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Effect of unconventional curing conditions and storage on pellets coated with Aquacoat ECD

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Abstract

Purpose: Purpose of this study was to develop storage stable pellets coated with the aqueous ethylcellulose dispersion Aquacoat ECD. *Methods*: The influence of accelerated curing/storage conditions on the release behavior of Aquacoat/HPMC-coated drug pellets were investigated as a function of various formulations (sealing, plasticizer content, and pore-former type/amount) and process parameters (process humidity, thermal curing, and organic processing). *Results*: Conventionally cured Aquacoat/hydroxypropyl methylcellulose-coated pellets were storage stable at ambient conditions and 25°C/60% relative humidity (RH) but showed a decreasing drug release at 40°C/75% RH, which is a required test condition according to ICH guidelines. *Conclusion*: Only organic processing of dried Aquacoat or unconventionally harsh curing conditions (60°C/75% RH or 80°C) improved the storage stability of Aquacoat-coated pellets at accelerated conditions.

Key words: *Aqueous dispersion; coating; ethylcellulose; pellet; storage stability*

Introduction

The preparation of modified release dosage forms through film coating with aqueous polymer dispersions offers several advantages over organic polymer solutions. The utilization of aqueous dispersions circumvents explosion hazards, as well as environmental or toxicity concerns, which are often associated with organic solvents. Moreover, processing times can be shortened with aqueous polymer dispersions, due to the low viscosities of polymer dispersions, which allow spraying at higher polymer contents compared to solutions[1].

The film formation process with aqueous dispersions of polymers, however, is fundamentally different from organic processing. In the latter case, solvent evaporation increases the polymer concentration to a point, where the polymer comes out of solution and forms a gel. Upon further evaporation of the solvent, the gel solidifies and forms a homogeneous film[2]. The film formation from aqueous colloidal polymer dispersions is more complex. The colloidal particles come into close contact upon water evaporation and form an ordered structure. The closely packed polymer particles will deform and then lose their individual character ('coalesce') as a result of surface tension and capillary forces[3]. Significant coalescence takes place only above the minimum film formation temperature (MFT), where a continuous and clear film is formed during drying[4,5]. However, a clear film does not mean that an interdiffusion of polymer chains between adjacent particles has taken place[4], which is necessary to form mechanically strong films[6]. An interpenetration of polymer chains occurs during 'curing' of the dry films at temperatures sufficiently above the glass transition temperature (T_g) of the polymer[3]. The latter can be lowered by coalescing aids (plasticizers). A reduction of the T_g is especially important for polymers with high glass transition temperatures, like ethylcellulose (T_g 133°C)[7], in order to enhance film formation and/or to reduce coating and curing temperatures[2]. Aquacoat ECD is a commercially available aqueous dispersion of ethylcellulose. One of the plasticizers recommended for Aquacoat ECD coatings is triethylcitrate (TEC)[8]. TEC reduces the T_g of ethylcellulose in the dispersion to values well below 60°C at

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concentrations around the recommended amount of 24% (w/w; based on latex solids)[7,8]. But even curing with dry heat above the T_g (e.g., at 60°C) as recommended by the supplier[7] does not necessarily ensure complete film formation. Changes of the release patterns on storage at ambient as well as at elevated temperatures and humidities were reported for formulations cured with dry heat[9–11]. However, stability under accelerated conditions is important for pharmaceutical dosage forms and official guidelines (e.g., ICH Guideline Q1A) require stability testing at 40°C/75% RH.

A decreased drug release of aqueous coated pellets upon storage at accelerated conditions was mostly attributed to an increased degree of polymer interdiffusion ('further gradual coalescence') in presence of water, which acts as an additional plasticizer for polymers[12]. However, other formulation and/or process parameters were reported to have effects on the storage behavior of Aquacoat-coated pellets. Thus, examples of formulations, which were stable at 40°C/75% RH, can be found in the literature[13]. It was, therefore, the goal of this study to investigate formulation and manufacturing parameters for a potential improvement of the storage stability of Aquacoat/hydroxypropyl methylcellulose (HPMC)-coated pellets.

Materials and methods

Materials

Compound A (Pfizer Ltd., Sandwich, UK), a salt of a weakly basic drug with a molecular weight of 569 g/mol, a melting point of 202°C, and solubilities of 117 mg/mL at pH 2 and 0.03 mg/mL at pH 7.5; micronized aspartic acid (Pfizer Ltd., Sandwich, UK); HPMC (Methocel E5; Colorcon, Orpington, UK); ethylcellulose aqueous dispersion (Aquacoat® ECD, FMC Biopolymer, Philadelphia, PA, USA); polyvinyl alcohol–polyethylene glycol graft copolymer (Kollicoat® IR, BASF, Ludwigshafen, Germany); TEC (Citroflex-2; Morflex, Greensboro, NC, USA), talc (micronized pharma grade; Luzenac, Toulouse, France), sugar beads (Suglets sugar spheres NF; 500–600 µm; NP Pharma S.A., Bazainville, France); and methanol and acetonitrile (HPLC gradient grade; Carl Roth GmbH and Co. KG, Karlsruhe, Germany) were used.

Methods

Preparation of drug cores

Drug cores were prepared using a fluidized bed coater (Aeromatic Strea-1; Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland) under the following conditions: inlet temperature, 68–70°C; outlet temperature, 40–42°C; air flow rate, 100–120 m^3/h; spray rate, 16 g/min; atomizing air pressure, 2.0 bar; spray nozzle diameter, 1.2 mm.

In the first step, aqueous aspartic acid dispersion (30%, w/w, solids) was sprayed onto 400 g nonpareils, with HPMC (10%, w/w, based on aspartic acid amount) as the binder. The weight gain was 100%. The drug was layered onto 400 g of the acid-layered beads from an aqueous solution (10%, w/w, solids) with HPMC as the binder (10%, w/w, based on drug). The weight gain was again 100%. The drug cores were optionally sealed with a 5% (w/w) aqueous HPMC solution to a weight gain of 10%.

Pellet coating

The aqueous ethylcellulose dispersion used for the coating of the pellets (standard composition) contained the following ingredients: Aquacoat ECD (30% ethyl cellulose dispersion), deionized (DI) water, HPMC (10%, w/w, solution in DI water), talc, TEC in a ratio of 450:450:150:52.5:37.5. Talc (35%, w/w, based on total polymer content) was added to reduce stickiness during coating and curing[12]. Finally, an ethylcellulose:HPMC ratio of 9:1 and a TEC concentration of 25% (w/w, based on the total polymer weight) was obtained. To obtain a 35% TEC concentration, the plasticizer portion was increased from 37.5 to 52.5 parts. According to previous report[13], talc was excluded for Aquacoat/Kollicoat IR and pure Aquacoat coatings. For the preparation of the coating dispersion, TEC was blended with DI water and the mixture was given to Aquacoat ECD. Then the HPMC solution and, thereafter, talc were added to the plasticizer containing dispersion and the dispersion was gently stirred overnight.

The coating dispersion was sprayed onto 500 g pellets using a fluidized bed coater (GPCG 1; Wurster insert; Glatt GmbH, Binzen, Germany). Final weight gains of 30% were targeted, but sampling was also performed at lower coating levels. The process parameters were as follows: product temperature, 39–41°C; actual air flow rate, 80–90 m^3/h; spray rate, 7 g/min; atomizing air pressure, 2.0 bar; and spray nozzle diameter, 1.2 mm. After coating the pellets were dried for 10 minutes and subsequently cured.

Curing conditions

The coated pellets were oven-cured directly after the coating step using dry heat (60°C and 80°C at ambient humidity) or combined heat/humidity [60°C/75% relative humidity (RH)]. The latter samples were therefore put into a desiccator containing saturated NH_4Cl solution, which was placed in an oven.

Storage testing

The cured drug-loaded coated pellets (2 g) were stored in 10 mL open glass vials covered with a filter paper to avoid condensed water droplets to fall into. Stability studies were performed under ambient conditions (21 ± 2°C/45

± 15% RH), 25°C/60% RH in a climatic chamber, 40°C in oven, and according to the ICH guideline for accelerated conditions at 40°C/75% RH in a climatic chamber. Ambient humidities correspond to RHs between 11% and 23% in a 40°C and between 4% and 9% in a 60°C oven. If not stated otherwise, ambient humidities were applied.

In vitro drug release studies

In vitro drug release from about 20 mg coated pellets was determined using the USP apparatus 2 (rotating paddle method) at 100 rpm and 37°C. If not stated otherwise, release studies were performed in 900 mL PBS buffer (pH 7.5). At predetermined time intervals, either 3 mL samples were withdrawn (Vankel 700/800; Varian, Inc., Palo Alto, CA, USA) and the drug concentration in the release medium was determined with a UV-spectrophotometer (HP-8453; Agilent Technologies, Palo Alto, CA, USA) or it was measured online (Vankel 7010 equipped with a Cary 50 UV-spectrophotometer; Varian, Inc., Palo Alto, CA, USA). In both cases the wavelength for quantification was 293 nm.

Plasticizer content determination

The plasticizer (TEC) was extracted from cured coated pellets as follows: 20.0 ± 2.0 mg pellets were accurately weighed into a flask. Acetonitrile (5 mL) was added and the flask was sonicated for 15 minutes. Thereafter, the flask was shaken horizontally (HS501 digital, IKA Werke GmbH & Co. KG, Staufen, Germany) at 100 rpm for 18 hours. The flask content (2 mL) was centrifuged at 28,110 × *g* for 15 minutes (Heraeus Sepatech Biofuge 22R; Haereus Holding GmbH, Hanau, Germany) and then the clear supernatant (1 mL) was diluted with DI water (1 mL). The diluted samples were again centrifuged at 17,000 rpm for 15 minutes before high-performance liquid chromatography (HPLC) analysis. TEC was quantified with a Shimadzu-HPLC (System Controller SCL-10Avp, Liquid Chromatograph LC-10ADvp (2×), Degasser DGU-14A, Column Oven-10ASvp, Diode Array Detector SPD-M10Avp; Shimadzu Deutschland GmbH, Berlin Germany), which was equipped with a C-18 column (Vertex Column Eurospher-100, 140 × 4 mm^2, 5 µm; Knauer GmbH, Berlin Germany). The following methanol (MeOH):water gradient was applied: 0–5 minutes, 50% MeOH; 7–23 minutes, 98% MeOH; 26–30 minutes, 50% MeOH). The flow rate was 1 mL/min. The column temperature was set to 30°C and 50 µL/run was injected. The detection wavelength was 220 nm.

Results and discussion

Storage at 25°C/60% RH or ambient conditions

Pellets coated with Aquacoat/HPMC 9:1 showed an almost linear drug release for about 18 hours at a coating level of 30% (Figure 1). The drug release profiles were stable upon storage at 25°C/60% RH for at least 6 weeks when cured for 2 hours at 60°C as recommended by the manufacturer of Aquacoat (Aquacoat product brochure) (Figure 1a). Pellets cured for 24 hours at 60°C also remained unchanged during 6 weeks at 25°C/60% RH (Figure 1b). Even 52 weeks storage at ambient

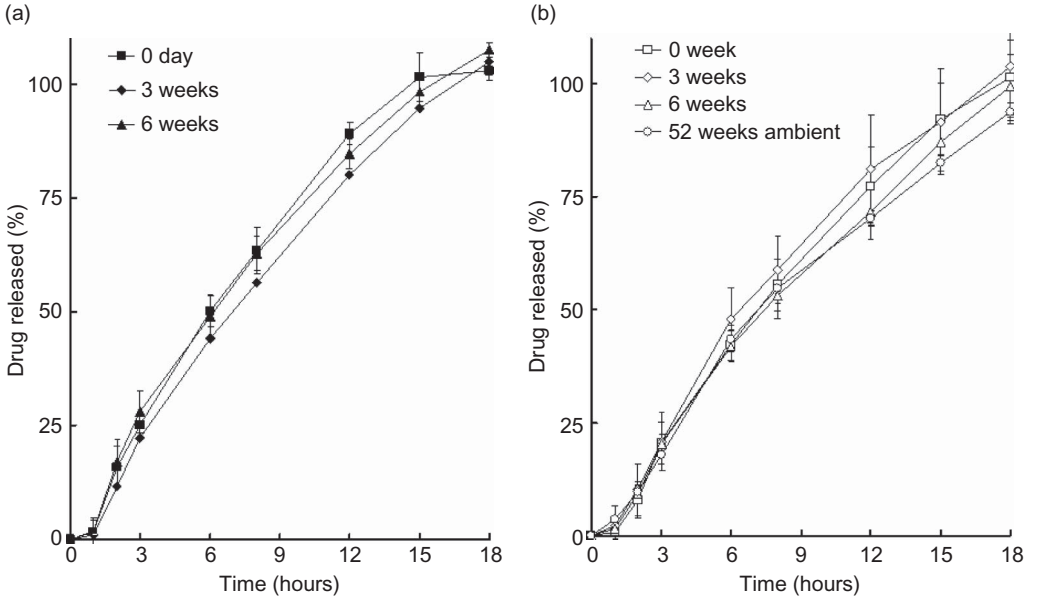

Figure 1. Drug release of 30% Aquacoat/HPMC-coated pellets cured for (a) 2 hours or (b) 24 hours 60°C/ambient humidity as a function of storage time at 25°C/60% RH or at ambient condition.

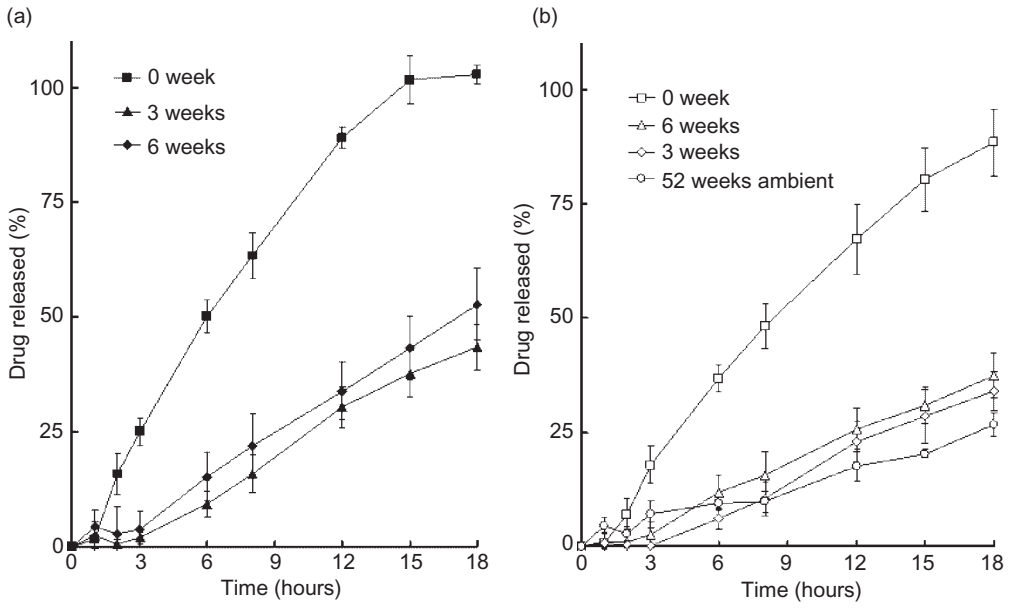

Figure 2. Drug release of 30% Aquacoat/HPMC-coated pellets cured for (a) 2 hours or (b) 24 h 60°C/ambient humidity as a function of the storage time at 40°C/75% RH.

temperature and humidity did not cause alterations of the release pattern.

Storage at 40°C/75% RH

Irrespective of the curing time at 60°C/ambient humidity, the drug release decreased upon storage at 40°C/75% RH (2 hours: Figure 2a or 24 hours: Figure 2b). The storage effect appeared to occur mainly within the first 3 weeks. Only minor changes of the release patterns occurred between 3 and 6 weeks. Continued storage for 1 year indicated that the release rate might even further decrease indicating an ongoing effect beyond a storage time of 6 weeks (Figure 2b). However, the difference to the 6 weeks time point was small.

Drying at 40°C for up to 1 week could not reverse the storage effect at 40°C/75% RH (data not shown), which suggested that the changes were not attributed to an increased water content of the functional coating.

Heat/humidity treatment at 60°C/75% RH

To distinguish whether the observed release changes upon storage of Aquacoat/HPMC-coated pellets at 40°C/75% RH were related to the elevated moisture or the higher temperature, a combined heat/humidity treatment at 60°C/75% RH was applied and the results were compared to the conventional curing at 60°C/ambient humidity. Incubation at 60°C/75% RH for 1 day resulted in a much slower release compared to curing at 60°C/ambient humidity (Figure 3), which revealed the importance of the humidity for the decrease of the release rate.

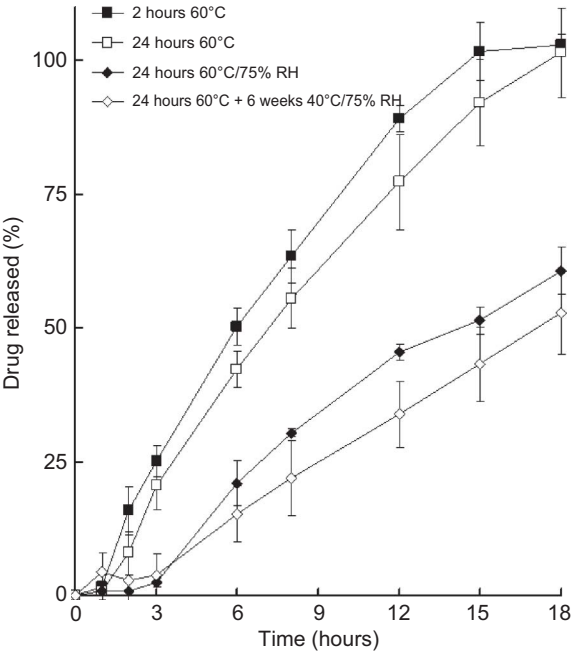

Figure 3. Drug release of 30% Aquacoat/HPMC-coated pellets as function of curing or initial curing with additional storage at accelerated conditions.

Interestingly, the release of pellets, which were conventionally cured (2 hours 60°C) and then stored at 40°C/75% RH for 6 weeks, was almost similar to pellets, which were subjected to 60°C/75% RH directly after coating. Such a correlation was suggested previously, where a heat/humidity treatment was applied to aqueous ethylcellulose coatings[9].

Formulation parameters with a potential stabilizing effect

Core sealing

Pellets with an additional barrier layer of HPMC (10%, w/w) between the drug and the functional coating were manufactured in order to suppress a potential drug migration during storage. In agreement with the formulation without the barrier coating, a large decrease of the release occurred within 6 weeks at 40°C/75% RH (Figure 4). Therefore, drug migration was excluded as the reason for the storage effect.

In contrast to 6 weeks storage at 40°C/75% RH, pellets stored at 40°C/ambient humidity or at ambient temperature and humidity for the same time showed drug release profiles, which were comparable to the initial profile. Thus, the elevated humidity was identified as key factor for the occurrence of a storage effect with Aquacoat/HPMC-coated pellets.

Incubation at 40°C/75% RH for only 24 hours was not sufficient to pick up the moisture sensitivity of the coated pellets, oppositely to 60°C/75% RH (Figure 5). Incubation at 60°C/75% RH for only 2 hours were also not enough to achieve stabilization at this condition (Figure 6). However, drug release did not change further upon a prolongation of the incubation time from 24 to 48 hours at 60°C/75% RH. Therefore, a period of 24 hours was chosen for the heat humidity/treatment. Due to the generally good correlation of Aquacoat/HPMC

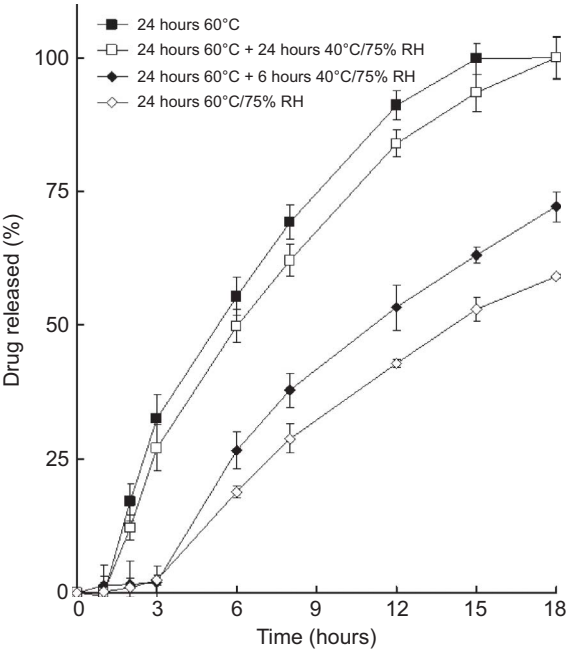

Figure 5. Drug release of 30% Aquacoat/HPMC-coated pellets either conventionally cured (24 hours at 60°C) and then stored at 40°C/75% RH or directly subjected to 24 hours at 60°C/75% RH after coating (formulation with a 10% HPMC seal coating).

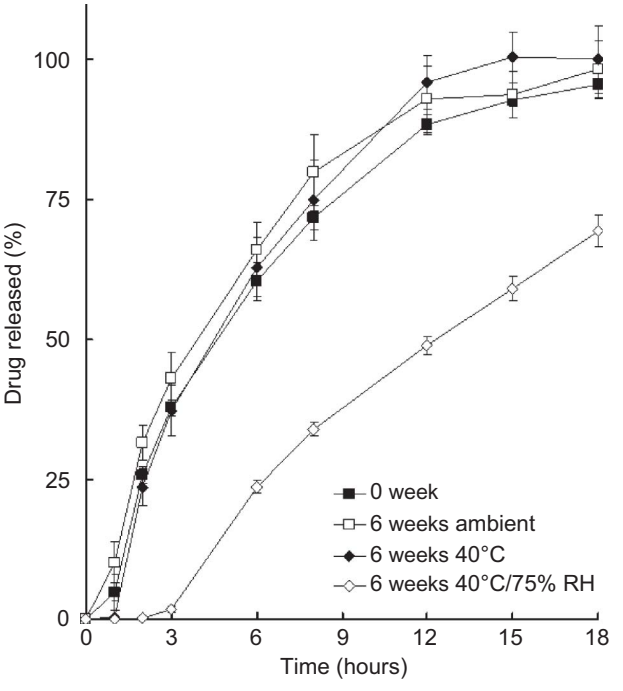

Figure 4. Drug release of 30% Aquacoat/HPMC-coated pellets cured for 2 hours at 60°C as function of the storage condition (formulation with a 10% HPMC seal coating).

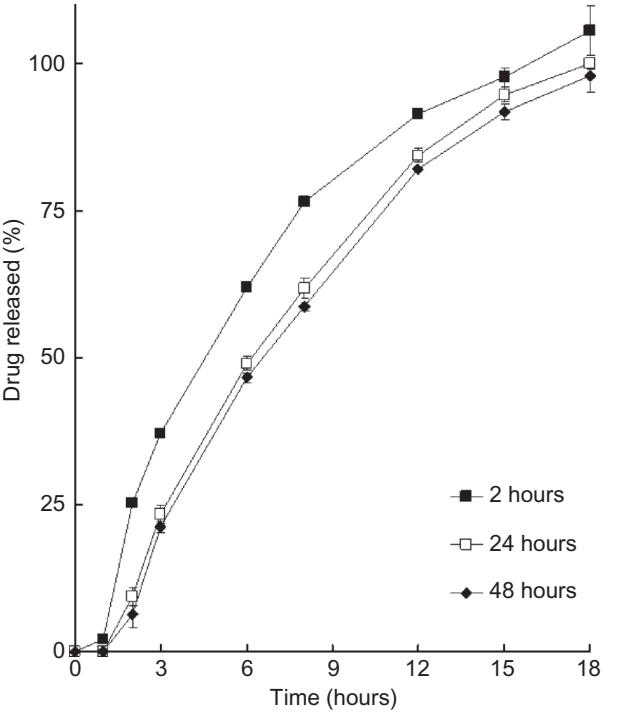

Figure 6. Drug release of 15% Aquacoat/HPMC-coated pellets as a function of incubation time at 60°C/75% RH after coating (formulation with a 10% HPMC seal coating).

pellets incubated at 60°C/75% RH for 24 hours with pellets stored at 40°C/75% RH for weeks, the short-term heat/humidity treatment was used as screening for the moisture sensitivity and thus for a possible storage instability of formulations under accelerated conditions. A correlation of an initial sensitivity of Aquacoat-coated pellets to the 60°C/75% RH treatment and changes of the release patterns upon longer time storage at 40°C/75% RH were reported[9].

Plasticizer amount

A possible explanation for the humidity effect was 'further gradual coalescence' in the Aquacoat/HPMC films in presence of water, which is known to act as an additional plasticizer for ethylcellulose[12]. To enhance the particle coalescence during the spraying process, the amount of plasticizer incorporated into the pseudo-latex was increased. A decrease in drug release was noticed upon increasing the plasticizer concentration from 25% to 35% (w/w, based on polymer). The formulation with 35% TEC (60°C curing) showed an 18 hours profile at a coating level of only 15% (w/w, weight gain based on polymer), whereas 30% coating was necessary to obtain a similar profile with the 25% TEC (Figure 7 versus Figure 1). The slower release could be attributed to an enhanced film formation at the higher plasticizer content. However, the moisture sensitivity of the Aquacoat/HPMC pellets was not improved (Figure 7).

Alternative pore-former

The water-soluble HPMC was used as the pore former for Aquacoat to obtain flexible release profiles over 18 hours at reasonable coating levels. HPMC is the recommended pore-forming agent for Aquacoat[8] and is therefore widely applied for release acceleration of ethylcellulose-coated formulations[10,12,14,15]. However, incorporation of HPMC into Aquacoat can cause flocculation of the ethylcellulose dispersion[16]. Alternative pore formers with improved compatibility to ethylcellulose (e.g., Kollicoat IR) have been suggested recently[13]. Therefore, HPMC was substituted with Kollicoat IR in a ratio Aquacoat/Kollicoat IR 9:1 without success (Figure 8). The superimposing release patterns of pellets, which were subjected to 60°C/75% RH either uncured or after an initial curing at 60°C/ambient humidity, suggested that an equilibrated profile was obtained and further supported the unsuitability of the conventional 'dry heat curing' at 60°C to stabilize the formulations against moisture. Aquacoat/Kollicoat IR- and even pure Aquacoat-coated pellets (Figure 9) were sensitive to moisture at 60°C. Thus, no improvement to Aquacoat/HPMC-coated pellets was obtained, which excluded flocculation of the Aquacoat before and during coating as the key reason for the humidity effect.

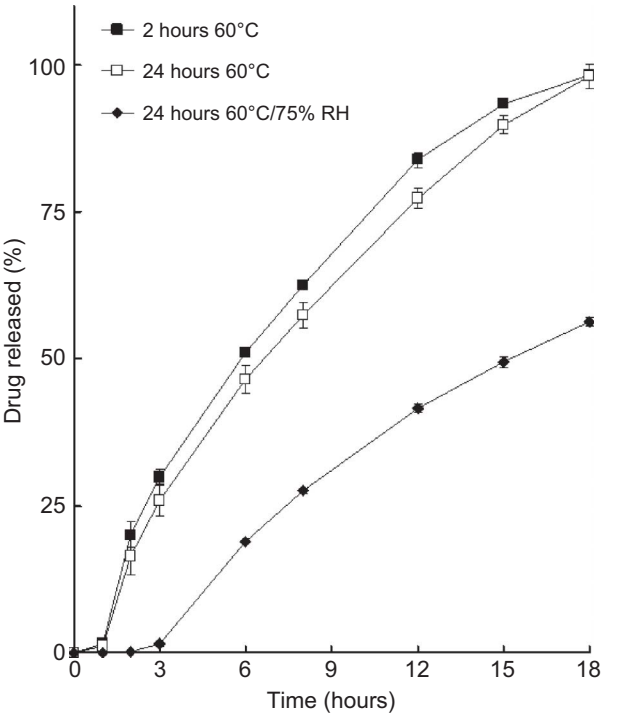

Figure 7. Drug release of pellets coated with 15% Aquacoat/HPMC-coated pellets containing 35% TEC as a function of curing.

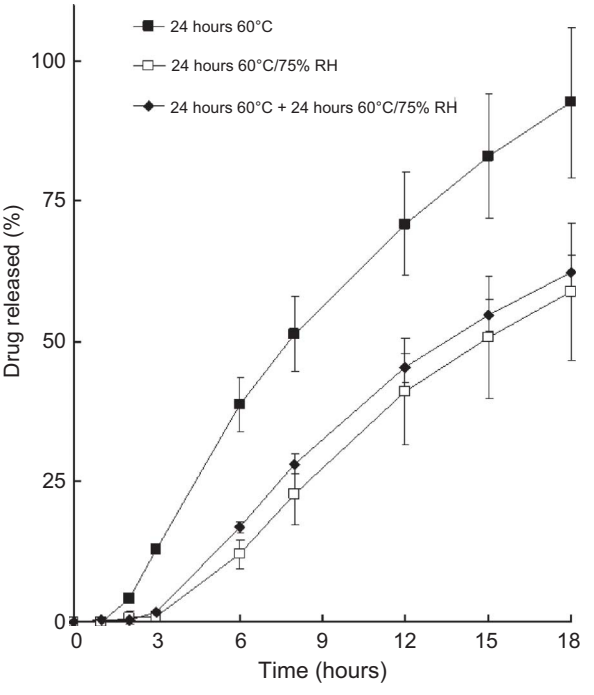

Figure 8. Drug release of pellets coated with 30% Aquacoat/Kollicoat IR 9:1 (weight increase based on polymer) as a function of curing.

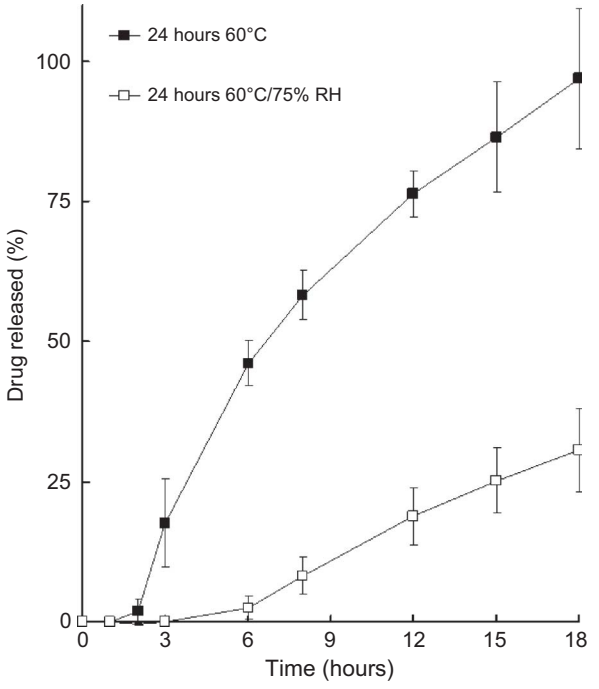

Figure 9. Drug release of pellets coated with 10% Aquacoat (weight increase based on polymer) as a function of the humidity during curing at 60°C.

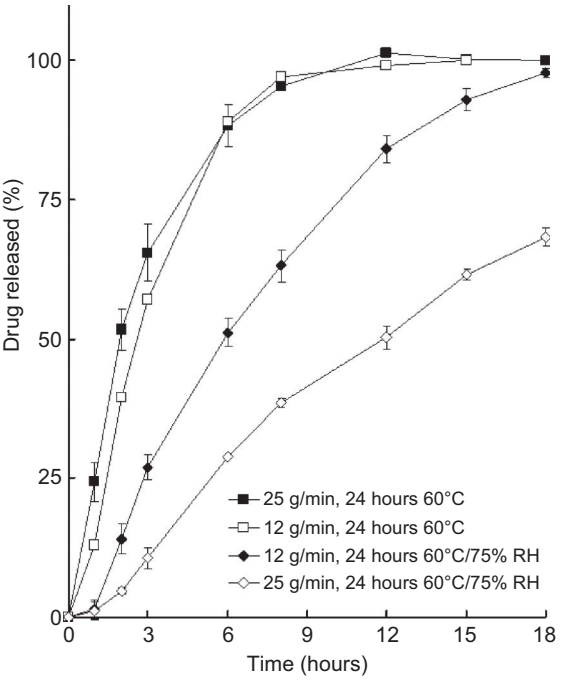

Figure 10. Drug release of 15% Aquacoat/HPMC-coated pellets as a function of spray rate during coating and curing.

Process parameters with a potential stabilizing effect

Process humidity

To improve the film formation and thus the moisture stability of the pellets directly during the coating process, the humidity in the coating chamber was increased. An increase of the spray rate from 12 to 25 g/min (product temperature of 40°C), which corresponded to an increase of the dew point from about 15°C to 26°C, did not improve the moisture sensitivity of the pellets (Figure 10). A limited success could be expected, since conditions like 40°C/75% RH and 60°C/75% RH, where the release was affected, corresponded to dew points of 35°C and 54°C, respectively. However, that the humidity effect even increased with pellets produced at the higher spray rate was unexpected. Besides an increase of the spray rate, also a decrease of the solid content from 15% to 10% failed to stabilize the formulation (data not shown).

Organic processing

In case of 'further gradual coalescence' being the reason for the susceptibility of Aquacoat/HPMC-coated pellets, a coating with an organic solution of both polymers should result in a formulation, which is insensitive to the heat/humidity treatment. Film formation out of organic solutions is fundamentally different from aqueous dispersions, since it does not involve polymer particle coalescence. In order to have a good comparison, pellets were coated with Aquacoat/HPMC from an ethanolic solution (ethanol:water 9:1, w/w). Therefore, dry Aquacoat ECD powder was prepared by drying at 40°C. In comparison to the original coating composition, only the Aquacoat/HPMC ratio was changed from 9:1 to 8:2, since slower release was expected for the solvent processing. Indeed, a 5% coating level (weight gain) was enough to achieve drug release over about 18 hours (Figure 11). The lower film permeability reflected the higher density usually seen with solvent-based film coatings[17]. Slightly faster release was obtained upon incubation of untreated pellets at 60°C for 24 hours, which might be due to the evaporation of some residual solvent. Oppositely to the aqueous formulations, the incubation at 60°C/75% RH did not affect the drug release from the organic coated pellets. The result strongly suggested that polymer interdiffusion as last stage of the film formation process was responsible for the observed humidity effect with Aquacoat/HPMC pellets. The reason why stable release patterns were obtained previously with Aquacoat/Kollicoat IR-coated and conventionally cured pellets[13] could be related to a lower mechanical stress on the external coating, due to a lower osmotic activity of the drug core. The drug core used in the previous study was based on cores, which contained 70% (w/w) of the low solubility drug theophylline ([S] ~10 mg/mL), whereas the highly osmotically active core investigated here contained 25% (w/w) sugar sphere ($[S]_{sucrose}$: 2000 mg/mL) and 45% (w/w) drug salt ($[S]_{Compound\ A}$: 117 mg/mL).

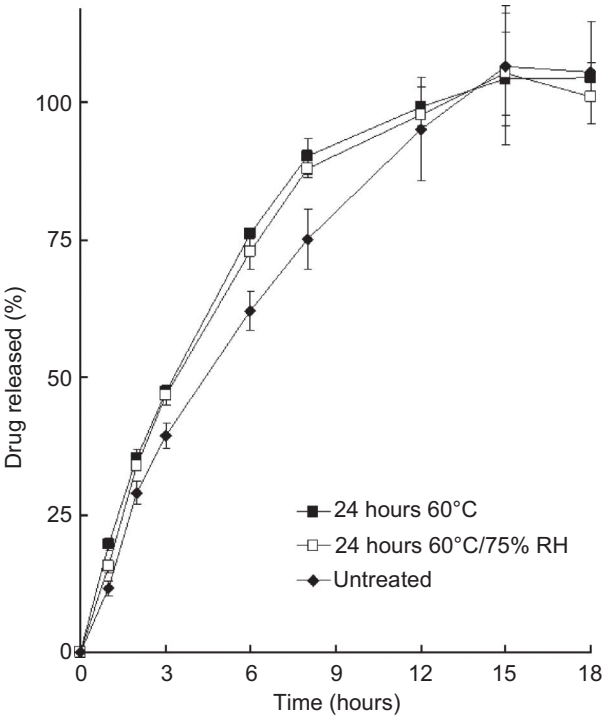

Figure 11. Drug release of pellets coated with an ethanolic solution of Aquacoat/HPMC 8:2 as a function of post-treatment (5% weight increase based on polymer).

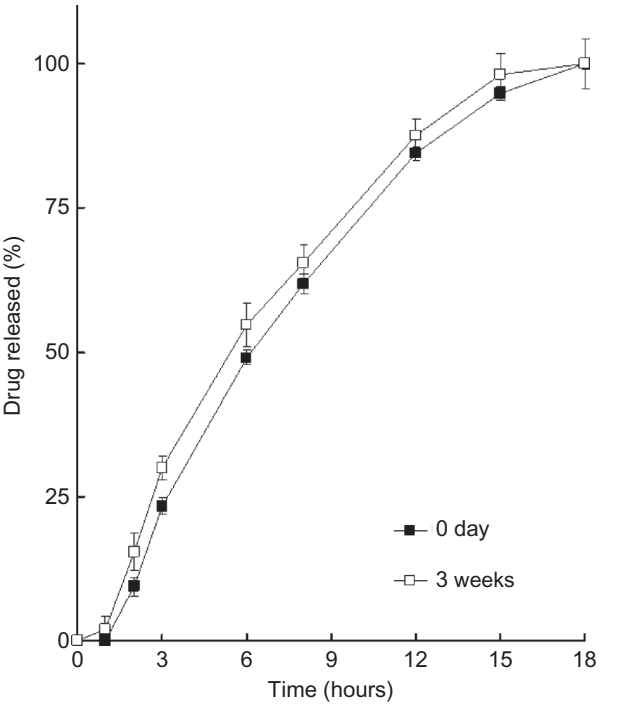

Figure 12. Drug release of 15% Aquacoat/HPMC-coated pellets cured for 24 hours at 60°C/75% RH as a function of storage time at 40°C/75% RH (formulation with a 10% HPMC seal coating).

Unconventional curing conditions

Heat/humidity curing. The high effectiveness of a combined heat/humidity treatment to accelerate polymer interdiffusion was previously described for film coatings obtained from aqueous ethylcellulose dispersions[9,17]. In agreement with the superimposing release profiles obtained after 24–48 hours incubation at 60°C/75% RH and 3–6 weeks at 40°C/75% RH (Figures 3 and 6), the short-term heat/humidity treatment could be expected to stabilize Aquacoat/HPMC pellets against storage at 40°C/75% RH. Thus, the heat–humidity treatment was applied to uncured pellets before subjecting them to 40°C/75% RH. These pellets showed indeed unchanged release pattern after storage at 40°C/75% RH for 3 weeks (Figure 12). Thus, the 24 hours 60°C/75% RH treatment applied as a curing step improved the storage stability of Aquacoat/HPMC-coated pellets at 40°C/75% RH. This stabilization was likely due to a water-assisted polymer interdiffusion responsible for the storage effects at elevated temperature and humidity.

Curing at 80°C/ambient humidity. A curing at an increased temperature was investigated as an alternative to incubation at 60°C/75% RH, which might compromise the stability of moisture-sensitive drugs. Interestingly, the drug release after curing at 80°C for 24 hours was faster compared to pellets cured for 24 hours at 60°C/75% RH (Figure 13). However, this did not

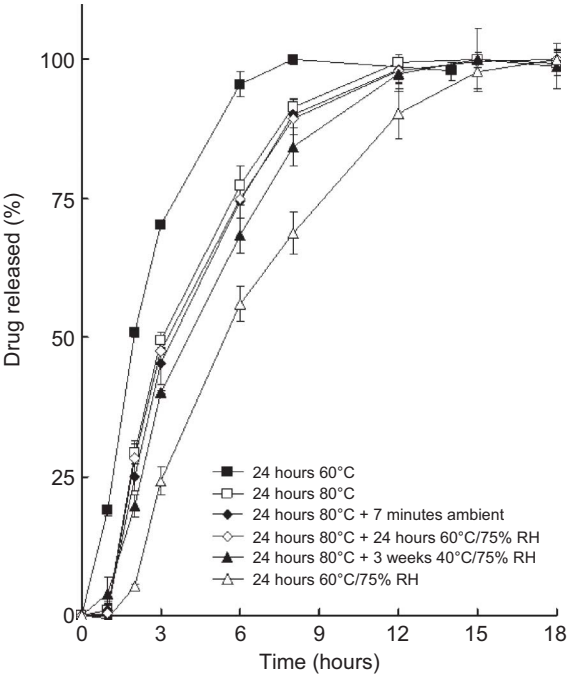

Figure 13. Drug release of 15% Aquacoat/HPMC-coated pellets as a function of curing and storage (formulation with a 10% HPMC seal coating, release in 0.01 N HCl).

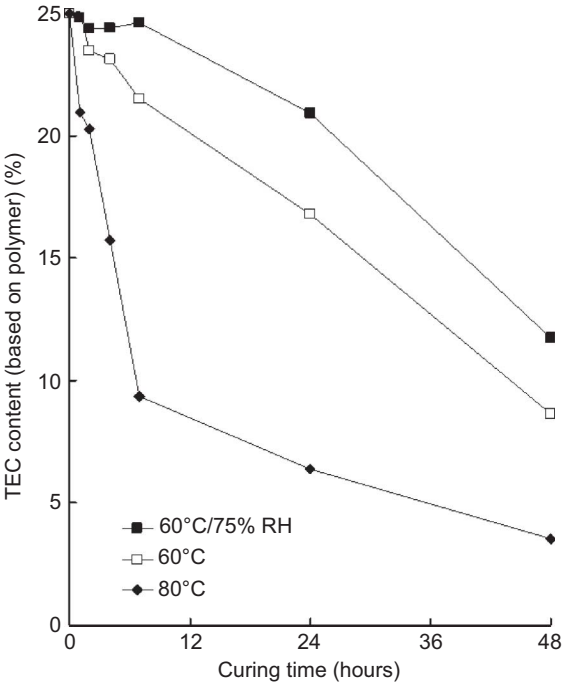

Figure 14. Amount of plasticizer in 30% Aquacoat/HPMC-coated pellets as function of curing time and condition.

necessarily correlate with a lesser extent of polymer interdiffusion obtained at 80°C. Aquacoat/HPMC pellets cured at 80°C were stable against a subsequently applied heat–humidity treatment and also against 3 weeks storage at 40°C/75% RH, which reflected a sufficient degree of film formation. The different release rates were probably due to different film compositions after both curings. It was previously reported that plasticizers, although being high-boiling liquids, could evaporate during curing[18], which could affect the drug release as shown above (Figure 1 versus Figure 7). The analysis of extracted pellets revealed differences in the plasticizer content (TEC) dependent on the applied curing condition. Only about 6% of the initial 25% TEC (based on polymer) remained in the pellets after 24 hours at 80°C (Figure 14), whereas 17% and 21% plasticizer remained in pellets after curing for 24 hours at 60°C/ambient humidity or at 60°C/75% RH, respectively. Thus, a lower plasticizer concentration was probably responsible for the accelerated release.

Conclusion

Conventionally cured Aquacoat-coated pellets (2 or 24 hours at 60°C) were stable at ambient conditions and 25°C/60% RH but showed slower release upon storage at accelerated conditions (40°C/75% RH). No storage effect at 40°C/ambient humidity was found, which showed that an elevated humidity at 40°C was important for the release changes on storage. A combined heat–humidity treatment (24 hours 60°C/75% RH) correlated reasonably well with storage stability at 40°C/75% RH and was therefore used as a screening for moisture sensitivity of pellet coatings as a function of formulation (core sealing, increased plasticizer content, and pore-former type/amount) and process parameters (process humidity and curing conditions). Aquacoat/HPMC pellets with improved storage stability at 40°C/75% RH were only obtained upon application of unconventionally harsh curing conditions (24 hours at 60°C/75% RH or at 80°C).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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