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STUDIES ON DEVELOPMENT OF ORAL COLON TARGETED DRUG DELIVERY SYSTEM OF MESALAMINE USING NATURAL POLYMER LOCUST BEANS GUM

SHOIB I QURESHI[1*], LAHOTI SR[1], S.F.ZEENAT FARHEEN SFZ[1], KATKE AP[2] AND SHAIKH SIRAJ N[3]

1: Department of Pharmaceutics Y B Chavan College of Pharmacy Aurangabad-431001 Maharashtra, India

2: Department of Pharmaceutics JSPM'S Rajarshi Shahu College of Pharmacy and Research Tathawade Pune- 411033. Maharashtra, India

3: Department of Pharmaceutics, Ali-Allana College of Pharmacy Akkalkuwa, Nandurbar - 425415, Maharashtra, India

***Corresponding Author: Shoib I Qureshi: E Mail: siqureshi.gmcp@gmail.com**

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ABSTRACT

The aim of the present research work was to develop and evaluate colon specific sustained release matrix tablet of Mesalamine using different concentrations of microbial-dissolvable polysaccharide Locust Beans Gum. The drug polymer compatibility studies were determined by using FTIR & DSC.Matrix Tablets of Mesalamine were prepared by wet granulation method & evaluated for Pre, Post compression parameters like tapped density, bulk density, Hauser's ratio, compressibility index, and compressibility index was studied.The hardness, friability, weight variation, drug content etc. Dissolution studies were performed in HCl buffer pH1.2, Phosphate buffer pH 7.4 and Phosphate buffer pH 6.8 Cecal content in order to mimic the conditions from mouth to colon. The FTIR spectra of pure Mesalamine and in the formulation were found to be identical. FTIR & DSC drug, polymer7 in Physical mixture shows no interaction between the drug and polymer. Preformulation study suggests powders blends shows acceptable flow properties. Developed colon targeted tablets possessed the required physicochemical parameters such as hardness, friability, weight variation, drug content. Formulated with Locust bean gum, F1&F2 only 6.4±0.15 and 5.21±0.52 % drug

release was observed in the upper part of the GIT. F1 batch showed better drug release, that is, 95.1±1.25%, at the end of the 12 hour of dissolution study in the presence of rat Cecal Contents, in comparison to batch F-2, which released 81.4±0.18%. The results of the present study have demonstrated that developed colon targeted tablet were promising vehicle for preventing rapid hydrolysis in gastric environment. Finally, the studies confirmed that microbial triggered locust bean gum based colon targeted matrix tablet of Mesalamine is a potential system to target the drug release in the colon for better treatment of ulcerative colitis.

Keyword: Mesalamine, Locust Beans Gum, Colon, Matrix, Tablet

INTRODUCTION

Oral administration of drugs is one of the most convenient routes and is associated with superior patient compliance compared to other routes of drug administration has many problems like short gastrointestinal transit time, fluctuation in blood plasma concentration, low bioavailability **[1]**. So there is a need for Targeted drug delivery. Targeting drug to a specific area not only increases the therapeutic efficacy of drugs but also it aims to decrease the toxicity associated with drugs **[2]**. One of the approaches of drug targeting Colon specific drug delivery. The colon specific drug delivery system should be capable of protecting the drug en route to the colon & having potential for delivering various drugs to combat the local diseases for colon **[3]**. The colon has microflora of 1011 - 1012 CFU per ml. The main bacterial population present is anaerobic bacteria which proliferate. The predominant species isolated are Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria, etc **[4]**. In recent studies, colon targeted drug delivery systems are gaining importance to treat local pathologies of the colon and also for the systemic delivery of protein and peptide drugs. Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs **[5, 6]**. The various approaches that have been studied for targeting orally administered drugs to the colon include use of pH-sensitive polymers time dependent

dosage forms and the use of carriers degraded by enzymes produced by colonic bacteria. of these approaches, the use of materials that are degraded by the colonic microflora has been found to be the most promising because of their site specificity **[6-8]**. Natural polysaccharides are now extensively used for the development of

solid dosage forms for delivery of drug to the colon. Several polysaccharides like, pectin, chondroitin sulphate, amylase, guar gum, xanthan gum and chitosan are being investigated as carriers for colon specific drug delivery **[9, 10]**.

The Locust bean gum is neutral polysaccharides having a molecular weight of 3,10,000 derived from the endosperm of the seed of the Ceratonia siliqua linn (Fam: Legminosae). Locust bean gum, also called carob bean gum, is extracted from the outer coating of the carobseed. It is a polysaccharide comprised of galactose and mannose units **[11]**.

Mesalamine is an anti inflammatory drug, for oral administration 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. Ulcerative colitis is the anti inflammatory disease of the colonic mucosa which is restricted to large intestine and is usually treated with salicylates or glucocorticoids. However, during periods of remission mesalamine is the drug of choice **[12, 13]**.

In the present research work was to develop Matrix tablets of Mesalamine by using naturally occurring, biodegradable, inexpensive and non-toxic polysaccharide polymer guar Locust bean gum for colon targeted delivery.

MATERIALS AND METHODS

Mesalamine was gift sample from Lupin Pharma Ltd. Aurangabad (India). Locust bean gum was purchased from Triveni-chemicals, Gujrat. All other chemicals were purchased from the Research Lab. Mumbai

Method

Drug and Excipient Compatibility Study [12, 13]

FTIR Study

To investigate the chemical interaction, Fourier transformed infrared (FTIR) analysis of Mesalamine and the chosen Locust bean gum & Physical mixture used in the formulation were carried out over the range of 400-4000 cm1 using FTIR spectrometer. The spectra obtained for pure drug alone and in combination with excipients were compared to confirm the interaction.

DSC Study

Method for estimating the physical interaction between Mesalamine and Locust bean gum used for the formulation of the dosage forms is a thermal analysis by DSC. In the present studies, the DSC analysis of drug Polymers and blend were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer-drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in an aluminum crucible and heated at a

constant rate of 10 ºC/min over a temperature range of 40 to 300 ºC. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

Formulation Development

The development of the formulation in the present study was mainly based and the drug selected. In this colonic delivery the microbial triggered and pH sensitive approach, both are selected. The matrix tablet of the drug with locust bean gum was prepared and to avoid drug release in upper GIT .in the colon, colonic bacteria degrade the locust bean gum and thus drug get release.

Preparation Matrix Tablets of Mesalamine

In this granulation were prepared by wet granulation technique using Microcrystalline cellulose was used as diluent and a mixture of Talc .magnesium stearate (2:1) was used as lubricant locust bean gum was included in the formulations in various proportions. All the ingredients were weighed separately. Mesalamine and all the excipient previously passed through sieve no.#60 . The powders were blended and granulated with 10% starch paste. The wet mass was passed through a mesh #12 and the granules were dried at 50 0C for 2 h. The dried granules were passed through a mesh #16 and these granules were lubricated with a mixture of talc–magnesium stearate (2:1). The lubricated granules were compressed at a compression force of 4500–5500 kg flat round punch of 8 mm sizes on a Rotary tablet compression machine **(Table 1) [12-14]**.

Table 1: Composition of Mesalamine Colon Targeted Matrix Tablet

Ingredients (mg)	F1	F2	F3
Mesalamine	250	250	250
Locust bean gum	100	120	-
Microcrystalline cellulose	115	95	215
Starch paste 10%	20	20	20
Magnesium stearate	5	5	5
Talc	10	10	10
Total (mg)	500	500	500

Evaluation of Mesalamine Matrix Tablet [16-19]

A) Evaluation of Pre compression parameters

1. **Determinations of Bulk Density and Tapped Density**

   10 g of the mixed blend (W) was introduced into a 50 ml measuring cylinder, and 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. The bulk density, and

tapped density were calculated using the following formulae;

Bulk density= weight of sample/Volume of sample
Tapped density = weight of sample /tapped volume

2. **Angle of repose**

Angle of repose is an indication of the frictional forces existed between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontal plane. The angle of repose was calculated using the following formula;

Where; θ = angle of repose, h = height of the powder heap, r = radius of the powder heap, θ = Tan-1h/r

3. **Carr's Index**

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20% has good flow property. Carr's Index was calculated using the following formula;

Carr's Index = tapped density-bulk density/tapped density x100

4. **Hausner's Ratio**

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density. Hausner's ratio was calculated using the following formula;

Hausner's Ratio = tapped density /bulk density x100

B) Evaluation of Post compression parameters

1. **Hardness Test**

Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated by using Pfizer Hardness tester. The hardness was measured in terms of kg/cm^2**.**

2. **Friability Test**

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Friabilator. It is expressed in percentage (%). Percentage friability was calculated by using the formula;

% loss = initial weight of tablet-final weight of tablet/ initial weight of tablet x 10

3. **Weight variation**

20 tablets are selected weight individually and together. The average weight was noted and standard deviation was calculated by formula.

Drug Content Determination

Ten tablets were weighed and powdered. An amount of the powder equivalent to 250 mg of Mesalamine was dissolved in 100 ml of pH 6.8 buffer, filtered, the solution was shaken 1 hr and kept for 24 hr.1 ml solution was taken in 10ml volumetric flask and volume is made with 6.8 phosphate buffer diluted suitably and analyzed for drug content at 300 nm using UV Visible spectrophotometer.

In Vitro Drug Dissolution Studies

Drug release studies were carried out using USP Dissolution Rate Test Apparatus. (Apparatus 1, 100 rpm, 37^0C). The tablets were tested for drug release for 2 h in 0.1 NHCl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced dissolution with pH 7.4 Sorensen's phosphate buffer (900 ml) and tested for drug release for 3 h as the average small intestinal transit time is about 3 h. The dissolution medium was changed to 100ml of phosphate buffer (Ph6.8)containing 2%(w/v) the rat ceacal content and supply continues CO_2 the drug release was studied for 19hr.the amount of drug release at each time interval was determined by UV analysis.

RESULTS AND DISCUSSION

The aim of the present research work was to develop and evaluate colon specific sustained release matrix tablet of Mesalamine using different concentrations of microbial-dissolvable polysaccharide Locust Beans Gum. Three formulations of Mesalamine were prepared using Locust Beans gum as a polymer. The evaluation of the formulation was done and the results obtained are presented in **Table 3**.

Drug Excipient Compatibility Study

Fourier transforms infra-red spectroscopy (FTIR) Study

FTIR obtained for pure Mesalamine and Locust bean gum it suggests all the characteristic peaks of Mesalamine and Locust bean gum were present in spectra, thus indicating confirmation drug & polymer. It shows that there was no significant change in the chemical integrity of the drug & polymer **(Figure 1-3)**.

On the basis of FTIR spectra of physical mixture it concluded that there was no chemical interaction between Mesalamine, Excipient and Locust bean gum and it can be concluded that the characteristics bands of Mesalamine were not affected.

Differential scanning calorimetry (DSC) Study

DSC of Mesalamine

The DSC shows was there is no interaction between the Mesalamine, Excipients and Locust bean gum in the solid state. The melting point range of Mesalamine is between 283^0C, thus indicating there is no change of Mesalamine in pure state,

physical mixture of drug and polymer **(Figure 4)**.

DSC of Locust bean gum

The locust bean gum is the carbohydrate hence sharp peak is not obtained **(Figure 5)**.

DSC of Physical mixture {Drug:Locst bean gum (1:1)

The Mesalamine and Locust bean gum having no chemical interaction so to obtained peak **(Figure 6)**.

Evaluation of Mesalamine Matrix Tablet

A) Evaluation of Pre compression parameters

B) Table Physical properties of the granules for formulation

Evaluation of Post compression parameters (Table 3)

Different type of granules properties have been employed to assess flow ability, of these, angle of repose is the most relevant. Angle repose of granules was investigated. the value of angle of repose (Ɵ) decreased after addition of lubricant .angle of repose is an indicative parameter of powder flow ability from hopper to diet cavity .the angle of repose of all formulations were within the range of 25-30 0, indicative of good flow ability bulk density may influence compressibility, tablet porosity ,dissolution and other properties and depends on the particle size, shape and density to particles to adhere together .the bulk density of granules.

The powder blend of various formulations shows good flow property. Results are shown in **Table 2**. Results of various formulations revealed that the powder blend can be directly compressed into tablets.

I) Thickness

The thickness of all the tablets was found within the range of 5.1±0.3 to 5.4±0.07 mm

II) Friability

The percent friability of all the prepared formulae was less than 1%. The results indicated that all formulations complied with the pharmacopoeial limits for these tests

III) Hardness Hardness of the formulations F1-F3 was observed within the range of 3.4 to 3.6 kg/cm2 as shown in **Table 2**.

IV*)* Uniformity of weight

The weight of all the tablets was found within the range 501.2±2.1to 509.2±3.6mg. Hence the weight of all formulations was found within the limit.

V*)* Drug content

The Drug content of all the tablets was found within the range 97.61±0.12 to 98.61±0.54 %.

In-Vitro Drug release from formulation F1-F3

Drug release studies were carried out using USP Dissolution Rate Test Apparatus (Apparatus I, 100 rpm, 37^0C). The tablets

were tested for drug release for 2 h in 0.1 N HCl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced dissolution with pH 7.4 Sorensen's phosphate buffer (900 ml) and tested for drug release for 3 h as the average small intestinal transit time is about 3 h. The dissolution medium was changed to 100ml of phosphate buffer (Ph6.8)containing 2%(w/v)and the rat ceacal content.the amount of drug release at each time interval was determined by UV analysis..The formulations F1, F2, F3 shows cumulative drug release *95.1±1.25*, *81.4±0.18*%, at 12 hrs & 61.85%, at 5 hrs respectively.

When the Mesalamine colon targeted tablet was formulated without Locust bean gum (F-3) 61.85% drug release was observed after 5 hrs hours in the *in vitro* drug release study. When it was formulated with Locust bean gum, F1&F2 only *6.4±0.15* and *5.21±0.52 %* drug release was observed in the upper part of the GIT. On the basis of result we observed the capability of Locust bean gum to protect the active medicaments to release in the upper part of the gastrointestinal tract. F1 batch showed better drug release, that is, *95.1±1.25*%, at the end of the 12 hour of dissolution study in the presence of rat cecal contents, in comparison to batch F-2, which released *81.4±0.18*% .I*n vitro* evaluation of the Mesalamine colon targeted tablet prepared using Locust bean gum shows that Locust bean gum is capable of protecting the drug from being released in the physiological environment of the stomach and small intestine. The result of in vitro evaluation shows that Locust bean gum is susceptible to the enzymatic action of cecal contents **(Table 4), Figure 7**.

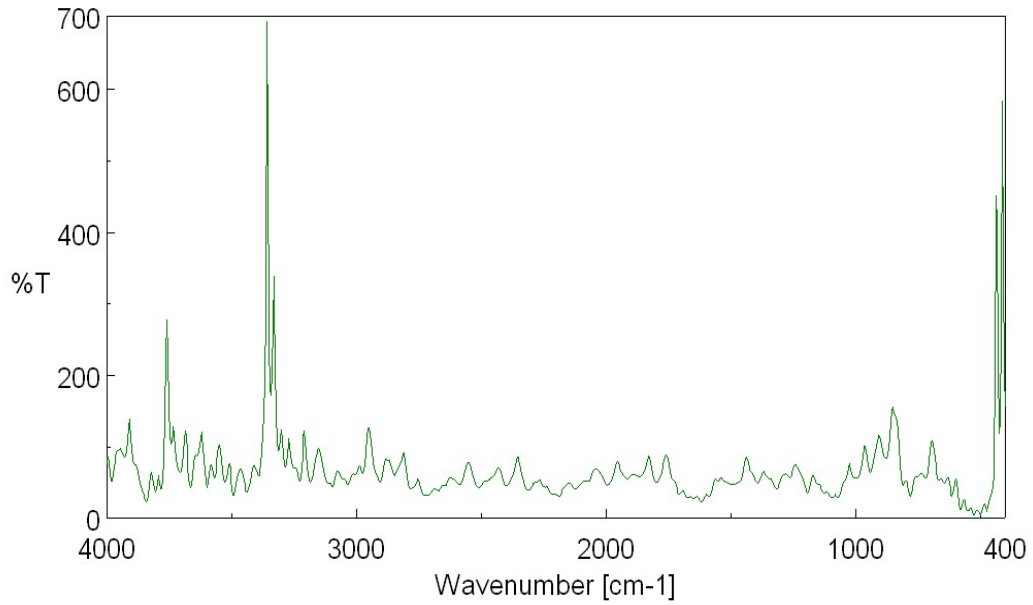

Figure 1: FTIR spectra of Mesalamine

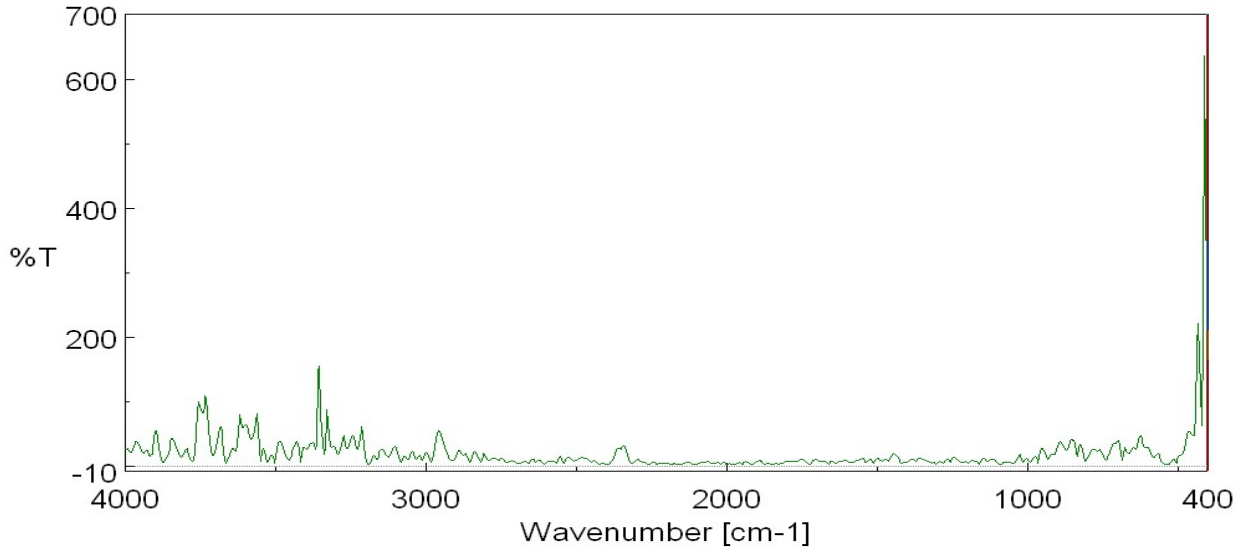

Figure: 2 FTIR spectra of Locust bean

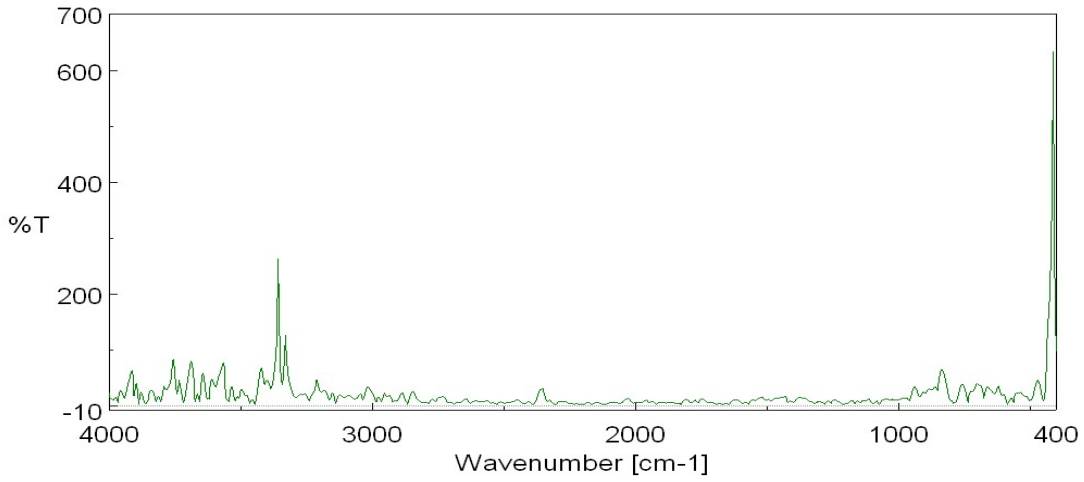

Figure 3: FTIR spectra of Physical mixture Drug:Locst bean gum(1:1)

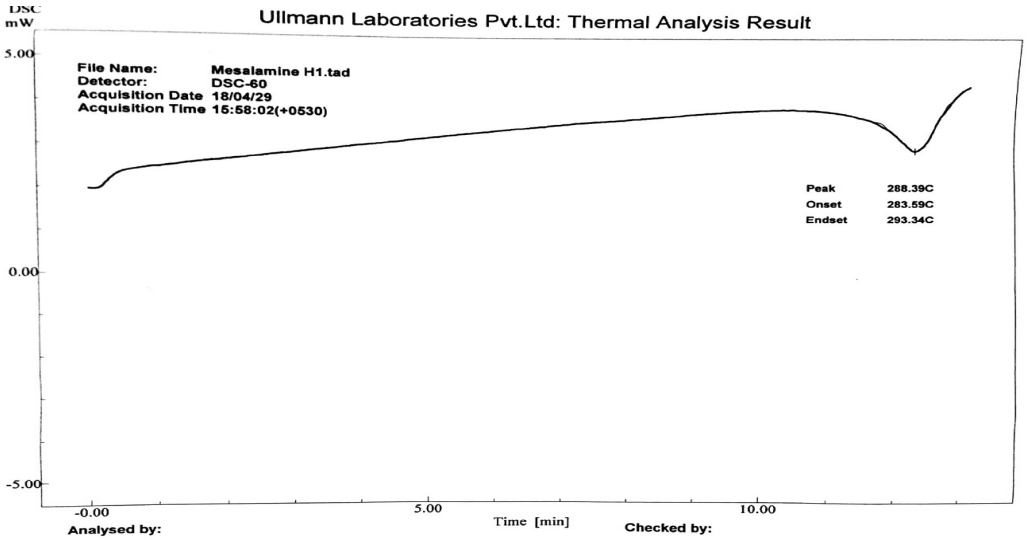

Figure 4: DSC of Mesalamine

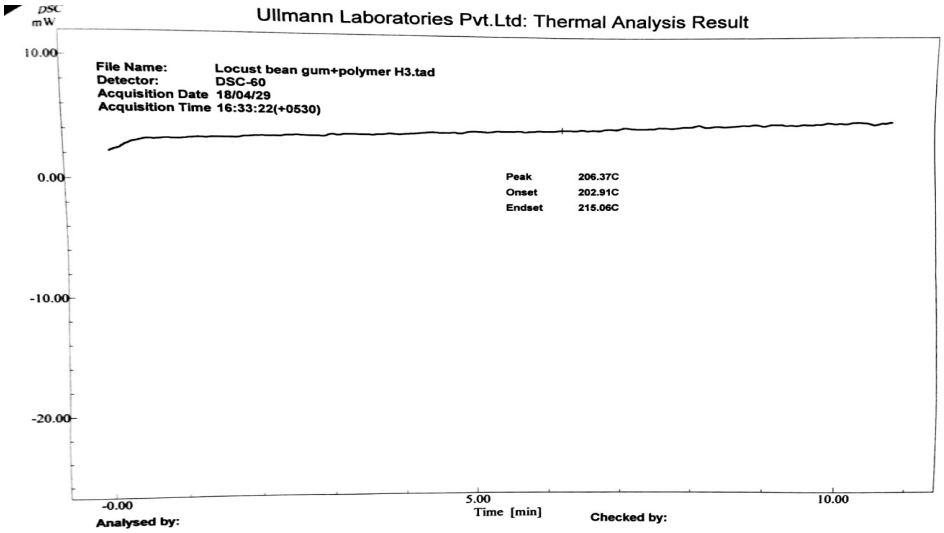

Figure 5: DSC of Locust bean gum

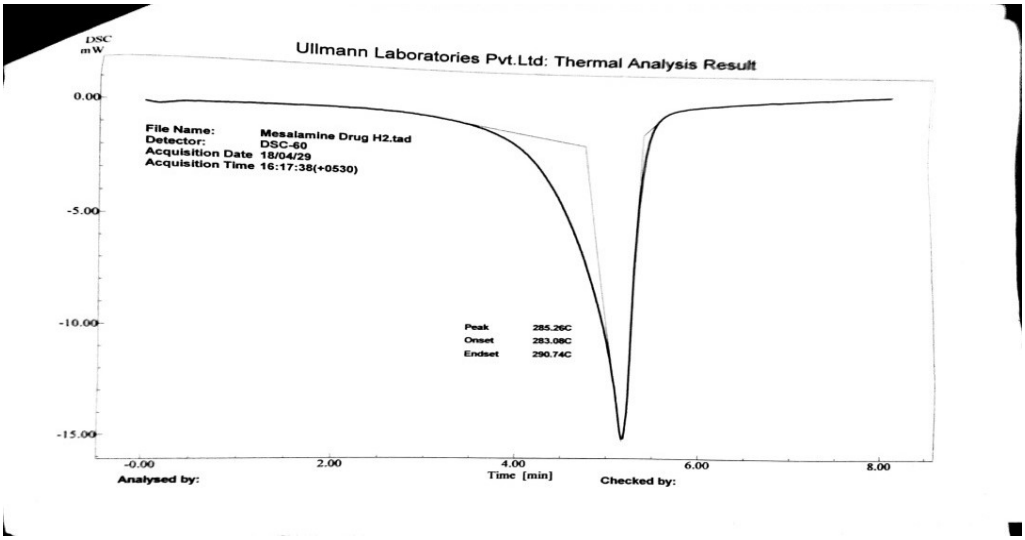

Figure 6: DSC of Physical mixture in formulation blend

Table 2: Evaluation of precompression parameters of granules blends

Parameters	F1	F2	F3
Bulk density	0.37±0.02	0.41±0.014	0.39 ± 0.04
Tapped density (gm/cm3)	0.43±0.02	0.50±0.007	0.45± 0.04
Carr's index (%)	13.95±0.32	18.2±1.5	13.4±1.7
Hausner's ratio	1.16±0.01	1.21±0.3	1.15±0.4
Angle of repose	28.16±0.90	24.69±2.63	27.44±2.61

Table 3: Evaluation of post compression parameters of Colon Targeted Matrix Tablet

Thickness (mm)	5.2±0.05	5.4±0.07	5.1±0.3
Friability (%)	0.71±0.08	0.84±0.02	0.59±0.06
Hardness	3.4	3.6	3.5
Uniformity of weight (mg)	501.2±2.1	509.2±3.6	506.4±5.9
Drug content	98.12±0.41	97.61±0.12	98.61±0.54

Table 4: In-vitro drug release study of formulation F1-F3

Time (hrs)	Cumulative % Drug Release		
	F1	F2	F3
0	0.00	0.00	0.00
1	0.80±0.41	0.57±0.36	12.1
2	3.32±0.12	2.06±0.76	23.87
3	5.04±0.13	3.15±08	32.76
4	5.50±0.14	4.09±0.11	46.1
5	6.4±0.15	5.21±0.52	61.85
6	18.9±0.19	15.9±0.45	-
7	31.52±0.14	23.66±0.90	-
8	49.64±0.45	34.32±0.49	-
9	52.50±0.16	46.22±0.18	-
10	81.9±0.41	65.8±0.76	-
11	90.22±0.14	77.85±0.16	-
12	95.1±1.25	81.4±0.18	

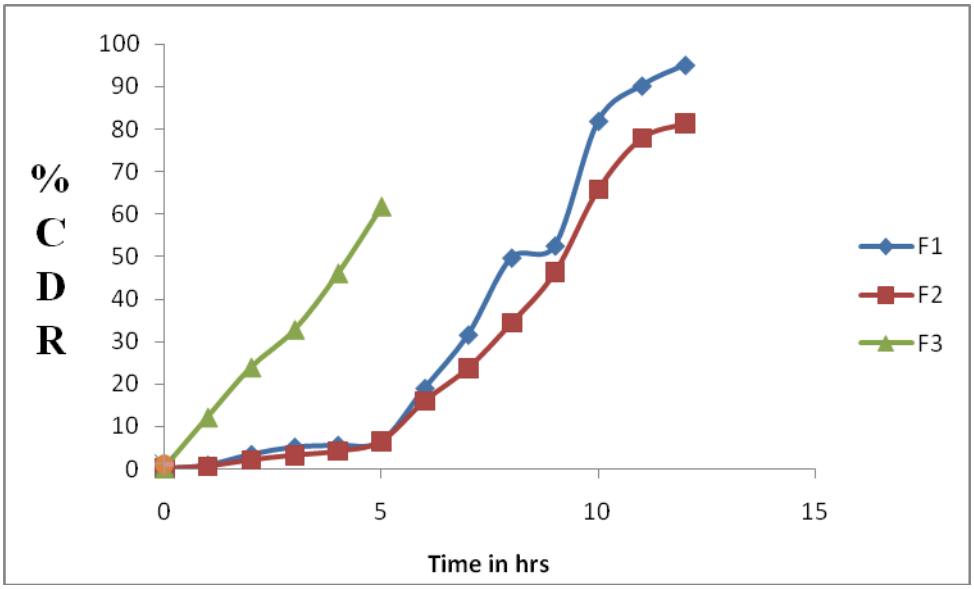

Figure 7: Graph of In-vitro drug release study of formulation F1-F3

CONCLUSION

The aim of the present study was to develop Matrix tablets of Mesalamine by using naturally polysaccharide polymer guar Locust bean gum for colon targeted delivery.Colon targeted matrix tablets of Mesalamine was prepared with different concentration of Locust Beans Gum & evaluated. FTIR &DSC The drug, polymer compatibility studies shows no interaction between the drug and polymer. Preformulation study suggests powders blends shows acceptable flow properties. Developed colon targeted tablets possessed the required physicochemical parameters such as hardness, friability, weight variation, drug content. When the Mesalamine colon targeted tablet was formulated without Locust bean gum (F-3) 61.85% drug release was observed after 5 hrs hours in the in vitro drug release study. When it was formulated with Locust bean gum, F1 & F2 only 6.4±0.15 and 5.21±0.52 % drug release was observed in the upper

part of the GIT. F1 batch showed better drug release, that is, 95.1±1.25%, at the end of the 12 hour of dissolution study in the presence of rat cecal contents, in comparison to batch F-2, which released 81.4±0.18 %. The results of the present study have demonstrated that developed colon targeted tablet were promising vehicle for preventing rapid hydrolysis in gastric environment. Finally, the studies confirmed that microbial triggered locust bean gum based colon targeted matrix tablet of Mesalamine is a potential system to target the drug release in the colon for better treatment of ulcerative colitis.

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