ZURÜCK

Poster

Screening of Polymorphic/Pseudopolymorphic Behaviour of Drugs

Steffen Neuenfeld and Ingrid Lochmann
Merck KGaA, Central Process Development
D-64271 Darmstadt
Germany

Tel +49 6151 727715
Fax +49 6151 726858
e-mail steffen.neuenfeld@merck.de
steffen neuenfeld@t-online.de

1 zurück

Introduction

Polymorphism is the ability of a substance to crystallise in different crystal forms resulting from different arrangements of the molecules in the solid state. Furthermore many compounds are able to incorporate solvent molecules in the crystal lattice. The effect of formation of solvates or in special case hydrates is called pseudopolymorphism.

The different solid state phases of a compound differ from one another in their crystal energies and show different solid state properties. The main physical properties affected are phase transitions like melting, density, solubility behaviour, crystal hardness, etc. Different polymorphs or pseudopolymorphs shows also a different solid state stability and different decomposition rates by treatment with heat or light or during a storage. Finally the different crystal forms cause a different pharmaceutical behaviour to example a different bioavaibility and formulation properties.

The knowledge of polymorphic or pseudopolymorphic properties of a drug structure is very important before the scale-up and synthesis of higher amounts for preclinical/clinical investigations and formulation studies will be started. The possible different process parameters in the lab scale and the pilot plant are able to result different crystal forms of a drug.

2 zurück

A so-called polymorphism screening is necessary to check the appearance of various polymorphic or pseudopolymorphic forms at an early stage.
An important question during the development of a drug is

„How many crystal forms exist?“

If a drug substance is able to exist in different crystal forms the question have to answer

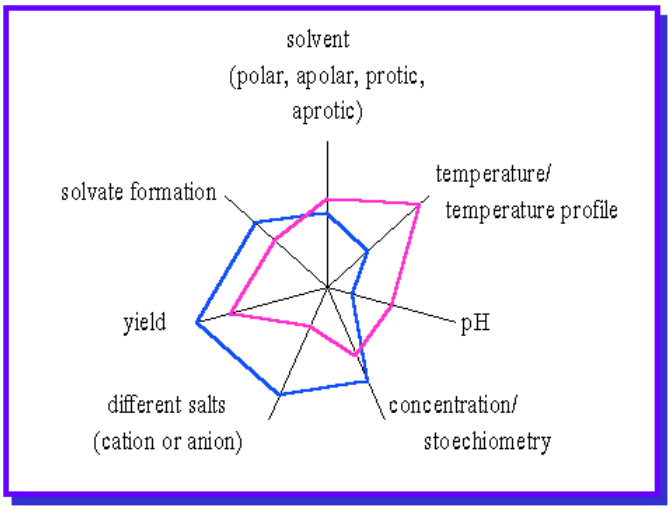
„What is the optimal crystal form for the further development?“

The selected crystal form has to be thermodynamic stable to avoid a transformation of a metastable form during storage or processing. Further the selected form has to be suitable for a scale up or formulation.

It turned out that the consideration of the last synthesis step (most a salt formation) is very effectively. The process conditions (e.g. temperature, dosing rate, solvents) are varied and their effect on the resulting crystal form will be investigated in view of a scale-up.

3 zurück

The main aim of the screening procedure is the discovering of possible different crystal forms under process relevant conditions. It must be noted that FDA guidelines state that solid state forms do not have to be created by techniques or conditions that are irrelevant to the synthetic process (1). It turned out that the consideration of the last synthesis step (most a salt formation) is very effectively. The process conditions (temperature, dosing rate, solvents, ...) are varied and the their effect on the resulting crystal form will be investigated in view of a scale-up. Additionally an optimization of a specific crystal formation in view of the scale-up ability and an assessment of the stability and reproducibility of the process is possible.



(1) Quality Control Reports “The Gold Sheet”, Vol. 30 (1996) 3

4 zurück

A. Preparation of the final drug compound under various conditions

Main aim

- discovering of possible different crystal forms (polymorphic/pseudopolymorphic forms)
- describing of the influence of process conditions on the crystal formation
- check the scale-up ability
- test of the stability and reproducibility of the crystallization/salt formation step

Methods

✗ **Precipitation of the final compound (salt formation)**
✗ **Recrystallization from various solvents (heating and cooling)**
✗ **Crystallization from various solvents (at room temperature)**
✗ **Solid state transformations**

5 zurück

A1. Precipitation of the final compound (salt formation)

Methods

- effect of various solvent (protic, aprotic, polar, apolar)
- effect of temperature/temperature profiles
- effect of pH variation
- influence of various concentrations/stoechiometric ratios
- different salt (e.g. sodium or potassium salt or hydrochloride, succinate, maleate...)
- optimization of precipitation/crystallization (yield)

A2. Recrystallization from various solvents (heating and cooling)

- effect of various solvent (protic, aprotic, polar, apolar)
- effect of cooling conditions (e.g. shock cooling, end temperature of heating or cooling)
- possibility of solvate formation

A3. Crystallization from various solvents (at room temperature)

- various solvents, solvate formation

A4. Solid state transformations

- thermal treatment at different temperatures
- crystallization of melt
- desolvation/dehydration of solvates/hydrates

6 zurück

B. Investigation of the properties of the different crystal forms

Main aim:

- detection of the thermodynamic stable form
- desciption of the stability relationships of different forms
- recognize of process relevant properties (thermal stability)
- selection of a practicable form in view of the process development/scale up

Methods:

Thermal Analysis
- different melting points, solid-solid transitions (monotropic or enantiotropic) melting behaviour
- desolvatation behaviour and kinetics
- decomposition behaviour and kinetics
- effect of thermal stress, long time stability
- thermodynamic calculations based on Gibbs equation

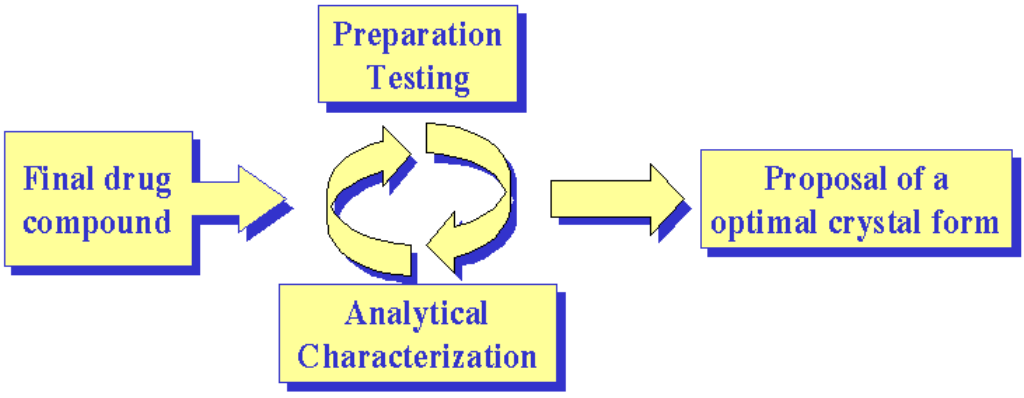
- solubility in various solvents, solubility profiles (time dependence)
- solid-solution equilibrium
- solid-vapour equilibrium
- effect of huminity (0 - 100 %)

- IR-Spectroscopy (identity, crystal form)
- Raman-Spectroscopy (identity, crystal form)
- X-Ray-Diffraction (crystal form)
- others (EA, NMR, MS - identity)

7 zurück

C. Conclusions

The specific search for possible polymorphs or pseudopolymorphs is an effective step of process development. The knowledge of the polymorphic and pseudopolymorphic behaviour enables a more purposeful selection of the desired crystal forms and its optimal process conditions of preparation. It minimizes the risk of random appearance of unknown crystal forms during the development and scale-up.



8 zurück

Example 1 - Effect of Temperatures

The precipitation of a development compound A from its sodium salt solution by acetic acid gives three different crystal forms (anhydrate A1, monohydrate H1 and dihydrate H3). In dependence on drying conditions three further crystal modifications were formed (monohydrate H2, anhydrate A2 and desolvate A3).

$$R\text{-}SO_3^- + H^+ \longrightarrow R\text{-}SO_3H \downarrow$$

Precipitation Temperature (°C)	Drying conditions 25°C	25°C + Vacuum	50°C + Vacuum	70°C + Vacuum
5	**H3**	**H3**	**A2**	**A2**
30	**H3**	**H3**	**H2**	**A2**
50	**H1**	**A3**	**A3**	**A3**
80	**A1**	**A1**	**A1**	**A1**

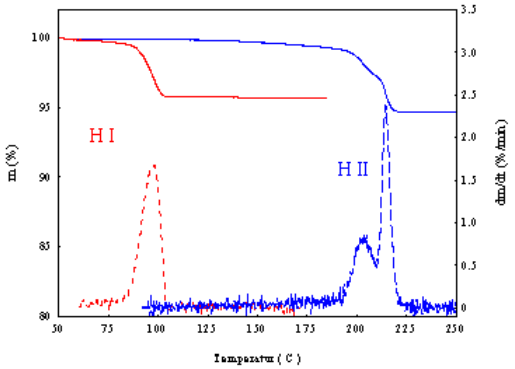
A1, A2, A3 = X; H1, H2 = X*H_2O H3 = X*2H_2O

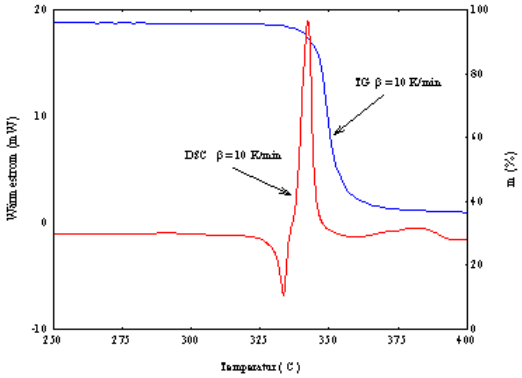
9 zurück

Example 2 - Polymorphic monohydrates

EMD 94246

Precipitation at 75°C gives the stable monohydrate HI. At lower temperatures the metastable monohydrate HII is formed. Both monohydrates show a very different thermal behaviour. The loss of water starts with monohydrate HI at 80°C and with monohydrate HII at 180°C in dynamic TG measurements. Monohydrate HII gives off water in two equal steps. Probably the dehydratisation proceeds over a hemihydrate intermediate. In both cases the dehydratisation gives the same anhydrous form. The resulting anhydrate I melts at 329°C under decomposition.





10 zurück

Example 3 - Effect of pH

Development compound B

- precipitation by conversion of a free amine base structure with aqueous hydrogene chloride
- pH > 1 - formation of a monohydrochloride form
- pH < 1 - formation of a dihydrochloride monohydrate form
- precipitation with ethanolic hydrogene chloride ("pH < 1") - formation of a dihydrochloride form

X·HCl X·2HCl X·2HCl·H_2O

Example 4 - Different salts and Hydrate formation

EMD 122946

- formation of a potassium and a sodium salt by precipitation with KOH and NaOH
- precipitation with KOH gives thermal instable solvates (ethanolate, hydrate)
- precipitation with NaOH gives a solvent free product
- the sodium salt forms an instable monohydrate by treatment with liquid water
- the sodium salt forms a trihydrate by treatment with vaporous water (100 % RH)

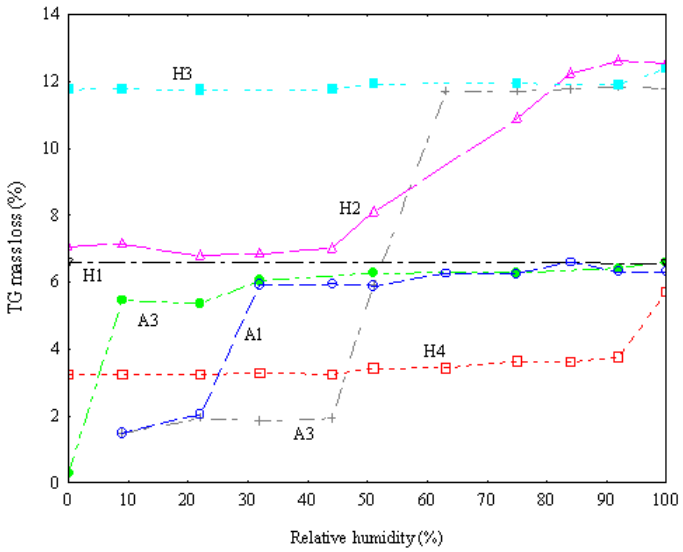
NaX NaX·H2O NaX·3H_2O KX·H2O KX·EtOH

11 zurück

Example 5 - Hygroscopicity

Development compound A

The polymorphic and pseudopolymorphic forms are able to differ by IR, XRD, DSC and TG measurements. Additionally every crystal modification is characterized by a specific hygroscopicity profil.



A1, A2, A3 = X

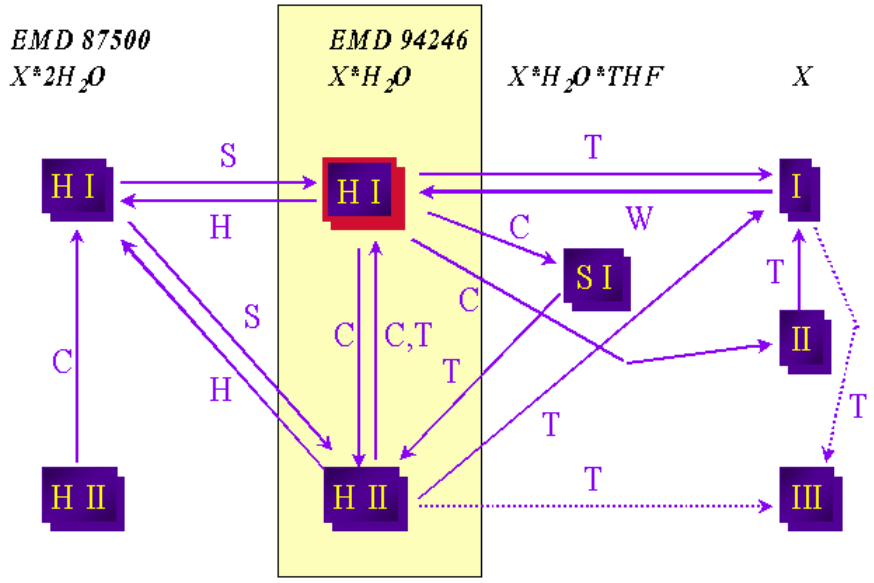
H1, H2 = X*H_2O

H3 = X*2H_2O

H4 = X*1/2H_2O

12 zurück

Example 6 - Stability relationships



C - crystallization, S - salt formation, T - thermal treatment, W -water treatment, H - hydrolysis

13 zurück

Example 7 - Effect of solvent / solid state transformations

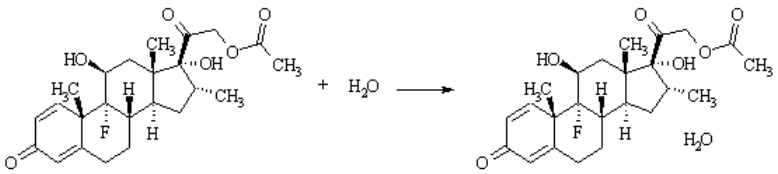
Development compound C (neutral molecule)

- crystallization from different solvents gives the stable form I
- precipitation from a methanolic solution by addition of water gives the metastable form II
- crystallization from melt gives form III

Example 8 - Effect of solvent / hydrate formation

Dexamethasone-21-acetate

- the hydrate formation is impossible by simple treatment of an anhydrate by water
- precipitation from ethanolic solution by addition of water gives the monohydrate only unter special conditions (temperature, concentration, ethanol-water ratio)
- three anhydrate formes (I - mp. 210°C, II - mp. 217°C, III - mp. 231°C

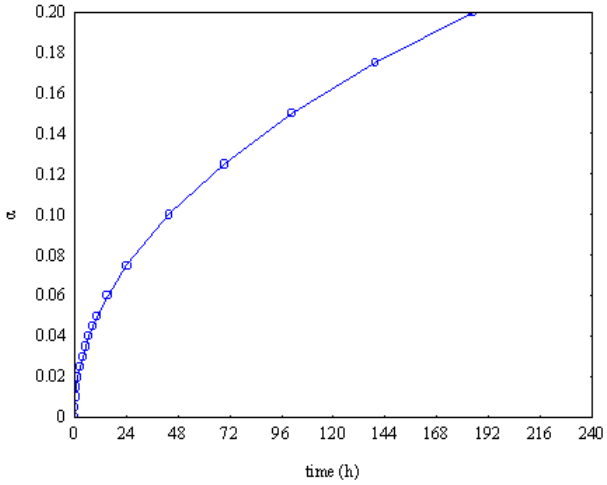


14 zurück

Example 9 - Decomposition kinetics

Development compound B

- the final compound decomposes during drying
- investigation of the decomposition reaction by isothermal TG measurements at different temperatures
- a kinetic analysis gives for a D4 model the best fit



$$\frac{d\alpha}{dt} = k \cdot \frac{3}{2} \cdot \frac{1}{(1-\alpha)^{-1/3} - 1}$$

5 % decomposition during 12 h drying at 60°C

15 zurück

Example 10 - Effect of Solvents EMD 94246

A variation of salt formation conditions yields to two different monohydrates (HI, HII). Monohydrate HI results from KOH/ethanol by precipitation at 75°C. The precipitation at lower temperatures than 50°C gives monohydrate HII. A reverse behaviour is found by crystallization/recrystallization experiments. Lower temperatures or a crystallization at room temperature yield favoured to monohydrate HI. A recrystallization (temperature treatment) gives monohydrate HII.

• Precipitation from different bases and solvents		
KOH/Ethanol	H I (75°C)	H II (<50°C)
KOH/Methanol	H I	
KOH/Water	H I	
$KOCH_3$/Ethanol		H II
$KOCH_3$/Methanol		H II
KO-tert.-C_4H_9/Ethanol		H II

• Crystallization/Recrystallization from different solvents		
	Crystallization at room temperature	Recrystallization
Ethanol	H I	H I + H II
Methanol	H I	
THF		H II
Aceton		H I + H II

16 zurück