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Design and Optimization of High-dose Colon-targeted Controlled Drug Delivery System for Mesalamine using Eudragit Coated Matrix Tablets

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ABSTRACT

Objective: Aim of the present work is to design and optimize a novel high-dose, colon-targeted controlled drug delivery system for Mesalamine, potentially suitable for once daily administration, using simple wet granulation method.

Methods: The proposed method is based on a core matrix tablet, which contains combination of hydrophilic hydrogel polymers such as Hydroxypropyl methylcellulose K100 LVCR and Sodium Carboxymethyl cellulose to manipulate drug release prepared by the traditional wet granulation technique, followed by coating with pH-dependent polymers such as Methyl Methacrylate Copolymers (Eudragit® L-100 and/ or Eudragit® S-100). Drug release from coated matrix tablets was evaluated in 0.1 N Hydrochloric acid, pH 6.4 and pH 7.2 Phosphate buffers.

Results & Conclusion: The optimised formulation was developed by employing 45mg and 54 mg of HPMC K100 LVCR and Sodium Carboxymethyl cellulose polymers respectively in the matrix core followed by application of 10%w/w Eudragit S-100 coating solution till 7.5%w/w weight gain. The results of dissolution studies indicated that optimized formulation exhibited drug release pattern very close to dissolution profile of marketed once a day tablet formulation, Vegaz OD 1.2g tablets and able to retard drug release in upper part of the GIT and sustain the drug release over eight hours in colonic region, hence can be concluded as a high dose once a day formulation is achieved.

Key words: Mesalamine, High-dose, Matrix tablets, Colon-targeted delivery, Eudragit.

INTRODUCTION

Mesalamine (5-aminosalicylic acid or 5-ASA or Mesalazine) is the first-line anti-inflammatory agent recommended for the treatment of active symptoms, induction of remission and maintenance of remission in patients with mild-to-moderate ulcerative colitis [1]. Mesalamine acts topically on the colonic mucosa but when orally administered, it is extensively and rapidly absorbed in the small intestine, leading to little localization of Mesalamine in the colon and hence, low efficiency with significant systemic side effects [2].

Consequently, three methods have been commonly used for targeting of Mesalamine to the colon: a pro-

drug concept, enteric coating, and/or prolonged release of the drug through semi permeable membrane [3].

The recommended daily dose of Mesalamine may reach 4.8 g in acute attack and 2.4 g in maintenance of remission in divided doses. Therefore, multiple daily dosing up to 12 tablets or capsules per day are required because of the low dosage strength of most currently commercially available Mesalamine formulations. Reduced patient compliance and disease control are the results of these inconveniences of frequent daily dosing and the number of tablets or capsules required per day [4]. Additionally, many traditional delayed-release formulations that lack any means for prolonging Mesalamine release are characterized by the

undesirable immediate release of Mesalamine once they reach the colon. This leads to a relatively smaller amount of Mesalamine delivered to the distal part of the colon, the area most commonly to be inflamed [5].

Multi-Matrix System (MMX) tablets with delayed-release technology was developed for the treatment of ulcerative colitis to deliver a higher dosages of drug with a view of improving patients compliance [6, 7]. The MMX technology involves incorporating drug into a lipophilic matrix, which is dispersed as micro-particles within a hydrophilic matrix. Then pH-dependent gastro-resistant film, designed to disintegrate when the pH is above 7, was applied to delay the dissolution [4, 8, 9].

The current study is aimed at developing and optimizing a novel delayed-controlled release matrix tablet of Mesalamine, suitable for once daily administration, employing a simpler method suitable for conventional tablets manufacture processes. The proposed method is based on a core matrix tablet, which contains combination of hydrophilic hydrogel polymers such as Hydroxypropyl methylcellulose K100 LVCR and Sodium Carboxymethyl cellulose to manipulate drug release prepared by the traditional wet granulation technique, followed by coating with pH-dependent polymers such as Methyl Methacrylate Copolymers (Eudragit® L-100 and/ or Eudragit® S-100).

MATERIALS AND METHODS

Materials:

Mesalamine was obtained as a gift sample from Inventis Drug Delivery Systems Pvt. Ltd., Hyderabad, India. HPMC K100 LVCR and Sodium Carboxymethyl cellulose, Eudragit L-100 and Eudragit S-100 were obtained as gift samples from Alphamed Formulations Pvt. Ltd., Hyderabad, India. All other excipients used were of laboratory grade.

Methods:

Preparation of Matrix Core Tablets:

Matrix core tablets of Mesalamine were prepared by wet granulation method using HPMC K100 LVCR and Sodium Carboxymethyl cellulose in combination as matrix forming agent in different proportions (Table 1). Microcrystalline cellulose PH-101 was used as diluent. Formulations were blended and granulated with polyvinyl pyrrolidone K-30 solution prepared by dissolving PVP in mixture of Purified water and Isopropyl alcohol at 1:1 ratio. The wet mass passed through #12 mesh and the granules were dried in hot air oven for 120 minutes at 50°C. The dried granules were sieved through #18 mesh, obtained granules were lubricated with Talc and Magnesium stearate. The lubricated granules compressed on a multi-punch tablet machine (Cad mach Machinery Co. Pvt. Ltd., India) using 21 × 9 mm capsule shaped punches with constant compression force around 200 N to 250 N. All the tablet formulations under study were assessed for their average weight, thickness, hardness, friability, disintegration, assay and in vitro drug release.

Coating of the Matrix Core Tablets:

Matrix core tablet formulation with dissolution profile similar to marketed product was chosen for delayed release coating trials. An organic polymer solution consisting of Eudragit® L-100 and Eudragit® S-100 in different proportions (Table 2) to achieve 10% w/w Methacrylic acid polymer in Isopropyl alcohol was used for the coating. Glycerol monostearate was incorporated in the coating solution as a plasticizer (10% w/w based on the polymer). An opacifier, titanium dioxide and Iron oxide red as colouring agent was added. An anti-adherent, talc to prevent adhering of tablets during the coating process was also added to the coating solution. Coating solution was prepared by stirring the mixture for 1 h to ensure homogeneous solution.

Table: 1 Composition of Mesalamine Control Release Core Matrix Tablets

Ingredients	Formulation (mg/ Tablet)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Mesalamine	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200
MCC PH-101	132	172	52	132	92	92	112	152	72	103
HPMC K100 LVCR	20	20	20	40	40	40	60	60	60	45
Sodium CMC	10	50	90	10	50	90	10	50	90	54
PVP K 30	20	20	20	20	20	20	20	20	20	20
Talc	14	14	14	14	14	14	14	14	14	14
Magnesium stearate	14	14	14	14	14	14	14	14	14	14
Granulating fluid*	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	1450	1450	1450	1450	1450	1450	1450	1450	1450	1450

* Mixture of Purified water and Isopropyl alcohol at 1:1 ratio

The outer delayed release coating layer was applied on the matrix core tablets using a Pharma R&D Coater (Ideal Cures Pvt. Ltd., India) to achieve the target weight gain of 7.5% (w/w).

Table: 2 Compositions of Delayed Release Coating Solutions

Ingredients	F11 (% w/w)	F12 (% w/w)	F13 (% w/w)
Eudragit L – 100	10.0	-	5.0
Eudragit S – 100	-	10.0	5.0
Glycerol monostearate	1.0	1.0	1.0
Talc	1.6	1.6	1.6
Titanium dioxide	0.5	0.5	0.5
Iron oxide red	0.4	0.4	0.4
Isopropyl alcohol*	q.s.	q.s.	q.s.

Characterization of Matrix Core Tablets:

The prepared matrix core tablets were evaluated for average weight, thickness, hardness, friability, disintegration, assay and in vitro drug release profiles. The hardness of 6 tablets was measured using Pharma Test's standard hardness tester. Friability was determined with 10 tablets by using Pharma Test's friability tester subjecting for 100 revolutions at 25 rpm. Disintegration time was evaluated on 6 tablets by using Electro labs tablet disintegration tester in 1000 mL of 0.1 N Hydrochloric acid, pH 6.4 and pH 7.2 Phosphate buffers at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$. For estimating drug content, 5 tablets were crushed and powdered. The aliquot of powder equivalent to 1200 mg of drug was weighed and dissolved in 1000 ml of 1 M hydrochloric acid. The resultant solution was filtered and suitably diluted, then analysed spectrophotometrically using Shimadzu UV-150 double beam UV-spectrophotometer at predetermined λ_{max} of 302 nm and drug content was calculated on average weight basis from the absorbance value [10].

Drug Release Studies on Matrix Core Tablets:

Drug release from matrix core tablets was studied using Electro labs multi station dissolution rate test equipment employing a paddle stirrer at 50 rpm in 900 ml of pH 7.2 Phosphate buffer at $37 \pm 0.5^{\circ}\text{C}$. Samples of 5 ml of each were withdrawn at different time intervals over a period of 8 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 332 nm for Mesalamine using a Shimadzu UV-150

double beam UV-spectrophotometer [10]. The drug release experiments were conducted in triplicate. For comparison purpose, drug release from a market formulation, Vegaz OD 1.2g tablets (Dr. Reddy's Laboratories, India) was also studied after peeling off the tablet coating manually.

Release data was analyzed as per zero order [11], first order, Higuchi [12, 13], Erosion equation [14] and Peppas [15, 16] models to assess the drug release kinetics and mechanism from matrix core tablets. Similarity factor (f_2) values were calculated to assess the similarity between test and market formulations.

Drug Release Studies on Coated-matrix Tablets:

Drug release from coated-matrix tablets was studied using Electro labs multi station dissolution rate test equipment employing a paddle stirrer at 50 rpm in 900 ml of 0.1 N Hydrochloric acid for 2 hours followed by 1 hour in pH 6.4 Phosphate buffer and 8 hours in pH 7.2 Phosphate buffer at $37 \pm 0.5^{\circ}\text{C}$. Samples of 5 ml of each were withdrawn at different time intervals and each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted with 0.1 N Hydrochloric acid, pH 6.4 Phosphate buffer & pH 7.2 Phosphate buffer and assayed at 302nm, 330nm and 332nm respectively for Mesalamine using a Shimadzu UV-150 double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate. To evaluate similarity with marketed formulation, drug release from Vegaz OD 1.2g tablets (Dr. Reddy's Laboratories, India) was also studied similar to coated-matrix tablets.

Drug release data from coated-matrix tablets was analyzed for Time for 2%, 30%, 50% & 90% Drug Dissolution, Mean Dissolution Time and Similarity factor (f_2) values.

Similarity Factor (f_2) Calculation:

The similarity factor (f_2) is defined as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles". f_2 value calculation is the simplest among the methods to evaluate the dissolution profile similarity between test and reference products drug release profiles. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f_2 [17].

$$f_2 = 50. \log \{ [1 + (1/n) \sum_{i=1}^n (R_i - T_i)^2]^{-0.5} \cdot 100 \}$$

Where ' R_i ' and ' T_i ' are the cumulative percentage dissolved at each of the selected n time point of the reference & test product respectively. Factor f_2 is

inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. If the f_2 value is in between 50-100 the release of the test and the reference are identical.

RESULTS AND DISCUSSION

Matrix core tablets each containing 1200 mg of Mesalamine prepared employing different proportions of HPMC K100 LVCR and Sodium Carboxymethyl cellulose hydrogels in combination as hydrophilic matrix forming agent by conventional wet granulation method. The tablets of different formulations were subjected to various evaluation tests like average weight, thickness, hardness, friability, disintegration time and drug content. Results of physicochemical evaluation of all the batches of Mesalamine matrix core tablets were presented in Table 3. Average weight of all the formulated batches, i.e. from F1 to F10, was found to be $1448 \pm 0.83\%$ to $1453 \pm 0.51\%$. Weight variation of all the formulated batches was less than 1% which was in acceptable range. Hardness of the tablets from the formulations was in the range of 221 to 273 Newton's. Thickness of the formulations was found to be between 8.07 and 8.20 mm. Friability of all the formulations was in acceptable range of less than 1%, ranging from 0.18% to 68%. All the tablets were found to be non-disintegrating in water and aqueous, acidic and alkaline fluids. As the formulated matrix core tablets were non-disintegrating in neutral, acidic and alkaline fluids, they are considered suitable for oral controlled release. Drug content of all the formulated batches was found to be between 98.092% and 101.47% and within $100 \pm 2\%$ of the labelled claim. As such the prepared tablets were of good quality with regard to drug content, hardness and friability.

Drug release parameters of the matrix core tablets are summarized in Table 4 and 5. The *in vitro* drug release profiles of matrix core tablets in pH 7.4 phosphate buffer are presented in Figure 1. F2 & F3 formulations showed complete drug release within 4 h, formulation F1 has release extended up to 5 h and F5 & F10 formulations extended the drug release up to 8 h and release was slow and spread over 8 h. Whereas release from F4, F7, F8 and F9 formulations is not complete within 8 h and release extended more than 8h.

When the release data was analysed as per zero and first order kinetic models, F1, F2, F3, F4, F7, F8 formulations showed the best fit and higher correlation with first order model indicating first order drug release kinetics. F5, F6, F9, F10 formulations showed the best fit and higher correlation with zero order model indicating zero order drug release kinetics. Drug release data from Mesalamine matrix core tablets computed as

per Higuchi, Erosion models & Peppas equation and F1, F2, F3, F4, F5, F7, F8 formulations showed non-fickian diffusion, F6, F10 formulations are following diffusion based super Case II transport and F9 formulation is following erosion based super Case II transport.

The similarity factor f_2 was calculated to check the dissolution profile similarity of matrix core tablets with Vegaz OD 1.2g tablets after peeling off the tablet coating manually. F1, F2, F3, F7, F8, F9 formulations showed f_2 values lower than 50 and are considered not similar to market formulation with respect to dissolution profile. F4, F5, F6, F10 formulations are considered similar to that of market formulation, with f_2 values above 50. And formulation F10 showed highest Similarity factor (f_2) value with best dissolution profile similarity with reference product and taken up for further trials of delayed releasing coating optimisation trials.

Matrix core tablets from F10 formulation was coated with different proportions of Eudragit® L-100 and Eudragit® S-100 to achieve 7.5% (w/w) weight gain. Drug release from coated matrix tablets was evaluated in 0.1 N Hydrochloric acid for 2 hours followed by one hour in pH 6.4 Phosphate buffer and 8 hours in pH 7.2 Phosphate buffer. Time for 2%, 30%, 50% & 90% Drug Dissolution (T2%, T30%, T50% & T90%), Mean Dissolution Time (MDT) and Similarity factor (f_2) values of test formulations were compared against the marketed formulation Vegaz OD 1.2g tablets.

Formulation F11 which is composed of Eudragit® L-100 coating and formulation F13 which contains combination of Eudragit® L-100 and Eudragit® S-100 in 1:1 ratio in coating were able to retard drug release in 0.1 N Hydrochloric acid but started significant drug release in pH 6.4 Phosphate buffer. Premature drug release from F11 and F13 formulations can be attributed to Eudragit® L-100 polymer which starts dissolving from above pH 6.0. Same phenomenon is reflected in Time for 2% Drug Release (T2%) values of F11 and F13 formulations showing T2% values of 2.20 & 2.81 hours respectively, which indicates significant drug release below pH 7.5. Formulation F12 which is comprised of Eudragit® S-100 in coating was able to delay the drug release in both 0.1 N Hydrochloric acid and pH 6.4 Phosphate buffer; drug release started in pH 7.2 Phosphate buffer dissolution media and extended up to 8 hours and T2% value also observed above 3 hours indicating no significant drug release below pH 7.5. Calculated Time for 30%, 50% & 90% Drug Dissolution (T30%, T50% & T90%) values are in the range 3.62 - 4.34, 4.78 - 5.62 and 7.94 - 8.89 hours respectively for F11, F12 & F13, where F12 formulation dissolution times are comparable with the

Table: 3 Results of Physico-chemical Properties of Core Matrix Tablets

Trial No.	Avg. Weight (mg $\pm$ % Deviation)	Thickness (mm)	Hardness (N)	Friability (%)	Disintegration Time (Minutes)	Drug content (%)
F1	1451 $\pm$ 0.80	8.11 – 8.18	235 – 246	0.57	Non-disintegrating	99.84
F2	1451 $\pm$ 0.61	8.13 – 8.16	221 – 252	0.33	Non-disintegrating	100.53
F3	1449 $\pm$ 0.42	8.07 – 8.10	228 – 270	0.18	Non-disintegrating	100.13
F4	1449 $\pm$ 0.66	8.08 – 8.16	236 – 268	0.68	Non-disintegrating	101.06
F5	1453 $\pm$ 0.51	8.15 – 8.20	223 – 255	0.46	Non-disintegrating	100.73
F6	1452 $\pm$ 0.56	8.10 – 8.18	240 – 273	0.55	Non-disintegrating	99.83
F7	1451 $\pm$ 0.53	8.12 – 8.17	239 – 263	0.44	Non-disintegrating	98.092
F8	1450 $\pm$ 0.48	8.10 – 8.15	238 – 249	0.63	Non-disintegrating	101.47
F9	1448 $\pm$ 0.83	8.09 – 8.14	222 – 251	0.64	Non-disintegrating	101.20
F10	1449 $\pm$ 0.61	8.11 – 8.16	234 – 262	0.51	Non-disintegrating	100.14

Table: 4 Correlation Coefficient (r^2) values of Mesalamine Matrix Core Tablets as per Various In-vitro Release Kinetic Models

Trial No.	Correlation Coefficient (r^2) Values				
	Zero Order	First Order	Higuchi Model	Erosion Model	Peppas Model
F1	0.803	0.947	0.973	0.992	0.984
F2	0.936	0.966	0.997	0.929	0.997
F3	0.944	0.954	0.981	0.969	0.990
F4	0.882	0.999	0.983	0.982	0.980
F5	0.950	0.931	0.976	0.966	0.994
F6	0.988	0.954	0.937	0.905	0.995
F7	0.942	0.996	0.981	0.986	0.986
F8	0.985	0.991	0.963	0.998	0.998
F9	0.999	0.928	0.925	0.972	1.000
F10	0.975	0.954	0.973	0.927	0.998

Table: 5 Drug Release Kinetics of Matrix Core Tablets

Trial No.	Release Rate Constant		Peppas Release Exponent (n)	Drug Transport Mechanism
	Ko (mg/h)	K ₁ (h ⁻¹)		
F1	15.189	0.777	0.462	First order, non-fickian diffusion
F2	23.616	0.700	0.494	First order, non-fickian diffusion
F3	25.273	0.908	0.722	First order, non-fickian diffusion
F4	11.276	0.335	0.698	First order, non-fickian diffusion
F5	12.906	0.444	0.769	Zero order, non-fickian diffusion
F6	17.572	0.375	1.030	Zero order, diffusion/ super Case II transport
F7	9.614	0.185	0.789	First order, non-fickian diffusion
F8	9.784	0.189	0.816	First order, non-fickian diffusion
F9	11.223	0.260	0.966	Zero order, erosion/ super case II transport
F10	12.722	0.339	0.781	Zero order, diffusion/ super Case II transport

Figure: 1 In-vitro % Drug Release Profiles for Mesalamine Core Matrix Tablets in pH 7.2 Phosphate buffer

Figure: 2 In-vitro % Drug Release Profiles of Mesalamine Coated Matrix Tablets

Table: 6 Similarity Factor (f2) Results for Dissolution Profile Comparison of Matrix Core Tablets

Trial No.	Similarity factor (f2)
F1	28.0
F2	26.6
F3	26.4
F4	57.7
F5	68.6
F6	54.4
F7	44.8
F8	39.8
F9	40.9
F10	77.7

Table: 7 Parameters for Characterizing Drug Release from Coated Matrix Tablets

Trial No.	T2%	T30%	T50%	T90%	MDT (hr)	Similarity factor (f2)
F11	2.20	3.62	4.78	7.94	5.01	45.64
F12	3.25	4.34	5.62	8.89	5.95	70.51
F13	2.81	3.93	5.09	8.21	5.40	62.75
Vegaz OD	3.13	4.28	5.26	8.60	5.68	-

Figure: 3 In-vitro % Drug Release Profiles Comparison of Mesalamine Coated Matrix Tablets with Marketed Formulation

reference product. Mean Dissolution Time (MDT) is 5.01, 5.95 & 5.40 hours respectively for F11, F12 & F13 formulations and MDT of F12 is close to reference product MDT of 5.68 hours. Similarity factor (f_2) values for F11, F12 & F13 formulations are 45.64, 70.51 & 62.75 correspondingly and formulation F12 showed highest Similarity factor (f_2) value with best dissolution profile matching against reference product.

CONCLUSION

It was concluded from the present study that appropriate combination of a hydrophilic polymers (HPMC K100 LVCR and Sodium Carboxymethyl cellulose) was suitable for preparing high-dose Mesalamine matrix tablets with a controlled drug release profile suitable for once daily administration and a pH-dependent polymer (Eudragit S-100) coating can be used to protect the drug release from being released in the upper region of the GI system. The optimised formulation (F12) was developed by employing 45 mg and 54 mg of HPMC K100 LVCR and Sodium Carboxymethyl cellulose polymers respectively in the matrix core followed by application of 10%w/w Eudragit S-100 coating solution till 7.5%w/w weight gain. The results of dissolution studies indicated that formulation F12, the most successful of the study, exhibited drug release pattern very close to dissolution profile of marketed once a day tablet formulation, Vegaz OD 1.2g tablets and able to retard drug release in upper part of the GIT and sustain the drug release over eight hours in colonic region, hence can be concluded as a high dose once daily formulation is achieved.

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