WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 7, 834-848. Research Article ISSN 2277–7105

FORMULATION AND ESTIMATION OF MESALAMINE BILAYER TABLET FOR COLON TARGETED DRUG DELIVERY

V. Ranjith*, Dr. S. K. Senthilkumar, P. Anitha, S. Aswini, R. Elavarasan, S. Gogulalakshmi and K. Janani

Arunai College of Pharmacy, Tiruvannamalai – 606 603, Tamilnadu, India.

Article Received on
04 Feb. 2025,

Revised on 25 Feb. 2025,
Accepted on 17 March 2025

DOI: 10.20959/wjpr20257-35997

***Corresponding Author**
V. Ranjith
Arunai College of Pharmacy, Tiruvannamalai - 606 603, Tamilnadu, India.

ABSTRACT

Ulcerative colitis is a chronic inflammatory bowel disease that affects the colon and rectum. Mesalamine, a 5-aminosalicylic acid (5-ASA), is a commonly used medication for the treatment of ulcerative colitis. However, its oral administration is associated with systemic side effects and low bioavailability in the colon. This study aimed to develop a bilayer tablet for colon-specific delivery of mesalamine to improve its therapeutic efficacy and reduce side effects. The bilayer tablet consisted of an immediate release layer containing mesalamine and a sustained release layer containing guar gum as a sustained release polymer. The tablets were enteric coated with Eudragit L100 to prevent release in the stomach and small intestine. The tablets were evaluated for their physical properties, in vitro drug release, and disintegration time. The results showed that the bilayer tablets exhibited good physical properties, with a weight variation of ±5%, friability of ≤1%, and hardness of 10 kg/cm². The in vitro drug release study revealed that the tablets releases of mesalamine in 9 hours in phosphate buffer pH 7.4, indicating its sustained release profile. In conclusion, the developed enteric coated bilayer tablet is a promising delivery system for colon-specific delivery of mesalamine, which can improve its therapeutic efficacy and reduce side effects. This formulation has the potential to provide a more effective treatment option for patients with ulcerative colitis.

KEYWORDS: Mesalamine, ulcerative colitis (UC), guar gum, eudragit L100, enteric coated bilayer tablet.

INTRODUCTION

Ulcerative colitis are inflammatory bowel diseases that cause chronic inflammation and damage in the gastrointestinal (GI) tract. Ulcerative Colitis is limited to the large intestine (colon) and the rectum. The inflammation occurs only in the innermost layer of the lining of the intestine. It usually begins in the rectum and lower colon, but may also spread continuously to involve the entire colon. Ulcerative colitis symptoms can vary, depending on the severity of inflammation and where it occurs. Signs and symptoms may include, rectal bleeding-passing amount of blood with stool, abdominal pain and cramping, rectal pain, urgency to defecate, inability to defecate despite urgency, weight loss, fatigue, fever. Health care providers often classify ulcerative colitis according to its location. Symptoms of each type often overlap. Types of ulcerative colitis include Ulcerative proctitis, Proctosigmoiditis, Left-sided colitis and Pancolitis. There are several mechanisms whereby colonic bacteria may influence the course of ulcerative colitis pathogenic mechanisms may involve an overwhelming presence of specific pathogenic bacteria, subtle imbalances in the ratio of beneficial to pathogenic bacteria (dysbiosis), a defective mucosal barrier and alterations in the gut immune response. Pathogenic bacteria may secrete enterotoxins capable of altering gut permeability and causing systemic effects, elaborate immunosuppressive proteins that interfere with normal gut immune responses, and may directly interfere with epithelial cell metabolism. Because no specific pathogen has been implicated in UC, alterations in gut immunity may play a significant role. A popular theory among researchers is that UC is characterized by an abnormal host response to normal colonic bacteria. For the treatment the severity of disease and patient preference dictate the appropriate treatment options. The initial treatment strategy in UC typically follows the traditional step-up approach. For definitions of severity of disease, see the section on severity and location of disease. Patients who present with moderate to severe symptoms are likewise often treated with corticosteroids to induce remission followed by a thiopurine to maintain remission. In cases of mild to moderate disease, 5-aminosalycilates (5-ASAs) are the treatment of choice. 5-ASAs can be administered orally, rectally, or in combination. The combination of oral and rectal 5-ASA is most effective. Mesalamine is an active ingredient of agents used for the long-term maintenance therapy to prevent relapses of crohn’s disease and ulcerative colitis, however, when mesalamine is administrated orally, a large amount of the drug is absorbed from the upper GI tract, and causes systemic side effects. Free mesalamine undergoes rapid and nearly complete systemic absorption from the proximal intestine depending on the concentration and local pH, followed by extensive metabolism. It is thus of tremendous importance to deliver

mesalamine locally in order to reduce influences by systemic drug absorption causing adverse effects and drug loss decreasing the probability for a therapeutic success. Hence, selective delivery of mesalamine into the colon is desirable. The effective use of most of the current 5-ASA formulation requires multiple daily dosing with up to 12 tablets or capsules. Reduced patient compliance and disease control are the results of this inconvenience of frequent daily dosing and the number of tablets or capsules required per day. Accordingly, in order to overcome these problems, formulating 5-ASA in a successful delivery system, it is tremendously important to minimize 5-ASA release in the upper gastrointestinal (GI) tract and to localize 5-ASA release in the colon as coated bilayer tablet manner. In the present study, Mesalamine was prepared as bilayer tablet containing immediate and sustained release. For immediate release provide loading dose and sustained release provide maintenance dose. Due to swelling property of guar gum it sustains the mesalamine drug release.

MATERIAL AND METHOD

Material

Mesalamine (5-ASA), Eudragit L100 was received as a gift sample, gaur gum as sustained release polymer, lactose, starch, PVP, talc, magnesium stearate was purchased from molychem, Mumbai.

METHODOLOGY

Preformulation study

Melting point

The melting point of mesalamine was determined by capillary tube method using digital melting point apparatus. one end of the capillary tube was sealed by heating gently using Bunsen burner and then a small quantity of mesalamine was filled into the sealed capillary tube. then this capillary tube was placed in the melting point apparatus. The temperature at which the drug starts melt was taken as melting point of the drug.

Determination of λ max

Accurately weighed mesalamine drug (10 mg) was dissolved in 10 ml volumetric flask containing methanol. Then volume was adjusted upto the level with sufficient quantity of methanol. This gave the concentration of 1000 µg/ml. It was diluted to 100µg/ml. Further, different aliquots were prepared with the stock solution. These aliquots were analyzed spectrophotometrically.

Preparation of Standard Curve

Mesalamine (10 mg) was accurately weighed and dissolved in 100 ml volumetric flask containing phosphate buffer (pH 1.2) and phosphate buffer (pH 7.4). Get a 100 µg/ml concentration (stock A). From the above solution 1 ml was taken and made upto 10ml to get 10 µg/ml solution (stock B). From the standard stock solution, different aliquots 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 ml were taken and made up to 10 ml with each buffer pH 1.2, and pH 7.4 individually in volumetric flask to produce 2, 4, 6, 8, 10, 12, 14, 16 18 and 20 µg/ml respectively. The solutions were filtered (Whatman filter paper 45µm) and absorbance was measured at 220 nm using a UV-spectrophotometer.

Solubility study

The solubility of mesalamine was determined using saturation solubility method. Solubility studies were carried out using different solvent such as distilled water, 0.1N HCl, methanol, DMSO, Acetone. in each case excess amount of drug was added to 5ml of solvent until it gets saturated and allowed to equilibrate for 24hrs. The samples were filtered using 0.45μm Millipore filter, diluted suitably and analyzed by using UV spectrophotometer.

Formulation of mesalamine immediate release tablet

The Mesalamine immediate release tablet was prepared by using direct compression method. All the ingredients are passed through sieve No: 44 weighed and mixed for 15 mins and compressed in a 16-station automatic punching machine with a punch size of 12.5 mm.

Table 1: Composition of Immediate release tablet.

Ingredient	IR1 Mg	IR2 Mg	IR3 mg
Mesalamine	150	150	150
Lactose	40	30	20
Microcrystalline cellulose	30	40	50
Polyvinylpyrrolidone	20	20	20
Talc	7	7	7
Magnesium stearate	3	3	3
Total weight	250	250	250

Formulation of mesalamine sustained release tablet

The Mesalamine sustained release tablet was prepared by using direct compression method. All the ingredients are passed through sieve No: 44 weighed and mixed for 15 mins and compressed in a 16-station automatic punching machine with a punch size of 12.5 mm.

Table 2: Composition of Sustained release tablet.

Ingredients	SR1 mg	SR2 mg	SR3 mg	SR4 Mg	SR5 mg	SR6 mg
Mesalamine	250	250	250	250	250	250
Guar gum	110	120	130	140	150	160
Lactose	90	80	70	60	50	40
Starch	20	20	20	20	20	20
Polyvinylpyrrolidone	20	20	20	20	20	20
Talc	7	7	7	7	7	7
Magnesium stearate	3	3	3	3	3	3
Total weight	500	500	500	500	500	500

Formulation of enteric coated bilayer tablet

The best immediate release formulation and sustained release formulation was compressed by direct compression method. The coating solution was prepared by mixing ethanol, polyethylene glycol 400 (5 percent w/v), Eudragit L100 coating solution (10 percent w/v) in water. The bilayer tablets were coated by dip coating technique.

Preformulation evaluation

Angle of repose

It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane the angle of repose was measured by fixed funnel method. Clean and dried funnel with flat tip was attached to the burette stand. A white paper was placed below the funnel on the clean, dry platform place. Lower tip of the funnel was adjusted above the paper at height of 2cm. Powder sample was poured carefully into the funnel with the help of spatula until cone shaped pile touch the lower tip of the funnel. Circumference of the pile of the sample was drawn with the help of pencil without disturbing the pile. Four points were marked on the circumference, at opposite to each other. Radius and height of the pile was recorded.

$$\Theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, h is height of pile, r is radius of pile

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed as

Bulk Density (g/mL) =M/Vo

Where, M is the mass of powder, V0 is the bulk volume of the powder

Tapped density

It is the ratio of total mass of powder to the tapped volume of powder. The after initial volume was measured by tapping the powder for 100 times and tapped volume was noted. It is expressed in g/cc and is given by

$$Dt = M/V_t$$

Where, M is the mass of powder, Vt is the tapped volume of the powder

Carr's index

The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 100 times. The percentage compressibility (Carr's index) was calculated by the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk density}}$$

Post formulation evaluation

Weight variation

Randomly 20 tablets were selected from prepared batch, the weight of individual tablet was noted. Measure the weight of 20 tablets together and average weight was calculated. Calculate the upper and lower limits at the % deviation stated, and at double that percentage as per IP.

$$\frac{\text{Initial Weight} - \text{Average weight}}{\text{Initial Weight}} * 100$$

Friability test

For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g. For tablets with a unit weight of more than 650mg,

take a sample of 10 whole tablets. Randomly required quantity of tablets were selected and dedusted and initial weight (Iw) carefully noted. Tablets were placed in friability drum and it operated at 25rpm for 4 minutes or up to 100 revolutions. Tablets were removed from drum, loose dust and broken tablets are removed carefully and final weight (Fw) was noted.

$$\textbf{Percentage friability} = \frac{\text{Initial Weight} - \text{Final weight}}{\text{Initial Weight}} * 100$$

Hardness test

Tablet was placed between the fixed jaw and moving jaw by adjusting the moving jaw, initial force was noted by adjusting scale on the barrel containing spring. The moving jaw was then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force by means of scale. The force of fracture was recorded, and the initial force reading is deducted from it.

Invitro drug release study

The ability of tablet to retard drug release in physiological environment of the stomach and small intestine was assessed by conducting drug release studies in phosphate buffer pH 1.2 and phosphate buffer pH 7.4. Dissolution study was conducted in USP Type II apparatus at 100 rpm and at 37° C, initially drug release was tested in 900ml of pH 1.2 for 2 hours followed by pH 7.4 for next 9 hours. Then dissolution was continued in phosphate buffer pH 7.4 till end of the test. 5ml sample was withdrawn at interval of 1 hours and filtered it was replaced with 5ml fresh medium to maintain the sink condition. The absorbance was recorded using UV-spectrophotometer at 220nm.

RESULT AND DISCUSSION

Melting point

Mesalamine API melting point was found to be 283° by capillary method.

Determination of λmax

The mesalamine dissolved in methanol to give solution of 100µg/ml which was spectrophotometrically analyzed at UV range. Solution shows maximum absorption peak at 220 nm. Thus, the wavelength was selected as λ_{max} for further study.

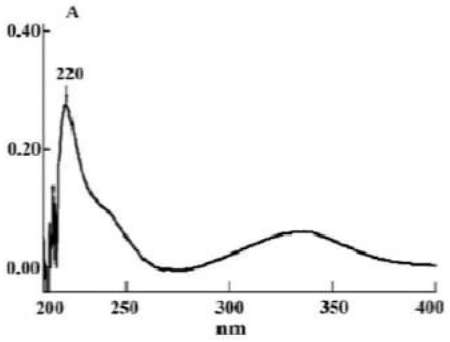

Figure 1: Lamda max.

Preparation of standard curve

The stock solution of mesalamine was diluted with phosphate buffer pH 1.2 and phosphate buffer pH 7.4 to get concentration range of 2 to 20 µg/ml of mesalamine. The absorbance was measured at 220 nm and calibration curve of mesalamine was plotted between absorbance and concentration for the 2 different buffer solution. The data were subjected to linear regression and the correlation co-efficient was found to be 0.991 for pH 1.2 and 0.993 for pH 7.4. Thus, the value of correlation coefficient indicates that the concentration range of 2 to 20 µg/ml of mesalamine obeys beer's lambert law.

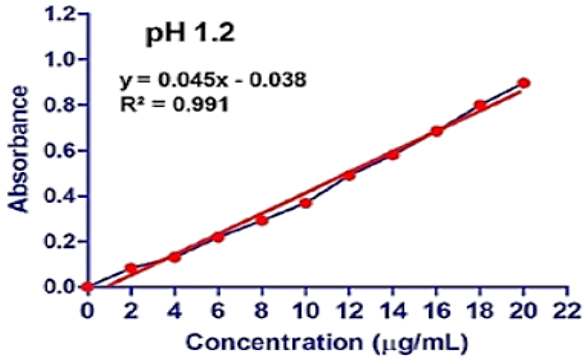

Figure 2: Standard graph at pH 1.2.

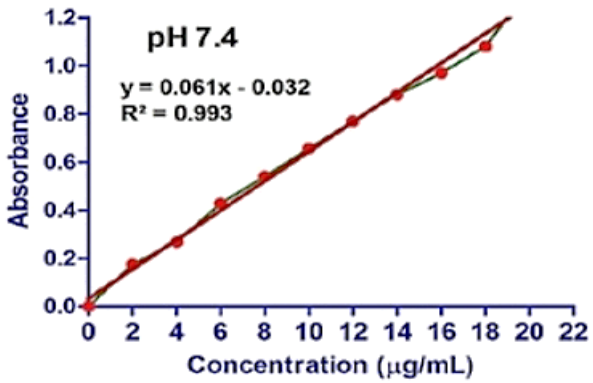

Figure 3: Standard graph at pH 7.4.

Solubility study

The solubility mesalamine in various solvents like acidic buffer of pH 1.2, Methanol, and dimethyl sulfoxide, acetone and distilled water was done by saturation solubility method and the inference are as follows. The result shows that drug is practically insoluble in water.

Table 3: Solubility study.

Solvent	Solubility
Distilled water	Insoluble
0.1N HCl solution	Insoluble
Methanol	Soluble
Dimethyl sulfoxide	Freely soluble
Acetone	Freely soluble

Preformulation evaluation

The study focused on the flow characteristic, particularly angle of repose, compressibility index, tapped and bulk density, Hausner's ratio. The bulk density value denotes well defined packing properties. The formulation's compressibility index suggests that the powder has good flow has good flow characteristics, which were additionally supported by measuring the angle of repose, which falls in.27.6° – 30.8° for immediate release and 25.9° – 30.1° for sustained release.

Table 4: Preformulation study of immediate release powder.

Formulations	Bulk density (mg/ml)	Tapped density (mg/ml)	Angle of repose (°)	compressibility index (%)	Hausner's ratio
IR1	0.70 ±0.3	0.79 ±0.5	25.9	11.3	1.12
IR2	0.69 ±0.3	0.78 ±0.5	28.6	11.5	1.13
IR3	0.68 ±0.3	0.77 ±0.5	30.1	11.6	1.13

Table 5: Preformulation study of sustained release powder.

Formulations	Bulk density (mg/ml)	Tapped density (mg/ml)	Angle of repose (°)	Compressibility index (%)	Hausner's ratio
SR1	0.62 ±0.3	0.71 ±0.5	27..6	12.1	1.14
SR2	0.62 ±0.3	0.72 ±0.5	27.9	13.8	1.16
SR3	0.62 ±0.3	0.73 ±0.5	28..5	15	1.17
SR4	0.62 ±0.3	0.73 ±0.5	29.6	15	1.17
SR5	0.62 ±0.3	0.73 ±0.5	29.7	15	1.17
SR6	0.62 ±0.3	0.74 ±0.5	30.8	16.2	1.19

Post formulation evaluation

The study focused on the physical strength, stability and hardness of the compressed tablet. The weight variation test to determine the content uniformity of the tablet all the tablet is within the limit as per IP. For the friability test tablet placed in the friability apparatuses were weighed and they are within the limit of less 1%. The hardness of the tablet was determined by using Monsanto hardness tester the values are within the limit of 5- 7 Kg/Cm^2. Disintegration test for all immediate release formulation are disintegrated within 30 minutes.

Table 6: Post formulation for immediate release tablet.

Formulations	Weight Variation (mg)	Friability (%)	Hardness (Kg/Cm^2)	Disintegration
F1	250 ± 5	0.56	5.0	Within 30 mins
F2	250 ± 5	0.52	6.5	
F3	250 ± 5	0.50	6.8	

Table 7: Post formulation for sustained release tablet.

Formulations	Weight Variation (mg)	Friability (%)	Hardness (Kg/Cm^2)
F1	500 ± 5	0.56	7.0
F2	500 ± 5	0.52	7.5
F3	500 ± 5	0.50	7.3
F4	500 ± 5	0.49	8.2
F5	500 ± 5	0.46	8.5
F6	500 ± 5	0.42	8.7

In vitro drug release study

In vitro drug release of immediate release formulation IR1, IR2 and IR3 shows 92%, 94% and 99% at 30 mins and sustained release formulation SR1, SR2, SR3, SR4, SR5 and SR6 shows 95%, 94%, 93%, 92%, 91% and 90% at 9 hours. Respectively, From the above results formulation IF3 shows good immediate release profile and formulation SF6 shows better sustained release. so, these formulations are selected and compressed into bilayer tablet.

Table 8: In vitro drug release for immediate release.

Time(mins)	Percentage drug release (%)		
	IR1	IR2	IR3
10	37.57	42.49	56.26
20	67.08	72.98	78.89
30	92.66	94.62	99.54

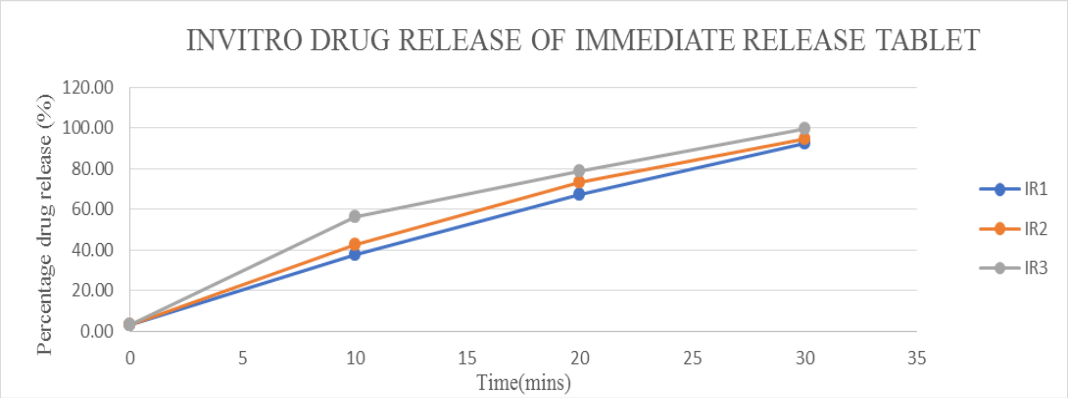

Figure 4: In vitro drug release of immediate release tablet.

Table 9: In vitro drug release for sustained release.

Time (hours)	Percentage drug release (%)					
	SR1	SR2	SR3	SR4	SR5	SR6
1	16	14	12	10	10	08
2	25	23	20	18	15	12
3	38	35	30	26	23	18
4	50	47	42	39	36	32
5	63	60	54	53	50	47
6	75	71	69	65	62	59
7	86	81	79	77	75	69
8	89	86	85	83	81	78
9	98	95	93	92	91	89

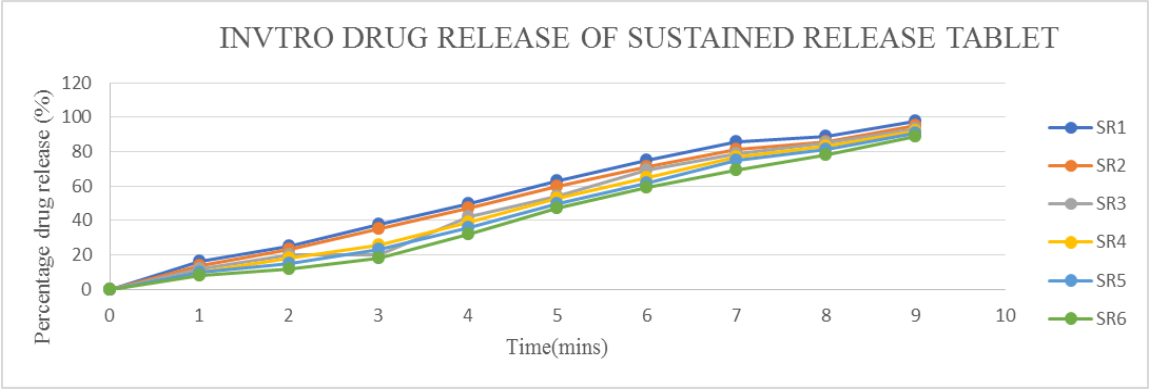

Figure 5: In vitro drug release of sustained release tablet.

Post formulation evaluation of bilayer tablet

The weight variation test of the bilayer tablet is within the limit of ±5% as per IP. For the friability test for bilayer tablet within the limit 1%. The hardness of the tablet was also within the limit. The disintegration test for bilayer tablet coated with eudragit is within 60 mins.

Table 9: Post formulation evaluation for bilayer tablet.

Formulation	Weight Variation (mg)	Friability (%)	Hardness (Kg/Cm^2)	Disintegration (Mins)
IR3SR6	750 ± 5	0.48	10	Does not disintegrate in 0.1 N HCl and disintegrate start at phosphate buffer pH 7.4

In vitro drug release study

In vitro drug release profile of ECIR3SR6 in phosphate buffer at different pH levels was investigated. The results showed that the drug release was significantly influenced by pH and time. In the acidic environment of pH 1.2, no drug release was observed within the first 2 hours, indicating a strong resistance of the ECIR3SR6 to acidic conditions. In contrast, at pH 7.4, a rapid dug release was observed, with 32.90% release within the first 30 minutes. The drug release continued to increase with time, reaching 85.65% at 10 hours and 90.44% at 11 hours. These findings suggest that ECIR3SR6 is pH-dependent and exhibits a delayed release profile in acidic conditions, which could be beneficial for targeted drug delivery applications. The rapid release at first 30 mins in pH 7.4, which shows immediate release and furthers increase in the drug release time, indicates that the drug can be effectively released in the body.

Table 10: In vitro drug release for enteric coated bilayer tablet.

Dissolution medium	Time(hours)	Percentage drug release (%)
		ECIR3SR6
Phosphate buffer pH 1.2	0	0
	1	0
	2	0
Phosphate buffer pH 7.4	2.30	32.90
	3	37.70
	4	41.02
	5	50.98
	6	59.09
	7	66.10
	8	75.32
	9	80.48
	10	85.65
	11	90.44

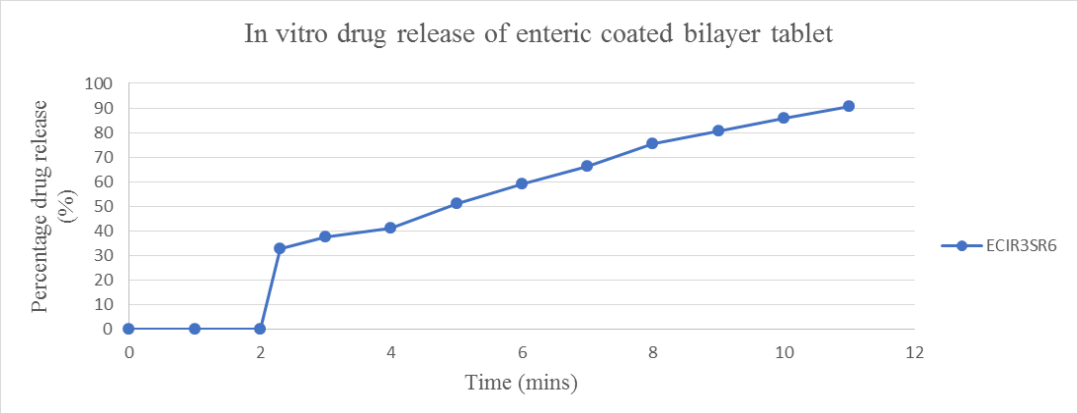

Figure 6: In vitro drug release of enteric coated bilayer tablet.

CONCLUSION

Ulcerative colitis is a chronic inflammatory bowel disease that affects the large intestine and rectum, leading to symptoms such as rectal bleeding, abdominal pain, and weight loss. The disease is characterized by an abnormal host response to normal colonic bacteria, and its treatment often involves the use of 5-aminosalicylic acid (5-ASA) medications, such as mesalamine. However, the systemic absorption of mesalamine from the upper gastrointestinal tract can lead to adverse effects and reduced therapeutic efficacy. In this study, we aimed to develop a bilayer tablet formulation of mesalamine that combines an immediate release layer with a sustained release layer, using guar gum as a sustained release polymer. The formulation was optimized through a series of pre formulation and post formulation evaluations, including angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The results showed that the optimized bilayer tablet formulation containing IR3 and SR6 exhibited good flow properties and passes post formulation. The enteric coating with Eudragit L100 further delay the release of mesalamine in the acidic environment of the stomach, ensuring its targeted delivery to the colon. The in vitro drug release study revealed that the bilayer tablet formulation achieved immediate releases of mesalamine in the first 30 minutes, followed by a sustained release over 9 hours. It shows that IR tablets provide the loading dose and SR tablets provide the sustained release over the next dose. Overall, our study demonstrates the potential of the bilayer tablet formulation of mesalamine as a promising therapeutic approach for the treatment of ulcerative colitis.

REFERENCE

1. Shilpa Sahu, Prasanta kumar Choudhury, Gourishyam Pasa, Padala Narasimha Murthy, Poonam Sahu, Renuka Verma, Modulation of mesalamine release from enteric coated

matrix tablets using natural polysaccharides for localized colonic delivery, JAPR, 13th April., 2024; 12: 93–108.

2. Whitney D. Lynch, Ronald Hsu, ulcerative colitis, NCBI, 2023, 5thJune.
3. Soni Nikita, Joshi Deepak, Jain Vikas and Pal pradeep, A review of application of bilayer tablet technology for drug combination, JDDT, 12thJan, 2022; 12.
4. Rohitas Dehmukh, Ranjit kumar Harwansh, Preformulation consideration development and Evaluation of mesalamine loaded polysaccharide based complex mucoadhesive beads for colon Targeting, IJPER, 2021; 20th Jan: 95-105.
5. Nikita chourey, Khushi Chouksey, Formulation and evaluation of enteric coated matrix tablets of Mesalamine for inflammatory Bowel Disease, JDDT, 2021, 28th December.
6. Ross J Porter, Rahul Kalla, Gwo- Tzer Ho, NCBI, 27th April, 2020.
7. Prasanthi D, prashant, Meghana G, Formulation and evaluation of press coated tablet of lansoprazole, IJAP, 11th April, 2019; 11: 49-56.
8. Diksha sharma, Dhruv Dev, Sustained release drug delivery system with the role of natural polymer, JDDT, 2019; 6th June, 9.
9. M. Manjunath, Anjali, D. V. Gowda, Praveen kumar, Atul Srivastava, Riyaz Ali Osmani, Chetan G. Shinde, and Siddaramaiah, Guar gum and its pharmaceutical and biomedical application, ASEM, 2016 August, 8: 1-14.
10. Niranjan Panda, A, Venkateswar Reddy, G. V. Subba Reddy, Afshan sultana, Formulation design and in vitro evaluation of bilayer sustained release matrix tablets of doxycycline, AJPCR, 8th August, 2015; 5: 5-48.
11. Vadlamudi H. C, Prasanna Raju Y, Rubia Y. B, Vulava. J, and Vandana K.R, In vitro characteristics of modified pulsincap formulation with mesalamine for ulcerative colitis treatment, ID, 2014; 31st Jan, 51: 35-43.
12. Dayse Fernanda de Souza, Karin goebel, Itamar Francisco Andreazza, Development of enteric coated sustained release minitablet containing mesalamine, BJPS, 2013, 3rd July, 49: 529-536.
13. Sharma Madhu, Joshi Baibhav, Bansal Monika, Goswami Manish, Formulation and Evaluation of colon targeted tablet of mesalazine, NICBI, 2012; 3rd Sep
14. Sharma Madhu, Joshi Baibhav, Bansal Monika, Goswami Manish, formulation and evaluation of colon targeted tablets of mesalamine, JDDT, 15 Sep., 2012; 2.
15. Spandann Kodati, Mrs. Jya, Dr. M. Chinna Eswaraiah, Formulation and evaluation of compression coated mesalamine tablet for colon specific drug delivery, IRJPAS, 7th November. 2012; 2: 1-11.

16. Sachin.S Kale, Saste. Prajkta L Ughade, Dheeraj T. Baviskar, bilayer tablet, IJPSRR, 01, August, 2011; 9: 25-30.
17. S. A Payghan, Dr. J. I. Disuza, Formulation, evaluation and development of Bilayer Tablet, IJPRD, December. 2011; 3: 80-87.
18. Kiran musle, S. A. Payghan, Dr. J. I. Disuza, Formulation, evaluation and development of bilayer tablet, IRJPAS, Dec., 2011; 2: 1-11.
19. P. B. Patil, A. A. Hajare and R. P. Awale, formulation for colon delivery, RJPT, November 2011; 4: 1751-1756.
20. Nirav V. Patel, Jayvandan K. Patel, Shreeja H. Shah, Jagruti J Patel, Design, Development and in vitro evaluation of mesalamine tablets containing pectin and Chitosan for colon specific drug deliver, IJRPS, 25th March, 2010; 1.
21. Rishabha Malviya, Pranati Srivastava, Mayank Bansal and Pramod Kumar Sharma, Formulation and optimization of sustained release tablets of Diclofenac Sodium using Guar gum as release modifier, IJPSR, 17th May 2010; 82-88.
22. Hiroaki Ito, MD, Mistuo lida, MD, Takayuki Matsumoto, MD, Yasuo Suzuki, Direct comparison of two different Mesalamine Formulation for the induction of remission in patient with Ulcerative colitis: A Doubleblind randomized study, NCBI, September 2010.
23. J.K. Patel, N.V. Patel and S.H. Shah: *In vitro* controlled release of colon targeted mesalamine from capitol ATO 888 based matrix tablets using factorial design, NCBI, Aug. 2009.
24. Monika C. Chuong, sustained delivery of intact drug to the colon mesalamine for mesalamine formulation and temporal gastrointestinal transit Analysis, NCBI, 2008; 28th September.
25. Y. S. R. Krishnaiah, R. S. Karthikeyan, V. GOURI Sankar, V. Satyanarayana, There layer guar gum matrix tablet formulation for oral controlled delivery of highly soluble trimetazidine dihydrochloride, JCR, 17th May 2002; 81: 45-56.