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MANUFACTURING AND INVESTIGATION OF COATED PELLETS CONTAINING WATER-SOLUBLE ACTIVE INGREDIENTS

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1. Introduction

Pharmaceutical dosage forms have to meet several requirements in order to be released on the market. Most of these involve parameters that, while key in determining product performance, are not specific to the product itself and have little to no connection to the natural laws and phenomena that determine the functionality of the final dosage form. While specific formulation properties and their investigation have received a lot of attention and several advanced characterization techniques have been developed a better understanding of the final product is required to improve design and manufacturing and thus avoid unnecessary batch failures and recalls.

Dissolution is arguably the most important parameter of a modern pharmaceutical formulation as it is the value that determines the efficacy of the product. Modified release formulations that are preferred nowadays by patients and prescribers are designed to provide a dissolution profile tailored to fit disease and patient characteristics, thus the factors influencing dissolution are of particular importance in their case. Our work attempts to investigate some properties of a model pellet formulation that potentially influence dissolution and translate the findings into a deeper understanding of the internal affairs of modified release multiparticulates.

2. Aims

Pellets are an increasingly popular choice in the development of drug delivery systems, yet comparatively few studies deal with their investigation even by methods routinely used elsewhere in the pharmaceutical industry. Our aim was to study the use of different analytical techniques in the investigation of different characteristics and phenomena influencing dissolution, develop new ones and determine the extent of usefulness of methods that, given their nature and required circumstances, appear to have a limited applicability on pellets.

The first section of this work describes the development of a Raman spectroscopic method for the determination of the film thickness of pyridoxine hydrochloride-containing coated pellets. Two different equipment set-ups were used for sample production and their impact on the outcome of the analysis was examined.

Section two deals with the investigation of an atypical thermal phenomenon observed in diltiazem hydrochloride-containing multilayer pellets. This is divided into two larger parts: the investigation of the thermal behavior and the underlying

recrystallization phenomenon and the development of a method to determine degree of crystallinity in intact pellets.

3. Materials

Diltiazem hydrochloride (Ph. Eur., a gift from EGIS Ltd., Budapest, Hungary) and pyridoxine hydrochloride (Ph. Eur.) were used as model drugs, Cellet 500 (Shin-Etsu Chemical Co., Ltd., Tokyo, Japan, granted as a gift from Harke Pharma) as nonpareil core material, Kollidon 25 (polyvinylpyrrolidone; BASF, Ludwigshafen, Germany) and Pharmacoat 606 (hypromellose; BASF, Ludwigshafen, Germany) was applied as a binder in the layering of the APIs, and Acryl-EZE (Colorcon, Dartford Kent, UK), a fully formulated enteric coating dispersion containing a methacryic acid copolymer, was used as coating material.

4. Samples

Samples' names consist of two or three letters and two numerical characters. The first letter represents the API contained in the sample where

D – indicates diltiazem hydrochloride

P – indicates pyridoxine hydrochloride.

The second letter indicates the binder used for the production of the sample such that

K – stands for Kollidon 25

P – stands for Pharmacoat 606.

In the case of samples labeled PP the third, additional letter represents the place of production where

S – is for Szeged, Hungary

D – is for Düsseldorf, Germany.

The first number will either be 0 or 1 which indicates the lack of or presence of coating. The second numerical character is the batch number.

5. Results and discussion

5.1. Section I – Pellets containing pyridoxine hydrochloride

5.1.1. Preparation of samples

Samples have been prepared in two different Strea 1 equipment pieces in the same batch sizes. The main differences between the two equipment were the use of the Wurster insert and the geometry of the column (see Table 1. for parameters). The

stainless steel column was set up to include the Raman probe described in the Methods section for inline measurements.

Table 1: Layering and coating parameters

	Strea 1 in Szeged	Strea 1 in Düsseldorf
Inlet temperature	50 °C	50 °C
Outlet temperature	43 °C	37 °C
Spray rate	6 ml/min	6 ml/min
Air volume	80 m^3/h (variable)	130 m^3/h (pre-set)
Nozzle diameter	1 mm	1 mm
Chamber material	Glass	Stainless steel
Wurster insert	Yes	No
Spraying installation	Bottom-spray	Bottom-spray

Yield was significantly higher in the Szeged equipment with values of 98-99% for API layering and 96-98% for coating. The lower values of 92-95% for API layering and 91-94% for coating observed in the Düsseldorf equipment are most probably aggravated by the difference in chamber geometry: the shape of the stainless steel chamber results in more collisions between particles and with the chamber wall.

5.1.2. Determination of drug content and film thickness

5.1.2.1. Particle size and film thickness

Pyridoxine-containing samples were measured with the Camsizer and the Leica equipment. For the Leica equipment three samples of 300 particles were measured, their results were compared against Camsizer analysis results of roughly 15000 particles separately and pooled for each sample.

Particle size and film thickness results between the two analytical methods show a fairly consistent behavior: while film thickness results can be said to be more or less equivalent between the two methods the mean particle sizes are usually larger when measured with the Leica equipment (and this difference is consistent between coated and uncoated samples as evident from the film thickness results). This is most probably explained by the different nature of the equipment: the Leica equipment employs a stereomicroscope focused on the stationary particles where the shadow cast by the particles distorts the image. The magnitude of the distortion also depends on the image recognition software and the resolution of the images taken of the particles. The Camsizer technology measures the shadow cast by the particles thus the distorting effects are taken into account during the calibration process.

The Camsizer film thickness results that were used in further studies show a linear correlation with coating polymer weight gain for both sample sets (R^2=0.9219) which suggests that the density of the films was not affected by the differences in the equipment used for production.

5.1.2.2. Dissolution

All samples showed a complete API release after 60 min in the pH 6.8 dissolution medium. Gastroresistance of the film coatings showed a relationship with their thickness where higher coating levels yielded better (in this case lower) results. Similar levels of coating showed similar levels of dissolution regardless of which equipment was used for sample production, indicating that the coating quality produced in different equipment (but with the same parameters) does not differ in this respect. Coatings of 35 μm or thinner were insufficient in achieving the Ph. Eur. requirements of gastroresistant films. The dissolution testing of Sample PPD11 (26.88 μm) was discontinued after observing over 50% drug release in artificial gastric acid.

The possibility of a linear correlation was observed between the percent of drug dissolved in gastric acid and the film thickness was examined but the coefficient of determination (R^2) proved to be poor (0.6667).

After excluding the data point from the discontinued dissolution test of Sample however the goodness of fit improved to R^2=0.8798 (see Fig. 1). Correlation between polymer weight gain and dissolution in artificial gastric acid yielded an R^2 of 0.6842 even after excluding the clearly outlying data point, suggesting that polymer weight gain is a bad indicator of dissolution results even though it is a good predictor of film thickness.

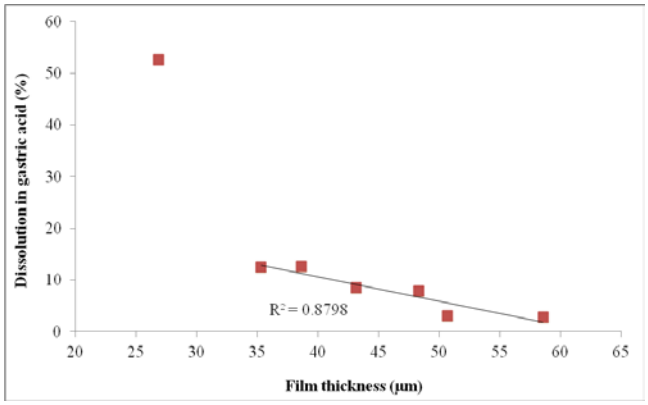

Figure 1: Correlation of film thickness and dissolution is gastric acid; line fitted with the first data point excluded

5.1.2.3. Raman spectroscopy

For the multivariate analysis spectra were SNV corrected and principal component analysis was performed to observe the variation between the peak structures not confounded by baseline and scaling differences. PLS regression was performed to find a common calibration curve.

SNV correction eliminates the basis of the expected first PC accounting for baseline differences by subtracting the baseline and normalizing the spectra thereby providing a better chance to see the latent structures of the peaks themselves. The first PC acquired from this analysis greatly resembles the Raman spectrum of titanium dioxide and corresponds to 91.44% of the variation between the spectra after SNV correction. The second PC is very similar to the spectrum of pyridoxine hydrochloride with a small negative trace of the 638.1 cm^{-1} peak of titanium dioxide. This PC explains 6.03% of the variations. The scores plot of the analysis shows that samples are located in order of increasing film thickness along the first PC axis.

According to the scree plot of the PLS analysis (not shown) two PLS-components were found to give the best results based on the SNV-corrected spectra without signs of overfitting with 97.4% of the spectral variation and 98.61% of the film thickness variation explained.

The first component again resembles the Raman spectrum of titanium dioxide. This component is responsible for 91.43% and 96.36% of the X- and Y-directional variations respectively, indicating that the use of just this component can result in a reasonably good model. The second PLS-component contains only 5.94% of spectral variation and is responsible for 2.25% of the variation in film thickness. The loadings of this component closely correspond to the Raman spectrum of pyridoxine hydrochloride in the negative. The two PLS-components thus indicate that the samples contain inversely proportional amounts of the film forming agent and the API and because of this only one significant PLS-component was expected before performing the analysis.

Our final model included two PLS-components and provided a root mean square error of calibration (RMSEC) of 1.15 and a root mean square error of cross-validation (RMSECV) of 2.29 using the leave-one-out method. The slope and y-intercept of the linear fit also indicate the validity of the model (see Fig. 2). It is worth to mention that using only the first PLS-components in the model also results in a

good correlation with an R^2 of 0.9636 but the inclusion of the second component further reduces the mean square error of the leave-one-out cross-validation somewhat.

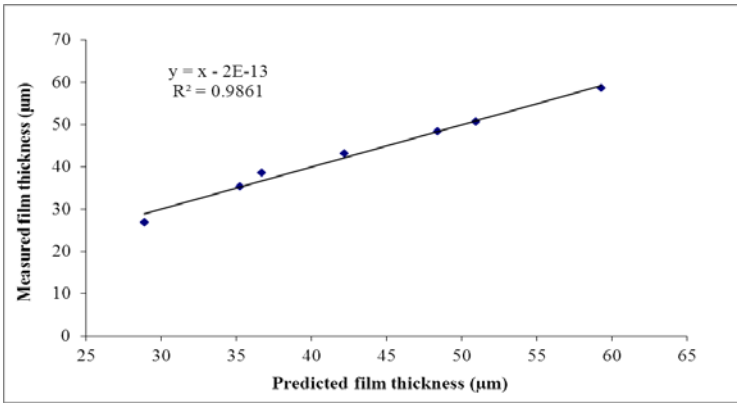

Figure 2: Linear model of the film thickness based on the PLS regression of the SNV-corrected Raman spectra

The lasers utilized for Raman spectroscopy have small sampling area and penetration depth. In our case the illumination area was 28.3 mm^2, which means that, calculating with the smallest size, less than 100 pellets were measured in every case. This is a significantly lower number of pellets than what the literature generally suggests and much less than the amount of particles measured with the Camsizer for the development of the method. Contrary to previous studies done on sustained release systems where film thickness was a good predictor of dissolution delayed release coatings appear to be more complicated. Our results suggest that there might be a threshold value above which a correlation exists. One of the reasons for this may be incomplete film formation. The greater mechanical stress the sample suffered in the bottom spray equipment compared to the Wurster coater could also have contributed to the poor dissolution performance through the formation of cracks and chips, which in the case of thin coatings (in this case Sample PPD11) could affect the preparation more adversely than in the case of thick coatings.

5.1.3. Summary

A Raman spectroscopic method was developed to assess film thickness prepared in two different types of fluid bed equipment. In the dissolution tests no indication of the films formed in the two equipment being different in quality were observed, however circumstances of preparation and Raman spectroscopic results suggest that differences may exist on some level. Multivariate analysis has visualized this as a difference in the slope of the baseline. Results suggest that above a threshold

value the results of a dissolution test may be estimated by the measurement of the coating thickness in gastroresistant pellets.

5.2. Section II – Pellets containing diltiazem hydrochloride

5.2.1. Preparation of samples

Diltiazem hydrochloride, being more water-soluble than pyridoxine hydrochloride, could be used in larger concentrations during API layering to reduce loading time. The utilization of this meant however that the viscosity of the Pharmacoat 606 – diltiazem hydrochloride solution increased so much that spraying it became very cumbersome. To reduce viscosity Kollidon 25 was used instead of Pharmacoat 606 as a binder in the production of some of the samples.

5.2.2. Study of the API migration and recrystallization

5.2.2.1. Thermal analysis

The DSC curves of the materials are presented on Fig. 3. The endothermic peak at 214°C indicates the melting of diltiazem hydrochloride; the second, broad endothermic peak on the curve can be attributed to API degradation. The broad endothermic peaks on the curves of Kollidon 25 and Pharmacoat 606 are related to the water loss of the polymers. No glass transition temperature could be determined which is probably due to overlapping and being obscured by the water loss peak and the changing plasticity caused by the water loss. The T_g of Acryl-EZE is visible at ~45°C, but no peaks characteristic of the excipients used in its composition appear on the curve.

As shown in Fig. 4, the melting point of diltiazem hydrochloride appearing in all the samples has shifted to about 10°C lower than observed in its pure form and an exothermic peak appeared at about 100°C on the DSC curves of the coated pellets. The T_g of Acryl-EZE did not shift significantly and the T_g of the binder polymers did not appear on the curves.

A slow weight loss starts approximately at 50°C that accelerates slightly at about 100°C. The previous value is somewhat higher in the case of coated samples. Total weight loss up to 100°C is only a few percent in all cases; this concurs with the water loss of the polymers described before and explains why the effect is delayed in coated samples where much of the water is contained beneath the coating. The

samples begin to lose weight fast above the melting point of diltiazem HCl which again concurs with our knowledge about the materials and the composition.

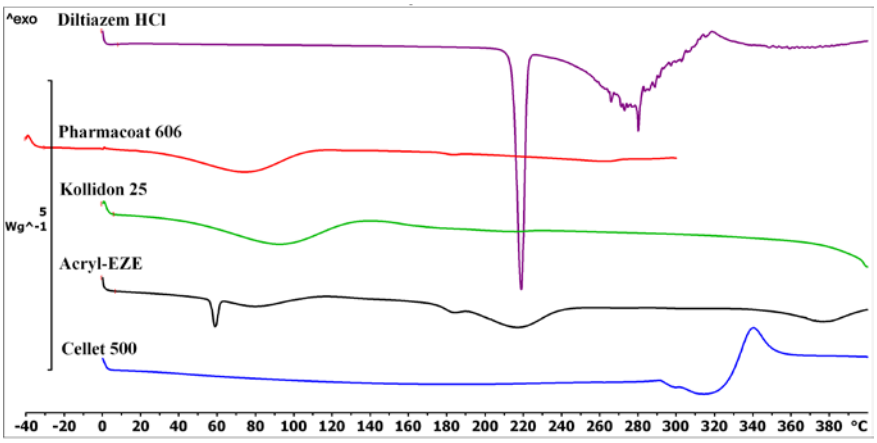

Figure 3: DSC curves of the raw materials

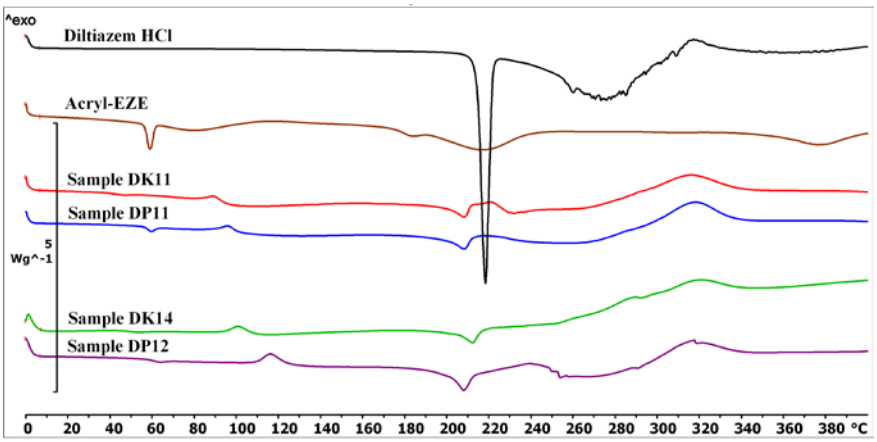

Figure 4: DSC curves of some representative samples containing diltiazem hydrochloride

5.2.2.2. X-ray analysis

The XRPD diffractogram of diltiazem HCl comprises several peaks; the larger ones that can also be seen in the samples' diffractograms are at 4.125° 2θ, 8.328° 2θ, 9.907° 2θ, 10.547° 2θ, 18.070° 2θ, 19.442° 2θ, 21.661° 2θ and 27.575° 2θ. Cellet 500, Kollidon 25 and Pharmacoat 606 are either polymeric or microcrystalline; hence only very broad peaks appear in their diffractograms which do not hinder the identification of the sharp peaks from other materials. Talc, listed as an ingredient of Acryl-EZE by the manufacturer, produced the two sharp peaks visible in the diffractogram of the coating system.

The XRPD diffractograms were detected at room temperature at baseline and heated to 120°C and to 200°C afterward. Results are presented in Fig. 5. a and b. The diffractogram of every coated sample shows a sharp peak at 25.648° 2θ. This was identified as titanium dioxide, used as white pigment in the Acryl-EZE coating system. Diltiazem hydrochloride peaks have become larger (or, in some cases, appeared) after heat treatment (in the case of the samples containing partially crystalline API only the peaks at 9.907° 2θ, 10.547° 2θ, 15.897° 2θ, 18.070° 2θ, 19.442° 2θ and 21.661° 2θ were prominently present before). In the case of the uncoated samples API peaks appeared/grew only after the heat treatment on 200°C whereas coated samples demonstrated the same after being heated to only 120°C.

The nature of the sample preparation process closely resembles the procedures employed during the solvent method of the preparation of solid dispersions. This implies that a solid dispersion can be formed during API layering that, depending on the composition and parameters, can contain the API in any and all physical states and forms.

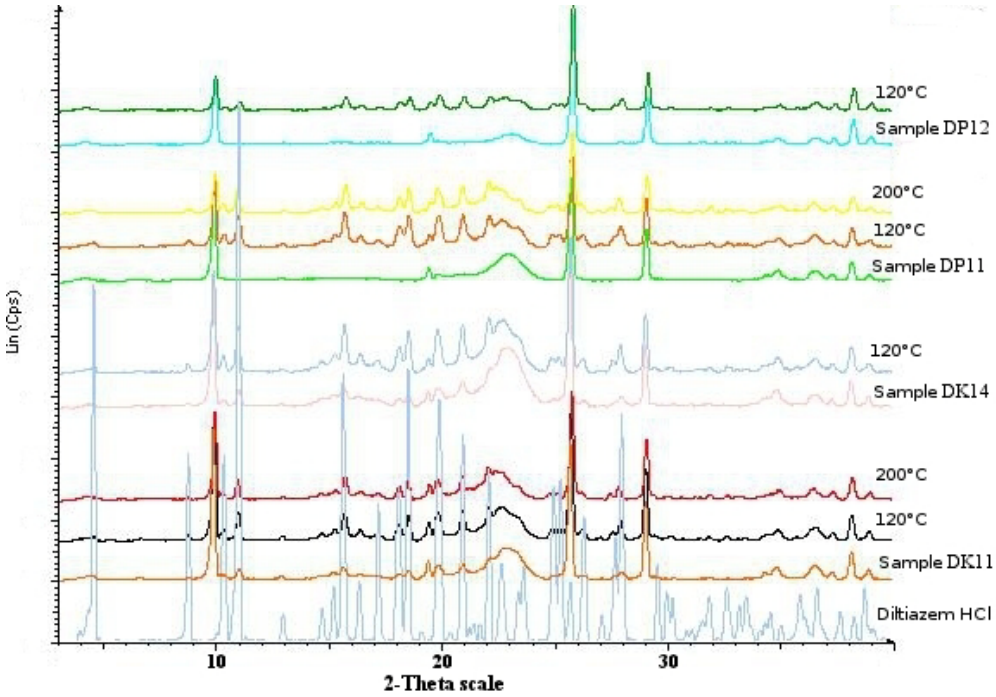

Figure 5.a, X-ray diffractograms of coated samples at different temperatures

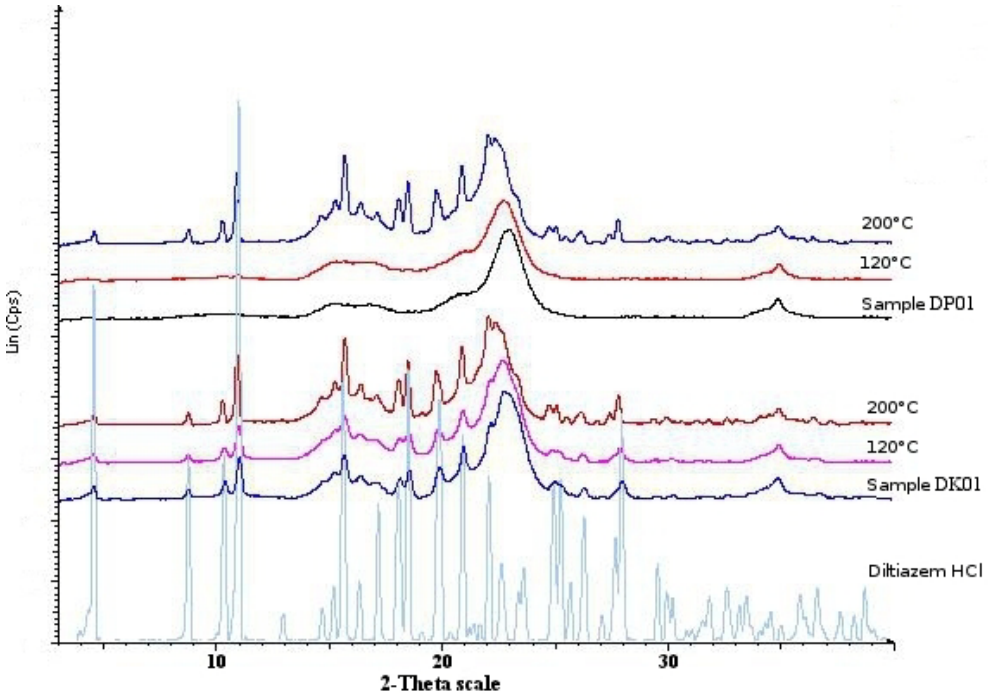

Figure 5.b, X-ray diffractograms uncoated samples at different temperatures

5.2.2.3. Hot-stage microscopy

The polarized light microphotograph of a piece of coating (Fig. 6) taken using crossed Nicol prisms shows that the polymeric film layer contains crystalline material even before heat treatment (left side). After the heat treatment (right side) the amount of birefringent particles in the coating increased which indicate that the crystalline material is diltiazem hydrochloride.

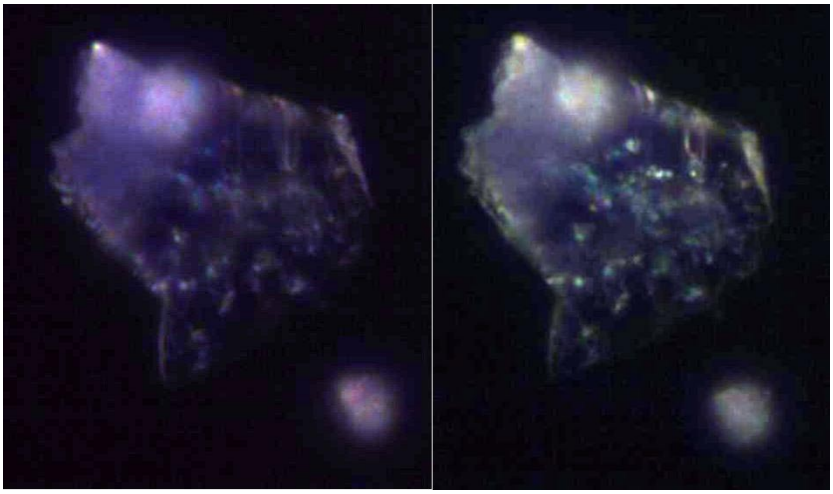

Figure 6: Coating fragment under the polarized light microscope before and after heat treatment

The API migrated into the coating and part of it remained amorphous that later crystallizes if subjected to heat treatment. The probable explanation for the migration is that the highly water-soluble diltiazem HCl dissolved into the droplets of coating suspension hitting the surface of the API-layered cores during the coating process. The plasticization mechanism described by Mizuno et al. can also play a role in the process. Binder polymers might also play a part by improving the speed of dissolution even further by forming solid dispersions with the API upon layering. This hypothesis is supported by the DSC analysis, which shows that no exothermic peak appears on the DSC curves of the coated sample prepared without a binder. The migration probably occurs mostly before a uniform coating layer forms on the drug-loaded cores and thus affects only a small fraction of the API.

Considering the fact that the drug layer already contains an amorphous fraction, migration does not explain the difference in the recrystallization behavior of the coated and uncoated samples. The DSC curves of the uncoated samples contain a broad endothermic peak that literature attributes to the loss of water in the binders, PVP and HPMC, respectively. This peak does not show up on the curves of the coated samples and the TG curves indicate that water loss in the coated samples starts only at boiling point indicating a watertight property of the coating at least on the timescale of the DSC analysis. The exothermic peak attributed to API recrystallization is in the thermal range of the boiling point of water. This raises the question: can water play a role in the recrystallization behavior of the API?

Several theories postulated by other authors can be used to explain the possible influence of water on the behavior of our coated samples. Many studies proved that water can act as a plasticizer in polymers; as such it can decrease the T_g of the polymer to the thermal range of our exothermic peak – which it cannot do for the uncoated samples as most of the water evaporates by the time the sample reaches the temperature range in question. Water can also be trapped in the pores of the microcrystalline cellulose core after API layering (wicking). Diltiazem hydrochloride, being highly water-soluble, can dissolve in the water migrating toward the surface of the pellet from the core and crystallize with the eventual evaporation of the solvent. As water boils in the thermal range of the recrystallization peak, the pressure of the forming steam in the pores of the pellet is expected to grow rapidly at the time of the event. As described before, water also acts as a plasticizer, so pores can be easily

expanded by the steam essentially removing the physical barriers of the polymer structure that stood in the way of recrystallization.

5.2.2.4. Stability

These mechanisms can and in reality probably do work independently from each other at the same time. This presents problems regarding the stability testing of samples of this nature. Studies should take into consideration that the high relative humidity used in accelerated stability tests will probably cause recrystallization by plasticizing the polymer that would not happen under ambient conditions.

To compensate for this hindrance samples were stored at 40˚C at 70% relative humidity, at 40˚C in a low humidity environment, at 75±5% relative humidity at room temperature (20˚C±2˚C) and at ambient conditions (45±5% and 20˚C±2˚C). Fully amorphous samples have fully recrystallized after a day at both humid conditions while samples stored at low humidity levels remained fully amorphous until the closing of the experiment 50 days later.

To evaluate the role of water loss in recrystallization a TG-DSC experiment with a low heating rate was performed. The 1°C/min heating rate was expected to provide enough time for the evaporated water to diffuse through the coating thereby equalizing the water loss trend with that of the uncoated pellets. DSC and TG curves have both fulfilled that expectation: weight loss rates were even between coated and uncoated samples with only a slight delay for the coated pellets and recrystallization occurs in both coated samples in the same thermal range as in their uncoated counterparts. This confirms that in our case the fast evaporation of water played a crucial part in causing the difference in recrystallization behavior.

5.2.3. Measurement of the degree of crystallinity

Six sub-samples were taken from Samples DK01-5 and their X-ray diffractograms collected. Diffractograms were then used to attempt to set up a calibration curve for the determination of the degree of crystallinity based on ssNMR results.

5.2.3.1. X-ray characterization of samples and starting materials

Samples DK01-5 contain only one crystalline compound, diltiazem hydrochloride, which produces the diffractogram displayed previously. The other

materials in the composition are amorphous or microcrystalline (Kollidon 25 and Cellet 500 respectively) and thus produce a broad halo in their diffractograms.

Sample DK03 turned out to be X-ray amorphous but the diffractogram showed no new halo features that could be definitively attributed to amorphous diltiazem hydrochloride. This can be a result of the halos of the polymer components overlapping over most of the 2θ range or differences in the intensity and concentration of the materials. In this case most probably both of these effects occur. Characteristic peaks of diltiazem hydrochloride are shifted in sample diffractograms and the extent of the shift is not consistent for all peaks and samples.

5.2.3.2. Determination of the crystalline content by univariate methods

Preliminary calculations were performed to choose the best-performing peaks and also to determine which peak parameter to use for further calculations. The characteristic peaks at 9.907° 2θ, 10.547° 2θ, 19.442° 2θ, 20.521° 2θ and 27.575° 2θ were chosen for their consistently good performance despite troubling characteristics. Results are summarized in Table 2.

Area methods generally provide better results than peak heights because of the wider 2θ range involved. In our case however peak heights almost always provided better results than peak areas. The previously shown formula was used to calculate results from total area parameters. Predicted crystallinities were plotted against the theoretical crystallinity obtained from the ssNMR measurements. The mathematical values used to describe the linear fit are the slope and y-intercept, the coefficient of determination (R^2) and the root mean square error of calibration and cross-validation. Zero intercept was not considered in these calculations but y intercepts indicate that correlation coefficients would not decrease much if zero intercepts were considered.

Table 2: Regression results for Savitzky-Golay smoothed diffractograms

	Crystalline/ amorphous area ratio	Sum of peak heights	Peak position (2θ)				
			9.907°	10.547°	19.442°	20.521°	27.575°
Slope	1	1	1	1	1	1	1
y intercept	$2*10^{-5}$	$8*10^{-5}$	$5*10^{-5}$	$1*10^{-4}$	$1*10^{-4}$	$3*10^{-5}$	$3*10^{-5}$
R^2	0.881	0.9028	0.9165	0.8846	0.8972	0.9277	0.9173
RMSEC	5.12	4.62	4.28	5.04	4.75	3.99	4.26
RMSECV	5.38	4.86	4.52	5.29	5.00	4.20	4.51

As ssNMR uses very small sample sizes compared to XRPD it is reasonable to assume that sampling errors are more likely to occur during the ssNMR measurement therefore the result may not necessarily be representative of the sample bulk. While the particles were mixed before sampling for XRPD measurements to reduce the chance of obtaining biased sub-samples the actual degree of crystallinity of the sub-samples can differ from each other and from the „theoretical value" for the samples obtained by ssNMR as flow properties and thus drying characteristics are inhomogeneous during production. Repeated ssNMR measurements would solve this issue but NMR measurements are both time-consuming and costly and therefore parallel measurements were not performed.

While promising, the overall results of the univariate analysis cannot be considered ideal or, in many cases, reliable based on the problems described above. Partial least squares regression was tested to overcome difficulties in parameter selection and to find a good fit based on not confounded information.

5.2.3.3. Determination of the crystalline content by multivariate methods

PLS analysis found three significant components that, while explaining 89.25% of the spectral variation which is roughly the same amount as examined by PCA, correspond to 95.81% of the differences in the degree of crystallinity. PLS component weights for the first two components closely resemble the diltiazem hydrochloride diffractogram with the both components containing the amorphous halo either in negative or in positive. The strongest feature of the third PLS-component is a negative shift that resembles an amorphous halo not attributable to microcrystalline cellulose and it also contains API peaks among some noise.

Score plots obtained for the PLS-components show the same clustering as PCA (see Fig. 7. a,). Samples are approximately in order of increasing degree of crystallinity along the first PLS-component axis. Samples DK02 and DK05 are merged along this axis but Sample DK02 is set apart by the third PLS-component as seen on Fig. 7. b.

The model obtained from the analysis shown on Fig. 8 supersedes all previous attempts to obtain a calibration curve with an RMSEC of 3.04 and an RMSECV of 3.88.

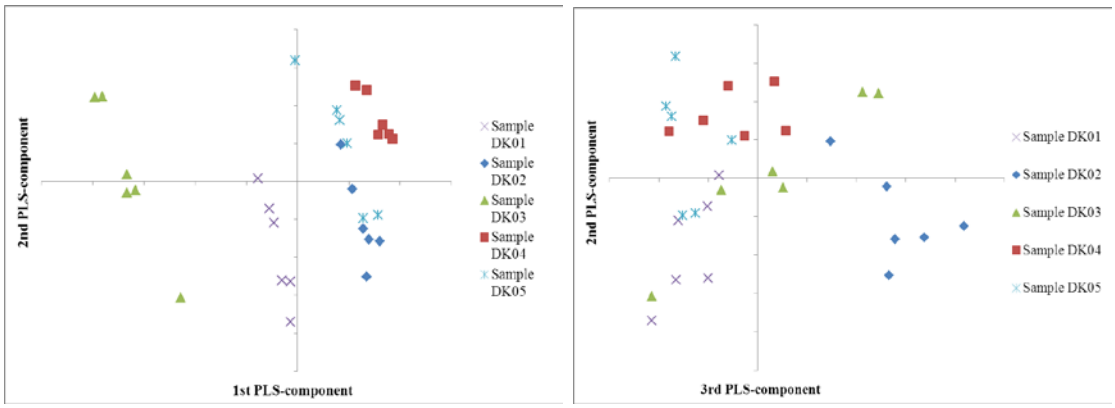

Figure 7. a-b, Score plots obtained from PLS-regression

These results have shown that the degree of API crystallinity of intact pellets can be examined by XRPD despite the initial difficulties. Univariate models obtained in the analysis varied in their predictive quality and often the best models came from the most dubious sources. This indicates that while univariate analysis in this case can be feasible the parameter it is built on has to be chosen very carefully. PLS analysis on the other hand provided better results and gave much less reason to worry about the validity of the obtained model. Building the PLS model was also less time-consuming due to the lack of preparatory work while for the univariate model not only the peak and halo separation needed to be done but also preliminary calculations were required to avoid choosing the most obvious but in reality not very predictive parameter.

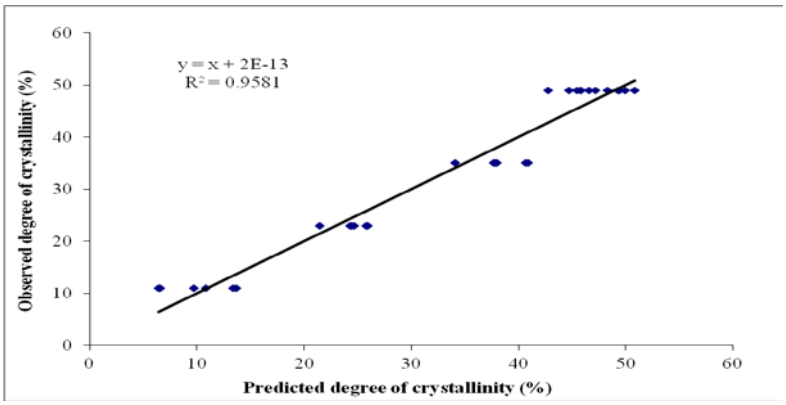

Figure 8: Linear model of the degree of crystallinity based on the PLS regression of the XRPD data of intact pellets

5.2.4. Summary

In this section diltiazem hydrochloride-containing pellets were investigated to find the reason of an atypical behavior and its impact on stability testing and

dissolution. We have also attempted to measure the degree of crystallinity of the uncoated samples from intact pellets with both univariate and multivariate methods.

6. Final conclusions, novelty, practical usefulness

The influence of various factors and phenomena on the dissolution of enteric coated pellets was investigated in this study. Pellets were manufactured by solution layering in a fluidized bed and subsequently coated with a fully formulated enteric coating system. Two model APIs and two model hydrophilic binder polymers were used and the four possible compositions were analyzed and their characteristics cross-referenced to see the effect of composition, process parameters and other phenomena on the behavior of multilayer pellets.

- API-layered and coated pellets were manufactured in fluid bed equipment in different compositions. Problems encountered during manufacturing were successfully solved and the transfer of the technology to a different device showed the procedure to be robust enough to withstand significant differences in manufacturing equipment.
- Two image analysis methods for the measurement of particle size were compared and evaluated. For the purpose of film thickness measurements the two methods gave similar results even though they differed substantially in the measurement of particle size characteristics. Results indicate that the automatized method using large sample sizes was more robust to sampling effects and sample characteristics.
- Raman spectroscopy proved to be a good tool for the measurement of the film thickness of coated pellets. Multivariate data analysis made it possible to differentiate samples based on their preparation conditions. It was shown that while the configuration of the fluid bed used for sample preparation probably has an effect on the Raman signal this difference does not indicate a difference in the performance of the coating. A relationship between film thickness and gastric resistance was postulated.
- An unexpected change in thermal behavior due to the addition of a coating layer was investigated. The effect of API migration on

dissolution was analyzed and the representativeness of some stability testing procedures was evaluated.

- A multivariate model was developed for the determination of the degree of API crystallinity from intact drug-layered pellets.
- Stability testing results emphasize the importance of packaging material and storage condition selection.

Part of the purpose of the study was to investigate the use of widespread analytical methods in the development of pellets. As multiunit systems are much less researched than traditional dosage forms analytical methods are not usually developed with the goal of making them easy and efficient to use in their development. Our results showed that nevertheless some tools primarily used in the development of other dosage forms can be efficiently employed for pellets if their unique nature is taken into consideration.

PUBLICATIONS RELATED TO THE THESIS

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