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FORMULATION AND DEVELOPMENT OF ER METOPROLAOL SUCCINATE TABLETS

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Abstract: In the present investigation an attempt was made to reduce the frequency of dose administration, to prevent nocturnal heart attack and to improve the patient compliance by developing extended release (ER) matrix tablet of Metoprolol succinate. Eight batches of ER matrix tablets of Metoprolol succinate were developed by using wet granulation technique and coated with hydroxy propyl methyl cellulose (KM 100) and hydroxyl methyl cellulose for extended release. Compressed tablets were evaluated for weight variation, hardness, friability and *in vitro* dissolution using paddle (USP type II) method. All formulation showed compliance with pharmacopoeial standards. Among the eight formulations, F8 showed extended release of drug for 20 hours with 87.1% drug release and subjected to stability studies for 3 months at 40□C/75% RH and 60□C/80%RH.

Keywords: Metoprolol succinate, wet granulation, *in vitro* dissolution.

1. Introduction:

Metoprolol succinate is a beta selected adrenoceptor blocking agent, for oral administration in the treatment of hypertension, aginapectoris and heart failure. It has a half life of 3 to 7 hours. When dose is missing it may causes nocturnal attack, so attention was made to develop the extended release tablets of Metoprolol succinate by utilizing hydroxy methyl cellulose. The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. In other words, they are able to exert a control on the drug release rate and duration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Among the hydrophilic polymers cellulose derivative such as methyl cellulose, hydroxypropyl cellulose and sodium corboxymethy cellulose are generally considered to be stable and safe as release retardant excipient in the development of oral controlled release dosage forms[1]. The dose release properties of matrix device may be dependent upon the solubility of the drug in the polymer matrix, the solubility in the sink solution within the particles pore network. Hydroxy methyl cellulose is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery[2]. While preparing ER tablets with HPMC, a change in the manufacturing variable yields a significant change in dissolution profile for the same formulation[3] .The objective of the present study was to develop Metoprolol succinate ER matrix tablets using hydroxyl propyl methyl cellulose and hydroxyl propyl cellulose polymer and elucidate the release behaviours.

2. Experimental:

2.1 Materials

The drug Metoprolol succinate was obtained from Alembic Pharmaceuticals., HPMC (hydroxyl propyl methyl cellulose) K100 M, HPC (hydroxyl propyl cellulose) supplied by Dow chemicals (Methocel),

Sodium CMC supplied by Reliance Chemical co. Lactose DMV International(Netherland), Povidone (BASF Tech.USA), Talc (Udaipur Minerals), Aerosil (Casot Summer Ltd)., Stearic Acid (Tauras Chemicals), Avicel pH101 (Sigachi Chemicals) were also used in the study. All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

2.2 Methods

2.2.1 Preparation of extended release tablets:

Eight batches of ER tablets, each containing 25mg Metoprolol succinate were prepared by wet granulation technique. The granules used for the preparation had good flow property and compressibility index. The total weight of tablet was constant for all the fabricated batches under experimental conditions of preparations. "Take in Table No 1"

Metoprolol succinate, lactose, avicel pH 101, HPMC K100 M (first portion) and sodium carboxy methyl cellulose were passed through sieve no #40 and thoroughly mixed in a polythene bag. Povidine in water was used as a binding agent. Which was added to the above mixer for granulation. Wet granules were passed through the sieve no #12 and slightly dried. Dried granules were again passed through the sieve no #20. The dried granules were prelubricated with rest of the portion of HPMC and HPC. Prelubricated granules were lubricated with aerosol, talc and stearic acid which were already passed through sieve no # 40 and compressed in to tablets on a 16 station single rotary machine using 7.9 mm N/C punch.

Iso propyl alcohol (IPA) was stirred in a colloidal mill and titanium dioxide was added slowly, avoiding powder floatation on the liquid surface. Methylene chloride was added and mixed well for thirty minutes to get a uniform dispersion. Finally the above solution was passed through 200 mesh nylon cloth. The core tablets were coated in the coating pan. "Take in Table No 2".

2.2.2 Evaluation of tablets:

The prepared ER matrix tablets were evaluated for their hardness, weight variation, thickness and friability.

2.2.3 *In vitro* drug release studies:

The *in vitro* dissolution studies were carried out using USP dissolution apparatus type II at 50 rpm. Dissolution test was carried out for a total period of 20 hrs using 500ml of phosphate buffer of pH 6.8. Analysis for Metoprolol succinate was done by HPLC detected at 280nm using phosphate buffer and acetonitrile in the ratio of 7.5:2.5 as a mobile phase.

2.2.4 Stability study:

The selected batch (F8) was kept at 40 °C with 75% RH and 60 °C with 85% RH and the samples were withdrawn at 30, 60 and 90 days for physical and *in vitro* evaluation of drug release.

3. Results and Discussion:

The results of hardness and friability of the prepared ER matrix tablets ranges from 4 to 8 Kg/cm^2 and 0.20 to 0.31 % respectively. "Take in Table No 3". All the batches of the fabricated tablets were of good quality with regard to hardness, friability and weight variation.

The results of dissolution studies of formulations were shown in "Take in Figure No 1 and 2". Among the *in vitro* drug release of the entire formulations F8 has satisfied drug release for the extended period of 20 hrs. "Take in Table No 4". The release of drug depends not only the nature of the matrix but also depends upon the drug polymer ratio. (The polymer concentration was gradually increased).

In all formulations, HPMC polymer was divided into two parts, first part was added before granulation and rest of the portion was added after granulation, but HPC polymer was added after granulation only. Comparing all the batches from F1 to F8, F8 batch gives satisfied release up to 87.1% at 20 hours. In the F8 batch 55% HPMC and 10% HPC were used to achieve the objective of the study. So F8 is considered as optimized formula for Metoprolol succinate ER tablets. The drug content is assayed for F8 batch by the HPLC method (95.5%).

Stability studies revealed that there was no significant change in drug release profile at 40 °C with 75% RH. But at 60 °C with 85% RH showed marked changes in drug release profile during the period of 90 days. It indicates that the Metoprolol succinate ER tablets should be stored at or below 40°C or at room temperature. "Take in Table No 5".

It may be concluded that the Metoprolol succinate ER tablets has been successfully formulated with good release profile for a prolonged period of time up to 20hrs. It decreases the frequency of dose administration, prevents nocturnal attack and improves patient compliance.

Table No 1: Formula for Metoprolol Succinate

S.No	Ingredients	Trials							
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
1	Metoprolol Succinate	24.25	24.25	24.25	24.25	24.25	24.25	24.25	24.25
2	Lactose	30.75	33.75	32.75	30.75	28.75	24.75	17.75	14.75
3	Sodium CMC	8.0	8.0	8.0	8.0	5.0	5.0	5.0	5.0
4	Avicel pH 101	45.0	40.0	30.0	25.0	20.0	15.0	10.0	5.0
5	HPMC K100M	40.0	40.0	45.0	50.0	55.0	60.0	65.0	70
6	Povidone	5.0	5.0	6.0	6.0	6.0	6.0	6.0	6.0
7	Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
8	HPMC K100M	20.0	22.0	25.0	27.0	30	33.0	35.0	38.0
9	HPC LH-11	3.0	5.0	8.0	10.0	12	15.0	20.0	20.0
10	Avicel pH101	10.0	8.0	7.0	5.0	5.0	3.0	3.0	3.0
11	Aerosil	2.50	2.50	2.50	2.50	2.50	2.50	2.5	2.5
12	Talc	2.50	2.50	2.50	2.50	2.50	2.50	2.5	2.5
13	Stearic acid	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0

Table No 2: Formula for Coating of Tablets

S.No	Ingredients	Quantity (mg)
1	HPMC 15 cps	6.980
2	Talc	1.300
3	Titanium dioxide	1.980
4	PG	0.740
5	IPA	qs

Table No 3: Physical Evaluation of Tablets

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Weight of the tablet(g)	0.198	0.201	0.200	0.201	0.199	0.201	0.200	0.199
Hardness (Kg/Cm^2)	4.5	5.0	4.5	6.0	5.5	5.0	6.5	5.5
Thickness (mm)	3.9	3.8	4.2	4.1	4.1	4.0	3.8	4.0
Friability (%)	0.20	0.31	0.28	0.25	0.28	0.30	0.21	0.29

Table No 4: *In Vitro* Drug Release Profile

S. No	Time (Hour)			Cumulative Drug Release (%)					
		F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
1	1	29.5	25.9	25.3	24.5	23.4	16.5	16.2	17.1
2	2	39.4	36.4	32.3	36.4	30.9	29.8	30.1	29.3
3	4	56.4	55.7	49.1	50.8	49.1	45.3	41.1	36.3
4	8	86.9	76.4	68.7	68.4	67.4	66.5	60.2	50.1
5	12	102.6	86.9	87.7	85.1	88.9	79.8	73.4	61.2
6	16	106.3	102.6	94.3	95.4	91.3	87.4	88.6	72.2
7	20	114.3	107.3	101.9	100.5	96.9	95.9	93.5	87.1

Table No: 5 Accelerated Stability Data of F8

Time in months	40ºC		60ºC	
	% Cumulative drug release*	Physical parameter	% Cumulative drug release*	Physical parameter
Initial	87.1%	+	87.1%	+
1	90.1%	+	79.6%	-
2	91.6%	+	73.9%	-

* - average of 6 determinations

Figure No 1 comparative Dissolution Profile of F1 to F5

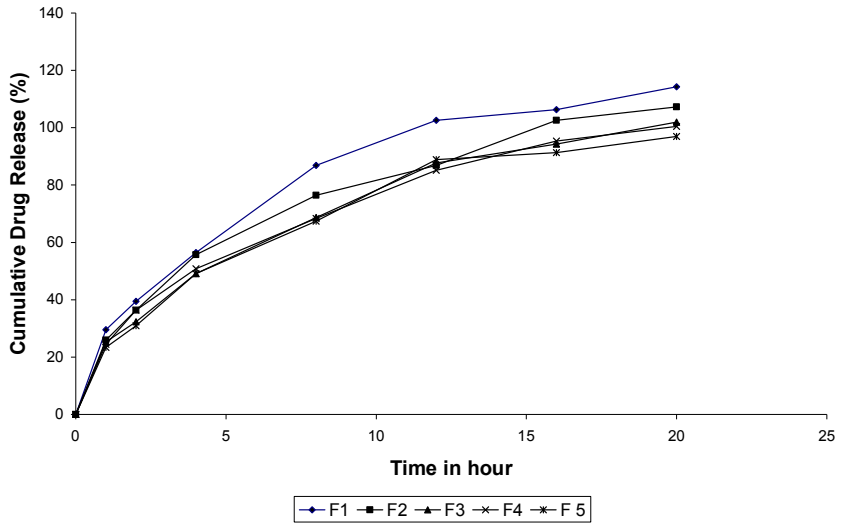
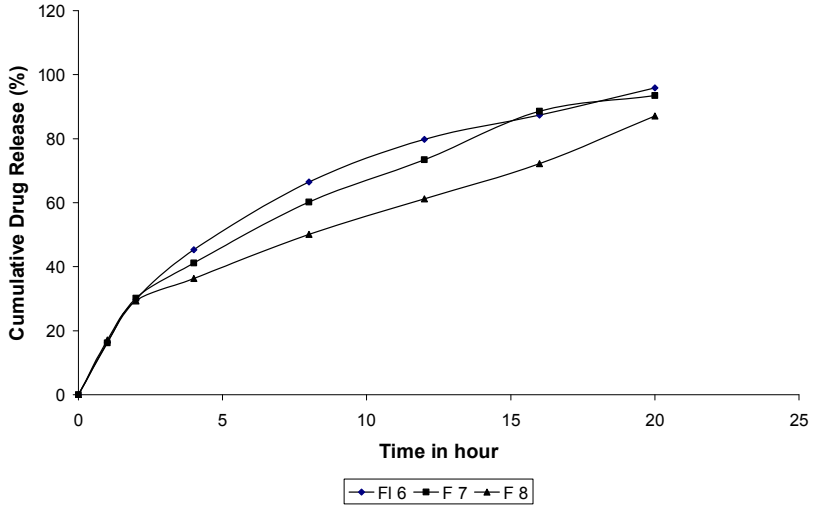


Figure No 2 comparative Dissolution Profile of F6 to F8



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