UNDERSTANDING SOLID-STATE TRANSFORMATIONS DURING DEHYDRATION: NEW INSIGHTS USING VIBRATIONAL SPECTROSCOPY AND MULTIVARIATE MODELLING

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LECTIO PRAECURSORIA

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SUMMARY

In this dissertation, the dehydration behaviour of pharmaceutical hydrates was assessed *in situ* and in a real process environment during fluidised bed drying. Near-infrared (NIR), Raman and terahertz pulsed spectroscopy (TPS) were used to monitor the solid-state transformations and multivariate data analysis was performed to interpret the spectral information. In addition, the *in situ* dehydration behaviour was investigated from compacts. The overall goal was to develop a method for monitoring the dehydration behaviour at the molecular level and predict and quantify the multiple solid-state transformations in-line during drying. The results obtained from qualitative experiments were used to develop a method and perform the quantification of the solid-state forms during processing-induced dehydration in a fluidised bed dryer. This dissertation demonstrated the utility of vibrational spectroscopy techniques and multivariate modelling to monitor and investigate dehydration behaviour *in situ* and during fluidised bed drying. NIR and Raman spectroscopy, and TPS, together with multivariate analysis techniques proved complementary in the study of dehydration. NIR spectroscopy models could quantify the solid-state forms in the binary system, but were unable to quantify all the forms in the quaternary system. Raman spectroscopy models on the other hand could quantify all four solid-state forms that appeared upon isothermal dehydration. The speed of spectroscopic methods makes them applicable for monitoring dehydration and the quantification of multiple forms was performed during phase transition. Thus the solid-state structure information at the molecular level was directly obtained.

INTRODUCTION

Drug substances may exist in several solid states. They can be either in different crystalline forms, thus exhibiting polymorphism, where the atoms and molecules are arranged in a repetitive manner in a crystal lattice and there is a long range order of molecules, or they may be amorphous, where no strict long-range order exists (Grant 1999). In addition, drug substances may exist in solvate or hydrate forms, where solvent molecules are included in the crystal lattice. Different solid-state forms may have different physicochemical properties, for instance, different melting point, compressibility, solubility and dissolution rate, which may lead to therapeutic, pharmaceutical, legal and commercial problems of a drug product (Bernstein 2002).

The selection of the most suitable solid state form of the drug in the initial stages of drug development is crucial to save time and cost associated with the drug development process. For instance, it is generally preferable to select thermodynamically the most stable form at ambient conditions for product development. This form will usually have the least liability for phase transformations. But in some cases the metastable form might be selected due to better performance or patent issues. However, when the forms are not properly characterised or stabilised, phase transformations, such as polymorphic transformation, interconversion to the amorphous form or hydrate formation and dehydration may occur under several conditions and stresses during manufacturing (Morris et al. 2001).

Crystalline hydrates are frequently encountered because water is prevalent in manufacturing of dosage forms. Active pharmaceutical ingredients (APIs) may become in contact with water and hydrates may be formed during several processing steps, such as crystallisation, wet granulation, and aqueous film-coating. Furthermore, water is always present as atmospheric humidity, thus the possibility of hydrate formation during storage under humid conditions needs to be evaluated. On the other hand, dehydration may occur and hydrates may lose their water either during drying, milling, mixing or tabletting, or during storage under high temperature or low humidity. Dehydration may comprise several consecutive reactions depending on the dehydration conditions and mechanisms. Heat, pressure or humidity may cause a phase transitions from hydrate to anhydrate or from higher hydrate to lower hydrate, or the dehydration may result in amorphous or metastable anhydrate forms. This process may be even more complicated and a mixture of different forms may be obtained (**Fig. 1**).

The main goal of pharmaceutical industry is

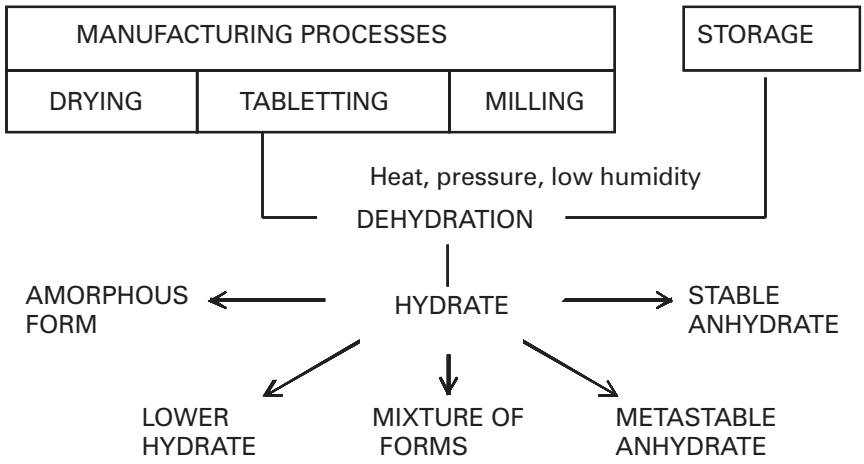

Figure 1. Conditions inducing dehydration and possible solid-state transformations.

to produce a pharmaceutical product that is satisfactory to the customer and that the safety and efficacy of the product are ensured at the minimum time and cost. To better understand, control, and predict the properties of the pharmaceutical, a thorough understanding of the underlying crystal structure and possible solid-state transitions need to be revealed. Several guidelines have been developed that reveal the regulatory perspective on this subject and give instructions to the pharmaceutical industry, what specific tests and validation methods are required for product development, manufacture and quality assurance (Byrn et al. 1995). On the Food and Drug Administration (FDA) initiative the concept of Process Analytical Technology (PAT) has been established, which main aim is to improve the product quality and process performance by using process analysis, monitoring and control together with process understanding. According to the guideline: "The product quality cannot be tested into products; it needs to be built in or it needs to be by the design"(FDA 2004). FDA PAT guideline does not give legally enforceable responsibilities to the industry, but it is meant to encourage industry towards innovative approach. PAT tools include the analytical techniques appropriate and applicable for continuous process monitoring, the proper analysis methods and the overall concept of process design and understanding, when these tools are used.

Several techniques can be used for dehydration studies, but spectroscopic techniques are now receiving a great attention. These techniques can be considered as PAT tools and they offer many advantages over the traditional methods to study the phase transitions. These methods offer the possibility to investigate the phase transformations at the molecular level. The main advantages are that these methods allow in-line process monitoring, are fast, non-destructive, and non-invasive. And these can be used to differentiate between the solid-state forms and for both qualitative and quantitative analysis, when used together with process analysis techniques.

MATERIALS AND METHODS

In this dissertation, the main goal was to investigate and increase the molecular level understanding of the dehydration behaviour of diverse hydrates using vibrational spectroscopy. Both qualitative and quantitative models were developed and used to explain the *in situ* dehydration. In addition, quantitative analysis was performed during fluidised bed drying using in-line NIR and Raman spectroscopy together with partial least squares (PLS) regression. In addition, different spectroscopic techniques were assessed and the effectiveness of NIR, Raman and teraherz pulsed spectroscopy (TPS) methods were compared to examine dehydration from compacts and investigate the effect of sample preparation (mixed, surface layer and middle layer compacts) on the dehydration behaviour of hydrates.

Piroxicam (PRX), carbamazepine (CBZ) and theophylline (TP) were used as model compounds. Hydrates of those APIs were prepared by crystallisation from hot saturated aqueous solutions. NIR and Raman spectroscopy, and TPS were used in solid-state analysis, and X-ray powder diffraction, variable temperature X-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis (TGA), Karl Fischer titrimetry and optical microscopy were used as reference methods. Data were analysed qualitatively using data visualisation, classification and reduction methods principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA), and quantitative analysis was performed using PLS regression. For model construction several spectral pre-treatment methods and different spectral regions were trialled. Model quality and performance was verified by looking at the specific model parameters that describe the accuracy, precision and robustness of the model.

RESULTS AND DISCUSSION

Firstly, the solid-state forms of model APIs (anhydrate forms and hydrate form) were characterised by NIR and Raman spectroscopy, and TPS, and secondly the dehydration was monitored *in situ* from powders and from compacts in first three publications [I, II, III].

Modelling of dehydration helped to predict the

behaviour of pharmaceutical hydrates and increase the understanding of the solid-state changes at the molecular level. *In situ* spectral data and model predictions revealed the dehydration behaviour of these model drugs and allowed identification of the solid-state forms during and after water removal.

This dissertation showed that it is important to determine the multiple solid-state forms which may occur during dehydration prior to quantification. In the model construction phase, all possible solid-state forms need to be considered. This knowledge was further used to develop the model for quantification. The intermediate forms (metastable or amorphous) or mixture of the forms can only be quantified during dehydration if all these forms are known and included during the model development stage. As an example, CBZ solid-state forms were quantified during isothermal heating on hot-stage (**Fig. 2**). It was revealed that the temperature affected not only the kinetics of dehydration, but also the amount of solid-state forms obtained during dehydration.

As a next step, the dehydration was investigated in-line during fluidised bed drying. The miniaturised fluidised bed dryer was used to mimic the real fluid-bed drying process, and NIR and Raman probes monitored the dehydration in-line through quartz sight window. In-line spectroscopic monitoring was performed in two last publications [IV, V]. It was possible to monitor and quantify multiple solid-state transformations during dehydration in fluidised bed dryer. As an example, fluidised bed drying at 323 K induced the dehydration of CBZDH granules and multiple solid-state forms were quantified during water removal (**Fig. 3**).

The dehydration from compacts was largely affected by the sample preparation method. TPS enabled to investigate the effect of sample preparation on the dehydration behaviour from compacts. Reflectance NIR and Raman spectroscopy were limited by their small sampling volume and interference from the polymer that formed the matrix of the compacts. However, the dehydration behaviour was monitored successfully with all three techniques (NIR and Raman spectroscopy, and TPS) using surface layer compacts, where the API layer was placed on top of the compact.

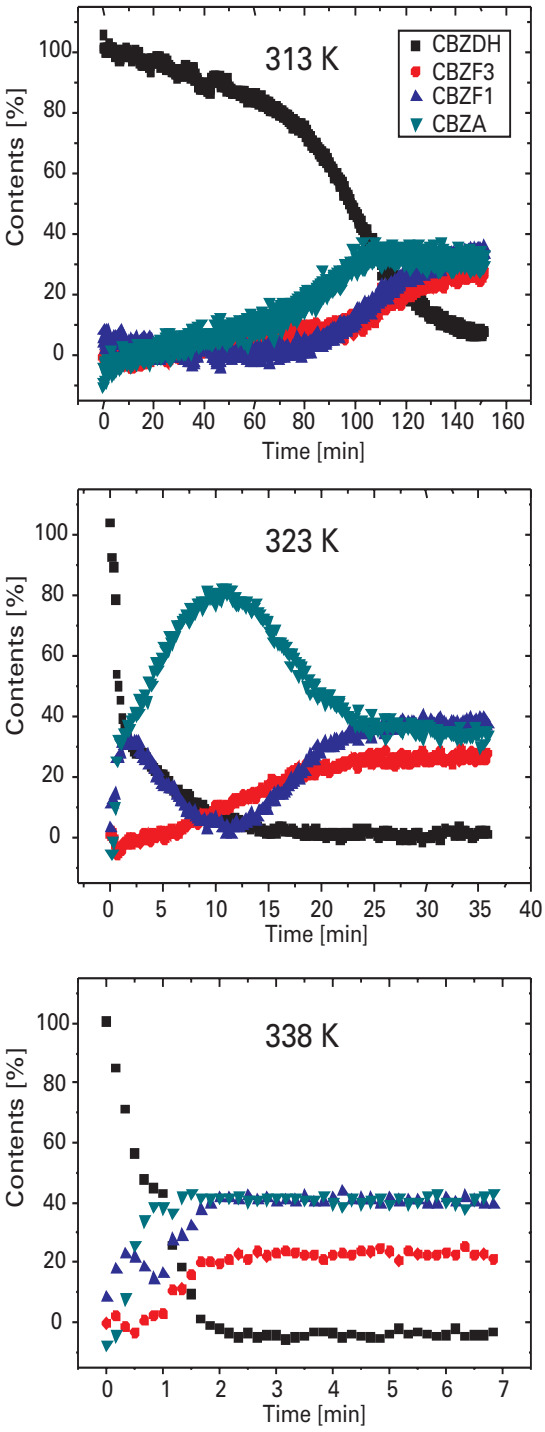

Figure 2. Quantification of CBZ solid-state forms during isothermal dehydration at 313, 323 and 338 K using Raman spectroscopy.

In this dissertation, the dehydration of pharmaceutical hydrates was investigated to obtain an understanding about the dehydration mechanisms encountered and that may also occur during manufacturing at higher temperatures. Although three model APIs were used in this study this kind of approach can also be used for other APIs, when vibrational spectroscopy is used. Vibrational spectroscopy techniques have characteristics needed for real time process monitoring and consequently for monitoring and controlling the process directly in-line. Deeper insight into the dehydration behaviour at the molecular level such as that obtained in this dissertation is needed for process control. The quality and performance of the API in a solid dosage form can be guaranteed only if the properties of an API are known under different processing steps and environmental conditions. The use of complementary techniques offers a good approach that can be used to increase the overall process and product understanding. However, not all techniques should always be used simultaneously. The choice of the technique(s) depends on the parameters that need to be monitored and controlled within the unit operation during manufacturing. Although, the approach developed in this dissertation is not yet a feed-back control method, it provides the basis for feed-back control. The overall control of the process can be achieved as a next step when the process parameters and conditions are known and understood.

CONCLUSIONS

The results presented in this dissertation revealed that vibrational spectroscopy together with multivariate modelling can be used to monitor and investigate dehydration behaviour *in situ* and in-line during the unit operation, fluidised bed drying. All three spectroscopic methods proved complementary in the study of dehydration, the speed of spectroscopic methods makes them suitable for monitoring dehydration and vibrational spectroscopy directly gives solid-state structure information. TPS detects the intermolecular phonon modes and Raman spectroscopy detects mostly the intramolecular vibrations. Both techniques revealed information about the crystal structure changes. Furthermore, the information about the molecular rotations of water in gaseous phase was obtained from TPS measurements. NIR spectroscopy, on the other hand was more sensitive to water content and the hydrogen bonding environment of water molecules.

Multivariate analysis methods (PCA and PLS-

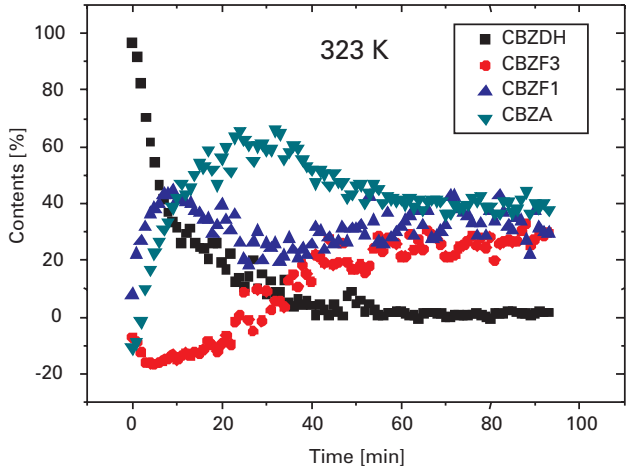

Figure 3. Quantification of CBZ solid-state forms during fluidised bed drying at 323 K using Raman spectroscopy.

DA) were found to be excellent tools to interpret the spectral changes. All possible solid-state forms need to be considered in construction of the quantitative models. PLS regression was found to be a good technique to conduct quantitative analysis of the spectral data. For the first time the quantification of four CBZ solid-state forms was performed using NIR and Raman spectroscopy. Raman spectroscopy was found to have higher spectral resolution which allowed quantifying two PRX forms and all four CBZ solid-state forms during isothermal dehydration. NIR spectroscopy, on the other hand, revealed complementary information about the dehydration from PRX monohydrate to PRX ahydrate form I, showing good agreement with Raman spectroscopy and TGA results. However, NIR spectroscopy was incapable of differentiating between the anhydrous solid-state forms of CBZ during dehydration. For TP monohydrate, both NIR and Raman spectroscopy allowed monitoring of dehydration and provided complementary information.

For the first time multiple spectroscopic techniques were used to monitor solid-state dehydration in compacts. Together, TPS and NIR and Raman spectroscopy simultaneously provided information on solid-state transformations, free water within and on the surface of the compact, and water vapour as it leaves the compact, thus increasing understanding of dehydration from within compacts. The sample preparation method affected the dehydration behaviour from compacts. The developed approach is proposed for improved process monitoring and understanding during pharmaceutical manufacturing, and this gives a basics to develop the continuous process control.

DISSERTATION WAS BASED ON FOLLOWING PUBLICATIONS:

I. Kogermann K, Aaltonen J, Strachan CJ et al.: Qualitative *in situ* analysis of multiple solid-state forms using spectroscopy and partial least squares discriminant modeling. J Pharm Sci 96: 1802–1820, 2007

II. Zeitler JA, Kogermann K, Rantanen J et al.: Drug hydrate systems and dehydration processes studied by terahertz pulsed spectroscopy. Int J Pharm 334: 78 –84, 2007

III. Kogermann K, Zeitler JA, Rantanen J et al.: Investigating dehydration from compacts using terahertz pulsed, Raman and near-infrared spectroscopy. Appl Spectrosc 61: 1265–1274, 2007

IV. Aaltonen J, Kogermann K, Strachan CJ, Rantanen J: In-line monitoring of solid state transitions during fluidisation. Chem Eng Sci 62: 408–415, 2007

V. Kogermann K, Aaltonen J, Strachan CJ et al.: Establishing quantitative in-line analysis of multiple solid-state transformations during dehydration. Accepted in J Pharm Sci, 2008

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KIDETILASSA TAPAHTUVIEN FAASIMUUTOSTEN YMMÄRTÄMINEN KIDEVEDEN POISTUMISEN AIKANA: UUSIA NÄKÖKULMIA SPEKTROSKOOPPISTEN MENETELMIEN JA MONIMUUTTUJAMALLINNUKSEN AVULLA

TIIVISTELMÄ

Lääkeaineet altistuvat eri olosuhteiden, kuten lämpötilan, mekaanisen stressin tai kosteuden, vaihteluille lääkevalmistuksen aikana, mistä voi seurata muutoksia lääkeaineen kiderakenteessa. Kiteinen lääkeaine voi muuttua amorfiseksi tai se voi kosteissa olosuhteissa muuttua hydraatiksi. Toisaalta hydraatista voi sen kuivuessa ja veden poistuessa muodostua joko anhydraattia tai metastabiilia muotoa. Eri kidemuodoilla on erilaiset fysikaalis-kemialliset ominaisuudet, kuten liukoisuus, hygroskooppisuus tai sulamispiste. On tärkeätä ymmärtää, mitä seurauksia näillä kidemuodon muutoksilla on lääkeaineen prosessoitavuudelle, säilyvyydelle tai terapeuttiselle vasteelle.

Dehydraatio eli kideveden poistuminen on yksi mahdollinen faasimuutos, joka voi tapahtua joko lääkkeen valmistusprosessin tai säilytyksen aikana. Väitöskirjassa käytettiin erilaisia spektroskooppisia menetelmiä ja monimuuttuja-analyysia dehydraatiomekanismien tutkimisessa. Dehydraatiota tutkittiin eri lämpötiloissa *in situ* sekä leijupetikuivauksen aikana. Dehydraation aiheuttamia muutoksia seurattiin Raman, lähialueen infrapuna- sekä terahertsispektroskopian avulla. Spektroskooppisilla tekniikoilla saadaan molekyylitason tietoa tutkittavasta näytteestä ja yhdistettynä monimuuttuja-analyysiin voivat auttaa kontrolloimaan lääkkeenvalmistusprosessia sekä ymmärtämään eri valmistusvaiheiden merkitystä lopputuotteen ominaisuuksiin.

Tämä tutkimus osoitti, että spektroskooppisia menetelmiä voidaan käyttää sekä dehydraation että leijupetikuivauksen aikaisten kiderakenteen muutosten seurantaan. Prosessinaikainen seuranta auttoi ymmärtämään lämpötilan ja muiden prosessiolosuhteiden muutosten aiheuttamia kiinteän tilan muutoksia. Tutkimuksesta kävi ilmi, että eri spektroskooppisilla tekniikoilla saadaan erilaista ja toisiaan täydentävää informaatiota. Spektroskooppisia menetelmiä voidaan käyttää myös eri kidemuotojen kvantitoinnissa. Terahertsispektroskopia on herkkä molekyylien välisille, kun taas Raman spektroskopia molekyylien sisäisille, vuorovaikutuksille. Molemmat menetelmät auttavat ymmärtämään kiderakenteen muutoksia molekyylitasolla. Lähialueen infrapunaspektroskopia on erittäin herkkä vedelle, joten sitä voidaan käyttää vesipitoisuuksien muutosten seurantaan. Tässä tutkimuksessa käytettyjä menetelmiä voidaan soveltaa dehydraation tutkimiseen eri lääkkeenvalmistusprosesseissa ja analyysimenetelmien kehityksessä.