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FORMULATION AND DEVELOPMENT OF MESALAMINE SUSTAINED RELEASE GUAR GUM MATRIX TABLETS FOR COLON SPECIFIC DRUG DELIVERY

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ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, for example, allow topical treatment of inflammatory bowel disease. Treatment could be made more effective if it were possible for drugs to be targeted directly on the colon. Systemic side effects could also be reduced. The aim of the work reported here was to develop a Matrix-unit colon-specific formulation for administration by mouth, using Natural gum polymers such as guar gum and the relevant excipients. It was aimed to prepare a formulation that allows drug absorption after a lag time of about 3 hours. The idea was that the polymers would prevent drug release and absorption in the upper gastrointestinal tract. Mesalamine Matrix tablets were prepared by wet granulation technique using guar gum alone as matrices (Table 1).The prepared tablet formulations (F1, F2, F3, and F4) are subjected to various evaluation parameters like hardness, friability, weight variation and disintegration test, which were found to be satisfactory. Drug dissolution was studied in vitro, at different pH levels.The drug release reports obtained from the dissolution that the formulation F3 shows maximum drug release and acquired all the required characteristics to be a sustained release matrix tablet. It was concluded that drug release and absorption can be targeted on the colon when Natural gum polymers were used as excipients in Matrix tablets.

Key words: *Matrix tablets, Mesalamine, Guar gum, Micro crystalline cellulose*

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INTRODUCTION

From the literature it is found that, there is an increasing interest in targeted delivery of drug to the colon via the oral route. To achieve successful colonic delivery continuous efforts have been focused on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accommodate different therapeutic needs. Many approaches have been demonstrated. All have some disadvantages. The large inter and intra- subject variation in G.I pH makes the pH dependent system less suitable. Microbially controlled systems which rely on conditions which are only encountered in the colon, these systems give true site specificity. Natural polymers such as pectin, guar gum, chitosan etc are more favorable carriers for these systems, but these naturally occurring polymers like pectin, chitosan etc. have inherent water solubility which can lead to decreased biodegradability. Guar gum being a natural biodegradable polymer acts as a disintegrating agent along with its binding activity and thus produces a matrix tablet with good hardness, which it finally enables for increased disintegration time so that the tablet formulation attains the sustained release nature. Mesalamine is the drug of choice for the treatment of mild-to-moderate ulcerative colitis and maintaining remission. As it is better tolerated and produces less adverse effects as compared to sulfasalazine, it is used in the present work to obtain the sustained drug release to colon region.

Experimental work:

1.1 Materials:

Mesalamine – Otto pharmaceuticals pvt Ltd, Mumbai, India.

Guar gum – Jyothi chemicals, modhinagar, India.

Micro crystalline cellulose - Otto pharmaceuticals pvt Ltd, Mumbai, India.

1.2 Preformultion tests: [1, 2, 3, 4, 5, 6]

The general preformulation tests for the tablet formulations include the following:

1. Bulk density
2. Compressibility index
3. Angle of repose

Bulk density:

Bulk density is defined as the mass of the powder divided by the bulk volume. The bulk density (gm/cm^3) of powder depends mainly on particle-size distribution, particle shape, and then tendency of the particles to adhere to one another.

It is given by following equation

$$D = M / V$$

Where,

D – Bulk density

M- Mass of the particles

V – Bulk volume

Compressibility Index :

The initial & final density's can be used to determined the percentage compressibility also called as compressibility index.

It is given by the equation:

$$I = (D_1-D_0/D_1)*100$$

Where,

I – Compressibility index

D_1 – Final density

D_0 – Initial density

The compressibility of a powder dictates its flow properties. A highly compressible powder exhibits less flow properties and vice-versa.

Angle of repose:

Angle of repose is defined as the maximum angle formed between the sides of the powder heap with the horizontal surface. It is a very simple technique which determines the flow properties of the powder. The equation is given as:

$$\text{Tan } \theta = H/R$$

Where,

θ - Angle of repose

R - Radius of powder bed

H -Height

1.3 Tablet formulation design:

The different Batches of tablet formulations are designed mainly to observe the release rate of the drug from gum Matrix so formed. It is mainly achieved by changing the polymer concentration.

Batch code	Drug (mg)	Guar gum (mg)	MCC (mg)	Starch (10%)(mg)	Magnesium state(mg)	Talc (mg)
F1	200	60	175	50	5	10
F2	200	100	135	50	5	10
F3	200	150	85	50	5	10
F4	200	80	155	50	5	10

Table 1: Formulation of Guar gum Matrix tablets of Mesalamine

Preparation of tablets[7,8]:

Matrix tablets, each containing 200 mg. Mesalamine[10] were prepared by wet granulation technique using guar gum alone as matrices (Table 1). Tablet formulations (F1–F4) were blended and granulated with 10% Starch (soluble) paste. The wet mass was passed through a mesh (1000 µm) sieve and the granules were dried in Hot air Oven at 50°C for 2–3 h. The dried granules were sieved (600 µm), lubricated with magnesium stearate: talc (1: 2) mixture and compressed on a single-punch tablet machine, (SISCO single punch tablet machine).

1.4 Evaluation test for the formulations[2, 3]

In vitro Dissolution test: [2, 3]

The in-vitro release of Mesalamine[10] from formulated tablets was carried out in the SECOR (Scientific engineering corporation, Delhi) India dissolution test apparatus, by using pH l.2 Hcl buffer (2 h) and pH 7.2 buffers (3 h) and pH 6.8 PBS without rat ceacal contents (19 h). The studies were performed in USP dissolution apparatus II (SECOR (Scientific engineering corporation, Delhi) India) at 37 ± 0.5° C and 100 rpm speed. Samples were taken at different time intervals and diluted to suitable concentration and analyzed for absorbance at 301.3 nm by using UV–visible spectrophotometer.

IR spectrum: [2, 3]

The IR spectrum for the drug (mesalamine[10]), polymer (guar gum) and the formulated tablet was performed to identify any incompatibility between the drug and the polymer.

Results and discussions:

Compressibility index of drug is determined as 40% which infers that the drug possess poor flow properties , the angle of repose is determined to be 60% and it conforms that the drug is poor flowing or cohesive product. The compressibility of a powder exhibits less flow properties. For each formulation, the hardness , friability , disintegration times of the formulations were reported in table 2.Mesalamine[10] matrix tablets (F1-F4) prepared in the present study complied with the official requirements for the drug content uniformity test according to B.P. and showed an acceptable mechanical strength (friability < 1%, hardness values in the range of 10–20 kg, Table 2). The ability of the various delivery systems, under study, to protect the drug in the physiological environment of the stomach and small intestine and allow its release into the colon was assessed by carrying out drug release studies in pH 1.2 Hcl buffer for 2 h, pH 7.2 buffer for 3 h and pH 6.8 in the absence and presence of rat ceacal contents for 19 h.

Formulation	Hardness	Friability	Disintegration time
F1	10	0.5	26min
F2	11.2	0.7	27min
F3	14	0.6	29 min
F4	12	0.8	28min

Table 2: Evaluation reports of different batches of mesalamine matrix tablets

Invitro Dissolution studies:

The test result indicates that the F1 tablet formulation could not attain the sustained release nature as like the F2 and F3 which have shown the sustained drug release. As the concentration of guar gum increased from (F1) to (F3) the rate of drug release fell relatively. Also a relative reduction in the extent of drug release. and the F4 formulation in which there was slight decrease in the polymer produced an increase in the rate of drug release, by this it confirmed that the increase in the concentration of the polymer decreased the

rate of drug release. The F3 formulation shows the sustained drug release nature in the gastric and intestinal region and thus enables the maximum drug release at the colon region by releasing the drug at that region. The drug release profile of the mesalamine matrix tablet formulations (F1-F4) is depicted in the figure 1.

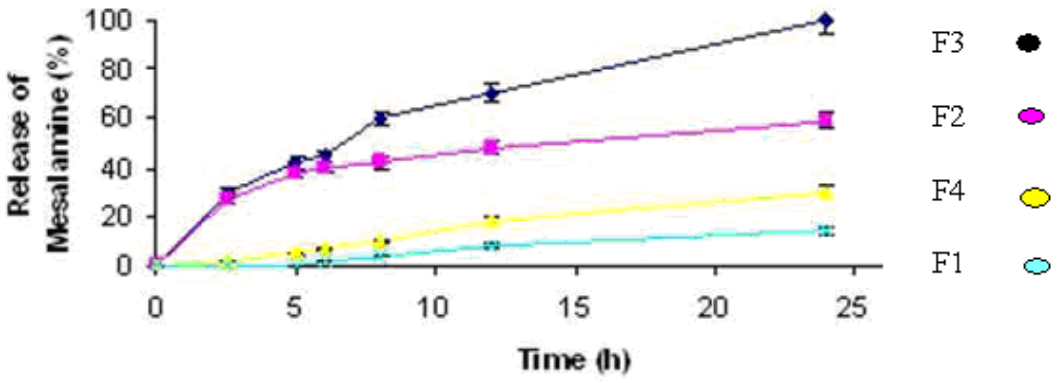


Figure 1: Release profiles of Mesalamine matrix tablets.

IR spectrum of pure drug (mesalamine):

The infrared spectrum of mesalamine **is shown** in Figure**,** The spectrum was obtained after dispersion in a potassium chloride disk, and the major bands are assigned in table 3:

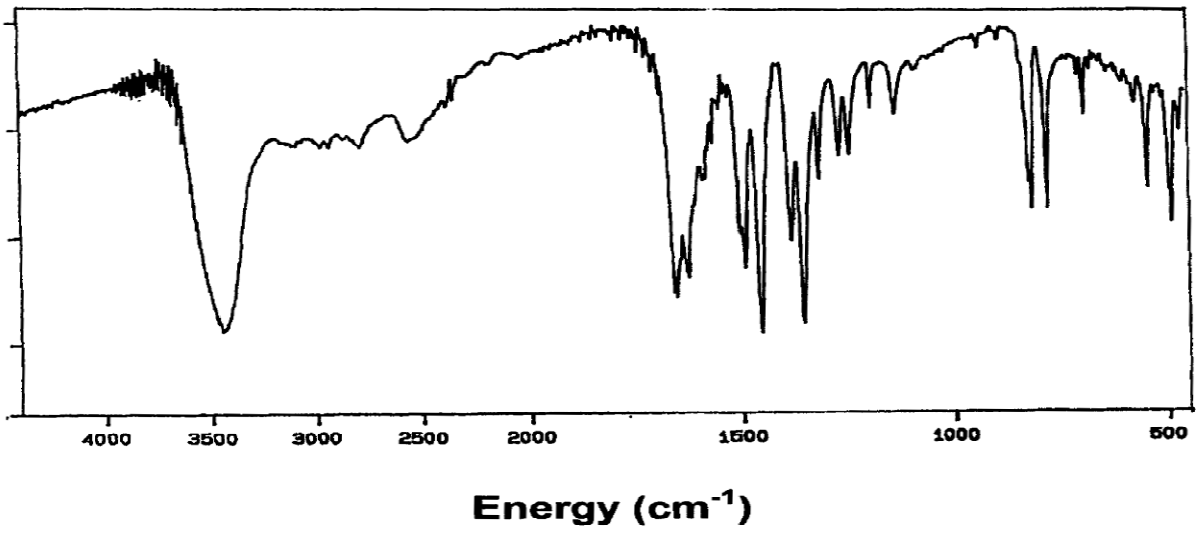


Figure 5. Infrared absorption spectrum of mesalamine.

Table 3: Assignments for the vibrational transitions of mesalamine

Energy	Relative Intensity	Assignment
3600 - 3200	Strong	O-H stretching mode associated with the hydroxyl groups
~ 3000	Strong	C-H stretch of the aromatic group
1619	Medium	C=C stretch of the aromatic group; N-H bond scissoring
1449, 1490	Strong	C-C stretching mode
1355, 1378	Strong	O-H deformation of the hydroxyl groups
1131	Medium	C-O stretching mode
1190 - 1267	Medium	In plane blending mode
685-808	strong	C-H bond out of plane blending mode; ring deformation of the aromatic group.

Figure 3: IR spectrum of guar gum

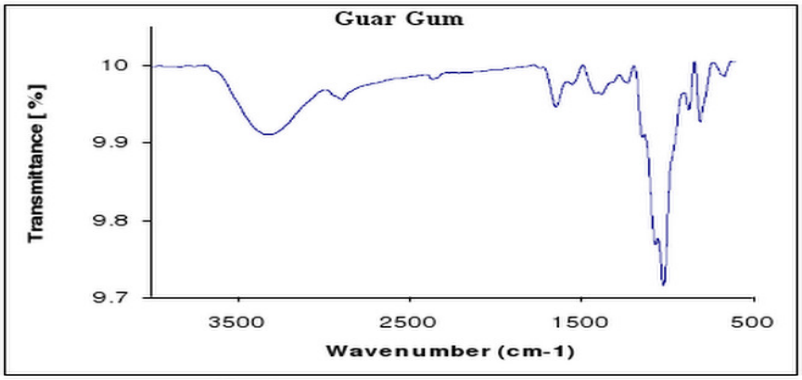
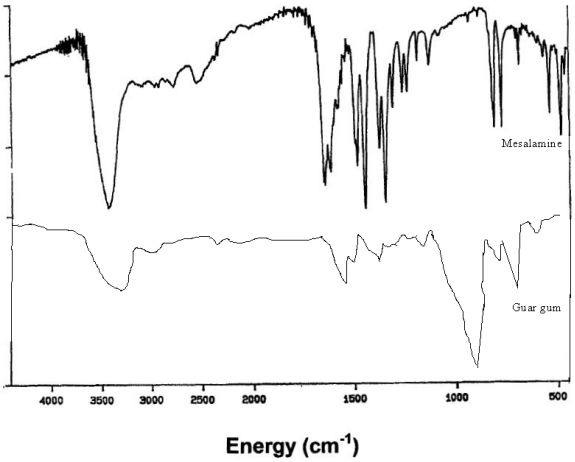


Figure IR of guar gum

Figure 4: IR spectrum of mesalamine tablet



CONCLUSION: Colon specific drug delivery has also gained increased importance for the delivery of drugs for the treatment of local diseases associated with the colon such as inflammatory bowel diseases (ulcerative colitis, Crohn's disease), some carcinomas, and gastrointestinal infections to maximize the effectiveness of these drugs. Colon is also a potential site for the systemic delivery of therapeutic peptide and proteins. Natural polymers such as pectin, guar gum, chitosan etc are more favorable carriers for these systems as release retardant and exhibit uniform release over longer period of time. The matrix tablet formulations (F1, F2, F3, and F4) were prepared and are subjected to various evaluation parameters like hardness, friability, weight variation and disintegration test, which were found to be satisfactory. The drug release reports obtained from the dissolution that the formulation F3 shows maximum drug release and acquired all the required characteristics to be a sustained release matrix tablet. It was concluded that drug release and absorption can be targeted on the colon when Natural gum polymers were used as excipients in Matrix tablets. The mesalamine tablet formulation is subjected to IR spectrum to test the incompatibility with the polymer. And the graph shows that there occurred no incompatibility between the drug and the polymer.

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