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ORIGINAL ARTICLE

Development and in vitro evaluation of mesalamine delayed release pellets and tableted reservoir-type pellets

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Abstract

Background: The basic objective of this study was to develop a novel technique that aids in compaction of coated pellets into tablets and obtain a release pattern from compressed pellets resembling the same pattern before compression. *Method*: Multi-unit dosage forms of mesalamine targeted to the colon were formulated by extrusion-spheronization, and then coated with Eudragit S (30%). These pellets were filled into gelatin capsules or further formulated and compressed into tablets. Tablets for colonic delivery of mesalamine were prepared by mixing the coated beads with cushioning agents like stearic acid and Explotab, or by applying an additional coat of gelatin (4% weight gain) onto the Eudragit S coated pellets, and then compressing into tablets (tableted reservoir-type pellets). Then additional coating of the tablets prepared by the coating technique was applied utilizing Eudragit L 100-55 (5% weight gain). *Results*: This technique provides additive protection for the coated beads to withstand the compression force during tableting. Excellent in vitro dissolution results were obtained, which were comparable to the results of the release of mesalamine from uncompressed beads filled in capsules. Mesalamine release from the capsules was 0.3% after 2 hours in gastric pH, 0.37% was released after an additional 1 hour in pH 6, and 89% was released after 1.5 hours in colonic pH 7.2. *Conclusion*: Various formulation and process parameters have to be optimized in order to obtain tableted reservoir-type pellets having the same release properties as the uncompressed pellets. The coating technique delays the release of mesalamine until the beads reach the terminal ileum and colon. Once released in the colon, mesalamine is minimally absorbed and can act locally to treat ulcerative colitis.

Key words: *Delayed-release; Eudragit S; extrusion–spheronization; gelatin; mesalamine; tableted reservoir-type pellets*

Introduction

Mesalamine (5-aminosalicylic acid), the therapeutically active moiety of sulfasalazine[1–3], is routinely employed in the treatment of inflammatory bowel disease, that is, ulcerative colitis and Crohn's disease. Orally administered mesalazine is rapidly and almost completely absorbed from the small intestine[4–6]. Hence, from immediate release dosage forms, only a small percentage of the drug reaches the lower gastrointestinal tract: ileac and colonic mucosa, which are the target regions for mesalamine action. The mechanism of action of mesalamine is unknown but appears to be local rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, that is, prostanoids, and through the lipoxygenase pathways, that is, leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon[7].

To provide controlled drug release and site-specific delivery to the intestinal target region, various delivery systems for 5-aminosalicylic acid have been developed, including tablets coated with an acrylic-based resin[8,9] or

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microgranules (pellets) coated with ethylcellulose[10,11]. Rudolph et al. have reported that mesalamine pellets coated with Eudragit S were resistant to gastric and upper intestinal pH effects but quickly released mesalamine at pH 6.8 and above[12]. They also reported that Eudragit FS 30D mesalamine-coated pellets were resistant to dissolution below pH 6.5, provided slow zero-order drug release between pH 6.5 and 7.2, released drug rapidly above pH 7.5, and thus were more appropriate than Eudragit S to provide mesalamine to the ileum and colon of ulcerative colitis patients.

Chuong et al.[13] also reported formulation of mesalamine in extruded beads with coatings of Eudragit S and obtained dissolution results consistent with those of Rudolph et al. Chuong et al. further related in vivo gastrointestinal transit times to in vitro dissolution results to show that Eudragit S-coated beads with identical dissolution patterns to Eudragit S-coated tablets produce dramatically different drug delivery profiles into the colon. Tablets meeting United States Pharmacopeia (USP) dissolution requirements for 'delayed release mesalamine' deliver drug as a bolus 'burst' delivery into the colon but identical dissolution pattern 'delayed release mesalamine' beads deliver drug into the colon in a controlled and sustained fashion, providing a prolonged and continual bathing of the colonic tissue with drug. Multiunit particulates are often preferable dosage forms compared with tablets but compaction of target-site-directed pellets into tablets is very challenging. Recently, there has been an increasing interest in the development of multiparticulate dosage form in the shape of tablets rather than hard gelatin capsules. The aim of most studies on the compaction of pellets is to convert multiple-unit dosage form into a single unit dosage form, which is able to disintegrate into the primary individual multiparticles[14].

Direct tablet compression of the beads formulated by Chuong et al.[13] produced slowly disintegrating tablets with drug release profiles that did not meet USP requirements for delayed release mesalamine tablets. Ideally, the tablets should disintegrate rapidly into individual pellets in gastrointestinal fluids. The pellets should not fuse into a nondisintegrating matrix during compaction, and drug release should not be affected by the compaction process. With reservoir-type-coated pellet dosage forms, the coating must be able to withstand the compression force; it can deform, but should not rupture, or must still provide controlled release even if ruptured[15]. Polymers used in the film coating of solid dosage forms fall into two broad groups based on either cellulosic or acrylic polymers. Most studies on the compaction of pellets coated with ethyl cellulose revealed damage to the coating with a loss of the controlled release properties. Drug release from compressed niacin/microcrystalline cellulose pellets coated with the aqueous colloidal ethyl cellulose dispersion, Surelease Y (7%, w/w), was much faster when compared with the release of the uncompressed pellets[16]. When compared to the ethyl cellulose films, the films prepared from acrylic polymers are more flexible and therefore more suitable for the coated pellets to be compressed into tablets[17]. Furthermore, although suitable for sustained release, ethylcellulose films are typically not suitable for delayed release dosage or delivery only into the colon, but acrylic polymers are available in pH-dependent forms for delivery into the colon.

This study was performed to delineate the formulation parameters for preparing delayed release pellets of mesalamine that can be compressed into tablets maintaining the desired drug release after compaction.

Materials and methods

Materials

Mesalamine (kindly supplied from Teva Pharmaceutical Company, Sellersville, PA, USA); Eudragit S 100, Eudragit FS, and Eudragit L 100-55 (Röhm Tech Inc., Malden, MA, USA); triethyl citrate (Aldrich Chemical Company, Inc., Milwaukee, WI, USA); microcrystalline cellulose [Avicel PH 101] (FMC Corporation, Philadelphia, PA, USA); sodium starch glycolate [Explotab] (Edward Mendell Company, Paterson, NJ, USA); polyvidone [kollidon 90] (BASF Corporation, Florham Park, NJ, USA); stearic acid and propylene glycol (J.T. Baker, Inc., Phillipsburg, NJ, USA); gelatin and sodium sulfate (Sigma Chemicals Co., St. Louis, MO, USA); gelucire 44/14 (Gattefossé, Saint-Priest, Cedex, France); sodium chloride, sodium phosphate tribasic, concentrated hydrochloric acid, sodium hydroxide, and concentrated ammonium hydroxide (Fisher Chemicals, Fair Lawn, NJ, USA); and sodium lauryl sulfate (Aldrich Chemical Company, Inc.) were used.

Pelletization using extrusion–spheronization

The composition of the mesalamine beads is presented in Table 1. Mesalamine beads were prepared according to the following protocol:

Table 1. Weight compositions (g) of different formulations for pelletization of mesalamine.

	Formulation			
Ingredients	I	II	III	IV
Mesalamine	90.5	90.5	90.5	90.5
Kollidon 90	5	5	5	5.5
Gelucire 44/14	4.5	4.5	4.5	4.5
Explotab	—	10	10	6
Avicel	—	—	10	6
Deionized H_2O	Q.S.	Q.S.	Q.S.	Q.S.

Q.S., quantity sufficient.

Formula I: Mesalamine (85.5 g) was placed in a mortar. Kollidon 90 (5 g) was mixed with 4.5 g of Gelucire 44/14 in a beaker, and 30 mL of deionized H_2O was added. The mixture was warmed on a hot plate until gelucire melted. Contents of the beaker were added portion wise to the mesalamine in the mortar with continuous mixing by hand. The remaining deionized H_2O (10 mL) was added dropwise until a mass of desired consistency was produced. The resulting wet mass was passed through a Caleva laboratory extruder model 10/25 (GEI international, Inc., Wayne, PA, USA) with a perforated (1 mm diameter) cylinder and pressure cylinder rotating at 10–18 rpm. Extrudes were cut at 1 cm in length using a spatula during extrusion. Sphere formation was facilitated using a Caleva laboratory spheronizer model 120 (GEI international, Inc.) rotating at 1800 rpm by mixing 5 g of mesalamine powder with the extrudates in the spheronizer for 5–10 minutes. Drug beads were dried overnight by tray drying in a hot air oven with temperature of 40–45°C and sieved through screen sized 25-μm mesh.

Formula II: Prepared by the same protocol as formula I, except that 10 g of Explotab was mixed with 5 g of mesalamine and then mixed with the extrudates before spheronization.

Formula III: The same procedures were applied, except that only 10 g of Avicel with 5 g of mesalamine was mixed with the extrudates before spheronization.

Formula IV: Mesalmine, Explotab, and Avicel were mixed together in a mortar, and then the same procedures performed as formula I except that no powders were mixed with the extrudates before spheronization.

Coating of mesalamine beads and tablets

The composition of all coating solutions used for coating the beads and the tablets are presented in Table 2.

Table 2. Composition in grams of different coating solutions for mesalamine beads and tablets.

	Formulation				
Ingredients	A	B	C	D	E
Eudragit S 100	13.44	30.00	—	—	—
Eudragit FS	—	—	100.00 mL	—	—
Eudragit L 100-55	—	—	—	—	10.00
TEC (70% dispersion)	9.40	21.00	3.00	—	(15%) 1.50
1.7% ammonium hydroxide	6.84	10.00	—	—	—
1 N NaOH (4%)	—	—	—	—	3.33
Gelatin	—	—	—	5	—
Sodium sulfate	—	—	—	1	—
Sodium lauryl sulfate	—	—	—	1	—
Propylene glycol	—	—	—	10	—
Deionized H_2O	70.00	100.00	—	110	44.50
Excipients					
Talc	1.34	3.00	5.00	—	—
Deionized H_2O	9.20	18.00	20.00	—	—

Eudragit FS coating dispersion

Triethyl citrate (Plasticizer) was added to Eudragit FS polymer dispersion. Talc was dispersed in 20 mL of deionized H_2O and then added to Eudragit FS dispersion under constant mixing.

Aqueous dispersion of Eudragit S

The process followed was provided by DeGussa-Evonik Company (GmbH, Essen, Germany). Deionized H_2O was placed in a beaker and an impeller stirrer inserted almost at the bottom of the beaker and set to stir slowly. Eudragit S powder was slowly added into the vortex formed because of gentle agitation and allowed to mix for 5–10 minutes. Ammonium hydroxide solution was added dropwise while stirring, and stirring continued for 60 minutes. Triethyl citrate was slowly added and mixed for another 60 minutes. Talc was suspended in 9.2 mL of H_2O for 15 minutes and mixed with high shear for at least 10 minutes until a homogenous dispersion was obtained, then added to Eudragit S dispersion with gentle stirring. Because ammonia is volatile, pH of the dispersion was adjusted with additional ammonium hydroxide solution to pH 6.3. The finished aqueous latex dispersion was passed through a screen (0.25 mm mesh wide) to eliminate agglomerates.

Aqueous dispersion of Eudragit L 100-55

The same processes were followed as for the preparation of Eudragit S coating dispersion, but NaOH was used instead of NH_4OH, and no talc was added.

Gelatin coating solution

In a beaker, deionized H_2O was heated to 60°C, and then propylene glycol was added, followed by addition of gelatin with continuous stirring, and then sodium sulfate (anti-drying agent) and sodium lauryl sulfate (protein precipitant) were added with stirring until a clear solution was obtained (about 20 minutes).

PEG 8000 coating solution

In a beaker, deionized H_2O was heated to 50°C and then 20 g of PEG 8000 was added with stirring until dissolved.

Coating of mesalamine beads

A weighed amount (100 g) of mesalamine beads was placed into the chamber of an aeromatic fluid bed spray coater (Niro-Aeromatic, model STREA-1, Niro-Aeromatic, Ltd., AG, Bubendorf, Switzerland) with a Wurster column insert and fluidized to equilibrate to the specified temperature. Table 3 shows process parameters of each coating solution/dispersion.

Table 3. Operating conditions and in process parameters for the coating experiments for mesalamine beads.

Operating conditions	Eudragit S dispersion	Eudragit FS dispersion	PEG 8000 solution	Gelatin solution
Inlet air temperature (°C)	27–30	38–40	45–50	50–55
Outlet air temperature (°C)	30–35	40–45	50–55	55–60
Nozzle diameter (mm)	1	1	1	1
Atomizing pressure (psi)	10–15	15–20	10–15	15–20
Application rate (mL/min)	1.1	1.3	1.4	1.3

Filling of the beads into capsules

The specified amounts of coated beads containing 400 mg of mesalamine were filled into capsules of size OOCS. The amounts of beads were determined according to drug content assay for each formulation, because it differs from formulation to formulation according to percentage weight (wt.) gain of the coating material.

Bead compaction into tablets

Mesalamine-coated beads were compressed into round flat tablets with a diameter of 11.1 mm and thickness of 5.2 mm using a Carver press fitted with a tablet punch and die at 1000 lbs pressure, and dwell time after target pressure was achieved for 10 seconds.

Four methods were used to prepare the mesalamine tablets; the first method was direct compression of Eudragit S-coated mesalamine beads. The second method is summarized as follows: coated beads were mixed with different types of additives before compression and then compressed into tablets. One approach was as follows: mesalamine beads coated with 30% Eudragit S were mixed with 20% Explotab gel (sodium starch glycolate). Explotab gel was prepared by slowly adding 2 g of Explotab powder to 10 mL of deionized H_2O in a beaker with continuous stirring by magnetic stirrer. The gel was formed and 100 mg of the gel was mixed with the beads gently, and then the beads were compressed into tablets. The tablets were kept in an oven at 40°C for 2 hours. Second trial: mesalamine beads were mixed carefully by spatula with 100 mg of stearic acid and 50 mg of Explotab powder, then filled into the tablet die while mixing to ensure homogenous mixing and then compressed into tablets by direct compression. Third trial: mesalamine beads were mixed by the same method as trial 2 with 100 mg of stearic acid and 100 mg of Explotab and compressed into tablets.

The third method involved spray-application of another coat over the Eudragit S-coated mesalamine beads using different coating agents and then compressed into tablets.

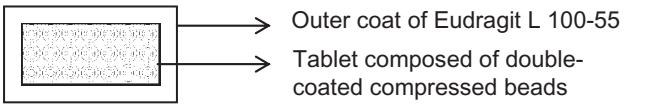

Figure 1. Schematic diagram representing the composition of mesalamine tablet prepared according to method 4.

In the fourth method, the compressed tablets containing double-coated beads were then spray coated with Eudragit L 100-55 as shown diagrammatically in Figure 1, providing the tablets an outer film coat.

Coating of mesalamine tablets

For the establishment of the suitable coating process, 10 mesalamine tablets were mixed with 40 plain tablets (of different color but of the same size and weight) and placed into the chamber of an aeromatic fluid bed spray coater with a short column insert and fluidized to equilibrate to 30°C. The outlet temperature was 30–35°C. The pressure was 20–40 psi, the nozzle diameter was 1 mm, and the flow rate of Eudragit L 100-55 coating solution was 1 mL/min. After completion of the coating process, the coated mesalamine tablets were separated from the coated plain tablets.

In vitro release studies for mesalamine beads, capsules, and tablets

In vitro drug release profiles from studied formulations were obtained using the USP XXV dissolution method for delayed release tablets of mesalamine, with apparatus 2, paddle method (VK 7000, Vankel Industries, Inc., Cary, NC, USA). Dissolution was studied at a paddle rotation speed of 100 rpm for gastric solution (pH 1.4) and phosphate buffer (pH 6.0), and 50 rpm for phosphate buffer (pH 7.2). Temperature of the dissolution bath was maintained at 37.5°C. Dissolution testing of all formulations was performed in triplicate.

Studied formulations were placed into dissolution vessels containing 500 mL of simulated gastric fluid (pH 1.4). Five-milliliter samples were withdrawn after 1 and 2 hours without medium replacement. At the end of the 2-hour period, the gastric solution was discarded and the dissolution vessels containing the tested formulations were filled with 900 mL of phosphate buffer (pH 6.0). Dissolution testing was continued in phosphate buffer for another 1 hour. One 5-mL sample was withdrawn at the end of 1 hour. Then this phosphate buffer solution was discarded and replaced with 900 mL of phosphate buffer (pH 7.2), and the rotation speed was changed to 50 rpm. Five-milliliter samples were withdrawn after 0.5, 1, and 1.5 hours without medium replacement. Samples were then filtered through membrane filters (0.45 μm) and measured using UV

spectrophotometer at 302 nm for gastric solution and at 330 nm for the phosphate buffers (pH 6.0 and pH 7.2). Amount of drug released was determined using an appropriate standard curve. Average drug releases and their standard deviations were calculated from three replications in all dissolution experiments. Dissolution profiles are presented as percent drug release versus time curves. Release patterns of mesalamine from beads, capsules, or tablets were compared to USP requirements for delayed-release mesalamine tablets.

Friability test

Ten tablets were weighed on an analytical balance and run in a Friability tester: model: 10809, Vanderkamp Industrial Inc., (Chatham, NJ, USA). Tablets were placed inside each side of the rotating drum that rotated at 25 rpm. The tablets were tumbled 100 times in the rotating drum. The friability was subsequently calculated as percentage of weight lost. A limiting value of 1% for friability tests of tablets has been suggested by the USP Pharmacopoeia.

Results

Formulation of mesalamine pellets

Mesalamine shows high stability in aqueous solutions[18], so deionized water was used in the preparation of mesalamine pellets. Formula I is based on earlier mesalamine formulations[13] but is modified to produce quite high drug content (90.5%) of mesalamine. The resulting beads, after drying at 40°C for 24 hours, were fragile and mostly rod-shaped and did not withstand further coating procedures. The beads of formula II were also fragile and rod-shaped but of good release pattern (more than 90% released after 30 minutes). In formula III, the resulting beads were very spherical and hard enough for further coating processes.

In the previous processes, a certain amount of dry powder (mesalamine in formula I, Explotab, and mesalamine in formula II or Avicel in formula III) was mixed with the extrudates, then spheronized to produce dry rods (formulae I and II) or spheres (formula III).

To avoid this extra process step, the amount of kollidon 90 (binder) was increased and the amounts of Explotab and Avicel were decreased as shown in formula IV. The resulting beads were true spheres of desirable hardness.

Release studies of mesalamine from different bead formulations

Release of mesalamine from the new beads (formulae I–IV) is shown in Figure 2. It is clear that mesalamine was relatively more retained in formula I, about 89.17% released after 1 hour compared with other formulae in pH 7.2 that show almost 100% release. Continuing for 1.5 hours, formula I showed 96.47% release. Formula II has a higher release rate than formula I because of Explotab (superdisintegrant). There is no significant difference in release of mesalamine from formula III or IV ($P > 0.05$). Formula III or IV may be used effectively to produce mesalamine beads. The method of preparation differs according to the formula used.

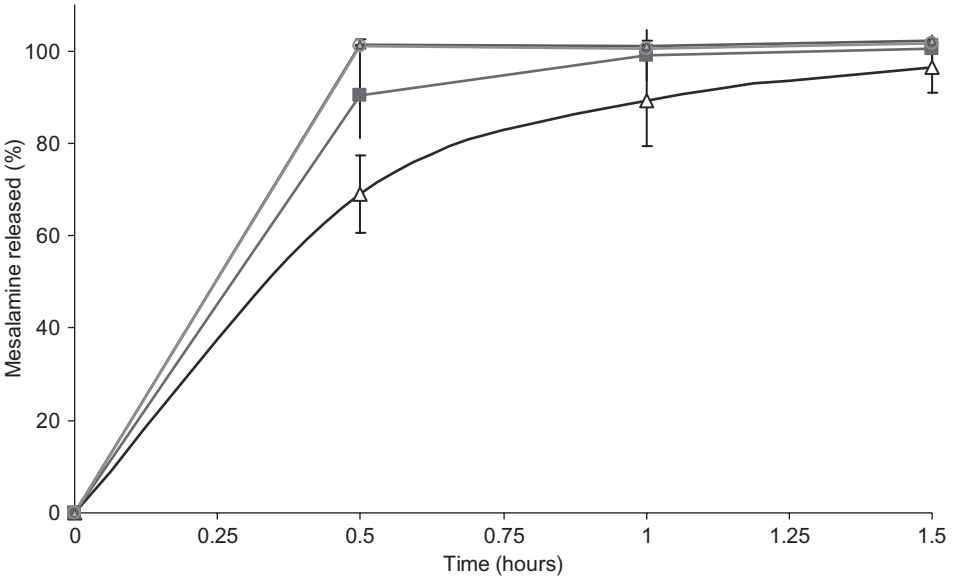

Figure 2. Release profiles of mesalamine from different formulations of mesalamine beads in pH 7.2 [(△) formula I, (■) formula II, (▲) formula III, (○) formula IV].

Release studies of mesalamine from the capsules containing the coated mesalamine beads

Formula III of mesalamine beads was coated with Eudragit FS (13% wt. gain) and with Eudragit S (13% wt. gain), and the release of mesalamine from the capsules containing these beads has been studied, and compared to the release from uncoated beads. Results are shown in Figure 3. The data are consistent with Rudolph et al.[12] who reported zero-order release of mesalamine from Eudragit FS-coated beads at pH 7.2 and faster release from Eudragit S coating than from Eudragit FS coating at pH 7.2.

Different coating thicknesses were applied to mesalamine beads using Eudragit S from 13% to 30% wt. gain. Release from these beads was compared using the requirements of the USP in different pHs, 2 hours in pH 1.4, 1 hour in pH 6.0, and 1.5 hours in pH 7.2. USP specifies the percentage released in each phase as follows: not more than 1% after 2 hours in gastric pH (100 rpm), not more than 1% in pH 6.0 for 1 hour (100 rpm), and not less than 80% in pH 7.2 within 1.5 hours (50 rpm).

Release of mesalamine from beads coated by Eudragit S with different percentage weight gain is shown in Figure 4. For 13% wt. gain, about 30.91% was released after 2 hours in gastric solution, 31.96% was released in pH 6, then 100% released after 1.5 hours in phosphate buffer (pH 7.2). For 17% wt. gain, 11.42% was released after 2 hours in gastric pH, 12.28% was released in pH 6, and 93.32% was released after 1.5 hours in phosphate buffer (pH 7.2). For 20% wt. gain, 10.4% was released after 2 hours in gastric pH, 11.76% was released in pH 6, and 93.04% was released after 1.5 hours in pH 7.2. So, none of 13%, 17%, and 20% wt. gain met the USP requirements. But the 30% wt. gain in Eudragit S coating satisfied the USP requirements as 0.30% mesalamine was released after 2 hours in gastric fluid, 0.37% was released after 1 hour in pH 6, and 89.13% was released after 1.5 hours in phosphate buffer (pH 7.2). These results are consistent with other studies in this laboratory[13], showing that it is desirable to coat mesalamine beads with Eudragit S (30% wt. gain).

In vitro release of mesalamine from tablets prepared by method 1

Mesalamine beads coated with Eudragit FS (13% wt. gain) and those coated with Eudragit S (30% wt. gain) were compressed into tablets by direct compression, each containing 400 mg of mesalamine. The release of mesalamine from the two formulations was compared in different pH media and also compared to the corresponding beads (before compression) as shown in Figure 5. The tablets of Eudragit FS-coated beads released 5.77% after 2 hours in gastric pH compared to 9.96% released from the beads before compression. Then, the release became 21.32% after 1.5 hours in phosphate buffer (pH 7.2), compared to 41.33% released from the beads before compression.

On the other hand, release of mesalamine from Eudragit S beads before compression into tablets was 0.3% after 2 hours in gastric pH solution but when compressed into tablets, the release increased to 26.07%. When the medium was changed to pH 6.0 for 1 hour, there is no difference in percentage released for both tablets. Then when the medium is changed to pH 7.2, only 45.64% was released from the tablets with Eudragit S-coated beads and only 21.33% from the Eudragit FS-coated beads. Eudragit S was selected for further study because it allows more rapid drug dissolution in pH 7.2.

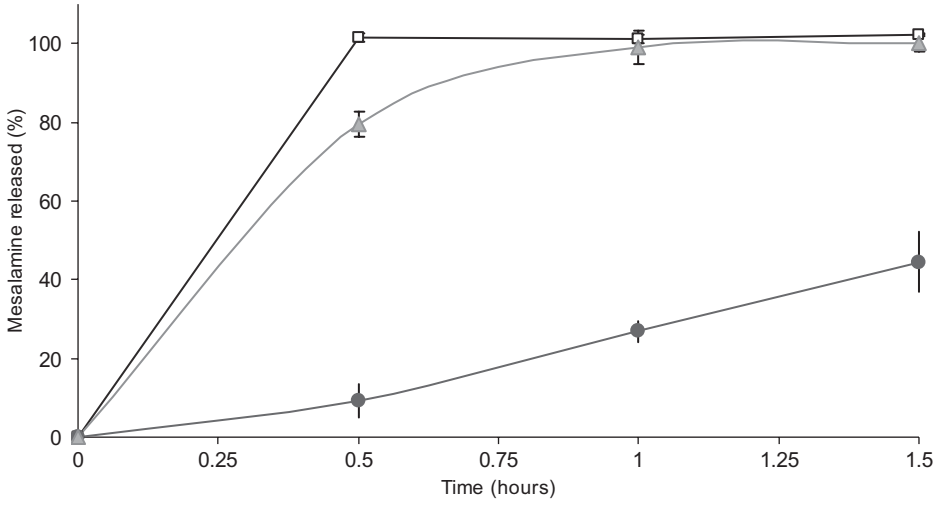

Figure 3. Release profiles of mesalamine from coated and uncoated mesalamine beads in pH 7.2 [(●) coated with Eudragit FS (13% wt. gain), (▲) Eudragit S (13% wt. gain), (□) uncoated beads].

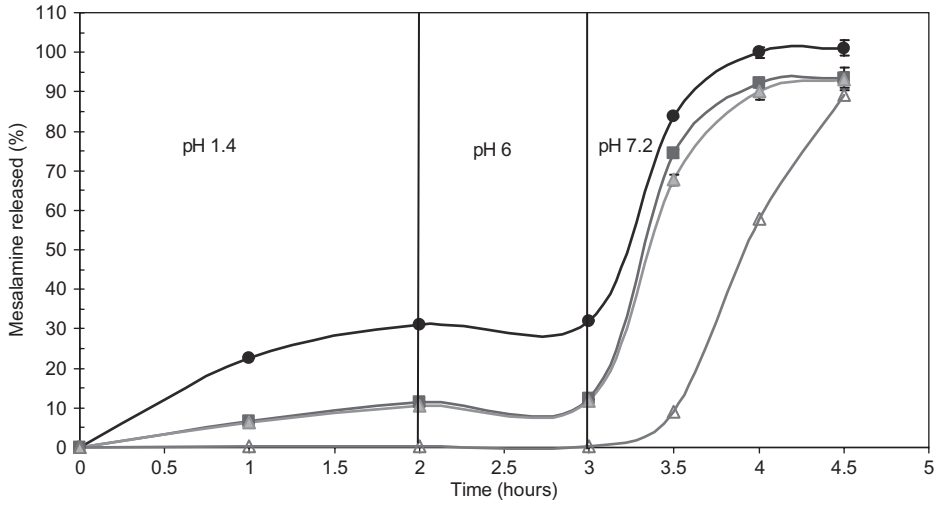

Figure 4. In vitro release of mesalamine from beads coated with Eudragit S [(●) 13% wt. gain, (■) 17% wt. gain, (▲) 20% wt. gain, (△) 30% wt. gain] in different pH media.

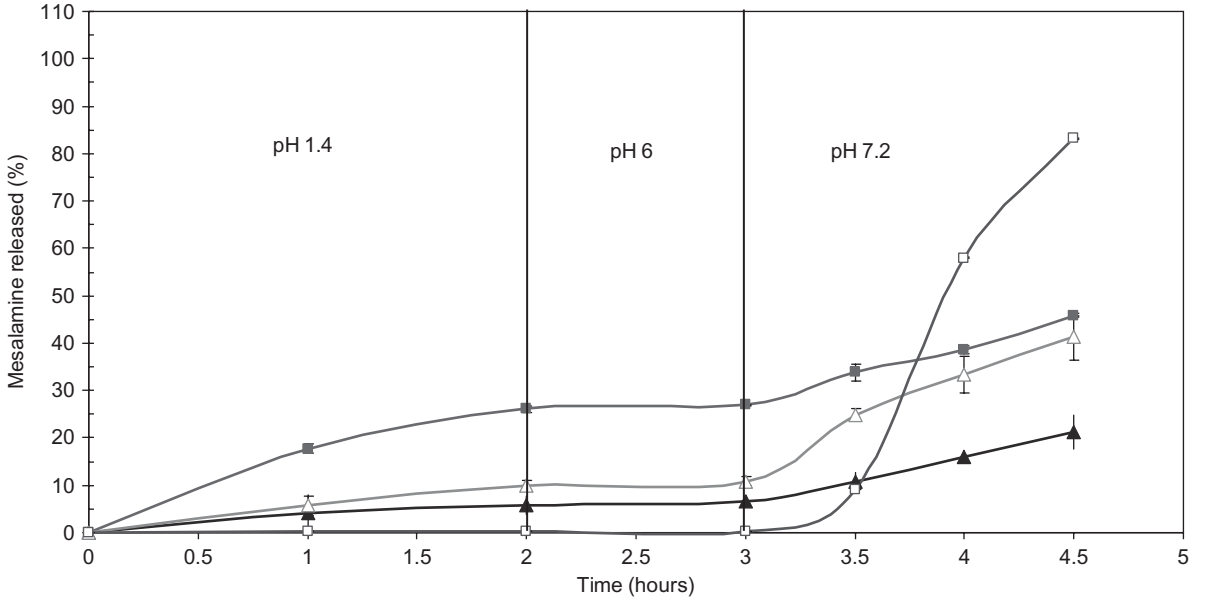

Figure 5. Release of mesalamine from tablets prepared by direct compression of coated beads [(▲) Eudragit FS (13% wt. gain), (■) Eudragit S (30% wt. gain)] and from uncompressed beads coated with [(△) Eudragit FS (13%), (□) Eudragit S (30%)] in different pH media.

In vitro release of mesalamine from tablets prepared by method 2

Release profiles of mesalamine in pH 1.4, 6, and 7.2 from tablets prepared as mentioned in trials 1–3 are presented in Figure 6. The mesalamine released was 11.7% in gastric pH from tablets prepared according to trial 1, but because of the presence of Explotab, the release of mesalamine became complete (98.77%) after 1.5 hours in pH 7.2. Mesalamine release was 3.19% and 1.97% in pH 1.4 from trials 2 and 3, respectively, 4.30% and 2.71% in pH 6.0, and 87.51% and 86.01% released in pH 7.2, which may be because of the effect of Explotab as a disintegrant.

Release of mesalamine from tablets prepared by method 3

Different coating solutions were used: first was Explotab solution (10% wt. gain), second was gelatin solution (8% wt. gain), third was gelatin solution (4%

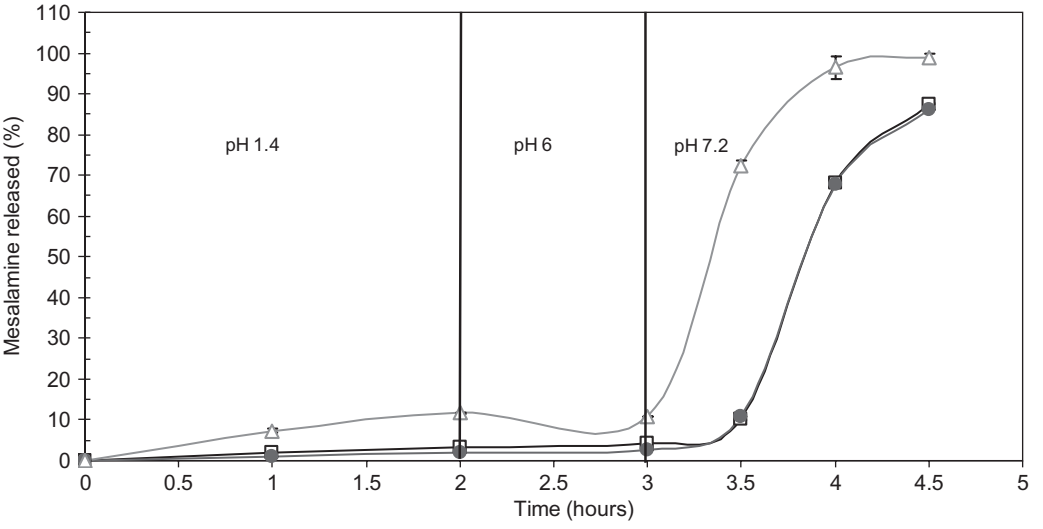

Figure 6. Release profiles of mesalamine from tablets formed of beads coated with Eudragit S (30%) mixed with different amounts of stearic acid and Explotab [(□) 100 mg stearic acid and 50 mg Explotab, (●) 100 mg stearic acid and 100 mg Explotab, (△) 100 mg 20% Explotab gel].

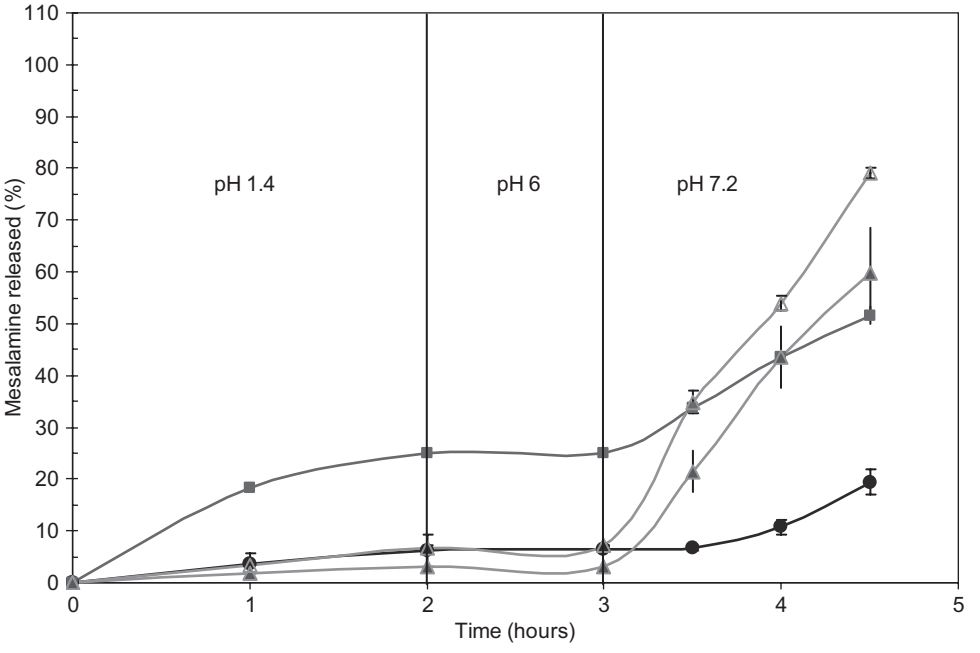

Figure 7. Release of mesalamine from tablets formed of beads double coated with different concentrations of Eudragit S and other coating materials [(△) 30% Eudragit S and 4% gelatin, (▲) 30% Eudragit S and 8% gelatin, (■) 30% Eudragit S and 10% Explotab, (●) 20% Eudragit S and 20% PEG 8000].

wt. gain), and the fourth was PEG 8000 (20% wt. gain). All of these coatings are aqueous based. All binder/disintegrant coatings were applied over beads coated with Eudragit S (30%) except PEG coating layer, which was applied over beads coated with Eudragit S (20%). In vitro release results for these tablets are shown in Figure 7.

It is obvious that Explotab coating solution (10% wt. gain) did not offer protection for the Eudragit S-coated mesalamine beads as 24.93% drug was released in pH 1.4 and is less effective than using Explotab as a gel with Eudragit S-coated beads. In pH 7.2, about 51.75% of mesalamine was released after 1.5 hours. When gelatin solution was applied as a second coating material for

mesalamine beads coated with Eudragit S (30% wt. gain), results from the dissolution curves in Figure 7 show that 3.14% was released from gelatin (8% wt. gain) after 2 hours in gastric solution, and no more release was detected at pH 6.0, and 59.80% released when transferred to pH 7.2 after 1.5 hours. It was observed that 8% gelatin coating thickness sticks the beads together and prevents tablet disintegration and the drug from complete release in pH 7.2. By reduction of gelatin percentage to 4% wt. gain, it was determined that about 6.77% drug was released in gastric pH, 7.23% was released in pH 6.0, but when transferred to pH 7.2, it was found that 79.12% was released, which is very close to USP requirements.

The release of mesalamine from PEG 8000 (20% wt. gain)-coated beads compressed into tablets was 6.14% in gastric fluid, 6.51% in pH 6.0, and 19.42% after 1.5 hours in pH 7.2 although the coating layer of Eudragit S was reduced to 20% wt. gain.

Release studies of mesalamine from tablets prepared by method 4

All tablets produced with compression pressure 1000 lbs had hardness 'tablet breaking forces' higher than 4 kg. This means that all tablets should be strong enough to resist chipping and breaking during coating and shipping process, whereas tablets coated with 30% Eudragit S and 10% Explotab were more fragile as 1.24% were lost during friability testing as shown in Table 4.

Eudragit L 100-55 has the property of dissolving at pH greater than 5.5 and can protect from dissolving in gastric solution. Two different coating amounts of Eudragit L 100-55 (5% and 10% wt. gain) were applied to tablets made by compression of the double-coated beads (Eudragit S, 30% and Gelatin, 4%). The release pattern is shown in Figure 8. There is almost no release in pH 1.4 (0.03% and 0.39%, respectively) or pH 6 (0.03% and 0.39%, respectively) from either formulation, but only 51.17% mesalamine was released from tablets with 10% wt. gain of Eudragit L 100-55 after 1.5 hours in pH 7.2, and 67.36% of the mesalamine was released from the 5% wt. gain Eudragit L-coated tablet after 1.5 hours in pH 7.2. It was found that 79.01% and 87.86% was released from Eudragit L (10% wt. gain) and Eudragit L (5% wt. gain), respectively, after an additional 0.5 hour in pH 7.2.

Discussion

During this study a new mesalamine pellet formulation was developed using extrusion–spheronization technique of high drug content (90.5%). In this laboratory-size spheronizer, addition of powder into the extruded rods before spheronization step facilitated spheronization.

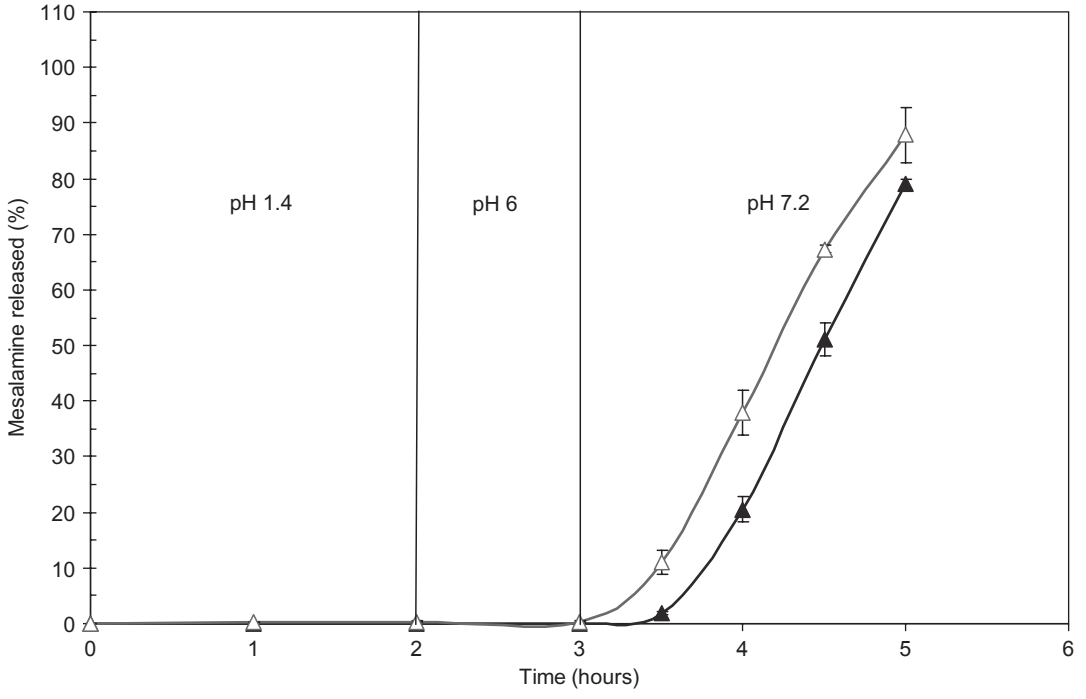

Figure 8. Release profiles of mesalamine from tablets composed of double-coated compressed beads and overcoated with [(△) 5% Eudragit L 100-55, (▲) 10% Eudragit L 100-55].

Table 4. Properties of mesalamine tablets formed of beads double-coated with different concentrations of Eudragit S and other coating materials.

Formulation	Friability test (% lost)	Hardness test (kg)
Tablets coated with 20% Eudragit S and 20% PEG 8000	0.82	4.57
Tablets coated with 30% Eudragit S and 10% Explotab	1.24	4.50
Tablets coated with 30% Eudragit S and 8% Gelatin	0.73	4.55
Tablets coated with 30% Eudragit S and 4% Gelatin	0.72	4.51

These pellets were spherical in shape and showed suitable hardness to withstand coating conditions. For formula I, 5 g of mesalamine powder was mixed with the rods after extrusion to help in drying of the spheres during the spheronization process, otherwise the extrudates stuck together and good spheres were not obtained in the small-scale laboratory equipment. In formula II, Explotab was mixed with the formed extrudates in the spheronizer because it is a superdisintegrant that has a role in increasing the release rate of mesalamine from the formed beads and in drying of the spheres. In formula III, Avicel was added and mixed with the extrudates in the spheronizer as Avicel has a high water-binding capacity and helps in the production of true spheres[19]. Formula III showed almost 100% release after 1 hour in pH 7.2, which indicates immediate release. Essentially, immediate release from the beads was preferred at this stage; so any later slow release, if found, could be attributed to the coating agent(s) being studied.

To meet the USP requirements for delayed release mesalamine formulations, the percentage release from the formulation must not be less than 80% within 1.5 hours in pH 7.2. In this study, mesalamine was released faster from beads coated with Eudragit S (13% wt. gain) than that coated with Eudragit FS (13% wt. gain) in pH 7.2. Also, beads coated with Eudragit FS have a tendency to agglomerate while standing after completing the coating process. Although Rudolph et al. discussed reasons that Eudragit FS-coated dosage form is most desirable for delivering mesalamine to treat ulcerative colitis, other authors report Eudragit S to be the most favorable coating in terms of achieving delayed delivery of mesalamine in the more distal part of the small intestine[20]. For these reasons, Eudragit S was chosen for further studies. Release of mesalamine from beads coated by Eudragit S with different percentage weight gain indicates that 30% wt. gain is required to achieve USP requirements. Release of mesalamine from tablets formed of beads coated with Eudragit FS (13% wt. gain) is lower than from uncompressed beads in pH 1.4, which is explained on the basis that the Eudragit FS coating fused the mesalamine beads together somewhat on compression, which decreased initial drug release from the tablets. Also at pH 7.2, the percent mesalamine released from the tablets was about one-half the percent released from the uncompressed beads. This occurs because Eudragit FS dissolves slower in pH 7.2 than Eudragit S,[12] and bead fusion during tablet compression prevents complete tablet disintegration and prevents mesalamine from complete release in the dissolution study time and so failed to satisfy USP requirements. Although in the case of Eudragit S, the percent released from the tablets was much higher than that of uncompressed beads in pH 1.4. This is because the Eudragit S coating layer did not offer an elastic-enough protective layer to withstand the force of compression. Because of these compression forces, the outermost coating layer was ruptured and allowed the drug to be released in gastric fluid. At higher pH 7.2, the polymers Eudragit S and FS both fuse coated beads because of the force of compression and form a relatively nondisintegrating matrix tablet that holds the drug in the center of the tablet. Neither of these two tablets meet USP requirements. The ideal filler materials used for the tableting of pellets should prevent the direct contact of the pellets (e.g., polymer coatings) and act as cushioning agent during compression. The excipients should also result in hard and rapidly disintegrating tablets at low compression forces and should not affect the drug release[14].

Adding different excipients to coated mesalamine beads may help in keeping the Eudragit S layer intact to prevent drug release in gastric pH and then completely release drug in pH 7.2. Sodium starch glycolate (Explotab) is widely used in oral pharmaceuticals as a disintegrant in tablet formulations[21,22]. It is commonly used in tablets prepared by either direct-compression[23,24] or wet-granulation processes[25,26]. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling[27]. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients, such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time[21]. Thus Explotab may help to withstand compression pressures and protect the Eudragit S coating layer. Stearic acid acts as binder and lubricant; it may prevent the direct contact of the pellets with each other and act as a cushion during compression, whereas Explotab acts as disintegrant.

The release patterns revealed that Explotab gel did not afford good protection from the compression forces during tableting. Addition of stearic acid in both trials 2 and 3 retarded the release of mesalamine in gastric pH as it is acting as a binder and also a protective for Eudragit S

bead coating layer from the forces of compression. The results reported by Abbaspour et al. showed that by increasing the pellet:filler ratio from 60% to 80%, ibuprofen tablet hardness, disintegration times, and percentage of friability increased[28]. Lundqvist et al.[29] and Debunne et al.[30] reported that increase in pellet ratio up to 60% in tablet formulation increased tablet friability and decreased the hardness and disintegration time.

In our study, preparation of tablets containing high pellets ratio up to 75% with suitable strength and disintegration time that give release profile similar to uncompressed pellets is achieved. These release patterns come very close to satisfying USP requirements, and the tablets are expected to be effective for delivery of mesalamine to the ileum and colon if administered to patients.

The process of method 2 works in the laboratory but is not useful in large-scale rapid production of tablets. Segregation will arise on a large scale while mixing ingredients of different particle size before tableting. This problem is solved by using method 3, which involves applying an extra coat over the Eudragit S coat in such a way that the beads become double coated. This extra coat may help in withstanding tablet compression forces and protect the Eudragit S layer, so that mesalamine release from these double-coated pellets becomes unaffected by compaction into tablets. This extra coating layer may deform and recover after compression without damage to the Eudragit S coating layer.

Gelatin layer is effective to form a protection to Eudragit S coating layer. However, spray application of the gelatin as a coating layer was difficult because of coating solution viscosity and required slow application with long drying times. On the other hand, PEG 8000 in this formulation promoted fusion of the PEG 8000 coating layer on beads during compression, forming a non-disintegrating matrix tablet that traps the drug inside.

None of the tablet formulations of method 3 satisfied the USP specifications for mesalamine dissolution, but applying extra enteric coat over the tablets prepared by compression of double-coated mesalamine beads should prevent dissolving in gastric conditions. Eudragit L 100-55 overcoat of 10% wt. gain is too much, but 5% wt. gain produces a tablet of hardness 6.23 kg and friability 0.2% with a release profile very close to USP requirements.

In conclusion, mesalamine pellets coated with Eudragit S (30% wt. gain) exhibited an in vitro release profile that meets USP requirements for delayed release formulations of mesalamine. Preparation of tableted reservoir-type pellets of the same delayed-release properties as uncompacted pellets is a substantial challenge. These pellets could be successfully compressed as a tablet using proper filler blends and excipients. The selected fillers (stearic acid and Explotab) provided desirable mechanical strength and disintegration time for the resulted tablets.

Compression of pellets into tablets can be also achieved by applying extra coats of gelatin coating (4% wt. gain) that are flexible enough to not rupture during compaction to offer a protecting effect to the coated beads and then applying an outermost coating to the tablets with an extra enteric coat using Eudragit L 100-55 (5% wt. gain). We hypothesize that this double-coating technique does not necessitate addition of fillers to the coated pellets to resist the mechanical stress during compaction.

However, further studies are required to optimize these coating techniques for delayed release mesalamine tablets comprising coated pellets to satisfy the USP dissolution specifications.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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