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Preparation and Characterization of Extended Release Matrix Tablets of Bisoprolol Fumerate Using Natural and Synthetic Polymers

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A B S T R A C T

The aim of the present study was to develop extended release formulation of Bisoprolol to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC K15M, Ethyl cellulose, Carbopol, Manugel were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. From the dissolution studies it was evident that the formulation (F4) showed better and desired drug release pattern i.e., 98.26% in 12 hours. It contains the HPMC K15M and Ethyl Cellulose combination polymer. It followed kars mayer peppas kinetics mechanism.

Keywords: Bisoprolol, HPMCK15M, Ethyl Cellulose, Carbopol 934, Manugel

A R T I C L E I N F O

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1. Introduction

Oral Drug Delivery:

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore

maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized:

1. Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.

2. Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3. Targeted-release drug products: A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

2. Materials and Methods

Materials: Bisoprolol fumerate, HPMC K15M, Manugel, Carbopol 934, Ethyl cellulose, PVP K 30, MCC pH 102, Magnesium stearate , Talc.

Methods

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose: The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Bulk density: Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density: After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density; M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility: The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$

Where, b = Bulk Density; Tap = Tapped Density

Formulation development of Tablets: All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Bisoprolol. Total weight of the tablet was considered as 100mg.

Procedure: Bisoprolol and all other ingredients were individually passed through sieve no≠60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Evaluation of post compression parameters for prepared Tablets: The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness: Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters:

Apparatus -- USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCl , p H 6.8 Phophate buffer

RPM -- 50

Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12

Temperature -- 37°c ± 0.5°c

Procedure: 900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 220nm (0.1N HCl) and 222nm (6.8pH) using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

3. Results and Discussions

Preformulation parameters of powder blend: Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.48±0.09 to 0.58±0.01 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57±0.06 to 0.69±0.05 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 14 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.25 indicating the powder has good flow properties. Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression tablet.

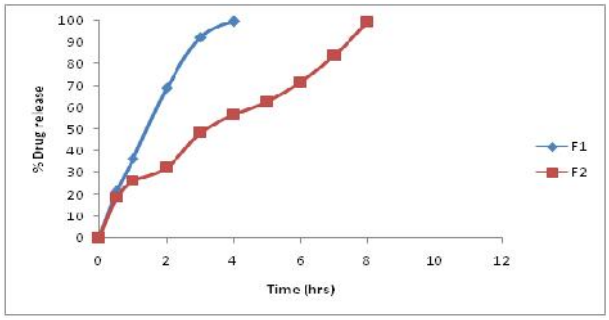

Figure 1: In-vitro drug release of F1 and F2 formulations containing HPMCK15M only

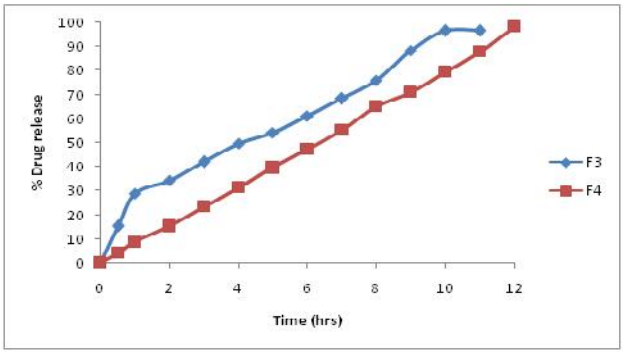

Figure 2: In-vitro drug release of F3 and F4 formulations

containing HPMCK15M and Ethyl Cellulose

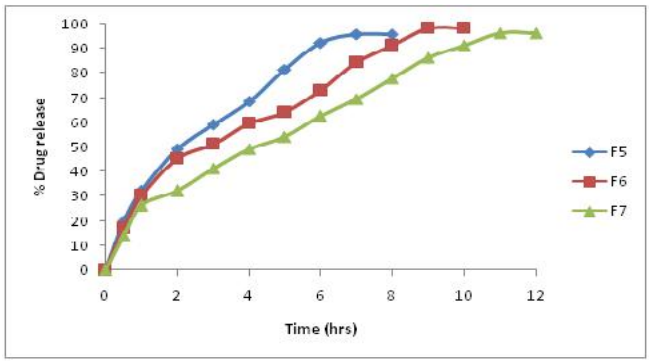

Figure 3: In-vitro drug release of F5, F6 and F7 formulations containing Manugel only

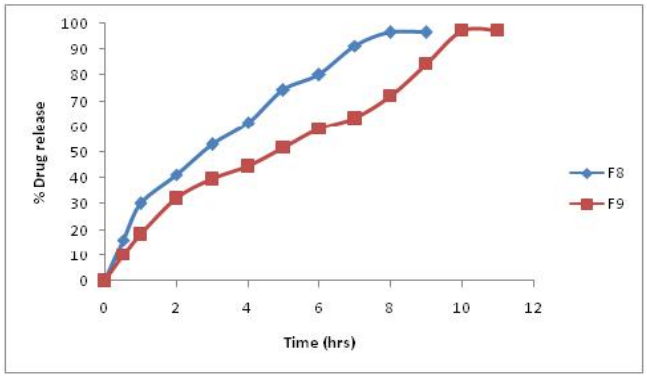

Figure 4: In-vitro drug release of F8 and F9 formulations containing HPMCK15 and Carbopol 940

From the dissolution data it was evident that the formulations prepared with HPMC K15 and Manu gel formulations were unable to retard the drug release up to 12 hrs. Whereas Combination polymer (HPMC K15 and Ethyl Cellulose) formulations were shown good drug release up to 12 hrs. Where Carbopol 940 replaced in place of Ethyl cellulose did not show good drug release. Among formulations F4 formulation containing combination polymers (20 mg of HPMC K 15 and 5 mg of Ethyl cellulose) was concluded as optimised formulation.

4. Conclusion

The present study was aimed to developing extended release tablets of Bisoprolol using natural and synthetic polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies. Tablet powder blend was subjected to various pre-formulation parameters such as angle of repose, bulk density, tapped density, cars Index and hausners ratio. All the formulations were showed good flow properties. Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compressed tablet. From the dissolution data it was evident that the formulation F4 was optimized formulation (containing HPMC K100 and Ethyl cellulose) Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model. it was evident that the formulation F4 was followed Kars mayer peppas mechanism.

Table 1: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.01±0.21	0.49±0.05	0.57±0.06	14.03±0.01	1.16±0.02
F2	26.8±0.35	0.56±0.04	0.67±0.08	16.41±0.00	1.19±0.05
F3	27.7±0.42	0.52±0.09	0.64±0.02	18.75±0.09	1.23±0.06
F4	25.33±0.48	0.54±0.05	0.64±0.04	15.62±0.05	1.18±0.08
F5	25.24±0.52	0.53±0.02	0.65±0.05	18.46±0.09	1.22±0.07
F6	28.12±0.35	0.56±0.03	0.66±0.02	15.15±0.02	1.17±0.05
F7	27.08±0.47	0.58±0.01	0.69±0.05	15.94±0.01	1.18±0.04
F8	25.12±0.51	0.48±0.09	0.57±0.05	15.78±0.05	1.18±0.06
F9	26.45±0.65	0.54±0.02	0.65±0.04	16.92±0.04	1.2±0.07

Table 2: *In-vitro* quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	98.8±1.48	2.5±0.06	0.40±0.08	2.79±0.05	95.1±0.15
F2	99.32±1.42	2.0±0.05	0.19±0.05	3.08±0.06	94.8±0.24
F3	102.88±2.28	2.5±0.07	0.08±0.04	3.05±0.06	91.34±0.32
F4	98.72±0.74	2.4±0.03	0.29±0.05	2.93±0.05	96.55±0.41
F5	98.42±0.85	2.5±0.05	0.30±0.05	2.79±0.07	94.13±0.15
F6	97.02±0.88	2.7±0.01	0.72±0.03	2.76±0.01	99.30±0.18
F7	96.9±1.01	2.3±0.03	0.41±0.04	2.74±0.06	94.82±0.32
F8	99.48±0.37	2.9±0.04	0.20±0.04	2.75±0.04	95.86±0.45
F9	98.4±1.19	2.5±0.06	0.19±0.04	2.76±0.06	96.55±0.25

Table 3: Containing HPMCK15

Time(hrs)	F1*	F2*	F3**	F4**	F5***	F6***	F7***	F8****	F9****
0.5	21.35	18.63	15.33	4.28	20.03	17.24	14.21	16.25	10.24
1	36.47	26.14	29.14	8.96	32.61	30.14	26.33	30.14	18.37
2	68.91	32.14	34.29	15.39	49.22	45.39	32.18	41.32	32.14
3	92.48	48.27	42.14	23.66	59.14	51.27	41.22	53.02	39.61
4	99.42	56.38	49.63	31.47	68.46	59.61	49.3	61.47	44.56
5		62.47	54.22	39.62	81.35	64.14	54.38	74.18	51.87
6		71.58	61.28	47.13	92.48	73.18	62.46	80.16	59.25
7		83.61	68.35	55.27	95.82	84.31	69.57	91.24	63.34
8		99.14	76.13	65.12	95.82	91.26	77.86	96.45	72.15
9			88.47	71.09		98.24	86.34	96.45	84.32
10			96.48	79.36		98.24	91.28		97.14
11			96.48	87.91			96.37		97.14
12				98.26			96.37		

** Containing HPMC K15 and Ethyl cellulose, ***Containing Manugel, **** containing HPMCK15 and Carbopol 940

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