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DESIGN, DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLETS OF METOPROLOL SUCCINATE USING EUDRAGIT POLYMERS.

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ABSTRACT

The objective of the study was to develop sustained release tablets of Metoprolol Succinate (MS) using two different grades of EUDRAGIT polymers called Drugcoat RLPO and Drugcoat RSPO and to evaluate pharmacokinetic parameters of the optimized product. Sustained release tablets of Metoprolol Succinate were prepared using combination of different ratios of Drugcoat RLPO and Drugcoat RSPO. Study of pre compression and post compression parameters facilitated the screening of a formulation with best characteristics. The granules were prepared by wet granulation method using non-aqueous vehicles. The granules were coated with coating solution containing EUDRAGIT polymers. *In-vitro* drug release studies were performed using USP apparatus type II. It was found that 93% of the drug was released at the end of 20hrs. *In-vitro* release studies was conducted based on the data that all formulations follows zero order release kinetics and higuchi's mechanism i.e. the drug was released by diffusion. Among all the 7 formulations F_7 was found to be best matched formulation with respect to the marketed formulation.

KEYWORDS: Sustained release, Metoprolol Succinate, DRUGCOAT RLPO, DRUGCOAT RSPO, β-blockers.

INTRODUCTION

Cardio vascular disease has become the leading cause of morbidity and mortality in India during the last three decades. On average, younger age are less likely to have cardiovascular

diseases and commonly seen in past middle age.[1] The genetic predisposition and acquisition of traditional risk factors at a rapid rate as a result of urbanization seems to be the major cause. Also, hypertensive heart diseases in India occur 10 – 15 years earlier than in western countries.[2] Similarly, there appears to be a steady increase in hypertension prevalence over the last 50 years which was found to be more in urban than in rural areas. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma level. Oral route has been the most convenient and commonly employed route of drug delivery. Indeed, for the sustained release systems received more attention in the design and testing of products.[3]

In the recent years focus on the development of sustained release drug delivery system has increased. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized, side effects are reduced and cure or control of the condition is achieved in the shortest possible time by using smallest quantity of drug administered by the most suitable route.[4] Sustained release (SR) products are designed to bring the blood level of a drug immediately to therapeutic concentrations by means of an initial dose portion and then sustained this level for a certain predetermined time with the maintenance portion.[5]

β- adrenergic blockers are one of the most frequently prescribed cardiovascular drugs.[6] Metoprolol is the prototype of cardio selective β- blockers with intrinsic sympathomimetic activity. It is one of the drugs which cross the BBB and it has been reported that in the cerebrospinal fluid it achieves 78% of plasma concentration. Only a small portion of it (12%) bound to human serum albumin. Metoprolol is most effective than other β- blockers. Metoprolol is approximately equipotent to propranolol in inhibiting β1 receptors in heart but 50 times less potent than propranolol in blocking β2 receptors.[7] Drugs that that blocks the β1 receptor have been developed to eliminate the unwanted bronchoconstrictor effects (β2) of propranolol seen among the asthmatic patients. Metoprolol antagonizes the β1 receptors at doses 50-100 times lesser than that required to block β2 receptors. This cardio selectivity is more at low doses and lost at high doses.

The drug is freely soluble at any pH, hence judicious selection of release retarding excipients is necessary for achieving constant in-vitro release. The most commonly used method of

modulating the drug release is to include the drug in matrix systems. Matrix based SR tablet formulations are the most popular and easy to formulate on a commercial scale in an industry. Reservoir type when compared to Matrix type provides better result in retarding the drug release but difficult to prepare on a commercial scale.[8]

In the present study combination of Reservoir and Matrix type system was formulated by wet granulation method. Influence of different ratio of polymer concentration on drug release was evaluated by keeping the drug substance concentration constant and altering the release retardant polymer concentration. Pre compression and post compression parameters were evaluated and optimized formulation was characterized.[9]

EUDRAGIT polymers are relatively new synthetic anionic and cationic release retarding agents consisting of methacrylic acid dimethylaminoethyl methacrylate and methacrylic acid esters in varying ratios. It is a white powder with slight amine like odor. It is suitable for Matrix devices and it exhibits pH independent swelling which helps in retarding the drug from the device.[10]

MATERIALS AND METHODS

Metoprolol Succinate was obtained from Paxmy chemicals, Mumbai. The EUDRAGIT polymers were obtained from Vikram thermolabs, Calcutta; Talc & Magnesium stearate was obtained from Loba chemie, Pvt. Ltd, Mumbai; MCC was obtained from Welming pharmaceuticals, India. Solvents and all other chemical reagents used were of analytical grade.

Preparation of SR tablets of Metoprolol Succinate.

Preparation of SR tablets of Metoprolol Succinate (F_1 to F_5)

Tablets were prepared by wet granulation method using the ingredients given in table. F_1 to F_5 trials were taken. The active ingredient Metoprolol Succinate and the following excipients like Micro crystalline cellulose, Magnesium stearate etc. were sifted separately through ASTM sieve no. 60. Aerosil was sifted through sieve no.24. Metoprolol Succinate and MCC were mixed thoroughly for 5min. DRUGCOAT RLPO, RSPO were mixed together and dissolved in mixture of IPA and Acetone. The above solution was used to form wet granules. The wet granules were open air dried at room temperature for 30min. The granules were passed through ASTM sieve no.12. The sifted granules were dried at 60^0C for 3hrs. To the dried granules, magnesium stearate and aerosil were added and mixed thoroughly. Finally,

the lubricated granules were compressed into tablets weighing 200 mg die cavity using the punch size of 10/32 SC' in a Cadmach double rotary tablet punching machine using appropriate size of standard concave punches to a hardness of 6 to 10 kg/cm^3. The compressed tablets were de dusted and evaluated for various tablet properties.

Preparation of SR tablets of Metoprolol Succinate (F_6, F_7)

Sustained release tablets of Metoprolol Succinate was prepared by wet granulation method The active pharmaceutical ingredient Metoprolol Succinate and the following excipients like talc, magnesium stearate were sifted separately through ASTM sieve no.60. Aerosil was sifted through ASTM sieve no.24. Metoprolol Succinate and talc was dry mixed previously. One third quantity of polymer DRUGCOAT RSPO was dissolved in the mixture of isopropyl alcohol and acetone. The above polymer solution was slowly added to the mixture of Metoprolol Succinate and talc to produce wet granules. The wet granules were kept for open air dry for 30min.The granules were then passed through ASTM sieve no.12.The sifted granules were then transferred to a pan and kept in an oven at 45^{0}C for 2 hours.

The remaining quantity of polymer DRUGCOAT RSPO was dissolved in a mixture of isopropyl alcohol and methylene chloride. For uniform distribution of the polymer into the solvent mixture the above mixture was homogenized. In the spray coating machine, the dried granules were placed in the coating pan. The above polymer solution was sprayed on to the dried granules at low pressure, in wide angle to overcome the flyover of particles. The coated granules were dried in oven at 60^{0}C for about 1 hr. The dried coated granules were then passed through ASTM sieve no. 18 and aerosil was added to the granules and lubricated. Finally, the lubricated granules were compressed into tablets weighing 200 mg die cavity using the punch size of 10/32 SC' in a Cadmach double rotary tablet punching machine using appropriate size of standard concave punches to a hardness of 6 to 10 kg/cm^3. The compressed tablets were dedusted and evaluated for various tablet properties.

Evaluation of Metoprolol Succinate S.R. tablets

Pre compression parameters

Initially the lubricated powder blend was evaluated for density parameters like bulk density, tapped density, compressibility index and Hausner's ratio was calculated to estimate the flow properties. The physical parameters of the lubricated powder blend from all the seven formulations were evaluated. From the data it was observed that, increased amount of

polymer concentration decreases the flow property and increases the compressibility of the lubricated powder blend.

Post compression parameters

The compressed tablets were characterized by their physical properties. The average tablet weight was determined from 20 tablets (USP, 2007). Tablet hardness was tested using Monsanto tablet hardness tester. Friability of the tablets was determined by Roche friabilator. Tablet friability was calculated as the percentages of weight loss of 20 tablets after 100 rotations (USP, 2007). The post compression parameters of the compressed tablets from all the seven trials were evaluated. Low hardness and little high friability were observed for formulations with low concentration of polymer and high concentration of active ingredient and this is due to low bulk density and low compressibility nature of Metoprolol Succinate.

Table no.1 Formula for Metoprolol Succinate S.R. tablets.

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1.	Metoprolol Succinate	47.5mg	47.5mg	47.5mg	47.5mg	47.5mg	47.5mg	47.5mg
2.	Microcrystalline cellulose	115.3mg	-	-	-	-	-	-
3.	Talc	-	115.3mg	106.8mg	78.3mg	70mg	96.3mg	98.3mg
4.	DRUGCOAT RLPO	3mg	3mg	3mg	-	-	-	-
5.	DRUGCOAT RSPO	30mg	30mg	38.5mg	70mg	78.3mg	52mg	50mg
6.	Magnesium stearate	2.1mg	2.1mg	2.1mg	2.1mg	2.1mg	2.1mg	2.1mg
7.	Aerosil	2.1mg	2.1mg	2.1mg	2.1mg	2.1mg	2.1mg	2.1mg
8.	Isopropyl alcohol	100ml	100ml	100ml	100ml	100ml	q.s	q.s
9.	Acetone	150ml	150ml	150ml	150ml	150ml	q.s	q.s
10.	Methylene chloride	-	-	-	-	-	q.s	q.s

Table no. 2: Evaluation of lubricated powder blend.

S. No.	Parameters	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1.	Angle of repose	$37^0$18'± 0.21	$25^0$79'± 0.34	$27^0$14'± 0.21	$33^0$51'± 0.03	$36^0$75'± 0.03	$28^0$16'± 0.06	$31^0$16'± 0.02
2.	Bulk density (g/ml)	0.642± 0.02	0.680± 0.01	0.652± 0.03	0.551± 0.01	0.529± 0.02	0.738± 0.01	0.742± 0.01
3.	Tapped density (g/ml)	0.741± 0.01	0.777± 0.03	0.744± 0.02	0.636± 0.02	0.640± 0.01	0.851± 0.04	0.829± 0.03
4.	Compressibility index (%)	17.45± 0.47	12.48± 0.14	12.41± 0.11	13.36± 0.26	18.38± 0.20	13.27± 0.18	10.49± 0.15
5.	Hausner's ratio	1.20± 0.01	1.14± 0.03	1.14± 0.02	1.15± 0.03	1.22± 0.01	1.15± 0.02	1.11± 0.01

Table no. 3: Evaluation of finished product

S.No	Test	Specification	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1.	**Description**	White colour, slightly concaved tablets	Complies	Complies	Complies	Complies	Complies	Complies	Complies
2.	**Thickness**	3.2 to 4mm	3.9±0.03	3.11±0.05	3.16±0.02	3.47±0.05	3.53±0.02	3.14±0.02	3.17±0.02
3.	**Hardness**	6 to 10 (kg/cm^2)	6.35±0.02	6.12±0.01	6.17±0.01	6.11±0.02	6.19±0.05	8.27±0.04	8.25±0.01
4.	**Friability**	NMT 1%	0.7	0.12	0.12	0.11	0.11	0.11	0.11
5.	**Weight Variation (mg)**	±7.5 from the average weight	203	202	200	200	201	200	201
6.	**Assay**	90-110%	98.86	98.21	99.64	98.75	99.34	98.71	98.78

Table No. 4. *In-vitro* dissolution data of formulations F1, F2, F_3, F_4, F_5, F_6 and F_7:

S. No.	Time in hours	Marketed Seloken XL	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1.	1	11.61±0.03	53.96±0.01	41.43±0.12	30.19±0.19	25.87±0.05	28.40±0.06	9.39±0.05	11.52±0.05
2.	4	24.77±0.06	88.29±0.05	62.34±0.16	61.76±0.23	52.58±0.09	59.31±0.1	25.11±0.08	27.39±0.03
3.	8	49.37±0.09	98.56±0.09	85.97±0.11	79.11±0.17	86.35±0.07	82.87±0.09	49.61±0.04	46.87±0.06
4.	20	83.18±0.04	87.11±0.07	79.54±0.14	96.84±0.21	89.49±0.11	87.62±0.11	80.64±0.09	93.44±0.03

Table no 5: Kinetic data of release profile of metoprolol succinate Sustained release tablets of optimized formulation.

S.No	Order of kinetics	Optimized formulation (F_7)	
		R^2	'n'
1.	Zero order	0.985	-
2.	First order	0.995	
3.	Higuchi plots	0.984	
4.	Korsmeyer Peppa's plots	0.994	0.7011

In-vitro dissolution study

In-vitro drug release study from the prepared S.R. tablets of Metoprolol Succinate was conducted for a period of 20 hours using six stations USP type II dissolution apparatus and the temperature of the medium was maintained at 37^0 ±0.5^0C with paddle rotation at 50rpm and 500ml of dissolution medium using pH 6.8 phosphate buffer. Samples of 2 ml were taken from the dissolution medium at appropriate time intervals. After filtration and appropriate dilution with the mobile phase (mixture of pH6.8 phosphate buffer and Acetonotrile in 85:15 ratio) the sample is injected into the HPLC column. Column used for reverse phase HPLC was Cromasil C18(250×4.6). The flow rate was maintained at 1.0ml/min. the sample injection volume was 20µl. The amounts of the drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Similarly, dissolution study was conducted for the reference product (i.e Seloken XL, Batch No: SWEJ001, Manufacturer: AstraZeneca) and compared with the test products. The dissolution profiles for the trials were provided in table no.3.

For the uncoated granules the increased polymer concentration could not retard the release of the drug in sufficient manner. Also the hardness and flow property was found to decrease in considerable amount. Similarly for coated granules flow property and hardness was found to be within the USP limits and there is evidence that the drug release was sufficiently retarded with even low polymer concentration. The drug release protocol of formulated trials of Metoprolol Succinate S.R. tablets from MS-1 to MS-7 is shown in (Table No.3). From these formulations MS-7 was found to be best formulation because the release pattern of F_7 batch was within the USP limits.

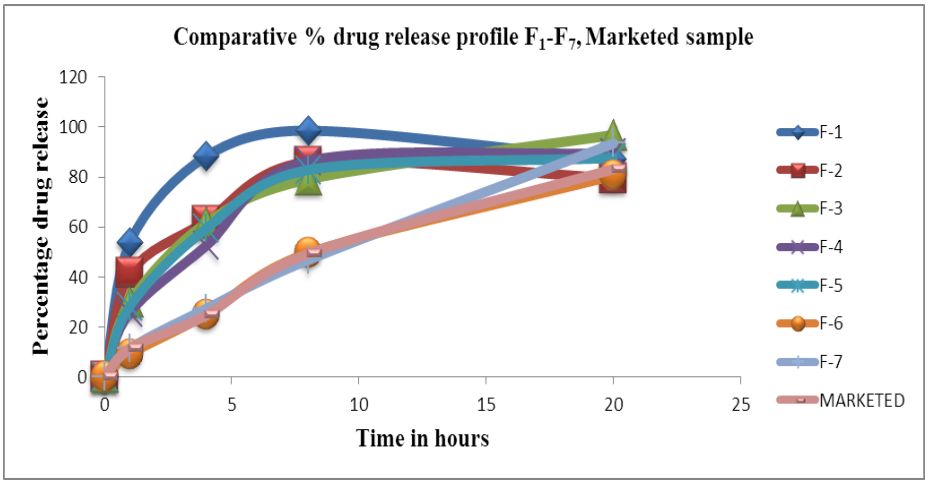

Figure no: 1 Comparative dissolution study of formulations F_1 - F_7 and marketed formulations.

Kinetic studies of Optimized formulation F_7.

The drug release data were subjected to mathematical treatment to check the release order kinetics. Plots of Percentage drug release Vs Time (Zero order Plot) Cumulative percentage drug release Vs Square root of time (Higuchi plot) are shown in graphs respectively. The kinetic data of dissolution studies of all formulations were presented in Table no 4. Plots of percentage drug release Vs Time were found to be linear indicating that the mechanism of drug release from these formulations was according to Zero order kinetics. To evaluate the drug release pattern of these formulations Higuchi plots were constructed. These plots were linear with formulations F_3, F_6, F_7 indicating that the drug release mechanism was Diffusion controlled but for the other formulations like F_1, F_2, F_4, F_5 non- linearity was observed indicating that the drug release was by Erosion.

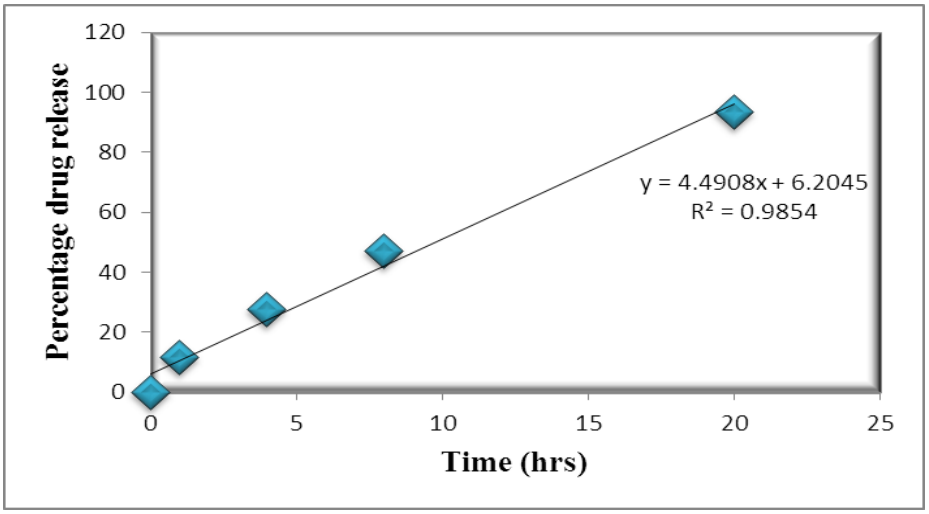

Figure no: 2 Zero order drug release plots of optimized formulation F_7.

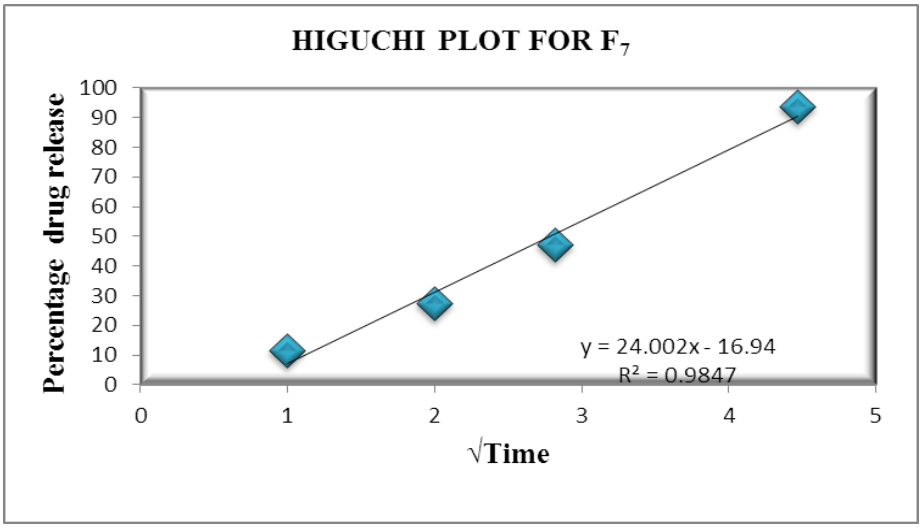

Figure No. 3 Higuchi's plots of optimized formulation F_7.

CONCLUSION

From the above observations it can be concluded that Metoprolol Succinate is an ideal candidate for converting into the sustained release dosage forms. Also, it shows the evidence that Eudragit polymers can be effectively utilized in the design of Metoprolol Succinate sustained release tablets using an optimum concentration for desired release profile and with good quality parameters.

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