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Formulation, Development and Evaluation of Colon Targeted Beads for Anti-Inflammatory Drug

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Abstract

Mesalamine is an anti-inflammatory drug used in treatment of Crohn'sdisease and ulcerative-colitis. Since Mesalamine islargely absorbed from the upper intestine, selective delivery of drugs into the colon may be regarded as a better method of drug delivery with fewer side effects and a higher efficacy.An objective of the present investigation is to prepare and evaluate Mesalamine microbeads for colon targeting. These microbeads were prepared by Ionotropic gelation method using physical mixtures of gellan gum locust bean gum and sodium alginate in ratio 1:3:2, 1:1:2 and 3:1:2. Eudragitcoated Mesalamine microspheres were evaluated for surface morphology, particle size analysis, percentage drug entrapment, percentage yield and in vitro drug, in-vivo drug release and stability studies. Drug release studies carried out in SGF (pH 1.2) for 2hrs, SIF (pH 6.5) for 5 hrs, SCF (pH 7.4) for 24hrs. The cumulative percent drug release after 24 hrs was found to 96.73%; 89.76%; 86.12% and 82.12%, 74.79%, 68.24% for F-1, F-2, F-3 of uncoated and CF1, CF2, CF3 of coated formulation respectively. By comparing the *in vitro* release pattern of all coated and uncoated formulations, it was found that the drug release from coated formulations was prolonged than uncoated beads. The drug release may be mainly controlled by drug diffusion through the natural gums matrix. The in vivo release performance of the developed colon specific formulation was carried out by gamma scintigraphy.The scintigraphy of the optimized formulation CF3 (92 ± 0.8% Radio labeling efficiency) was performed using rabbits (animal model) in order to establish its colon targeting potential. Scintigram shows the residence of beads in colon more than 12 hrs. These results showed that Eudragit S-100 coated beads formulation may be useful for targeting mesalamine to the colon. Stability studies indicated that the optimized formulation does not show any significant change with respect to shape, color, surface and in vitro drug release.It is concluded from the present investigation that Mesalamine microspheres are promising controlled release carriers for colon-targeted drug delivery.

Keywords: Mesalamine, Gellan gum, Locust bean gum, sodium alginate, Eudragit, colon targeted drug delivery system

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1. Introduction

Dosage forms that deliver drugs into the colon rather than upper gastrointestinal tract (GIT) offers number of advantages [1]. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. Mesalamine is an anti-inflammatory drug used to treat inflammation of the digestive tract ulcerative colitis and mild-to-moderate Crohn's disease. Mesalazine is a bowelspecific aminosalicylate drug that acts locally in the gut and has its predominant actions there, thereby having few systemic side effects [2,3].

Gellan gum, are natural biodegradable and biocompatible gums shows a significant promise for colon targeting of drug. The locust bean gum is a hydrophilic polymer which is used to prolong release of drug from the formulation. Due to ionic gelation process that affects the entrapment efficiency of the drug. This limitation is overcome by the use of mixture of gum in which one gum has improved ionic gelation property such as gellan gum, sodium alginate etc. Several investigators proved, work on mixture of the natural polysaccharide in different proportion for the development of colon targeted drug delivery system.

The various approaches were used for development of the colon targeted system includes coated formulation with pH sensitive copolymer and with the release of the drug started in alkaline pH of intestine. This was the most common approaches which was used by several investigators in past and other approach also suggested that use of biodegradable polymer's coating which degrades by the action of the colonic bacteria and release of drug at the colon[4,5].

The objective of present study was to develop a colon targeted microspheres of Mesalamine with a view of retarding the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon with an improved patient compliance, lesser side effects, and most aspects of an ideal drug delivery system.

2. Materials and Methods

2.1. Materials

Mesalamine and Eudragit S-100 was procure as a gift sample from the Wallace Pharmaceuticals Pvt Ltd, Goa and EvonikRoehm Pharma Ltd., Mumbai, Locust bean gum was purchased from the Himedia Laboratories Pvt. Ltd, Mumbai. Gellan gum and sodium alginate was purchased from SRL chemicals Pvt. Ltd, Mumbai, S.D. Fine Chemical Ltd, Mumbai respectively. Pepsin, Pancreatin and Galactomanase was purchased from Himedia Laboratories and Sigma Aldrich, Mumbai respectively.Healthy white male rabbits (male) weighing 2.5-3kg was selected for the *in vivo* studies. Ethical committee clearance was obtained prior to the study from the Institutional Animal Ethics Committee.

2.2. Method of ionotropic gelation/Bead Formation

For encapsulation of drug in gellan-locust-alginate beads, physical mixtures of gellan gum locust bean gum and sodium alginate in ratio 1:3:2, 1:1:2 and 3:1:2 were dispersed in 40ml of double-distilled water by magnetic stirring. Mesalamine (750mg) was suspended in gel mixture (1:1 ratio with gums) and vigorously stirred for 1hr. Then using a No.20 hypodermic needle, drug-gel solution was added dropwise into 1M $CaCl_2$ solution. The solution was continuously stirred with help of magnetic stirrer for half an hour; beads were filtered from the solution and kept for drying [6].

Table 1: Formulation Plan for Mesalamine Beads

Formulation Code	Ratio of drug and polymer (Drug: Polymer)	Ratio of Gums Used (GG:LBG)	Ratio of Sodium alginate and gum Used
F-1	1:1	1:3	1:2
F-2	1:1	1:1	1:2
F-3	1:1	3:1	1:2

2.2.1. Coating of Beads (Dip Coating)

Gellan beads were coated with 10% eudragit solution in chloroform : methanol mixture (72:28 v/v) by typical solvent evaporation method. Dip Coating was followed to develop the beads [7]. The beads was alternatively dipped in 10% eudragit solution and dried. After drying , the weight of beads was mesured and the coating was ruled with an acurate weight again of 8-12%.

2.3 Characterisation of Mesalamine Beads

2.3.1 Percentage yield

Percentage practical yield is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production [8]. The percentage yield of prepared beads was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practicalyield}}{\text{Theoretical yield}} \times 100$$

2.3.2. Drug content determination

Fifty mg of uncoated sample is first extracted with 10ml of SCF by continuously stirring for at least 1 hour in a glass jar. Then 10 ml of simulated colonic fluid (pH 7.4) with little quantity of gamanase enzyme add into the glass jar. Pipette out 1ml of this solution in 100ml volumetric flask and diluted with simulated colonic fluid and measure the absorbance in UV- Visible Spectrophotometer. By use of this absorbance we can calculate the drug content of the formulation [9,10].

2.3.3. Drug entrapment efficiency

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment (PDE) as per the following formula [11]

$$\% \text{ Entrapment Efficiency} = \frac{\text{Mass of Drug in Beads}}{\text{Mass of Drug Used in Formulations}} \times 100$$

2.3.4 Particle size

Particle size of beads is determined by the verniercaliper [12]. Take 25 beads from each batch and measure the diameter of beads by calibrated verniercalliper.

2.3.5. Surface morphology

Surface morphology of the specimens were determined by using a SEM, Hitachi model SU 1500. The dried samples were mounted on brass specimen studies, using double sided adhesive tape [13]. Gold-palladium alloy of 120^0A knees was coated on the sample using sputter coating unit (JEOL JFC-Model 1100E, Japan) in Argon at ambient of 8-10 Pascal with plasma voltage about 20MA. The sputtering was done for nearly 5 min. The SEM was operated at low accelerating voltage of about 10KV with load current of about 80MA. The condenser lens position was maintained between 4.4-5.1° and the working distance, WD=13mm.

2.3.6 Compatability studies

The evaluation of potential interactions between an active component and various additives is a vital aspect of the pre-formulation in any stage of formulation development [14,15]. Pure substance under study, Eudragit L100, S100, Fruit mucilage of AbelmoschusEsculentus, Guar Gum, Xanthan Gum, HPMC K_4 M and Maltodextrin, physical mixing of substance under study and polymer and Mesalaminebeads were powdered and combined with potassium bromide having IR-grade in a 1:100 ratios. In hydraulic systems, 10 metric tones of pressure were employed to analyze the corresponding beads. The microbeads were scanned employing a Fourier transform infrared spectrophotometer on a wavelength span of 4000–400cm^{-1}. (Hadi MA *et al.*, 2012)

2.3.7. *In Vitro* drug release

Preparation of dissolution media

The *in vitro* drug release carried out in three different mediums. They are as follows

- Simulated Gastric Fluid (SGF, pH 1.2)
- Simulated Intestinal Fluid (SIF, pH 6.5)
- Simulated Colonic Fluid (SCF, pH 7.4)

***In Vitro* method**

Drug release studies of coated and uncoated beads were carried out using a USP XXIII dissolute ion rate test apparatus (Apparatus 1, 100 rpm, 37 °C) for 2 hr in SGF as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with pH-6.5 in SIF for 3hr, the average small intestinal transit time is about 3 hr. After 5 hr, the dissolution medium was replaced with pH 7.4 SCF and tested for drug release up to complete drug release. At the end of the specific time period (1Hrs). 10 ml of the samples were taken and analyzed for Mesalamine content. A 10 ml Volume of fresh and filtered dissolution medium was added to make the Volume after each sample withdrawal. Sample was analyzed using UV spectrophotometer at 330 nm [16,17].

2.3.8. Kinetic treatment of dissolution data

Order to study the exact mechanism of drug release from uncoated beads formulation, drug release data was analyzed according to Zero Order Kinetics, First order kinetiscs, Higuchi square root equation, Hixon – Crowell equation [18,19]. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

- Cumulative percentage release of substance under study against time-Zero order
- Log Cumulative percentage retained against Time -First order
- Cumulative percentage release of substance under study against $\sqrt{T}$ - Higuchi Equation
- Cumulative percentage release of substance under study against $\sqrt[3]{T}$ – Hixson Crowell Equation
- Log of Cumulative percentage release of substance under study Vs. Log time –Peppas equation.

Table 2: Drug transport mechanis with release exponent

Release Exponent (*n*)	**Drug Transport Mechanism**
$n = 0.5$	Fickian diffusion or square root of time kinetics
$0.5<n<1$	Anomalous (non- Fickian) diffusion,
$n=1$	Case –II transport
$n>1$	Super Case II transport.

2.3.9*In vivo* studies

In vivo studies of prepared formulations were carried out by determining the *in vivo* behavior of dosage forms in animals. The Scintigraphy of the optimized formulation (CF-3) coated with radiolabel coating and filled in capsule and activity were perform on rabbits in order to establish its colon targeting potential. From the Scintigraphy images, it can be interpreted that the beads were completely intact in the stomach up to 2 hrs. Images indicate that when beads containing mesalamine (CF3) were in the small intestine the radioactivity was concentrated in a very small area indicating that little release had occurred. The mean transit time from stomach to colon was found to be 6.0±0.47 hrs. The bead started to disintegrate in colon after 6.0 hrs. Once the beads entered the ascending colon, there was considerable spreading of radioactivity from ascending colon toward the transverse colon which was most likely caused by the action of the bacterial enzymes in the colon degrading the gellan gum and accelerating the release of radioactivity. Scintigram shows the residence of beads in colon more than 12 hrs. These results showed that CF-3 formulation can be useful for targeting mesalamine to the colon [20].

2.3.10.Stability study

The optimized formulation (CF-3) was packed in aluminium foil. It was than stored at 40°C / 75 % RH according to ICH guidelines [21]. Samples were withdrawn after three months and evaluated for change in drug release pattern.

3. Results and Discussion

3.1. Percentage yield

Percentage yield of all formulations, F-1 to F-3, were calculated and the percentage yield was found to be 92.5, 93.3 & 93.4 % respectively. The results are shown in Table 3.

Table 3: Percentage Yield of Mesalamine Beads

Formulation	Theoretical yield (gms)	Practical Yield (gms)	% Yield
F-1	1.50	1.388	92.5
F-2	1.50	1.385	92.3
F-3	1.50	1.401	93.4

3.2 Drug Content and Entrapment Efficiency

The results of drug content and entrapment efficiency shows that both are increase with increase in proportion of gellan gum in the ratio of natural gum mixture this is due to the gellan gum has good in ionic gelation so drug could not come out in the gelation medium (1M $CaCl_2$). The results of drug content and Entrapment efficiency are given in Table no.15. Due to the poor solubility of mesalamine in water shows the better results in the entrapment efficiency. NB singh et al (2003) reported that an increase in calcium ion concentration, the drug loading efficiency decreases almost proportionally.

Table 4: Drug Content and Drug Entrapment Efficiency of Mesalamine Beads

Formulation	Drug Content	Entrapment Efficiency (%)
F-1	39.79	79.57
F-2	41.16	82.32
F-3	41.54	83.08

3.3. Particle Size

The size of the beads was measured by simple verniercalliper method. The particle sizes of all formulations are shown in Table 5. The particle size of Mesalamine beads was found to be 1.34mm, 1.28mm and 1.26mm for the uncoated beads of formulation F1 to F3. When these beads coated with the Eudragit S100 by dip coating method the diameter of beads was increase. The size of the beads after coating was found to be 1.56, 1.49 and 1.50mm of three formulations CF1, CF2 & CF3 respectively.

Table 5: Particle Size of Mesalamine Beads

Formulation	Particle Size
F-1	1.34±0.20
F-2	1.28±0.17
F-3	1.26±0.22
CF-1	1.56± 0.19
CF-2	1.49±0.15
CF-3	1.50±0.22

*****Mean ±SD (n=10)

3.4. Surface Morphology

Scanning Electron Microscopy was used to observe the surface structure of the gellan, locust bean gum and sodium alginate bead before and after coating The SEM analysis revealed that the beads prepared in this study were mostly spheres with rough surfaces. Fig. 1 shows the appearance of the white spots on the surface of alginate/gellan gum/locust bean gum beads. The size of spherical beads ranged from 1.26 to 1.50mm.

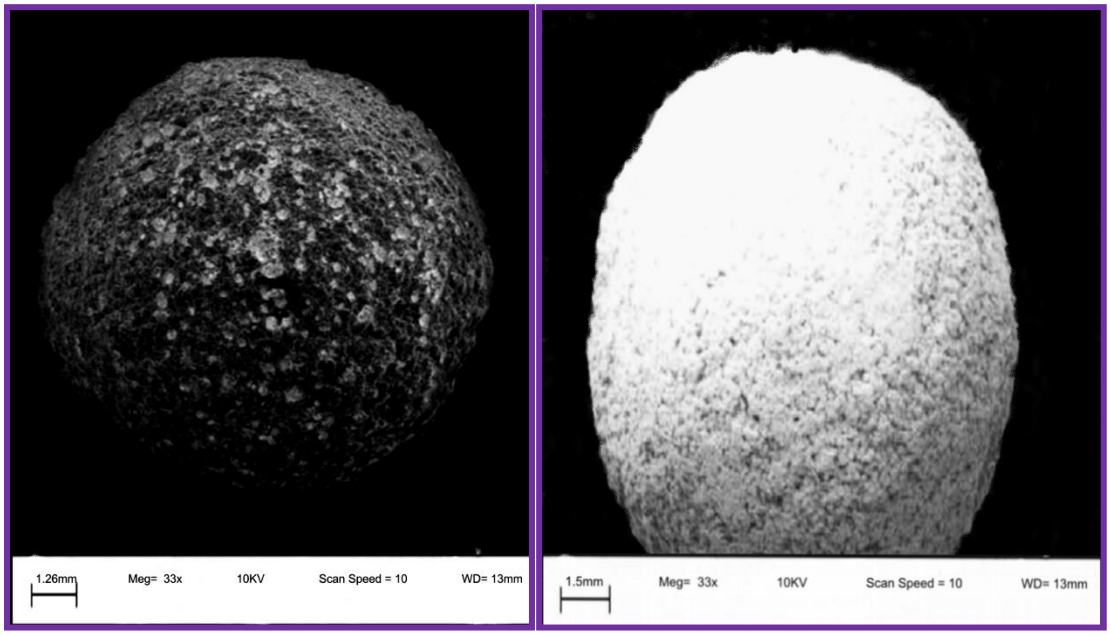

Figure 1: SEM Photographs of Mesalamine Beads.

3.5 Compatibility Studies

The FT-IR spectra of pure drug mesalamine and combination of drug and polymer were obtained which are shown in Figure 2, 3 & 4 respectively. From the obtained spectra it was observed that all the characteristics peaks of Mesalamine were present in the combination spectra thus indicating the compatibility of the drug with the polymer used.

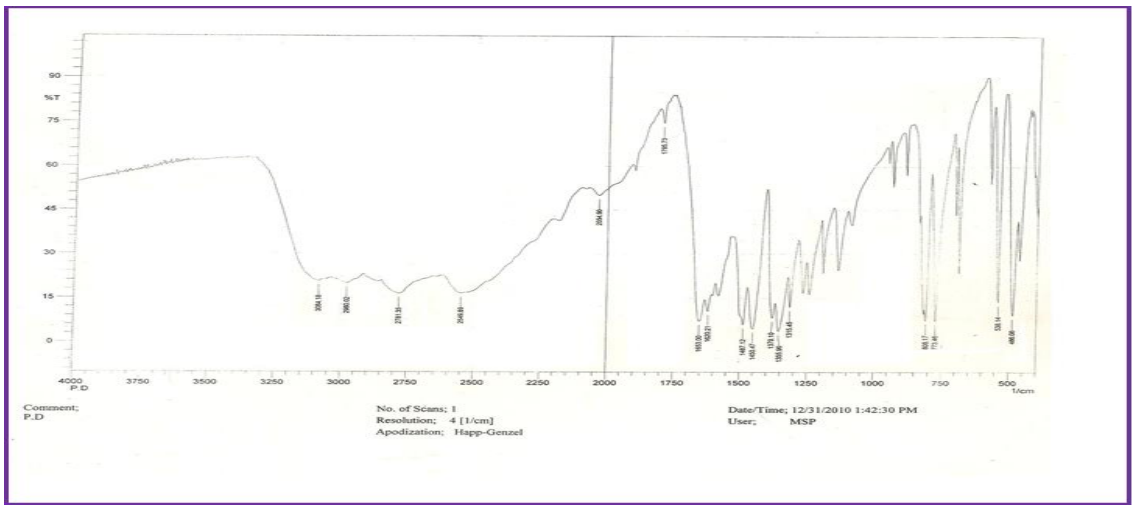

Figure 2: IR Spectrum of Mesalamine

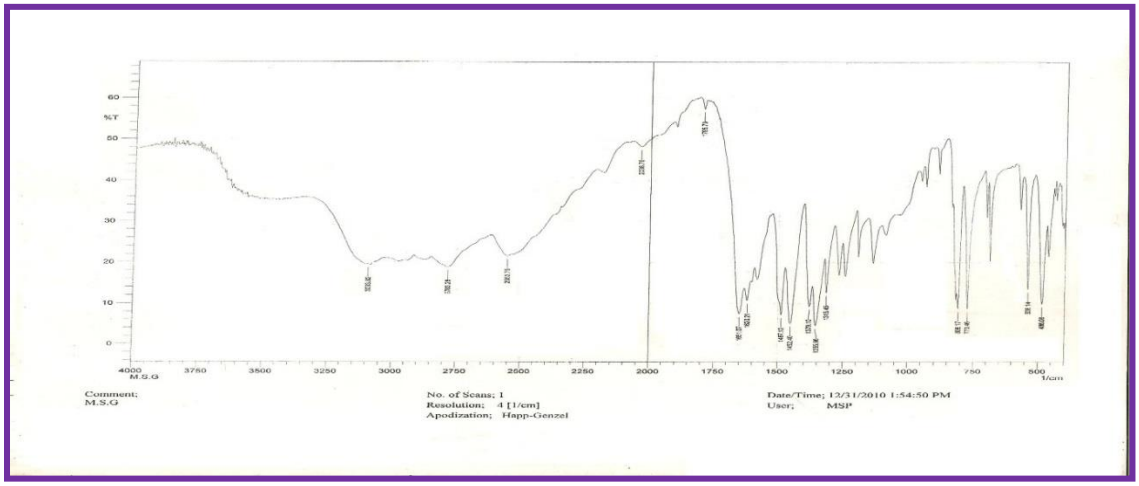

Figure 3: IR Spectrum of Mesalamine + Sodium alginate +Gellan gum+ locust bean gum (Physical Mixture)

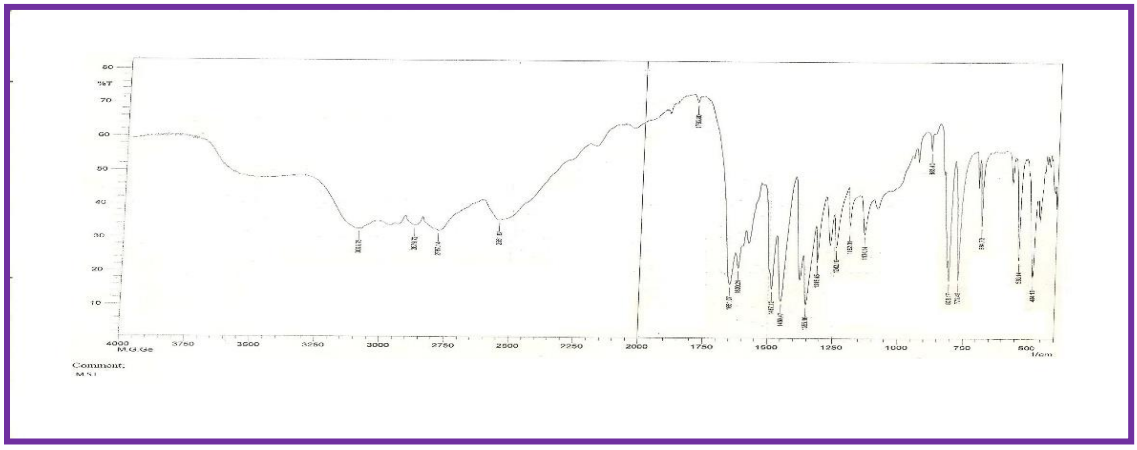

Figure 4: IR Spectrum of Optimized formulation

In Vitro Drug Release

The dissolution study on all the formulations of Mesalamine beads was carried out in three different mediums namely SGF, SIF & SCF. The cumulative percent drug release after 24 hrs was found to 96.73%; 89.76%; 86.12% and 82.12%, 74.79%, 68.24% for F-1, F-2, F-3 of uncoated and CF1, CF2, CF3 of coated formulation respectively.

Table 6: *In Vitro* Release Profile of Mesalamine Uncoated Bead

Dissolution medium	Time (hrs)	% Cumulative Drug Release		
		F1	F2	F3
SGF(pH=1.2)	1	19.7 ± 1.57	15.90±2.47	21.38±2.72
	2	32.69±1.00	23.88±2.66	34.27±3.18
SIF(pH=6.6)	3	39.24±1.58	27.49±1.75	37.58±3.51
	4	44.83±1.49	39.07±2.74	42.47±2.97
	5	50.66±1.16	45.56±2.55	50.41±3.08
SCF(pH=7.4)	6	52.36±1.08	49.57±2.09	53.25±2.38
	7	53.9±1.43	51.62±2.19	55.21±1.85
	8	62.79±1.38	57.21±1.93	58.66±2.21
	9	65.82±1.37	63.04±1.06	64.45±2.68
	10	70.67±1.27	69.37±2.09	68.34±2.78
	11	76.4±1.00	74.35±2.23	74.08±2.91
	12	81.09±1.26	79.08±2.50	76.61±2.44
	24	96.73±0.93	89.76±2.18	86.12±2.64

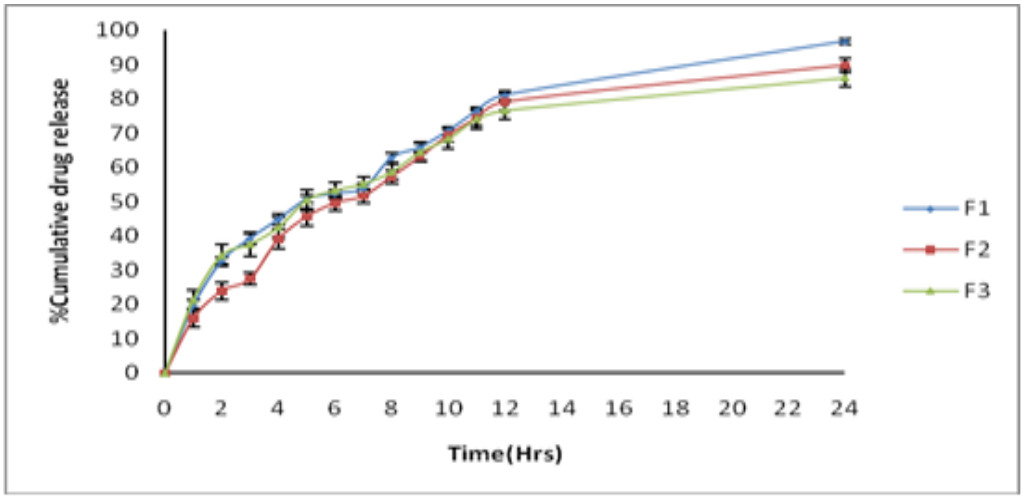

Figure 5: *In Vitro* Release Profiles of Mesalamine
(Uncoated Formulation F-1, F-2 & F-3)

Table 7: *In Vitro* Release Profile of Mesalamine Coated Bead

Dissolution medium	Time (hrs)	% Cumulative Drug Release		
		CF1	CF2	CF3
SGF(pH=1.2)	1	0.61±0.05	0.31±0.07	0.43±0.0.16
	2	0.78±0.03	0.31±0.08	0.49±0.07
SIF(pH=6.6)	3	0.80±0.03	0.36±0.09	0.50±0.07
	4	0.87±0.04	0.37±0.08	0.52±0.09
	5	0.89±0.05	0.57±0.12	0.60±0.04
SCF(pH=7.4)	6	37.65±3.01	47.23±1.95	40.25±2.58
	7	43.54±3.09	50.46±2.32	43.14±2.21
	8	47.72±3.55	52.58±2.12	47.81±0.02
	9	51.00±3.42	55.21±2.04	50.77±0.64
	10	55.40±3.98	57.24±2.95	54.46±1.79
	11	59.32±3.24	60.23±2.06	57.05±2.36
	12	64.88±4.29	62.36±2.02	60.19±3.06
	24	82.12±3.49	74.79±2.69	68.24±3.65

*Each value represents Mean ± S.D of three determinations (n=3)

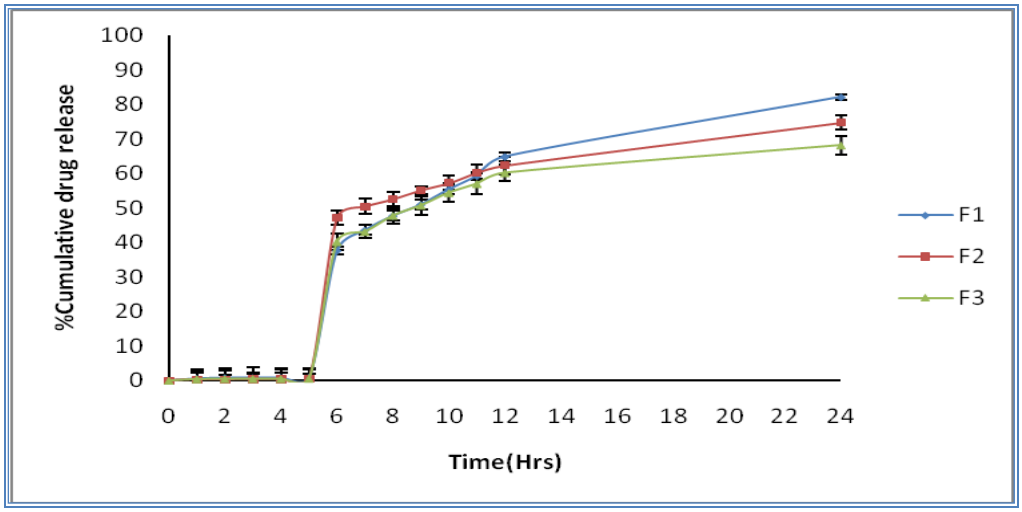

Figure 6: *In Vitro* Release Profiles of Mesalamine
(Coated Formulation CF-1, CF-2 &CF-3)

From the results it was observed that, the uncoated beads realeses the drug more than eudragit coated beads in first five hrs. The results show that the drug releases for uncoated beads take place more than 50% of drug in the area of upper intestine due to an initial burst effect. This burst effect is consistent with earlier findings of Quigley and Deasy (1992) who suggested that burst effect is due to poorly entrapped drug on the surface of gellan gum beads. By comparing the *in vitro* release pattern of all coated and uncoated formulations, it was found that the drug release from coated formulations was prolonged than uncoated beads. The drug release may be mainly controlled by drug diffusion through the natural gums matrix.

Data Analysis

Calculated regression co-efficient for different formulations are shown in Table 8. These values were compared with each other for model fitting equation. The model giving a regression coefficient close to unity was taken as order of release.The best fit model was observed to be Higuchi matrix for formulations F-1, F-2, F-3 the '*n'* values for F-1, F-2 and F-3 were respectively, as the values are between 0.5 & 1 the mechanism was found to be non Fickian diffusion.

Table 8: Best Fit Models for All Formulations

Uncoated beads	**Zero Order**	**First Order**	**Higuchi Matrix**	**Peppas Plot**	**Hixson Crowell**	**'n' Values**	**Best Fit Model**
F-1	0.9297	0.9708	0.9913	0.6123	0.9882	0.6018	Higuchi Matrix
F-2	0.9712	0.9872	0.9763	0.5881	0.9778	0.5718	Higuchi Matrix
F-3	0.9195	0.9766	0.9928	0.6837	0.9926	0.6218	Higuchi Matrix

***In Vivo* Studies**

In order to investigate out the in vivo performance of the coated alginate/gellan/ locust bean gum beads, a gamma scintigraphic study was carried out. The scintigraphy of the optimized formulation F3 (92 ± 0.8% Radio labeling efficiency) filled in enteric coated capsule was performed using rabbits (animal model) in order to establish its colon targeting potential. From the scintigraphic images (Figure 20) it can be interpreted that the beads were completely intact in the stomach up to 2 hrs. Images indicate that when beads of mesalaminewas in the small intestine the radioactivity was concentrated in a very small area indicating that little release had occurred. The mean transit time from stomach to colon was found to be 6.0±0.47 hrs. The beads started to disintegrate in colon after 6.0 hrs. Once the beads entered the ascending colon, there was considerable spreading of radioactivity from ascending colon toward the transverse colon which was most likely caused by the action of the bacterial enzymes in the colon degrading the gellan gum and accelerating the release of radioactivity. Scintigram shows the residence of beads in colon more than 12 hrs. These results showed that Eudragit S-100 coated beads formulation may be useful for targeting mesalamine to the colon.

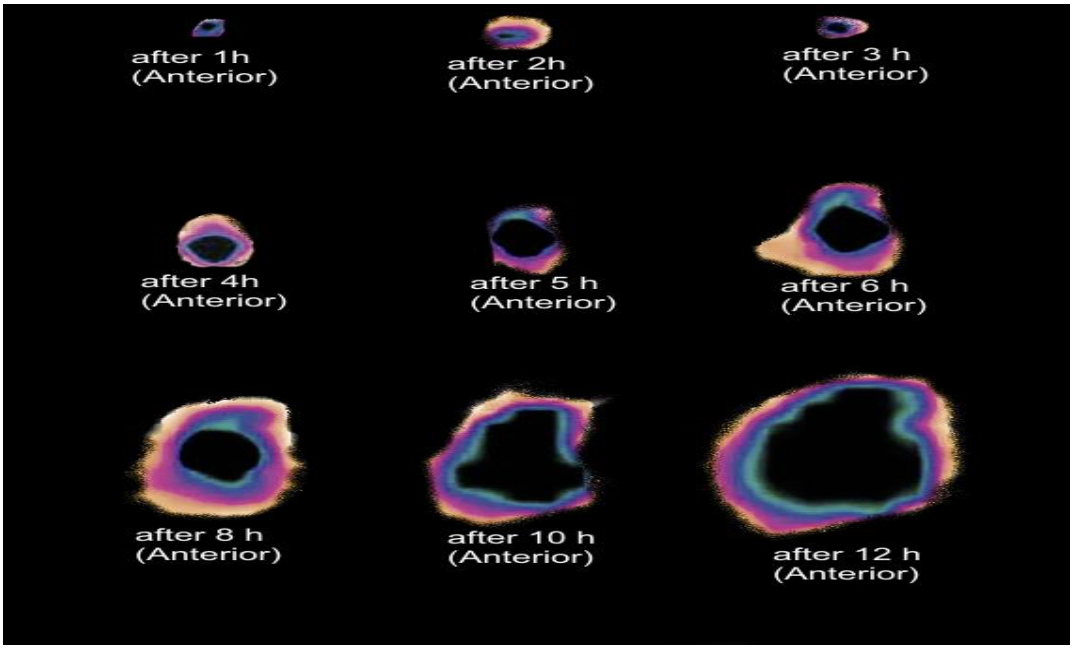

Figure 7: Gamma scintigraphic images of mesalamine loaded gellan beads in rabbit at different time intervals

Stability studies

The optimized formulation does not show any significant change with respect to shape, color, surface and in vitro drug release. The results of drug release are shown

Table 9: Stability studies of optimized formulation

Dissolution medium	**Time (hrs)**	**Percentage of MZ released from CF3 Formulation**	
		Before storage	**After storage (40^0C/75% RH)**
SGF(pH=1.2)	**1**	0.43±0.16	0.32±0.03
	2	0.49±0.07	0.41±0.03
SIF(pH=6.5)	**3**	0.50±0.07	0.48±0.03
	4	0.52±0.09	0.54±0.03
	5	0.60±0.04	0.71±0.07
SCF(pH=7.4)	**6**	40.25±2.58	32.40±2.30
	7	43.14±2.21	35.62±1.47
	8	47.81±0.02	40.94±1.61
	9	50.77±0.64	45.92±1.24
	10	54.46±1.79	50.58±1.42
	11	57.05±2.36	53.69±1.54
	12	60.19±3.06	55.91±2.6

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