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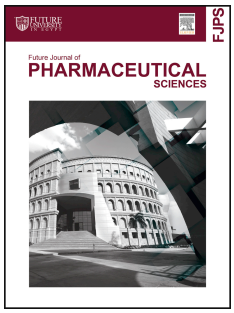

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Swapnoleena Sen, Moumita Das, Bijaya Ghosh, L.K. Ghosh

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Design, development and in vitro evaluation of sequentially optimized mesalamine tablets for optimum colonic delivery.

Swapnoleena Sen[1], Moumita Das[1], Bijaya Ghosh[2], L.K Ghosh[1]

1-Department of Pharmaceutical Technology, Jadavpur University. Kolkata- 700032

2-NSHM College of Pharmaceutical Technology, 124 BL Saha Road, Kolkata-700053

Corresponding author-

Moumita Das

Department of Pharmaceutical Technology, Jadavpur University. Kolkata- 700032

E mail: mmtdas@yahoo.co.in

Phone: +91 9051117332

1. Introduction

Mesalamine has been used for treatment of diseases like ulcerative colitis and chron's disease which affect the colonic lumen and require local drug action, rather than systemic effect [1, 2]. Several research workers have worked on delayed release devices (with enteric coatings which can bypass the upper gastrointestinal tract) which can thereafter release the drug immediately or sustain drug release in the form of matrix tablets, capsules, pellets or multiparticulate systems [3, 4, 5, 6]. They utilized pH dependent, time dependent approaches or polysachharide based systems or osmotic delivery systems [7, 8, 9].

For colon targeted systems, two aspects have to be considered. First, the delivery device should be able to avoid drug release in the upper parts of gastrointestinal tract including the stomach and small intestine and secondly, the dosage form should be able to supply the drug in optimum therapeutic concentrations in the colonic lumen for intended duration of time. The retention time of dosage forms in the stomach usually averages to 2 h and in the small intestine from 3-4 h. Therefore, the lag time of drug release should be around 5-6 h [10]. This can be done with enteric coating with suitable enteric polymers like Eudragit S100. However, Eudragit coated formulations may start releasing the drug in the small intestine, above pH 7 [11]. Therefore, the coating formulation should be optimized such that the effective drug release starts after 6 h of dissolution. After the enteric coat gives way to the core tablet and drug release starts, the drug release should be sustained in a manner that the drug is available at the site of action for required duration. In case of ulcerative colitis, the affected part may extend from small sections to the entire colon [12]. Therefore the dosage form designed should be able to release drug at a sustained rate while travelling through the entire length of colon. The colonic residence time

again varies from 6 to 48 h [13]. Therefore, the dosage form intended to serve the entire colonic lumen should have a sustained release property to maintain the release throughout the day.

The volume of colonic fluid is much less than that of the upper parts of the gastrointestinal tract (stomach and small intestine) and varies from about 12-13 ml (fasted state) to about 18-26 ml (fed state) or an average volume of 15 ml [14]. From the pharmacokinetic data, previously obtained for the drug it has been found that, a 3 g tablet attains a concentration of 1500 µg/ml of the drug in the colonic fluid [15].Considering the data, a target was set to achieve a total concentration of drug of around 22,500 µg/ml or 22.5 mg/ml in the colonic fluid through sustained drug release and this concentration should be maintained to achieve optimum therapeutic efficacy with the developed formulation.

Therefore, in the present study, sustained release formulation would be developed and optimized such that the drug release starts after 6 h of dissolution and thereafter sustained maintaining a drug concentration of above 22.5 mg/ml in the dissolution media.

2. Materials

Mesalamine (98 % from Lab solution, Kolkata, India), Hydroxypropylmethylcellulose K15M (99 % pure from LobaChemie, Mumbai, India), Eudragit S100 and Trisodium orthophosphate (98 % and 99.99 % pure respectively from Yarrow Chemicals, Mumbai, India), Microcrystalline cellulose (99 %), Talc (98.99 %), Magnesium Stearate (99%), Acetone (99.9 %), Isopropyl alcohol (99.9 %), Dibutyl Pthalate (99.9 %), Potassium Chloride (98.99 %), Hydrochloric acid (37.5 %) were commercially procured from Lab Solution, Kolkata, India .

3. Methods

3.1. Drug-Excipients compatibility study

For ensuring compatibility between drug and different excipients, FTIR spectrum of drug, FTIR spectrum of polymers (HPMC and Eudragit) and FTIR spectrum of physical mixture of drug with all other excipients were obtained. The physical mixture was prepared using drug and excipients in the same quantities as used for preparation of core and coated tablets (400 mg of drug, 30 mg of HPMC K15 M, 183 mg of MCC, 6 mg of talc and magnesium stearate, 27.5 mg of Eudragit S100 and 6.05 mg of dibutylphthalate). FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Bruker Alpha T spectrophotometer. Samples were prepared in KBr disks by means of a hydrostatic press. The samples (Mesalamine, physical mixtures) were previously ground and mixed thoroughly with potassium bromide, at 1:20 (Sample: KBr) ratio, respectively. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

3.2. Formulation of core matrix tablets

Initially six batches of core matrix tablets were formulated and the best was chosen with respect to sound physical parameters and suitable drug release profile including burst release and sustained drug delivery from the tablets. Coating optimization was then performed with the chosen formulation.

For formulation of matrix tablet of mesalamine, Hydroxypropylmethylcellulose K15M (HPMC K15M) was chosen as matrix forming release retardant polymer, Microcrystalline cellulose (MCC) as diluent, talc as glidant and magnesium stearate as lubricant. The percentage of HPMC K15M was varied to get optimal sustained release property of tablet. The tablets were prepared by wet granulation method. Initially drug, polymer, MCC were measured and sifted through sieve #40 and then granulated with purified water. After drying in the hot air oven till constant

weight reached, the granules were passed through sieve #20. Talc and magnesium stearate were passed through sieve #60 and the mixture was blended homogeneously with the granules to obtain the final mix, which was then compressed by tablet punching machine using flat punches (10 mm).

3.3. Evaluation of core matrix tablet

The core tablets were evaluated with respect to various physical parameters including weight variation, hardness, thickness and diameter, friability and content uniformity tests and in-vitro drug release. For determination of weight variation, the weights of a batch of 30 tablets were taken and the average calculated. The difference in weights of individual tablets from the average weight was determined. Hardness of the tablets was measured with Monsanto hardness tester for a batch of 10 tablets to determine the crushing strength of the tablets. Thickness and diameter of the tablets were measured with the help of digital vernier calipers for batch of 10 tablets. The friability of the tablets was determined in a Roche friabilator to determine the percentage of chipping or breakage of the tablets.

To determine the release profile of 5-Fluorouracil, 400 mg of the drug was mixed with microcrystalline cellulose (188 mg), 6 mg of talc and 6 mg of magnesium stearate and directly compressed. In-vitro release study was performed for this formulation and all the other core tablets using USP dissolution type II apparatus, in 900 ml of phosphate buffer pH 6.4 at 75 rpm and 37±0.5°C. Evaluating the release profiles of the core tablets, the best one was chosen and coating formulations were applied on it.

Evaluation of release kinetics

The release data of the tablets were fitted into different release kinetics model equations like zero order, first order, higuchi and korsemeyer-peppas model equations to determine the release mechanism from the matrix tablets.

3.4. Coating with Eudragit S 100 solution

Six coating formulations, with different concentrations of Eudragit S 100 and Dibutyl phalate were developed and coatings were applied on the chosen core tablet [16, 17]. Thereafter, sequential simplex optimization was used to optimize the coating formulation, based on the responses obtained for the initial formulations.

Coating solutions were prepared in the solvent system consisting of acetone: isopropyl alcohol in 1:1 proportion and the solutions were stirred for 17 h to achieve proper plasticization of the polymer [18]. The stirring time was optimized to achieve proper plasticization of Eudragit S100. The core matrix tablets were dipped into the coating solution and air dried for 30 min repeatedly, till the desired weight gain of the tablets was obtained. The tablets were then left overnight in petri dishes, so that complete removal of solvent may take place.

3.5. Evaluation of coated tablets

The coated tablets were evaluated for various physical parameters like weight variation, hardness, thickness and diameter and in-vitro dissolution studies, using standard procedures. Dissolution studies were conducted in changing media (HCl buffer, pH 1.2, phosphate buffer pH 7.4 and phosphate buffer, pH 6.4). The change in pH of the dissolution medium was obtained adding trisodium orthophosphate in suitable amounts [19]. The other conditions for the study were similar as in the case of core matrix tablets.

To compare the release profile of optimized tablet against a marketed formulation, dissolution tests were carried out on six tablets of a marketed formulation, MESACOL, carrying 400 mg drug.

3.6. Optimization of coated tablets

In the present work, sequential simplex design was used for optimization of coating with respect to two parameters, namely, cumulative release during lag time of 6 h and hourly drug release rate after lag time. The high and low ranges of the formulation factors were defined and six initial formulations were designed. The levels of factors for the initial set of experiments were given in Table 1.

Table 1. Levels of factors for various coating formulations

Batch No.	Eudragit S 100 %(w/v)	Dibutyl phthalate % w/w of Eudragit S 100	Weight gain of core matrix tablet (%)
C1	10	10	8
C2	10	20	8
C3	15	10	5
C4	15	10	8
C5	15	20	5
C6	15	20	8
C7	11	22	5.6

3.6.1. Evaluation of response

The responses of the various formulations were evaluated by the following equations.

$$R_n = \frac{H-X}{H-M} \times 100 \qquad \text{Eq. 1}$$

$$R_n = \frac{X-M}{H-M} \times 100 \qquad \text{Eq. 2}$$

Here Rn was the normalized response, X was the original unnormalized value and M and H were the lowest and the highest values respectively for the specific response. Cumulative release during lag time was normalized using Eq. 1 and hourly drug release rate after lag time was normalized using Eq. 2. The overall response of the formulations was determined by the following equation.

$$Rt = 0.50R_1 + 0.50R_2 \qquad \text{Eq. 3}$$

Here, Rt represents the total response whereas, R1 and R2 represent the normalized response for, cumulative release during lag time of 6 h and hourly drug release rate after lag time, respectively [20].

3.6.2. Calculation of response and designing coating formulations for optimization of coating

Sequential simplex design was used to optimize the three factors such as the percentage of polymer and percentage of plasticizer in the coating solution and percentage of weight gain of coated tablets. The high and low of the factors were decided and initial six formulations were designed. According to the principal of sequential simplex the batch giving worst response was

eliminated and the factors of the retained batches were averaged (P). W was the level of factor for the worst batch.

The level of factors for the first derived formulation was obtained from the equation:

{P+(P-W)} Eq. 4

The new sets of formulations (the previously retained formulations + new set of formulation) were graded in terms of response. If the new formulation got the first rank (best response) then equation 5 was used to calculate levels of factors in the next derived formulation.

{P + 2(P-W)} Eq. 5

If it got the $(n+1)^{th}$ rank or $(n+2)^{th}$ rank, then equations 6 and 7 were used for derivation of the next formulations, respectively [21].

{P + 0.50(P-W)} Eq. 6

{P-0.50(P-W)} Eq. 7

The process was continued until a suitable formulation with calculated response close to the target response of 100 was obtained.

4. Results and discussions

4.1. FTIR compatibility studies

Observations from the FTIR spectra were enlisted in Table 2. From comparing the spectra of drug and physical mixture of drug and excipients (Fig 1), it was observed that all the major peaks in the spectrum of drug were also present in the spectrum of the physical mixture. Mechanism of action of mesalamine involves reversible binding to the active sites of cyclooxygenase enzymes

COX 1 and COX 2. The presence of carboxyl group attached to a hydrophobic aromatic group is important for interaction with the COX active site [22]. Thus, the carboxylic acid group is the major contributor in the activity of mesalamine, apart from other functional groups like hydrophobic aromatic groups, C=C, C-H, O-H groups, etc. Therefore, modification of these functional groups due to incomaptibilities between drug and excipients may result in loss of activity of drug [23]. However, the FTIR studies proved that the major functional groups were present in the physical mixture and therefore, no significant interaction was reported between drug and excipients.

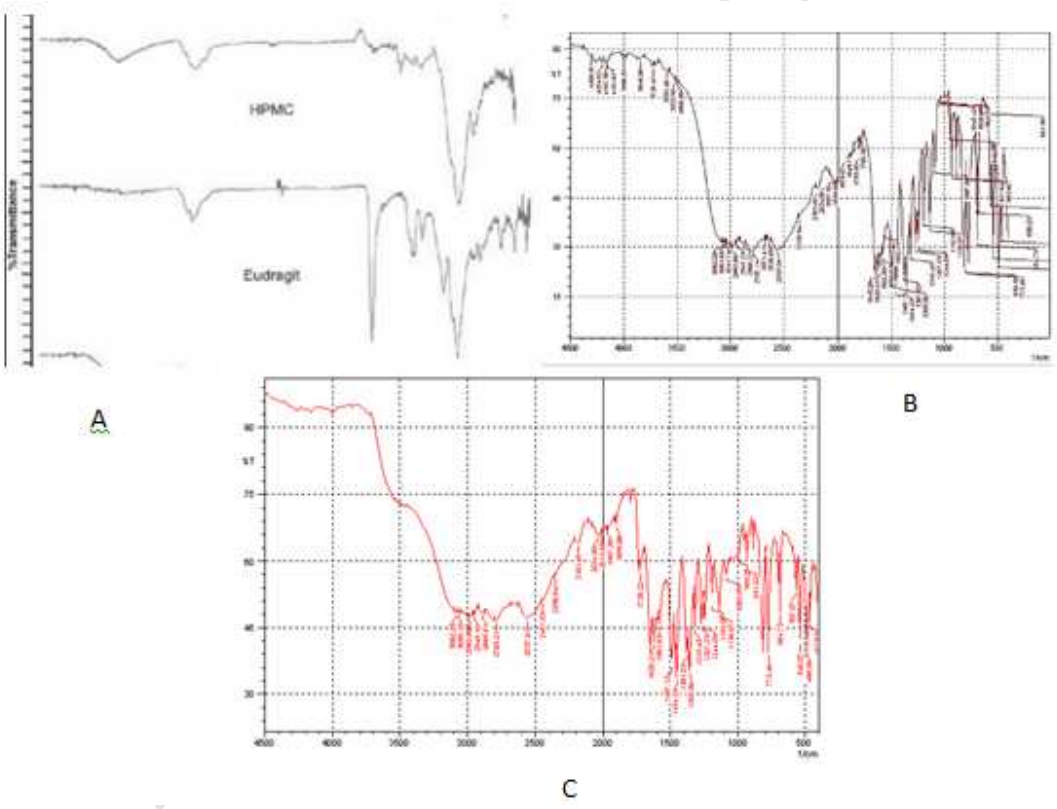

Fig. 1. FTIR spectrum of A- HPMC and Eudragit; B-Mesalamine; C- Physical mixture of Mesalamine with excipients

Table 2. Observations and analysis from FTIR studies

Functional groups	Absorption range	Matching peaks
COO-H	3200-2200	2358.94
C-H	3100-2700	3082.25, 2983.88,
C=O	1850-1640	1899.88
C=C	1680-1590	1620.21
Aromatic	1600-1500	1581.63

4.2. Formulation and evaluation of core matrix tablets

Mesalamine (400 mg), talc (6 mg) and magnesium stearate (6 mg) were used in fixed quantities to prepare the core matrix tablets. The amounts of the variables in the core matrix tablets were presented in Table 3. The final weight of the tablet was 600 mg. HPMC K15M was used as a release retardant in the tablets and it also served as a binder. Therefore, no additional binder was used in the preparation of the tablets. The tablets possessed good amount of hardness and friability, and the content uniformity was high with less weight variation (Table 4).

Table 3. Compositions of core matrix tablets of mesalamine

Batch code	HPMC K15M (mg)	HPMC K15M (%)	MCC (mg)
F1	120	20	93
F2	75	12.5	138
F3	60	10	153
F4	45	7.5	168
F5	30	5	183
F6	12	2	213

Table 4. Physical parameters for various core formulations

Batch code	Friability (%)	Hardness (Kg/Sq. cm)	Tablet Diameter (mm)	Tablet Thickness (mm)	content uniformity (%)
F1	0.25±0.15	3.20±0.10	10.96±0.05	5.50±0.07	96.00±1.50
F2	0.26±0.09	3.30±0.07	10.97±0.10	5.50±0.05	95.80±0.99
F3	0.49±0.43	2.90±0.25	10.95±0.08	5.46±0.12	97.20±1.25
F4	0.30±0.66	3.00±0.15	10.97±0.11	5.48±0.09	94.60±0.87
F5	0.35±0.25	3.10±0.44	10.97±0.07	5.56±0.04	98.50±1.05
F6	0.32±0.06	3.40±0.34	10.98±0.09	5.52±0.05	94.70±0.54

The directly compressed tablet containing 5-Fluorouracil released the whole drug within 1 h in the dissolution study. Six batches of core tablets were prepared with the variant HPMC K15M in the range of 2 % w/w to 20 % w/w (Table 3). The formulations F1 to F4 contained greater amounts of HPMC K15M, which is a high molecular weight diffusible polymer. Thus, these formulations exhibited slower release. The formulation F5 (with 5 % w/w of HPMC K15 M) gave a moderate burst release and sustained release thereafter, with approximately 70% drug release within 10 h (Fig. 2). Formulation F6 with only 2 % w/w of the polymer could not sustain the release as required. Therefore, batch F5 was chosen for coating optimization.

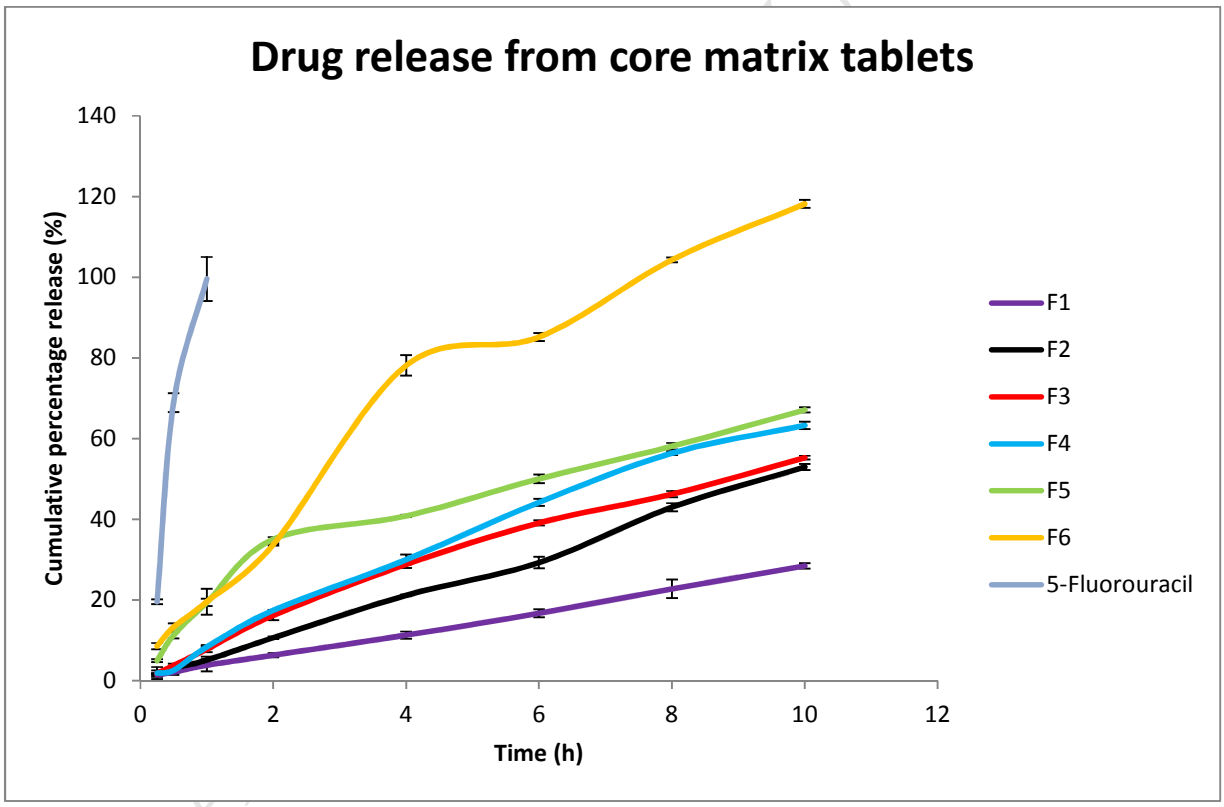

Fig. 2. Drug release from core matrix tablets

Evaluation of release kinetics

Formulations F1, F2 and F4 followed zero order kinetics (release was independent of drug concentration) whereas F3, F5 and F6 followed higuchi model (drug release from matrix system occured through diffusion). 'n' values of F1, F5 and F6 were <0.89, which indicates non-Fickian transport. 'n' values of F2, F3 and F4 were >0.89, which indicated super case II transport [24].

Table 5. R^2 values for Formulations according to different kinetic models

Batch No.	Zero order	First order	Higuchi model	n value
F1	0.999	0.884	0.959	0.823
F2	0.997	0.876	0.955	0.922
F3	0.983	0.781	0.994	0.931
F4	0.988	0.785	0.982	1.001
F5	0.925	0.699	0.983	0.657
F6	0.957	0.832	0.988	0.745

4.3. Formulation and evaluation of coated tablets

The coating solution was prepared with Eudragit S100 as enteric polymer, Dibutyl phthalate as plasticizer and Aceone/IPA as solvent system. The amounts of polymer, plasticizer and weight gain of the coated tablets to achieve desired release profile was optimized using sequential simplex optimization technique, which gives optimization of the results with fewer batches and is based on simple mathematical calculations.

The dissolution studies for the coated tablets were performed in changing buffer media, starting with HCl buffer, pH 1.2. The pH of the stomach in human beings ranges from 1.0-3.5. Thus, pH 1.2 HCl buffer was chosen to mimic the pH conditions of the stomach. The pH of the small intestine (including duodenum, jejunum and ileum) ranges from 5.5-7.5. Hence, the phosphate buffer chosen to mimic the conditions of the small intestine was of pH 7.4. Lastly, the pH of the

colon ranges from 6-7. Hence the pH of the buffer for colonic conditions was chosen to be 6.4 [25].

4.4. Optimization of coated tablets

According to the objective of the study, the coated tablets had to maintain a lag time of drug release within the first 6 h (limits 0-10% cumulative drug release) and thereafter had to maintain a near to constant drug release rate (limits 4-7% per hour average release, accounting to 16 mg to 28 mg of drug release per hour) throughout the day. The lag time should be maintained in order to avoid any drug release in stomach or small intestine and thereafter a constant drug release rate should be maintained to achieve optimum therapeutic efficacy in the colon, as discussed earlier. Therefore, the coating composition and weight gain of the coat should be optimized in such a way that during the lag time, minimum drug release would occur, and thereafter, the release occurs at a controlled rate, which was a challenging task.

Coated formulations C1 and C2 were prepared with same quantity of Eudragit S100 (10 % w/v) and same weight gains but different amounts of plasticizer- 10 % w/w and 20 % w/w of polymer, respectively. The drug release was almost similar, C2 being slightly slower. A burst release was observed after which sustained release was obtained. In case of C3 and C4, the polymer and plasticizer amounts were same (15 % w/v Eudragit S100 and 10 % w/w of plasticizer), but weight gain of C4 was higher than C3. Therefore, the release was sustained more in case of C4, whereas C3 released the whole drug within 8 h. Again for C5 and C6, the polymer and plasticizer amounts were same (15 % w/v Eudragit S100 and 20 % w/w of plasticizer), but weight gain of C6 was higher than C5. As a result, the rate of drug release was low for C6 as compared to C5. From the dissolution results of the six initial coated formulations, it was

observed that drug release was not much affected by amount of plasticizer (dibutyl phthalate), but amount of Eudragit S100 affected the release. Dibutyl phthalate is only slightly soluble in water and did not facilitate the dissolution of the coating [26]. The more the weight gain of tablets and the more the amount of Eudragit S100, the slower was the release [27]. After the six initial formulations were analyzed by sequential simplex, C7 was developed with 11 % w/v of Eudragit S100 and 22 % w/w plasticizer. The formulation was able to avoid drug release in the first 6 h and thereafter sustained the release till 24 h (Fig. 3).

The compositions of initial six batches of coated tablets as per sequential simplex method were given in Table 1. From the dissolution data of these formulations, the responses were evaluated and normalized using equations 1 and 2. The overall response was calculated using equation 3 (Table 5). From the observations of the responses of the initial formulations, C4 was identified as the worst batch. Therefore with equation 4, next formula C7 was derived with 11 % w/v of Eudragit S100 and 22 % w/w (of Eudragit S100) as plasticizer and a coat weight gain of 5.6%. This batch gave the best response of 99.3, when data was evaluated. As it was close to the target of 100, the process of optimization was stopped at this point and formulation C7 was optimized.

Table 6. Response obtained for coated formulations

Batch No.	Response (R)
C1	97.42
C2	91.57
C3	90.32
C4	74.31
C5	85.46
C6	97.09
C7	99.30

When the marketed formulation was evaluated for drug release profile as a comparison, following similar method of in vitro dissolution studies, the drug release started after 4 h of dissolution and release was complete within 1-2 h after that (Fig. 3).

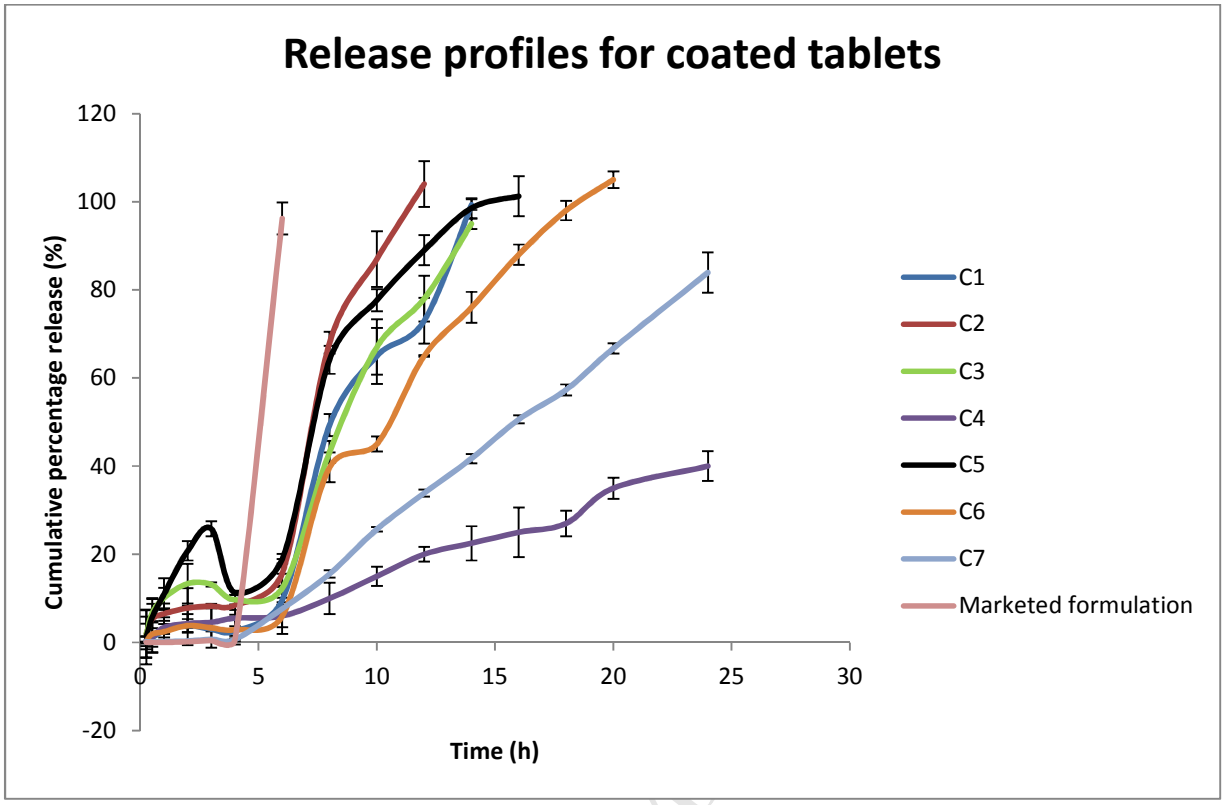

Fig. 3. Drug release comparison of optimized formulation and marketed formulation

5. Conclusion

The aim of the project was to formulate a delayed release tablet better than marketed formulation, which releases the drug at higher pH rapidly and fails to achieve controlled release. The present work deals with the formulation of a controlled release matrix tablet of mesalamine which maintains a lag time of 6 h and ensures sustained release at a rate to achieve desired concentrations of the drug in the colonic lumen and fluid. To meet the conditions, a suitable core tablet was chosen among six initial formulations and then the core tablet was coated with various coating formulations. The coating formulation was optimized by sequential optimization, such that the above conditions were met well.

In the present work, C7 with Eudragit S100 and dibutyl phthalate at concentrations of 11% w/v and 22% w/w of Eudragit S100 and a weight gain of 5.6 % was able to achieve the desired characteristics of the formulation.

6. Acknowledgement

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7. Declaration of Conflicts of interest

The authors report no conflicts of interest.

This article does not contain any studies with human and animal subjects performed by any of the authors.

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