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DESIGN AND *IN VITRO* EVALUATION OF COLON TARGETED DRUG DELIVERY SYSTEM OF A MODEL NSAID FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

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ABSTRACT: The objective of the present research work is to formulate and optimize the colon targeted tablet formulations of Mesalamine HCl using time-dependent and natural bio degradable polymers like Chitosan, HPMC K4M and Sodium CMC as carriers. Matrix tablets containing various proportions of chitosan, HPMC K4M and sodium CMC were prepared by wet granulation technique using PVP K30 as a binder. IR spectrum showed no interaction between Mesalamine and chitosan, HPMC K4M and sodium CMC. All the formulations were evaluated for hardness, drug content uniformity, stability study and were subjected to *in vitro* drug release studies. The amount of Mesalamine released from the matrix tablet at different time interval was estimated by UV method. Colon targeted matrix tablets of Mesalamine containing 20% of chitosan, 70% HPMC K4M and 10% sodium CMC released 2.14% of Mesalamine in 0.1 N HCl, 6.77% in phosphate buffer pH 7.4 and 103.90% in the phosphate buffer pH 6.8 for 14 hours. The tablets are enteric coated using a combination of Eudragit L100 and Eudragit S100. The dissolution study was continued in simulated colonic fluids, the matrix tablets containing 20% chitosan, 20% HPMC K4M and 10% sodium CMC released the same amount of Mesalamine after degradation into 2-3 pieces at the end of 14h study. The colon targeted matrix tablet of Mesalamine showed no change either in physical appearance, drug content or in dissolution pattern after storage at 30ºC±2˚C / 65±5% RH for 60 days.

Keywords: Mesalamine HCl *USP*, Chitosan, HPMC K4M, Colon targeted matrix tablet, Enteric-coating.

1. INTRODUCTION

Among the controlled delivery systems, colon targeted drug delivery systems have been the focus of interest for the last decade, which is useful not only for local but also for systemic therapy. By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). The site specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome, intestinal amoebiasis and colon cancer. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon[1, 2, 3.] The drug release in the colon of the gastrointestinal tract locally accumulates the drug in a high concentration without involving absorption in the small intestine, which leads to reduction of systemic side effects. Delivery to the colon would ensure direct treatment at the disease site, lower dose with fewer systemic side effects.

In addition to local therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation [4-12]. The term inflammatory bowel disease represents the disorders that occur in the region of small intestine and colon in which the intestines become inflamed (red and swollen), probably as a result of an immune reaction of the body against its own intestinal tissue. The disease is characterized by chronic, relapsing inflammation of the gastrointestinal tract and often are associated with extra intestinal manifestations. Inflammatory bowel disease is characterized by two symptoms Ulcerative colitis and Crohn's disease[13] . Mesalamine is an anti-inflammatory drug used for the treatment of colonic disorders like inflammatory bowel disease and in Arthritis. It reduces the inflammation by blocking the cyclooxygenase and inhibits prostaglandin production.[14] The polymers Chitosan facilitates biodegradable approach and HPMC K4M facilitates time dependent approach. The usage of polymers Eudragit L100 and Eudragit S100 facilitates pH dependent approach which prevents the absorption of drug in acidic environment of stomach.

2. MATERIALS AND METHODS:

Materials	Source
Mesalamine	D.K. Intrachem Pvt. Ltd and BEC Chemicals Pvt. Ltd. Mumbai.
Chitosan	Hi Media chemicals, Mumbai
HPMC K4M	Yarrow chem, Mumbai
Sodium CMC	Yarrow chem, Mumbai
Eudragit L100 and S100	Evonik India, Mumbai
PVP K-30	Karnataka fine chem, Bangalore
Magnesium stearate	Karnataka fine chem, Bangalore
Talc	Karnataka fine chem, Bangalore

FORMULATION OF COLON TARGETED TABLETS OF MESALAMINE

Mesalamine HCl *USP*, HPMC K4M, Chitosan, sodium CMC, PVP-K30, Microcrystalline Cellulose (MCC), Magnesium stearate and Talc were taken in required quantities. Batch of 50 tablets was prepared by wet granulation method. Dry screening of all the raw materials is done using sieve #80. Drug in dry state was mixed with HPMC K4M (10% in ethanol) and Chitosan (1%w/v in Lactic acid) and MCC (half quantity) and then made into granules using PVP K-30 (6% in isopropyl alcohol) as granulating agent. Granules are then passed through sieve # 22/44. Remaining amount of disintegrant, magnesium stearate are added to granules and then compressed to tablet using 12mm diameter biconcave punch in 10 station Rimek minipress-I tablet punching machine and evaluated for their physicochemical properties and for *invitro* release profile. The optimum batch of tablets are enteric coated using Eudragit L100 and Eudragit S100 by dip coating method.[15] The detailed compositions of the prepared tablet formulations are given in (Table 2 and 3).

EVALUATION OF PREFORMULATION PARAMETERS:

i) Micromeretic properties[16, 17, 18]

a) Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules are allowed to flow through funnel freely onto the surface. The diameter of the granule cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h/r.$$

Where, θ = angle of repose, h = height of the pile and r = radius of the pile base.

b) Bulk density

Both loose bulk density (LBD) or bulk density and tapped bulk density (TBD) were determined. Granules from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted

Bulk density is calculated by using formula:

$$\text{Bulk density} = \frac{Weight\ of\ the\ Powder}{\text{Bulk } volume \text{ of Powder}}$$

$$\text{Tapped density} = \frac{Weight\ of\ the\ Powder}{Tapped\ volume\ of\ the\ Powder}$$

c) Carr's index

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by

Carr's index (%) = [(TBD-LBD) * 100]**/**TBD where

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

ii) Compatibility studies

Fourier Transform – Infrared spectroscopy (FTIR)

The FTIR spectra of pure drug, polymers and combination of drug and polymer were obtained using FTIR spectrophotometer (Bruker Optic, Tensor 27, and USA).

iii) Physicochemical parameters[19]

a) Tablet hardness

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.

b) Tablet thickness

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using Vernier calipers on 3 randomly selected samples.

c) Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 min dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were re-weighed and the percentage loss in tablet weight was determined.

d) Weight variation

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the (Table 9) and none deviates by more than twice that percentage.

e) Uniformity of drug content

Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder weight equivalent to 300 mg drug was dissolved in pH 6.8 Phosphate buffer solution and the volume was made up to 100 ml with pH 6.8 Phosphate buffer solution (stock-1). From the stock solution, 10 ml solution was taken in 100 ml volumetric flask and the volume was made with pH 6.8 phosphate buffer solution (stock-2). From the stock-2 solution 1 ml was taken and the volume is made up to 10 ml with pH 6.8 Phosphate buffer. The absorbance was measured spectro-photometrically at 331.5 nm against blank correction media. Amount of drug present in one tablet was calculated.

f) Dissolution studies[20]

The release rate of Mesalamine HCl from Chitosan matrix tablets were determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of simulated gastric fluid (0.1 N HCl, 0.2% NaCl) for 2 hours, pH 7.4 Phosphate buffer saline for 3 hours and in pH 6.8 Phosphate buffer till the tablet disintegrates at 37 ± 0.5 °C and 100 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The withdrawn samples were made up to 10ml using particular buffer solutions. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug at 232.5 nm (for 0.1N HCl) 329.5nm (pH 7.4 Phosphate buffer) and 331 nm (pH 6.8 Phosphate buffer).

g) Drug release kinetic studies[21, 22]

From time to time, various authors have proposed different types of drug release mechanisms from matrices. It has been proposed that drug release from matrices usualy implies water penetration in the matrix, hydration, swelling and diffusion of the dissolved drug. Several kinetic models relating to the drug release from matrices, selected from the most important mathematical models, are described over here. However, it is worth mention that the release mechanism of a drug would depend on the dosage form selected, pH, nature of the drug and the polymer used.

4) Stability studies for the most satisfactory formulation of colon targeted tablets of Mesalamine

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, stability studies were done according to ICH guidelines.

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 °C / 65 ± 5 % RH for two months. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters.[23]

3. RESULTS

FTIR (ATR) spectrum of pure Mesalamine drug

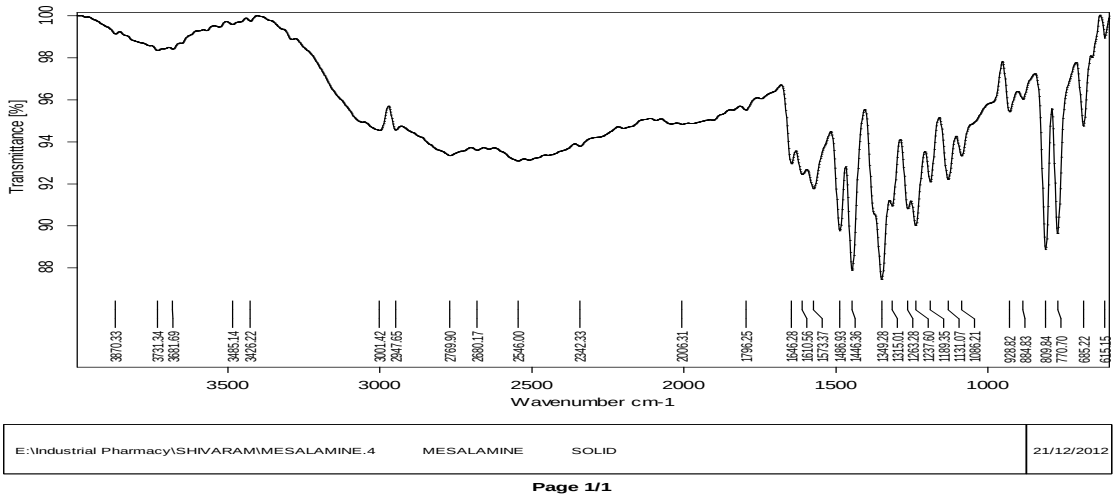

Fig 1. FTIR (ATR) spectrum of Mesalamine+Chitosan

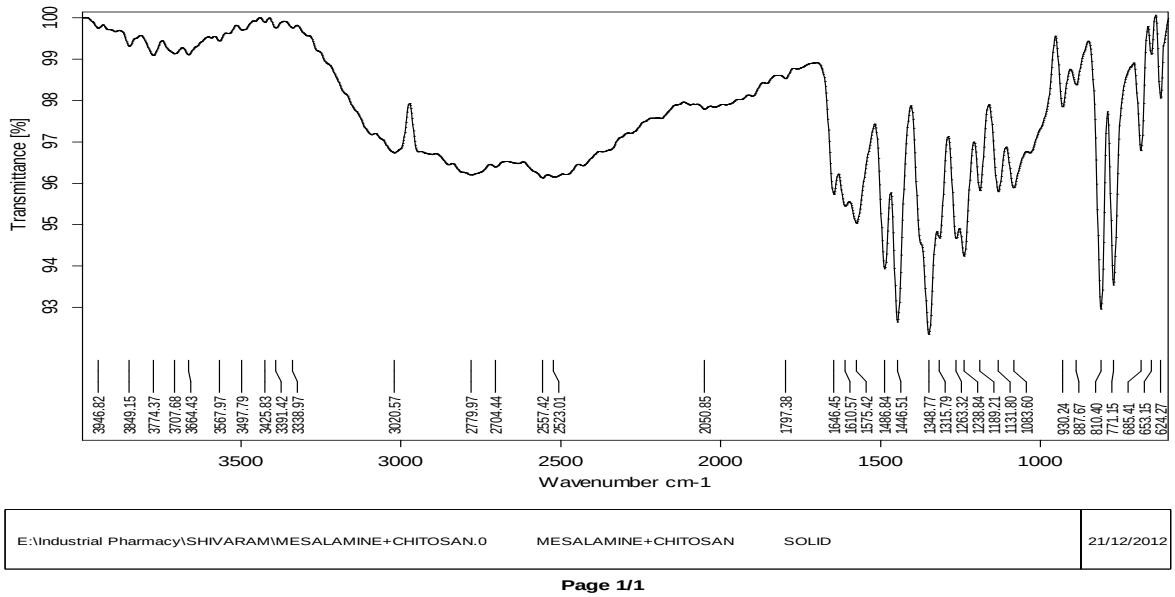

Fig 2. FTIR (ATR) spectrum of Mesalamine + HPMC K4M

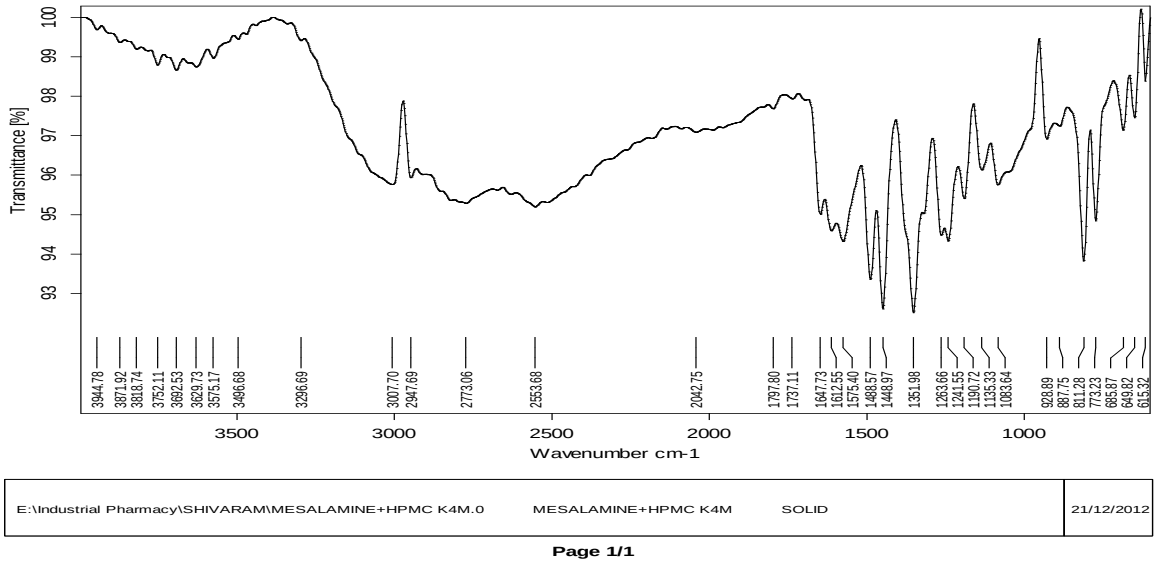

Fig 3. FTIR spectrum of Mesalamine + Sodium CMC

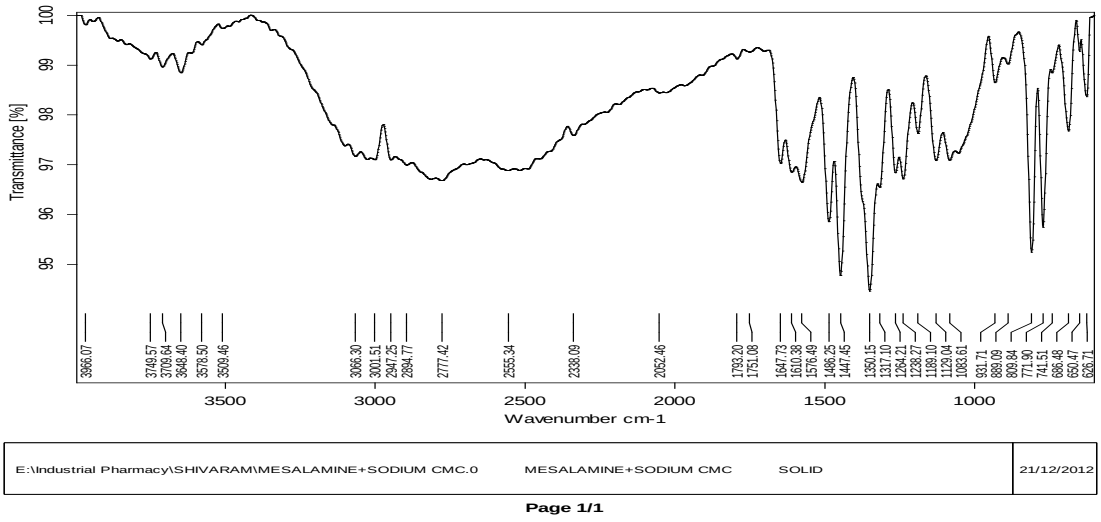

Fig 4.FTIR spectrum of Mesalamine + Eudragit L100

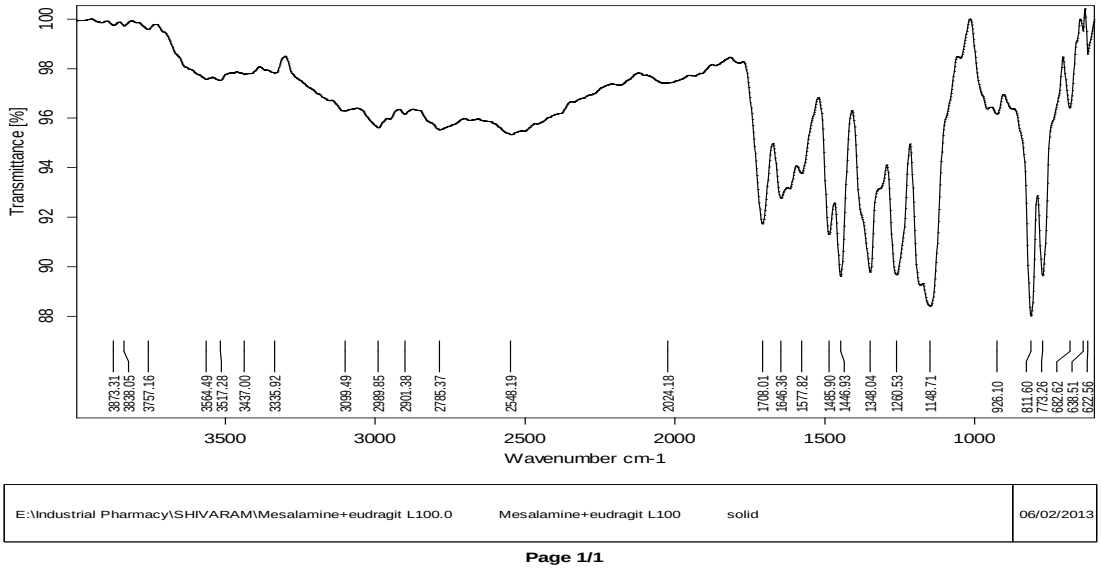

Fig 5. FTIR spectrum of Mesalamine + Eudragit S100

Table 1: FTIR (ATR) spectral data of Mesalamine and polymer combination

Mesalamine	Mesalamine + Chitosan	Mesalamine + HPMC K4M	Mesalamine + Sodium CMC	Mesalamine + Eudragit L100	Mesalamine + Eudragit S100	Functional Group
3485.14	3489.15	3496.88	3509.46	3437.00	3514.24	O-H stretch
3001.42	3020.57	3007.70	3001.51	2989.85	3001.18	C-H stretch
1610.56	1610.57	1612.55	1610.38	1646.36	1644.98	N-H stretch
1446.36, 1486.93	1446.51, 1486.84	1448.57, 1488.57	1446.93, 1485.90	1444.52, 1482.78	1444.52 1482.78	C-C stretch
1349.28	1348.77	1351.98	1350.15	1351.99	1351.99	O-H bend
1131.07	1131.80	1135.33	1129.04	1151.36	1151.36	C-O stretch
1189.35-1263.28	1189.21-1263.32	1190.72-1263.66	1189.10-1264.21	1260.53	1251.97	In plane bending
685.22-809.84	685.41-810.40	685.87-811.28	686.48-809.84	682.62-811.60	687.84-812.78	C-H bond out of plane bending

***All values are in cm^{-1}**

Table 2: Detailed formulation chart of colon targeted matrix tablets of Mesalamine

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7
Mesalamine HCl	300	300	300	300	300	300	300
Chitosan	60	120	-	60	80	60	100
HPMC K_4M	60	-	120	-	80	60	100
PVP K-30	30	30	30	30	30	30	30
Sodium CMC	60	-	40	120	40	-	30
Mg. stearate	25	25	25	25	10	25	10
Talc	25	25	25	25	10	25	10
Total weight of tablet	600	600	600	600	600	600	600

***All values are in mg**

Table 3: Enteric coating formula for tablets of Mesalamine

Ingredients	Quantity
Eudragit S-100	16gm
Eudragit L-100	16gm
Triethyl citrate	4gm
Acetone/Isopropyl alcohol	250gm

Evaluation of Parameters

Table 4: Micromeretic properties of granules of Mesalamine matrix tablets

Formulation code	Precompression properties				
	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (º)	Compressibility index (%)	Hausner's ratio
F1	0.35 ± 0.01	0.36 ± 0.009	31.56 ± 0.47	15.88 ± 1.20	1.02 ± 0.01

F2	0.39 ± 0.005	0.39 ± 0.002	34.36 ± 0.40	10.66 ± 1.05	1.01 ± 0.03
F3	0.45 ± 0.02	0.52 ± 0.008	32.28 ± 1.47	12.66 ± 1.27	1.14 ± 0.09
F4	0.55 ± 0.004	0.60 ± 0.007	34.60 ± 0.26	10.25 ± 1.19	1.09 ± 0.04
F5	0.52 ± 0.005	0.56 ± 0.006	30.05 ± 0.17	10.45 ± 0.008	1.09 ± 0.001
F6	0.53 ± 0.005	0.35 ± 0.004	28.36 ± 0.06	18.42 ± 0.088	1.05 ± 0.001
F7	0.58 ± 0.005	0.59 ± 0.06	27.98 ± 0.20	10.10 ± 0.10	1.11 ± 0.012

* **All values are mean of 3 readings ± SD**

Table 5: Physicochemical parameters of colon targeted enteric coated tablets of Mesalamine

Formulation code	**Tablet properties**				
	Hardness * (kg/cm^2)	**Thickness *(mm)**	**Friability (%)**	**Weight variation * (mg)**	**Drug content (%)**
F1	6.5 ± 0.35	6.06 ± 0.17	0.182	600.77 ± 1.18	91.90
F2	6.2 ± 0.11	6.02 ± 0.12	0.251	601.45 ± 0.82	99.04
F3	6.4 ± 0.15	6.12 ± 0.11	0.477	604.15 ± 1.06	99.35
	6.4 ± 0.17		0.276	601.87 ± 2.80	

F4		6.01 ± 0.10			91.26
F5	6.2 ± 0.15	6.05 ± 0.02	0.334	600.95 ± 2.83	101.61
F6	6.1 ± 0.15	5.9 ± 0.10	0.36	592.17 ± 2.77	104.57
F7	6.1 ± 0.05	6.03 ± 0.02	0.569	598.85 ± 2.04	99.74

*** All values are mean of 3 readings ± SD**

Table 6: Comparative drug release profiles of formulation F1-F4

Sl No	**Time (H)**	**Cumulative % Drug Release ± SD**			
1		F1	F2	F3	F4
2	0.5	3.78±0.84	6.86±2.12	6.22±0.71	6.69±2.0
3	1	5.96±2.60	8.25±3.02	8.63±2.54	7.81±2.95
4	1.5	7.09±2.73	10.38±3.41	10.56±1.02	10.15±2.04
5	2	9.56±3.75	13.33±2.34	12.65±1.79	14.04±1.24
6	3	5.83±2.81	8.12±0.03	13.76±2.41	11.36±0.04
7	4	8.64±2.13	9.89±1.13	16.32±1.16	17.22±3.39
8	5	14.01±0.6	13.85±1.94	28.14±2.49	23.50±1.91
9	6	19.67±0.21	18.73±2.51	16.29±1.75	16.16±1.98
10	7	30.41±2.05	27.75±2.33	25.06±1.29	32.04±2.40
11	8	46.95±4.08	39.01±1.97	37.24±1.45	48.71±0.94
12	9	71.52±1.54	48.02±1.52	53.30±2.80	66.13±1.04
13	10	93.47±3.43	60.95±3.52	67.23±2.76	83.31±0.71
14	11	110.26±2.35	77.01±0.68	92.26±2.60	94.98±1.07
15	12	-	95.34±2.63	103.36±2.54	102.55±1.85

16	13	-	-	-	-
17	14	-	-	-	-

* All values are mean of 3 readings ± SD

Table 7: Comparative drug release profiles of formulation F5-F7

Sl No	Time (H)	Cumulative % Drug Release ± SD		
1		F5	F6	F7
2	0.5	0.67±0.65	4.21±1.76	3.18±2.79
3	1	1.14±0.30	7.81±2.95	3.96±3.43
4	1.5	1.35±0.30	10.15±2.04	5.07±4.39
5	2	2.14±0.31	14.04±1.24	5.63±4.87
6	3	3.83±1.20	8.83±2.29	19.14±6.19
7	4	4.09±1.19	12.62±1.4	23.53±7.33
8	5	6.77±2.01	16.11±5.08	27.77±5.64
9	6	9.02±0.98	16.92±3.20	27.82±5.88
10	7	19.69±1.22	29.55±2.67	35.08±7.00
11	8	28.64±0.22	39.70±3.50	45.59±6.82
12	9	41.70±1.98	54.33±2.58	53.93±5.82
13	10	57.56±2.07	67.15±2.08	66.20±9.19
14	11	77.98±2.05	82.86±2.20	82.62±1.04
15	12	88.95±2.98	108.86±2.78	95.70±1.71
16	13	99.46±2.42	-	99.90±0.65
17	14	103.90±0.80	-	-

* All values are mean of 3 readings ± SD

Comparative drug release profiles of F1-F7 colon targeted Mesalamine tablets

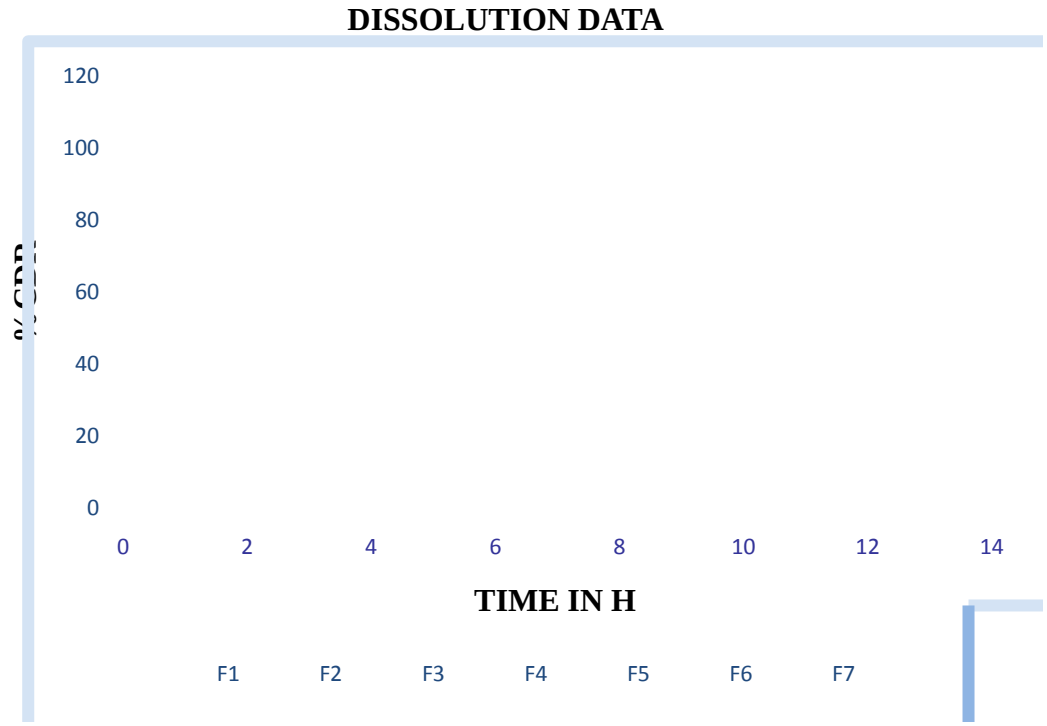

Table 8: Drug release kinetic studies based on different kinetic models

Formulation code	Zero order	First order	Higuchi model		Peppas model	
	r^2	r^2	r^2	N	r^2	N
F5	0.978	0.867	0.740	33.62	0.917	1.658

The *in vitro* release data obtained were fitted into various kinetic models. Correlation coefficients of formulation F5 showed higher correlation with zero order plots than first order, Higuchi model and Peppas model. The 'n' value was found to be 1.658 which corresponds to super case-II transport or release system. So, predominant drug release mechanism was found to be of sustained and case-II (Non-Fickian) type.

Table 9: Physicochemical parameters of most satisfactory formulation F5 during/after stability studies

Time in days	Formulation code	Hardness (kg/cm^2)	Drug content (%)
0	F5	6.2±0.15	101.61
30 (A)	F5	6.2±0.11	100.79
60 (B)	F5	6.0±0.18	100.14

A= 30 ± 2˚C/ 65 ± 5% RH

B = 40 ± 2˚C/ 75 ± 5% RH

Table 10: Drug release profile for most satisfactory formulation F5 during stability studies

Sl No	Time (h)	AFTER 30 DAYS	AFTER 60 DAYS
		F5 (%) ± SD	F5 (%) ± SD
1	0.5	1.67±0.22	1.77±1.14
2	1	2.22±0.58	2.45±1.38
3	1.5	2.31±1.55	2.74±1.59
4	2	2.85±1.74	3.21±1.54
5	3	3.77±1.26	3.97±2.15
6	4	4.24±1.03	4.82±1.54
7	5	7.03±1.37	6.97±1.25
8	6	10.15±0.80	10.74±2.07
9	7	20.23±0.58	19.72±1.19
10	8	27.91±1.56	27.75±1.74
11	9	42.15±2.18	43.57±1.03
12	10	55.76±2.71	59.24±1.45
13	11	78.34±0.75	79.47±0.52
14	12	89.65±1.7	88.14±2.57
15	13	99.85±0.78	100.57±1.27
16	14	102.78±0.95	102.17±1.48

*All values are mean of 3 trails ± SD

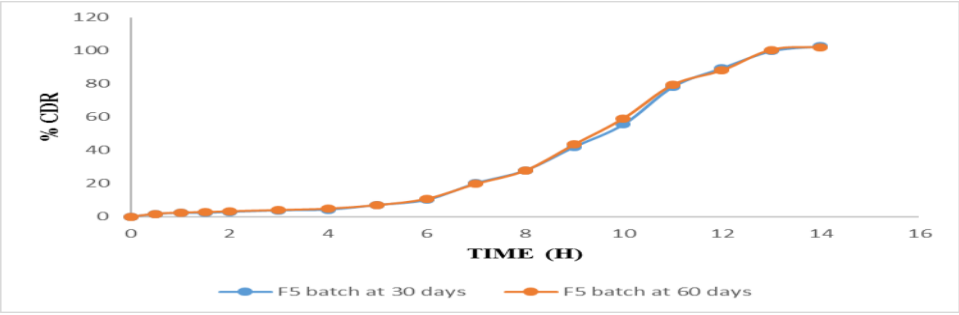

Fig 7. *In vitro* drug release profile of F5 after stability studies

4. DISCUSSSION

In the present study, an attempt was made to formulate colon targeted matrix tablets of Mesalamine HCl *USP* using a combination of natural polysaccharide Chitosan and time dependent methacrylic polymer HPMC K4M as carriers to deliver the drug directly into the colon. The tablets are enteric coated using Eudragit L100 and S100 to prevent the drug release in the stomach. A total of seven formulations of matrix tablets of Mesalamine HCl was prepared by wet granulation method. The preformulation studies such as bulk density, tapped density, angle of repose, compressibility index and Hausner ratio were evaluated which were found to be within prescribed limits and indicated good to poor flowing property. The data obtained from physicochemical parameters such as hardness, friability, weight variation, drug content and *in vitro* drug dissolution are shown in table (4, 5 and 6).

Preformulation studies

Estimation of Mesalmine HCl *USP* was carried out by using SHIMADZU-1700 UV spectrophotometer at λ_{max} of 232.5 nm in 0.1N HCl (pH 1.2) and in Phosphate buffers pH 6.8 and pH 7.4 at λ_{max} of 329.5 and 331nm respectively. The linear coefficients were found closer to 1. By using the regression coefficient equation, the drug content and % CDR were calculated.

UV spectrum analysis of Mesalamine HCl *USP*

Mesalamine HCl *USP* showed maximum absorption at a wavelength 232.5 nm in 0.1N HCl and in Phosphate buffers pH 6.8 and pH 7.4 at 329.5 and 331 nm respectively. Standard calibration curve when subjected to regression analysis, the value of regression coefficient was found to be 0.999 and 0.998 which showed linear relationship between concentration and absorbance.

Any formulation development work has to be preceded by preformulation studies. This preformulation study includes drug polymer compatibility study and analytical investigation of the drug. FTIR (ATR) studies showed that there was no interaction between drug and polymer. So, the drug and polymers were found to be compatible.

Formulation development

The matrix tablets of Mesalamine HCl were prepared by wet granulation technique using 10 % PVP K-30. Microcrystalline cellulose was used as diluent and the mixture of talc and magnesium stearate at 1:1 ratio was used as lubricant. The composition of different matrix formulation used in the study containing 300 mg of Mesalamine is given in table 2. In the present study, chitosan and HPMC K4M were incorporated at various percentages to retard the drug release in the environment of stomach and small intestine. The granules were prepared by the method of wet granulation. The drug release in stomach is prevented by enteric coating using a combination of Eudragit L100 and Eudragit S100.

Micromeretic properties

Angle of repose

The angle of repose value for formulation F1 – F7 ranged from 27.98 ± 0.20 to 34.60 ± 0.26° (table 4) which indicate the good flow properties of granules.

Bulk density and Tapped density

The value of bulk density and tapped density for formulation F1 – F7 ranged from 0.35 ± 0.01 to 0.58 ± 0.005 gm/ml and 0.35 ± 0.004 to 0.60 ± 0.007 gm/ml respectively (table 4).

Compressibility index

The compressibility index values for formulation F1 – F7 ranged from 10.10 ± 0.10 to 18.42 ± 0.08 % (table 4). These values indicate that the granules of all batches exhibited excellent to fair characters and hence, they were suitable for wet granulation.

Evaluation of physicochemical properties

Tablet Hardness

Hardness of the developed formulations varied from 6.1±0.15 to 6.5±0.35 kg/cm^2 (table 5) in all formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling.

Thickness

Thickness for all formulations varied from 5.9±0.10 mm to 6.12±0.11 mm (table 5) and the average thickness was within the range of ± 5%. Each sample was analyzed in triplicate.

Friability

The loss in total weight of the tablets due to friability was in the range of 0.1 to 0.5 % (table 5) in all the formulation and the friability value was less than 1% which ensured that formulated tablets were mechanically stable.

Weight variation

The average weight of 20 tablets was calculated for formulation F1 – F7 and it varies from 592.17±2.77 to 604.15±1.06 mg (table 5) and none of the formulations showed a deviation more than ± 5 % for any of the tablets tested which complied with the official limit of the *IP*.

Uniformity of drug content

The amount of drug present for formulation F1 – F7 ranged from 91.26 to 104.57 (table 5) which is within the official limit of *IP* i.e. 85 - 115%.

***In vitro* drug release studies**

All the colon targeted matrix tablet formulations of Mesalamine were evaluated for *in vitro* dissolution studies as per the procedure described in above section. In the formulation F1, The highest *in vitro* dissolution profile at the end of 14 h (103.90%) was shown by F5 containing 2:2:1 of Chitosan, HPMC K4M and Sodium CMC respectively (table 7) and F7 containing 2:1:2 ratio of Chitosan, HPMC K4M and Sodium CMC showed 99.90% (table 7) and the other formulations like F2 containing only Chitosan showed 99.34% only in 5 h in intestinal conditions and F3 containing only HPMC K4M showed 103.36% only in 5 h in intestinal conditions (table 6).

From the *in vitro* dissolution studies it can be discussed that the colon targeted matrix tablets containing 2:2:1 ratio of Chitosan, HPMC K4M and sodium CMC respectively as the best formulation to target Mesalamine to the colon in the treatment of inflammatory bowel disease. It may be due to the presence of colonic bacteria which act on the Chitosan and digests it.

Kinetics modeling of drug release profile

The *in vitro* release data obtained were fitted in to various kinetic models and the best formulation was selected. The correlation coefficient of formulation F5 batch was higher for zero order plots (table 8) than first order, Higuchi model and Peppas model. The 'n' value was found to be 1.658

which corresponds to non Fickian case 2 transport system. So, predominant release mechanism was found to be of sustained and non Fickian case 2 transport system.

Stability study

The optimized formulation (F5) was subjected for accelerated stability studies. Tablet is packed in aluminum foil and kept in humidity chamber maintained at 30 ± 2 °C/65 ± 5 % RH for 60 days. Samples were withdrawn at the interval of 1 month and were analyzed for the hardness, drug content and *in vitro* release rate (table-28 and 27). There was no statistically significant difference in hardness, drug content and *in vitro* release pattern at various sampling points during the stability studies.

5. Conclusion

The objective of the present study was to develop a polymeric combination for colon targeted tablets of Mesalamine HCl *USP* and to implement a design of experiments principle in developing formulation for better stability and high production feasibility and excellent patient acceptability.

The micromeretic evaluation such as angle of repose, compressibility index and Hausner ratio showed good to satisfactory flow properties. The physicochemical evaluation of different formulations were carried out as per IP and the results obtained were in accordance with IP limits. Various formulations were developed by using release retarding and gel forming polymers like HPMC K4M, Chitosan and Sodium CMC in single by wet granulation method. Different proportions of Chitosan and HPMC was associated with decrease in overall cumulative drug release rate. The highest viscosity polymeric combination (20% Chitosan with 70% HPMC K4M and 10% Sodium CMC-F5 batch) has seen to inhibit the initial burst release of Mesalamine. From the result, it is evident that Chitosan and HPMC by forming a matrix retards the release rate of drug. In the formulation F5, Chitosan (20% of tablet weight) and HPMC (70% of tablet weight) were used. F5 showed 103.90% drug release in 14 h and initial drug release was minimized by enteric coating. Based on the result obtained it concluded that Chitosan, HPMC K4M and Sodium CMC is suitable to get desired release pattern.

The *in vitro* release data obtained were fitted in to various kinetic models and the best formulation was selected. The correlation coefficient of formulation F5 batch was higher for zero order plots (table 8) than first order, Higuchi model and Peppas model. The 'n' value was found to be 1.658 which corresponds to non Fickian case 2 transport system. So, predominant release mechanism was found to be of sustained and non Fickian case 2 transport system. The most satisfactory formulation F5 was subjected to short term stability studies by placing in varied conditions for sixty days. It was concluded that there was no significant changes in drug content or physical properties. The *in vitro* drug release of formulation F5 showed no noticeable changes confirming that the formulation was stable after a period of 60 days.

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