Stability And Excipient Compatibility Studies

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Outline

• Introduction
• Solution stability
• Solid state stability
  – Kinetic treatment
  – Chemical stability
  – Physical stability
• Excipient compatibility study
• Concluding remarks
Introduction

Importance of stability

• Extensive chemical degradation $\Rightarrow$ a substantial loss of potency
• Degradation products may result in adverse events or be unsafe
• Instability may cause
  – Undesired change in performance, i.e. dissolution/bioavailability
  – Substantial changes in physical appearance of the dosage form causing product failures
• Requirement for approval by regulatory agencies
Introduction

Factors Affecting Formulation Stability

Drug & Excipient
- chemical structure
- impurity profile
- physical form
- moisture content
- particle size
- surface area
- morphology

Formulation
- drug:excipient ratio
- processing method
- mixing/milling
- powder packing

Environment
- temperature
- relative humidity
- packaging
- light
- oxygen

Solid dosage forms are multi-component, and multi-phase system, therefore, their (in)stability is complex!
Solution Stability

Fundamental characterization of the compound

- Providing necessary information for product development
  - Early understanding of the system and the complexity for development
  - Dosage form selection
  - Formulation design
  - Analytical method development

Many “solid state reactions” are in deed occurring in the solution state
Solution Stability

Kinetics of reactions

• First order reactions

\[- \frac{dC}{dt} = kC \quad \rightarrow \quad \ln \frac{C}{C_0} = -kt\]

• Second order reactions

\[- \frac{dC}{dt} = kC^2 \quad \text{or} \quad - \frac{dC}{dt} = kC_A C_B \]

\[\frac{1}{C_0} - \frac{1}{C} = -kt\]
Solution Stability

Kinetics of reactions

- Complex reactions
  - Consecutive reactions

\[ \text{A} \rightarrow \text{B} \rightarrow \text{C} \]

\[
\text{Cefotaxime Na, aqueous solution, UV 254 nm}
\]

\[
\begin{align*}
\text{Time (hour)} & \quad \text{10000 x concentration (M)} \\
0 & \quad 0 \\
1 & \quad 20 \\
2 & \quad 40 \\
3 & \quad 60 \\
4 & \quad 80 \\
5 & \quad 100 \\
6 & \quad 120 \\
\end{align*}
\]

Solution Stability

Kinetics of reactions
• Complex reactions
  – Parallel reactions

\[
\begin{array}{ccc}
A & \xrightarrow{\text{reaction}} & B \\
& & \setminus \\
& & C
\end{array}
\]

Notari & DeYoung, J Pharm Sci 64 (1975) 1148.
Factors affecting reaction rate

• Temperature
  – Arrhenius equation: $k = Ae^{-E_a/RT}$
  – The Arrhenius plot
    • lnK against 1/T
    • $E_a$ can be obtained from the slope
    • Basis for the accelerated stability testing
  – Underlying assumption
    • Reaction mechanism does not change as a function of temperature, i.e., $E_a$ is independent of $T$
    • May not be valid for some reactions, especially the complex reactions
Solution Stability

Factors affecting reaction rate

- **Solvent**
  - pH of aqueous solvents
    - Acid, base, and water catalyzed reactions, mostly hydrolysis
    - Leading to various kinetic profiles: L, V, U
    - More complex shapes of kinetic profiles if the compound has (multiple)ionizable functionality
  - Composition: medium effect on chemical reactions
    - Non-traditional dosage forms: e.g. co-solvents, soft gel, lipid based systems
Solution Stability

Factors affecting reaction rate

- Light
- Oxygen
- Co-solutes
  - Buffer salts: catalysis
  - Surfactants: different environment in the micelles
  - Complexation agents: different environment, e.g. cyclodextrin
  - Antioxidants and/or chelating agents
Solution Stability

Common degradation routes

- **Solvolyis/hydrolysis**
  - Most frequently encountered hydrolysis - ester
  - Typically pseudofirst order
  - Intramolecular catalysis and steric factors

- **Photolysis/oxidation**

- **Racemization**
  - May cause substantial decrease in biological activities: e.g. Pilocarpine, tetracycline

- **Others**
  - e.g. decarboxylation
Solid State Stability: Kinetic Treatment

Solid state reaction kinetic models:

\[
\frac{d\alpha}{dt} = k(T) f(\alpha) = A e^{\frac{E_a}{RT}} f(\alpha)
\]

<table>
<thead>
<tr>
<th>Model Designation</th>
<th>Differential Form, ( f(\alpha) )</th>
<th>Integral Form, ( g(\alpha) )</th>
<th>Corresponding Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>( 2(1-\alpha)[-\ln(1-\alpha)]^{1/2} )</td>
<td>( -\ln(1-\alpha)^{1/2} )</td>
<td>Avrami-Erofeev, ( n = 2 )</td>
</tr>
<tr>
<td>A3</td>
<td>( 3(1-\alpha)[-\ln(1-\alpha)]^{2/3} )</td>
<td>( -\ln(1-\alpha)^{1/3} )</td>
<td>Avrami-Erofeev, ( n = 3 )</td>
</tr>
<tr>
<td>A4</td>
<td>( 4(1-\alpha)[-\ln(1-\alpha)]^{3/4} )</td>
<td>( -\ln(1-\alpha)^{1/4} )</td>
<td>Avrami-Erofeev, ( n = 4 )</td>
</tr>
<tr>
<td>D1</td>
<td>( 1/2\alpha )</td>
<td>( \alpha^2 )</td>
<td>One-dimensional diffusion</td>
</tr>
<tr>
<td>D2</td>
<td>( [-\ln(1-\alpha)]^{-1} )</td>
<td>( (1-\alpha)\ln(1-\alpha) + \alpha )</td>
<td>Two-dimensional diffusion</td>
</tr>
<tr>
<td>D3</td>
<td>( 1.5(1-\alpha)^{1/3}[(1-\alpha)^{-1/3} - 1]^{-1} )</td>
<td>( [1 - (1-\alpha)^{1/3}]^2 )</td>
<td>Three-dimensional diffusion (Jander)</td>
</tr>
<tr>
<td>D4</td>
<td>( 1.5[(1-\alpha)^{-1/3} - 1]^{-1} )</td>
<td>( 1 - 2\alpha/3 - (1-\alpha)^{2/3} )</td>
<td>Three-dimensional diffusion (Ginstling-Brounshtein)</td>
</tr>
<tr>
<td>F1</td>
<td>( 1 - \alpha )</td>
<td>( -\ln(1-\alpha) )</td>
<td>First-order reaction</td>
</tr>
<tr>
<td>F2</td>
<td>( (1-\alpha)^2 )</td>
<td>( 1/(1-\alpha) - 1 )</td>
<td>Second-order reaction</td>
</tr>
<tr>
<td>P1</td>
<td>( \alpha(1-\alpha) )</td>
<td>( \ln[\alpha/(1-\alpha)] )</td>
<td>Prout-Tompkins</td>
</tr>
<tr>
<td>PL2</td>
<td>( 2\alpha^{1/2} )</td>
<td>( \alpha^{1/2} )</td>
<td>Power law ((n = 1/2))</td>
</tr>
<tr>
<td>PL3</td>
<td>( 3\alpha^{2/3} )</td>
<td>( \alpha^{1/3} )</td>
<td>Power law ((n = 1/3))</td>
</tr>
<tr>
<td>PL4</td>
<td>( 4\alpha^{3/4} )</td>
<td>( \alpha^{1/4} )</td>
<td>Power law ((n = 1/4))</td>
</tr>
<tr>
<td>R1</td>
<td>( 1 )</td>
<td>( \alpha )</td>
<td>One-dimensional phase boundary</td>
</tr>
<tr>
<td>R2</td>
<td>( 2(1-\alpha)^{1/2} )</td>
<td>( 1 - (1-\alpha)^{1/2} )</td>
<td>Two-dimensional phase boundary</td>
</tr>
<tr>
<td>R3</td>
<td>( 3(1-\alpha)^{2/3} )</td>
<td>( 1 - (1-\alpha)^{1/3} )</td>
<td>Three-dimensional phase boundary</td>
</tr>
</tbody>
</table>

\( \alpha \): fraction transformed

Solid State Stability: Kinetic Treatment

Solid $\rightarrow$ Liquid + Gas and Solid $\rightarrow$ Solid + Gas

Same system may exhibit different kinetics and mechanism at different temperatures!

Many “solid state” reactions occur in solution

Major source of the solvent

- Residual moisture or solvent from wet granulation
- Moisture sorbed (in)onto excipients, such as starch and lactose
- Moisture in the capsule shell may migrate, through direct contact or vapor phase
- A melt of the drug itself or an ingredient in the formulation that has a low melting point
- A solvate or hydrate that loses its lattice solvent with time and temperature fluctuation
Solid State Stability: Chemical

Factors: particles
• Physical form
  – Differences in intrinsic activity
  – Difference in mobility
• Particle size/surface area
  – Oxidation
  – Many solid state reactions are initiated on the surface
• Morphology
  – Representation of the functional groups are different on various crystal faces
  – Different reactivity if certain functional group(s) is (are) reactive
• Defects concentration
  – Solid state reaction usually initiate at high energy sites ("hot spots")
  – Surface can be considered “hot spots”
• Impurities
  – Lattice stain surrounding the incorporated impurity → “hot spots”
Solid State Stability: Chemical

Factors: environment

• Temperature
  – More complicated compared to solution state, e.g. Prout-Tompkins vs. Bawn kinetics
  – Vaporization of the reaction products
  – Melting points of the various components

• Relative humidity
  – Directly determine the water content in(on) the solid

• Packaging

• Light
  – Wavelength and intensity

• Oxygen
Solid State Stability: Chemical

Factors: excipients

- Acting as surface catalysts
- Altering the pH of the moisture layer
- Undergoing direct chemical reactions with the drug
  - Drug:excipient ratio
  - Powder mixing and packing
    - Impact both physical contact of the reactive species and the diffusion matrix (porosity and tortuosity)
    - Physical mixing vs. granulation
    - Granules vs. compacts
# Solid State Stability: Chemical

## Known incompatibilities

<table>
<thead>
<tr>
<th>functional Group</th>
<th>Incompatibilities</th>
<th>Type of Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary amine</td>
<td>mono and disaccarides</td>
<td>amine-aldehyde and amine-acetal</td>
</tr>
<tr>
<td>ester, cyclic, lactose</td>
<td>basic components</td>
<td>ring opening, ester-base, hydrolysis</td>
</tr>
<tr>
<td>carbonyl, hydroxyl,</td>
<td>silanol</td>
<td>hydrogen bonding</td>
</tr>
<tr>
<td>aldehyde</td>
<td>amine, carbohydrates</td>
<td>aldehyde-amine, Schiff base or glycosylamine formation</td>
</tr>
<tr>
<td>carboxyl</td>
<td>bases</td>
<td>salt formation</td>
</tr>
<tr>
<td>alcohol</td>
<td>oxygen</td>
<td>oxidation to aldehydes and ketones</td>
</tr>
<tr>
<td>sulfhydryl</td>
<td>oxygen</td>
<td>dimerization</td>
</tr>
<tr>
<td>phenol</td>
<td>metals</td>
<td>complexation</td>
</tr>
<tr>
<td>gelatin capsule shell</td>
<td>cationic surfactants</td>
<td>denaturation</td>
</tr>
</tbody>
</table>
Solid State Stability: Chemical

Method of Stabilization

• Assumption
  – Reaction occurs in solution state in the solid dosage forms
  – Reaction rate is proportional to the amount of dissolved drug
  – Amount of dissolved drug = volume of available solvent x saturated solubility of the drug

• Altering the properties of the solid drug
  – Increasing melting point
  – Choosing a non-hygroscopic form (crystal or salt form)
  – Reducing solubility by choosing a less soluble salt
  – Micellar inclusion
  – Complexation
  – Engineering of the particles (shape)
Solid State Stability: Chemical

Method of Stabilization

• Minimizing the level of moisture in the formulation
  – Choice of excipients
  – Co-solvents
  – Manufacturing conditions
  – Storage conditions
  – Packaging

• Changing the micro-environment around the drug particles in the formulation
  – Adjusting the pH by using acids, bases, or buffer salts
  – Incorporating complexation agents to inactivate trace metal ions
  – Displacing oxygen with nitrogen or argon
  – Incorporating antioxidants
Solid State Stability: Chemical

Method of Stabilization

• Physically separating the reacting species
  – Minimizing the contact among the interacting drug(s) and excipients, and water
  – Techniques:
    • Coating with polymers/ microencapsulation
    • Multi-layer tablet
    • Tablet in a tablet
    • Tablet in a capsule
Examples

I. Enzyme X: effect of temperature (momentary)
   • When loosely mixed with excipients, the enzyme is stable
   • When compressed, however, the frictional heat generated was sufficient to degrade the labile substance

II: Captopril: importance of drug:excipient ratio
   • Drug-excipient compatibility studies showed decomposition in the present of Mg stearate
   • However, High strength (100 mg) tablets prepared containing Mg stearate are table
   • Lower strength (2 mg) tablets, on the other hand, showed significant oxidative decomposition
Examples

III: Moexipril: stabilizing via new solid phase

- This n-carboxylalkyl dipeptide undergoes intramolecular aminolysis in solution at pH’s less than 4.5 and ester hydrolysis at pH’s greater than 10
- In the dry state most excipients were showed to be incompatible, moisture and basic agents were the destabilizing factors
- In wet granulations, however, basic agents were found to suppress drug degradation even in the presence of moisture
- A possible explanation is that new salt form was created through ion exchange during the wet granulation process

Solid State Stability: Physical

Physical degradation routes

• Polymorphic transition
• Hydrate/solvate formation
• Crystallization of amorphous material
• Vaporization
  – e.g. Nitroglycerin
• Sorption
• Particle sedimentation
  – For suspensions, emulsions, creams and ointments
Solid State Stability: Physical

Tendency of transformation is defined by the stability phase diagram. Kinetic, however, could be drastically different.

- **Process dependent**
  - Slow for solid state phase transition
  - Facilitated by temperature, defects, and seeds
  - Fast for adsorption, evaporation, etc.

- **Environment dependent**
  - Temperature
  - Relative humidity for dehydration, amorphous crystallization
  - Excipients (solubilization in the amorphous matrix, inhibiting nucleation, etc.)

- **Particle dependent**
  - Particle size
Examples

I. Form conversion during milling
   • Calcium antagonist CGP28727
   • Form I
     – Melting point: 155-157°C
     – Solubility in water at 25°C: 3.8 μg/mL
     – Cream color
   • Form II
     – Melting point: 170-172°C
     – Solubility in water at 25°C: 7.4 μg/mL
     – Yellow color
   • Form I and Form II are enantiotropically related
   • Micronization by a jet mill not successful
   • Milling in a pin mill reduced particle size only marginally but resulted in Form II
Examples

II: Hydration Kinetics: seeding effect

- Carbamazepine
- Readily convert to dihydrate in water (in minutes)
- Very slow hydration with atmospheric water vapor (take 5 weeks to see any conversion at 97% RH)
- After wet granulation and drying (maybe insufficient) traces of the dihydrate are retained, act as seed material, and rehydration takes place faster and would also happen at lower humidity values
- takes 25 days for complete hydration at 93% RH

Examples

III: Enalapril: sorption

- Incompatible with microcrystalline cellulose
  - caused dissociation of the amine maleate, which resulted in wicking of the oil away from the anion
  - The free amine is unstable

- Compatible with Ca Phosphate
  - No such preferential adsorption occurred


IV: Ibuprofen: vaporization

- Forms eutectic in the presence of stearates which sublimes

- Film coating the tablets eliminate this problem

Excipient Compatibility Study

Tiered approach for formulation development

- Excipient compatibility screening
- Model formulation design and stability testing
- Formulation optimization
Excipient Compatibility Study

Why screen excipients for compatibility?

• Formulation stability studies are time consuming and expensive
• Need to minimize the number of model formulations
• Provide rational basis for selecting excipients used in model formulations
• Goal: Identify excipients that
  – Are not compatible with the active
  – Do not have any impact on the stability of the active
  – Can stabilize the drug substance - A myth
    • solid state reactions are generally heterogeneous reactions which occur only at points of contact between drug and excipients. To expect a stabilizer to interpose at these points of contact on a random basis is rather simplistic.
  – Assign a relative risk level to each excipient within a functional class
Excipient Compatibility Study

Experimental Design

• Prototype formulations
• Binary mixture at extreme ratios
  – Need to reflect those expected to be present in the final product
• Part of the mixture can be compacted, e.g., in a Carver press, to simulate forces encountered in a tablet operation
• Expose to 40 or 50°C/75% RH
• Addition of water (5-20% water as a worst case)
• Analysis by HPLC
Excipient Compatibility Study

Experimental Design

- Other analytical methods:
  - DSC Screening
    - Thermal events usually at high T
    - Often not predictive of chemical interactions at RT
  - Isothermal calorimetry (Thermal Activity Monitor, TAM)
    - Highly sensitive, therefore, experiments are performed at lower T → better extrapolation to RT
    - No or minimum sample treatment required
    - Non-destructive
    - Non-specific → less method development
    - Non-specific → can be misleading (Enthalpy differences across reactions, physical processes not related to compatibility, i.e., evaporation, dissolution, phase changes)
  - Non-representative conditions as in formulations
Concluding Remarks

Predicting Product Stability from Chemical Structure

• Qualitative ranking and rationalization is possible
• Quantitative prediction is still difficult
  – Diverse possible reactions and interactions
  – Too many factors affecting drug stability in a pharmaceutical product during its self-life
  – Multiple phases (e.g. a tablet) make it difficult to model the reaction rate
Concluding Remarks

Developing a stable formulation requires

• Thorough investigation of the intrinsic stability of the compound in preformulation stage of development
  – Thermal and photo
  – Against oxidation

• Relevant excipient compatibility studies
  – Identify low risk excipients

• Detailed stability studies of the prototype formulations
  – Accelerated conditions
  – Understand the stability in formulations

• Optimize formulation based on the stability and other quality attributes