Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Research Article

Preparation and Characterization of Colon Targeted Drug Delivery System of Non-Steroidal Anti-inflammatory drug.

Tejas J. Vhora[*, 1], Tejeswini V. Deshmukh[2]

[1]Department of Pharmaceutics, SVPM's College of Pharmacy, Malegaon (BK II), Baramati, Pune- 413115, Maharashtra, India.

[2]Department of Pharmaceutics, SVPM's College of Pharmacy, Malegaon (BK II), Baramati, Pune- 413115, Maharashtra, India.

Received 31 July 2019; received in revised form 12 September 2019; accepted 18 September 2019

***Corresponding author E-mail address:** *tejas.vhora@gmail.com*

ABSTRACT

Colon Targeted drug Delivery system of Mesalamine was successfully formulated by compressional coating method. Initially Mesalamine core tablets were prepared by direct compression technique and subsequently core tablets were coated by using different proportion of Eudragit RS 100 as a P^H sensitive polymer and Sodium Alginate as a delayed release polymer. Mesalamine core tablets were prepared coated with polymeric coating solution. Mesalamine and excipient powdered mixture were evaluated by pre-compression parameters such as Bulk Density, Tapped Density, Hausner's ratio, Compressibility index and Angle of Repose. Powdered mixture of core Tablet formulations were showed acceptable results for pre-compression parameters. Polymeric Coating solutions were prepared by using Sodium alginate and Eudragit RS 100. Coated tablets were evaluated by different Post-compression parameter such as Hardness, Thickness, Diameter, Appearance, Friability test etc. Disintegration test were performed for prepared Core Tablets as well as Coated Tablets by using 0.1N HCL as well as phosphate buffer P^H 7.4. The Compression Coated tablets were evaluated by different IPQC and QC Tests like weight variation test, In-Vitro Dissolution study, Drug content uniformity, and stability study. All the prepared formulations shows appreciable amount of drug content and disintegration time. Drug and polymer compatibility were evaluated by FTIR study. The FTIR studies indicated that there was no interaction between drug and polymers. In In-Vitro dissolution studies different Dissolution models were studied for study of drug release kinetics of prepared optimized formulations of Colon Targeted drug delivery system. Optimized formulations F3 and F4 were showed the drug release according to First Order Model and Korsemeyer Peppas model.

KEYWORD

pH Sensitive Drug Delivery System, Colon Targeted Drug Delivery System, Mesalamine, Mesalazine, 5-Aminosalicylic Acid.

1. INTRODUCTION

The principle goal of the site specific delivery is to deliver the drug in the specific organ of body. The colon drug delivery has a number of important implications in the field of pharmacotherapy [1]. The therapeutic advantages of targeting the drug to the diseased organ include:

1. Targeted delivery of the drug in its intact form as close as possible its site of action.
2. Reduces conventional dose and frequency
3. Reduced incidence of adverse side effects.

Various diseases of colon such as ulcerative colitis, Crohn's disease, carcinoma and infections require local therapy. So that, the development of locally acting colon targeted drug delivery systems may revolutionize the treatment of colonic diseases [2]. In the recent times, the colon specific delivery systems are also gaining importance for the systemic delivery of protein and peptide drugs [3]. The peptide and protein drugs are destroyed and inactivated in acidic environment of the stomach and/or by pancreatic enzymes, the colon is considered to be more suitable for delivery of peptides and protein in comparison to small intestine. Further, drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of diseases that have peak symptoms in the early morning such as nocturnal asthma, angina, and arthritis [4].

Mesalamine (5-aminosalicylic acid, 5-ASA) was widely used in long-term treatment of ulcerative colitis by its topical mode of action on the inflammation in colonic mucosa. In order to achieve effective oral 5-ASA treatment with minimal side effect and acceptable patient compliance; the delivery system had to overcome many obstacles. Upon oral administration, 5-ASA exhibits rapid and nearly complete absorption from the upper intestine, resulting not only in systemic side effects but also in lowering the dose reaching the colon with the subsequent decreased probability of therapeutic success. Furthermore, in the case of ulcerative colitis, inflammation is observed in all regions of the colon. Therefore, if 5-ASA is released in a pulsatile manner in the ascending colon, 5-ASA would be diluted during its passage in the colon, consequently insufficient concentration of 5-ASA could be delivered to the transverse and descending colon resulting in decreased clinical effectiveness [5]. 5-ASA exhibits amphoteric property, its solubility is increased at acidic pH values (pH<2) in the stomach and at more alkaline values (pH>5.5) in the lower part of the small intestine.

1.1. Objective

1. To Sustain / Targeted Drug Delivery System.
2. To increase Solubility at Targeted site.
3. Combination of polymers and other components, and deeper understanding of human physiology are important for development of pH- and ion-sensitive polymeric DDS products for patients.
4. Targeted and controlled release system to be achieved.
5. Sustained / prolonged release polymer combination should be selected in such way that it should release the control amount of drug in specific time interval in order to reduce dosing frequency.

1.2. Criteria for drug selection

1. Drugs used for local effects in colon against GIT diseases.
2. Drugs poorly absorbed from upper GIT.
3. Drugs for colon cancer.
4. Drugs that degrade in stomach and small intestine.
5. Drugs that undergo extensive first pass metabolism.
6. Drugs for targeting

2. MATERIALS AND METHODS

2.1. Materials

Mesalamine was procured as gift sample from Wallace pharmaceuticals, Goa. Eudragit RS 100, PEG 6000 and HPMC K4M were procured from Evonik India, Mumbai. Starch, Sodium Alginate, Aerosil, magnesium stearate, Sodium di-hydrogen phosphate were obtained from Loba Chemicals, Mumbai. All other chemicals and reagents used were of chemical grade.

2.2. Methods

Mesalamine (5-aminosalicylic acid, 5-ASA) was widely used in long-term treatment of ulcerative colitis by its topical mode of action on the inflammation in colonic mucosa [6].

Mesalamine and polymer blend were prepared as per composition reported in table no.1 and pass through sieve no 44. Tablets were prepared on Karnavati (Rimek mini press -1, 8mm punch) rotary punching machine by Direct Compression method. The compression pressure is adjusted to obtain tablet with hardness in range of 4-5 kg/cm^2.

Table 1. Composition of Formulation design for Core Tablets.

Ingredient	**Formulation code**	
	Formula I (for Coating)	**Formula II (For FMT)**
Mesalamine	**150**	**150**
NaCl	**--**	**15**
Crosscarmellose (Ac-Di-Sol)	**--**	**08**
Starch	**40**	**--**
Microcrystalline cellulose	**60**	**--**
Talc	**05**	**06**
Magnesium stearate	**10**	**06**
Aerosil	**05**	**05**
Total weight	**250**	**190**

2.3. Coating composition

Table 2. Coating Composition for core Tablets

Ingredient	**F1**	**F2**	**F3**	**F4**	**F5**
PEG 6000	100 mg	100 mg	100 mg	100 mg	100 mg
Hydroxy Propyl Methyl Cellulose K4M	1 %	1%	1%	1%	1%

Sodium Alginate	2.5 %	2.5 %	12.5 %	12.5 %	1.5%
Eudragit RS 100	2.5 %	12.5 %	2.5 %	12.5 %	1.5%
Purified Water : Isopropyl Alcohol (19:1)	q.s.	q.s.	q.s.	q.s.	q.s.

Table 3. Coating Composition for Multilayer Tablet of Mesalamine.

Ingredient	FMT I	FMT II
Core Tablet	190	190
PEG 6000	5	5
Hydroxy Propyl Methyl Cellulose K4M	20	20
Sodium Alginate	100	----
Eudragit RS 100	40	40
Eudragit RL 100	----	100
Total Weight	355	355

Drug Mesalamine and all Ingredients were dried at 105°C in oven for 2 hours. All the powdered ingredients were weighed and mixed. This mixture was thoroughly blended manually and passed through a 44# sieve number. Then screened powder mixed with binder and lubricants and stored at room temperature for tableting.

2.4. Multilayer Tablet Process

The multilayer Tablets are mostly used for time release drug delivery. Core tablets were prepared by using Formula 2 in Table no 1, then the second layer of polymeric mixture composition were prepared and punched over the core tablets. The formulation FMT I and FMT II were prepared as Multilayer Tablet I (FMT I) and Multilayer Tablet II (FMT II).Tablet was punched in 8 mm diameter punches.

2.5. Characterization of Powdered Mixture

Before compression, powders were evaluated for their Characteristic parameters. Angle of repose was determined by funnel method. Bulk and tapped density were determined by cylinder method, Carr's index (CI) and Hausner's Ratio was calculated using following formula (4) and (5)

2.5.1. Angle of Repose [7]

A funnel was fixed at a particular height on a funnel stand. A graph paper was placed below the funnel on the table. The powdered drug passes through the funnel until it forms a pile. The radius of pile is noted. Angle of repose of the powder material was calculated using the formula.

Angle of repose $\theta = \tan^{-1}(h/r)$ --- Formula 1

Where h = Height of pile,

r = Radius of pile

2.5.2. Bulk density [8]

It is the ratio of total mass of powder to the bulk volume of powder. It is measured by pouring the weighed powder in to a measuring cylinder and the initial volume was noted. This initial volume is called as bulk volume. From this the bulk volume was calculated according to formula mentioned below. It was expressed in g/cc and is given by

Bulk density = Weight of powder in gm /Volume in ml --- Formula 2

2.5.3. Tapped density

It is ratio of mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 50 times. Then the tapping was done for 100 times and the tapped volume was noted. It is expressed in g/cc and is given by

Tapped density = Weight of powder in gm/Tapped volume in ml --- Formula 3

2.5.4. Carr's index (% compressibility) [8]

Based on the apparent bulk density and tapped density, the percentage compressibility of drug was determined by using the following formula.

$$\boldsymbol{CL} = \frac{(\boldsymbol{Tapped\ Density - Bulk\ Density})}{\boldsymbol{Tapped\ Density}} \boldsymbol{x\ 100}$$ --- Formula 4

2.5.5. Hausner's ratio [8]

Hausner's ratio of microparticles was determined by the comparing tapped density to the bulk density using the equation

$$\boldsymbol{Hausner's\ ratio} = \frac{\boldsymbol{Tapped\ density}}{\boldsymbol{Bulk\ density}}$$ --- Formula 5

All the experiments were done in triplicate.

2.6. Compatibility Study of Drug and Polymers by Fourier – transform infrared (FT – IR) Spectroscopy

Compatibility studies of drug – polymer were performed in order to confirm the drug excipient compatibility. It mainly included Fourier – transform infrared (FT – IR). FTIR spectrum of pure drug Mesalamine (Fig. 1(A)) and Polymer such as Eudragit RS 100 (Fig. 1 (B)) and Sodium alginate (Fig. 1 (C)) was studied and compared with physical mixture of polymer and drug. In this the physical mixture of the drug with polymer is prepared and used in compatibility study. The results were reported in Fig. 1(D)

2.7. Preparation of Tablets

Tablets weighing 250mg containing 150mg of Mesalamine were compressed on ten-station rotary machine (Karnavati, Rimek mini press -1, 8mm punch) 8mm round, concave, plain die-punch.

2.8. Evaluation of prepared colon specific Tablet Formulations by In Process Quality Control (IPQC) and QC tests [9]

The properties of the compressed tablets, such as diameter, thickness, hardness, friability, Weight variation and content uniformity were determined using reported procedure. Briefly, diameter, thickness were determined by Varnier calliper (Mitutoyo, CD-6 CS), hardness was determined using Monsanto hardness tester (Campbell Electronics, Mumbai, India) and friability was determined Campbell friability testing apparatus. Drug content studies were carried out to evaluate the amount of drug present in the prepared tablet.

2.9. Determination of drug content [9]

Randomly, 20 tablets were selected from each formulation and tested for its drug content. The tablets were finely powdered; quantities of powder equivalent to 10 mg of Mesalamine were accurately weighed and transferred to 100 ml volumetric flask. The flask was filled with a 0.1 N HCl solution and mixed thoroughly. 1ml of filtrate was further diluted to 10ml of 0.1 N HCl and was measured the absorbance of resulting solution at 303 nm using UV- Visible double beam spectrophotometer (1700, Shimazdu, Japan).

2.10. Preparation of Polymeric Coated Tablets

Polymeric Coating Solutions were prepared by using different composition of Eudragit RS 100 and Sodium alginate. Tablet core formulation Formula 1 was selected to optimize the coating solution formula. Various formulations for coating solution are as mentioned in table no. 2. Distilled Water is used as solvents, PEG 6000 as plasticizer, HPMC K4M used for coating uniformity, Sodium Alginate as delay release polymer and Eudragit RS100 as pH sensitive polymer. All the coating ingredients were sieved through 60# and Coating solution was prepared by aqueous (Purified Water: Isopropyl Alcohol (19:1)) Solution prepared of Sodium Alginate and Eudragit RS100 with constant stirring. Small amount of Isopropyl alcohol used for the preparation of solution of Eudragit RS 100. Core tablets were coated with coating solution in an automatic perforated coating pan. Initially pan was rotated at low speed (3-5rpm) and heated air was passed through tablet bed. Coating process was started only if outlet temperature was reached to 30°C. Coating pan rpm was maintained in a range of 15-20 rpm and coating solution was applied at a rate of 5-7 ml/min. Coating process was continued until desired weight was gained on tablet core. For all formulations, coated tablets were dried at 40°C for 3 hours before evaluation.

2.10.1. Viscosity Test

The coating sample was taken and placed on the stage of Digital Brookfield viscometer and the spindle no 1 used for evaluation of polymeric coating solution.

2.10.2. Appearance

Appearance of Compression coated tablets was studied by visual inspection. It is required for uniform polymeric coating of tablet.

2.10.3. Percentage Weight Gain

% Weight gain defined by difference between weight of tablets after coating (W_{ta}) and weight of tablets before coating (W_{tb}) divided by weight of tablets before coating. It was calculated by following equation.

$$\%Weight\ Gain = \frac{Wta - Wtb}{Wtb} \times 100$$ ---Formula 6

2.10.4. Disintegration Test [9]

Disintegration testing of coated dosage forms was carried out in the six tablet basket rack USP disintegration apparatus. One tablet was introduced into each tube of the basket rack assembly of the disintegration apparatus without disc. The assembly was positioned in the beaker containing 0.1N HCl (pH 1.2) maintained at 37±2°C and operated the apparatus for 2 hours. After 2 hours 0.1N HCl was replaced with phosphate buffer 7.4 pH. A disc was added to each tube and operated for further 60 minutes. The disintegration time of each tablet was recorded.

2.11. In vitro drug release study

The in vitro release study was carried out in the USP XXIV dissolution test apparatus (Campbell electronics; TDT 08L Dissolution tester USP) type II (PADDLE).

For In- Vitro release study two dissolution medium such as 0.1 N HCl Phosphate buffer pH 6.0 and Phosphate buffer pH 7.4.

1. For first two hours 0.1 N HCl was selected as a dissolution medium.
2. After two hours dissolution medium was replaced by Phosphate buffer 6.0 for three hours.
3. Consecutively, after three hours in Phosphate buffer pH 6.0 dissolution medium was replaced by phosphate buffer pH 7.4.

Set of parameter for dissolution study of different formulations of Mesalamine Tablet:

1. Apparatus used :- TDT 08L Dissolution tester USP Type II (Paddle)
2. Dissolution Medium :- 0.1 N HCl, Phosphate buffer pH 6.0 and Phosphate buffer pH 7.4
3. Volume of Dissolution medium:- 900 mL
4. Set Temperature:- 37±0.5 ^{o}C
5. Set RPM :- 75 RPM in 0.1N HCl and phosphate buffer pH 6.0, 100 RPM for Phosphate Buffer pH 7.4
6. Sampling Interval: - 1hrs, 2hrs, 3hrs, 4hrs, up to 10 hrs.
7. Volume of sample withdraw:- 1 ml
8. Dilution factor:- 50
9. Strength of tablet:- 150 mg of Mesalamine

The sample were removed at different time intervals, diluted with either HCl / Phosphate buffer and finally analysed by using UV Spectrophotometer (Shimazdu UV 1800) at 303 and 330 respectively.

2.12. In vitro Release kinetics of Compression Coated Tablets

To study release kinetics, data obtained from in vitro drug release studies was plotted in various kinetics models; Zero Order as cumulative percentage of drug unreleased Vs. time, First order as a log cumulative percentage of drug remaining Vs. time, Hixson-Crowell Cube Root Law Model as the cube root of percentage of drug remaining in the matrix Vs. time, and Higuchi Model [10] as the square root of time Vs. % drug release. The dissolution data was also fitted to the

exponential equation of Peppas Korsemeyer model, which is often used to describe drug release behavior from polymeric systems [11].

This study was determining the best fit mathematical model for formulations F1 to F5. R^2 values for different mathematical models were determined. The model for which the R^2 value was the highest was considered the best fit model for the concerned formulation.

2.13. Accelerated Stability Study [12]

Stability of a drug can be defined as the time from the date of manufacture and the packaging of formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency (90%) and its physical characteristics have not changed appreciably. ICH specifies length of study and storage conditions.[109 Stability] Study was carried out as per ICH guidelines. The optimized formulation were wrapped in the laminated aluminum foils and was placed in the accelerated stability chamber at elevated temperature and humidity conditions of 40 ^{0}C/ 75% RH and a control sample was placed at an ambient condition for a period of three months. Sampling was done at a predetermined time of initial 0, 1, 2 and 3 months interval respectively.

3. RESULTS AND DISSCUSSION

3.1. Evaluation of Powder Flow Properties [7]

The Formulation were evaluated by measuring the parameters such as bulk density, tapped density, angle of repose, Hauser's ratio, compressibility index and drug content. The results are shown in table 4.

3.1.1. Angle of Repose

The results of angle of repose (<30) indicate good flow properties and the value for prepared formulations ranges from 27.4^o - 29.79^o

3.1.2. Hausner's Ratio

The value of Hausner's ratio is under satisfactory ranges such as 1.17 - 1.24, that was in good flow property

3.1.3. Compressibility or Carr's index

The values indicate good flow properties and values for all formulation range from 15.22 % - 18.56%.

All these results obtained indicate that the powder possessed good flow properties.

Table 4. Values of Pre-Compressive Parameter.

Formulation Code	Angle of Repose	Bulk Density (g/ml) ± S.D	Tapped Density (g/ml/)±S.D	Hausner's Ratio ± S.D	Carr's Index (%) ± S.D
F1	27.4± 0.98	0.1941±0.000	0.24±0.0013	1.237±0.001	19.18±0.8
F2	29.88±1.00	0.1931±0.001	0.235±0.003	1.216±0.01	17.81± 0.5
F3	27.56±1.84	0.1926±0.000	0.2272±0.0023	1.179±0.017	15.22± 1.2
F4	29.19±0.33	0.1931±0.001	0.2372±0.0046	1.228±0.032	18.56± 2.9

F5	29.79±1.23	0.1922±0.001	0.2328±0.0012	1.205±0.015	17.04± 1.0
FMT I	29.24±0.98	0.194±0.0002	0.2024±0.0012	1.216±0.017	17.81±1.1
FMT II	29.39±1.18	0.1918±0.003	0.2007±0.0032	1.246±0.006	19.77± 0.4

3.2. Compatibility Study of Drug and Polymers by Fourier – transform infrared (FT – IR) Spectroscopy

3.2.1. FTIR spectrum of Mesalamine

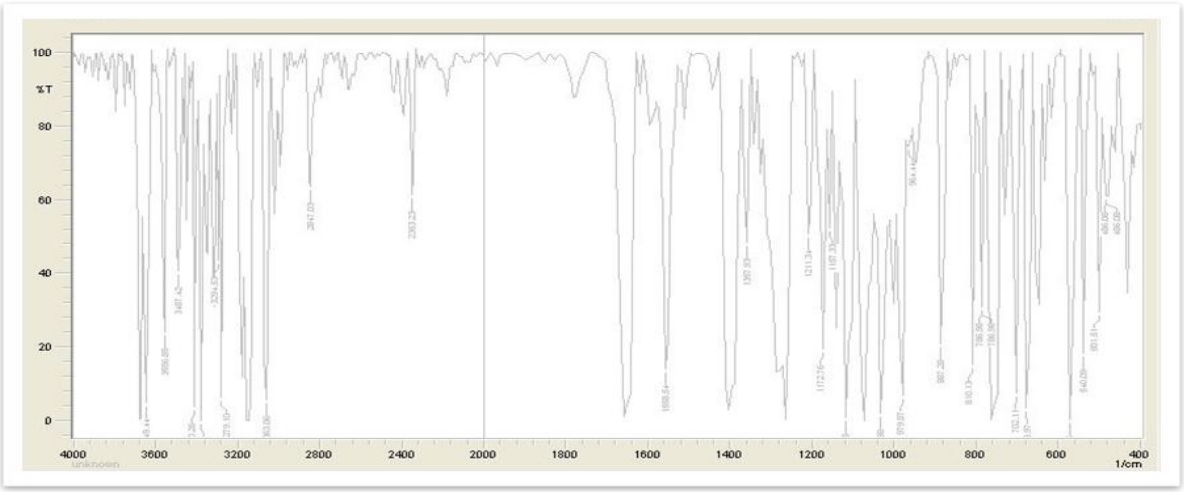
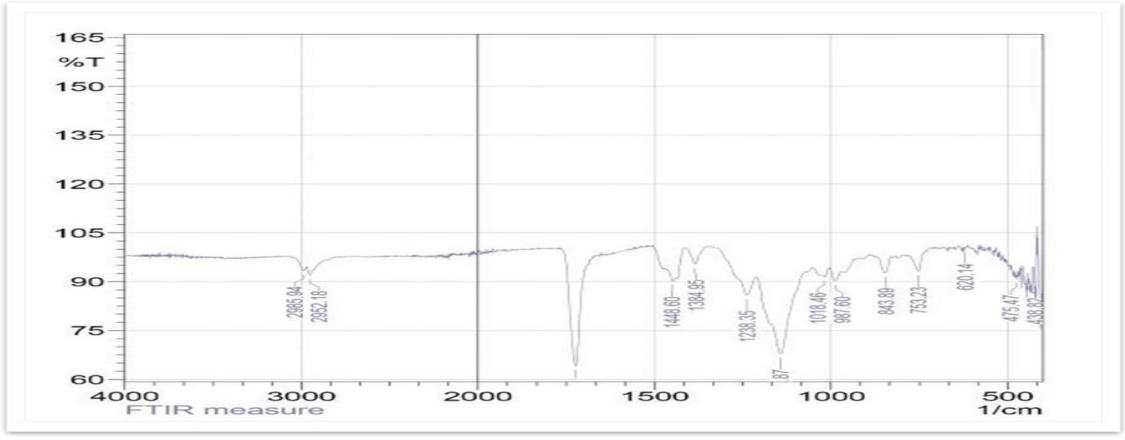


Fig. 1. FTIR Spectrum of Mesalamine.

3.2.2. FTIR Spectrum Of Eudragit RS100



.

Fig. 2. FTIR Spectrum of Eudragit RS 100.

3.2.3. FTIR Spectrum of Sodium Alginate

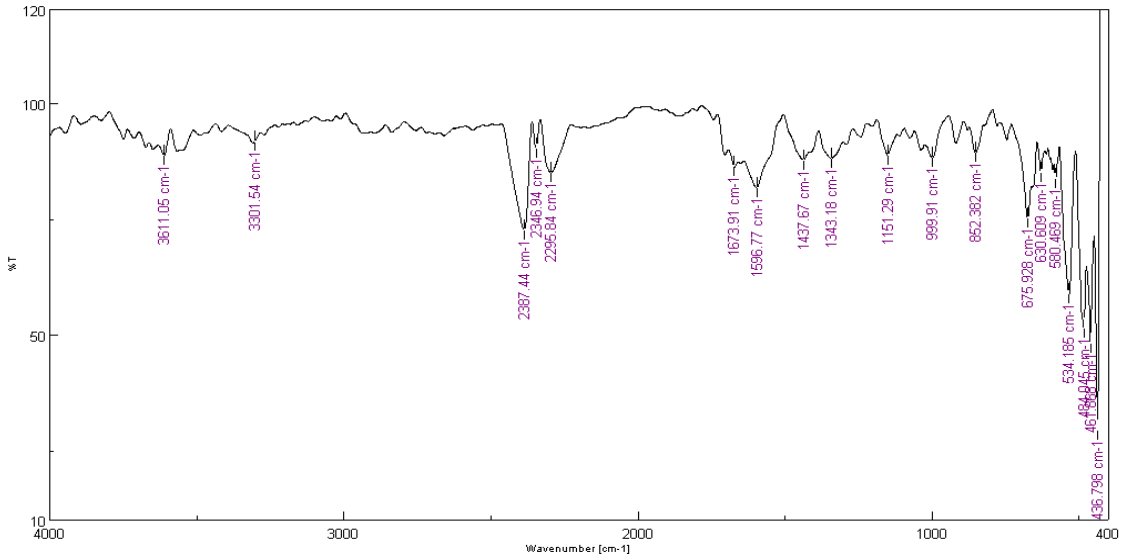


Fig. 3. FTIR interpretation of Sodium Alginate.

3.2.4. Drug – polymers compatibility studies: Mixture of Mesalamine +Eudragit RS 100+ Sodium Alginate.

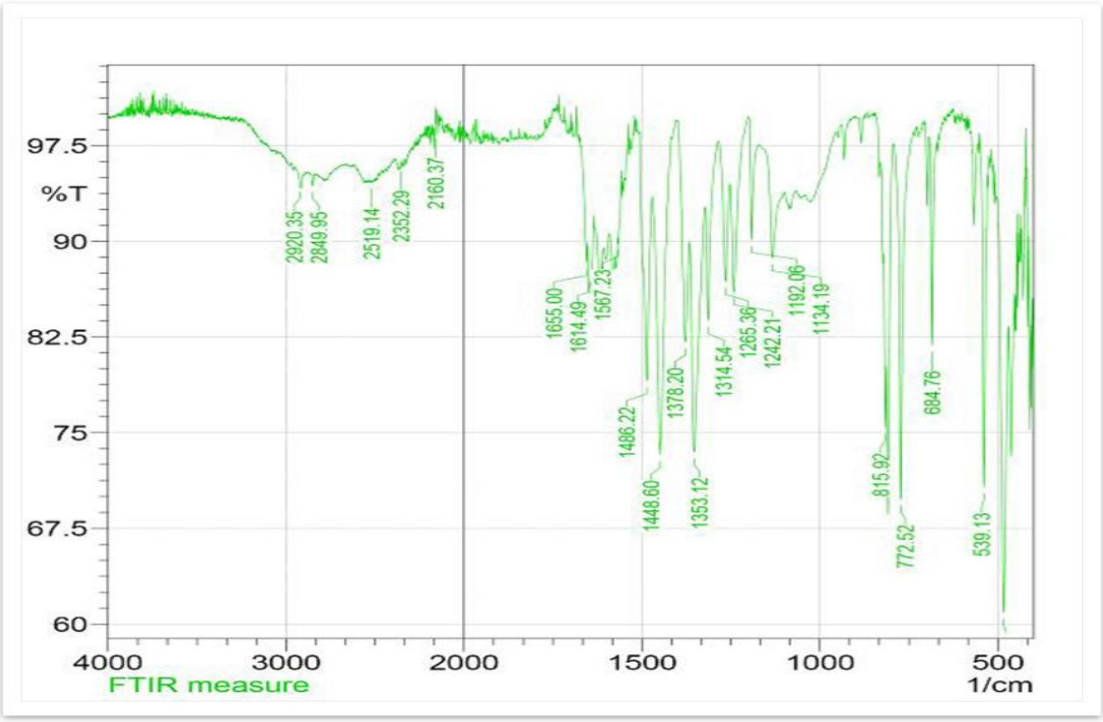


Fig. 4. Drug-polymer compatibility study: Mixture of Mesalamine +Eudragit RS 100+ Sodium Alginate.

In Spectra of (A) Mesalamine, medium and sharp peak at 3649.44 cm^{-1} observed O-H stretching, weak C-O stretching at 1211.34 $cm^{-1}$was alkenes group attached to Mesalamine. Medium =C-H stretching observed at 3379.40 cm^{-1} , 3294.53 cm^{-1}, 3279.40 cm^{-1} of alkynes group, where –CH rocking at 1358.54 cm^{-1}. Weak NH group observed at 810.13 cm^{-1} and 887.28 cm^{-1} due to presence of amine group in drug.

In spectra of (B) Eudragit RS100 , medium C-H stretching observed at 2985.94 cm^{-1} and 2958.18 $cm^{-}1$, where medium bending observed at 1448.6 cm^{-1} of methyl Alkane group and strong bending at 753.23 cm^{-1} of 1,2- Disubstitution. Strong C=O stretching observed at 1723.47 $cm^{-1}$of aldehyde group.

In spectra of (C) Sodium alginate, strong O-H stretching observed at 3301 cm^{-1} of carboxylic acid. Medium C-H wagging observed at 1151.3 cm^{-1} of alkyl group, where as medium =CH bending obtained at 999.9 cm^{-1} of alkenes functional group and low C-H peak observed at 862.3 cm^{-1} of Alkane.

In physical mixture of Mesalamine + Eudragit RS 100 + Sodium alginate(D), 2920.35 cm^{-1} and 2849.95 cm^{-1} were observed as strong and broad peak of N-H stretching of amine salts from drug molecule. Ketene group –C=C- was confirmed by strong peak of 2160.37 $cm^{-1.}$ 1655 cm^{-1} was observed medium peak of cis 1,2- Disubstitution of C=C, where O-H bending observed at 1448.60 cm^{-1} appeared in medium peaks of carboxylic acid compound. C-O Stretching observed by 1134.19 cm^{-1} and 1192.06 due to saturation of bonds where medium bending observed at 1314.64 cm^{-1} of aromatic group.

3.3. Evaluation of prepared colon specific Tablet Formulations by In Process Quality Control (IPQC) and QC tests [9]

The tablet formulations were subjected to various posts – compressive evaluation tests. Such as Drug Content, Hardness, Friability, Weight variation. The results for all formulations were shown in Table 5-7.

3.3.1. Hardness

The general specification for Hardness of modified release tablets should lies between 3.5 Kg/cm^2 and 8.0 Kg/cm^2. The prepared core tablet showed hardness in between 3.567 Kg/cm^2 to 3.944 Kg/cm^2 and Coated Tablet were 4.533 Kg/cm^2 to 5.266 Kg/cm^2. Hence it complies with general specification for hardness of tablet.

Table 5. Tablet Hardness of uncoated and coated tablets.

Formulation Batches	**Core /Uncoated Tablet Hardness Mean ± S.D (Kg/cm^2)**	**Coated Tablet Hardness Mean ± S.D (Kg/cm^2)**
F1	3.66 ± 0.28	4.56 ± 0.05
F2	3.87 ± 0.11	4.93 ± 0.11
F3	3.83 ± 0.35	5.26 ± 0.11
F4	3.56 ± 0.05	4.53 ± 0.23
F5	3.76 ± 0.05	5.06 ± 0.11
FMT I	3.71 ± 0.17	4.27 ± 0.35
FMT II	3.94 ± 0.24	4.67 ± 0.47

[All values was expressed as Mean± SD (n=5)]

3.3.2. Thickness

The prepared core tablet showed thickness in between 5.61 mm to 5.76 mm similarly for coated tablets were 5.69 mm to 5.79 mm. similarly Core Formulation FMT I and FMT II were 3.84 mm and 3.92 mm in multilayer 6.26 mm to 6.46 mm.

Table 6. Tablet Thickness of uncoated and coated tablets.

Formulation Batches	Core / Uncoated Tablet Thickness Mean ± S.D (mm)	Coated Tablet Thickness Mean ± S.D (mm)
F1	5.68 ± 0.34	5.69 ± 0.30
F2	5.78 ± 0.16	5.79 ± 0.12
F3	5.75 ± 0.15	5.79 ± 0.08
F4	5.76 ± 0.15	5.76 ± 0.24
F5	5.61 ± 0.08	5.73 ± 0.32
FMT I	3.84 ± 0.42	6.46 ± 0.16
FMT II	3.92 ± 0.35	6.26 ± 0.24

[All values was expressed as Mean± SD (n=5)]

3.3.3. Diameter

Table 7. Tablet Diameter of uncoated and coated tablets.

Formulation Batches	Uncoated Tablet Diameter Mean ± S.D (mm)	Coated Tablet Diameter Mean ± S.D (mm)
F1	8.63 ± 0.01	8.72 ± 0.02
F2	8.71 ± 0.005	8.87 ± 0.11
F3	8.67 ± 0.11	8.80 ± 0.06
F4	8.74 ± 0.01	8.96 ± 0.06
F5	8.77 ± 0.08	8.92 ± 0.12
FMT I	8.47 ± 0.2	9.12 ± 0.18
FMT II	8.51 ± 0.11	9.08 ± 0.27

[All values was expressed as Mean ± S.D (n=5)]

The prepared core tablet showed diameter in between 8.63 mm to 8.77 and for coated tablet were 8.72 mm to 8.96 mm. similarly FMT I and FMT II were in core were 8.47 mm to 8.51 mm and in multilayer 9.08mm to 9.12 mm.

3.4. Evaluation of Prepared Compression coated Tablet

The prepared colon specific Tablet Formulation was showed the weight variation within limit of 250 ± 18.75 mg as per IP. The prepared formulations F1-F5 and FMT I and FMT II colon targeted tablets shows weight variation in between 0.38% to 0.58%.

The Friability limit as per IP and USP were 1% and prepared Formulation were shows 0.4978% - 0.5698%. Hence formulation F1 – F5 were complies with IP and USP.

The Disintegration test were carried out for which given formulation disintegrates with respect to time, Disintegration test was performed using two different medium 0.1 N HCl and phosphate buffer pH 7.4.

Table 8. Evaluation of prepared compression coated Tablet by weight variation, Friability and Disintegration Test.

Formulation Code	Weight Variation (%)	Friability (%) Mean	Disintegration Test (min)	
			0.1 N HCl (2 hrs.)	Phosphate Buffer pH 7.4 (1 hr.)
F1	± 0.58	0.530	No Change	32.4 ± 0.5
F2	± 0.45	0.514	No Change	31.35 ± 0.5
F3	± 0.53	0.497	No Change	35.45 ± 0.45
F4	± 0.51	0.569	No Change	34.46 ± 1.5
F5	±0.38	0.541	No Change	3.3 ± 0.52
FMT I	±0.43	1.278	39 ± 1.45	---
FMT II	±0.81	1.626	46 ± 1.2	---

[All values was expressed as Mean± SD (n=3)]

Formulation F1-F5, showed disintegration time more than 2 hours in 0.1 N HCl; while disintegration time in between 31.35 min to 35.45 min in phosphate buffer pH 7.4.

According to IP and USP specifications delay release tablets should not disintegrate in 1-2 hrs in 0.1N HCl hence formulations F1 – F5 complies with specifications While in case of FMT I and FMT II both formulations were disintegrated within 45 min in 0.1N HCl and hence does not complies with IP and USP specifications for disintegration time and hence not studied further.

3.5. Drug Uniformity [9]

The delayed release or sustained dosage form of Mesalamine was according to I.P. contains 95% - 105% drug content. While the prepared formulation of Mesalamine for colon specific tablet showed percentage drug content in between 95.73%-99.93%. Hence all formulation complies with drug uniformity test according to I.P.

3.6. Evaluation of Coating Formulations by Viscosity Test

The viscosity of polymeric coating solutions were determined by using digital Brookfield viscometer. As the polymer concentration increased the viscosity of polymeric coating solutions were increased as shown in following table 10. The obtained viscosity of different coating solution was shown in between 21 CP to 35 CP at 25^{o}C.

Table 9. Viscosity of Coating solution.

Formulation Code	F1	F2	F3	F4	F5
Viscosity (at 25^{o}C) C.P.	**21**	**19**	**28**	**35**	**18**

During application of polymeric coating solution in tablet coating process it was observed that all the batches except batch F3 showed difficulty during application of polymeric coating solution

uniformly around the surface of tablets as well as difficulty like sticking of tablets to one another and difficulty during drying. F3 and F4 both formulations were showed higher viscosity as compared to other formulations because the proportions of sodium alginate in both formulations were 12.5%. But F4 formulation shows highest viscosity as compared to F3 formulation because the polymers, sodium alginate and Eudragit were used in higher proportion i.e. 12.5% and hence F4 batch shows orange peel effect and drying problem due to highest viscosity. But batch F3 shows uniform distribution of polymeric coating solution and faster drying due to optimum viscosity i.e. 28 CP and hence more superior results as compared to other batches. Hence, it can be concluded that on the basis of coating technique F3 batch was optimized batch.

3.7. Evaluation of Coated Tablets by Appearance

Table 10. Appearance of Compression Coated Tablets.

Formulation Code	**F1**	**F 2**	**F 3**	**F 4**	**F 5**
Appearance	Rough thin Surface	Rough thin surface	Uniform thick Surface	Rough uneven Surface	Rough thin surface

The appearance of compression coated tablets were visually observed and shown in above table 11. All the formulations were showed thin or thick layer which can determine or predict the drug release performance of tablet. The formulation F3 showed more uniform distribution of polymeric coating solution as well as formation of thick coating layer of polymeric solution which may retard the drug release. While F4 batch showed unequal distribution of polymeric coating solution also found more difficulty during coating process due to high viscosity of polymeric solution i.e. 35CP**.**

3.8. Evaluation of Coated Tablets by Percentage Weight Gain

After coating process, different formulations of Mesalamine tablets were evaluated by % weight gain. The % weight gain was found in between 6.1 % to 11.79% for formulation F1 to F5. According to previously reported research articles[120] maximum % weight gain after coating should lies in between 5% - 60%.

Table 11. Tablet % Weight gaining.

Formulation Code	F1	F 2	F 3	F 4	F 5
% Weight Gain	7.11	9.14	11.79	11.32	6.1

3.9. In Vitro Drug Release Study

Formulation from F1 to F5 and FMT I, FMT II all showed different result because of different concentration of polymer used. As the concentration of Sodium Alginate and Eudragit RS100 were changed. The drug release affect and gets changed. All the formulation were added to 900 mL of dissolution medium thermostated at 37 ± 0.5 C and stirred at 75 rpm, which was varied

according to the following sequence, in order to mimic the gastrointestinal transit, 2 h artificial gastric juice (pH 1.2, 0.1 N HCl solution); 3 hrs in phosphate buffer pH 6.0; 6 hrs artificial colonic fluid (Phosphate Buffer pH 7.4). As percentage cumulative drug release, of F3 batch shows 3.8% drug releases at 2 hrs. in 0.1N HCl and 102 in 3 hrs in Phosphate buffer 6.0 and sequentially Phosphate Buffer pH 7.4 at the end of 9 hr.

Table 12. Cumulative (%) Drug Release of Formulation F1-F5 batches.

Time	**Time (min)**	**Cumulative % Drug Release**				
(Hrs.)	0.1N HCl	F1	F2	F3	F4	F 5
0	0	0.0	0.00	0.00	0.00	0.00
1	60	3.1	2.5	2.3	3.3	3.2
2	120	5.3	4.2	3.8	4.8	5.8
Phosphate Buffer pH 6.0						
3	180	7.11	6.7	5.4	6.17	7.8
4	240	8.8	8.43	6.9	8.1	9.1
5	300	10.81	10.49	8.64	9.7	11.4
Phosphate Buffer pH 7.4						
6	360	74.4	69.1	37.4	46.8	81.8
7	420	101.1	100.2	57.8	63.5	99.9
8	480	---	---	86.7	81.4	---
9	540	---	---	102	98.1	---

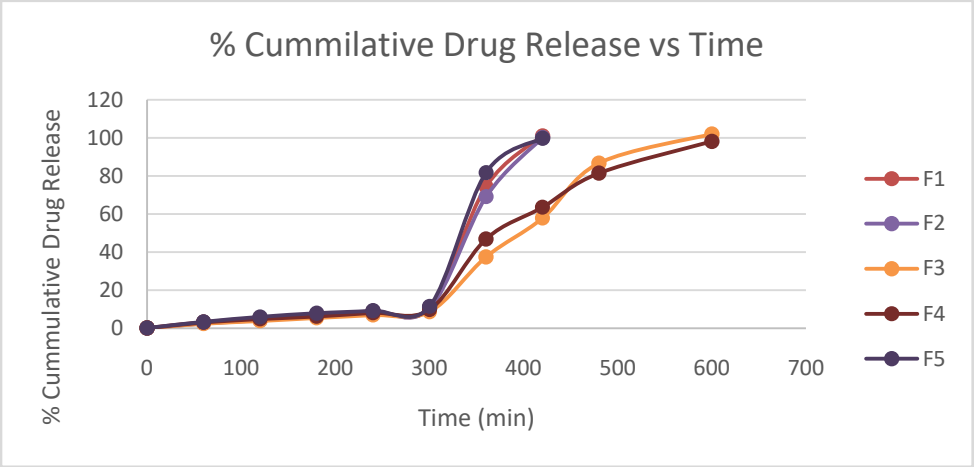


Fig. 5. Dissolution Study of F1-F5.

All 5 formulations from F1 to F5 showed different result. Reason may be beacause of changed proportion of sodium alginate and eudragit RS 100. The ability of the compression coated tablets to remain intact in the physiological environments of the stomach and small Instinstine was assessed by conducting drug release studies under varying pH according to mouth-to-colon transit. Drug release studies were carried out using an USP dissolution rate test apparatus (apparatus 1, 50/100 RPM, 37^{o}C) for 2 hours in 0.1 N HCl (900 ml) as the average gastric emptying time is about 2 hrs. Then the dissolution medium was replaced with phosphate buffer

pH 6.0 (900 ml) and tested for drug release for 3 hours as the average small Instestine transit time is about 3 hours. Finally dissolution medium was replaced with phosphate buffer pH 7.4 (900ml) and tested for drug release for 7 hours.

Hydration of sodium Alginate matrix quickly forms the viscous gel layer in the presence of water or aqueous medium to produce controlled drug release. Eudragit RS 100 was selected as additional coating Polymer to resist the lower pH values to upper Gastrointestinal tract (GIT),but since eudragit RS 100 is a pH sensitive polymer. Hence, dissolves in moderately alkaline pH of the lower GIT.

To identify the best proportion of sodium Alginate and eudragit RS 100 as compression coated polymers and to determine the optimum amount of eudragit RS 100 to produce colon specific delivery of mesalamine in the compression coat (F1-F5), In Vitro drug release studies were performed. The formulation containing 12.5% sodium Alginate and 2.5% eudragit RS 100 was considered as a better formulation as compared to other formulations to produce the colon specific delivery of mesalamine. In all formulations the proportion of HPMC K4M and PEG 6000 were used in same proportion i.e. 1% and 100 mg respectively. PEG 6000 was used as a plasticizer and HPMC K4M was used as film former.

Amongst the all formulations, formulations F3 and F4 showed best results for percentage drug release in phosphate buffer pH 7.4. but in formulation F3 the proportion of sodium Alginate and eudragit RS 100 were used 12.5% and 2.5% respectively.

But in case of F4 formulation the proportion of sodium Alginate and eudragit RS 100 were used in highest proportion i.e. both were used in same proportion i.e. 12.5 % respectively.

According to the data of percentage drug release study of formulation shows less than 11.4 % drug release in 0.1N HCl (refers stomach environment) as well as in phosphate buffer pH 6.0 (refers small intestine environment). As expected in phosphate buffer pH 7.4, the formulation F3 and F4 shows 100% drug release at the end of 7 hours.

According to data of obtained results the concentration of sodium Alginate and eudragit RS 100 were 12.5% and 2.5% respectively in F3 batch and 12.5% and 12.5% respectively in batch F4. As seen in drug dissolution data, the both batches were shown expected drug release in 7 hrs, in phosphate buffer pH 7.4. But as compared to F3 batch F4 batch containing high proportion of Euragit RS 100 while F3 batch contained only 2,5% Euragit and hence showed excellent results as compared to Formulation F4. Hence, the batch F3 selected as optimized batch.

3.10. Dissolution Kinetics of Formulation

The dissolution data of all formulation, was obtained, and was fitted to various kinetics models like Zero order, First order, Higuchi model, Korsmeyer-peppas model.

3.10.1. First – Order Dissolution Model

Fig. 6. First Order Kinetic Model.

In F3 Formulation the sodium alginate was higher as12.5% and Eudragit RS 100 was low as 2.5%. The high concentration of sodium alginate was cause increase in viscosity, so that the mixture of Eudragit RS 100 and sodium alginate form the perfect coating viscosity. As we seen in cumulative drug concentration at 9 hours was 102%. The first order drug release was concentration gradients release and the regression values were 0.949 and were show slight sigmoid curve. The Korsemeyer Peppas model was perfectly obey by the F3 formulation batch. The highest regression value means steady state drug release. The regression value was found to be 0.9707 and 'n' value define supercase II transport drug diffusion kinetics. The given F3 Formulation had 2.762 that were above 1 and shows supercase II drug release. So that given models shows the Formulation F3 batch was Supercase II transport drug Diffusion release kinetics.

In F4 Formulation, Eudragit RS 100 and sodium alginate was in their highest concentration as designed in table 2. The higher concentration can cause higher viscosity of the coating solution. Hence Formulation was show the uneven rough tablet coating. The drying process was prolonged and easy to coat the tablets. The percentage of cumulative drug release was at 9 hours and concentration was 98.1% much lower than other batches. First order drug release, as we saw, was depending on concentration gradients, regression value was 0.964.The Korsemeyer Peppas model regression value was 0.9659 and 'n' value which defines Supercase II transport kinetics and was 2.68.

3.10.2. Korsemeyer Peppas Model

Korsemeyer-Peppas model studied by equation and model of fit, the given diagram shows a compared study of the given equation. Model of fit are the predicted value calculated from equation. The standard deviation between % CDR and Model of fit shows the non-linearity so that we can assure the drug release are fickian lies between $0 < 0.45$ are shows the uniformity.

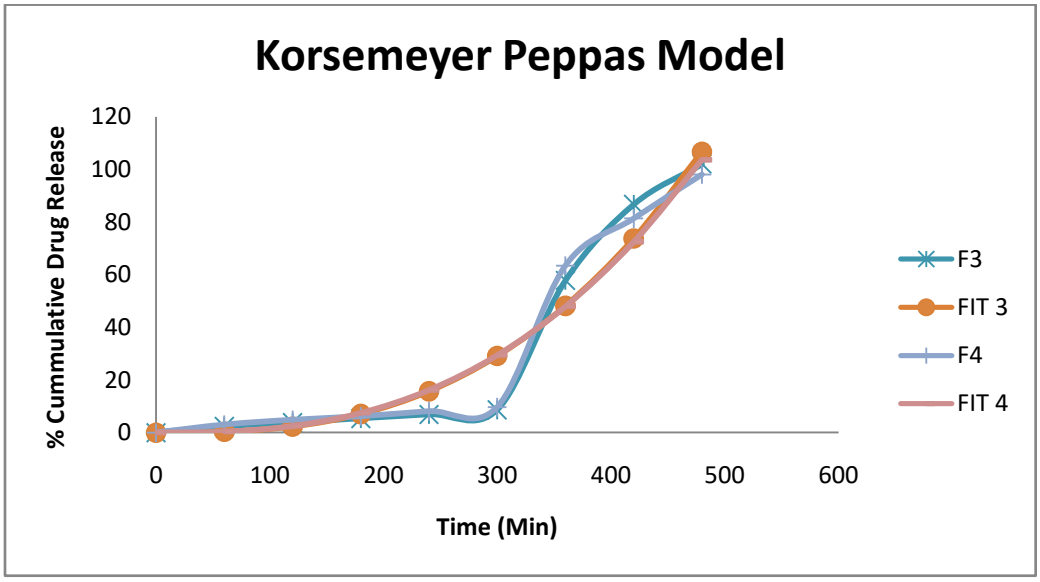


Fig 7. Korsemeyer Peppas Model Plot.

The above plot were contains the F3 and F4 percentage cumulative drug concentration and predicted value calculated from formula of Korsemeyer Peppas model ($M_t/M_{oo}=Kt^n$). The predicted value was defined by 'FIT'. The calculated FIT value was close to respected Formulations. The correlation between Formulation and predicted FIT curve values were calculated. And this regression R^2 was show in table 14.

The optimized Formulation F3 was showed the Korsemeyer Peppas model in Super Class II non fickian diffusion state, and regression value was 0.9706 and n value was 2.7931.

By plotting Log (%CDR) vs. Log (Time) Shows the given formulation are passes the Korsemeyer Peppas model for dissolution. The plots are shown as per following figure 8;

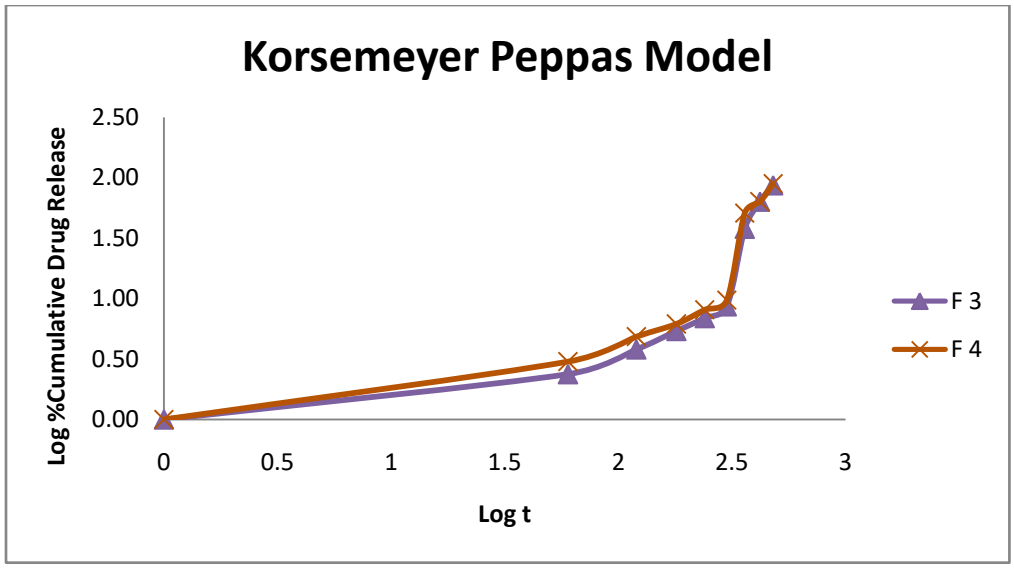


Fig. 8. Logarthmatic plot of Korsemeyer Peppas model.

3.11. Dissolution Kinetics Profile

The release kinetics of formulation was determined by various models like Zero-Order; first order model, Higuchi model, Korsmeyer - Peppas Model. The best fitting model was determined from the regression coefficient (R^2) and exponent (n). The formulations F1-F5 was followed the Korsemeyer Peppas Dissolution kinetic model. The regression coefficient (R^2) and release exponent (n) of all formulation were reported in the table no. 14.

Table 13. Dissolution Kinetic Profile.

Code	**R^2 Values of Dissolution Kinetic model**			**Best Fit Model**
	First Order Kinetics	**Korsemeyer Peppas model**		
	R^2	**n**	**R^2**	
F1	0.916	2.901	**0.9560**	K.P. Model
F2	0.933	2.773	**0.9565**	K. P. Model
F3	**0.949**	2.762	**0.9707**	First order, K. P. Model
F4	**0.964**	2.68	**0.9659**	First order , K. P Model
F 5	0.911	2.793	**0.9461**	K. P. Model

The n value obtained from the Korsemeyer Peppas model is used to characterize the release mechanism was compared with the standard Values [10]. The value n was greater than 1 hence the formulation follows the Super case II Transport release.

Drug release data of F3 formulation showed good fitted in first order equation (r^2=0.949), partially fitted in zero order equation (r^2=0.835), and high linearity in Korsemeyer equation (r^2=0.9706), value of release exponent *n* determined for F3 in differential pH environment is 2.707 indicating combined effect of diffusion and predominantly erosion mechanism for controlled release.

3.12. Accelerated Stability Study [11]

The stability of compressed coated Tablets was evaluated for 0, 30 and 60 days. The Drug stability was shown by formulation in table 15. Stability of Compression Coated tablet formulation F1 to F5 was carried out at $37^o \pm 0.5^o$ C temperature and at 75 ± 5 % RH as per ICH guidelines. The drug Contents were found out in between 94.5% - 98.7% after one month and 92.2% - 96.6% after two months.

Table14. Evaluation of formulation F3 kept for stability study at 40±2 ^{o}C and 75±5% RH.

Parameters	**Initial**	**After 1st month**	**After 2nd month**
Shape	Round, oval	No Change	No Change

Colour	Pinkish-gray	No Change	No Change
Odour	Characteristics	No Change	No Change
Weight Variation (%)	± 0.49%	± 0.64%	± 0.65%
Hardness (kg/cm^2)	4.9± 0.2	4.7 ± 0.6	4.6± 0.3
Friability (%w/w)	0.371%	0.41%	0.443%
% Drug content	99.1%	98.7%	98.6%

The Tablets were evaluated for hardness, friability, weight variation and % drug content. The results of stability studies showed the physical and chemical properties of the tested tablets (F3) were not altered significantly in that formulation. So these may considered as stable formulation.

4. CONCLUSION

Compression coated tablets of Mesalamine were prepared using Sodium alginate as delay release polymer and Eudragit RS 100 as pH sensitive polymer. In this study, Sodium Alginate and Eudragit RS 100 compression coated tablets were prepared to retard the drug release in lower GIT to gain colon targeting. From the FT-IR spectra, the interference was verified and found that Mesalamine did not interfere with the excipients used and accelerated stability studies showed the stability of tablet.

Core tablets of Mesalamine (F-3) were successfully prepared by direct compression method using polymers like Magnesium stearate, microcrystalline cellulose, and starch as excipients and binder, respectively. Disintegration Test of optimized batch F3, formulation was found no any change in tablet in 0.1 N HCl while in phosphate buffer it showed disintegration within 35.45 min. The batch F3 shows uniform distribution of polymeric coating solution and faster drying due to optimum viscosity i.e. 28 CP. The percentage weight gain of compressed coated tablet were in between (F1)6.1 to (F3) 11.79.

All 5 formulations from F1 to F5 showed different result. Reason may be beacause of changed proportion of sodium alginate and eudragit RS 100.

To identify the best proportion of sodium Alginate and eudragit RS 100 as compression coated polymers and to determine the optimum amount of eudragit RS 100 to produce colon specific delivery of mesalamine in the compression coat (F1-F5), In Vitro drug release studies were performed. The formulation containing 12.5% sodium Alginate and 2.5% eudragit RS 100 was considered as a better formulation as compared to other formulations to produce the colon specific delivery of mesalamine. In all formulations the proportion of HPMC K4M and PEG 6000 were used in same proportion i.e. 1% and 100 mg respectively. PEG 6000 was used as a plasticizer and HPMC K4M was used as film former.

Amongst the all formulations, formulations F3 and F4 showed best results for percentage drug release in phosphate buffer pH 7.4. but in formulation F3 the proportion of sodium Alginate and eudragit RS 100 were used 12.5% and 2.5% respectively. But in case of F4 formulation the

proportion of sodium Alginate and eudragit RS 100 were used in highest proportion i.e. both were used in same proportion i.e. 12.5 % respectively.

Based on Dissolution studies, F3 Formulation showed significant level of drug release in the colon without loss in upper GIT for 9 hrs. Drug release data of F3 formulation showed good fitted in first order equation (r^2=0.949), partially fitted in zero order equation (r^2=0.835), and high linearity in Korsemeyer equation (r^2=0.9706), value of release exponent *n* determined for F3 in differential pH environment is 2.707 indicating combined effect of diffusion and predominantly erosion mechanism for controlled release. Drug release from the Optimized formulation follows First order and Korsemeyer peppas (supercase II transport) drug release kinetics.

5. ACKNOWLEDGEMENT

I would like to thank SVPM's College of Pharmacy (Malegaon BKII) for providing me platform for this work. I am also thankful to all my colleagues, teaching & non teaching faculty.

6. ETHICAL ISSUE

Not Applicable

7. CONFLICT OF INTEREST

None Declared

8. REFERENCES

1. Gupta, B.P., Thakur, N., Jain, S., Patel, P., Patel, D., Jain, N., Jain, N.P. (2010) A comprehensive Review: colon specific drug delivery system. *Int J Pharmatec Res.*, 3:1625-9.
2. Basit, A. W. (2005). Advances in colonic drug delivery. *Drugs*, *65*(14), 1991-2007.
3. Rao, D. S., et al. (2015) Formulation and evaluation of Benazepril pulsatile drug delivery system. *Journal of Chemical and Pharmaceutical Sciences,* 8(4); 664-666
4. Anuj, S., & Amit, J. K. (2010). Colon targeted drug delivery using different approaches. *Int J Pharm Stud Res*, *1*(1), 60.
5. Hua, Z., Kimura, G., Ito, Y., Mawatari, S., Shimokawa, T., Yoshikawa, H., ... & Takada, K. (1999). Technology to obtain sustained release characteristics of drugs after delivered to the colon. *Journal of drug targeting*, *6*(6), 439-448.
6. Frieri, G., PIMPO M, T., PALUMBO G, C., Onori, L., Viscido, A., Latella, G., & Caprilli, R. (1999). Rectal and colonic mesalazine concentration in ulcerative colitis: oral vs. oral plus topical treatment. Aliment. Pharmacol. Ther. 1999; 13: 1413-1417.
7. Aulton, M.E., Taylor, K. (2012) Aulton's Pharmaceutics: Pharmaceutics the science of dosage form design. 2nd edition. Churchill, Livingston, Edinburgh, London.
8. Lachman, L., Liberman, H., Kanig, J. (1987) The theory and practice of industrial pharmacy, 3rd Edition; Varghese publishing House, Bombay, pp297, 249.

9. Government of India Ministry of Health and Family Welfare. (2014) The Pharmacopoeia of India. Delhi, India: Controller of Publication.

10. Higuchi, T. (1963). Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of pharmaceutical sciences*, *52*(12), 1145-1149.

11. Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. *International journal of pharmaceutics*, *15*(1), 25-35.

12. ICH Q1A. (2003) Stability testing guidelines: stability testing of new drug substances and products, CPMP/ICH/380/95, 1-13.