Polymorphism

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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 Characteristics:**
  - Polymorph
  - Salt form
  - Solvate
  - 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”

7 unsolvated forms

frequently occur concomitantly

distinguishable by color and habit

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 CH$_3$CN by slow evaporation
- thermodynamic crystallization
- transparent
- mixed stacks
- semiconductor

Black Form

- from CH$_3$CN by rapid cooling of saturated solution; use seeds for larger crystals
- 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
- Be aware of literature and use it
- Don’t hesitate to use unconventional measures
- Potential for new technologies, e.g. combinatorial chemistry; high throughput technology
- If 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 spectra
- NMR 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 metastable 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 & orthrh)

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

Time consuming approaches to drug production important... → ... manufacturing processes yield poorly reproducible products

Polymorphic variability is a key issue... → ... regulators e.g. FDA demand 100% polymorphic purity for drugs

Why? Polymorphs exhibit different chemical stability, physical properties and hence bio-availability

How are different polymorphs formed? → Via variability in pharmaceutical production process operations...

Commercial implications! → ... crystallisation, filtration, drying, granulation, compaction, milling...

Increased profits e.g. $1B/annum for LOSEC, VIAGRA, ZANTAC
Different Solubility - Different Bio-availability

Dissolution profile

Bio-availability profile

... producing the correct polymorph means.

... safer drug dosage with prolonged therapeutic effect!
Batch Crystallisation Process Science

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

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

Economics
- environmental impact
- production cost
- time to market

Product Specifications
- particle size and shape
- polymorphic form
- crystal purity

Molecular Scale
- nucleation rate
- growth rate
- growth mechanism
- yield

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

... multi-technique measurements critical!
Batch Crystallisation Processes

A nice cup of hot tea... time passes & tea temperature drops...

plenty of sugar... with a little stir sugar easily dissolves in the hot tea...

... sugar recrystallises out of tea solution and settles at the bottom...

... it's the phone, there goes my cuppa!

... the very same process underpins manufacture of most speciality chemical products...

... process seems very simple but underlying science and its control are surprisingly complex!
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
CBB Programme: Integrated In-Process Analytics

Chemometrics
- FTIR
- USS
- Video microscopy
- UVvis
- XRD
- LDA/PIV
- CFD
- Supersaturation
- Nucleation kinetics
- MSZW
- Polymorphic form
- Process conditions
- Mixing & scale-up
- Heat transfer
- Batch process monitoring & control
- Reactant rheology
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**
Particles Made to Measure

Particle size affects product properties → Bio-availability (Drugs)
Texture (Foods)
Surface activity (Catalysts)

Control of particle size is CRITICAL → Key step

Nucleation dominant → small crystals
Growth dominant → large crystals

...supersaturation controls particle size of product crystals...

... meanwhile back at the tea cup...
Simultaneous Multi-Technique In-Process Measurements during Batch Crystallisation

- Turbidity probe - crystallisation onset
- Infra-red spectroscopy - supersaturation
- X-ray diffraction - polymorphic form
- Ultrasonic spectroscopy - particle size

... simultaneous multi-technique measurements during crystallisation process...
In-process Monitoring of Crystal Shape within a Stirred Reaction Vessel

- Needle crystals
- Prismatic crystals

Microscopy reveals shape of crystals within vessel

Hydrodynamics leads to enhanced attrition of crystals

Slow stir
Fast stir

CHEMICAL ENGINEERING @ LEEDS
Video Microscopy: Observing Process Events

Agglomeration

Attrition

0 s
+ 8 s
+ 51 s
+ 90 s
+ 116 s
**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 $\Rightarrow$ higher interfacial free energy $\Rightarrow$
  higher free energy barrier for nucleation $\Rightarrow$
  wider metastable zone $\Rightarrow$ lower nucleation rate
Growing prenucleus or crystal

- 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:
    $\log c = e + a\delta + b\pi^* + c\Sigma\alpha + d\Sigma\beta$
  
  – For sulfamerazine Polymorph II
    $\log c = -4.46 - 0.00133\delta + 1.63\pi^* + 2.90\Sigma\beta$ \hspace{1cm} 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

Milled for 2 h with 5% NSMZ
Milled for 2 h without NSMZ
SMZ Form I, starting material

Intensity

2 theta angle
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 structurally-related 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, isoelectric 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...

<table>
<thead>
<tr>
<th>Technique</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crystallography</strong>: single crystal, XRPD</td>
<td>Crystal structure, polymorphic identities</td>
</tr>
<tr>
<td><strong>Microscopy</strong>: optical, polarizing optics, thermal, electron</td>
<td>Information on habit, shape, topography, optical properties RI, phase transitions</td>
</tr>
<tr>
<td><strong>Thermal</strong>: TGA, DTA, DSC</td>
<td>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</td>
</tr>
</tbody>
</table>
## Characterization...

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<td><strong>Molecular Motion:</strong> Spectroscopy</td>
<td><strong>FTIR:</strong> 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: for symmetric vibrations and low polar groups, sharp bands with well resolved spectral features, more facile characterization of structural differences in polymorphs.</td>
</tr>
<tr>
<td>Molecular Motion: Vibrational spectroscopy</td>
<td></td>
</tr>
<tr>
<td><strong>Infrared absorption, Raman,</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Chemical Environment:</strong> Nuclear magnetic resonance spectrometry</td>
<td>Required for individual nuclei to exist in 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.</td>
</tr>
</tbody>
</table>
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

Analysis

- Large numbers of experiments
- Miniaturized scale
- Automation of tedious operations

- Informatics software for experimental Design
- Process control

- Automated sample preparation & processing
- End-to-end tracking

- Data mining
- Identification of trends, learning
High Throughput Polymorph Screening (continued)

• **Hardware**: 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

- 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 minimum in 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, infringement, 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