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Amylopectin as a subcoating material improves the acidic resistance of enteric-coated pellets containing a freely soluble drug

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Abstract

The effect of an aqueous amylopectin subcoating on the acidic resistance and dissolution behaviour of enteric-coated pellets was studied. Freely water-soluble riboflavin sodium phosphate (RSP) was used as a model drug, and microcrystalline cellulose (MCC) and lactose as fillers in the pellet cores. The pellets were subcoated with 5% aqueous amylopectin solution or with 5% hydroxypropyl methylcellulose (HPMC) solution, and subsequently film-coated with aqueous dispersion of cellulose acetate phthalate (CAP). Drug release of enteric-coated pellets was investigated by confocal laser scanning microscopy (CLSM). Dissolution tests showed that amylopectin subcoating improved the acidic resistance of the enteric-coated pellets in 0.1 N hydrochloric acid (HCl) compared with HPMC subcoating. As the amylopectin subcoating load was increased to 4% and the aqueous CAP coating load to 35%, the coated pellets resisted in 0.1 N HCl solution for approximately 1 h (the amount of drug released was below 10%), and they dissolved in the SIF without enzymes in less than 10 min. Confocal microscopy images and profiles of mean fluorescence intensities of RSP (obtained in the range of the interface of the pellet core and the film and the film coating surface) showed consistent results with dissolution tests. It seems that amylopectin subcoating can prevent the influx of the dissolution medium into the pellet core, and thus decrease the premature dissolution and release of the drug from the enteric-coated pellets in 0.1 N HCl solution. The drug release mechanism appeared to be osmotically driven release, and followed by diffusion through the polymer film.

Keywords: Acidic resistance; Amylopectin; Aqueous CAP dispersion; CLSM; Enteric coating; Subcoating

1. Introduction

Aqueous polymeric dispersions and solutions of alkali salts have been used extensively for enteric film coating of pharmaceutical solid dosage

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forms. These coating systems have numerous advantages over e.g. organic solvent-based systems with respect to ecological, toxicological and manufacturing safety concerns. However, the major limitation related to many aqueous enteric coating formulations is probably the risk of premature drug release (permeation) through the enteric coat in the stomach. This can be due to an increased permeability of aqueous film coating (Chang, 1990) or to a high water solubility of the drug (Bianchini et al., 1991).

In our previous study, waxy maize starch (amylopectin) as a co-filler in the pellet cores decreased premature migration of a freely water-soluble drug from the core into the (enteric) film coating layer. The enteric-coated pellets containing amylopectin as a filler had a good acidic resistance in 0.1 N HCl solution for at least 1 h, while the respective film-coated pellets containing lactose failed the dissolution test for enteric products. Since lactose is one of the most commonly used starting materials in pellet manufacture, it would be interesting to find out whether amylopectin as a subcoating can prevent premature drug release of enteric-coated pellets containing lactose as a co-filler in the core.

Research work on the behaviour and function of oral film-coated drug delivery systems has mostly focused on the properties of individual material components and on the importance of film coating process parameters. Little work has been done on techniques that can improve our understanding of the drug release mechanisms related to the controlled-release film-coated systems (Wilding et al., 1991). Confocal laser scanning microscopy (CLSM) is a potential powerful technique because of its non-invasive nature and ability to visualise the internal structure of samples.

In the present study, the effect of amylopectin as a non-traditional subcoating material on gastric resistance and dissolution of aqueous enteric-coated pellets was studied. Furthermore, the CLSM technique was applied in investigating drug permeability and release mechanisms of enteric-coated pellets exposed to an acidic environment.

2. Materials and methods

2.1. Materials

Riboflavin sodium phosphate (RSP) (Ph. Eur.) was used as a model for freely water-soluble drug. Microcrystalline cellulose (MCC), (Emcocel®, type 90M, E. Mendell, Nastola, Finland) and lactose monohydrate (Pharmatose®, type 80M, DMV International, Veghel, Netherlands) were used as excipients in pellets. Purified water was used as a granulation liquid. Five percent (w/w) waxy maize starch solution (Amioca®, National Starch & Chemical GmbH, Neustadt, Germany) and 5% (w/w) hydroxypropyl methylcellulose (HPMC), (Methocel E5®, Dow Chemical, USA) solution were used as subcoating solutions. The aqueous enteric coating solution contained cellulose acetate phthalate (CAP), (Aquateric, FMC Corporation, Philadelphia, USA), triacetin (Fluka Chemie AG, Buchs, Switzerland), Tween 80 (Fluka Chemie AG, Buchs, Switzerland) and purified water.

2.2. Preparation of pellets

The composition (%) of core pellets was as follows: RSP 0.1, MCC 70.6 and lactose 29.3. The pellets were made with the extrusion/spheronization technique (Nica M6L mixer/granulator; Nica E170 extruder; Nica S320 spheronizer; Nica System AB, Mölndal, Sweden). The pellets were prepared in batches corresponding to granulation of 15 s. The die dimension was 1 mm. In the granulator the speed of the powder feeder was 35 rpm, and the speed of the liquid input pump was 159–160 rpm. During extrusion the speed of the extrusion head was 35 rpm and that of the feeder 45 rpm. The diameter of the apertures in the screen was 1.0 mm, the thickness was 1.25 mm, the spheronization speed was 900 rpm and the spheronization time was 3 min. At the spheronization stage, 300 g of the extrudate was rounded off. Pellets were dried for 24 h in a drying oven at 32 °C. The dry pellets were sieved manually, and those between 0.71 and 1.25 mm in diameter were selected for subsequent film coating.

2.3. Film coating of pellets

2.3.1. Subcoating

Aqueous amylopectin coating solution was prepared in a thermal and pressure reactor equipped with a blade mixer (VTT Automation, Espoo, Finland). Five percent of amylopectin was first dispersed in cold water. Once loaded in the reactor the solution was mixed and gradually heated to 160 °C at a pressure of about 3 bars to ensure that amylopectin remained in a soluble form. Heating was then stopped and the solution was cooled to 95 °C. After that the chamber containing amylopectin solution was taken out from the reactor. When the temperature of amylopectin solution was about 75 ± 5 °C, it was ready for subcoating. Five percent HPMC solution was used as a subcoating reference.

The pellets were coated using an Aeromatic air-suspension film coater (Areomatic Strea-1, Aeromatic AG, Muttenz, Switzerland). Each coating batch comprised 300 g pellets. The pellet cores were preheated for 10 min. The inlet air temperature was adjusted to 78 ± 2 and 60 ± 2 °C, the outlet air temperature to 50 ± 2 and 42 ± 2 °C for amylopectin and HPMC subcoating, respectively. The pneumatic spraying pressure was 1.4 bar, and the air flow rate was 100 m^3/h. The pump rate of the coating solution was 2.0 g/min until a theoretical 2% increase in coating weight was obtained. When a theoretical 4% increase in coating weight of the amylopectin subcoating was used, 0.1% magnesium stearate (Ph. Eur.) was added to the amylopectin solution to prevent the tackiness of amylopectin during the coating process.

2.3.2. Enteric coating

The composition (% w/w) of the aqueous enteric coating dispersion was as follows: Aquateric 11.0, triacetin 3.9, Tween 0.1 and water 85.0. After subcoating, the nozzle and spraying tube were carefully washed and subsequent enteric coating was started. The pneumatic spraying pressure and air flow rate were the same as in the subcoating. The pump rate of the coating solution was 3.2 g/min until a 2% increase in coating weight was obtained, then proceeding at a pump rate of 6.4 g/min to complete the coating run. The inlet air temperature was adjusted to 40 ± 2 °C and the outlet air temperature to 30 ± 2 °C for the Aquateric film coating. After spraying, the inlet air temperature (68 °C) and outlet air temperature (56 °C) were maintained for an additional 2 h in the drying phase. The pellets were then cured in an oven at 60 °C for 2 h. The theoretical amounts of coating were 30 and 35% (w/w) of the total weight of the pellets.

2.4. Evaluation of pellets

The in vitro release tests were performed using an USP apparatus I (basket method). The dissolution medium was 500 ml of 0.1 N hydrochloride acid (HCl) and simulated intestinal fluid (SIF) without enzyme (USP, 1995) maintained at 37 ± 0.3 °C. The basket rotation speed was kept at 50 rpm. The samples were filtered through a filter and assayed by UV spectrophotometry (Perkin–Elmer, Bodenseewerk, Perkin–Elmer GmbH, Uberlingen, Germany) at 444 nm for RSP.

For CLSM analysis, pellets were individually removed from the baskets after 20, 40 and 60 min and immediately dried for 30 min at 60 °C. They were individually placed in a cover glass without further preparation. Images were made with the Bio-Rad Lasersharp MRC-1024 (Bio-Rad, UK) attached to a microscope (Axiovert 135M, Zeiss, Germany) using a Zeiss Plan–Neofluar $10 \times /0.30$ N.A. air lens. A 488 nm line of a krypton–Argon laser and a laser power of 0.45 mW were used. The box size was 512×512 pixels. The iris, black, gain control and all other settings were kept constant during all experiments. Kalman for $N = 6$ frames per Z level was set prior to initiation of the Z series. Images were recorded at intervals of 5 μm in the Z direction.

Parallel tests were performed by quantification of RSP from the film-coated pellet surface to the core. Each stack of pictures was evaluated using an image analysis system (ImageSpace, Molecular Dynamics, Inc., USA). An area of about 0.01 mm^2 of the image was measured by determining the mean fluorescence intensity of RSP in the film. Exactly the same size of image was determined for images at different points of distance.

3. Results and discussion

The release profiles of RSP pellet cores and enteric-coated pellets in 0.1 N HCl are shown in Fig. 1. Amylopectin-subcoated pellets had a more distinct acidic resistance than HPMC-subcoated pellets. Surprisingly, the release rate was higher for HPMC-subcoated pellets than for pellets without subcoating. During the subsequent aqueous CAP coating process, the HPMC film might dissolve in the CAP dispersion due to the hydrophilic nature of HPMC. This might be also contributed by the difference in coating processing temperatures between subcoating and enteric coating. Govender et al. (1995) reported that HPMC inclusion in the polymer film coating had increased the salbutamol release rates due to its hydrophilic nature that had promoted the formation of pores and cracks on the polymer films. Ragnarsson et al. (1992) showed that increasing the proportion of HPMC in the composition of ethylcellulose decreased the reflectivity and increased the permeability of the membrane. It also lowered the tensile stress required to induce convective permeability.

Dissolution profiles for amylopectin-subcoated and subsequent CAP-coated pellets in 0.1 N HCl for 1 h, and subsequently in SIF are shown in Fig. 2. Both batches of coated pellets were shown to improve the acidic resistance in 0.1 N HCl medium and dissolve at SIF in less than 10 min. Increasing the amount of amylopectin subcoating could delay the drug release under 10% for more than 50 min in 0.1 N HCl medium. The molecular weight of amylopectin is about 10^7–10^9 and the side chains of amylopectin form double helices (De Meuter et al., 1999). The branched structure of amylopectin with all its attached chains yields a much larger molecule. Consequently, amylopectin is better at building viscosity. A high viscosity may contribute to good adhesion to the pellet core. The branched amylopectin gives steric hindrance and, therefore, can prevent RSP migration during the coating process.

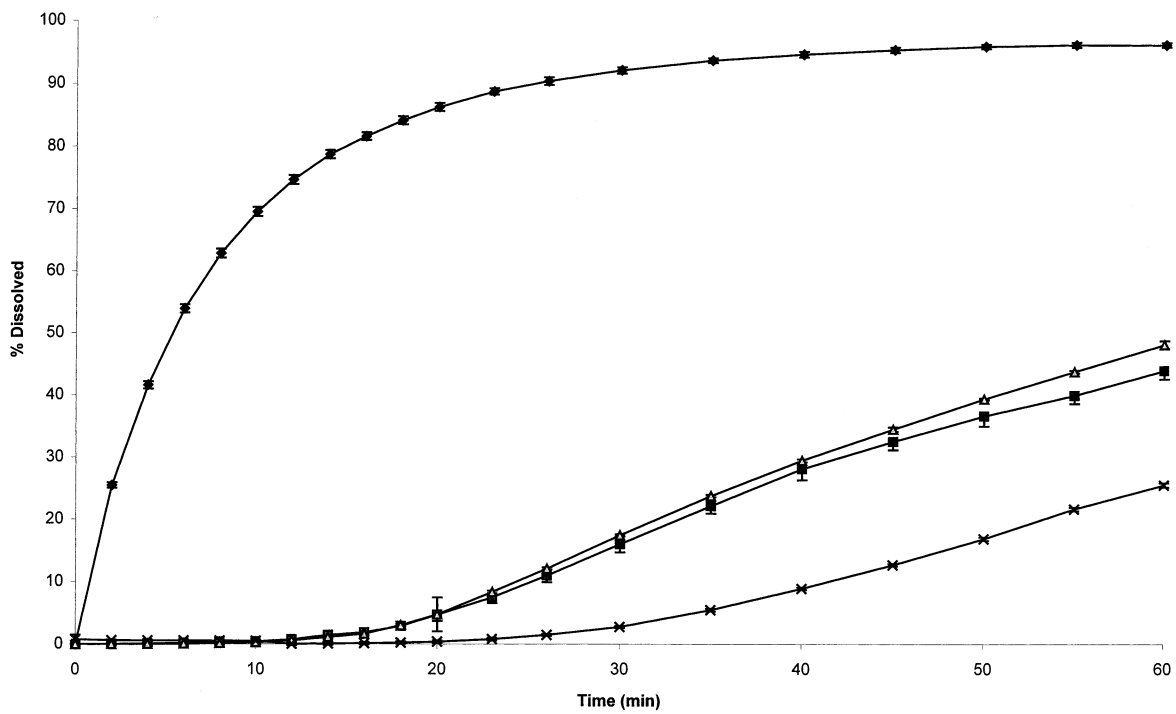

Fig. 1. Dissolution of pellets in 0.1 N HCl medium ($n = 5$). (◆) uncoated pellets, (■) 30% enteric-coated pellets, (△) 2% HPMC subcoat and 30% enteric-coated pellets, (×) 2% amylopectin subcoat and 30% enteric-coated pellets.

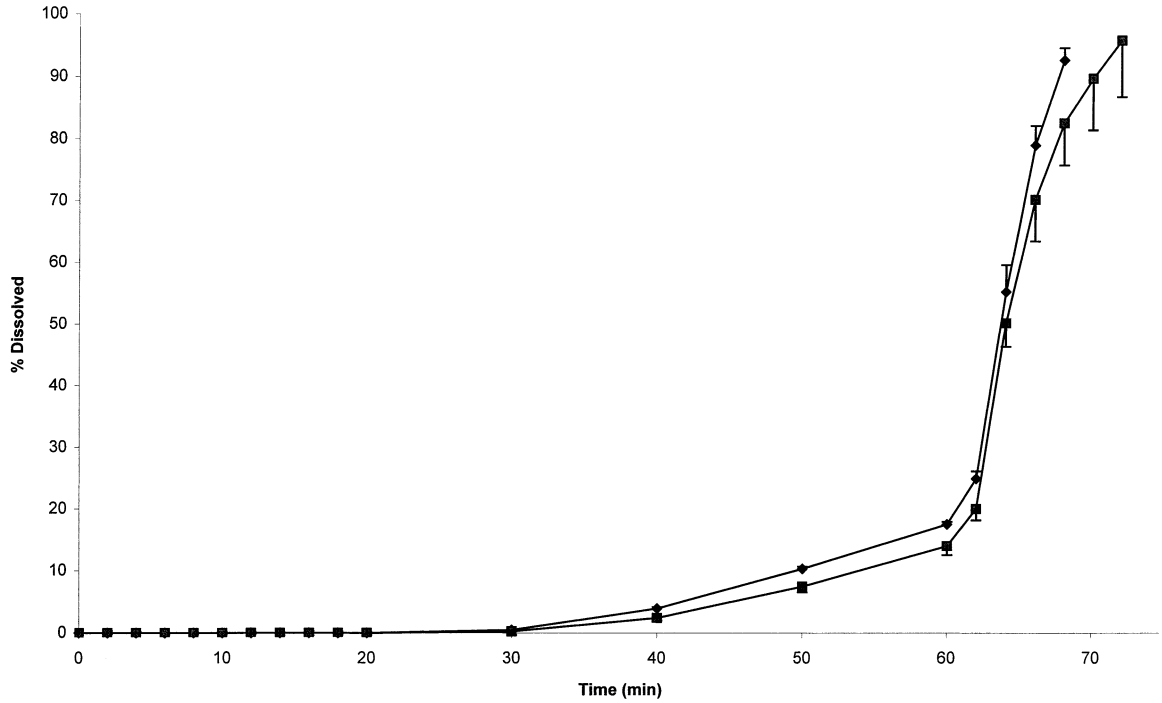

Fig. 2. Dissolution of pellets containing amylopectin subcoat in 0.1 N HCl and SIF media ($n = 5$). Key: (◆) 2% amylopectin subcoat and 35% enteric-coated pellets, (■) 4% amylopectin subcoat and 35% enteric-coated pellets.

In order better to understand the drug release mechanism of amylopectin-subcoated pellets, a dissolution test was carried out for amylopectin-subcoated and 30% aqueous CAP-coated pellets. Samples were collected at intervals of 20, 40 and 60 min for confocal microscopy. Fig. 3 shows confocal images and corresponding fluorescence intensities of RSP from the pellet coat surface to the pellet core. No fluorescent drug in the film coating of the pellets was seen at 20 min. The relatively longer distance from pellet surface to pellet core explained that the dissolution medium probably expanded the film at this point (Fig. 3a). At 40 min the image showed the irregular shape of the pellet (Fig. 3b). This indicates that the drug had dissolved unhomogeneously. It was probably due to amylopectin hindering the influx of medium. The higher viscosity and the branched-molecular amylopectin affected the capacity of the medium, making it more difficult to dissolve the drug. At 60 min, 0.1 N HCl had penetrated further in the pellet core, dissolving the drug and making the drug homogeneously distributed in the pellet (Fig. 3c). At this point, it seemed that the drug in the pellet core was almost completely dissolved and further diffused on the surface of the film. It was seen that the drug diffusion proceeded gradually from the pellet core to the film surface. Fig. 4 shows the confocal image and respective fluorescence intensity profiles for HPMC- subcoated and subsequently 30% CAP-coated pellets at 20, 40 and 60 min of dissolution. At 20 min, the drug in the pellet cores had already dissolved and started to diffuse towards the pellet surface. The irregular shape of the pellets was not as obvious as the amylopectin subcoated pellets at 40 min of dissolution (Fig. 4a). At 40 min, most of the drug had released to the 0.1N HCl medium, and small amounts of drug remained in the film (Fig. 4b). At 60 min, much less drug was measured in the pellet core and film compared with amylopectin-subcoated pellets (Fig. 4c).

Based on the above results it is likely that the dissolution medium (0.1 N HCl) first permeated

and expanded the film coatings (Fig. 3a). In the literature (Thoma and Bechtold, 1999; Thoma and Kräutle, 1999), tablets coated with an aqueous dispersion of CAP coating agents showed massive swelling due to penetration of test medium into the core when acid permeability was evaluated in a 2 h resistance test in 0.1 N hydrochloric acid (HCl). At this point, the mechanism of drug release was primarily induced by osmotically driven release because of the influx tendency of medium. This is consistent with the coated pellets with a membrane of ethylcellulose and HPMC. The more soluble salts induced a higher osmotic influx rate of water into the pellet. At the same time they generated a more rapid expansion of the surrounding membrane (Thoma and Bechtold, 1999). After the inflow medium had dissolved the drug in the core, diffusion appeared to be the major mechanism of drug release (Fig. 3b Fig. 3c). These confirm well the release from PPA HCl pellets coated with an ethylcellulose-based film, which appeared to be a combination of osmotically driven release and diffusion through the polymer and/or aqueous pore (Ozturk et al., 1990). The confocal image (Fig. 3b) shows that the amylopectin subcoating can prolong medium influx to the core due to its high viscosity and hydrophobic properties.

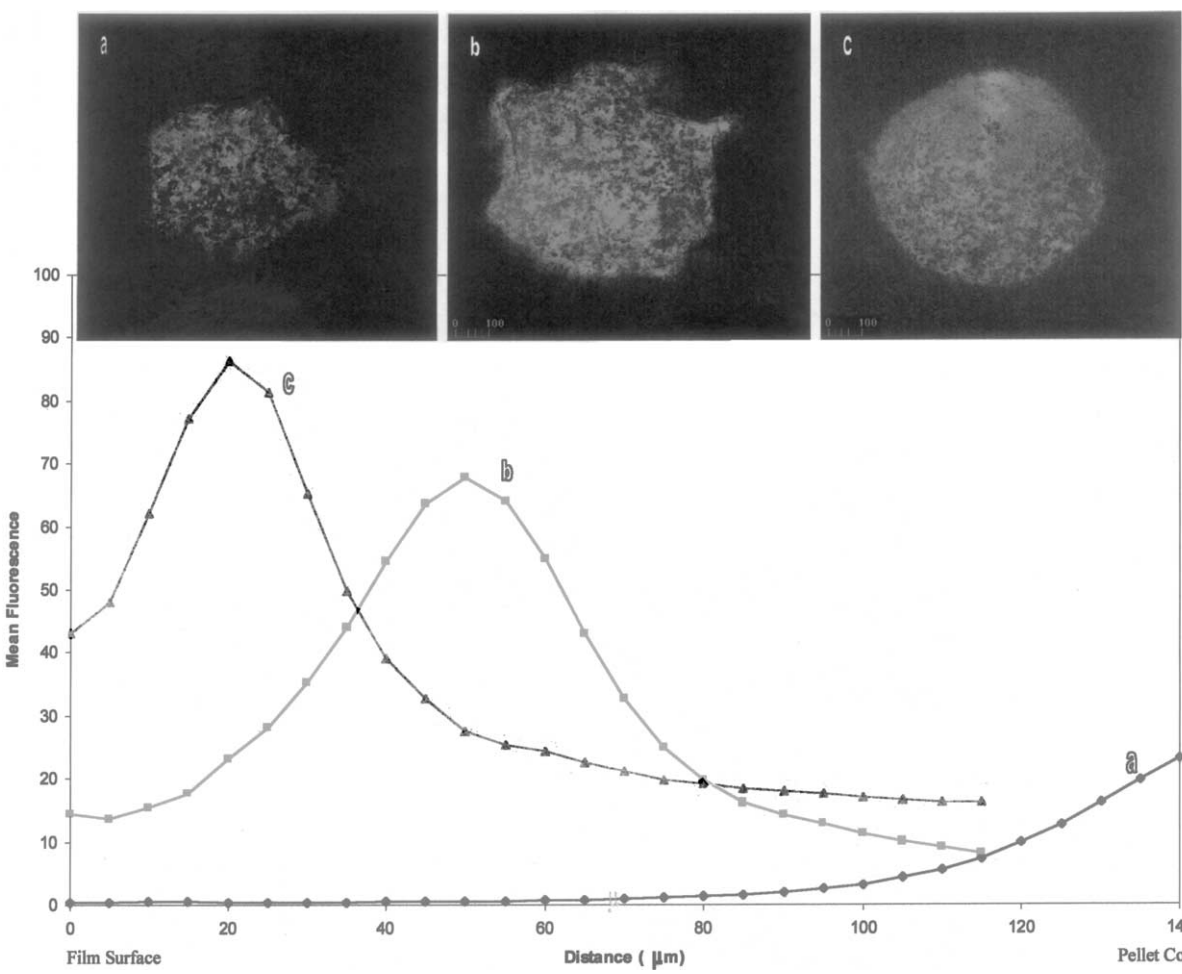

Fig. 3. Mean fluorescence intensity of RSP quantified from the pellet core to the film coat and images after (a) 20 min, (b) 40 min and (c) 60 min of dissolution of the amylopectin-subcoated pellets.

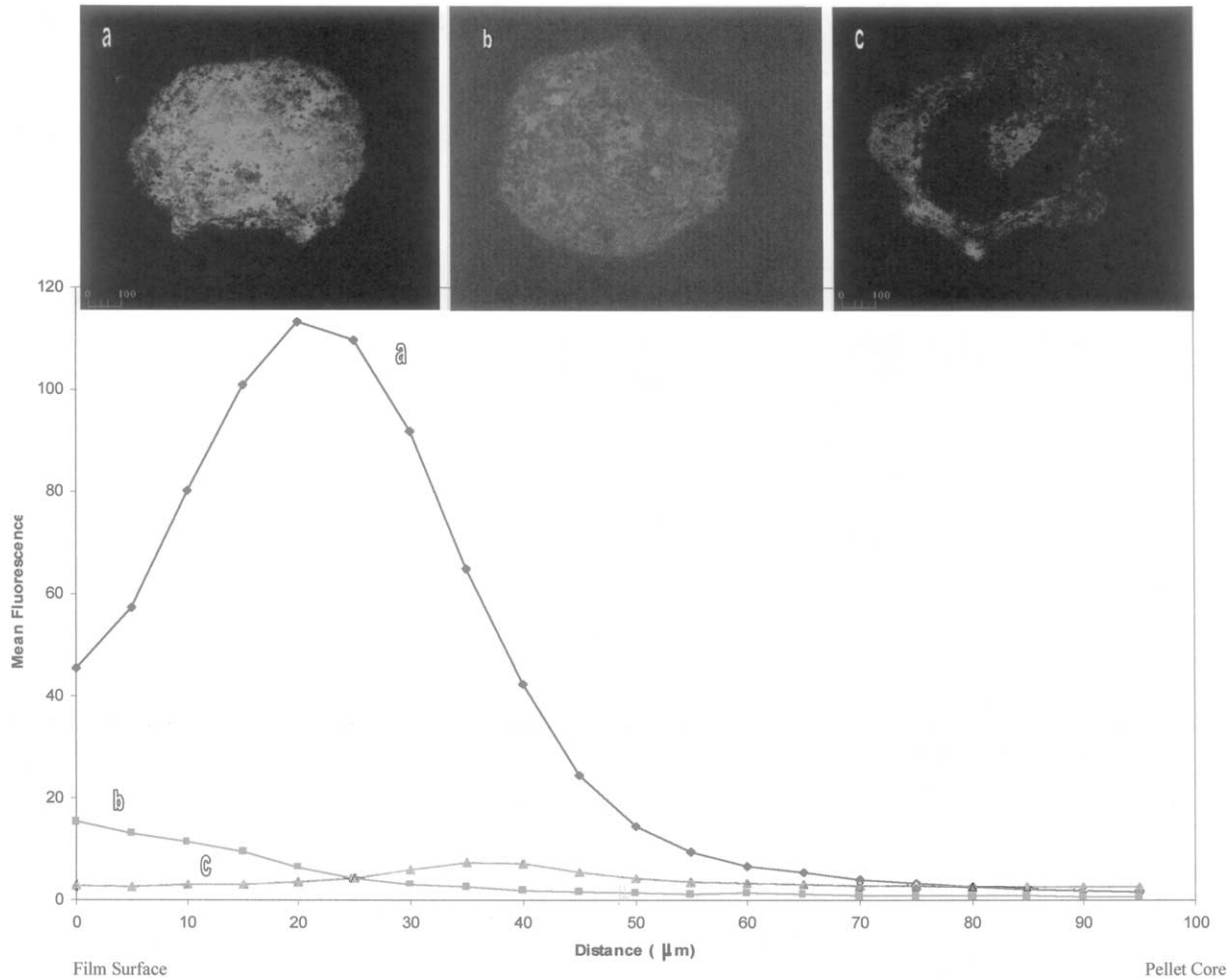

Fig. 4. Mean fluorescence intensity of RSP quantified from the pellet core to the film coat and images after (a) 20 min, (b) 40 min and (c) 60 min of dissolution of the HPMC-subcoated pellets.

4. Conclusions

Application of amylopectin as a subcoating in the pellets subsequently coated with aqueous enteric CAP dispersion can efficiently prevent premature release of freely water-soluble drugs in 0.1 N HCl medium. By increasing the load of amylopectin subcoating or subsequent enteric coating the acidic resistance of the coated pellets can be improved. The confocal microscopy studies agreed very well with the respective dissolution studies. The drug release mechanism of the present enteric-coated pellets appeared to be osmotically driven release followed by diffusion-controlled.

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