University of Szeged
Doctoral School of Pharmaceutical Sciences

Educational Program: Pharmaceutical Technology
Head: Prof. Dr. habil. Piroska Szabó-Révész Ds.c.

Department of Pharmaceutical Technology
Supervisor: Dr. habil. Zoltán Aigner Ph.D.

Péter Láng

POLYMORPH SCREENING OF A FORMER DRUG CANDIDATE

Final Exam Committee:

Head: Prof. Dr. István Erős Ds.C., University of Szeged, Department of Pharmaceutical Technology

Members: Dr. István Zupkó Ph.D., University of Szeged, Department of Pharmacodynamics and Biopharmacy

Dr. Miklós Vecsernyés Ph.D., University of Debrecen, Department of Pharmaceutical Technology

Reviewer commitee

Head: Prof. Dr. György Dombi, University of Szeged, Department of Pharmaceutical Analysis

Reviewers: Prof .Dr. Etelka Tombácz Ds.C., University of Szeged, Department of Physical Chemistry and Materials Science

Dr. Imre Markovits Ph.D., Egis Pharmaceutical Company

Members: Dr. Ildikó Csóka, University of Szeged, Department of Drug Regulatory Affairs

Dr. Péter Doró, University of Szeged, Department of Clinical Pharmacy

SZEGED
2016

1. INTRODUCTION

Investigations of the polymorphism of APIs are currently essential in pharmaceutical research and production. This process is known as "polymorph screening". The polymorph screening of organic materials is an extremely complex and multifaceted field, which poses considerable challenges for innovators and generic companies from the aspects of both pharmaceutical and intellectual property rights.

Polymorphism is a common phenomenon among APIs. Some literature sources suggest that it occurs in 32-51 % of solid materials (Hilfiker, 2006), whereas other surveys indicate that ~ 90 % of crystalline active ingredients have polymorphs (Theyer, 2007). The physico-chemical properties of polymorph modifications such as melting point, hardness, solubility, dissolution rate, etc. can differ as a consequence of the different crystal structures and this may influence the formulation, the storage, the absorption, the toxicity, the efficiency and finally the bioavailability of the API. The importance of polymorph screening is outstanding since the drug registration authorities require a precise description of the characteristics of a solid-state API and a drug candidate can be placed on the market only in the case of a specific polymorph for which long and expensive biological, toxicological and clinical studies have been carried out (Byrn et al., 1995, Huang et al., 2004, Raw et al. 2004).

Pharmaceutical dosage forms contain both active ingredients and excipients. Although excipients must be inert, they may influence the absorption and bioavailability of the drug in such a way as to increase the stability of the formulation, to faciliate the liberation of the API, etc. (Jackson et al., 2000). Additives and impurities can influence the kinetic stability of a polymorph in a solution or a suspension by affecting both the nucleation and the growth rate (Gu et al., 2002, Hilfiker et al., 2006). Polymorph screening that is performed with additives may therefore lead to different results from a screening performed with a pure batch (Hilfiker et al., 2006). Among the additives currently utilized in the pharmaceutical industry are the SEs, which have likewise long been preferred in the food and cosmetic industries too. They can be applied as emulsifiers, solubility and dissolution rate enhancers, gel-formers and crystal growth enhancers or inhibitors (Mitsubishi Co., 1982, Akoh, 1992, Mutoh et al., 2007, Oh et al., 2006, Garti et al. 2000, Kato et al. 1971, Awad et al., 2002). Szűts et al. reported that a certain type of SE influenced the degree of crystallinity of a model drug (Szűts et al., 2011). Accordingly, since SEs can affect the crystal structure of the API, it is useful to investigate the structural changes during crystallization processes when SEs are used as additives.

2. AIMS

Polymorph screening is a very complex process during preformulation research. It is not sufficient to investigate merely the effects of the organic solvents and the temperature. The presence of the different additives, such as the SEs, must also be considered. These surfactants may cause changes in the polymorphic form during crystallization, and these may finally affect the bioavailability of the drug.

The aim of my PhD work was therefore to develop a polymorph screening method on a model drug and to investigate the influence of different SEs during the crystallization process.

A. The main aim of my investigations was to develop a polymorph screening method on a failed drug candidate. Different crystallization and transformation methods were used to generate the polymorphs of the model drug. Eight polymorphs were obtained and were characterized by light microscopy, SEM, XRPD, DSC and Raman spectroscopy. A special dissolution test was developed with which the eight polymorphs could be well distinguished.

B. After the characterization of the different polymorphs, their relative stabilities were investigated by means of a slurry conversion method, VH-XRPD, VT-XRPD and DSC.

C. Finally, different types of SEs (widely used as additives at present) were studied during the crystallization of the polymorphs in order to establish their polymorph-changing effects.

3. MATERIALS AND METHODS

3.1. Materials

My Ph.D. work related to the polymorphism of a failed drug candidate, 3-[2-({[1-(2-cyclohexylethyl)-5-(2,5-dimethoxy-4-methylphenyl)-1H-1,2,4-triazol-3-yl]amino}carbonyl)-6-methoxy-4,5-dimethyl-1H-indol-1-yl}propanoic acid (Sanofi Pharmaceutical Company, Budapest, Hungary).

In the first step relating to the crystallization of the various polymorphic forms of the model drug, I used different organic solvents of analytical grade.

After crystallization of the model drug in the pure solvents, the same method was repeated in the presence of SEs (Mitsubishi-Kagaku Foods Corporation, Japan) with low (S 370 and L 595) or high HLB values (S 1570, O 1570 and D 1216).

3.2. Sample preparation

Preparation of polymorphs by crystallization

Different techniques were used for the preparation of the polymorphs (**Table 1**). **Crystallization by shock cooling**: ~ 100 mg of the raw material was dissolved at the boiling point of the solvent to give a saturated solution which was then diluted with a small amount of the solvent. The hot solution was filtered by a "Canula 10 μm" filter into a vial immersed into crashed ice.

Crystallization by slow cooling: The same process of dissolution was used, but the filtered, hot solution was cooled down slowly (- 3 °C/h).

Crystallization by slow evaporation: The products were the dried residues of the clear filtrates of the samples prepared by shock cooling.

Preparation of polymorphs by heating transformation

Two of the former drug candidate's polymorphs (Form II and IVb) could be generated by heating processes at various temperatures for different periods of time from the polymorphs generated by crystallization. When Form I was heated on 160 °C during 6 hours, it transformed to Form II. In case of Form IVb the same process was applied on Form IVa, but on higher temperature (205 °C).

Table 1 The techniques used for the preparation of the polymorphs

Form	Method	Solvent	Circumstances
I	crystallization	96 %, abs. ethanol	shock cooling
II	heating	-	160 °C/6 h (from Form I)
III	crystallization	isopropanol, 2–butanone, butylacetate, ethylacetate, toluene	shock cooling
IVa	crystallization	methanol	shock cooling
IVb	heating	-	205 °C/6 h (from Form IVa)
V	crystallization	chloroform	shock cooling, slow cooling, slow evaporation
VI	crystallization	acetone, methanol, dichlormethane, 1,4–dioxane	shock cooling, slow cooling, slow evaporation
VII	crystallization	acetonitrile	shock cooling

Preparation of polymorphs by crystallization in the presence of sucrose esters

After the differentiation of the polymorphic forms by means of analytical examinations, the single-solvent recrystallizations were repeated in the presence of one or other SE. The different SEs were chosen on the basis of their HLB values (**Table 2**).

Table 2 SEs and solvents used during the additive-induced crystallizations

SE	Solvent	HLB	API:SE mass ratios
S 370	chloroform, dichloromethane	3	1:1
S 1570	chloroform	15	1:1
O 1570*	96%, abs. ethanol, butyl acetate, methanol, chloroform, dichloromethane, 2-butanone, isopropanol	15	1:1, 1:2, 1:4, 2:1, 4:1
L 595*	96%, abs. ethanol, butyl acetate, methanol, chloroform, dichloromethane, 2-butanone, isopropanol, ethylacetate, toluene, acetone	5	1:1, 1:2, 1:4, 2:1, 4:1
D 1216	96%, abs. ethanol, 2-butanone, isopropanol, methanol, chloroform, acetone	16	1:1

* In the cases of the SEs O 1570 and L 595, which had polymorph-changing effects, and additional ratios were also tested.

3.3. Polymorph investigation methods

The particle size distribution of the drug candidate was investigated by **light microscopy** using a LEICA Image Processing and Analysis System (LEICA Q500MC, LEICA Cambridge Ltd., Cambridge, United Kingdom).

The morphology of the particles was examined by **SEM** (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan) having a magnification of 1000x. A sputter coating apparatus (Bio-Rad SC 502, VG Microtech, Uckfield, United Kingdom) was applied to induce electric conductivity on the surface of the samples. The air pressure was 1.3-13.0 mPa.

Raman spectra were recorded at room temperature by using a Bruker SENTERRA Dispersive Raman Microscope (Bruker Optik GmbH, Ettlingen, Germany) equipped with Nd-YAG (532 nm) and diode (785 nm) excitation lasers and a cooled CCD detector.

XRPD spectra were recorded with a BRUKER D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) system with Cu Kα1 radiation (λ = 1.5406 Å) over the interval 2.5-40 °/2θ.

DSC curves were obtained by a Mettler Toledo DSC27HP apparatus (Mettler-Toledo AG, Greifensee, Switzerland) using a heating rate of 10 °C/min from 25 °C up to 250 °C.

Dissolution rate was also studied by a modified paddle dissolution apparatus (Pharmatest, Hainburg, Germany). An appropriate dissolution medium had to be developed, because of the poor solubility of the model drug. The concentration of each polymorph solution was determined spectrophotometrically at 324 nm (Unicam UV/vis spectrophotometer, Unicam Limited, Cambridge, United Kingdom).

3.4 Relative stability examination of the polymorphs

Slurry conversion method

An automatic laboratory reactor system (Avantium Crystal 16, Amsterdam, The Netherlands) was used to investigate the relative stabilities of the different polymorphs in suspension. The different polymorphs were stirring in suspension in 96 % ethanol and in silicone oil. The polymorphs were examined for a maximum of 130 days at room temperature, 50 or 70 °C (in the case of ethanol) or at 200 °C (in case of silicone oil). Samples of the suspensions were taken out from time to time and the crystals obtained were measured by XRPD.

Variable humidity and temperature X-ray powder diffractometry

VH/VT-XRPD patterns were recorded with a Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) system with Cu Kα1 radiation (λ = 1.5406 Å) in the interval 2.5-40 °/2θ. The diffractometer was equipped with a hot-humidity chamber (MRI Physikalische Geräte GmbH, Karlsruhe, Germany) controlled by an Ansyco Sycos H-Hot (Analytische Systeme und Componenten GmbH, Karlsruhe, Germany) and a Våntec 1 line detector (Bruker AXS GmbH, Karlsruhe, Germany), which indicated the phase transitions of the polymorphs directly in the diffractometer chamber. The parameters of the VH-XRPD investigations: humidity between 20 and 80 RH% in 10 RH% increments, and repeated measurement at 20 RH%. The temperature was 30 °C. The VT XRPD studies were carried out between 30 and 230 °C, in increments of 5 °C. After the series of measurements, the samples were cooled back to 30 °C and measurements were repeated immediately after cooling and one day later.

Differential scanning calorimetry

The DSC analysis was carried out with a Mettler Toledo STARe thermal analysis system, version 9.30 DSC 821e (Mettler-Toledo AG, Greifensee, Switzerland), at a linear heating rate of 1, 10 or 30 °C min^{-1}. The examinations were performed in the temperature interval 25-250 °C. The MTDSC parameters were as follows: temperature interval: 25-250 °C; heating rate: 10 °C min^{-1}; amplitude: 0.5 or 1 °C; period: 0.5 or 1 min.

4. RESULTS

4.1. Characterization of the polymorphs

Light microscopy

Most of the particles had sizes in the range 10-25 μm. The smallest particles were those of Form IVa, and the largest were those of Form VI. Form I and II gave very similar average results. Form V exhibited the smallest roundness value which explains the best dissolution profile. Form II and IVb were prepared by heating, transforming one polymorph into another, and there was no significant difference in particle size.

Scanning electron microscopy

The SEM pictures reveal that the crystals of the polymorphs present differences in size, morphology and surface. Form I resulted in long needle-shaped crystals. When Form I was heated to 160 °C, the transformation led to a new morphology. Form II contained prismatic crystals in size range of 25-60 μm. Form III gave mostly irregular trapezoid crystals with a smooth surface around 50 μm. Form V crystals are around 25 μm, with a nearly ditrigonal morphology. The morphology of Form IVa and Form IVb (obtained by heating of Form IVa) were very similar, involving slender ditrigonal and ditetragonal prisms. The crystals of Form IVa were smaller than those of Form IVb. The crystals of Form VI and Form VII were very irregular and varied in size.

Raman spectroscopy

The model drug contains Raman-sensitive C-O-C, C=O, C-N(-N-), methyl and carboxyl groups and cyclohexane, triazole, aromatic and indole rings. There are clear differences between the Raman spectra of the polymorphs in the ranges 3,200-2,800 cm^{-1} and in particular 1,800-900 cm^{-1} (Fig. 1). The Raman spectra of Forms I and IVb demonstrate low Raman intensities (5,000 and 900) relative to the other forms (16,000-40,000). Moreover, Form IVb exhibits an unfavourable signal-to-noise ratio and slight fluorescence behaviour.

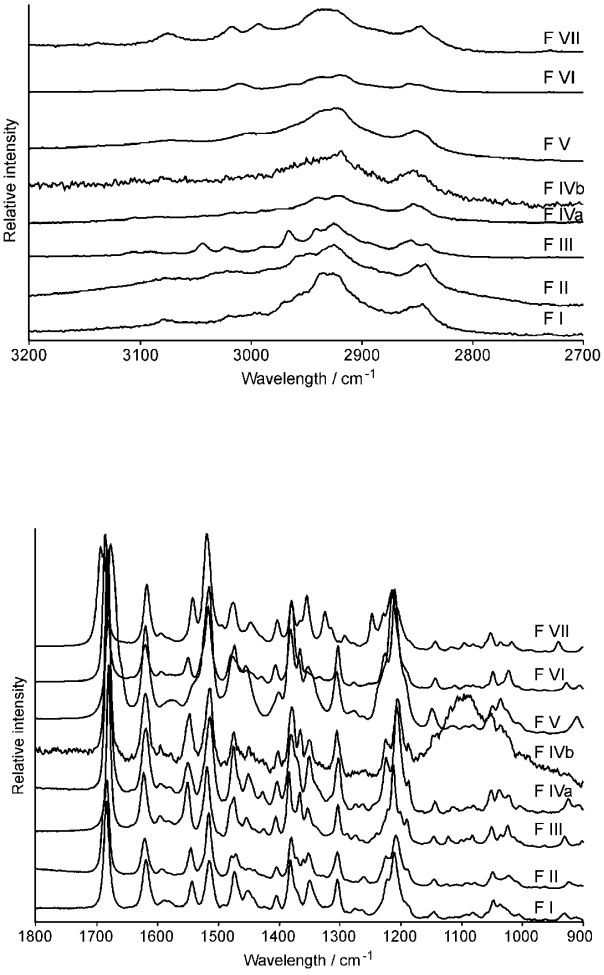

Fig. 1 Raman spectra of the eight polymorphs

X-ray powder diffractometry

The XRPD patterns of the eight polymorphs are shown in Fig. 2. The characteristic peaks are situated between 4 and 26° 2θ. All the eight polymorphs (with the exception of Forms IVa and IVb) exhibit clear XRPD differences, but these two forms can be well distinguished by other methods, though the crystal structure of Form IVa and IVb were very similar.

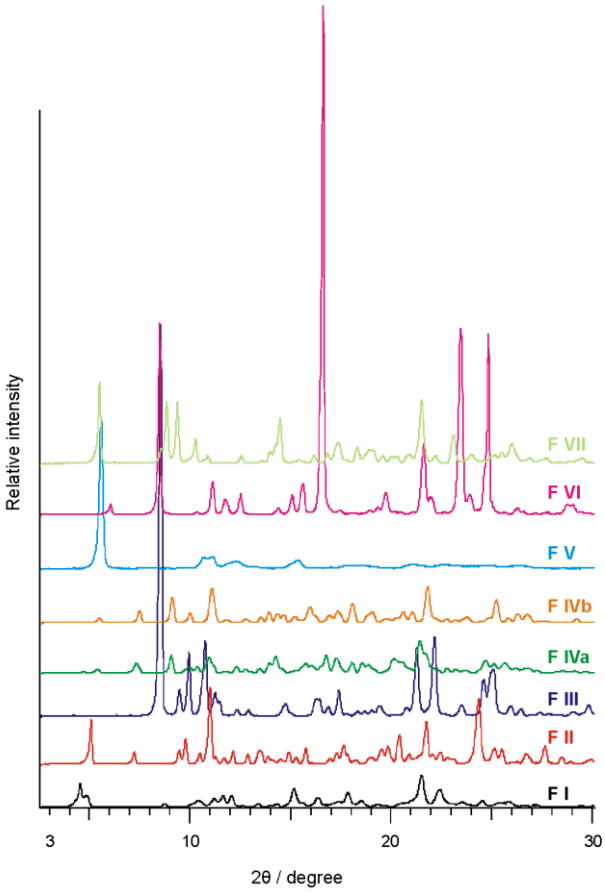

Fig. 2 The XRPD patterns of the eight polymorphs

Differential scanning calorimetry

The eight forms give different DSC patterns, except for Form I and II which display a single endothermic peak at about 232 °C (under the DSC conditions, Form I is converted to Form II). Forms III, V, VI, and VII have multiple peaks (endotherms and exotherm) which illustrate transformation by heating via melting. These four polymorphs furnish a common peak at around 232 °C which corresponds to Form II. Therefore five out of the eight polymorphs transformed to Form II by heating via melting (monotropy) or without it (enantiotropy). For Form IVa, two endothermic peaks are observed at 219 and 227 °C, whereas Form IVb gives

only one endothermic peak at 227 °C, which indicates the transformation caused by heating from Form IVa to IVb.

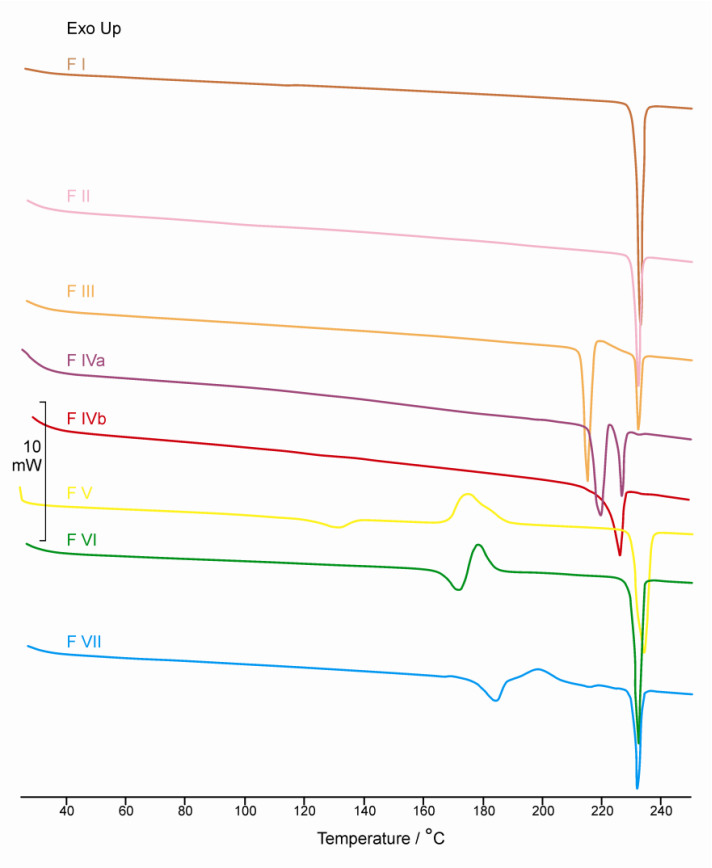

Fig. 3 The DSC curves of the eight polymorphs

Dissolution rate study

Dissolution rate study was an additional analytical investigation to distinguish the polymorphs generated. In the developped dissolution medium, the rates could be well distinguished (Fig. 4). The fastest dissolution and the largest amount of dissolved compound were seen for Form V, whereas Form III displayed the slowest dissolution, but the lowest amount dissolved belonged to Form IVa. At Forms IVa and IVb a “burst effect” was observed at the beginning of the curve. This is in connection with the small particle size of these two polymorphs.

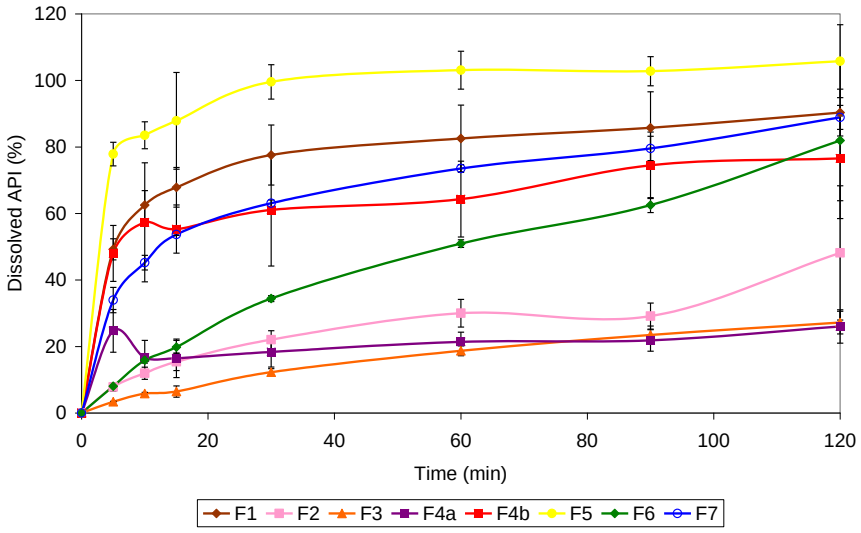

Fig. 4 The extents of dissolution of the eight polymorphs

4.2. Relative stability examinations

The relative stabilities of the polymorphs generated were investigated by three different analytical methods. All the solids could be stored without any change in morphology for at least 2 years.

Slurry conversion

When the ethanol suspensions were slurried at room temperature Forms I, V, VI and VII turned into Form III, whereas Forms II, III, IVa and IVb did not undergo any change within 130 days. At 50 °C, Form I was transformed to Form III and Form III was transformed to Form IVb. The other forms investigated (Forms II, IVa and IVb) remained unchanged during the investigation time. At 70 °C, Form I turned into Form II, Form III into Form IVb, and Form IVa into Form IVb, while Forms II and IVb did not change during the investigated period.

When the polymorphs of the model drug were slurried in silicone oil at 200 °C, only Forms I and III turned into Form II. As expected Form IVa changed into Form IVb. The other forms were not investigated. No interchange was observed between Forms II and IVb.

Variable-humidity and temperature X-ray powder diffractometry

The *in situ* VH-XRPD analyses did not revealany changes in the eight polymorphs. All of them were stable in the range 20-80 RH% and at 20 RH% in the repeated measurements.

By contrast, the in situ VT-XRPD investigations yielded interesting results as concerns the polymorph transformation screening process. The intensities of the diffraction peaks of Form I decreased continuously during heating. The transformation of Form I started at about 155 °C and was completed at about 190 °C (Fig. 5).

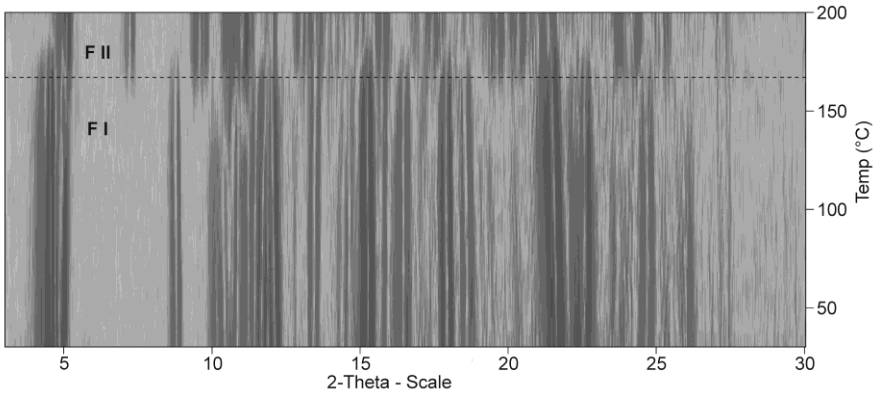

Fig. 5 2D VT-XRPD diffractogram of Form I in the interval 30-200 °C

The VT-XRPD investigation indicated that Form II was the stable one, and this was confirmed by DSC studies. The phase transition of Form III started at about 215 °C and after recooling; Form II was identified. Increase of the temperature did not cause any changes in the Form IVa and IVb polymorphs up to 225 °C, but after cooling back to 30 °C the samples became amorphous. The heating of Form V resulted the appearance of a new form (Intermediate I) at about 150 °C, differed from that of any other polymorph. During further heating of the material, a phase transition process started at about 190 °C, resulting in a second new form (Intermediate II), and Form II finally crystallized (Figs 6).

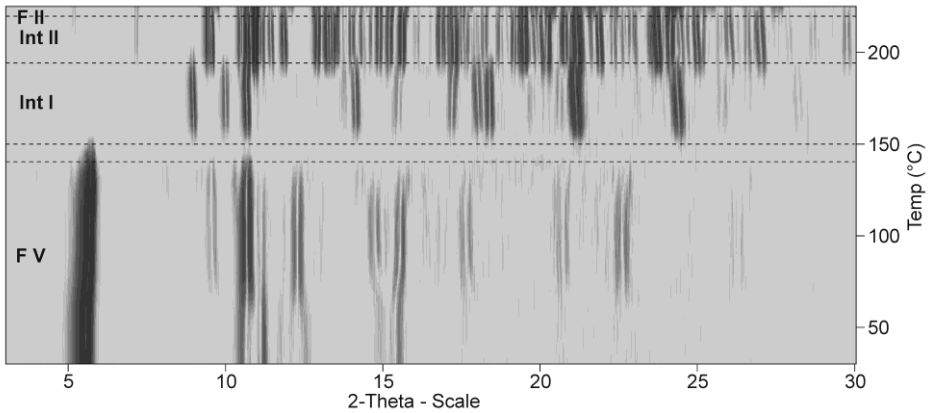

Fig. 6 2D VT-XRPD diffractogram of Form V in the interval 30-230 °C

During the heating of Form VI, two phase-transition processes were detected (Intermediate I, and Form II). Finally, similarly to Form I, Form VII was transformed to Form II.
Intermediates I and II could not be prepared in this investigation: although the heating was stopped at the given temperature, the transformation process continued. These two forms are unstable forms; all attempts to isolate them resulted in the stable Form II.

Differential scanning calorimetry

DSC investigations of all the polymorphic forms were performed at several heating rates. The results confirmed the findings of the XRPD investigations. The DSC studies carried out at different heating rates led to different results. Both the low (1 °C min^{-1}) and the high (30 °C min^{-1}) heating rate studies provided additional information on the phase-transition processes.

The two intermediate forms of Form V were also seen in the DSC curve, but only at higher heating rate (Fig. 7).

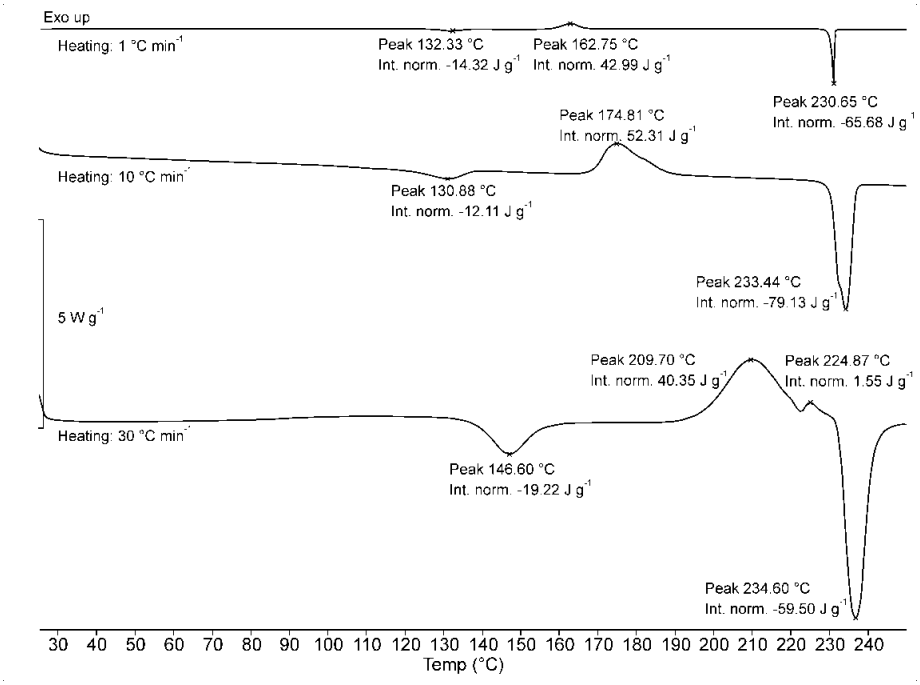

Fig. 7 DSC curves of Form V at different heating rates

The phase-transition process of Form VI could be also detected in the DSC curve at a heating rate of 10 °C min^{-1}. The endothermic and exothermic pair at about 178 and 186 °C corresponded to the appearance of Intermediate I.

The MTDSC investigations did not provide more information on the relative stability of the polymorphs, and these results are therefore not presented in my PhD work.

The enthalpy of the melting endotherm for Form II proved to be the highest, and that of Form V the lowest.

4.3. The influence of sucrose esters on the polymorphism of the model drug

In the first five samples evaluated, the ratio of the model drug and the SE was 1:1. In each case, XRPD was used to identify the forms and to compare the samples containing SE with the pure polymorphs. Two SEs, sucrose laurate L 595 (HLB 5) and sucrose oleate O 1570 (HLB 15), were found to modify the original Form IVa to Form III (Fig. 8). The other three selected SEs (S 370, S 1570 and D 1216) did not affect the polymorphism.

In the second step, the influence of L 595 and O 1570 on the polymorphism was examined at four other concentration ratios. Both SEs gave the same results: the transformation of Form IVa to Form III occurred except when the quantity of the SE was 4 times that of the model drug in the sample. In that case, no characteristic peaks were seen in the X-ray powder diffractograms, which can be explained by the crystallization-inhibiting property of these SEs.

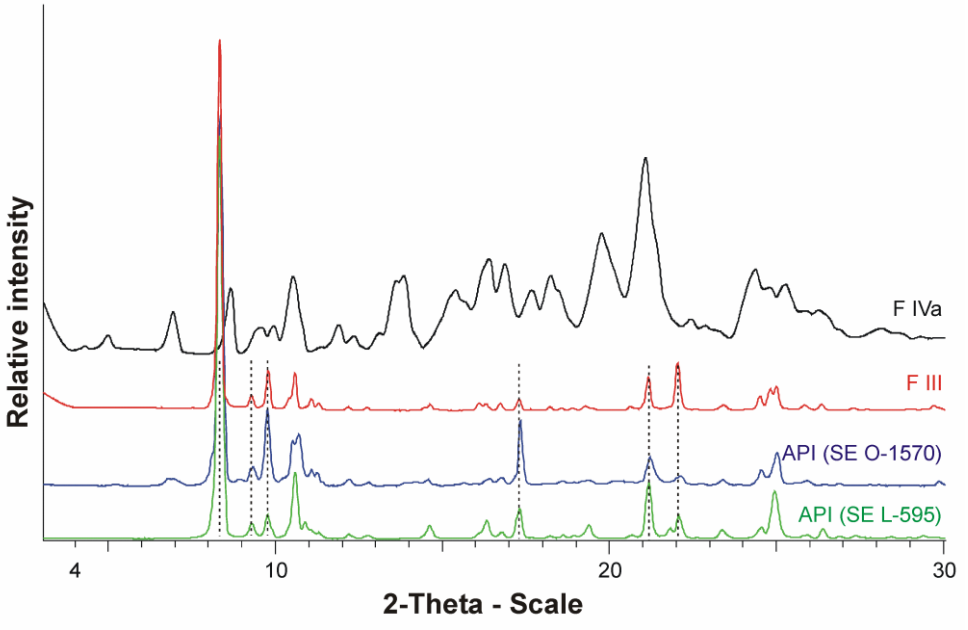

Fig. 8 The XRPD patterns of the samples crystallized in the presence of SE O-1570 or L-595 compared with the original Forms III and IVa

5. SUMMARY

The main aim of my Ph.D. work was to develop a polymorph screening method on a model drug and to investigate the influence of different SEs during the crystallization process.

A. Preparation and identification of polymorphs

A failed drug candidate obtained from Sanofi Pharmaceutical Company (Hungary) was investigated to explore its polymorphism by means of analytical examinations. The primary objective was to develop a polymorph screening method. Through crystallization and transformation methods, eight polymorphs were obtained and were characterized by light microscopy, SEM, XRPD, DSC and Raman spectroscopy. The different polymorphs exhibit different solubilities, which affects the bioavailability of the drug, and it is therefore important to perform dissolution studies with the different polymorphs. Because of the poor water-solubility of the model drug, a special dissolution medium was developed in which the eight pure polymorphs could be well distinguished.

XRPD is always the definitive method for the identification of polymorphs, but in some cases (Forms IVa and IVb) other analytical examinations were also required to characterize the individual forms.

B. Analysis of the polymorph changes

After the preparation and structural characterization of the polymorphs, their relative stabilities were also studied by an isothermal suspension equilibration method, VH-XRPD, VT-XRPD and DSC.

For the isothermal suspension equilibration study the Avantium Crystal 16 automatic laboratory reactor system was complemented with XRPD to identify the morphologies. Its main advantage that the effects of solvent- and temperature-mediated polymorphic transformations can be investigated.

In DSC tests, the application of different heating rates is recommended in order to obtain appropriate information relating to the details of phase-transformation processes. The literature findings indicate that the use of MTDSC may also give additional data, but in our case it did not provide more information.

The model drug was not sensitive to humidity, and variation of the relative humidity therefore had no influence on the polymorphic transformations.

The in situ VT-XRPD investigations yielded new routes in the polymorph transformation screening process. Two new unstable intermediate forms appeared during the heating of Forms V and VI, though they could not be prepared by crystallization. Overall, it may be noted that VT-XRPD is a very useful in situ technique for the analysis of phase-transition processes. The results of the relative stability studies are presented in a flowchart (Fig. 9).

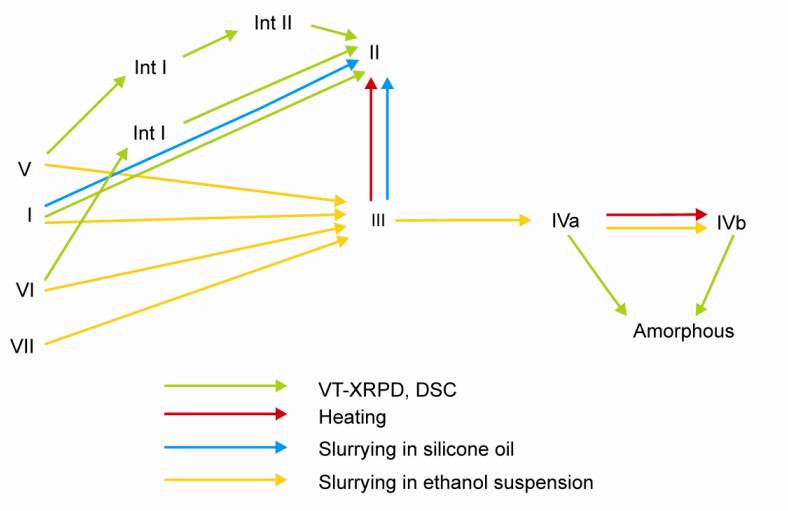

Fig. 9 Flowchart of phase-transition processes

C. The influence of SEs on polymorphism

Finally, different SEs were studied from the aspect of their HLB values during the crystallization of the polymorphs to demonstrate their polymorph-changing effects. Two of the SEs used modified the original polymorphic form, and this modifying effect was demonstrated at different concentrations. This property of the SEs does not depend on the HLB value.

6. PRACTICAL RELEVANCE OF THE RESULTS

The results presented in this thesis furnish information that can be utilized in the polymorph screening of drug candidates and generic APIs. During the development of pharmaceuticals, it is essential to investigate polymorphism for both economic and therapeutic reasons. The accurate establishment of thermodynamic stability relations is also very important, because unexpected polymorphs can appear. VT-XRPD can be a very useful technique for such stability studies.

In the course of the polymorph screening process, it is not sufficient to use only conventional crystallization methods, where the solvent and the temperature affect the formation of the crystals. The effects of the different additives used during the pharmaceutical production, and especially the surfactants, such as the SEs, must also be considered. The use of SEs in the pharmaceutical industry is increasing, because of their advantageous properties, such as solubility enhancement or emulsification. As this Ph.D. work reveals, these commonly used additives can influence polymorphic phase-transformations, which can lead to undesirable changes in the product.

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

1. Szűts, A.; **Láng, P.**; Ambrus, R.; Kiss, L.; Deli, M. A.; Szabó-Révész, P.: Applicability of sucrose laurate as surfactant in solid dispersions prepared by melt technology

Int. J. Pharm., 410 (2011) 107-110.

IF: 3.650

2. **Láng, P.**; Kiss, V.; Ambrus, R.; Farkas, G.; Szabó-Révész, P.; Aigner, Z.; Várkonyi, E.: Polymorph screening of an active material

J. Pharm. Biomed. Anal., 84 (2013) 177–183.

IF: 2.979

3. **Láng, P.**; Várkonyi, E.; Ulrich, J.; Szabó-Révész, P.; Aigner, Z.: Analysis of the polymorph changes of a drug candidate

J. Pharm. Biomed. Anal., 102 (2015) 229-235.

IF: 2.979 (2014)

PRESENTATIONS RELATED TO THE SUBJECT OF THE THESIS

Oral presentations

1. **Láng, P.**; Kiss, V.; Szabó-Révész, P.; Aigner, Z., Várkonyi, E., Potenciális farmakon-jelölt polimorfia szűrése:

MKE Kristályosítási és Gyógyszerformulálási Szakosztály Kerekasztal Konferenciája, Balatonszemes, 26-28. October 2012.

2. Aigner, Z., **Láng, P.**; Szabó-Révész, P.; Várkonyi, E.: Polimorf származékok relatív stabilitás vizsgálata különböző fűtési sebességű DSC és hőmérséklet + páratartalom beállítására alkalmas porröntgen berendezéssel, MKE Kristályosítási és Gyógyszerformulálási Szakosztály Kerekasztal Konferenciája, Balatonszemes, 26-28. October 2012.

3. **Láng, P.**; Várkonyi, E.; Ulrich, J.; Szabó-Révész, P.; Aigner, Z.: Hatóanyag-jelölt polimorf módosulatainak vizsgálata, MKE Termoanalitikai Szakcsoport Termoanalitikai Szemináriuma, Szeged, 21. November 2014.

Poster presentations

1. **Láng, P.**; Kiss, V.; Ambrus, R.; Farkas, G.; Szabó-Révész, P.; Aigner, Z.; Várkonyi, E., Screening of polymorph forms of a former drug candidate: 8th Word Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Istanbul, Turkey, 19-22. March 2012., Solid State Characterisation /P-184/

2. **Láng, P.**; Várkonyi, E.; Szabó-Révész, P.; Aigner, Z.: Relative stability of a former-drug candidate's polymorphs, 9th Word Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, Portugal, 31 March-3 April 2014., Starting materials /P-254/