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Research Paper

Safety and Robustness of Coated Pellets: Self-Healing Film Properties and Storage Stability

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Purpose. Aim of the study was to verify the safety of chlorpheniramine maleate pellets, coated with blends of poly(vinyl acetate) and poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer. Therefore, the impact of mechanical forces and storage conditions on the drug release was investigated.
Results. Similar release profiles before and after compression of the pellets to tablets underlined the high film robustness. A damage of the film coat with a razor blade resulted in a premature release, but without a burst. After a similar damage with a needle, the release profile remained almost unchanged, which indicated a swelling based self repair mechanism of the film. Additional studies were dedicated to the storage stability at three different conditions. A slightly delayed release was obtained after 6 months storage at 25°C and a marginally accelerated release was measured after storage at elevated temperatures. No drug migration into the coating layer was detected during storage by confocal Raman microscopy. ^{1}H-NMR analysis during storage demonstrated, that no polymer or drug degradation had occurred and the plasticizer concentration remained constant.
Conclusion. The polyvinyl based coating blend for modified release pellets demonstrated a high safety, due to their high robustness and compressibility as well as their satisfying storage stability.

KEY WORDS: confocal Raman microscopy; Kollicoat®; pellet; safety; storage.

INTRODUCTION

Whenever a functional film coat is used to achieve a modified release from pellets, a major focus has to be set on the safety of the dosage form. Safety in this case means to verify, that the functionality of the film coat is guaranteed over the shelf life of the dosage form. A loss of the film coat functionality will result in a burst release after administration. This burst release can cause intensified local side effects and can even lead to life-threatening side effects in case of a narrow therapeutic window.

The functionality of the film coat can be damaged by mechanical forces during manufacturing (e.g. during tablet compression) or by inappropriate handling by patients (e.g. splitting of coated tablets). Additionally, alteration of the film coat during storage, especially at elevated temperatures, can also cause a loss of film functionality (1). Therefore, a high robustness of the film coat against mechanical forces and during storage is required to ensure its functionality until the end of the shelf life and beyond.

In general, a high flexibility of the film coat improves its resistance against mechanical forces. A high mechanical robustness of the film is of major importance, to guarantee a stable release, which also ensures the safety of the dosage form for patients. Some frequently used polymers for modified release, like ethyl cellulose (EC), show a high brittleness and weak resistance to mechanical forces (2). An advantageous high flexibility has been demonstrated for poly(vinyl acetate) (PVAc), a water insoluble polymer for modified release applications (3,4). Dashevsky *et al.* investigated the compressibility of propranolol pellets, coated with PVAc or EC, with and without plasticizer (5). The addition of a suitable plasticizer in an appropriate concentration increased the film coat flexibility of the different polymers and thereby prevented damage and premature release after compression (2,6).

Apart from damage by mechanical forces, the functionality of the film coat can also be lost by film coat alteration during storage. Several factors have been reported in literature for different film coat materials, which can affect the release during storage. Besides migration processes of the drug or the plasticizer within the coated dosage forms (7,8), the alteration of film coats at elevated temperatures in combination with a high humidity was in the main focus of interest. The impact of storage time and storage temperature on the release from coated dosage forms is published thoroughly in literature, using cellulose based polymers (9,10), polymethacrylate based polymers (11–13) or polyvinyl based polymers (14,15).

In general, the drug release from pellets, coated with polyvinyl based films (e.g. PVAc), can be adjusted via the film

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coat thickness, the type and concentration of plasticizer (14) as well as by addition of a soluble pore former to the film coat composition (16). The successful use of poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA-PEG) as pore forming polymer, in blends with PVAc, has been reported for modified release tablets (17,18) as well for modified release pellets (19,20). Event though, the compressibility and storage stability of PVAc coated dosage forms was already investigated (6,14), the influence of the addition of PVA-PEG on storage stability and compressibility is still unexplored.

Three procedures were implemented to verify the safety and robustness of PVAc/PVA-PEG coated pellets. Primarily, the resistance of coated pellets against the mechanical forces during a tablet compression process was analyzed. In a second series, an inappropriate handling of the pellets was imitated. The film coat was damaged manually to clarify the robustness of coated pellets. Finally, the pellets were stored for 6 months at different climate conditions, to clarify their storage stability.

During storage, alterations in the film coat structure were analyzed using confocal Raman microscopy (CRM). Raman spectroscopy is one well-established technique for identification and characterization of solid states of pharmaceuticals. It is a robust and reliable method yielding information of high quality with a low detection limit of 0.1–1% (21). In addition it requires minimal sample preparation and is suitable for high throughput screening and automatization. In combination with an optical microscope, Raman spectroscopy can be implemented to map a specimen and to provide spatially resolved chemical information on the underlying species. In recent years, progress in laser equipment, development of high quality holographic filters and gratings as well as advances in charge couple device (CCD) technology has led to an advent of Raman microscopy (22). Employing the principle of confocality, modern Raman microspectrometers allow rapid chemical mapping with high spatial and spectral resolution. It is possible to reveal the exact composition and spatial distribution of complex mixtures of components. Nowadays, modern confocal Raman microscopy was successfully applied in many fields of pharmaceutical sciences (23–25). Nevertheless its use in the field of pellet coating has been rarely published (26,27).

MATERIALS AND METHODS

Materials

Chlorpheniramine maleate (CPM) was delivered from SelectChemie AG, Zürich, Switzerland. Hydroxypropyl methyl-cellulose (Methocel™ E3 Premium, 3 cps) was delivered from Dow Chemical Company; Midland, MI, USA. Cellulose starter cores (Cellets® 700-1000 μm) were received from PharmaTrans Sanaq AG, Basel, Switzerland. Talc was delivered from Luzenac val Chisone, Porte, Italy. Titanium dioxide (TiO_2) was purchased from Kronos Titan GmbH & Co, Leverkusen, Germany. Propylene glycol was delivered from Sigma-Aldrich Chemie GmbH, Steinheim, Germany. Microcrystalline cellulose (Vivapur PH 102) was purchased from JRS Pharma GmbH & Co, Rosenberg, Germany. Spray dried lactose (316 Fast-Flo Lactose) was delivered from Foremost Farms USA, Baraboo, WI, USA. Aerosil® 200 was purchased from Evonik Degussa GmbH, Rheinfelden, Germany. Magnesium stearate was delivered from FACI SpA, Carasco, Italy. Poly(vinyl acetate) (PVAc; Kollicoat® SR 30D) and poly(vinyl alcohol)–poly (ethylene glycol) graft copolymer (PVA-PEG; Kollicoat® IR) were received from BASF AG, Ludwigshafen, Germany. All other used chemicals were of reagent grade.

Preparation of Film Coated Pellets

Chlorpheniramine maleate (CPM) pellets were manufactured in a fluidized bed coater (Mycrolab; OystarHüttlin GmbH, Schopfheim, Germany) by spraying an aqueous drug-binder solution onto cellulose starter cores. The CPM pellets were coated in the same fluid bed coater to different film coat thickness, using three coating dispersions with different PVAc/PVA-PEG ratios (Table I, samples I–IV). The process parameters from pellet layering and coating as well as the preparation of the coating dispersion were published in a previous article (20).

Compression of Pellets to Tablets

CPM pellets were compressed to tablets to clarify their compressibility. Coated CPM pellets (sample I) were blended with a direct compression powder blend (25% *w*/*w*) in a turbula blender for 5 min. The powder blend comprised spray dried lactose (50% *w*/*w*), microcrystalline cellulose (48.5% *w*/*w*), Aerosil® 200 (0.5% *w*/*w*) and magnesiumstearate (1.0 % *w*/*w*). Biplane shaped, round tablets with 15 mm diameter, 1.2 g tablet mass and 160 mg CPM content were compressed, using an EK 0 single punch press (Korsch AG, Berlin, Germany). Tablets were compressed at two compression forces of 10.5–13 and 16.5–18.5 kN, resulting in a tablet hardness of 85 and 170 N, respectively.

Table I. Compositions and Coating levels of Investigated CPM Pellets

	Sample			
	I	II	III	IV
Performed study/aim	Compressibility	Robustness	Storage stability	Storage stability
CPM drug load[a]	57%	54%	63%	49%
PVAc/PVA-PEG ratio	9:1	9:1	9.5:0.5	8.5:1.5
Coating thickness[b]	18%	20%	13%	23%
Plasticizer concentration[b]	5%	5%	5%	5%

[a] Percent (w/w) after coating
[b] Percent (*w*/*w*) based on dry polymer

Robustness of Film Coat to Mechanical Forces

The surface of PVAc/PVA-PEG coated CPM pellets (sample II) was manually treated to damage the film coating. The integrity of the coating was either compromised by manually puncturing it with a needle (size 26G 3/8) or by slicing with a razor blade. Additionally, CPM pellets were cut in two half's as a positive control. The drug release from damaged CPM pellets was compared to undamaged pellets.

Scanning Electron Microscopy (SEM)

Treated pellets and sectioned tablets containing pellets, were fixed on a small metal stub and sputtered with gold, using a SCD500 high vacuum sputtering device (BAL-TEC, Balzers, Liechtenstein). The samples were analyzed, using a Supra™ 40 electron microscope (Carl Zeiss NTS GmbH, Oberkochen, Germany).

Long-term Stability Studies

Five grams of coated CPM pellets (samples III & IV) were filled in 30 ml HDPE bottles with self sealing cups and were stored in a stability test chamber VB Pharma (Vötsch Industrietechnik GmbH, Balingen-Frommern, Germany), which were equilibrated at three climate conditions, 25°C/60% relative humidity (rH), 30°C/65% rH and 40°C/75% rH (28). After predetermined time intervals, the pellets were analyzed using dissolution testing, confocal Raman microscopy and ^{1}H-NMR spectroscopy.

Dissolution Rate

The drug release from coated pellets was analyzed, using an USP XXIII rotating paddle method at 37°C medium temperature and 50 rpm rotation speed over a 9 h period. Dissolution studies (n=5) were carried out in 750 ml of hydrochloric acid / sodium chloride solution (pH 1.2). After 2 h, the media pH was changed from pH 1.2 to 6.8 to simulate the gastric transition, according to the European pharmacopoeia (29). The content of CPM was measured spectrophotometrically at 265 nm (pH 1.2) and 262 nm (pH 6.8).

Confocal Raman Microscopy (CRM)

Film coated pellets were embedded using LR White Resin (Electron Microscopy Sciences, Hatfield, PA, USA). Cross sections thereof were prepared using a glass knife microtome (Leica EM UC 6, Leica Microsystems AG, Glattbrugg, Switzerland). The cross sections were analyzed, using an upright confocal dispersive laser scanning Raman microscope CRM200 (Witec GmbH, Ulm, Germany) equipped with a frequency doubled Nd:YAG laser (532 nm, 50 mW). A long working distance Plan-Neofluar® objective (20×, numerical aperture 0.4; Carl Zeiss AG, Oberkochen, Germany) and a thermoelectrically cooled CCD detector DV401 (Andor Technology, Belfast, Nothern Ireland) were employed. Data was processed using the software Witec Project 1.90 (Witec GmbH, Ulm, Germany).

Nuclear Magnetic Resonance Spectroscopy (NMR)

Five coated pellets were filled into a small vial and 600 µl d_6-Dimethylsulfoxide (d_6DMSO) were added. The samples were dissolved in d_6DMSO under periodical shaking for four hours, whereby solely the cellulose cores, talc and TiO_2 remained insoluble. 400 µl of the sample was transferred into a tube and a ^{1}H-NMR spectra was recorded, using a DMX 500 MHz system (Bruker BioSpin GmbH, Rheinstetten, Germany). The complete analysis was carried out in duplicate. The NMR spectra were evaluated using ACD SpecManager, Version 9.06 (Advanced Chemistry Development Inc., Toronto, Ontario, Canada).

RESULTS

Compressibility of Coated CPM Pellets

After compression, some coated pellets (sample I) were visible on the surfaces and edges of the tablets, which appeared visually undamaged. A closer look was made on the coated CPM pellets (sample I) inside the tablets, which were also undamaged after compression (Fig. 1a, b). SEM pictures showed an undamaged surface, without any cracks or deformations, independently from the applied compression force. Additionally, the pellets were homogeneously distributed inside the tablets (pictures not shown). The release from the pellets compressed to tablets was almost similar to the release from single pellets. All three profiles demonstrated a sigmoid shaped release pattern, comprising a lag-time of 2 h with a fast and continuous release afterwards, reaching a complete drug release after 7 h (Fig. 2). The different compression forces did not show a huge impact on the release profile. Some small differences were obtained, comparing the release from single pellets and pellets compressed into tablets. The tabletted pellets showed a marginally faster release between 2 and 3 h and contrarily a slower release at the end of the release between 4 and 6 h. However, the differences were only significant for tablets of 170 N hardness.

Robustness of Film Coat to Mechanical Damage

SEM pictures of coated CPM pellets (sample II) showed a tremendous damage of the film coat after treatment with a needle. Several craters with approximately 50–100 µm diameter were detected (Fig. 1c). The damage seemed to affect only the film coat without reaching the drug layer. The razor blade treatment resulted in an even worse damage of the film coat. Several long cuts were detected on the film coat surface (Fig. 1d). In some cases, the complete film coat was damaged and the cut reached the drug layer.

Very surprisingly, the release profile from pellets after treatment with a needle was similar to the release from undamaged pellets (Fig. 3). The damaged pellets showed a slow increase of the release to 7% after 2 h, whereby the undamaged pellets did not show a release upon that time. After 2.5 h, untreated and needle punctured samples demonstrated a fast and continuous release, leading to a complete release after 7 h. A different release profile was obtained after the razor blade treatment (Fig. 3). The shape of the release profile had changed and an almost linear release (r^2=0.9932) over 7 h was obtained with an increase of 15–20% release per hour. The release was initiated immediately and ended after 7 h. Interestingly, both

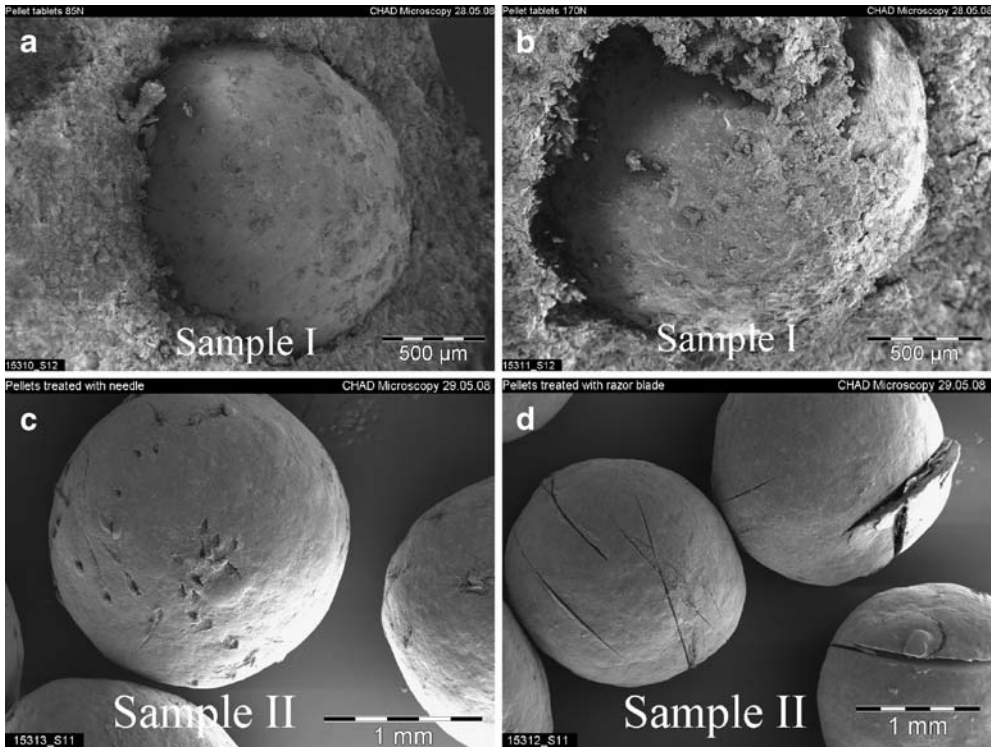

Fig. 1. Coated CPM pellets after compression into tablets with 85 N hardness (**a**) and 170 N hardness (**b**) and after treatment with needle (**c**) and razor blade (**d**).

treatments did not result in a burst release. The positive control with CPM pellets, cut in two half's, showed an immediate release, reaching 100% release after 15 min (Fig. 3).

Long Term Stability after 6 Months

Drug Release

Two samples of CPM pellets (samples III & IV) were used to investigate the long term stability (Table 1). Both samples showed a lag-time of approximately 1.5 h, but the release afterwards was different (Fig. 4a, b). Due to the higher coating level (23%), sample IV showed a slower release, whereby >95% release was achieved after 6 h instead of 3 h at 13% coating level (sample III). The release from both samples (sample III and IV) was not affected by the media change after 2 h from pH 1.2 to 6.8 (Fig. 4a, b), which underlined the pH independent drug release from PVAc/PVA-PEG coated CPM pellets, reported in various previous publications (19,20).

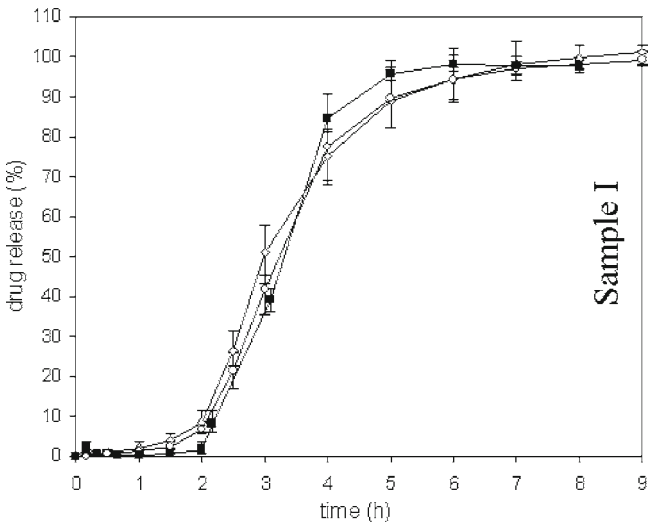

Fig. 2. Release from coated CPM pellets after compression to tablets with 85 N (*open diamond*) and 170 N hardness (*open circle*) in comparison to release from single pellets (*closed square*).

The pellet color and visual appearance remained unchanged after storage at 25°C/60% rH. The release profiles after 1 month storage at 25°C were identical with the release before storage with the same sigmoid shape and the same lag-times (Fig. 4a). Solely, sample III showed a minor delayed release, whereas >95% drug release was achieved after 4 h instead of 3 h (before storage). A prolonged storage time of 3 and 6 months at 25°C (sample III) demonstrated a minor impact on the release profiles, whereby a delayed release with a marginally extended lag-time was obtained. However, a complete drug release was achieved after the same time. CPM pellets (sample IV) demonstrated no change of the release profile between 1 and 3 months storage. Solely after 6 months storage at 25°C, the release was delayed with a little extended lag-time (Fig. 4a).

After storage at 40°C/75% rH, the pellet color changed from white to slight yellow. A sticking of pellets in their bottles was observed, whereby a gentle shaking was sufficient to separate the pellets from each. Solely after 6 months storage at 40°C, a more intense agitation was necessary for separation of the sticking pellets. The shape of the release profiles from both samples remained sigmoid after storage at 40°C/75% rH. However, CPM pellets from sample III showed

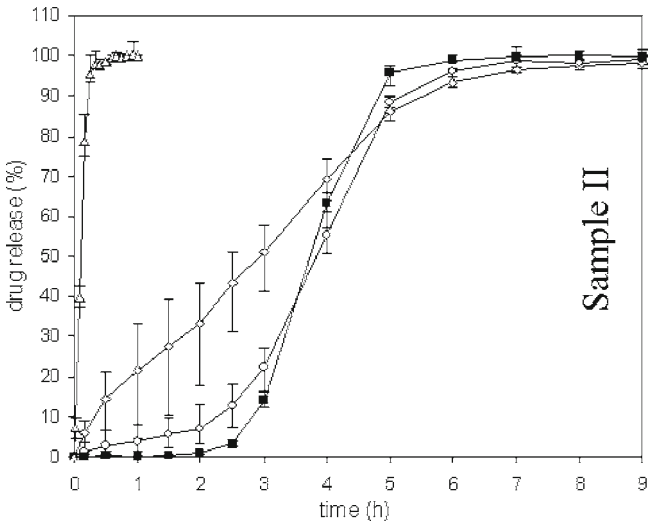

Fig. 3. Release from undamaged coated CPM pellets (*closed square*), after needle damage (*open circle*), after razor blade damage (*open diamond*) and from CPM pellets cut in two half's (*open triangle*).

a delayed release with an extended lag-time already after 1 month storage (Fig. 4b). Interestingly, the release was not further delayed but contrarily marginally faster after 3 and 6 months storage, compared with release after 1 month. CPM pellets from sample IV showed a similar behavior. After 1 month storage at 40°C/75% rH, the release was delayed and the lag-time was extended (Fig 4b). In contrast, the release after 3 months was almost similar to the release before storage and was even faster after 6 months with a reduced lag-time, compared to release before storage. Nevertheless, the differences of the release profiles before and after storage were small. At higher film coat thickness (sample IV), a smaller deviation (<10%) was obtained than with lower film thickness (sample III, 10–20% deviation). However, the shape of the release profile was not affected significantly by the storage time or the storage temperature.

Interface Between Drug Layer and Coating Layer

A sharp interface between the drug and the coating layer before storage was confirmed for sample III and IV by confocal Raman microscopy (Fig. 5a). Furthermore, the images demonstrated the homogeneity of the drug (Fig. 5b, in red) and the coating layer of PVAc/PVA-PEG (Fig. 5c, in green) as well as the homogeneous distribution of talc (Fig. 5d, in orange) and titanium dioxide (Fig. 5e, in pink) in the coating layer. The film coat material was partly dissolved by the embedding resin (Fig. 5f, in blue), resulting in a diffusion and migration of film coat material into the resin. This diffusion and migration was related to the embedding conditions of the pellets and not to the storage conditions. The images after 6 months storage at 25°C/60% rH and 40°C/75% rH demonstrated a similar clear intersection between drug layer and film coat, respectively (Figs. 6a–c and 7a–c). Neither the storage time nor the storage temperature caused a migration of drug into the film coat. Clear intersections were detected at all samples, investigated during the stability study (data not shown). Additionally, the homogeneous distribution of talc (in orange) in the film coat was not affected by storage time nor storage temperature (Figs. 5d, 6d and 7d).

The clear intersection between the drug and coating layer can be visualized more precisely by plotting the Raman signal intensities from CPM, PVAc/PVA-PEG and embedding resin along the transverse cross section of the picture (supplementary information). The red line (drug signal) increases abruptly from 0 to >1,200 cts at the drug layer's boundary. The diffusion of coating material into the embedding resin can be also visualized. Both lines, the green film coat signal and the blue resin signal increase or decrease much gentler.

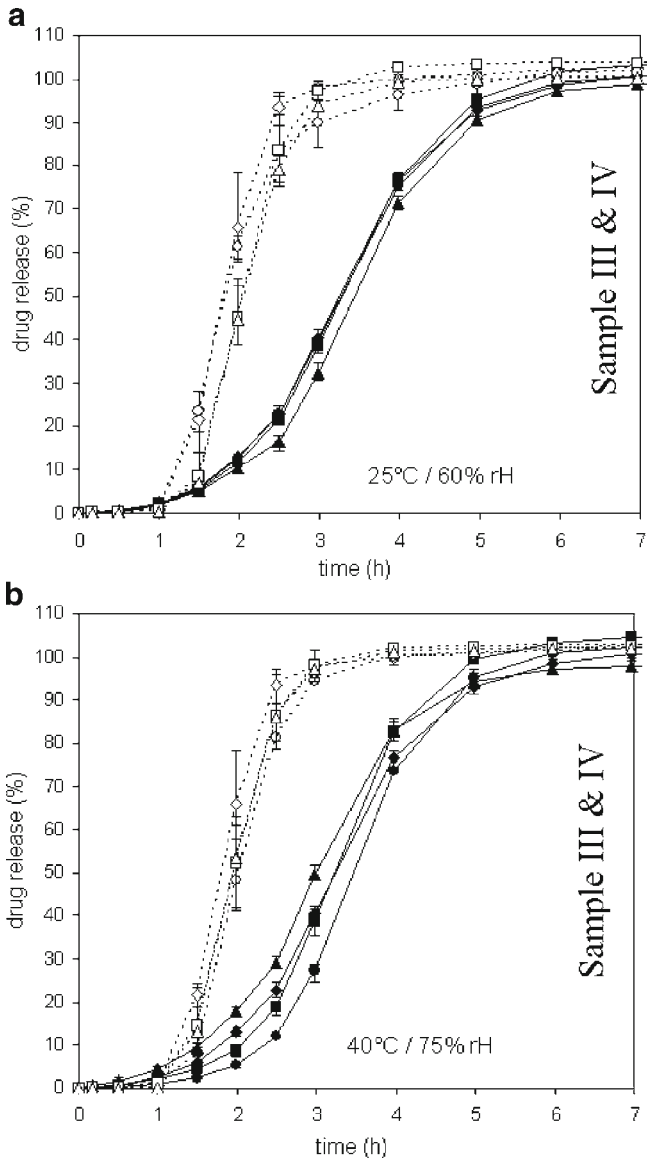

Fig. 4. **a** Release profile from coated CPM pellets with 13 % (*open symbols*) and 23 % coating level (*closed symbols*) before storage (*diamond*) and stored at 25°C/60% rH for 1 month (*circle*), 3 months (*square*) and 6 months (*triangle*). **b** Release profile from coated CPM pellets with 13 % (*open symbols*) and 23% coating level (*closed symbols*) before storage (*diamond*) and stored at 40°C/75% rH for 1 month (*circle*), 3 months (*square*) and 6 months (*triangle*).

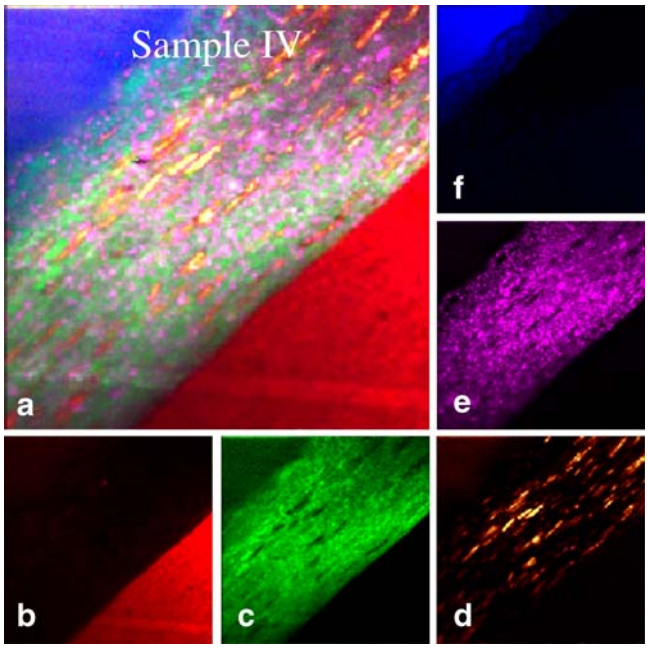

Fig. 5. Confocal Raman microscopic mapping of coated CPM pellet cross section (sample IV) before storage: overlay (**a**); single component visualizations of CPM (**b** *red*), PVAc/PVA-PEG (**c** *green*), talc (**d** *orange*), TiO_2 (**e** *pink*) and resin (**f** *blue*). Edge length 200 μm.

In both samples (III and IV), small clusters of film coat material and titanium dioxide were observed after 6 months of storage (Figs. 6c, e, 7c and e). These clusters, visible as bright green and pink domains (indicated with arrows) are areas of higher density of the respective material. The clusters are not visible in the image before storage (Fig. 5a) and are also not detected after 1 and 3 months storage at 25°C/60% rH (data not shown). These clusters were discovered firstly after 3 months storage at 30°C or 40°C and after 6 months, at all three storage conditions. The amount and size of detectable clusters was differing from sample to sample, making a clear conclusion on impact of storage conditions on size and number of clusters impossible.

Degradation of Drug, Polymer and Plasticizer

NMR analysis was implemented to detect possible degradation processes and a possible migration of the plasticizer, propylene glycol. The weight of five coated pellets, used for the analysis, differed only marginal before and after storage (20.9 mg *versus* 20.7 mg). A significant weight difference from sample to sample was measured with a standard deviation of 1.21 and 0.72, respectively (n=10). Therefore, NMR spectra were evaluated qualitatively, since a quantitative evaluation comprised a high risk of failure.

^{1}H-NMR spectra from CPM pellets after 6 months storage 40°C/75% rH were compared with the spectra before storage (Fig. 8). Both spectra comprised 29 NMR signals of different intensities, which could be assigned to the different components (drug, binder, film coat materials and plasticizer). The signal intensities after 6 months storage were marginally reduced, which was probably caused by the differences in pellet weight. The chemical shift of the signals was unchanged and no additional signals were detectable after 6 months storage. Furthermore, no signals disappeared or were reduced significantly. The signal of propylene glycol at 0.98 and 0.99 ppm (doublet from methyl protons) was detectable with similar signal intensity even after 6 months storage at 40°C/75% rH (Fig. 8). Both propylene glycol signals were visible at all stability samples (data not shown).

DISCUSSION

Compressibility of Coated CPM Pellets

It was demonstrated successfully, that a film coating of PVAc and PVA-PEG in 9:1 ratio was robust enough to survive a tablet compression process. Compression forces of 10–18 kN did not cause a damage of the film coat on the pellets inside the compressed tablets. As a consequence, the release profile from pellets compressed to tablets was very similar to the release profile of single pellets. ANOVA studies of the release profiles showed only one (85 N hardness) and three release values (170 N hardness) with significant difference. Previous publications have demonstrated the high robustness and compressibility of PVAc coated pellets, after addition of 10 % plasticizer (triethyl citrate) (5,30). It was shown, that a reduced concentration of 5 % plasticizer (propylene glycol) in PVAc/PVA-PEG film blends was sufficient to ensure compressibility and to preserve sthe resistance of the film coat to mechanical damage. The risk of a burst release after compression of PVAc/PVA-PEG coated pellets was minimized, confirming successfully their high safety. However, further compression studies using different PVAc/PVA-PEG film blend ratios and different pellet ratios inside the tablets are necessary to demonstrate thoroughly the safety of coated pellets.

Robustness of Film Coat to Mechanical Damage

A burst release, as it was expected and shown for a complete damage of the film coat (pellets cut in two half's), was not obtained after treatment with a needle or a razor blade. It is well known, that PVAc/PVA-PEG film coats start to swell after exposure to water (17). This swelling can obviously repair the damages in the film coat, by reducing the holes, craters and clefts. Since the needle damages were less grave and affected the outer parts of the film coat, the reparation by swelling was much more efficient, resulting in an almost unchanged release profile. The damages from razor blade treatment had a much higher impact and comprised also the inner parts of the film coat, close to the drug layer. In this case, the self repair mechanism of PVAc/PVA-PEG film coats was not strong enough to fully compensate these damages, resulting in the almost linear drug release over 7 h. Nevertheless, the repair mechanism was strong enough to prevent a burst release, which ensures a preserved functionality of the film coat and the safety of the coated dosage form. A similar self repair mechanism was reported by Meyer *et al.* for tablets, coated with PVAc/PVA-PEG film coat blends (31). Meyer *et al.* demonstrated the self repair mechanism at tablets with thicker film coat (12 mg/cm^2) and higher PVA-PEG content (7:3 blend of PVAc/PVA-PEG). Comparing the results from Meyer *et al.* with own results, the same self repair

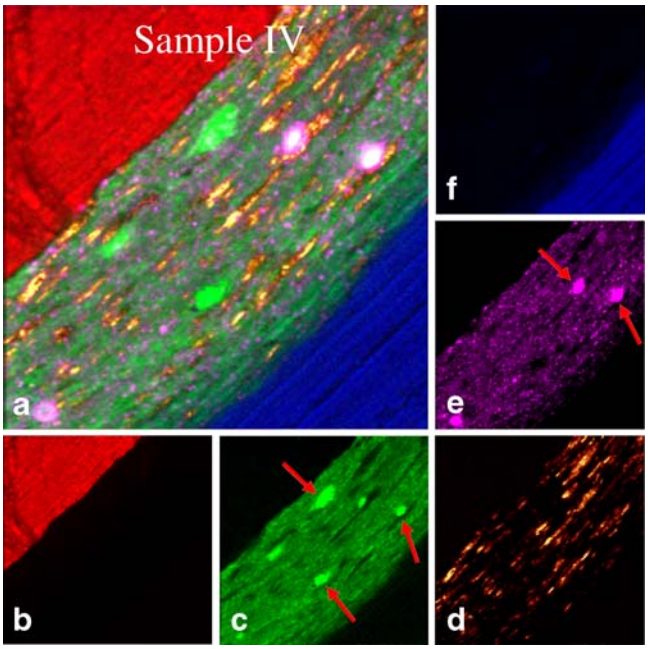

Fig. 6. Confocal Raman microscopic mapping of coated CPM pellet cross section (sample IV) after 6 months storage at 25°C/60% rH: overlay (**a**); single component visualizations of CPM (**b** *red*), PVAc/PVA-PEG (**c** *green*), talc (**d** *orange*), TiO_2 (**e** *pink*) and resin (**f** *blue*). Edge length 200 μm. *Red arrows* (**c**, **e**) indicate clusters of PVAc/PVA-PEG and TiO_2 respectively.

mechanism of was demonstrated successfully for PVAc/PVA-PEG coated pellets, even at the use of a thinner film coat (7.5 mg/cm^2 at pellets) and a reduced PVA-PEG content (9:1 blend of PVAc/PVA-PEG). However, an impact of PVA-PEG or plasticizer content in the film coat on the efficiency of the self repair mechanism could not be verified within the presented data.

Long Term Stability after 6 Months

The observed sticking of pellets after storage was mainly caused by the storage temperature above or at the glass transition temperature (Tg). The Tg describes the temperature range, where the polymer passes from a glassy to the rubbery state. PVAc showed a Tg of 40–42°C, whereby the addition of PVA-PEG decreased the Tg to 33–35°C, depending on the blend ratio (32). Storage conditions above Tg caused an increased stickiness of the polymers, which lead to the enhanced pellet sticking during storage at 40°C/75% rH.

Two different effects were reported from release analysis after storage. A long time storage at 25°C resulted in a delayed release with a extended lag-time, becoming significant after 6 months (Fig. 4a), whereas a storage at 40°C resulted in unexpected inverting results with a marginally faster release, in some cases even faster than before storage (Fig. 4b). The delayed release after storage was probably caused by a curing of the film coat. During curing, the film coat becomes denser, due to a proceeding coalescence of the film coat particles, accelerated at elevated temperatures. Additionally, the stickiness of the film coat increased at elevated temperatures, leading to agglomeration of the pellets. The removal of pellet sticking by agitation probably caused a minor damage of the film coat, which had an opposite effect on the release. This damage in the film coat might compensate the effect of the proceeding film coalescence and resulted in the observed contrarily, slightly faster release after storage at 40°C (Fig. 4b). This behavior during storage was reported for both investigated samples III and IV, independently from the PVAc/PVA blend ratio (Fig. 4b).

Studies by Shao *et al.* on the stability of diphenhydramine pellets, coated with pure PVAc, showed a different behavior during storage (14): after 2 months storage at 25°C, the release profile was unchanged and not affected by the storage time or temperature. In contrast, PVAc coated pellets showed a delayed release even after 1 week storage at 40°C (14). Those results can be compared with observations from the current stability study, since the same plasticizer and a similar coating level was used. Solely, a post-coating thermal treatment was applied on the PVAc coated diphenhydramine pellets (14).

In the current study, the addition of PVA-PEG to a PVAc film demonstrated a positive effect on the storage stability at elevated temperatures of 40°C. A fast delayed drug release after storage at 40°C, as presented by Shao *et al*, was not observed, underlining the positive effects of PVA-PEG on the storage stability. A similar improved storage stability was reported by Siepmann *et al.* for EC films after addition of PVA-PEG (33). The previously reported Tg reduction after the PVA-PEG addition (32,33) might be the reason for the observed positive effect on the storage stability and played definitely a major role during storage of PVAc/PVA-PEG films.

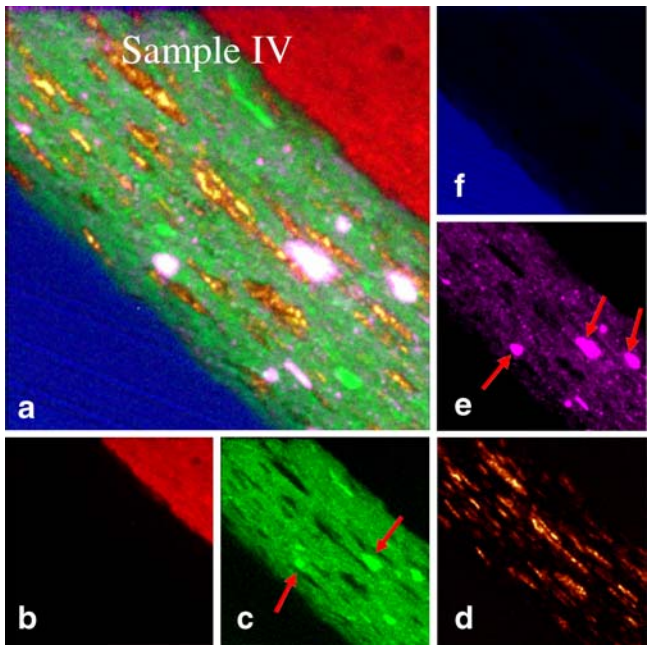

Fig. 7. Confocal Raman microscopic mapping of coated CPM pellet cross section (sample IV) after 6 months storage at 40°C/75% rH: overlay (**a**); single component visualizations of CPM (**b** *red*), PVAc/PVA-PEG (**c**, *green*), talc (**d**, *orange*), TiO_2 (**e** *pink*) and resin (**f** *blue*). Edge length 200 μm. *Red arrows* (**c**, **e**) indicate clusters of PVAc/PVA-PEG and TiO_2 respectively.

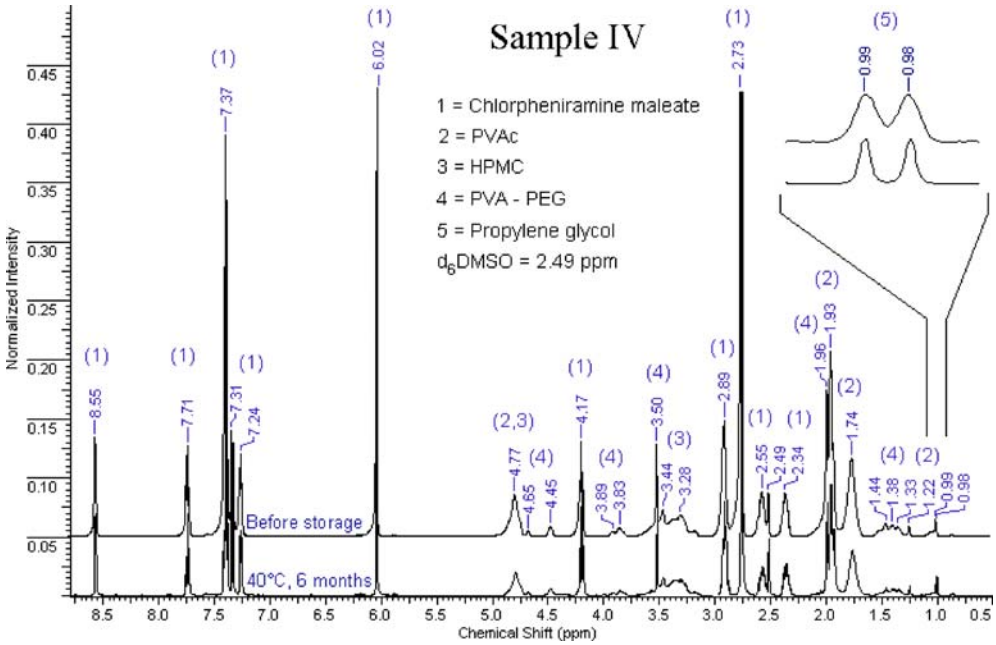

Fig. 8. ^{1}H-NMR spectra from coated CPM pellets (in d_6DSMO) before storage and after 6 months storage at 40°C/75% rH (sample IV).

A faster release during storage, as mentioned in the previous section, can also be caused by drug migration into the film coat (3,8,15), which was investigated by CRM. In a previous article, the EDX technique was used for a similar purpose (19). The major advantage of CRM is its possibility to detect, distinguish and map different compounds, whereas EDX is limited to different atoms. In the case of coated pellets, the drug distribution within the different layers can be detected easily with both methods, since the drug comprises a characteristic atom, chlorine. Similarly, the distribution of talc and titanium dioxide in the coating layer can also be detected with both methods. The film coat polymers, PVAc and PVA-PEG, can be solely visualized by EDX, using the elements O and C, which are both not specific for the film coat polymers. For that reason, CRM was implemented to distinguish and detect the distribution of the film coat polymers as well as changes thereof within storage.

In the current study, CRM analysis displayed a distinct interface between drug layer and film coat and no drug migration into the film coat. Due to the hydrophilic nature of the drug, a migration into the film coat was not expected. Interestingly, small clusters were detectable in the film coat after three and 6 months storage by CRM analysis. These clusters were not composed of degradation products but an assignment to clusters of highly concentrated PVAc/PVA-PEG material and TiO_2 was possible, based on the emitted Raman signals. Furthermore the qualitative evaluation of the ^{1}H-NMR analysis verified that neither the storage time nor temperature caused a degradation of film coat components. No additional NMR signals or changes of signal intensity and chemical shifting were detectable. Both would be clear indications for degradation products. The exact reason for the formation of clusters in the film coat is therefore unknown. The storage above the polymer Tg might be a likely explanation. The change of the internal polymer structure might lead to phase separation in the film coat layer, visible as clusters. Since clusters were detectable in both samples from stability analysis, the cluster formation is not influenced by the polymer ratio or film thickness. Further investigations have to clarify the reason for the cluster formation.

^{1}H-NMR signals from propylene glycol were detected with similar signal intensity within all samples throughout the stability study. Consequently, a similar plasticizer concentration remained in the coated pellets during the six months storage. Due to the low vapor pressure of propylene glycol (0.7 mbar at 30°C) a plasticizer volatilization during storage was eliminated. Unfortunately, the implemented setup for the NMR study did not enable to distinguish between plasticizer in the film coat or migrated in the drug layer. The plasticizer migration was also not measurable by CRM, since the limit of detection is insufficient for the very weak Raman scattering of propylene glycol. Therefore, a possible migration of plasticizer (propylene glycol) from the film coat in to the pellet core could not be clarified and has to be investigated by further studies.

CONCLUSION

The presented study emphasized the safety of the novel film coat blend of PVAc and PVA-PEG for modified release pellets. A swelling based self repair mechanism was postulated, which prevented successfully a burst release, even after a huge damage of the film coat. Additionally, similar release profiles with minor deviations before and after storage underlined a sufficient storage stability of the film coat. The self repair mechanism and the sufficient storage stability are two new advantages of PVAc/PVA-PEG films for pellet coating. Using PVAc/PVA-PEG films, high safety for patients can be achieved and ensured over a long time period. In summary, film blends of PVAc and PVA-PEG have become an interesting alternative film coating polymer, especially for

pellets with modified drug release and a mechanically stressful manufacturing processes (e.g. tablet compression). However, the efficacy of the self repair mechanism and the stability of the film coat during storage have to be further investigated using different drug pellets and other blends of PVAc and PVA-PEG.

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