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Evaluation of the drug release patterns and long term stability of aqueous and organic coated pellets by using blends of enteric and gastrointestinal insoluble polymers

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ABSTRACT

The major aim of this study was to identify an efficient tool to adjust drug release patterns from aqueous and organic ethylcellulose (a gastrointestinal insoluble polymer) coated pellets and to evaluate the long term stability of the film coatings. Drug release was monitored during open and closed storage at 25 °C/60% RH (ambient conditions) and 40 °C/75% RH (stress conditions) for up to 24 months. Release of vatalanib succinate, a poorly soluble drug that demonstrates pH-dependent solubility, from pure ethylcellulose coated pellets was slow irrespectively of the type of coating and release medium. By addition of the enteric polymer methacrylic acid/ethyl acrylate copolymer (applied as aqueous Kollicoat MAE 30 DP dispersion or organic solution of Kollicoat MAE 100 P) to ethylcellulose broad ranges of drug release patterns could be achieved. For aqueous film coatings the addition of Kollicoat MAE 30 DP to ethylcellulose dispersions resulted in unaltered drug release kinetics during closed storage at ambient and stress conditions. The storage stabilizing effect of the added enteric polymer might be explained by the more hydrophilic nature of Kollicoat MAE 30 DP compared to ethylcellulose trapping water during film formation and improving polymer particle coalescence. However, during open storage of aqueous coated ethylcellulose:Kollicoat MAE 30 DP pellets at stress conditions drug release decreased due to further gradual polymer particle coalescence. In contrast, drug release rates from organic coated ethylcellulose:Kollicoat MAE 100 P pellets stored at ambient and stress conditions did not change which could be explained by differences in the film formation process. This clearly indicates that the presented concept of the addition of methacrylic acid/ethyl acrylate copolymer to ethylcellulose film coatings in combination with an organic coating process is able to achieve broad ranges of drug release patterns and to overcome storage instability.

1. Introduction

Polymeric film coatings are commonly used to mask unpleasant tastes, to protect drugs against moisture and to control drug release from solid oral dosage forms (Mc Ginity, 1997). Polymers such as hydroxypropyl methylcellulose, polyacrylate/polymethacrylate copolymers, polyvinylacetate/polyvinylpyrrolidone, or ethylcellulose have been demonstrated to be suitable coating materials, providing various types of drug release (Van Savage and Rodes, 1995; Bussemer et al., 2003). To obtain the desired drug release patterns different formulation and processing parameters can be varied, e.g. coating level, type of polymer and type and amount of added plasticizer (Frohoff-Hülsmann et al., 1999; Okarter and Singla, 2000). However, the variation of these parameters is generally restricted. For example, too low or too high coating levels must be avoided to prevent film rupturing and dose dumping and too long processing times. Polymers that are used should be non-toxic and addition of too high amounts of plasticizer would result in sticking of the coated dosage form whereas too low amounts of plasticizer could result in brittle film coatings thus leading to dose dumping.

An interesting approach to overcome these restrictions is based on blending different polymers (Siepmann et al., 2008a,b,c). Blends of gastrointestinal (GIT) insoluble polymers (Eudragit RL and Eudragit RS) were investigated by Amighi and Moes (1995). By varying the polymer:polymer blend ratio, the resulting film coating properties were effectively adjusted and broad ranges of drug release patterns were obtained. Another example of the combination of different polymers in film coating is the use of ethylcellulose and hydroxypropyl methylcellulose (Chan et al., 2005). In contrast to the GIT-insoluble ethylcellulose, hydroxypropyl methylcellulose is water soluble thus increasing drug release rates from ethylcellulose coated dosage forms significantly. However, it must be pointed out that when using aqueous dispersions of ethylcellulose for film coating (e.g. Aquacoat ECD or Surelease), the coating

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formulation can flocculate and sedimentation can occur upon addition of hydroxypropyl methylcellulose (Wong and Bodmeier, 1996). Furthermore, even films prepared from organic polymer solutions were inhomogeneous, showing ethylcellulose- and hydroxypropyl methylcellulose rich domains (Sakellariou and Rowe, 1995).

Recently, it has been shown that the addition of water-soluble poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer to ethylcellulose did not cause flocculation of the aqueous polymer dispersion but increased theophylline release from ethylcellulose coated pellets drastically (Siepmann et al., 2007a). Stable drug release patterns were obtained irrespectively of the type of release medium, coating level, and polymer blend ratio during 6 months open storage at room temperature and 40 °C/75% RH (Siepmann et al., 2008a). Similar observations were made when transferring this approach to the freely water-soluble diltiazem HCl (Muschert et al., 2009). However, hybrid coatings of GIT-insoluble polymers with water-soluble polymers increase drug release at low and high pH, thus they are not able to compensate pH-dependent drug release patterns.

To overcome these pH-dependent drug solubility effects, film coatings with blends of GIT-insoluble polymers and enteric polymers have been suggested. At low pH both polymers are insoluble whereas at high pH the enteric polymer is soluble thus compensating pH-dependent solubility especially of weak bases (which are poorly soluble at high pH). Lecomte et al. (2003) obtained broad ranges of drug release patterns from aqueous ethylcellulose:Eudragit L coated pellets by varying the polymer blend ratio. Dashevsky et al. (2004) was able to overcome pH-dependent release of a basic drug from pellets coated with the aqueous extended release polymer dispersion Kollicoat SR 30 D and the enteric polymer dispersion Kollicoat MAE 30. However, in both cases no data on long term stability were provided. Especially for polymer blends consisting of Kollicoat SR 30 D and Kollicoat MAE 30 long term stability could be critical as both dispersions coagulated/flocculated in contact with each other. Furthermore, enteric polymers such as propylene glycol alginate and carrageenan have been efficiently modified drug release from ethylcellulose coated dosage forms (Siepmann et al., 2007b, 2008c). Once again, long term stability at of the aqueous coated dosage forms at increased temperature and humidity seem to be critical.

In addition to the composition of the film coatings the type of coating technique (using aqueous dispersions or organic solutions) can significantly affect the properties of the resulting polymeric membranes (Lorck et al., 1997; Wesseling and Bodmeier, 1999; Lecomte et al., 2004). The use of aqueous polymer dispersions is advantageous from a toxicological and processing point of view but is critical with respect to film formation and storage stability. Hence, particular attention of the study was focused on the curing conditions of aqueous formulations. In addition, drug release patterns and long term stability was also investigated after organic coating processes.

The major aim of the present study were (i) to use blends of a GIT-insoluble and an enteric polymer for pellet coating, (ii) to study the effect of the polymer blend ratio and type of coating process (organic versus aqueous), and (iii) to study the long term stability of the coated dosage forms. Ethylcellulose was chosen as non-toxic, nonirritant GIT-insoluble polymer. Aqueous Kollicoat MAE 30 DP dispersions or organic solutions of Kollicoat MAE 100 P were chosen as enteric polymers. Both are copolymers derived from methacrylic acid/ethyl acrylate. As Kollicoat MAE 100 P is manufactured from Kollicoat MAE 30 DP similar copolymer ratios and molecular weights can be expected. Vatalanib succinate (molecular weight: 464 g/mol, molecular formula: $C_{20}H_{15}ClN_4C_4H_6O_6$) is a potent tyrosine kinase inhibitor with good oral bioavailability and activity against the vascular endothelial growth factor receptor (VEGFR) family, platelet-derived growth factor receptor β and c-Kit receptor kinases. Numerous clinical trials are in progress evaluating vatalanib succinate alone or in combination in several types of cancer as well as myelodysplastic syndromes and age-related macular degeneration. In this study the compound was chosen as a weakly basic model drug that is soluble at low pH but almost insoluble at pH values above 4.5. Hence, film coatings with blends of GIT-insoluble polymers and enteric polymers might be an effective tool to overcome these pH-dependent drug solubility effects.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: vatalanib succinate ((4-chlorophenyl)[4-(4-pyridylmethyl)phthalazin-1-yl]ammonium hydrogen succinate, Bayer Schering Pharma, Berlin, Germany), ethylcellulose (Ethocel Standard 10 Premium, Dow Chemical Company, Midland, USA), Aquacoat ECD 30 (an aqueous ethylcellulose dispersion) and microcrystalline cellulose (Avicel® PH 101, FMC, Cork, Ireland), Kollicoat MAE 30 DP (an aqueous methacrylic acid/ethyl acrylate copolymer dispersion) and Kollicoat MAE 100 P (a redispersible methacrylic acid/ethyl acrylate copolymer powder, BASF, Ludwigshafen, Germany), sucrose (Nordzucker GmbH, Braunschweig, Germany), talcum (Herwe Chemisch-technische Erzeugnisse, Sinsheim-Dühren, Germany), triethyl citrate (TEC, Morflex, Greensboro, USA), hydroxypropyl-β-cyclodextrine (HP-β-CD, Roquette Services Techniques Laboratoires, Lestrem, France), and purified water. All chemicals were reagent grade or higher.

2.2. Preparation of core pellets

Pellets were prepared by extrusion/spheronization. Dry powder blending of drug substance (60), microcrystalline cellulose (25) and sucrose (15) was done in a Turbula® mixer (W.A. Bachhofen AG, Basel, Switzerland) at 22 rpm (all quantities are given in % and based on the total weight of the dry powder blend). The dry powder blending was done on a 2000 × *g* scale. Content uniformity studies indicated homogeneous distribution of vatalanib succinate throughout the dry powder blend after blending for 10 min. Therefore, this mixture time was used throughout the study. For the discontinuous extrusion/spheronization process the dry powder blend was divided into smaller fractions. Wet granulates were made in a Nica™ high shear mixer (ML 6, Lejus, Mölndal, Sweden) by adding an appropriate amount of purified water. The wet mass (300 g) was then extruded through a ring die with 1 mm holes by using a Nica™ extruder (Lejus, Mölndal, Sweden) at a feeding speed of 75 rpm. Finally, the extrudate was processed in a Nica™ spheronizer (SP 300, Lejus, Mölndal, Sweden) fitted with a cross-hatched friction plate rotated at 400 rpm for 2–8 min. After spheronization the pellets were dried in a fluid bed coater (GPCG-1, Glatt, Binzen, Germany) at an inlet temperature of 60 °C until the relative humidity of the outlet air was constant for 5 min (followed by an additional drying step for 24 h at 60 °C and ambient relative humidity in an oven). Pellets in a size range of 800–1250 μm were used throughout the study.

2.3. Coating of pellets

For the coating process fractions of 500 g of pellets were coated with blends of ethylcellulose and methacrylic acid/ethyl acrylate copolymer in a fluid bed coater (GPCG-1, Glatt, Binzen, Germany) using bottom spray and Wurster insert until a theoretical coating level of 10%, or 20% (w/w, based on core pellets) was reached. Talcum (0.5%) was added as anti-tacking agent (w/w, based on core pellets). Ethanolic polymer solutions of ethylcellulose and Kollicoat

MAE 100 P were prepared by addition of 10% TEC (w/w, based on the total polymer mass). The aqueous polymer dispersions of ethylcellulose and Kollicoat MAE 30 DP were plasticized overnight with 25% TEC (w/w, based on the total polymer mass) and adjusted to 15% (w/w) polymer content prior to coating. The following ethylcellulose:methacrylic acid/ethyl acrylate copolymer blend ratios were investigated: 100:0, 85:15, 75:25, 72:28, 65:35, and 55:45 (w/w). Coating conditions: inlet temperature 40 °C (aqueous dispersions) or 25 °C (ethanolic solutions), nozzle diameter 1.2 mm, spray pressure 1.0 bar, spray rate 3–4 g/min. After coating aqueous coated pellets were cured for 24 h/48 h at 60 °C and ambient relative humidity (RH) or for 24 h/48 h at 60 °C and 75% RH.

2.4. Drug release studies

In vitro drug release was determined using the USP XXIX rotating paddle method (Distek Inc., North Brunswick, USA) in 0.1N HCl or phosphate buffer pH 6.8 at 50 rpm (1000 ml dissolution medium, 37 °C, 372 mg pellets, $n = 3$). Prior to dissolution studies the dissolution tester was calibrated according to the Apparatus Suitability Test described in the USP. No differences in in vitro dissolution results were observed when doubling the number of samples. In order to maintain sink conditions 5% HP-β-CD were added to the buffer medium pH 6.8 (solubility of vatalanib succinate at pH 6.8 after addition of 5% HP-β-CD = 5.7 mg/ml). The solubility of vatalanib succinate in 0.1N HCl is higher than 100 mg/ml, thus indicating perfect sink conditions in all cases. Upon release testing the pH of the media remained unchanged as indicated by pH measurements. At predetermined time intervals, 3 ml samples were withdrawn and analyzed UV-spectrophotometrically at 316 nm. Vatalanib succinate solutions of known concentration were used to calculate the amount of drug released. The dissolution method including UV assay was validated with respect to linearity ($r > 0.99$), precision (<3% RSD) and accuracy (<3% RSD).

3. Results and discussion

3.1. Drug release from aqueous film coated pellets

Intermediate drug release profiles (more than 50% drug release upon 6 h) could not be obtained when using ethylcellulose only at coating levels of 10% or 20% (Fig. 1A–D). Irrespectively of the type of release medium (0.1N HCl or phosphate buffer pH 6.8) and coating level vatalanib succinate release was slow. One possibility to increase drug release rates is to coat very thin polymer films and/or to use imperfect film coatings (e.g. uncured pellets). However, poor reproducibility (slight variations of the coating level would result in significant changes of the drug release profiles) and instable drug release patterns upon storage (due to further polymer coalescence) could be expected.

To increase vatalanib succinate release from coated pellets Kollicoat MAE 30 DP was added to ethylcellulose. The addition of 15–45% Kollicoat MAE 30 DP accelerated drug release significantly, irrespectively of the coating level and type of release medium. Increased dissolution rates at low pH can be attributed to the higher permeability of Kollicoat MAE 30 DP for the drug compared to ethylcellulose. In buffer pH 6.8 the effect of the polymer blend ratio on drug release was even more pronounced. This can be explained with the leaching of the enteric polymer at higher pH resulting in porous film coatings upon dissolution testing thus finally leading to increased release rates of vatalanib succinate. Similar observations (increasing drug release rates especially at higher pH) have been made when combing the extended release polymer ethylcellulose with the pH sensitive compound propylene glycol alginate

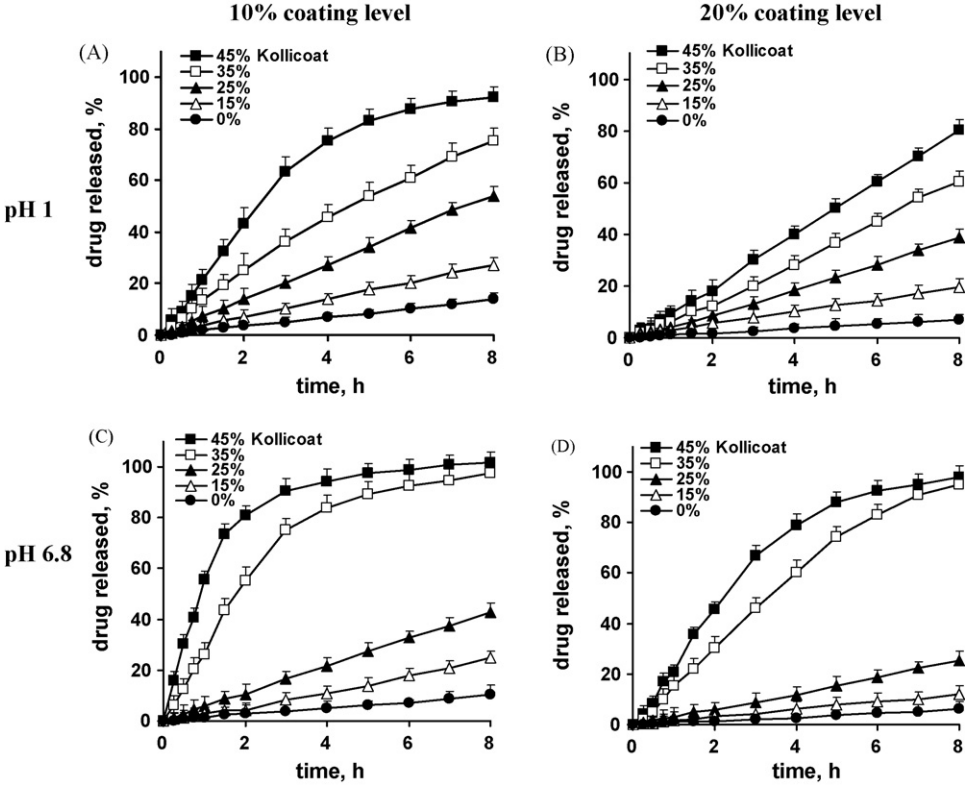

Fig. 1. Drug release from pellets coated with aqueous ethylcellulose dispersions containing various amounts of Kollicoat MAE 30 D in (A) 0.1N HCl, 10% coating level; (B) 0.1N HCl, 20% coating level; (C) buffer pH 6.8, 10% coating level; and (D) buffer pH 6.8, 20% coating level (curing: 2 d at 60 °C).

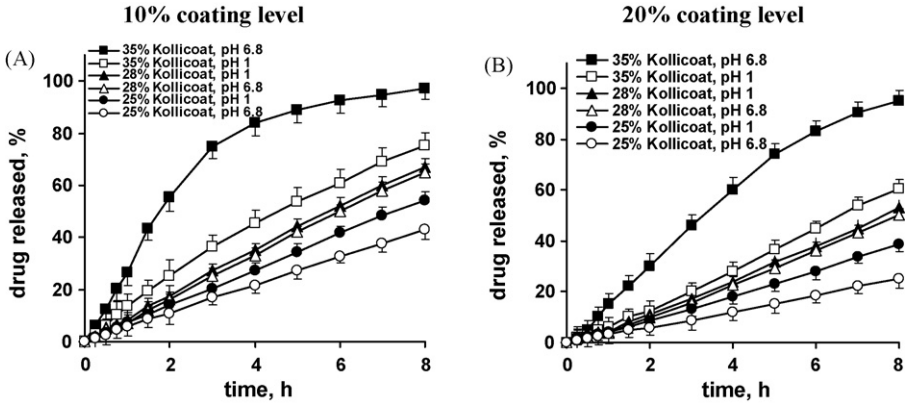

Fig. 2. Effect of the type of release medium on the drug release from pellets coated with aqueous ethylcellulose dispersions containing 25%, 28% or 35% Kollicoat MAE 30 D at (A) 10% coating level; and (B) 20% coating level (curing: 2 d at 60 °C).

for theophylline coated pellets (Siepmann et al., 2008c). Furthermore, Fig. 1A–D illustrates that the variation of the coating level can also be used to alter the drug release profiles. Drug release rates decreased with increasing coating thickness due to increasing length of diffusion pathways. In all cases, vatalanib succinate release remained almost constant upon initial drug release (zero order kinetics). This can be explained with the presence of an excess of drug within the pellet core leading to constant drug concentration gradients upon dissolution testing at perfect sink conditions.

Importantly, vatalanib succinate release in 0.1N HCl was faster than in buffer pH 6.8 from pellets coated with polymer blends containing 15% and 25% Kollicoat MAE 30 DP (Figs. 1 and 2). In contrast, for pellets coated with polymer blends with 35% and 45% Kollicoat MAE 30 DP the drug release was faster at pH 6.8 compared to 0.1N HCl. Fig. 2 shows a direct comparison of vatalanib succinate release from pellets coated with 75:25 and 65:35 ethylcellulose/Kollicoat MAE 30 DP blends at a coating level of 10% and 20%. The reversal of the drug release profiles can be explained with the weakly basic nature of the drug leading to higher solubility of the compound at lower pH values and the carboxylic groups in Kollicoat MAE 30 DP resulting in better solubility of the polymer at higher pH. Hence, at higher pH the lower solubility of vatalanib succinate was compensated by a simultaneous increase in the permeability of the film coating. This effect is more pronounced when using polymer blends with higher Kollicoat MAE 30 DP content. Furthermore, almost overlapping release profiles were observed for pellets coated with 72:28 ethylcellulose/Kollicoat MAE 30 DP blends at a coating level of 10% and 20% (Fig. 2). These findings clearly demonstrate that hybrid coatings of the extended release polymer ethylcellulose and the gastrointestinal insoluble polymer Kollicoat MAE 30 DP are a powerful tool to overcome pH-dependent drug release profiles of weakly basic drugs.

3.2. Effect of curing conditions on drug release from aqueous coated pellets

Curing conditions are crucial when using aqueous polymer dispersion for film coating. Generally, if curing conditions are not sufficient further polymer coalescence will occur upon storage thus leading to decreasing drug release rates. Drug release rates of uncured and cured (1 or 2 d at 60 °C as well as 1 or 2 d at 60 °C/75% RH) pellets are given in Fig. 3. The effect of the curing conditions on the drug release in 0.1N HCl and buffer pH 6.8 was investigated on pellets coated with ethylcellulose films containing 35% Kollicoat MAE 30 DP at 10% and 20% coating levels. An ethylcellulose:Kollicoat MAE 30 DP ratio of 65:35 was chosen for all further experiments as intermediate drug release profiles (more than 50% drug release after 6 h) were expected irrespectively of the coating level. For all investigated formulations curing reduced the initial drug release significantly thus indicating that film formation was not complete directly after film coating. Importantly, the effect of the curing time (1 d versus 2 d) on the drug release profiles was negligible whereas curing at accelerated humidity resulted in further decreased drug release rates. Decreased vatalanib release rates at accelerated humidity can be explained with the plasticizing effect of water thus facilitating further polymer particle coalescence upon curing. It also indicates that curing at ambient humidity can lead to partially coalesced thermostable but moisture sensitive pellet formulations. Improved polymer particle coalescence has also been observed for heat humidity cured cellulose acetate phthalate pellets (Liu and Williams, 2002). In contrast, heat humidity treatment did not affect the release of theophylline from pellets coated with ethylcellulose containing poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG-graft-copolymer) (Siepmann et al. (2007a). Differences between the observed results might be explained with the different nature of polymer and/or polymer combination resulting in different film formation temperatures.

Higher release rates at higher pH again can be attributed to the carboxylic groups in Kollicoat MAE 30 DP thus overcompensating the weakly basic nature of vatalanib succinate. Interestingly, irrespectively of the release medium the effects of the curing conditions on the drug release were more pronounced at a coating level of 10% compared to a coating level of 20%. This can be explained with the differences in film coating thickness and involved number of polymer particles layers. In thin film coatings (with less polymer layers), incomplete polymer coalescence resulted in porous coatings with a high probability of interconnected pores. Hence, vatalanib succinate was released through water-filled channels. In contrast, at higher coating levels (with a higher number of ethylcellulose:Kollicoat MAE 30 DP layers) the probability of interconnected pores and existence of continuous water-filled pores is reduced even after incomplete polymer coalescence. Therefore, the effects of the curing conditions on the drug release were less pronounced at 20% coating level.

3.3. Storage stability of aqueous coated ethylcellulose:Kollicoat MAE 30 DP pellets

The open storage stability of pellets coated with ethylcellulose:Kollicoat MAE 30 DP 65:35 blends is shown in Fig. 4. The storage conditions (25 °C/60% RH or 40 °C/75% RH) are given on top of the figure. The coating level was 10%, the curing conditions were 2 d at 60 °C/75% RH and the release medium was buffer pH 6.8. Similar tendencies were observed for pellets coated with ethyl-

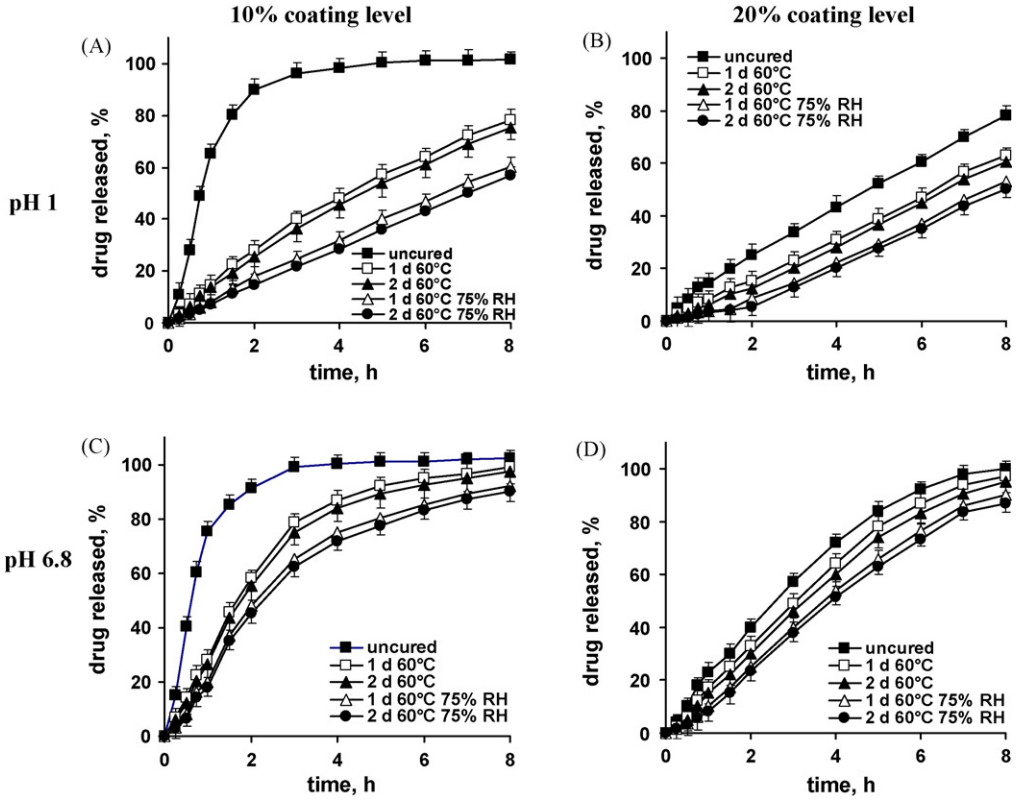

Fig. 3. Effects of the curing conditions on drug release from pellets coated with aqueous ethylcellulose dispersions containing 35% Kollicoat MAE 30 D upon exposure to (A) 0.1N HCl, 10% coating level; (B) 0.1N HCl, 20% coating level; (C) buffer pH 6.8, 10% coating level; and (D) buffer pH 6.8, 20% coating level.

cellulose:Kollicoat MAE 30 DP at a coating level of 20% (data not shown). As it can be seen, the drug release for formulations stored for up to 24 months at 25 °C/60% RH was constant. In contrast, drug release rates from pellets coated with ethylcellulose only decreased significantly even when stored at 25 °C/60% RH for 24 months (data not shown). Hence, the presence of Kollicoat MAE 30 DP allowed the formation of ethylcellulose:Kollicoat MAE 30 DP films that did not alter at these conditions. However, significant time dependent changes in release rates were observed for pellets stored at 40 °C/75% RH. The significantly increased mobility of the ethylcellulose chains at elevated temperature and humidity (water acts as a plasticizer) resulted in further polymer particle coalescence during storage. Finally, this resulted in denser film coating structures with lower permeability for water and drug. Increased storage stability upon open storage at 40 °C/75% RH has been described in the literature for aqueous coated ethylcellulose:PVA–PEG-graft-copolymer pellets (Siepmann et al., 2008a). The improved storage stability was explained with an improved film formation process. However, the storage stability was investigated for up to 6 months only thus long term open storage stability (up to 2 years) remains unclear.

Next, the storage stability of pellets coated with ethylcellulose:Kollicoat MAE 30 DP 65:35 blends was investigated upon storage in aluminum blisters (Fig. 5). Again the storage conditions (25 °C/60% RH or 40 °C/75% RH) are given on top of the figure. The coating level, curing conditions and release medium were kept constant compared to Fig. 4. In contrast to pellets stored under open conditions the release profiles of pellets stored in aluminum blisters did not alter even when stored at 40 °C/75% RH. This clearly indicates that humidity (which was excluded by closed storage in aluminum blisters) was the main driver for further polymer coalescence leading to decreasing vatalanib release rates upon stor-

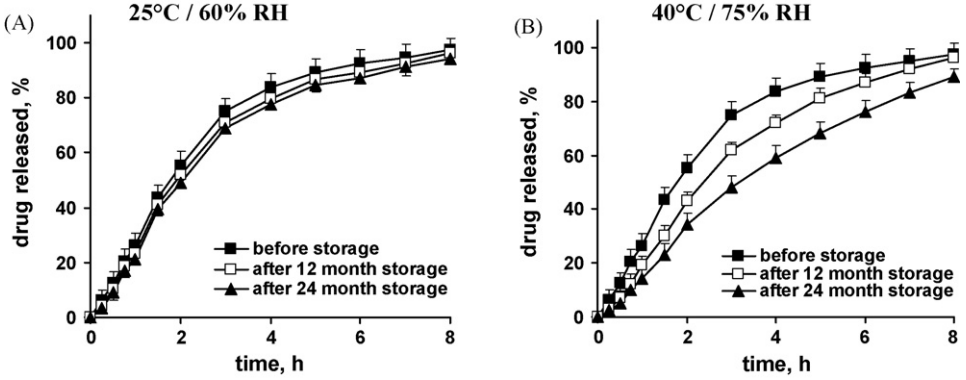

Fig. 4. Open storage stability of aqueous coated ethylcellulose:Kollicoat MAE 30 D (polymer ratio: 65:35) pellets in buffer pH 6.8 (curing: 2 d at 60 °C; 10% coating level). The storage conditions are given on top of the figure.

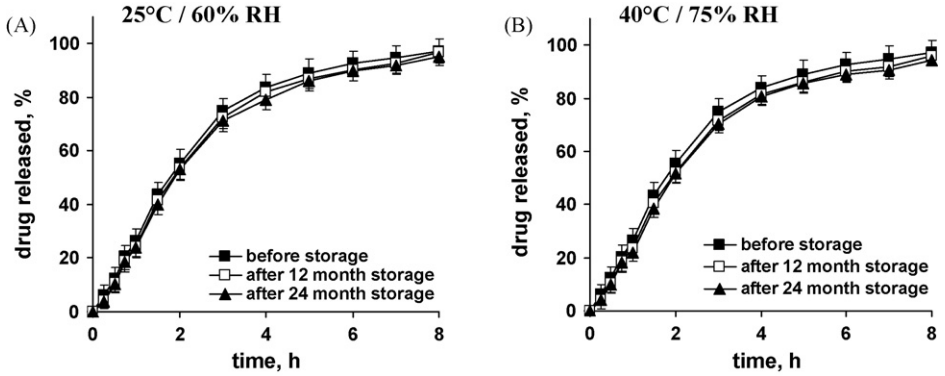

Fig. 5. Closed storage stability of aqueous coated ethylcellulose:Kollicoat MAE 30 D (polymer ratio: 65:35) pellets in buffer pH 6.8 (curing: 2 d at 60 °C; 10% coating level). The storage conditions are given on top of the figure. Pellets were stored in aluminum blisters.

age. Irrespectively of the pH of the release medium constant drug release rates (zero order kinetics) were observed for the initial observation period. This can be explained with saturated vatalanib succinate solutions at the inner surface of the pellets and perfect sink conditions at the outer surface of the pellet coatings. Hence, the resulting drug concentration gradients and drug release rates were constant as the thickness and density of the film coating did not alter upon storage under closed conditions. Again, for pellets coated with ethylcellulose only decreasing drug release rates were observed upon storage in aluminum blisters at 25 °C/60% RH and

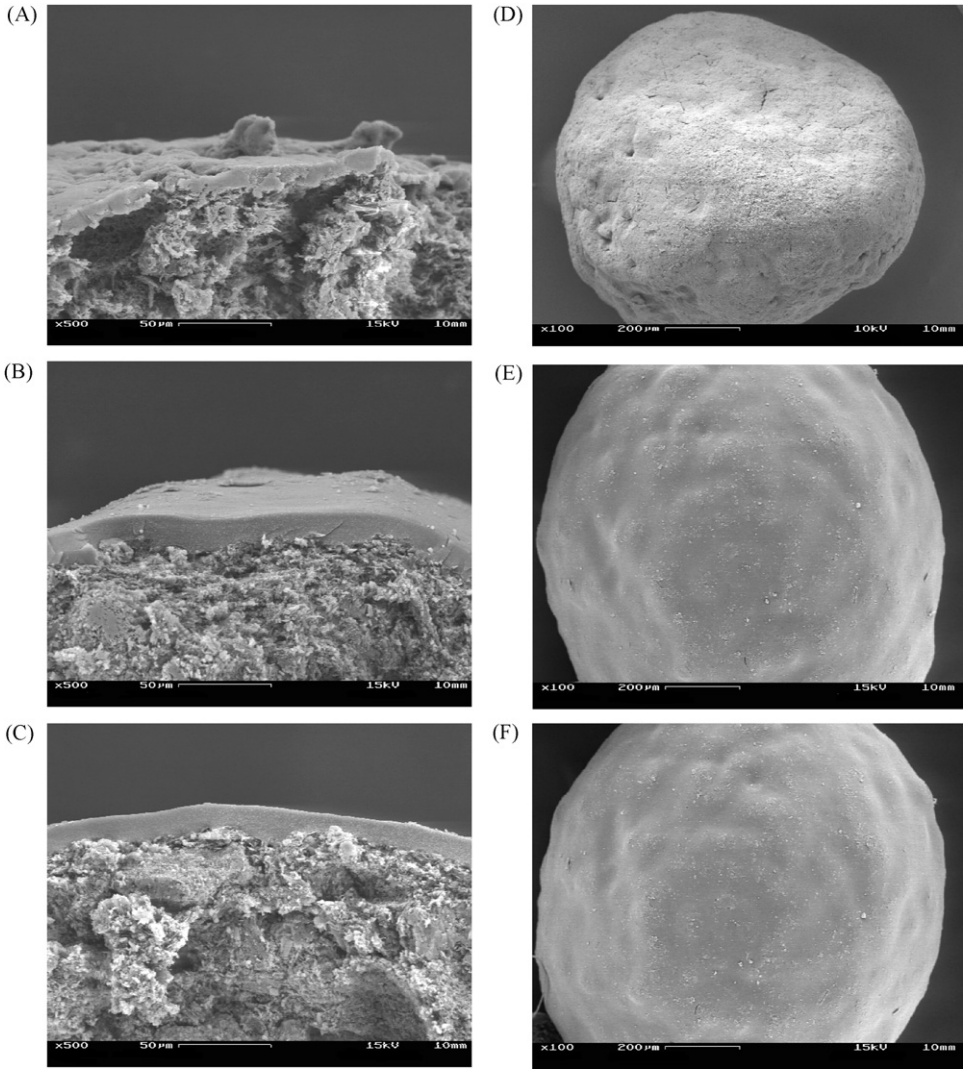

Fig. 6. Scanning electron micrographs of cross-sections of aqueous coated ethylcellulose:Kollicoat MAE 30 D (polymer ratio: 65:35, 10% coating level) pellets (A) prior to curing; (B) after curing for 2 d at 60 °C; and (C) after 24-month closed storage at 40 °C/75% RH. Scanning electron micrographs of surface properties of these pellets (D) prior to curing; (E) after curing for 2 d at 60 °C; and (F) after 24-month closed storage at 40 °C/75% RH.

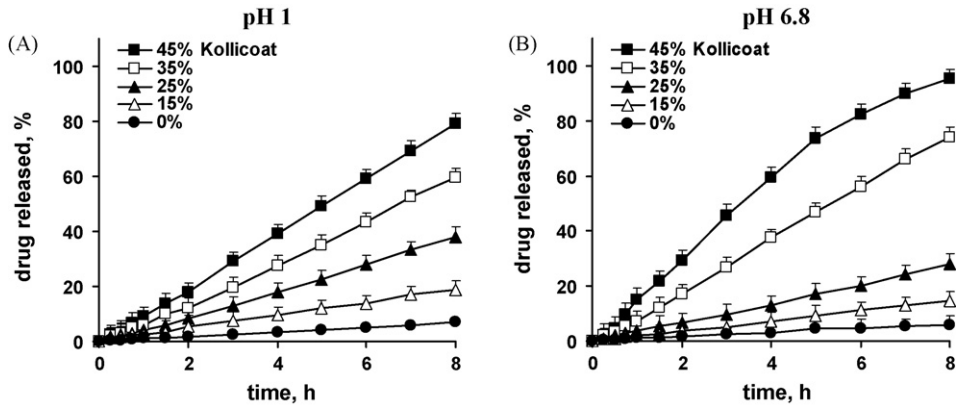

Fig. 7. Drug release from pellets coated with organic ethylcellulose solutions containing various amounts of Kollicoat MAE 100 P in (A) 0.1N HCl; and (B) buffer pH 6.8 (no curing; 10% coating level).

40 °C/75% RH for up to 24 months (data not shown). Improved long term stability of pellets coated with ethylcellulose:Kollicoat MAE 30 DP polymer blends might be explained with the more hydrophilic nature of Kollicoat MAE 30 DP trapping water during film formation and acting as plasticizer. Finally, upon film formation this resulted in increased mobility of the macromolecules and improved polymer particle fusion. An alternative explanation might be that Kollicoat MAE 30 DP particles between ethylcellulose particles might sterically hinder further polymer particle coalescence at long term storage.

To better understand drug release phenomena, to be able to explain increased drug release rates from uncured pellets and unchanged release profiles of cured pellets that were stored for up to 24 months in aluminum blisters SEM pictures were taken (Fig. 6A–F). Aqueous coated ethylcellulose:Kollicoat MAE 30 D (polymer ratio: 65:35, 10% coating level) beads showed a porous pellet surface with small cracks distributed all over the extended release film coat prior to curing (Fig. 6A and D). In contrast, these pellets showed a smooth and non-porous surface after curing for 2 d at 60 °C that did not change upon storage in aluminum blisters for 24 months (Fig. 6E and F). SEM cross-sections of cured pellets taken directly after curing or storage for 24 months are indicating a relatively homogeneous and dense polymer film (Fig. 6B and C). Consequently, for uncured pellets drug diffusion not only occurred through the extended polymer layer but also through water-filled pores and cracks thus explaining increased drug release rates from uncured pellets (Fig. 3). Importantly, curing resulted in further polymer coalescence thus explaining decreasing drug release rates from cured pellets that did not alter upon storage in aluminum blisters (Figs. 3 and 5).

3.4. Drug release profiles from organic coated ethylcellulose:Kollicoat MAE 100 P pellets

For organic coated pellets broad ranges of vatalanib succinate release patterns were obtained at low and high pH by varying the polymer blend ratio (Fig. 7A and B). Comparable to aqueous coated pellets the drug release from ethylcellulose coated pellets only was slow. The addition of 15–45% Kollicoat MAE 100 P significantly accelerated drug release. Again, increased dissolution rates at low pH can be attributed to the higher permeability of Kollicoat MAE 100 P for the drug compared to ethylcellulose. At high pH increased dissolution rates are explained by leaching of the enteric polymer. Similar to aqueous coated pellets, vatalanib succinate release in 0.1N HCl was faster than in buffer pH 6.8 from pellets coated with polymer blends containing 15% and 25% Kollicoat MAE 100 P. In contrast, with coatings containing 35% and 45% Kollicoat MAE 100 P drug release was faster at pH 6.8. This phenomenon once more can be explained by the pH-dependent solubility of vatalanib succinate which is overcompensated by the better solubility of Kollicoat MAE 100 P at higher pH.

Importantly, the shape of the release profiles from organic coated pellets were similar to the profiles obtained with aqueous coated pellets (zero order release kinetics upon initial drug release) whereas the slope of the release profiles strongly dependent on the coating technique. At comparable coating level (10%) and ethylcellulose:Kollicoat MAE 100 P ratio drug release from organic coated pellets was significantly slower compared to drug release from aqueous coated pellets (Fig. 1 versus Fig. 7). This observation can be explained based on the different film formation mechanisms. In organic polymer solutions, the two types of macromolecules are highly mobile. Hence, it can be expected that the different types of macromolecules are intimately blended and distributed throughout the solution. Upon solvent evaporation, the polymer chains approach each other and finally form a strong film with high degree of polymer–polymer-interpenetration. In contrast, separated pure ethylcellulose and Kollicoat MAE 30 DP domains exist at the beginning of the film formation process when aqueous polymer dispersions are used. Due to restricted mobility of the macromolecules within the colloidal particles, the polymer chains cannot completely interdiffuse. Only in regions close to particle surfaces polymer–polymer blending can be expected. Therefore, upon water evaporation polymeric films with pure ethylcellulose and pure Kollicoat MAE 30 DP domains are formed. Finally, the resulting polymer–polymer interaction in aqueous systems is weaker compared to organic solutions and different film coating microstructures are obtained. In systems with high degrees of ethylcellulose:Kollicoat MAE 100 P chain entanglement, the polymer structure is denser and water uptake and drug release is more effectively hindered. Similar observations have been made when using polymer blends of ethylcellulose and Eudragit L for aqueous or organic coated propranolol HCl loaded pellets (Lecomte et al., 2004). As the polymer structure upon organic coating was denser, decreased drug release rates for organic coated propranolol HCl loaded pellets were observed when compared to aqueous coated pellets.

3.5. Storage stability of organic coated ethylcellulose:Kollicoat MAE 100 P pellets

The open storage stability of organic coated pellets is shown for ethylcellulose:Kollicoat MAE 100 P 65:35 blends (Fig. 8). The storage conditions (25 °C/60% RH or 40 °C/75% RH) are given on top of the figure. Comparable to the aqueous coating process the coating level was 10% and the release medium was buffer pH 6.8. As curing did not alter the drug release profiles (data

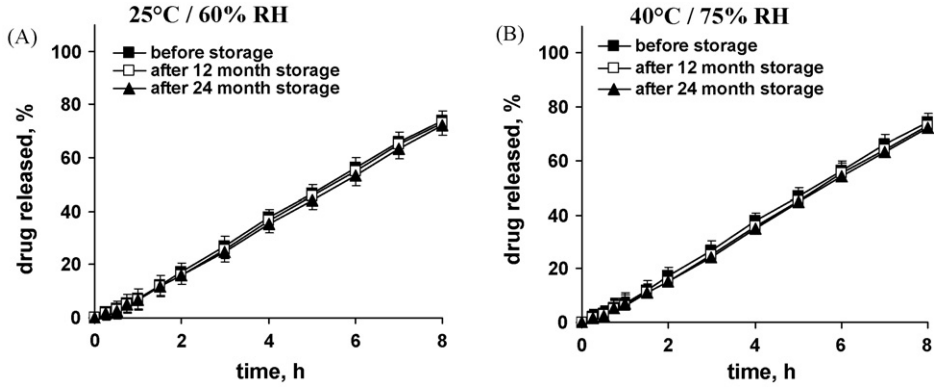

Fig. 8. Open storage stability of organic coated ethylcellulose:Kollicoat MAE 100 P (polymer ratio: 65:35) pellets in buffer pH 6.8 (no curing; 10% coating level). The storage conditions are given on top of the figure.

not shown) the storage stability of organic coated pellets was investigated on uncured pellets. As it can be seen, the drug release for formulations stored for up to 24 months at 25 °C/60% RH and 40 °C/75% RH did not change. Similar tendencies were obtained for organic coated pellets with ethylcellulose:Kollicoat MAE 100 P 75:25 and 85:15 blends and for drug release studies in 0.1N HCl (data not shown). Clearly, this indicates that upon organic coating of ethylcellulose:Kollicoat MAE 100 P blends no further polymer particle coalescence (leading to denser and less permeable films and finally decreased drug release rates) as well as drug migration into the film coating (leading to increased concentration gradients and finally increased drug release rates) is involved even under storage at stress conditions (40 °C/75% RH). Improved long term stability of organic coated pellets under open storage at stress conditions compared to aqueous coated pellets can be explained with the differences in the film formation process and resulting polymer microstructures as already discussed in Section 3.4.

4. Conclusions

By adding Kollicoat MAE 30 DP to aqueous ethylcellulose dispersions broad ranges of drug release patterns could be achieved. The presented concept was able to overcome storage instability of aqueous coated pellets stored in aluminum blisters at 25 °C/60% RH or 40 °C/75% RH. Under open storage conditions the drug release of aqueous coated ethylcellulose:Kollicoat MAE 30 DP blends did not change when stored at 25 °C/60% RH but decreased when stored under stress conditions (40 °C/75% RH). For organic coated ethylcellulose pellets the drug release patterns again could be varied in a broad range by the addition of Kollicoat MAE 100 P. Drug release rates for organic coated ethylcellulose:Kollicoat MAE 100 P pellets stored at stress conditions did not change. This clearly indicates that the presented concept of the addition of methacrylic acid/ethyl acrylate copolymer to ethylcellulose film coatings in combination with an organic coating process is able to achieve broad ranges of drug release patterns and to overcome storage instability.

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