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Research Article

Formulation Development and Evaluation of Transdermal Patches of Metoprolol

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Abstract-

Transdermal drug delivery patches offers many advantages over conventional administration such as enhanced potency, increased safety, greater convenience, improved patient compliance and absence of hepatic first pass metabolism. UV spectrogram of metoprolol succinate scanned from 200- 400 nm, λmax found at 220nm**.** All the formulated transdermal patches were evaluated and foundunder limits, average thickness was 0.15mm found and average tensile strength was 0.9 Kg /cm2. The dissolution study of all formulation shows the percentage drug release were found to be F1-93.10%, F2 - 95.25%,F3- 96.16%, F4- 93.95%, F5-96.91% and F6-88.25%, in 24 hour. **F-3** and **F-4** formulations shows excellent drug release profile in steady way.

Keywords: Metoprolol,Ttransdermal patches, Reformulation

Introduction

Transdermal drug delivery patches have been in the market for over a decade.1. Classified into two types, first is passive transdermal delivery system and second type is called the active transdermal delivery system. The Transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs2. It offers many advantages over traditional administration such as enhanced efficacy, increased safety, greater convenience, improved patient compliance and absence of hepatic first pass metabolism3,4. It excludes the variables that affect drug absorption from the gastrointestinal tract such as pH, enzymatic activity and drug food interactions5. This approach of drug delivery is more pertinent in case of chronicdisorders, such as hypertension, which require long term dosing to maintain therapeutic drug concentration6,7.

Metoprolol is a selective β1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension[8]. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias and myocardial infraction. It is almost completely absorbed after oral administration, although the systemic bioavailability varies widely owing to extensive presystemic metabolism. Peak plasma concentrations are achieved after 2-3 hours[9]. The plasma half life is about four hours, which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for long term treatment. The transdermal route of administration is capable of avoiding the hepatic first pass effect, thus achieving higher systemic bioavailability of drug[10].

Materials and Methods

Metoprolol succinate was obtained as a gift sample from Ranbaxy, Devas M.P. Hydroxy Propyl Methyl Cellulose (HPMC) from SulabVarodara, polyvinyl pyrrolidone (PVP) and poly ethylene glycol (PEG) from Rankem Mumbai. All other chemicals were used of analytical grade.

Reformulation Studies

Organoleptic properties: are the aspects that can be experienced through one's senses like taste, smell, sight, and touch. It includes a recording of the color, odour, and taste of the drug.

Solubility: solubility determine by drug dissolve in different solvent systemlikeethanol, methanol, chloroform, acetone, etc. and check according to solubility chart given in IP

Partition co-efficient: partition coefficient is method to determine the lipophilicity and hydrophilicity of the drug. 10 mg drug dissolve in 25 ml water phase and 25 ml of Octanol in a separating funnel and mix well then allow standing for a time, so the two layers separate. One by one layer separate from funnel in separate beakers. Each layer diluted and takes absorbance to detect solubility, then partition coefficient calculated by following formulae

Partition coefficient = (concentration of drug in aqueous phase) / (concentration of drug in oily phase)

Melting Point: Melting point of Metoprolol was determined by taking a small amount of drug in capillary tube sealed at one end using a Bunsen flame. The tube was put in melting point apparatus and the temperature at which the drug melts was noted by thermometer with it.

Scanning For Ultraviolet Absorption Maxima

Ultraviolet absorption in the rage 200 to 800 nm of a 1000 µg/ml solution in 7.4 pH phosphate buffer was measured. The wavelength at maximum absorption (λmax) of Metoprolol in this solution was found to be 220 nm.

Calibration curve of metoprolol

Metoprolol (10 mg) was dissolved in 1ml 7.4 pH phosphate buffer and volume was made up to 10 ml volumetric flask using 7.4 pH phosphate buffers. Five micro liters of stock solution (1 mg/ml) was further diluted with 7.4 pH phosphate buffer, up to 10 ml. This solution (100µg/ml) was further diluted to 7.4 pH phosphate buffer, to obtain solutions of 2 to 10 µg/ml. Absorption of each solution was measured at 220 nm using Systronics UV-2203 UV/Vis double beam spectrophotometer and 7.4 pH phosphate buffer, as a reference standard. Same process repeated with water.

Drug- excipient compatibility:

Physical incompatibility: color changes, dissolution, solubility, sedimentation rate, liquefaction, phase separation or immiscibility.

Chemical incompatibility: undesirable reaction between drug and excipients to monitor if compounds undergo hydrolysis, oxidation, reduction, precipitation, decarboxylation, and racemization.

Therapeutic incompatibility:theinteractions which are observed after administration of the medication. Examples of biopharmaceutical interactions are premature breakdown of enteric coat, interactions due to adjunct therapy and increase in gastrointestinal motility.

Formulations

Method of preparation of transdermal patch of metoprolol

Transdermal patch of metoprolol was prepared by solvent casting methods. Accurately weighed polymers were dissolved in 10 ml of, 1:1 ratio of water and ethanol and kept aside for clear solution. Then drug dissolved in mixture and mixed it until clear solution obtained. Polyethylene glycol 400 was used as plasticizer. The resulted uniform solution was cast on the Petri dish (4.2 cm diameter and area 13.85 cm2) which was lubricated with glycerin and dried at room temperature for 24 h. An inverted funnel was placed over the Petri-dish to prevent fast evaporation of the solvent. After 24 h, the dried patches were taken out and stored in a desiccator for further studies.

Table no. 1: Formulation of Transdermal patches of Metoprool succinate

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6
Metoprolol (mg)	10	10	10	10	10	10
HPMC	5	4	3	2	1	0
PVP	0	1	2	3	4	5
PEG (plasticizer)	3	2	2	2	2	2
Methanol: water (1:1) %w/w	3	3	3	3	3	3

Methods of evaluation of TDDS

Thickness: Patch thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated.

Tensile Strength: The tensile strength of the patch was evaluated by using the Densitometer. It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 1x1cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

Percentage Moisture Content: The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and determined the percentage moisture content from the below mentioned formula:

$$\%\ \textbf{moisture content} = \frac{(\text{initialweight} - \text{final weight})}{\text{final weight}} X\ 100$$

Percentage Moisture Uptake: The weighed films were kept in a desiccator at room temperature for 24 h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, the films were reweighed and determine the percentage moisture uptake from the below mentioned formula:

$$\%\ \textbf{moisture uptake} = \frac{(\text{final weight} - \text{initial weight})}{\text{initialweight}} X\ 100$$

Weight variation: As weight variation between the formulated patches can lead to difference in drug content and in-vitro behaviour, a study was carried out by weighing 6 patches in an electronic balance. The average weight of a patch and its standard deviation was calculated by using their formulas.

Drug Content:A specified area of patch (1cm2) was dissolved in 100 ml ethanol and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometric ally at wavelength of 220 nm and determined the drug content.

In-vitro Drug Release Studies: In-vitro drug release studies were carried out using the paddle over disc method. Dry films of known thickness were cut into circular shape, weighed, and fixed over a glass plate with an adhesive. The plate was then placed in a 900 ml phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32°C ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50rpm, and samples (5 ml aliquots) were withdrawn at appropriate time intervals up to 24 h and analyzed for drug content at 220 nm using double beam UV -visible spectrophotometer. The experiment was performed in triplicate, and the mean value was calculated.

In-vitro skin permeation study: An in-vitro permeation study was carried out by using Franz diffusion cell. The cellophane membrane was carefully mounted between donor and recipient compartments of diffusion cell. Then the formulated patches were positioned over the membrane toward the donor compartment. The receptor

compartment of the diffusion cell was filled with phosphate buffer (pH 7.4) and every 1 h, 5 ml of sample was taken and replaced the same with receptor fluid, and the sample was analyzed for drug content at 220 nm using double beam UV -visible spectrophotometer.

Kinetic modeling of dissolution data: Drug release kinetics were analyzed by various mathematical models such as a zero-order and first-order kinetic models; Higuchi and Korsmeyer–Peppas models to ascertain the kinetics of drug release.

Zero order kinetics: $Q_1 = Q_0 + K_0 t$

Where Q is the amount of the drug dissolved in time t, Q is the initial amount of drug in the solution (most times, Q50) and K is the zero order release constant.

First order kinetics: $\ln Q_1 = \ln Q_0 - K_1 t$

Where Qt is the amount of drug released in time t, Q0 is the initial amount of drug in the solution and K is the first order release constant.

Higuchi model: $Q_t = K_H t_{1/2}$

Where Qt is the amount of drug released in time t, KH is release rate constant.

Korsmeyer–Peppas model: $Q_t/Q_\infty = at^n$

Where n is the release exponent and the function of t is Q /Q (fractional release of the drug)

Result and Discussion

During Preformulation study the metoprolol succinate characterized as white powder freely soluble in water, 0.1N NaOH, 0.1N HCl, 7.4pH buffer and insoluble in ethyl acetate. Having melting point at 122OC and partition coefficient was 0.868. UV spectrogram of metoprolol succinate scanned from 200- 400 nm, λmax found at 220nm. Calibration Curve prepared in 7.4pH buffer and water with R2 value 0.996 and 0.999 respective also calculated Linear equation. FT-IR study indicated on the basis of peaks of both metoprolol(pure) and metoprolol + (HPMC + PVP +PEG), that there is no drug excipient interaction.

Evaluation of transdermal patches: all the formulated transdermal patches are evaluated and found, all are flexible smooth and translucent, weight variation was under limits, average thickness was 0.15mm found, average tensile strength was 0.9 Kg/cm2 found, drug content was 0.73 mg/cm2 average, moisture content % and moisture uptake % also evaluated.

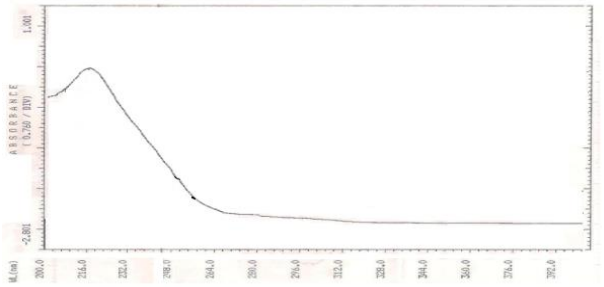

Fig no.1: UV spectrogram of metoprolol succinate scanning from 200- 400 nm

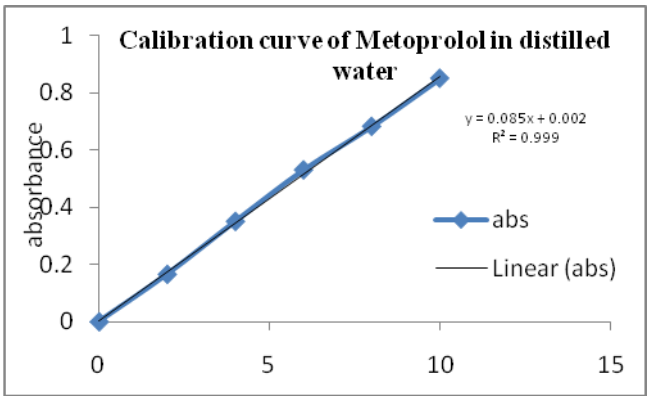

Fig. no.2: Calibration curve of Metoprolol in distilled water

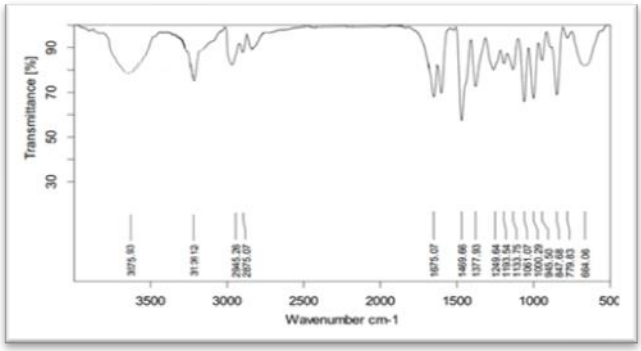

Fig. no.3: FT-IR spectrogram of Metoprolol succinate

In-Vitro Release Profile: all the formulated transdermal patches were evaluated for their In-Vitro Release. The dissolution study of all formulation shows the percentage drug release were found to be F1-93.10%, F2 - 95.25%,F3- 96.16%, F4- 93.95%, F5-96.91% and F6-88.25%, in 24hours. According to drug release studied F-3 and F-4 formulations shows excellent drug release profile in steady way.

Drug release kinetic: kinetic modeling of release profile have done. From the data of drug release, it was found that all the formulations follow diffusion mechanism for the drug release.

Conclusion

The prepared transdermal patches preparations had shown excellent promising results for all the evaluated parameters. Based on the in-vitro drug release and drug content results, F-3 and F-4 formulations has excellent drug release profile as compare to other formulationswhich shows higher percentage of drug release in linear way.In-vitro release profile was applied on various kinetic modeling orders like Zero order, First order and Higuchi model. The best fit with highest regression coefficient was found with Zero order Kinetics. The rate constants are calculated from the slop of the respective plots the release mechanism of transdermal patches. F-3 and F-4 formulations can be further study for preclinical and clinical evaluations. Then can launch in market

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A) Zero order kinetics

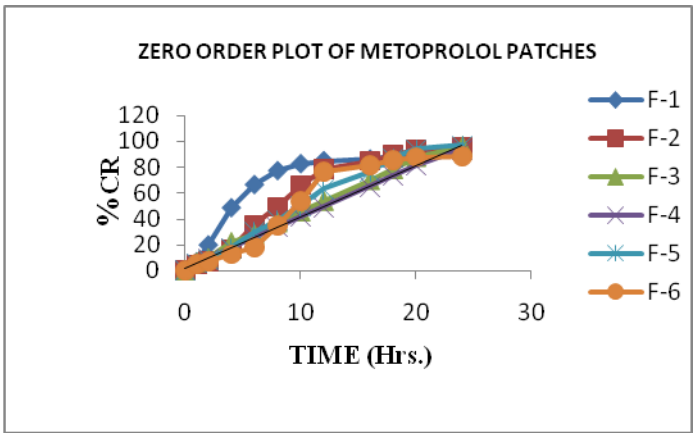

Fig. no.4: Zero Order plots of metoprolol patches (F-1 to F-6)

B) First order kinetics

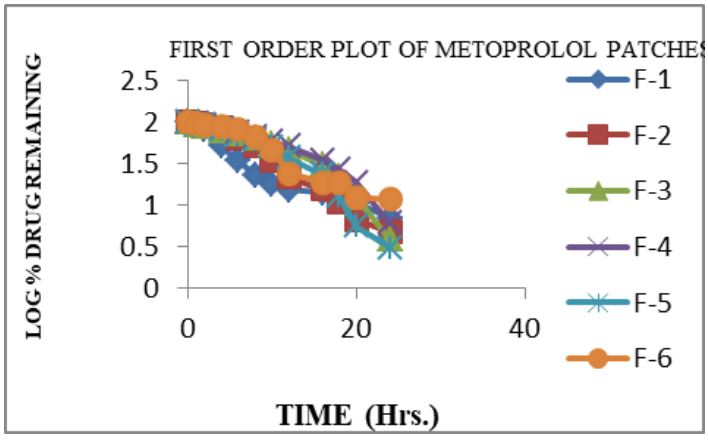

Fig. no. 5: First order plots of Metoprolol patches (F-1 to F-6)

Table no.2: Physico-chemical parameters of the formulated transdermal patches of Metoprolol

Formulation code	Physical appearance	Weight variation (gms)	Thickness (mm)	Tensile strengths (Kg/cm^2)	Moisture content (%)	Moisture uptake (%)	Drug content (mg/cm^2)
F-1	Translucent flexible smooth	0.550 ± 0.028	0.175 ± 0.009	0.846	3.31 ± 0.18	5.43±0.01	0.734
F-2	Translucent flexible smooth	0.562 ± 0.017	0.184 ± 0.013	0.922	2.77 ± 0.164	4.97±0.04	0.713
F-3	Translucent flexible smooth	0.521 ± 0.019	0.147 ± 0.003	0.932	2.09 ± 0.49	3.77±0.09	0.724
F-4	Translucent flexible smooth	0.516 ± 0.009	0.152 ± 0.008	0.955	2.59 ± 0.43	3.15±0.01	0.734
F-5	Translucent flexible smooth	0.498 ± 0.014	0.167 ± 0.015	0.934	1.24 ± 0.57	2.64±0.02	0.741
F-6	Translucent flexible Smooth	0.542 ± 0.013	0.195 ± 0.021	0.882	2.83 ± 0.17	4.05±0.001	0.787

C) Higuchi model of drug release kinetics

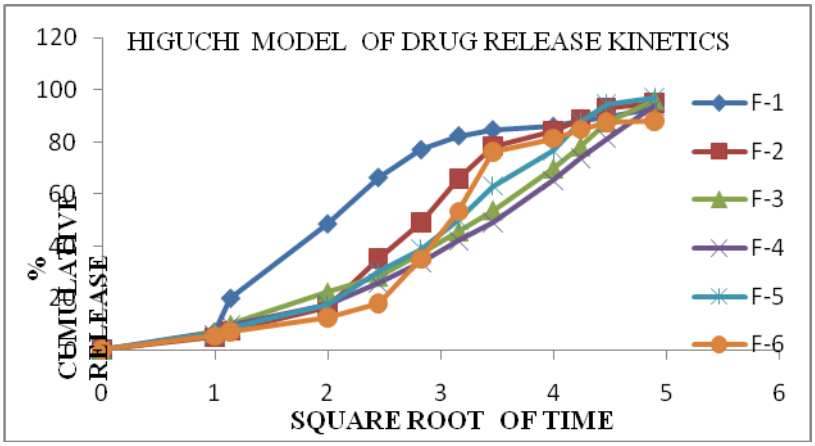

Fig. no. 6: *Higuchi* model plots of metoprolol patches (F-1 to F-6)

D) Peppas model of drug release kinetics

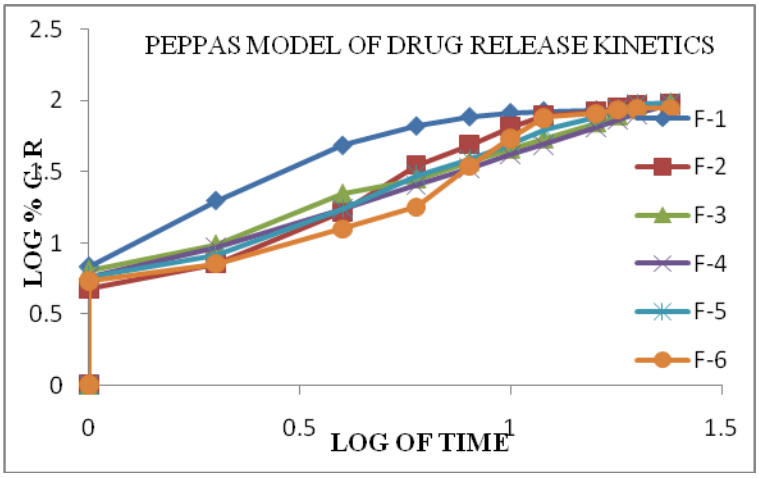

Fig. no.7: *Peppas* model plots of metoprolol patches (F-1 to F-6)