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EFFECT OF LUMINAL pH CHANGES ON GUAR GUM-HPMC E15 LV MIXED MATRIX TABLETS FOR MESALAMINE DRUG DELIVERY TO COLON AND STUDY ON *IN- VITRO* CHARACTERISTICS IN TWO DIFFERENT DISSOLUTION MODELS vs. MARKETED FORMULATION

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ABSTRACT

The study was designed to investigate the impact of colonic pH changes on formulated colon targeted Mesalamine matrix tablets in the treatment of inflammatory bowel disease (IBD). Mesalamine tablets were fabricated with guar gum as Polymer system. The different batches of Mesalamine tablets (GMM1-GMM6) were compressed with increasing proportion of guar gum and HPMC E15 LV. The different buffer conditions were chosen to mimic the pH changes in terminal part of the ileum as well as the colon. A separate two *in vitro* studies were conducted in all the formulations. The impact of the pH changes on the coated tablets in normal pH condition and reduced pH condition (pH reduced during IBD) were compared. In IBD the pH of the colon falls below its normal level. The extent of pH change depends on the severity of the disease. The study was designed to evaluate the *in vitro* dissolution characteristics of Mesalamine matrix tablets in a variety of simulated fluids (pH range 1.2, 6, 6.8, 7.2, 5). The results indicated that the impact of pH changes on drug release profile was not affected in the diseased and normal pH condition of the colon. The present treatment methods of IBD mostly depend on pH sensitivity polymers or enteric coating technique. These pH sensitive polymers based colonic devices may not serve the patient needs successfully because the influence of colonic pH on pH sensitive polymer based devices plays an important role in triggering the drug release in target site. The lowered pH condition in diseased state could not trigger the drug release in pH sensitive polymer based devices as it was not the threshold pH of the particular coated polymer. In case of enteric coating there may be a possibility of disintegration of the tablet before reaching the colon due to the contractile movement of GI tract and fluctuation in the GI pH. The present matrix tablets were prepared with guar gum, which cannot be affected by the pH changes of the colon, maintained its integrity better than enteric coated tablets and release the drug in the pre determined pattern and can be used successfully against IBD for better targeting properties. The study results indicate that the formulations of guar gum colon targeted tablets can be used successfully for IBD treatment and better alternate for synthetic polymer based marketed formulations.

INTRODUCTION: Colon targeted drug delivery systems are used for the variety of reasons and providing most effective therapy in colon related diseases such as inflammatory bowel disease (IBD) [1]. In recent advancements, colon drug delivery can be used for chronotherapy such as asthma, hypertension, cardiac arrhythmias and arthritis are characterized by circadian rhythm [2]. Small luminal surface area restricting the transit of the material through colon but the longer residence time of the material through the colon some extent compensate this problem.

The GI residence time was influenced by many physiological factors. The pH of the lumen in healthy volunteers was observed as pH 7.5± 0.4 in duodenum a decrease in ceacum (pH 6.4± 0.4) then a slight rise in the left to the right colon with final value of pH 7.0±0.7. The change in the colonic pH was reported in the various inflamed conditions especially in IBD, this should be considered in the development of colonic devices [3, 4].

The present treatment of inflammatory bowel disease mostly based on pH sensitive polymers based delayed release dosage forms that are expected to dissolve at particular threshold pH. The different studies indicate that there is significant fall in the colonic pH due to diseased condition of the colon [5-8]. Preparing a colon targeted drug delivery system with the natural polymers especially in diseases such as inflammatory bowel disease can avoid the problem of poor drug release profile in the colonic region caused by the affected pH of the colon.

Guar gum is available naturally and is non-ionic in nature. It is a polysaccharide derived from the seeds of *Cymompsis tetraganololbus* from the family of leguminacaea [9]. Guar gum is a hydrophilic natural polymer swell in the water and upon soaking forms the colloidal dispersion. The gelling property of the guar gum can be used for the variety of purposes like controlled release, microsphere formation, and colon specific targeting carriers [10, 11].

MATERIALS AND METHODS: Mesalamine – Sarex overseas ltd, Guar gum, Micro crystalline cellulose, PVP K_{30},Magnesium Stearate, Talc, HPMC, Propylene glycol-Merck.

Equipments: Electronic weighing balance, -Shimadzu corporation, Compression machine-Cadmach 16 station rotary tablet punching machine, Digital vernier caliper-Mitutoyo-Digimatic caliper,Hardness tester-Dolphine, Friability tester, Secoa-India, UV visible spectrophotometer-Elico SL 164 (double beam), Digital Dissolution test apparatus-Lab India DS 8000,Sifter(manual).

Methods:

FTIR Analysis: The FTIR spectra of drug raw material, drug with various excipients used in the formulation were recorded using Perkin Elmer (USA), from 4000-400 as scanning range between wave number (cm^{-1}) and % transmittance. Samples were prepared in KBr discs (2mg sample in 200mg KBr) with hydro static press at force of $5cm^{-2}$ and the resolution was 4 cm^{-1}. Experiments were duplicated to check the reproducibility.

Fabrication of Guar Gum Matrix Tablets: Mesalamine matrix tablets were prepared by conventional granulation method. Along with active pharmaceutical ingredient (Mesalamine) Micro crystalline cellulose, HPMC E15 LV and polymer (Guar gum) were mixed according to the formula as **table 1** and formulations (GMM1-GMM6) were developed.

TABLE 1: FORMULA OF MESALAMINE GUAR GUM MATRIX TABLETS

Ingredients (mg)	Formulations					
	GMM1	GMM2	GMM3	GMM4	GMM5	GMM6
Mesalamine	400	400	400	400	400	400
Micro Crystalline Cellulose	170	140	110	140	110	80
Guar gum	120	140	160	120	140	160
HPMC E15LV	0	10	20	30	40	50
Talc	18	18	18	18	18	18
Magnesium Stearate	9	9	9	9	9	9
Total weight	717	717	717	717	717	717

Guar gum and HPMC E15 LV was incorporated in the formulation by constant increments to assess the influence of proportion of polymers on the colon targeting and drug release profile. Granulation was carried out by using HPMC 15cps (10%) as binding agent and water as the granulating medium. After a thorough mixing of all ingredients the damp mass was prepared and passed through 16#. The wet granules were collected and dried in a tray drier with inlet temperature of 45^{o}C/hr. Immediately after drying, collected granules were passed through 44 # to get granules suitable for tablet compression. Previously the dried granules were lubricated with magnesium stearate and talc. The tablets were prepared by using 12mm round shaped punches by using 16 station tablet punching machine.

***In-vitro* Drug Release Studies:**

***In-vitro* drug release study design for colonic pH changes in normal and inflamed conditions of colon:** Experiments were designed to study the effect of;

(i) Coating of formulation

(ii) Impact of dissolution medium (normal & diseased pH condition of the colon) on coated tablets.

The *in-vitro* release study was carried out by buffer change method using USP XXIII test apparatus (paddle method) and the conditions of 75 rpm, 37±0.5^{o}C were maintained throughout the experiments. The USP apparatus was used for all the experiments and buffer stages were adjusted according to the purpose of the study. The drug release study was started with 500 ml of 0.1N HCl (2hours) and followed by buffer stage 1 and 2, (pH 6 phosphate buffer -2 hour and followed by 7.2 pH phosphate buffer).

The pH of the solution was indicating the normal pH condition of stomach, intestine and colon. The dissolution studies were continued up to 17 hours. In diseased condition (IBD), the pH of the colon expected to be decreased so that the following pH conditions were chosen for the study. Initially 500 ml of 0.1N HCl followed by pH 6.8 phosphate buffers (2h) and 5 pH (decreased colon pH) were used as dissolution medium for up to 17 to 20 hours.

Aliquots were collected manually at pre determined time intervals and analyzed for Mesalamine content using a U.V Spectro photo meter (Perkin -Elmer). The readings were taken at 302, 330 and 332nm for samples tested in 0.1 N HCl and the buffer Medias respectively. The drug concentration was determined by using standard calibration curve prepared from the standard of known concentration of Mesalamine.

Buffer change procedure: The dissolution test was carried out as per USP 2005. *Acid Stage* – After 2 hours of operating, withdraw an aliquot for the fluid, discard the remaining solution, and retain the tablets in proper order, so that each will be returned to its respective vessel later on, Blot the tablets with a paper towel to dry, and proceed immediately as directed for buffer stage 1. The amount of Mesalamine dissolved was analyzed by employing UV absorption at the wavelength of maximum absorbance at about 302nm on filtered portions of the solution under test, suitably diluted with dissolution Medium.

1. **Buffer stage 1:** Transfer pH 6.0 Phosphate buffer (use buffer that has been equilibrated to a temperature of 37±0.5^{o}C) to each of the dissolution vessels, and place each tablet from the acid stage into its respective vessel. After 1 hour remove a 50ml aliquot, and proceed immediately as directed for Buffer stage 2. The amount of Mesalamine dissolved was determined by employing UV absorption at the wavelength of maximum absorbance at about 330nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium.

2. **Buffer Stage 2:** Add 50ml of Sodium hydroxide solution to each dissolution vessel to adjust to a pH of 7.2, and continue the run Procedure. The amount of Mesalamine dissolved was determined by employing absorption at the wavelength of maximum absorbance at about 332nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium.

Procedure for preparation of rat ceacal contents medium: Six Albino rats weighed 120- 160 gm were maintained in the normal diet conditions were chosen for the study to collect rat ceacal contents. The study on the animals was carried out after the scrutiny and

approval of institutional animal Ethical committee (IAEC). The study was designed to assess the enzymatic activity of the colonic bacteria on the matrix tablets. To assess the enzymatic activity, drug release studies were performed in the pH media mimicking the colonic pH conditions in the presence of rat ceacal contents. Previously rats were induced for the enzymes in the colon by giving the guar gum dispersion. Normal diet conditions were maintained for the rats. But the guar gum dispersion (4% W/V) was given orally to induce the enzymes in the colon to act on guar gum.

From this, 1 ml of 2% w/w guar gum dispersions provides the best conditions for the colonic degradation by bacteria [12, 13]. The procedure involves the oral administration of 2% w/v guar gum dispersions for 7days to induce guar gum degrading enzymes in the colon. The guar gum dispersion was administered by inserting the Teflon canula directly in to the colon. Around an hour before the commencement of *in-vitro* drug release studies albino rats were sacrificed and ceacal contents were collected by opening the abdomen. The ceacal was ligated both the ends with the help of thread and removed carefully and weighed separately.

The contents were immediately transferred in to 6.8 pH phosphate buffer saline bubbled with carbon dioxide. Finally 4% w/v of ceacal dilution was prepared by pooling the ceacal contents of four albino rats. The 4% w/v ceacal content was introduced in to the dissolution process after four hours of study. The samples were collected in the pre determined time intervals and medium was replaces with fresh media bubbled with carbon dioxide as the ceacum is naturally anaerobic. The withdrawn samples were centrifuged to remove solid contents. The supernatant liquid was collected and filtered through bacteria proof filter. The Mesalamine contents were analyzed by double beam UV spectrophotometer at wave length of 330 and 332 nm.

Release Kinetics: Each batch of the tablet dissolution data is treated with different kinetic models to characterize the drug release from hydrophilic matrices. The zero order $Q = K_0 t$; First order $\text{Log } Q_t = \text{Log } Q_0 + kt/2.303$, Higuchi square root time $Q = K_H t^{½}$; Korsemeyer-Peppas $Mt / M\infty = K_M t^n$; Hixson- Crowell $Q_0^{⅓} - Q_t^{⅓} = K_{HC} tt$; where Q is the amount of drug released at time t, K_0, K are the zero order and first order release constants respectively. K_H is Higuchi's release constant. $Mt/M\infty$ is the fraction of drug released at time t. K_M is the constant incorporating geometric and structural characteristics of tablets and 'n' are the diffusion exponent indicative of release mechanism. In case of tablets (cylindrical shape) a value of $n< 0.45$ indicates fickian diffusion or case I release; $0.45<n<0.89$ for non fickian or anomalous release; $n = 0.89$ for case II release; and $n>0.89$ indicates super case II release.

RESULTS AND DISCUSSION: The present study was undertaken to formulate Mesalamine matrix tablets. The dosage form study includes pre-formulation of drug and excipients. The overall objective of pre-formulation testing is to generate information useful to the formulation development of stable and bio available dosage forms. Study was carried out to analyze drug excipients interactions for formulation process development to prepare a final optimized formulation.

The results of pre-formulation study were optimized the new formulation design. Drug and excipients involved in the formulation were also analyzed under IR spectra analysis to find out the compatibility of drug and excipients (**Figure 1-5**). Based on the spectra derived from IR analysis the drug Mesalamine was stable with the used excipients and no interaction was reported. By using these excipients, final optimized formulation was developed.

Mesalamine colon targeted tablets were prepared by using guar gum, micro crystalline cellulose, HPMC E15 LV, talc and magnesium stearate. Since guar gum having poor flow properties and the amount present in the tablet formula was very high it was chosen to be prepared by conventional wet granulation technique. The prepared solid dosage form was stable, elegant and has no abnormalities or defect in the appearance.

The prepared matrix tablets were evaluated for various physical characteristics such as size, shape, thickness, hardness, friability. The vital evaluation parameter such as content uniformity was evaluated and found in satisfactory limits. The essential results were presented in the **table 2**.

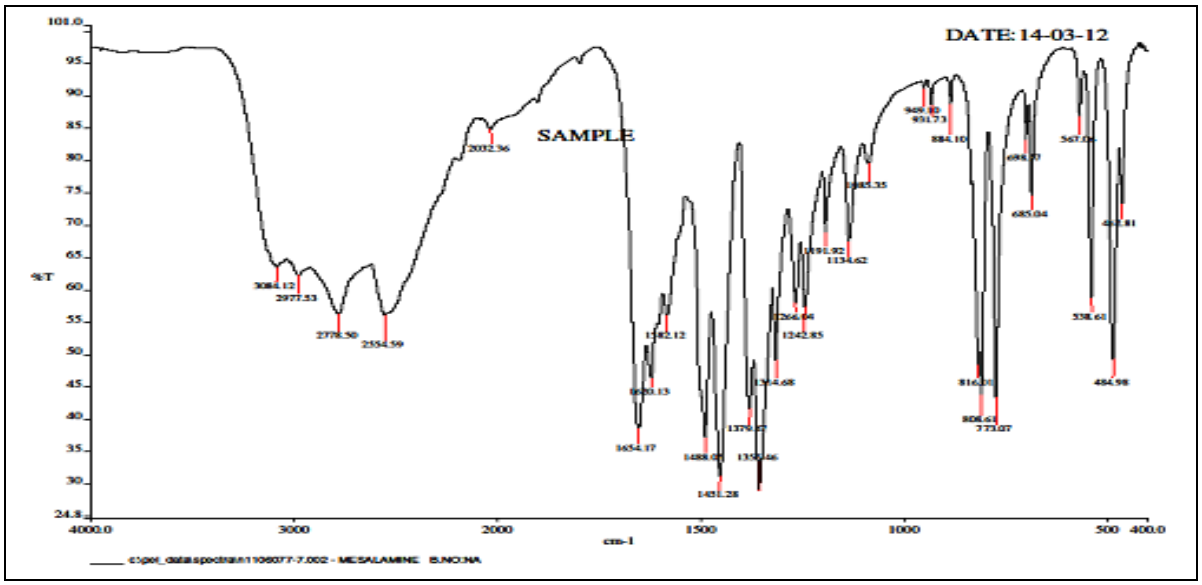

FIGURE 1: IR SPECTRUM OF MESALAMINE DRUG

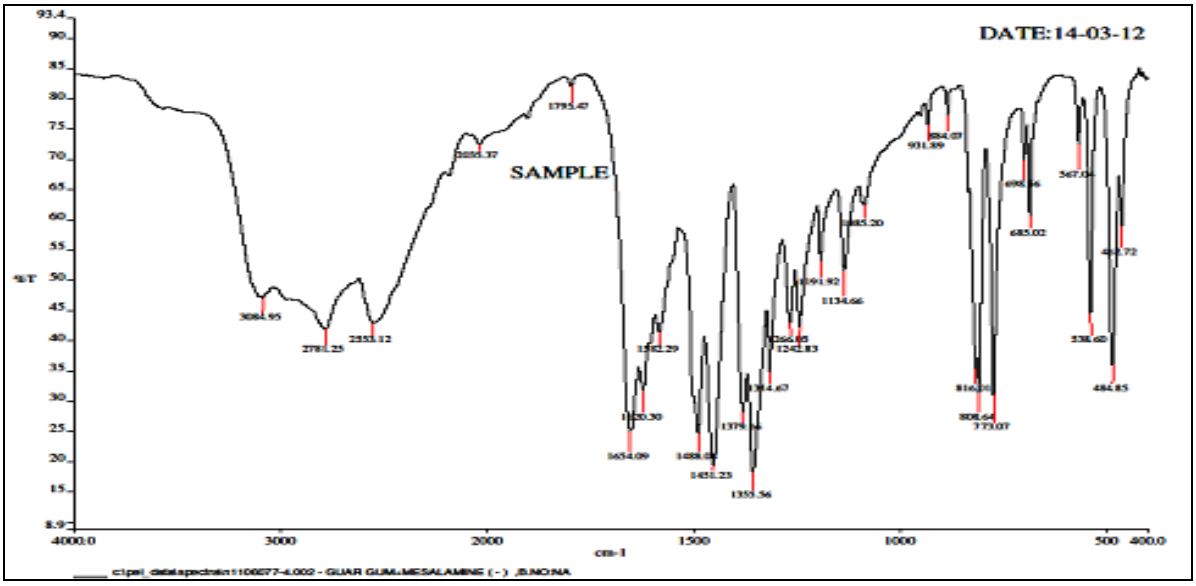

FIGURE 2: IR SPECTRUM OF MESALAMINE -GUAR GUM

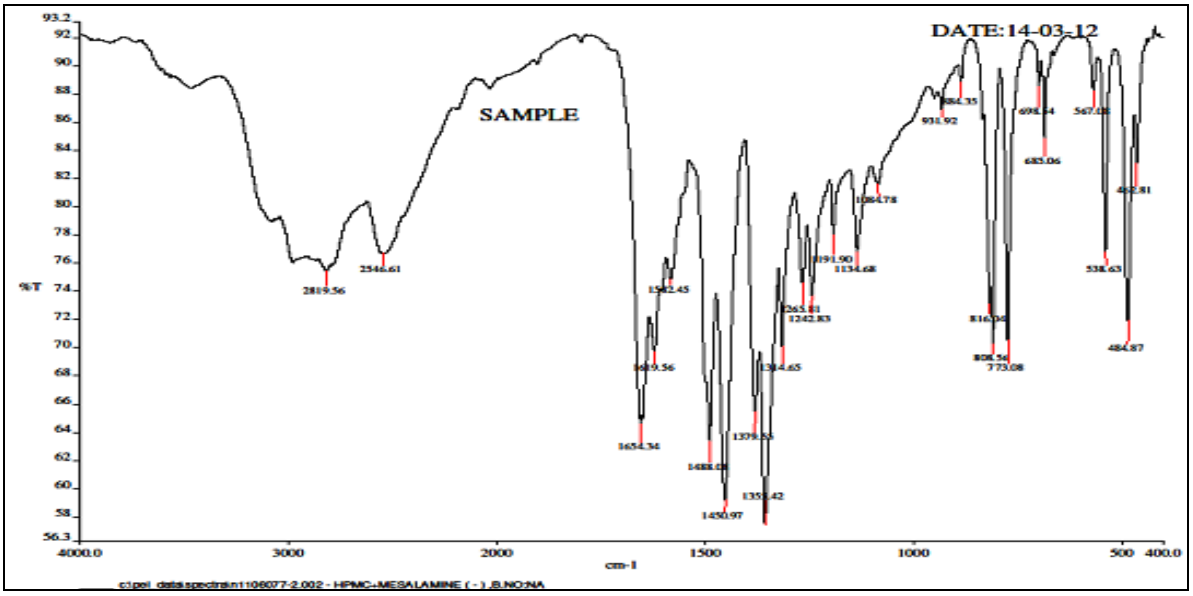

FIGURE 3: IR SPECTRUM OF MESALAMINE-HPMC

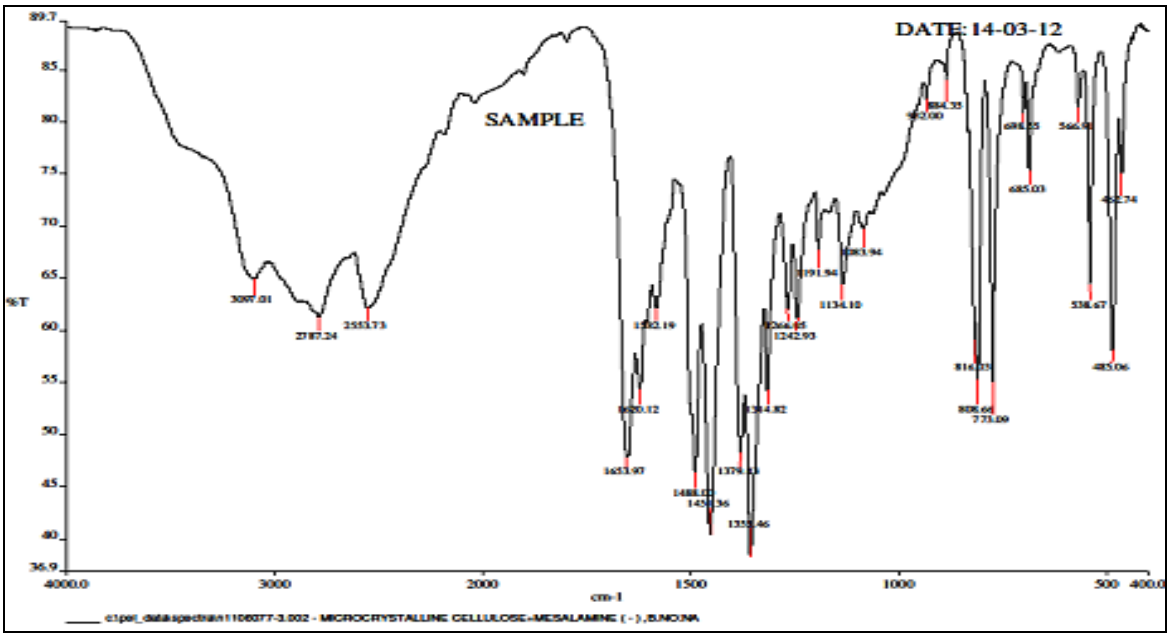

FIGURE 4: IR MESALAMINE-MICRO CRYSTALLINE CELLULOSE

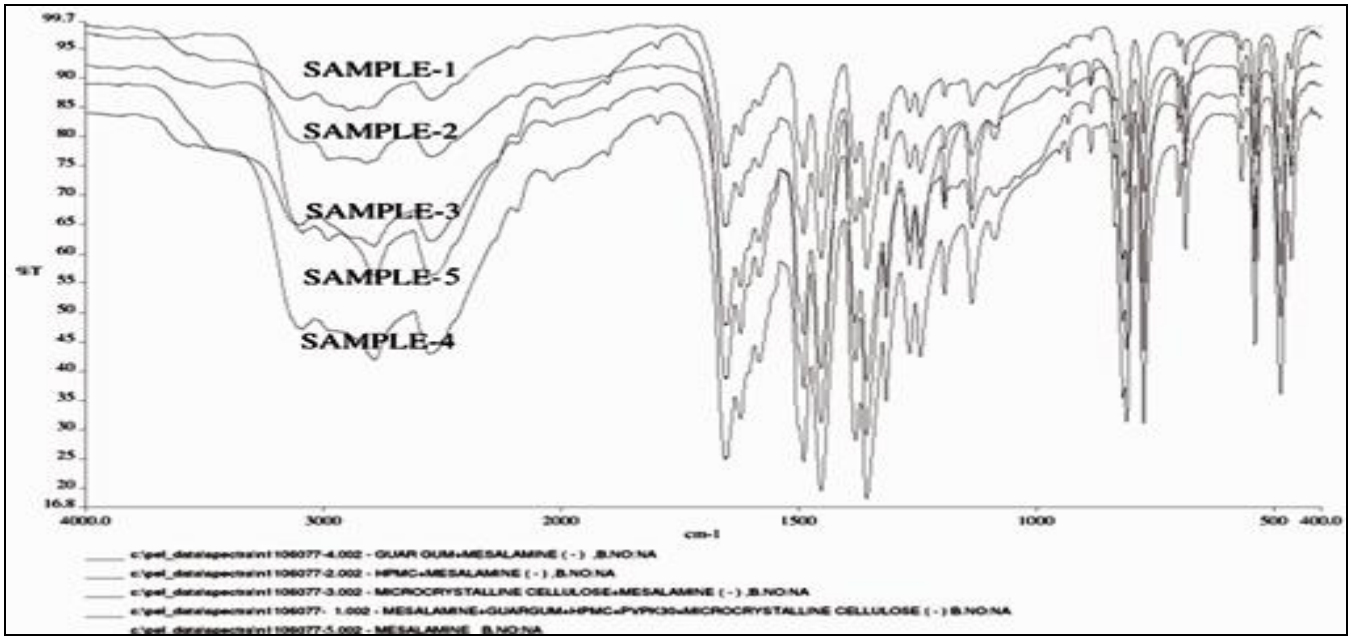

FIGURE 5: IR OVER LAY SPECTRUM OF MESALAMINE WITH OTHER INGREDIENTS

TABLE 2: PHYSICOCHEMICAL CHARACTERISTICS OF THE TABLETS

Formulations	Parameters			
	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Content uniformity (%)
GMM1	4.59±0.988	0.416	717.2±1.54	102.22±2.83
GMM2	5.71±0.627	0.716	717.1±1.72	104.04±3.19
GMM3	6.35±0.662	0.817	717.4±1.17	102.61±0.72
GMM4	5.27±1.018	0.925	717.9±1.96	102.80±2.12
GMM5	5.24±0.227	0.367	718.2±1.68	101.76±2.41
GMM6	6.51±0.435	0.634	718.8±1.54	102.14±1.55

The *in-vitro* studies were carried out for the Mesalamine colon targeted tablets as per USP method as it was mentioned under Mesalamine delayed release tablets. The drug release study was conducted in the different pH conditions (pH 1.2, 6, &7.2) and the results were shown in the **table 3** and **figure 6**.

TABLE 3: DISSOLUTION PROFILE OF GUAR GUM MATRIX TABLETS (USP DISSOLUTION METHOD)

pH condition	Time(h)	Cumulative % drug released						
		GMM1	GMM2	GMM3	GMM4	GMM5	GMM6	MKT
1.2	**2**	3.62	3.24	3.78	8.15	7.11	8.99	8.09
6	**3**	4.57	4.29	4.91	12.33	8.89	12.13	15.16
6	**4**	9.63	9.48	10.28	23.78	17.29	23.64	45.06
7.2	**5**	10.51	9.51	10.53	34.81	19.15	27.88	67.09
7.2	**6**	10.9	9.76	11.19	45.67	22.98	39.15	75.34
7.2	**7**	12.22	11.13	12.71	57.98	31.11	46.17	85.35
7.2	**8**	13.25	11.93	13.1	69.92	43.09	59.12	97.19
7.2	**9**	13.46	12.1	13.9	82.11	54.23	63.14	
7.2	**10**	14.7	16.23	16.38	96.39	67.12	78.9	
7.2	**11**	19.79	19.23	17.47		72.15	93.14	
7.2	**12**	21.42	20.86	21.09		94.11		
7.2	**13**	25.68	27.87	29.09				
7.2	**14**	35.46	32.17	42.08				
7.2	**15**	57.09	49.99	51.71				
7.2	**16**	74.72	64.08	59.34				
7.2	**17**	82.06	73.33	64.56				

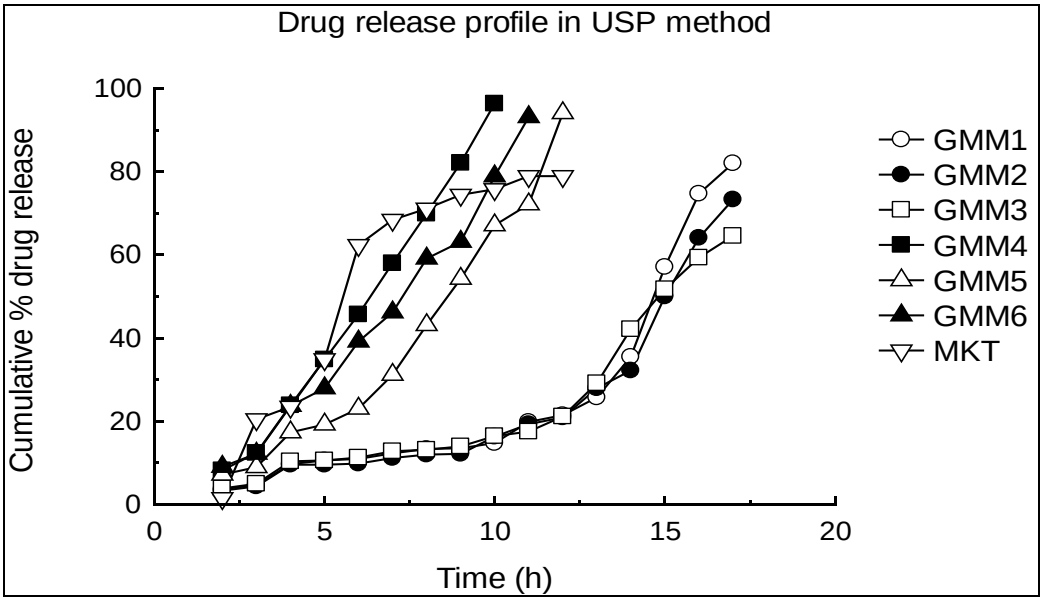

FIGURE 6: CUMULATIVE % DRUG RELEASE IN USP DISSOLUTION METHOD

In order to mimic the different pH conditions of the GI tract, alternative method with other pH (pH 1.2, 6.8 & 5)) were also adopted to assess the release characteristics and targeting property of the fabricated dosage form in varying luminal pH conditions and the results were presented in the **table 4** and **figure 7**. The pH of alternative method collected from literature review [14, 15]. The drug release profile from all the dosage forms are examined carefully and compared with the marketed delayed release (MKT) formulation. The all guar gum colon targeted tablets showing the controlled dissolution profile.

The drug release was controlled in the upper GI tract. In USP method the dissolution was carried out first in the 0.1 N HCl. All the six formulations were released a negligible amount of the drug in this dissolution condition. This indicates all the formulations of guar gum Mesalamine matrix tablets passed the enteric performance test. The prepared tablets maintained its intactness and integrity up to 2h of dissolution study at acidic conditions. After the completion of study in acidic environment the 6 pH phosphate buffer solution was replaced 0.1N HCl. The drug release studies continued for two hours in this pH environment

TABLE 4: DISSOLUTION PROFILE IN ALTERNATE DISSOLUTION CONDITIONS

pH conditions	Time (h)	Cumulative % drug released						
		GMM1	GMM2	GMM3	GMM4	GMM5	GMM6	MKT
1.2	**2**	3.637	3.207	4.05	5.16	9.35	8.12	0.114
6.8	**3**	4.7	4.36	4.71	11.22	8.89	14.84	11.08
6.8	**4**	11.25	10.53	11.16	12.33	18.12	25.17	11.24
6.8	**5**	11.5	10.93	11.16	15.15	20.56	27.34	12.21
5/6.8	**6**	12.95	11.78	12.56	18.76	24.67	37.36	12.89
5/6.8	**7**	13.34	12.48	14.02	25.29	32.11	45.91	13.158
5	**8**	13.72	13.11	14.23	37.78	45.92	57.18	13.64
5	**9**	14.31	13.75	14.42	45.32	57.6	66.83	14.1
5	**10**	17.81	17.12	14.97	55.34	69.19	79.5	14.182
5	**11**	19.03	17.98	15.19	69.2	75.15	95.13	
5	**12**	18.98	18.34	18.93	85.11	91.29		
5	**13**	27.09	25.07	21.63	95.82			
5	**14**	45.19	39.06	32.06				
5	**15**	67.06	55.09	46.79				
5	**16**	71.06	67.06	52.45				
5	**17**	85.09	77.01	59.91				

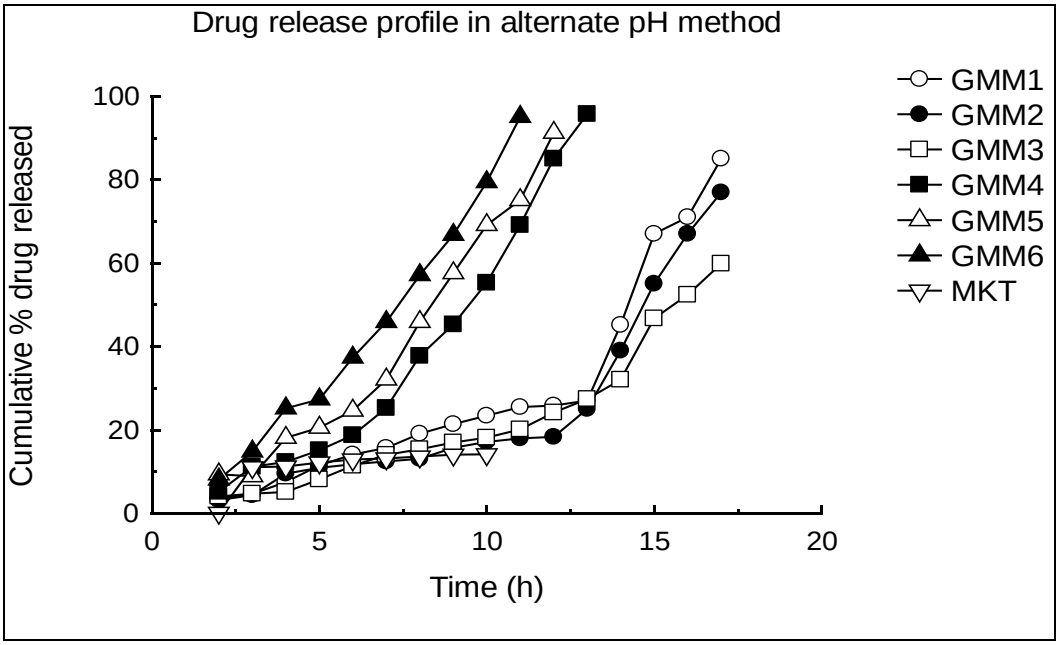

FIGURE 7: CUMULATIVE % DRUG RELEASE IN ALTERNATE DISSOLUTION METHOD

The reports indicate that drug release was found to be more in this buffer conditions as compared to the drug release in the acidic conditions. The guar gum matrix tablets already exposed to the acidic media more than 2h had softens the matrix formation and when it was exposed to the buffer conditions the leaching of drug from the matrix leads to appearance of more drug release in the 6pH phosphate buffer. Once the completion of study on buffer stage 1 (pH 6 phosphates buffer) the 50ml buffer was removed from the dissolution apparatus and freshly prepared NaOH solution was introduced for buffer stage 2 and the pH of the buffer solution in this stage was adjusted to 7.2 pH, and at the 5th hour of the dissolution process rat ceacal contents (4% w/v) were introduced as per the procedure. The drug release study was continued at 7.2 pH until the tablets releases the maximum amount of the drug from the dosage form. Guar gum a natural polysaccharide polymer specifically degraded by the colonic enzymes. So degradation of the guar gum in the upper GI tract was not possible but the fluid penetration and softening the polymer leads to the small amount drug release in the upper GI tract.

In buffer stage two, there was an excellent drug release observed because integrity of the matrix was already disturbed and rat ceacal content also influenced the drug release. The drug release profile in all the formulation was analyzed carefully and the influence on the incorporation of the HPMC E15 LV also studied. The formulation of tablets with guar gum alone was found problematic in tablet compression and the hardness of the tablet was found to be low and the tablets are soft and easily breakable.

More over, the surface of the tablet was not uniform in appearance. The incorporation of the second polymer HPMC E15 LV increased the tablet hardness in to optimum level and the appearance of the tablet also improved. Dug release profile was more are less same in the first three formulations in two dissolution methods. In both dissolution models, the formulations GMM1-GMM3 released less than 15 % of the drug in first five hours of the dissolution study. The dissolution profile indicates the drug release profile was controlled in two dissolution method in maximum extent.

The drug release was controlled for the extended period and the drug release was not significant even after 10 hours of the dissolution profile. The colon drug delivery system expected to release the drug after a lag time and maximum amount of drug should be released in the colon as soon as the dosage form reaches the colon. The formulation GMM1-GMM3 not released the drug as expected and the drug release was poor upto 12 hours of dissolution where less than 30% drug release was noted and it takes fifteen hours to release the 80% of the drug in the formulations GMM1 and GMM2. Incase of GMM3 less than 60% of drug was released from this formulation after seventeen hours of dissolution profile.

The reason for poor dissolution profile in GMM3 is presence of maximum amount of guar gum in this formulations and the quantity of second polymer HPMC E15 LV could not modified the release as the high proportion of guar gum totally controlled the drug release from all these three formulations. The formulation GMM4-GMM6 shown the moderate drug release profile as the proportion of polymer HPMC E15 LV played a significant role in modifying drug release. After five hours of dissolution drug release was found to be less than 30%.

Almost all the tablets from GMM4-GMM6 released maximum amount of the drug within 12 % hours of dissolution profile. The pattern of release indicated that the drug release was maximum after the lag time when the tablets expected to reach the terminal part of the ileum as well as colon. The drug release pattern in GMM5 was found to be better and showing good colon targeted properties as compared to the other formulations.

The varying pH conditions have no significant effect on all the formulations (GMM1-GMM6). But the dissolution profile of the marketed tablet 'Cosacol' showed the entirely different dissolution profile in both dissolution models. The first dissolution method (USP Mesalamine delayed release method) data indicated the drug release profile was normal and the drug release was proportionately increased as the time increases. The pattern of drug release confirmed the colon targeting properties of the dosage form. But when the marketed tablet was exposed to the alternate pH condition the drug release was drastically reduced in all the tablets subjected to drug release study.

The drug release was as low as 14% after 10 hours of dissolution study. This confirmed the impact of pH changes in the colonic region significantly influenced the drug release from the dosage form. The availability of the threshold pH is essential for triggering the drug release from the dosage form. As many marketed tablets designed for colonic delivery depend on pH sensitive polymer to release the drug in colon may pass the enteric performance test but could not release the maximum amount of drug as expected when the threshold pH is not available. The conditions like IBD there are several researches proved the remarkable lowered pH in colonic region.

On such conditions the natural polymer based devices serves better targeting properties which was not affected by varying pH conditions. The incorporation of HPMC E15 LV in the matrix tablets increased the quality of matrix formation, consistency in the drug release profile in repeated drug release studies, minimized batch to batch variation in dissolution profile, improved hardness and elegant appearance. Usually the reproducible results were not observed when the guar gum used alone in formulations and it

was confirmed during the trials of formulation development. The reason for limited commercial usage of guar gum in controlled release formulation is also the same. The overall integrity and quality of the tablet was increased by the addition of HPMC E15 LV polymer with consistent dissolution profile. The physical changes of the tablets were presented in **figure 8 and 9** for USP dissolution method and alternate dissolution method respectively. This was confirmed in the present study after preparing the matrix tablets with Guar gum alone and in combination with HPMC E15 LV. The formulation GMM5 was subjected to stability studies.

FIGURE 8: PHYSICAL CHANGES IN THE TABLET AFTER 6H OF DISSOLUTION (USP METHOD)

FIGURE 9: PHYSICAL CHANGES IN THE TABLET AFTER 6H OF DISSOLUTION (ALTERNATE METHOD)

Drug Release Kinetics: Various release kinetics parameters of different batches of guar gum Mesalamine were presented in **Table 5.** Different batches of guar gum formulations shows different degree of fit to each model. The release kinetic parameter of GMM1, GMM2 and GMM3 could not be explained because of their poor fit with models. GMM4 drug release kinetics was related by zero order, Higuchi, Korsemeyer-Peppas. But the most dominant release mechanism was zero order. This was confirmed by its Korsemeyer-Peppas 'n' value of 1.63 which indicates super case II release kinetics (a clear indication of zero order kinetics).

TABLE 5: THE VARIOUS RELEASE MODELS AND THEIR RELEASE PARAMETERS

Batch	Zero order		First order		Higuchi		Korsemeyer-Peppas		Hixson-Crowell	
	K_0	R^2	K_1	R^2	K_H	R^2	n	R^2	K_{HC}	R^2
GMMI	4.41	0.741	0.035	0.612	23.55	0.645	1.124	0.889	0.101	0.657
GMM2	3.94	0.778	0.027	0.667	21.09	0.685	1.242	0.89	0.083	0.706
GMM3	3.73	0.822	0.006	0.752	20.13	0.731	1.180	0.883	0.076	0.776
GMM4	11.29	0.992	0.144	0.78	51.61	0.964	1.636	0.987	0.366	0.893
GMM5	8.43	0.945	0.089	0.708	40.57	0.886	1.352	0.962	0.225	0.817
GMM6	9.23	0.983	0.101	0.793	43.55	0.946	0.591	0.981	0.254	0.884

In GMM5 drug release was fitted with zero order, Korsemeyer – Peppas in a predominant manner with the 'n' value of 1.35 which indicates the zero order drug release with super case II release. In formulation GMM6 zero order, Higuchi, Korsemeyer-Peppas release kinetics are observed and 'n' value was 0.591 indicated anomalous non fickian release.

It was observed that GMM4, GMM5 and GMM6 obeyed Korsemeyer-Peppas release mechanism and zero order and had at least two different release kinetics model in operation, thus Korsemeyer-Peppas release kinetics and 'n' value was used to validate the release kinetics to confirm which release mechanism or mechanism in operation. Zero order release is ideal in controlling the drug release and it has been reported that that was not to be common with matrix system. This was being endorsed to time dependent changes in drug depleted matrix surface area and diffusional path length [16]. To achieve linear or zero order release kinetics with matrix system under several manipulations in the design of the dosage form is required to make structural and geometric changes on the tablets [17-19].

CONCLUSION: The Mesalamine matrix tablets were prepared with natural polymer guar gum and evaluated for various parameters. The result was revealed that guar gum based matrix tablets can be launched to colon successfully. The drug release profile of the various tablets revealed that formulations shown the desirous release pattern along with other tablet quality control parameters. The batch GMM5 showed better release pattern with predominant super

case II release. From these overall experiments, the particular concentration and proportion of drug and polymer used in GMM5 were found to be satisfactory and good for colon targeted drug delivery. The usage of HPMC E15 LV modified the drug release pattern and confirmed the consistent and reproducible dissolution profile. And Guar gum can be replaced for various marketed pH sensitive polymers based colon targeted tablets.

The natural polymer based colon targeted tablets release pattern cannot be affected by pH changes in the colon, and integrity of the GMM5 was better than marketed enteric coated delayed release tablets. And the present formulation able to replace the various marketed synthetic polymer based products. The batch GMM5 was subjected to short term stability study at 75% RH/ 40^0C was found to be stable at the end of three months and no significant variation reported in drug release profile. But the further detailed studies on stability of the dosage form were recommended for long term storage conditions.

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