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A novel pH- and time-based multi-unit potential colonic drug delivery system. I. Development

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Abstract

A novel delivery system was developed for delivering drugs to the colon by selecting polymethacrylates with appropriate pH dissolution characteristics for the distal end of the small intestine and relying upon the relatively constant transit time of the small intestine. Pellets were prepared by powder layering of 5-aminosalicylic acid (5-ASA) on nonpareils (0.5–0.6 mm) in a conventional coating pan. Drug-layered pellets were coated with an inner layer of a combination of two pH-independent polymers Eudragit® RL and RS (2:8), and an outer layer of a pH-dependent polymer, Eudragit FS. Scanning electron micrograph (SEM) pictures of the coated pellets showed the uniformity of both the coatings. The release profile of 5-ASA was studied in three phosphate buffers after a simulated gastric pre-soak for 2 h in pH 1.2 media. There was no drug release for 12 h at pH 6.5. There was a sustained release of 5-ASA for over 12 h both at pH 7.0 and 7.5 after a lag time at pH 7.0 and no lag time at pH 7.5. The release rate was faster at pH 7.5 than at pH 7.0. The delivery system demonstrated its potential for colonic delivery by resisting drug release until pH 6.5 and the combination of Eudragit RL and RS proved successful for the sustained delivery of 5-ASA at the expected pH of the colon.

Keywords: Controlled-release; Site-specific delivery; Colonic delivery; Pellets; Polymethacrylates; Eudragit

1. Introduction

Although oral drug dosing is the most widely accepted route of administration, the gastrointestinal (GI) tract presents several formidable barriers to drug delivery. Colonic drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases of colon but also for its potential for the delivery of proteins and peptides. The colon presents less hostile conditions for drug delivery because of less diversity and intensity of enzymatic activities and a near neutral pH (Mrsny, 1992a; Ashford and Fell, 1994; Rubinstein, 1995; Van den Mooter and Kinget, 1995; Watts and Illum, 1997). In addition, the residence time of dosage forms is longer in the

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colon; this can be useful for prolonged drug delivery.

The large intestine may indeed be the best site for the delivery of agents to cure the local diseases of colon, however, the large intestine is difficult to reach because of its location which requires the passage of the dosage form through the stomach and up to 6 m of small intestine (Ashford and Fell, 1994). The pH of the GI tract gradually increases as one moves down the GI tract from stomach (pH 1.5–3) to terminal ileum (pH 7–8). However, the pH of the colon drops to 5.5–7.0 because of the acidification of the colonic contents caused by the products of bacterial fermentation (Haeberlin and Friend, 1992).

In order to develop a reliable colonic drug delivery system, the transit time of dosage forms through the GI tract needs to be well understood. The transit through the GI tract is highly variable and depends on many factors (Hunter et al., 1982; Davis et al., 1984; Devereux et al., 1990; Price et al., 1993; Meier et al., 1995; Brown et al., 1998). Gastric transit of single-unit non-disintegrating dosage forms has been reported to vary from 15 min to more than 3 h (Kaus et al., 1984). However, it is widely agreed that small intestinal residence time is fairly constant at 3–4 h. The mean colonic transit time in humans is reported to be 33 h in men and 47 h in women (Hinton et al., 1969).

Most of the previous literature reports on colonic targeting have focused on the development of a colonic delivery system based on one of these three approaches – pH-dependent systems, time-dependent systems, and bacterially-degradable systems (Ashford and Fell, 1994; Wilding et al., 1994; Watts and Illum, 1997).

The objective of this study was to develop a multi-unit delivery system of a model drug for the majority of drug release to occur in the colon in a sustained-release fashion. Based on literature review it was concluded that a colonic delivery system which is based only on time in the GI tract or only pH-dependence would not be reliable because of the inherent variability of pH and emptying times from the GI tract. It was decided to take advantage of relatively constant transit time of the small intestine (3–4 h) and high pH of the distal small intestine (7–8) and hence combine pH characteristics of different Eudragit polymers and transit time in the small intestine to develop a reliable multi-unit colonic delivery system. In the present study, Eudragit FS30D was used to provide an outer coating to the pellets. Eudragit FS30D dissolves at pH 6.8; since the pH at ileum and ileo-caecal valve is reported to be 7–8, it is expected that Eudragit FS30D will dissolve in that region, and can be used to control the site of release of a pellet system previously coated with an Eudragit RL–RS layer for sustained-release of a drug in the colon (Gupta et al., 2000). The schematic of the delivery system is shown in Fig. 1. Because of the known benefits of aqueous systems over organic systems, it was decided to use only aqueous coating systems for the present study.

5-ASA was used as a model drug in this study because there is a therapeutic benefit for the colonic delivery of this drug for the treatment of inflammatory bowel disease (IBD) and in addition, it possesses necessary physico-chemical properties for formulation in a sustained-release product (Dash and Brittain, 1998). Pellets were chosen for development because they spread out over a large area of intestine; this makes pellets more effective for the treatment of local diseases of colon and may improve absorption possibilities for large molecules (Li et al., 1997; Amighi et al., 1998; Mrsny, 1992b).

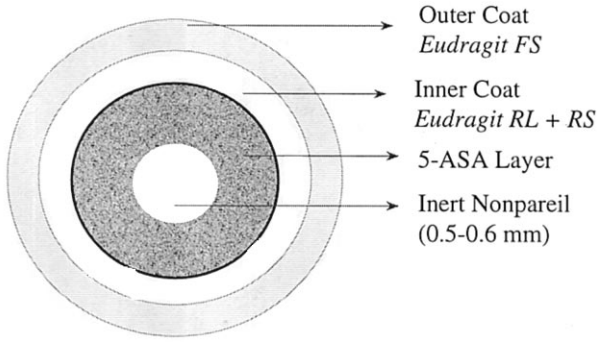

Fig. 1. Schematic of the delivery system (not to scale).

Table 1
Composition of 5-ASA pellets (%)

I. Cores	
Nonpareils (0.5–0.6 mm)	40
II. Layering powder	
5-ASA	50
Lactose D80	8
Aerosil 200	0.5
Kollidon 25	1.5
Total	100
III. Binder solution	
5% Kollidon 25 in water	q.s.

2. Materials and methods

2.1. Materials

Mesalazine (5-aminosalicylic acid) was purchased from Chemie-S.p.A, Italy. Eudragit RL30D, RS30D, FS30D were obtained in-house from Röhm GmbH, Chemische Fabrik, Germany, and the nonpareils were purchased from Hans G. Werner GmbH, Germany. Other excipients used to prepare pellets and for coating were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

2.2. Preparation of pellets

Pellets were prepared by powder layering of 5-ASA on nonpareils (nuclei) in a 35-cm diameter, conventional coating pan (Erweka, Germany). The composition of the pellets and the parameters for the powder-layering process are listed in Table 1 and Table 2, respectively.

Excipients of the powder layering composition were sieved through a 400 μm screen and mixed for 15 min in a double cone mixer. After mixing, the powder mixture was again sieved through a 400 μm screen and mixed again for 10 min. Binder solution was prepared by dissolving Kollidon 25 (polyvinyl pyrrollidone) in water with magnetic stirring. Binder solution was continuously sprayed on the moving nonpareils by means of a peristaltic pump and a Walther-Bingo type spray-nozzle with a 1-mm orifice. The powder addition was started after a 2-min lag time of the binder solution. At fixed intervals, fixed amounts of the powder composition were layered onto the particles. The drug-loaded pellets were dried in an oven at 40°C for 24 h after which sieve analysis was done and the fraction of 0.8–1.0 mm was separated for coating.

2.3. Preparation of spraying dispersion for coating

Eudragit FS is relatively a new polymer – it is an anionic copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid. The polymer is pH-sensitive; the carboxylic groups are transformed to carboxylate groups above pH 6.5 and the polymer dissolves. Eudragit RL and RS30D are cationic copolymers of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride. Eudragit RL and RS have the same chemical structure except that Eudragit RL has double the number of hydrophilic quaternary ammonium groups than Eudragit RS. Since the release of most drugs is faster from Eudragit RL than from Eudragit RS, dosage forms can be coated with different combinations of Eudragit RL and RS to provide various degrees of sus-

Table 2
Layering conditions for the preparation of 5-ASA pellets in a conventional coating pan

Charge load (nonpareils) (g)	800
Target quantity of drug to layer (g)	1000
Spray gun (type)	Walther 'Bingo' Air Spray Gun
Nozzle bore (mm)	1
Pan speed (rpm)	40
Inclination angle pan (°)	30
Distance: pellet bed − spray gun (cm)	10–15
Atomising pressure (bar)	0.2–0.6
Binder spraying time (min)	50–70
Binder spray rate (g/min)	0.2–0.25
Layering time (min)	50–70
Amount per layer (g)	15–20
Drying in the equipment after layering (min)	5
Final drying in an oven	24 h, 40°C
Yield calculated after processing (%)	95–98

tained-release of the drug. Both the polymers are pH-independent; they swell and become permeable after coming in contact with digestive juices (Lehmann, 1997; Röhm GmbH and Rohm America, 1999).

Eudragit RL–RS dispersion: The coating formula contained Tween 80 ($\approx 0.2\%$ of dry polymer) as surfactant, glyceryl monosterate ($\approx 0.5\%$ of dry polymer) as glidant, and triethyl citrate ($\approx 20\%$ of dry polymer) as plasticizer. Tween 80 was dissolved in water and the solution was heated to about 70°C. Glyceryl monostearate was slowly added to the above solution while stirring and the mixing was continued for another 30 min. The solution was allowed to cool to room temperature after which triethyl citrate was homogenized in the above solution using a homogenizer (Ultra Turrax® T50, Janke & Kenkel, Germany). Eudragit RL30D and RS30D were separately mixed and the pre-dispersion was slowly added to the Eudragit dispersion using magnetic mixer. The dispersion was blended for about 10 min.

The amount of triethyl citrate was 20% of dry polymer because both Eudragit RL and RS are "hard" (lower *Elongation at Break*) polymers and hence require higher amounts of plasticizer for elastic films.

Eudragit FS30D dispersion: The coating formula and the method of preparation for Eudragit FS30D dispersion were the same as for Eudragit RL–RS dispersion except that the Eudragit FS30D dispersion did not contain any plasticizer. Since Eudragit FS is a "flexible" polymer (higher *Elongation at Break*), it gives flexible coatings without the addition of a plasticizer.

Compositions of Eudragit RL–RS and Eudragit FS coating dispersions for 8% and 30% coating thickness are shown in Table 3 and Table 4, respectively.

2.4. Coating of pellets

For the inner coat, the pellets were coated with a combination of Eudragit RL–RS in a fluidized-bed coating apparatus (GPCG 1.1, Glatt, Germany). In-process samples at various coating levels (% polymer weight gain) were taken to check the morphology of coating and to do dissolution. Coating was continued until complete polymer weight gain was achieved. After the coating, the pellets were gently fluidized for about 5 min after which they were cured in an oven for 24 h at 40°C. For the initial development, the proportion of 2:8 for mixing Eudragit RL and RS and the coating level of 8% for the inner layer were chosen after reviewing the previous literature reports about the sustained-release work done using these polymers.

Table 3
Coating formula for 8% Eudragit RL–RS inner coating[a]

Ingredients	Amount (g)	Dry substance (g)
Eudragit RL30D	43	13
Eudragit RS30D	170	51
Glyceryl monostearate	3	3
Triethyl citrate	13	13
Tween 80, 33% aq.	3	1
Water	173	–
Total	405	81

[a] Amount of pellets to be coated: 800 g; solids content of spraying suspension: 20%; polymer applied: 8%; total solids applied: 10%; samples taken after: 2%, 4%, and 6% polymer weight gain.

For the outer coat, the cured pellets containing inner coat of Eudragit RL–RS were further coated with Eudragit FS30D in the fluidized-bed processor. In-process samples at various coating levels were taken and the coating was continued until complete polymer weight gain was achieved. After the coating, the pellets were gently fluidized for about 5 min after which they were cured in an

Table 4
Coating formula for 30% Eudragit FS outer coating[a]

Ingredients	Amount (g)	Dry substance (g)
Eudragit FS30D	800	240
Glyceryl monostearate	12	12
Tween 80, 33% aq.	15	5
Water	458	–
Total	1285	257

[a] Amount of pellets to be coated: 800 g; solids content of spraying suspension: 20%; polymer applied: 30%; total solids applied: 32%; samples taken after: 15%, 20%, and 25% polymer weight gain.

Table 5
Coating conditions for inner coating with Eudragit RL–RS30D and outer coating with Eudragit FS30D in fluidized-bed coating apparatus

Batch size (g)	800
Nozzle bore (mm)	1.2
Distance: pellet bed − spray gun	Low
Atomising pressure (bar)	2
Inlet air (m^3/h)	80–95
Inlet air temperature[a] (°C)	30–40
Exhaust air temperature (°C)	26–30
Pellet bed temperature (°C)	23–26
Spray rate (g/min)	10
Drying in the equipment after coating (min)	5
Final drying in oven	24 h, 40°C
Yield calculated after processing (%)	96–98

[a] The inlet air temperature was changed in order to keep the pellet bed temperature at 23–26°C.

oven for 24 h at 40°C. Usually, a 15% coating level of Eudragit FS is recommended by the manufacturer for enteric-coating. However, as the present dosage form was intended for colonic delivery and was thus expected to pass through small intestine causing minimal drug release, it was decided to study the coating level of Eudragit FS until a maximum of 30%.

To prevent the coated pellets from sticking together, 0.5% Aerosil 200 was added to all the samples and the finished product after both inner and final coatings. Various parameters of the fluidized-bed coating process are listed in Table 5.

2.5. Product yield and powder layering efficiency

Product yield (%) was calculated by dividing the actual weight of drug-layered pellets obtained after drying with the sum of charge load of nonpareils, and the layering powder and multiplying by 100.

Powder layering efficiency was calculated by dividing the actual drug content with theoretical drug content and multiplying by 100. The actual drug content was determined by assay of the drug in pellets. Theoretical drug content was calculated by dividing the amount of drug present in the layering powder with the total of charge load of nonpareils and the amount of the powder layering composition used. As the moisture content of the drug-loaded pellets was low (1–2%), the possibility of change of the moisture content of pellets during the layering process was considered to be low and therefore not taken into account. Moisture contents were determined as a percentage loss of weight upon drying at 100°C using a moisture analyzer.

2.6. Scanning electron micrograph studies

The surface characteristics of the pellets were observed by taking scanning electron micrographs (SEM) (Jeol, JSM-840A, Germany). The pellets were sputter coated with Au/Pd alloy for 6–7 min in a Hammer sputter-coating machine. The pictures were taken at an excitation voltage of 5.0 kV using a TMAX 100-speed film.

2.7. Dissolution studies

Dissolution studies were carried out using modified USP XXIII, Method B for enteric-coated products (paddle method, 100 rpm, 37°C). For the Acid Stage, 200 mg of pellets ($n = 6$) were added to 700 ml of 0.1 N hydrochloric acid and dissolution was done for 2 h. At the end of 2 h, 200 ml of 0.20 M tribasic sodium phosphate was added to all the dissolution vessels and the pH was adjusted to either 6.5 or 7.0 or 7.5 using either 0.1 N sodium hydroxide or 0.1 N hydrochloric acid. Dissolution was continued for another 12 h for the Buffer Stage. The dissolution apparatus (DT 80, Erweka, Switzerland) was attached to the UV spectrophotometer for automated sampling and online analysis.

3. Results and discussion

3.1. Preparation of pellets

The three important factors for the successful preparation of pellets using powder layering technique are – application of binder solution to produce a uniform wetted surface, balancing the powder and binder application rates, and maintaining the cascading flow of pellets in the pan as the pelletization progresses (Vuppala et al., 1997).

Uniform wetting of the pellet bed was achieved by using a fine droplet size. Balancing the applica-

tion rate of layering powder and binder solution was critical. When the spray rate of binder solution was too high, the pellet bed became so wet that it resulted in agglomeration. When the rate of addition of layering powder was too high, the product bed became too dry and powder-layering efficiency decreased. The rate of powder and binder addition was optimized in order to prevent agglomeration, get adequate seeding of pellets, and get good layering efficiency. The point of application of the binder solution and powder was also important. The binder solution was sprayed on the top one-third of the bed and powder was applied at the bottom of the bed in such a way that the wet pellets rolled out on the powder and led to the seeding of the pellets.

3.2. Product yield, powder layering efficiency, processing time, and sieve analysis

Product yield of uncoated drug-layered pellets was 96–98% and the powder layering efficiency was 95–98%. The loss of 2–5% product was due to the formation of some agglomerates and fines in the product bed, and the loss of layering powder to exhaust. The total processing time for layering 1000 g of drug on 800 g of nonpareils was 55–65 min. These times were far less than the processing times reported for layering using a rotary fluid bed processor, or solution layering of the same amount of drug (Vuppala et al., 1997).

Approximately 88–90% of the uncoated pellets and 84–86% of coated pellets (8% inner coating and 30% outer coating) were within the size range of 0.6–1.0 mm and 0.8–1.0 mm respectively. When coating is based on polymer weight gain, the thickness of coating is dependent on the surface area of the pellets on which the coating is applied. To reduce the in-batch and batch-to-batch variability, drug-layered pellets of similar sieve-cut were used for coating. Approximately 15% of the product was lost when pellets of similar sieve-cut were used.

3.3. Drug content

Uncoated and coated pellets (8% inner coating and 30% outer coating) had a drug content of 48–50% and 34–36%, respectively. Low variability of drug content in the six replicate samples (RSD $< 4\%$) was indicative of uniform drug layering.

It must be kept in mind that the thrust of this work was on the applicability of multiple coatings of polymethacrylates for site-specific release in the colon followed by sustained-release of a model drug. Formulators may decide to make changes by choosing 5-ASA granules instead of nonpareils as the starting material to increase the drug loading.

3.4. Characterization of coating

Fig. 2 is the section of a drug-layered pellet at $60\times$; the nonpareil and a uniform layer of drug deposited during the layering process can be seen. The uniformity and homogeneity of both inner and outer layers can be observed in Fig. 3; it is the SEM of a pellet containing 8% inner coat and 30% outer coat. A thin porous layer of Aerosil can be spotted between inner and outer coating. Aerosil was added as anti-adherent after both inner and outer coating.

3.5. Dissolution studies

Before applying outer coat on the pellets, the effect of the amount of inner coat on the retardation of release was studied. As shown in Fig. 4, the values of t_{60} (time for 60% drug release)

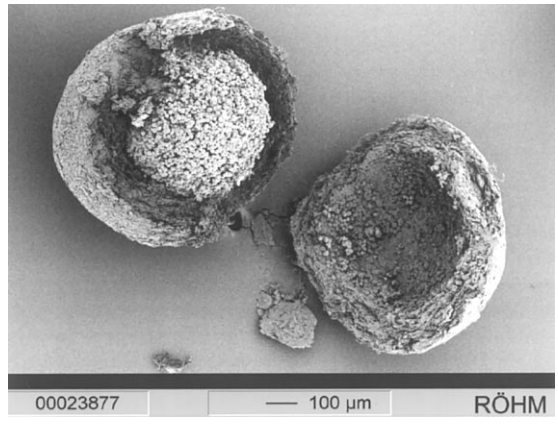

Fig. 2. SEM picture of uncoated 5-ASA pellet (magnification $60\times$).

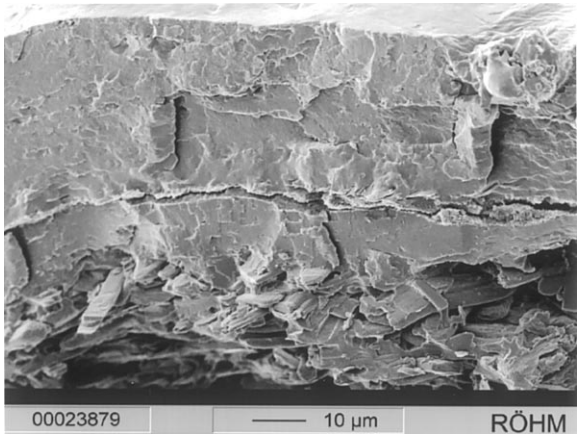

Fig. 3. SEM picture of the coatings (8% inner coating and 30% outer coating) of 5-ASA pellet (magnification 1000 ×).

increased with an increase in the thickness of inner coating of Eudragit RL–RS (2:8). Eudragit RL and RS are water-insoluble but water-swellable polymers over the entire pH range; the active ingredients are gradually dissolved by penetrating dissolution media and the release is primarily diffusion-controlled. The release rate was slower at higher coating levels because of the increased diffusion path-length and tortuosity at higher coating levels.

Eudragit FS30D was successful in the enteric coating of the pellets at all coating levels studied – 15, 20, 25, and 30% – as evident from less than 1% drug release in pH 1.2 dissolution media. There was no drug release at pH 6.5 for 12 h at all

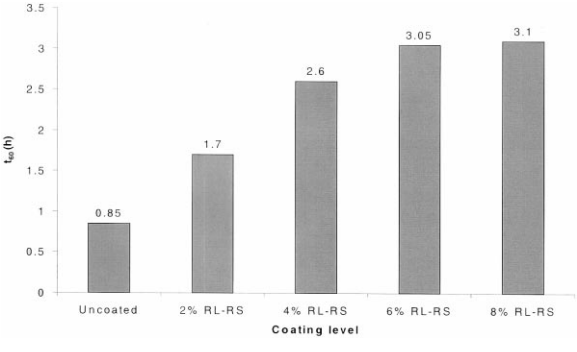

Fig. 4. Effect of the amount of inner coat on the rate of drug release from 5-ASA pellets at pH 7.0.

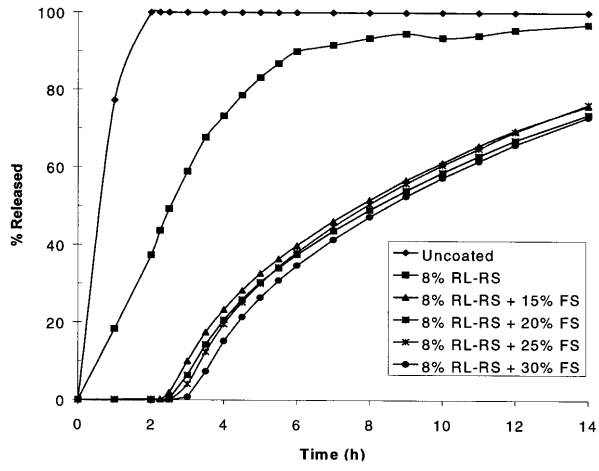

Fig. 5. Dissolution of 5-ASA pellets for the first 2 h at pH 1.2 followed by pH 7.0 USP phosphate buffer.

the coating levels. This is significant because, if the objective of majority of drug release in the colon can be achieved with a lower coating level of the polymer, it leads to lower cost, reduction in processing time, and lower weight and smaller size of the final dosage form. At pH 7.0, there was a sustained release of 5-ASA after a lag time of 15–60 min (Fig. 5). Similarly, at pH 7.5 there was a sustained-release of 5-ASA, however, there was no lag time at any of the coating levels (Fig. 6). This can be explained by the fact that Eudragit FS30D is an anionic polymer containing carboxyl groups that ionize in neutral to alkaline media. There is faster ionization of the carboxyl groups at pH 7.5 than at 7.0, and hence Eudragit FS dissolves faster at higher pH. The lag time increased with an increase in the coating level of Eudragit FS30D (30 min at 15% and 90 min at 30%). The increased lag time at higher levels of coating demonstrated the effect of coating thickness on the dissolution rate; it was expected due to the longer time taken to solubilize thicker films.

The low variability (RSD $< 4\%$) in the release profiles of six replicates during dissolution was an indication of uniformity during the layering and coating processes.

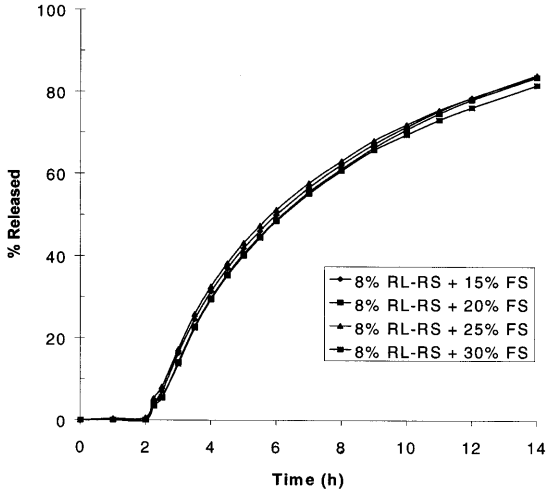

Fig. 6. Dissolution of 5-ASA pellets for the first 2 h at pH 1.2 followed by pH 7.5 USP phosphate buffer.

3.6. Tailoring drug release at other regions of GI tract

This delivery system can also be tailored to release drug at other regions of GI tract like the proximal small intestine, where the pH is lower than 6.5–7.0. One way to do that is by partial neutralization of the polymer. Eudragit FS starts dissolving at pH 6.8; however, the pH at which Eudragit FS dissolves can be changed by partial neutralization of the anionic carboxyl groups. The pH value at which a polymer like Eudragit FS that contains –COO groups dissolves is dependent upon its *Acid Value*. *Acid Value* is defined as the amount of alkali (potassium hydroxide, mg) required to completely (100%) neutralize the acid groups contained in one gram of polymer. By neutralizing some of the acid groups, a polymer can be made to dissolve at a lower pH depending on the extent of neutralization. Partial neutralization could also be useful for tailoring drug release in patients suffering from IBD and Crohn's disease who are known to have lower pH in distal intestine.

As was seen in Fig. 5, $\approx 30\%$ drug released at pH 7, the expected pH of mid to distal small intestine. In order to reduce the amount of undesired drug release before the colonic arrival of the delivery system, *Acid Value* of the polymer can be increased by chemical modification of the polymer. However, it is significant to mention here that when pH is used as the release trigger, a delivery system is more reliable if the release of drug commences before the arrival of dosage form in the colon. Since the pH in colon drops to 5.5–6.0, if the delivery system did not release drug in the distal small intestine, it may not release drug anywhere further in the GI tract. Human data would indeed be helpful in striking a balance and further refinement of the delivery system.

4. Conclusions

A novel pH- and time-based drug delivery system for potential colonic delivery was developed using multiple coatings of aqueous polymethacrylates on drug-layered pellets. The delivery system might prove successful for delivery of drug to the colon in a sustained-release fashion. This system can be easily manufactured on a large-scale in a reasonable processing time using conventional powder-layering and fluidized-bed coating techniques. From regulatory viewpoint, all the ingredients comprising the delivery system, except Eudragit FS (new polymer), are official in United States Pharmacopoeia (USP). The delivery system does not require organic solvents for preparation; it results in reduced cost, less environmental pollution, and reduced work hazard.

For successful colonic delivery, any possible change in the residence time of dosage forms in the GI tract of a patient suffering from IBD or Crohn's disease must also be borne in mind. The delivery system developed in this study should not be seriously affected by an increase or a decrease in the residence time because the outer coat is pH-dependent and not time-dependent. However, changes in pH to values below 6.8 in terminal ileum would decrease or prevent drug delivery.

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