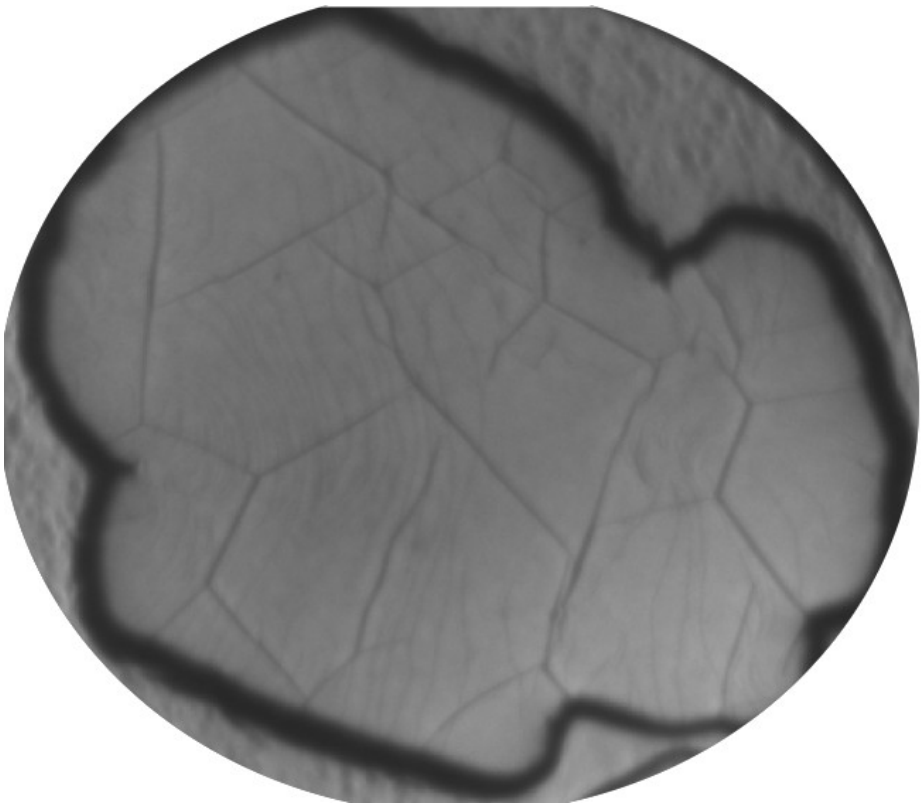
FACET

Informatieblad van de NVKG

dutch association for crystal growth
DACG
nederlandse vereniging voor kristalgroei

26 oktober 2009
nummer 2



FACET

informatieblad van
de NVKG, sectie van
de KNCV en de NNV

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Omslagfoto/Cover

Een Lage Energie Electronenmicroscopie (LEEM) opname van een grafeen kristal dat gegroeid is op een Ir(111) oppervlak. Het grafeenlaagje is 1 atoomlaag dun en wordt alom gezien als toekomstig materiaal voor het fabriceren van electronische schakelingen met verbeterde eigenschappen t.o.v. Si. In het kristal is een lijnstructuur zichtbaar. Deels zijn dit atomaire stapranden van het onderliggende substraat die door het grafeen heen zichtbaar zijn. Duidelijker zijn een aantal dikke lijnen te zien op het grafeen. Dit zijn kreukels die ontstaan zijn t.g.v. spanning die ontstaat na het afkoelen van het grafeen van de groeitemperatuur naar kamertemperatuur.

De figuur is aangeleverd door Raoul van Gastel van de Universiteit Twente.

Electronische verzending FA*C*ET

Ten behoeve van de verzending van de FA*C*ET is het van belang dat de NVKG beschikt over een geldig emailadres. Indien U deze FA*C*ET niet via de reguliere mailing aan de NVKG-leden heeft ontvangen, vragen wij U om aan de redactie van de FA*C*ET een geldig emailadres door te geven, danwel kenbaar te maken of U de FA*C*ET in papieren vorm wilt blijven ontvangen.
De FA*C*ET verschijnt uiteraard ook nog altijd gelijktijdig met de emailversie op de website van de NVKG. De meest recente FA*C*ET kan daar te allen tijde uit het FA*C*ETtenarchief gedownload worden. Net zoals de vorige elektronische FA*C*ETten, bevat ook dit exemplaar weer handige, automatische links voor web en e-mail.

Redactioneel

Voor u ligt de tweede FA*C*ET van het jaar 2009 met daarin vooral aandacht voor het aanstaande jaarsymposium van de NVKG. Dit jaar zal dat gehouden worden op 13 november bij PANalytical te Almelo, waarbij de lezingen gecombineerd zullen worden met een interessant bedrijfsbezoek.

Een vast item op deze plek is de oproep voor input voor de FA*C*ET. Wat kunt u bijdragen ?

- Aankondigingen van lezingen, symposia en congressen (niet alleen de activiteiten die u zelf organiseert, maar ook activiteiten waarover u langs andere weg bent geïnformeerd)
- Verslagen van (kristalgroei)-conferenties
- Artikelen (mag ook heel kort zijn!) over een opmerkelijke ontdekking
- Advertenties: bijvoorbeeld i.v.m. vacature
- Omslagfoto's (met toelichting). Telkens zal de beste ingezonden foto op de omslag van de FA*C*ET worden afgedrukt samen met een korte toelichting aan de binnenzijde van het blad. Bovendien zullen de foto's op de fotogalerij van onze webstek worden gepost.

De drempel voor uw bijdragen is *zeer laag*: aanleveren kan per brief, fax, e-mail, of telefoon. En we staan natuurlijk open voor alle direct of indirect met de NVKG verwante onderwerpen. De volgende FA*C*ET verschijnt volgens schema begin mei 2010.

Tenslotte rest mij dan nog U aan te kondigen dat ik na vijf jaar de redactie van de FA*C*ET over ga doen aan iemand anders. Allereerst wil ik U op deze plaats bedanken voor alle feedback en kopij die ik over de jaren heb ontvangen en op heb mogen nemen in de FA*C*ET. Ten tweede wil ik U aankondigen dat bij de jaarvergadering een discussie gepland is over de vormgeving van de FA*C*ET als puur electronische nieuwsbrief van de NVKG, en die frequenter verschijnt dan de huidge twee edities per jaar. Uw input is daarbij zeer gewenst en ik hoop U dan ook 13 november te kunnen begroeten bij PANalytical te Almelo.

Raoul van Gastel

DACG Annual Symposium 2009

De aanmelding voor het najaarssymposium geschiedt via het aanmeldformulier op de website van de NVKG.

Wanneer:	13 November 2009
Waar:	PANalytical Lelyweg 1 7602 EA Almelo
Thema:	X-ray diffraction in crystal growth
Organizatoren:	Hans te Nijenhuis and Raoul van Gastel

Programma

10.00 Coffee

10.30 Welcome
Hans te Nijenhuis (PANalytical)

10.45 Growth of millimeter-sized graphene flakes of a single orientation visualized with slow electrons
Raoul van Gastel (UT)

11.20 Surface microscopy
Speaker to be announced (UL)

11.55 Pulsed laser deposition of perovskites: in-situ XRD studies
Paul Tinnemans (RU)

12.30 lunch

13.00 DACG Annual Meeting

13.30 Visit to the application laboratories and production facilities
Hans te Nijenhuis (PANalytical)

14.30 Thin film crystal growth of $KY(WO_4)_2$
Shanmugan Aravazhi (UT)

14.45 Pair distribution function analysis of nanocrystalline, and amorphous organic and inorganic compounds using high-energy X-rays
Milen Gateshki (PANalytical)

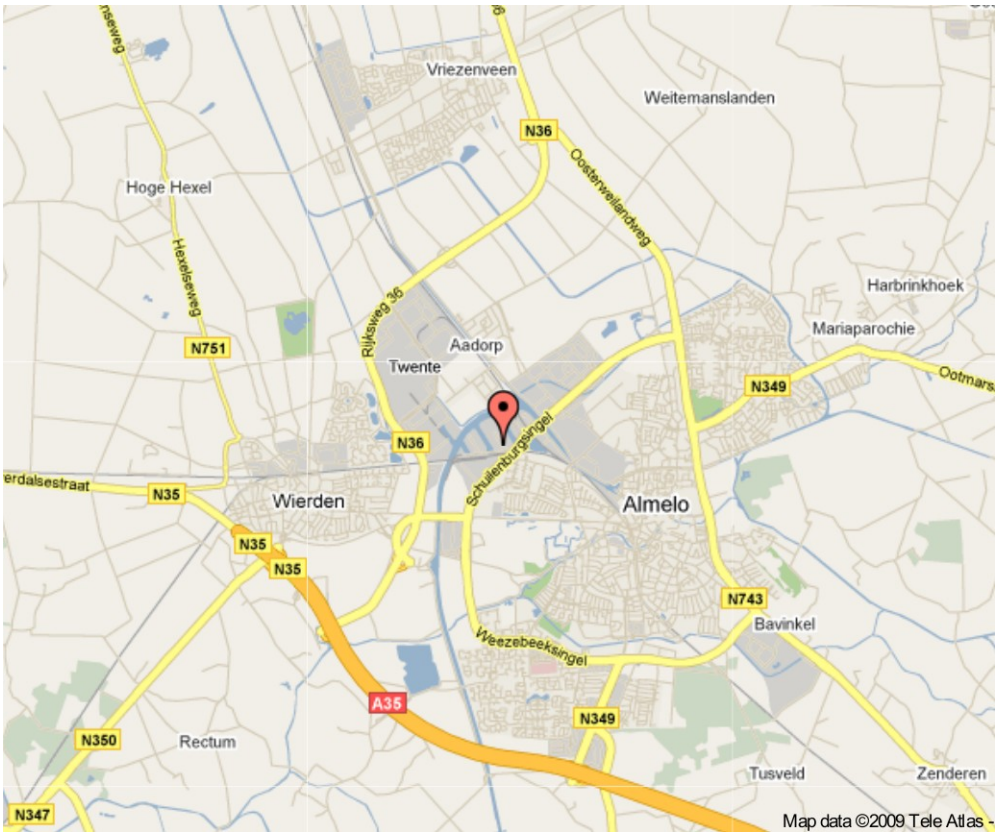
15.20 Crystallization of nanocrystal solids. Insights from molecular simulations.
Philipp Schapotshnikow (TUD)

15.55 X-ray diffraction analysis for the study of crystallization processes
Detlef Beckers (PANalytical)

16.30 Closing/borrel

Route to PANalytical

Het symposium wordt gehouden bij de vestiging van PANalytical te Almelo aan de Lelyweg 1 in het havengebied langs het Twentekanaal, zie het onderstaande kaartje.



Op de website van PANalytical is een applicatie beschikbaar die routeinstructies genereert al naar gelang uw vertrekpunt.

Zie http://www.panalytical.com/index.cfm?pid=1050&itemid=203&contentitemid=1

Jaarverslag Nederlandse Vereniging voor Kristlagroei (NVKG) November 2008 - November 2009

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Ledenbestand:
Het ledenaantal is momenteel ongeveer 130.

Bestuur:
De taakverdeling binnen het bestuur was als volgt.

Dr. ir. J.H. ter Horst	Voorzitter
Dr. M.J. Rost	Secretaris
Dr. P. Verwer	Penningmeester
Dr. R. van Gastel	FA*C*ET en web-pagina
Dr. P. Vonk	Lid
Dr. H. Meekes	Lid
Dr. P. van Hoof	Lid

Het bestuur heeft twee maal vergaderd in het verslagjaar.
Besluitenlijsten van de bestuursvergaderingen worden gepubliceerd in de FA*C*ET.

Verenigingsblad
Het verenigingsblad FA*C*ET is, zoals gewoonlijk, twee maal per jaar verschenen. Het blad is bedoeld om de communicatie tussen onderzoekers en gebruikers van kristallisatie in Nederland te bevorderen. Het blad bevat onder meer samenvattingen van relevante proefschriften, 'mooie' plaatjes uit kristalgroeionderzoek en data van congressen en activiteiten die voor kristalgroeiers interessant zijn. Initiatieven, besluiten en plannen van de NVKG worden in de FA*C*ET gepubliceerd. De FA*C*ET wordt zoveel mogelijk elektronisch verspreid. Leden van de NVKG worden uitgenodigd kopij in te leveren.

Webpagina
Op de webpagina www.dacg.nl wordt informatie gegeven over de structuur en activiteiten van de NVKG. Verder zijn alle nummers van FA*C*ET sinds 2000 in elektronische vorm beschikbaar en worden links naar de Nederlandse onderzoeksgroepen op het gebied van kristallisatie en naar buitenlandse zustervereniging gegeven. Suggesties voor aanvullingen zijn welkom en kunnen aan Raoul van Gastel worden doorgegeven.

Jaarvergadering en excursie 2008
Deze zijn gehouden op vrijdag 14 november 2008 bij Friesland Foods in Deventer. De organisatie was in handen van Sabine Fischer van Friesland Foods en Elias Vlieg (RU Nijmegen). De jaarvergadering met ongeveer 25 deelnemers was een succes. Met lezingen van de gastsprekers Pieter Walstra van Universiteit Wageningen en Paul Smith van Cargill en een rondleiding door het lab is het een zeer interessante dag geworden.

Kristalgroeisymposium 2009
Het kristalgroeisymposium is vooral bedoeld om jonge onderzoekers kennis te laten nemen van elkaars werk. Het jaarlijkse kristalgroeisymposium is dit jaar komen te vervallen.

Jaarvergadering en excursie 2009
Deze zullen worden gehouden op vrijdag 13 november 2009 bij Panalytical in Almelo. De organisatie is in handen van Hans te Nijenhuis van Panalytical en Raoul van Gastel (Universiteit Twente). Het programma zal onder meer de rol van X-ray diffractie in kristallisatieonderzoek belichten.

KNCV/NVKG Kristalgroeiprijs 2007 en 2010
De kristalgroeiprijs wordt eens per twee jaar uitgereikt. De prijs wordt gesponsord door de KNCV. De prijs wordt tijdens de jaarvergadering uitgereikt aan een jonge onderzoeker voor hoogstaand wetenschappelijk onderzoek op het gebied van de kristalgroei. De KNCV/NVKG kristalgroeiprijs 2007 is gewonnen door Yohana Perez de Diego voor haar proefschrift "Production of controlled drug

delivery microparticles using supercritical CO2". In 2010 zal er weer een Kristalgroeiprijs worden uitgereikt.

Ondersteunende activiteiten
De NVKG stimuleert dat voor kristalgroei belangrijke congressen in en/of mede door Nederland georganiseerd worden. Daartoe geeft het bestuur advies en ondersteuning aan leden die bij de organisatie van evenementen als BIWIC, JANE en andere kristalgroeimeetings betrokken zijn. De NVKG is aangesloten bij de internationale kristalgroeiorganisatie IOCG. Veel leden bezoeken de driejaarlijkse ISSCG zomerscholen en ICCG congressen.
Een aantal bestuursleden was direct betrokken bij de organisatie van het grote internationale industriële kristallisatiecongres ISIC 2008. Het bestuur heeft morele en financiële steun gegeven. Hiertoe is de Stichting ter bevordering van de Kristalgroeicongressen gereactiveerd.
Verder geeft de NVKG soms bescheiden financiële ondersteuning aan wetenschappelijke symposia en andere activiteiten die van belang zijn voor de kristalgroeiwetenschap.
Het bestuur werkt aan de instelling van een kristalgroeiwedstrijd voor middelbare scholieren. In België is een dergelijk initiatief een groot succes gebleken. De KNCV heeft belangstelling getoond om bij de organisatie betrokken te worden.

Agenda jaarvergadering NVKG

Te houden op 13 november 2009 (PANalytical, Almelo)

1. Opening
2. Vaststelling agenda
3. Ingekomen stukken
4. Notulen jaarvergadering 2008
5. Jaarverslag 2008/2009
6. Financieel Jaarverslag 2008
7. Mededelingen bestuur
8. Activiteiten 2009:

    Kristalgroeisymposium 2010
    DACG Annual meeting 2010

9. Bestuurssamenstelling en verkiezing nieuwe kascommissieleden

    Aftredend en niet herkiesbaar zijn:
    Raoul van Gastel (FA*C*ET)
    Paul Verwer (Penningmeester)

    Functiewissel wordt door het bestuur voorgesteld voor:

    Arie van Houselt (FA*C*ET)
    Menno Deij (Penningmeester)

10. Vormgeving FA*C*ET
11. Rondvraag
12. Sluiting

Crystallization lectures by Dimo Kashchiev and Roger Davey

Monday, November 2, 2009
Crystal Nucleation
Rudolf Diesel Room
Process & Energy
3mE, TU Delft
Leeghwaterstraat 44
2628 CA Delft

14:00 hr Nucleation rate of crystals and crystalline monolayers
Prof. Dimo Kashchiev
Bulgarian Academy of Sciences

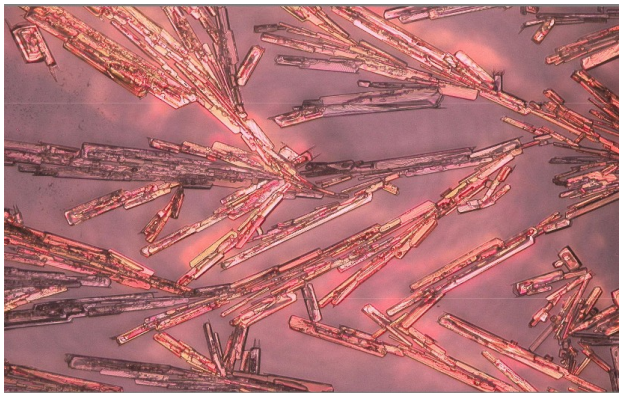
15:00 hr Nucleation, solution chemistry and polymorphs
Prof. Roger Davey
University of Manchester

Please register by sending an email to Joop ter Horst: J.H.terHorst@tudelft.nl

Recente proefschriften

Dr. Shanfeng Jiang
"Crystallization Kinetics in Polymorphic Organic Compounds"
Promotor: prof.dr.ir. P.J. Jansens
Co-promotor: dr.ir. J.H. ter Horst

Summary
Polymorphism is frequently encountered in many pharmaceutical, chemical, and food products. Polymorphs have the same chemical composition but different crystal structures, and therefore differ in their physicochemical properties such as stability, solubility, and bioavailability. These property differences can influence the product performance. Thus, the production of specific and well-defined polymorphs is crucial, especially in the pharmaceutical industry. This thesis focuses on how to establish control over the polymorph formation. Crystallization kinetics, especially nucleation kinetics and thermodynamics, were studied to improve the understanding of polymorphic crystallization behavior. Using the improved fundamental understanding, control over the polymorphism of model organic compounds has been successfully established.



Dr. Natalia Panina
"Crystal Structure and Morphology Prediction of Organic Pigments"
Promotor: prof.dr. E. Vlieg
Co-promotores: dr. H. Meekes en dr. G. Deroover
Verdedigd op: 23 maart 2009

Summary
Organic pigments are coloured organic compounds that are used in the form of

insoluble powders in colouring of textile, paper, plastic and other materials, as well as in coatings. Colour is the most important characteristic of a pigment and depends strongly on the structure and morphology of the crystalline particles. The research presented in this thesis focuses on these two characteristics of organic pigment crystals.

Organic pigments, generally, have a very low solubility. This is one of the reasons why it is difficult to grow large enough single crystals, and consequently, it is in many cases not possible to determine the crystal structure using single crystal X-ray diffraction. Crystalline powders of pigments are also of low quality. The small particle size, and often the preferred orientation of the crystallites in the powder, result in low quality X-ray powder diffraction patterns, not suitable for structure determination. An alternative method, namely crystal structure prediction, can only be used for small molecules with few degrees of freedom and is rarely successful.

In chapter 2 the combination of crystal structure prediction and X-ray powder diffraction is presented as a powerful method, and used to predict the crystal structures of the three polymorphic forms of the organic pigment quinacridone (Pigment Violet 19). This combined method turns out to be rather successful for quinacridone, which can be explained by the rigid molecular structure and, thus, the limited degrees of freedom. The results show that all three polymorphs of quinacridone were found within the first fifteen structures ranked in energy. Since the crystal structure of the stable gamma polymorph was known, it served as a test to evaluate the quality of the prediction. The structures of the beta and alpha polymorphs were not known at the moment of the study and the predicted crystal structure of the beta polymorph was later confirmed experimentally.

After the method was shown to be successful in predicting the crystal structure of the quinacridone polymorphs in chapter 3, three more pigments from different classes, Pigment Violet 23, Pigment Red 202 and Pigment Yellow 139, were subjected to the same prediction method. This was done to evaluate its general feasibility for pigment crystal structure prediction. For Pigment Violet 23, a bright blue pigment used in inks, the method solved the previously unpublished structure. The structure of the stable beta polymorph was predicted as number one in energy ranking and has, strikingly, no hydrogen bonds present in the structure, which is very unusual for organic pigments. The crystal structure of Pigment Red 202, which is widely used for outdoor applications, was predicted as number two in the ranking. Pigment Red 202 is a substituted quinacridone, and its structural features resemble largely the structure of its unsubstituted analogue quinacridone. Finally, for Pigment Yellow 139, a pigment with an unknown crystal structure, number one in the ranking fitted best, having an unusually high symmetry space group Cmca. The structure was shown to consist of layers of strongly bonded molecules with a dense hydrogen bond network.

In chapter 4 a study on the crystal morphology of the blue pigments copper and metal-free phthalocyanine is presented. Both phthalocyanine pigments can be grown by sublimation at about 500C as long dark blue needles with a violet shine. The crystal morphology was indexed using optical goniometry. The crystals have a large flat basal face and several small side faces. The basal face was also investigated using Atomic Force Microscopy which revealed growth spirals on some of the crystals. Such long, thin anisotropic morphologies are usually not predicted well by conventional morphology prediction methods like the attachment energy method. Therefore, more sophisticated methods - kinetic Monte Carlo simulations and a step energy approach - were used to explain the crystal morphology of phthalocyanines. The results show that the time consuming kinetic Monte Carlo simulations, which simulate the growth of crystal faces for chosen driving force and temperature, lead to the most accurate prediction of the morphology. The calculations based on the step energies of the crystal faces, was shown to give reasonable results in a much shorter time.

Chapter 5 deals with polymorphism of quinacridone. In earlier crystal growth experiments the polymorph stability and nucleation order were not fully understood. The prediction of the crystal structures of three polymorphs of quinacridone in chapter 1 made it possible to investigate the nucleation

behaviour of the polymorphs in a simulation study. For that, three-dimensional kinetic Monte Carlo simulations were conducted on the crystal structures of the three quinacridone polymorphs. The growth probability of three-dimensional molecular clusters at different driving forces and temperatures was determined. The gamma polymorph was found to be the most stable form, followed by the beta and alpha polymorphs. This stability order was confirmed by slurry experiments. In the simulations it was found that at high driving forces the beta polymorph has a lower surface energy, which results in a higher growth probability compared to the other polymorphs. This explains why only the beta polymorph was formed during sublimation, as in such experiments the driving force is very high. Furthermore, Ostwald's rule of stages was reversed by applying continuous grinding of the crystals in solution. In this way it was possible to obtain crystals of the metastable polymorph, starting from the stable gamma-form.

Chapter 6 deals with the crystal morphology of the three polymorphs of quinacridone and its three derivatives - Pigment Red 122, Pigment Red 202 and Pigment Red 209. The crystal structures of these pigments have several common features and were expected to show similar morphologies. The crystals were grown from the vapour and from solution. Solution experiments were performed by choosing a suitable solvent from the class of ionic liquids which turned out to enable the dissolution of the pigment in an amount sufficient for crystal growth experiments. The grown crystals had a very thin platelet morphology. Morphology prediction with the conventional attachment energy method did not succeed in reproducing the large anisotropy of the morphology. Therefore, the kinetic Monte Carlo and step energy methods used in chapter 4 were applied, giving much better results. The morphology of unsubstituted quinacridone was, however, found to be complicated due to twin formation.

Chapter 7 describes the growth spirals observed using Atomic Force Microscopy on the largest face of the needle crystals of metal-free phthalocyanine. The spirals were analysed and compared with kinetic Monte Carlo simulations and a step energy analysis. A model describing an anisotropic rectangular growth spiral was proposed, relating step distances and step energies to the driving force for crystal growth. The spirals obtained using Monte Carlo simulations showed fair resemblance in anisotropy with the experimentally observed growth spirals. The model made it possible to estimate the experimental driving force which turned out to be much lower than was expected when using the Clausius-Clapeyron equation, based on the sublimation enthalpy. In case the experimental driving force is well known, the model can be used together with the step distances determined in the experiment, in order to find the anisotropy in the step energies on surfaces of anisotropic crystals.

Dr. Carmen Guguta
"Structures and conversions of pharmaceutical compounds"
Promotor: prof.dr. E. Vlieg
Co-promotor: dr. R. de Gelder
Verdedigd op: 6 april 2009

Summary

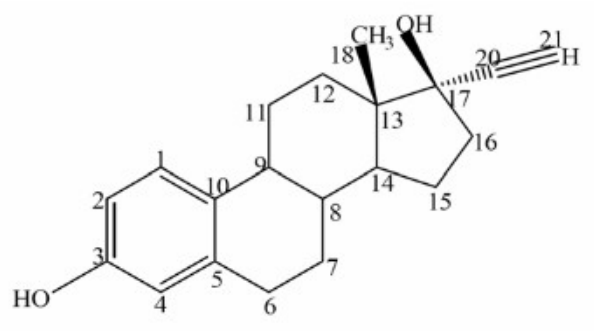
Pharmaceutical compounds have the tendency to crystallize in various polymorphs, solvates or hydrates as a function of the crystallization medium, temperature and humidity. This can cause many practical problems, including changes in stability, dissolution rates, bioavailability, morphology, vapor pressure, and packaging: the key factors to the development of appropriate dosage forms. Therefore, understanding polymorphism and solvate or hydrate formation at the molecular level is of particular interest. It critically depends, however, on the availability of powerful structure elucidation methods and other methods for solid-state analysis.

This thesis presents a new strategy for crystal structure determination from powder diffraction data that circumvents the difficulties associated with separate indexing, one of the major bottlenecks in the powder method. Moreover, this thesis deals also with application of different solid-state techniques in combination with crystal structure determination for the study of solvate and

hydrate formation of pharmaceutical compounds and excipients.

Chapter 2 and 3 deal with aspartame, a sweetener and excipient in drug formulation. The crystal structure of aspartame anhydrate was determined successfully by collecting X-ray powder diffraction data. Comparison of the structures of the hydrates and the anhydrate reveals a remarkable similarity between the structures of IA and IB on the one hand and between IIA and IIB on the other hand. Minimization experiments suggest that another hemi-hydrate polymorph exists and that the ordering of the water molecules inside the channels is an essential step in the dehydration mechanism of the hemi-hydrate. The hydration/dehydration behavior of aspartame was investigated using hothumidity stage X-ray powder diffraction (XRPD) and molecular mechanics modeling in combination with differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The results are compared to earlier studies on aspartame as described in literature. It is shown that earlier transition studies were hampered by incomplete conversions and wrong assignment of the forms. The combination of the techniques applied in this study now shows consistent results for aspartame and yields a clear conversion scheme for the hydration/dehydration behavior of the four forms. The systematic study on aspartame as presented in this thesis may be of importance for a further understanding of the formation of hydrates and shows that the availability of crystal structures together with analytical data provides a detailed insight into the hydration/dehydration behavior of compounds.

Chapter 4 presents the crystal structures of four new ethinyl estradiol solvates together with a structural study of H-bond formation and isostructurality. The characteristic H-bonds formed by the ethinyl estradiol pseudo-polymorphs are between the –OH groups attached to C(3) and/or C(17) and the corresponding solvent molecules, as well as hydrogen bonds between different ethinyl estradiol molecules, namely between the –OH groups attached to C(3) and those attached to C(17).



The molecular structure of ethinyl estradiol

Ethinyl estradiol forms pseudo-polymorphs mainly with solvents having Hbond accepting or both accepting and donating propensity and shows a remarkable flexibility in forming distinctly different hydrogen-bonding patterns, resulting in a diverse set of solvate structures. A high degree of similarity can be observed between the crystal packing of the nitromethane and dioxane solvates, forming isostructural sheets of ethinyl estradiol molecules arranged parallel in a head-to-tail fashion.

In Chapter 5 the crystal structures of naloxone monohydrate and four new anhydrate forms of morphine, naloxone, and their hydrochloride salts, all determined from X-ray powder diffraction data, are presented. These new structures, together with already known structures from the Cambridge Structural Database, enabled us to investigate the influence of the subtle molecular differences between these agonist and antagonist, the role of water and the effect of the chloride counter-ion on structural properties of morphine and naloxone in the solid state. The results suggest that the introduction of water or counter-ions like chlorine generate structures with higher ensional hydrogen bonding networks than the corresponding anhydrate or free base structures. The counter ion Cl- takes over the role of the water molecules in the anhydrates forming H-bonds with the N atom as well. When water molecules are present, Cl- prefers the water molecules instead of the N atom. If water molecules and the counter ion are not present, intermolecular H-bonds are formed between different -OH groups. The allylic group of the naloxone molecule takes over the role of the counter ion Cl- only in its absence. Further more, the N atom can act as a H-bond donor as well as an acceptor.

Chapter 6 deals with two antagonists, naloxone and naltrexone, chemically and structurally related. All known hydrate and anhydrate forms of naltrexone and naloxone hydrochloride crystallize in the orthorhombic space group P212121, although the crystal packings show clear differences. Dehydration causes in both cases no breaking of the symmetry but the change in unit cell is for naltrexone profoundly different from naloxone. Dehydration of naltrexone hydrochloride tetra-hydrate takes place with shrinkage of the volume of the unit cell, while dehydration of naloxone hydrochloride di-hydrate results in an expansion of the unit cell. The H-bonding patterns corresponding to the two antagonists seem to be footprints for the crystal structures and also for their hydration/dehydration behavior. Despite naltrexone and naloxone hydrochloride are chemically and structurally related and show similarities in their biological behavior, the overall hydration and dehydration process is fundamentally different.
In Chapter 7 a new methodology for structure determination is proposed for non-indexable powder patterns. FIDDLE is a method for determination of crystal structures from powder diffraction data that circumvents the difficulties associated with separate indexing. Structure determination from powder diffraction data can be seen as a process of global optimization of all model parameters, including the unit cell parameters. This strategy is applied in the FIDDLE program. For the simultaneous optimization of the parameters that describe a crystal structure a genetic algorithm together with a pattern matching technique based on auto and cross correlation functions is used. This "one-pot" strategy for indexing and structure determination, as applied in FIDDLE, was successfully used for determining the unknown crystal structures of ethinyl estradiol anhydrate, naloxone monohydrate and creatine anhydrate, cases for which indexing was problematic.

Dr. Zjak van Eupen
"Enanatiomers and polymorphism in Venlafaxine and Odansetron"
Promotor: prof.dr. E. Vlieg
Co-promotor: dr. H.L.M. Meekes
Verdedigd op: 14 oktober 2009

In this thesis different aspects of polymorphism, the ability of a substance to crystallize in more than one crystal form, are studied. Because physical properties, e.g. melting enthalpy, heat capacity, and solubility, of two polymorphs can differ, the pharmaceutical industry spends a lot of money and effort in studying the phenomenon of polymorphism, because especially the solubility difference between two polymorphs can have influence on the effectivity, the bio-availability and the safety of drugs. A lot of effort is invested to find the most stable polymorph, although one is never certain that the most stable polymorph has been found. A recent example, in which the difference in bio-availability was of importance, is ritonavir. After having been on the market for almost two years, a more stable polymorph with a lower solubility and, therefore, a lower bio-availability was found. Especially the thermodynamic aspects, that play an important role concerning polymorphism of active pharmaceutical ingredients of drugs, are studied in this thesis.
After a general introduction about the phenomenon of polymorphism, the thermodynamic theory of solubility of compounds in solvents is described, with the emphasis on compounds exhibiting polymorphism. The relation between phase diagrams and solubility is treated. Starting with simple models describing the thermodynamics of solutions, assuming no mixing between the solvent and the solute in the solid state, the large variety of possible solubility curves, describing the temperature dependent solubility, are explained. In addition, pseudo polymorphs, that is solvates, are treated. The models result in a formula which makes it possible to estimate the transition temperature for an enatiotropically related system. For this only the melting temperature and the melting enthalpy of the two polymorphs are needed. Both are simply determined using Differential Scanning Calorimetry (DSC).

In the third chapter the phase behaviour of the free base of Venlafaxine, the active ingredient of a drug used to treat stress, is described. Both the polymorphic phase diagram as well as the thermodynamic relations between the three forms are studied, using DSC, X-ray Powder Diffraction (XRPD), slurry experiments and solubility measurements. The solubility of Venlafaxine was determined in several solvents, focussing on deviations of the solubility as compared to the ideal solubility according to the van 't Hoff equation. The nature of the deviation of the solubility was such that attributing the stability regions for polymorphs I and II, on the basis of solubility data would lead to a wrong attribution of these regions. This turned out to be the result of the concave shape of the solubility curves, a form that, from a theoretical viewpoint, is described in more detail in chapter 2. The transition temperature of polymorph I and II of Venlafaxine free base was calculated using the earlier mentioned equation to estimate the transition temperature and compared with the values extracted from the solubility data. The concave shape of the solubility curves is the result of a non neglectable temperature dependence of the melting enthalpy.

In chapter 4 the remarkable behaviour of the free base of Venlafaxine with respect to polymorphism and chiral resolution is studied. Using different complementary techniques, the three forms of Venlafaxine free base were characterized. The crystals of all the three forms are composed of almost identical enantiomerically pure layers, only the stacking of the layers is different. In case of form I alternating bi-layers of R and S layers were found, while form II consisted of alternating double bi-layers of R and S enantiomers. In case of form III, the form with the highest melting point, the enantiomer separation is complete, resulting in a racemic conglomerate. The racemic conglomerate can be obtained from solution, or via a solid-solid phase transition of the lowest melting form. Remarkably, during this phase transition the shape of the crystal is conserved. It is hypothesized that, during the phase transition occurring, the chiral separation takes place via a local melting process. Locally the melting point is lower as the result of crystal defects. Because of the local melting process, molecules are able to migrate over relatively large distances between the layers in the crystal.

The results of a morphology prediction for the three forms of the free base of Venlafaxine are presented in chapter 5. Three different methods, the Bravais-Friedel-Donnay-Harker method, the attachment-energy method and a Monte Carlo growth simulation are used for that. A comparison of the predicted and the experimentally found morphologies shows that the Monte Carlo simulation gives a semi-quantitative result for form I and II. In case of form III the correct morphology was found, but some of the predicted indices did not correspond with the experimentally found indices.

In chapter 6 the polymorphic behaviour of the free base of Ondansetron is studied. For Ondansetron, an active pharmaceutical ingredient used to treat vomiting and nausea during chemotherapy, two different crystalline forms are known: ODS-1 and ODS-2. Both forms have been grown from solution. Even using different techniques; XRPD, Nuclear Magnetic Resonance (NMR), and DSC turned out to be not sufficient to determine if Ondansetron shows polymorphism or not. Using a combination of a badly resolved crystal structure of a vapour grown crystal, ODS-3, and molecular modelling, it was hypothesized that the crystal structure of ODS-3 best can be interpreted as a locally ordered solid solution of enantiomers. Because the similarities between the XRPD patterns of the three batches it was assumed that also ODS-1 and ODS-2 are locally ordered solid solutions of enantiomers. Different incorporations of enantiomers on a mesoscopic scale, in the solid state give rise to slightly different forms of Ondansetron. The amount of water present during the crystal growth induces subtle but important local order in the disorder. The results show in this case that although different ODS forms show different physical properties, one cannot speak of polymorphism.

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"Model-Based Control of Industrial Batch Crystallizers: Experiments on Enhanced Controllability by Seeding Actuation"
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The main objective of this thesis is to design, implement, and evaluate a real-time model-based control strategy for controlling the process performance in general and the product characteristics in particular in the course of a batch crystallization process.

An introduction to (batch) crystallization and challenges in control of batch crystallizers is given in **Chapter 1**. In this introductory chapter, the research problem is formulated and decomposed into smaller research questions. An approach to address the research objective is also outlined therein.

In **Chapter 2** of this work, modeling of the relations between the process inputs and the process performance measures using first principles is treated. Before both comprehensive and reduced models are presented, the importance of making a model for a particular purpose is emphasized. While a detailed rigorous model is derived to support the process controllability analysis, a reduced model is needed for on-line model-based control purposes. Model reduction possibilities are introduced and discussed. A summary of the implementation details is given as well.

Two crystallizers of different scale and type are introduced in **Chapter 3**. Each crystallizer is analyzed with respect to the actuating techniques it offers for control of the crystal properties and the product yield. A review of the available techniques for measurement of supersaturation and the CSD is given together with a brief description of each measurement method. At the end of that chapter, an industrial control system installed at the pilot facilities is presented.

The model validation is the subject of **Chapter 4**. The text presented therein expands on the adopted procedure for parameter estimation and validation of the predictive capabilities of both population balance and moment models. The chapter is concluded with a discussion on how to improve the estimate of the kinetic parameters by designing improved experiments.

A two-step controllability analysis of the studied process systems is presented in **Chapters 5 and 6**. The focus of the material in Chapter 5 is on establishing qualitative possibilities for fulfilling the selected control objectives. Preliminary control strategies are derived based on the analysis of a semi-analytical solution of the population balance model. The benefits of the identified control strategies are quantified through simulation and optimization studies whose settings and results are given in Chapter 6.

From the controllability analysis of the previous chapters, it turned out that seeding has a potential of having a larger influence on the process than other actuators. Therefore, a separate chapter was dedicated to experimental evaluation of seeding as a process actuator. The purpose of **Chapter 7** is to design an optimal seeding procedure. In addition, two control strategies outlined in Chapter 5 are explored by using various seeding techniques. The results of the experimental evaluation confirm that, for the given system, seeding is an effective method for controlling the characteristics of the end product and increasing reproducibility of batches.
A number of methods for obtaining the seed crystals were studied. A valid conclusion for each of the preparation method is that the seed preparation procedure is critical for obtaining the seed particles with desired properties. The control of the crystal properties during the seed preparation is as important as control during the seeded process itself.
Fig. 1 illustrates the dynamics of crystal size and shape during residence of seed crystals in a saturated solution of the seeding vessel prior to their introduction into the crystallizer. The following is evident from the Scanning Electron Microscope (SEM) images. The fine crystals of the original sieve fraction (Fig. 1a) dissolve in a first few minutes in a saturated solution (Fig.

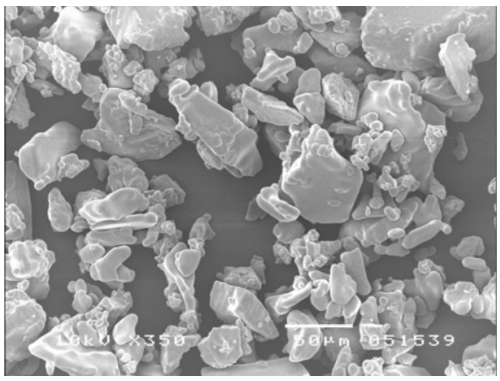
1b). Larger crystals not only grow at the expense of dissolving smaller crystals, but also fracture upon collisions with the stirrer of the agitated seeding vessel (Figs. 1cd). The challenge is to find a favorable balance among the dominant phenomena in order to create a desired seed population.

An optimal seeding protocol was obtained taking into account the crucial steps of the seed preparation procedure.

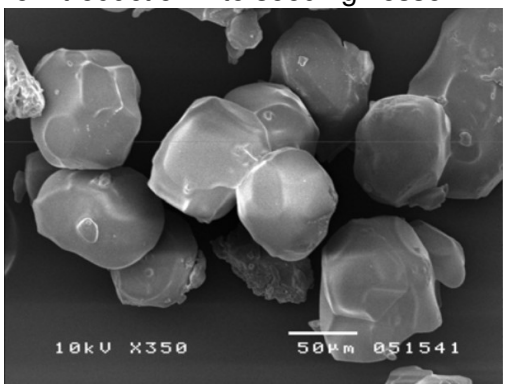
In **Chapter 8**, a comparative study of different approaches for state estimation suitable for process monitoring and state-based control of nonlinear systems is given. From the abundance of methods, nonlinear estimation techniques are considered. The nonlinear Luenberger observer is compared to the extended Kalman filter. Finally, one state estimation technique is chosen for the use in the model-based control systems discussed in the next chapter.

Chapter 9 concludes the development and validation of the model-based control strategies for batch crystallization. Three optimal control strategies are presented and compared to each other. The first optimal control policy is an open-loop implementation of an optimal trajectory computed off-line. The two remaining policies deal with closed-loop optimal control using the model predictive control technology.

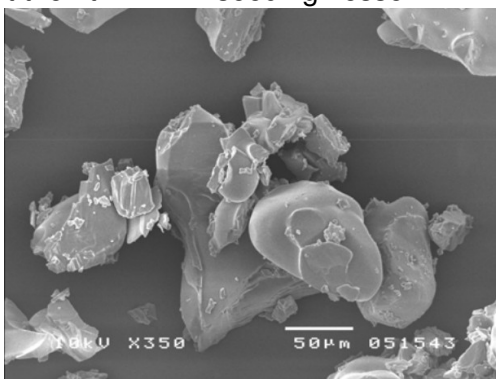
The thesis is concluded with **Chapter 10**, in which conclusions and perspectives are summarized. The research questions posed in the beginning of Chapter 1 are revisited. The main conclusion of the realized research program is that model-based control of industrial batch crystallizers is feasible. Despite the nonlinear nature of batch crystallization, the resulting model-based control strategy is not necessarily based on nonlinear control techniques. The availability of robust in- or on-line sensors is a prerequisite for a successful implementation of the model-based control in industrial conditions. The presented model predictive control system can also be implemented using commercially available advanced control solutions.



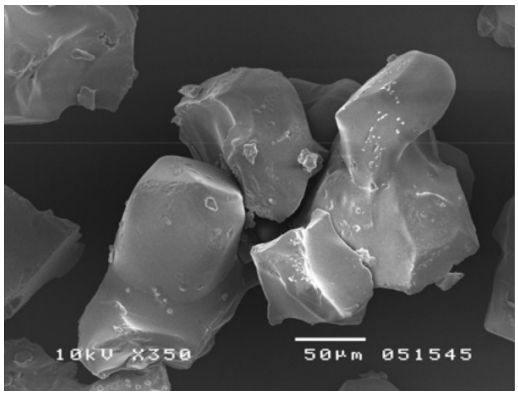
(a) Sieve fraction of 75–90 µm before introduction before introduction into seeding vessel



(b) At the 4th min in seeding vessel



(c) At the 15th min in seeding vessel



(d) At the 120th min in seeding vessel

Figure 1: SEM pictures of experiment SV_M03

AANKONDIGING CONGRESSEN EN SYMPOSIA

NVKG Annual meeting,
November 2009, PANalytical, Almelo
Organizer: Hans te Nijenhuis, PAnalytical
Zie de aankondiging in deze FACET voor meer details

International conference on the Crystal Growth of Organic Materials (CGOM)
Where: Singapore, 2010
Nadere details in de volgende FACET

International Conference on Crystal Growth, ICCG-16,
8-13 August 2010, Beijing, China
Details op de IOCG website