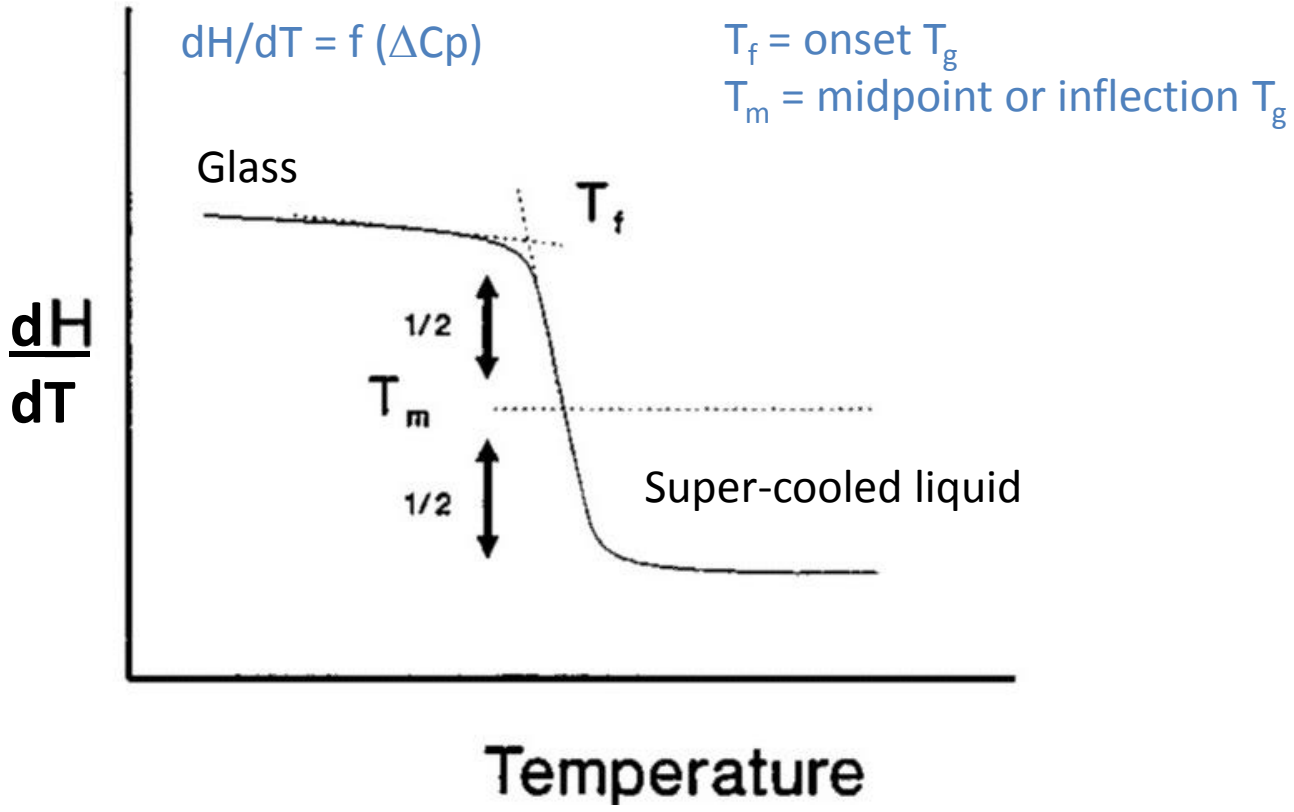
- ET diagram for volume (V) or enthalpy (H)
- Depending on thermal history, glass can form with slightly different energies, resulting in variable T_gs
- This is not polyamorphism, just different energy levels of the glass



Bhurg and Pikal. *J. Pharm. Sci*. **2008**, *97*, 1329-1349

Glass Transition Temperature

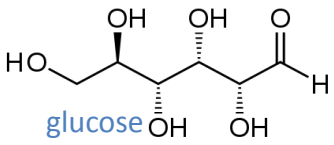
Commonly measured with differential scanning calorimetry (DSC) or modulated DSC

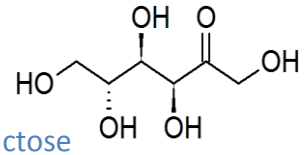


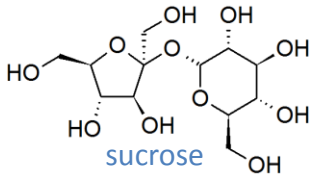
Glass Transition Temperature

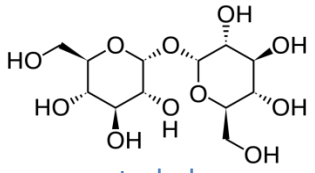
- Common sugars

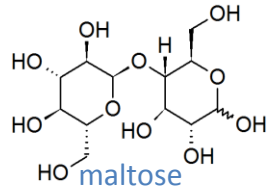
Sugar	Molecular Weight (g/mol)	T_g (° C)
Glucose	180	30
Fructose	180	13
Sucrose	342	74
Trehalose	342	115
Maltose	342	100
Lactose	348	102
Raffinose	504	108
Maltodextrin	860	169
Dextran	10K	197

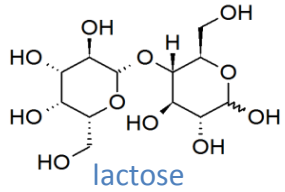

glucose

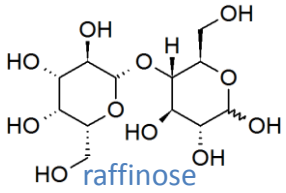

fructose

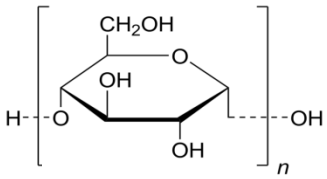

sucrose


trehalose

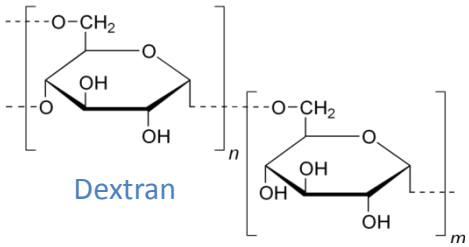

maltose


lactose


raffinose


maltodextrin

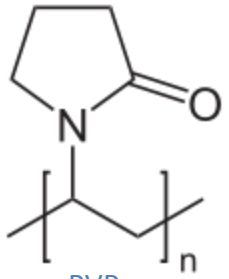
$2 < n < 20$


Dextran

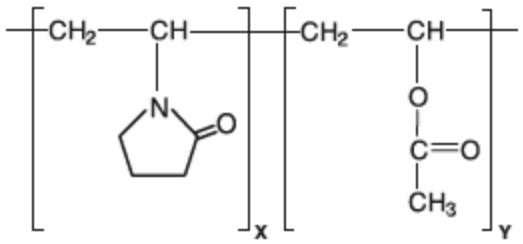
Glass Transition Temperature

- Different grades of poly(vinylpyrrolidone) (PVP)

Sample	Molecular Weight (g/mol)	T_g (° C)
PVP K90	1500 K	177
PVP K30	50K	156
PVP K17	10K	136
PVP K12	2K	101
PVP/VA (60:40)	50K	102



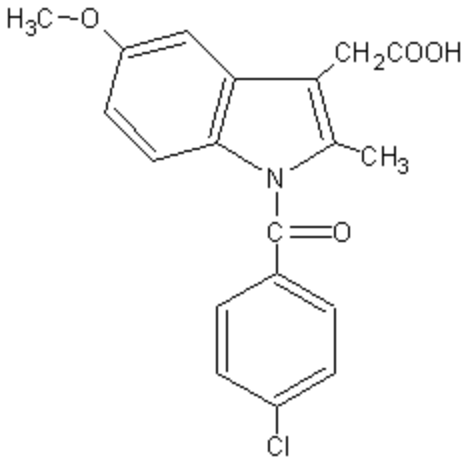
PVP

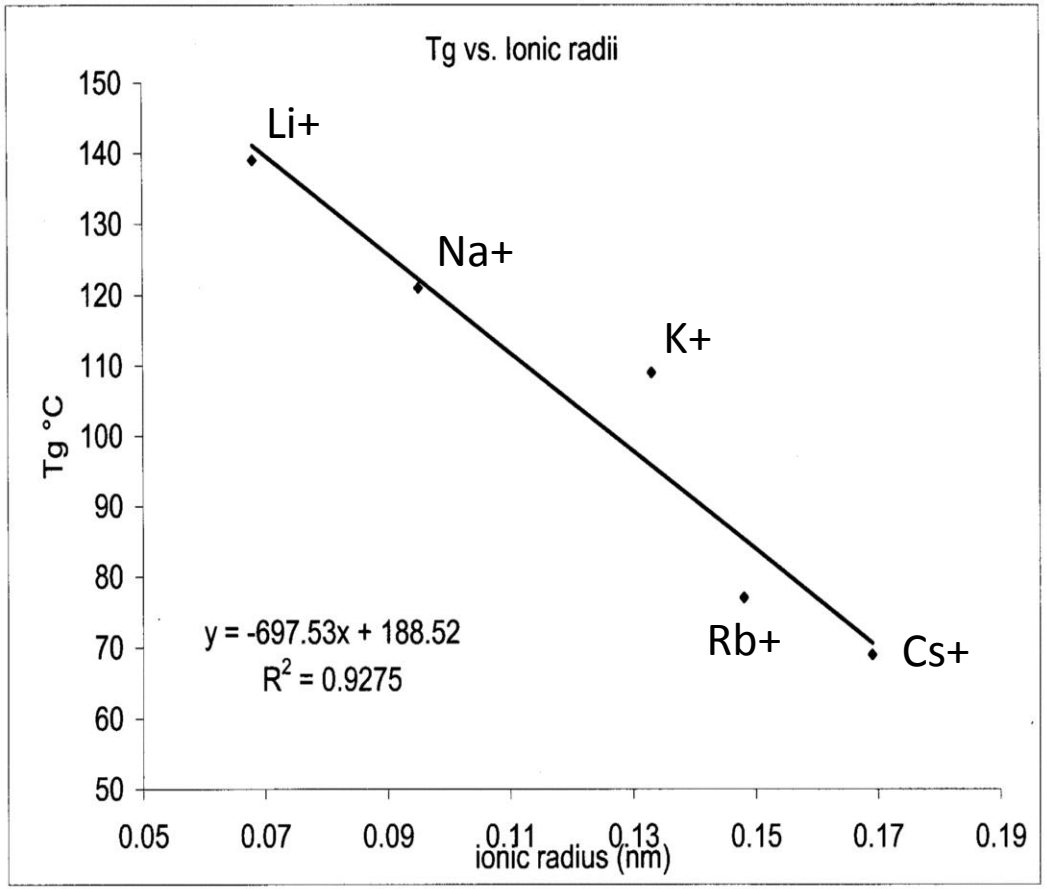


PVP/VA

Glass Transition Temperature

- Effect of different counterions on the Tg of indomethacin salts





Tong et al, *Pharm.Res*. **2002**, *19*, 649-654.

Glass Transition Temperature

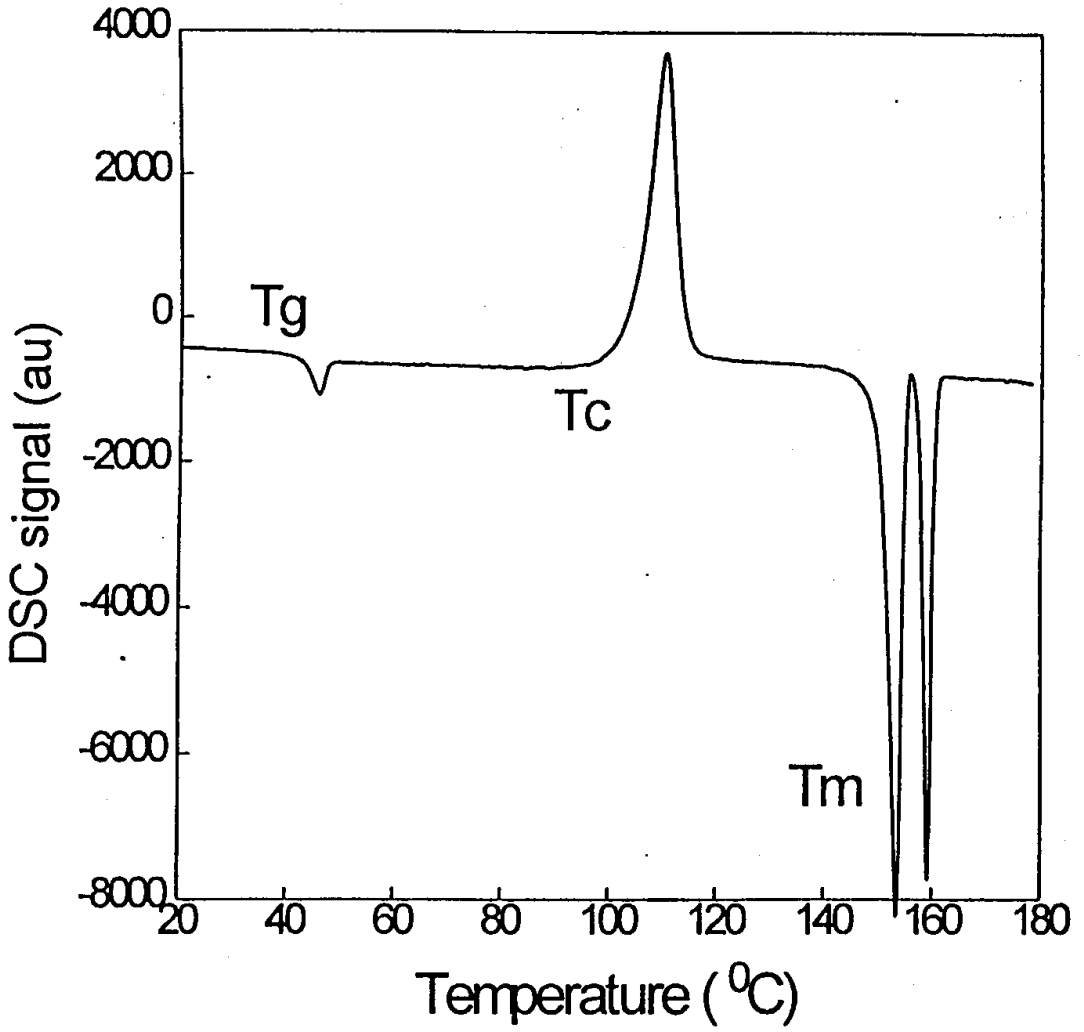
- Estimation of T_g
  - T_g is roughly (0.67)T_m (the melting temperature of the crystalline material
  - "2/3 rule"

Sample	Tg (K)	Tm (K)	Tg/Tm
Poly(ethylene terephthalate)	343	538	0.64
Nylon 66	333	538	0.61
Polyacrylonitrile	378	590	0.64
Isotactic polypropylene	268	435	0.62
Aspririn	243	408	0.60
Indomethacin	315	434	0.73
Sodium indomethacin	393	543	0.72
Nifedipine	323	447	0.72
Cholocalciferol	293	352	0.84

Amorphous Indomethacin

DSC can also give information on changes with temperature

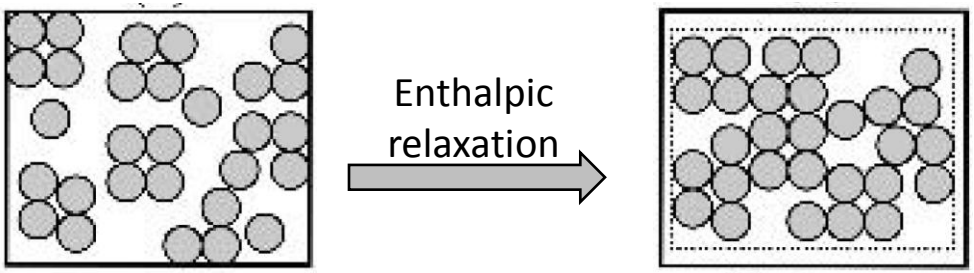
- Exotherm: crystallization of amorphous (T_c)
- Endotherm: melt of crystalline indomethacin (T_m)



Hancock and Zografi. *J. Pharm. Sci*. **1997**, *86*, 1-12

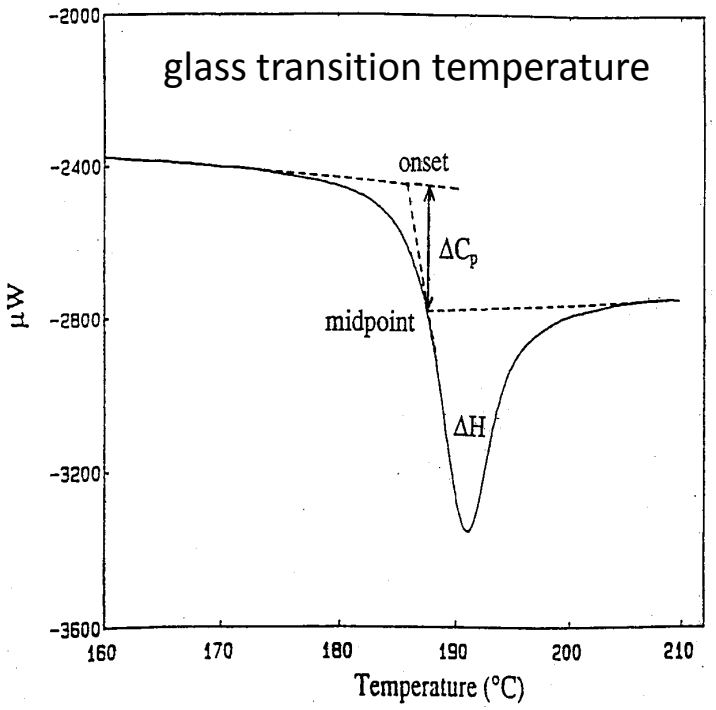
Relaxation

- Amorphous materials can age or relax over time
- DSC shows an enthalpy relaxation endotherm
- Upon relaxation
  - Density increases
  - Free volume decreases



Unaged amorphous matrix

Aged matrix
↑ density
↓ free volume

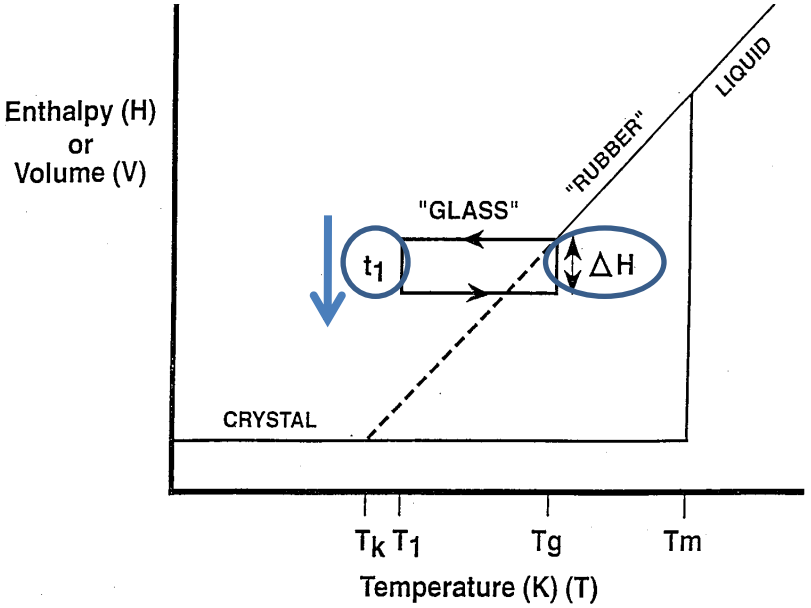


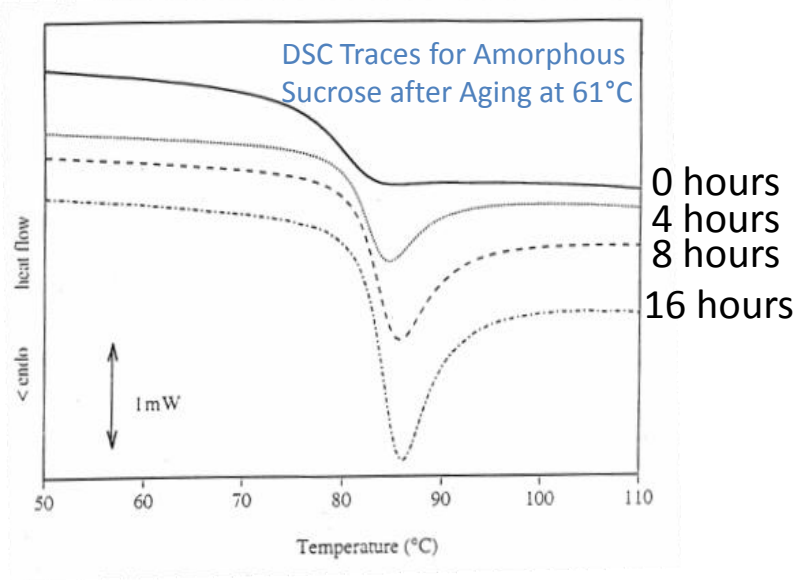
Hancock and Zografi. *J. Pharm. Sci*. **1997**, *86*, 1-12

Surana et al. *Pharm. Res*. **2004**, *21*, 867-874.

Relaxation

- Once the glass is formed, it can be aged or annealed at a specific temperature (t_1) for a period of time
- The relaxation results in a decrease in H or V
- Upon reanalyzing the material, enthalpy of relaxation is seen as and endotherm (ΔH)
- Longer aging times will result in larger enthalpy relaxation

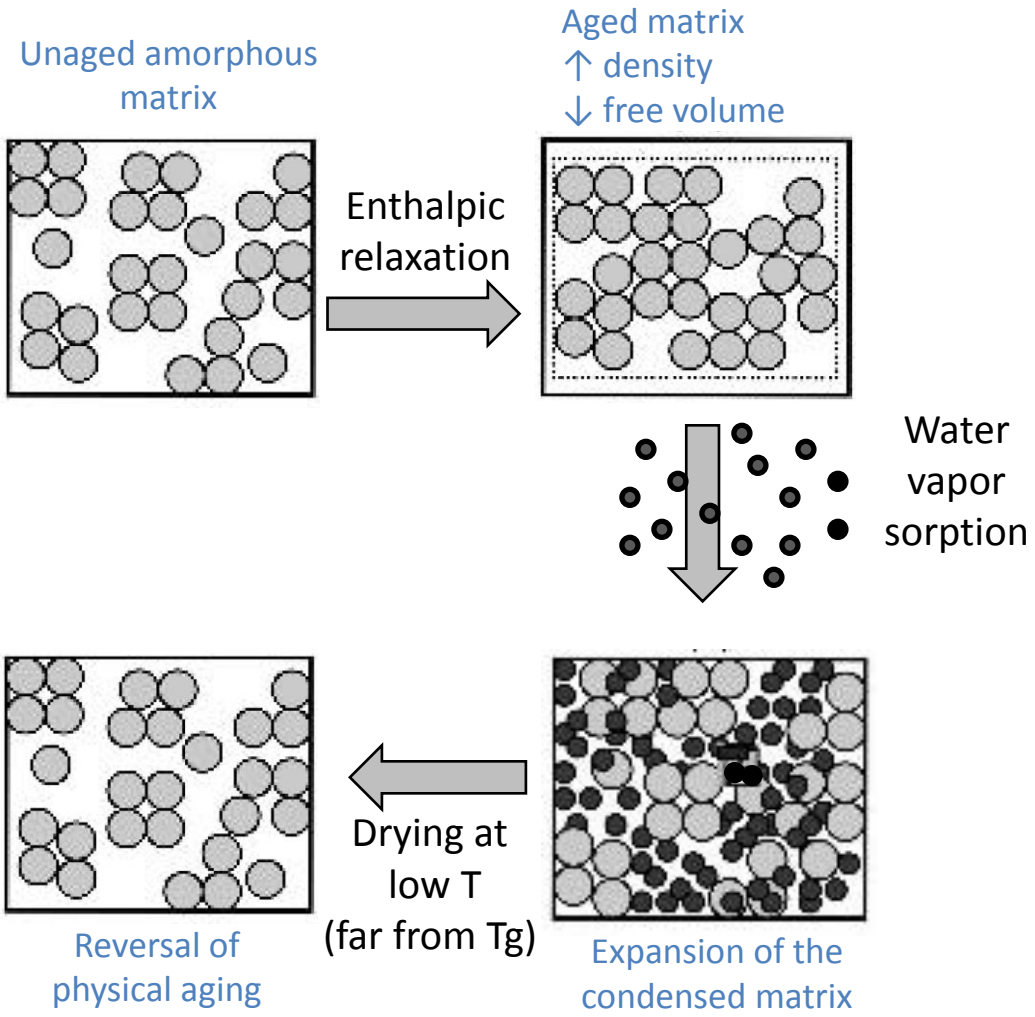




Hancock et al. *Pharm. Res*. **1995**, *12*, 799-806
Shamblin and Zografi. *Pharm . Res*. **1998**, *15*, 1828-1834

Relaxation

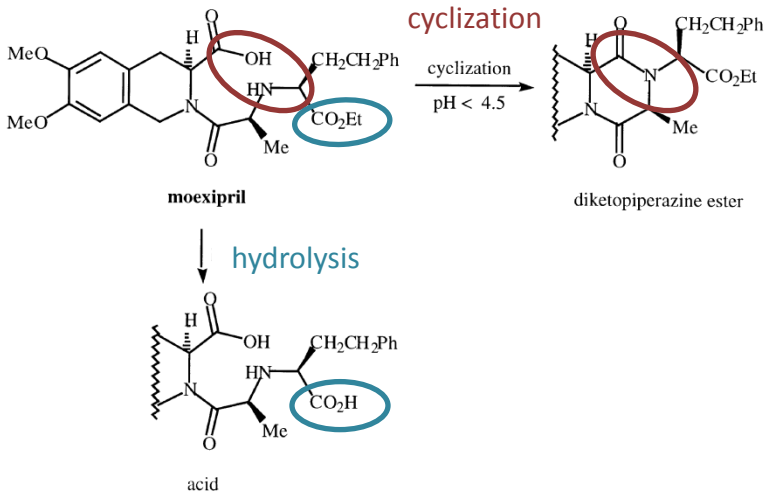
- Aged materials show decreased physical and chemical reactivity compared to unaged materials
- Exposure to water can reverse the aging of an amorphous material and make it more reactive

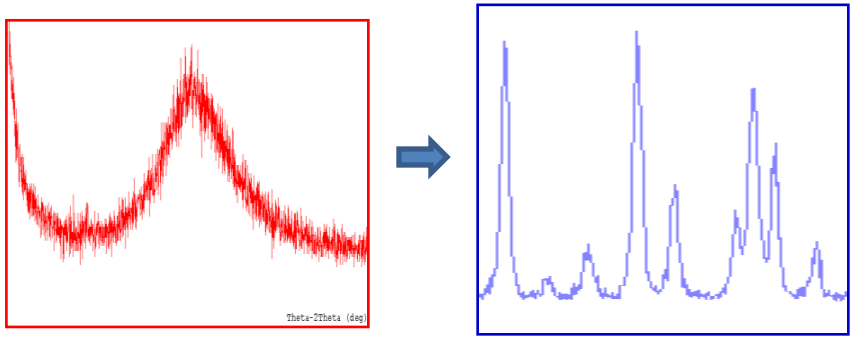


Surana et al. *Pharm. Res*. **2004**, *21*, 867-874.

Stability

- Chemical stability
  - Amorphous materials can be less chemically stable than crystalline materials
- Physical stability
  - Amorphous materials are less physically stable and will tend to crystallize over time and under stress (temp, RH, etc)

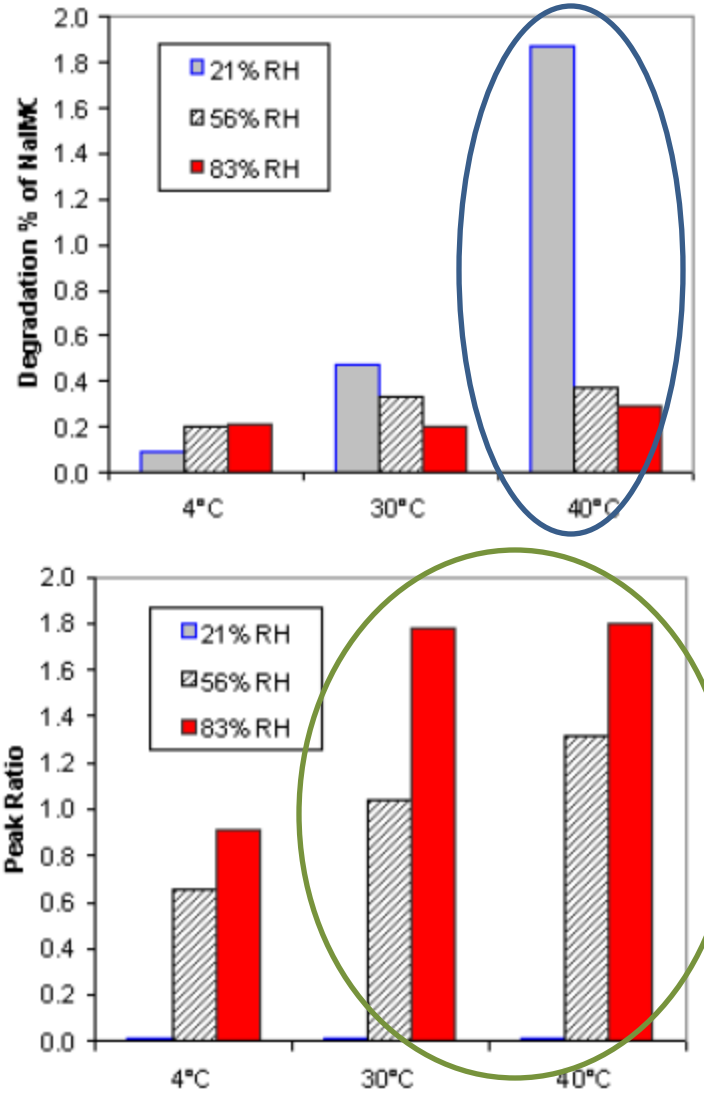




Stability

Amorphous Na indomethacin

- T_g of 121 °C dry, 53 °C at 21% RH
- 15 days at elevated temperature (below T_g) and RH
- Amorphous material remained amorphous at 21% RH and 40 °C
- Amorphous material had highest chemical decomposition highest temperature, closer to T_g
- Crystallization increased with higher T and RH conditions



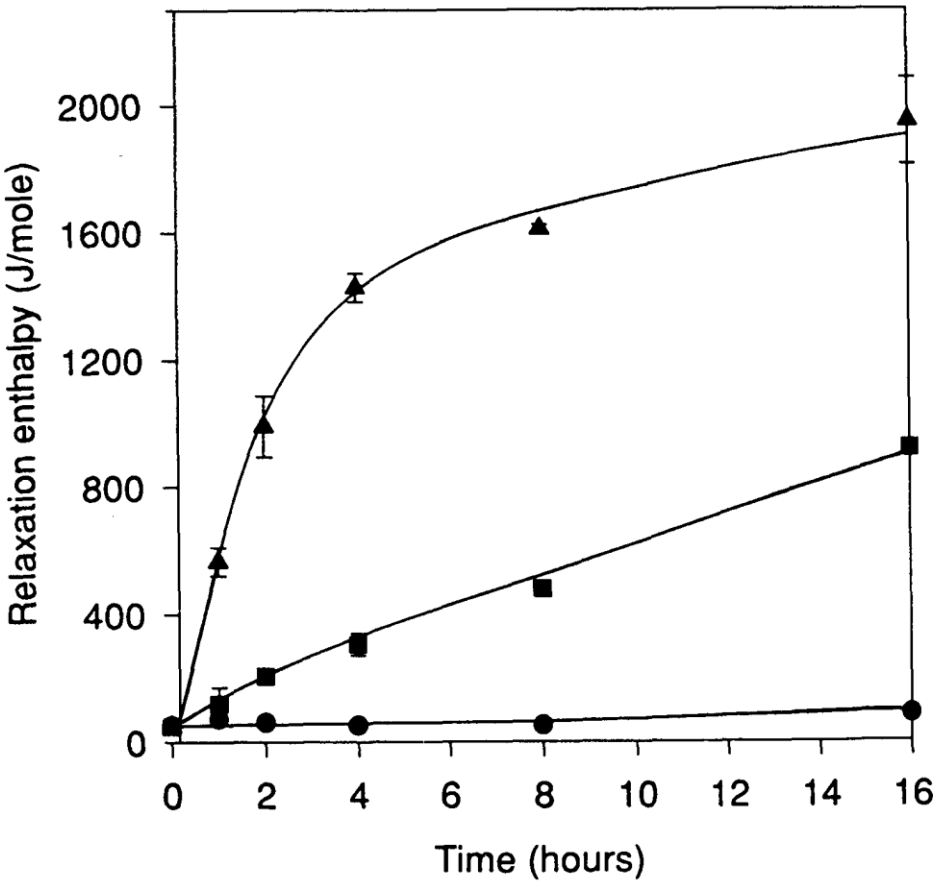
Peak ratio of crystalline Na indomethacin trihydrate vs crystalline LiF standard

Tong et al. *AAPS PharmSciTech*, **2003**, *5(2)*, article 26.

Physical Stability

Temperature

- Sucrose stored at 47, 32, and 16 °C below T_g
- Enthalpy relaxation measured over time
- Samples stored at T_g-47 showed no change
- Rule of thumb: store amorphous samples 50 °C below T_g to minimize changes



Variation of the relaxation enthalpy with storage time for sucrose (● Tg-47, ■ Tg-32, ▲ Tg-16).

Hancock et al. *Pharm. Res*. **1995**, *12*, 799-806

Physical Stability

- Water can absorb (dissolve) into amorphous solids via hydrogen bonding due to the disordered structure
- Water has low T_g
  - 135 K (-138 °C)
  - Plasticizing effect
  - Lowers Tg of most pharmaceutical systems
- Estimation of Tg
  - Fox Equation :

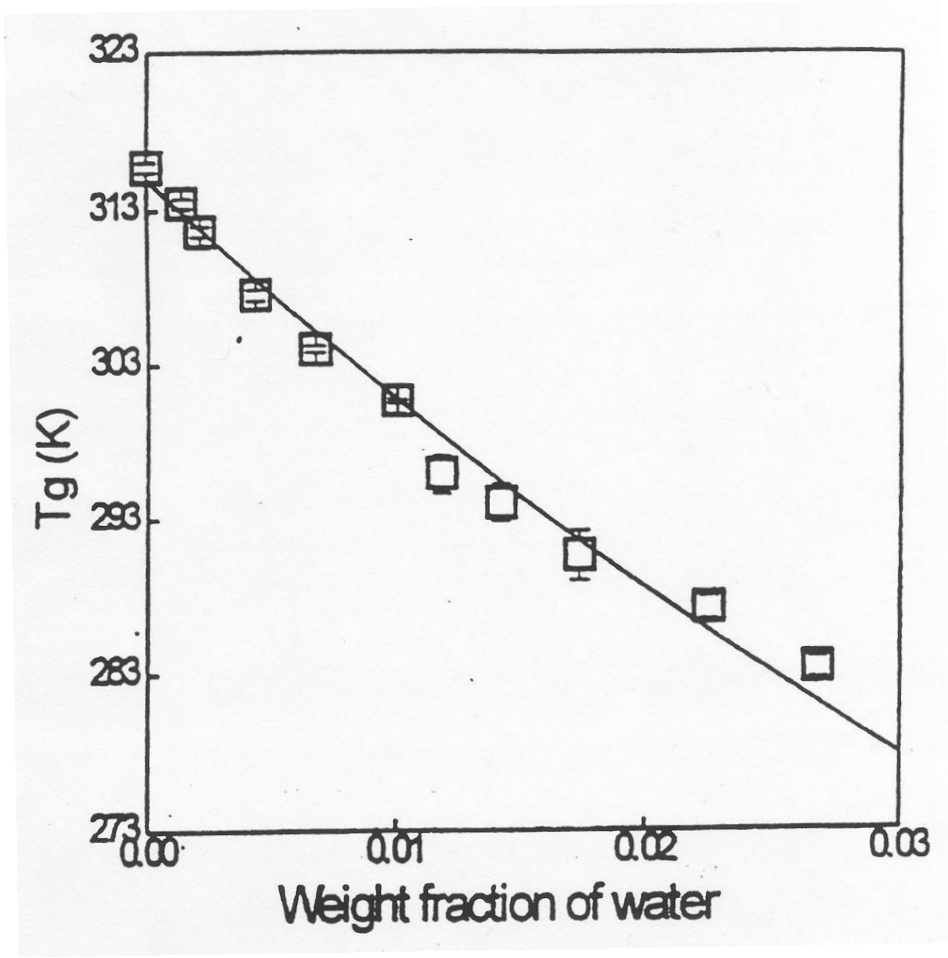
    $1/Tg_{mix} = (w_1/Tg_1) + (w_2/Tg_2)$

    where w = weight fraction

Water content: 5.0% w/w
Tg: 50 °C (323K)
$1/Tg_{mix} = (0.05/135) + (0.95/323)$
Tg_{mix} = 302K or 29 °C

Physical Stability

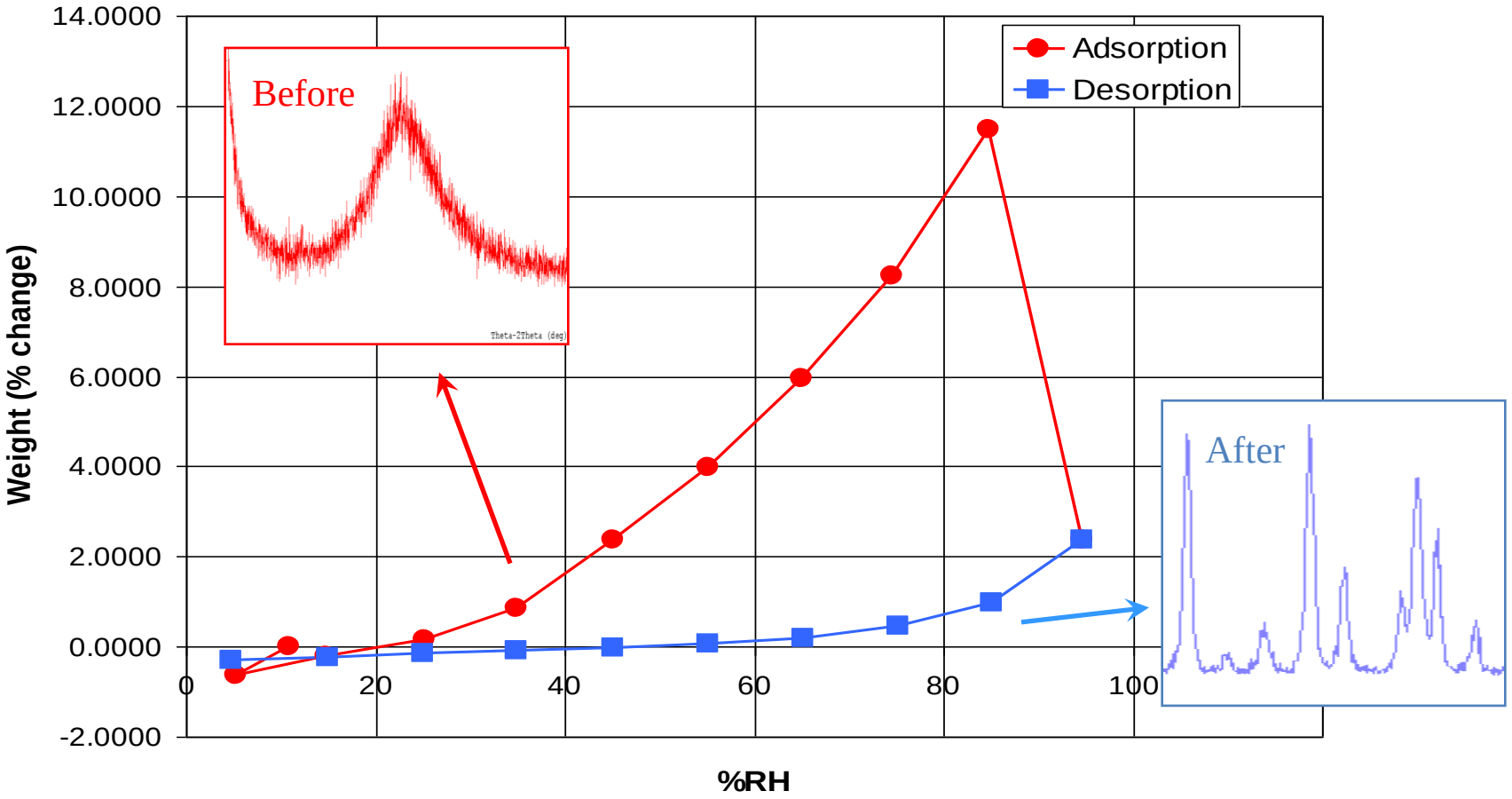
- Indomethacin-water
- Absorbed water lowers the T_g of an amorphous solid
- Rule of thumb: 1% water will decrease T_g by about 10 deg



Andronis et al., *J.Pharm.Sci.* **1997,** *86,* 346-351

Physical Stability

Loss of water at 85% RH indicative of amorphous material crystallizing into Form A



Molecular Mobility

- For any physical or chemical transformation to take place in the solid state
  - must be a thermodynamic driving force
    - a net loss in free energy
    - sufficient diffusional motion (translational and rotational) over the desired time scale
- Generally, molecular mobility follows the order: liquid > super cooled liquid > glass > crystal

- Molecular motions
  - Primary Relaxations
    - α relaxations
    - "slow" cooperative diffusion translational and rotational motion of whole molecules or polymer segments)
    - corresponds to Tg
  - Secondary Relaxations
    - β relaxations
    - "faster" non-cooperative local motions associated with individual molecules or polymer main-chain segments, as well as with polymer side-chains
    - *Important secondary relaxations are often called "Johari-Goldstein" relaxations. They are precursors to the primary α relaxations*

Johari and Goldstein. *J. Chem. Phys*. **1970,** *53,* 2372

Molecular Mobility

- Molecular mobility is best expressed in terms of a relaxation time, t_s
  - t_s represents the time scale over which a unit dynamic event occurs
- Rate of relaxation expressed as "the fraction unrelaxed" or the relaxation parameter, $\phi(t)$
  - $t = 0$, $\phi(t) = 1$
  - $t = t$, $\phi(t)$ = between 1 and 0
- In a disturbed system, observe rate of return to equilibrium

$$\phi(t) = \exp(-t/\tau_s)$$

- Methods to Measure Relaxation Time
  - Dynamic Mechanical Analysis
  - Dielectric Relaxation
  - Enthalpy and Volumetric Relaxation
  - NMR
  - Dynamic Light scattering
  - Dynamic Neutron Scattering
  - Optical Probes
- In combination these cover $t=10^{+6}$ to 10^{-12} s

Molecular Mobility

- Kohlrausch, Watts, Watkins (KWW) stretch exponential relationship:

$$\phi(t) = \exp\left[-\frac{t}{\tau_{KWW}}\right]^{\beta}$$

$\beta = 1$ for single relaxation mode

$0 \geq \beta\ 1$ for multiple modes

$\beta \simeq 0.3\text{-}0.5$ near Tg; approaches 1.0 at high temperatures

relaxation parameter, $\phi(t)$

relaxation time, t_{KWW}

- Critical considerations in estimating relaxation times for predicting molecular mobility
  - The values of τ_s obtained experimentally are average values
  - There are multiple modes of relaxation reflected in the value of β from the KWW equation

Fragility

- Fragile:
  - greater the change in molecular mobility with temperature, and the more non-Arrhenius it is, the more “fragile” the system is considered
- Strong:
  - Less change with temperature and the more Arrhenius-like this change the more the system is considered to be a “strong liquid”

Vogel, Tamman, Fulcher (VTF) Equation

$$\log \tau_s = \log \tau_o + [(DT_o) / (T-T_o)]$$

τ_s = structural relaxation time at T = T

τ_o = structural relaxation time at T = ∞

D = strength parameter

T_o = temperature at infinite relaxation time

D = 2-30 “Fragile Liquid”

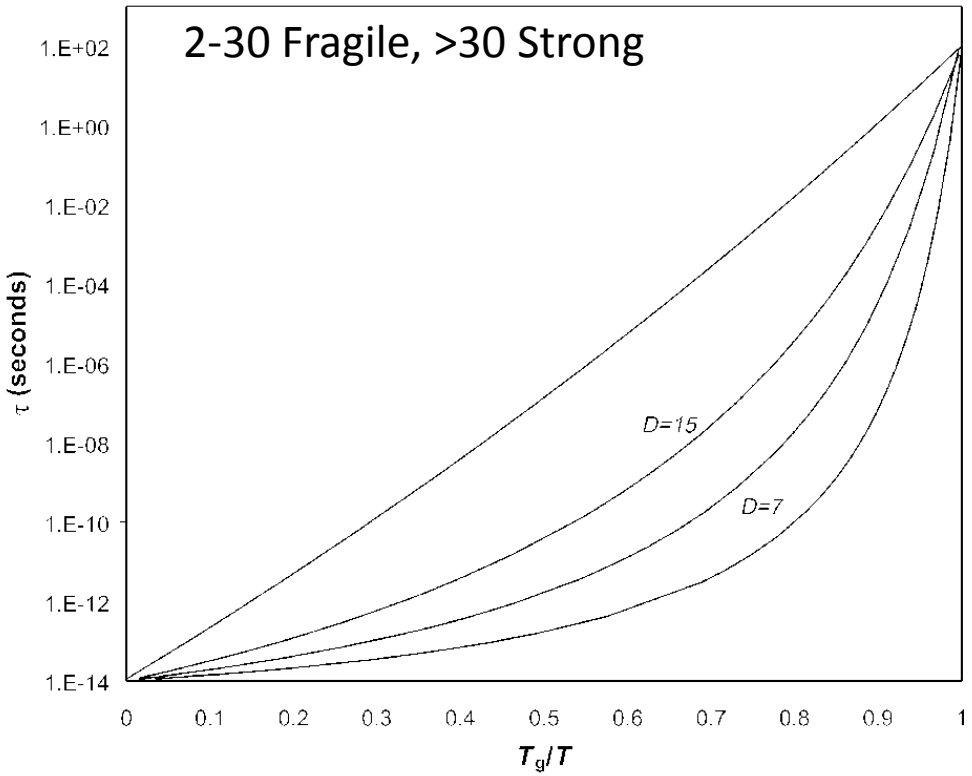
D = > 30 indicates a “Strong Liquid

Angel. *Polymer*. **1997**, *38*, 6261

Fragility

Relaxation time vs temperature scaled to Tg described by VTF

D values



Material	T_g (K)	T_o (k)	D
B_2O_3	557	320	27
sorbitol	270	214	9
o-terphenyl	249	195	10
indomethacin	317	237	13
Na indomethacin	389	276	15
nifedipine	322	228	15
diazepam	398	249	10
felodipine	416	247	10

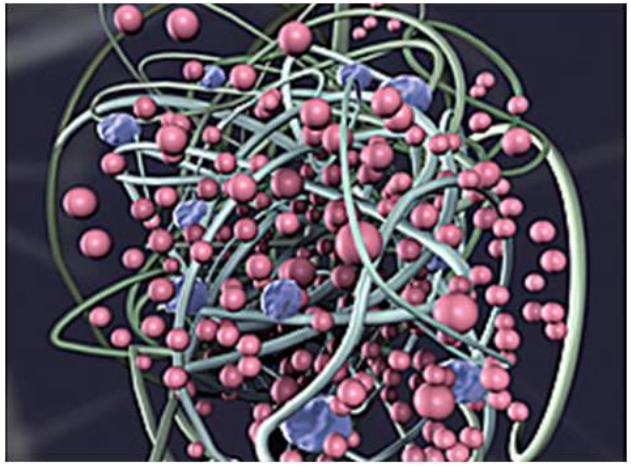
Similar D values means similar $T_m - T_g$ values, and therefore, similar T_g/T_m

Crowley and Zografi. *Thermochimica Acta* **2001**, *380*, 79-83

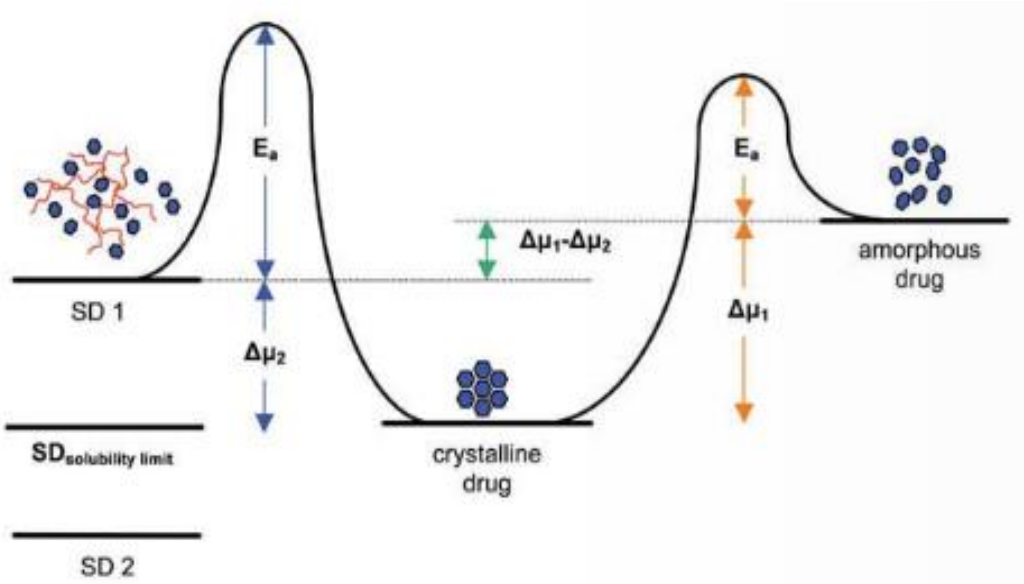
Amorphous Solid Dispersions

Amorphous solid dispersions

- Amorphous drug with polymer
- Polymer stabilizes amorphous drug
- Results in better stability, higher apparent solubility, faster dissolution
- Usually prepared on large scale by spray drying or melt extrusion



Molecular Pharmaceutics cover, December 2004.



Schematic hypothetical energy cartoon showing the amorphous drug, crystalline drug, and several single phase amorphous solid dispersions (μ represents the chemical potential of the drug and E_a represents the activation energy barrier for crystallization).

Harmon et al. *AAPS Newsmagazine*, **2009**, *Sept*, 14-20.

Amorphous Products

Amorphous active pharmaceutical ingredients (APIs) marketed as drug products:

- Accolate® (zafirlukast)
- Ceftin® (cefuroxime axetil)
- Accupril® (quinapril hydrochloride)
- Viracept® (nelfinavir mesylate)

Amorphous solid dispersions marketed as drug products:

- Cesamet® (nabilone)
- Gris-PEG® (griseofulvin)
- Isoptin® (verapamil)
- Kaletra® (lopinavir/ritanovir)
- Sporanox® (itraconazole)
- Rezulin® (troglitazone)

Terms

- Early literature referred to **solid dispersions** as mixtures of polymer and *crystalline* drug
  - Small particle size of crystalline drug would sometimes help improve dissolution
- **Amorphous solid dispersion** is used to describe solid mixtures of polymer and *amorphous* drug
- Other terms that have been used
  - Amorphous dispersion
  - Amorphous solid solution
  - Molecular dispersion
- Need to determine the type of system that is being described when reading literature reports
  - Review characterization data to determine if API is amorphous or crystalline

Polymers

Wide variety of polymers available

- Polymers used as excipients can be used for dispersions
- Handbook of Pharmaceutical Excipients
- Other polymers can be used; tox properties need to be evaluated

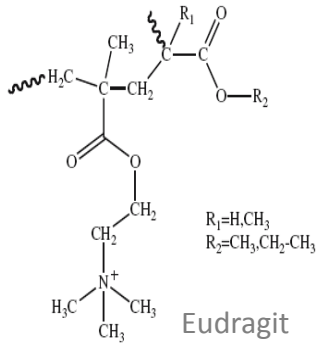
carboxymethylethylcellulose	CMEC
cellulose acetate phthalate	CAP
D-alpha-tocopheryl polyethylene glycol 1000 succinate	TPGS
ethyl cellulose	EC
gelucire 44/14	
hydroxyethyl cellulose	HEC
hydroxypropyl cellulose SL	HPC-SL
hydroxypropylmethyl ellulose	HPMC
hydroxypropylmethyl ellulose acetate succinate	HPMC-AS
hydroxypropylmethyl cellulose phthalate	HMPCP
methacrylic acid copolymer (Eudragit)	
methylcellulose	MC
pluronic F-68	
poloxamer 188	P188
polyethyene glycol	PEG
polyethyene glycol monomethyl ether	PEG MME
polyoxyethylene (40) stearate	S40
polyoxyethylene–polyoxypropylene copolymers (Poloxamer® 188)	
polysorbate 80	
polyvinyl acetate phthalate	PVAP
polyvinylacetal diethylaminoacetate (AEA®)	
polyvinyl pyrrolidone	PVP
polyvinylpyrrolidone vinylacetate	PVP/VA

Note: representative list only

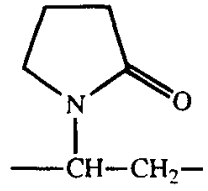
Polymers

Polymer selection

- Empirical approach- choose common polymers
- Manufacturing- need low melting polymers for melt extrusion, need solubility in solvent for spray drying
- Interactions- look at common H-bonding motifs or ion dipole interactions between drug and polymer
  - try to disrupt bonding in crystalline material (example PVP disrupts indomethacin dimers)
- Miscibility and solubility using Flory-Huggins theory- miscible systems show melting point depression, non-msicible systems do not show signficant melting point depression
- Melting point (T_m) and glass transition (T_g) ratio (T_m/T_g)-high ratios may crystallize more easily

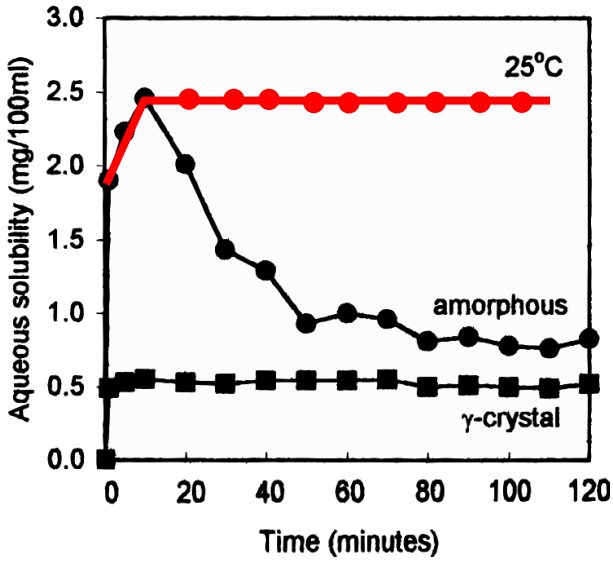


Eudragit


PVP

olymers

- Polymers stabilize amorphous drug in solid-state
- Upon exposure to aqueous media, dissolution is believed to generate a supersaturated state due to the amorphous state of the drug
- Matrix polymer is believed to have a role in preventing precipitation or crystallization from the supersaturated state
  - Drug-polymer interactions
  - Preventing or retarding nucleation and crystal growth



Aqueous solubility profiles for amorphous (●) and α-indomethacin crystal form (■)

Dispersions

Tg of an Ideal Molecular Dispersion

- Assume Ideal Mixing :

$$Tg_{mix} = V_1 Tg_1 + V_2 Tg_2$$

where V = volume fraction

- On the basis of weight fraction (w)

$$Tg_{mix} = \{(w_1 Tg_1) + (K w_2 Tg_2)\} / (w_1 + K w_2)$$

where : $K \sim \rho_1 Tg_1 / \rho_2 Tg_2$ (Gordon-Taylor where ρ is density)

or : $K \sim \Delta Cp_1 / \Delta Cp_2$ (Couchman-Karasz where Cp is heat capacity

- Fox Equation

when $\rho_1 = \rho_2$ in the Gordon Taylor Equation

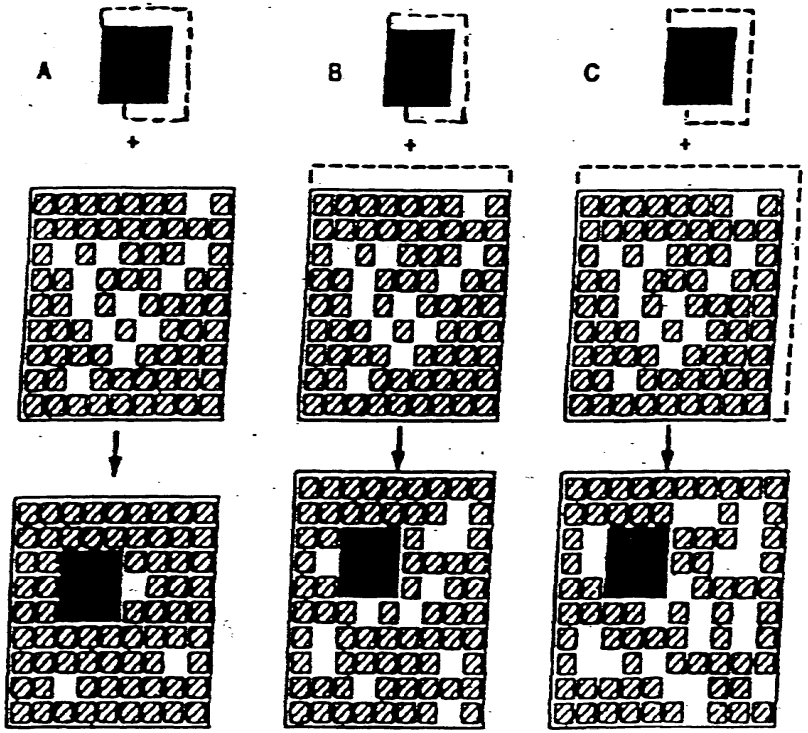
Useful for approximate estimates

$$1/T_{gmix} = w_1/T_{g1} + w_2/T_{g2}$$

Dispersions

Why does non-ideal mixing lead to a greater or smaller Tg than expected?

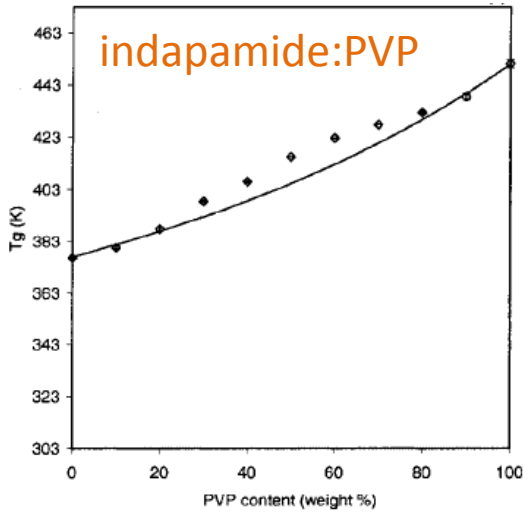
- Depends on the net free volume change

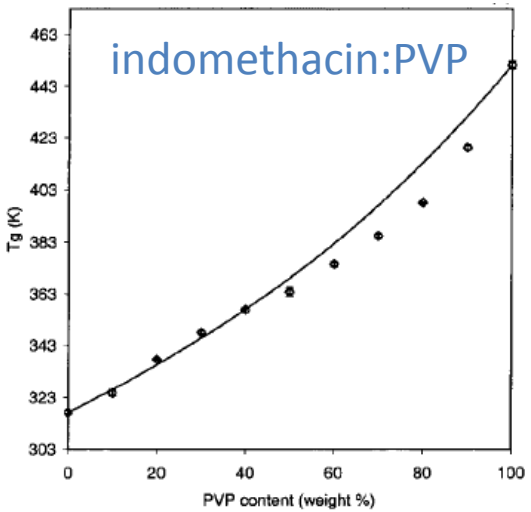


(Tg mix > Tg ideal)

(Tg mix = Tg ideal)

(Tg mix < Tg ideal)





solid line represent Tg values predicted from Gordon-Taylor

Crowley et al. J. Pharm. Sci. 2002, 91, 2150-2165

Manufacture

- Small scale
  - Solvent methods
    - Fast evaporation, rotary evaporation, spray drying
  - Thermal
    - Melt
  - Other
    - Supercritical fluid, lyophilization, ultra-rapid freezing
- Large scale
  - Spray drying
  - Melt extrusion

http://www.mybuchi.com/

http://www.niro.com/niro/cmsdoc.nsf/WebDoc/ndkk5hvdwpPRODUCTIONMINORSprayDryersize

http://www.leistritz.com/extrusion/en/04_products/pharmaextruder.html

Characterization

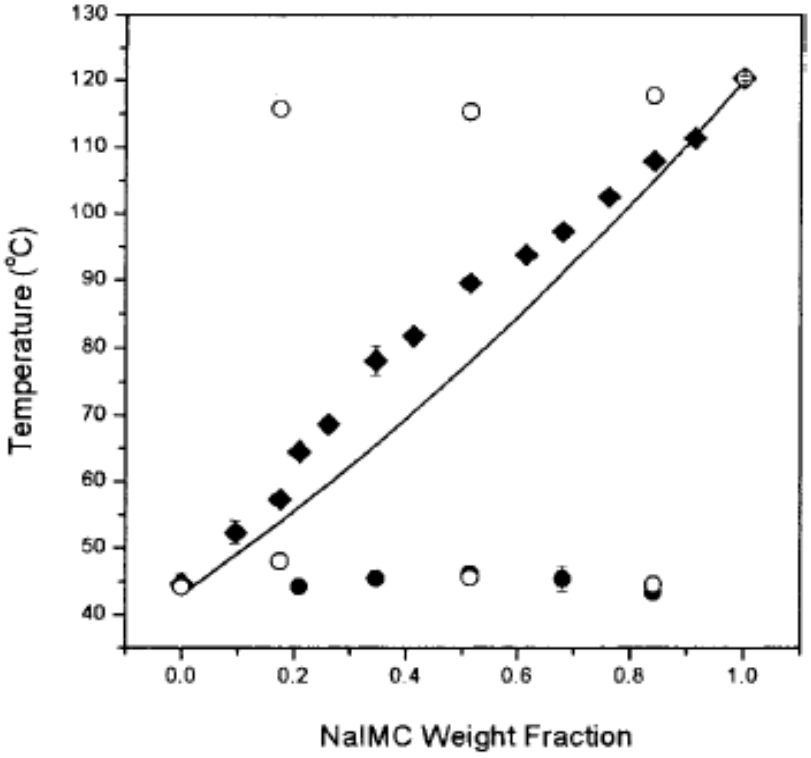
- Diffraction
  - Powder diffraction, low angle scattering, computational methods
- Thermal
  - DSC, Dynamic mechanical analysis (DMA), dielectric analysis (DEA)
- Spectroscopic
  - IR, Raman, NMR spectroscopy
- Solution calorimetry
- Microscopy
  - Optical, scanning electron microscopy (SEM), atomic force microscopy (AFM)
- etc

Miscibility

- Miscible system more stable than physical mixtures
- Ways to investigate miscibility
  - DSC
    - One Tg indicates miscible system
  - XRPD Computational
    - Pair distribution function (PDF)
    - XRPD data cannot be described by individual components indicates a miscible system
  - Spectroscopy
    - Shows association of molecules in a miscible system

Miscibility

- A physical mixture will give two glass transition (Tg) temperatures
- A solid amorphous dispersion will give a single Tg that will change with composition
- Can have positive or negative deviations from theory
- May be a spacial resolution limit with DSC (30 nm)
- Thermal data and other characterization data may not agree



Glass transition temperature for different types of amorphous mixtures of NaIMC and IMC. (●) T_g of physical mixtures measured by DSC and (○) by MTDSC. (◆) T_g of coprecipitated mixtures measured by DSC. The solid line is the predicted value of T_g, assuming ideal mixing behavior, by the Gordon-Taylor equation.

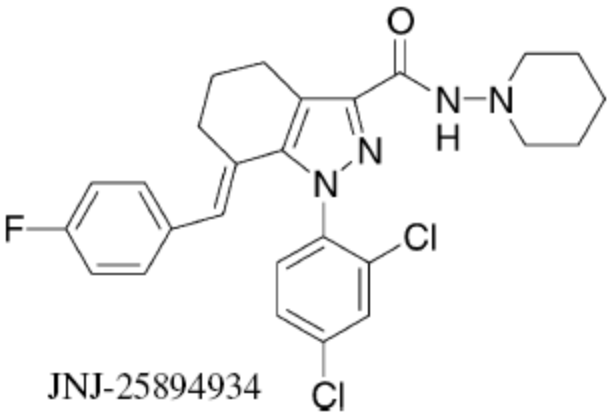
Tong and Zografi. J. Pharm. Sci. 2001, 90, 1991-2004

Dispersion Screening

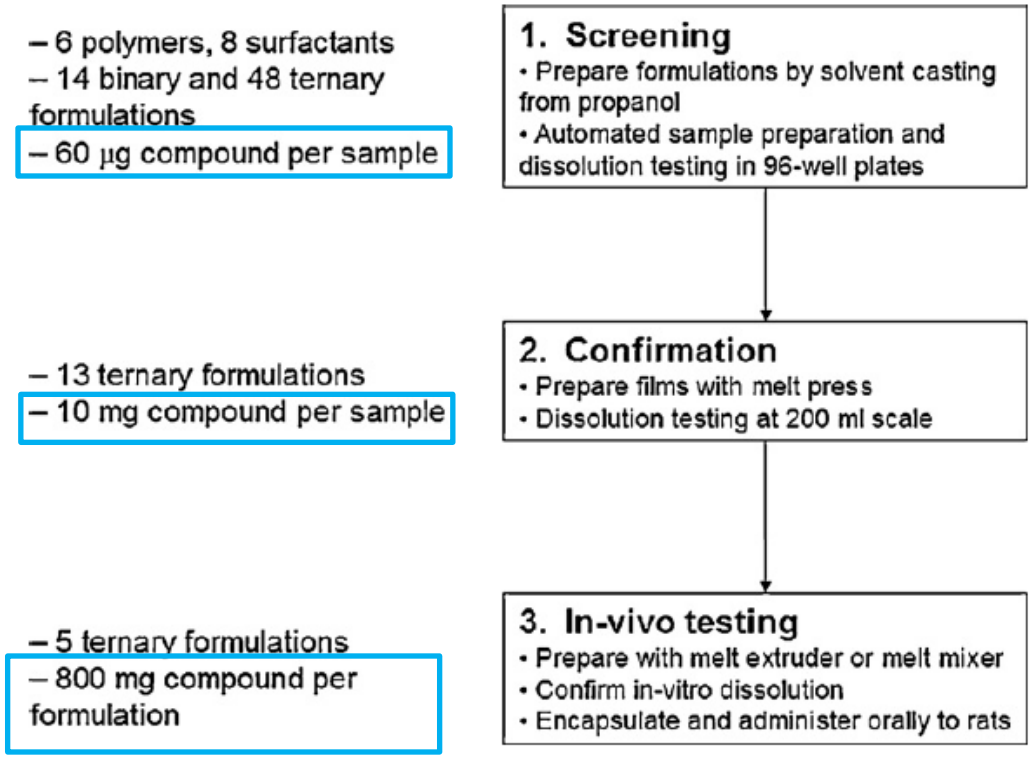
- Variables
  - Different polymers
  - Drug:polymer ratio
  - Binary vs ternary mixtures
  - Solvent
  - Preparation conditions
    - Solvent (evaporation, freeze drying)
    - Melt
- Manual and automated (plate) methods available

Dispersion Screening

- Plates used initially
- Scaled up to melt press and then melt extruder
- Included in-vivo testing on five formulations



JNJ-25894934

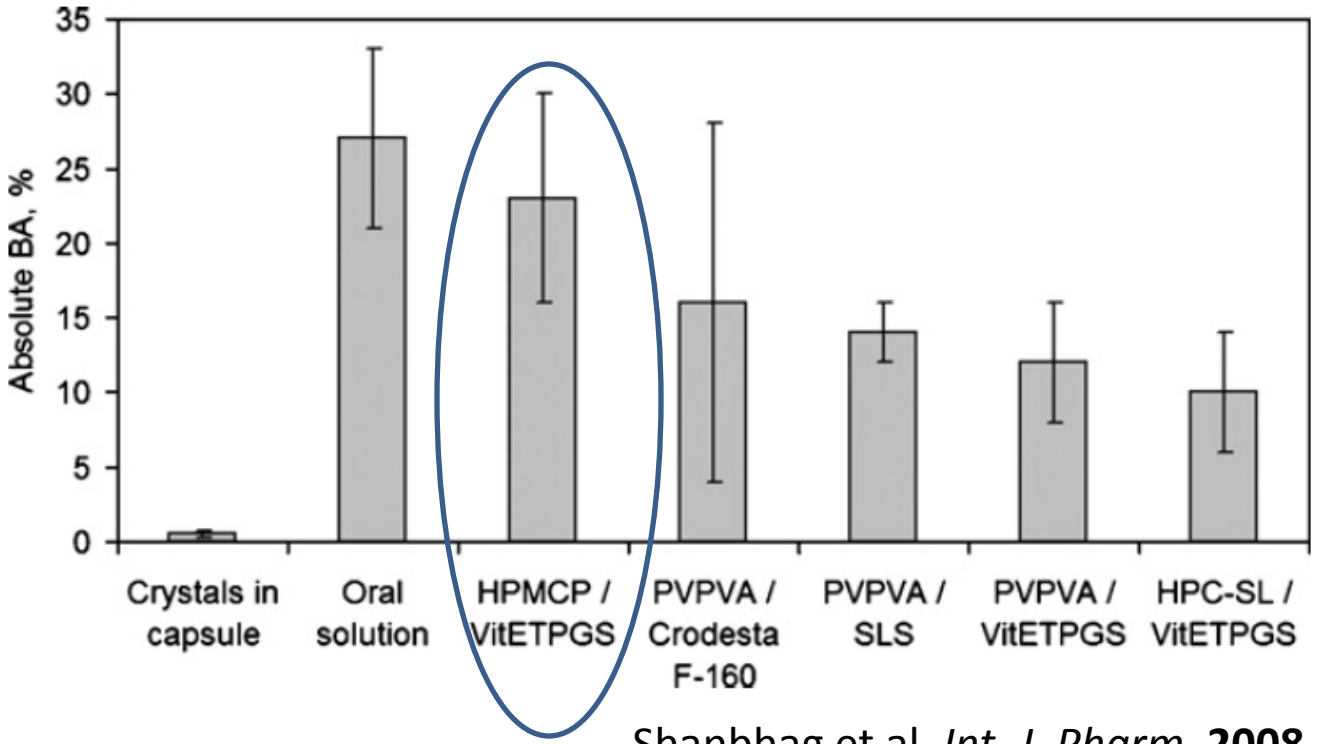


Schematic illustration of the different stages of experimentation. At each subsequent stage, fewer samples are examined; the samples are larger and more compound is used per sample; and the formulation preparation and characterization methods become more relevant to traditional scale formulation development work.

Shanbhag et al. *Int. J. Pharm.* **2008**, *351*, 209-218.

Dispersion Screening

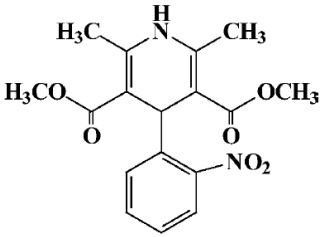
- Oral bioavailability tested for five dispersions and compared to IV
  - HPMCP/TPGS was closest to oral solution for absolute bioavailability
- Did not look at crystallinity or physical stability as part of selection process



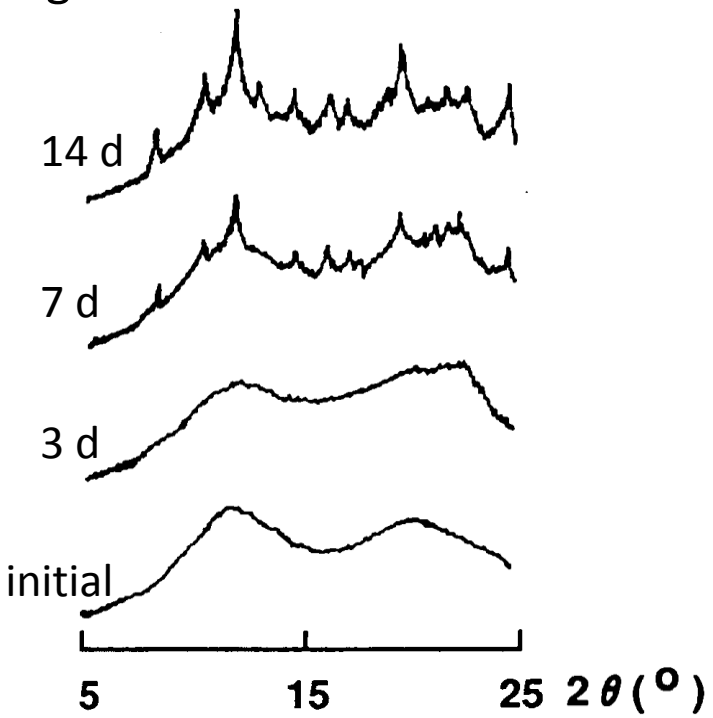
Shanbhag et al. *Int. J. Pharm.* **2008**, *351*, 209-218.

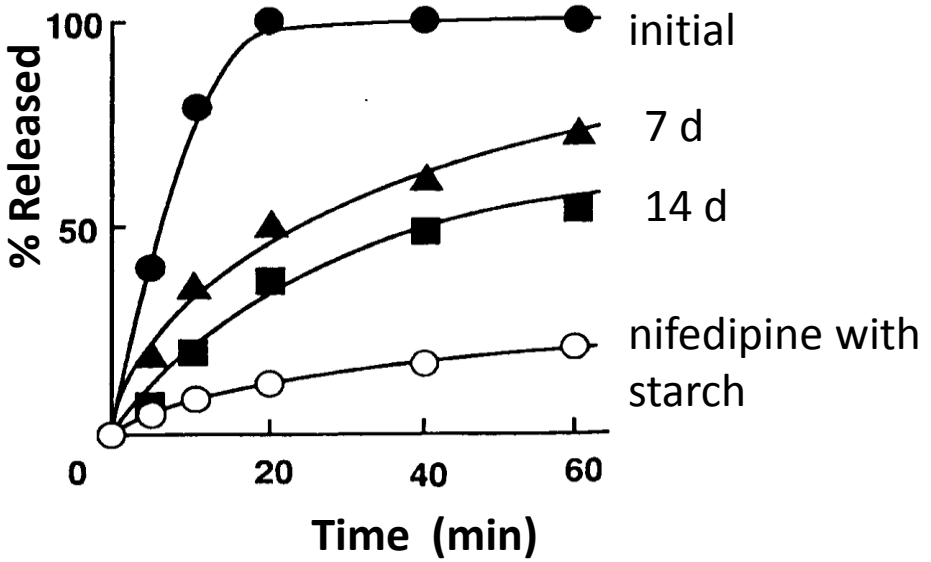
Properties

Physical Stability



- 1:4 Nifedipine:PVP amorphous dispersions compressed into tablets
- Stored at 60°C/75% RH
- Dissolution measured in 900 mL of water with 0.1% surfactant at 37°C
- Slow down in dissolution due to crystallization of nifedipine during storage



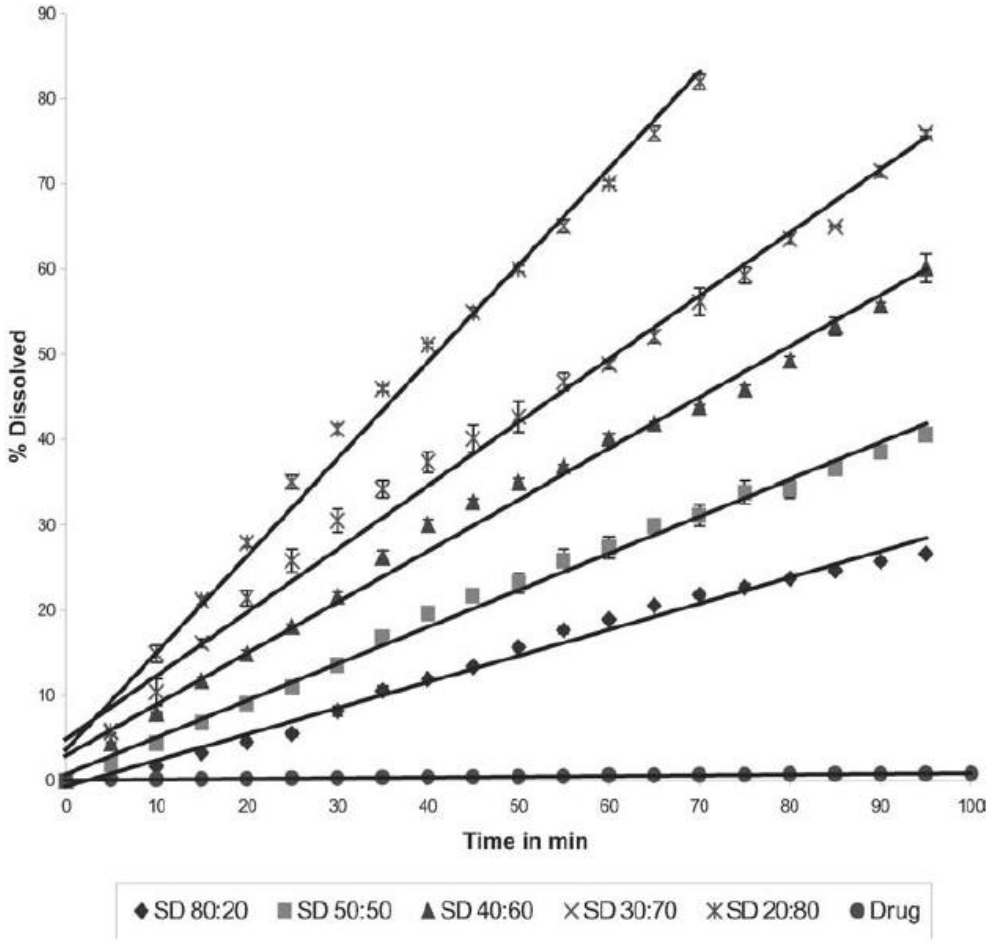


Uekama et al *J. Pharm. Pharmacol*. **1992**, *44*, 73-78

Properties

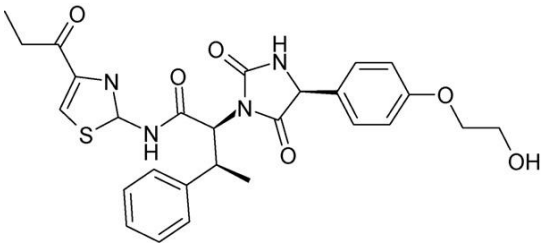
Dissolution

- Dispersions with polaxamer 188 (P188)
- Dissolution in SGF at 37 °C
- No crystallization observed
- Significant increase over API



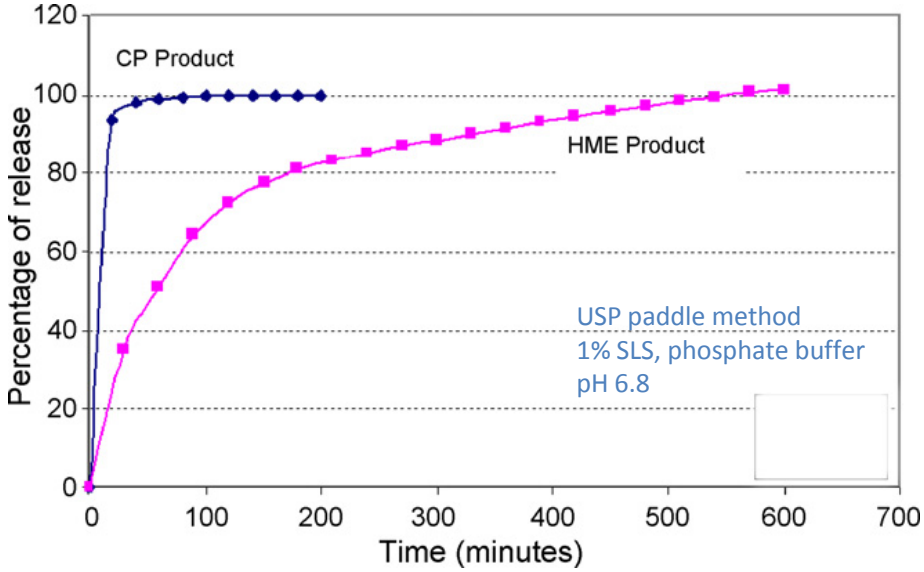
Chokshi et al. *Drug Delivery* **2007**, *14*, 33-45

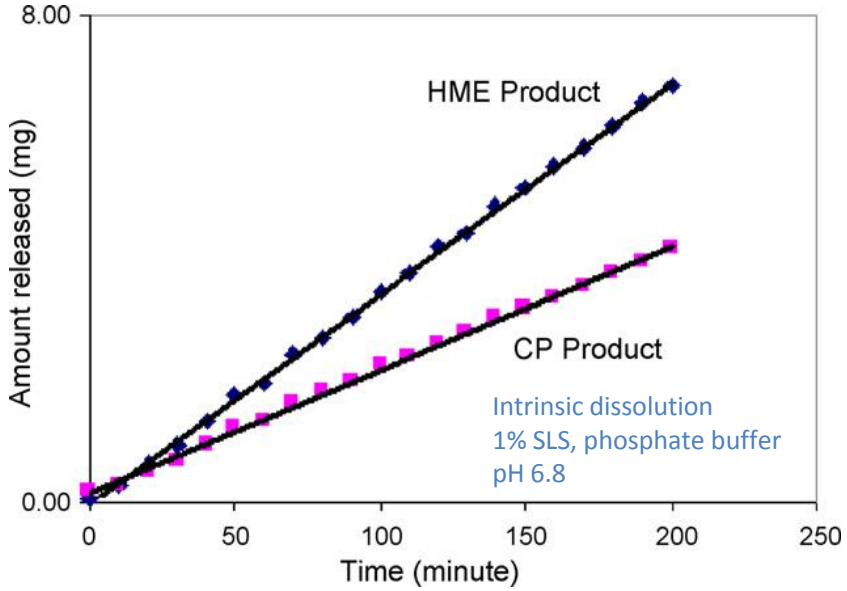
Properties



Dissolution

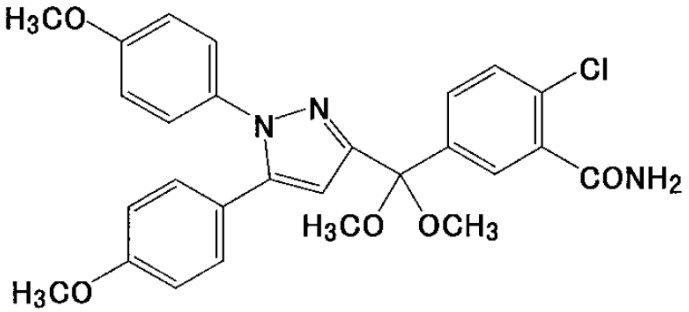
- Dispersions with HPMCAS made from hot melt extrusion (HME) and coprecipitation (CP)
- 40% drug loading
- Physical properties similar except for surface area
  - CP 6.19 m^2/g; HME 0.13 m^2/g
- Dissolution rate different for the preparations





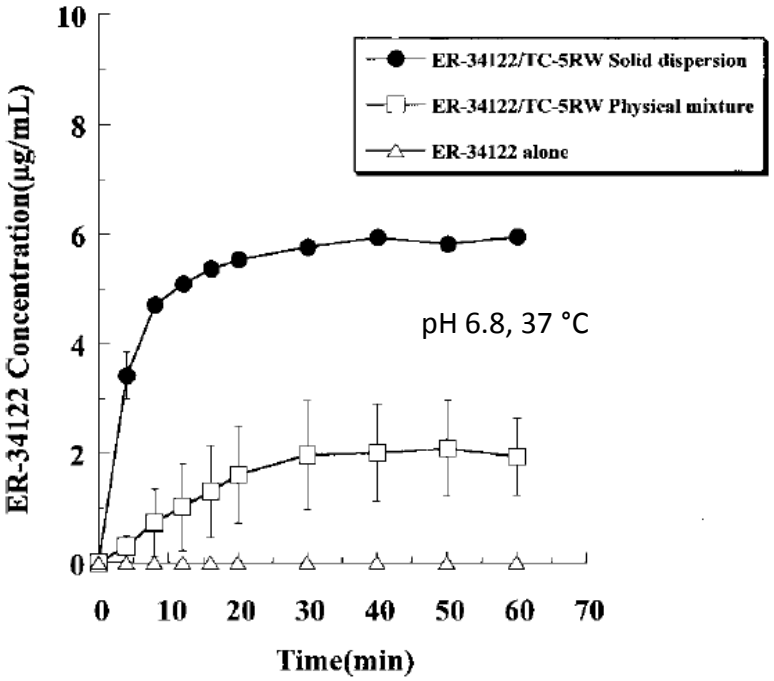
Dong et al. *Int. J. Pharm*. **2008**, *355*, 141-149

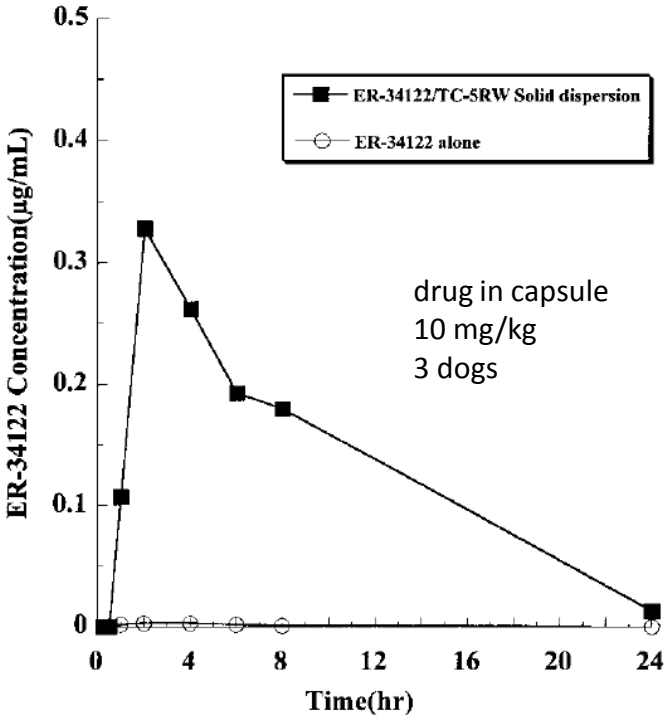
Properties



Bioavailability

- 1:1 ER-34122:HPMC (*TC-5RW*™)
- Dispersion showed faster dissolution and higher bioavailability than crystalline material



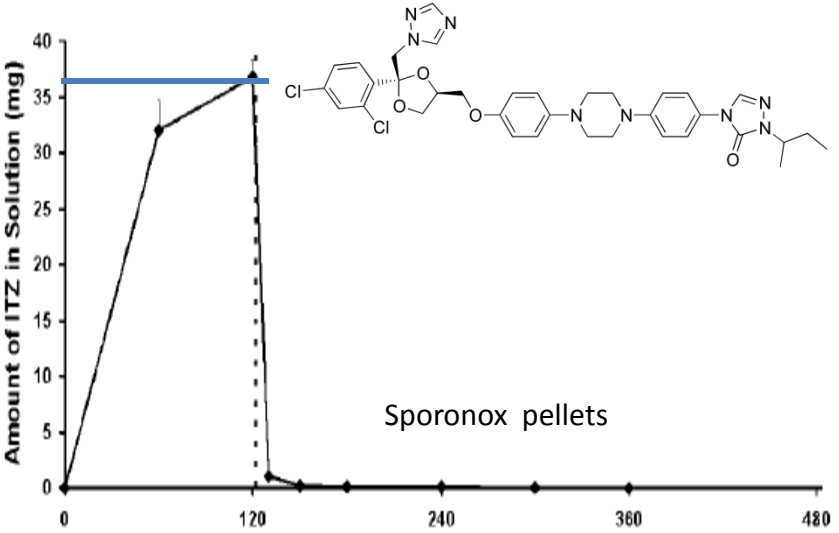


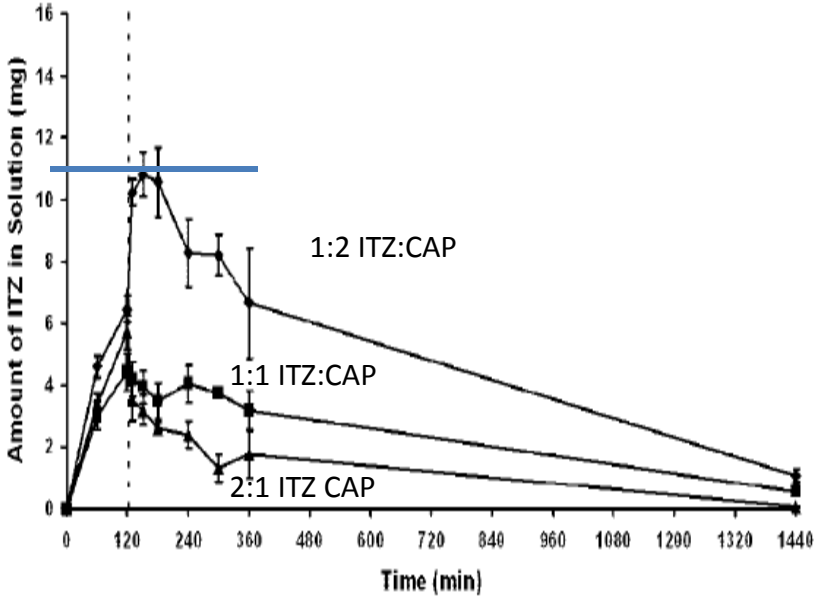
Kushida et al. *J Pharm. Sci*. **2002**, *98*, 251-256.

Properties

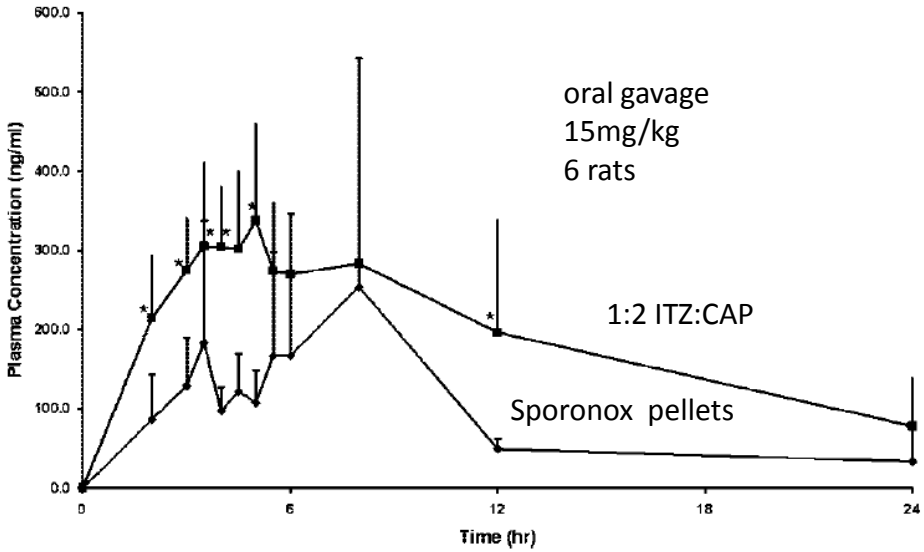
Bioavailability

- Itraconazole (ITZ): CAP dispersions
- Sporonox faster dissolution and higher concentration
- 1:2 ITZ:CAP dispersion gave better bioavailability
- No IVIVC (in vitro-in vivo correlation)





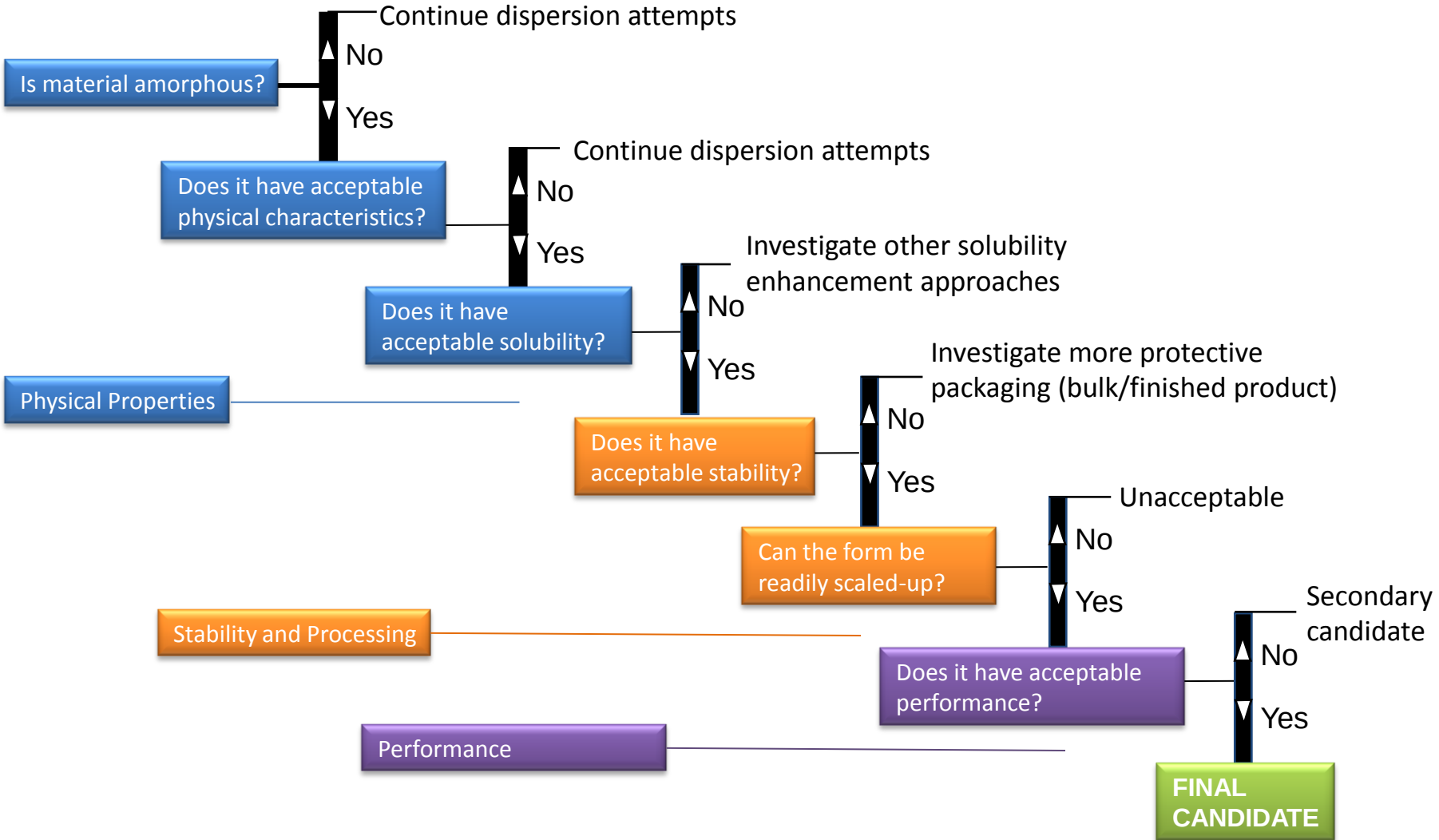
Testing in 0.1N HCl for 2 hours followed by pH adjustment to 6.8 + 0.5 with 250 mL of 0.2 M tribasic sodium phosphate solution. Dashed lines indicates time of pH change.



Dinunzio et al. *Mol. Pharm*. **2008**,*5*,968-980

Dispersion Selection

Decision tree for dispersion screening



What Have We Learned

- Amorphous
  - Exhibits increased apparent solubility and dissolution rate compared to crystalline materials
  - Can result in poor physical and chemical stability
  - Characterization can include Tg, enthalpy relaxation, fragility
- Amorphous solid dispersions
  - Polymers added to stabilize amorphous material
  - Can perform screens to find possible dispersions
  - Manufacture: spray drying vs melt extrusion for larger scale
  - Performance
    - Dissolution, stability, bioavailability
    - May or may not have in vitro-in vivo correlation (IVIVC)
    - Can use simple prototype formulations (powder in capsule) for early studies; additional work may be needed for later studies

Resources

Amorphous

Hancock and Zografi, J. Pharm . Sci. 1997, 86-1-12

Bhugra and Pikal. J. Pharm. Sci. 2008, 97, 1329-1349

Yu. Adv. Drug Deliv. Rev 2001, 48, 27-42

Taylor and Shamblin. Amorphous Solids In "Polymorphism in Pharmaceutical Solids", 2nd edition, Ed. H. Britain, 2009

Amorphous Solid Dispersions

Leuner and Dressman. *Europ. J. Pharm. Bioparm*, **2000**, *50*,47-60

Serajuddin. *J. Pharm. Sci*. **1999**, *88*, 1058-1066

Friesen et al. *Molec. Pharm*. **2008**, *5*, 1003-1019

Curatolo et al. *Pharm. Res*. **2009**, *26*, 1419-1431

Qian et al. *J. Pharm. Sci*. **2010**, early view, 10.1002/jps.22074

Chiou and Riegelman, *J. Pharm. Sci*. **1971**, *60*, 1281

Marsac et al. *Pharm. Res*. **2009**, *26*, 139-151.

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