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Formulation and Evaluation of Matrix Tablet of Mesalazine with HPMCAS

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ABSTRACT

Mesalazine is considered as a gold standard anti-inflammatory agent for treatment of inflammatory bowl diseases. It is mostly utilized for treatment and maintenance of remission in mild to moderate Ulcerative colitis. Orally ingested Mesalazine is efficiently absorbed by small bowel and rapidly clear from circulation, with elimination half-life of only 1 hour. Therapeutic concentration in colon can be achieved by oral ingestion of delayed or slow released matrix preparations. In the present study slow released matrix tablets of Mesalazine were prepared using pH sensitive polymer HPMCAS-HF with six 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. Invitro release studies revealed that Mesalazine formulations F3, F4, F5, and F6 qualified first stage of release while all the formulations qualified second stage of drug release. The release profiles were affected by variable concentration of matrix forming polymer and hence, the release of Mesalazine retarded with increase in proportion of HPMCAS. As HPMCAS is a pH sensitive polymer with threshold value 6.8 because of which it could effectively prevent the escape of drug at both acid stage and buffer stage 1.

Keywords: Mesalazine, HAPC-AS, Ulcerative colitis, wet granulation.

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INTRODUCTION

Colonic drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases of colon such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis (UC) but also for its potential for the delivery of proteins and therapeutic peptides like insulin [3, 10].

Ulcerative colitis is a chronic inflammation of the large intestine (colon). It is a disease that causes inflammation and sores, called ulcers, in the lining of the rectum and colon. Ulcers are formed at sites where inflammation has killed the cells that usually line the colon, which then bleed and produce pus. It is closely related to another condition of inflammation of the intestine called Crohn's disease. Together, they are frequently referred to as inflammatory bowel diseases (IBD) [8].

Mesalazine is used as anti-inflammatory agent for treatment of inflammatory bowel diseases. It is mostly utilized for treatment and maintenance of remission in mild to moderate Ulcerative colitis. Orally ingested Mesalazine is efficiently absorbed by small bowel and rapidly clear from circulation, with elimination half-life of only 1 hour [4]. Therapeutic concentration in colon can be achieved by oral ingestion of delayed or slow released matrix preparations. The delayed released matrix tablets were formulated to minimize escape of drug mesalazine in upper part of GIT and provide maximum amount to the colon. As HPMCAS is a pH sensitive polymer with threshold value 6.8 because of which it could effectively prevent the escape of drug at both acid stage and buffer stage 1 [6].

MATERIALS AND METHODS

Materials

Mesalazine was Kind gift from Sarex pharma Mumbai India. HPMC-AS, Povidone (PVP-K30) & microcrystalline cellulose gifted by Signet chemical corporation, Mumbai. Talc and Magnesium stearate were procured from Emcure House M.I.D.C. Pune. All other chemicals and reagents used were of analytical grade.

Preparation of Mesalazine S.R. 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 drug were mixed in various proportions and mixtures were assigned different formulation codes presented in table-1 [2].

The active ingredients Mesalazine, the polymers, Hydroxypropylmethylcellulose acetate succinate –HF were passed through screen (60 #). The physical mixtures of 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 (3% w/v and 5% w/v) 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 following flow properties bulk density, tapped density, compressibility index (C.I.) & Angle of repose (θ).

Table-1: Formulations of the matrix tablets of Mesalazine

Sr. No.	INGREDIENTS (%W/W)	Formulation codes					
		F1	F2	F3	F4	F5	F6
1	Mesalazine	50	50	50	50	50	50
2	HPMC-AS	15	15	25	25	35	35
3	PVP K-30	3	5	3	5	3	5
4	Magnesium state	1	1	1	1	1	1
5	Aerosil	1	1	1	1	1	1
6	Talc	30	28	20	18	10	8
Weight of one tablet is 500mg							

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 / m2. The batch size prepared for each formulations was of 25 tablets.

Evaluation of matrix tablets of Mesalazine

Weight variation

This test was performed as per 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 [5].

Friability

The friability of 10 tablets of each formulation type was noted using Roche friabilator following the procedure described in standard text book [5]. And the weight loss (% w/w) was calculated using following formula,

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

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Drug contents

The contents of Mesalazine were estimated using 5 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 from UV absorbance of these solutions at 331 nm using previously prepared calibration curve of Mesalazine in phosphate buffer pH 7.2 [1].

***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). The 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 below stated test conditions represented in table-2.

Stability Studies

Stability studies were carried out to assess the stability of all formulated sustain release Mesalazine tablets [4]. The prepared tablets were kept at $45^{o}\pm2^{o}C$, 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.

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 & frequency of withdrawn of 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

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 HPMCAS, revealed different behaviour of each formulation blend expressed in table-3. Thus, the values for granules of Mesalazine with HPMC AS (HF) are more consistent. However, all these values are still suggestive of good flowability of blends.

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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)
F1	0.512±0.0192	0.568±0.004	9.85±0.005	27.21±0.012
F2	0..463±0.0194	0.513±0.003	9.76±0.004	26.12±0.o142
F3	0.478±0.0195	0.587±0.008	18.56±0.003	28.34±0.123
F4	0.512±0.0184	0.579±0.004	11.63±0.002	26.83±0.134
F5	0.489±0.018	0.580±0.004	15.68±0.006	24.60±0.034
F6	0.510±0.0194	0.589±0.008	13.41±0.004	25.73±0.124

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

Values of loose bulk density and tapped bulk densities for Mesalazine granules ranged between HPMC AS (HF): 0.463-0.512 and 0.513-0.589 gm/ml. The Carr's index values ranged between 9.85-18.56, the values of angle of repose 24.60-28.34. 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 HPMC-AS (HF) were characterized for various tablet characteristics as per the monograph mentioned in table-4.

Table-4: Characterization of matrix tablets of Mesalazine

code	Avg. weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug Content (%)
F1	499±1.56	12.89	3.33	**8.0**	**0.23**	99.42±0.123
F2	500±0.85	12.88	3.34	8.0	0.38	99.45±0.066
F3	497±1.92	12.90	3.33	8.5	0.36	98.35±0.107
F4	501±2.25	**12.88**	3.33	8.0	0.39	98.26±0.126
F5	498±1.87	12.86	3.39	8.5	0.45	99.62±0.129
F6	502±0.95	12.85	**3.30**	8.5	0.26	99.85±0.132

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

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 12.85-12.90mm. Thickness of the matrix tablets was in the range of 3.30-3.39 mm. Hardness of matrix tablets was in the range of 8-8.5 Kg/cm^2 **,** Friability of the matrix tablets of Mesalazine with 0.23-0.45 %. 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 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 % drug contents for tablets of Mesalazine is not less than 98% and not more than 101% of the labelled amount. (USPNF 2004). The percent drug contents for Mesalazine formulations with HPMCAS (HF) ranged between 98.26-99.86 Hence, the tablets complied with the official specifications

***In vitro* release of Mesalazine from matrix tablets**

The USP specifications for % 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 labelled amount)

***In vitro* release of Mesalazine from matrix tablets prepared with variable concentration of HPMCAS.**

The formulations F3, F4, F5, and F6 qualified the first stage of release while all the 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 HPMCAS (table-5, fig. 1.1. a, b, c). HPMC-AS is a pH sensitive polymer with threshold value of 6.5 because of which it could effectively prevent the escape of drug at both the acid stage and buffer stage 1.

Table-5: Dissolution data of matrix tablets of Mesalazine with variable concentration of HPMC-AS

Dissolution phase & duration.	Time (min.)	Cumulative (avg.) % drug release					
		HPMCAS: PVP K30	HPMCAS: PVP K30	HPMCAS: PVP K30	HPMCAS: PVP K30	HPMCAS: PVP K30	HPMCAS: PVP K30
		15:3 (%)	15:5 (%)	25:3 (%)	25:5 (%)	35:3 (%)	35:5 (%)
		F1	F2	F3	F4	F5	F6
Acid stage pH= 3 (120 minutes)	0	0	0	0	0	0	0
	30	7.9±1.14	7.21±1.05	5.86±1.21	7.44±1.14	6.98±1.12	5.77±1.19
	60	10.37±1.08	9.92±1.15	8.45±1.15	9.49±1.08	8.30±1.44	8.10±1.44
	90	13.41±0.32	12.95±0.32	9.37±0.62	11.40±0.32	10.50±0.91	10.22±0.91
	120	15.96±0.82	15.57±1.12	11.91±0.52	12.56±0.68	12.05±2.02	12.10±1.36
Buffer stage-1 pH-6 (60 minutes)	150	17.98±0.61	18.38±0.61	13.68±1.13	14.98±0.98	13.23±1.61	12.94±2.20
	180	21.03±1.35	22.08±1.74	16.52±1.74	21.48±1.35	15.60±0.54	14.59±1.20
Buffer stage 2 pH= 7.2 (90 minutes)	210	52.63±1.78	53.24±2.25	45.26±1.81	39.96±2.18	34.12±1.90	35.63±1.90
	240	63.31±2.05	61.18±2.11	56.23±2.23	51.19±2.21	45.93±1.63	47.62±1.56
	270	89.14±1.61	87.39±1.63	67.12±1.31	64.21±1.61	59.86±2.13	58.39±2.12
	300	99.68±1.55	98.52±1.53	76.39±1.23	75.96±2.51	71.20±1.38	72.28±1.38
	330	--	--	89.84±1.98	88.53±2.14	83.26±2.56	85.98±0.81

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

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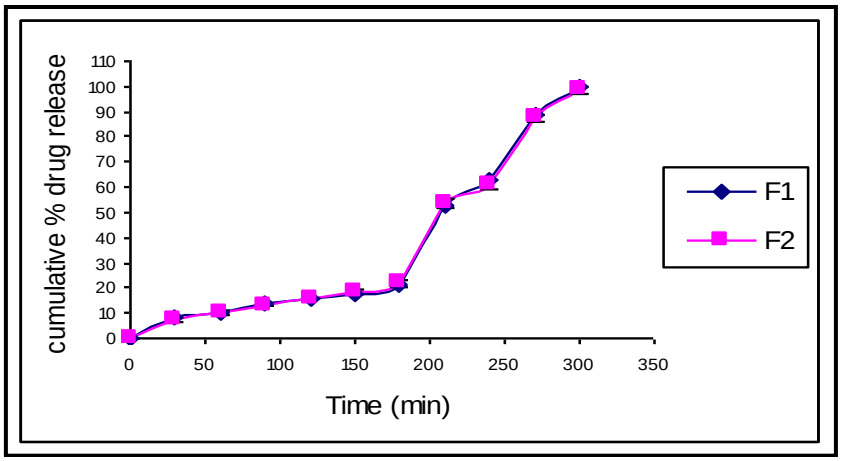

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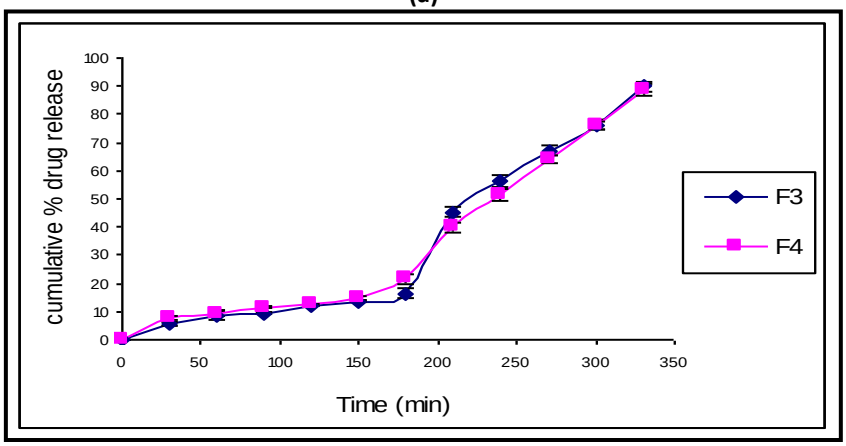

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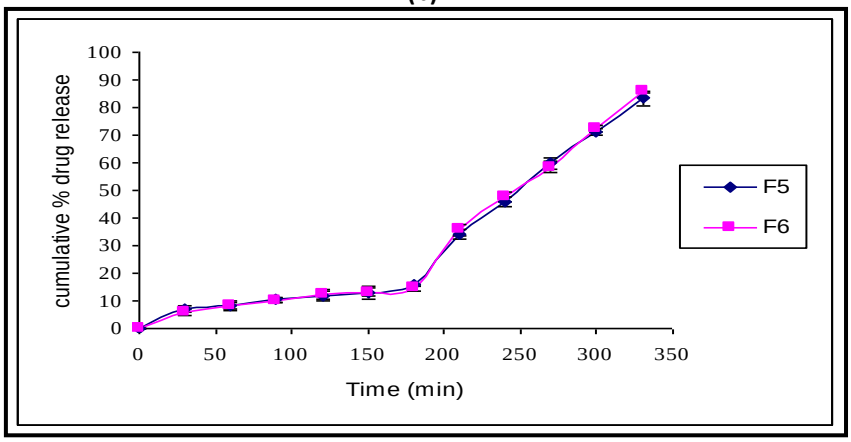

(c)

Fig-a, b and c: *In vitro* release of Mesalazine from matrix tablets prepared with HPMC-AS.

Stability Studies

Mesalazine matrix tablets from all the formulations were stored at 45^{o}± 2^{o}C, 75 ± 5% RH upto 45 days. Tablet evaluation tests were carried out at every 15 days intervals. All the formulations are physically stable. There were no deviations found in the tests and all are 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, tablet evaluation tests are within the acceptable limits. The dissolution profile indicate that formulation F3, F4, F5 & F6 prevent escape of Mesalazine in acidic pH, of not more than 12% of labeled amount. All other formulations minimize escape of Mesalazine in buffer stage 1(pH 6) i.e. not more than 30% of labeled amount. HPMCAS offered better protection from escape of Mesalazine in precolonic pH stages. Hence matrix tablets of Mesalazine with optimum concentration of HPMC-AS were successfully developed.

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