Polymorphism

G. SHANMUGAM M.Sc., M.PHIL., (PH.D)

Contents

- Polymorphism:
- Some concepts
- Making of polymorphs
- Some Thermodynamic concepts
- Characterization
- Computational predictions....status
- Legal aspects

- What is Polymorphism?
- Polymorphism is the ability of a solid substance to crystallize into more than one different crystal structure.
- Different polymorphs have different arrangements of atoms within the unit cell, and this can have a profound effect on the properties of the final crystallized compound.
- Polymorphic transformation: The change that takes place between crystal structures of the same chemical compound is called polymorphic transformation.

Polymorphism: Some more thoughts

- **Definition:** A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecule of that compound in solid state. W C McCrone (1965)
- "..... every compound has different polymorphic forms and The number of forms known for a given compound is proportional to the **time and energy** spent in research on that compound." W C McCrone
- "With accumulation of data there is a developing a gradual realization of the generality of polymorphic behavior, but to many chemists **polymorphism is strange and unusual phenomenon.** M J Buerger (1937)
- "But not to be able to find something is no proof of its non existence".....a philosophical view point

The General Situation

- What is the frequency of occurrence of polymorphism and/or different crystal forms?
- How do we prepare different crystal forms in a controlled and reproducible manner?

What are the similarities and differences of properties of the different crystal forms?

The General Situation



Meeting room for a conference on polymorphism *ca*. 1963

Meeting room for a conference on polymorphism 2006

Importance of polymorphism

- Business Scenario
- 1. Most stable form patented by the inventor
- 2. Barriers set to block entries
- 3. As a generic player our opportunity lies in prior art or novel form
- 4. Competitor generic companies coming up with large number of forms at final stages of our development cycle resulting in loss of opportunity and development cost
- 5. Such output is not possible by conventional methods. Competitors are using such techniques, to compete we have to access such techniques

Impact of Crystal form on Drug product

- Solid Form Characteristic:
- Polymorph
- Salt form
- Solvate
 Solvate
 Selected Form
- Hydrate
- Habit
- Particle size

Dosage Form Attributes: drug solubility dissolution rate bioavailability manufacturing methods dosing regimen delivery options shelf life time to market market image intellectual property

- Optimal form selected for above desired properties
- Form can vary for different routes of administration

A recent example -"ROY"



5-Methyl-2-(2-nitro-phenylamino)thiophene-3-carbonitrile



- 7 unsolvated forms
- frequently occur concomitantly
- Istinguishable by color and habit

Yu et al., J. Am. Chem. Soc. **122**, 585-591 (2000); J. Phys. Chem. A**106**, 544-550 (2002)

Occurrence of polymorphism in molecular crystals

- The existence of more than one crystal form (polymorphs and/or solvates) of any substance is not obvious and is not yet predictable. However, it is not surprising when new crystal forms are discovered, either by systematic searching, or by serendipity.
- Keep eyes and mind open, even if not involved in a conscious effort to prepare new crystal forms.

Comparison of Red and Black Forms of TMTSF:TCNQ

Red Form

from CH₃CN by slow evaporation

thermodynamic crystallization

- Transparent
- mixed stacks
- semiconductor

from CH₃CN by rapid cooling of saturated solution; use seeds for larger crystals

Black Form

kinetic crystallization

opaque

segregated
stacks
conductor

Polymorphism and electrical conductivity of molecular complexes

Two polymorphs of TMTSF and TCNQ

Red Form Mixed stacks

Black Form Segregated stacks





Some suggestions for preparing different crystal forms in a controlled manner

- Use thermal information from microscopy and DSC/TGA to determine trial conditions for crystal growth
- Try kinetic as well as thermodynamic conditions
- Use molecular and crystal structural data to generate crystallization conditions (solvent, solvent mixtures and 'tailor-made' additives) to prevent or induce particular forms
- Avoid seeds of undesired forms, but use seeds of desired forms
- The aware of literature and use it
- Don't hesitate to use unconventional measures
- Potential for new technologies, e.g. combinatorial chemistry; high throughput technology
- Tf it works, it's fair game

Physical and chemical properties that may vary among polymorphs (partial list)

melting point
vapor pressure
hardness
optical, electrical, magnetic properties

- Color
- IR spectraNMR spectra

molecular conformation
photochemical reactivity
thermal stability
filtration and drying characteristics
dissolution rate
bioavailability

Some Thermodynamic concepts

- Why thermodynamics: In order to answer questions like,
- How many polymorphs have been crystallized from a given substance?
- Which crystal form is thermodynamically stable at ambient conditions, how it can be obtained?
- Are the polymorphic modifications enantiotropic (reversible) or monotropic (not reversible), what is the transition point?
- How stable is a particular meta stable form, can it be used to better pharmaceutical properties?
- These questions can be answered from the semi-quantitative graphical solution of Gibbs-Helmoltz equation, ... dG = dH TdS, which are the Energy-Temperature diagrams.
- These can be constructed by knowing the order of relative stability of polymorphs at 0 K and the higher temperatures (melting point).

Thermodynamic concepts (continued)

- Some thumb rules:
- Heat of Fusion Rule: If the higher melting form has the lower heat of fusion, the two forms are most probably enantiotropic, otherwise monotropic.
- Heat of Transition Rule: If an endothermal transition is observed at some temperature, it may be assumed that there is a transition point below it that is the two forms are related enantiotropically. If an exothermal transition is observed at a given temperature, it may be assumed that there is no transition point below it, suggesting monotropic polymorphs.
- **Density Rule**: If a polymorph has a lower density than another one, then it may be assumed that at absolute zero this crystal form is less stable.
- **Infrared Rule**: If the first absorption band in the IR spectrum of a hydrogen bonded molecular crystal is higher for a polymorph than the other one, that form may be assumed to have the larger entropy.

Making of polymorphs.....consistently

- The most universal way is isolation from solution, crystallization, reactive precipitation, solvent-antisolvent techniques, etc.
- Other techniques like evaporation, flash evaporation, grinding, milling, etc also exist.
- Making polymorphs in a reproducible and consistent manner is a challenging task.
- In this section we will briefly see how do we ensure, what kind of techniques we use to make polymorphs consistently.

Organic Crystal Chemistry & Polymorphism

Organic crystals formed from large, flexible & non-spherical molecules hence

 big(ish) crystal unit cells involving intermolecular packing within low symmetry structures (tricl, monocl & orthorh)

Organic crystals mostly held together via weak & undirected van der Waals forces plus some H-bonding

 produces relatively soft crystals capable of adopting a number of "stable" structures (polymorphs) each having very similar energetic stabilities

Impurities effect nucleation & crystal growth processes & can impact upon resultant polymorphic form produced

as product purity improves during process work-up the "stable" polymorphic form can change!

Polymorphism in Pharmaceuticals

drug production important... poorly reproducible products Polymorphic variability ... regulators e.g. FDA demand is a key issue ... 100% polymorphic purity for drugs Polymorphs exhibit different chemical stability. Why? physical properties and hence bio-availability Via variability in pharmaceutical How are different production process operations... polymorphs formed? ... crystallisation, filtration, drying, **Commercial implications!** granulation, compaction, milling ... eased profits e.g. \$1B/annum for LOSEC, VIAGRA, ZANTAC

Different Solubility - Different Bio-availability

Dissolution profile

Bio-availability profile



Batch Crystallisation Process Science

... batch prepared crystals are notoriously difficult to prepare in reproducible manner...

Economics

environmental impact
 production cost
 time to market

Process Variables

- supersaturation
- solute concentration
- temperature
- cooling ramp
- solvent/additives
- seeding

... many process related factors need optimisation...

Product Specifications

particle size and shape
 polymorphic form
 crystal purity

Molecular Scale

- nucleation rate
- growth rate
- growth mechanism
- yield

... multi-technique measurements critical!



Product vs Process - Need for Measurements

- Process engineering design relies on manipulation of thermodynamic state functions such as P, V, T, H
 - e.g. can improve process energy (H) efficiency via variation of state functions
- Product dependent parameters (polymorphic form, porosity, morphology, bio-availability, etc.) usually not directly driven by state functions

Paradigm shift: can't ONLY optimise the process flowsheet -MUST make measurements to optimise product properties



Reactor Scale-Up Effects on Nucleation Processes

Nucleation can be promoted via number of potential nucleation sites within batch reactor such as:

- Walls of vessel & at liquid free surface
- Stirrer & reactor internals such as baffle surfaces
- Heteronuclei, e.g. impurities, particulates, seeds
- Attrition fragments from particle/particle & reactor/particle collisions
- Effects of hydrodynamics & intense reactor mixing

Fundamental understanding of nucleation processes vs reactor scale essential if NPI timescale to be met









In-process Monitoring of Crystal Shape within a Stirred Reaction Vessel





Solvent-mediated polymorphic transformation

Metastable form $\xrightarrow{\text{Dissolution}}$ Solution $\xrightarrow{\text{Nucleation}}$ Stable form

- Efficient technique to
 - discover and prepare the most stable polymorph
 - eliminate the metastable polymorph in a polymorphic mixture
 - determine the relative stability of polymorphs
 - check the phase purity of a polymorph



 Lower solubility ⇒ higher interfacial free energy ⇒ higher free energy barrier for nucleation ⇒ wider metastable zone ⇒ lower nucleation rate



- Stronger solvent-solute interactions lead to
 - higher energy required for desolvation of the solute molecule
 - stronger binding to the solute clusters to inhibit them from growing into stable nuclei

- Types of interactions
 - Hydrogen bond interactions
 - Van der Waals interactions
- Solvent-solute interactions are stronger in the solvent giving higher solubility
 - Linear free energy approach to predict solubility: log $c = e + a\delta^2 + b\pi^* + c\Sigma\alpha + d\Sigma\beta$
 - For sulfamerazine Polymorph II log $c = -4.46 - 0.00133\delta^2 + 1.63\pi^* + 2.90\Sigma\beta$ $r^2 = 0.975$
- Stronger solvent-solute interactions in the solvent giving the higher solubility may reduce the transformation rate

Conclusions from Solvent Effects

- The balance between solubility and strength of the solute-solvent interactions determines the rate of solvent-mediated polymorphic transformation
 - Polymorphic transformation rate is generally lower in the solvent giving the lower solubility
 - Stronger interactions in the solvent giving the higher solubility may reduce the transformation rate
 - Hydrogen bond interactions play an important role
 - The transformation rate may be adjusted using solvent mixtures

The impurity is adsorbed onto the surface of a growing prenucleus or crystal where it inhibits nucleation or crystal growth



Stabilization of SMZ Form I during ball milling



Intensity

Conclusions from Impurity Effects

- Trace amounts of impurities may stabilize the metastable polymorph both in the solution and in the solid state
- The inhibitory effect of the impurity depends on the ability of the impurity molecules to disrupt the hydrogen bond network of the host crystal
- The inhibitory effect of the impurity may be predicted by the surface binding energy
- The inhibitory effect of the impurity may be described by the model based on the Langmuir adsorption isotherm

General Implications

•To prepare a more stable polymorph, a solvent giving high solubility and a moderate hydrogen bonding propensity is preferred.

•To prepare a metastable polymorph by recrystallization from solution, a solvent giving a low solubility is preferred.

•Purity is an important factor to be considered during polymorph screening.

•Metastable polymorph may be stabilized by a structurallyrelated additive.

Effect of pH:

- pH is known to affect polymorph selectivity, e.g Glycine has three polymorphs: alpha, beta, and gamma.
- Alpha form: aqueous solution, isolelectric point,centric.
- Gamma form: most stable, acidic basic solutions,polar.
- Alpha forms in pH range from 3.8 to 8.9, otherwise gamma is preferred
- Why gamma nucleates at extreme pH : (1) inhibition of growth of alpha form, (2) prevention of nucleation of alpha form, (3) induced nucleation of gamma form.
- Charged species in solution can modify growth of alpha form.

Analysis and Characterization of Polymorphs:

- Host of techniques based on various principles of crystallography,microscopy, thermal analysis, solubility studies, vibrational spectroscopy, nuclear magnetic resonance are being used.
- The defining criterion for existence of different crystal forms is a non equivalence of crystal structures, implying a non equivalent XRPD pattern for each suspected polymorphic variation.
- All other methods can be considered as sources of supporting and ancillary information, they cannot be taken as definitive proof for the existence of polymorphism by themselves alone.

Characterization...

Technique	Application
Crystallography :si ngle crystal, XRPD	Crystal structure, polymorphic identities
Microscopy: optical, polarizing optics, thermal,electron	Information on habit, shape, topography, optical properties RI, phase transitions
Thermal: TGA, DTA, DSC	 TGA: thermally induced weight loss, for solvates, hydrates, decomposition, stability, DTA: phase changes, structural changes, decomposition, desolvation DSC: phase changes, enthalpies, stability, kinetics, transitions, glass transitions

Characterization...

Technique	Application		
Molecular Motion: Vibrational spectroscopy- Infrared absorption,	FTIR: no major differences in solid state forms, particularly useful when solvent molecules are incorporated in crystal lattice, hydrogen bonding related changes, study of multiple anhydrates, hydrates, solvates.		
Raman,	Raman: for symmetric vibrations and low polar groups, sharp bands with well resolved spectral features, more facile		
Chemical Environment: Nuclear magnetic resonance spectrometry	characterization of structural differences in Required for individual nuclei to exist in polymorphs nonequivalent magnetic environment within two crystal structures. Used to deduce nature of polymorphic variations, differentiate polymorphs and solvates, quantitative phase compositions, molecular mobility, order, stability.		

High Throughput Polymorph Screening

- Concept: Crystallization from solution by suspension or controlled evaporation are the chosen methods for HTPS. These crystallization techniques enable investigation of thermally stable and unstable substances.
- The use of a number of solvents and solvent mixtures creates different nucleation and crystal growth conditions such that stable and metastable forms can be produced. In addition, the stability of hydrates and solvates as a function of water and solvent activity can be investigated by equilibration of solvent mixtures.

Benefits of HT Crystallization



Streamlined End-to-end Process

	Design	Execution	An	alysis	
•	 Informatics software for experimental Design Process control 	•Automated san preparation & p •End-to-end tra	nple processing cking	 Data minin Identificati trends,learn 	ng on of ing

High Throughput Polymorph Screening (continued)

- Hard ware: Automated crystallizer station, automated screening stations (HPLC,Microscopy, Raman spectroscopy, XRD, DSC-TGA, FTIR,etc).
- **Software:** For data mining, trend analysis, and experimental design.
- Few examples:
- (1) Sumatriptan succinate: not recognized as polymorphic, HTPS studies: 1200 conditions, 24 solvents, 350 solids formed, 2 new forms discovered.
- (2) Acetaminophen:2 forms known, 10,000 experiments,24 solvents, third form found, crystal structure derived
- (3) **Ritonavir:** latent polymorphism, 2 known forms,HTPS studies: 2000 experiments, 32 solvents,>50 solids isolated, 3 new forms found, reproducible methods of making.

HT Crystallization Impact on Pharmaceutical Value

Drug Preclinical Clinical Marketing Regulatory Manufacture Sales Development Development, Discovery/

- HT crystallization allows rapid discovery of crystal form diversity
 - Large number of experiments
 - Miniaturized scale
 - Multitude of processing options
 - Rapid analysis
 - Data mining and knowledge generation



Better decisions; Better products

Sample Generation for HTPS without automated crystallizer

• Solvent-based Crystallizations

Fast and slow evaporations and cools, temperature variation, solvent variation, water activity variation, slurry experiments, antisolvent crashes, concentration studies, supersaturation studies, vapor diffusion, others

• Non-Solvent and Specialized Experiments

Lyophilization, grinding, melt experiments, impurity studies, seeding and epitaxial studies, thermal studies, amorphous crystallizations, sublimation, seed-free conditions, others

Computational polymorph prediction...an Overview

- Objective: To predict crystal structures of polymorphs and conditions under which they can be successfully made, to have this information before the synthesis of the molecule!
- For polymorphs requirements are phase diagrams plus meta-stables
- Basic Assumptions: The experimental crystal structure will correspond to the global minimumin the static lattice energy, a crude) K thermodynamic model. Any competitive local minima are possible polymorphs, within 2 kcal/mol of global minimum.
- Many approaches from first principles are under study, readymade softwares also exist e.g DMAREL, MOLPAK, Accelrys, but strong limitations exist in these predictions.
- Unless thermal, kinetic, solvent, impurity, effects are included in the models realistic predictions are difficult.
- Still more understanding in the areas of thermodynamics, kinetics, structure-property relationships, and more working knowledge of polymorph systems is required to arrive at meaningful predictions.

Some Legal aspects:

- To make use of ANDA process, a generic need not market the identical product but must show only 'bioequivalence'.
- General patent laws of novelty, obviousness, infringence, apply to polymorphs also.
- The burden is on the patentee to produce evidence that product infringes claims.

Legal aspects....

- Lessons for the researcher:
- Find and patent all possible polymorphs and crystal forms with all possible techniques.
- Characterize by all possible techniques and include as evidence while filing patent.

Thank Q for Patience