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Formulation Development Of Time Release Dosage Form For Beta Blocker Propranolol.

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ABSTRACT: The objective of the present research work was to develop time-release dosage form for beta-blocker propranolol associated with the heart disease. propranolol is a beta-blocker. Beta-blockers affect the heart and circulation Propranolol is used to treat tremors, angina (chest pain), hypertension (high blood pressure), heart rhythm disorders, and other heart or circulatory conditions. It is also used to treat or prevent heart attack, and to reduce the severity and frequency of migraine headaches. The most commonly used method of modulation the drug release is to include it in a matrix system. For poorly water soluble, drugs, it is necessary to include it in a hydrophilic 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. Hence, in the present work an attempt has been made to develop once daily sustained –release matrix tablets of Propranolol using hydrophilic matrix materials such as hydroxyl propyl methyl cellulose (HPMC) and hydrophobic wax material as hydrogenated castor oil flakes.

Keywords. Propranolol, Anti-hypertensive, hydrophilic matrix tablet, Hydroxy propyl methyl cellulose (HPMC 9000cps).

I. INTRODUCTON.

In the last two-three decades interest in sustain release drug delivery systems is remarkably increasing. This has been due to various factors viz.

- Developing new drug entities.
- Expiration of international patents
- Discovery of new polymeric materials suitable for prolonging the drug release,
- Need of therapeutic efficacy and safety achieved by sustain release drug delivery.

The subject of sustain release has been reviewed by various authors. Several books have been published on it. These reviews and books provide not only the mechanisms and technology of production of dosage forms but also the information on clinical evidence and performance. Propranolol has a half-life of 2 hours and the usual oral dosage regimen is 40 mg taken 2 times a day. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of Propranolol is desirable. The hydrophilic matrix tablet of Propranolol BP containing Hydroxy propyl methyl cellulose (HPMC 9000cps) is suitable for preparation of sustain release tablet. Hence study demonstrated that Hydroxy propyl methyl cellulose (15%-HPMC 9000cps) can be used as a matrix for preparation of once daily formulation of Aceclofenac.

II. MATERIALS AND METHOD.

2.1 Materials: Hydroxy Propyl Methyl Cellulose (HPMC), Hydrogenated Castor Oil Flakes, cetyl alcohol, Dibasic Calcium Phosphate dehydrate, Magnesium stearate, Talc,Carboxypolymethylene, Lactose monohydrate and Sodium Lauryl Sulphate,

2.2 Methods:

2.1 Characterization of Propranolol Pure drug:

2.1.1 Melting point determination:

The melting point of Propranolol was determined by Melting point apparatus using capillary method.

2.1.2. Solubility Determination of Propanol:

The solubility was determined in distilled water and phosphate buffer pH 6.8 The procedure is detailed as follows, in separate 25mlvolumetric flasks, 10mlof distilled water and phosphate buffer pH 6.8 were transferred. Excess quantity of drug was added to each flask. Then by using ultra sonication, the flasks were shaken/sonicated for 48 hours. Mixtures in flasks were filtered. The filtrate was diluted with appropriate mediumand analyzed by using UV spectrophotometer at 290 nm

2.2. Spectroscopic studies:

2.2. a. UV spectroscopy: (Determination of λ max.)

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50mg of Propranolol was accurately weighed and was first dissolved in 50ml methanol AR grade. 2ml of this solution was then diluted to 100ml using phosphate buffer (pH- 6.8) to get a final solution of conc. 20µg/ml. This solution was kept in fused silica cell and UV spectrum was recorded in the wavelength range 200- 400 nm. The wavelength of maximum absorbance (λ max.) was found to be 290 nm.

2.2 b. IR spectrums Interpretation:

The dry sample of Propranolol was mixed by triturating with dry potassium bromide (A.R. Grade) and placed in sample cell. The IR spectrum of the drug sample was recorded and the spectral analysis was done.

III. PREPARATION OF STANDARD CURVE (CALIBRATION CURVE) OF PROPANOL:

A standard curve was prepared by dissolving 50 mg of Propranolol in 50ml of methanol (AR Grade). It was further diluted with dissolution medium i.e., phosphate buffer pH – 6.8 to get solutions in concentration range of 10 to 100µg/ml. The absorbances of these solutions were determined spectrophotometrically at 290 nm.

IV. FORMULATION OF SUSTAINED RELEASE TABLETS:

4.1.I)HYDROPHILIC MATRIX TABLET:

The hydrophilic matrix tablets were preparedby using of Semi-synthetic polymersas HPMC (9000cps) in conc. 10%, 15%, 20%.

Table 1: Each Hydrophilic Matrix Tablet contains Propranolol BP 200mg

Sr. No.	Ingredients	F1 (10%)	F2 (15%)	F3 (20%)
01	Propranolol BP	40 mg	40 mg	40 mg
02	HPMC (9000cps)	12.8 mg	19.2 mg	25.6 mg
03	Dicalcium Phosphate IP	50.8 mg	44.4 mg	38 mg
04	Lactose IP	8 mg	8 mg	8 mg
05	Poly vinyl Pyrrolidone	3.2 mg	3.2 mg	3.2 mg
06	Talc	0.8 mg	0.8 mg	0.8 mg
07	Magnesium stearate	0.4 mg	0.4 mg	0.4 g
08	Sodium laurel sulphate	2.4 mg	2.4 mg	2.4 mg
09	Sodium starch glycolate	1.6 mg	1.6 mg	1.6 mg
10	Isopropyl alcohol	q.s.	q.s.	q.s.
	Total Weight	120 mg	120 mg	120 mg

Procedure:

The tablets were prepared by wet granulation techniques (Formulations F1, F2, F3- Table 5). Drug and other Excipients excluding lubricants were granulated with PVP K-30 using isopropyl alcohol as granulating agent. The wet mass formed was dried and passed through sieve# 16. The granules were lubricated and compressed into round shaped tablets using 8-station rotary tablet compression machine (Model Mini Press- II MT, Make- Rimek). Each tablet contained 200mg of Propranolol BP which is confirmed by content of uniformity test and other pharmaceutical ingredients.

4.1.II) HYDROPHOBIC WAX-MATRIX TABLET:

Table 2: -Each Hydrophobic Wax- Matrix Tablet contain Propranolol200mg

Steps	Ingredients	F4
1	Propranolol BP	10
	Cetyl Alcohol	10
	Hydrogenated Castor Oil Flakes	10
2	Propranolol BP	10

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	Microcrystalline Cellulose	6
	Lactose IP	3.6
	Ethyl Cellulose	16
	Isopropyl alcohol	qs
3	Propranolol BP	20
	Starch IP	13.6
	Microcrystalline Cellulose	16
	HPMC (E5 LV)	4
	Dicalcium Phosphate	8
	Lactose IP	1.6
	PVP K-30	0.4
	Isopropyl alcohol	10
Total weight		129.2 **mg**

Procedure:

Step 1.-The formulations of Wax-Matrix tablets are listed in Table 6. Hydrogenated Castor Oil Flakes and Cetyl alcohol were mixed homogeneously; the blend was heated (85-90^{0}C) in a water bath with continuous agitation. Hydrogenated Castor Oil Flakes and Cetyl alcohol were melted at about 80-90^{0}C. to this melt at 70^{0}C Propranolol was added and the hot molten mass was spread on a tilt glass plate. The mass was allowed to solidify at room temperature. The congealed solid was passed through sieve # 16. The granules obtained were kept for 1 hour at room temperature.

Step 2.- Drug, Microcrystalline Cellulose, Lactose was granulated with Ethyl cellulose using isopropyl alcohol as a granulating agent. The mass was dried at room temperature and passed through sieve # 16. The granules obtained were air dried for 1 hour at room temperature.

Step 3.- Drug and other excipients were granulated with solution of PVP K-30 in Isopropyl alcohol as a granulating agent. The mass was dried and pass-through sieve # 16. The granules obtained were air dried for 1 hour at room temperature. Granules of step 1, 2, 3 were mixed homogeneously in polybag, and lubricated using talc (2%) and magnesium stearate (1%). The granules were compressed into round shaped tablets using 8-station rotary tablet compression machine (Model Mini Press- II MT, Make- Rimek). Each tablet contained200mg of Propranolol BP which is confirmed by content of uniformity test.

4.2.III) FORMULATION CONTAINING POLYMER CARBOMER (C934):

Table 3: Each Tablet formulation prepared using Carbomer (C934) contains Propranolol BP 200mg

Ingredients	**F5C934 3%)**	**F6 (C934-7%)**	**F7(C934-10%)**
Propranolol	40	40	40
HPMC (5 cps) E5 LV	8	8	8
Microcrystalline cellulose	32	32	32
Dicalcium Phosphate	16	16	16
Lactose	24	24	24
PVP K-30	0.8	0.8	0.8
Isopropyl alcohol			
Talc	2.4	2.4	2.4
Magnesium stearate	1.2	1.2	1.2
Carbomer 934	3.6	8.4	12
Total Weight	128	132.8	136.4

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Procedure:

- The tablets were prepared by wet granulation techniques (Formulations F5, F6, F7 Table 7) Drug and other Excipients were granulated with PVP K-30 solution in isopropyl alcohol as granulating agent. The mass formed was dried at room temperature and passed through sieve # 16.
- The granules were first lubricated with Carbomer (C934) for 15 min. and then using talc and magnesium stearate for 2min. in each formulation. These granules were compressed into round shaped tablets using 8-station rotary tablet compression machine (Model Mini Press- II MT, Make- Rimek).
- Each tablet contained 200mg of Propranolol BP which was confirmed by assay and other pharmaceutical ingredients.

The granules were evaluated for following parameters.

1. Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation:

Tan□ = H /R

Where, H = Pile Height.
R = Radius of Pile

Therefore; □ **= tan –1 H / R**

4.3 EVALUATION OF GRANULES:

Table 4:Relationship between Angle of repose (Ø) and flowability

Angle of repose (Ø)	Flowability
< 20	Excellent
20-30	Good
30-34	Acceptable
> 40	Very poor

2. Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2g of granules from each formula was lightly shaken to break agglomerates if any and then was introduced into a 10ml-measuring cylinder. It was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2- second intervals. The tapping was continued until no further change in volume was noted. Loose bulk density (LBD) and tapped bulk density (TBD) was calculated using the following formulae:

LBD = Weight of the granules/Volume of the packing

TBD = Weight of the granules/Tapped volume of the packing

3. Compressibility index:

The compressibility indices of the formulation blends were determined using Carr's compressibility index formula:

Car's compressibility index (%) = (TBD-LBD) X 100
TBD

Table 5: Relationship between % compressibility and flowability

% Compressibility	**Flowability**
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
<40	Very very poor.

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4.4 EVALUATION OF TABLETS:
A: PHYSICAL PARAMETER.
1. Thickness:
The thickness of the tablets was determined using a vernier caliper. Five tablets from each type of formulation were used and average values were calculated.

2. Weight variation test:
To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Table 6.Specifications for tablets as per Pharmacopoeia of India.

Sr. No.	Average Weight of Tablet	% Deviation
1	80 mg or less	10
2	More than 80 mg but less that 250 mg	7.5
3	250 mg or more	5

3. Hardness: For each type of formulation the hardness values for 6 tablets were determined using Monsanto hardness tester.
4. Friability:
Tablets have a tendency to cap during handling and transportation which affects the quality, appearance, drug content, coating requirements and hence friability test is carried out. The apparatus used is Roche friabilator, which consists of a rotating disk 12 inch in of diameter, rotating at speed 100r.p.m. Tablets to be evaluated are added into disc and rotated for 100 revolutions. The percent friability was determined using following formula-

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight 100 r. p. m.}}{\text{Initial weight}} \times 100$$

Limits for friability = < 1%of their weight

B. Chemical Parameters:
1. Uniformity of drug content:
Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 50mg of Propranolol was weighed and dissolved in 50ml methanol. This was the stock solution from which 2ml sample was withdrawn and diluted to 100ml with phosphate buffer (P^H6.8). The absorbance was measured at wavelength 290 nm using double beam UV-Visible spectrophotometer.

2 In vitro dissolution of sustained release matrix tablets of Propranolol:
The study was carried out using dissolution apparatus USP Type-II (paddle)
Dissolution Medium :
Phosphate buffer pH 6.8, 900ml.
Speed of Paddle : 100rpm.
Temperature of Dissolution Medium : 37^0C $\pm 0.5^0$C.

Tablets were placed in the dissolution medium and apparatus was run. At intervals of 0.5,1,1.5, 2, 2.5, 3……. 10 hours, for suitability of dilutions 12.5 ml aliquots were withdrawn and replacement was made each time with 12.5ml of fresh dissolution medium maintained at the same temperature. Each 12.5 ml sample solution was filtered through Whatman filter paper No-41. 12.5ml sample filtrate was diluted to 250ml with phosphate buffer pH 6.8 and the absorbance was measured at 290 nm. Drug concentration in the samples was determined from the standard calibration curve. Cumulative percent of drug dissolved was found out at each time point.

V. CONCLUSION:

Propranolol has a half-life of 2 hours and the usual oral dosage regimen is 40 mg taken 2 times a day. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of Propranolol is desirable. The most commonly used method of modulation the drug release is to include it in a matrix system. For poorly water soluble, drugs, it is necessary to include it in a hydrophilic 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. Hence, in the present work an attempt has been made to develop once daily sustained –release matrix tablets of Propranolol using hydrophilic matrix materials such as hydroxyl propyl methyl cellulose (HPMC) and hydrophobic wax material as hydrogenated castor oil flakes.
The objectives of the study were,

- To design sustained release release tablets of aceclofenac, that will release the drug upto 24 hrs.
- To investigate the effect of polymer concentration on release of Propranolol from different formulation.
- To investigate the effect of type of polymers and effect of various schemes on release of Propranolol from different formulations.
- To arrive at better formulations based on comparison among the studied ones.
- To carryout concurrent process validation of selected better formulation of Propranolol sustained release tablet.

As all the above objectives were successfully studied and confirmed that hydrophilic matrix tablet of Propranolol BP containing Hydroxy propyl methyl cellulose (HPMC 9000cps) is suitable for preparation of sustain release tablet. Hence study demonstrated that Hydroxy propyl methyl cellulose (15%-HPMC 9000cps) can be used as a matrix for preparation of once daily formulation of Aceclofenac.

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