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Modified release from hydroxypropyl methylcellulose compression-coated tablets

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ABSTRACT

The goal of this study was to obtain flexible extended drug release profiles (e.g., sigmoidal, pulsatile, increasing/decreasing release rates with time) with hydroxypropyl methylcellulose (HPMC) compression-coated tablets. Drugs of varying solubility (carbamazepine, acetaminophen, propranolol HCl and chlorpheniramine maleate) were incorporated into the tablet core in order to evaluate the flexibility/limitations of the compression-coated system. The HPMC-compression-coating resulted in release profiles with a distinct lag time followed by different release phases primarily determined by the drug solubility. Carbamazepine, a water-insoluble drug, was released in a pulsatile fashion after a lag time only after erosion of the HPMC compression-coat, while the more soluble drugs were released in a sigmoidal fashion by diffusion through the gel prior to erosion. With carbamazepine, increasing the molecular weight of HPMC significantly increased the lag time because of the erosion-based release mechanism, while, in contrast, molecular weight did not affect the release of the more soluble drugs. The lag-time and the release rate could also be well controlled by varying the HPMC amount in and the thickness of the compression-coating. A pulsatile release could also be achieved for water-soluble drugs by introducing an enteric polymer coating between the drug core and the HPMC compression-coating. This novel concept of introducing an enteric subcoating eliminated drug diffusion through the gelled HPMC layer prior to its erosion. Incorporating drug in the compression-coating in addition to the tablet core in varying ratios resulted in release profiles with increasing, decreasing or constant release rates. In conclusion, a versatile single-unit delivery system for a wide range of drugs with great flexibility in release profiles was presented.

1. Introduction

Time-controlled or pulsatile drug delivery systems are often based on rupturable (Bussemer et al., 2003; Sungthongjeen et al., 2004) or erodible coatings/matrices (Gazzaniga et al., 1994; Krögel and Bodmeier, 1998). A time-controlled delivery system named Chronotopic® system (Gazzaniga et al., 1994; Sangalli et al., 2001) is based on a drug-containing core spray-coated with the water-soluble polymer hydroxypropyl methylcellulose (HPMC). Upon contact with gastrointestinal fluids, the coating underwent swelling and lipophilic drugs were released after erosion of the gel layer. Pulsatile release profile cannot be obtained with water-soluble drugs, because they are released already prior to erosion of the gel by diffusion through the gel layer. However, coating with high molecular weight HPMC presents some challenges. Spray-coating of the viscous and low concentrated coating solution requires long processing time; hydro-alcoholic HPMC solutions were used to reduce this problem (Maffion et al., 1993).

Compression-coating presents an attractive alternative to spray-coating techniques for high molecular weight polymers. Thick coatings can be applied rapidly and it is a solvent-free coating process (Bose and Bogner, 2007). Compression-coating has been used in the pharmaceutical field for different purposes: (1) to protect hygroscopic, light-sensitive, oxygen-labile or acid-labile drugs (Picker, 2002); (2) to combine and separate different therapeutic drugs (Maggi et al., 1993; Waterman and Fergione, 2003) and (3) to modify a drug release pattern (delayed, pulsatile and programmable release of different drugs in one tablet) (Halsas et al., 2001; Lopes et al., 2007).

Various materials have been investigated as compression-coatings to obtain time-controlled release: HPMC (Conte et al., 1993; Sirkiä et al., 1994; Wu et al., 2007), hydroxypropyl cellulose (Fukui et al., 2000), polyethylene oxide (Sawada et al., 2004), micronized ethyl cellulose (Lin et al., 2001, 2002), Eudragit® RS (González-Rodríguez et al., 2003), behenic acid (Peerapattana et al., 2004). Bimodal drug release usually obtained with multi-layered matrix tablets (Streubel et al., 2000) can also be obtained

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with compression-coated tablets (Sirkiä et al., 1994; Lopes et al., 2007).

In this study, HPMC-compression-coated tablets were investigated to obtain flexible modified release profiles for model drugs covering a wide range in solubility. One objective was to obtain a pulsatile release with this system also for water-soluble drugs by inhibiting the drug release through the gelled layer prior to erosion.

2. Materials and methods

2.1. Materials

Acetaminophen, carbamazepine and propranolol HCl (BASF AG, Ludwigshafen, Germany), chlorpheniramine maleate (STADA GmbH, Bad Vilbel, Germany), hydroxypropyl methylcellulose 2208; 400 cps (HPMC 400) (Metolose® 90SH-400, Shin-Etsu Chemical, Tokyo, Japan), HPMC 2208; 4000 cps (HPMC K4M) (Methocel® K4M Premium) and HPMC 2910; 50 cps (HPMC E50) (Methocel® E50 Premium LV) (Colorcon Ltd., Orpington, UK), methacrylic acid–ethyl acrylate copolymer (1:1) (Eudragit L) (Eudragit® L100-55, Evonik Industries AG, Darmstadt, Germany), triethyl citrate (TEC, Morflex, Greensboro, NC, USA), direct compressible lactose (Ludipress®, BASF AG, Ludwigshafen, Germany), magnesium stearate (Herwe Chemisch-technische Erzeugnisse GmbH, Sinsheim-Dühren, Germany) were used as received.

2.2. Methods

2.2.1. Drug solubility

The solubility of drugs was determined by adding an excess amount of drug in vials with 5 ml phosphate buffer pH 7.4 and shaking in a 37 °C incubator (GFL® 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany). After 48 h incubation, the drug suspensions were adjusted to pH 7.4, if necessary, and further shaken. The suspensions were filtered, and the filtrate was diluted and analyzed UV-spectrophotometrically (Shimadzu UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany) at wavelengths of 243.6, 285, 290 and 261 nm for acetaminophen, carbamazepine, propranolol HCl and chlorpheniramine maleate, respectively.

2.2.2. Preparation of tablet cores

Acetaminophen and carbamazepine biconvex tablet cores (6 mm diameter, 15 mg drug, 85 mg Ludipress®, 0.5 mg magnesium stearate), propranolol HCl and chlorpheniramine maleate tablet cores (6 mm diameter, 40 mg drug, 60 mg Ludipress®, 0.5 mg magnesium stearate) were prepared by direct compression (compression force: 15 kN, hardness: 30 N; Korsch EKO, Korsch AG, Berlin, Germany). The drug content in the cores was different in order to allow UV detection without dilution of the dissolution samples. Prior to compression, drug and Ludipress® were blended in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min and additionally blended with 0.5% magnesium stearate for 2 min.

Eudragit L-subcoated cores were prepared by spray-coating a solution of Eudragit L (7.5%, w/w, solid content in ethyl alcohol:water, 95:5, v/v) and 10% (w/w) TEC (based on polymer) on the acetaminophen cores in a fluidized bed coater (Uni-Glatt®, Glatt GmbH, Binzen, Germany) to obtain coating levels of 4.7, 9.5, 14.3 mg/cm^2. The coating conditions were: inlet temperature 26–28 °C, outlet temperature 24–26 °C, nozzle diameter 1.2 mm, spray pressure 1.6 bar, spray rate 1.5 g/min and final drying at 40 °C for 15 min. The coated tablets were equilibrated at ambient temperature for 1 day and stored in desiccators for further studies.

2.2.3. Compression-coating of tablet cores

6 mm diameter tablet cores (acetaminophen, carbamazepine, propranolol HCl, chlorpheniramine maleate, Eudragit L-subcoated

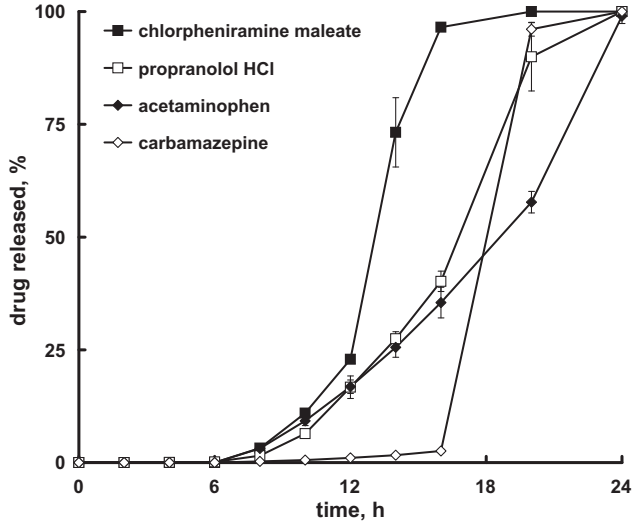

Fig. 1. Effect of type of drug on the drug release from HPMC 400 compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force).

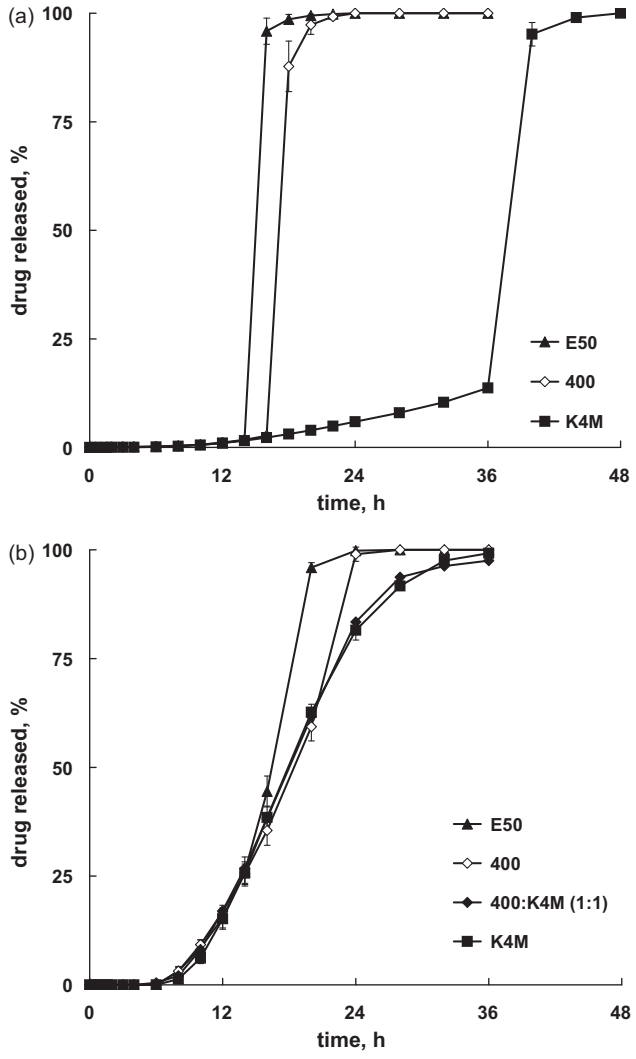

Fig. 2. Effect of HPMC-type on drug release from HPMC compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) carbamazepine and (b) acetaminophen.

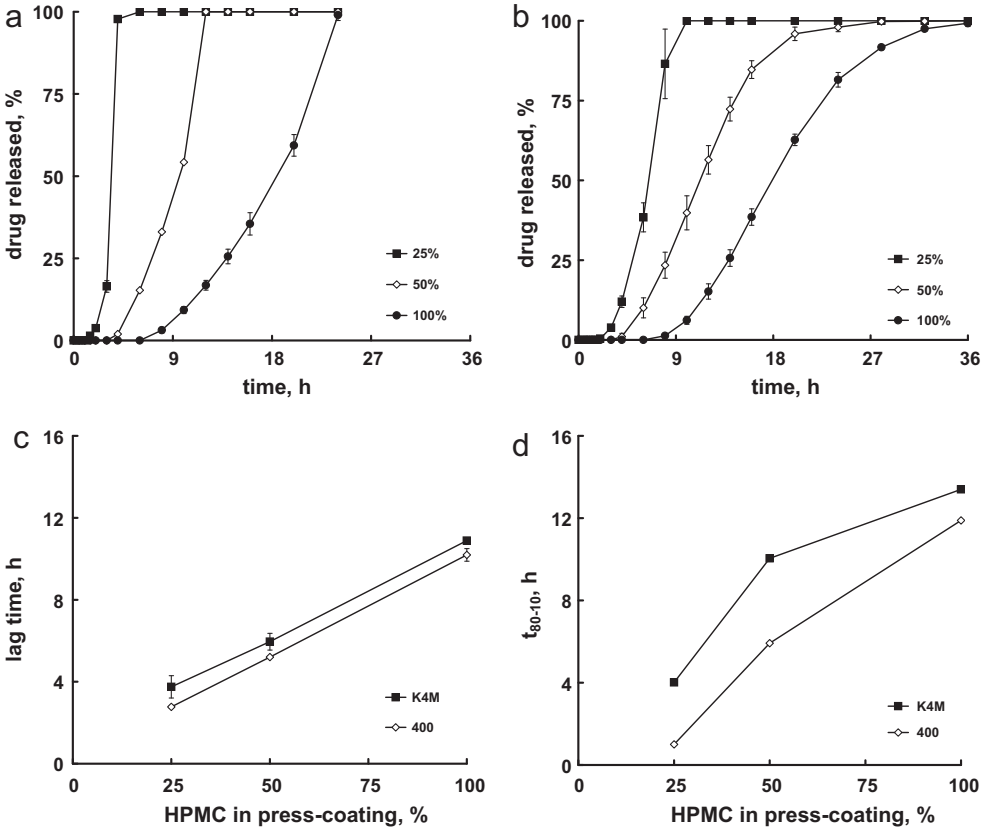

Fig. 3. Effect of HPMC content in compression-coating on acetaminophen release (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) HPMC 400, (b) HPMC K4M, (c) lag time and (d) release time (t_{80-10}).

acetaminophen cores) were compression-coated into 9 mm diameter tablets using various HPMC compression-coating formulations (200 mg; 50–200 mg of HPMC E50, HPMC 400 and HPMC K4M and 0–150 mg of Ludipress® for 25–100% HPMC compression-coating). The compression-coated tablets (core:coat, 1:2) were prepared by first filling one-half (100 mg) of compression-coated powders in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half (100 mg) of the polymer powder on top and then by compression at 25 kN (Korsch EKO, Korsch AG, Berlin, Germany), unless other compression forces were mentioned. For the compression-coating amount (thickness) study, 100, 200 and 400 mg of HPMC 400 and HPMC K4M were compression-coated on 6 mm acetaminophen tablet cores to obtain 8, 9 and 11 mm compression-coated tablets, respectively.

300 mg compression-coated tablets comprising HPMC 400 compression-coatings and different amount of drugs in the core and compression-coating (15:100, 15:50, 15:15, 15:7.5, 15:0 and 15:0 for acetaminophen; 40:0, 40:40 and 0:40 for chlorpheniramine maleate) were prepared to study the influence of drug distribution between core and coat.

2.2.4. Drug release study

Drug release was studied in a paddle apparatus (USP XXIV) (Vankel® VK 700, Vankel Industries, Edison, NJ, USA) [100 rpm, 37 °C, 900 ml, 50 mM of phosphate buffer pH 7.4, $n = 3$]. Drug release was measured by UV spectrophotometer (Shimadzu UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany) at the same wavelengths used for drug solubility determination. The lag time (t_{10}) and release time (t_{80-10}) were defined as the times in h of 10% and 80–10% drug released, respectively.

3. Results and discussion

The goal of this study was to obtain flexible extended drug release profiles (e.g., sigmoidal, pulsatile, increasing release rate with time) with HPMC compression-coated tablets. Drugs of varying solubility (solubilities of carbamazepine, acetaminophen, propranolol HCl and chlorpheniramine maleate are 0.2, 20, 253 and 562 mg/ml, respectively) were incorporated into the core in order to evaluate the flexibility/limitations of the compression-coated system with regard to different drug candidates.

All tablet cores (without compression-coating) resulted in complete drug release within 15 min (data not shown). The HPMC-compression-coating resulted in release profiles with a distinct lag time followed by a complete release with different release rates (Fig. 1). The HPMC compression-coating hydrated and swelled around the drug cores. Depending on their solubility, drugs are released from HPMC matrix tablets by diffusion through and/or erosion of the gelled HPMC matrix (Siepmann et al., 2002). Carbamazepine, the least water-soluble drug, was released in a pulsatile fashion after a long lag time. It was thus released after erosion of the HPMC compression-coating and not by diffusion through the gel. The release of the other, more water-soluble drugs started after a shorter but similar lag-time for these drugs. The drug release then increased with increasing drug solubility (chlorpheniramine maleate > propranolol HCl > acetaminophen), pointing to an increasing diffusional release component with increasing drug solubility. Other drug properties such as molecular weight and particle size were considered of having a minor/no influence on the comparative drug release profiles when compared to the dominating factor of drug solubility.

Next, the effect of various changes in the HPMC compression-coating on the drug release was investigated.

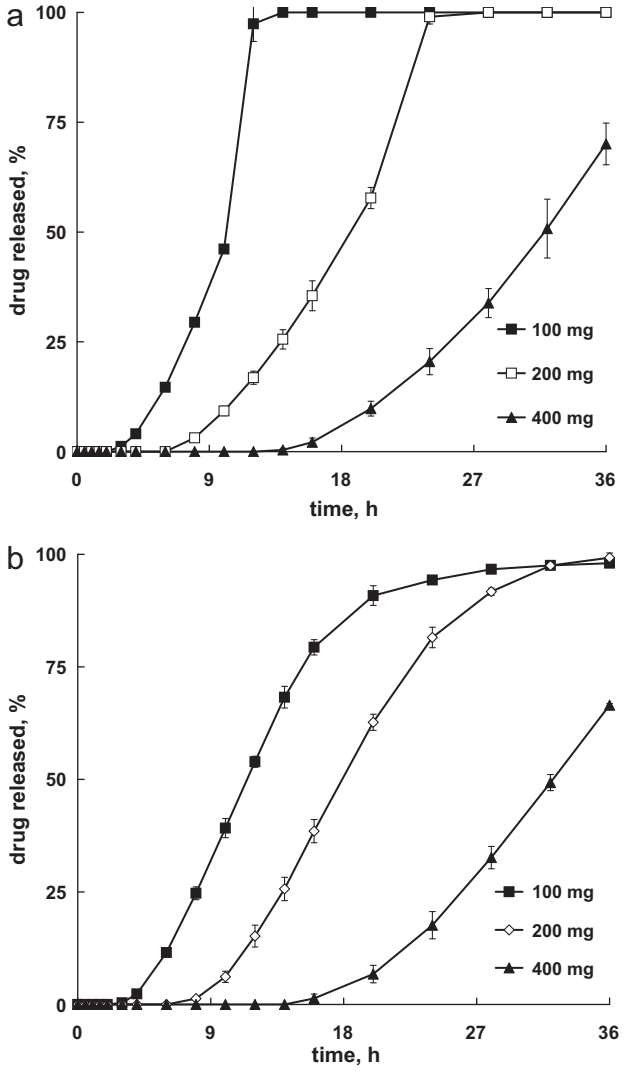

Fig. 4. Effect of amount of compression-coating on acetaminophen release from HPMC compression-coated tablets: (a) HPMC 400 and (b) HPMC K4M.

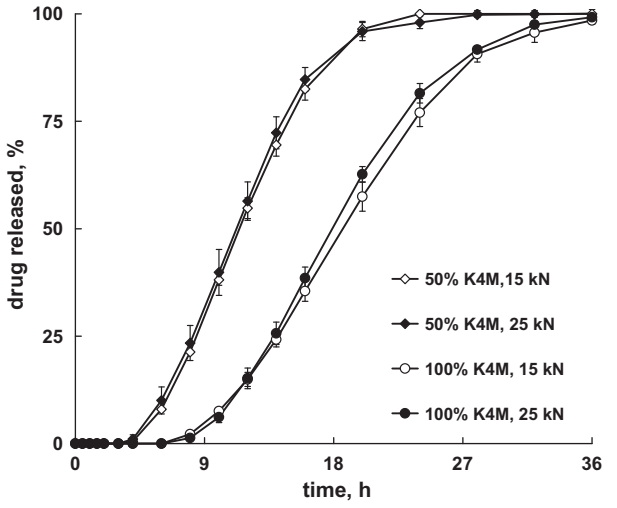

Fig. 5. Effect of compression-coating compression force on acetaminophen release from HPMC K4M compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets).

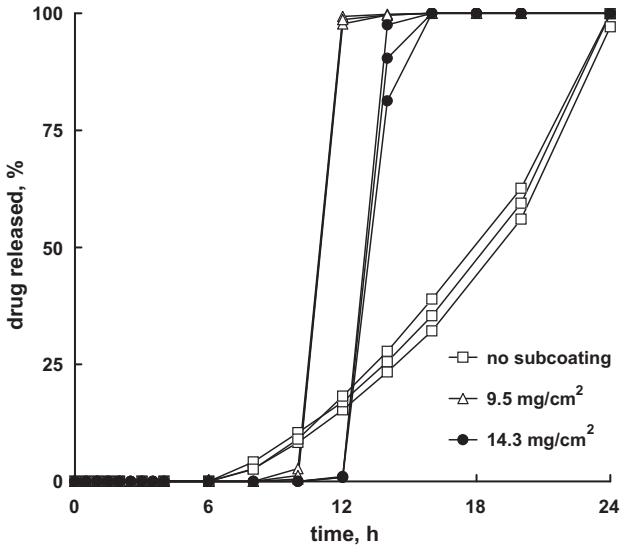

Fig. 6. Effect of Eudragit L subcoating level (mg/cm^2) on acetaminophen release from HPMC 400 compression-coated tablets (core:coat, 1:2, 6 mm Eudragit L subcoated tablets cores in 9 mm compression-coated tablets, 25 kN compression force) ($n = 3$, individual release profiles shown).

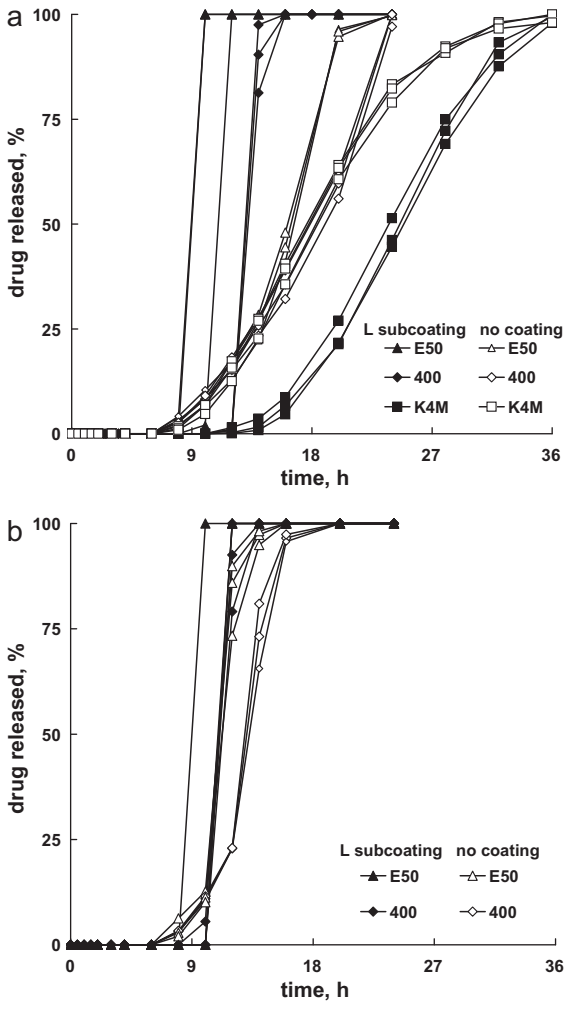

Fig. 7. Effect of HPMC type and Eudragit L subcoating on drug release from compression-coated tablets (core:coat, 1:2, 6 mm tablets cores in 9 mm compression-coated tablets, 25 kN compression force) ($n = 3$, individual release profiles shown): (a) acetaminophen and (b) chlorpheniramine maleate.

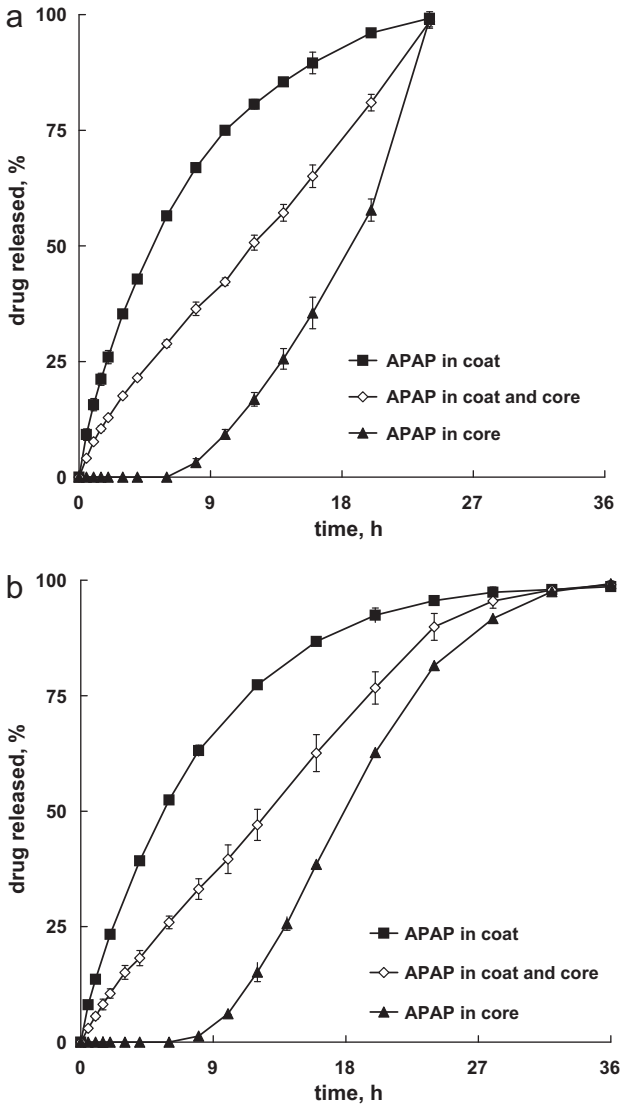

Fig. 8. Acetaminophen release from (a) HPMC 400 and (b) HPMC K4M compression-coated tablets with acetaminophen (APAP) amount in core:coat, 1:1 (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force).

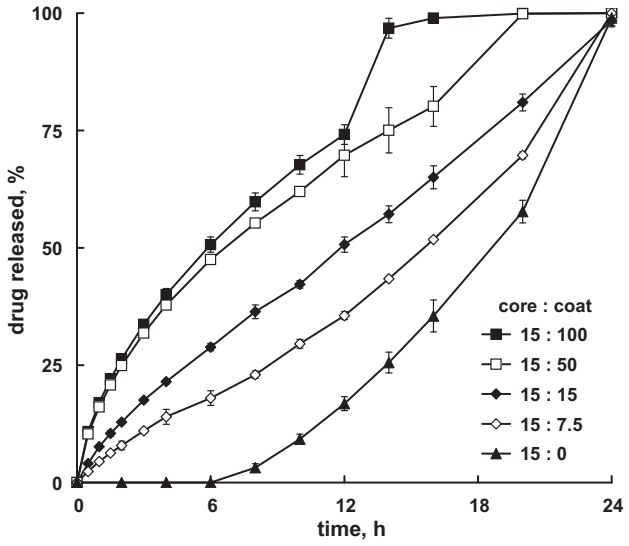

Fig. 9. Effect of drug distribution in the core:coat on acetaminophen release from HPMC 400 compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force).

With the water-insoluble carbamazepine, increasing the molecular weight of HPMC significantly increased the lag time because of the erosion-based release mechanism and the stronger gel and slower erosion with the higher molecular weight HPMC grades (Fig. 2a). In contrast, increasing the viscosity grade (molecular weight) of HPMC in the compression-coating did not affect the release of the more soluble acetaminophen much (Fig. 2b). The initial release phase was the same with the different HPMC grades because of a release mechanism of diffusion through the gel. Only at the later stages did the lower viscosity grade HPMC E50 erode faster and thus resulted in an earlier completeness in release.

The lag-time and the release rate could also be well controlled by varying the composition (ratio HPMC/lactose-Ludipress®) and the amount (thickness) of the compression-coating (Figs. 3 and 4). Increasing the HPMC amount prolonged the lag time and extended the release phase (less steep profiles) because of a higher gel strength (slower erosion) and a higher diffusional resistance (Fig. 3a and b). Slight differences in lag time between HPMC 400 and K4M were observed (Fig. 3c); however, larger differences with regard to the steepness of the release phase (t_{80-10}) were observed because of the faster erosion of the lower molecular weight HPMC 400 (Fig. 3d). As expected, increasing the amount of the compression-coating (decreasing core:coat ratio) resulted in an increasing lag time and decreasing release rate (Fig. 4) because of an increase in gel thickness and thus diffusional path length.

The compression-coating compression force did not affect the drug release in the range investigated (15–25 kN) (Fig. 5). HPMC quickly formed a gel layer on the surface, thus eliminating the potential effect of minor differences in densities obtained with different compression forces. This confirms findings of previous studies with HPMC matrix tablets (Hiremath and Saha, 2008) and pectin-HPMC compression-coatings (Turkoglu and Ugurlu, 2002).

A pulsatile release from HPMC compression-coated tablets, as obtained with the water-insoluble carbamazepine (Fig. 1) would also be desirable for water-soluble drugs. This could be achieved by introducing an enteric polymer layer of Eudragit L between the drug core and the HPMC compression-coating (Fig. 6). The Eudragit L subcoating eliminated drug diffusion into the gelled HPMC layer prior to erosion of the layer; the enteric polymer completely dissolved after erosion of the HPMC compression-coating in intestinal pH-ranges/regions. The lag time increased with increasing Eudragit L coating level because of a slower dissolution of the thicker Eudragit L coating (Fig. 6).

The HPMC type in the compression-coating also affected the drug release from Eudragit L subcoated cores. Pulsatile release was obtained with the lower molecular weight HPMC E50 and 400, but extended release with longer lag time with from HPMC K4M (Fig. 7a). Extended release from HPMC K4M compression-coated tablets was explained by drug diffusion through the partially dissolved Eudragit L subcoat and swollen HPMC K4M compression-coating having higher gel strength compared with HPMC E50 and 400. Pulsatile release from HPMC compression-coated tablets with Eudragit L subcoating was also obtained with the highly water-soluble chlorpheniramine maleate (Fig. 7b).

To further gain flexibility in the drug release profile, drug was also incorporated in the compression-coating in addition to the tablet core (Fig. 8). A constant zero-order drug release profile was obtained with 50% drug each in the core and compression-coating. The individual release curves from drug present in the compression-coating only resulted in a typical matrix-type release profile with a decreasing release rate, while the drug present in the core only resulted in a profile with an increasing release rate.

The decreasing and increasing release rates of the compression-coating and the core then summed up to a constant release rate. Increasing the drug loading in compression-coating resulted in an increased drug release due to a decreased HPMC amount in the compression-coating (Fig. 9). The drug release rate changed from increasing release rates to decreasing release rates with increasing drug loadings in the compression-coating.

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