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Compression of pellets coated with various aqueous polymer dispersions

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Abstract

Pellets coated with a new aqueous polyvinyl acetate dispersion, Kollicoat® SR 30 D, could be compressed into tablets without rupture of the coating providing unchanged release profiles. In contrast, the compression of pellets coated with the ethylcellulose dispersion, Aquacoat® ECD 30, resulted in rupture of the coating and an increase in drug release. Plasticizer-free Kollicoat® SR coatings were too brittle and ruptured during compression. The addition of only 10% w/w triethyl citrate as plasticizer improved the flexibility of the films significantly and allowed compaction of the pellets. The drug release was almost independent of the compression force and the pellet content of the tablets. The inclusion of various tabletting excipients slightly affected the drug release, primarily because of a different disintegration rate of the tablets. The core size of the starting pellets had no influence on the drug release. Pellets coated with the enteric polymer dispersion Kollicoat® 30 D MAE 30 DP [poly(methacrylic acid, ethyl acrylate) 1:1] lost their enteric properties after compression because of the brittle properties of this enteric polymer. Coating of pellets with a mixture of Kollicoat® MAE 30 DP and Kollicoat® EMM 30 D [poly(ethyl acrylate, methyl methacrylate) 2:1] at a ratio of 70/30 and compaction of the pellets resulted in sufficient enteric properties.

Keywords: Aquacoat® ECD; Coating; Compaction of pellets; Ethylcellulose; Extended release; Kollicoat® MAE 30 DP; Kollicoat® SR 30 D; Polyvinyl acetate

1. Introduction

Multiple unit extended release dosage forms such as pellets offer several advantages when compared to single unit dosage forms such as coated tablets or capsules (Bodmeier, 1997; Ghebre-Sellassie, 1994; Bechgaard and Nielson, 1978). The multiparticulates spread uniformly throughout the gastrointestinal tract, resulting in less variable bioavailability and a reduced risk of local irritation. Various drug release profiles can be obtained by simply mixing pellets with different release characteristics or incompatible drugs can be easily separated.

The compaction of pellets is a challenging area. Only a few multiple unit-containing tablet products are available, such as Beloc® ZOK (Sandberg et al., 1988) and Antra® MUPS (Petersen and Schmutzler, 1999). Beloc® ZOK is an extended release multiple unit tablet formulation, containing the antihypertensive drug metoprolol succinate, which releases the drug over a wide range with zero order kinetics (ZOK). Antra® MUPS is a multiple unit pellet system (MUPS)

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consisting of micropellets of the proton pump inhibitor omeprazol.

Ideally, the compacted pellets should not fuse into a non-disintegrating matrix during compaction and should disintegrate rapidly into individual pellets in gastrointestinal fluids. Importantly, the drug release should not be affected by the compaction process. With reservoir-type coated pellet dosage forms, the polymeric coating must be able to withstand the compression force; it can deform, but it should not rupture.

Polymers used in the film-coating of solid dosage forms fall in two broad groups based on either cellulosic or acrylic polymers (McGinity, 1997; Cole et al., 1995). The acrylic polymers are marketed under the trade names Kollicoat® or Eudragit® and the major cellulosic polymer used for extended release is ethyl cellulose. Many of these polymers have been formulated into aqueous colloidal dispersions (e.g. latexes or pseudolatexes) in order to overcome problems associated with the use of organic polymer solutions.

Most studies on the compaction of pellets coated with ethyl cellulose revealed damage to the coating with a loss of the extended release properties. The drug release from compressed niacin/microcrystalline cellulose pellets coated with the aqueous colloidal ethyl cellulose dispersion, Surelease®, was much faster when compared to the release of the uncompressed pellets (Bansal et al., 1993). At higher compression pressures, the pellets were fractured and simultaneously underwent fusion. This resulted in a slight decrease in drug release when compared to the release from compacts compressed at lower compression pressures.

When compared to the ethyl cellulose films, films prepared from acrylic polymers are more flexible and therefore more suitable for the compression of coated pellets (Bodmeier and Paeratakul, 1994). Elongations of more than 75% were obtained with the acrylic polymers, Eudragit® RL/RS, and compression of pellets without damage to the coating was achieved (Lehmann et al., 1993). Crystals, granules and pellets were coated with various aqueous acrylic polymer dispersions (Eudragit® NE 30 D, RS/RL 30 D and L 30 D-55) and compressed into fast disintegrating tablets (Lehmann et al., 1994; Lehmann, 1997). Multiparticulates coated with flexible polymers (Eudragit® NE 30 D) and plasticized Eudragit® RS/RL 30 D could be compressed without significant damage to the coating. Enteric coatings based on Eudragit® L 30 D-55, a methacrylic acid–ethylacrylate copolymer, were brittle and the compression of the pellets resulted in film damage. This damage could be avoided by mixing the enteric polymer with the flexible Eudragit® NE 30 D (Beckert et al., 1996).

This study investigated the use of a new colloidal polymer dispersion, Kollicoat® SR 30 D for extended release pellets and mixtures of Kollicoat® MAE 30 DP and Kollicoat® EMM 30 D for enterically coated pellets, which were subsequently compressed into tablets.

2. Materials and methods

2.1. Materials

Aqueous dispersion of polyvinyl acetate, Kollicoat® SR 30 D; poly(ethyl acrylate, methyl methacrylate) 2:1, Kollicoat® EMM 30 D; poly(methacrylic acid, ethyl acrylate) 1:1, Kollicoat® MAE 30 DP; cross-linked polyvinylpyrrolidone, Kollidon® CL-M; vinylpyrrolidone–vinyl acetate copolymer, Kollidon® VA 64; polyethylene glycol, Lutrol® 4000; coprocessed compound of 93% lactose, 3.5% polyvinylpyrrolidone and 3.5% cross-linked polyvinylpyrrolidone, Ludipress®; propylene glycol (BASF AG, Ludwigshafen, Germany); triethyl citrate, TEC (Morflex, Greensboro, NC, USA); microcrystalline cellulose, Avicel® PH 200; aqueous ethylcellulose dispersion, Aquacoat® ECD 30 (FMC Biopolymer, Philadelphia, PA, USA); lactose monohydrate, Flowlac® 100 and Granulac® 200 (Meggle, Wasserburg, Germany); hydroxypropyl methylcellulose, Methocel® E5 (Colorcon, Orpington, England); sugar spheres, Suglets (500–600, 600–710, 710–850, 850–1000 μm, NP Pharma, Bazainville, France); magnesium stearate (Herwe, Chem-techn Erzeugnisse GmbH, Sinsheim-Dühren). Propranolol HCl, acetaminophen and acetylsalicylic acid were used as model drugs (BASF AG, Ludwigshafen, Germany).

2.2. Methods

2.2.1. Mechanical properties of Kollicoat® SR films

Kollicoat® SR films were prepared by casting a 10% w/v aqueous dispersion onto Teflon plates (14 cm × 14 cm), followed by oven-drying at 30 °C for 48 h.

The films (350–400 μm thick) were cut into pieces of 4 cm × 4 cm and were stored in a dessicator until further use. Mechanical properties of the films in the dry state were measured by a puncture test with an Instron® 4466 mechanical testing device (Instron Wolpert, Ludwigshafen Germany) using a metal probe with a hemispherical end (diameter 5 mm). The load at break and the maximum displacement of the film samples were determined ($n = 6$) and then converted to puncture strength (MPa) and elongation at puncture (%) (Bodmeier and Paeratakul, 1994).

2.2.2. Drug layering

The model drugs were layered on sugar pellets using an ethanol/water (60:40 w/w) solution of HPMC (Methocel® E5) (1.5% w/v) as a binder and PEG (Lutrol® 4000) (10% w/w based on HPMC) as plasticizer in a fluidized bed coater Glatt GPCG-1 (Glatt GmbH, Binzen, Germany) to achieve a 10% w/w drug content. The layering conditions were—batch size: 800 g, inlet temperature: 30 °C, product temperature: 26 °C, air flow: 130 m^3/h, nozzle diameter 1.2 mm, spray pressure: 1.2 bar, spray rate: 8.5 g/min, final drying at 40 °C for 15 min.

2.2.3. Coating of drug-layered pellets

The drug-layered pellets were coated with Aquacoat® ECD, Kollicoat® SR 30 D, Kollicoat® MAE 30 DP, or mixtures of Kollicoat® MAE 30 DP and Kollicoat® EMM 30 D (15% w/w solid content) with a plasticizer (TEC) (if necessary) in the fluidized bed coater Glatt GPCG-1 to a predetermined weight gain. The coating conditions were—batch size: 800 g, inlet temperature: 55 °C, product temperature: 40 °C, air flow: 130 m^3/h, nozzle diameter 1.2 mm, spray pressure: 1.2 bar, spray rate: 7.8 g/min, final drying at 40 °C for 15 min.

Because of the incompatibility of the aqueous dispersions Kollicoat® SR 30 D and Kollicoat® MAE 30 DP, two separate nozzles were used to spray the dispersions using the ball coater Hüttlin HKC 05 (Hüttlin Coating-Technik, Steinen, Germany). The coating conditions were—batch size: 600 g, inlet temperature: 46 °C, product temperature: 39 °C, two nozzles: 0.8 mm diameter, spray pressure: 0.5 bar, microclimate pressure: 0.2 bar, spray rate (total for both nozzles): 5.0 g/min, final drying at 40 °C for 15 min.

2.2.4. Compression of coated pellets

Coated pellets were mixed with different amounts of filler (mostly Avicel® PH 200) and 0.5% w/w magnesium stearate was added as a lubricant. The tablets were compressed on an instrumented tablet press (Korsch EKO, Korsch Pressen GmbH, Berlin, Germany) with different compression forces (punch diameter 10 mm). The hardness of the tablets was tested with a hardness tester (PTB 311, Pharma-Test, Hainburg, Germany).

2.2.5. Drug release

The drug release from the coated and compressed pellets was investigated in a paddle apparatus (USP XXIV) (Vankel® VK 300, Vankel Industries, Edison, NJ, USA) (900 ml 0.1N HCl or buffer pH 6.8 Pharm. Eur. 1997, 100 rpm, 37 °C, $n = 3$). Samples were withdrawn at predetermined time points and measured UV-spectrophotometrically (propranolol HCl $\lambda = 269$ nm, acetaminophen $\lambda = 244$ nm). Pellets and tablets containing acetylsalicylic acid were investigated in a paddle apparatus (Vankel® VK 300) under the following conditions: (100 rpm, 37 °C, 600 ml 0.1N HCl for 2 h, 200 ml 0.2N tribasic sodium phosphate were then added and the pH was adjusted using 2 N NaOH or HCl to a pH of 6.80 ± 0.05 (USP XXIV). Samples were withdrawn at predetermined time points and measured UV-spectrophotometrically at $\lambda = 279$ nm (0.1N HCl) and $\lambda = 267.5$ nm (pH 6.8).

2.2.6. Scanning electron microscopy

Broken tablets were sputtered with gold palladium for 230 s and then observed with a scanning electron microscope (SEM) (Philips SEM 515, Typ PW6703, Philips Optical electronics, Eindhoven, Netherlands).

3. Results and discussion

Coated extended release pellets are mostly filled into hard gelatin capsules or compressed into tablets as final dosage forms. The polymeric coating of the pellets must remain intact during compression in order to retain its extended release properties. The mechanical properties of the particular polymer coating have to be determined in order to investigate its suit-

ability for the coating of pellets, which are intended to be compressed into tablets.

3.1. Compression of Aquacoat® ECD 30 coated pellets

The propranolol HCl release from compressed pellets, which were coated with an aqueous ethylcellulose dispersion, Aquacoat® ECD 30 (plasticized with 25% w/w triethyl citrate) was significantly faster than from the original pellets irrespective of the compression force or the pellet content of the tablets (Figs. 1 and 2). The release increased with increasing compression force and increasing pellet content (less filler Avicel® PH 200), indicating more damage to the coated pellets during compression. This could be explained by the weak mechanical properties of ethylcellulose films, which ruptured during compression. Ethylcellulose films cast from the plasticized dispersion, Aquacoat® ECD 30, were very brittle and weak with low values for puncture strength and elongation (Bodmeier and Paeratakul, 1994).

3.2. Compression of Kollicoat® SR 30 D coated pellets

Kollicoat® SR 30 D is a new colloidal polyvinyl acetate dispersion for the preparation of extended release dosage form and has several advantages when compared to other colloidal polymer dispersions. Kollicoat® SR 30 D coated pellets usually do not require plasticizers for film formation and also not a curing step (thermal after-treatment) because of the low minimum film formation temperature. The pellets also have a pH-independent drug release and are easily processed (Dashevsky et al., 1999).

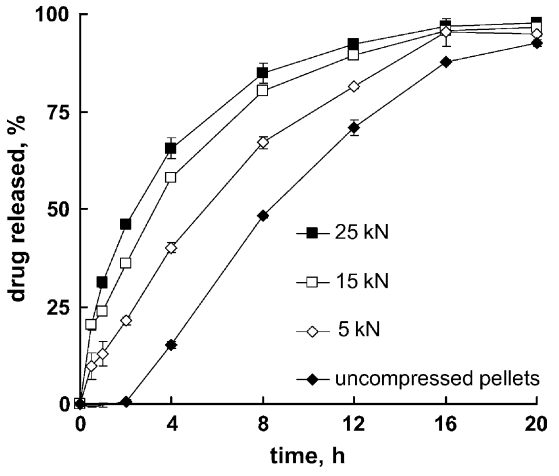

Fig. 1. Influence of compression force on the propranolol HCl release from tablets compressed from Aquacoat® ECD (25% w/w triethyl citrate) coated pellets and Avicel® PH 200 (coating level 20% w/w, pellet content 50% w/w).

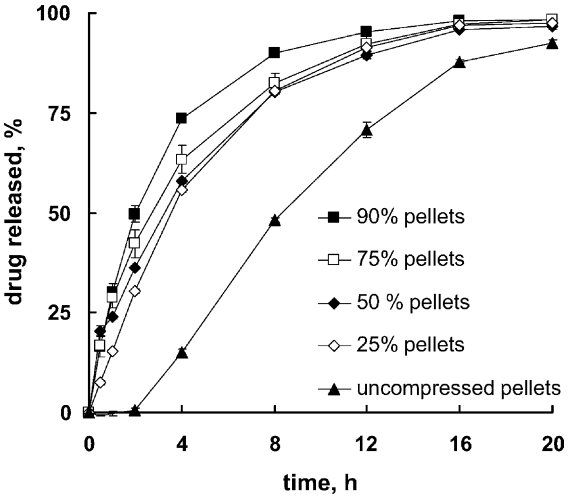

Fig. 2. Influence of pellet content on the propranolol HCl release from tablets compressed from Aquacoat® ECD (25% w/w triethyl citrate) coated pellets and Avicel® PH 200 (coating level 20% w/w, compression force 15 kN).

3.2.1. Effect of plasticizer/pellet content

The pellets were initially coated with Kollicoat® SR 30 D without a plasticizer. However, like with Aquacoat® pellets, the drug release from the compressed pellets was higher than the release from the original pellets, indicating damage to the Kollicoat® SR coating (Fig. 3). Plasticizer-free Kollicoat® SR films were very brittle (elongation approximately 1%). The flexibility of the coatings was dramatically improved by the inclusion of a plasticizer, elongation values up to 137% were obtained with relatively low amounts of plasticizer (10% w/w TEC) (Table 1). TEC was a more efficient plasticizer than propylene glycol. The addition of only 10% TEC to Kollicoat® SR 30 D resulted in almost unchanged drug release profiles at different compression forces because of the improved mechanical properties (Fig. 4). The drug release was also almost independent of the pellet content (Fig. 5).

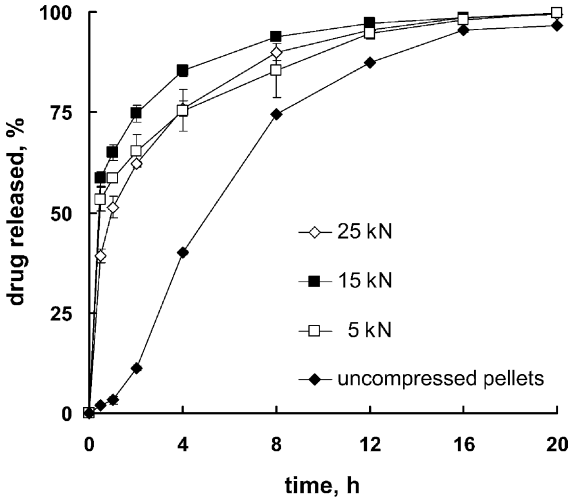

Fig. 3. Influence of compression force on the propranolol HCl release from tablets compressed from Kollicoat® SR 30 D coated pellets and Avicel® PH 200 (coating level 20% w/w, pellet content 50% w/w).

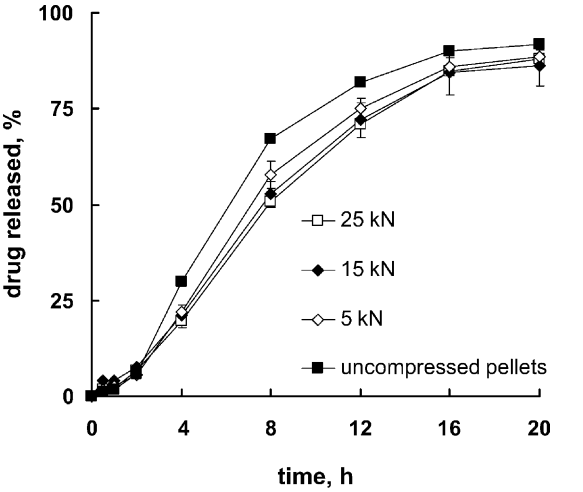

Fig. 4. Influence of compression force on the propranolol HCl release from tablets compressed from plasticized Kollicoat® SR 30 D (10% w/w triethyl citrate) coated pellets and Avicel® PH 200 (coating level 20% w/w, pellet content 50% w/w).

3.2.2. *Effect of filler*

Besides the flexibility of the coating film, the properties of the filler can also influence the compression of pellets. The ideal filler used for the tabletting of pellets should prevent the direct contact of the pellets (e.g., polymer coatings) and act as a cushion during compression. The excipients should result in hard and rapidly disintegrating tablets at low compression forces and should not affect the drug release (Bodmeier, 1997).

The protective effect of different tabletting excipients on the compression of propranolol HCl pellets coated with Kollicoat® SR 30 D was studied indirectly through dissolution studies (Fig. 6). At a pellet/excipient ratio of 1:1, the drug release from the tablets was slightly higher in the case of Kollidon® CL-M, showing a lower protective property of this excipient. In contrast, the release from Kollidon® VA 64 containing tablets was slightly decreased; this was caused by the longer disintegration time of the tablets.

Table 1
Mechanical properties of cast Kollicoat® SR 30 D films (thickness 350 μm)

Plasticizer (%)	Puncture strength (Mpa, m.v. ± S.D.)	Elongation (%, m.v. ± S.D.)
No plasticizer	1.0 ± 0.3	1.1 ± 0.16
Propylene glycol (5)	0.6 ± 0.1	3.0 ± 0.4
(10)	3.8 ± 1.6	21.4 ± 9.4
Triethyl citrate (5)	11.2 ± 1.9	31.3 ± 7.2
(10)	9.3 ± 1.1	136.8 ± 14.2

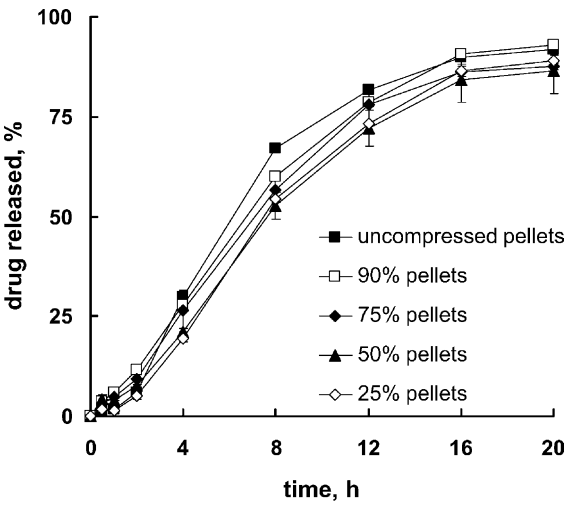

Fig. 5. Influence of pellet content on the propranolol HCl release from tablets compressed from Kollicoat® SR 30 D (10% w/w triethyl citrate)-coated pellets and Avicel® PH 200 (coating level 20% w/w, compression force 15 kN).

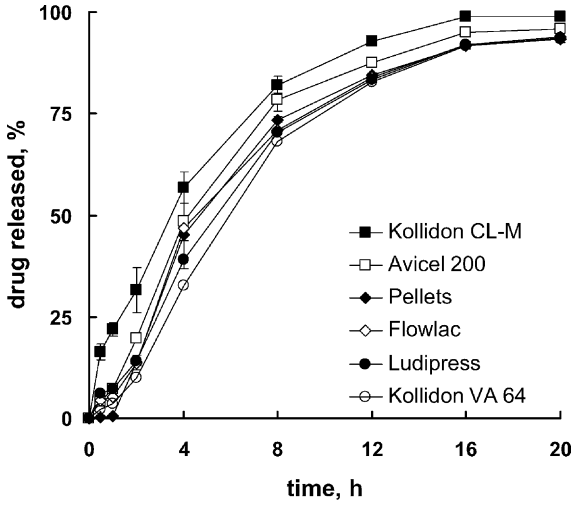

Fig. 6. Influence of different tableting excipients on the propranolol HCl release from tablets compressed from Kollicoat® SR 30 D (10% w/w triethyl citrate) coated pellets (coating level 20% w/w, pellet content 50% w/w, compression force 15 kN).

Avicel® PH 200, Flowlac® and Ludipress®, which are frequently used as direct compression excipients, showed very good cushioning properties. No damages of the pellets were visible (as exemplified with Avicel® PH 200 in Fig. 7) and the drug release from the tablets was almost identical to the original pellets.

3.2.3. *Effect of pellet size*

Pellet size potentially can affect the compaction process and the drug release. Coated smaller pellets individually undergo a lower mechanical stress under compression because of the better distribution in the void space, but have a thinner coating at the same weight gain in coating level because of the higher surface area of the smaller pellets. The propranolol HCl release from Kollicoat® SR 30 D coated pellets decreased with increasing pellets size, however, the release from compressed and uncompressed pellets was very similar at the same pellet size (Fig. 8).

Fig. 7. SEM photographs of the broken tablets containing propranolol HCl pellets, coated with Kollicoat® SR 30 D (10% w/w triethyl citrate, coating level 20% w/w, tableting excipient Avicel PH 200, pellet content 50%, compression force 15 kN).

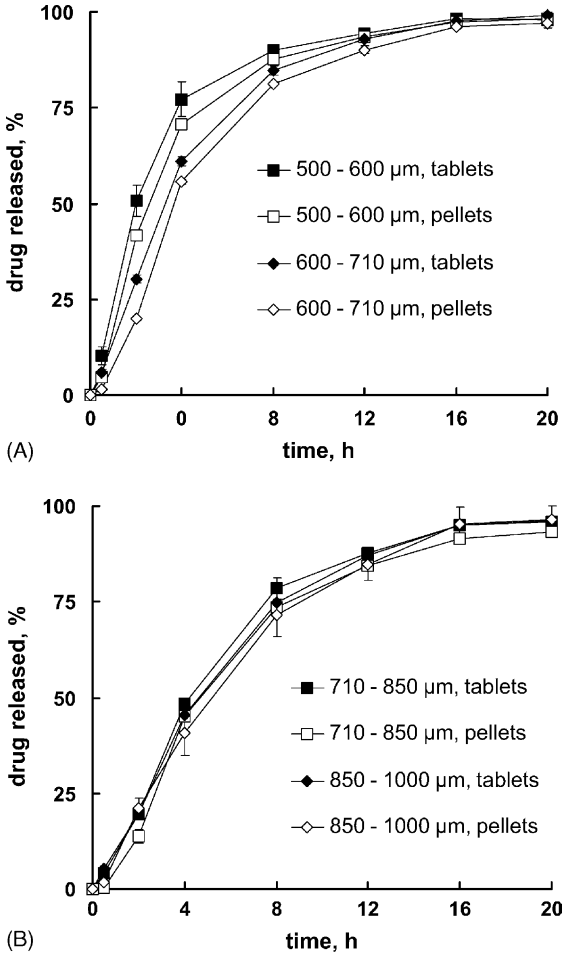

Fig. 8. Propranolol HCl release from pellets of different size (A: 500–600, 600–710; B: 710–850, 850–1000 μm coated with Kollicoat® SR 30 D (10% w/w triethyl citrate) and from compressed pellets (tablets) and Avicel® PH 200 (coating level 20% w/w, pellet content 50% w/w, compression force 15 kN).

3.3. Compression of enterically coated pellets

Acetylsalicylic acid pellets, which were coated with the enteric polymer dispersion, Kollicoat® MAE 30 DP [poly(methacrylic acid, ethyl acrylate) 1:1] and 10% (w/w) TEC as plasticizer, lost their enteric properties after compression into tablets (Fig. 9A). The polymer is very brittle in the dry state and therefore not flexible enough to withstand the compression force. Mixing the enteric polymer with the highly flexible Kollicoat® EMM 30 D [poly(ethyl acrylate, methyl

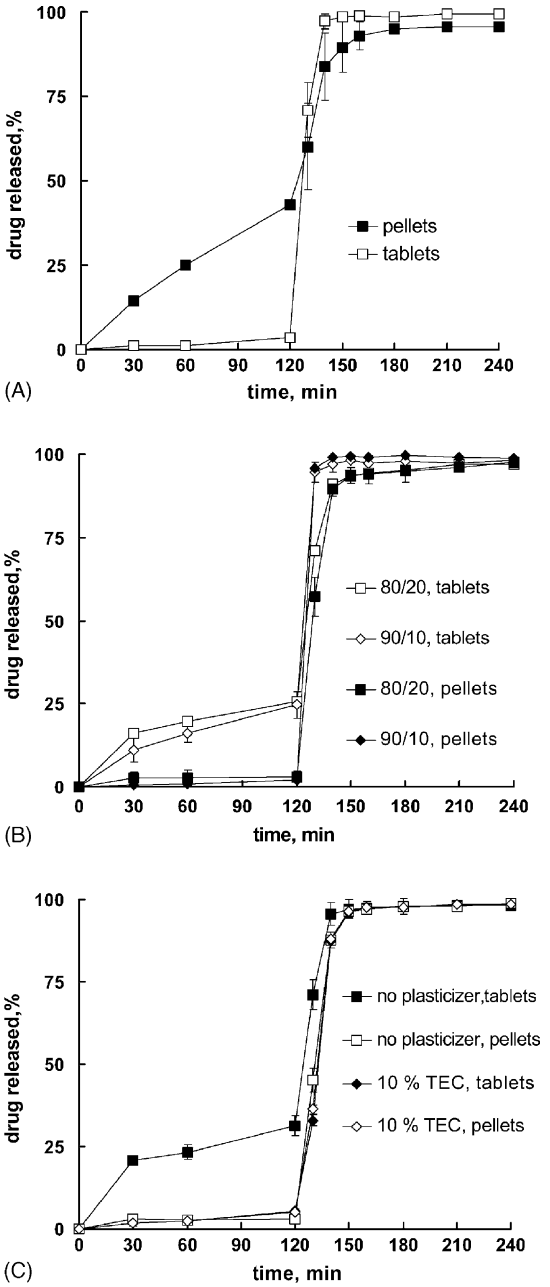

Fig. 9. Acetylsalicylic acid release from pellets coated with A: Kollicoat® MAE 30 DP B: Kollicoat® MAE 30 DP/Kollicoat® EMM 30 D 80/20 and 90/10 and C: Kollicoat® MAE 30 DP/Kollicoat® EMM 30 D 70/30 with and without plasticizer and from tablets compressed from these pellets and Avicel® PH 200 (10% w/w triethyl citrate, coating level 20% w/w, pellet content 50% w/w, compression force 15 kN) for 2 h in 0.1N HCl followed by phosphate buffer pH 6.8.

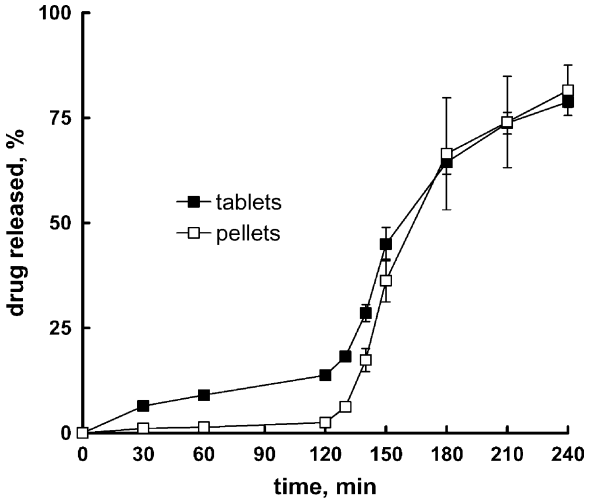

Fig. 10. Acetylsalicylic acid release from pellets coated with Kollicoat® MAE 30 DP/Kollicoat® SR 30 D 90/10 and from tablets compressed from these pellets and Avicel® PH 200 (10% w/w triethyl citrate, coating level 20% w/w, pellet content 50% w/w, compression force 15 kN) for 2 h in 0.1N HCl followed by phosphate buffer pH 6.8.

methacrylate) 2:1] in ratios of 90/10, 80/20 and plasticizing (10% w/w/TEC) could not eliminate the loss in enteric properties (Fig. 9B). Good gastric protection was achieved for compressed pellets coated with a ratio of Kollicoat® MAE 30 DP/Kollicoat® EMM 30 D of 70/30, but only when using 10% TEC as a plasticizer (Fig. 9C). Kollicoat® SR 30 D with 10% TEC was suitable for the compression of the pellets into tablets. But the mixture of Kollicoat® MAE 30 DP and Kollicoat® SR 30 D in a ratio of 90/10 for the coating of acetylsalicylic acids pellets did not improve the mechanical properties to achieve gastric protection after compression into tablets (approximately 13% drug was released after 2 h in 0.1N HCl) (Fig. 10). Moreover, the drug release was retarded in buffer pH 6.8, within 1 h only approximately 80% was released for both pellets and from compressed tablets. Increasing amounts of Kollicoat® SR 30 D in the polymer mixture increasingly retarded the drug release in phosphate buffer pH 6.8 (data not shown).

In summary, Kollicoat® SR 30 D, a new aqueous colloidal dispersion of polyvinyl acetate, with small amounts of plasticizer resulted in flexible coatings and was a suitable polymer for the coating of pellets, which were compressed into tablets.

Acknowledgements

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