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Research Article

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Design, Development and Characterization of Extended Release Multiunit Particulate System of Anti-Inflammatory Drug

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ABSTRACT

Multi unit particulate system has long been employed to improve the bioavailability of drugs. Mesalamine pellets were prepared by Coating drug solution on sugar sphere followed by various functional coating. The influence of rate controlling membrane made up of Eudragit RSPO and Eudragit RLPO in combination with delay release polymer coating with Eudragit L_{100} in different proportions on drug release kinetics was studied. Pellets were for the various parameter like Physical characteristics, assay and *in-vitro* dissolution profile. The study confirmed that mesalamine can be delivered by multi unit particulate system into lower part of intestine. Optimized formulations were evaluated for In-vitro release profile. The optimized formula was stable at accelerated storage condition 40°C / 75 % RH. Prepared Pellets can be used in the treatment of the ulcerative colitis.

Keywords: Mesalamine, Eudragit RSPO and Eudragit RLPO, Eudragit $L_{100,}$ *in vitro* release.

INTRODUCTION

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi spherical units, referred to as pellets [1]. Pellets range in size, typically, between 0.5 – 1.5 mm, though other sizes could be prepared. Pellets are for pharmaceutical purposes and produced primarily for the purpose of oral controlled-release dosage forms having gastro resistant or sustained-release properties or the capability of site-specific drug delivery. For such purposes, coated pellets are administered in the form of hard gelatin capsules or disintegrating tablets that quickly liberate their contents of pellets in the stomach. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function. Pellets may be manufactured by using different methods according to the application and the choice of producer. The most widely used processes are extrusion and Spheronization and solution or suspension layering, and powder layering. One of the new classes of drug delivery systems, multi unit particulate system, which offer many advantages over conventional dosage forms, like increased GI residence, possibility of releasing drug at a slow and constant rate, accurate dosing and increased shelf life. [2- 3]

Mesalamine (5-aminosalicylic acid) is the active component of sulfasalazine; the specific mechanism of action of mesalamine is unknown; however, it is thought that it modulates local chemical mediators of the inflammatory response, especially leukotrienes; action appears topical rather than systemic. [4]

The aim of the present investigation is to study the drug release kinetics of mesalamine from pellets with rate controlling membrane made up of Eudragit RSPO and Eudragit RLPO.

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MATERIALS AND METHODS

Mesalamine was obtained as gift sample from Cadila health care Ltd. Moraiya, Gujarat. Eudragit RSPO, Eudragit RLPO and Eudragit L_{100} were obtained as a gift sample from Relax Pharmaceuticals, Baroda, Gujarat.

Preparation of drug layered Pellets

Drug layered pellets were prepared by aqueous drug layering coating method. In the present study two different type of drug layered pellets. F_1 and F_2, were prepared. The detail compositions are given in Table 1.

Preparation of delay release coating on ER polymer coating

Table 1: Formulation of Aqueous drug layering on Sugar sphere.

Ingredients	F01 (530%)	F02 (796%)
Sugar sphere	600	400
Mesalamine	3000	3000
HPMC 50 cps	144(4% w/w)	144(4% w/w)
Talc	24	24
PEG - 400	16	16
Purified water	9552	9552
Total	3784	3584

All quantity in gm

Table 2: Formulation of extended release polymer coating on drug loaded pellets.

Ingredients	F02A (10%) (7:3)	F02B (12%) (6:4)	F02C (10%)	F02D (14%)	F02E (7%) (7:3)	F02F (10%) (7:3)	F02G (15%)
Drug loaded pellets (F01 & 02)	250	250	250	250	250	250	275
Ethyl Cellulose 7 cps	17.5	18.0	--	--	--	--	--
Hypromellose 3 cps	7.5	12.0	--	--	--	--	--
Eudragit NE 30 D*	--	--	83.30	--	--	--	--
Eudragit RLPO	--	--	--	35.0	5.25	7.5	--
Eudragit RSPO	--	--	--	--	12.25	17.5	--
Eudragit L_{100}	--	--	--	--	--	--	41.25
Acetyl mono Glycerate	1.0	1.2	--	--	--	--	--
Tri ethyl Citrate (20%)	--	--	--	7.0	3.50	5.0	8.25
Talc (30%)	--	--	7.50	10.5	5.25	7.5	12.38
Isopropyl Alcohol	222.3	266.76	--	301.87	151.0	215.6	569.2
Acetone	--	--	--	301.87	150.0	215.6	--
Methylene Chloride	222.3	266.76	--	--	--	--	--
Purified water	49.4	59.28	83.4	--	--	--	142.30
Total							

All quantity in gm

- Solid of 25 g of Eudragit NE 30 D ≈ 83.30 g of Eudragit NE 30 D Solution

Preparation of extended release polymer coating

The pellets were taken from the optimized drug loaded pellets. Here formulation for polymer coating on drug loaded pellets was carried out by taking different coating levels. Different concentration of different polymers used for controlling the release of drug from the drug loaded pellets. The composition of formulation of trial series for obtaining extended drug release from pellets was shown in the Table 2.

This delay release coating was applied on the extended release polymer coated pellets because formulation have target to release the drug in colon for local effect. The delay release coating will be done with Eudragit L_{100}. The film of Eudragit L_{100} is not degrade in stomach and protect the formulation from the acidic environment and also soluble in basic pH. So, different coating was done with the Eudragit L_{100} polymer to get the desired release profile. The most recommended plasticizer is Triethyl citrate in the concentration of 20%. The detail compositions are given in Table 3.

Evaluation of pellets [5, 6, 7]

The above pellets were evaluated for various parameters like, Physical Description, Density, Particle size Analysis, Aspect ratio, Assay, Related Substances and In-vitro dissolution profile. The pellets were free flowing; light pink in color with rough surface. Particle size analysis was done by the Sieve analysis by USP sieve shaker. Pellets were passed from the #16 and retained from the #30 sieve. Assay of mesalamine was carried out by the HPLC method by dissolving the drug to 150 ml of water and sonicate with occasional shaking for about 45 minutes. . Make volume up to the mark with water. Dilute 5.0 ml 0f this solution to 25 ml with water and mix. Filter the solution through 0.45 µm Millipore PVDF filter; collect the filtrate and analyzed for mesalamine content at 220 nm in HPLC.

***In-vitro* Release studies**

In-vitro drug dissolution study was performed for the % drug release of the mesalamine from the formulation at the regular time interval. The detail of % drug release from various formulations is given in Table 4.

Capsule filling of pellets

Capsules were filled with two different kinds of pellets in different percentages. The detail of capsule filling was given in Table 5.

Stability study

The optimized formulation was packed in aluminum foil. It was than stored at 40°C / 75 % RH and 60°C / 85 % RH according to ICH. Samples were withdrawn after three month and evaluated for change in drug release pattern. The detail of stability study was given in Table 6.

Table 3: Formulations for Delay release Pellets

Ingredients	$F02F_a$ (5% w/w)	$F02F_b$ (10% w/w)	$F02F_c$ (15% w/w)
SR coated pellets (F08)	300	300	300
Eudragit L_{100}	15	30	45.0
Talc (30%)	4.5	9.0	13.5
Tri ethyl citrate (20%)	3.0	6.0	9.00
Isopropyl Alcohol	207.0	414.0	621.0
Water	51.5	103.0	155.0
Total	322.5	345.0	367.5

All quantities are in gm

Table 4: Result of in vitro drug release from pellets

Medium	TIME (Hrs.)	% DRUG RELEASE F02G	F02Fc	F02G (20%) and F02Fc (80%)
0.1 N HCl	0	0	0	0
	2	0	0	0
pH 6.8 Phosphate Buffer	3	17.3	36.1	36.2
	4	31.8	46.9	50.7
	5	45.7	57.7	63.5
	6	58.8	67.3	71.2
	7	70.7	77.6	79.9
	8	78	80.1	84.7

Above results are averages of the 6 samples.

Table 5: Filled composition in Capsule

Ingredients	Quantity	Quantity per capsule
Pellets of F02Fc	80%	485.2 mg
Pellets of F02G	20%	110.0 mg
Total	100%	595.2

Table 6: Dissolution profile of stability batch

Medium	TIME (Hrs.)	% DRUG RELEASE		
		Controlled	40° C / 75% RH	60° C / 85% RH
0.1 N HCl	0	0.0	0.0	0.0
	2	0.0	0.0	0.0
	3	36.2	36.1	35.9
	4	50.7	50.5	50.3
pH 6.8 Phospahte Buffer	5	63.5	63.6	63.4
	6	71.2	71.0	70.9
	7	79.9	79.7	79.5
	8	84.7	84.5	84.3

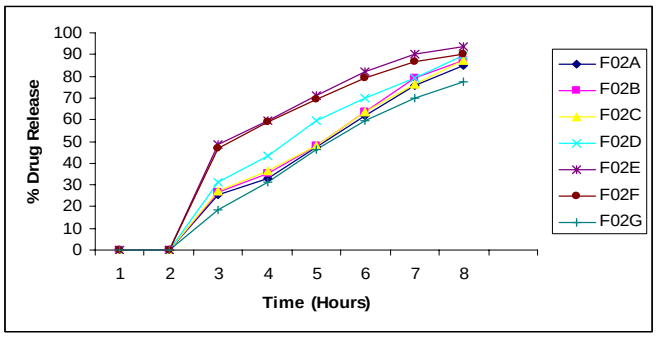

Fig. 1: Graphical presentation of %Drug dissolution versus Time (h)

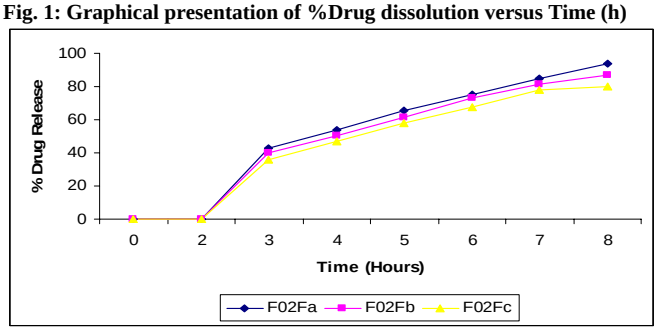

Fig. 2: Graphical presentation of %Drug dissolution versus Time (h)

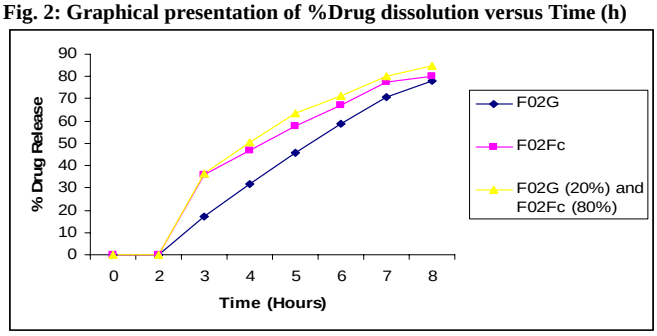

Fig. 3: Graphical presentation of %Drug dissolution versus Time (h)

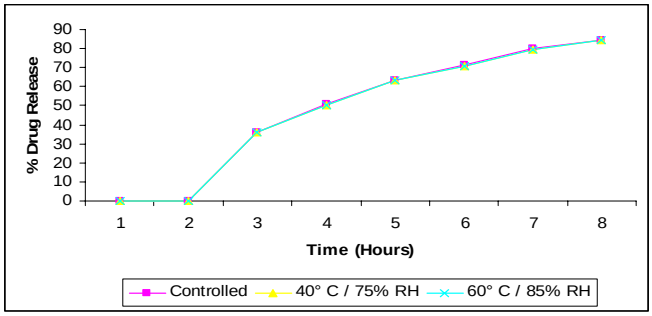

Fig. 4: Graphical presentation of % Drug dissolution of stability batch

RESULT AND DISSCUSSION

The prepared pellets were free flowing, light pink in color, uniform in appearance and with slightly rough surface. The drug content was consistent in all batches. The formulation containing 796% drug loading on sugar sphere followed by coated with Eudragit L100 (15%) and Eudragit RSPO & RLPO (10% in ratio of 7:3) separately. Eudragit RSPO & RLPO polymer Coated pellets were coated with delay release polymer Eudragit L_{100} (15%). The pellets were filled in hard gelatin capsule and evaluated for In-vitro drug release study. Multiunit particulate drug delivery system gives unique release pattern. This product was further subjected to stability study, the results of which indicated no significant change with respect to Shape, color, surface and in vitro drug release.

Developed pellets achieved the targets of present study, such as increased residence time, prolonged release profile, reduction in frequency of administration, an thus improve patient compliance.

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