ORIGINAL ARTICLE

Formulation development, optimization and study on drug release kinetics of Eudragit® L100-HPMC E15 LV mixed film-coated colon-targeted Mesalamine tablets

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The study was designed to evaluate the *in vitro* dissolution characteristics of pH-sensitive polymer - HPMC E 15 LV-coated tablets - in various simulated fluids (pH range 1.2, 6, 7.2). The Mesalamine tablets were fabricated by mixing the drug with microcrystalline cellulose and other ingredients. The fabricated Mesalamine tablets were coated with Eudragit L100 polymer and HPMC E 15 LV. The fluctuation in colonic pH conditions during inflammatory bowel disease and the nature of less fluid content in the colon may limit the expected drug release in the colon. Addition of HPMC E 15 LV may control this problem by hydrophilic nature and excellent film-forming characteristics like ductility and elasticity. The different batches of Mesalamine tablets (FM1-FM5) were coated with increasing concentration of Eudragit L100 and HPMC E 15 LV. The coating was given up to 8% TWG(Total weight gain) of the uncoated tablet. Drug release studies were conducted in different pH conditions in the presence of rat ceaecal contents. The different buffer conditions were chosen to mimic the pH changes in the terminal part of the ileum as well as in the colon. The drug release profile was analyzed for colon-targeting performance *in vitro*. The release profile of the tablets indicates that the drug release was retarded in the tablet by film coating. The addition of HPMC E 15 LV ensures the channels for allowing colonic fluids to penetrate into the core and subsequent drug release at the target site. The kinetics of the drug release also evaluated the release pattern that was best fitted with Higuchian release. The results of the mechanism of release revealed that drug release was found to be a complex one with diffusion, erosion and swelling.

Key words: *Colonic delivery, Eudragit L100, HPMC E 15 LV, IBD, Mesalamine*

INTRODUCTION

It has been reported that at least one million Americans are believed to have inflammatory bowel disease (IBD), with 15,000–30,000 new cases identified yearly.[1,2] The causes of IBD are multifactorial, which is because of inflammatory responses and genetic factors, such as multiple genetic factor, candidate gene and chromosome location. Dietary factors such as saturated fats, milk products and allergic foods may also impel IBD. The common term IBD includes two diseases: Ulcerative colitis and Crohn's disease. The etiology and pathophysiology of IBD are thought to result from inappropriate and ongoing activation of the mucosal immune system, driven by the presence of normal lumina flora. These abnormal responses are likely to be alleviated by the defects in the barrier function of the intestinal epithelium and the mucosal immune system. The major types of idiopathic IBD were defined based on the clinical manifestations; investigators have been struggling to identify the fundamental pathophysiologic process underlying this enigmatic disorder and

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clinicians have struggled to provide effective therapy for the often-dismaying clinical manifestations.[3]

Colon drug delivery systems (CDDS) are providing more effective therapy in the colon-related diseases like ulcerative colitis, Crohn's disease, bowel cancer, some infections and constipation, which need local delivery of the drugs.[4] Besides local therapy, the colon can also be used for entry of drugs into the systemic circulation.[5,6] Prophylaxis to the colon cancer and in treating nicotine addiction, administration of proteins, peptides such as insulin, calcitonin, vasopressin as cytokinin inhibitor and antibiotics are explored for colonic delivery. Delivery of vaccine is also explored possibly because it is rich in lymphoid tissue and provides the natural environment to the vaccine.[7] Colonic drug delivery is desirable for chronotherapy to treat diseases such as asthma, hypertension, cardiac arrhythmia's, arthritis and inflammation.[8] The need and advantages of the CDDS have been well accepted and revealed by the various researchers.[9-12] In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH 6.6 ± 0.5) to the terminal ileum (pH 7.5 ± 0.4), a decrease in the ceacum (pH 6.4 ± 0.4) and then a slow rise from the right to the left colon with final value (pH 7.0 ± 0.7).[13,14] Some reports suggested that the change in the gastrointestinal (GI) profile may occur in patients with IBD, which should be considered in developing delayed release formulations.[15] The dissolution and release from colonic formulations is thought to decrease more in the colon than in the small intestine, which may be because of less fluid content in the colon.[16] The small luminal surface area and transit of the material through the colon can be restricted or slowed by constricted lumen of the colon. It is assumed that the colon could restrict drug transport to across the mucous and into the systemic circulation, but the longer residence time may compensate this limitation of the colon to a certain extent.[17] The GI residence time of the dosage form is another important factor in a pH-dependent CDDS, and many physiological and other factors were believed to influence the GI residence time.[18,19]

There are various techniques for targeting orally administered drug to the colon. The technique includes prodrugs (sulfasalazine, balslazide, osalazine) to deliver the 5-ASA locally in the colon to treat IBD. Coating with pH-sensitive polymer (Mesalamine, corticosteroids), time-release system to release the drug after a lag time is predominant in the colon. Drug-loaded carriers that are specifically degraded by colonic bacteria can be targeted to the colon provided the colon contains over 400 distinct species of bacteria having a population of 10^{11} to 10^{12} CFU/mL with bacterioids, Bifidobacterium, Eubacterium and lactobacillus being abundantly present than other species. The pH-dependent systems are based on the existence of pH gradients in the GI tract. The pH-sensitive polymers most commonly used are Eudragit L100, Eudragit S100 and combined Eudragit L100 and Eudragit S100. According to various studies worldwide, it was revealed and suggested that there was a fluctuation in the pH of the colon because of various reasons and diseased conditions. Mesalamine tablets manufactured by different companies have a different release profile when tested in various pH media.[20] The behavior of various pH-sensitive polymer-coated marketed products (Pentasa®, Asacol®, Salofalk®) with human subjects indicates that there was a marked individual variation in urinary recovery of the drug observed in patients after administration of Pentasa® tablets.[21,22]

The main objective of the present study is to prepare a most suitable coating formula of Eudragit L100 in combination with another film-forming polymer. The aim of the combination in formula was to improve the coating characteristics and targeting property to release the drug in the colon. Eudragit L100 is expected to offer a good release profile in combination rather than when used alone. Because there are several factors limiting the release profile, colon-targeted devices are prepared only with a pH-sensitive polymer. Many studies have indicated the considerable variation in pH gradient in the GI tract; therefore, completely depending on the pH sensitivity of the polymer alone may not be sufficient to trigger the drug release at a specific site. To overcome this, a novel combination of another good film-forming polymer, HPMC E15 LV, was incorporated in the coating formula. In this research work, the Mesalamine tablets were coated with varying proportions of Eudragit L100 and HPMC E15 LV and studied *in vitro* for their release profile in various pH conditions. The superiority of the formulation was compared with that of the marketed products. The drug release kinetics were studied by using various kinetic studies available, such as Higuchi, Korsemeyer-Peppas, Hixon-Crowell, zero order and first order kinetics. The results of the overall study, release kinetics and mechanism of drug release were elaborately discussed in this work.

MATERIALS AND METHODS

Material

The model drug was Mesalamine (5-amino salicylic acid), procured from Sarex Overseas, Maharashtra, India. Eudragit L100 was from Lab Chemicals, Chennai, India. HPMC E 15 LV and titanium dioxide were from Loba Chemie Pvt. Ltd., Mumbai, India. Microcrystalline cellulose from Merck, Mumbai, India; PEG 400, PVPK 30, talc and magnesium stearate from Sisco Research Laboratories, Mumbai, India; and iso propyl alcohol were obtained from RFCL Limited, New Delhi, India.

Fabrication of mesalamine tablets

Granules of Mesalamine were produced by the wet granulation technique. The appropriate amounts of Mesalamine and microcrystalline cellulose were weighed as shown in Table 1 and blended thoroughly. A weighed quantity of polyvinyl pyrollidone K-30 was dispersed in water as granulating fluid that was used to form a wet mass. The damp mass formed was

Table 1: Formula of Mesalamine tablets coated with Eudragit L100 and HPMC

Ingredients (mg)/tablet	FM1	FM2	FM3	FM4	FM5
Mesalamine	400	400	400	400	400
Microcrystalline cellulose	303.5	303.5	303.5	303.5	303.5
Polyvinyl pyrrolidone	21.25	21.25	21.25	21.25	21.25
Talc	9	9	9	9	9
Magnesium stearate	9	9	9	9	9
Coating	**C1**	**C1**	**C1**	**C1**	**C1**
Eudragit L100:HPMC 15 LV	1:0.25	1.5:0.5	2:0.75	2.5:1	3:1.25
% weight gain of Eudragit L100:HPMC	8%	8%	8%	8%	8%
Total weight after coating	802.17	802.17	802.17	802.17	802.17

then forced through a sieve no. 18 and dried at 45°C for 1 h in a tray dryer to remove moisture. The dry mass was forced through a sieve no. 22 and stored in desiccators until further use. The granules were taken out and lubricated using talc and magnesium stearate, which was already passed through a sieve no. 60. The final resultant blend was then compressed by a 16 station tablet compression machine (Cadmach®-India) using 19 mm × 9 mm capsule shaped plain punches.

FTIR Fourier transform infrared spectroscopy study

The FTIR spectra of the drug raw material and drug with various excipients used in the formulation were recorded using a Perkin Elmer-(USA) scanner from 4000 to 400 as the scanning range between wave number (cm^1) and % transmittance. Samples were prepared in KBr discs (2 mg sample in 200 mg KBr) with hydrostatic press at the force of 5 cm^2 and the resolution was 4 cm^1. The samples of pure drug and granules containing different polymer and excipients were scanned individually. Experiments were duplicated to check the reproducibility.

DSC Differential scanning colorimetryanalysis

Thermal analysis using the DSC method was carried out on Mesalamine and physical mixture of Mesalamine with other ingredients. A Seiko, Japan, DSC 200 c model differential scanning calorimeter was used for the study. Samples of 1–4 mg were sealed hermetically in flat-bottomed aluminum cells or pans. These samples were then heated over a temperature of 30–450°C in an atmosphere of nitrogen (30 mL/min) at a constant rate of 10°C/min using alumina (standard material of DSC supplied by Shimatzu Corporation-USA) as the reference standard.

Preparation of eudragit L100–HPMC E15 LV coating systems

The coating solution was prepared using Eudragit L100 and HPMC E 15 LV as per the quantities mentioned in Table 2. Basing on the ratio of Eudragit L100 and HPMC E15 LV (1:0.25, 1.5:0.5, 2:0.75, 2.5:1, 3:1.25) in the formulations, they were named FM1, FM2, FM3, FM4 and FM5. Eudragit L100 was dispersed in iso propyl alcohol and kept in a propeller for 1 h to get a homogenized coating solution. After 1 h of mixing in the propeller, HPMC E15 LV was introduced into the coating solution and kept in the propeller for another 1 h. Previously, HPMC E15 LV was soaked in water for around 3 h to form a transparent jelly and then it was kept in the solution of water and iso propyl alcohol (3:1) under mechanical stirring for 1 h to form a homogeneous solution. It was then incorporated in the coating solution of Eudragit L100 by small amounts while it was kept in a propeller under high RPM. During mixing, the plasticizer, castor oil, and opacifying agent, titanium dioxide, were mixed in small quantities to improve the aptness of the coating solution.

Table 2: Formula of the coating solution

	Quantity/1000 mL				
Ingredients	**FM1**	**FM2**	**FM3**	**FM4**	**FM5**
Eudragit L100	4	6	8	10	12
HPMC E15 LV	1	2	3	4	5
Castor oil	0.9	1.2	1.5	1.8	2.1
Titanium di oxide	0.48	0.64	0.8	0.96	6.75
Iso propyl alcohol	qs	qs	qs	qs	qs

Coating of Mesalamine tablets with the Eudragit L100–HPMC E 15 LV coating

The polymer solutions prepared with different concentrations of the polymer were coated on the tablets. The desired volume of coating solution was sprayed on the prewarmed (temperature 40°C) tablet bed (batch size 500 g) in a pan coater (Kalweka, Gujarat India). The coated tablets were dried with the help of inlet air (temperature 45–50°C). The coating processes were achieved with 8% weight gain by the weight of the uncoated tablet. The percent mass increase of the tablet on coating was taken to be indicative of the coat thickness. The same procedure was carried out for various coating solutions with varying proportions of polymers to be coated on the Mesalamine tablets.

Preparation of rat ceacal contents medium

Before carrying out the study on animals, the study protocol was scrutinized by an institutional animal ethical committee (IAEC) and was approved by the same. The susceptibility of the enzymatic activity of the colonic bacteria on matrix tablets was assessed by performing the drug release study in a medium containing rat ceacal contents. Albino rats weighing 180–200 g were chosen to collect rat ceacal contents for the

study. The normal diet conditions were maintained. Around 45 min before the drug release studies, rats were sacrificed to open the abdomen to collect the rat ceacal contents. The ceacal contents were transferred to the phosphate buffer solution that was already chosen for colonic studies and the media was bubbled with carbon dioxide. The ceacal contents were collected individually from the animal and weighed separately, and a final 4% w/v ceacal dilution was prepared by pooling the ceacal contents of five Albino rats. The 4% ceacal contents were introduced into the dissolution media after the 5th hour of the study and studied up to 20 h or until 95% or more drug release was observed. The samples were collected at the predetermined time intervals and analyzed, which were then replaced with the fresh media bubbled with carbon dioxide to maintain sink conditions. The withdrawn samples were diluted and centrifuged to separate the solid contents. The supernatant liquid was collected and filtered through the bacteria-proof filter and the filtrate was analyzed for Mesalamine contents using a double-beam UV spectrophotometer at wavelengths of 330 and 332 nm.

Stability studies

The formulation FM3, which meets all the desirable tablet quality control parameters and shows better colon targeting drug release profile, was selected and subjected to stability studies for 3 months. The tablets were packed with Al/PVC and exposed to 40°C/75% RH in a stability chamber. These samples were again subjected to drug release studies, physical properties and assay at the different time intervals.

In vitro studies

The *in vitro* release study was carried out by a buffer change method in the presence of rat ceacal contents using a USP XXIII test apparatus (paddle method) and the conditions of 75 RPM, 37 ± 0.5°C were maintained throughout the experiments. The USP apparatus (Lab India disso 8000-India) was used for all the experiments and buffer stages were adjusted differently according to the purpose of the study. The drug release study was started with 500 mL of 0.1 N HCl (2 h), followed by the buffer stage and 0.2 M phosphate buffer pH 6 (1 h), and the rest of the experiment was conducted in 0.05 M phosphate buffer (pH 7.2) as dissolution media. The pH of the solution indicated the normal pH conditions of the stomach, intestine and colon. The dissolution studies were carried out up to 20 h. Aliquots were collected manually at predetermined intervals and analyzed for Mesalamine content using a UV spectrophotometer (Perkin Elmer). The readings were taken at 302, 330 and 332 nm for samples tested in 0.1 N HCl and the buffer medias, respectively. The drug concentration was determined using a standard calibration curve prepared for the standard of the known concentration of Mesalamine.

Procedure for dissolution

The dissolution test carried out as per the United States Pharmacopoeia (USP). After 2 h of operation in 0.1 N HCl for acid stage, an aliquot was withdrawn for the fluid and the remaining solution was discarded. The Mesalamine dissolved was analyzed by employing UV absorption at the wavelength of maximum absorbance, about 302 nm, on filtered portions of the solution under test suitably diluted with the dissolution medium. Tablets were retained in proper order so that each could be returned to its respective vessel later. To dry, the tablets were blotted with a paper towel and then, immediately, for the buffer stage pH 6 was performed. After 1 h, the 50 mL aliquot was removed. The Mesalamine dissolved was determined by employing UV absorption at the wavelength of maximum absorbance, about 330 nm, on filtered portions of the solution under test suitably diluted with the dissolution medium. In the buffer stage pH 7.2, 50 mL of sodium hydroxide solution was added to each dissolution vessel to adjust to a pH of 7.2. The Mesalamine dissolved was determined by employing absorption at the wavelength of maximum absorbance about 332 nm on filtered portions of the solution under test, suitably diluted with the dissolution medium.

Mechanism of drug release and data analysis

The cumulative amount of Mesalamine release from the formulated tablets at different intervals were fitted to the following plots, cumulative % drug release versus time (zero order kinetic model); log cumulative of % drug remaining versus time (first order kinetic model); cumulative % drug release versus square root of time (Higuchi model); log cumulative % drug release versus log time (Korsmeyer model) and cube root of % drug remaining in matrix versus time (Hixson-Crowell cube root law) to characterize the mechanism of drug release.

In zero order kinetics, it describes the system in which the drug release rate is independent of its concentration.

$$Qt = Q_0 + K_0 t \quad (1)$$

Where, Qt = amount of drug dissolved in time t and the $Q_{0 =}$ initial amount of drug in the solution, which is often zero and K_0 is the zero order release constant. If the zero order drug release kinetics is obeyed, then a plot of Qt versus t will give a straight line with a slope of K_0 and an intercept at zero.

First order kinetics describe the drug release from the systems in which the release rate is concentration dependent.

$$\text{Log } Qt = \log Q_{0 +} \text{ Kt / 2.303} \quad (2)$$

Where Qt is the amount of drug released in time t. Q_0 is the initial amount of drug in the solution and k is the first order release constant. If the first order drug release kinetics is obeyed, then a line with a slope of Kt/2.303 and an intercept at t = 0 of log Q_0 is obtained.

In the Higuchi model, the fraction of drug release from an insoluble matrix proportional to the square root of the time-dependent process based on Fickian diffusion is described.

$$Mt / M\alpha = kH\ t^{1/2} \quad (3)$$

Where Mt and Mα are cumulative amounts of drug release at time t and infinite time, and K_H is the Higuchi dissolution constant reflection formulation characteristics. If the Higuchi model of drug release (that is Fickian diffusion) is obeyed, then a plot of Mt/M α versus $t^{1/2}$ will be a straight line with a slope of K_H.

The Korsmeyer–Peppas model or the power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in the following equation:

$$Mt / M\infty = Kt^n \quad (4)$$

$$Log\ [Mt / M\infty] = log\ k + n\ log\ t \quad (5)$$

Where Mt and M α are cumulative amounts of drug release at time t and infinite time (that is the fraction of drug release at time t), k is the constant incorporating structural and geometrical characteristics of the controlled release device and n is a diffusion release exponent indication of the mechanism of drug release for drug dissolution. To characterize the release mechanism, the dissolution data {Mt / M ∞ < 0.6} are evaluated. A plot of log {Mt / M∞} versus log t will be linear with a slope of n and intercept, giving the value of log k. Antilog of log k gives the value of k.

Korsemeyer derived a simple relationship that described the drug release from a polymeric system Eq. (5). To determine the mechanism of drug release, first, 60% drug release data were fitted in the Korsmeyer–Peppas model:

$$Mt/ M\infty = Kt^n \quad (6)$$

Where Mt / M∞ are fractions of drug released at time t, k is the rate constant and n is the release exponent. The "n" is an exponent used to characterize different release mechanisms for cylindrical-shaped matrices. If the exponent is $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is a non-Fickian anomalous diffusion. An exponent value of 0.89 indicates case-II transport or typical zero order release. If $n > 0.89$, it is super case transport.

In the Hixon–Crowell cube root law, the equation can be written as follows:

$$Q_0^{1/3} - Qt^{1/3} = K_{HC}\ t \quad (7)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the tablet and K_{HC} is the rate constant for the Hixson–Crowell rate equation. The Hixson–Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles of tablets.

Statistical analysis

Linear regression analysis was performed to compare the mechanism of drug release rate of the different formulations.

RESULTS AND DISCUSSION

Tablets were compressed successfully after preformulation studies and did not require any change in the formula. The prepared uncoated tablets were smooth and shiny and any tablet manufacturing defects were not observed. The FTIR analysis indicates that there is no significant difference in the spectra of drug raw material and drug mixed with other excipients used in the formulations. The drug and various excipient mixtures also exhibited all characteristic bands as in the spectrum of Mesalamine, excluding the possibility of any interaction, chemical and functional group change during the processing of the formulation [Figures 1 and 2].

DSC provides the information on the physical characteristics of the sample. Any significant changes in the thermal behavior of either a drug or a polymer demonstrates the possible interaction of the drug and the polymer. According to the thermograms, Mesalamine presented a sharp endothermic peak at 286.6°C, corresponding to the melting point of the amorphous drug. However, the melting point was observed with less intensity at 286.16°C [Figures 2 and 3] as there was not much difference in the thermal behavior of the drug in the thermogram of the drug and that of the formulation. It can be confirmed from the DSC analysis that the drug is in the pure state in the formulation without interacting with the polymer [Figures 3 and 4].

All batches of Mesalamine tablets were coated with pH-dependent polymer (Eudragit L100) and HPMC E15 LV. The pH-sensitive polymer Eudragit L100 was chosen to coat the tablet because of its pH sensitiveness in the colonic region, where it dissolves to release the drug. Eudragit L, S and FS types are used as an enteric coating soluble at different pH values, e.g. Eudragit L is soluble at pH > 6, whereas Eudragit S and F are soluble at pH > 7. It was decided to choose Eudragit L100 for coating because it is soluble in intestinal fluid, and the progressive increase in the GI pH may influence the tablet to start dissolve when it reaches the intestinal fluid and, by the time it reaches the large intestine, maximum drug release can be achieved. In the coating solution, HPMC E 15 LV was added in all five formulations (FM1-FM5) to improve the perfection and quality of the coating. The purpose of incorporation HPMC E 15 LV to the coating was to improve the physicochemical property of the coating film, such as ductility, toughness and elasticity.[23,24] Such film may provide expected controlled release of the drug in the small intestine by offering the increased permeability properties of the fluids present in the colon.[25,26] The Eudragit L100 proportion was proportionately increased when the proportion of HPMC E 15 LV increased by meager quantities. The percentage weight gain of the tablet after the coating was maintained at 8% for

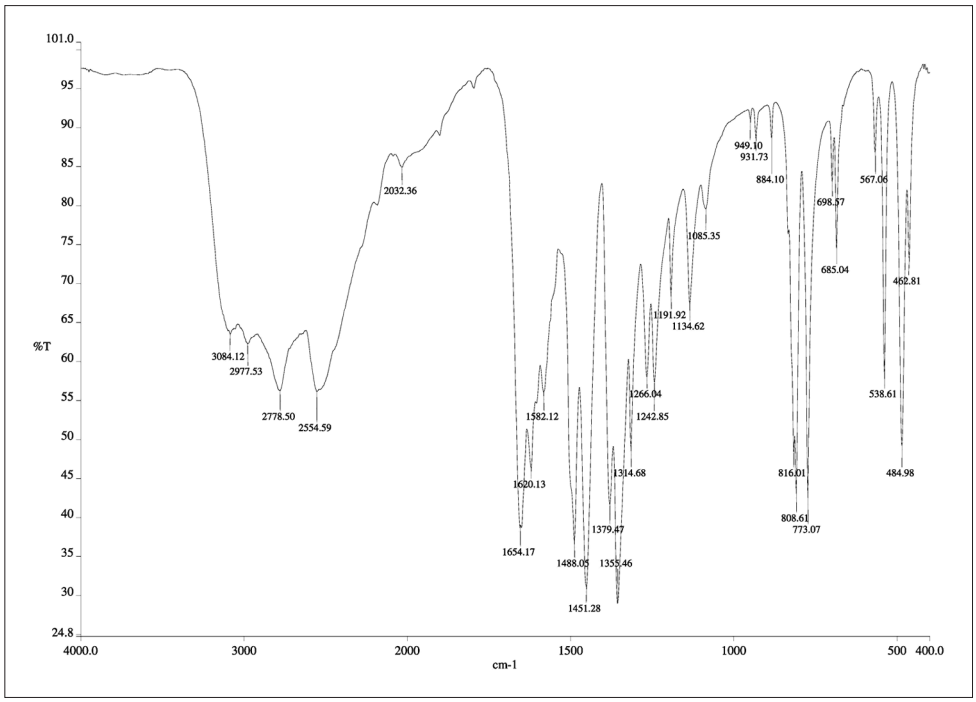

Figure 1: Infrared spectrum of Mesalamine

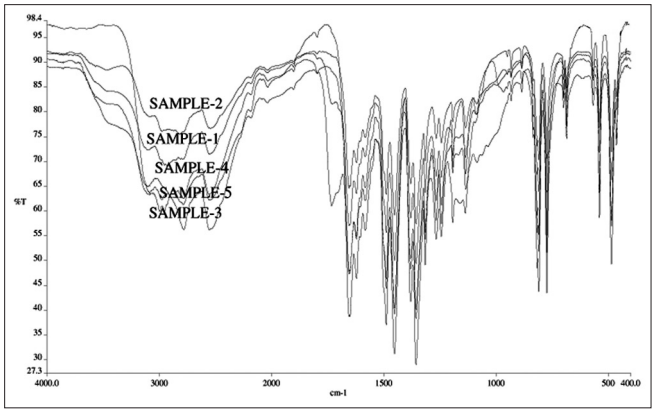

Figure 2: Overlay spectrum of Mesalamine with other ingredients - samples: (1) Eudragit L100 + Mesalamine, (2) HPMC + Mesalamine, (3) MCC(Micro crystalline cellulose) + Mesalamine, (4) Mesalamine + Eudragit L100 + HPMC + PVP k30 + MCC, (5) Mesalamine

all the tablet formulations. Coating with polymer solution more than this concentration was found to be problematic, and significant tablet agglomeration was experienced during coating because of the thermoplasticness and tackiness of the Eudragit coating system. Because of this, the formulations FM4 and FM5 appeared with uneven coating and the surface of the tablet was rough after coating. In the case of FM1, FM2 and FM3, the coating was smooth and elegant. This was decided after assessing the variety of the formulation parameter (concentration of the polymer coating solution, proportion of polymer) and processing factors (spray rate, atomizing pressure and bed temperature), and suitable parameters were adopted to improve the quality of the coating. It was understood from the trials that coating could be possible below 8% and, above this concentration, there will be difficulties in getting the successful coating (without agglomeration and uniform coating thickness) on the tablet. The physicochemical parameters of the coated tablets are shown in Table 3. The weight variation was within the acceptable limit, and the hardness was set to 5–7 kg ± 5 kg. The friability was found to be within limits. The length and breadth of the tablet were found to be fixed according to punch size. Size and thickness were controlled as well by fixing the tablet weight and thickness constant; the surface area and volume were essentially made constant. The thickness of the tablet after coating was found to be between 5.78 mm and 6.07 mm, and the length of the tablet was between 19.01 mm and 19.15 mm. Almost all the tablets contained 400 ± 5 mg of Mesalamine, which was confirmed by suitable the UV spectrophotometric assay procedure. The mean drug content value was found to be satisfactory with pharmacopoeial limits. The drug release in tablets was found to vary with increasing concentration of the Eudragit L100. The different pH conditions had different impacts on the drug release.

All the formulations (FM1–FM5) of Mesalamine tablets were coated with coating solution up to 8% total weight gain of the tablet. In order to meet the USP criteria for the enteric performance, the tablets were tested in 0.1 N HCl (for 2 h). All the coated tablets passed the enteric performance test at the selected level of 8% of the coating. The release pattern of Mesalamine-coated tablets of different batches (FM1-FM5) is shown in Figure 5. The data clearly showed that the delayed release pattern was achieved with 8% weight gain. The tablets

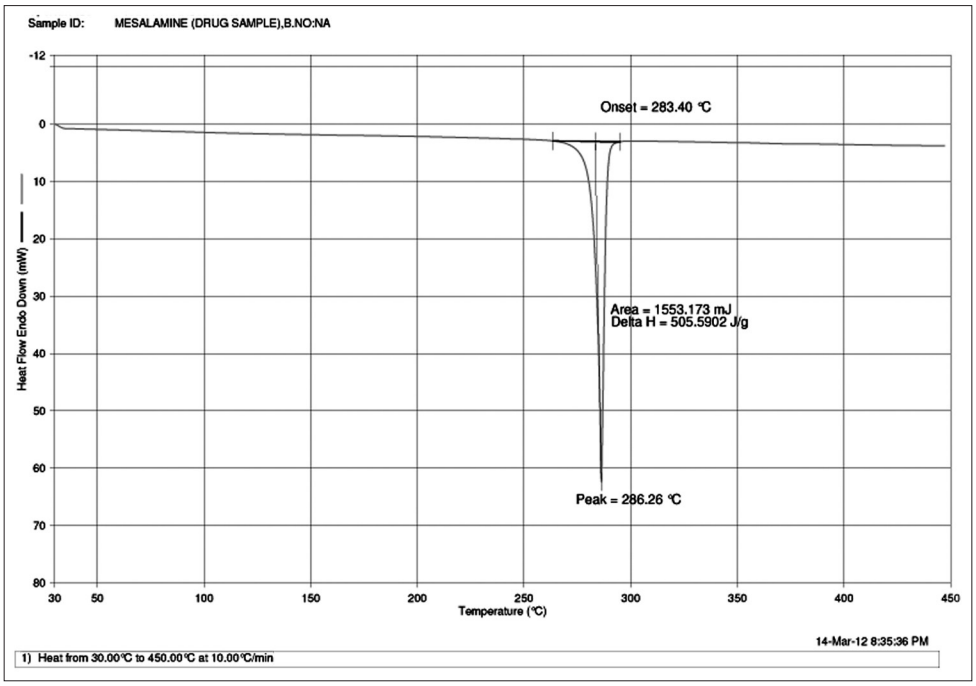

Figure 3: DSC thermogram of Mesalamine pure drug

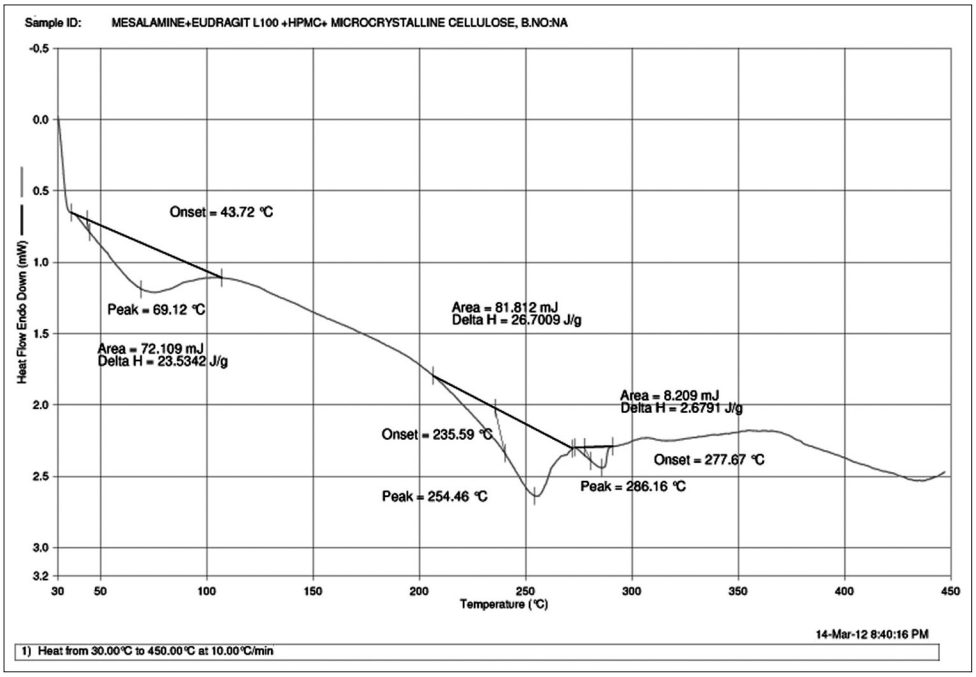

Figure 4: DSC thermogram of Mesalamine with ingredients in the formulations

Table 3: Physicochemical parameters of Mesalamine tablets coated with Eudragit L100

Batches	Content uniformity (%)	Uniformity of weight (mg)	Hardness (kg)	Friability (%)
FM1	99.87±0.12	824±0.010	6.1±0.53	0.0234
FM2	100.79±1.24	802±0.005	5.1±0.89	0.0435
FM3	102.66±3.02	803±0.012	5.7±0.67	0.0623
FM4	98.01±4.99	801±0.030	6.2±0.43	0.0409
FM5	106.10±0.90	804±0.005	6.2±0.32	0.0311

coated with Eudragit L100 could control the drug release from all the batches of the tablets until then the tablets reach the colon. A dissolution study was designed based on the pH condition of the colon. The study was conducted with the pH of 0.1 N HCl with two buffer stages, namely pH 6 and 7.2 according to the USP. All the batches (FM1–FM5) were subjected to drug release profile studies. All the batches of tablets were exposed to 0.1 N HCl, and the amount of drug released in this acid stage was found negligible. It reveals that all the batches passed the enteric performance test. The batches FM1 and FM2 released more or less the same amount of the drug after 10 h, which were about 57% and 49%, respectively.

As anticipated, the difference in pH profiles significantly influenced the drug release profiles of the tablets. Surprisingly, in case of FM4 and FM5, it was diverse even although the polymer (Eudragit L100) was higher in these formulations but the drug release profile was a bit quicker than the FM2 and FM3, and it was unexpected. It may be that because of the particular concentration, the higher amount of polymer (Eudragit L100) formed the more uneven coating on the tablet. This uneven surface is observed with thin coating areas that are considered as weak points or thin areas of coating. These pores formed were acting as the point for early penetration of media into the core tablet, resulting in quicker disintegration of the tablet by breaking or damaging the polymer film (Walker *et al*. 1997). However, if we see the picture of the tablets [Figure 6] FM1, FM2 and FM3, the polymer coatings were expanded and the pores present in that coating increased in diameter or size, which allowed the passage of the medium inside the core and simultaneous leaching of dissolved drug outside the coating through the pores. In FM4 and FM5, there was a clear damage and appearance of core tablet was observed after the few hours of dissolution experiment. This is indicative of coating film damage, which encourages the quick disintegration of the tablet in these batches. Not just a single tablet but all the tablets that were taken to the dissolution studies faced the same problem of quicker coating film damage on the surface of the tablet. This problem was not controlled even after reducing the RPM of the paddle. This clearly indicates that poor coating on the surface of the tablet leads to this quick film damage. The poor coating was the combined effect of the various factors, among which concentration of the solution was the significant one. Between five-formulation higher concentrations of Eudragit L100 were used in FM4 and FM5, which led to agglomeration and damaged the film surface. The drug release from formulation FM4 and FM5 were 44% and 62%, respectively, after 10 h of the drug release study. The concentration of polymer used in the FM3 was ideal for proper colonic delivery with elegant coating appearance, which released less than 5% of the drug after 4 h of the study, and the drug release was extended up to 20 h. The drug release was constantly increased with progression of time. After 10 h, the drug release was 45%. Although the formulations FM1 and FM2 appear to be good in the coating, but the drug release profile and pattern of drug release was found to be better in FM3, and it was subjected to stability studies.

Stability studies

The coated tablets of FM3 were observed for changes in the physical nature and tested for drug content. The in vitro drug release studies were also performed again to analyze and determine whether the storage of the tablet caused any impact on the drug release profile or not. No remarkable physical changes in the tablet were observed. The drug content analysis indicated that there was no change in the content with 99.4 ± 2.4. The dissolution testing reports before the storage of the FM3 batch was found to be 78.06% ± 0.3.1 mg, whereas after the storage the drug release was found to be 80.1% ± 0.37 mg. There was no significant difference observed in the mean Mesalamine release from the FM3-coated tablets after being stored for 3 months at 40°C/75% RH. Stability study reports indicated that the tablet was stable at the different storage conditions, but that elaborate studies were required to determine the exact shelf-life.

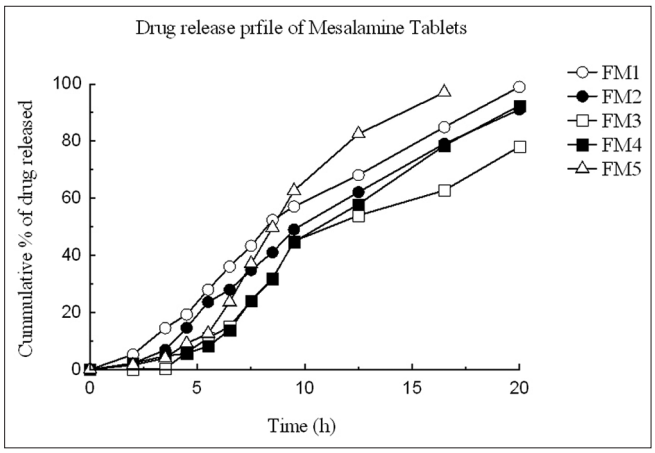

Figure 5: Drug release profile of Mesalamine colon-targeted tablets

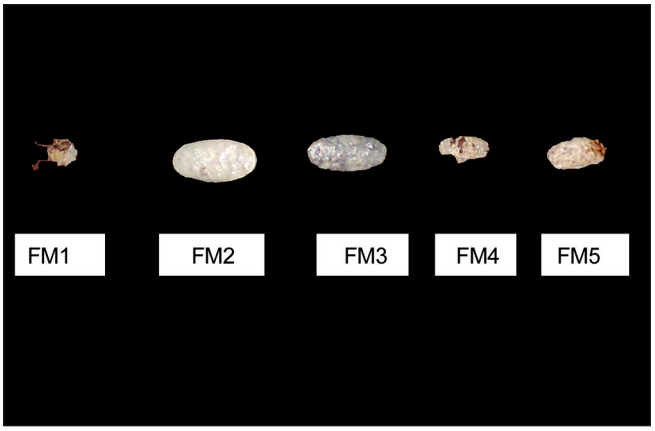

Figure 6: Physical changes in the tablets after 8 h of dissolution

Release kinetics and mechanism of drug release

Drug release kinetics were fitted with different mathematical models such as zero order, first order, Higuchi, Korsemeyer–Peppas and Hixson–Crowell release. This demonstrates the pattern of the drug release. The release constant value, R^2, and "*n*" value of release Korsemeyer–Peppas of all the formulations are depicted in Table 4. The release of drug from the formulations fitted with various models in different degrees. The formulation FM1 fits with all the release kinetic models in which Korsemeyer–Peppas was found to be the predominant release mechanism, followed by the Hixson–Crowell release model. Formulations FM2 and FM3 showed the combination of all the kinetics. In formulation FM2, the Hixson–Crowell release model was found to be the principal release mechanism. Formulation FM4 and FM5 obeyed all the release models. The predominant release mechanism was Korsemeyer–Peppas release in FM5, whereas in FM4 the Hixson–Crowell release kinetics dominated the remaining mechanisms.

By incorporating the first 60% of the drug release data, the mechanism of drug release can be revealed according to Korsmeyer–Peppas when "n" is the release exponent, which indicates the mechanism of drug release; Fickian diffusion release and a case II report relaxational release are the limits of this phenomenon. Fickian diffusion release occurs by the usual molecular diffusion of the drug due to chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stress and state transition in glassy polymers that swell in biological fluids. This also includes polymer destanglement and erosion. The mechanism of drug release was as described earlier, and ranges were given for the cylindrical shape (e.g., tablet). The "*n*" values of FM1–FM5 found to be 1.54, 2.01, 1.86, 1.94 and 2.47, respectively, were an indication of significant super case II transport. Almost all the mechanisms the release involved in the drug release of the formulations (FM1–FM5) were subjected to drug release studies. The zero order release was demonstrated by almost all the formulations, indicating that drug release was independent of concentration and time. First order release was observed with all the formulations except FM5, which revealed that along with zero order release, concentration-dependent release also takes place. All the formulations showed the Hixson–Crowell release mechanism as the principal or a predominant release mechanism in the release of the drug, which shows the progressive dissolution taking place as a function of time. This was responsible for the changes in the surface area of the tablets. The Hixson–Crowell cube root model describes the changes in the surface area of the coated tablets. All formulations obeyed Korsemeyer–Peppas release, confirming that the diffusional release constant "*n*" value can be considered for explaining the exact release mechanism of the formulations. The results revealed that the super case II transport is a significant release mechanism involved in the release of many formulations. The applicability of the formulation of the equation indicated that the change in surface area and diameter of the tablet with the progressive dissolution of the core tablet through the expanding tablet was a function of time. The value of the release exponent in FM2 and FM5 was found beyond the limits of the Korsemeyer–Peppas model (power law). The power law can only give limited insight into the exact release mechanism of these formulations.

CONCLUSION

Mesalamine delayed release tablets was prepared successfully by coating with Eudragit L100 and HPMC E15 LV as polymers to retard the drug release and achieve a required dissolution profile. The drug release studies revealed that the pH-sensitive Eudragit L100 can retard the drug release from the tablet until the tablet reaches the colon. But, the fluctuations in the pH of the GI tract and lowered pH in the diseased state may limit the drug release from the polymer. The presence of HPMC E15 LV may increase the hydrophilicity of the coating film and ensure the proper drug release in the target site though the lowered colonic pH condition in diseased state and less fluid content of the colonic area is the limiting factor for the drug release. The coated tablets of FM3 released maximum amount of drug in pH conditions of the colon and the terminal part of the intestine. Drug release kinetics indicated that drug release was best fitted to the Hixson–Crowell release kinetics. The

Table 4: Release kinetics parameters of Mesalamine colon-targeted tablets

Model	Parameter	FM1	FM2	FM3	FM4	FM5
Zero order	Ko (h^{-1})	5.27	5.01	4.46	4.46	6.99
	R^2	0.977	0.982	0.950	0.960	0.937
First order	K_1 (h^{-1})	0.054	0.55	0.03	0.06	0.10
	R^2	0.979	0.959	0.970	0.922	0.896
Higuchi	K_H ($h^{-1/2}$)	31.93	31.08	28.34	33.84	42.05
	R^2	0.992	0.99	0.958	0.951	0.939
Peppas	*n*	1.54	2.01	1.86	1.94	2.47
	R^2	0.994	0.971	0.918	0.951	0.98
Hixson–crowell	K_{HC} ($h^{-1/3}$)	–0.14	–0.14	–0.10	–0.15	–0.24
	R^2	0.993	0.989	0.976	0.966	0.930

"*n*" value of Korsmeyer–Peppas confirmed that the complex mechanism of swelling diffusion and erosion was involved in the drug release. Hence, drug release was controlled by more than one process. This study suggests that this simple coating technique may be considered as an alternate method for delivery of drug to the colon to achieve better targeting and pharmacological effects in the treatment of IBD.

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