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Original Research Article

Formulation and Evaluation of Extended Release Matrix Tablets of Metoprolol Succinate Using Natural Polymers

Vivel Battu[1], S. Padma Priya[2]

[1]Department of Pharmaceutics, Vels College of Pharmacy, Chennai
[2]Department of Pharmaceutics, College of Pharmacy,
Mother Theresa Postgraduate and Research Institute of Health Sciences, Puducherry, India

Corresponding Author: S. Padma Priya

ABSTRACT

The objective of this study was to design and evaluate an oral extended drug delivery system for Metoprolol succinate using natural hydrophilic gums such as Xanthan Gum, Guar Gum, Pectin and Carrageenan as a release modifier. Twenty four batches were prepared by using in combination of 1:1, 1:2 and 2:1 ratios of Natural polymers and Avicel RS 581. Matrix tablets were prepared by wet granulation method and granules are coated with rate release polymers like Ethyl cellulose and Hydroxy propyl methyl cellulose. The formulations were evaluated for angle of repose, bulk density, tapped density, Compressibility Index, % LOD (Pre compression properties) and weight variation, content uniformity, friability, hardness, thickness, *in vitro* drug release studies(Post compression properties). Among the formulations studied formulation H - MSG_1 containing combination of Guar Gum and Avicel RS 581 (1:1) showed extended release of drug for 24 hrs with cumulative percent release of 99.46% ± 0.01%. The kinetic treatment showed that the optimized formulation followed first order kinetics and the release exponent (n) 1.199 through Korsmeyer and Peppas equation shown that the formulation follows super case II. The matrix formulation H – MSG_1 showed sustained release of Metoprolol succinate by the diffusion mechanism. On comparison with the marketed formulation, the best formulation H - MSG_1showed similarity factor (f_2) of 80.09 indicted more significant in drug release behaviour.

Keywords: Extended release, Xanthan Gum, Guar gum, Pectin, Carrageenan, Coated granules, in vitro drug release, Similarity factor.

INTRODUCTION

Among various dosage forms, matrix tablets are widely accepted for oral Extended release (ER) as they are simple and easy formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed (Chien, 2005). In fact, matrix is defined as a well composite of one or more drugs with a gelling agent i.e. hydrophilic polymer. Past research therefore acknowledged various hydrophilic natural gums like Agar, Konjac, Guar Gum, Chitosan, Sodium alginate and Locust bean gum in alone or in combination (Derle *et al*., 2006). Hydrophilic natural gums are high molecular weight substances, usually insoluble in alcohol, but can be made to dissolve, swell or disperse in water to give viscous or mucilaginous solutions. The varied structure and chemistry of polymers provide ample opportunity for complexes to form in solution (Salsa et al., 1997). When solutions of polysaccharides (hydrophilic gums) are mixed, they interact with each other; this can result in an increase in viscosity, which becomes greater than the viscosity of each solution individually.

Under certain conditions, they may even form a gel. Such a phenomenon is often called as rheological synergism. A standard technique for manufacturing oral sustained-release dosage forms consists of coating drug-containing granules or beads with aqueous, colloidal latex or pseudolatex polymeric dispersions (Lordi, 1986). A certain amount of plasticizer is always added to the polymers in order to improve the mechanical properties of the coating shell. (Lee and Robinson, 1978) Metoprolol succinate, β_1- selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6hrs and in normal course of therapy drug administration is required every 4-6hrs, thus warrants the use of extended release formulation.

In the present study, the influences of various types of natural polymers like Xanthan Gum, Guar Gum, Pectin and Carrageenan upon the release of Metoprolol Succinate from its matrix and the selection of best polymer suitable for extended release of drug.

MATERIALS AND METHODS

Materials:

Metoprolol succinate was obtained from Tristar pharmaceutical Ltd, Pondicherry as a gift sample. The Xanthan gum, Guar Gum and Pectin were obtained from Loba Chemie, Mumbai and Carrageenan was obtained from HiMedia, Mumbai. Solvents and all other reagents used were of analytical grade. Double distilled water was used throughout the study.

Preparation of Matrix tablet:

The matrix tablets were prepared by granule coated technology. Twelve formulations (MSX_1, MSX_2, MSX_3, MSG_1, MSG_2, MSG_3, MSP_1, MSP_2, MSP_3, MSC_1, MSC_2, and MSC3) of varying constituents were prepared as shown in table 1. The polymer used for the extended release is the combination of Avicel RC 581 and the natural polymers like Xanthan Gum, Guar Gum, Pectin and Carrageenan. First three formulations MSX_1, MSX_2, MSX_3 Consisted of 1:1, 1:2 and 2:1 ratios of Xanthan Gum and Avicel RC 581. The other formulations are also chosen like in this manner. (Naikwade et al., 2008)

Preparation of drug loaded granules

Metoprolol succinate and all other polymers sifted through sieve no. 40.The sifted materials were hand mixed in a polythene bag. PVP K 30 (5%) was dissolved in Isopropyl alcohol and was used for granulation. The mixed materials were granulated using granulating solution. The mixture is mixed thoroughly to get a damp mass, passed through sieve no.22. The above granules were air dried for 15 min. And finally dried in hot air oven (SEMCO, Chennai) at 45^o-50^oc till LOD is < 2 %.

Preparation of coated granules

Ethyl cellulose and Hydroxypropyl methyl cellulose are selected for coating of granules. The coat polymer solutions were prepared in a mixture of Methylene chloride and Isopropyl alcohol in the ratio of 3:2. 10% Dibutyl phthalate was added as a plasticizer. The quantity of granules equivalent to the therapeutic dose of metoprolol succinate are calculated by the means of assay and the same quantity of granules are coated. Ethyl cellulose of 5% and Hydroxyl propyl methyl cellulose of 4% are used for coating and the other ingredients used are listed in table 2 and 3.

Ethyl cellulose (5%) coated twelve formulations of Xanthan Gum, Guar Gum, Pectin and Carrageenan granules and Hydroxy propyl methyl cellulose (4%) coated twelve formulations of Xanthan gum, Guar Gum, Pectin and Carrageenan granules were transferred to compression stage.To this lubricated granules sodium starch glycolate as a superdisintegrant was added and made the total weight to 350mg and those coated granules were compressed in 9 mm circular punches using rotary punching machine.

Table 1 Composition of Metoprolol Succinate Granules

INGREDIENTS	FORMULATIONS											
	QUANTITY (mg)											
	1:1	1:2	2:1	1:1	1:2	2:1	1:1	1:2	2:1	1:1	1:2	2:1
	MSX_1	MSX_2	MSX_3	MSG_1	MSG_2	MSG_3	MSP_1	MSP_2	MSP_3	MSC_1	MSC_2	MSC_3
Metoprolol succinate	100	100	100	100	100	100	100	100	100	100	100	100
Xanthan Gum	100	66.4	133.6	-	-	-	-	-	-	-	-	-
Guar Gum	-	-	-	100	66.4	133.6	-	-	-	-	-	-
Pectin	-	-	-	-	-	-	100	66.4	133.6	-	-	-
Carrageenan	-	-	-	-	-	-	-	-	-	100	66.4	133.6
Avicel RC 581	100	133.6	66.4	100	133.6	66.4	100	133.6	66.4	100	133.6	66.4
Poly vinyl pyrrolidone K30	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Isopropyl alcohol (ml)	5	5	5	5	5	5	5	5	5	5	5	5
Total weight (mg)	300.25	300.25	300.25	300.25	300.25	300.25	300.25	300.25	300.25	300.25	300.25	300.25

Table 2 Formula for Ethyl cellulose coating of formulations

INGREDIENTS	FORMULATIONS											
	QUANTITY (mg)											
	E - MSX_1	E - MSX_2	E - MSX_3	E - MSG_1	E - MSG_2	E - MSG_3	E - MSP_1	E - MSP_2	E - MSP_3	E - MSC_1	E - MSC_2	E - MSC_3
Drug loaded granules Metoprolol quantity equivalent to 100 mg	294.82	293.04	298.44	295.14	299.04	297.84	296.04	292.74	298.74	289.14	294.54	297.84
Ethyl Cellulose	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Dibutyl phthalate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methylene Chloride	30	30	30	30	30	30	30	30	30	30	30	30
Isopropyl Alcohol	20	20	20	20	20	20	20	20	20	20	20	20
Total weight build up (mg)	297.82	296.04	301.44	298.14	302.04	300.84	296.04	295.74	301.74	292.14	297.54	300.84

Table 3 Formula for Hydroxy propyl methyl cellulose coating of formulations

INGREDIENTS	FORMULATIONS											
	QUANTITY (mg)											
	H - MSX_1	H - MSX_2	H - MSX_3	H - MSG_1	H - MSG_2	H - MSG_3	H - MSP_1	H - MSP_2	H - MSP_3	H - MSC_1	H - MSC_2	H - MSC_3
Drug loaded granules Metoprolol quantity equivalent to 100 mg	294.82	293.04	298.44	295.14	299.04	297.84	296.04	292.74	298.74	289.14	294.54	297.84
HPMC E 15	2	2	2	2	2	2	2	2	2	2	2	2
Dibutyl phthalate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methylene Chloride	30	30	30	30	30	30	30	30	30	30	30	30
Isopropyl Alcohol	20	20	20	20	20	20	20	20	20	20	20	20
Total weight build up (mg)	297.32	295.64	299.94	297.64	301.54	300.34	295.04	295.24	301.24	291.64	297.04	300.34

Table 4 DSC thermogram values

Name of ingredients and physical mixtures used in formulation	Temperature at which peak obtained
Metoprolol succinate	159.2^0C
Xanthan gum	108.9^0C
Guar gum	101.6^0C
Pectin	91.1^0C
Carrageenan	92.0^0C
Metoprolol succinate + Xanthan gum	155.3^0C
Metoprolol succinate + Guar gum	159.7^0C
Metoprolol succinate + Pectin	$160.^0$C
Metoprolol succinate + Carrageenan	152^0C

Table 5 Pre-compression properties of Metoprolol Succinate Uncoated Granules

FORMULATIONS	ANGLE OF REPOSE	BULK DENSITY(g/c.c)	TAPPED DENSITY(g/c.c)	COMPRESSIBILITY INDEX (%)	% LOSS ON DRYING
MSX_1	28.38 ± 0.21	0.64 ± 0.01	0.72 ± 0.01	14.28 ± 0.3	0.64 ± 0.02
MSX_2	26.45 ± 0.48	0.66 ± 0.03	0.71 ± 0.01	13.88 ± 0.6	0.82 ± 0.36
MSX_3	27.31 ± 0.17	0.66 ± 0.02	0.74 ± 0.02	15.14 ± 0.6	1.06 ± 0.41
MSG_1	27.08 ± 1.06	0.65 ± 0.02	0.74 ± 0.01	15.31 ± 0.08	0.96 ± 0.58
MSG_2	26.64 ± 0.43	0.63 ± 0.01	0.74 ± 0.03	14.46 ± 0.4	0.62 ± 0.02
MSG_3	27.48 ± 0.71	0.64 ± 0.01	0.73 ± 0.03	14.34 ± 0.02	0.88 ± 0.37
MSP_1	27.24 ± 0.17	0.66 ± 0.03	0.73 ± 0.03	14.60 ± 0.24	1.15 ± 0.51
MSP_2	28.33 ± 0.31	0.63 ± 0.01	0.75 ± 0.04	14.57 ± 0.54	1.1 ± 0.40
MSP_3	26.27 ± 0.13	0.64 ± 0.01	0.73 ± 0.03	14.48 ± 0.21	1.03 ± 0.34
MSC_1	27.33 ± 0.16	0.64 ± 0.01	0.71 ± 0.05	15.56 ± 0.36	1.08 ± 0.40
MSC_2	29.26 ± 0.12	0.64 ± 0.01	0.72 ± 0.01	15.57 ± 0.24	1.00 ± 0.34
MSC_3	27.19 ± 0.09	0.66 ± 0.02	0.74 ± 0.03	14.08 ± 0.20	0.82 ± 0.46

n=3, the values are mean ± S.D, $p < 0.001$

Table 6 Pre-compression properties of Metoprolol Succinate Ethyl cellulose coated Granules

FORMULATIONS	ANGLE OF REPOSE	BULK DENSITY(g/c.c)	TAPPED DENSITY(g/c.c)	COMPRESSIBILITY INDEX (%)	% LOSS ON DRYING
E-MSX_1	26.25 ± 0.11	0.68 ± 0.01	0.76 ±0.01	15.39 ± 0.21	0.64 ± 0.02
E-MSX_2	25.13 ± 0.01	0.68 ± 0.01	0.74 ± 0.01	15.39 ± 0.21	0.82 ± 0.36
E-MSX_3	27.43 ± 0.50	0.65 ± 0.02	0.74 ± 0.03	13.31 ± 0.08	1.06 ± 0.41
E-MSG_1	29.38 ± 0.26	0.63 ± 0.02	0.72 ± 0.01	14.34 ± 0.02	0.96 ±0.58
E-MSG_2	28.40 ± 0.25	0.63 ± 0.01	0.73 ± 0.02	14.43 ± 0.38	0.63 ± 0.02
E-MSG_3	27.13 ± 0.01	0.65 ± 0.02	0.73 ± 0.01	13.31 ± 0.08	0.89 ± 0.37
E-MSP_1	27.38 ± 0.24	0.66 ± 0.02	0.72 ± 0.01	15.09 ± 0.39	1.16 ± 0.51
E-MSP_2	27.13 ± 0.02	0.66 ± 0.02	0.74 ± 0.03	14.25 ± 0.06	1.10 ±0.40
E-MSP_3	28.38 ± 0.15	0.65 ± 0.01	0.74 ± 0.03	15.35 ± 0.01	1.03 ±0.34
E-MSC_1	29.44 ± 0.18	0.63 ± 0.01	0.75 ± 0.04	14.33 ± 0.02	1.08 ±0.40
E-MSC_2	26.37 ± 0.06	0.65 ± 0.03	0.75 ± 0.02	15.55 ± 0.37	1.00 ±0.34
E-MSC_3	26.26 ± 0.10	0.62 ± 0.01	0.73 ± 0.03	15.29 ±0.04	0.82 ± 0.36

n=3, the values are mean ± S.D, $p < 0.001$

Table 7 Pre-compression properties of Metoprolol Succinate HPMC coated Granules

FORMULATIONS	ANGLE OF REPOSE	BULK DENSITY(g/c.c)	TAPPED DENSITY(g/c.c)	COMPRESSIBILITY INDEX (%)	% LOSS ON DRYING
H-MSX_1	25.22 ± 0.16	0.62 ± 0.01	0.74 ± 0.03	15.31 ± 0.1	1.02 ± 0.36
H-MSX_2	26.33 ± 0.02	0.63 ± 0.01	0.72 ± 0.02	14.28 ± 1.05	1.08 ± 0.40
H-MSX_3	26.33 ± 0.22	0.65 ±0.12	0.73 ± 0.01	14.55 ± 1.00	1.10 ± 0.40
H-MSG_1	26.27 ± 0.11	0.64 ± 0.01	0.72 ± 0.01	14.80 ± 1.17	1.03 ± 0.36
H-MSG_2	27.13 ± 0.02	0.66 ± 0.02	0.73 ± 0.03	14.26 ± 0.05	1.08 ± 0.34
H-MSG_3	26.23 ± 0.18	0.67 ± 0.03	0.75 ± 0.03	14.73 ± 0.50	1.06 ± 0.37
H-MSP_1	25.14 ± 0.03	0.64 ± 0.02	0.74 ± 1.36	14.78 ± 0.73	0.87 ± 0.39
H-MSP_2	25.30 ± 0.28	0.65 ± 0.01	0.76 ± 0.01	14.20 ± 0.90	0.85 ± 0.33
H-MSP_3	25.28 ± 0.13	0.64 ± 0.01	0.75 ± 0.01	15.00 ± 1.14	0.90 ± 0.47
H-MSC_1	25.36 ± 0.32	0.63 ± 0.01	0.75 ± 0.03	15.09 ± 0.69	1.11 ± 0.41
H-MSC_2	25.45 ± 0.15	0.63 ± 0.03	0.75 ± 0.04	15.32 ± 1.05	1.09 ± 0.40
H-MSC_3	25.20 ± 0.10	0.62 ± 0.03	0.74 ± 0.03	16.52 ± 0.30	1.07 ± 0.41

n=3, the values are mean ± S.D, $p < 0.001$

Table 8 Post compression properties of Ethyl cellulose granule coated matrix tablets

FORMULATIONS	THICKNESS (mm)	WEIGHT VARIATION(mg)	HARDNESS(kg/cm2)	FRIABILITY (%)	ASSAY (%)
E-MSX_1	3.52 ± 0.11	352.00 ± 1	5.53 ±0.11	1.31 ± 0.10	100.19 ± 0.97
E-MSX_2	3.57 ± 0.13	349.33 ± 2.08	5.50 ± 0.17	1.24 ± 0.15	99.19 ± 0.51
E-MSX_3	3.35 ± 0.17	352.00 ± 2	5.47 ± 0.30	1.15 ± 0.07	98.42 ± 1.01
E-MSG_1	3.15 ± 0.05	350.33 ±2.51	5.40 ± 0.17	1.35 ±0.05	97.77 ± 1.26
E-MSG_2	3.48 ± 0.05	351.33 ± 2.30	5.20 ± 0.26	1.44 ± 0.02	97.53 ± 1.82
E-MSG_3	3.53 ± 0.28	350.33 ± 1.52	5.37 ± 0.20	1.38 ± 0.06	99.82 ± 0.33
E-MSP_1	3.54 ± 0.18	351.67 ± 1.15	5.13 ± 0.05	1.30 ± 0.12	100.55 ± 0.58
E-MSP_2	3.50 ± 0.12	347.33 ± 1.52	5.17 ± 0.20	1.22 ± 0.10	100.25 ± 2.94
E-MSP_3	3.41 ± 0.25	352.67 ± 1.15	5.33 ± 0.05	1.29 ± 0.15	99.40 ± 0.94
E-MSC_1	3.49 ± 0.30	351.00 ± 2.64	5.67 ± 0.25	1.31 ± 0.10	101.63 ±1.50
E-MSC_2	3.61 ± 0.05	352.33 ± 2.08	5.63 ±0.28	1.18 ± 0.12	100.05 ± 0.36
E-MSC_3	3.61 ± 0.06	351.00 ± 2.64	5.10 ± 0.21	1.32 ± 0.18	100.47 ± 0.92

n=3, the values are mean ± S.D, $p < 0.001$

Table 9 Post compression properties of Hydroxy propyl methyl cellulose granule coated matrix tablets

FORMULATIONS	THICKNESS (mm)	WEIGHT VARIATION(mg)	HARDNESS(kg/cm2)	FRIABILITY (%)	ASSAY (%)
H-MSX$_1$	3.60 ± 0.19	352.33 ± 1.52	5.57 ± 0.25	1.31 ±0.10	100.49 ± 2.40
H-MSX$_2$	3.64 ± 0.01	349.00 ± 1.73	5.33 ± 0.05	1.28 ± 0.15	98.53 ± 1.91
H-MSX$_3$	3.58 ± 0.11	352.33 ± 1.52	5.23 ± 0.35	1.14 ± 0.07	101.23 ± 0.09
H-MSG$_1$	3.40 ± 0.26	348.33 ± 1.5	5.33 ± 0.25	1.32 ±0.18	99.60 ± 0.04
H-MSG$_2$	3.58 ± 0.10	350.67 ± 1.15	5.10 ± 0.1	1.32 ± 0.17	100.44 ± 0.94
H-MSG$_3$	3.67 ± 0.05	349.67 ± 2.08	5.23 ± 0.20	1.33 ±0.12	99.91 ±1.44
H-MSP$_1$	3.47 ± 0.22	351.33 ± 1.52	5.33 ± 0.05	1.30 ± 0.16	98.63 ± 1.46
H-MSP$_2$	3.40 ± 0.06	347.33 ± 2.30	5.53 ± 0.32	1.31 ± 0.10	98.40 ±1.79
H-MSP$_3$	3.42 ± 0.25	352.33 ± 0.57	5.67 ± 0.32	1.24 ± 0.15	98.86 ±1.96
H-MSC$_1$	3.37 ± 0.13	353.33 ± 0.57	5.33 ± 0.40	1.15 ± 0.07	99.85 ± 0.38
H-MSC$_2$	3.58 ± 0.14	352.67 ± 2.30	5.33 ± 0.25	1.35 ± 0.05	100.78 ± 1.18
H-MSC$_3$	3.58 ± 0.11	351.00 ± 2.64	5.20 ± 0.26	1.32 ± 0.18	100.55 ± 0.80

n=3, the values are mean ± S.D, $p < 0.001$

Table 10 Comparative drug release of formulations

Formulations	**Percentage cumulative Drug release at the end of 24thhr**			
Ethyl cellulose coated formulations				
Ratios		**1:1**	**1:2***	**2:1**
Xanthan gum	E-MSX$_1$	95.37		
	E-MSX$_2$		No release	
	E-MSX$_3$			93.79
Guar Gum	E-MSG$_1$	98.46		
	E-MSG$_2$		No release	
	E-MSG$_3$			89.01
Pectin	E-MSP$_1$	93.80		
	E-MSP$_2$		No release	
	E-MSP$_3$			93.10
Carrageenan	E-MSC$_1$	87.24		
	E-MSC$_2$		No release	
	E-MSC$_3$			86.01
Hydroxy propyl methyl cellulose coated formulations				
Ratios		1:1	1:2	2:1
Xanthan gum	H-MSX$_1$	97.72		
	H-MSX$_2$		No release	
	H-MSX$_3$			96.20
Guar Gum	H-MSG$_1$	99.46		
	H-MSG$_2$		No release	
	H-MSG$_3$			93.80
Pectin	H-MSP$_1$	93.59		
	H-MSP$_2$		No release	
	H-MSP$_3$			90.50
Carrageenan	H-MSC$_1$	85.42		
	H-MSC$_2$		No release	
	H-MSC$_3$			88.39

Preformulation studies:

Differential scanning calorimetry

In this technique the difference in energy inputs into a substance and reference material is measured as a function of temperature as the specimens are subjected to controlled temperature program. (Beckett et al., 2003)

Evaluation of Matrix tablets:

The precompression properties like angle of repose, bulk density, tapped density, Compressibility Index, and % LOD was calculated for both coated and uncoated granules. The post compression properties like thickness, Weight variation, hardness, friability and assay were calculated for the Matrix tablets.(Gilbert et al., 1990)

In vitro drug release

Acid stage:

The dissolution media used was 750ml of 0.1N HCl (pH 1.2) solution at 37 ± 0.5° for first 2 h. The samples are withdrawn at time intervals 0.5h, 1h, 1.5h and 2h and are calculated for drug content at 280 nm spectrophotometrically.

Buffer stage:

To the above dissolution fluid 250 mL of of 0.2 M of Tribasic sodium phosphate was added and pH was adjusted to 6.8 ± 0.05 using 2N Hydrochloric acid or 2 N sodium hydroxide and the operation

was continued and samples were withdrawn at 4h, 6h, 8h, 10h, 12h, 16h, 20h and 24 h and are calculated for drug content at 280 nm spectrophotometrically using UV spectrophotometer (Schimadzu159 series). During the dissolution the paddle speed was maintained at 50 rpm and the temperature of the whole process was maintained at 37ºC ± 0.5.

The dissolution studies were performed for 24 h and the cumulative percentage of drug released from the tablets was calculated and plotted against time. (Salomon et al., 2002)

Release kinetic studies:

The rate and mechanism of release of Metoprolol Succinate through the prepared matrix tablets were analyzed by fitting the drug release data into Zero order equation $Q = Q_0 - K_0t$, Q is the amount of drug remaining undissolved at time t, Q_0 is the amount of drug undissolved at t = 0 and K_0 is the corresponding release rate constant and First order release equation $\ln Q = \ln Q_0 – K_1t$, Where M is the amount of drug undissolved at time t, M_0 is the amount of drug undissolved at t = 0 and K_1 is the corresponding release rate constant. Higuchi Square Root Law equation $Q = K_2t^{0.5}$, Q (Q = 100 - M) is the amount of drug dissolved at time t and K_2 is the diffusion rate constant. The diffusion data was further analyzed to define the mechanism of release by applying the diffusion data into Korsmeyer - Peppas equation $M_t/ M_\infty = K t^n$,M_t / M_∞ is the fraction of drug released at time t, K is the Korsmeyer release rate constant and n characterizes the mechanism of drug release from formulations during diffusion process. If n = 0.45 it is case I or Fickian diffusion, 0.45, n, 0.89 is for anomalous diffusion or non- Fickian transport, n = 0.89 for case II transport, n .0.89 for super case II transport.(Peppas et al., 1989) The results were shown in table 10

Comparison of dissolution profiles

The similarity factor (f_2) was employed to evaluate the release profiles of various formulations compared with the ideal release profile.

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} X\ 100 \right\}$$

The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the experimental drug release T_t and the ideal drug release R_t for over all time points ‘n’. The similarity factor fit the result between 0 and 100. It is approached 0 as the dissimilarity of the test and the reference profile increased, whereas, it attained 100 when the test and the reference profile were identical. The two profiles were believed to be similar when the f_2 value of them was larger than 50 for which the mean deviation over all the time points ‘n’ was less than 10% based on above equation.

RESULTS AND DISCUSSION

Preformulation studies:

The output of a DSC is a plot of heat flux (rate) versus temperature at a specified temperature rate. DSC provides information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and polymers in formulations. According to the thermograms, Metoprolol succinate presented a sharp endothermic peak at 159.2ºC corresponding to the melting point of the drug and the combination of Metoprolol Succinate with other polymers shows a slight variation in the endothermic peak value in the thermograms as shown in Table 4. Thus the thermograms of drug were in its amorphous form and also there is no interaction between the Metoprolol succinate and the polymers which were employed in the formulations and thus showed the peaks corresponding to the drug molecules when present in the mixture.

Evaluation of Matrix tablets:

The angle of repose of the uncoated granules are ranged from 26º.45±0.48 to 29.26±0.12, Ethyl cellulose coated granules are ranged from 25.13±0.01 to 29.44±0.18

and the hydroxyl propyl methyl cellulose coated granules are ranged from 25.14 ± 0.03 to 27.13 ± 0.02. This shown that all formulated granules are having the good flow rate. The values of tapped and bulk density shown that the granules are tightly the granules are granules are not tightly and it should not affect the dissolution of the drug. The compressibility index of the granules were found to comply within the limits and shown good compressibility index. The formulations the % LOD of the granules were found to comply within the limits and it should not affect the coating of the granules. The post compression properties of these tablets are within the limits as specified conditions under USP.

***In vitro* drug release:**

All the formulations are Ethyl cellulose and HPMC coated and they shown the minimum drug release in the 0.1 N Hcl of 1.2 pH. It showed that 4.64 ± 0.80 % for E -MSX_2 had least drug release in 0.1 N Hcl and 5.50 ± 0.66 % for E -MSC_1 had highest drug release for ethyl cellulose granule coated matrix tablets. It showed that 4.00 ± 2.00 % for H -MSP_3 had least drug release in 0.1 N Hcl and 5.31 ± 0.54 % for H -MSG_2 had highest drug release for Hydroxy propyl methyl cellulose granule coated matrix tablets. Hydroxy propyl methyl cellulose granule coated matrix tablets shown less drug release in 0.1 NHcl of 1.2 pH compared to the Ethyl cellulose granule coated matrix tablets. This is may be the HPMC is hydrophilic and EC is hydrophobic in nature. The HPMC will swell and then the drug is release by diffusional way, where as in the EC coated formulations the drug is released in the form of erosion. It showed that 86.01 ± 0.34 % for E -MSC_3, it is the minimum drug release in phosphate buffer 6.8 pH at 24hr and 98.46 ± 0.36% for E -MSG_1 had maximum drug release in phosphate buffer 6.8 pH at 24hr for Ethyl cellulose granule coated matrix tablets. It showed that 85.42 ± 0.36 % for H -MSC_1, it is the minimum drug release in phosphate buffer 6.8 pH at 24hr and 99.46 ± 0.01 % for H -MSG_1 had high drug release in phosphate buffer 6.8 pH at 24hr for Hydroxy propyl methyl cellulose granule coated matrix tablets. The hydroxyl propyl methyl cellulose granule coated tablets containing 1:1 of Guar Gum and Avicel RS 581 showed the 99.46 ± 0.01 % at the end of the 24th hr in phosphate buffer pH 6.8.The combination of the Guar Gum with the Avicel RC 581 in 1:1 ratio that is coated with the HPMC shows the 99.46% in 24hrs. The polysaccharide polymer chain is well relaxed in the case of Guar gum compared to the other formulations and hence it has maximum release.

Metoprolol Succinate is mostly absorbed from the upper parts of the intestine, so the granules containing the combination of natural polymer and Avicel RC 581 are coated with the Ethyl cellulose and HPMC E 15; it causes slow release in gastric pH and also further extension of drug release. Avicel RC 581 is the combination of MCC and Sodium CMC which is having the combination of disintegrant and the cellulose derivative which turns into viscous when contact with biological fluids. When it is combined with the natural gums and formulated, the drug is released from its matrix slowly by the diffusion process as it contains the Sodium CMC which is hydrophilic in nature and the use of MCC is to penetrate the water into this Sodium CMC to cause it to swell. The use of natural polymers is to slow down the drug release so it is also hydrophilic and it is combined with Avicel RC 581. Out of the four polymers that are selected the Xanthan Gum and Carrageenan have the high compressibility index compared to the others so the porosity of this granules are less and the permeation of dissolution fluid into this formulations are less and hence these formulations shown the less drug release compared to that of Guar Gum. Moreover the acidic nature of Carrageenan due to sulphate groups it hindered the release of cationic Metoprolol Succinate.

The combination of the pectin with the cellulose polymers cause the slow relaxation of the polymer chains compared

to that of others polymers causes the improper diffusion of the drug from its matrix that's why it shows the less release compared to the Guar Gum. The Guar Gum in the combination of Avicel RC 581(1:1) showed the best drug release in the 24hrs. The result shown that some cellulose ethers had physical properties (e.g., Viscosity), Yet when present with this polysaccharide give proper diffusion of the drug from its matrix. Hence a polymer - polymer interaction at a molecular level might be at the base of these characteristics.

Here in this results the 1:1 combinations of all polysaccharides and cellulose ethers shown good results when compared to that of 1:2 or 2:1 of the polysaccharides and cellulose ethers, because in 1:2 combinations the concentration of the MCC and Sodium CMC is more and hence the drug is released fast before 24hrs and moreover for 2:1 combinations the concentration of the polysaccharides are increased and the drug is released slowly and in 1:1 combinations there is equal concentration of polysaccharides and Avicel RC 581.so the relaxation of the polymer chains of polysaccharides are widely happen and drug is diffused in an extended manner.

All formulations are coated with EC and HPMC because to slow the drug release at the stomach pH. In stomach minute amounts Metoprolol is only absorbed and mostly it is absorbed from the upper parts of the intestine. The EC is hydrophobic in nature and HPMC is hydrophilic in nature. On contact with the dissolution fluid the HPMC swells and slowly uptakes the fluid and it reaches to the polymer matrix and cause the polymer relaxation. Hence this HPMC coated granules shown the best release at 24hrs. While in EC coated granules on contact with dissolution fluid it erodes away and there by the fluid reaches the polymer and relaxation occurs. Hence it shows less drug release compared to HPMC coated granules.

Release kinetic studies:

These values are fitted to the first order plot and its regression values are ranges from 0.942 to 0.992, as its value nearer to the '1' it is conformed as it follows the slow first order release. The mechanism of drug release is further confirmed by the Korsmeyer and Peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non – Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The 'n' values are ranges from 1.037 to 1.314 for all formulations, these values are characteristic of super case II transport, suggesting that more than one mechanism may be involved in release kinetics. High the value of 'n' high is the polymer relaxation and swelling / erosion and drug is release in this fashion. For H-MSG_1 the 'n' value is high shown that drug is released by high polymer relaxation and swelling / erosion.(Korsmeyer et al., 1981)

Comparative study with marketed formulation:

All formulations are compared with marketed formulation for similarity studies. The formulation H-MSG_1 had somewhat same drug release when compared to the marketed formulation. The similarity factor (f_2) of all the formulations is ranging from 58.32 to 80.09. The similarity factor of H-MSG_1 is high when comparing to other formulations so, it is more similar to that of marketed formulation for which the similarity factor is 80.09.

CONCLUSION

From the data it is concluded that the natural polymer plays a major role in the design of extended release matrix tablet. The study reveals that the extended release of Metoprolol Succinate is possible for choosing the Guar gum (natural polymer) as matrix former also shows anomalous diffusion.

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