

A synchronous colon-specific drug delivery system for orally administered mesalamine

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Abstract

The aim of the present investigation is to develop a time and pH-dependent system for colon specific drug delivery of mesalamine. The colon specific drug delivery system (CDDS) is designed such that the innermost part consists of a core tablet of mesalamine which is then compression coated with a pH-independent hydrophilic polymer (Hydropropylmethyl cellulose). This is then coated with a pH-dependent methacrylic acid copolymer (Eudragit® S100). The concentration (coating level) of Eudragit® S100 was optimized to provide an enteric coat that allows the tablet to pass intact through the stomach and is targeted to the colon. The coating thickness and grades of HPMC were optimized to set a desired lag time in the intestine. From the in vitro evaluation it can be revealed that the developed CDDS can exhibit site-specific drug targeting to the colon.

Key words: Colonic specific drug delivery, compression coating, enteric coating, mesalamine.

Introduction

The oral CDDS have recently gained importance for delivering a variety of drugs. Colonic drug delivery may be achieved by either oral or rectal administration. Rectal dosage forms (enemas and suppositories), are not always much effective due to high variability in the distribution of drug administered by this route (Patel et al. 2007). Therefore, the oral route is the most preferred. Conventional oral formulations dissolve in the stomach or intestine and are absorbed from these regions. The major obstacle with the delivery of drugs by oral route to the colon is the absorption and degradation of the drug in the upper part of the gastrointestinal tract (GIT) which must be overcome for successful colonic drug delivery (Lee 1991).

In conditions where localized delivery of the drugs is required in the colon or drugs which are prone to degradation in the environment of the upper GIT, colonic drug delivery may be valuable. Drug release at this site will ensure maximum therapeutic benefits. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or help to avoid unnecessary systemic absorption of the drug. Ulcerative colitis is the inflammatory disease of the colonic mucosa which is usually treated with salicylates or glucocorticoids. However, during the periods of remission, mesalamine is the drug of choice. In this case it is desirable to localize the release of mesalamine to the afflicted site in the colon (Watts et al. 1997, Sinha et al. 2001, Qi et al. 2000). Thus, mesalamine was used as a model drug in the present study.

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As mentioned previously CDDS need to protect the drug during transit through the stomach and small intestine before allowing rapid release on entry into the colon. Various approaches have been used for oral delivery of drugs to the colon, which include time dependent delivery, pH dependent delivery, and delivery systems that use bacteria that colonize in the colon or produce enzymes to affect the drug release (Ahrabi et al. 2000, Macleod et al. 1999, Lorenzo-Lamoza et al. 1998, Rodrigues et al. 1998).

Despite widespread use of pH dependent systems for colon targeted delivery of drugs, there has always been a controversy about their usefulness for the intended purpose, mainly because of high pH variability of the gastrointestinal tract among individuals and lack of proper coating materials that would dissolve at the desired pH of the colon. Although methacrylic acid copolymers such as Eudragit[®] L100 and Eudragit[®] S100 have commonly been used as pH dependent polymers for coating solid dosage forms (because of their solubility at pH 6.0 or higher and 7.0 or higher respectively), none of them is suitable for use alone for coating of dosage forms that would start releasing the drug specifically at pH 6.4 which is generally considered as the suitable pH for colon targeted drug delivery (Kun et al. 2005, Khan et al. 1999, Khan et al. 2000). A major drawback of Eudragit[®] coated pH dependent formulation is premature release of drug in the small intestine (Nugent et al. 2001).

Time-controlled delivery has been achieved by applying coats onto drug cores which are capable of delaying the release through different mechanisms (Narisawa et al. 1994, Bussemer et al. 2001, Pozi et al. 1994, Krogel et al. 1999, Ueda et al. 1994) or alternatively designing of dosage forms based on capsule shape (MacNeil et al. 1990) or osmotic type of devices (Gupta et al. 1996). Time controlled release systems have been used for colonic delivery, but lack the site specificity due to variation in the gastric emptying time.

These problems could be overcome by using a combination of enteric and controlled release properties of polymers. Thus, a formulation needs to be developed that offers protection to the drug until it reaches to the small intestine (pH 7.0 or higher) using an enteric type of polymer, while also avoiding the complete drug release in the ileum using a polymer with controlled release properties.

The objective of this study is to develop formulations using a combination of time and pH dependent system for delivering mesalamine to the colon and to demonstrate its site specificity in the colon.

The CDDS consists of three parts (Figure 1). The innermost part consists of the core tablet of mesalamine. The core tablet is then compression coated with a pH independent hydrophilic polymer like hydroxypropylmethyl cellulose (HPMC) which would serve as a time dependent factor. Finally it is enteric coated with a pH dependent methacrylic acid copolymer (Eudragit[®]). In this system the enteric film layer was designed to minimize the influence of the stomach emptying time on drug release and to guarantee that the tablet could enter the small intestine intact. The compression coating layer was adopted to delay the drug release for about 2 to 3 hours and to allow the tablet to pass intact through the small intestine to the colon.

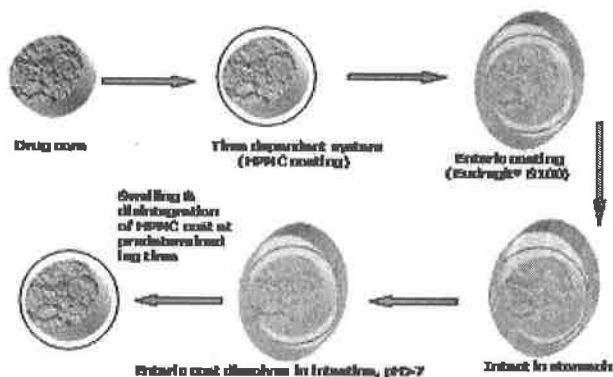


Figure 1. Time and pH dependent colon targeted drug delivery system.

Materials and Methods

Materials

The compounds obtained as a gift samples: Mesalamine from Sun Pharmaceutical Industries, India. Eudragit[®] S100 from Degussa, Rohm Pharma, India. Sodium starch glycolate from Torrent Pharmaceuticals Pvt. Ltd., India. Polyvinyl pyrrolidone K 30 (PVP) from S. D. Fine Chemicals Ltd., India. HPMC E3, E5, E15 and K4M from Colorcon Asia Pvt. Ltd, India. All the other chemicals and solvents used were of laboratory reagent grade.

Methods

Preparation of mesalamine core tablets

Weighed quantity of mesalamine, 60# dicalcium phosphate dihydrate and sodium starch glycolate (5 %w/w) were mixed and granulated using a binder polyvinyl pyrrolidone (5 %w/w) in isopropyl alcohol. The mass was passed through 22# sieve and the granules were dried in a tray drier (Labline, Sun Instruments Pvt. Ltd., Ahmedabad, India) for 10 – 15 min at 60°C. Perfectly dried granules were passed through 22# and were mixed uniformly with 2 %w/w of talc and 1 %w/w magnesium stearate. Granules (300 mg) were compressed on a rotary tablet machine (Rimek, Karnavati Engineering Pvt. Ltd., Ahmedabad, India) using 11 mm concave punches. Tablet cores of mesalamine were characterized for weight variation, hardness, friability and disintegration time.

Preparation of mesalamine colon targeted tablets

Core tablets of mesalamine were press coated for the inner coating layer using different grades of HPMC (K4M, E3, E5, and E15). One half quantity of the polymer required per tablet was filled into the die cavity of a rotary tablet machine having a 13 mm concave punch. The core tablet was then placed in the centre of the die cavity on the polymer mixture bed. The remaining half quantity of the polymer mixture was again filled in the die cavity, on the core tablet. The tablet was then compressed and the press coated tablets were evaluated and used for further coating.

The outer coating layer was applied on the press-coated tablets using dip coating method. An organic polymer solution consisting of 5 %w/v Eudragit[®] S100 in acetone was used for the coating. Castor oil was incorporated in the coating solution as a plasticizer (20 %w/w based on the polymer). An opacifier, titanium dioxide (0.05 %w/w) and an antiadherent, talc (5 %w/w) to prevent adhering of tablets during the coating process were also added to the coating solution.

In vitro dissolution studies

In vitro dissolution studies were performed for the mesalamine tablets using USP dissolution apparatus II (paddle method, Electrolab, Tablet Dissolution Tester, TDT – 06 T, Mumbai, India) at 100 rpm, 37°C ± 0.5°C

and 900 ml dissolution medium. In order to simulate the pH changes along the GIT, four dissolution media with pH 1.2, 6.0, 7.2 and 6.4 (colonic pH) were sequentially used, referred to as the sequential pH change method (Table 1). When performing the *in vitro* release experiments, pH 1.2 medium was first used for 2 h which was then replaced with fresh pH 6.0 dissolution medium and kept for 1 h. This medium was again replaced by pH 7.2 dissolution medium. After 2 h, pH 7.2 dissolution medium was removed and finally pH 6.4 dissolution medium was added. Samples were withdrawn at regular time intervals. The sample solutions were filtered using Whatman filter paper (45 μ). Samples were estimated using UV/VIS spectrophotometer (Elico SL-164 – Double beam UV/VIS Spectrophotometer) at 303 nm and 330 nm for mesalamine estimation in simulated gastric fluid (pH 1.2) and for other phosphate buffer media, respectively. The cumulative percentage release for mesalamine was calculated over the sampling times using Beer Lambert's curve generated in the respective medium. Studies were performed in triplicate and the mean cumulative percentage of drug calculated (\pm SD) and plotted against time.

Table 1. Dissolution conditions and λ_{max} of mesalamine coated tablets.

PH	λ_{MAX} (NM)	Time (H)	Simulated GIT Region
1.2	303	2	Stomach
6.0	330	1	Duodenum
7.2	330	2	Terminal ileum
6.4	330	5	Colon

Results and Discussion

As discussed earlier core tablets of mesalamine were prepared by using dicalcium phosphate dihydrate as a diluent, as lactose was reported to give maillard reaction with amine containing drugs. As the drug has poor flow property, the tablets were prepared by wet granulation method. Since the main function of colon is absorption of water, the viscosity of colonic contents increases appreciably as one move down from the colon; this may impede the drug release from the dosage as time progresses. Thus, sodium starch glycolate was added as a superdisintegrant to facilitate disintegration.

Enteric coating of mesalamine tablets

Currently Eudragit[®] S100 seems to be the most favorable coating polymer in terms of achieving a delayed delivery of mesalamine in the more distal parts of the small intestine. Taking this into consideration the core tablets of mesalamine were enteric coated with Eudragit[®] S100 to obtain tablets with a coating level of 5, 6, 7, 8 and 9 %w/w (Batch S1 to S5)

Figure 2 shows the dissolution profile of batches S1 to S5 which reveals that a minimum of 5 % w/w coating level of Eudragit[®] S100 was required to impart an enteric effect. Further more, it was observed that the dissolution rate was inversely proportional to the thickness of the coat applied. At a coat concentration of 5%, the percent drug release in the first 4.5 h of dissolution at pH 7.2 was 66.6 \pm 3.23%. Increasing the coat thickness to 6%, 7%, 8% and 9% reduced the drug release to 41.67 \pm 3.20%, 36.74 \pm 2.13%, 18.47 \pm 3.76% and 6.47 \pm 2.30% respectively. All the coated tablets showed a nearly complete drug release within 6 to 7 h i.e. in the next 3 h. A significant difference was observed in the percentage of drug released for different coating concentrations, from 3 h to 7 h during dissolution study. These results are in general agreement with the results of Sinha et al. (2003), who demonstrated that an increase in the coat thickness of Eudragit[®] S100 shows a decrease in the dissolution rate of the drug indomethacin. This could be attributed to the fact that increasing the coat concentration made the coat more impermeable due to which drug release was retarded. Slowly as the coatings solubilized at higher pH, drug dissolution was facilitated.

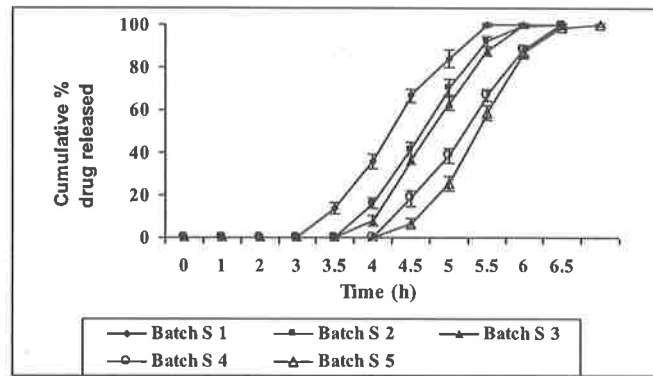


Figure 2. Comparison of dissolution profile of batches S1 to S5 (data shown as mean \pm standard deviation, $n=3$).

Figure 3 shows lag time profile of batches S1 to S5 which reveals that increasing the coating level of Eudragit® S100 increases the lag time for drug release. At a coat concentration of 5 %, a lag time of 3 h was obtained. Increasing the coat thickness to 6 % and 7 % a lag time of 3.5 h and to 8 % and 9 % a lag time to 4 h was obtained, however this lag time would not be sufficient for the tablet to reach intact to the colon. Thus, an additional coat of HPMC was needed to be applied on the core tablets to further delay the drug release. The coating was done by compression coating method to prevent the premature release of drug in the terminal ileum. Since the batches S3, S4 and S5, could prevent the drug release for about 4 h; these batches seems to be more promising and were used for compression coating.

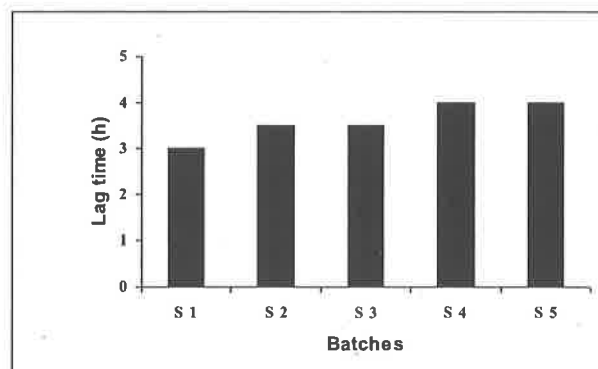


Figure 3. Lag time profile of batches S1 to S5.

Compression coating of mesalamine tablets (Delayed Release System)

As discussed above tablet cores containing mesalamine were compression coated with HPMC K4M, E3, E5, and E15. The compression coating layer was adopted to delay the drug release for about 2 to 3 h and to allow the tablet to pass intact through the small intestine to the ileo-cecal junction or proximal colon. Tablets coated with HPMC K4M did not release the drug for about 8 to 10 h and hence this grade of HPMC was not used for further studies.

Tablets of mesalamine were compression coated with HPMC E3 to obtain batches with % weight gain of 33.33, 50.00, 66.66 and 83.33 (Batches H1 to H4). *In vitro* evaluation of compression coated tablets was carried out at pH 7.2, since it is this pH at which the HPMC coat gets exposed after

solubilization of the enteric coat in the upper part of GIT. The dissolution profile of batches H1 to H4 revealed that this grade of HPMC was not found suitable as it could prevent the drug release for only about 0.5 h (Figure 4). The low viscosity grade of HPMC E3 was not sufficient to retard the release. Thus, a higher viscosity grade HPMC E5 was used in further trials (Batches H5 to H8, with % weight gain of 33.33, 50.00, 66.66 and 83.33 respectively).

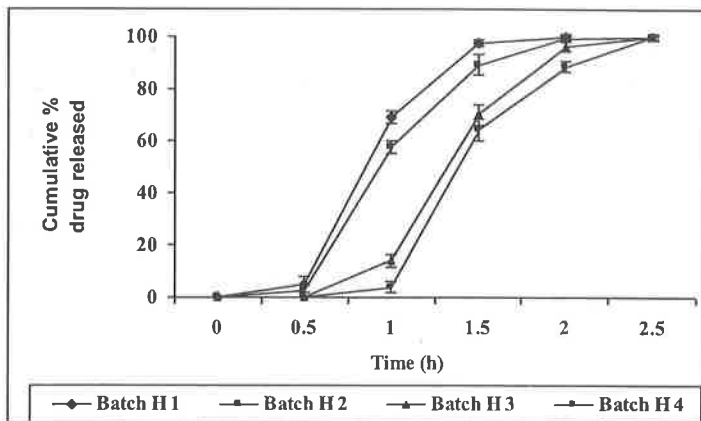


Figure 4. Comparison of dissolution profile of batches H1 to H4 (data shown as mean \pm standard deviation, $n = 3$).

The dissolution profile of batches H5 to H8 revealed that even at higher concentrations of HPMC E5, the drug release was retarded for only 1 h (Figure 5), but this would not be sufficient to retard drug release for 2 to 3 h. Thus, further studies were conducted using yet a higher viscosity grade of HPMC; HPMC E15 (Batches H9 to H12, with % weight gain of 33.33, 50.00, 66.66 and 83.33 respectively).

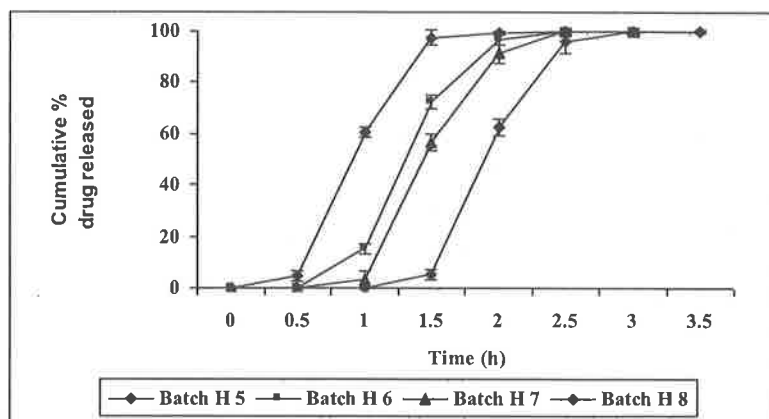


Figure 5. Comparison of dissolution profile of batches H5 to H8 (data shown as mean \pm standard deviation, $n = 3$).

The dissolution profile of batches H9 to H12 revealed that as the thickness of the compression coat increases, the release of the drug decreases (Figure 6). It was observed that at % weight gain of 66.66 to 83.33 %w/w of core tablets with HPMC E15 (batches H11 to H12) could prevent the drug release for 2 to 3 h. Batches H9 and H10 showed a premature drug release. The coating thickness demonstrated an inversely proportional effect on the drug release i.e. as the coat thickness increases

the drug release decreases and lag time of 2 to 3 h could be obtained with batches H11 and H12. Thus, batches H11 and H12 could be considered as promising batches and were used for applying enteric coat. The grade of HPMC E15 was found to be sufficient to give the desired lag time.

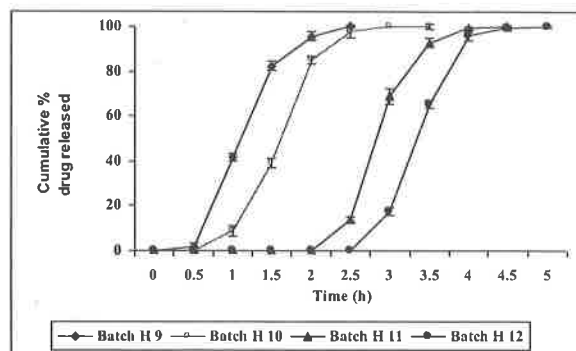


Figure 6. Comparison of dissolution profile of batches H9 to H12 (data shown as mean \pm standard deviation, $n = 3$).

The dissolution profile of batches H1 to H12 revealed that the viscosity grade of HPMC and the coat level had a significant effect on the lag time and drug release rate. The lag time of drug release was delayed with the increase of the viscosity grade of HPMC and the release rate was decreased. For the system presented, it was designed to release the drug at the scheduled time and then release most of the drug within a short time period in the colon. A higher viscosity grade of HPMC was not suitable for this purpose.

Formulations containing combination of time and pH dependent systems for colon targeted mesalamine tablets

The core tablets of mesalamine were compression coated with HPMC E15 (66.66 to 83.33 %w/w). These were further coated with Eudragit[®] S100 (7, 8 and 9 %w/w) polymer so as to prevent the drug release in stomach and small intestine. Table 2 shows specifications for combination of time and pH dependent system.

Table 2. Specifications of time and pH dependent system.

BATCH	MS1	MS2	MS3	MS4	MS5	MS6
Compression coating level (%w/w)	66.66	66.66	66.66	83.33	83.33	83.33
Eudragit [®] S100 coating level (%w/w)	7	8	9	7	8	9
Lag time (h)	4.5	5	5	5.5	5.5	6
Amount of drug release (%) in first 6 h	52.88 \pm 1.57%	43.76 \pm 1.63%	34.77 \pm 2.11%	17.66 \pm 1.67%	8.51 \pm 2.28%	No drug released

The dissolution (Figure 7) as well as the lag time profiles of batches MS1 to MS6 reveals that the thickness of the coat applied had a significant effect on the drug release characteristics. Batch MS1 and MS4 with 7 %w/w coat level of Eudragit[®] S100 and 66.6 and 83.33 %w/w of HPMC coat level shows a lag time of 4.5 h and 5 h with 52.88 \pm 1.57% and 17.66 \pm 1.67% of drug release respectively in first 6 h. Batch MS2 and MS5 with 8 %w/w coat level of Eudragit[®] S100 and 66.6 and 83.33 %w/w of HPMC coat level shows a lag time of 5 h and 5.5 h with 43.76 \pm 1.63% and 8.51 \pm 2.28% of drug release respectively in first 6 h. Batch MS3 and MS6 with 9 %w/w coat level of Eudragit[®]

S100 and 66.6 and 83.33 %w/w of HPMC coat level shows a lag time of 5 h and 6 h with $34.77 \pm 2.11\%$ and no drug release respectively in first 6 h. Thus, from the above results we can conclude that, by keeping the coating level of Eudragit® S100 constant and by increasing the coat level of HPMC, the lag time for drug release can be increased and the amount of drug release can be decreased. All the formulations could withstand the acidic pH and no drug release occurred in simulated gastric fluid. After the dissolution of the enteric coat in simulated intestinal fluid, the HPMC starts to interact with the dissolution medium. Finally, the release of the active principle from the system is dependent on duration of the lag time as a function of the applied amount of the hydrophilic polymer.

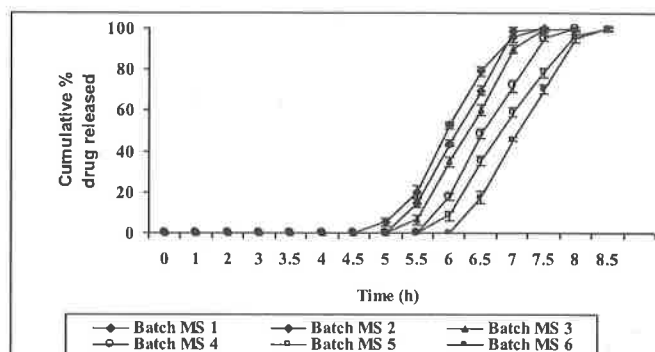


Figure 7. Comparison of dissolution profile of batches MS1 to MS6 (data shown as mean \pm standard deviation, $n = 3$).

The *in vitro* evaluation revealed that, except batch MS1, all the other batches could fulfill the selection criteria for delivering mesalamine to the colon through oral targeted tablets. Batch MS6 was selected as the best batch as it could prevent the drug release for upto 6 h.

Comparison with marketed product

The best batch of the CDDS (Batch MS6) was compared with that of the formulation available in the market, Asacol. The marketed product contains a core of mesalamine (400 mg) coated with a pH-sensitive acrylic polymer called Eudragit® S, which delays release of mesalamine until the tablet reaches an environment of pH 7 or above. The marketed product, which typically dissolves in the terminal ileum or colon, is designed to deliver effective concentrations of mesalamine to the colon with low systemic absorption²⁰. As discussed earlier the major drawback of using Eudragit® alone for coating using basis of a pH dependent formulation, is the premature release of drug in the small intestine ($68.554 \pm 3.02\%$ drug was released in the small intestine from the marketed product).

The dissolution profiles of the best batch MS6 was compared with the marketed product (Asacol) and f_2 value was determined (Figure 8). The f_2 value obtained by comparing the dissolution profile of batch MS6 with Asacol was found to be 11.34. The value of similarity factor, f_2 was less than 50, thus it can concluded that there is a significant difference between the dissolution profiles of the marketed product and the formulated product.

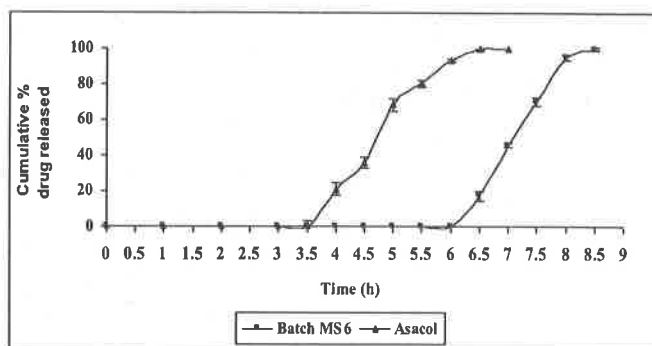


Figure 8. Comparison of dissolution profile of batch MS6 with marketed product (data shown as mean \pm standard deviation, $n = 3$).

Conclusion

A novel pH- and time-dependent delivery system was developed for delivering drugs after oral administration to the colon. The dosage form could carry the drug intact through the stomach and small intestine to the distal end of the small intestine and begin to release the drug in the colon. The in vitro studies revealed that the novel system could release the drug at a predetermined time, which was mainly controlled by the coating layers of the system. Comparing the best batch with that of the marketed product showed a significant difference between the dissolution profiles (f_2 was less than 50). Thus, it can be concluded that the developed CDDS, can give more site specific release of mesalamine in the colon.

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