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### Design and Evaluation of Novel High-load Mesalamine Multi-particulate Formulations for Colon-targeted Controlled Drug Delivery

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#### ABSTRACT

**Objective:** Aim of the present work is to design and evaluate novel high-load multi-particulate systems of Mesalamine for colon-targeted controlled drug delivery suitable for once daily administration.

**Methods:** The proposed method is based on multi-particulate system coated with a combination of pH-dependent and rate controlling polymers. Manufacturing involves densification of API using wet granulation with polymers to get drug polymer premix and drug layering employing centrifugal fluid-bed equipment; followed by coating with a combination of pH-dependent and rate controlling polymers. Drug release profiles from core and coated pellets were evaluated in 0.1 N Hydrochloric acid, pH 6.4 and pH 7.2 Phosphate buffers as appropriate.

**Results & Conclusion:** Granulation with HPMC K100 M followed by drying and subsequent milling gives drug polymer premix with improved flow properties and bulk density; centrifugal drug layering technique is suitable to achieve high drug loading efficiencies. Combination of a Eudragit® S 100 and Eudragit® RS PO polymers at 1:1 ratio in coating can be used to protect the drug in acidic GI conditions and subsequent prolonged release profile suitable for once daily administration in colonic pH environment. The results indicated that formulation MSP08, exhibited drug release pattern very close to marketed once a day formulation, Vegaz OD 1.2g tablets. The major advantage of the developed high-load pellets is ease of dose titration and administration of large doses to geriatric patients. Hence it can be concluded that, a high-dose once daily formulation is achieved.

**KEY WORDS:** Mesalamine, Drug polymer premix, High-load, Multi-particulate, 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 Ulcerative colitis (UC) and Crohn's disease (CD) (collectively termed inflammatory bowel disease - IBD) [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]. Various

Mesalamine drug delivery systems are developed to deliver varying amounts of drug to the intended site of action, which may have an effect on the bio-availability and therapeutic efficacy. The available oral 5-ASA products are developed using mainly three types of drug delivery systems: a pro-drug concept, enteric or delayed release coating, and/or prolonged release formulations [3].

pH dependent delayed-release formulations start the drug release when the pH of gastric environment is above pH 6-7.

**Table: 1 Different Drug Delivery Systems of Mesalamine Available in Market**

Brand Name	Dose (mg)	Drug Delivery Technology	Drug Release	Site of delivery
<b>Pentasa</b>	500, 1000, 2000	Ethylcellulose coated micro granules	Controlled	Duodenum to rectum
<b>Asacol MR</b>	400	Tablets coated with Eudragit S	Delayed; > pH 7	Terminal ileum, colon
<b>Asacol HD</b>	800	Tablets coated with Eudragit L & S	Delayed; > pH 6 - 7	Terminal ileum, colon
<b>Mezavant/ Lialda</b>	1200	Multi-matrix tablet coated with combination of Eudragit L & S	Prolonged; > pH 6.8	Colon
<b>Salofalk</b>	250, 500	Eudragit L-coated tablets	Delayed; > pH 6	Terminal ileum, colon
<b>Salofalk</b>	500, 1000, 1500, 3000	Eudragit NE 40 D matrix granules coated with Eudragit L	Prolonged; > pH 6.8	Terminal ileum, colon
<b>Ipocol</b>	400	Tablets coated with Eudragit S	Delayed; > pH 7	Terminal ileum, colon
<b>Salazopyrin</b>	500	5-ASA linked to sulfapyridine by azo bond	Cleavage by intestinal flora	Colon
<b>Colazal</b>	750	5-ASA linked to 4-aminobenzoyl-b-alanine by azo bond	Cleavage by intestinal flora	Colon
<b>Dipentum</b>	250	5-ASA dimer linked by azo bond	Cleavage by intestinal flora	Colon

Controlled-release drug delivery system such as Pentasa contains micro-granules coated with Ethylcellulose semipermeable membrane that slowly release the Mesalamine throughout the gastrointestinal tract. Multi-Matrix System (MMX) tablets with delayed-release technology was developed for the treatment of ulcerative colitis to deliver a higher dosages of drug allowing for once-daily dosing with a view of improving patients compliance [4, 5]. The MMX technology involves incorporating the drug into a lipophilic matrix, which is dispersed as micro-particles within a hydrophilic matrix. Then pH-dependent gastro-resistant film designed to dissolve when the pH is above 7 was applied to delay the dissolution [6-8]. In pro-drug approach Azo-bonded formulations such as Colazal (Balsalazide), Dipentum (Olsalazine) and Salazopyrin (Sulfasalazine) contains a 5-aminosalicylate active moiety that is linked by azo bond, which is cleaved by azo-reductase enzyme of colonic bacteria [9].

The recommended daily dose of Mesalamine may reach up to 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 low dosage strengths of most of the conventional Mesalamine formulations currently available in market. 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 [6].

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 [10, 11].

Multi-particulate systems (MUPs) contains discrete particles that make up a multiple unit system. In multi-particulate dosage forms the active ingredient is distributed in to a number of small independent sub-units and each sub-unit acts as an independent dosage form. To deliver the target dose of active, these sub-units are filled into a sachet or encapsulated into capsules or compressed into a tablet. MUPs provide many advantages over conventional single-unit systems because of their small size and large number. Multi-particulates are less dependent on gastric emptying time, resulting in minimum inter and intra-subject variability during gastrointestinal transit and shows better reproducible pharmacokinetic profiles than conventional single unit formulations. MUPs are also better distributed than single unit systems and less prone to cause local irritation [12].

Patient safety because of dose dumping is also improved by using multi-particulate dosage forms, especially for modified release dosage forms. In single-unit (monolithic or reservoir) system, once the rate controlling technology is failed or damaged, it may

lead to severe lead to severe complications because of reduced drug stability, dose dumping and no release of drug at all. By contrast MUPs formulation avoids all or none phenomenon; the drug release mechanisms are incorporated into each single subunit. Any possible damage, only affects the release characteristics of that single subunit involved; which represents a very small portion of the total dose administered, reducing the likelihood of safety and efficacy problems [13].

Another main reason for formulating a drug as a multi-particulate system is to facilitate easy swallowing of comparatively large doses than the single unit systems, which can improve compliance in paediatric and geriatric patients.

Current study is aimed at the development and evaluation of novel high-load multi-particulate formulations suitable for once daily administration of Mesalamine with more than 90% drug loading and also capable of release the drug in a predetermined controlled manner to the colon, which is the intended target site of pharmacological action; employing suitable cost effective conventional pellet manufacture process. The proposed manufacturing process consists of three primary steps: preparation of drug polymer premix using traditional wet granulation technique, followed by drug layering onto the sugar spheres and final coating with pH dependent and/ or pH independent release controlling polymers such as Eudragit® S 100 and/ or Eudragit® RS PO.

## MATERIALS AND METHODS

### Materials:

Mesalamine was obtained as a gift sample from Inventis Drug Delivery Systems Pvt. Ltd., Hyderabad, India. Hypromellose (HPMC) K100 M, Hypromellose (HPMC) 5 cps, Polyvinylpyrrolidone K-30, Eudragit® S 100 and Eudragit® RS PO were obtained as gift samples from Alphamed Formulations Pvt. Ltd., Hyderabad, India. All other excipients used were of laboratory grade.

### Methods:

#### Preparation of Drug Polymer Premix:

Mesalamine API is available as light tan to pink colour needle - shaped crystals, because of this crystal habit Mesalamine has very low bulk density and shows poor flow ability, compatibility and compression characteristics [14, 15, 16]. To improve flow properties and bulk density, Mesalamine was granulated using different polymers in sufficient quantity to achieve dough mass (Table 2). The wet mass passed through #12 mesh and the granules were dried in hot air oven at 50°C for two hours. The dried granules were

pulverized and sieved through #60 mesh to obtain fine drug polymer premix powder. All premix formulations were assessed for Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of Repose.

#### Preparation of Drug Loaded Core Pellets:

Pelletization by drug layering technique was employed using centrifugal fluid-bed equipment (rotary processor) of Umang Pharmatech Pvt. Ltd., India. Weighed quantity of sugar spheres were loaded into processing chamber and moistened by spraying small quantities of polymer binder solutions along with simultaneous application of drug polymer premix onto the sugar spheres to achieve the core pellet composition as per the table 3. Process parameters maintained during the drug layering step was given in table 4. After the completion of drug layering, the core pellets were retained in the processing chamber for another 15 minutes under rotation to improve surface morphology of the pellets.

The obtained drug loaded pellets were withdrawn from the processing chamber and were dried in a hot air oven at 50°C for two hours. The dried pellets were passed through #16 and #24 meshes to remove fines and/ or agglomerates and the uniform sized pellets were separated by collecting fraction retained between #16 and #24 meshes. Collected core pellets were evaluated for parameters like mean pellet size, friability, percent drug content and drug loading efficiency.

#### Coating of Drug Layered Pellets:

Drug layered core pellets with highest drug loading efficiency was chosen for colon-targeted controlled release coating trials. Polymer solution compositions (Table 5) consisting of 10% w/w Eudragit® RS PO and Eudragit® S 100 polymers in mixture of Isopropyl alcohol/ Acetone (2:1) were used for the coating. Triethyl citrate was incorporated in the coating solution as a plasticizer (10% w/w based on the polymer). An anti-adherent, Glycerol monostearate to prevent adhering of pellets to each other during the coating process was also added to the coating solution. Coating solution was prepared by stirring the mixture for 1 hour to ensure homogeneous solution.

The colon-targeted controlled release coating layer was applied on the core pellets using a R&D Fluid Bed Processor of Umang Pharmatech Pvt. Ltd., India. Core pellets were loaded into product container/ bowl of fluid bed processor and pre-warmed to a product temperature of 30°C. The colon-targeted controlled release coating solution was sprayed onto the pre-warmed core pellets at an inlet temperature of 50°C while maintaining the product temperature between

**Table: 2 Composition of Drug Polymer Premix**

Ingredients	Concentration (% w/w)				
	MSP01	MSP02	MSP03	MSP04	MSP05
Mesalamine	93.72	91.24	99.72	94.43	90.42
Polyvinylpyrrolidone K-30	6.28	-	-	-	-
Eudragit® RS PO	-	8.76	-	-	-
Hypromellose K100 M	-	-	0.28	-	-
Hypromellose 5 cps	-	-	-	5.57	-
Ethyl cellulose	-	-	-	-	9.58
Purified water	q.s.	-	q.s.	q.s.	-
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.

**Table: 3 Compositions of Drug Loaded Core Pellets**

Ingredients	Concentration (% w/w)				
	MSP01	MSP02	MSP03	MSP04	MSP05
Sugar spheres	2.20	2.07	2.44	2.23	2.03
Mesalamine	82.36	75.34	97.15	84.09	73.54
Polyvinylpyrrolidone K-30	15.44	-	-	-	-
Eudragit® RS PO	-	22.59	-	-	-
Hypromellose K100M	-	-	0.41	-	-
Hypromellose 5 cps	-	-	-	13.68	-
Ethyl cellulose	-	-	-	-	24.43
Purified water	q.s.	-	q.s.	q.s.	-
Isopropyl alcohol	-	q.s.	q.s.	q.s.	q.s.

25°C and 35°C. The modified release coating was carried out using bottom spray (Wurster process) coating mode to achieve final weight build-up of 7.36% w/w. After completion of coating, coated pellets were dried at reduced fluidization air flow of 20 to 40 cfm with an inlet air temperature of 45°C. The dried pellets were passed through #16 and #24 meshes to remove fines and/ or agglomerates and the uniform sized pellets were separated by collecting fraction retained between #16 and #24 meshes. Collected coated pellets were evaluated for mean pellet size, percent drug content and dissolution. Table 6 presents the summary of process parameters employed during coating trials.

**Table: 4 Process Parameters for Drug Layering of Core Pellets**

Process Parameter	Setting
Rotor speed (rpm)*	100 - 200
Slit air (Lit/ min)	150
Spry air (Lit/ min)	12
Spray air pressure (kg/cm <sup>2</sup> )	0.6
Spray rate (mL/ min)*	10 - 28
Premix dropping rate (g/min)*	3 - 6

\*Adjusted to avoid over wetting and agglomerates.

#### Evaluation Pellet Size and Shape:

Determination of pellet size was carried out by sieve analysis method. Accurately weighed quantity of pellets were transferred into a sieve shaker equipped with US standard sieves #14, #16, #20, #24, #28 & #32 and shaken for 15 min. Weight of the fraction of pellets retained on the each sieve was recorded and mean pellet size was calculated.

#### Friability:

Friability of un-coated core pellets was evaluated using Pharma Test's friability tester. 10 g accurately weighed ( $W_1$ ) de-dusted pellets were collected along with 25 spherical glass beads of 3 mm diameter and samples were placed in the friabilator drum and rotated for 100 revolutions at 25 rpm. Pellets were carefully collected from the drum and loose dust was removed using #40 mesh and then reweighed ( $W_2$ ). Pellets friability is calculated by using below equation and is expressed as percentage.

$$\% \text{ Friability} = \left[ \frac{W_2 - W_1}{W_1} \right] \times 100$$

Where  $W_1$  is the weight of pellets before revolutions and  $W_2$  is the weight of the pellets after revolutions.

**Table: 3 Compositions of Drug Loaded Core Pellets**

Ingredients	Concentration (% w/w)				
	MSP06	MSP07	MSP08	MSP09	MSP10
<b>Core Pellets</b>					
Sugar spheres	2.26	2.26	2.26	2.26	2.26
Mesalamine	90.00	90.00	90.00	90.00	90.00
Hypromellose K100M	0.38	0.38	0.38	0.38	0.38
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.
<b>Coating Solutions</b>					
Eudragit® RS PO	6.00	4.50	3.00	1.50	0.00
Eudragit® S 100	0.00	1.50	3.00	4.50	6.00
Triethyl citrate	0.60	0.60	0.60	0.60	0.60
Glycerol monostearate	0.76	0.76	0.76	0.76	0.76
Acetone	q.s.	q.s.	q.s.	q.s.	q.s.
Isopropyl alcohol*	q.s.	q.s.	q.s.	q.s.	q.s.

**Assay (or) % Drug Content:**

Collect 2.5 grams of pellets and grind pellets using a clean mortar & pestle in to a fine powder.

500 mg of accurately weighed powder was transferred into a 1000 mL volumetric flask and the contents were dissolved using 100 mL of Methanol by sonication and volume was made up to 1000 mL with 1 M hydrochloric acid. Then sample solution was passed through a Whatman cellulose filter paper.

Suitable dilutions were made and absorbance of sample solutions were measured using a Shimadzu UV-150 double beam UV-spectrophotometer at 302 nm and content of Mesalamine was calculated [17].

**Drug Release Studies of Drug Loaded Core Pellets:**

Drug release from core pellets was studied using Electrolabs multi station dissolution rate test equipment employing a paddle stirrer at 50 rpm in 900 mL of pH 7.2 Phosphate buffer at 37±0.5°C. Dissolution study was carried out by transferring the pellets equivalent to 1200 mg of Mesalamine into the dissolution bowels and samples of 5 ml of each were withdrawn at different time intervals. 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 [17]. The drug release experiments were conducted in triplicate.

**Drug Release Studies on Coated Pellets:**

Drug release from coated pellets was studied using Electrolabs 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±0.5°C.

Dissolution study was carried out by transferring the pellets equivalent to 1200 mg of Mesalamine in to the dissolution bowels and samples of 5 ml of each were withdrawn at different time intervals. 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 302 nm, 330 nm and 332 nm respectively for Mesalamine using a Shimadzu UV-150 double beam UV Spectrophotometer [17]. 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 pellets.

Release data was analyzed as per zero order [18], first order, Higuchi [19, 20], Erosion equation [21] and Peppas [22, 23] models to assess the drug release kinetics and release mechanism from the coated pellets. Drug release data from coated pellets was also analyzed for time for 2%, 30%, 50% & 90% dissolution, mean dissolution time and similarity factor (f2) values [24] to assess the similarity against marketed formulation.

**Table: 6 Process Parameters for Coating of Drug Layered Pellets**

Process Parameter	Setting
Nozzle insert diameter (mm)	0.8
Filter shaking mode	Asynchronous
Filter shaking interval (Sec)	8
Filter shaking Pause (Sec)	300
Fluidization air (cfm)	40 - 50
Inlet air Temperature (°C)	50
Product Temperature (°C)	25 - 35
Atomization air Pressure (Bar)	1 - 2
Wurster column height (mm)	25
Spray rate (mL/ min)	20 - 40

**Similarity Factor (f2) Calculation:**

Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profiles of test and reference products. The similarity factor (f2) 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” [17]. f2 value calculation is the simplest among the methods to evaluate the dissolution profile similarity between test and reference products drug release profiles.

$$f2 = 50 \cdot \log \left\{ \left[ 1 + \left( \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \cdot 100 \right] \right\}$$

Where ‘R<sub>t</sub>’ and ‘T<sub>t</sub>’ are the cumulative percentage dissolved at each of the selected ‘n’ time point of the reference and test products respectively. Factor f2 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 f2 value is in between 50 and 100, then the drug release from the test and the reference drug products can be considered identical.

**RESULTS AND DISCUSSION**

Mesalamine is a very low dense, fluffy material and exhibits poor flow properties because of its needle-shaped crystals. Poor flow ability is a major challenge during powder drug layering technique and necessitates addition of glidants to improve the flow properties of drug layering powder and also uniformity of pellets size, shape and other morphological properties. Poor density and compactibility are the further challenges, which have deleterious effect on the size and drug loading efficiency of pellets. To overcome above said challenges, Mesalamine API was subjected to wet granulation to get drug polymer premix with improved flow properties, density and compactibility. Mesalamine was granulated using different polymers and then the wet granules were dried, pulverized to achieve fine drug polymer premix powder. The needle-shaped Mesalamine crystals were broken down during granulation and subsequent milling to yield drug polymer premix with significantly improved flow properties and bulk density, to ensure uniform drug layering and achieve high drug load pellets. Drug polymer premix formulations were assessed for micrometrics and results were presented in table 7.

Mesalamine core pellets were prepared employing centrifugal drug layering technique by applying different drug polymer premix formulations onto the sugar spheres. The core pellets of trial formulations were subjected to various evaluation tests like mean pellet size, friability, percent drug content and drug loading efficiency; results of physicochemical

evaluation of core pellet trials were presented in table 8. Mean pellet size of all the formulated batches was found to be 876 μm to 922 μm. Friability of all the formulations was in acceptable range of less than 1%, ranging from 0.14% to 58% and formulation MSP03 composing high viscous grade HPMC K100 M showed lowest friability. Drug content of all the formulated batches was found to be in the range of 70.62% to 96.83% and drug loading efficiencies in the range of 90.59 % to 99.65 %, supporting suitability of centrifugal drug layering technique to achieve high process efficiency. The *in-vitro* drug release profiles of core pellets in pH 7.4 phosphate buffer are presented in figure 1. MSP01 and MSP04 formulations showed complete drug release within 45 minutes, MSP03 formulation had release extended up to 2 hours and drug release from MSP02 and MSP05 formulations was slow and spread over 3 hours. Formulation MSP03 was found with highest percent drug content and drug loading efficiency, hence chosen for further colon-targeted controlled release coating trials.

Core pellets from MSP08 formulation was coated with the 10% w/w Eudragit® RS PO and Eudragit® S 100 polymer solutions to achieve 7.36% w/w weight gain. The coated pellets were evaluated for mean pellet size and percent drug content and the results were presented in table 9. Mean pellet size of all the formulated batches was found to be between 878 μm and 890 μm. Drug content of all the formulated batches was found to be in the range of 89.43% to 92.02%. Drug release from coated pellets 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 (Figure 2) and correlation coefficient (r<sup>2</sup>) values as per *in-vitro* release kinetic models and drug release rate constants with transport mechanism were reported in table 10 and 11 respectively. Time for 2%, 30%, 50% & 90% drug, mean dissolution time and Similarity factor (f2) values of test formulations were compared against the marketed formulation Vegaz OD 1.2g tablets and the results given in table 12.

Formulation MSP06 which is composed of Eudragit® RS PO coating and formulation MSP07 which contains combination of Eudragit® RS PO and Eudragit® S 100 in 3:1 ratio in coating were not able to retard drug release in 0.1 N Hydrochloric acid and started significant drug release in 0.1 N Hydrochloric acid. Premature drug release from these formulations can be attributed to Eudragit® RS PO polymer which is a rate controlling polymer and do not possess any gastro-resistant characteristics. Same phenomenon is reflected in time for 2% drug release (T2%) values of MSP06 and MSP07 formulations showing T2% values of 0.08 & 0.57 hours respectively, which indicates significant

Table: 7 Results of Micromeritic Parameters of Drug Polymer Premix

Trial No.	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio	Angle of Repose (Degrees)
API	0.164	0.368	55.43	2.24	53.29
MSP01	0.478	0.567	15.70	1.19	32.08
MSP02	0.380	0.511	25.64	1.34	35.36
MSP03	0.538	0.612	12.09	1.14	28.64
MSP04	0.493	0.591	16.58	1.20	31.81
MSP05	0.358	0.526	31.94	1.47	36.07

Table: 8 Results of Physico-chemical Properties of Core Pellets

Trial No.	Mean Pellet Size ( $\mu\text{m}$ )	Friability (%)	Drug Content (%)	Drug Loading Efficiency (%)
MSP01	887	0.34	82.04 $\pm$ 1.32	95.97
MSP02	922	0.58	71.15 $\pm$ 2.06	93.11
MSP03	876	0.14	96.83 $\pm$ 1.84	99.65
MSP04	891	0.22	82.21 $\pm$ 2.92	97.76
MSP05	913	0.53	70.62 $\pm$ 2.37	90.59

Table: 9 Results of Physico-chemical Properties of Coated Pellets

Trial No.	Mean Pellet Size ( $\mu\text{m}$ )	Drug Content (%)
MSP06	890	91.08 $\pm$ 2.14
MSP07	878	89.43 $\pm$ 1.82
MSP08	885	89.62 $\pm$ 1.99
MSP09	889	90.94 $\pm$ 2.62
MSP10	882	92.02 $\pm$ 2.08

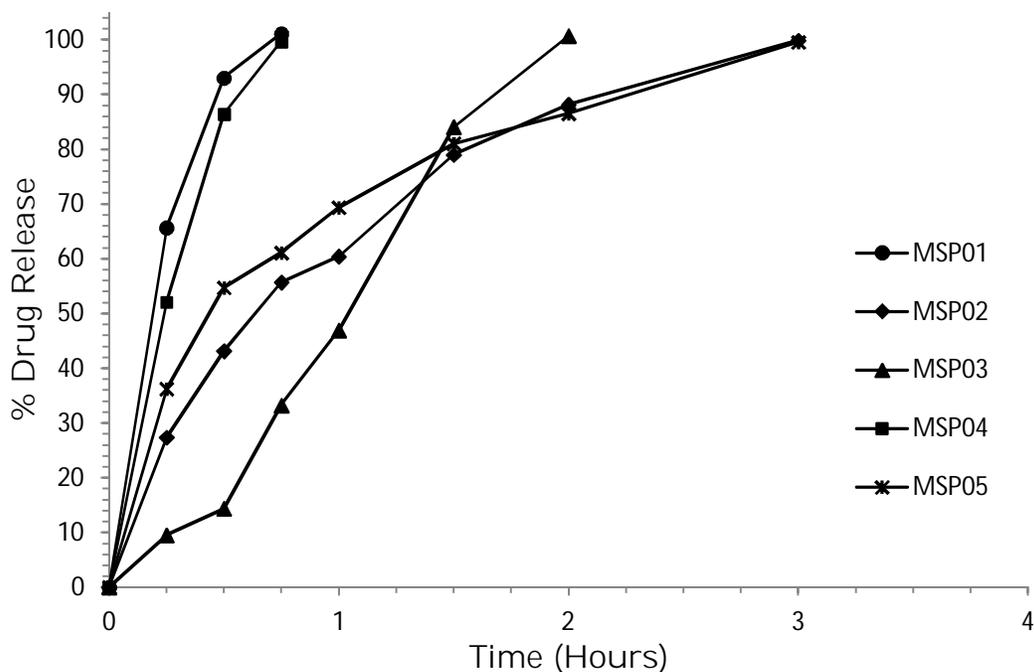


Figure: 1 In-vitro % Drug Release Profiles for Core Pellets in pH 7.2 Phosphate buffer

**Table: 10 Correlation Coefficient Values of Coated Pellets as per *In-vitro* Release Kinetic Models**

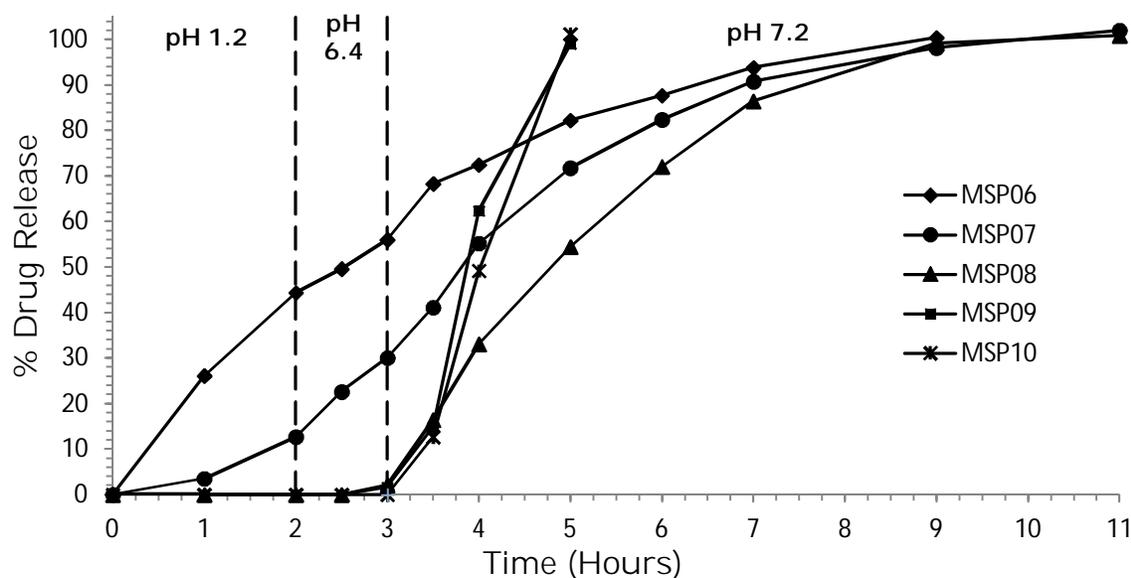
Trial No.	Correlation Coefficient ( $r^2$ ) Values				
	Zero Order	First Order	Higuchi Model	Erosion Model	Peppas Model
MSP06	0.892	0.977	0.981	0.996	0.976
MSP07	0.911	0.905	0.879	0.964	0.925
MSP08	0.884	0.967	0.936	0.988	0.745
MSP09	0.924	0.730	0.905	0.747	0.994
MSP10	0.983	0.893	0.977	0.904	0.902

**Table: 11 Drug Release Kinetics of Matrix Core Tablets**

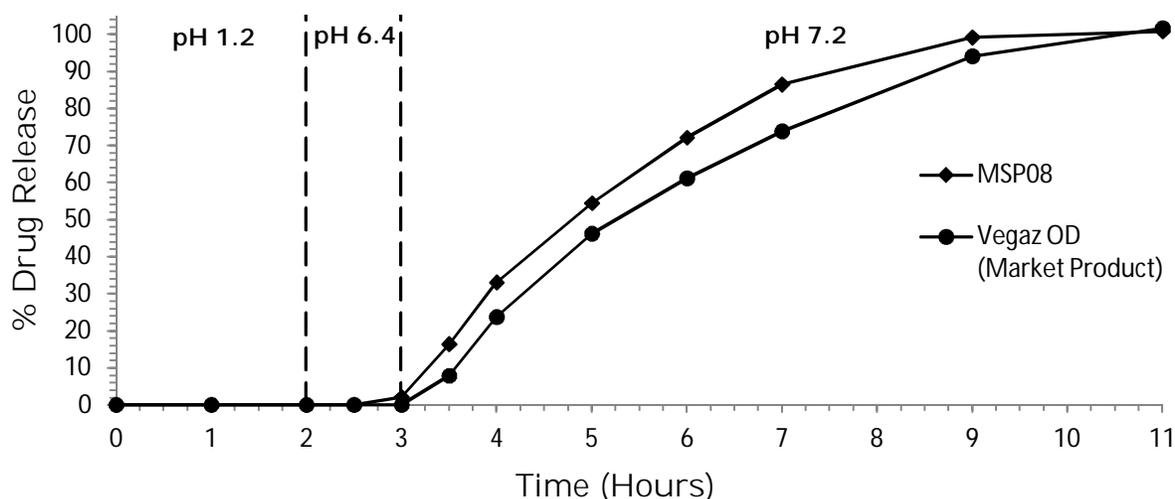
Trial No.	Release Rate Constant		Peppas Release Exponent (n)	Drug Transport Mechanism
	$K_0$ (mg/h)	$K_1$ ( $h^{-1}$ )		
MSP06	10.803	0.388	0.735	First order, non-fickian diffusion
MSP07	10.964	0.442	1.928	Zero order, super case II transport
MSP08	13.156	0.446	4.581	First order, super case II transport
MSP09	43.541	0.616	12.690	Zero order, super case II transport
MSP10	52.697	0.677	5.562	Zero order, super case II transport

**Table: 12 Parameters for Characterizing Drug Release from Coated Pellets**

Trial No.	T2%	T30%	T50%	T90%	MDT (hr)	Similarity factor ( $f_2$ )
MSP06	0.08	1.21	2.53	6.38	2.91	19.40
MSP07	0.57	3.00	3.81	6.91	4.24	33.31
MSP08	2.97	3.91	4.79	7.56	5.13	54.12
MSP09	3.01	3.66	3.87	4.75	3.92	24.10
MSP10	3.08	3.74	4.02	4.78	3.89	22.70
Vegaz OD	3.13	4.28	5.26	8.60	5.68	-



**Figure: 2 *In-vitro* % Drug Release Profiles of Coated Pellets Marketed Formulation**



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

drug release in gastric environment. Formulation MSP09 which contains combination of Eudragit<sup>®</sup> RS PO and Eudragit<sup>®</sup> S 100 in 1:3 ratio in coating and MSP10 formulation which is composed of Eudragit<sup>®</sup> S 100 in coating were able to retard drug release in 0.1 N Hydrochloric acid and pH 6.4 Phosphate buffer, but the drug release in pH 7.2 Phosphate buffer was rapid. This release behaviour can be assigned to Eudragit<sup>®</sup> S 100 polymer which provides gastric resistance but lacks rate controlling properties and similar indication can be observed with time for 90% drug release (T90%) values of MSP09 and MSP10 formulations showing T90% values of 3.92 & 3.89 hours respectively, which indicates the dose dumping with uncontrolled drug release once entered into the colonic pH environment. Formulation MSP08 which consists of combination of Eudragit<sup>®</sup> RS PO and Eudragit<sup>®</sup> S100 in 1:1 ratio in coating was able to achieve desired target dissolution profile with no significant drug release in both 0.1 N Hydrochloric acid and pH 6.4 Phosphate buffer and drug release in pH 7.2 Phosphate buffer is extended up to 6 hours. Observed T2% value 2.91 hours which is near to 3 hours indicates that, there is no significant drug release below pH 7.2 and based on the T30%, T50% & T90% values it can be concluded that the drug release is slow and spread over 6 hours. Mean dissolution time (MDT) is in the range of 2.91 - 5.13 hours for test formulations and among this MDT of MSP08 is close to reference product MDT of 5.68 hours. Similarity factor (f<sub>2</sub>) values for MSP06, MSP07, MSP08, MSP09 & MSP10 formulations are 19.40, 33.31, 54.12, 24.10 & 22.70 correspondingly and formulation MSP08 showed highest Similarity factor (f<sub>2</sub>) value meeting acceptance criteria with best dissolution profile matching against reference product.

## CONCLUSION

It was concluded from the present study that appropriate combination of a hydrophilic hydrogel polymers (HPMC K100 M), pH-dependent (Eudragit<sup>®</sup> S 100) and rate controlling (Eudragit<sup>®</sup> RS PO) polymers were suitable for preparing high-load Mesalamine multi-particulate formulations for colon-targeted controlled drug delivery. The granulation with HPMC K100 M and subsequent milling to prepare drug polymer premix is found to be suitable to significantly improve the flow properties and bulk density and high drug loading efficiencies supported the suitability of centrifugal drug layering technique. Appropriate combination of a pH-dependent (Eudragit<sup>®</sup> S 100) and rate controlling (Eudragit<sup>®</sup> RS PO) polymers in control release coating can be used to protect the drug being released in the upper region of the GI system and subsequent prolonged release profile suitable for once daily administration in colonic pH environment. The optimised formulation MSP08 was developed by employing HPMC K100 M during drug polymer premix preparation and Eudragit<sup>®</sup> S 100 & Eudragit<sup>®</sup> RS PO polymers in 1:1 ratio in control release coating. The results of dissolution studies indicated that formulation MSP08, the most successful of the study; exhibited drug release pattern very close to dissolution profile of marketed once a day formulation, Vegaz OD 1.2g tablets and able to retard drug release in upper part of the GIT and sustain the drug release in colonic region. The added major advantages of the developed high-load Mesalamine multi-particulate formulation is, unlike currently available Multi-Matrix System (MMX) tablets with delayed-release technology, dose of the multi-particulate formulations can be titrated individually and can be easily administered in large

doses to geriatric patients with difficulty in swallowing large tablets or capsules. Hence it can be concluded that, a high-dose once daily Mesalamine multi-particulate system for colon-targeted controlled drug delivery is achieved.

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