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Formulation and evaluation of alginate based mesalazine matrix tablets for intestinal delivery

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ABSTRACT:

The aim of this study is to develop alginate based mesalazine matrix tablets for intestinal delivery. Sodium alginate is a biocompatible natural polymer, with pH sensitive gel forming ability. Matrix tablets of Mesalazine were prepared using Sodium alginate with three different concentrations by wet granulation method. The granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausners ratio. The tablets were subjected to weight variation, hardness, friability and drug content test. The in vitro release characteristics of mesalazine from alginate tablets were compared with those of the commercial product Asacol.

The cumulative amount of released drug of S3 formulation was found to be almost the same as the of commercial product in acidic and basic media. The release profiles were affected by variable concentrations of Sodium alginate and hence, the release of Mesalazine was prevented in upper GIT with increase in the proportion of Sodium alginate. Mesalazine-alginate matrix tablet formulations can deliver drug to the small and large intestine. Thus, it may be a promising system for the treatment of Ulcerative colitis.

Keywords:
Mesalazine, Sodium alginate, Intestinal drug delivery, ulcerative colitis.

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INTRODUCTION:

Oral administration is the most convenient and proffered means of drug delivery into systemic circulation. (Hwang *et al*., 1998). The natural pH environment of GI tract varies from acidic to slight alkaline. pH-sensitive hydrogels may be an alternative for site specific drug delivery (Wilding, 2000). A variety of synthetic and natural polymers with acidic or basic pendent groups have been used to fabricate pH sensitive hydrogels. Among them, alginate is one of the most commonly used natural polymer. (Lin *et al*., 2005). Alginates are naturally occurring substances mostly used in pharmaceutical dosage formulations, particularly as vehicle for controlled drug delivery. The formulation of a matrix, upon hydration, causes a gelatinous layer which can act as a drug diffusion barrier (Bajpai, 2004). Mesalazine has been used for several years in the treatment of inflammatory bowel disease. When pure mesalazine, administered directly in proximal part of small bowel or orally as conventional tablet, it is rapidly and almost completely absorbed, with little drug reaching the distal small intestine and colon (Prakash, 1999). Therefore premature absorption of mesalazine can be prevented by the preparation of enteric coated tablets. Orally administered delayed-release mesalazine, act locally from within the lumen of the inflamed bowel and is partly absorbed in systemic circulation. To prevent proximal small intestinal absorption, and to allow mesalazine to reach the inflamed small bowel/colon, a variety of mesalazine delivery systems have been developed (Altamash *et al*., 2005). The aim of the present study was to develop a site specific matrix tablet of mesalazine with sodium alginate and to investigate the in vitro release characteristics of the tablets and compare them with those of the commercial product Asacol.

MATERIALS AND METHODS

Materials

Mesalazine was obtained from Sarex Overseas, Mumbai, India, Sodium alginate from Alembic Pharmaceuticals Ltd., Baroda, Povidone (PVP-K30) and microcrystalline cellulose from Signet chemical corporation, Mumbai for free of cost. Talc and Magnesium stearate were procured from Emcure House M.I.D.C. Pune. All the other chemicals and reagents used were of analytical grade. The commercially available mesalazine product, Asacol was procured from A. Birla hospital (Pune).

Measurement of viscosity

Viscosity measurement of 1% W/V aqueous dispersion of sodium alginate was carried out using Brookfield viscometer (Brookfield viscometer LVTD USA) at 25°C.

Preparation of Mesalazine matrix tablets

For preparing matrix tablets, the content of Mesalazine was maintained at 250 mg, in each type of formulation. The accurately weighed quantities of selected polymers and the drug were mixed in various proportions and the mixtures were assigned different formulation codes presented in table-1 (Aultons, 1998).

The active ingredients Mesalazine, the polymers, sodium alginate were passed through screen (60 #). The physical mixtures of the drug, polymers and excipients were prepared by blending the accurately weighed quantities of each of them with Mesalazine in geometric proportions in glass mortar for 15 minutes. Ethnolic solutions of PVP K-30 were used as binders which were added gradually to powder blends with trituration until a coherent moist mass was formed. This mass was passed through screen (22#) to get moderately coarse granules. The wet granules were dried at 50°C for 1 hour. The dried granules were again passed through screen (44#) to obtain fine granules. The resulting granules were lubricated with magnesium stearate and then evaluated for the following flow properties bulk density, tapped

Table-1. Formulations of the matrix tablets of Mesalazine.

Sr. No.	Ingredients (%W/W)	Formulation codes		
		S1	S2	S3
1	Mesalazine	50	50	50
2	Sodium alginate	15	30	45
3	PVP K-30	3	3	3
4	Magnesium state	1	1	1
5	Aerosil	1	1	1
6	Talc	30	15	0

Total weight of one tablet is 500mg

density, compressibility index (C.I.) and Angle of repose (θ).

The granules of each formulation type were compressed into matrix tablets using S.S. punches (diameter 13 mm flat surface) on rotary tablet press. The compression force was maintained in such a way that the hardness of resulting tablets ranged between 7-8 Kg/m^2. The batch size prepared for each formulation was of 25 tablets.

Evaluation of matrix tablets of Mesalazine

Weight variation

This test was performed as per the procedure described in Indian Pharmacopoeia (1996) using 10 tablets of each formulation type. The tablets were weighed individually and their mean weight was calculated. The deviation of individual weight from the mean was expressed as standard deviation. The compliance of tablets with recommended allowances for variations in weight was judged on the basis of official specifications.

Hardness:

Hardness of three tablets of each formulation type was determined using Monsanto hardness tester following the procedure described in standard text book (Liberman, 2001).

Friability:

The friability of 10 tablets of each formulation type was noted using Roche friabilator following the procedure described in standard text book (Liberman, 2001,). And the weight loss (% w/w) was calculated using the following formula,

% Friability = (Loss in weight/ Initial weight) x 100

Drug contents

The contents of Mesalazine were estimated using five tablets of individual formulations. The tablets were weighed individually, and were crushed in mortar. From this, the powder equivalent to 250 mg of Mesalazine was taken in volumetric flasks and dissolved in sufficient quantity of phosphate buffer (pH 7.2) and the final volume was made up to 100 ml. Appropriate dilutions of the resulting solutions were carried out and the contents of Mesalazine were estimated using UV absorbance of these solutions at 331 nm using previously prepared calibration curve of Mesalazine in phosphate buffer pH 7.2 (Acarturk and Demiroz, 2007).

In vitro release of Mesalazine from matrix tablets

The test was conducted using three matrix tablets of each type of formulation using USP (23) dissolution apparatus (Apparatus I). (Watts and Illum, 1997) The

Table-2: The experimental conditions used for *in vitro* release of Mesalazine from matrix tablets.

Phases	Type and volume of Dissolution Medium	Speed of Rotation (rpm)	Duration (min)	λ max used for Recording absorbance	Volume withdrawn and frequency of withdrawn aliquots
Phase I Acid stage	0.1N HCl 500ml pH- 3	100 rpm	120	303.0	10ml at intervals of 30min
Phase II Buffer stage-1	Phosphate buffer 900ml pH- 6	100 rpm	60	330.0	10ml at intervals of 30min
Phase III Buffer stage-2	Phosphate buffer 900ml pH-7.2	50 rpm	90	331.0	10ml at intervals of 30min

Table-3: Flow properties of granules of Mesalazine with individual pH sensitive HPMC polymers and their combination with sodium alginate.

Code	Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Carr's Compressibility Index. (%)	Angle of repose(Ø)
S1	0.155±0.0190	0.183±0.004	15.30±0.005	25.81±0.021
S2	0.147±0.0190	0.184±0.011	19.78±0.002	24.25±0.022
S3	0.164±0.0195	0.185±0.005	11.35±0.013	25.97±0.016

All values are expressed as mean± SD, n=3

tablets of each type of matrix formulations were kept in baskets which were placed successively in below mentioned dissolution media. The dissolution apparatus was run maintaining test conditions are stated below in table 2. (Liew *et al*., 2006). The release profiles of matrix tablets were compared with those of the commercial product Asacol (Acarturk and Demiroz, 2007).

Stability Studies

Stability studies were carried out to assess the stability of all formulated sustain release Mesalazine tablets (Melia and Davies1995). The prepared tablets were kept at 45°±2°C, 75±5% RH for 45 days. At 15 days intervals the tablets were evaluated for all physical parameters. The percentage of Mesalazine content and Invitro drug release studies were also determined.

RESULTS AND DISCUSSION

Evaluation of Mesalazine Granules:

The values for loose bulk density, tapped bulk density, compressibility index and angle of repose of granules of Mesalazine prepared with Sodium alginate, revealed different behaviour of each formulation blend expressed in table 3. However, all these values are still suggestive of good flowability of blends.

Values of loose bulk density and tapped bulk densities for Mesalazine granules ranged between 0.147-0.164, and 0.183 to 0.185 respectively. The Carr's index values ranged between 11.35-19.78, the values of angle of repose 24.25-25.97. All the flow characteristics are satisfactory for subsequent processing of granules for preparation of matrix tablets of Mesalazine.

Evaluation of Mesalazine Tablets

The matrix tablets of Mesalazine prepared with Sodium alginate were characterized for various tablet characteristics as per the monograph mentioned in table 4.

The pharmacopoeial specifications for deviation in weight from average weight for tablets weighing more than 250 mg are ±5%. The percentage deviation in the weight of prepared tablets (weighing 500 mg) was within the specified limits for all the formulation types and hence, they complied with the test for weight variation. Diameter of the matrix tablets was in the range of 12.87-12.89mm. Thickness of the matrix tablets was in the range of 3.32-3.38 mm. Hardness of the matrix tablets was in the range of 8-8.5 Kg/cm^2, Friability of the matrix tablets of Mesalazine was within 0.33-0.48%.

The matrix tablets of different formulations possessed consistent dimensions and hardness values and all of them complied with the specified limits for friability (<1%). The higher values of hardness may be justified since the drug is targeted for colon and the inclusion of pH sensitive polymer would ensure its release in the destined organ. The pharmacopoeial specifications for permissible allowances for deviation in

Table-4: Characterization of matrix tablets of Mesalazine.

Code	Avg. Wight (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug Content (%)
S1	499±1.63	12.88	3.38	8.0	0.44	97.35±0.122
S2	501±0.95	12.87	3.34	8.0	0.48	98.88±0.183
S3	501±1.25	12.89	3.32	8.5	0.33	98.56±0.155

All values are expressed as mean ± SD, n=3

Table-5: Dissolution data of matrix tablets of Mesalazine with variable concentration of sodium alginate

Dissolution Phase and duration	Time (min)	Cumulative (Avg.) % drug release		
		S1	S2	S3
		15%	30%	45%
Acid Stage pH= 3 (120 min)	0	0	0	0
	30	9.50±0.48	7.72±0.98	3.21±1.20
	60	11.47±0.84	9.46±1.12	5.61±1.10
	90	13.97±0.37	11.20±0.44	6.46±0.49
	120	15.64±1.94	13.31±2.12	9.78±1.62
Buffer Stage-1 pH-6 (60 min)	150	18.90±1.19	15.18±1.41	11.78±1.13
	180	22.87±0.94	18.54±1.74	13.52±1.41
Buffer Stage 2 pH= 7.2 (150 min)	210	29.26±1.69	26.42±1.38	21.28±2.23
	240	43.62±2.45	37.92±1.90	32.49±1.91
	270	55.28±1.56	48.77±1.43	44.69±1.26
	300	69.12±1.13	60.17±1.43	57.12±1.20
	330	83.24±0.82	71.34±2.78	69.21±2.30
	360	97.41±1.21	86.55±1.32	83.14±1.78

***The dissolution studies were extended by 60 minutes in buffer stage 2 (pH 7.2) for estimating the time taken for complete release of drug contents.**

% of drug contents for tablets of Mesalazine is not less than 98% and not more than 101% of the labelled amount. (USPNF 2004). The percent of drug contents for Mesalazine formulations with sodium alginate ranged between 97.35-98.88 Hence, the tablets are complied with the official specifications.

In vitro release of Mesalazine from matrix tablets

The USP specifications for % of cumulative release of drug from colon targeted dosage forms are;

- Acid stage: Not more than 12% of LA.
- Buffer stage 1: Not more than 30% of LA (LA is labeled amount)

In vitro release of Mesalazine from matrix tablets prepared with variable concentration of Sodium alginate.

The formulations S3 qualified the first stage of release while all formulations qualified the second stage of drug release. The release profiles were affected by variable concentrations of matrix forming polymer and hence, the release of Mesalazine retarded with increase in proportion of sodium alginate (table 5, fig. 1). Sodium alginate has pH sensitive gel forming ability because of that it could effectively prevent the escape of drug at both the acid stage and buffer stage 1.

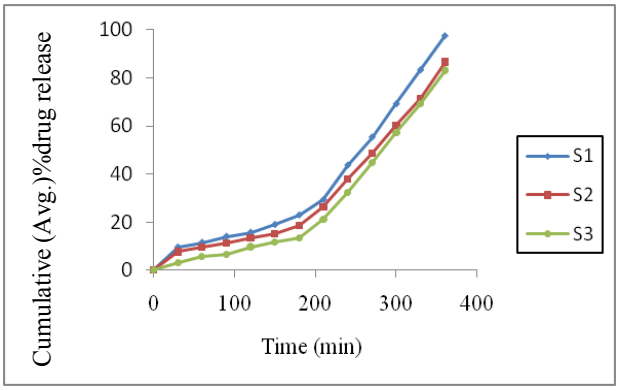

Fig 1: *In vitro* release of Mesalazine from matrix tablets prepared with Sodium alginate.

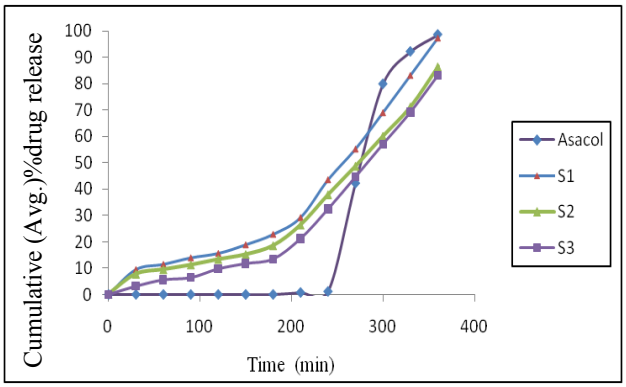

Fig 2: Comparative evaluation of Mesalazine matrix tablets with marketed formulation Asacol*

Table-6: Comparative evaluation of Mesalazine matrix tablets with marketed formulation Asacol*

Dissolution Phase and duration	Time (min)	Cumulative (Avg.) % drug release			
		Asacol*	S1	S2	S3
			15%	30%	45%
Acid Stage pH=3 (120 min)	0	0	0	0	0
	30	0	9.50±0.48	7.72±0.98	3.21±1.20
	60	0	11.47±0.84	9.46±1.12	5.61±1.10
	90	0	13.97±0.37	11.20±0.44	6.46±0.49
	120	0	15.64±1.94	13.31±2.12	9.78±1.62
Buffer Stage-1 pH=6 (60 min)	150	0	18.90±1.19	15.18±1.41	11.78±1.13
	180	0	22.87±0.94	18.54±1.74	13.52±1.41
Buffer Stage 2 pH=7.2 (150 min)	210	0.73	29.26±1.69	26.42±1.38	21.28±2.23
	240	1.147	43.62±2.45	37.92±1.90	32.49±1.91
	270	42.18	55.28±1.56	48.77±1.43	44.69±1.26
	300	79.82	69.12±1.13	60.17±1.43	57.12±1.20
	330	92.12	83.24±0.82	71.34±2.78	69.21±2.30
	360	98.54	97.41±1.21	86.55±1.32	83.14±1.78

***The dissolution studies were extended by 60 minutes in buffer stage 2 (pH7.2) for estimating time taken for complete release of drug contents.**

The comparison of in vitro release profile of the formulation with those of the commercial product Asacol showed that the matrix tablets released 22.87% of drug during the first two hours, in acidic and one hour in buffer stage 1 at pH-6. No mesalazine release was found from Asacol* (Fig 2). The increasing amount of alginate results in the increase in viscosity of gel layer, which retards the drug diffusion from the tablet. (Liew *et al.*, 2006)

Stability Studies:

Mesalazine matrix tablets of all the formulations were stored at 45°±2°C, 75±5% RH upto 45 days. Tablet evaluation tests were carried out at every 15 days intervals. All the formulations were physically stable. There were no deviations found in the tests and all were within the limits. There were no significant change in the drug content and Invitro drug release profiles. It showed that all the formulations are chemically stable.

CONCLUSION:

The results of experimental studies of Mesalazine matrix tablets proved that the granules of Mesalazine showed good flow properties and that the, tablet evaluation tests are within the acceptable limits. The dissolution profile indicates that formulation S3 prevents escape of Mesalazine in acidic pH, of not more than 12% of the labeled amount. All the other formulations minimize escape of Mesalazine in buffer stage 1 (pH 6) i.e. not more than 30% of the labeled amount. Sodium alginate offered better protection from escape of Mesalazine in precolonic pH stages. Hence matrix tablets of Mesalazine with optimum concentration of Sodium alginate were successfully developed. It was concluded that Mesalazine-alginate matrix tablet formulation can deliver the drug to small and large intestine.

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