Stability of Solid Dosage Forms

Eric J. Munson
Department of Pharmaceutical Chemistry
University of Kansas

Outline
I. Motivation for Studying Solid Dosage Forms
II. Introduction to Solid Forms of Drugs/Excipients
III. Problems with Different Solid Forms
IV. Solid-State Stability - Kinetics
V. Polymorphism - Professor Richard Prankerd
VI. Amorphous Forms - Professor Thomas Rades
VII. Solid-State NMR Spectroscopy - Professor Eric Munson
Why Study Solid Dosage Forms?

- Most drugs are marketed in the solid state (70-90%)
- Stability of dosage forms critical to proper drug release
  - Physical and Chemical Stability
  - Solubility and Dissolution Rate
  - Bioavailability
  - Processability
- Complex nature of dosage forms make them difficult to study (heterogeneous)

Complexity of Solid Dosage Forms

- Active Pharmaceutical Ingredient (API)
  - Usually chosen to be in most stable form
  - Problem - most stable form is also the least soluble form
- Excipients
  - Added to formulation for a variety of reasons - diluent, glidant, binder, etc.
  - Usually want avoid interactions of excipients with API
- Processing steps
  - Milling, grinding, blending, compaction, tabletting, coating, etc.
  - May cause change in form of API and/or excipient
Polymorphic forms of drugs
- Polymorphism is defined as the ability of a compound to adopt two or more conformations/arrangements of molecules in the crystal lattice
- Polymorphism is observed for ~70% of most drug compounds (reported number varies)
- Only one crystal form is the most thermodynamically stable form - all other forms are metastable
- Different polymorphs must have different solubilities

Solubility is related to the enthalpy of solution, $\Delta H$
\[
\ln [S] = - \frac{\Delta H}{RT} + \beta
\]
- Different polymorphs have different enthalpies of solution, hence different solubilities
- Temperature can determine which polymorph is the most stable (monotropic vs. enantiotropic)
- Change in solubility of compound on polymorphic form can vary
- For Ritonavir, change in polymorphic form forced recall of product because of solubility issues
Different Forms of API

- Pseudopolymorphic forms of drugs
  - Pseudopolymorphs refer to solvated forms of compounds (solvates or solvatomorphs)
  - Different pseudopolymorphs have different enthalpies of solution, hence different solubilities
  - Pseudopolymorphs can often have a much larger effect upon the solubility than polymorphic form
  - For example, hydrates of drug compounds are often less stable than are the anhydrous forms
  - Solvation and/or desolation can have a dramatic effect upon form of drug

- Amorphous forms of drugs
  - Amorphous forms can be defined as a form that is not crystalline, or lack long-range order
  - In general, the amorphous state has a higher dissolution rate and higher solubility than does the crystalline state
  - Amorphous materials can also crystallize and are usually more prone to chemical degradation
  - Methods vary to produce amorphous materials, including melt quenching, lyophilization, spray drying, desolvation, and attempts to recrystallize from different solvents
Processing of API/Excipients

- Particle size reduction
  - Really affects dissolution rate more than solubility
  - Noyes Whitney equation

\[ \frac{dM}{dt} = k A (S - C) \]

where:
- \(M\) = mass
- \(t\) = time
- \(k\) = intrinsic dissolution rate constant
- \(A\) = planar surface area
- \(S\) = solubility
- \(C\) = concentration in solution at time \(t\)

Processing of API/Excipients

- Particle size reduction
  - Noyes Whitney works for planar surface
  - Use Hixson-Crowell equation for particles (3D)
  - Assumes monodisperse, spherical powder dissolving under sink conditions

\[ 1 - \left( \frac{M}{M_0} \right)^{1/3} = K t \]

where:
- \(M\) = mass
- \(t\) = time
- \(K\) = particle cube root rate constant
- \(M_0\) = initial mass (\(t = 0\))
Concerns with API Forms

- Polymorphic forms
  - Usually most stable polymorph is chosen to avoid possible change in form upon processing, i.e. physical and chemical stability is chosen over improved solubility
  - Often metastable polymorphic form will dissolve, and then be followed by crystallization of more stable form, which is less soluble

- Pseudopolymorphic forms
  - Often are less soluble than anhydrous forms
  - Desolvation can lead to formation of different forms, including polymorphs, pseudopolymorphs, anhydrates, and amorphous material
  - Desolvated crystals may contain significant numbers of defect sites
Concerns with API Forms

- Amorphous forms
  - Gains in solubility are contrasted with reduced stability
  - Crystallization is the largest concern with amorphous materials
  - Chemical stability may also be an issue
  - Recrystallization can lead to significantly reduced solubilities
  - Small amount of amorphous material may be generated during processing

Concerns with Processing of API/Excipients

- Reduced particle size
  - Similar problem to amorphous state in that gains in solubility are contrasted with reduced stability
  - Aggregation/recrystallization is the largest concern with reduced particle size materials
  - Chemical stability may also be an issue
  - Recrystallization can lead to significantly reduced solubilities
  - Small amount of amorphous material may be generated during processing
Solid-State Stability

- Two types of stability - Physical and Chemical
- Physical Stability
  - Conversion from one form to another
  - Crystallization, change in polymorphic form, desolvation are common
- Chemical Stability
  - Can be intramolecular or intermolecular
  - Hydrolysis, oxidation, photolysis are possible

Solid-State Stability

- Amorphous material - generally less stable
- Basic properties of an amorphous material
  - Defined as a non-crystalline solid
  - Can also be referred to as a supercooled liquid
  - Can exist in either the “glassy” or “rubbery” state
  - Above the glass transition temperature, $T_g$, the material is in the rubbery state and is highly mobile
  - Below the glass transition temperature, the material is in the glassy state, and mobility is significantly reduced
  - The $T_g$ can change based upon moisture content, etc.
Solid-State Stability

- Crystalline material - generally more stable
- Basic properties of a crystalline material
  - Defined as a solid form that is crystalline
  - Has a defined repeating unit
  - Crystal shape is referred to as morphology or habit
  - Mobility is usually much less than in an amorphous form
  - Will usually have a defined solvent stoichiometry, e.g. monohydrate, dihydrate, 2.5 hydrate
  - Can also have variable solvent stoichiometry

Solid-State Stability

- Characterization of the amorphous state
  - PXRD - Lack of long range order results in an amorphous halo in diffraction pattern
  - Moisture sorption isotherm - amorphous materials are usually much more hygroscopic than crystalline form
  - Isothermal microcalorimetry - can monitor heat of crystallization
  - Modulated differential scanning calorimetry (MDSC) - can detect small amounts of amorphous
  - Spectroscopic methods - includes Raman, Infrared, Solid-State NMR
Solid-State Stability

- Characterization of the crystalline state
  - Single crystal XRD - Long range order results in well-defined diffraction pattern - makes it possible to determine molecular conformation and packing
  - PXRD - usually used to characterize crystalline material - diffraction pattern is a fingerprint of the crystal form
  - Moisture sorption isotherm - can be used to determine the change in weight upon change in relative humidity - useful for determining water stoichiometry

Solid-State Stability

- Characterization of the crystalline state
  - Differential scanning calorimetry (DSC) - useful for determining the thermodynamic relationship between polymorphs
  - Particle size measurement - provides information about size and distribution of particles in the solid state
  - Microscopy - particle size, birefringence tells crystallinity
  - Spectroscopic methods - includes Raman, Infrared, Solid-State NMR - provides fingerprint, quantitation of forms
Solid-State Stability

- Physical stability of the amorphous state
  - Crystallization much more likely above $T_g$
  - General “guideline” is that amorphous materials are stable at temperatures 50 °C below $T_g$
  - Stability of amorphous form greatly depends on how is it prepared
  - Presence of residual crystallinity (defect sites) can be source for nucleation
  - In general, grinding/milling produces least stable amorphous form, followed by lyophilization/spray drying, followed by melt-quench

Solid-State Stability

- Physical stability of the crystalline state
  - Polymorphic transformation and solvation/desolvation biggest problems
  - Stability of polymorphic form may depend upon temperature (monotropic vs. enantiotropic)
  - Mixtures of polymorphic and pseudopolymorphic forms possible
  - Presence of moisture can promote polymorphic and pseudopolymorphic transformations
  - Polymorphic and pseudopolymorphic changes are often observed upon scaling up a process
Solid-State Stability

- Chemical stability of the amorphous state
  - Reactivity much more likely above $T_g$
  - Above $T_g$, reactions in the amorphous state may be thought of as a continuation of reactions in the melt (follow same Arrhenius plot)
  - Hydroscopic nature can promote hydrolysis reactions
  - May also be more sensitive to oxidation and photochemical degradation
  - It has been proposed that small amounts of amorphous material is the source of many stability problems observed (both physical and chemical)

Solid-State Stability

- Chemical stability of the crystalline state
  - Four steps to a solid-state reaction
    1. Loosening of molecules at the reaction site - necessary distortion of reaction cavity
    2. Molecular change - breaking and forming of chemical bonds
    3. Solid-solution formation - reactant and product both present in crystal
    4. Separation of product - production of new product crystals
Solid-State Stability

- Chemical stability of the crystalline state
  - Topochemical postulate
    “reactions in crystals occur with a minimum of atomic and molecular movement”
  - Molecular mobility - necessary to understand factors responsible for solid-state reactions
  - Mobility can be enhanced by presence of defect sites
  - Common reactions in the solid state include hydrolysis, oxidation, and photolysis

Solid-State Stability

- Reaction Kinetics
  - Reaction kinetics in solid state much more complicated than in solution
  - Multiple models exist to describe reaction, and choice of model may not be clear cut from fitting of data
  - Noted by Carstensen*
    “It is difficult to distinguish between reactions orders in the solid state on pure statistical grounds, and other information must be available before a mechanistic model can be assigned”
    “It is emphasized here that sorting out mechanisms by statistical analysis can be fallacious”

*Carstensen, Advanced Pharmaceutical Solids
Solid-State Stability

- Reaction Kinetics
  - Nucleation-based mechanisms commonly used
  - Nucleation site is a site of high mobility (disorder)
  - Prout-Tompkins equation:

\[
\ln \left( \frac{x}{1-x} \right) = k \cdot t + c
\]

where:
- \( x \) = percent decomposition
- \( t \) = time
- \( k \) = rate constant
- \( c \) = constant

Solid-State Stability

- Reaction Kinetics
  - Nucleation-based mechanisms commonly used
  - Dimensionality is incorporated into A-E equation
  - Avrami-Erofeyev equation:

\[
[- \ln (1-x)]^n = k \cdot t
\]

where:
- \( x \) = percent decomposition
- \( t \) = time
- \( k \) = rate constant
- \( n \) = 1/4, 1/3, 1/2, 2/3, 1
Solid-State Stability

- Reaction Kinetics
  - Other reactions
  - Phase boundaries (one, two, three dimensions)
  - Diffusion controlled reactions (one, two, three dimensions)
  - Power law equations
  - Reaction order
  - Note: some of these reaction rates (e.g. power law) have no basis in theory, but just fit the data
  - Reflects the difficulty in studying kinetics in the solid state
Methods for Characterizing Pharmaceutical Solids

- **Thermal methods**
  - Differential Scanning Calorimetry (DSC)
  - Thermogravimetric Analysis (TGA)
  - Hot stage microscopy

- **Solubility methods**
  - Solubility
  - Dissolution rate

- **Diffraction methods**
  - Single-crystal X-ray diffraction
  - Powder X-ray diffraction
  - Neutron diffraction

- **Spectroscopic methods**
  - Infrared spectroscopy
  - Raman spectroscopy
  - Solid-state NMR spectroscopy

Why Use Solid-State NMR Spectroscopy to Characterize Pharmaceuticals?

- Non-destructive and non-invasive
- Quantitative and Selective
- Structure
- Dynamics
Why Use Solid-State NMR Spectroscopy to Characterize Pharmaceuticals?

Non-destructive and non-invasive

- Bulk drugs
- Drug formulations
  - Drug - different chemical shift from excipient
- Inclusion compounds
  - Host-guest interactions
- Polymer matrices
  - Crystalline drugs, proteins, and peptides
  - Chemical reactions

Why Use Solid-State NMR Spectroscopy to Characterize Pharmaceuticals?

Quantitative and Selective

- Quantitation of Forms
  - Crystalline vs. amorphous
  - Mixtures of forms
  - Don’t need standard!
- Selective Labeling
  - Drug-excipient interactions
  - Changes upon formulation
  - Amorphous $\Rightarrow$ crystalline
Why Use Solid-State NMR Spectroscopy to Characterize Pharmaceuticals?

**Structure**

- Crystalline
  - Number of crystallographically inequivalent sites
  - Conformation
  - Hydrogen bonding
  - Packing arrangement
- Amorphous
  - Degree of disorder
- Mixed phases
  - Liquids in solids

**Dynamics (mobility)**

- Crystalline
  - Determine mobility in lattice
- Amorphous
  - T_g
  - Plasticizers
- Formulations
  - Drug
  - Excipient
  - Polymer
Why Isn’t Solid-State NMR Spectroscopy Used More to Characterize Pharmaceuticals?

- Requires expertise to use properly
- Expensive
- Non-routine
- Difficult to automate
- Insensitive
- Long analysis times
- Assigning peaks problematic
  - Chemical shifts can vary by more than 10 ppm from their solution values
  - Relating chemical shifts to structure complicated

Characterization of Polymorphic Forms

- Solid-state NMR (SSNMR) spectra are strongly influenced by the conformation and arrangement of molecules in the crystal lattice
- Influence of packing vs. conformation on the chemical shift is unclear, but conformation probably dominant
- Each carbon may have multiple peaks in SSNMR spectra, reflecting multiple crystallographically inequivalent sites in unit cell
- Tentative assignments can be made based upon expected chemical shifts and theory
Aspartame

13C CP/MAS NMR Spectra of Aspartame Polymorphs

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Identification: PXRD vs. Solid-State NMR

- Powder X-ray diffraction viewed as “gold standard” of polymorphic identification
- Very sensitive to changes in unit cell parameters, which almost always vary between polymorphs
- Requires long-range order to identify polymorphic change, i.e. diffraction grating
- Solid-state NMR is sensitive to short range order, and is therefore complementary to PXRD for identification of polymorphic changes
- Occasionally two techniques will give different answers

13C NMR Assignments for Neotame Monohydrate
13C Solid-State NMR Spectra of Neotame

- Monohydrate (4.8% H₂O)
- 12 hrs at house vac, 60 °C (0.73% H₂O)
- 3 days at 1 Torr (0.73% H₂O)
- Melted at ~95 °C and 1 torr (0.99% H₂O)

Phenyl Region of 13C Solid-State NMR Spectra of Neotame

- Monohydrate (4.8% H₂O)
- 12 hrs at house vac, 60 °C (0.73% H₂O)
- 3 days at 1 Torr (0.73% H₂O)
- Melted at ~95 °C and 1 torr (0.99% H₂O)
**Powder X-ray Diffraction Patterns of Neotame**

- Monohydrate (4.8% H$_2$O)
- 12 hrs at house vac, 60 °C (0.73% H$_2$O)
- 3 days at 1 Torr (0.73% H$_2$O)
- Melted at ~95 °C and 1 torr (0.99% H$_2$O)

**Phenyl Region of $^{13}$C Solid-State NMR Spectra of Neotame**

- Monohydrate (4.8% H$_2$O)
- 12 hrs at house vac, 60 °C (0.73% H$_2$O)
- 3 days at 1 Torr (0.73% H$_2$O)
- Melted at ~95 °C and 1 torr (0.99% H$_2$O)
**13C Solid-State NMR Spectra of Conversion Experiment**

3 days at 1 torr (0.73% H₂O)
in jar 2 days (0.98% H₂O)
in jar 4 days (0.96% H₂O)
in jar 6 days (1.2% H₂O)
in jar 8 days (1.2% H₂O)
84% RH for 12 days

**Powder X-ray Diffraction Patterns of Conversion Experiment**

3 days at 1 torr (0.73% H₂O)
in jar 2 days (0.98% H₂O)
in jar 4 days (0.96% H₂O)
in jar 6 days (1.2% H₂O)
in jar 8 days (1.2% H₂O)
84% RH for 12 days
Phenyl Region of $^{13}$C Solid-State NMR Spectra of Neotame

Quantitation: Mixtures of Anhydrous Neotame Polymorphs

- Ideally, amount of signal (i.e. peak area) is proportional to the number of nuclei
- Problem: Cross polarization spectra are rarely quantitative
- Peak area and intensity are governed by cross polarization rates and relaxation rates ($T_{CP}$ and $T_{1p}$)
- At short to optimum contact times (CT), cross polarization rates increase signal detected. At longer CT, signal decays by proton $T_{1p}$ relaxation
$^{13}$C Solid-State NMR Spectra of Neotame Forms A and G

Form A

Form G

$^{13}$C Solid-State NMR Spectrum of a 50/50 Wt.% Mixture of Neotame Forms A and G

Form A

Form G

$^{13}$C Solid-State NMR Spectrum of a 50/50 Wt.% Mixture of Neotame Forms A and G

Form A

Form G
Quantitation: Mixtures of Anhydrous Neotame Polymorphs

- Requires resolution of peaks between forms. (Carbon 7 - quaternary aromatic)
- For mixtures of two polymorphs, peak areas are only quantitative if CP dynamics are the same
- To determine absolute intensities, plot CT vs. ln[relative peak area] at long contact times and extrapolate to CT = 0
Quantitation: Mixtures of Anhydrous Neotame Polymorphs

- For mixtures of two polymorphs, peak areas are only quantitative if CP dynamics are the same.
- Requires resolution of peaks between forms. (Carbon 7 - quaternary aromatic)
- To determine absolute intensities, plot CT vs. ln[relative peak area] at long contact times and extrapolate to CT = 0.
- Example:
  - Intercept A = 4.8556; e^{4.8556} = 128.46 (50.27%)
  - Intercept G = 4.8449; e^{4.8449} = 127.09 (49.73%)
### Comparison of Solid-State NMR Integration Values vs. Weight Percent of Neotame Forms A and G

#### Table

<table>
<thead>
<tr>
<th>Sample</th>
<th>Form</th>
<th>Mass (g)</th>
<th>Wt. %</th>
<th>Rel. Area</th>
<th>R²</th>
<th>Exp. %</th>
<th>Diff (abs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>A</td>
<td>0.0064</td>
<td>2.37</td>
<td>1027</td>
<td>0.9843</td>
<td>4.55</td>
<td>2.18</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.3385</td>
<td>97.63</td>
<td>21556</td>
<td>0.9974</td>
<td>95.45</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>A</td>
<td>0.0478</td>
<td>12.62</td>
<td>1478</td>
<td>0.9996</td>
<td>13.64</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.3309</td>
<td>87.38</td>
<td>9340</td>
<td>0.9899</td>
<td>86.34</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>A</td>
<td>0.0759</td>
<td>21.20</td>
<td>141.9</td>
<td>0.9992</td>
<td>22.00</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.2822</td>
<td>78.80</td>
<td>503.1</td>
<td>0.9906</td>
<td>78.00</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>A</td>
<td>0.1034</td>
<td>29.71</td>
<td>134.2</td>
<td>0.9928</td>
<td>29.36</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.2445</td>
<td>70.29</td>
<td>321.5</td>
<td>0.9852</td>
<td>70.64</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>A</td>
<td>0.1273</td>
<td>39.12</td>
<td>154.2</td>
<td>0.9979</td>
<td>39.36</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.1981</td>
<td>60.88</td>
<td>203.1</td>
<td>0.9956</td>
<td>62.14</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>A</td>
<td>0.1507</td>
<td>49.73</td>
<td>128.5</td>
<td>0.9994</td>
<td>50.27</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.1982</td>
<td>50.27</td>
<td>127.1</td>
<td>0.9954</td>
<td>49.73</td>
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</tr>
<tr>
<td>60%</td>
<td>A</td>
<td>0.1954</td>
<td>61.56</td>
<td>130.1</td>
<td>0.9995</td>
<td>62.28</td>
<td>0.72</td>
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<tr>
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<td>G</td>
<td>0.1220</td>
<td>38.44</td>
<td>78.8</td>
<td>0.9990</td>
<td>37.72</td>
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<tr>
<td>70%</td>
<td>A</td>
<td>0.2413</td>
<td>75.29</td>
<td>132.6</td>
<td>0.9981</td>
<td>74.41</td>
<td>1.12</td>
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<tr>
<td></td>
<td>G</td>
<td>0.1620</td>
<td>24.71</td>
<td>53.1</td>
<td>0.9476</td>
<td>26.59</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>A</td>
<td>0.2966</td>
<td>89.88</td>
<td>131.4</td>
<td>0.9951</td>
<td>89.87</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.0703</td>
<td>10.12</td>
<td>25.1</td>
<td>0.9955</td>
<td>10.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>0.2961</td>
<td>88.41</td>
<td>132.0</td>
<td>0.9996</td>
<td>88.04</td>
<td>0.35</td>
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<tr>
<td></td>
<td>G</td>
<td>0.0388</td>
<td>11.59</td>
<td>78.8</td>
<td>0.9996</td>
<td>11.05</td>
<td></td>
</tr>
</tbody>
</table>

#### Graph

- The graph shows a linear relationship between the calculated weight percent and the integration values.
- The equation of the line is: $y = 1.0068x + 0.1128$.
- The coefficient of determination ($R^2$) is 0.9992.

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