Module 2: Preformulation

PHYSICO-CHEMICAL PROPERTIES OF API

Impact on Formulation Development

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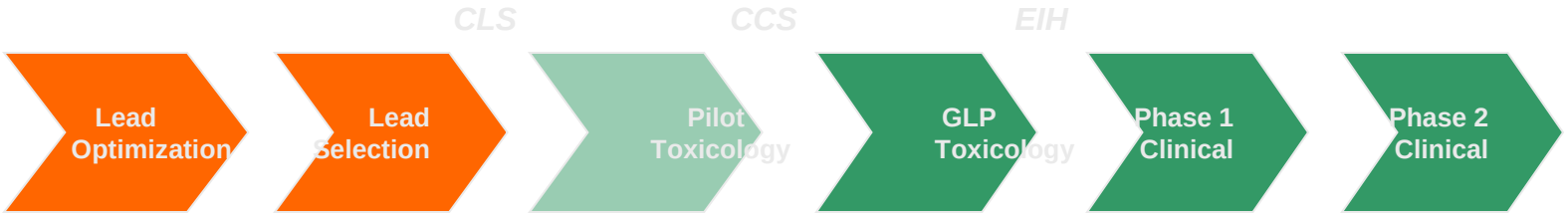
Overview

- 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

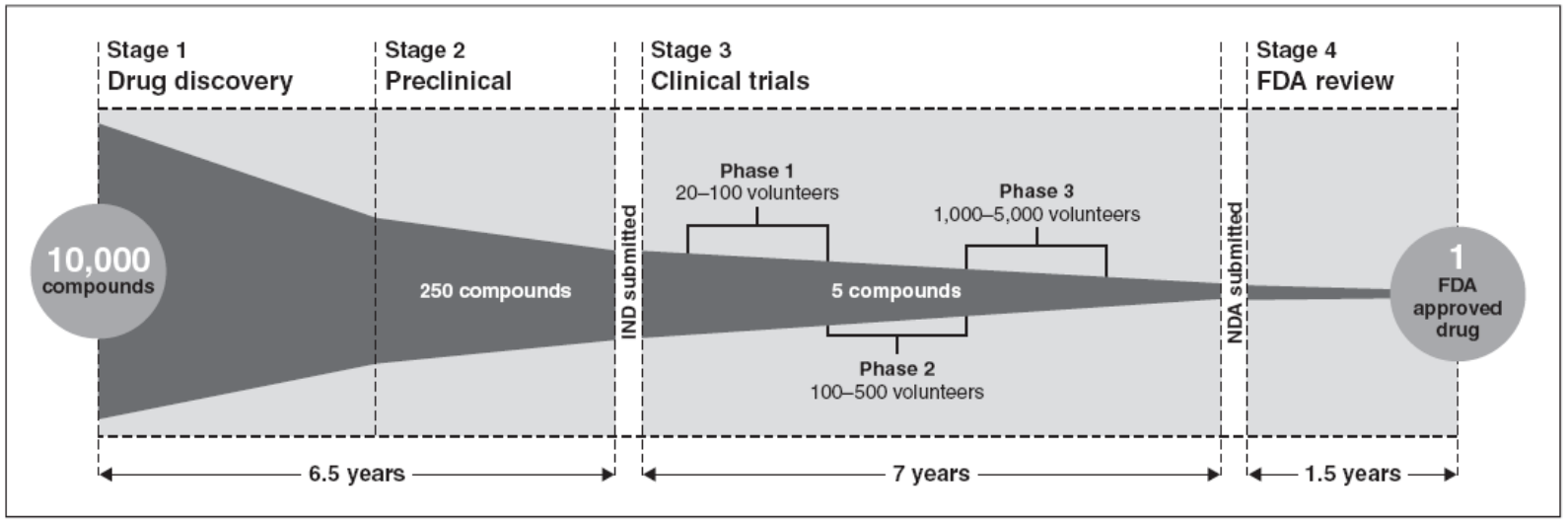
Preliminary Preformulation

- 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



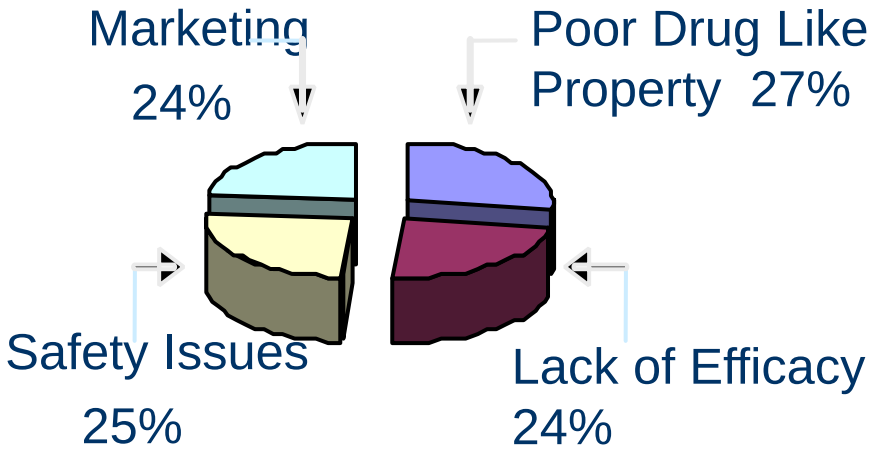
Source: Pharmaceutical Research and Manufacturers of America.

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

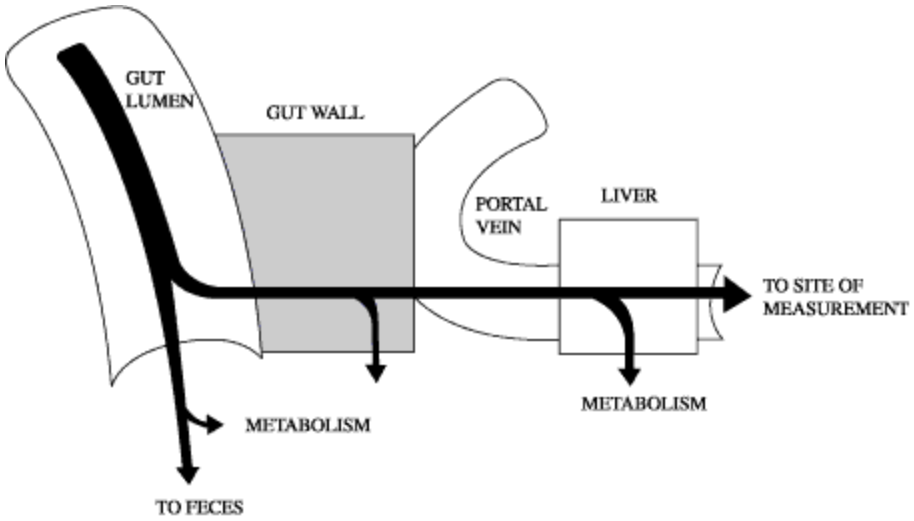
Molecular Wt

H Bonding

Solubility

Polar Surface Area

Stability



pKa

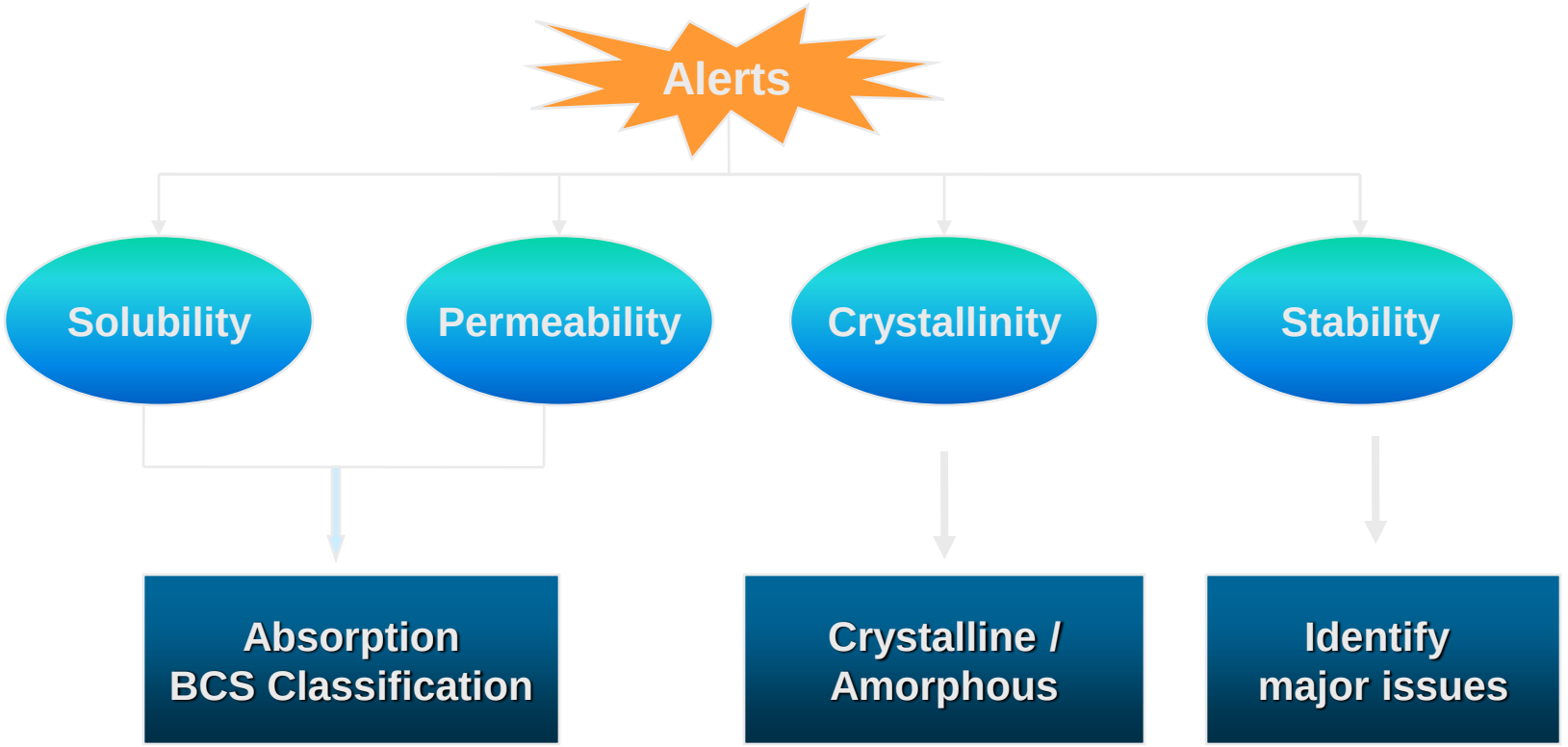
Lipophilicity (Log P / D)

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

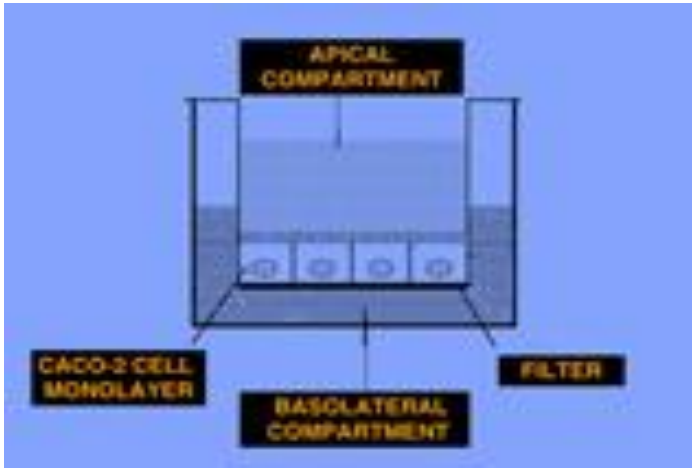
- Extent of absorption in humans:
  - Mass-balance pharmacokinetic studies.
  - Absolute bioavailability studies.

- 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)

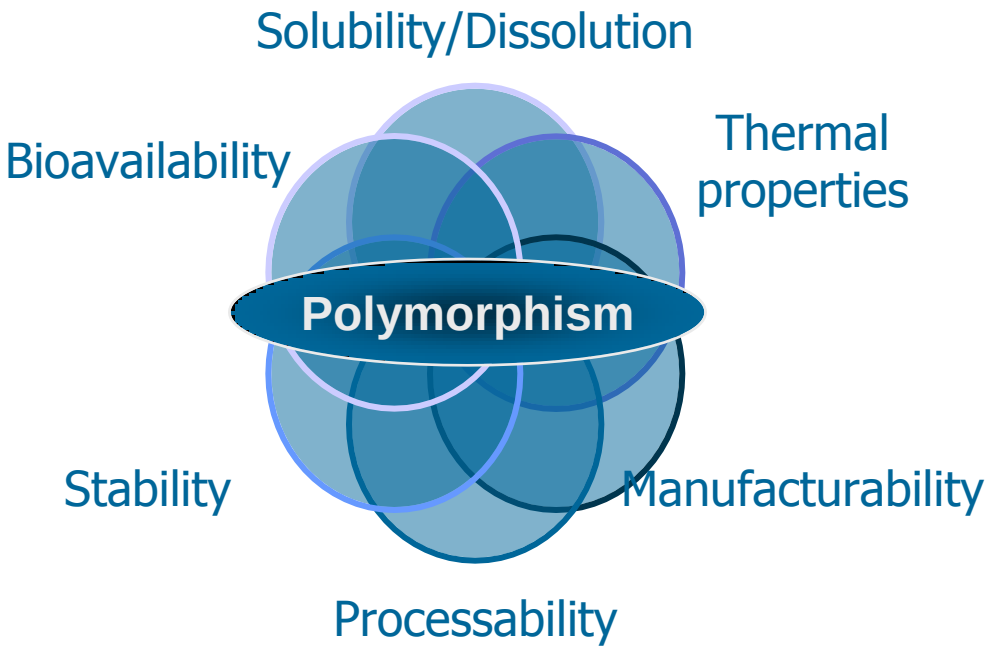
- Example
  - Ranitidine
    - Dose = 300 mg
    - Cs = 100 mg/mL
    - Do = 300 mg / 100 mg/mL / 250 mL = 0.006 : high solubility
  - Acetaminophen
    - Dose = 750 mg
    - Cs = 0.1 mg/mL
    - Do = 750 mg / 0.1 mg/mL / 250 mL = 30 : low solubility
  - Digoxin
    - Dose = 0.25 mg
    - Cs = 0.01 mg/mL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

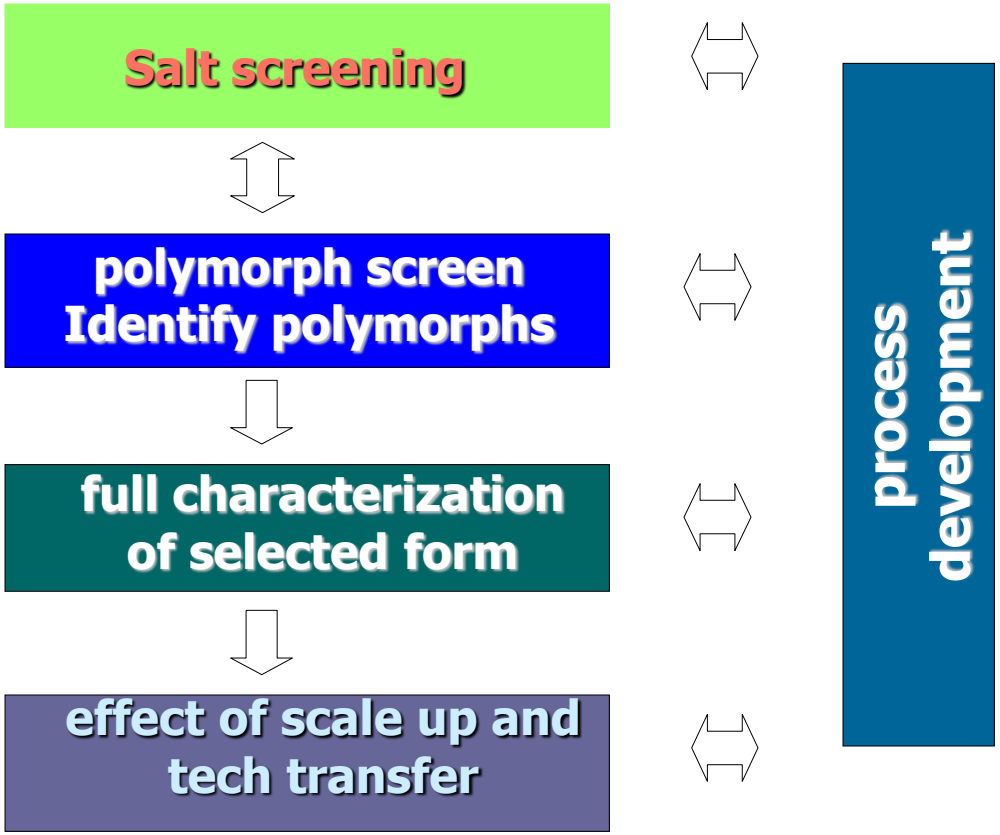
- It is regulatory requirement
- It provides strong IP position
- Polymorphs have different mechanical property impacting on manufacturability of drug
- Polymorphs have different solubility and dissolution rates, potentially leading to lower or higher biological activity than desired.
- Polymorphs can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

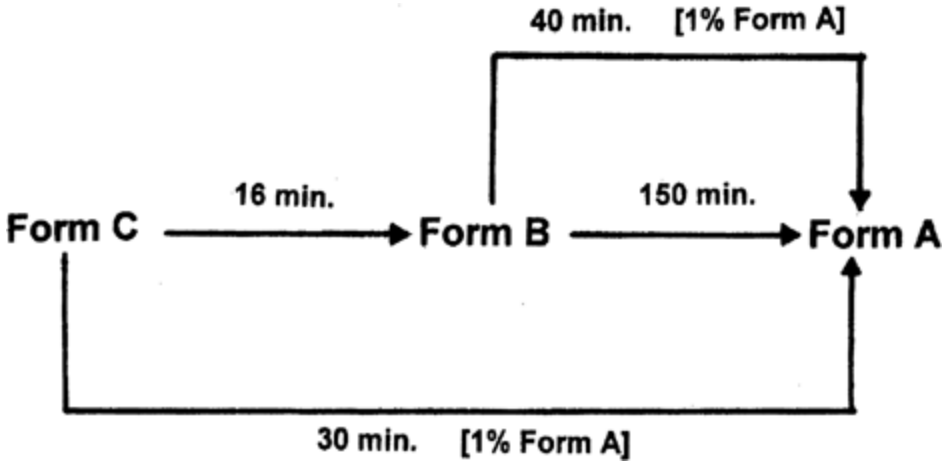
- Solvent composition and polarity
- Drug concentration and degree of supersaturation
- Temperature and cooling rate
- Presence of seed crystals and nucleation sites
- Additives to modify crystalline lattice
- Agitation rate, pH, salt
- Processing time
- Presence of impurities

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%

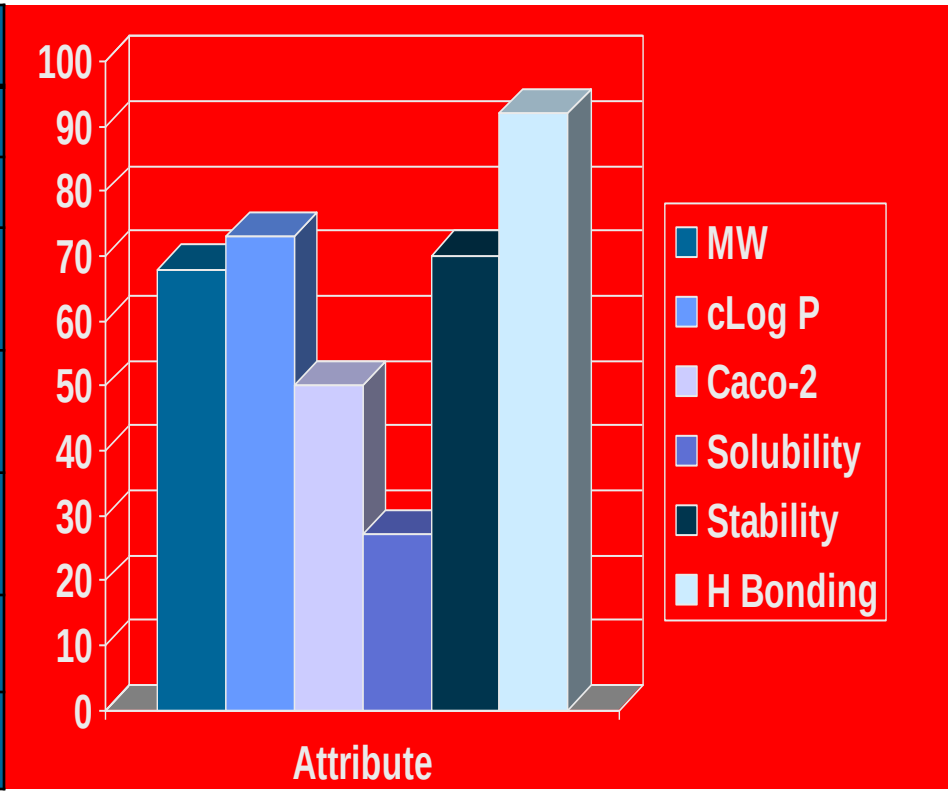
Pro-Drug Design

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

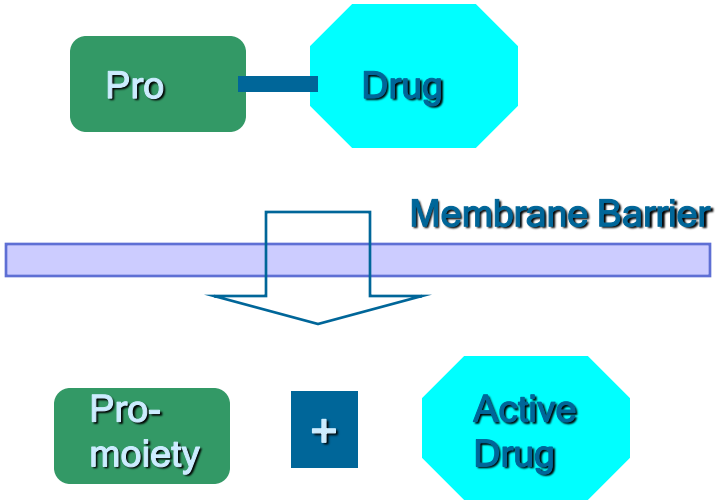
- Total 25 pro-drugs were synthesized and evaluated for drug like properties
  - Biological properties
    - Plasma stability, TDI, Caco-2, etc.
  - Physicochemical properties
    - Solubility, melting point, stability, etc.

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

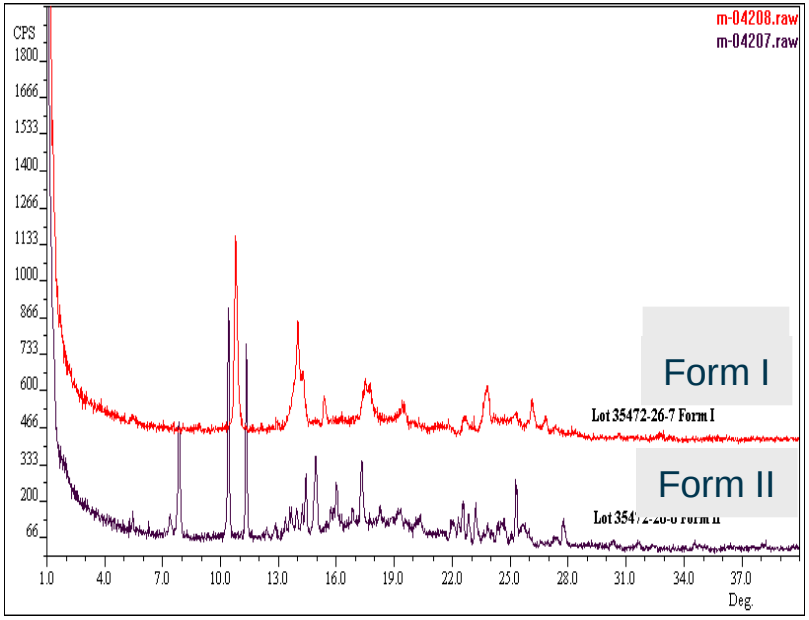
Property	Value
MW (FB)	570
Melting Point	248 °C
pKa (basic)	8.3
Caco-2	87 x10^{-7} cm/sec
Intrinsic Solubility	3 mg/mL
Bio in Rats	33%
Bio in Dogs	41%

Salt and Polymorph Selection

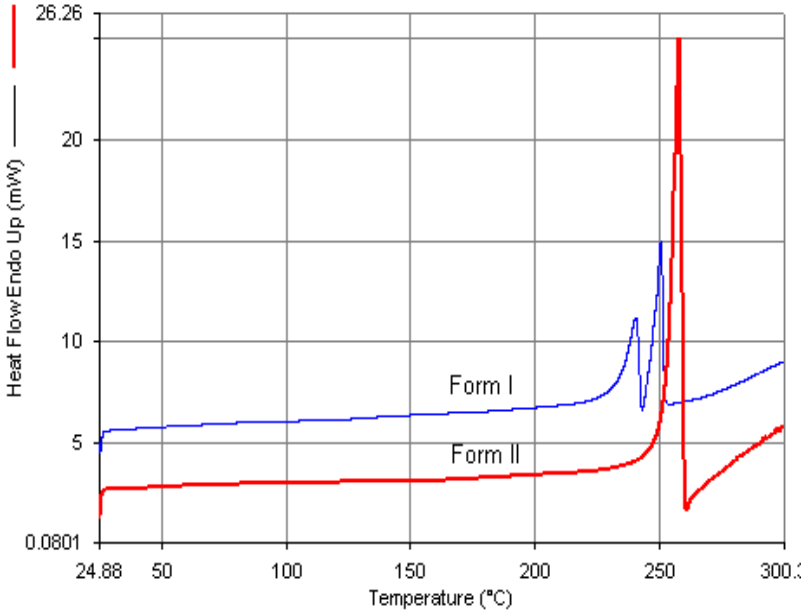
- Following selection of a drug candidate with good pharmacological and physicochemical properties, salt screening was performed
  - HCl salt was selected as final salt form
  - Good solubility and acceptable solid state stability
  - Non hygroscopic
  - Pharmaceutically process-able
- Preliminary polymorph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

Result of Polymorph Screening

Powder XRD showed two distinctive patterns



DSC showed two distinctive thermal transitions



Polymorph Characterization

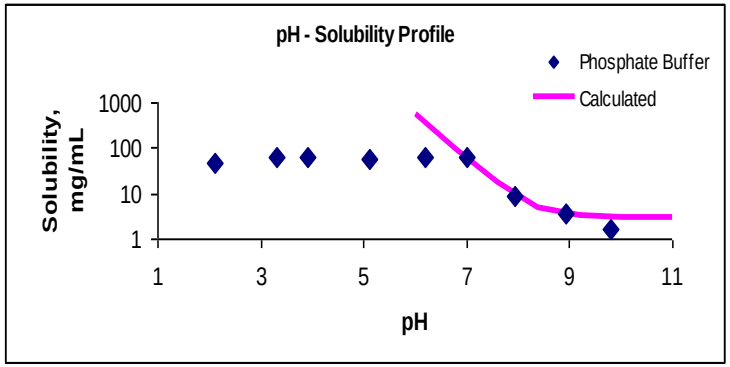
- Solvent mediated transformation study
  - At room temperature, Form I + Form II slurry mixture converted to Form II
  - Form I + II mixture converted to Form II at reflux

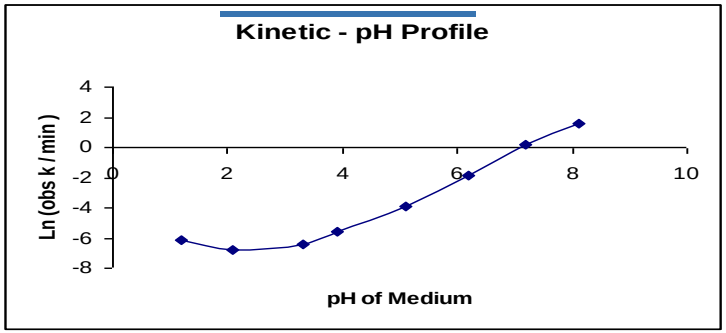
- Aqueous solubility at 25 ºC

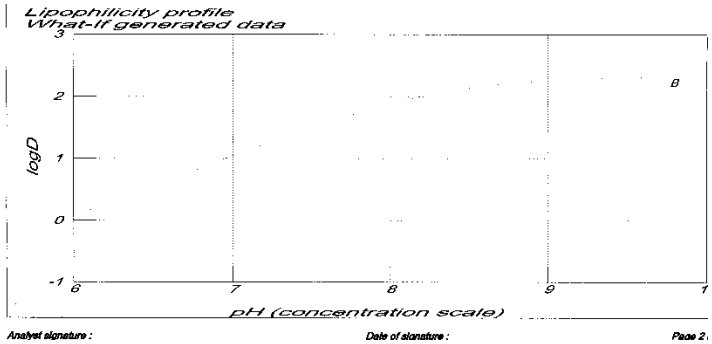
	SGF	SIF	Water
Form I	45 mg/mL	78 mg/mL	86 mg/mL
Form II	28 mg/mL	63 mg/mL	72 mg/mL

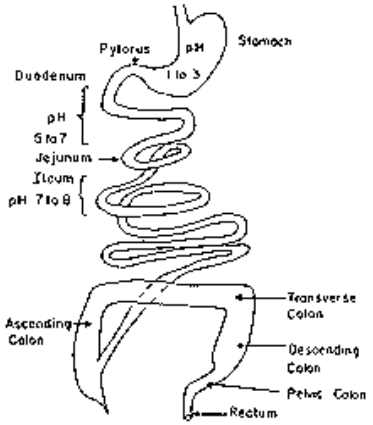
Form II is more stable form (monotropically related)

Physicochemical Property (Form II)



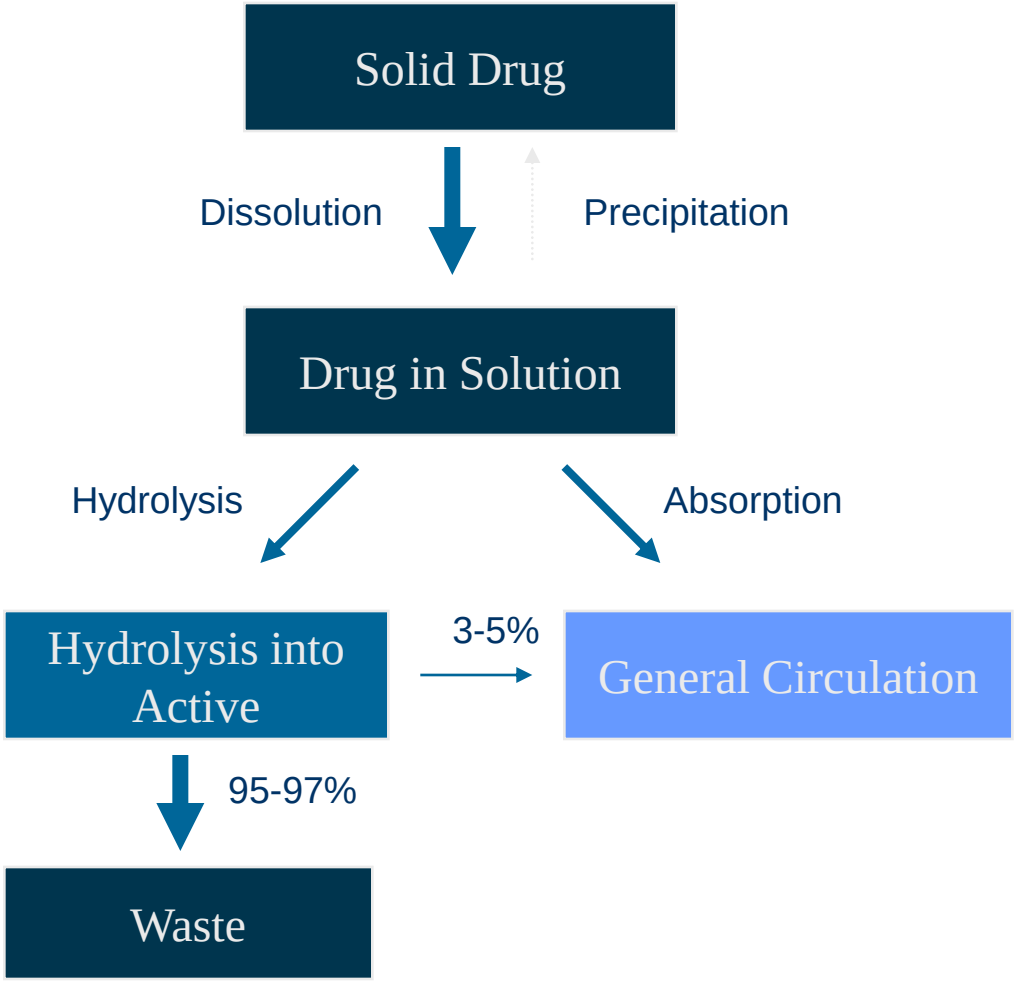


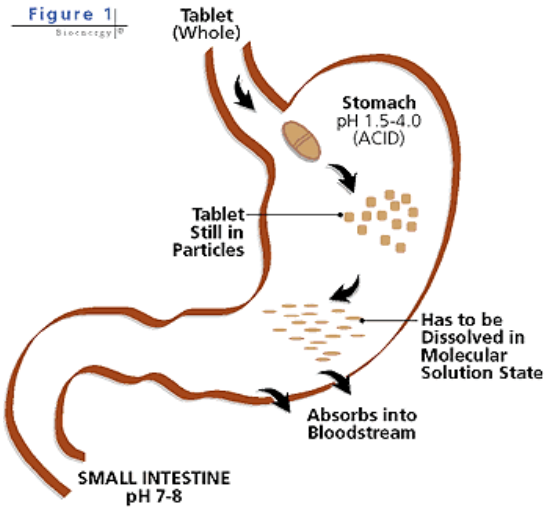




- Good solubility in physiological pH (So = 3 mg/mL)
- Hydrolyzes rapidly at pH > 7, but reasonably stable in pH 2 – 7
- Good partition coefficient, Log D at pH 7.4 = 1.4

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

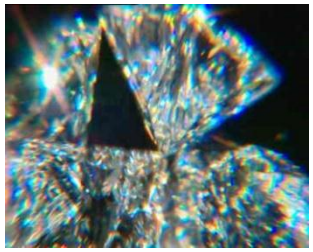
Excellent Team Work
Good Clinical Candidate

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

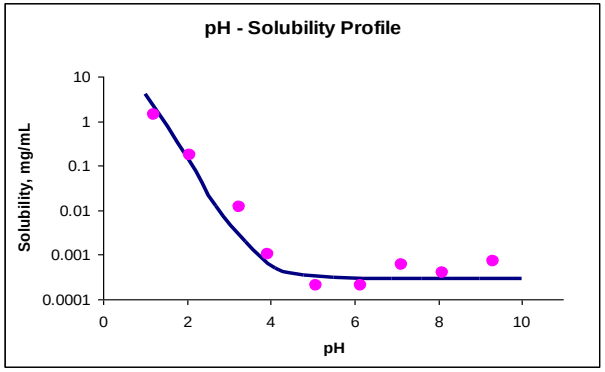
	B-1	B-2	B-3
pK (basic)	4.3	3.9	3.8
Solubility in SGF (pH 1.2)	2.0 mg/mL	> 5 mg/mL	1.4 mg/mL
Solubility in SIF (pH 7.4)	0.0052 mg/mL	0.010 mg/mL	0.0005 mg/mL
Stability in SGF & SIF	Stable	Stable	Stable
cLog P	2.2	2.1	2.3
Caco-2 (10^{-7} cm/sec)	249	51	84
Melting Point	201 °C	185 °C	218 °C
Crystallinity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

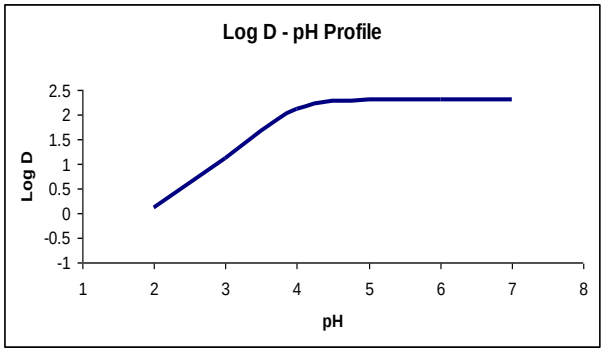
After careful evaluation of all data presented, project team endorsed B-3 as clinical candidate

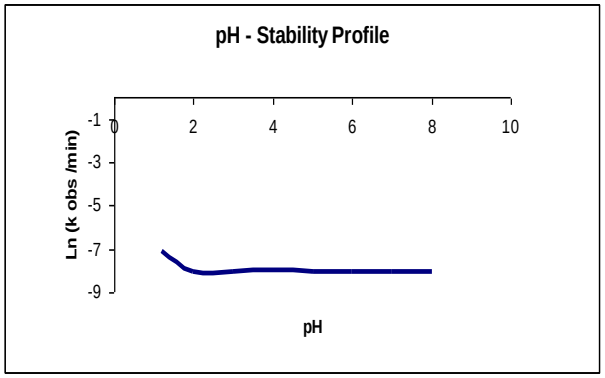
Selection Criteria

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

Physicochemical Property





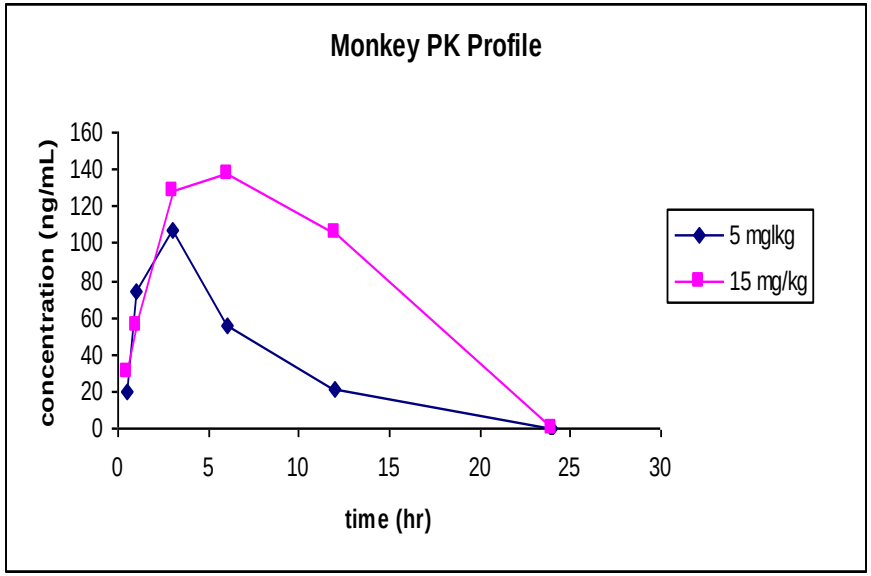


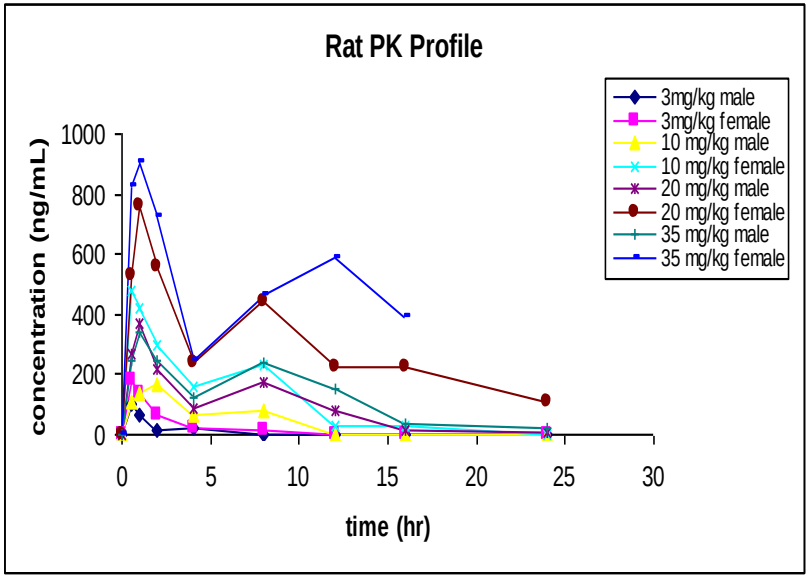
- Reasonable solubility in acidic media but poor solubility in pH greater than 4 (So = 0.0005 mg/mL)
- Good partition coefficient in intestinal pHs (Log D = 2.3 at pH 7.4)
- Chemically stable in gastro intestinal pH range

Dissolution limited absorption is expected

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

Monkey & Rat SD PK Profile

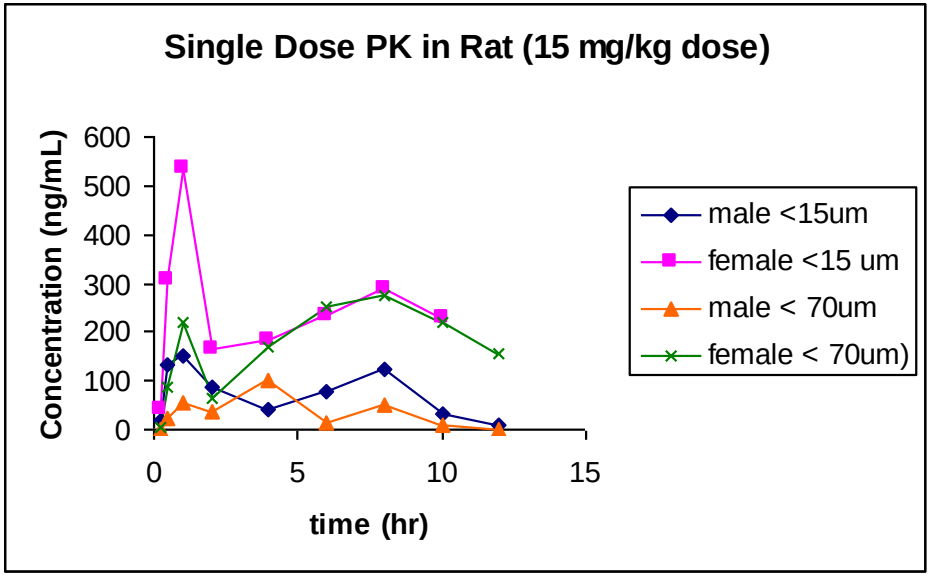




- Bioavailability in rat = 20%
- Bioavailability in monkey = 6% - 10%

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

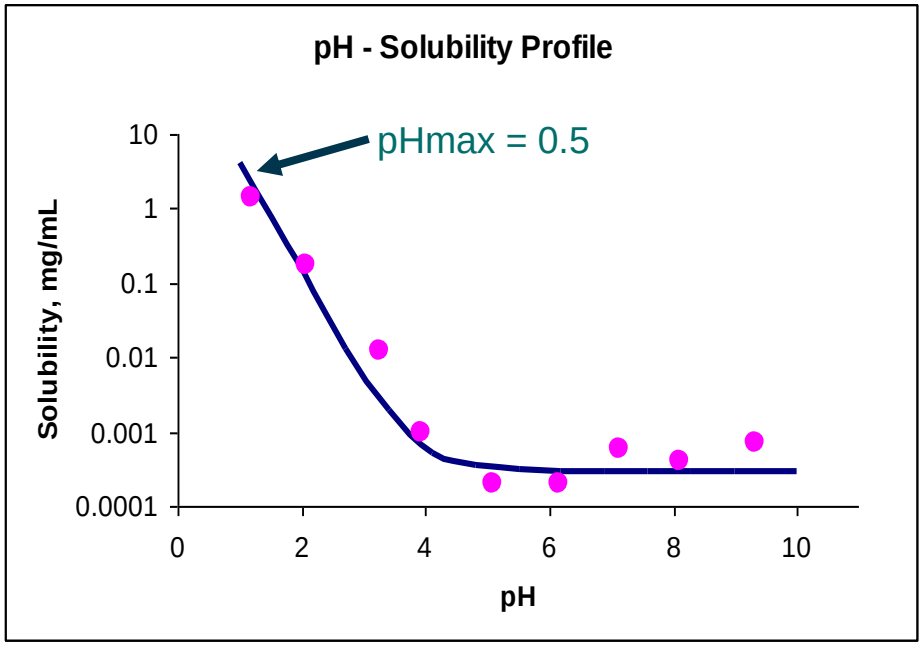
Can salt form provide desired properties?

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

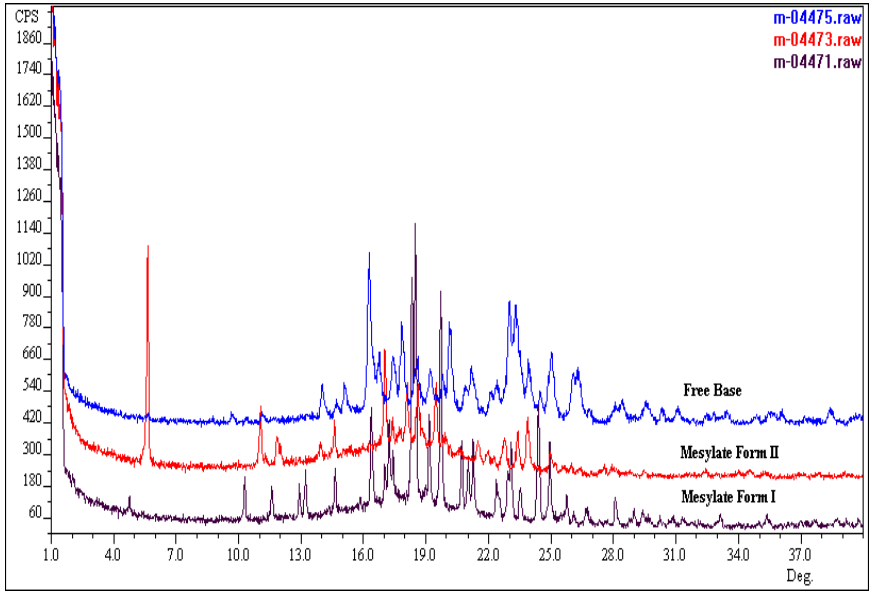
When we put all physicochemical data together

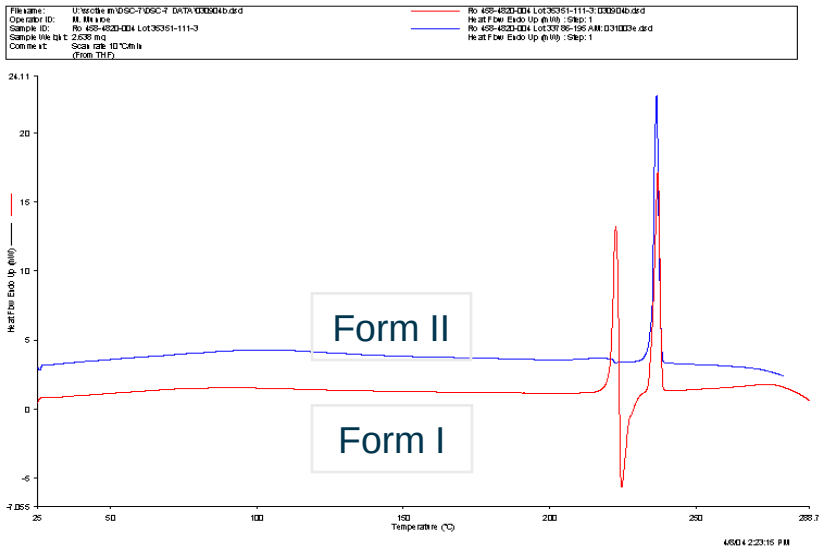
Mesylate Salt

was the winner

Polymorph screening of mesylate salt found two polymorphs

Polymorph Characterization of Mesylate Salt





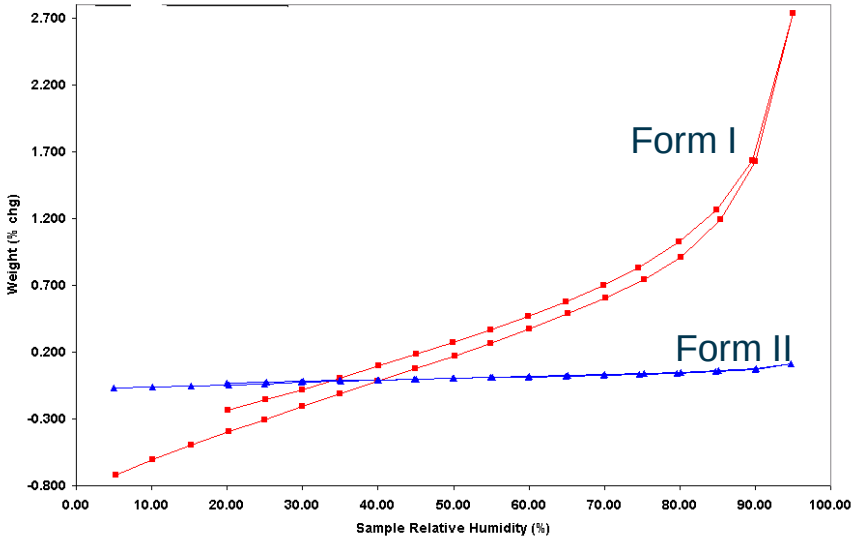
Polymorphs have different PXRD Patterns.

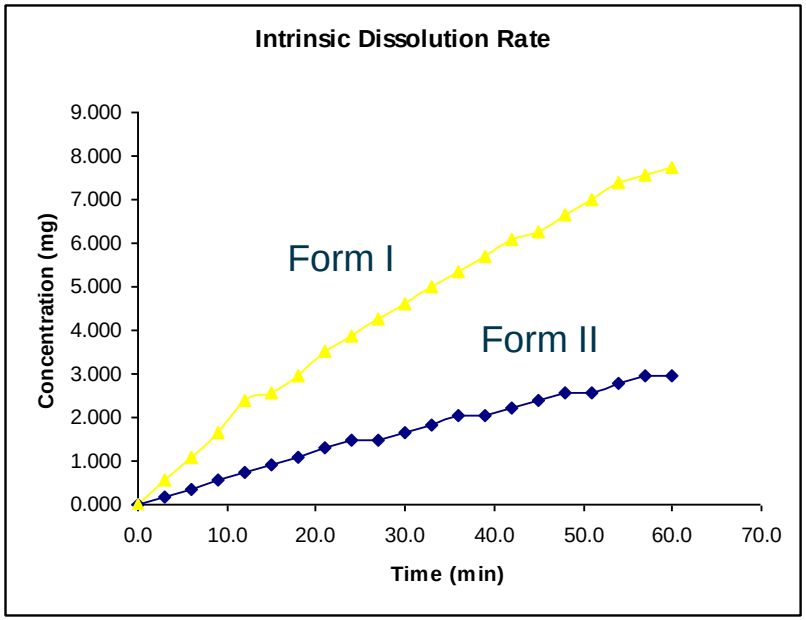
Two XPRD patterns of mesylate salt are shown against free base

Polymorphs have different melting points.

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

Polymorph Characterization of Mesylate Salt





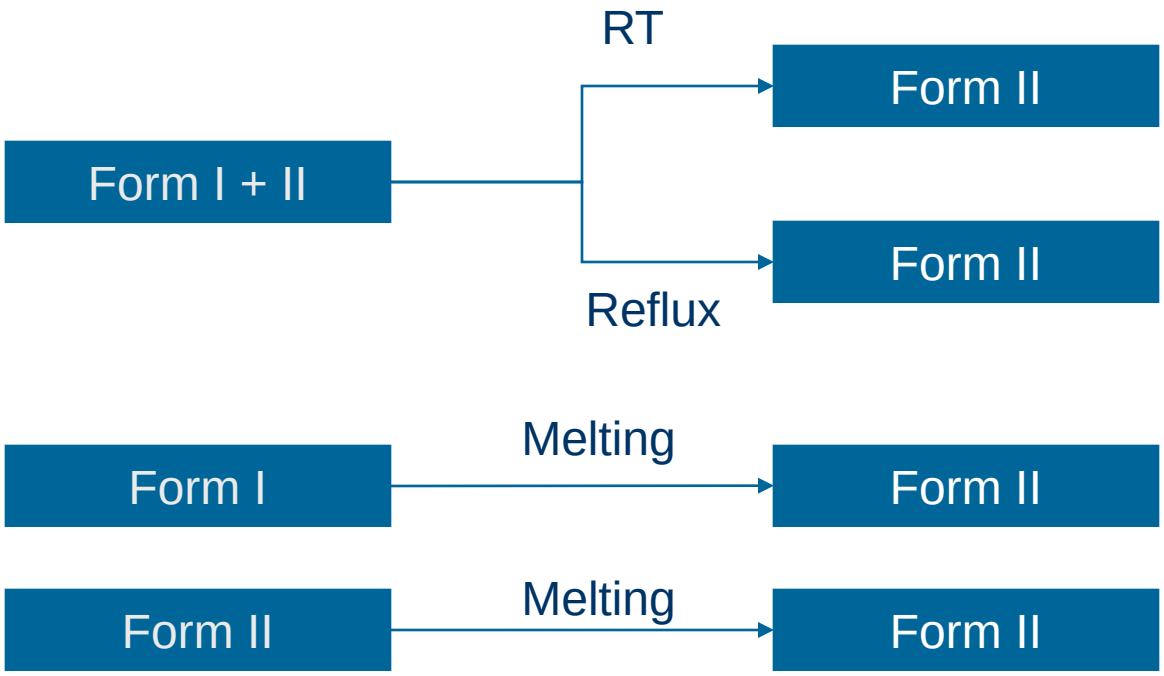
Polymorphs may have different hygroscopicity.

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

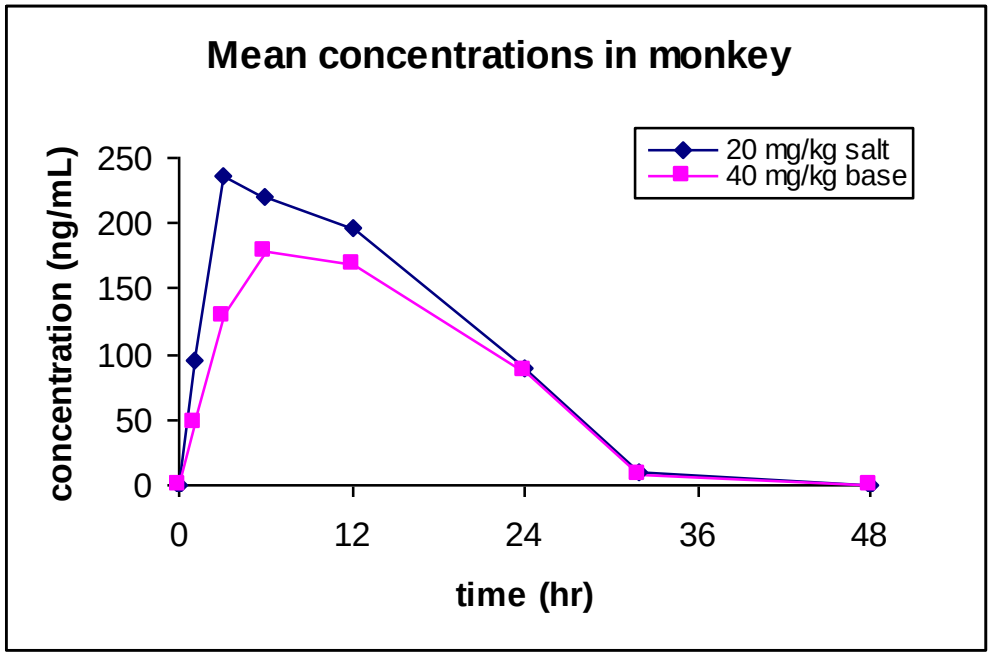


- Form I and II are monotropically related
- Form II is more stable form

Monkey PK Study Result

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

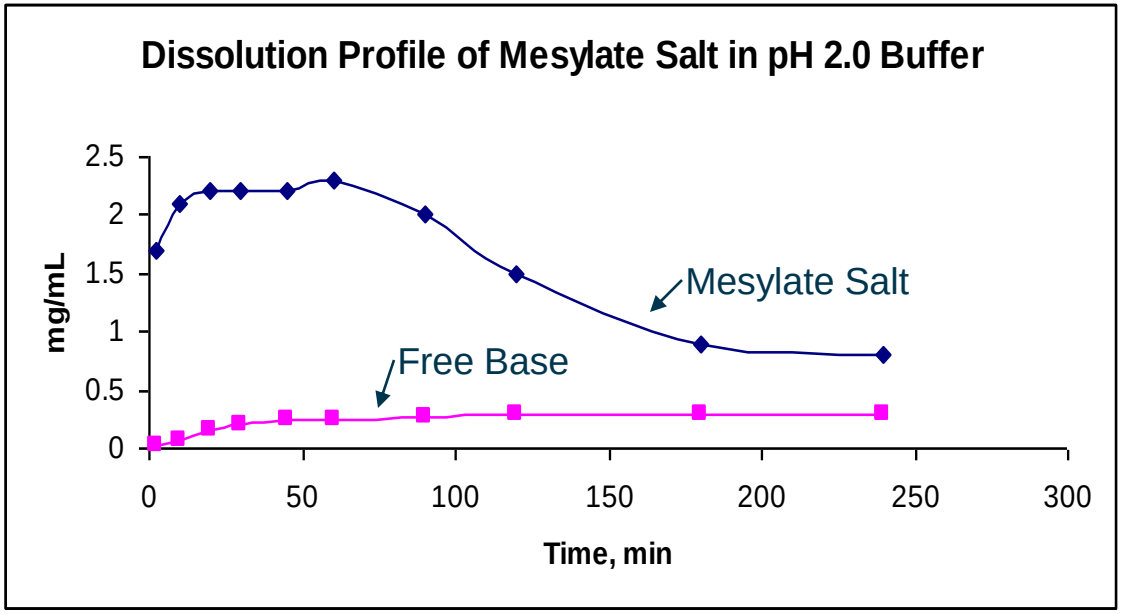
Single Dose PK Study in Monkey
(Mesylate vs. Free Base)



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

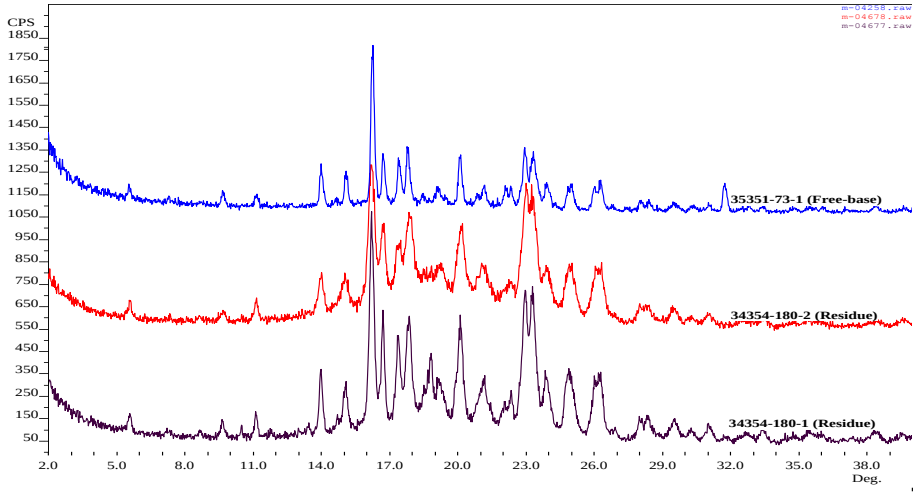
	AUC (ng*hr/mL)	CV (%)	Cmax (ng/mL)
40 mg/kg free base	3502	27	190
20 mg/kg mesylate	4310	32	250

Dissolution Profile of Mesylate Salt



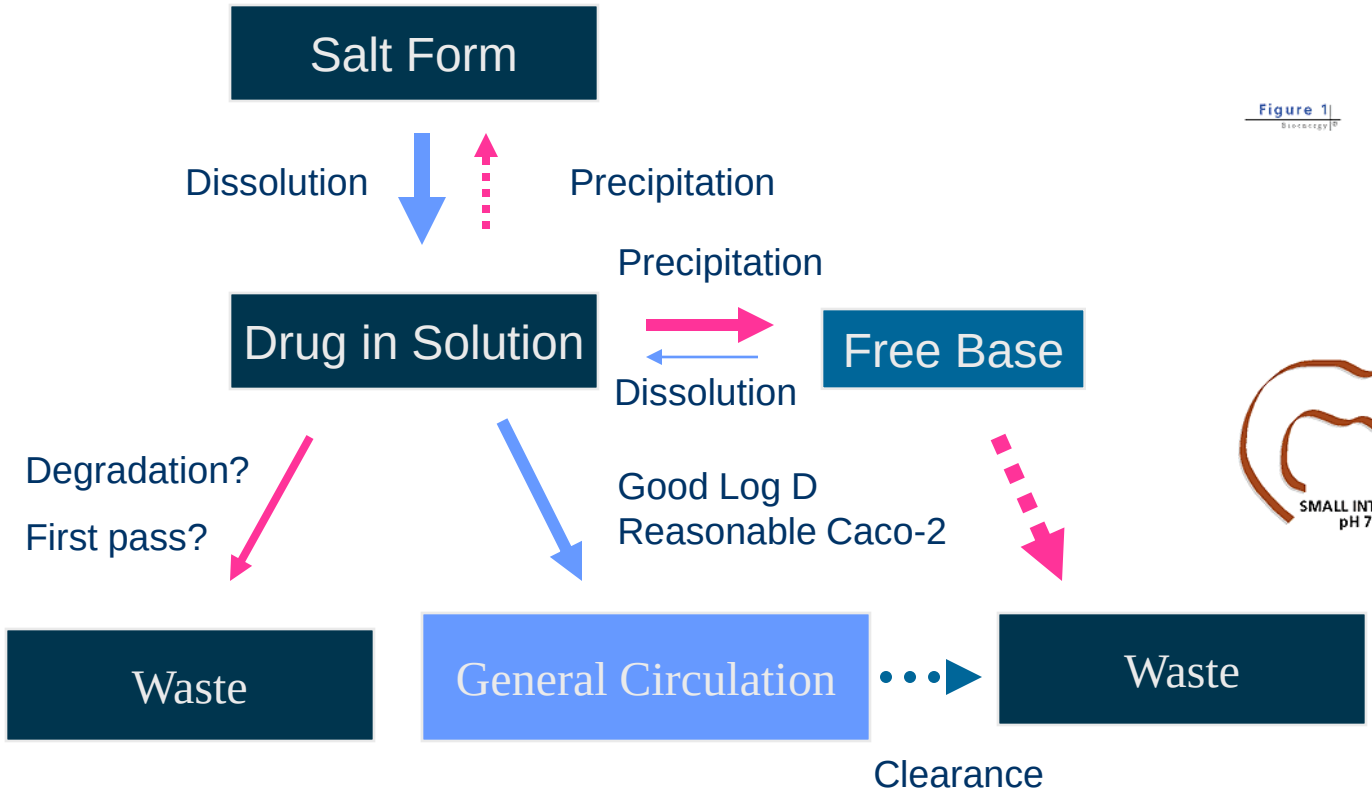
- Mesylate salt dissolves rapidly into a transient equilibrium state in 20 min, and begins to precipitate after 2 hours.
- Free base dissolves gradually into an equilibrium state in an hour.

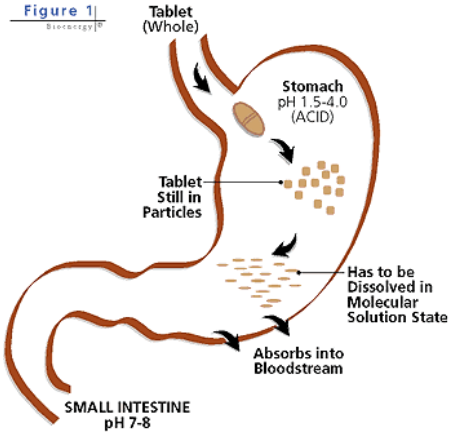
Mesylate Residue in Aqueous Media



- 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?

Practical Uses of Amorphous Materials; Features and Stability

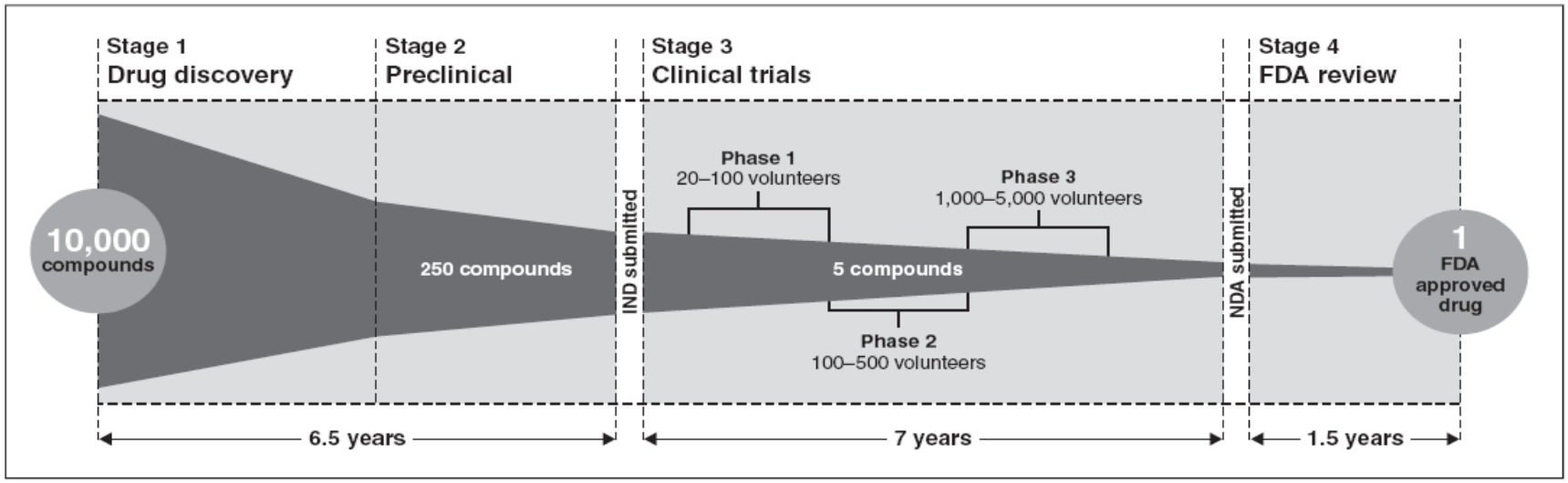
Duk Soon Choi, Ph.D.

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



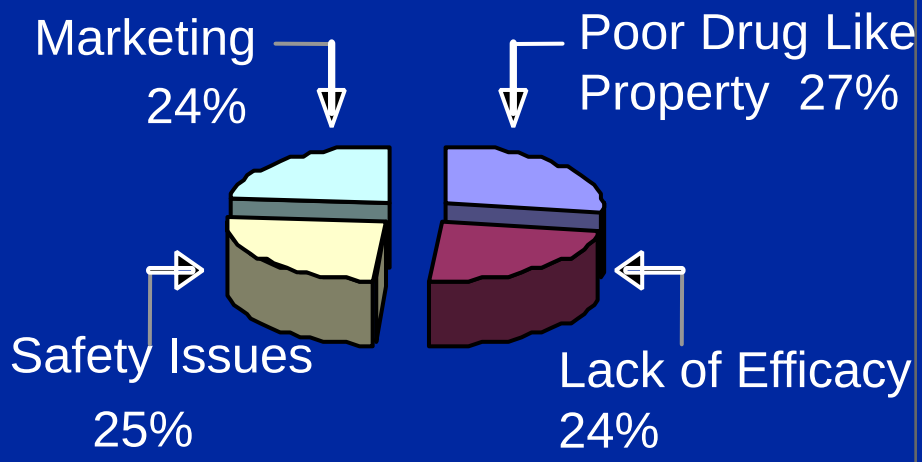
Source: Pharmaceutical Research and Manufacturers of America.

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**

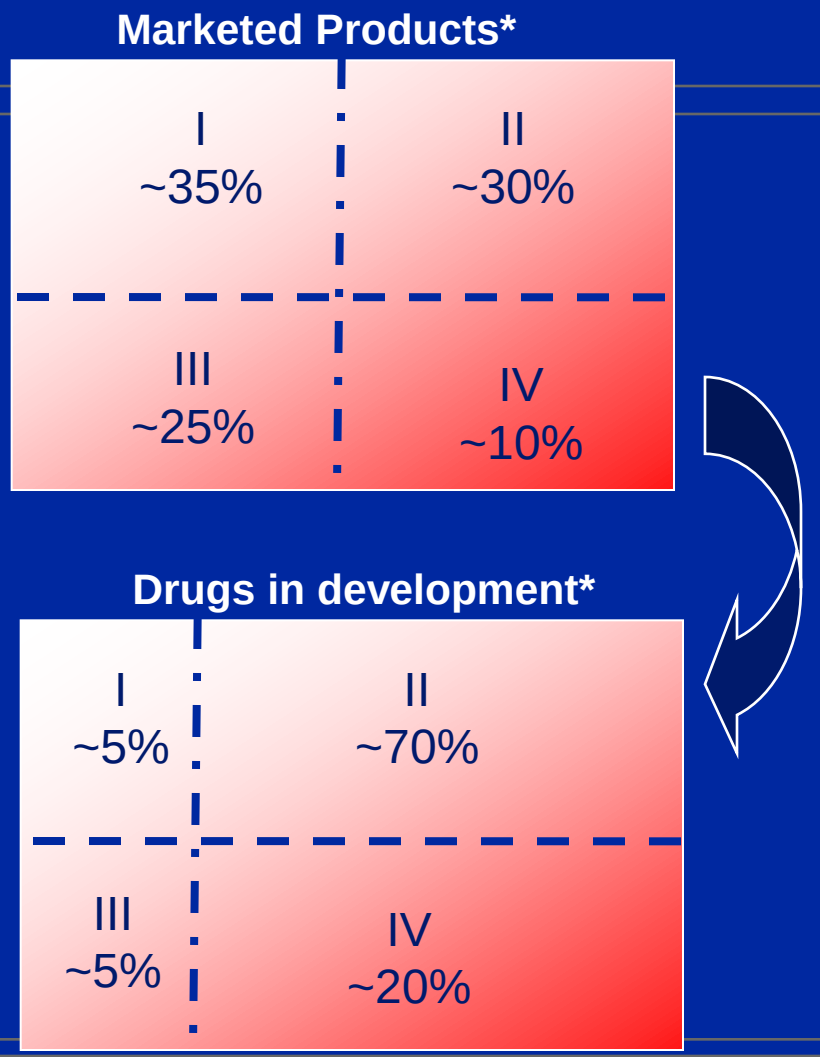


- **Reasons for slowdown**
  - Synthetic complexity
  - Low potency
  - Ambiguous toxicity findings
  - Complex target indication
  - Manufacturability – stability and consistency
  - **Poor drug like properties**

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

Poorly Water Soluble Compounds; A growing challenge

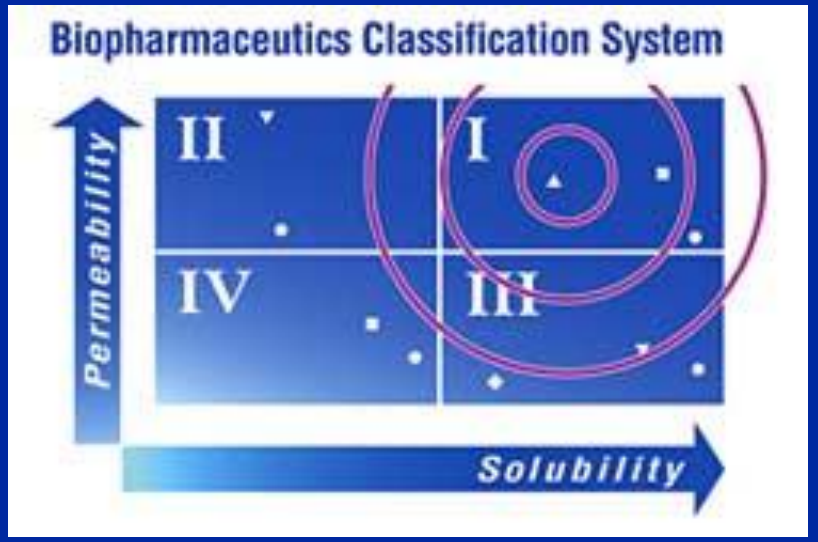
- About 40% of drug in market is poorly water soluble (BCS 2/4)
- Percentage of poorly water soluble APIs in development is further increasing owing to HT screening, combinatorial chemistry, and paradigm shift!
- Numerous APIs don't even enter development due to extremely low solubility
- BCS 2/4 compounds, 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

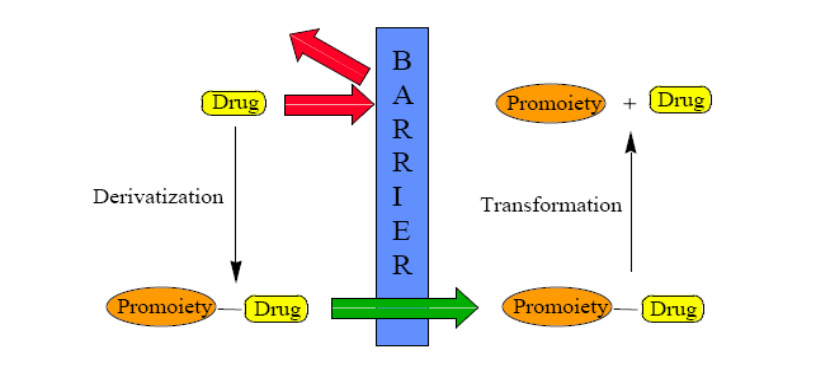
Approaches to Address BCS 2/4 Drugs

- 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

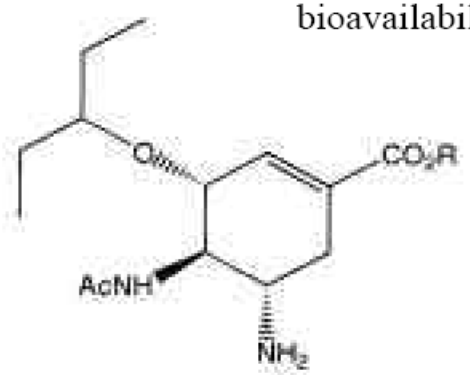


Approaches to Address BCS 2/4 Drugs

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.



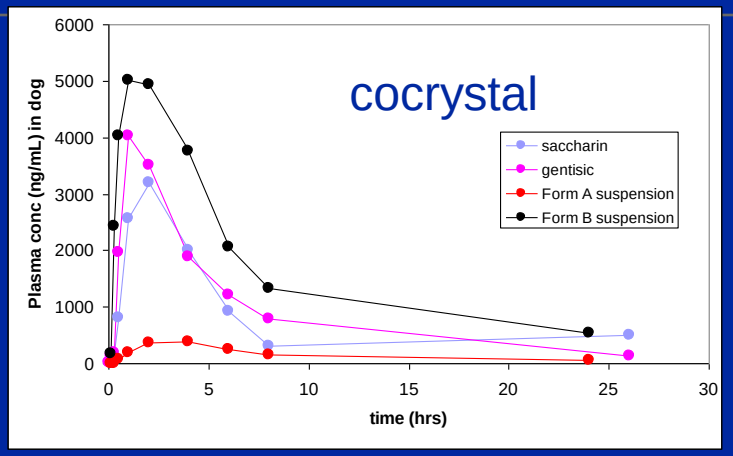
	Bioavailability
Oseltamivir carboxylate, R = H	**4.3% ± 1.6**
Oseltamivir ethyl ester, R = CH_2CH_3	**35% ± 11**

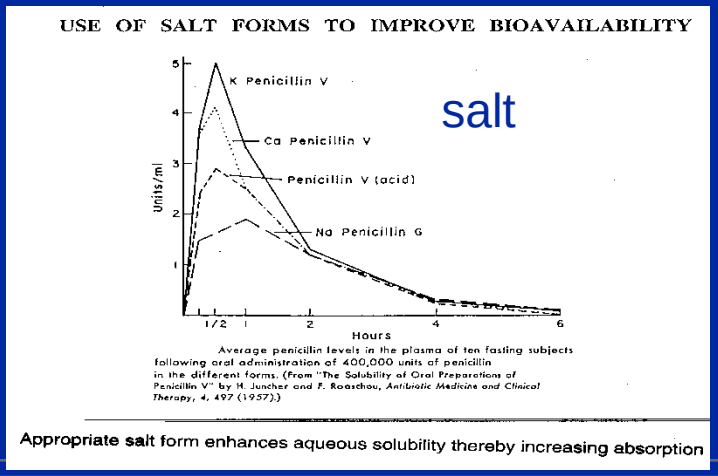
Prodrug can improve solubility and permeability; thus bioavailability

Approaches to Address BCS 2/4 Drugs

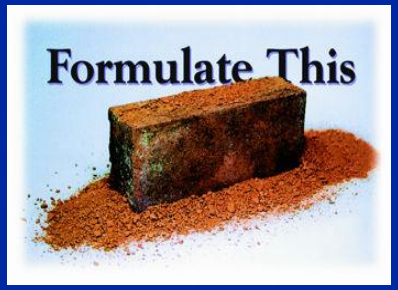
Chemical Form Modification - Salt / Cocrystal

- 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



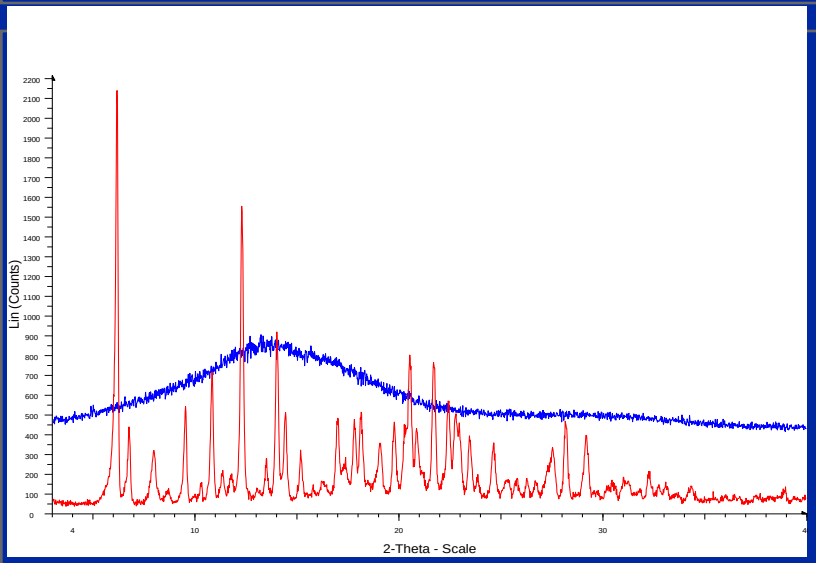
Examples of Amorphous Products

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



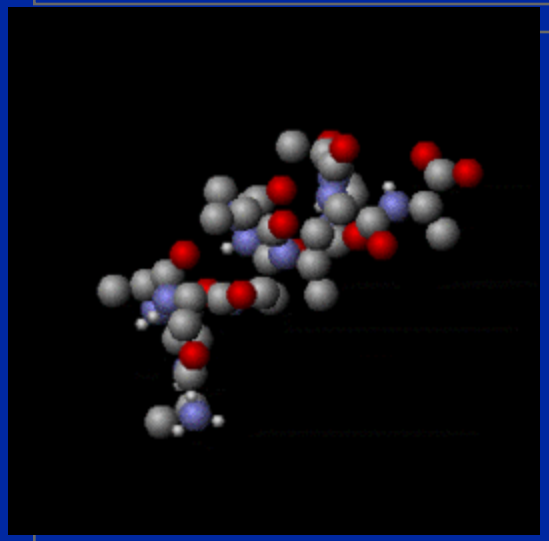
In most pharmaceutical application, a material is called amorphous if it exhibits XRPD profile that devoid sharp peaks

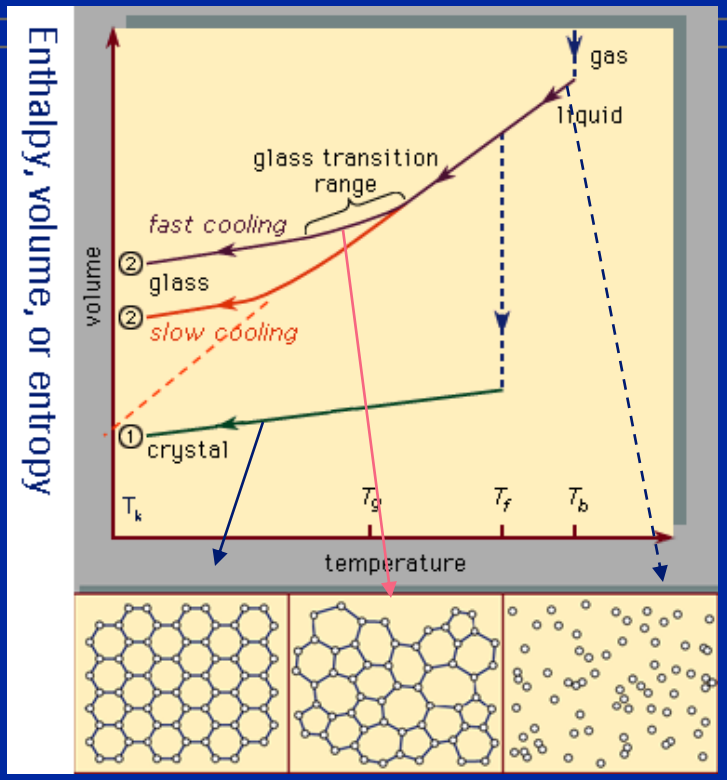
Attributes	Crystalline State	Amorphous State
Melting	Has defined melting	Has **no** melting; usually has glass transition temperature
Birefringence	Except cubic, crystal is anisotropic and exhibits birefringence	Amorphous is isotropic and exhibits **no** birefringence
X-Ray Diffraction	Reflect X-ray 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

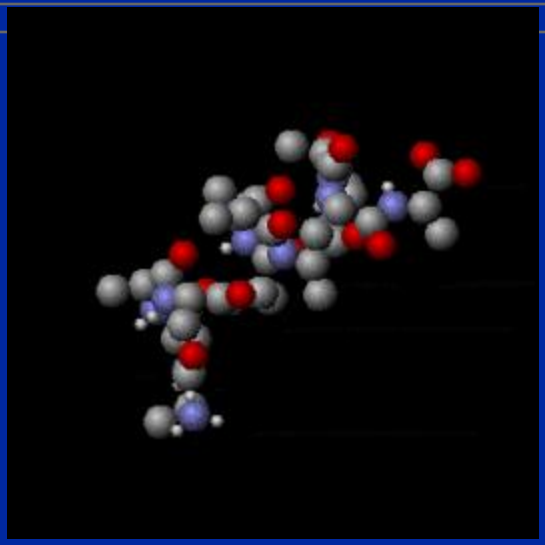
Amorphousness is **NOT** measured directly; only implied/derived from absence of

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

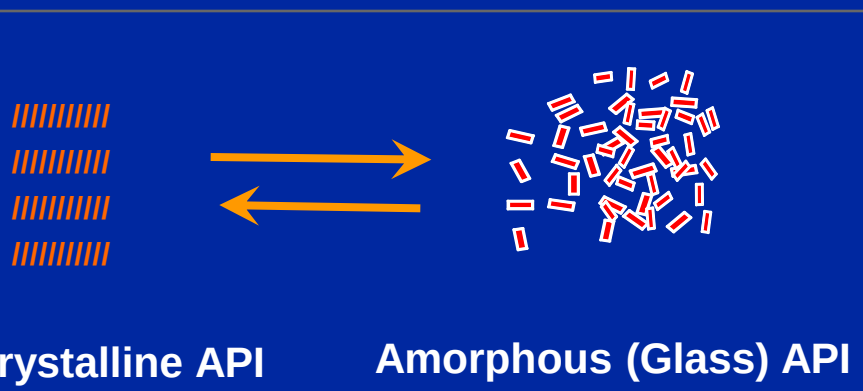
* Hancok and Parks, Rham Res 17, 2000

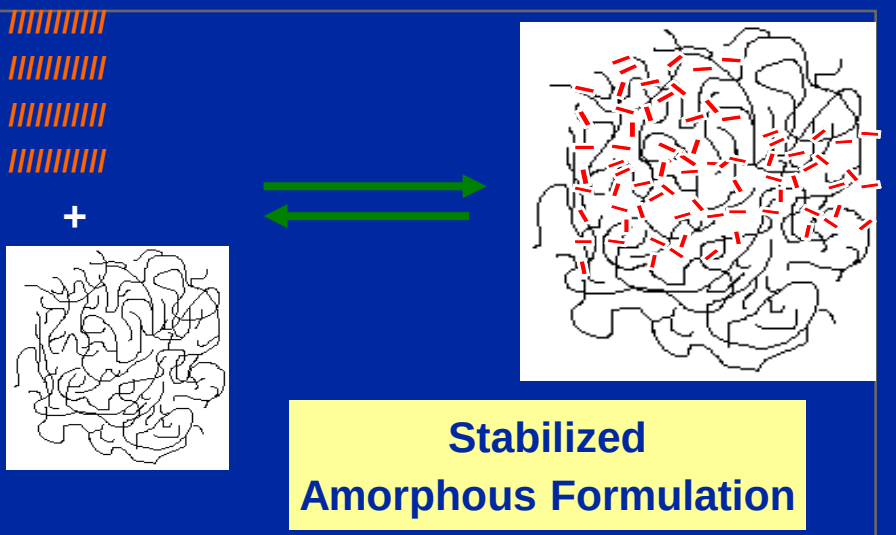
Concerns with Amorphous API

- 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)



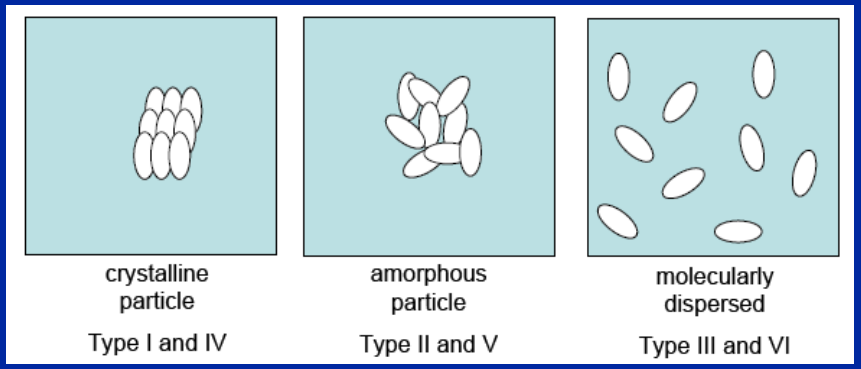


- Higher chemical potential results in higher dissolution rate and solubility but also makes them thermodynamically unstable
- API, without protection from matrix, may revert back to crystalline state
- Selection of polymer and process are crucial in designing amorphous formulations

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

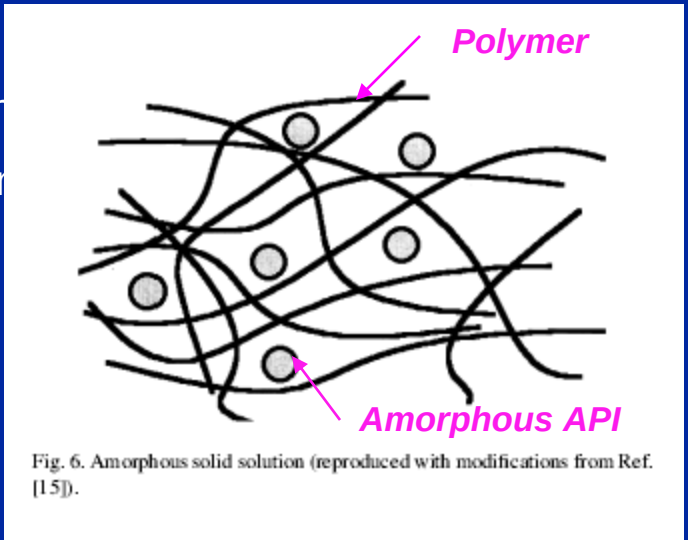


Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

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

50: 47-60 (2000).

Factors in Selection of Polymer

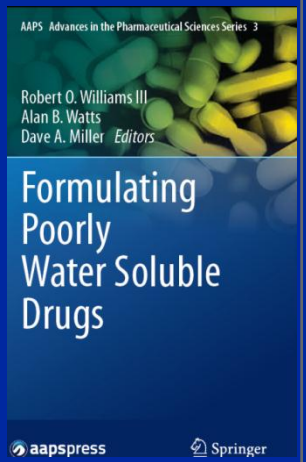
What to look for?

- 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

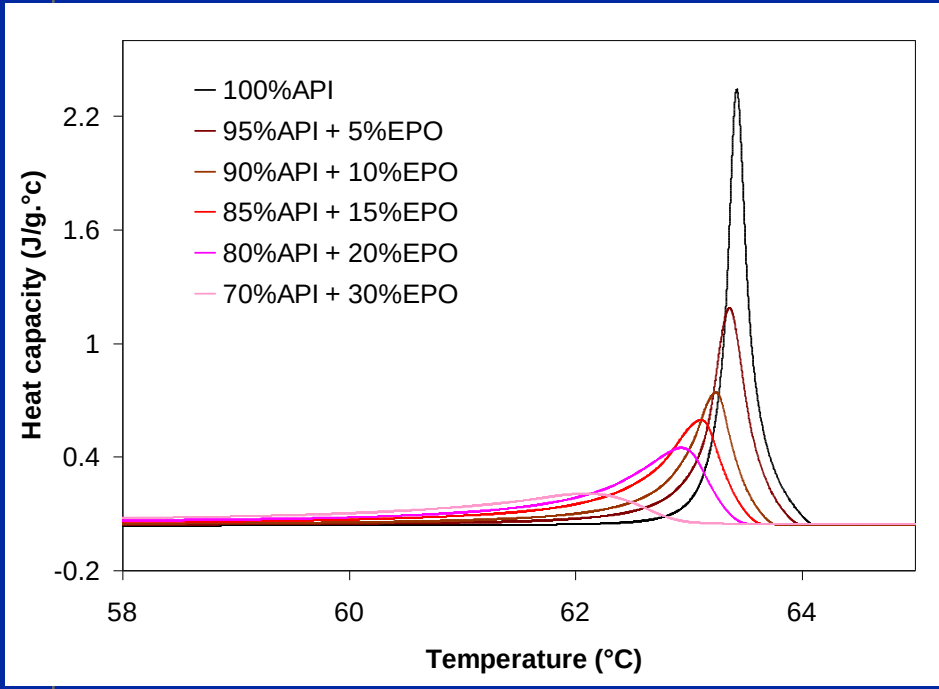
- Hildebrand Parameter
- Hansen Parameter
- Hoftyzer / van Krevelen Parameter
- Hoy Parameter

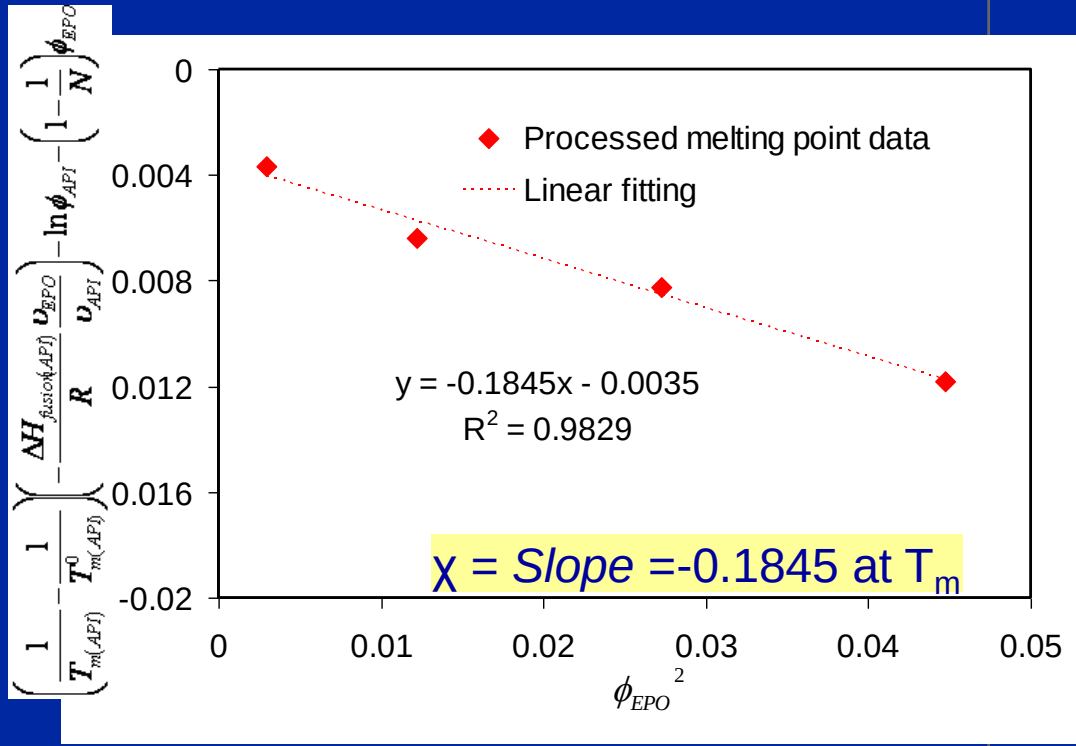
* Calculated using Molecular Modeling Pro

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

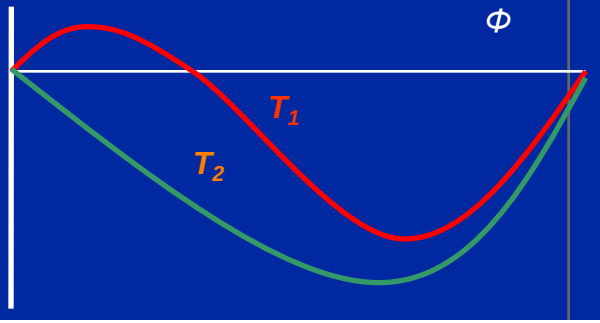
(χ_1 at T_1) and (χ_2 at T_2)

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

Flory – Huggins

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

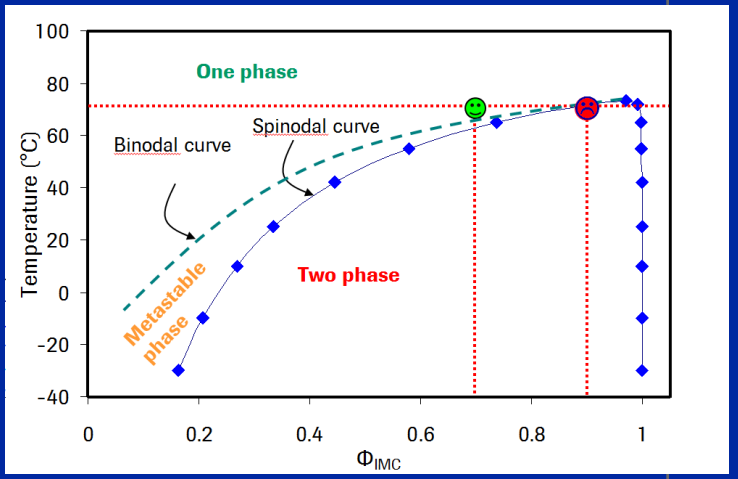
$$\frac{\Delta G_m}{RT}$$



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)

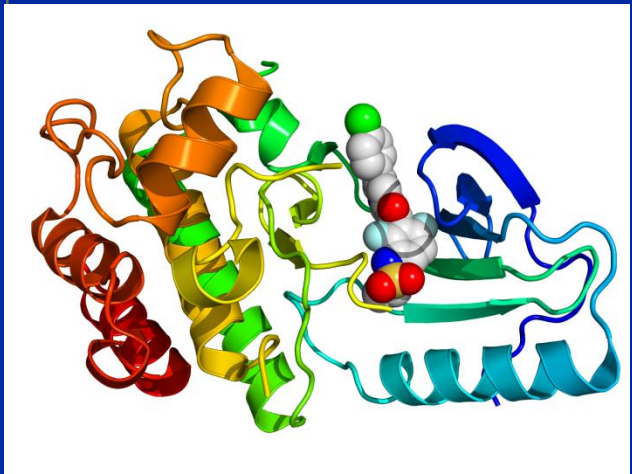
Melt Methods

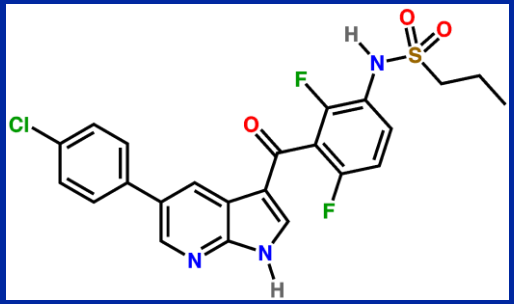
- Glass transition temperature (Tg) and melting point of both API and polymer
- Molecular weight and viscosity of the polymer
- Thermal stability
- Interaction of API and polymer (plasticizing or antiplasticizing)

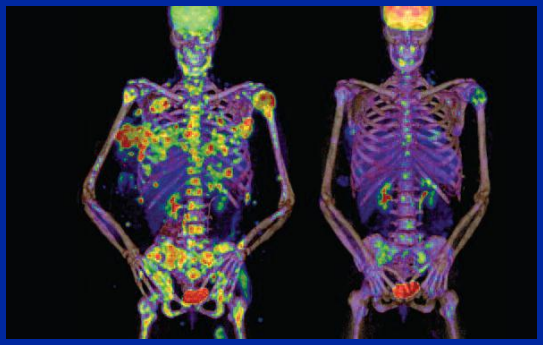
Characterization Techniques

- **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

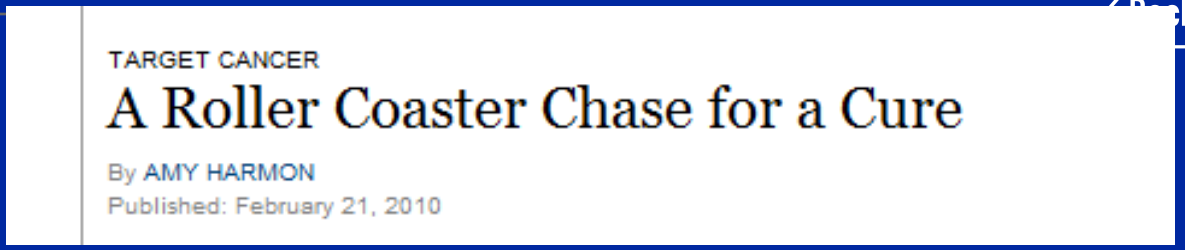
Case Studies (Vemurafenib)







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

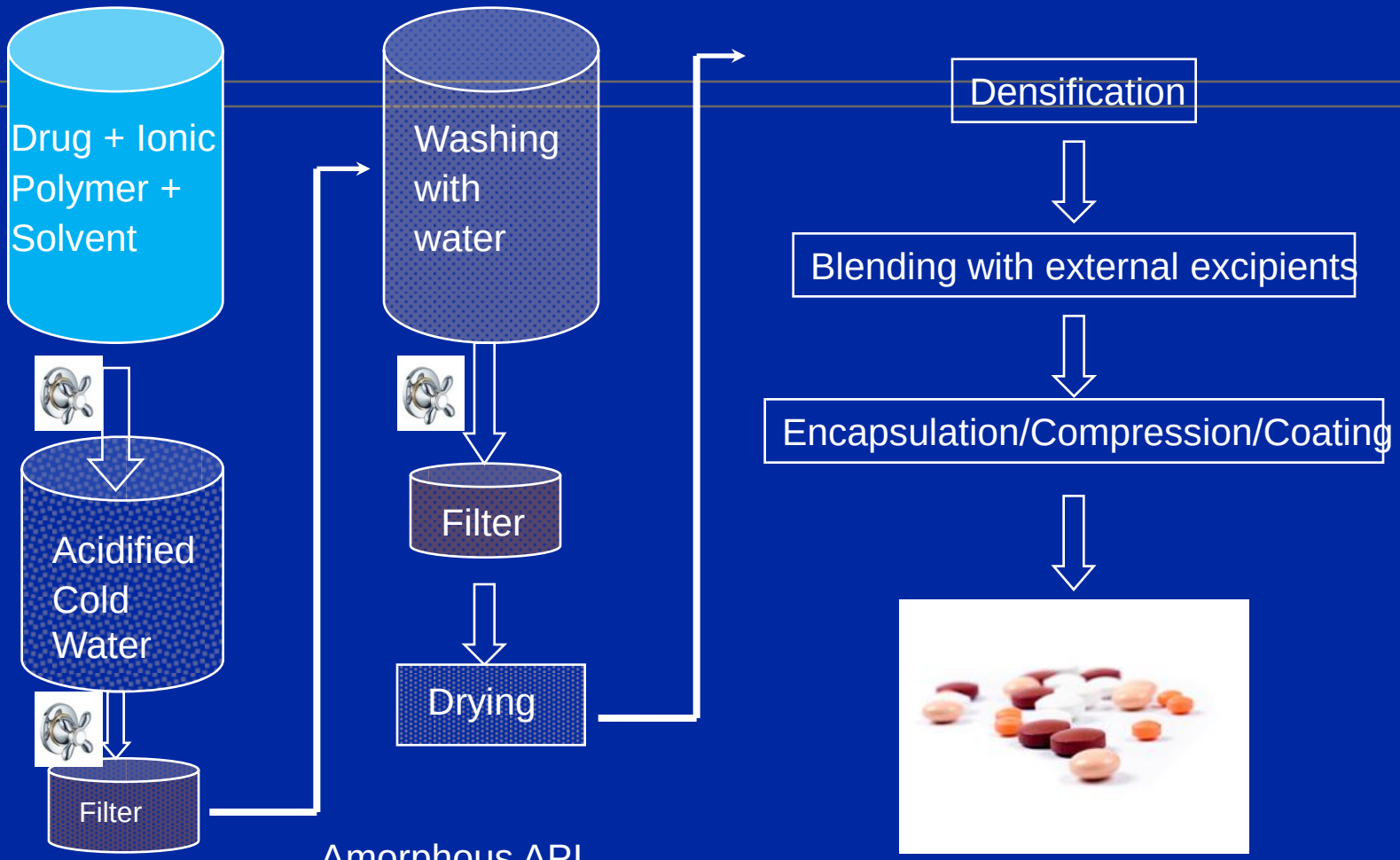
- *In-silico* prediction and modeling suggested HPMC-AS as candidate

Manufacturing Technology

- Evaluation of physicochemical properties suggested MBP as viable process

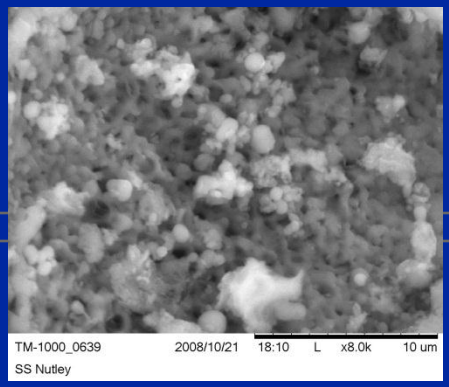
Overall Assessment

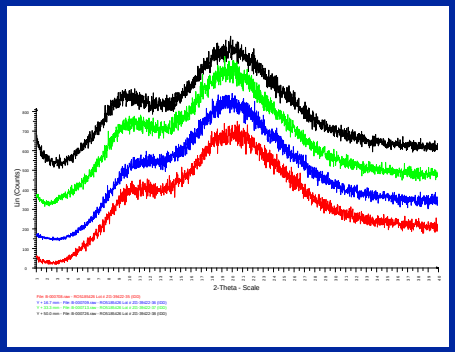
MBP Manufacturing Scheme

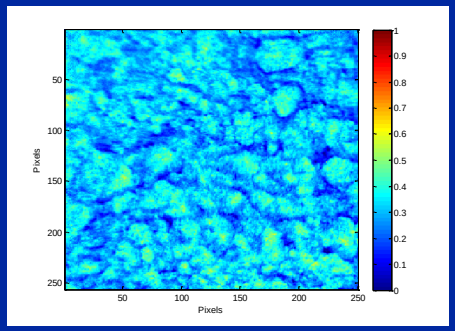


Characterization

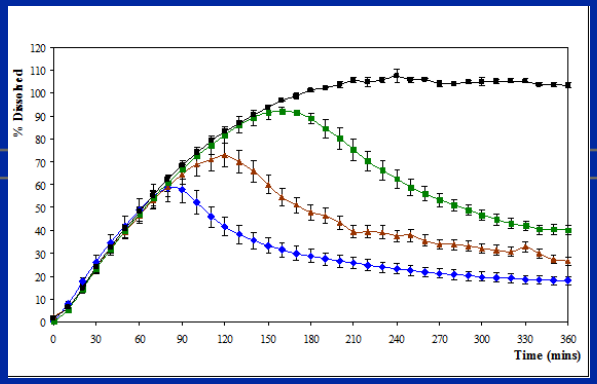
- XRPD indicates MBP is amorphous and stays amorphous
- Spectroscopy (IR, Raman and ssNMR) suggests disruption of drug – drug interaction and existence of drug – polymer interaction.
- TEM, EDAX, AFM and NIR CI indicate molecular distribution of drug molecules within polymer matrix without sign of heterogeneity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

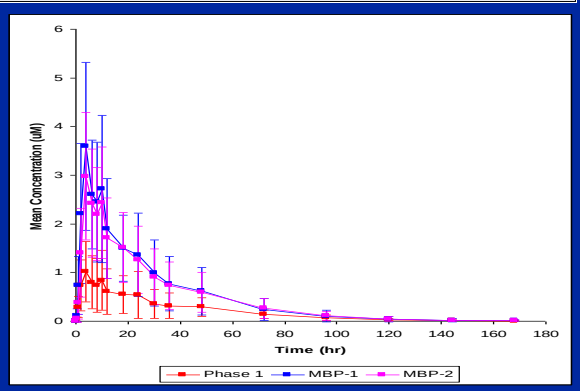






Performance

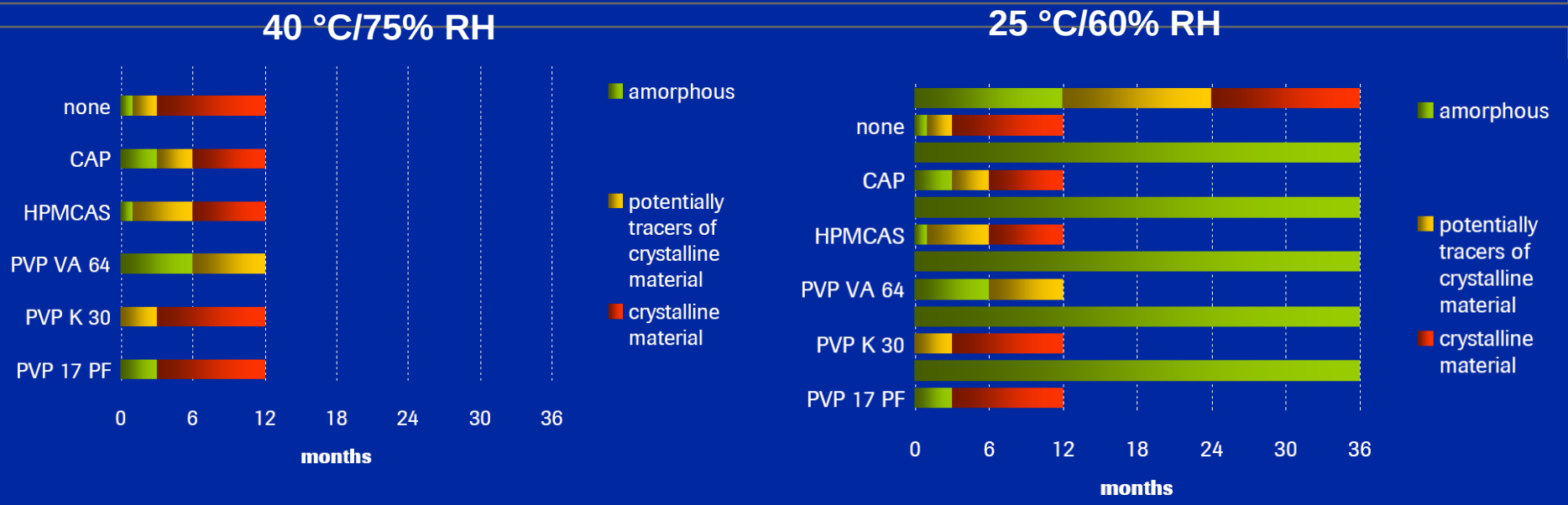




- MBP formulation maintained supersaturation during dissolution for up to 4 hours
- MBP formulation provided satisfactory PK profile
- MBP formulation demonstrated satisfactory physical stability
- MBP formulation successfully scaled up to commercial scale

Stability Prediction

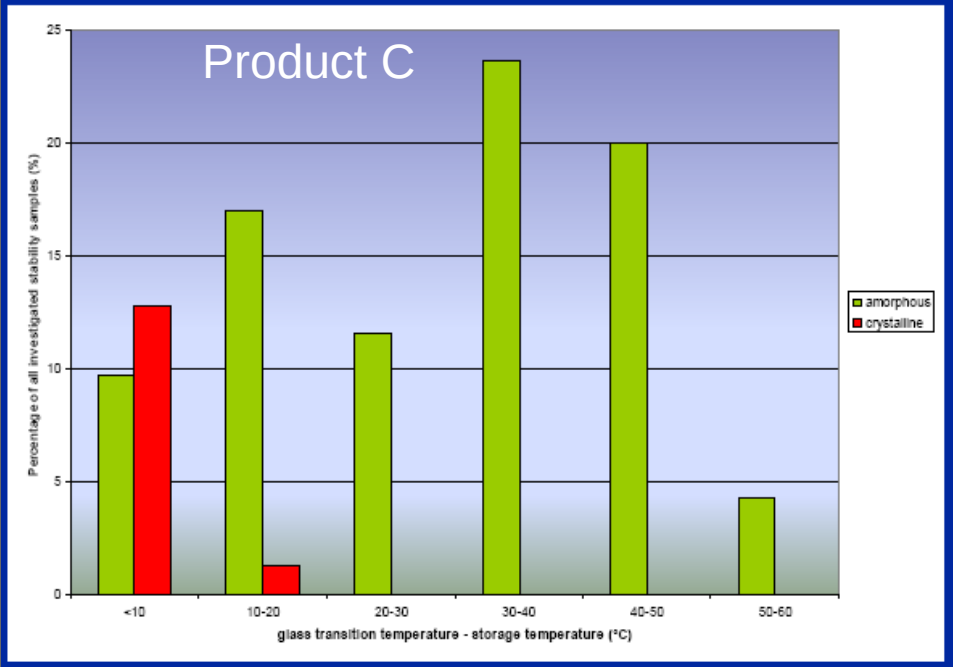
Storage Condition - 40 °C/75% RH vs 25 °C/60% RH Open

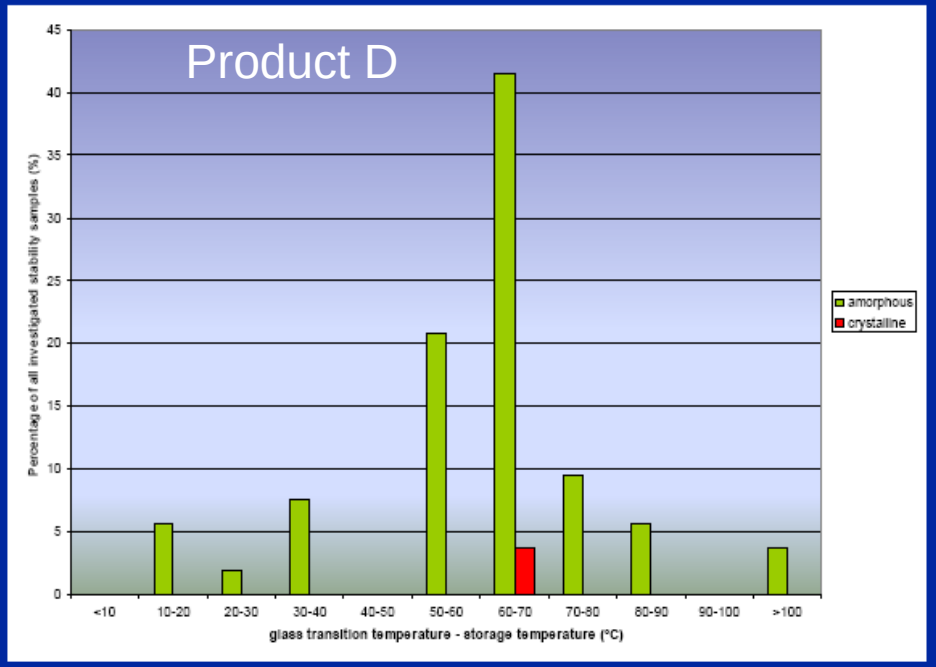


- Amorphous formulations showed instability at an accelerated stability condition (40°C/75% RH, 12 months); but good stability at room temperature (25°C/60% RH, 36 months)
- Accelerated stability condition is not predictive for long term stability

Solid State Stability Prediction

Glass transition temperature vs and storage temperature

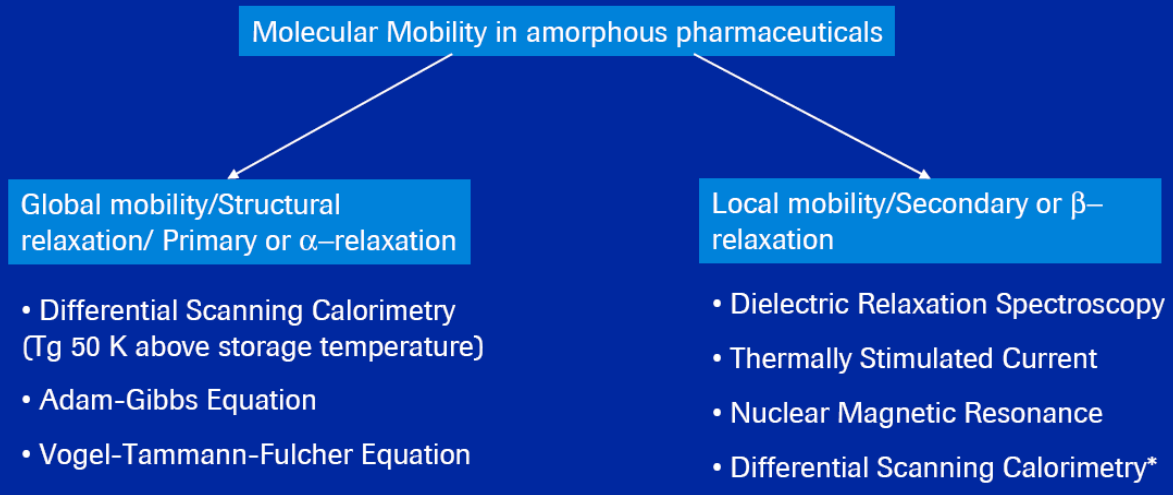




- The rule of thumb that a stable solid dispersion is obtained when the glass transition temperature is 50 K above the storage temperature worked nicely for one compound, but not for the other one.

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