Crystal Engineering for Product & Process Design

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Role of Engineer in Industry

To make, evaluate and justify technical decisions in support of business
Why Crystals?

• Crystalline organic solids ubiquitous in
  ➢ chemicals & specialty chemicals
  ➢ home & personal care
  ➢ food and pharma

• Almost 100% of small MW drugs are isolated as crystalline materials

• Over 90% of ALL pharmaceutical products are formulated in particulate, generally crystalline form

• Pharma industry worldwide > $300 billion/year sales
Why Modeling?

“If you can’t model your process, you don’t understand it. If you don’t understand it, you can’t improve it. And, if you can’t improve it, you won’t be competitive in the 21st century.”

Jim Trainham, DuPont
Perspectives

- Engineers believe that their models approximate nature

- Scientists believe that nature approximates their models

- Mathematicians don’t give a damn either way
Outline

1. Phase diagrams & crystal quality
2. Material properties & product functionality
3. Design for desired material properties
   - crystal engineering for product design
4. Scale up & process synthesis
Solid – Liquid Equilibrium

$P = 1 \text{ atm}$

$T \ (°C)$

$0 \ (°C)$

$188 \ (°C)$

Solvent (Water)

Solute (Succinic Acid)

$x_{\text{solute}}$

Solid solute in equilibrium with liquid solution

Solubility of Succinic Acid (Based on Qiu and Rasmuson 1990)
Succinic Acid

- Metastable
- 2.2 °C (Hofmann & Doherty)
- ~5 g/L solution (Qin & Rasmusm)

C (g/L solution)

T (°C)

24 (°C) 30 (°C)
Apparatus after experiment of 30 min, 0.8K below the metastable zone width (succinic acid saturated at 24 C)
Polymorphism

• The polymorph that is selected can affect:
  Solubility, Shape, Melting Point, Bioavailability, Compressibility, Growth and Dissolution Rate, Taste, Color, Stability, Flowability, Patentability…

• The transition from one polymorph to another usually occurs more easily in a solution mediated mechanism, rather than a direct solid-solid transition.
Solution-Mediated Polymorphism

Time lapse photos of a transition between forms 1 and 2 of dihydroxybenzoic acid (Davey et al.)
Polymorphs of Ritonavir

- Ritonavir – Main component in an Abbott Labs HIV drug
  - Early 1998 – Many final product lots began to fail a dissolution test
- A new, previously unknown, thermodynamically more stable and much less soluble crystalline form (polymorph) appeared after two years of production
  - They were no longer able to produce the marketed form.
  - US-FDA web site 1998, “Abbott Laboratories is experiencing manufacturing difficulties with the capsule formulation of our HIV protease inhibitor, Norvir (ritonavir), which will result in a shortage of capsules. We have encountered an undesired formation of a Norvir crystalline structure that affects how the capsule form of Norvir dissolves …”
- It is vital to know about polymorphs as early as possible, and it is important to understand their interconversion for processing.

Crystal Shape - Ibuprofen

Gordon & Amin US Patent 4,476,248 issued to The Upjohn Company

- Objective of the invention: “an improved crystalline habit and crystal shape of ibuprofen”
- Method of crystallization from polar solvents, such as methanol, ethanol (instead of hexane or heptane).
- Faster dissolution rate, larger particle size, lower bulk volume, reduced sublimation rates and improved flow properties.

Ibuprofen grown out of hexane

Ibuprofen grown out of methanol
Crystal Size

- Beta-carotene – food colorant. Color shade is determined by the narrow size distribution in the submicron range
- New brilliant ink pigments in the nanoparticle size range
- Tungsten carbide particles – narrow size distribution in the 5-7 micron range
Key Issues for Process Development

• How to design for the desired material properties?
  - crystal purity
  - mean particle size and particle size distribution
  - polymorph
  - particle shape
  - enantiomer

• How to scale up?
  - vessel design
  - system design & process synthesis
Equilibrium Crystal Growth & Shape

- Idealized shape at infinitesimal supersaturation and loooooooong times
- Gibbs equilibrium condition for shape of facetted crystals (1877-78)
  \[ \min \sum_{i} \gamma_i A_i, \quad s.t. \ fixed \ V \]
- Wulff (1901) construction - solves the Gibbs minimization problem

Wulff Construction
Reservations About the Theory

Gibbs (Collected Works, pp. 325-326)

“On the whole it seems not improbable that the form of very minute crystals in equilibrium with solvents is principally determined by the condition that \( \sum \gamma_i A_i \) shall be a minimum for the volume of the crystal, but as they grow larger (in a solvent no more supersaturated than is necessary to make them grow at all), the deposition of new matter on the different surfaces will be determined more by the orientation of the surfaces and less by their size and relations to the surrounding surfaces. As a final result, a large crystal, will generally be bounded by those surfaces alone on which the deposit of new matter takes place least readily. But the relative development of the different kinds of sides will not be such as to make \( \sum \gamma_i A_i \) a minimum”.

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Reservations About the Theory

Landau & Lifshitz (Statistical Physics, p. 520)

“It must be emphasized that the crystal shape observed under ordinary conditions is determined by the condition of growth of the crystal and is not the equilibrium shape.”
Steady-State Growth Shapes

Real growth shapes at low supersaturation

Chernov Condition

Facetted Growth

Crystal Shape and Growth Models

- Crystals grow by the flow of steps across the faces
- Sources of steps
  - 2-D nuclei - birth and spread model
  - spirals growing from screw dislocations
- Sources of edges – strong bond chains (PBC’s)
- Sources of docking points for solute incorporation – kinks on edges (missing molecules along bond chains)
Spiral Growth of Organic Crystals

Figure 10.4: Part of the \{001\} surface of an n-C_{40}H_{82} crystal with several polygonal spirals imaged by TM-AFM.

Acknowledgement
The cover design represents the \{101\} face of a tetragonal hen egg white lysozyme. R. Price, B. Donohoe, G. L. Taylor and P. J. Halfpenny (University of Strathclyde, UK).
Step Formation

Spirals from a Screw Dislocation (BCF)

2-D Nucleation / Birth & Spread

BCF Growth Model

Rate of growth normal to face $hkl$

$$R_{hkl} = (v_i \cdot d / y_i)_{hkl}$$

$i = \text{edge } i \text{ on face } hkl$

$(y_i)_{hkl} \text{ depends on shape of spiral and step velocities}$

$$(v_i)_{hkl} \propto a_p \left[1 + 0.5 \exp\left(\phi_{hkl}^{kink}, i / RT\right)\right]^{-1}$$

$$R_{hkl} \propto \frac{d_{hkl}}{(y_i)_{hkl}} a_p \left[1 + 0.5 \exp\left(\phi_{hkl}^{kink}, i / RT\right)\right]^{-1}$$
Boltzmann Distribution of Kinks

\[
\begin{align*}
\frac{p(\text{kink}, i)}{p(\text{no kink})} &= e^{-\frac{\phi_{1}^{\text{kink}}}{kT}} / e^{-\frac{0}{kT}} = e^{-\frac{\phi_{1}^{\text{kink}}}{kT}} \\
\end{align*}
\]
Kinks on Steps of Ferritin Crystal

KAI CHEN AND PETER G. VEKILOV

(a)

200 nm

(b) Frequency of Occurrence

\( \bar{n}_k = 3.5 \)

(c)

Net growth
2 molecules

Time [s]

Surface Coordinate [nm]
Solid State and Solvent Effects

Face velocities depend on:

- crystallography (unit cell, space group, etc)
- atom-atom pair potentials (including charge distribution)
- bond chains (we have a fast, automated new method for finding them) and kink energies
- growth unit
- solvent

\[ \gamma_{ls} = \gamma_l + \gamma_s - W_A = \gamma_l + \gamma_s - 2 \left( \gamma_l^d \gamma_s \right)^{0.5} \]
General Principle

The **faster** the rate of growth of a face, the **smaller** its size on the crystal

Fast faces grow out and do not appear on the final steady growth shape
The Model

\[
\frac{dH_i}{dt} = G_i
\]

\[
x_i = \frac{H_i}{H_{\text{ref}}} \quad R_i = \frac{G_i}{G_{\text{ref}}} \quad d\xi = \frac{G_{\text{ref}}}{H_{\text{ref}}} dt
\]

\[
\frac{dx_i}{dt} = \frac{G_{\text{ref}}}{H_{\text{ref}}} (R_i - x_i)
\]

\[
\frac{dx_i}{d\xi} = R_i - x_i, \quad i = 1, \ldots, N - 1
\]

Eigenvalues = -1

Unique Stable Steady State
Steady States

\[
\frac{dx_i}{d\xi} = R_i - x_i
\]

\[
R_i - x_i = 0
\]

\[
\frac{R_1}{x_1} = \frac{R_2}{x_2} = \cdots = \frac{R_N}{x_N} = 1
\]

\[
\frac{G_1}{H_1} = \frac{G_2}{H_2} = \cdots = \frac{G_N}{H_N} = \text{constant}
\]

Chernov Condition
Discrete Events at Vertices

- Geometric Elements
  - Crystal: 3-D polyhedron bounded by flat faces
  - Edges: intersection of 2 faces
  - Vertices: intersection of 3 or more faces

- Euler's Polyhedral Rule
  - Convex polyhedron \( F + V - E = 2 \)
  - Under shape changes \( \Delta F + \Delta V - \Delta E = 0 \)
  - Number of virtual faces, edges

\[
\Delta V_{\text{max}} = ^N C_3 - 1, \quad \Delta E_{\text{max}} = ^N C_2 - E^V
\]

\( N = \) number of faces that meet at the vertex under consideration

\( E^V = \) number of edges that meet at the vertex under consideration = \( N \)
Effect of Random Seed Shape
Succinic Acid Grown from Water

Seeds: 450 – 500 μm

1 hr

2:15 hrs

3:30 hrs

Steady state shape from an independent experiment
3-D Shape Evolution: Adipic Acid
Application - Ibuprofen

Storey & York (1997)
Ibuprofen grown from methanol

Predicted – ibuprofen grown from hexane (top) and methanol (bottom)
Application – alpha glycine

alpha-glycine grown from aqueous solution


  (b) dimer growth unit
  (c) monomer growth unit
Population Balance Modeling

- **Shape Factor:** 
  \[ k_v(h_{hkl}) = \frac{V_{\text{cryst}}}{h_{hkl}^3} = f(h_{hkl}, h_{hkl}^0) \]

- **Link:** Shape Evolution Model \( k_v(h_{hkl}), G_{hkl} \rightarrow \) PBM

- **One Dimensional MSMPR Crystallizer**

  Population Balance: 
  \[ \frac{\partial n}{\partial t} = -G_{hkl} \frac{\partial n}{\partial h_{hkl}} - \frac{n}{\tau} \]
  
  Solute Mass Balance: 
  \[ \frac{dc}{dt} = \frac{(\rho - c)}{\tau} + \frac{(c_{in} - \rho)}{\epsilon \tau} + \frac{\rho - c}{\epsilon} \frac{d\epsilon}{dt} \]

  \[ \epsilon = 1 - \int_0^\infty n k_v(h_{hkl}) h_{hkl}^3 dh_{hkl} \]
Size & Shape Evolution – Succinic Acid

Initial and steady-state distribution

Size distribution transient dynamics
Initializing the Model: Nucleation & Polymorph Selection

Gibbs-Thomson Theory

\[ \Delta G = -\frac{4}{3} \pi r^3 \frac{\Delta \mu_{solute}}{\nu_{solute}} + 4\pi r^2 \gamma \]  

(1)

3D Nucleation of \( \alpha \)-glycine

Critical Diameter = 600 nm
Recent Experiments

Observations

• Critical nucleus sizes are in the range of 10’s of nm, e.g., 40 nm for apoferritin

• Molecular arrangement within the nucleus is similar to that in the bulk crystal

• “Contrary to the general belief, the observed nuclei are not compact molecular clusters, but planar arrays of several rods of 4-7 molecules set in 1 or 2 monomolecular layers. Similar unexpected nuclei structures might be common, especially for anisotropic molecules. Hence, the nucleus structure should be considered as a variable by advanced theoretical treatments.” (Yau & Vekilov)
Additional Important Issues

- **Scale-up**
  - CFD – spatially non-uniform conditions

- **Optimization & control**
  - Compartmental models (Bermingham et al., Delft)
  - Exchange rates between cells?

- **Process synthesis**
  - Douglas, Ng, et al.
  - Crystallization paths are useful
  - Process alternatives selected on the basis of economics

- **Material properties (product design) not yet considered (other than size)**
Opportunities

- Polymorphic phase transformations
- Additives & impurities
- Nucleation and polymorph selection
- Solvents/co-solvents/anti-solvents
- Complex bond chains, H-bonds, growth units
- Racemic mixtures, enantiomeric resolution
- From single particles to suspensions
- Process models & process systems engineering
- Process intensification by division of tasks
- Experiments
  - on surfaces for model validation
  - for polymorph selection
  - growth units & precursors
Molecules to Products