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# Process-Induced Phase Changes and Potential Impacts on Drug Product Performance

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# Outline

- Pharmaceutical Solid Forms
- Pharmaceutical Processing & Potential Phase Transformations
- Case Studies
- Anticipation and Mitigation

# Basic Regulatory Requirements

- Safety & Efficacy
  - Pharmacological properties
  - Drug concentration (bioavailability)
  - Impurity and level (stability)
- Bioavailability (BA)
  - Physiology of absorption site(s)
  - Biopharmaceutical properties
  - Physicochemical properties
    - Solubility, dissolution rate, stability
- Stability
  - Physically and chemically

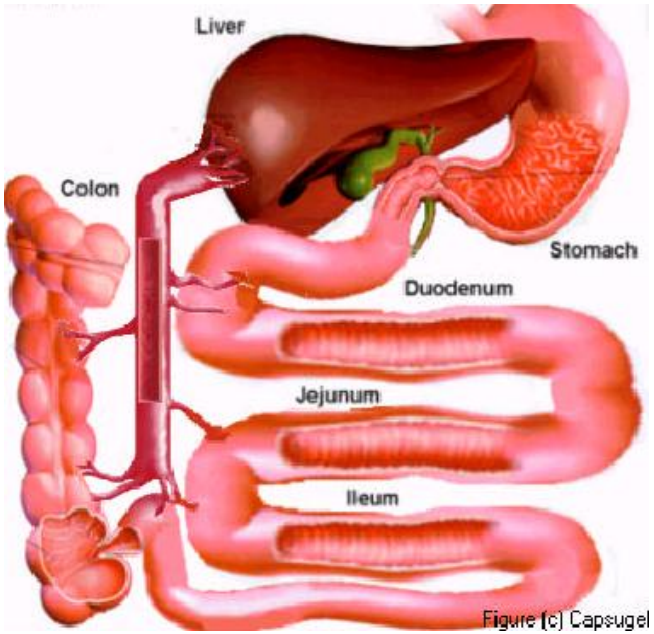


Figure (c) Capsugel

# Impacts of Solid Phases

Solid phases may differ

- Packing: Molecular volume and density; Refractive index; Conductivity, electrical and thermal; Hygroscopicity
- Thermodynamic: Melting and sublimation temperatures; Internal energy; Enthalpy; Heat capacity; Entropy; Free energy and chemical potential; Thermodynamic activity; Vapor pressure; Solubility
- Spectroscopic: Electronic transitions (UV); Vibrational transitions (IR/Raman); Rotational transitions (Far IR/Microwave); Nuclear spin transitions (NMR)
- Kinetic: Dissolution rate; Solid state reaction rate; Stability
- Surface: Surface free energy; Interfacial tensions; Habit
- Mechanical: Flow, Tensile strength; Compactibility; Handling

Directly related to CQAs: stability, bioavailability, efficacy and safety

# Solid Form Selection

Thermodynamically stable phase is usually preferred

Meta-stable phases selected for special considerations

- Apparent solubility/ dissolution rate → Bioavailability
- Chemical stability
- Mechanical property (e.g. acetaminophen)
- API Manufacturability

Importance of thorough screening /characterization

- Polymorph: Crystal lattice
- Salt/parent: Lattice + counterion
- Anhydrate/hydrate: Water activity/RH

# Importance of Controlling Solid Forms during Processing

Inadvertent solid phase changes may impact:

- physical and/or chemical stability
- dissolution characteristics
- in vivo performance (bioavailability, efficacy, and safety)

May defeat the purpose of form selection.

May introduce a time bomb.

- Kinetics in solid-state may vary significantly

Process-induced phase transformations may be responsible for many observed drug product performance issues

# Common Pharmaceutical Processing

Active Pharmaceutical Ingredient (API) size reduction

- Impact mill
- Fluid energy mill

Granulation/size enlargement

- Wet granulation (low/high shear mixing, fluid-bed mixing, pelletization)
- Dry granulation (slugging, roller compaction, etc.)
- Melt granulation

Spray (and freeze) drying

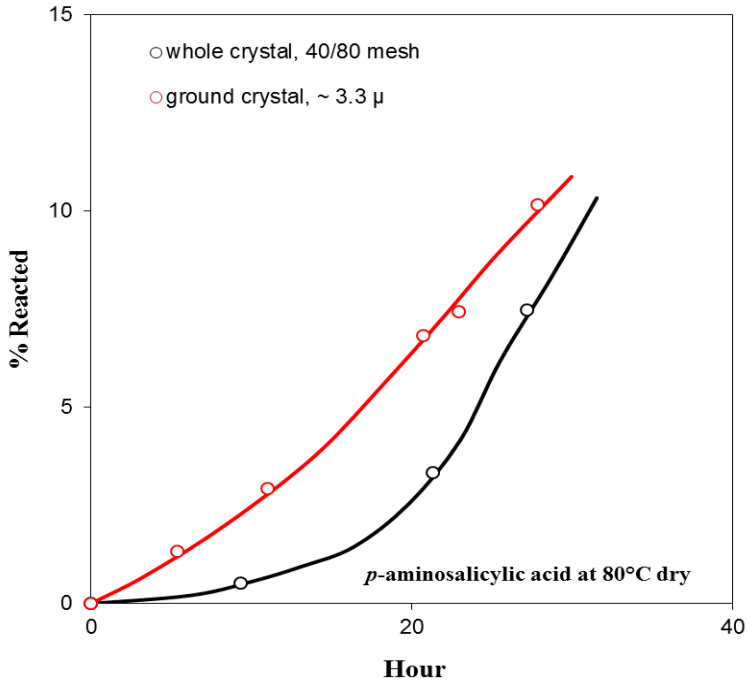
Compression and encapsulation

Coating (functional or non-functional)

# API Size Reduction

Often necessary first step

- Facilitates subsequent processing
- Enhances performance




Kornblum and Sciarrone (1964)

Mechanical and thermal stresses

- Shearing/cutting
- Compacting
- Impacting
- Attrition

- Dehydration
- Partial melting / crystallization
- Metastable phases
- Defect ,disorder, amorphous

# Wet Granulation and Drying

## Improves

- Densification  and flowability
- Cohesiveness
- Compressibility

## Solvent, thermal, mechanical stresses

- Dissolution/Crystallization
- Drying/crystallization/amorphization

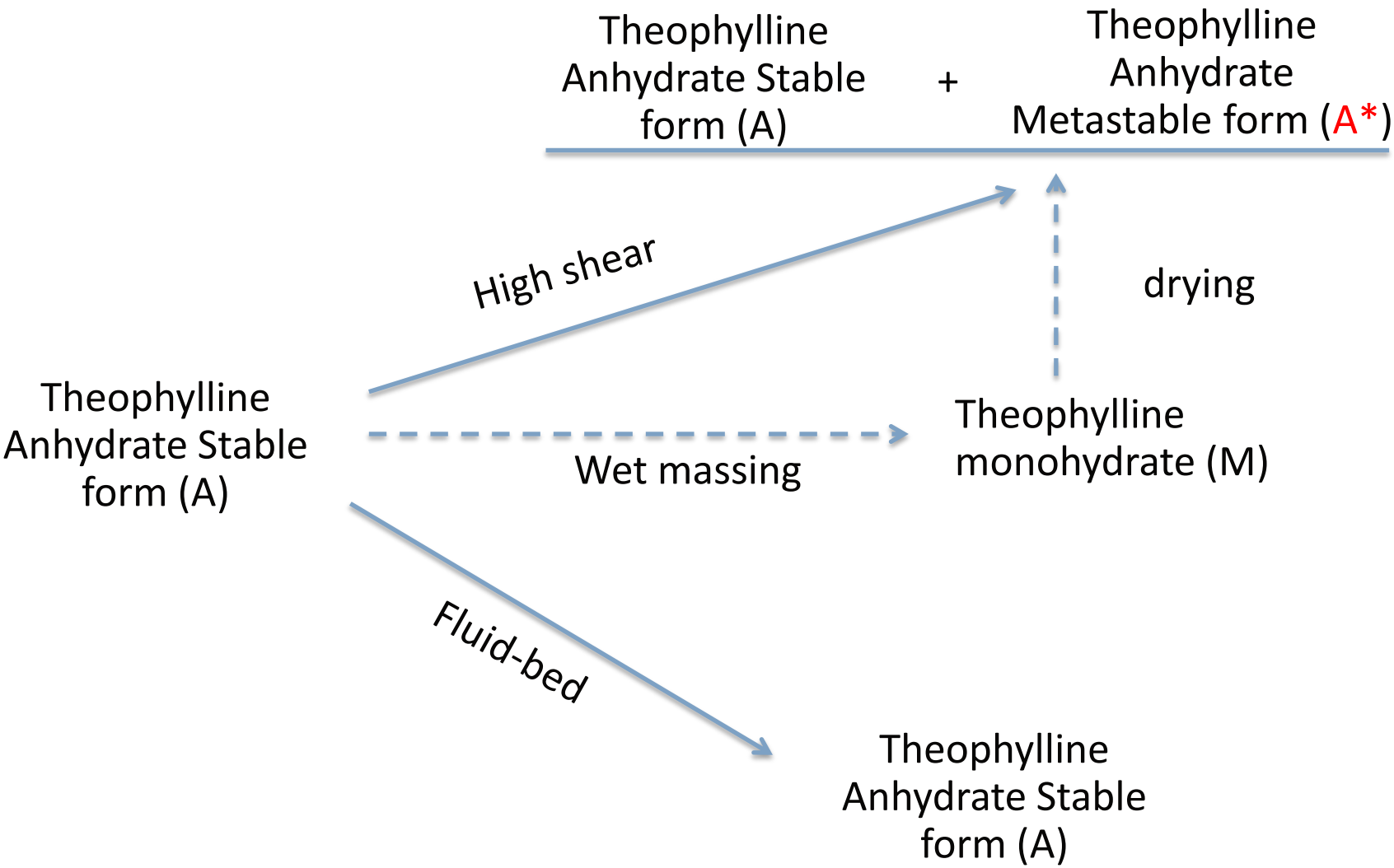
## Potential phase changes

- Conversion to stable phases
- Conversion to metastable phases
- Hydration/dehydration
- Defect/disorder /amorphous

**Function of**

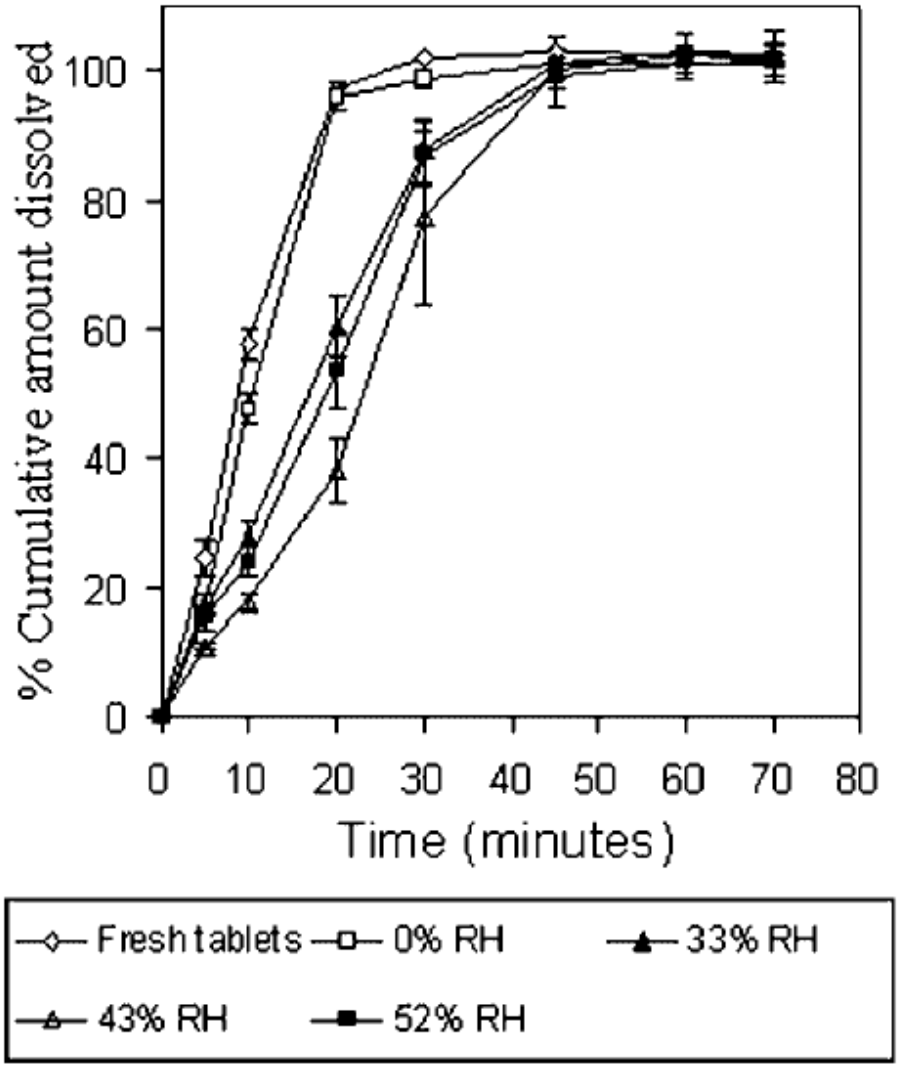
- Solubility of the drug
- Amount of liquid
- Granulation time
- Drying time / Rate

# Wet Granulation Example




Tantry, Tank, Suryanarayanan, J. Pharm. Sci. 96, 1434-1444 (2007)

# Theophylline Example (Cont)




Dissolution after 2 week storage

Tantry, Tank, Suryanarayanan, J. Pharm. Sci. 96, 1434-1444 (2007)

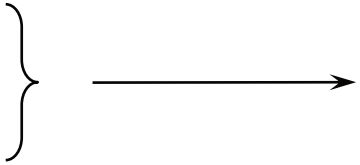
# Dry Granulation (Slugging & Roller Compaction)

Method of choice for granulation when

- Moisture sensitive API
- Continuous manufacturing

Mechanical stresses

- Compacting
- Shearing
- Attrition



- Polymorph conversion
- Defect/disorder /amorphous

Example: Drug S (25 µg)

- Wet Granulation: Chemical stability as primary challenge
- Roller Compaction: Even worse stability
  - Destruction of the crystalline API during RC

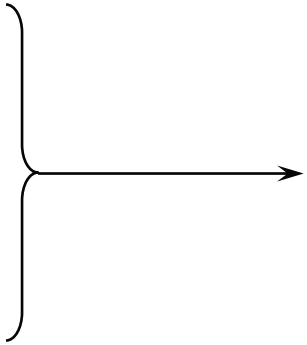
# Melt Granulation / Melt Extrusion

## Method of choice

- Solvent-free method particularly when dry granulation is not suitable
- Intentionally generate a metastable phase, e.g. amorphous

## Mechanical and thermal stresses

- Shearing
- Temperature
- Amount of granulating agent
- Granulation time
- Congealing time



- Solid state
- Melt
- Solution
- Solution-mediated

# Spray (Freeze-) Drying

## Useful

- Homogeneous
- Porous
- Uniform particles
- Produce metastable phase

## Solvent and thermal stresses

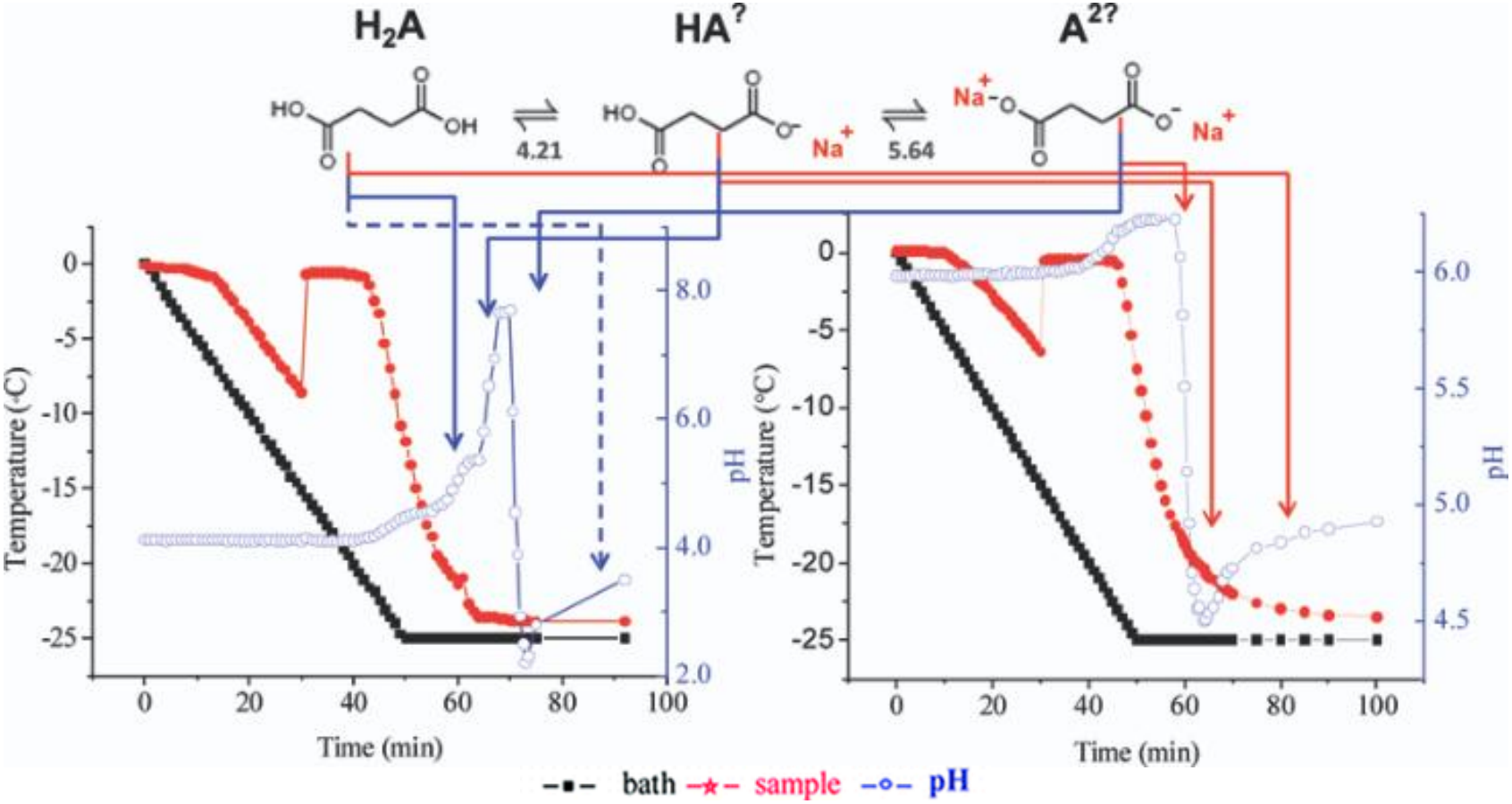
- Convert to stable phases
- Conversion to meta-stable phases
- Hydration/dehydration
- amorphization

**Function of**

- Solubility
- Amount of liquid
- Evaporation rate
- temperature

Be aware of phase transformation of excipient during freeze-drying

# Example: Excipient Crystallization during Freeze-Drying




Sundaramurthi, Shalaev, Suryanarayanan, J. Phys. Chem. B 114: 4915-4923 (2010)

# Compression/Encapsulation

## Compression

- Compression pressure
- May cause phase transformation
  - Caffeine
  - Sulfabenzamide
  - Maprotiline hydrochloride
- Creation of defect / disorder is common

## Encapsulation

- Low stress introduced
- Phase transformation seldom encountered

# Coating

Nonfunctional

- Aqueous or solvent based
- Minimal interaction between core and coating liquid
- Minimal risk of transformation

Active coating

- Solution or suspension of the drug may be used
- Solution or solution-mediated transformation possible
- Pay attention to amorphous content created

The defect / disorder / amorphous contents created is a common theme and cause to drug product performance issues

# Analytical Tools and Challenges

Powder X-ray Diffraction (PXRD)

- Gold standard

Microscope

- Optical, electronic, atomic force

Thermal Analysis

- DSC, TGA

Spectroscopy:

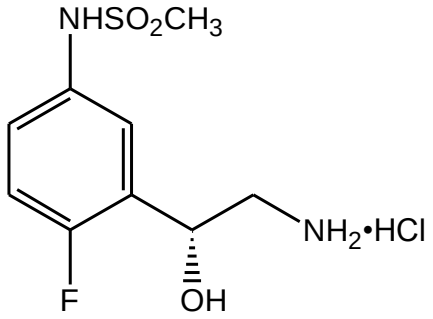
- IR, Raman, NMR

Challenges:

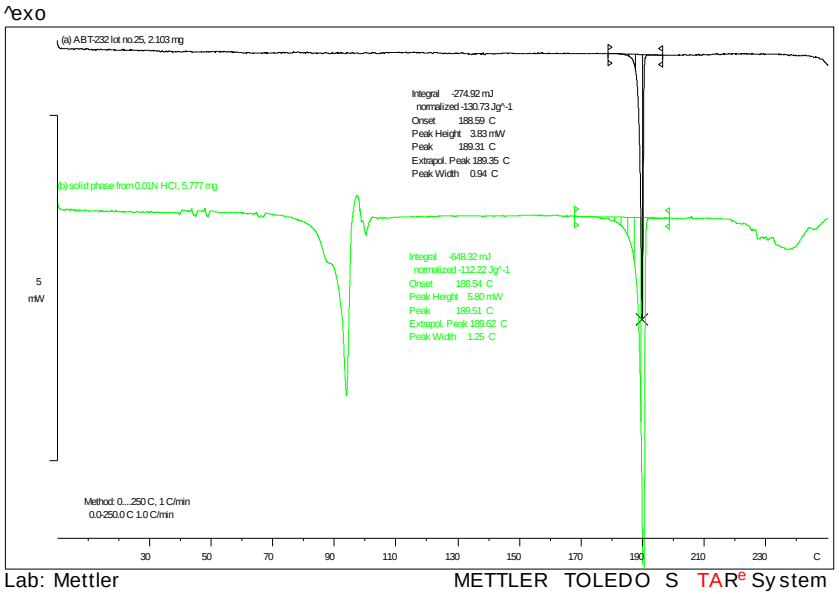
Low level of phase transformation is very difficult to be detected and/or quantified in real formulations

# Case Study: ABT-232

- Highly water soluble HCl salt
- Solid forms
  - Anhydrate
    - Tm: ~ 189 °C
    - Non-hygroscopic
    - Chemically stable (solution)
    - Solid-state stable 40°C/75%
    - Compatible with excipients
    - Selected for development
  - Monohydrate
    - Crystallized from aqueous solutions
    - Dehydrates @ 80 – 90 °C, and converts to anhydrate




$C_9H_{14}ClFN_2O_3S$
MW = 284.7

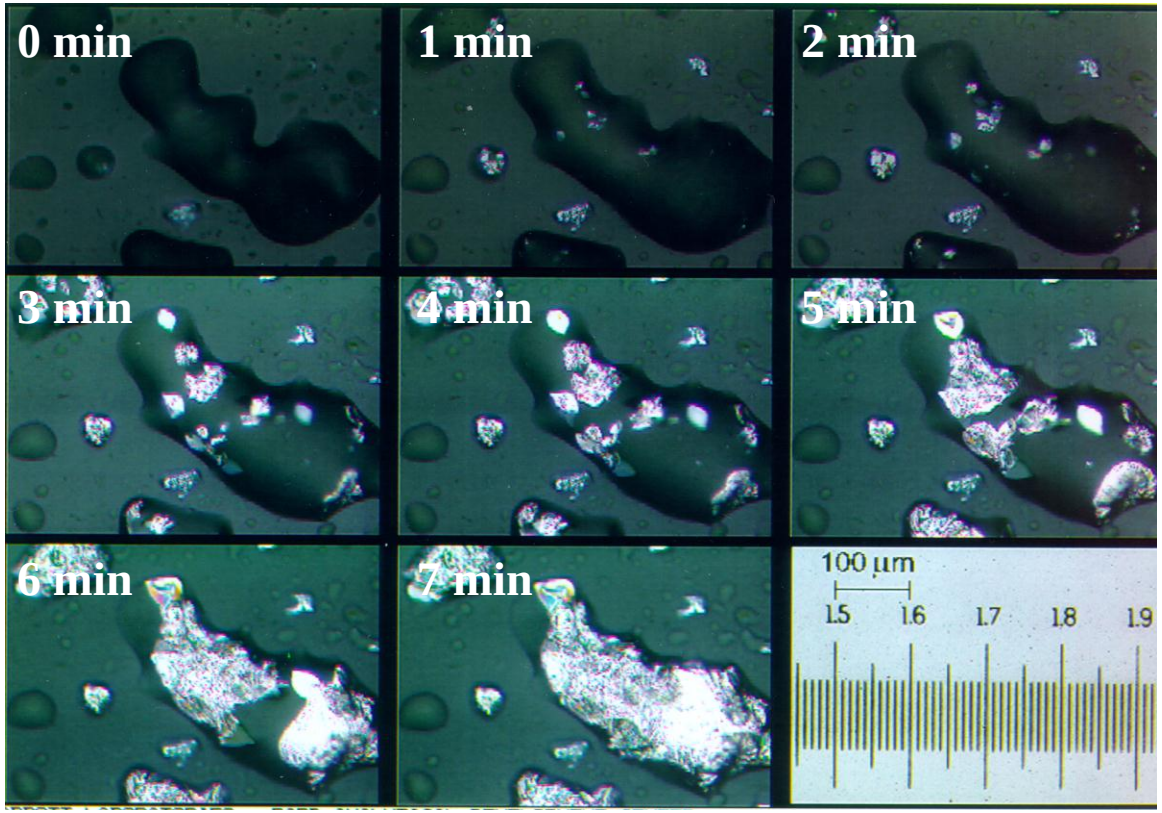



Wardrop J et al, J. Pharm. Sci. 95, 2380–2392 (2006)

# ABT-232: Physicochemical Properties of Amorphous Form

## Amorphous

- Tg: 62 °C
- Very hygroscopic
- Crystallizes readily




Wardrop J et al, J. Pharm. Sci. 95, 2380–2392 (2006)

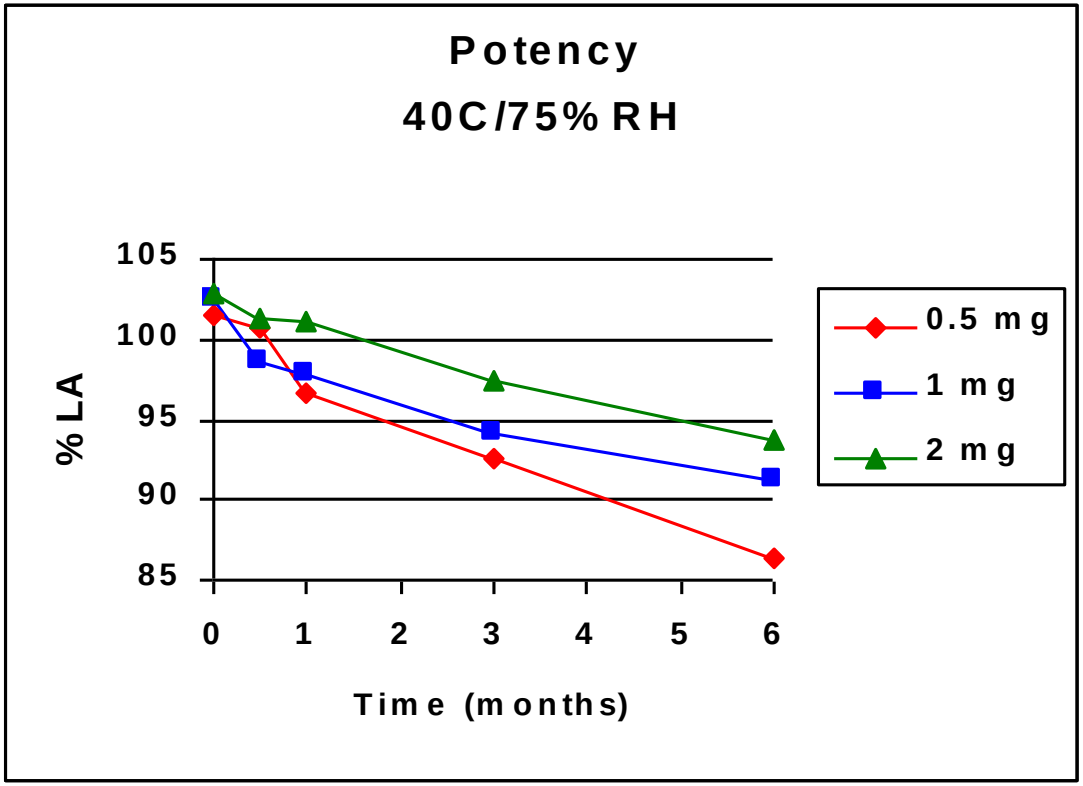
# ABT-232: Formulation

- Immediate release tablet formulation
- low drug loading
  - Low dose: 0.5, 1, 2 mg
  - 0.25 to 1% (w/w) drug loading
  - Challenge: content uniformity
- Formulation excipients
  - Pre-gelatinized starch, mannitol, Avicel 101, sodium starch glycolate, magnesium stearate
- Wet granulation process
  - Excellent content uniformity achieved
  - Hydrate expected to crystallize and dehydrate to the anhydrate
  - Amorphous phase expected to crystallize to anhydrate (if formed)

# ABT-232 : Formulation Stability @ 40 °C / 75% RH

Issue

- Unacceptable chemical stability
- Although API is chemically stable and is compatible with the selected excipients




Wardrop J et al, J. Pharm. Sci. 95, 2380–2392 (2006)

# ABT-232 : Stability Investigation

Hypotheses:

Wet granulation /drying unintentionally generated amorphous phase

- Anhydrate → dissolution → amorphous (drying)
  - Excipients inhibited the crystallization from amorphous phase
- Anhydrate → dissolution → monohydrate → amorphous (drying)

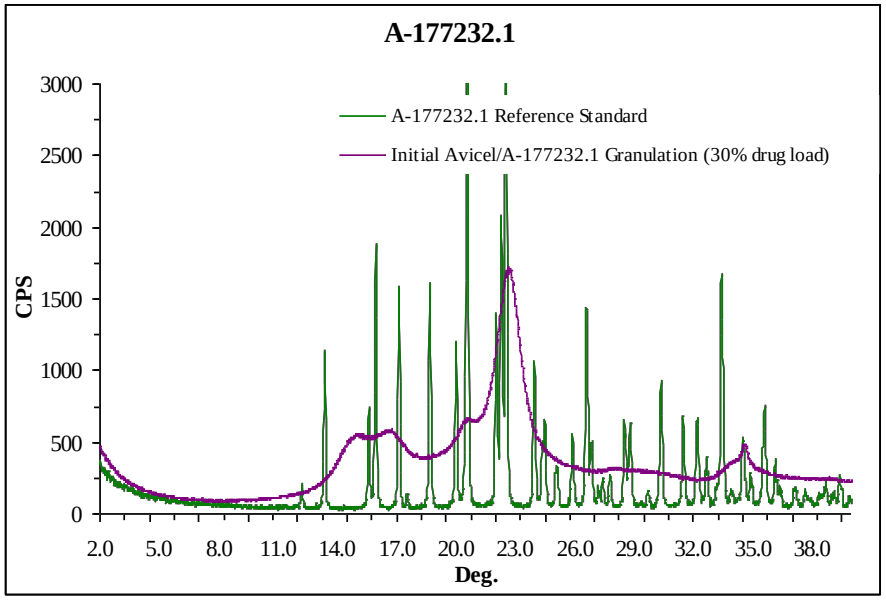
Amorphous content led to accelerated degradation

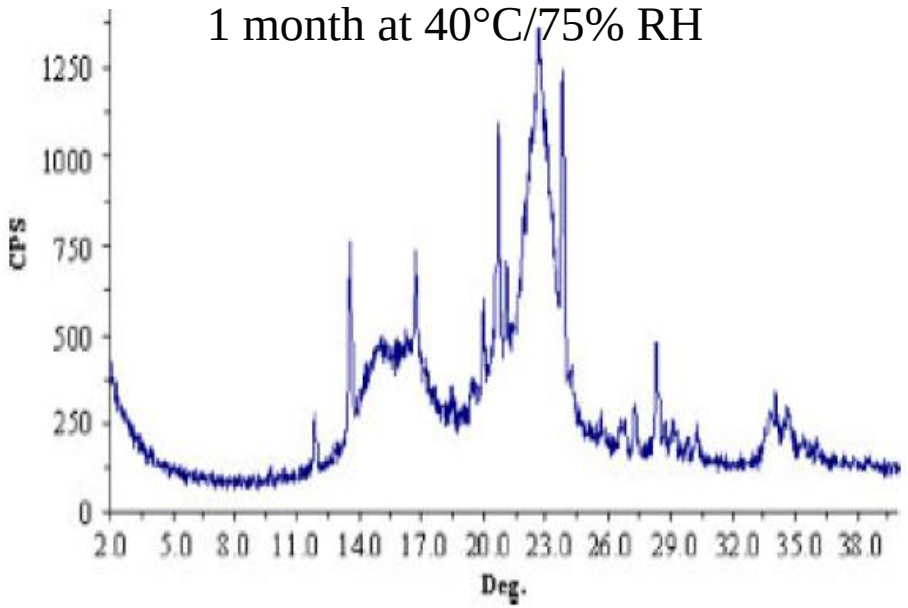
- Chemical stability not demonstrated for amorphous phase during physicochemical characterization
- Difficulty in performing solid state stability experiments for pure amorphous API due to rapid crystallization

# ABT-232: Investigation

Demonstrate the formation of amorphous phase

- Extremely low drug loading: 0.25 – 1%
- Use model formulation with increased drug loading of 30%




- Amorphous phase generated at 30% loading → more likely at lower loading
- Crystallization from amorphous phase in formulation is sluggish
  - No crystallinity seen after 5 months in a capped bottle (RT)

# ABT-232: Mitigation

Avoid the formation of amorphous will improve chemical stability

- Use processes that eliminate the use of water
- Direct compression
  - Crystallinity demonstrated by PLM and Raman
- Accelerated stability testing: 1 mg strength

| 40 °C / 75% RH | Wet Granulation | | Direct Compression | |
|---|---|---|---|---|
| Time (Weeks) | Potency (%) | Related substances (% w/w) | Potency (%) | Related substances (% w/w) |
| 0 | 102.4 | 0.3 | 100.5 | 0.3 |
| 4 | 97.4 | 1.02 | 100.2 | 0.4 |

Much improved chemical stability

# ABT-232 : Summary

Phase transition occurred during wet granulation and drying

- Amorphous phase was unintentionally generated, and was sustained in the product on stability testing
- Instability originates from the amorphous phase

Formulation excipients altered the course of phase transitions

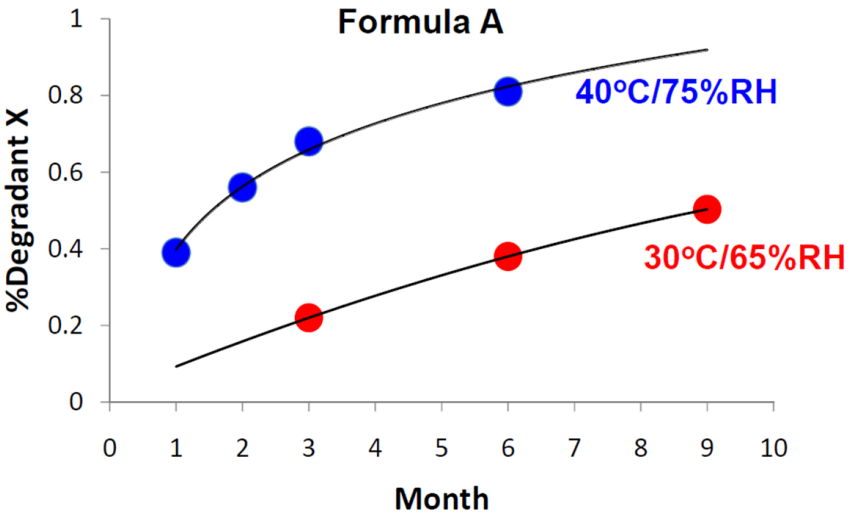
- Inhibited nucleation

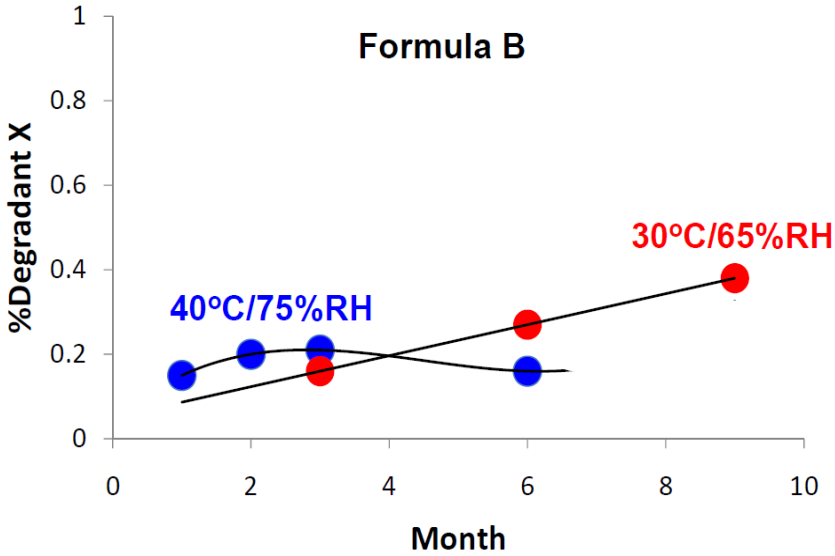
Direct compression produced stable product

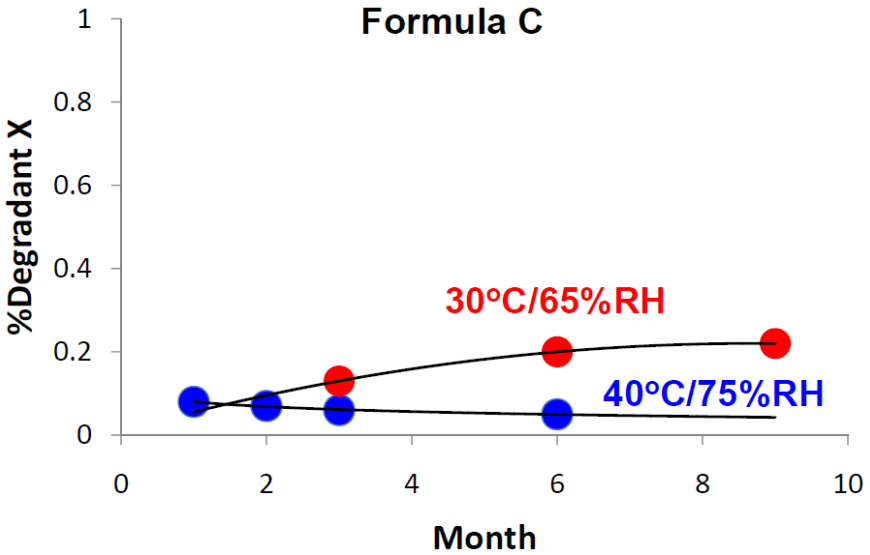
- Avoid wet granulation due to high solubility of API
- Eliminated the formation of amorphous phase

**What if amorphous phase is not very physically stable in formulation?**

# Drug X – A Conference Example




Xiao KP et al. AAPS Workshop on Current Trends in Stability-2009

# Annealing: Improving Physical / Chemical Stability

What is annealing ?

- Holding of drug product intermediate for certain duration under appropriate conditions (e.g. temperature, humidity) prior to further processing

Why annealing?

- Promote phase transformations
- Mitigate risks associated with incomplete phase transformation during processing and phase transformations during subsequent storage.

Where it is usually done?

- Conditioning for dry powder inhalation (DPI) product
- Elsewhere when appropriate

# Annealing Example: Gabenpentin


gabapentin gaba-L

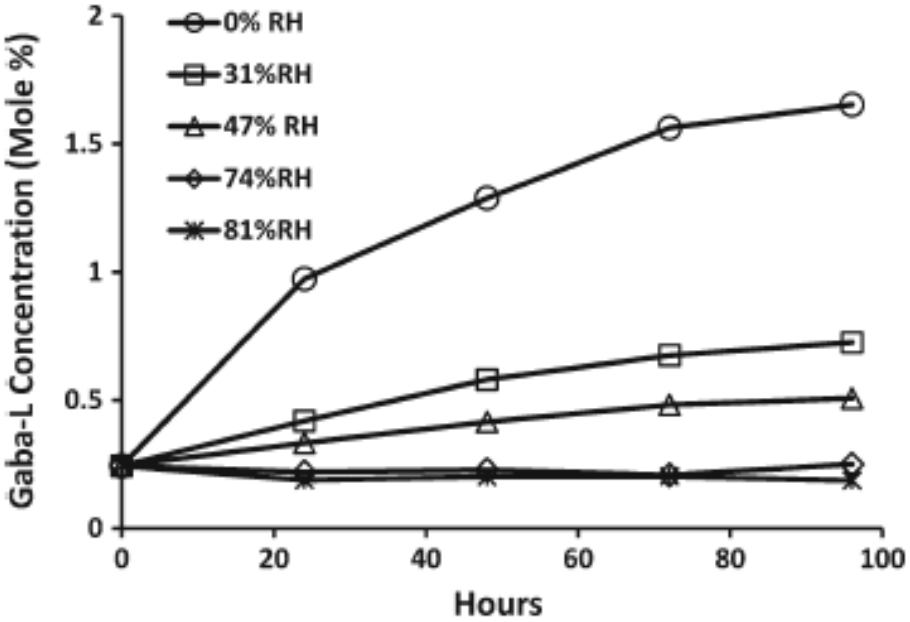



**Fig. 4.** Gaba-L formation from 60 min milled gabapentin sample at 50°C and different relative humidity

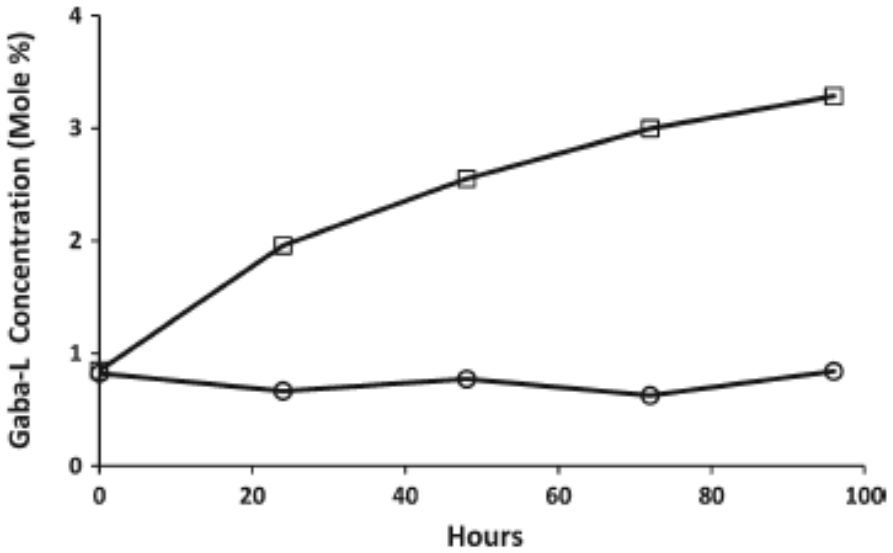



**Fig. 7.** Gaba-L formation from moisture pretreated gabapentin sample. *Empty square* sample was stored at 25°C 0% RH for 24 h before thermal stress, *empty circle* sample was stored at 25°C 81% RH for 24 h before thermal stress

Zong et al, AAPS PharmSciTech 12, 924–931 (2011)

# Drug Y: Impacts on Dissolution

Small molecule

moderate water solubility

- ~18 mg/mL

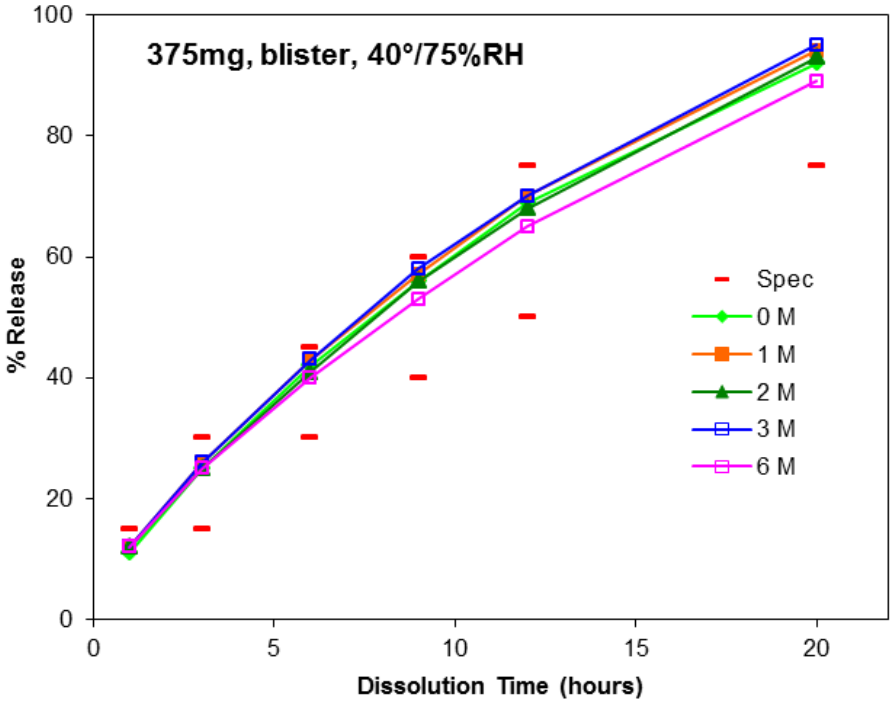
Extended release tablet

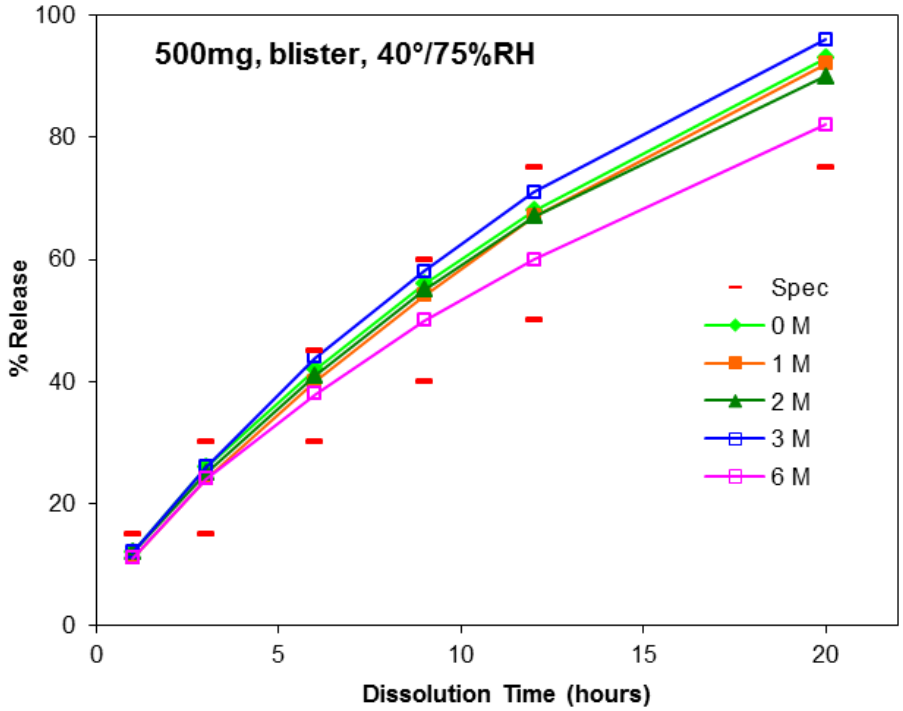
- Hydrophilic matrix (HPMC)
- Strengths: 375, 500, 750, 1000 mg

Manufactured by wet granulation

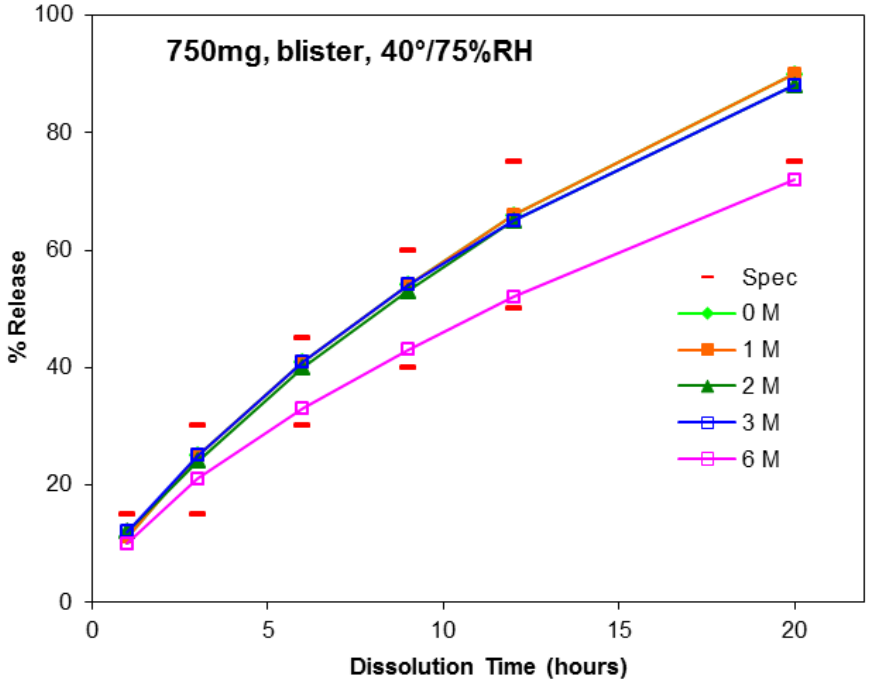
- Common granules
- Differ in amount of extra-granular HPMC to achieve release objectives

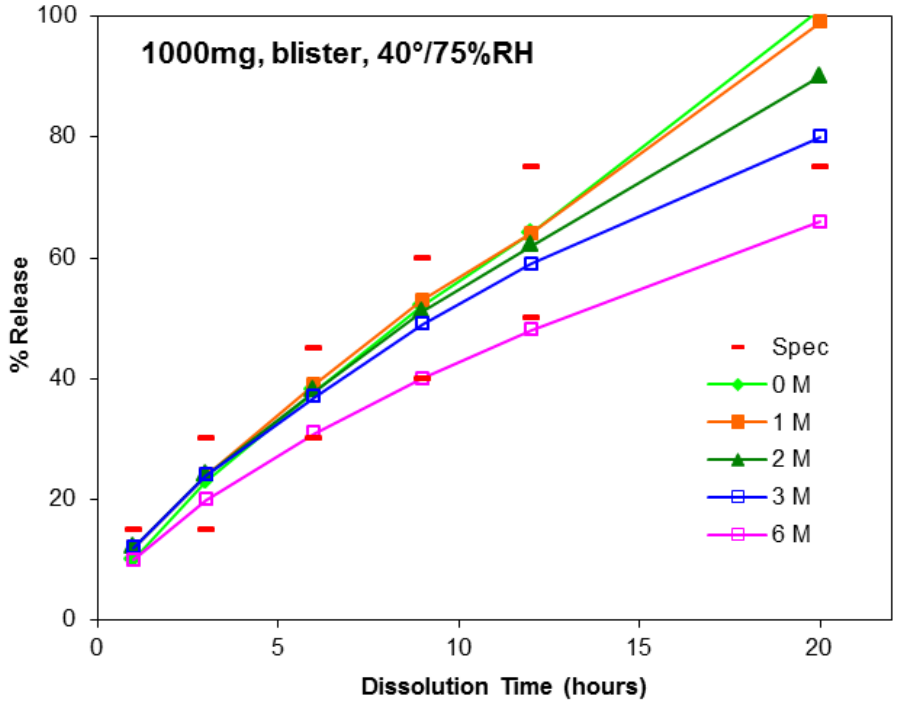
# Drug Y: Release during Stability



# Drug Y: Release during Stability (Cont)



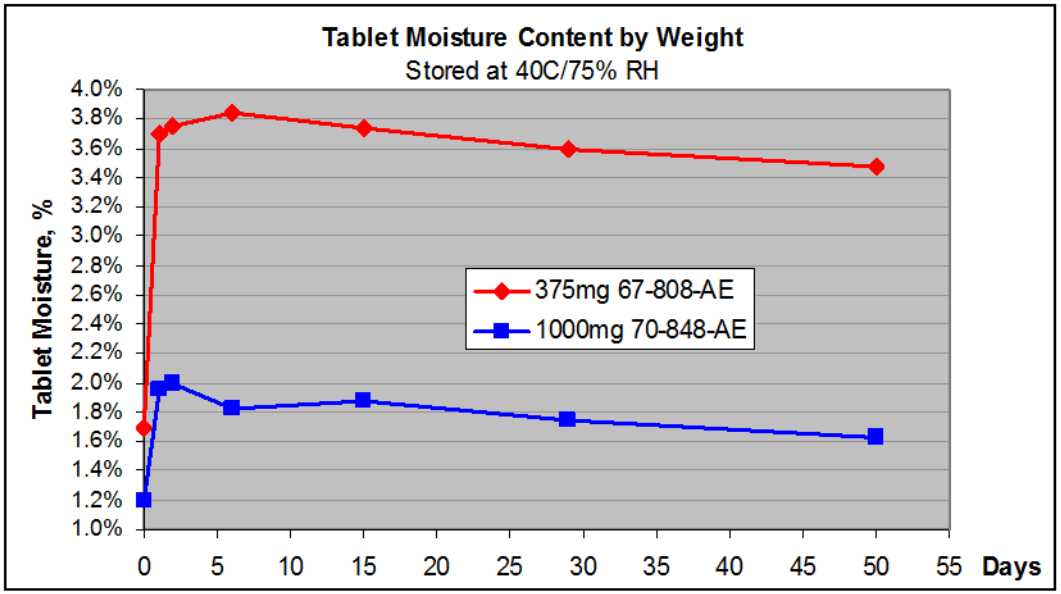
# Drug Y: Release during Stability (Cont)

Possible causes

- Crystal form: polymorph/hydrate not reported before
- Partial amorphous API during WG
- Interactions between API and HPMC/PVP during WG/storage

No clear cause identified

- PXRD
- Raman
- NIR
- Moisture sorption



# Anticipating and Mitigating Phase Transformation: — API Selection

- Understand design objectives
  - Target product profile
- Understand drug molecule
  - Intrinsic physicochemical properties: solubility, stability
- Understand solid-state properties of the API
  - Polymorph, salt, hydrate, amorphous etc
  - Solid-state properties including reactivity
  - Interrelationship of conversion
- Select appropriate form to accomplish TPP
  - Identify challenges: bioavailability, stability, manufacturability
  - Address challenges with appropriate solid form selection
  - Understand potential impact to design objectives if there is a solid-form change

# Anticipating and Mitigating Phase Transformation: — Process, Formulation, Packaging

Understand what may happen during various processes

- General process understanding
- Considerations for specific drug molecule
- Anticipate what may be the consequences

Select a process that can achieve the design objective while

- Minimize unwanted phase transformation
- Minimize impacts on product performance
  - Facilitate transformation if needed

Always stay vigilant about the potential of phase changes

Formulation manipulation

Packaging

# Acknowledgement

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