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FORMULATION AND EVALUATION OF ONCE DAILY MATRIX TABLETS OF METOPROLOL SUCCINATE USING HYDROXYPROPYL METHYL CELLULOSE BY WET GRANULATION TECHNIQUE

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ABSTRACT

The aim of the current study was to develop once-daily sustained-release matrix tablets of metoprolol succinate, Selective β_1- blocker used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), polyvinylpyrrolidone K30 were used as granulating agents along with hydrophilic matrix polymer hydroxypropyl methylcellulose (HPMC K100M). The granules were evaluated for angle of repose, bulk density, compressibility index and drug content. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. The results of dissolution studies indicated that batch AH_3 (Drug-to-HPMC K100M, ethyl cellulose solution (4%W/V, as granulating agent) could extend the drug release up to 24 hours. Batch AH_3 showed highest f_2 value 84.95 and MDT 8.9 hrs similar to that of reference product. The dissolution data were subjected to model fitting analysis and best fitted model was Higuchi model. All the formulations (except batch AH_3) exhibited diffusion-dominated drug release. The mechanism of drug release from batch AH_3 was diffusion coupled with erosion.

INTRODUCTION: Hypertension and angina pectoris, the most common cardiovascular diseases, require constant monitoring. β_1 - Selective blockers are presently considered an important class of drugs for hypertension and angina pectoris. Metoprolol Succinate is used in Hypertension, Angina pectoris and stable, symptomatic heart failure of ischemic, hypertensive, or cardiomyopathic origin [1]. Successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired. Metoprolol Succinate is BCS Class-I drug which is freely soluble in water. The absolute oral bioavailability is 12% and biological half-life is 3-7 hrs [2]. Its chemical name is (±) 1-(isopropylamino) - 3- [p- (2- methoxyethyl) phenoxy]- 2- propanol succinate. The usual initial dosage is 25 to 100 mg daily in a single dose. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of metoprolol succinate is desirable. The drug is freely soluble in water, and hence judicious selection of release-retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are

widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance [3].

Hence, in the present work, an attempt has been made to develop once-daily sustained-release matrix tablets of metoprolol succinate using putative hydrophilic matrix materials such as hydroxypropyl methylcellulose (HPMC) in different concentrations hence it works as a pH independent gelling agent [4]. The drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained-release dosage forms.

Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications. Therefore, in this study, the hydrophilic polymer was used as matrix material, and the solutions of polymers like ethylcellulose (EC), polyvinylpyrrolidone (PVP) were used as granulating agents. The objective of the study was to investigate the performance of hydrophilic matrix system prepared by HPMC in controlling the release of this freely soluble drug, and to investigate the effect of granulating agents such as ethanolic solutions of EC, PVP on the release rate of metoprolol succinate.

MATERIALS AND METHODS:

Materials: Metoprolol Succinate was obtained as gift sample from Torrent Pharmaceuticals Ltd. Hydroxy propyl methyl cellulose (Methocel® K100M) was obtained as gift sample from Ms. Colorcon (Mumbai, India). Ethylcellulose (14 cps) was purchased from SD Fine Chemicals Ltd (Mumbai India). PVP (K30) was procured from Loba Chemie (Mumbai, India). Dibasic calcium phosphate (DCP), Magnesium stearate, Cab-O-Sil was purchased from Ms. SD Fine Chemicals (Mumbai, India). All the other chemicals used were of high analytical grade.

Methods:

Preparation of Matrix Tablets: Firstly, drug excipient compatibility studies were conducted. For the compatibility-testing program, binary powder mixtures were prepared in 1:1 ratios with bulk excipients and 1:10 ratio with trace excipients (lubricants). The binary mixture were ground in a mortar, and screened through mixture was filled in the vial and sealed. All samples were stored at 55^{o}C for 10 days. Sampling was done after every 2days. Samples were analyzed for drug content, and UV spectra.

The tablets were prepared by wet granulation method. The corresponding amount of drug, hydroxypropyl methylcellulose, ethyl cellulose, PVP K30, magnesium stearate and talc were accurately weighed. The powders were screened through screen #60. The screened powders were transferred to mortar and mixed for 10 minutes. The powder mixture was granulated using granulating solutions i.e. ethyl cellulose and PVP K30. The wet mass was passed through sieve # 16 and granular material was dried in oven for 12 hours at 45°C. The dried mass was passed through sieve # 20. After addition of lubricant and glidant, compression was carried out using 9 mm flat-faced circular punches on single station tablet press (Cadmach Machinery, Ahmedabad, India). The total weight of the tablet was 500 mg. The composition of various formulations is given in **table 1**.

TABLE 1: Composition of metoprolol succinate matrix tablets

Batch code	Metoprolol succinate (mg)	Methocel K100M (mg)	DCP* (mg)	Mg-Stearate (mg)	Cab-O-Sil (mg)	Ethyl cellulose (%W/V)	PVP (K30) (%W/V)
AH_1	95	50	345	5	5	4	-
AH_2	95	100	295	5	5	4	-
AH_3	95	150	245	5	5	4	-
AH_4	95	200	195	5	5	-	10
AH_5	95	225	170	5	5	-	10
AH_6	95	250	145	5	5	-	10

DCP* = Dibasic calcium Phosphate

Evaluation of granules: Granules prepared by wet granulation method were evaluated for angle of repose, bulk density and drug content.

Angle of Repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [5]:

$$\text{Tan } \theta = H/R$$

Where, H and R are the height and radius of the powder cone respectively.

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas [6]:

LBD= Weight of the Powder/Volume of packing

TBD= Weight of the Powder/Tapped volume of packing

Compressibility Index: The compressibility index of the granules was determined by Carr's compressibility index [7].

Carr's index (%) = [(TBD - LBD) X 100/TBD]

Drug Content: An accurately weighed amount of powdered Metoprolol tartarate granules (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane (Nunc, New Delhi, India). The absorbance was measured at 275.7 nm after suitable dilution.

Evaluation of tablets:

Tablet dimensions and crushing strength: The diameter, thickness and crushing strength of ten randomly selected tablets per batch were determined using Dr. Scheleuniger® (Pharmatron 8M, Germany) hardness tester.

Friability: Twenty tablets were rotated in a friabilator (Model EF2, Electro lab, India) at 25 rpm for 4 min. The tablets were then dedusted, and the loss in weight due to fracture or abrasion was recorded as percentage weight loss (% friability).

Weight Variation Test: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AX 200 Shimadzu) and the test was performed according to the official method [8].

Drug Content: Five tablets were weighed individually, and the drug was extracted in water. The drug content was determined as described above.

***In vitro* Drug Release Study:** The in vitro dissolution study of marketed product (Seloken XL 100 mg) and the formulated metoprolol succinate matrix tablets were carried out using USP apparatus Type-II in 500 ml of phosphate buffer solution (pH 6.8) at $37^0C \pm 0.5^0C$ at a rotational speed 50 rpm [9]. At 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 24 h after starting the test, 10 ml sample of dissolution medium were withdrawn and analyzed spectrophotometrically at 275.7 nm by using Shimadzu-1700 UV/visible spectrophotometer. An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r =0.9995).

Analysis of Release Data: The dissolution parameter used for comparing the different formulations was mean dissolution time (MDT), measure of the rate of the dissolution process that is calculated from the amount of drug released to the total cumulative drug release. Higher the MDT, slower the drug release rate. Linder and Lippold found that application of MDT provides a more accurate drug release rate than the t_x % approach [10]. The following equation was used to calculate the MDT from the mean data.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} * \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where i, dissolution sample number; n, the number of observation; t_{mid}, the time at the midpoint between i and i − 1 and ΔM, the additional amount of drug dissolved between i and i − 1. The similarity factor f_2 was calculated from the mean dissolution data according to the following equation:

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

Where n, the number of pull points; R_t, the reference profile at time point t and T_t, the test profile at the same time point. Where n, the number of pull points; R_t, the reference profile at time point t and T_t, the test profile at the same time point. The value of f_2 should be between 50 and 100. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases.

Model Fitting Kinetic: To know the mechanism of metoprolol succinate release from the sustained release matrix tablets, the dissolution data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's [11] (cumulative percentage of drug released vs square root of time), and Korsmeyer *et al*., [12] (log cumulative percentage of drug released vs. log time) equations along with zero order (cumulative amount of drug released vs. time) pattern.

RESULTS AND DISCUSSION: The granules of different formulations were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, and drug content (**Table 2**). The results of angle of repose and compressibility index (%) ranged from 23.42 ± 0.02 to 29.85 ± 0.02, and 12.92 ± 0.04 to 13.75 ± 0.02, respectively (table 2). The results of LBD and TBD ranged from 0.283 ± 0.03 to 0.506 ± 0.02 and 0.325 ± 0.06 to 0.582 ± 0.04, respectively (table 2). The drug content in a weighed amount of granules of all formulations ranged from 96.79 ± 0.04 to 98.55 ± 0.03% (table 2).

TABLE 2: EVALUATION OF GRANULES

Batch Code	Angle of Repose (θ)	LBD(g/ml)	TBD (g/ml)	Carr's Index (%)	Drug content
AH_1	24.50±0.02	0.506±0.02	0.582±0.04	13.08±0.02	98.55±0.03
AH_2	24.11±0.03	0.283±0.03	0.325±0.06	12.95±0.03	96.79±0.04
AH_3	23.95±0.01	0.304±0.02	0.349±0.02	12.92±0.04	98.55±0.02
AH_4	24.52±0.04	0.304±0.03	0.349±0.04	12.92±0.02	97.96±0.02
AH_5	29.85±0.02	0.289±0.03	0.335±0.04	13.75±0.02	97.54±0.02
AH_6	23.42±0.02	0.306±0.04	0.352±0.02	13.08±0.03	95.60±0.03

The thickness of the tablets ranged from 3.34 ± 0.03 to 3.45 ± 0.02 mm (**Table 3**). The average percentage deviation of 20 tablets of each formula was less than ±5% (TABLE 3). Drug content was found to be uniform among different batches of the tablets and ranged from 95.60 ± 0.02 to 99.55 ± 0.15 (table 3). The hardness and percentage friability of the tablets of all batches ranged from 4.0 ± 0.23 to 4.9 ± 0.23 kg/cm^2 and 0.65 ± 0.06 to 0.85 ± 0.06%, respectively (table 3).

TABLE 3: EVALUATION OF TABLETS

Batch code	Thickness (mm)	Deviation in weight variation test (%)	Drug content (%)	Hardness (Kg/cm^2)	Friability (%)
AH_1	3.39±0.02	2.987±0.03	96.37±0.02	4.0±0.23	0.85±0.06
AH_2	3.45±0.02	2.567±0.03	98.55±0.13	4.6±0.16	0.72±0.05
AH_3	3.38±0.03	3.125±0.02	96.51±0.03	4.6±0.16	0.73±0.04
AH_4	3.45±0.01	2.987±0.04	97.50±0.04	4.8±0.24	0.68±0.12
AH_5	3.34±0.03	2.689±0.03	99.55±0.15	4.9±0.23	0.65±0.06
AH_6	3.42±0.03	3.895±0.03	95.60±0.02	4.5±0.20	0.75±0.02

***In-vitro* Drug Release Study:** The results of drug release study composed of HPMC K100M and prepared with granulating agents prepared with ethyl cellulose (4%W/V) and PVP K30 (10%W/V) are shown in **table 4**. The dissolution study of the reference drug product is also shown in table 4. The formulations AH_4-AH_6 prepared with PVP K30 as granulating agent released 28.60%, 24.30%, 32.45% respectively at the end of 2 hrs and 95.28%, 97.29%, 96.97% at the end of 24 hrs respectively (table 4). The formulations AH_1-AH_3 were further modified by incorporating ethyl cellulose (4%W/V) as granulating agent showed release of metoprolol succinate 33.79%, 27.01% and 25.76% respectively at the end of 2 hrs and 99.76%, 98.07%, 99.98% at the end of 24 hrs respectively (table 4). The incorporation of ethyl cellulose (4%W/V) better retarded the release of metoprolol succinate as compared to PVP K30.

TABLE 4: COMPARATIVE *IN VITRO* DISSOLUTION PROFILE OF BATCHES AH_1-AH_6 WITH REFERENCE PRODUCT

Time (hrs)	AH1	AH2	AH3	AH4	AH5	AH6	Reference product
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	29.39	24.32	22.85	18.93	12.82	16.77	18.73
2	33.79	27.01	25.76	24.20	16.99	27.78	21.72
3	42.34	36.11	32.38	28.60	24.30	32.45	26.92
4	49.55	44.28	40.36	34.05	28.81	36.77	32.71
5	58.44	53.57	49.70	40.58	35.98	43.44	39.45
6	69.65	63.65	56.52	45.75	42.29	49.76	44.37
7	75.48	69.26	63.70	50.77	48.48	53.44	49.61
8	88.45	71.89	65.75	55.27	51.35	58.99	53.83
10	92.49	77.74	72.70	60.32	55.96	63.89	58.86
12	99.57	86.00	79.41	65.08	59.92	69.78	62.38
24	99.76	98.07	99.98	95.28	97.29	96.97	97.97

Analysis of Release Data: Once a day modified release tablet should perfectly release the loading dose in first hour (Y_{60}= 20 ± 5 %) and the remaining drug should be released at a fairly constant rate. The 24 h release pattern obtained from the reference product i.e. Seloken XL 100 mg, which meets all criteria of dissolution profile as per USP was considered as a reference release pattern. The constrains were chosen for the selection of acceptable batches are: a) 15 % < Y_{60} < 20 %,

b) 20 % <Y_{240} < 40 %, c) 60 % < Y_{720} < 70 %, d) 8 h < MDT < 10. From the **table 5**, we can conclude that Batch AH_3 fulfills all the desired optimized batch criteria and having highest **f_2 value** (84.95) as well as very closer MDT value (8.9 h) to that of reference product. From the figure 1 it is clearly seen that the release profile of Batch AH_3 is very similar to that of reference product. So Batch AH_3 is considered as the best batch.

TABLE 5: ANALYSIS OF RELEASE DATA SHOWING F_2 VALUE AND MEAN DISSOLUTION TIME

Batch code	f_2 value	MDT Value in (hr)
AH1	31.3	4.31
AH2	39.47	5.65
AH3	84.95	8.9
AH4	50.05	6.95
AH5	75.77	9.48
AH6	66.89	7.56

Model Fitting Kinetic: As clearly indicated in figure 1 the formulations did not follow a zero-order release pattern. The release rate kinetic data for all the other equations can be seen in **table 6**. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid depending on the concentration. As gradient varies, the drug is released, and the distance for diffusion increases.

This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi model. In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi model, as the plots showed high linearity (R^2= 0.994) (table 6).

TABLE 6: FITTING ANALYSIS

Zero order release		First order release		Higuchi Model		Korsmeyer Peppas		Hixon Crowell model		Release mechanism
K_0	R^2	K_1	R^2	K_H	R^2	N	R^2	K_{HC}	R^2	
8.07	0.935	0.071	0.983	27.47	0.994	0.505	0.993	0.199	0.943	Anomalous transport

To confirm the diffusion mechanism, the data were fit into Korsmeyer *et al.,* equation. The formulations AH_1 to AH_6 showed good linearity (R^2=0.993), with slope (*n*) value 0.505 indicating that diffusion is the dominant mechanism of drug release with these formulations. This *n* value, however, appears to indicate a coupling of diffusion and erosion mechanisms so called anomalous diffusion. Hence, diffusion coupled with erosion may be the mechanism for the drug release from batch AH_3.

CONCLUSION: Controlled release following Higuchi kinetics attained in the current study indicates that the matrix tablet of metoprolol succinate prepared using HPMC K100M and ethyl cellulose solution can successfully be employed as once-a-daily oral controlled release drug delivery system. Both the polymer and binder plays a major role for the sustained release of metoprolol succinate. All the formulations showed diffusion dominated drug release.

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