Journal of Pharma Research
Available online through
www.jprinfo.com
Vol. 14 Issues 06, 2025 ISSN: 2319-5622

Original Article

# DESIGN AND EVALUATION OF COLON SPECIFIC DRUG DELIVERY SYSTEM OF MESALAMINE

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**Received on: 01-10-2025 Accepted on: 02-11-2025**

***ABSTRACT***

*As Mesalamine (5ASA) is rapidly absorbed from small intestine, selective delivery of drug to the colon may be regarded as better delivery of drug with fewer side effects and higher efficacy. The aim of the present investigation was to formulate enteric coated sesbania matrix tablets of mesalamine using combined approaches of biodegradable microflora activated systems of sesbania matrix with pH sensitive polymeric coating. FTIR showed no drug polymer interactions. Matrix tablets of mesalamine were prepared by wet granulation with different ratios of sesbania gum. Compressed tablets were prepared and evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, in vitro dissolution using paddle method. All formulations showed compliance with Pharmacopoeial standards. Among different batches formulations showed sustained release of drug for 12 hours with and without rat cecal contents in pH 7 were selected. Optimized formulation is coated with different percentages of Eudragit L 100 and Eudragit S 100 as pH sensitive polymers with 5, 10, 15 and 20% weight gain. The results of drug release studies performed using 0.1N HCl for 2 hrs, phosphate buffer pH 6.8 buffer for 3 hours then the medium was replaced with phosphate buffer pH 7.4 containing rat cecal contents. The drug release of tablets coated with Eudragit S 100 with 20% weight gain showed 99.50% due to the microbial enzymatic activity and therefore site specificity of the dosage form consequently sustained the release of the drug over the period of 24 hours. Formulations containing mesalamine, sesbania gum coated with 6% Eudragit S 100 with 20% total weight gain was a promising formulation for the targeted and extended drug delivery to the colon.*

***Keywords:*** *Mesalamine, Sesbania gum, Colon, Eudragit L 100 and Eudragit S 100.*

## INTRODUCTION

Drug delivery specifically to the colon of the git has gained considerable importance in recent years. A number of colonic diseases could be treated more efficiently by delivering the drug locally in the colon, such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon, and irritable bowel syndrome. Several methods have been developed for confining drug release to the colon. One of the oldest and the most commonly employed method uses enteric polymers as coating materials over tablets, granules, or pellets. These rely upon the difference in pH values in the gastrointestinal tract (GIT).[2] Others include time-controlled release systems,[3] pressure controlled release systems,[4] prodrugs,[5] polysaccharide-based delivery systems[6,7] and osmotically controlled release systems.[8]

Mesalazine, or 5-aminosalicylic acid (5-ASA), has been used for several years in the treatment of inflammatory bowel disease. When pure mesalazine is administered directly in the proximal part of the small bowel or orally as a conventional tablet, it is rapidly and almost completely absorbed, with little drug reaching the distal small intestine and colon [9]. Therefore the premature absorption of mesalazine can be prevented by the preparation of enteric coated tablets or colon-specific dosage forms. Orally administered delayed-release mesalazine acts locally from within the lumen of the inflamed bowel and is partly absorbed into systemic circulation. To prevent proximal small-intestinal absorption, and allow mesalazine to reach the inflamed

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**DOI:** https://doi.org/10.5281/zenodo.17555960

small bowel and/or colon, a variety of mesalazine delivery systems have been developed [9, 10].

Sesbania gum is one of the natural polymers which can be used as a substitute for arabic gum or guar gum because of its similar performances and relatively low price. Sesbania gum is extracted from the seeds of sesbania. It contains high molecular weight hydrocolloidal polysaccharides composed of galactan and mannan units combined through glycosidic linkages are completely digested by colonic bacteria. However, their solubility and swelling properties in aqueous media make them unable to efficiently avoid the release of drugs during the transit through the upper gastrointestinal tract, and imply the combined use of insoluble polymer to assess their integrity until they reach the colon region.[3]

Eudragit polymers are widely used as coating materials in order to achieve either modification of drug release behaviour or taste masking. For the purpose of coating, polymeric films are generally applied to the solid dosage forms using the spray atomization technique. Eudragits are extensively employed as pH-dependent coating polymers in order to attain either enteric effect or colon targeting of drugs. The pH-dependent systems are conventionally designed on the generally accepted view that pH of the human gastrointestinal tract increases progressively from stomach (2.0 -- 3.0) to small intestine (6.5 -- 7.0) to colon (7.0 -- 8.0) [28] (though it has been reported that pH drops slightly in colon and is highest in ileocecal junction [29]). Thus, it is expected that the polymer used as coating material for colon targeting should be able to withstand lower pH value of upper gastrointestinal tract and disintegrate at neutral or slightly alkaline pH of terminal ileum, preferentially ileocecal junction. The most commonly employed Eudragit grades include Eudragit L 100 and S 100. Eudragit L dissolves at pH > 6 and is used for enteric coating, whereas Eudragit S, which dissolves at pH > 7 (attributed to the presence of higher amount of esterified groups in relation to carboxylic groups) is used for colon targeting.

The aim of the present study was to formulate sesbania gum matrix tablets coated with Eudragit S100 and Eudragit L 100 for site specific delivery of Mesalamine using natural polysaccharide and pH-sensitive polymer (EudragitS100 and EudragitL 100) for the treatment of ulcerative colitis in colon. This system is anticipated to protect the drug loss in the upper GI tract, which results from the inherent property of Eudragit S100, and deliver Mesalamine in the colon only. The use of enteric polymer EudragitS100 coated sesbania matrix tablets makes them able to release the drug at the particular pH of colonic fluid. A combined mechanism of release is seen, which combines specific biodegradability of polymer and pH-dependent drug release from the coated matrix tablets.

The Colonic Drug Delivery Systems have recently gained importance for delivering a variety of drugs. Colonic drug delivery may be achieved by either oral or rectal administration. Rectal administrations of drugs for colon targeting always face high variability in the distribution of drug, when they are administered in form of dosage forms like enemas and suppositories, which are not always effective. 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. [1]

In general, four primary approaches have been proposed for targeted colon delivery; namely, prodrugs, pH, time dependent systems and microflora-activated systems. Microflora-activated systems appear more promising, since the abrupt increase of the bacteria population and associated enzyme activity in the colon represent a non-continuous event, independent of gastrointestinal (GI) transit time. [2] Large number of polysaccharides has already been tried for their potential as colon-specific. Sesbania gum (SG) is derived from the endosperm of seeds of the plant sesbania grandiflora belonging to family Leguminosae (Papillionaceae). It contains high molecular weight hydrocolloidal polysaccharides composed of galactan and mannan units combined through glycosidic linkages are completely digested by colonic bacteria. However, their solubility and swelling properties in aqueous media make them unable to efficiently avoid the release of drugs during the transit through the upper gastrointestinal tract, and imply the combined use of insoluble polymer to assess their integrity until they reach the colon region. [3]

Mesalamine, an anti-inflammatory agent used in the treatment of ulcerative colitis and in mild to moderate Crohn`s disease undergoes rapid &extensive hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability between 20 % and 30 %. It has a half-life of 5 h after initial dose and 7 h at steady state, so patients are advised to administer Mesalamine formulation for several times a day. Such frequent drug administration may lead to patient incompliance and reduced therapeutic efficacy. Hence formulations containing Mesalamine which target the drug release to colon with sustained drug release have been formulated in this study for the treatment of ulcerative colitis.[5]

The aim of the present study was to formulate sesbania gum matrix tablets coated with Eudragit S100 and Eudragit L 100 for site specific delivery of Mesalamine using natural polysaccharide and pH-sensitive polymer (EudragitS100 and EudragitL 100) for the treatment of ulcerative colitis in colon. This system is anticipated to protect the drug loss in the upper GI tract, which results from the inherent property of Eudragit S100, and deliver Mesalamine in the colon only. The use of enteric polymer EudragitS100 coated sesbania matrix tablets makes them able to release the drug at the particular pH of colonic fluid. A combined mechanism of release is seen, which combines specific biodegradability of polymer and pH-dependent drug release from the coated matrix tablets.

 

## MATERIALS AND METHODS:

### Materials

The compounds obtained as a gift samples: Mesalamine was received as a gift sample Aurobindo Pharma, Vizag. Eudragit S 100 and Eudragit L 100 were obtained from Degussa Pharma Polymers, Germany. Sesbania gum was obtained from Yucca enterprises, Mumbai. PVP K 30, Di calcium phosophate, Magnesium stearate and Talc were purchased from SD fine chemicals, Mumbai. Tri ethyl citrate and Isopropyl alcohol from procured from Finar Chemicals, Mumbai.

### Methods

### Preparation of mesalamine core tablets

Core tablets of Mesalamine were prepared by wet granulation technique. Dicalcium phosphate was used as diluent, and the mixture of talc and magnesium stearate (1:1 ratio) was used as lubricant. Sesbania gum was included in the formulations in various proportions. The composition of different formulations used in the study containing 250 mg of Mesalamine in each case was shown in Table 1. In all the formulations, sesbania gum, di calcium phosphate and mesalamine were passed through sieve no. 60 separately and mixed homogenously. The mixture was then granulated using a binder solution of PVP K-30 which was dissolved in isopropyl alcohol. The wet mass was passed through sieve no. 22 and the resulted granules were dried in a tray drier for 15 min at 50oC. The dried granules were passed through sieve no. 22 and mixed with a mixture of talc and magnesium stearate. Tablets were compressed, using the Cadmach tablet machine with a 12 mm flat-faced punch. Each tablet with an average weight of 600±10 mg contained 250 mg of mesalamine. Core Tablets of mesalamine were tested for weight variation, hardness, thickness, friability and drug content (Table 2).

### Preparation of coating solution

Coating solutions containing Eudragit S-100 (6%w/v) and Eudragit L-100 (6%w/v) were prepared by dissolving in isopropyl alcohol, using Triethyl citrate (33.3%) as plasticizer. Talc was used as an anti-adherent. The whole mixture was constantly stirred for 1 hr on magnetic stirrer and the stirred coating solution was filtered through muslin cloth, a clear solution was obtained. Composition of coating solution was shown in Table 3.

### Coating of Mesalamine core tablets

About 100 gm of compressed mesalamine tablets were de-dusted and loaded in an 8 cm width mini stainless steel coating pan which was fixed on VJ instruments laboratory coating machine (R&D Coater, VJ Instruments, Mumbai, India), 25 rpm was maintained. The tablets loaded bed was pre-heated at 60°C. The prepared Eudragit S-100 (6%w/w) and Eudragit L 100 coating solution was sprayed on the tablet bed, spay gun nozzle 0.52 mm diameter, air pressure at 1 bar (10 psi), spray rate 2 ml/ min and the hot air was applied inside coating pan at 50-60°C. The coating process was continued until the desired tablet coating weight was achieved. Coated tablets were evaluated for weight variation, hardness, friability, drug content and in vitro dissolution study.

### Physical characterization of designed formulations

The designed formulations were studied for their physicochemical properties such as weight variation, hardness, thickness friability drug content and in vitro dissolution study. For estimation of drug content, ten tablets were finally powdered, and quantity of the powder equivalent to 100 mg of Mesalamine was accurately weighed and transferred to a 100 mL volumetric flask containing 50 mL of pH 7.4 phosphate buffer and allowed to stand for 5 hr with intermittent sonication to ensure complete solubility of the drug. The solutions were made up to volume with pH 7.4 phosphate buffer and filtered. The solution was suitably diluted and estimated for mesalamine at 330 nm by UV- Visible spectrophotometer.

### In vitro release studies:

In vitro dissolution studies were carried out by USP type I (basket) apparatus (Electrolab TDT- 6P, Mumbai, India) at 50 rpm, 37±0.5oC. The tablets were tested for drug release for 2 h in 0.1 N HCl (900 ml), due to the fact that the average gastric emptying time is supposed to be between 0.5-2 h. Then, the dissolution medium was replaced by pH 6.8 phosphate buffer (900 ml) and tested for 3 h, bearing in mind that the average small intestine transit time is 3 h. At the end of these time periods, the dissolution medium was replaced by pH 7.4 (900 ml) in order to simulate drug release in the colon without caecal contents. At selected times, 5 ml aliquots were withdrawn and replaced by the same volume. Data were corrected for dilution. The drug concentration was determined by UV spectrophotometry (λ = 330 nm). The assays were performed in triplicate.

### Drug release studies of coated tablets in colonic conditions

### Preparation of rat cecael medium

Male Wister rats (weighing 150 – 180 g each) were purchased from Mahaveer Enterprises, Hyderabad, India, and were maintained in an air-conditioned room at 22 ± 20C and relative humidity of 45 – 55 % in a 12/12 h light/dark cycle. The animals had free access to standard food pellets and water was available ad libitum. All the animal experiments were conducted according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Chennai, India and the study protocol was approved by Institutional Animal Ethical Committee of Vaagdevi College of Pharmacy, Warangal, India (ref no. 1047/ac/07/CPCSEA). International guidelines issued by the International Council for Laboratory Animal Science were also followed. Thirty minutes before starting drug

 

release studies, six rats were sacrificed by spinal traction. Their abdomens were opened, the caecum was isolated, and tied at both ends, before being dissected and immediately transferred into pH 6.8 which had been previously bubbled with CO2. The caecal bags were then opened and their contents were individually weighed, pooled, and suspended in PBS to give a final dilution of 4% w/v. As caecum is naturally anaerobic, all the operations were carried out under a CO2 atmosphere.

**Drug release studies in presence of rat cecal contents**

The susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in rat caecal content medium. Drug release studies was performed in 900 ml of 0.1N HCl (pH 1.2) for 2 hr, followed by pH 6.8 for 3 hr. After which, cecael content equivalent to 8 gm was added to give a final cecal dilution of 4%. The dissolution was carried out in cecal content media upto 24 hr in phosphate buffer pH 7.4 medium. 5ml aliquots were withdrawn at different time intervals, maintained under anaerobic conditions, and is replenished into the dissolution media. The samples were centrifuged and micro filtered before analyzing in UV spectrophotometer.

**Drug release data model fitting**

Data obtained from the in vitro release studies of compression coated tablet of Mesalamine formulations were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsmeyer- Pappas model using following equations: Q = Q0 – K0t (For Zero order model), ln Q = ln Q0 – K1t (for First order model), Q = K2t1/2(for Higuchi model), and Q/Q0 = Ktn (for Korsmeyer - Pappas model). Where, K0 to K2 were release rate constants, Q/Q0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled), n ≤ 0.5; for non- Fickian (anomalous/ zero order) release, 'n' value is in between 0.5 to 1.0; for zero order release, n=1.0; for super case transport II, n > 1.0.

**RESULTS & DISCUSSION:**

The physical properties of weight, crushing strength, thickness, and friability of core tablets and Eudragit-coated tablets were given in Table 2. All tablets were of high quality and complied with pharmaceutical standards.

Mesalamine is a typical anti-inflammatory drug has been used for the treatment of ulcerative colitis and Crohn's disease. It is rapidly absorbed from the small intestine and there is little localization of mesalamine in the colon relative to small intestine. As such the drug from a conventional dosage form does not reach the site of action i.e., colon in sufficient quantities and/or larger doses are needed for effective concentration levels in the colon. To overcome this disadvantage the use of polysaccharides coated with pH-sensitive polymers is used.

The use of enteric polymer Eudragit S 100 coated sesbania matrix tablets makes them able to release the drug at the particular pH of colonic fluid. The combination of these two polymers in a various ratio makes it possible to manipulate drug release within pH range of 6.0 to 7.0. The matrices of natural polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine. But once they reach the colon, they are acted upon by the bacterial polysaccharidases and result in the degradation of the matrices and release of the embedded drug. Sesbania gum has been reported to possess ideal qualities for sustained release of the drug to the targeted site (colon). Colon-specific delivery of the investigational drug (Mesalamine) was aimed through single unit systems (tablets) in order to ascertain the efficacy of these formulations for delivery of drug to the colon. Sesbania gum in varying concentrations F1 (1:0.25), F2 (1:0.5), F3 (1:0.75) and F4 (1:1) was used to prepare tablets.

FT IR analysis shows that the drug Mesalamine is compatible with the polymers used. There was no drug- excipient interaction in the physical mixture. It also suggests that the drug did not undergo any degradation or interaction through the whole of the coating process.

The method employed for tableting in this study was wet granulation and compression for which the granules should possess good flow and compacting properties. The optimum value for Carr's index (%) is upto 15%. Values for angle of repose (θ) less than or equal to 25 generally indicate free flowing material. By means of pilot studies it was found that pure mesalamine exhibited angle of repose value of 31.18± 0.52 indicating extremely poor flow property. It was further supported by high Carr's index value of 47.09 ± 0.27. All the prepared granules Possessed good flow properties as indicated by low values of Angle of repose (21°26'±1.34–24°18' ± 1.84) and Carr's index (13.88 ± 0.28-19.90 ± 0.09). Since, the flow properties of the powder mixture are important for the uniformity of dose of the tablets. The tablets of different batches showed varied thickness (4.02 ± 0.2 to 4.05 ± 0.1), and hardness (5.47 ± 0.45 kg/cm3 to 6.17 ± 0.29). The friability (0.12 to 0.19 %) and weight variation (%deviation: 599.3±1.63 to 599.8 ± 1.76) of different batches of tablets were found within the prescribed limits. The drug content was found to be uniform (> 98%) within the batches of different tablet formulations. Thus, various concentration of sesbania gum did not influence the physical characteristics of the tablets however; the swelling appears to be dependent on its concentration.

The evaluation of release profile is recommended as an important tool in the development and optimization of drug formulations. Release studies of core tablet were carried out in pH 7.4 with and without rat cecal contents. The release of drug in SCF is very high due to the presence of enzymes. The drug release from F3 (93.53%) was high, while it was low for F4 (72.60) for 12 hrs. The reason for this may be low concentration of Sesbania gum in F3 and high concentration in F4 which causes hydration of sesbania gum particles in neutral medium resulted

 

in extensive swelling. This caused initially well separated particles to come into contact and then the swollen particles coalesced. This resulted in a continuous viscoelastic matrix which fills the interstices, maintaining the integrity of the tablet and retarding further liquid penetration. As a result of a high swelling, sesbania gum matrix tablets containing high proportions of sesbania gum i,e F4 formulation can sustain the drug release in SCF. Sesbania gum has a substantial ability to swell and form a hydrogel in neutral medium hence the initial drug release takes place in SIF. Whereas the enteric polymers remain insoluble in the gastric pH and intestinal pH and thus controlling the release of drug within the desired range.

The second part of the formulation focused on the pH dependent polymeric coating of the sesbania gum tablets. The coating polymers were, Eudragit S-100 and Eudragit L-100, dissolves above pH 7.0 and pH 6 respectively, thereby protecting the drug from releasing from the core before reaching the colonic region. Once the enteric coating dissolves, it is expected that drug release would be by microbial dependent of sesbania gum in the target area. Taking into account the dissolution profile of sesbania gum mesalamine matrix tablets, the F4 was an optimized formulation as its dissolution profile was akin to the expected requirements of the study.

Core tablet i,e F4 is coated with 4, 6, 8 % of Eudragit S 100 and Eudragit L 100. Among different concentrations 6% showed good characters such as luster of film and elegance. 6% of Eudragit S 100 and Eudragit L 100 are enteric coated to achieve 5, 10, 15, 20% weight gain separately. The weight variation, hardness and the drug content of all the formulations was found to be within the official limit. From the dissolution data it was observed that all the formulations showed little or no significant release at pH 1.2 (i.e., <1% drug release). Release started in pH 6.8 buffer for all the formulations. This may be attributed to the fact that the threshold pH (pH at which dissolution occurs) of Eudragit L-100 is 6. The lag time for drug release in pH 6.8 buffer was found to be dependent on the level of coating 5, 10, 15 and 20% (coating level in TWG) corresponding to batches EL9 a, EL9 b, EL9 c and EL9 d respectively showed significant drug release (i.e., >20%) after a lag time of 4 hr., 5 hr., 5.5 hr. and 5.5 hr. respectively and drug release in pH 7.4 containing rat cecal contents is >90% for EL9 a, EL9 b, EL9 c in 18 hours and >90% for EL9 d in 24 hours.

Formulations coated with ES-100 TWG 20% showed no release in pH 6.8 buffer (i.e., <1% drug release). However, the release for formulations coated with ES 100 TWG 5%, 10% started in 7.4 buffer with rat cecal contents. Also, the lag time for drug release in pH 6.8-7.4 buffer was found to be dependent on the level of coating. 5, 10, 15, 20% (coating level in TWG) corresponding to batches ES3 a, ES3 b, ES3 c and ES3 d showed significant drug release (i.,e > 25%) after a lag time of 5 hr. (in pH 6.8 medium), 5.5 hr., 6 hr. and 8 hr. (in pH 7.4 medium with rat cecal contents) respectively. Drug release in pH 7.4 containing rat cecal contents is >90% for ES3 a, ES3 b in 18 hours and >90% for ES3 c EL9 d in 24 hours.

Formulation ES3 d coated with 20% TWG of Eudragit S- 100 showed the most desirable properties. EL9 d also performed better in vitro but ES3 d was considered more superior because of the former's dependence of GI transit for drug release and was not specific to pH of the colon. Hence ES3 d was considered as the optimized formulation for colonic drug delivery.

The mechanism of drug release from matrices containing swellable polymers is either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms. When hydrophilic matrix system enters an in-vitro dissolution medium, drug particles initially pass into solution from the surface. The solid matrix also begins to swell as soon as hydration with solvent molecules, diffusion of the dissolved drug and erosion of viscous polymer layer into aggregates or granules and these in turn de aggregate into fine particles that also release their drug content by dissolution. The release mechanism is also influenced by porosity and tortuosity of the matrix. In this study, drug release kinetics was evaluated by fitting with different models, zero-order, first-order, Higuchi, or Korsmeyer-Peppas. According to the Table 34, it is observed that ES3 d formulation was best fitted with zero order model indicating their release kinetics is not dependent on the concentration of drug in the depot. The drug release data were fitted to the power law or the Korsmeyer–Peppas equation. In this study, the mesalamine release, in neutral medium, from sesbania gum tablets showed a good fit into the Korsmeyer-Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release. It exhibited a correlation coefficient (r2) greater than 0.98. In the case of matrix tablets, $0.45 < n$ corresponds to a Fickian diffusion mechanism and $n = 0.89$ indicates a purely relaxed controlled delivery which is referred to as Case II transport. Intermediate values $0.45 < n < 0.89$ indicate an anomalous behavior (non-Fickian kinetics corresponding to coupled diffusion/polymer relaxation). Occasionally, values of $n > 0.89$ have been observed, which has been regarded as Super Case II kinetics. The mechanisms of drug release is (super case-II), since they fitted well with Korsmeyer–Peppas models as their r2 values in the range of 0.999 with n value above 1. This indicates that the drug release depends on swelling, relaxation and erosion of polymer with zero order release kinetics.

## CONCLUSION

Mesalamine core tablet was prepared using different ratios of polysaccharide sesbaniga gum. The results from this study clearly shows that mesalamine and polysaccharide sesbania gum in F4 (1:1) ratio showed sustained release. Core tablet is coated with 6% polymeric solution of Eudragit L 100 and Eudragit S 100 to obtain 5, 10, 15, 20% weight gain for colonic drug delivery. Formulation ES3 d coated with 20% TWG of Eudragit S- 100 showed the most desirable properties. EL9 d also performed better in vitro but ES3 d was considered more superior because of the former's dependence of GI transit for drug release and was not specific to pH of the colon. Mesalamine Eudragit coated sesbania matrix formulation can be promising system for the treatment of colon disease, such as Ulcerative colitis.

 

**Table 1. Various formulations tried for optimization of core tablets**

| Ingredients | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) |
|---|---|---|---|---|
| Mesalamine | 250 | 250 | 250 | 250 |
| Sesbania gum | 62.5 | 125 | 187.5 | 250 |
| PVP K 30 | 20 | 20 | 20 | 20 |
| Di calcium phosophate | 257.5 | 195 | 132.5 | 70 |
| Magnesium stearate | 5 | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 | 5 |
| Total weight | 600 | 600 | 600 | 600 |

**Table 2. Characterization of tablet powder blend**

| Formulation code | Angle of repose (θ) | Bulk density (gm/cm3) | Carr's Index (%) |
|---|---|---|---|
| F1 | 21º26'±1.84 | 0.51±0.037 | 13.88±0.28 |
| F2 | 23º21'±1.64 | 0.54±0.044 | 17.24±0.33 |
| F3 | 23º47±1.36 | 0.61±0.038 | 17.28±0.59 |
| F4 | 24º54'±1.55 | 0.62±0.042 | 19.90±0.09 |

Table 3. Characterization of compressed core tablet

| Formulation code | Thickness (mm) | Hardness (kg/cm3) | Weight variation (mg) | Friability (%) | %Drug content |
|---|---|---|---|---|---|
| F1 | 4.02±0.1 | 5.47±0.45 | 599.35±1.63 | 0.18 | 99.33±0.47 |
| F2 | 4.05±0.1 | 6.17±0.29 | 599.5±1.36 | 0.14 | 99.70±0.16 |
| F3 | 4.01±0.2 | 5.67±0.76 | 599.8±1.76 | 0.19 | 101.40±0.68 |
| F4 | 4.03±0.1 | 5.83±0.29 | 599.6±1.5 | 0.15 | 100.40±0.15 |

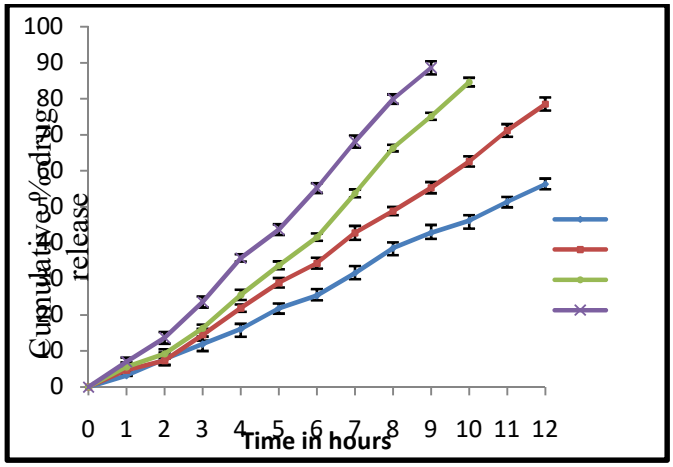


**Figure 1 . Cumulative percentage drug release of core tablets without rat cecal contents**

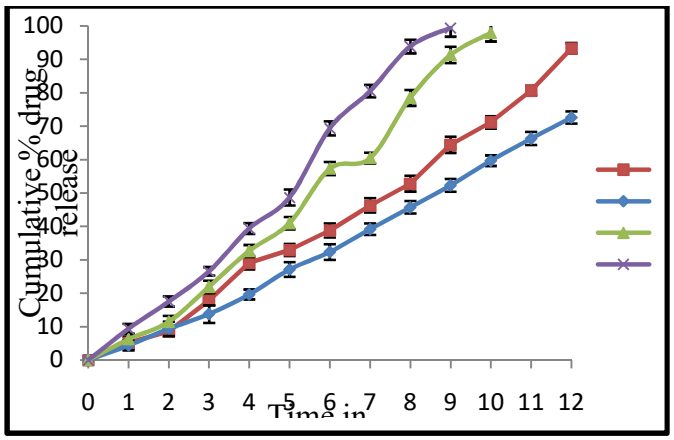


**Figure 2. Cumulative percentage drug release of core tablets with rat cecal contents**

**Table 4. Optimization of coating solution**

| Ingredient | ES1 | ES2 | ES3 | ES4 | ES5 | ES6 | ES7 | EL8 | EL9 |
|---|---|---|---|---|---|---|---|---|---|
| Eudragit S 100 (gm) | 6 | 6 | 6 | 8 | 4 | 6 | 6 | - | - |
| Triethyl citrate (mL) | 2 | 2 | 2 | 2 | 2 | 3 | 1.6 | 2 | 2 |
| Isopropyl alcohol (mL) | 30 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Acetone (mL) | 60 | - | - | - | - | - | - | - | - |
| Talc (gm) | - | - | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Eudragit L 100 (gm) | - | - | - | - | - | - | - | 8 | 6 |

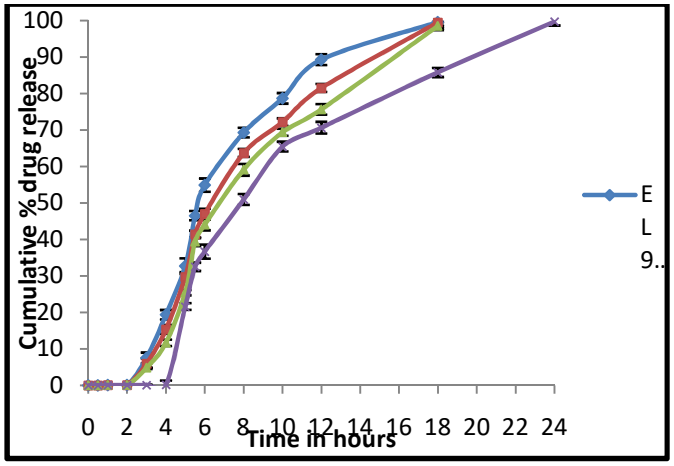


**Figure 3. In vitro drug release profiles of tablets coated with Eudragit L- 100**

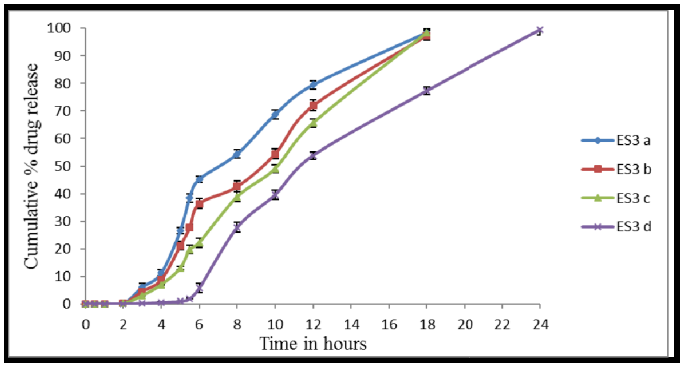


**Figure 4. In vitro drug release profiles of tablets coated with Eudragit S- 100**

**Table 5. Physical characteristics of coated formulations**

| Formulation code | Thickness (mm) | Hardness (kg/cm2) | % Drug content |
|---|---|---|---|
| **Eudragit L 100** | | | |
| **EL9 a** | 4.15±0.05 | 7.8±0.3 | 98.64±0.43 |
| **EL9 b** | 4.27±0.04 | 7.3±0.2 | 101.31±0.29 |
| **EL9 c** | 4.34±0.02 | 7.6±0.1 | 99.94±0.46 |
| **EL9 d** | 4.48±0.05 | 6.9±0.3 | 99.83±0.68 |
| **Eudragit S 100** | | | |
| **ES3 a** | 4.19±0.06 | 7.6±0.18 | 101.49±0.72 |
| **ES3 b** | 4.32±0.01 | 7.5±0.33 | 101.27±0.43 |
| **ES3 c** | 4.38±0.05 | 7.1±0.15 | 101.27±0.45 |
| **ES3 d** | 4.49±0.01 | 7.5±0.12 | 101.33±0.27 |

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**How to cite this article:**

**Chandra Shekhar Reddy Bonepally*, DESIGN AND EVALUATION OF COLON SPECIFIC DRUG DELIVERY SYSTEM OF MESALAMINE J Pharma Res, 2025; 14(06): 17-26. DOI: https://doi.org/10.5281/zenodo.17555960**

**Conflict of interest**: The authors have declared that no conflict of interest exists.

**Source of support:** Nil

 