Stress Testing to Assess Stability Differences among the Physical Forms of an Active Substance.

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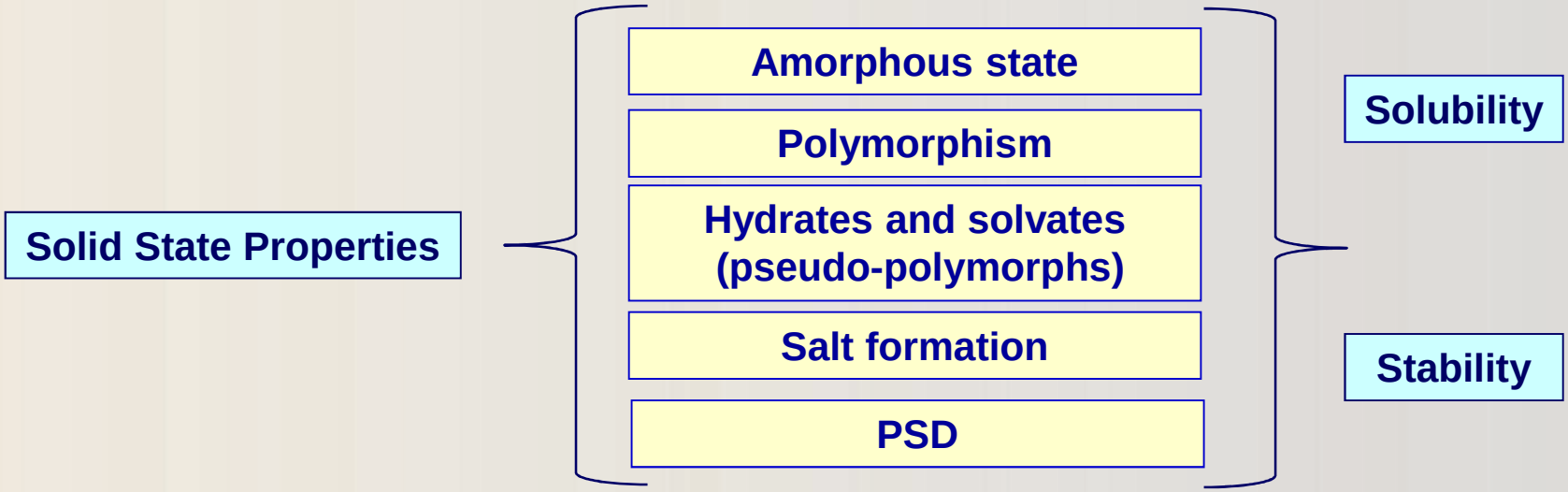
La caratterizzazione dello stato solido degli API, Milan 2013

Outline

- **Differences in stability among drug substance physical forms and corresponding impact on Drug Development.**
- **Design of the stress conditions for a comparative stability study.**
- **Considering the main pros and cons for different stress testing conditions.**
- **Impact of the study time length, practical and regulatory constraints.**
- **Overcoming the key challenges experienced when defining and designing stress conditions and limits.**
- **Impact of the excipients and formulation on stability: how stress conditions can be of help in the assessment**

Solid State Properties & Development

Drug Substance Solid State Properties: a Critical Issue during Development



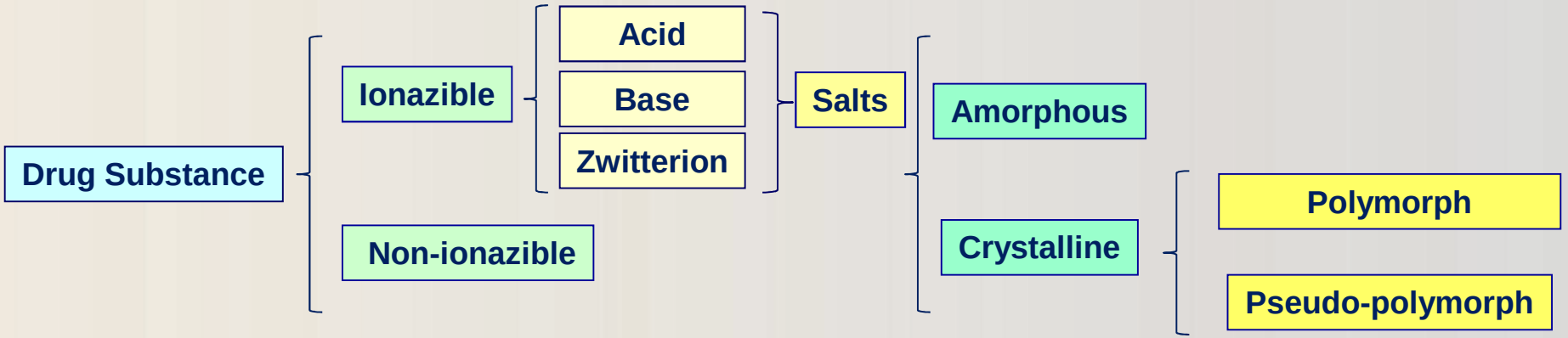
ICH Q6 A; Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, May 2000; paragraph 3.3.1, decision trees (3) and (4, 1-3).

S. Byrn et al., Pharmaceutical Solids a Strategical Approach to Regulatory Considerations, Pharmaceutical Research, 1995, 945-954.

D. Lettani, T.J. DiFeo, The European Clinical Trials Directive – A Regulatory Approach for filing Drug Substance Information, Development and Industrial Pharmacy, 31: 709-718, 2005.

The Drug Physical Form

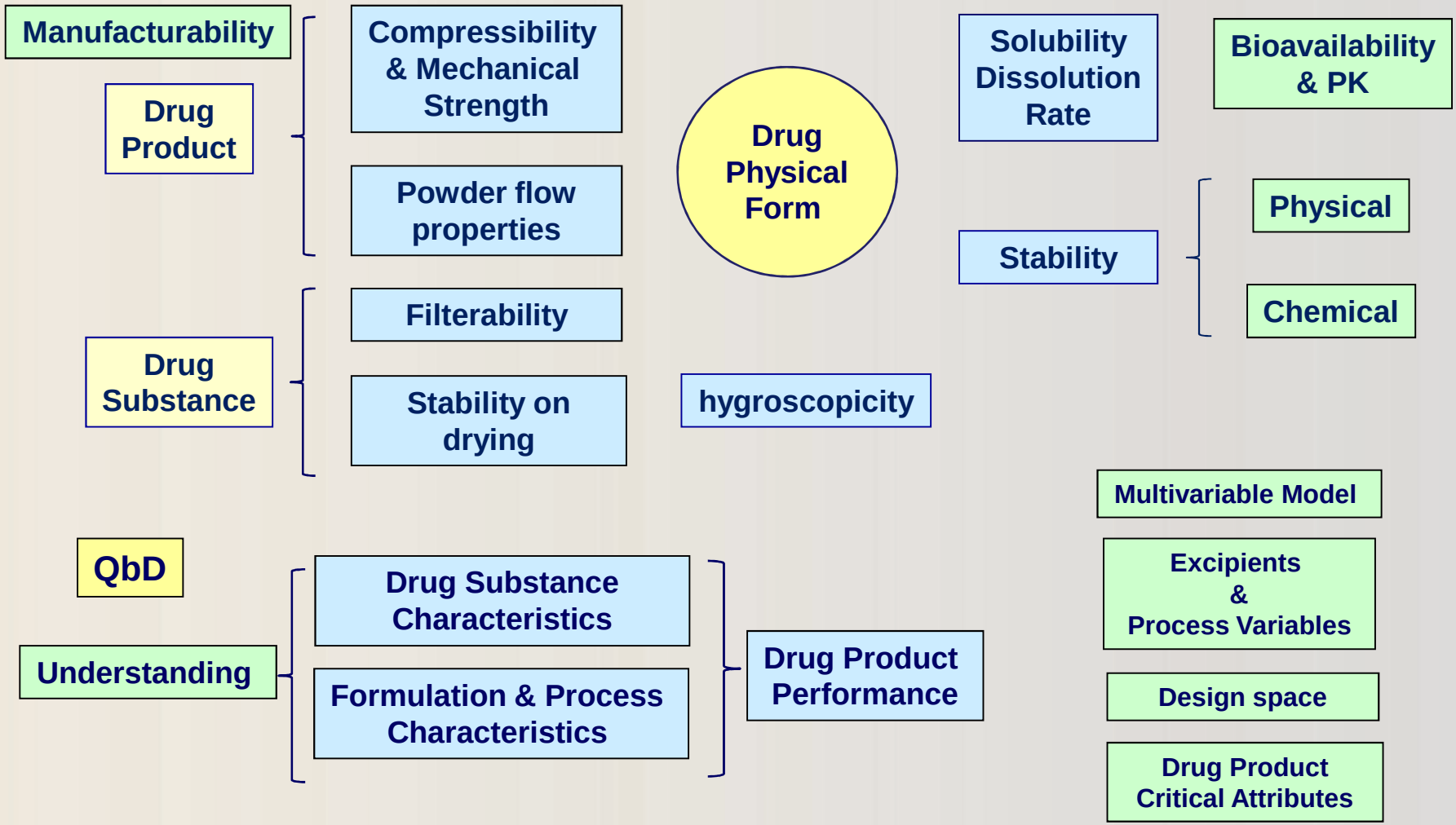
A critical element of Drug Development is the selection of the appropriate Drug Form



L.F. Huang, T. Tong, Impact of solid state properties on developability assessment of Drug Candidates, Adv. Drug Del. Rev., 2004, 65, 321.

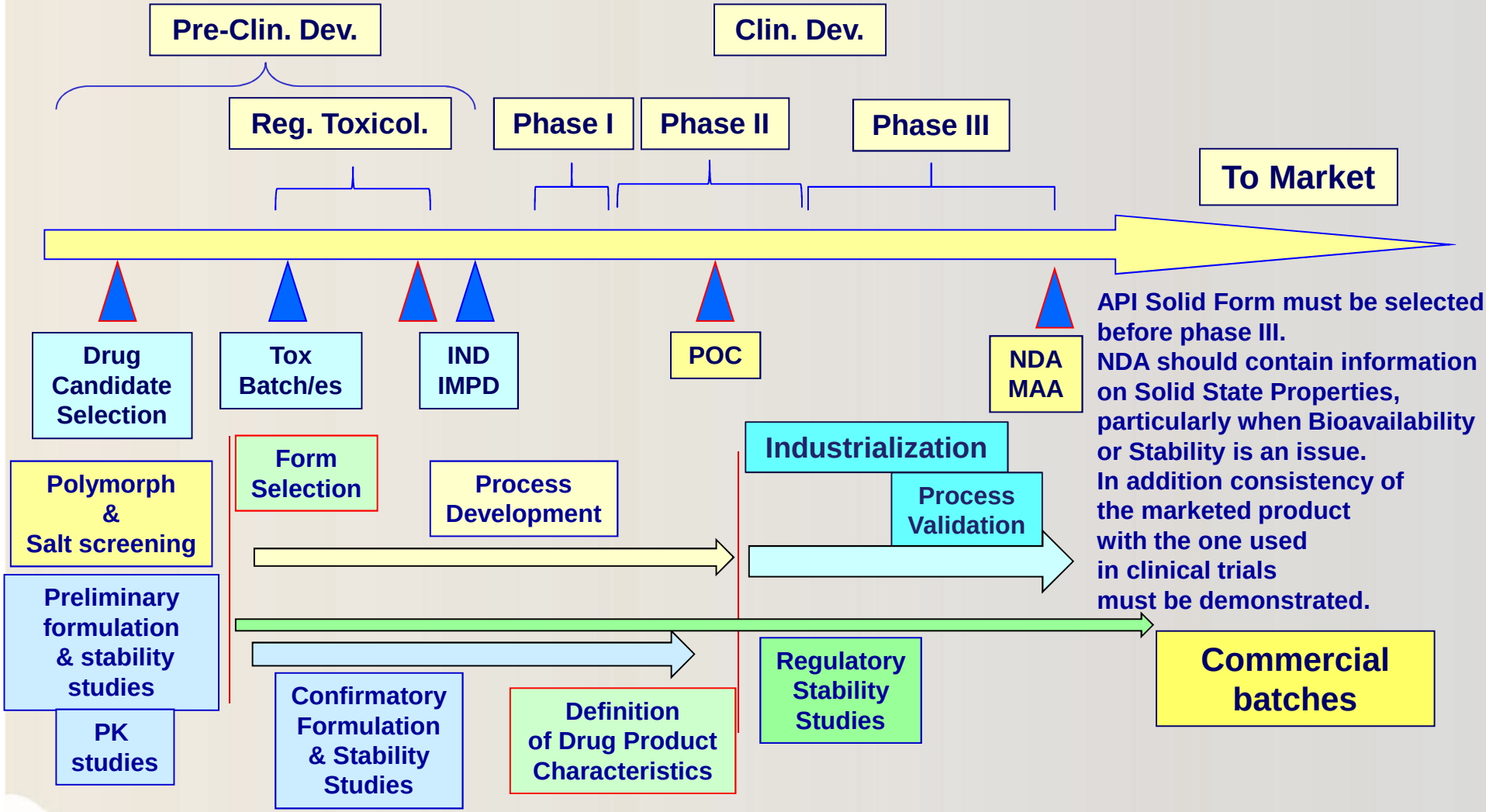
D. Singhal, W. Curatolo, Drug Polymorphism and Dosage Form Design: a practical perspective, Adv. Drug Del. Rev., 2004, 335-347.

Drug Substance Physical Form & Drug Product



S. L. Lee et al., Significance of Drug Substance Physicochemical Properties in Regulatory Quality by Design, Drug Pharmaceutical Science, 2008, 178, 571-586.

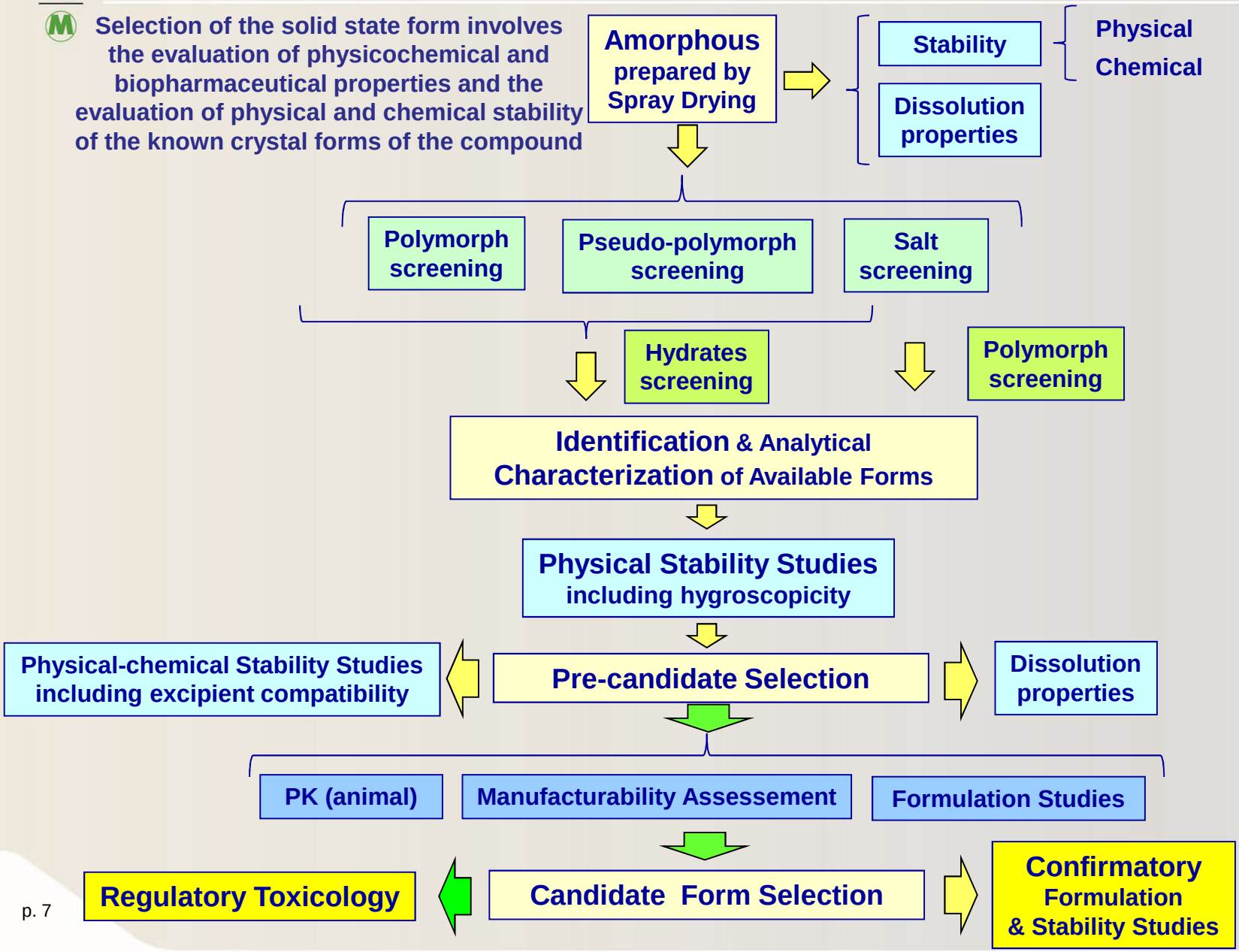
When the Form Selection should be Addressed ?



M. Paluki et al., Strategies at the Interface of Drug Discovery and Development: Early Optimization of the Solid State Phase and Preclinical Formulations for Potential Drug Candidates, J. Med. Chem. , 2010, 5897-5905.

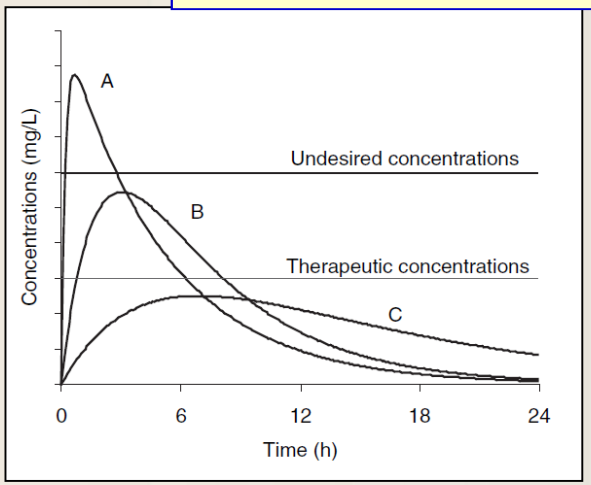
Identification of the Solid State Form: the Tier Approach

Selection of the solid state form involves the evaluation of physicochemical and biopharmaceutical properties and the evaluation of physical and chemical stability of the known crystal forms of the compound

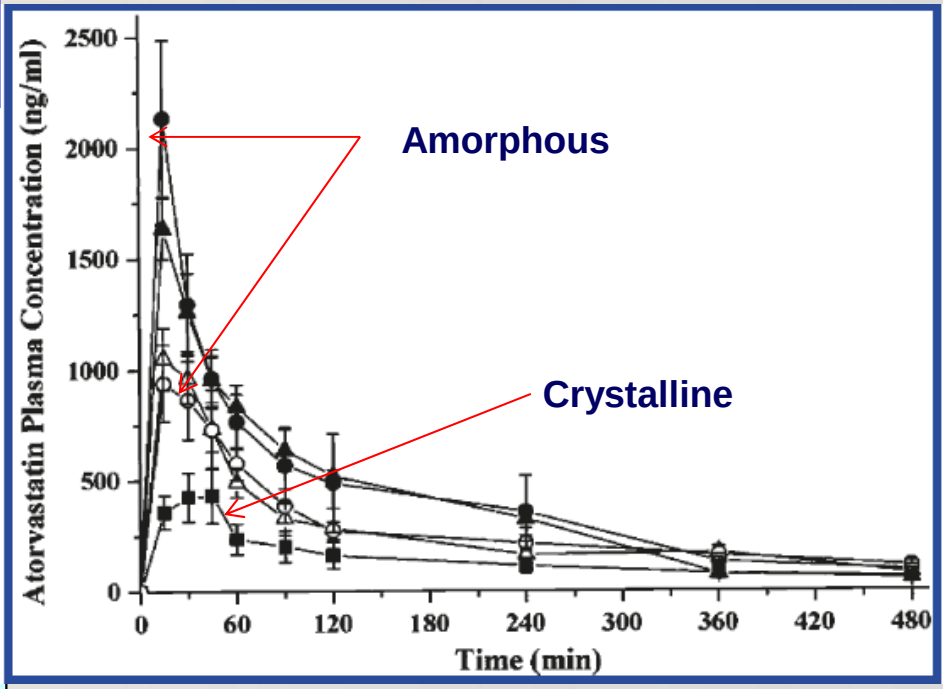


Physicochemical Properties & Bioavailability

The intrinsic solubility of a substance depends on its solid phase.

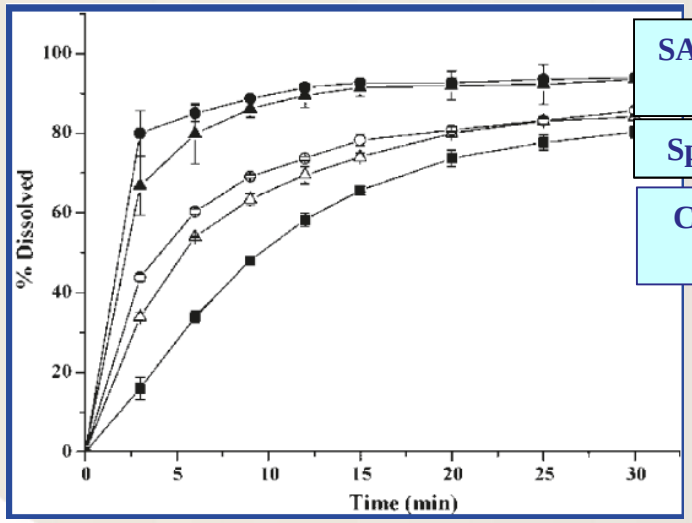


P.L. Toutain et al., Bioavailability and its assessment, J. Pharmacol. Ther., 2004,455-466.



Plasma concentrations after amorphous and crystalline Atrovastatin calcium administration

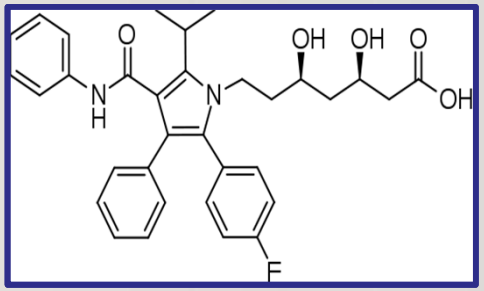
Dissolution profiles of crystalline and amorphous Atrovastatin calcium



SAS precipitated amorphous

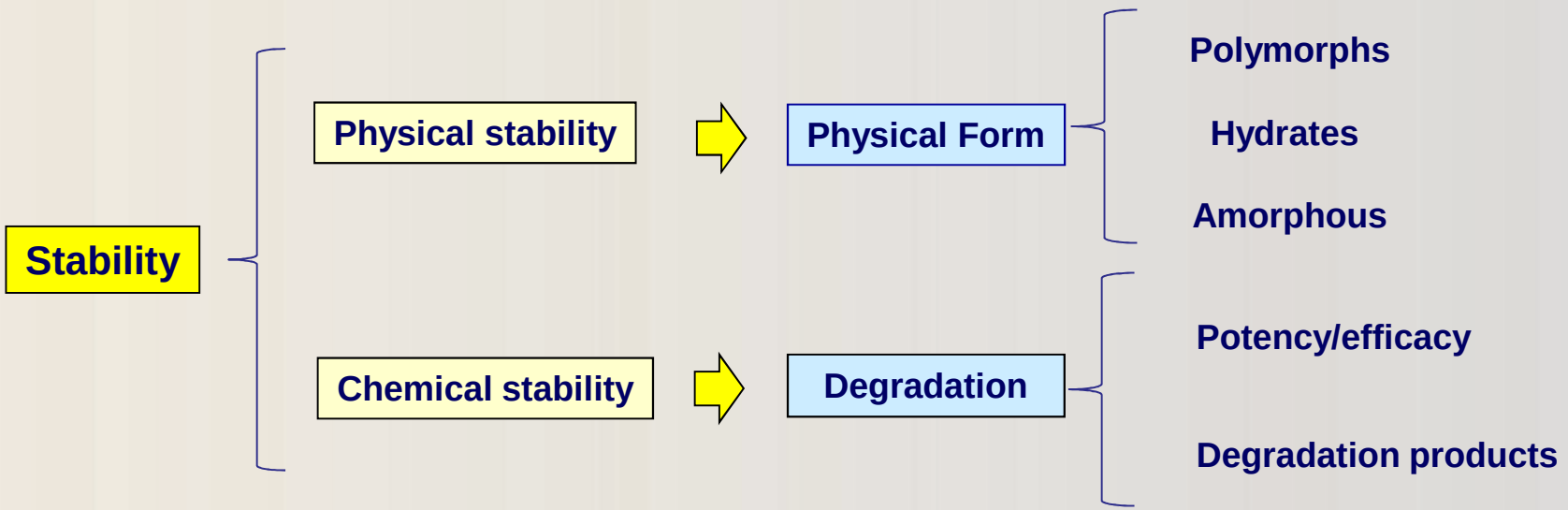
Spray dried amorphous

Cystalline Atrovastatin Calcium



J.S. Kim et al.. Physicochemical properties and oral bioavailability of amorphous atrovastatin calcium using spraying drying and SAS processes. Int. J. Pharm., 2008, 211-219.

Physicochemical Properties & Stability



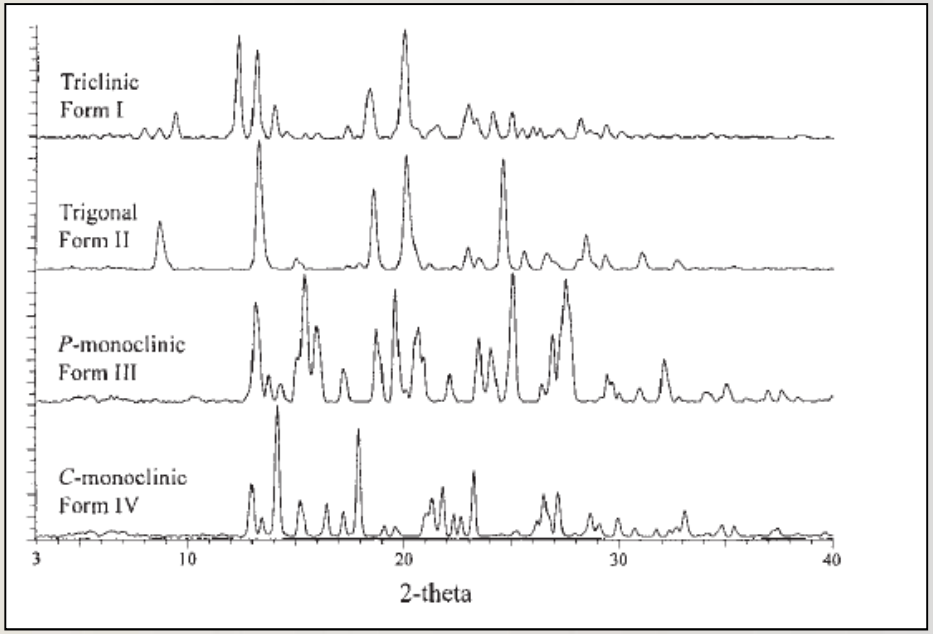
Often chemical stability is function of the physical form, thus the two items cannot be considered independently

Solid State and Stability: Carbamazepine

Polymorphs and pseudo-polymorphs of several drugs are characterized by a different chemical stability, this is due to differences in crystal packing which give rise to different density, molecular mobility and different exposure of reactive groups.

Carbamazepine

- Form I (Triclinic)
- Form II (Trigonal)
- Form III (P-monoclinic)
- Form IV (C-monoclinic)



XRPD patterns of four CBZ polymorphs

Form II { About 15% degradation 90 days, 40° C, 75% RH

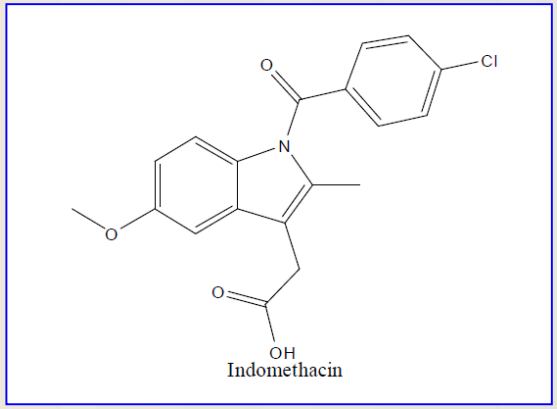
Form III { Stable

Photostability of form I is higher than that of form II and III

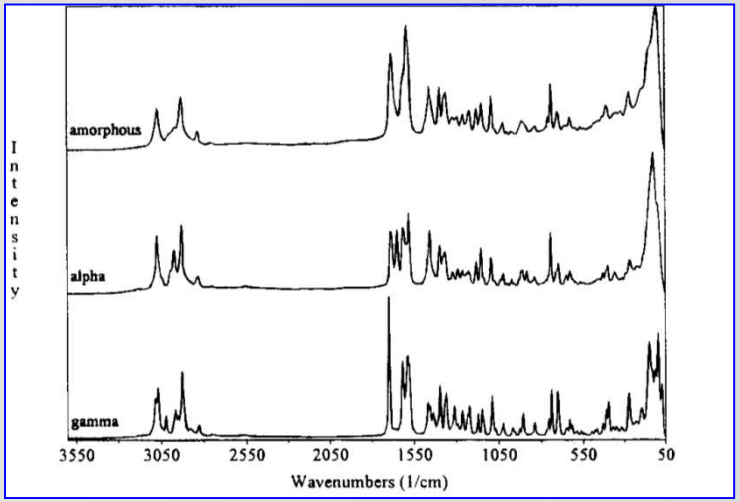
R Teraoka et al., Int. J. Pharmaceutics , 2004, 286, 1-8

A. L. Grzesiak et al., J. Pharm Sci, 2003, 92, 2260-2271

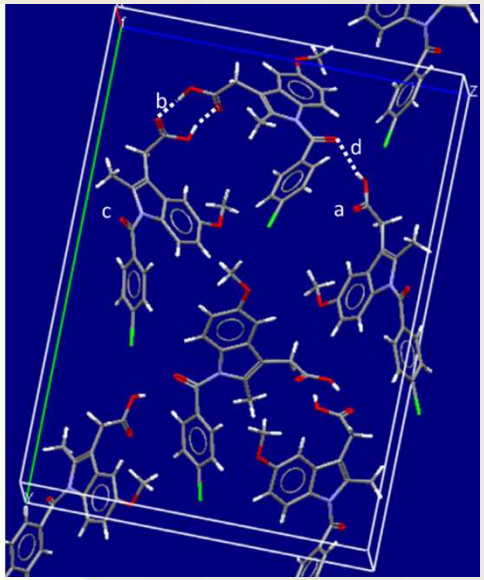
Indomethacin Solid State Forms & Reactivity



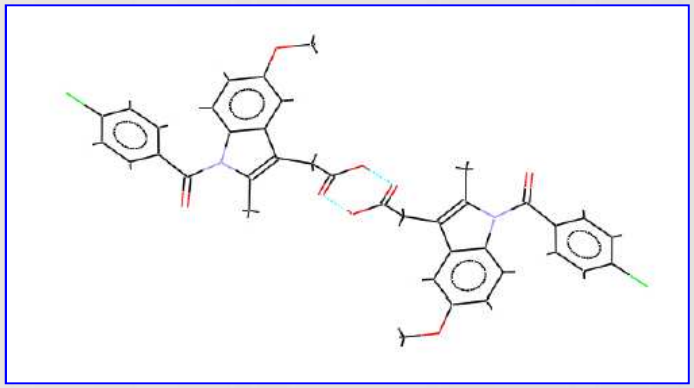
Raman of Indomethacin Forms



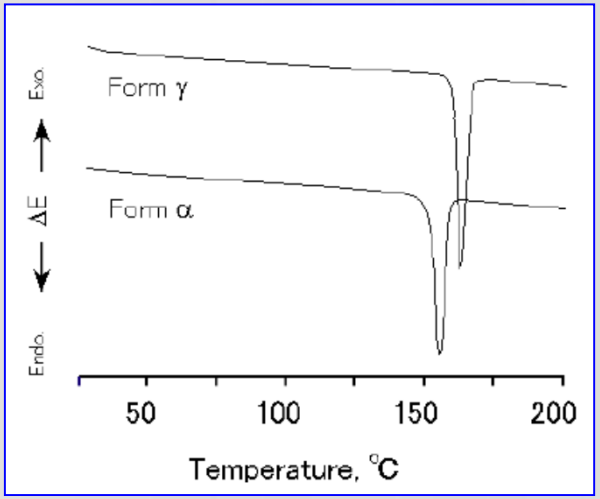
α-Form: H-Bonding and packing



γ- Form: H-Bonding



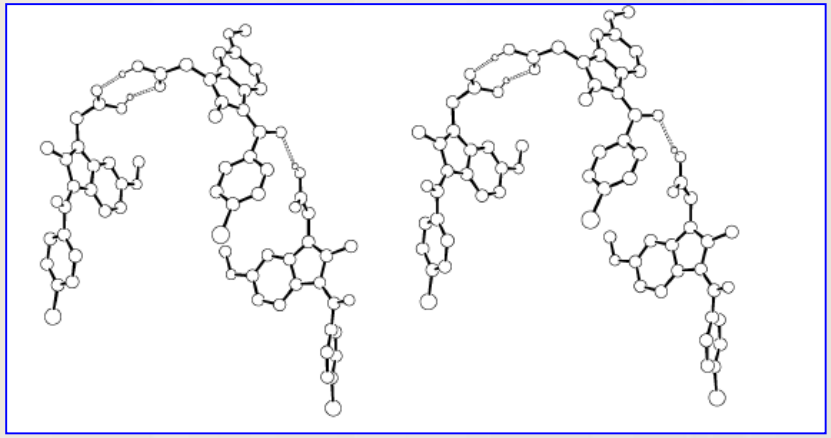
Indomethacin Crystal Forms DSC



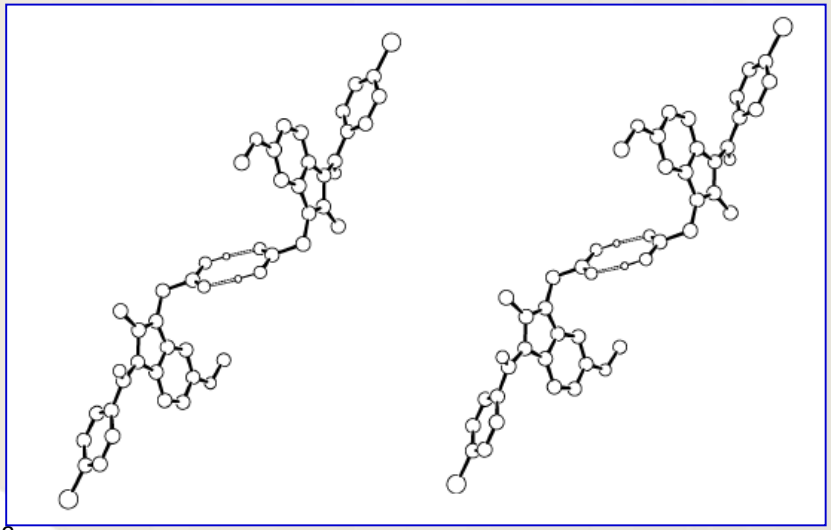
B. Van Eedenburgh, L.S. Taylor. J. Pharmaceutics, 2011, 3-16.

Indomethacin Solid State Forms & Reactivity

Indomethacin, form α,
stereoview of hydrogen-bonding trimers

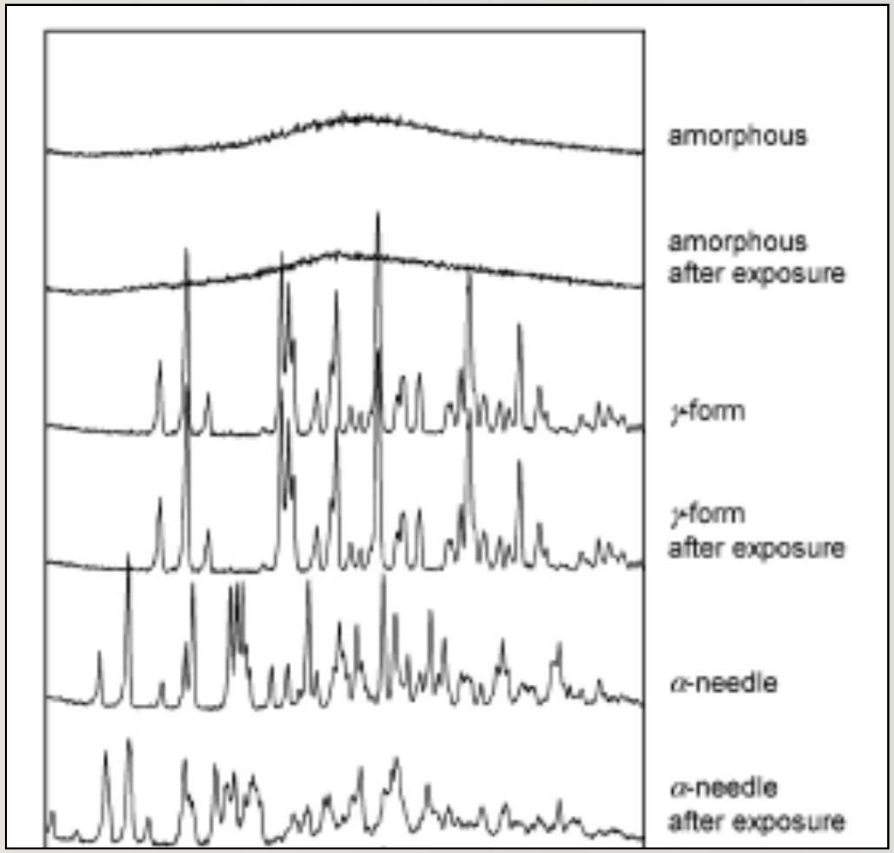


Indomethacin, form γ,
stereoview of hydrogen-bonding dimers



Indomethacin:
differences in crystal structure,
differences in reactivity

While the γ- form doesn't react with ammonia gas
the α-form quickly gives rise to the ammonium salt

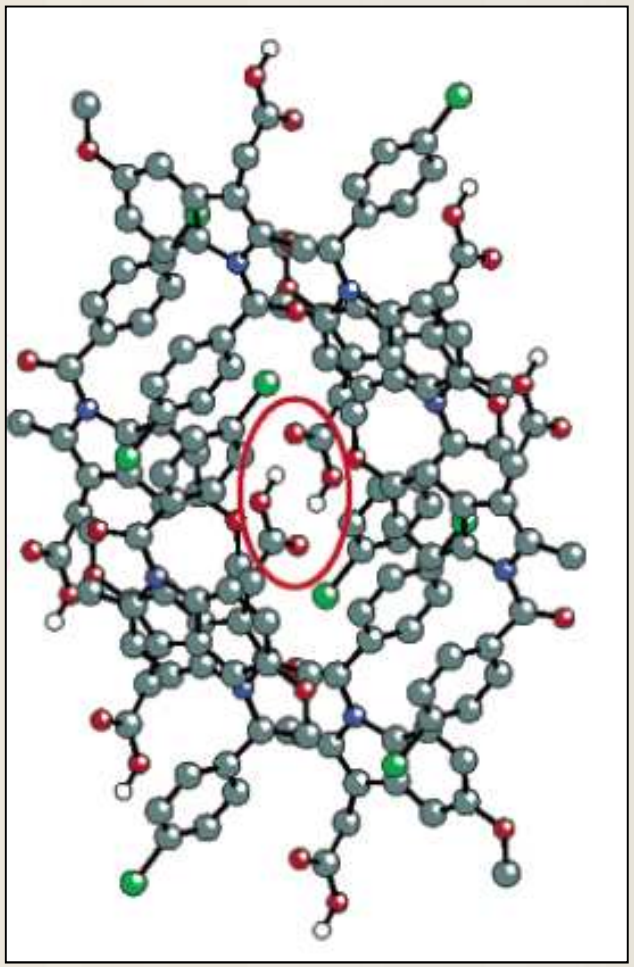


Chen et al., Reactivity Differences of Indomethacin solid forms with Ammonia Gas, J.Am.Chem.Soc., 2002, 124, 15012-19

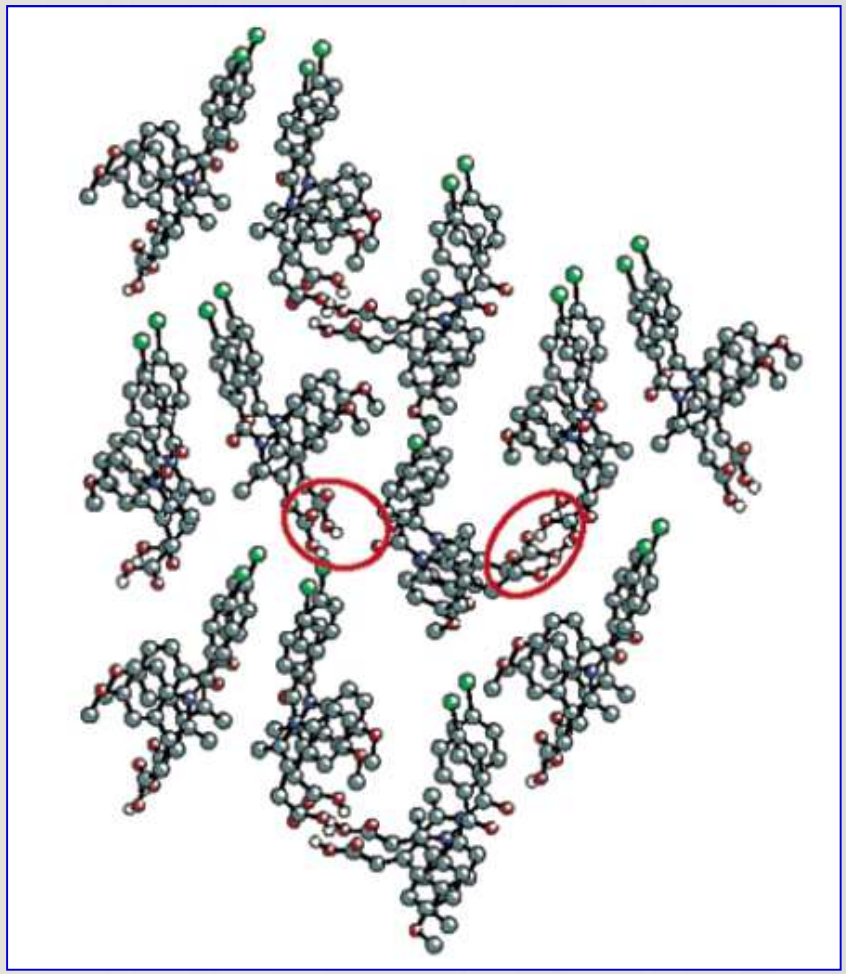
Indomethacin Solid State Forms & Reactivity

Changes in crystal packing can produce a large change in reactivity at the solid state

Stereoview of γ-indomethacin crystal packing



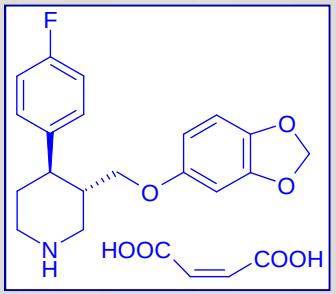
Stereoview of α-indomethacin crystal packing

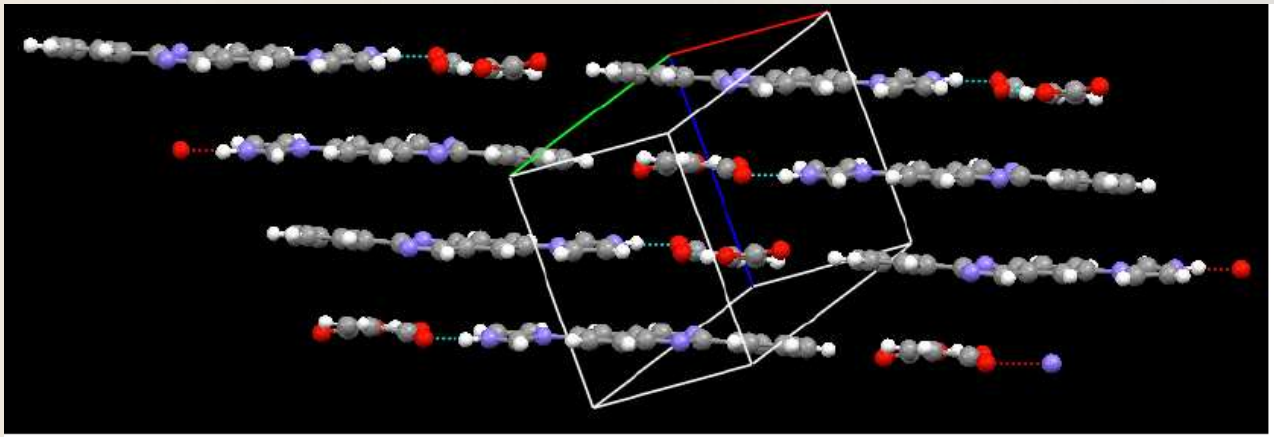


Chen et al., Reactivity Differences of Indomethacin solid forms with Ammonia Gas, J.Am.Chem.Soc., 2002, 124, 15012-19

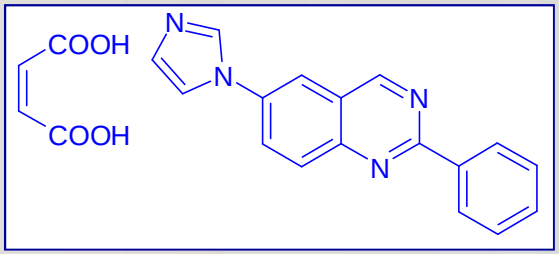
Solid State Forms & Reactivity

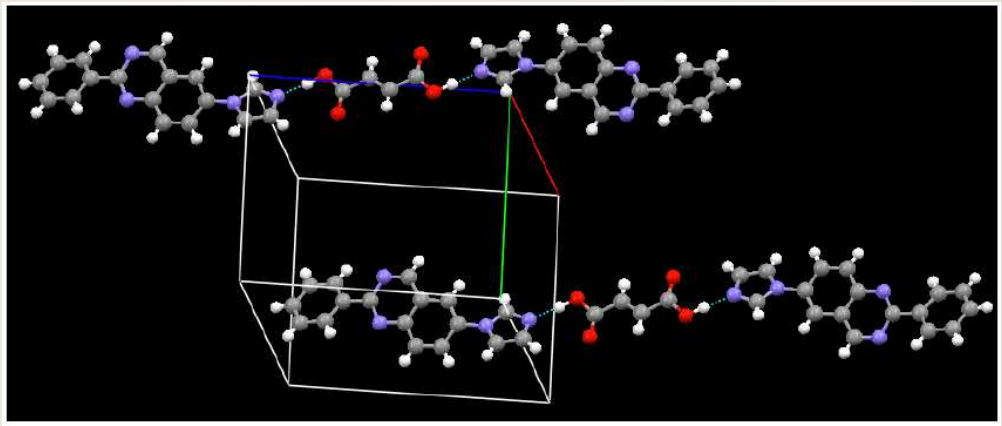
Paroxetine Maleate — **Form A**, **Form B** — **chemically more stable**



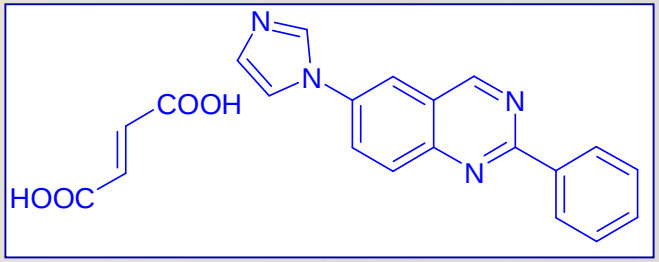


CR4056 Maleate





CR4056 Fumarate



A. Diez et al., Paroxetine maleate polymorps and pharmaceutical compositions cointaing them, 2002, US 6,440, 459

A. Giordani et al., Crystalline forms of 6-(1H-imidazol-1-yl)-2-phenyl quinazoline and its salts, 2009, WO2010140139,

Stress Testing: a Powerful Tool for Physical Form Selection

Stress Testing is fundamental for a fast identification of stability issues during physical form selection

Stress Testing is used for:

- Assessing specificity when developing stability indicating analytical methods
- Providing information about degradation products and degradation pathways
- Assessing stability differences among physical forms

Impact of the Physical Form on Chemical Stability

Samples

- Particle Size
- Physical Form

Solid State forced degradation studies

What happens during the stress testing

- Amorphization
- Crystalline form inter-conversion
- Hydrates formation

Selected Form

«Undesired» Form/s

Extent of Degradation

Degradation Path. Impurity Profile → **Impact on Safety**

Consistency in stress testing results can be assured when consistency in the used physical form is assured.

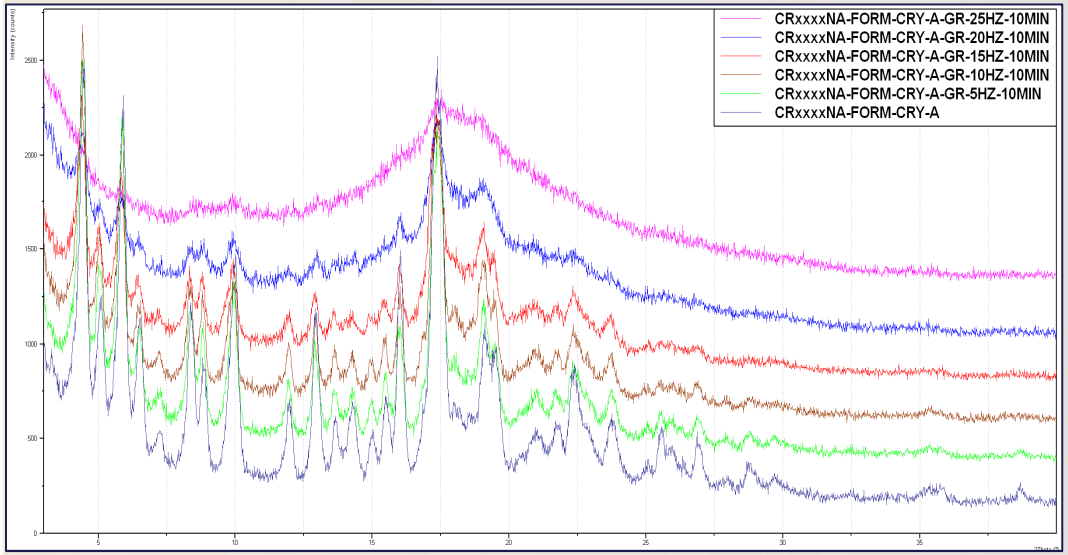
Impact on Stability Results

B.R. Matthews, Regulatory aspects of stability testing in Europe, Drug dev. Ind. Pharm., 1999, 831-856.

D. W. Reynolds et al., Available Guidance and Best Practice for Conducting Forced Degradation Studies, Pharmaceutical Tech., 2002, 48-54

Sample History: Impact of the Amorphous Phase

XRPD: CRXXX-Na Form A, 10 min. grinding, 5 to 25 Hz



CRXXX-Na: several crystalline forms

CRXXX-Na Form A

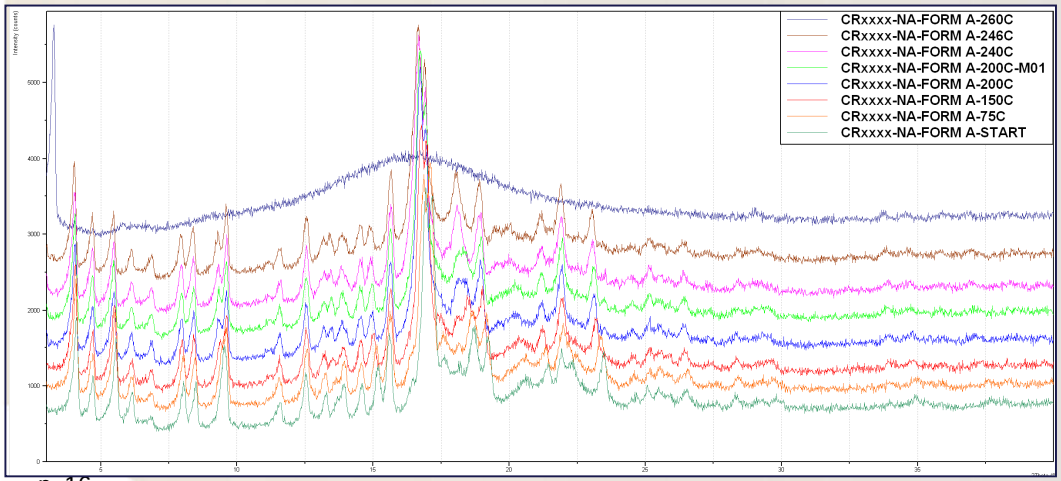
Mechanical liability Vs. amorphous

Amorphous Lower Chemical Stability

Which is the «mechanical history» of the sample ?

Are the «Physical characteristics» of the sample for solid state stress testing representative of the standard product ?

VT-XRPD: CRXXX-Na Form A, RT to 260° C

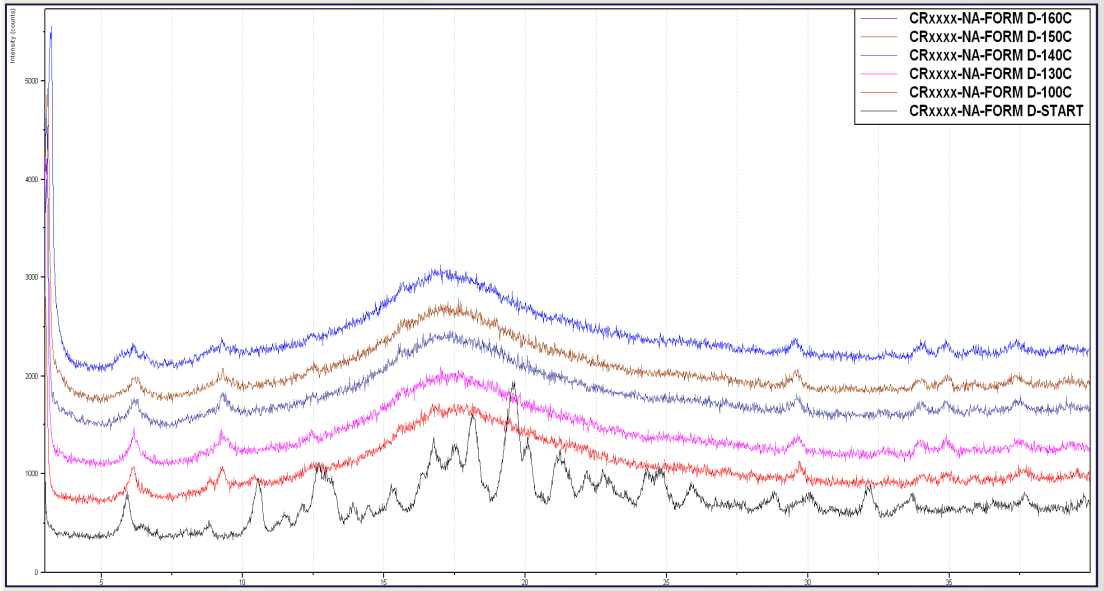


No thermal liability Vs. amorphous

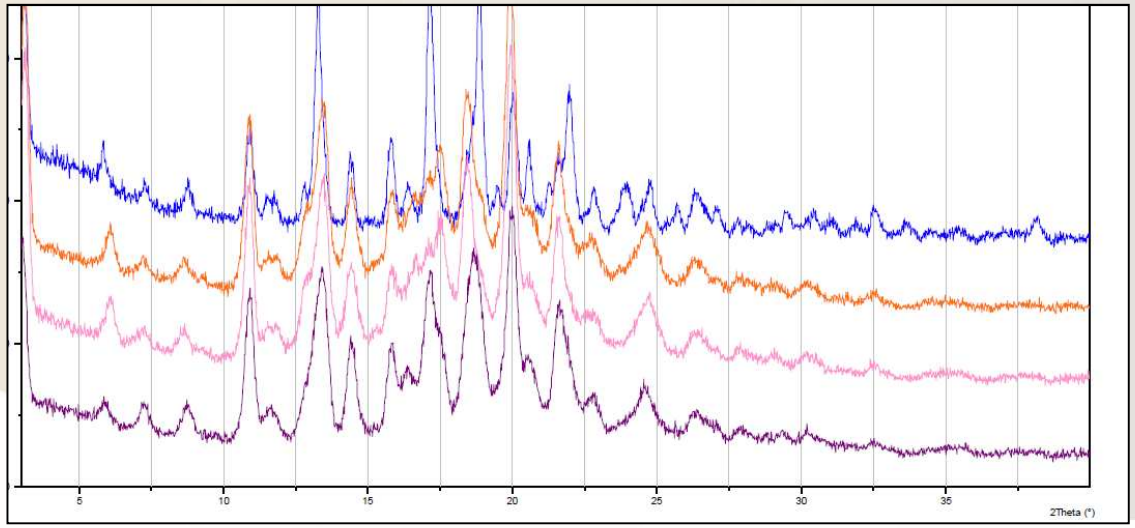
No impact is expected In thermal stress testing

Sample History: Impact of the Amorphous Phase

VT-XRPD: CRXXX-Na Form D, RT to 160° C



XRPD: CRXXX-Na Form D, 10 min. grinding, 10 to 30 Hz



CRXXX-Na Form D

Thermal liability vs. amorphous

Amorphous Lower Chemical Stability

Are the conditions used during solid state stress testing sigificative?

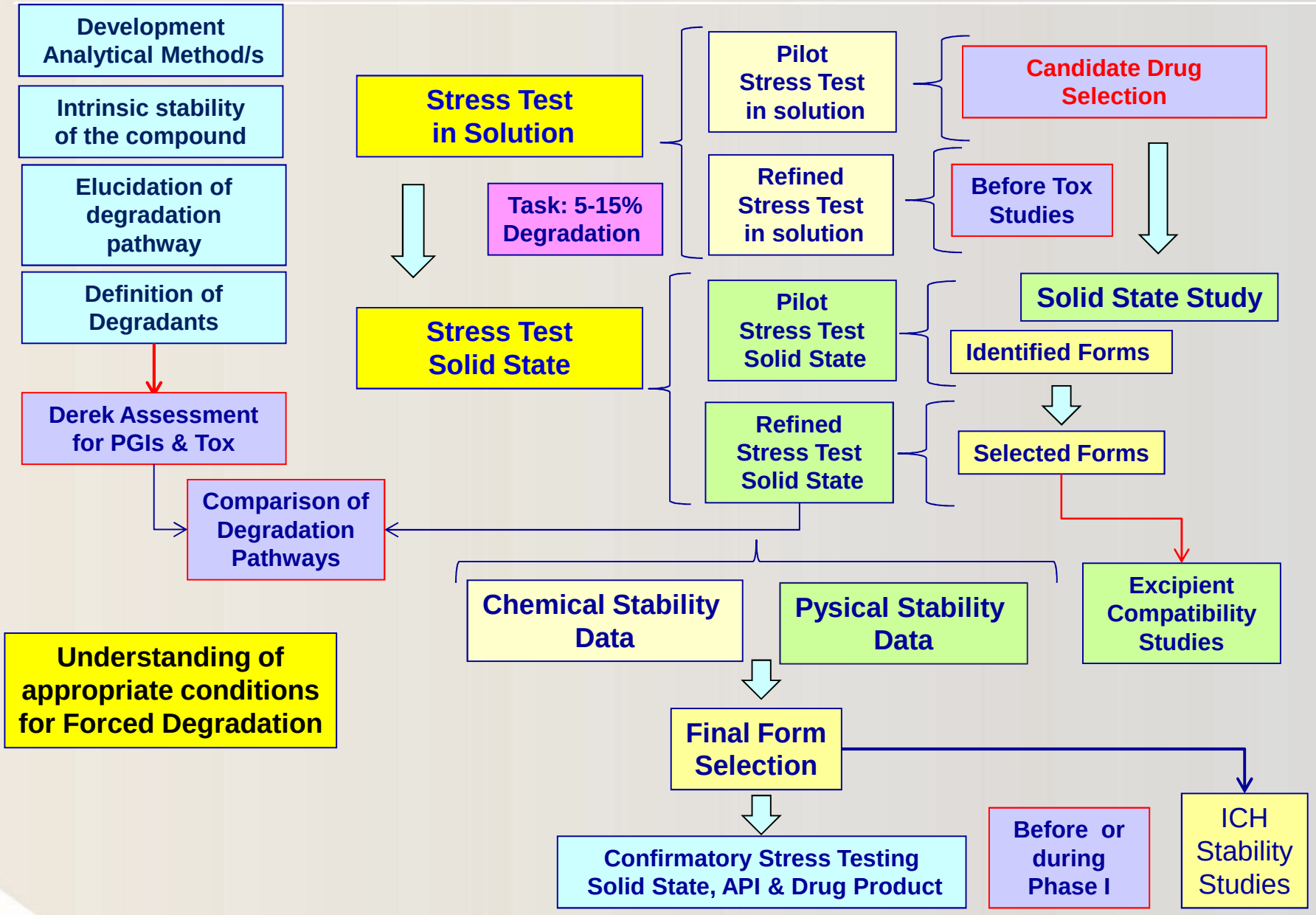
Important when stress testing results are used for kinetic evaluation

Fine-tuning of the thermal stress conditions taking into account the physical transformation of the sample

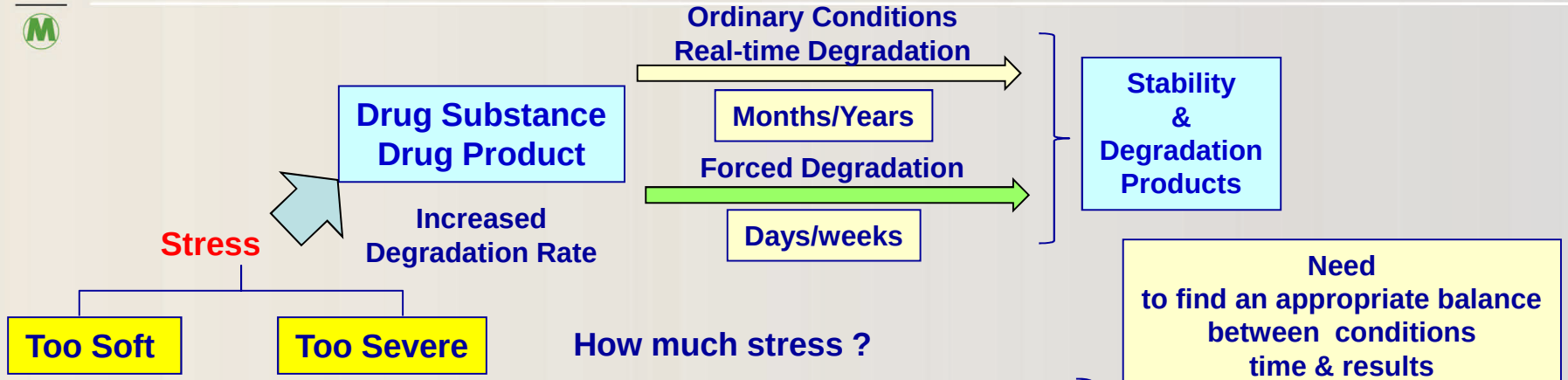
No mechanical liability Vs. amorphous

The «mechanical history» of the sample is not an issue in this case

Combining Stress Testing with Development



Focusing on Appropriate Conditions for Forced Degradation



Long time

Overestimating Stability

Very complicated degradation profiles

Secondary degradation products

Pathways not activated under normal storage conditions

Not useful information

The goal is to generate a degradation profile that mimics what would be observed in formal stability studies under ICH conditions

Relevant ICH Guidelines

Q1A	Stability testing of New Drug Substance and Products
Q1B	Stability testing: Photostability testing of New Drug Substances and Products
Q1C	Stability testing of New Dosage Forms
Q1D	Bracketing and Matrixing Designs for stability testing of Drug Substances and Products
Q1E	Evaluation of Stability data.

S. Klick et al., Toward a Generic approach for Stress Testing of Drug Substances and Drug Products, Pharm. Tech., 2005, 48-66.

Focusing on Appropriate Conditions for Forced Degradation

A benchmarking study about conditions used for Stress Testing by 20 Pharmaceutical Companies was published

Stress testing in solution (hydrolysis)

50% of the companies explore the range **pH 1-13**

5% cover only ranges **pH 1-2** and **12-13**

20% only **< 2** and **>12**

25% explore **pH 0-2; 5-9; 10 - > 12**

Temperature range: RT to 70°C

no degradation observed → 80-90°C or higher

Target degradation : 5-20%

Hydrogen peroxide (1-3%) is used for oxidative degradation

Temperatures: RT to 30°C

Catalysts such as transition metals or AIBN

can be used as radical initiators.

Thermal-humidity studies (drug substance)

typical range : 51-70°C (70% companies)

if no degradation occurs:

stress the sample at T> 90°C (50% companies)

in the range 71-90°C (25% companies)

The typical humidity range is 51-75% RH.

If the sample degradation is negligible about 50% of the companies stress the sample at RH>75%.

It was frequently observed that although one stress condition was too soft for one compound it led to massive degradation for another compound.

It is difficult to generate the relevant degradation products with a fixed set of stress conditions some fine-tuning of applied stress conditions or stress duration is often necessary.

K.M. Alsante et al., A Stress Testing Benchmarking Study, Pharm. Tech., 2003, 60-72.

D. W. Reynolds et al., Available Guidance and Best Practice for Conducting Forced Degradation Studies, Pharmaceutical Tech., 2002, 48-54

K.M. Alsante et al., The role of degradant profiling in active pharmaceutical ingredients and drug products , Adv. Drug Del. Rev., 2007, 29-37.

Stress Testing : The Screening

Screening approach, 28 samples x drug, carried out at the time of CD selection

Hydrolytic

Co-solvents: THF (DMSO), acetic acid, alcohols for not reactive compounds
Concentration: 0.1-1 mg/mL

1) 0.1N HCl/NaOH 8 hrs, 24 hrs, 48 hrs @ 25°C
2) 2 N HCl/NaOH 8 hrs, 24 hrs, 48 hrs @ 25°C
3) 0.1 N HCl/NaOH 4 hrs, 8 hrs @ 50°C
4) 0.1 N HCl/NaOH 4 hrs, 8 hrs @ 80°C
5) 2 N HCl/NaOH 4 hrs, 8 hrs @ 50°C
6) 2 N HCl/NaOH 4 hrs, 8 hrs @ 80°C

Comparative Intrinsic Stability among pre-candidate Drugs

Preliminary information about Degradation Rates

Preliminary information about Relevant Degradants

Samples are controlled using at least two orthogonal HPLC systems (RP & HILIC or Chromolith/Phenyl)

Results are reported as A% drug remaining; samples are quenched, analyzed and frozen

Optionally: samples with relevant degradants are analyzed for structure elucidation (LC-MS)

Information about differences in reaction rate between acidic and alkaline hydrolysis is also useful for formulation development.

P. Bojana et al., Microwave-assisted forced degradation using high-throughput microtiter platforms, J. Pharm. Biomed. 2011, 867-873.

M. Argentine, Strategies for the investigation and control of process-related impurities in drug substances, Adv. Drug Del. Rev.59, 2007 12-28

Liu et al., Geometric approach to factor analysis for the estimation of orthogonality and practical peak capacity in comprehensive two-dimensional separation, Anal. Chem. 67 (1995), 3840-45

Stress Testing : The Screening

Screening approach, 16 sample x drug, carried out at the time of CD selection

Oxidative

1% H_2O_2, 8 hrs, 24 hrs, 48 hrs @ 25°C

1% H_2O_2, Fe^{+3} or Cu^{++} (5% mol) , 8 hrs, 24 hrs, 48 hrs @ 25°C

1% H_2O_2, AIBN (5% mol), 8 hrs, 24 hrs, 48 hrs @ 25°C

3% H_2O_2, 8 hrs, 24 hrs @ 40°C

6% H_2O_2, 8 hrs, 24 hrs, 48 hrs @ 25°C

Co-solvent: CH_3CN

Comparative Intrinsic Stability among Drugs

Preliminary information about Degradation Rates

Preliminary information about Relevant Degradants

MainTasks of the Screening

When possible information on the structure of degradants

Comparative Intrinsic Stability → **Monitor Degradation**

Identify suitable conditions for refined studies on degradation → **Degradation of 5-15%**

Find conditions for the development of a stability-indicating method → **Information from Orthogonal Methods**

Info obtained by the Screening

Hydrolytic Conditions

Conditions		Time (hours) vs. A%				
HCl (N)	Temp. (°C)	0	4	8	24	48
0.1	25	99.3	-	99.4	99.3	99.0
2	25	99.3	-	98.6	96.6	93.5
0.1	50	99.3	97.7	96.2	-	-
0.1	80	99.3	93.1	86.5	-	-
2	50	99.3	96.6	93.8	-	-
2	80	99.3	88.2	77.2	-	-

Conditions		Time (hours) vs. A%				
NaOH (N)	Temp. (°C)	0	4	8	24	48
0.1	25	99.3	-	99.1	98.6	96.4
2	25	99.3	-	94.5	84.5	63.2
0.1	50	99.3	83.8	71.3	-	-
0.1	80	99.3	68.7	31.3	-	-
2	50	99.3	80.1	43.2		-
2	80	99.3	51.3	<30%	-	-

Assess mass balance, if significant mass loss is observed :
Response factors, volatile or highly retained products

Conditions leading to degradation of about 20% were identified

The Compound was more stable under acidic than alkaline conditions

Degradation profile under acidic conditions did not completely match that under basic conditions (at same temperature)

For acidic contitions, Degradation Profile/Pathway at lower temperature (25° C) matched with those at higher temperatures (secondary degradants highlited at 80° C).

For alkaline conditions Degradation Profile/Pathway at lower temperature (25° C) did not match with the one at 80° C.

Fine-tuning of Conditions in Refined Stress Test

Suitable degradation at a lower temperature in a reasonable time

Conditions		Time (hours) vs. A%				
HCl (N)	Temp. (°C)	0	4	8	24	48
0.1	25	99.3	-	99.4	99.3	99.0
2	25	99.3	-	98.6	96.6	93.5
0.1	50	99.3	97.7	96.2	-	-
0.1	80	99.3	93.1	86.5	-	-
2	50	99.3	96.6	93.8	-	-
2	80	99.3	88.2	77.2	-	-

Conditions		Time (hours) vs. A%				
NaOH (N)	Temp. (°C)	0	4	8	24	48
0.1	25	99.3	-	99.1	98.6	96.4
2	25	99.3	-	94.5	84.5	63.2
0.1	50	99.3	83.8	71.3	-	-
0.1	80	99.3	68.7	31.3	-	-
2	50	99.3	-	80.1	43.2	-
2	80	99.3	-	<30%	-	-

About 5 % Degradation:

2N HCl @ 25°
2N HCl @ 50° C
0.1N HCl @ 80° C
2N NaOH @ 25° C

About 15 % Degradation:

0.1N HCl @ 80°
2N HCl @ 80° C
2N NaOH @ 25° C
0.1 N NaOH @ 50° C

Selected Acidic Conditions:

4N HCl @ 30° C

About 5% degradation @ 8 hrs.

4N HCl @ 50° C

About 15% degradation @ 8 hrs.

Selected Basic Conditions:

2N NaOH @ 30° C

About 5% degradation @ 8 hrs, about 15% @ 12 hrs.

2N NaOH @ 50° C

About 5% degradation @ 2 hrs, about 20% @ 8 hrs.

Need to ensure that the degradation profile at the experimental temperature is consistent with the one at r.t.

Check Intermediate pH ranges : 3- 9

Degradation in the Solid State

Degradation In the Solid State

- Thermal Degradation
- Thermal-humidity Degradation
- Photo-degradation

→ Hydrolysis, decarboxylation, isomerization, rearrangement, polymerization and oxidation

→ Oxidative / Non-oxidative

Humidity

- Rate of Hydrolytic Reactions
- Increase in Molecular Mobility

Stress Testing in the Solid State

Degradation

HPLC
LC-MS

Formation of Degradation Products

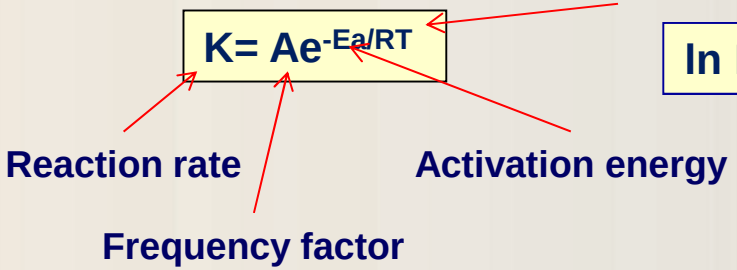
Thermal	Changes in form	XRPD VT-XRPD DSC
Increasing Temperature		
Thermal-humidity	Formation of hydrates	XRPD DVS DSC
Increasing Temperature & RH%		
Photoirradiation	Changes in form	XRPD DSC
hν		
(Mechanical Stress)		
Pressure, milling, grinding		

During Processing →

Physical Form Consistency

Solid State Kinetics

Effect of Temperature on Reaction Rate is described by the Arrhenius equation:



$\ln K_T = \ln(A) - E_a/RT$

Genton & Kesselring
modified Arrhenius model

$\ln K_T = \ln(A) - E_a/RT + Bh$

Effect of RH on
the Rate of Degradation

$$B = \frac{\ln (K1/K2)}{RH1-RH2}$$

The activation energy represents the quantitative relationship between reaction rate and temperature

The average activation energy for most drug substances is 10-20 kcal/mole

Making measurements at three different conditions of temperature and relative humidity, by the modified Arrhenius equation is possible to estimate the time-to-failure at any other temperature and relative humidity

**Ea= 10 kcal/mol
the increase of reaction rate
is in the range 2-3 times
for every 10° C increase**

**Storage at 70° C for 14 days, Ea= 10 Kcal/mole
can be kinetically equivalent to a storage
at 40° C for 6 months**

S.W. Baertschi, Pharmaceutical Stress Testing: Predicting Drug Degradation, Taylor&Francis, 2005

G. Scrivens, Mean Kinetic Relative Humidity: A New Concept for Assessing the Impact of Variable Relative Humidity on Pharmaceuticals, Pharm Tech., 2012,52-57.

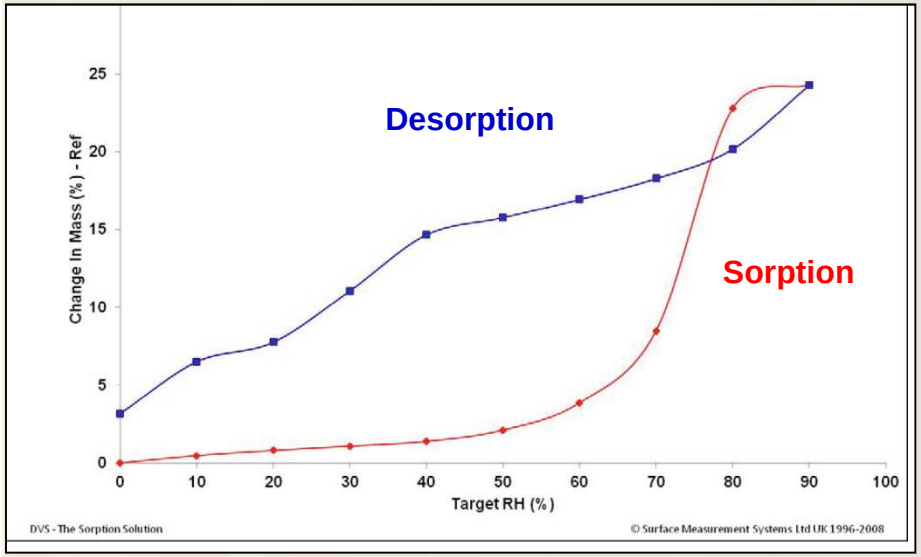
A. Vyazovikin, C.A. Wigth, Kinetics in Solids, Ann. Rev. Phys. Chem., 1977, 48, 127.

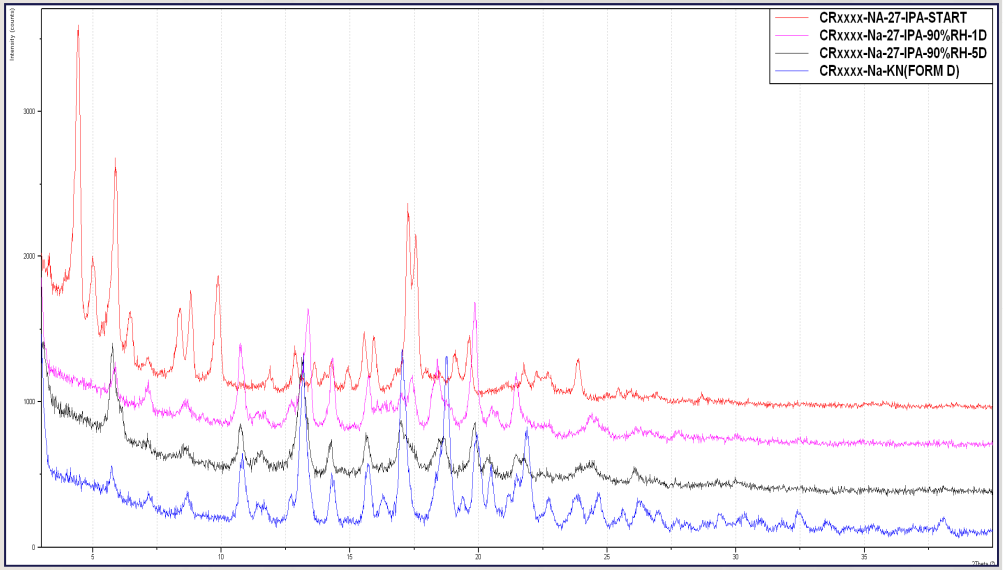
Thermal-Humidity: Hydrate Formation Assessment

Hydrates are often less chemically stable than corresponding anhydrous form.
Formation of hydrates should be assessed before thermal-humidity stress testing

Sometimes hydrate screening methods in solution are not able to highlight hydrates which are formed by interaction with moisture in the solid state.

DVS jointly with XRPD can highlight the hydrate formation





Y. Cui et al., Evaluation of Hydrates Screening Methods, J. Pharm. Sci., 2008, 97(7), 2730.

D. Giron et al., Solid State Characterization of Pharmaceutical Hydrates, J. Therm. Anal. Cal., 2002, 68, 453.

Solid State Stress Testing

Thermal: Temperatures higher than 50° C such as 70-90° C can be applied to rapidly generate data during development.

Samples stored at lower temperatures for longer times can provide information about consistency of the degradation pattern.

Use the highest thermal stress that does not result in a change of physical form.

Thermal-humidity

ICH Q1A(R2) (2003)

Long Term (12 months): 25±2 °C, 60±5% RH,

Accelerated (6 months): 40±2°C,75±5% RH,

"intermediate" : 30±2 °C, 65% RH (backup data)

Another widely used protocol:

70° C, 75% RH; 70° C, 20% RH; 2-4 wks

Protocol for accelerated shelf-life estimation

T (°C)	RH (%)	Sampling Time (days)	
50	75	4	14
60	5	14	21
60	40	4	21
70	5	4	21
70	75	1	2
80	40	1	4

K. Waterman et al., Improved protocol and data analysis for accelerated shelf-life estimation, Pharm. Res., 2007, 24(4), 780-790.

Solid State Stress Testing : the Screening

For Stress Studies in the solid state a screening is used to identify appropriate conditions

Physical Form Stability and Melting Point are the key factors to be taken into account for the selection of the higher temperature to be used .

Thermal and Thermal-humidity studies are carried out sequentially

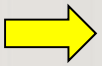
The Sample is exposed

50° C for 14 days (dry) (sampling: 7, 14)
70° C for 14 days (dry) (sampling: 7, 14)
60° C / 75% RH for 4 weeks
90° C / 75% RH for 4 weeks

90° C for 5 days (dry) (sampling: 3, 5)
120° C for 4 days (dry) (sampling: 2, 4)
60° C / 85% RH for 4 weeks
90° C / 85% RH for 4 weeks

Comparative Stability Data among Forms

Preliminary Stability Data for each Form



Depending on the results two sets of suitable lower temperatures, RH% conditions and longer times are selected for the refined stress testing

Example: Difference in Stability among CRXXX Forms

Thermal

Starting	90°C / 5 days	120°C / 4 days
1. 99.3 %	1. 98.8 %	1. 92.0 %
2. 99.3 %	2. 99.3 %	2. 98.9 %
3. 99.3 %	3. 99.2 %	3. 98.9 %
4. 99.5 %	4. 99.4 %	4. 98.8 %
5. 99.3 %	5. 99.0 %	5. NA

Less Chemically Stable Form

No Stability Differences

Amorphous Quite Stable

1. CRXXX solvate desolvated
2. CRXXX-Na (form D)
3. CRXXX-Na (form A)
4. CRXXX-HCl (form A)
5. CRXXX amorphous

Form 2-4
90° C
1 month
70° C
2 months

Example: Difference in Stability among CRXXX Forms

Thermal-humidity

Initial results	1 week	2 weeks	3 weeks	4 weeks
1. 99.3 %	1. 99.2 %	1. 99.2 %	1. 99.1 %	1. 99.1 %
2. 99.3 %	2. 99.2 %	2. 99.2 %	2. 99.2 %	2. 99.3 %
3. 99.3 %	3. 99.2 %	3. 99.2 %	3. 99.2 %	3. 99.1 %
4. 99.5 %	4. 99.4 %	4. 99.4 %	4. 99.4 %	4. 99.4 %
5. 99.3 %	5. 99.2 %	5. 99.1 %	5. 99.2 %	5. 99.0 %

Stability study @ 60° C/85% RH

1. CRXXX solvate desolvate
2. CRXXX-Na (form D)
3. CRXXX-Na (form A)
4. CRXXX-HCl (form A)
5. CRXXX amorphous

Initial results	1 week	2 weeks	3 weeks	4 weeks
1. 99.3 %	1. 96.2 %	1. 96.1 %	1. 94.3 %	1. 94.3 %
2. 99.3 %	2. 99.2 %	2. 99.3 %	2. 98.9 %	2. 99.1 %
3. 99.3 %	3. 99.1 %	3. 99.1 %	3. 98.7 %	3. 99.1 %
4. 99.5 %	4. 99.3 %	4. 99.3 %	4. 98.4 %	4. 98.9 %
5. 99.3 %	5. 98.1 %	5. 96.7 %	5. 96.2 %	5. 86.6 %

Stability study @ 90° C/85% RH

Forms 2-4
70° C
75% RH
3 months
90° C
75% RH
2 months

Confirmatory stress test in the solid state not more than 3 months

Impurity Pattern Assessment

Main degradation products (≥ 0.1 %):

Form	90° C	120° C	60° C/85%RH[1]	90° C/85%RH[1]
1	RRT1.06: 0.6 %	RRT0.65: 0.8 % RRT1.06: 0.7 % RRT1.09: 0.3 % RRT1.21: 0.5 % RRT1.44: 0.4 % RRT1.68: 1.3 % RRT1.86: 0.5 %	RRT1.06: 0.5 %	RRT0.65: 0.6 % RRT1.06: 0.5 % RRT1.09: 0.4 % RRT1.21: 0.4 % RRT1.44: 0.4 % RRT1.68: 0.7 % RRT1.86: 0.3 %
2	RRT1.06: 0.6 %	RRT1.06: 0.9 % RRT1.09: 0.1 %	RRT1.06: 0.6 %	RRT1.06: 0.6 %
3	RRT 1.06: 0.7 %	RRT1.06: 0.9 % RRT1.09: 0.1 %	RRT 1.06: 0.8 %	RRT1.06: 0.8 %
4	RRT0.99: 0.1 % RRT1.06: 0.4 %	RRT0.99: 0.1 % RRT1.06: 0.6 % RRT1.09: 0.1 %	RRT0.99: 0.2 % RRT1.06: 0.3 %	RRT0.99: 0.2 % RRT1.06: 0.6 %
5	RRT0.95: 0.1 % RRT0.99: 0.3 % RRT1.06: 0.2 % RRT1.08: 0.1 %	-	RRT0.99: 0.3 % RRT1.06: 0.2 % RRT1.08: 0.1 %	RRT0.65: 1.0 % RRT0.98: 0.4 % RRT1.04: 0.8 % RRT1.06: 0.3 % RRT1.08: 0.4 % RRT1.22: 0.7 % RRT1.27: 0.8 % RRT1.44: 0.5 % RRT1.48: 0.7 % RRT1.49: 0.6 % RRT1.69: 2.1 % RRT1.87: 0.6 %

[1] After four weeks

Photostability

Photolytic Degradation

- **Non-oxidative** → isomerization, cyclization, rearrangements, dimerization, homolytic cleavage of X-C hetero bond (X=N, O, halogen)
- **Oxidative**
  - $^1O_2$ → Reaction with unsaturated bonds to form photoxidative addition products
  - $^3O_2$ → Radicals reactions giving rise to peroxides

The photo-degradation rate depends on the intensity of incident light and on the wavelenght of the radiation.

The overall illumination NLT 1.2 million lux/hour ⇒ **NMT 6 million lux/hour**

Commonly used wavelength: 300-800 nm

Integrated Energy NLT 200 Watt/ hrs. /m^2

ICH Q1B, Stability Testing of New Drug Substances and Products, November 1996.

Example: Difference in Photostability among CRXXX Forms

Sample	Initial	Photostab. 12hrs Control (65° C)	Photostab. 12hrs Test Sample
CRXXX-Na Form A	99.2%	99.2%	98.5%
CRXXX-Na Form D	99.2%	99.2%	92.4%
CRXXX.HCl Form A	99.3%	99.3%	98.2%
CRXXX Amorphous	99.4%	99.4%	81.6%

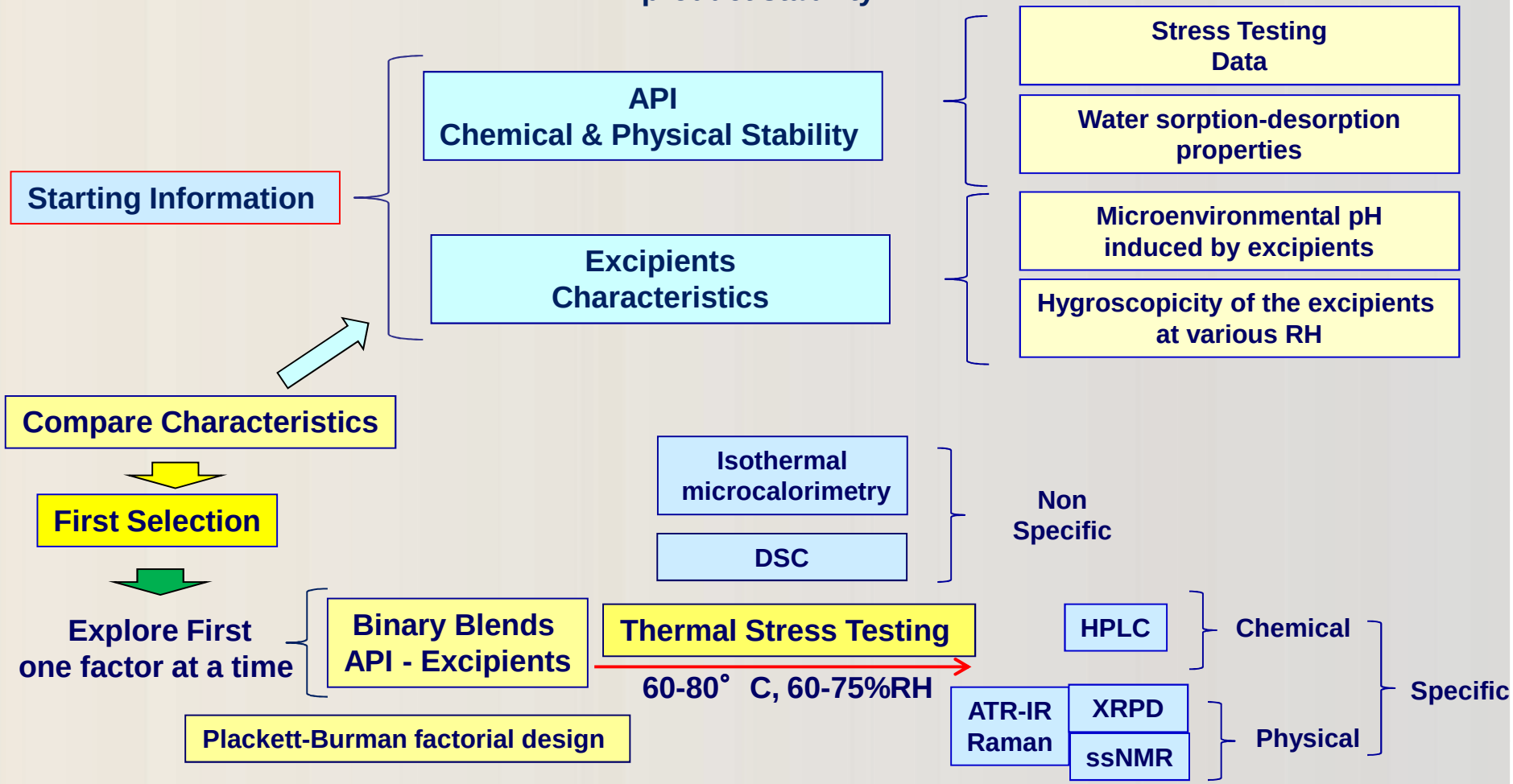
- Test Sample: powder distributed on Qz plate
- Control: sample wrapped in aluminum foil (for evaluation of thermal degradation)

Xenon lamp; Irradiance value: 765W/h/m^2
1st Trial: exposition for 12 hrs.
2nd trial: exposition for 48 hrs.(4xICH)

Sample	Purity (A%)
Amorphous (t=0)	99.4
Photostability Control_12hrs	99.4
Photostability_12 hrs	82.0
Photostability_48 hrs	52.1

Excipient Compatibility Testing

Selection of appropriate excipients for drug substance formulation is important in ensuring drug product stability.



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A. S. Narang et al., Impact of Excipient Interactions on Solid Dosage Form Stability, Pharm. Res. 2012, 2660.

S. J. Carreira et al., A new approach to accelerated drug-excipient compatibility testing, Pharm. Dev. Tech., 2003, 119.

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