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Research paper

A new 5-aminosalicylic acid multi-unit dosage form for the therapy of ulcerative colitis

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Abstract

The aim of the present study was to develop a multi-unit dosage form containing 5-aminosalicylic acid (5-ASA) for the treatment of ulcerative colitis (UC), optimised on the basis of recent studies indicating that UC patients have higher intestinal pH than was previously thought to be the case. Pellets with a drug content of 77.4% were prepared by a granulation and spheronization process and then coated with a new pH sensitive poly(meth)acrylate copolymer (Eudragit® FS 30D) to achieve site specific drug release close to the ileocecal valve. Dissolution tests were carried out in a paddle dissolution apparatus in media simulating pH conditions at various locations in the gastrointestinal tract. The pellets released rapidly at pH values above 7.5. Between 6.8 and 7.2 drug release was found to be zero order, while at pH 6.5 and below no release occurred. In a biorelevant medium which simulates the fasting proximal small intestine fluid it was shown that neither surfactants (sodium taurocholate and lecithin) nor changes in ionic strength trigger drug release. Compared to 5-ASA pellets coated with the well established Eudragit® S, and to currently marketed products licensed for the treatment of UC, the multi-unit dosage form coated with the new polymer exhibited an in vitro dissolution profile more appropriate to the pH profile of the ileum and the colon observed in UC patients.

Keywords: Ulcerative colitis; 5-Aminosalicylic acid; Poly(meth)acrylate copolymer; Eudragit® FS 30D; Multi-unit dosage form; Pellets; Dissolution test; Coating

1. Introduction

In recent years much interest has been focussed on site specific delivery to the colon. Many approaches have been taken, including biodegradable polymers which exploit metabolism by the intestinal microflora to release the drug [1,2], time dependent approaches based on the gastrointestinal transit time [3,4] and pH dependent approaches utilizing the changes in pH along the gastrointestinal (GI) tract [5,6].

Ulcerative colitis (UC) is an inflammatory disease of the colonic mucosa, in which site specific delivery offers several advantages. Acute flare-ups of UC are usually treated locally with salicylates or glucocorticoids in the form of rectally applied foams, suppositories or enemas. However, when the inflammation spreads above the left flexure (pancolitis), and during periods of remission, 5-aminosalicylic acid (5-ASA) is often administered orally (2–4 g/day) [7]. In this case, it is desirable to localise release of 5-ASA insofar as possible to the afflicted sites in the colon. Release of drug in the proximal GI tract should be avoided to circumvent absorption from the small intestine and consequent drug wastage and systemic side effects [8]. Any drug that is absorbed from the small intestine will be distributed throughout the body, with only a small proportion reaching the inflamed tissue in the colon. Much higher serum peaks have been observed following administration of conventional formulations of 5-ASA than when release first occurs in the distal part of the small intestine or in the colon [9]. These high serum peaks appear to be associated with intestinal nephritis, one of the more serious side-effects of 5-ASA [10]. Therefore, an appropriate release pattern appears to be key to providing effective therapy with minimal side-effects in this long lasting – often life long – maintenance therapy. Poly(meth)acrylates (PMMA) are well established in the formulation and development of dosage forms with pH dependent drug release. In fact, the use of pH-sensitive

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Table 1
Marketed products used in the study and their formulation concepts

Product	Dosage form	Polymer type[a]	Trade name	Release pH
Salofalk®	Coated tablets	MA:MM (1:1)	Eudragit® L	> pH 6
Claversal®	Coated tablets	MA:MM (1:1)	Eudragit® L	> pH 6
Asacolitin®	Coated tablets	MA:MM (1:2)	Eudragit® S	> pH 7
Pentasa®	Coated pellets	Ethylcellulose	Surelease®	Release via microgranules diffusion

[a] MA, methacrylic acid; MM, methacrylate.

acrylate based polymers represents the leading formulation approach to the oral treatment of inflammatory bowel diseases, with three of the four products on the German market utilising PMMA to modify the release profile of 5-ASA. The fourth product is a slow release preparation, in which the 5-ASA is encapsulated in microspheres of ethylcellulose. Table 1 illustrates the various marketed products and their formulation approaches.

A relevant consideration for optimisation of the dosage form design for UC is that, in contrast to earlier findings [11], it now appears that the pH in the ileum and proximal colon of UC patients tends to be higher than in healthy individuals [12]. Furthermore, since the gastric residence time of monolithic dosage forms is strongly influenced by the presence and caloric content of food in the stomach and the motility pattern of the different digestive and interdigestive phases [13], we opted for a multi-particulate dosage form design.

In this article we describe the manufacture and release characteristics of 5-ASA containing pellets coated with a new resin composed of methacrylic acid, methylacrylate and methylmethacrylate (Eudragit® FS 30D). This polymer dissolves rapidly at pH $\geqq$ 7.5 (data on file, Röhm GmbH), which should lead to site-specific release in the ileocecal region in patients with UC. We also compared the release behaviour of the pellets coated with the new polymer with that of pellets coated with the well established polymer Eudragit® S, and with the four currently marketed products for the treatment of UC.

2. Materials and methods

2.1. Materials

Mesalazine drug substance (lot# U60554) was purchased from Chemie-S.p.A, Italy. Lactose (lot# 791) was obtained from Meggle, Wasserburg, Germany. Polyvidone (Kollidon® 25) (lot# K23404877) was purchased from BASF, Ludwigshafen/Rh., Germany. Eudragit® FS 30D (lot# 1270514144) and Eudragit® S100 (lot# 1270205103) were donated by Röhm GmbH, Darmstadt, Germany. Glycerol monostearate (Cutina®) (lot# 704001), Polysorbate 80 (Tween® 80) (lot# 744441), Pentasa®, Claversal®, Asacolitin® and Salofalk® were donated by their manufacturers (Ferring Arzneimittel, Kiel, Germany, Merckle GmbH, Ulm (Donau), Germany, Henning Berlin GmbH, Berlin, Germany and Dr Falk Pharma GmbH, Freiburg, Germany, respectively). Lecithin, 99,1% pure (lot# 12091-1) was a donation from Lipoid GmbH, Ludwigshafen, Germany, while sodium taurocholate 97% pure (lot# 59H52254) was purchased from Sigma-Aldrich Chemie, Deisenhofen, Germany. Potassium dihydrogen phosphate, potassium hydrogen phosphate, sodium chloride, sodium hydroxide and hydrochloric acid were all of analytical grade and purchased from E. Merck, Darmstadt, Germany.

2.2. Preparation of the 5-ASA pellets

Lactose (20%) and mesalazine (80%) were thoroughly mixed in a high speed mixer (DIOSNA Typ P 10, Dierks, Osnabrück, Germany) and the granulating fluid (aqueous solution of Kollidon® 25) was added in small increments until a homogenous mass was achieved. The wetted powder mixture was passed through a granulator sieve (Typ SK M/R, Alexanderwerk, Remscheid, Germany). Thereafter the granules were spheronized (Spheronizer Typ 15, Caleva, Ascot, UK) for 10 min until spherical pellets were obtained. The pellets were then dried in a vacuum oven (VT 650, Pink Thermosysteme, Wertheim, Germany) at 40°C for 24 h.

2.3. Eudragit® FS 30D Coating dispersion

Glycerol monostearat (GMS) (20 g) as a glidant and polysorbate 80 (16 g) as an emulsifier were added to 75°C water (525 g) and stirred until a fine, homogenously dispersed emulsion was obtained. The emulsion was added in small increments to the Eudragit® FS polymer dispersion (667g) under constant mixing. The proportion of solids in the final dispersion was 19% (w/w). The percentage of GMS was 10% based on the dry weight of the polymer.

Since Eudragit® FS 30D exhibits a minimum film-forming temperature (MFT) of 14°C no plasticizer was needed in the formulation.

2.4. Aqueous dispersion of Eudragit® S

A redispersed aqueous polymer dispersion was obtained by incremental addition of 200 g of Eudragit® S 100 Powder in 1500 g of water under constant stirring. Addition of 102 g of 1 M ammonia drop-wise to the aqueous suspension over

Table 2
Operating conditions and in process parameters for the coating experiments

Operating conditions	Eudragit® S organic solution of polymer	Eudragit® S aqueous dispersion of polymer	Eudragit® FS 30D aqueous dispersion of polymer
Inlet air temperature (°C)	44–46	40–44	48–52
Product temperature (°C)	n.d.	31–35	38–41
Outlet air temperature (°C)	38–40	29–33	34–37
Total spraying time (min)	358	340	207
Spraying rate	17.9 g/ml	5.9 g/min	5.6 g/min
Curing after coating	10 min in fluid bed, 24 h at 40°C	10 min in fluid bed, 24 h at 40°C	10 min in fluid bed, 24 h at 40°C

15 min resulted in neutralisation of 15% of the carboxyl groups on the polymer, as calculated using a theoretical mean acid value of 190 mg KOH. During this time the powder particles disappeared and a milky latex was formed. After additional stirring for 1 h, 100 g of triethyl citrat (TEC) was added as a plasticizer. The resulting dispersion was stirred overnight. At this point, a talcum suspension which had been homogenized for 10 min in water using a high speed stirrer was added to the polymer dispersion. The proportion of solids in the final dispersion was 20% (w/w).

2.5. Organic solution of Eudragit® S

To prepare an organic solution of the polymer, talcum (100 g) and TEC (20 g) were first added to 1480 g of a mixture of isopropanol/acetone/water (23.5:15.5:1) and gently homogenized. The resulting dispersion was added in small increments to 1600 g of a 12.5% solution of Eudragit® S (Eudragit® S 12.5). The total solids content in the final dispersion was 10% (w/w).

2.6. Coating of the 5-ASA pellets

A Glatt WSG 5 (Glatt GmbH, Binzen, Germany) was used as a coating apparatus for processing the organic Eudragit® S solution. All other coating experiments were conducted in a Glatt GPCG 1 (Glatt GmbH, Binzen, Germany) coating apparatus. In each run, the spraying nozzle was used in the'top-spray' mode, the diameter of the nozzle was 1.2 mm and the spraying pressure was 2 bar. Table 2 shows the process parameters of each coating run.

2.7. Scanning electron microscopy

The morphology of the surface and the film thickness were examined by scanning electron microscopy (SEM) (Jeol 840 A, Jeol, Ltd., Japan). Samples were gold coated using a sputter coater. To evaluate the film thickness, pellets were radial sheared before the sputter coating was applied.

2.8. Dissolution tests

An ERWEKA Type DT 80 dissolution tester, Apparatus 2 (ERWEKA, Heusenstamm, Germany) was used for all dissolution studies. The volume of media was 900 ml at 37 ± 0.5°C and a stirring rate of 100 rev/min was employed.

The dissolution test was conducted over at least four hours, corresponding to the mean transit time of solids through the small intestine. All studies were performed at least in triplicate and results are expressed as mean % dissolved at the given sampling time. To simulate pH conditions in the GI tract, one biorelevant medium and five compendial media were used. The ionic strength of the compendial media was in the range of 0.1–0.2 M. A biorelevant medium which simulates the small intestinal fluid in the fasting state (FaSSIF) was chosen in order to evaluate whether the dissolution behaviour is influenced by the presence of bile salts and lecithin. FaSSIF consists of an isoosmolar phosphate buffer solution, pH 6.5, sodium taurocholate (NaTC) (3 mM) and lecithin (LEC) (0.75 mM). These concentrations and pH conditions reflect the usual composition of chyme in the fasted state in the proximal small intestine [14]. The media was freshly prepared and used within 24 h. In order to investigate the influence of the ionic strength (IS) on the dissolution behaviour, blank FASSIF medium (i.e. phosphate buffer pH 6.5) adjusted to hypoosmolar (80 mOsm), isoosmolar (270 mOsm) or hyperosmolar (600 mOsm) values with potassium chloride was used. An overview of the various media used is given in Table 3.

2.9. Detection of released 5-ASA

In cases where no NaTC was used in the media, the concentration of dissolved 5-ASA was measured by UV spectroscopy. In SGFsp the measuring wavelength was 232 nm; for all other media the wavelength was 331 nm. When NaTC was included, a HPLC method was utilised to determine the amount of drug released. The system consisted of an RP 18 column, Lichrosphere® 100 (5 μm) (Merck, Darm-

Table 3
Dissolution media used for the dissolution tests

Dissolution media	pH	Reference
Simulated gastric fluid without pepsin (SGFsp)	1.2	USP XXIII
Phosphate buffer	6.0	DAB 10
FaSSIF	6.5	[14]
Phosphate buffer	6.8	DAB 10
Phosphate buffer	7.2	DAB 10
Simulated intestinal fluid (SIFsp)	7.5	USP XXIII

stadt, Germany), a HPLC-pump (L-7100, Merck Hitachi, Darmstadt, Germany), an autosampler (L-7200, Merck Hitachi), a degassing unit (Bischoff SDU 2003, Bischoff Analysentechnik, Leonberg, Germany), a UV/VIS detector (L-4250, Merck Hitachi) and an integration software system (Borwin, Groß-Umstadt, Germany). As mobile phase a solution of methanol:phosphate buffer pH 4.6 (1:1) was used. The flow rate was 1.0 ml/min, the injection volume was 100 μl and the detection wavelength was 297 nm. Under these conditions, 5-ASA typically eluted at 2.8 min.

3. Results and discussion

3.1. Manufactured pellets

The drug content of the spheronized 5-ASA pellets was 77.4%. The pellets possessed a tap density of 0.705 g/ml and a Hausner factor of 1.042. The friability was 0.24%. The fraction between 0.8 and 1.25 mm was used for the coating experiments. The pellet morphology is depicted in Fig. 1a. After coating, the pellets possessed a spherical form and a smooth surface. The film thickness of the coatings was approximately 55 μm in each trial. These findings are in a good agreement with calculated values and reflect the high efficiency and reproducibility of the coating process. Fig. 1b–d illustrates SEM of the pellet surface and cross-sections of the various batches of coated pellets. Homogenous and uniform polymer films were observed for all formulations and completion of the film formation process can be assumed, since the coated pellets were subjected to post column heating for 24 h at 40°C in a tray dryer. Although no plasticizer was used in the Eudragit® FS 30D formulation, the polymer film exhibited a tendency to agglomerate during the curing process. To prevent this agglomeration and to ensure free flow characteristics of the pellets, we subsequently mixed 0.5% (w/w) Aerosil 200 into the pellet batch before initiating the drying process.

3.2. Dissolution tests of Eudragit® FS 30D and Eudragit® S pellets

Currently Eudragit® S seems to be the most favourable coating in terms of achieving a delayed delivery of 5-ASA in the more distal parts of the small intestine [15]. Taking into consideration that the intestinal pH tends to be higher in patients with UC [12], the release from of Eudragit® S coated products is likely shifted to a more proximal region of the gut in these patients. Comparative in vitro dissolution studies with Eudragit® FS 30D were conducted to investigate whether the new polymer exhibited a more appropriate release pattern than Eudragit® S.

Fig. 2a shows the release profiles at different pH values from 5-ASA pellets coated with Eudragit® FS 30D. Release is very slow at pH 6.8, averages about 20% an hour at pH 7.2 and is complete within 2 h at pH 7.5. No release was observed at pH 6.5, pH 6.0 or 1.2. Fig. 2b shows the release

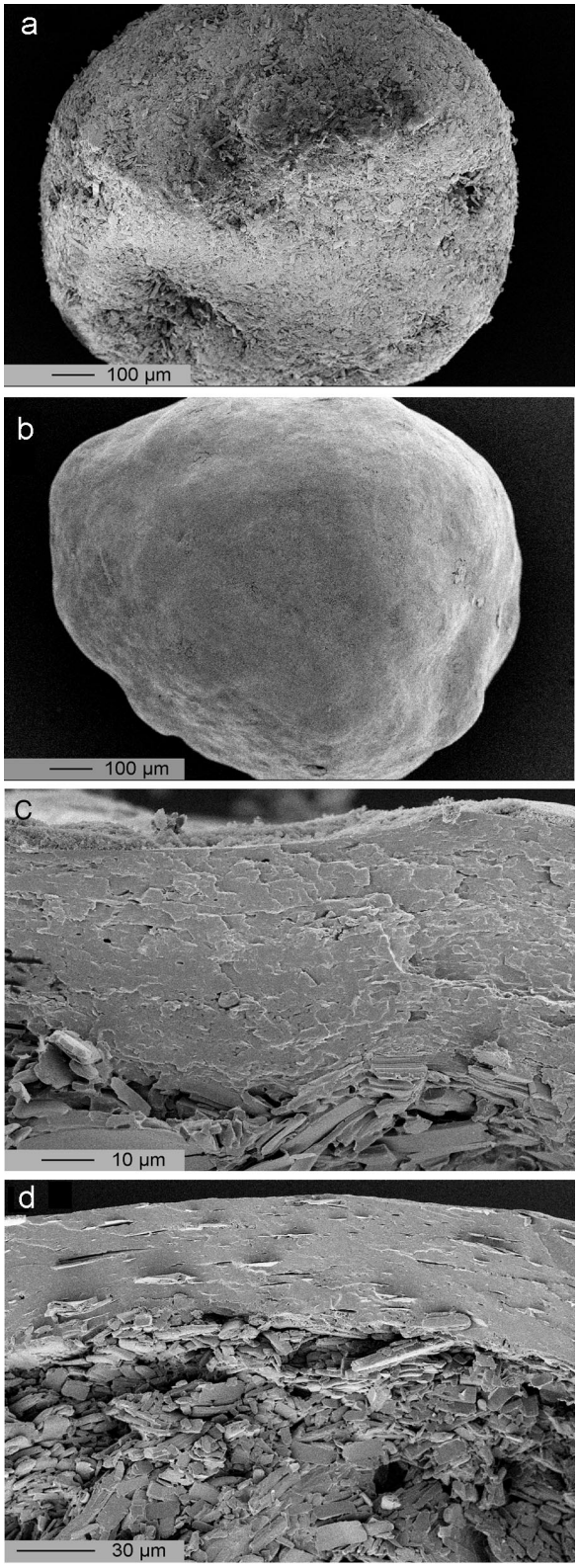

Fig. 1. (a) SEM of the 5-ASA pellet surface without coating (magnification 80×). (b) SEM of the 5-ASA pellet surface after coating with Eudragit® S (magnification 80×). (c) SEM cross section of a 5-ASA pellet coated with Eudragit® FS 30D (magnification 1000×). (d) SEM cross section of a 5-ASA pellet coated with Eudragit® S from an aqueous dispersion (magnification 500×).

profiles of 5-ASA pellets coated with Eudragit® S, either from an organic solution or from an aqueous dispersion in various phosphate buffers (pH 7.5, 7.2 and 6.8). No release was observed at pH 6.5, 6.0 or 1.2. For pellets coated with the aqueous dispersion, rapid release was observed at pH values above 7. Pellets coated from an organic solution tended to exhibit slower release than those from aqueous dispersions. In the case of the aqueous dispersion, partial neutralisation of the dispersion may result in partial salt formation of the polymer and hence faster release.

At pH values below 7, no significant release of drug was observed from any of the Eudragit® S or FS 30D formulations, whereas at pH 7.5, all formulations release fast. The intermediate pH, 7.2, appears to discriminate the best between the various formulations, as shown in Fig. 3. Both Eudragit® S formulations release faster than the Eudragit® FS 30D formulation at pH 7.2. These findings in vitro would be commensurate with high 5-ASA concentrations in the small intestine and hence, systemic absorption. By contrast, the minor release of 5-ASA from the Eudragit® FS 30D formulation under pH conditions typical of the jejunum/ileum should lead to a minimal absorption of 5-ASA from the small intestine. In most patients with UC, the pellets should release the drug a shortly before or at the ileocecal valve. Even in those patients who do not achieve a pH of 7.5 in the ileum, the steady release rate at pH values above 7 should ensure adequate release of 5-ASA in the proximal and transverse colon.

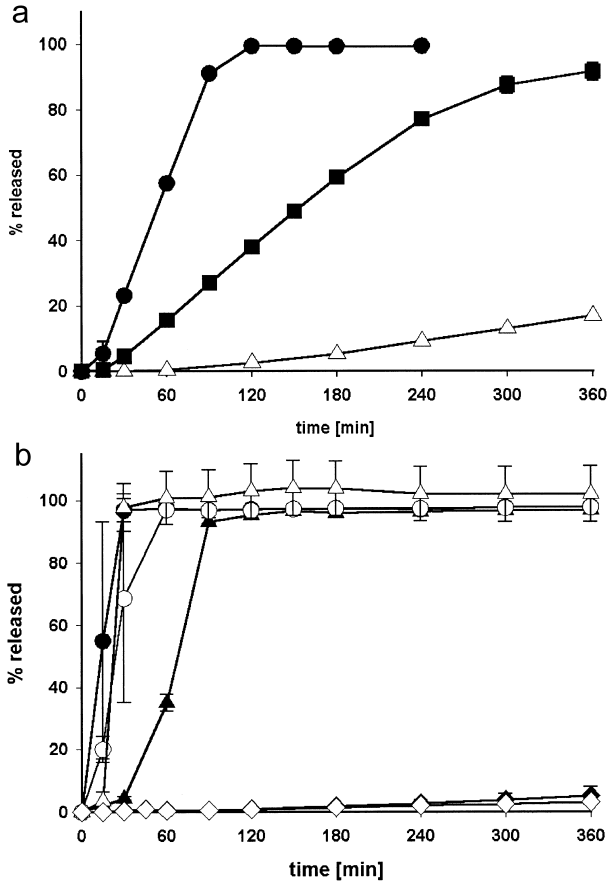

Fig. 2. (a) Mean dissolution profiles (±SD) of 5-ASA pellets coated with Eudragit® FS 30D in various phosphate buffers: (●) pH 7.5; (■) pH 7.2; (△) pH 6.8. (b) Mean dissolution profiles (±SD) of 5-ASA pellets coated with Eudragit® S from an organic solution (closed symbols) and an aqueous dispersion (open symbols) in various phosphate buffers. Circles (●, ○) represent data at pH 7.5, triangles (▲, △) at pH 7.2 and diamonds (◆, ◇) at pH 6.8.

3.3. Influence of osmolarity and added surfactants

The effects of buffer capacity on disintegration and dissolution of salicylic acid tablets coated with Eudragit® S have been investigated by Ashford and co workers [6], but they used a high pH (7.5) phosphate buffer. They found a linear relationship between the buffer capacity and the dissolution rate. In addition to buffer capacity, the IS can affect dissolution of the polymer. We used blank FaSSIF (pH 6.5) for our osmolarity studies. Blank FaSSIF has a pH more typical of duodenal pH conditions. In this region the osmolarity is likely to fluctuate according to which fluids or meals are administered with the dosage form. Deeper in the GI tract, where the pH is higher, the osmolarity is more tightly regulated to isoomolar by means of secretion of water (in the case of hypertonic meals/fluids) or water absorption (in the case of coadministration of water with the dosage form).

The PMMA polymer matrix can swell according to osmotic swelling pressure and ion exchange kinetics [16]. To examine whether the IS has an influence on the process of polymer dissolution, we kept the buffer capacity constant and varied IS with potassium chloride. We found that varying the osmolarity with potassium chloride did not modify the release pattern from pellets coated with either Eudragit® S or Eudragit® FS 30D. Further, when NaTC and LEC were included in the medium (FaSSIF), no effect was observed on the release rate. Osmotic and surfactant independent zero

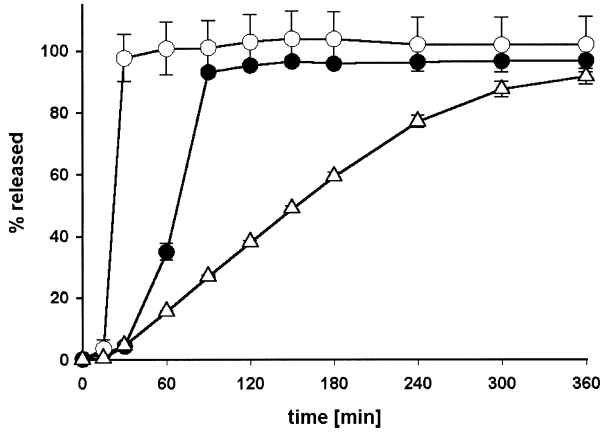

Fig. 3. Mean dissolution profiles (±SD) of 5-ASA pellets coated either Eudragit® S or Eudragit® FS 30D at pH 7.2:, (●) Eudragit® S, organic solution; (○) Eudragit® S, aqueous dispersion; (△) Eudragit® FS 30D, aqueous dispersion.

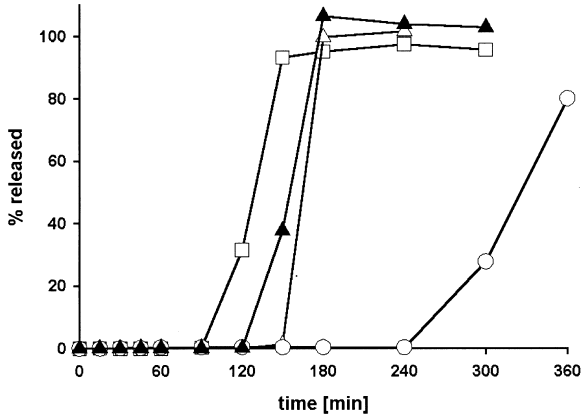

Fig. 4. Mean dissolution profiles of Claversal® tablets in FaSSIF and blank FaSSIF with varying osmolarity (all experiments conducted at pH 6.5). ((▲) FaSSIF; (△) blank FaSSIF, isoosmolar (270mOsm); (○) blank FaSSIF, hypoosmolar (80mOsm); (□) blank FaSSIF, hyperosmolar (600mOsm))

order release was also observed for Pentasa®. In the case of Eudragit® L coated Salofalk® and Claversal® tablets, an osmotic pressure dependent dissolution behaviour was observed. The dissolution profiles of Claversal in FaSSIF and blank FaSSIF with varying osmolarity are depicted in Fig. 4. The lag time increases with decreasing IS and with inclusion of NaTC and lecithin in the medium. Similar results were obtained for Salofalk® but the profiles are not statistically significant (results not shown). During the dissolution studies with the commercial products, we observed that the onset of drug release correlates to formation of a leakage at the tablet edge. Therefore we determined the film thickness at various locations on the tablets. In both Claversal® and Salofalk® the thinnest film thickness was found at the tablet edge (approximately 100 μm for Salofalk® and 250 μm for Claversal®).

3.4. Dissolution tests of marketed products

Comparative dissolution tests of the marketed products

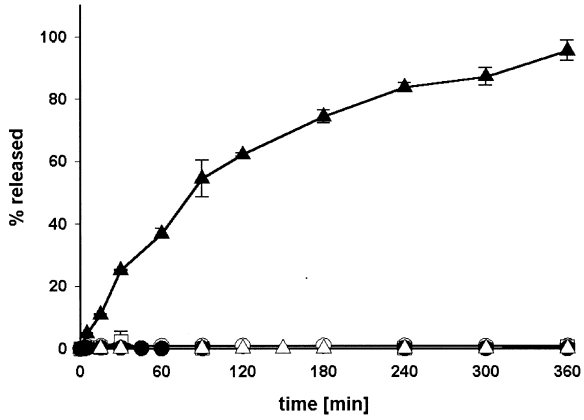

Fig. 5. Comparative dissolution profiles in SGsp., expressed as mean ± SD. ((●) Salofalk®; (□) Claversal®; (○) Asacolitin®; (▲) Pentasa®; (△) Eudragit® FS 30D pellets).

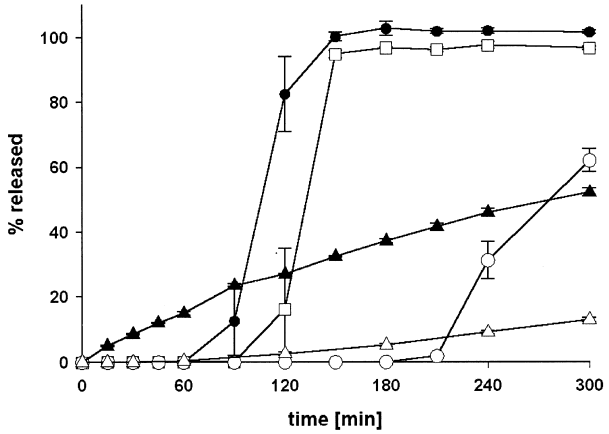

Fig. 6. Comparative dissolution profiles in phosphate buffer pH 6.8, expressed as mean ± SD. ((●) Salofalk®; (□) Claversal®; (○) Asacolitin®; (▲) Pentasa®; (△) Eudragit® FS 30D pellets).

and the pellets coated with Eudragit® FS 30D were conducted to evaluate and compare dissolution behaviour at several pH values reflecting various locations along the small intestine. From the acrylate coated products no release was observed in SGF, whereas with the ethylcellulose coated microgranules (Pentasa®) 60% was released after 2 h (Fig. 5). The higher release rate at pH 1.2 than at intestinal values reflects the higher solubility of 5-ASA at pH 1.2 [17]. The relatively high release of 5-ASA from Pentasa® under gastric conditions may lead to a substantial wastage of drug before reaching the inflamed area.

At pH 6.0 and 6.5, corresponding approximately to duodenum, substantial release was observed for Pentasa® via diffusion through the polymer film. At pH 6.0, release after a lag time of 120 min also occurred in the case of Salofalk®. During the test period of 6 h Claversal® did not release 5-ASA at pH 6.0 (profiles not shown). However, both Claversal® and Salofalk® released 5-ASA rapidly at pH 6.5 after a lag time of 120 and 60 min, respectively.

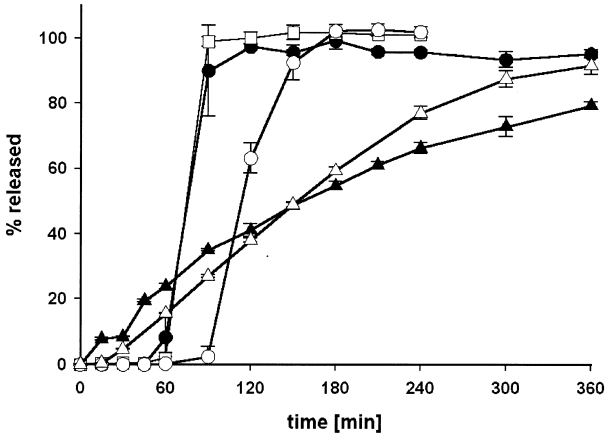

Fig. 7. Comparative dissolution profiles in phosphate buffer pH 7.2, expressed as mean ± SD. ((●) Salofalk®; (□) Claversal®; (○) Asacolitin®; (▲) Pentasa®; (△) Eudragit® FS 30D pellets).

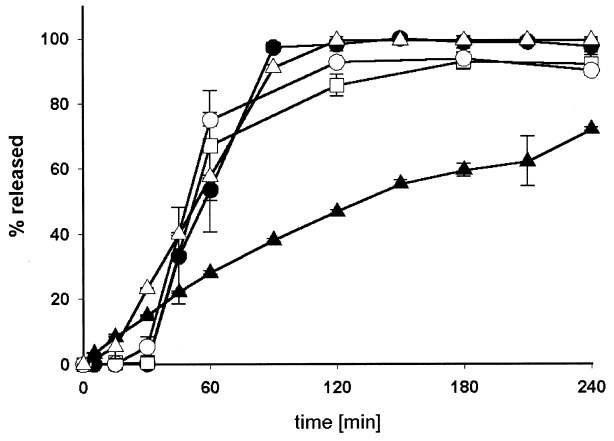

Fig. 8. Comparative dissolution profiles in phosphate buffer pH 7.5, expressed as mean ± SD. ((●) Salofalk®; (□) Claversal®; (○) Asacolitin®; (▲) Pentasa®; (△) Eudragit® FS 30D pellets).

These lag times correlate well with the different film thickness of the two formulations.

The pH 6.8 medium reflects the jejunal region of the small intestine. Formulations Salofalk® and Claversal® released drug completely within 120 min (Fig. 6). A lag time of 210 min was observed for Asacolitin®, followed by first-order release. Slow, zero order release was observed for Eudragit® FS 30D pellets, after a lag time of 60 min, and for Pentasa®.

The transition from the jejunal to the ileal segment was simulated using a pH 7.2 buffer (Fig. 7). The approximately zero order release profiles for Pentasa® and Eudragit® FS 30D pellets are comparable and display no lag-time. Claversal®, Salofalk® and Asacolitin® exhibit a very rapid release after a lag-time ranging from 60 to 90 min. Asacolitin® is coated with Eudragit® S, which possesses fewer carboxyl groups and has a higher pK_a value than Eudragit® L (Claversal®, Salofalk®). As ionization of the polymer occurs at higher pH values, the lag-time is somewhat prolonged.

At pH 7.5, which simulates the mid to distal ileum in UC patients, all pH-sensitive acrylate based formulations release drug quickly (Fig. 8). Release from Pentasa® is, by contrast, diffusion controlled. In fact, Pentasa® possesses a diffusion controlled release mechanism at all pH values tested, with little or no lag time, suggesting that substantial release and absorption would occur well before the dosage form reaches the colon.

In summary, the fast release from Salofalk® and Claversal® at pH 6.8 indicates that drug will be released at relatively proximal sites in the small intestine resulting in high systemic absorption. In UC patients, Asacolitin® may also release 5-ASA prematurely, since release is rapid at pH 7.2. By contrast, Eudragit® FS 30D pellets release 5-ASA quickly only at pH 7.5; at lower pH values the release is zero order and slow compared with GI transit. These characteristics should lead to a less substantial absorption in the small intestine, yet provide consistent release in the colon, thus optimizing chronic drug therapy with 5-ASA.

4. Conclusions

5-ASA pellets coated with Eudragit® FS 30D exhibited a promising in vitro dissolution profile for the therapy of ulcerative colitis. Compared to the currently marketed products, the release profile appears to be more appropriate to the GI pH profile observed in patients with ulcerative colitis. In vivo investigations are needed to verify the superiority of this dosage form to the currently marketed products.

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