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FORMULATION OF POROUS BASED OSMOTIC DRUG DELIVERY SYSTEM OF METOPROLOL SUCCINATE

Pharmaceutical

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ABSTRACT

Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a pre determined rate and for a predetermined time. The majority of controlled release formulation are designed for oral administration. The objective of the present study is to design Controlled Porous Osmotic Pump Tablet (CPOPT) of Metoprolol Succinate. It was observed that predominantly the drug was released through the pores at a constant rate. The drug is freely soluble in water and administered at a dose of 47.5 mg daily. Half life of Metoprolol Succinate is 3-4 hrs. Hence, an attempt is made to formulate a Porous Osmotic Pump to regulate the release of Metoprolol Succinate by using CPOP system to reduce dosing frequency, avoid dose dumping and maintain uniform plasma concentration of drug and improve the patient compliance. The present study aimed to develop a porous osmotic drug delivery system for controlled release of highly water soluble drug Metoprolol Succinate . core tablet of Metoprolol Succinate containing the mixture of osmogens i.e., Lactose and Fructose with different ratios were formulated and coated with Cellulose Acetate to form nonporous coating membrane. Further 0.4 mm delivery orifices were drilled on one side of the tablet, to select best formulation for further characterization. The present study to analyze the feasibility to consider metoprolol succinate in the form of porous osmotic drug delivery system and sustained release, clearly confirmed that this type of formulation can be administered safely for the treatment of anti-hypertension with improved therapeutic efficacy. Osmotically controlled oral delivery system can be used as once-a day controlled release formulation,thus improved patient compliance.

KEYWORDS

metoprolol succinate, osmogen, pore forming agent, coating material

INTRODUCTION

Novel Drug Delivery Systems (NDDS) constitute the mainstay of pharmaceutical research and development. The focus in NDDS includes design of NDDS for new drugs on one hand and on the other NDDS for established drugs to enhance commercial viability. Although a number of NDDS have been successfully commercialized, per oral controlled release system continue to hold the major market share. A significant milestone in oral NDDS is the development of the osmotic drug delivery system, an innovative and highly versatile drug delivery system[1] The reason for this paradigm shift is relatively low development cost and time required for introducing a NDDS ($20 - 50 million and 3 - 4 years, respectively) as compared to new chemical entity (approximately $500 million and 10 - 12 years, respectively). In the form of NDDS, an existing drug molecule can get a `new life' thereby, increasing its market value competitiveness, and patent life[2].For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. Traditionally, the oral drug delivery has been popular as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs.[3] Conventional drug delivery system have little control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentration[4]. In the recent years, pharmaceutical research has led to the development of several novel drug delivery system. The role of drug development is to take a therapeutically effective, molecule with sub–optimal physicochemical and/or physiological properties and develop an optimized product that will still be therapeutically effective. Controlled drug delivery system should be primarily deemed to achieve more predictable and increased bioavailability[5] Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a pre determined rate and for a predetermined time. The majority of controlled release formulation are designed for oral administration. Recently, such devices has also been introduced for parenteral administration ocular insertion, and for transdermal applications[6].

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field, because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, the patient, the length of the therapy and the properties of the drug. Most of the oral controlled drug delivery systems relay on diffusion, dissolution (or) combination of both mechanisms, to release the drug in a controlled manner to the gastrointestinal tract (GIT).

OBJECTIVES OF THE STUDY

The objective of the present study is to design Controlled Porous Osmotic Pump Tablet (CPOPT) of Metoprolol Succinate. The Controlled Porosity Osmotic Pump Tablets (CPOP) was developed during 1991. The CPOP Tablet is complementary in design to the EOP. However the CPOP is desirable for the delivery of water soluble drugs. It was observed that predominantly the drug was released through the pores at a constant rate. The drug is freely soluble in water and administered at a dose of 47.5 mg daily. Half life of Metoprolol Succinate is 3-4 hrs. When Metoprolol Succinate conventional tablets are administered with food rather than on an empty stomach, peak plasma concentration are higher and the extent of absorption of the drug is increased. The maintenance of a constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic response.Hence, an attempt is made to formulate a Porous Osmotic Pump to regulate the release of Metoprolol Succinate by using CPOP system to reduce dosing frequency, avoid dose dumping and maintain uniform plasma concentration of drug and improve the patient compliance.

METHODS AND MATERIALS

PREFORMULATION STUDIES:

- Determination of λ max of metoprolol succinate.
- Calibration Curve for the drug in pH 1.2 and phosphate buffer saline pH 7.4.
- Preparation of Core tablets with different osmogens (Lactose and Fructose) 1:1 of varying concentration i.e., 1:1(1:1.5), 1:1(3:1), 1:1 (1:3), etc.

EVALUATIONOF GRANULES

Physico chemical parameter of granules

- Bulk Density
- Tapped bulk Density
- Compressibility Index
- Angle of Repose
- Drug content analysis

To prepare the Controlled Porosity Osmotic Pump Tablet using different concentration of pore forming agent.

Evaluation of CPOP Tablets : Determination of physio-chemical parameter of prepared CPOP Tablets like:

- Hardness
- Diameter
- Thickness
- Weight variation
- Friability
- Drug content

EVALUATION OF TABLETS

Determination of physico-chemical parameter of prepared tablets.

- General appearance
- Thickness Diameter
- Hardness Friability
- Weight variation
- Content uniformity.

DETERMINATION of λmax BY UV SPECTRUM:

UV spectrum obtained from 10 µg/ml concentration solution of metoprolol succinate in standard buffer solution.From the spectrum it have been concluded that the maximum absorption takes place at 222nm.

PREPARATION OF STANDARD CALIBRATION CURVE FOR METOPROLOL SUCCINATE:

100 mg of Metoprolol Succinate was accurately weighed and transferred to a small quantity of Hydrochloric Acid buffer in a 100 ml standard flask and made upto the volume. From this primary stock solution 10 ml was pipetted out and made upto 100 ml with Hydrochloric acid buffer pH 1.2 to form the secondary stock solution containing 100 µg/ml.

PREPARATION OF METOPROLOL SUCCINATE CORE TABLETS[7]

Eight formulations of metoprolol Succinate were prepared. Out of which, seven formulations were developed by using two different osmogens separately and in combination with varying proportions of other ingredientsThe eighth formulation is prepared as reference without osmogen used for further comparative studies.

GRANULATION PROCEDURE :

The dry granulation technique is employed for the preparation of granules. In dry granulation process, the powder mixture was compressed without using heat and solvents. Metoprolol Succinate and Dicalcium Phosphate were mixed well by geometric dilution without slugging and passed through sieve No.60. The other ingredients were added and mixed thoroughly using suitable binder PVPK30. Finally the powder mixture was lubricated with 1% Talc and 1% Magnesium Stearate. Then the powder mixture was kept ready for direct compression.

PRE-COMPRESSION PARAMETERS:[8,9,10]

i) DETERMINATION OF BULK DENSITY (g/ml) :

Bulk density is the ratio between a given mass of powder (w) and its bulk volume (V0). Apparent bulk density was determined by pouring the weighed granules into a graduated cylinder by using funnel and measuring the volume. Bulk Density was calculated using the following formula: Mass of the powder

ii) TAPPED DENSITY: (g/ml)

Tapped density is the ratio between a given mass of powder and the constant or final volume of powder after tapping. It was determined by tapping a graduated cylinder containing a known mass of granules for a fixed number of taps until the powder volume has reached minimum.

ASSESSMENT OF FLOW PROPERTIES:

iii) COMPRESSIBILITY INDEX (I):

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from the bulk and tapped density determinations.

iv) ANGLE OF REPOSE :

The flow property was assessed by determining the angle of repose measured by allowing the granules to fall over a paper placed on a horizontal surface through a funnel kept at a suitable height (of about 6 cm from paper). The angle of repose θ is the maximum angle between the surface of a pile of powder and horizontal plane. It is determined by fixed funnel method and different ranges of flow ability in terms powder/granules.

V) ESTIMATION OF DRUG CONTENT

The powdered mixture equivalent to 100 mg of metoprolol succinate was accurately weighed and added with 10 ml of Ethanol in which the drug freely soluble. The mixture was shaken well and filtered. This filtrate was transferred to a 100 ml standard flask and made up with pH 7.4 buffer resulting solution was measured at 222nm. Equivalent weight granules to be taken for each tablet was estimated.

COMPRESSION OF TABLETS

The resulting granules were then compressed into tablet on 8.0 mm round concave punches using single punch table machine. The weight of each tablet was determined to be within the range of 247.5 mg. Each tablet theoretically contains 47.5 mg Metoprolol Succinate (equivalent to 50 mg of Metoprolol Tartrate) and the compression pressures was adjusted so that the average hardness of the tablets after compression was 5 to 6 kg/cm2.

PREPARATION OF COATED TABLETS

PREPARATION OF COATING SOLUTION:

4% w/w of solution of Cellulose Acetate in Acetone and IPA 4:1% was used to coat the tablets as it showed required permeability characteristics and also the coat showed rigidity after 12 hours. To this solution an optimized concentration of 30% w/v of Cellulose Acetate was used. Diethylphthalate was added as a plasticizer.

COATING OF TABLET CORE:[11,12]

The tablets were coated using pan coating machine. A stainless steel pan with a diameter of about 30 cm was used at a rotational speed of 25 rpm. The coating solution was sprayed using an automizer spray gun at a rate of 5 ml/mg. The tablets were coated to a target thickness of about 0.2 mm. The coated tablets were evaluated for film thickness and % weight increase during the coating process.

Further the tablet are drilled delivery orifce size 0.4mm to be made on one side of the surface of the tablet to select the best formulation based on the release charactertics for further development.

POSTCOMPRESSION PARAMETERS[13,14]

1. **General Appearance of tablets:** The tablets prepared were white, slightly biconvex circular, beveled edge coated tablet consistency, odour, taste etc.
2. **Thickness and Diameter:** During punching of tablets thickness and diameter can vary with no change in weight due to difference in the density of granulation and the pressure applied to tablets as well as speed of tablet compression. Diameter and tablet thickness were measured by using Vernier caliper and the results were tabulated in Table No.16. A plus or minus 5% may be allowed for standard value.
3. **Hardness:** The ability of a tablet to withstand handling during packaging and shipping operations. The hardness of the tablet was determined by using Monsanto Hardness tester.
4. **Weight Variation:** Twenty tablets from each formulation were selected randomly and weighed individually. The average weight was then determined for each formulation. Not more than two of the individual weights should deviate from the official standard (limit ± 5%).
5. **Friability:** It measures the ability of the tablet to withstand abrasion during handling .A number of tablets were weighed and placed in the friability apparatus and rotated for 100 times. The weight loss is measured not less than 1% for official limit.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES:

I.DETERMINATION OF λ_{max} FOR METOPROLOL SUCCINATE:

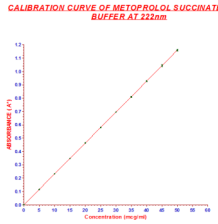
The UV-Spectrum of pure drug in dissolution medium concluded that the maximum absorption at222nm

II.STANDARD CALIBRATION CURVE FOR METOPROLOL SUCCINATE:

By using UV Spectrophotometer method metoprolol succinate was

analysed at the λ_{max} 222 nm. Standard calibration curve were prepared in Hydrochloric acid buffer pH1.2, Phosphate buffer pH7.4. A linear relation in the concentration of 5-50 µg/ml was observed. The correlation co-efficient value was found to be γ=0.999997498, γ=0.999998695.

Figure No:1: Calibration Curve Ofmetoprolol Succinate In Ph 1.2 Buffer At 222 Nm



PRECOMPRESSION PARAMETERS

The granules of F1-F8were prepared and evaluated for the pre-formulation parameters such as Bulk Density, Tapped Density, Compressibility Index, Angle of repose and also the percentage yield and percentage drug content.

1.Bulk Density:

Figure 1:FORMULATION PARAMETERS

Formulation Code	FORMULATION PARAMETERS (Average Values)								
	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Angle of Repose (θ)	Hardness (Kg/cm2)	Thickness (mm)	Diameter (mm)	Friability (%)	Drug Content
F1	0.4431 ± 0.0076	0.5253 ± 0.103	15.65 ± 1.57	27.87 ±0.99	5.2 ±0.464	4.3 ±0.471	8.0 ±0.047	0.693	99.85 ±0.4006
F2	0.4549 ± 0.0081	0.5354 ± 0.0113	15.01 ± 0.268	29.82 ±0.4716	5.3 ±0.471	4.3 ±0.471	8.0 ±0.000	0.628	100.1 ±0.4006
F3	0.4733 ± 0.0004	0.5581 ± 0.0116	15.20 ± 0.268	26.63 ±0.9029	6 ±0.816	4.5 ±0.081	8.1 ±0.047	0.630	99.42 ±0.2027
F4	0.5433 ± 0.0113	0.6383 ± 0.0000	14.89 ±1.772	29.93 ±0.2875	5.3 ±0.471	4.3 ±0.081	8.0 ±0.000	0.669	99.56 ±0.1970
F5	0.5746 ± 0.0012	0.6569 ± 0.0168	12.48 ±2.107	29.23 ±0.942	5.3 ±0.471	4.4 ±0.081	8.1 ±0.047	0.646	99.71 ±0.5318
F6	0.5166 ± 0.0103	0.6239 ± 0.0149	12.86 ±0.256	29.45 ±0.4665	5.3 ±0.471	4.4 ±0.081	8.0 ±0.000	0.665	99.28 ±0.2027
F7	0.5158 ± 0.0010	0.591 ± 0.0013	12.86 ±0.259	29.09 ±0.3064	5.3 ±0.471	4.4 ±0.041	8.0 ±0.000	0.647	99.71 ±0.5318
F8	0.4503 ± 0.0008	0.5298 ± 0.0111	15.01 ±0.268	29.30 ±0.159	5.1 ±0.000	4.4 ±0.047	8.0 ±0.047	0.601	99.71 ±0.5318

The powder mixture of all formulation were evaluated for loose bulk density . The result were found between 0.4431-0.5746 g/ml

2. **Tapped Density:**The Tapped Density for all formulations of powder mixture were also evaluated. The results were found between 0.5253-0.6569 g/ml
3. **Compressibility Index:** The percentage compressibility Index was found to be with in the range of 12.86% -15.65% and had good flow property.
4. **Angle of Repose:** The Angle of repose of prepared granules was found to be 26.63%-29.30% indicated good flow property

CONCLUSION:

The present study aimed to develop a porous osmotic drug delivery system for controlled release of highly water soluble drug Metoprolol Succinate . core tablet of Metoprolol Succinate containing the mixture of osmogens i.e., Lactose and Fructose with different ratios were formulated and coated with Cellulose Acetate to form nonporous coating membrane. Further 0.4 mm delivery orifices were drilled on one side of the tablet, to select best formulation for further characterization. The present study to analyze the feasibility to consider metoprolol succinate in the form of porous osmotic drug delivery system and sustained release, clearly confirmed that this type of formulation can be administered safely for the treatment of anti-hypertension with improved therapeutic efficacy.0smotically controlled oral delivery system can be used as once-a – day controlled release formulation, thus improved patient compliance.

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