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Metoprolol Tartrate-An Ideal Drug Candidate for Transdermal Antihypertensive Therapy: It's Preliminary Preformulation Screening

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Metoprolol tartrate is the antihypertensive drugs that have been explored for its transdermal delivery potential in the present preliminary preformulation screening. Metoprolol tartrate is a selective adrenergic blocking agent, has become a widely used therapeutic agent for mild and moderate hypertension. Plasma elimination half-life (< 4 h), molecular weight (< 750) and poor bioavailability (40-60 %) due to extensive first pass metabolism, makes metoprolol tartrate a suitable candidate for transdermal drug delivery. However the transdermal route of administration cannot be employed for a large number of drugs therefore before going into the actual formulation of transdermal drug delivery system of metoprolol tartrate, other parameters has also been investigated in the present paper *i.e.*, drug identification by advanced techniques like FTIR/DSC, determination of λ_{max} and plotting of calibration curve of the drug, physicochemical properties of the drug (solubility, melting point, partition coefficient log P), *in vitro* permeation study through porcine skin *via* determination of steady-state flux, permeability coefficient, diffusion coefficient, lag time and permeation enhancement study by permeation enhancers such as SLS, DMSO and oleic acid. The results suggested that metoprolol tartarate is the ideal drug for transdermal drug delivery system and SLS, DMSO and oleic acid induced a significant increase in drug permeation, with DMSO showing the highest enhancing effect at the lowest concentration (5 %) applied and hence may assist in the development of an effective transdermal formulation of metoprolol tartrate for use in humans.

Key Words: Metoprolol tartrate, Hypertension, Preformulation, Solubility, Melting point, Partition coefficient, Porcine skin, Steady-state flux, Permeability coefficient, Diffusion coefficient, Lag time.

INTRODUCTION

Hypertension, a cardiovascular disease accounts for a large proportion of all deaths and disability worldwide. Global Burden of Disease (GBD) study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries. Transdermal systems are ideally suited for diseases that demand chronic treatment. Transdermal drug delivery systems (TDDS) are defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. Transdermal drug delivery systems in comparison to conventional pharmaceutical dosage forms, offer many advantages, such as the possibility of achieving controlled zero order absorption, simple mode of administration and the option of easy withdrawal of dose in case of adverse manifestations and elimination of first-pass metabolism make them desirable in antihypertensive therapy.

Metoprolol tartrate (MT) is a selective adrenergic blocking agent. It is used in the prevention of myocardial infarction, tachycardia, coronary heart disease (prevention of angina attacks), heart failure and hypertension. However, its oral application leads to intensive first-pass hepatic metabolism and it has a short biological half-life (> 4 h). As a result of its intensive first-pass metabolism, frequent dosing is needed to maintain the therapeutic blood level. To overcome these characteristics the administration of metoprolol should be carried out *via* the transdermal route. Metoprolol tartrate has been explored for its transdermal delivery potential in the present preliminary preformulation screening. The relative impermeability of the stratum corneum provides the principal resistance to percutaneous absorption of most drugs. Percutaneous absorption enhancers are therefore required to develop effective formulations of metoprolol tartrate for percutaneous use. The effect of 3 penetration enhancers (5 % SLS, 5 % oleic acid and 5 % DMSO) on the percutaneous absorption of metoprolol tartrate through porcine skin was evaluated *in vitro* using Franz type diffusion cells[1-6].

EXPERIMENTAL

Various preliminary preformulation screening tests have been performed for metoprolol tartrate including tests for physical appearance and organoleptic properties, drug identification by FT-IR and DSC, solubility, analytical methods, estimation using UV spectroscopy, melting point, partition coefficient and permeability coefficient and steady state flux.

IR spectra for pure drug metoprolol tartrate was recorded in a Fourier transform infrared (FTIR) spectrophotometer (Shimadzu Corporation 8600, Japan) with KBr pellets. The measurement of the heat of fusion and the melting point by differential scanning calorimetric (DSC) were performed using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan). The entire samples were run at a scanning rate of 10 ºC/min from 50-300 ºC[7-13]. The UV spectrophotometric analytical methods were developed for the metoprolol tartrate using a Shimadzu (UV-1700) double beam UV spectrophotometer[14]. 100 mg of metoprolol tartrate was accurately weighed and dissolved in sufficient amount of phosphate buffer saline (PBS) pH 7.4 in 100 mL volumetric flasks and diluted appropriately to get the concentration ranging from 1-5 µg/mL. The absorbance was measured at 274 nm against blank phosphate buffer saline pH 7.4. Sample analysis were carried out in triplicate.

Partition coefficient: The *n*-octanol:water partition coefficient is a measure of the relative lipophilic nature of a compound. *n*-Octanol and phosphate buffer saline pH 7.4 were presaturated with each other for atleast 24 h before the experiment. To the pre-equilibrated phosphate buffer saline pH 7.4 (10 ml), known quantity of drug is dissolved. Ten mL of octanol was added to equal volume of phosphate buffer saline pH 7.4 of drug in a separating funnel. The system was kept for 24 h with intermittent shaking. Then aqueous phase (phosphate buffer saline pH 7.4) was separated, centrifuged for 10 min at 2000 rpm. The aqueous phase was assayed before and after partitioning using UV spectrophotometer to get partition coefficient.

Partition coefficient = C_o/C_w, where C_o is the concentration of drug in the octanol and C_w is the concentration of drug in phosphate buffer saline pH 7.4. Experiment was carried out in triplicates and data expressed as mean ± standard deviation of three determinations[15-17].

Determination of drug permeability through porcine ear skin: The permeability study of the drug was carried out across the porcine ear skin using a Franz diffusion cell. The excised skin was mounted between the half-cells with the dermis in contact with receptor fluid (pH 7.4 phosphate buffer) and was equilibrated for 1 h. The receiving chamber had a volume of 20 mL and the area available for diffusion was *ca.* 3.14 cm^2. The donor cell was covered with an aluminum foil to prevent the evaporation of vehicle. The fluid in the receptor compartment was maintained at 37 ± 0.5 ºC. The skin sections were initially left in the Franz cells for 2 h in order to facilitate the hydration of membranes. After this period, A 2 mg/mL drug suspension was prepared in phosphate buffer pH 7.4 and 2 mL of the above suspension was taken in the donor compartment.

The entire assembly was kept on a magnetic stirrer and the solution in the receiver compartment was stirred continuously using a magnetic bead. The sample solution was withdrawn from the receptor compartment (replaced with phosphate buffer saline pH 7.4 to maintain sink condition)at regular intervals and estimated spectrophotometrically (UV) at 276 nm after suitable dilutions to determine the amount of drug diffused.

Data analysis: The permeation of metoprolol tartrate was measured over 12 h and plots of the cumulative amount of drugs permeated per unit skin surface area was plotted against time and the slope of the linear portion of the plot was estimated as the steady-state flux (J_{ss}).

The permeability coefficient (K_p) of the drug diffused through the porcine skin was calculated using the equation:- $K_p = J_{ss}/C_d$ where, J_{ss} = steady-state flux, C_d is the total donor concentration of the solute. The diffusion coefficient (D) was calculated according to the following equation: $D = h^2/ 6.LT$, where h is the skin thickness measured as 0.078 cm. LT is the lag time in hours which is calculated as the intercept on the time axis in the plot of cumulative amount permeated (µg/cm^2) *versus* time (h). The permeation-enhancing activities were expressed as the enhancement factor (EF) of each penetration enhancer as the ratio of steady state drug flux in presence of the enhancer to the steady state flux in absence of the enhancer (control)[18-20].

RESULTS AND DISCUSSION

Organoleptic properties: Table-1 shows the organoleptic properties of the drug.

TABLE-1

Test	Specification	Practical observation
Colour	White crystalline powder	White crystalline powder
Taste	Tasteless	Tasteless
Odour	Odourless	Odourless

FTIR analysis of metoprolol tartrate: The pure drug metoprolol tartrate exhibited characteristic "OH" absorption at 3454 cm^{-1} which is the normal range of absorption for aliphatic hydroxyl group. Secondary immine (NH) has given a weak absorption and Merged with aromatic C-H at 3030 cm^{-1} and aliphatic C-H of CH_3 and OCH_3 at 2980 cm^{-1}. The C-O absorption is found at 1589 cm^{-1} merged with C=C of aromatic (Table-2).

TABLE-2

Assignment of bands	Specification (literature values)	Practical observation
$-NH_2$ + -OH aliphatic and aromatic –CH stretching	3600-2300	3454-2445
Carboxylic acid salt	1580, 1573	1589, 1510 1572
Aromatic ring	1250, 1015 1249, 1109	1247, 1174, 1298
1,4-Disubstituted benzene	1100 1109	1051,1112,823

DSC Analysis of metoprolol tartrate: The DSC thermogram (Fig. 1) shows that when the drug metoprolol tartrate is taken to study its properties at higher temperature it has exhibited the melting endotherm at 125.29 ºC with very little

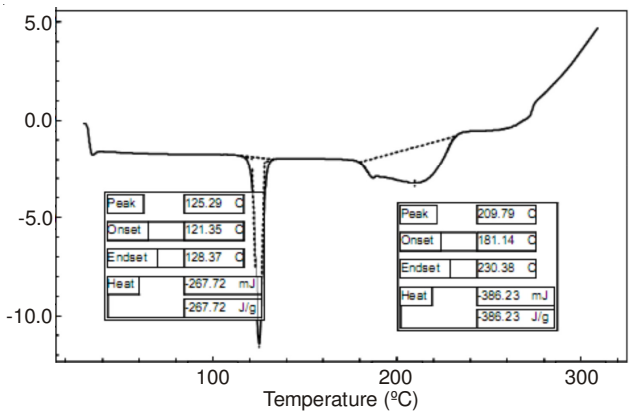

Fig. 1

variation with the literature reported temperature. The value agreed with the literature value of 122.3 ºC, the fusion temperature of metoprolol.

Solubility: Table-3 below shows the solubility of the drug in the different solvents (Fig. 2).

TABLE-3

Solvent code	Solvent system	Solubility* (mg/mL)
1	Distilled water	1034 ± 8.082904
2	Phosphate buffer saline ph 7.4	973 ± 6.658328
3	Ethanol	592 ± 6.506407
4	Methanol	564 ± 8.888194
5	Chloroform	450 ± 7.549834
6	Acetone	354 ± 5.567764

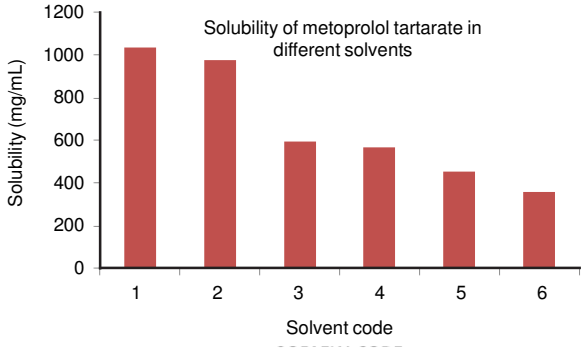

Fig. 2

Calibration curve: The solution of 10 µg/mL was scanned between the wavelength ranges of 200-400 nm in Shimadzu UV spectrophotometer against phosphate buffer saline pH 7.4 as blank and the peaks were recorded at 220 and 274 nm. In the literature, 223 and 274 nm wavelengths were reported. Wavelength of 274 nm was selected for the analytical work.

From the standard curve of metoprolol tartrate (Table-1, Fig. 3), it was observed that the drug obeys Beer's law in concentration range of 1-5 µg/mL in phosphate buffer saline pH 7.4. The linear regression equation (Y = mx + c) generated was used for the calculation of amount of drug.

Partition coefficient: It is widely acknowledged that for a compound to permeate the skin in significant quantities it should possess a log P of *ca.* 1-3. If log P of a permeant is outside of this range it may not easily partition from the formulation into the skin, thus it will exhibit a low transdermal

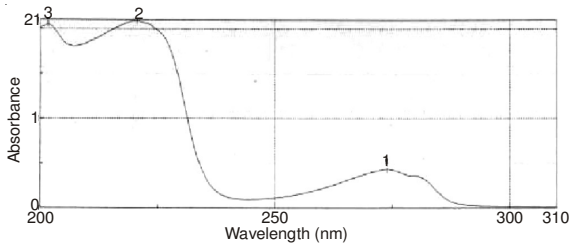

Fig. 3

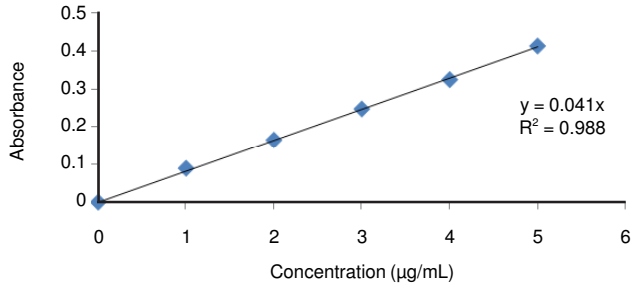

Fig. 4. Calibration curve of metoprolol tartarate

flux. The log P of metoprolol tartrate is around 1.9 which shows the suitability of metoprolol tartrate for transdermal formulation[21].

TABLE-4

Solvent system	Partition coefficient* (log P)
n-Octanol/PBS pH 7.4	1.9 ± 0.015275

*Study conducted in triplicate.

Melting point: Melting point obtained in this work corroborates with the literature value (122.3 ºC). The above melting point is less than 200 ºC which shows the suitability of metoprolol tartrate for tdds. m.p. 125.666 ± 0.57735 ºC.

Data analysis of permeation study using porcine skin: *In vitro* permeation of control drug preparation and other preparations containing permeation enhancers through porcine ear skin indicates that metoprolol tartrate has got good skin permeation property as shown in Table-5.

Conclusion

In this study an attempt was made to explore the transdermal delivery potential of metoprolol tartrate and a study was undertaken regarding its preliminary preformulation screening. In this work the candidate drug was characterized for its physico-chemical properties like melting point, solubility in various solvents, partition coefficient and *in vitro* permeation studies across porcine skin was conducted in phosphate buffer saline initially to assess the permeability of the drug with a blank preparation containing drug only and compared it with the preparations using 3 different permeation enhancers namely- SLS (5 %), DMSO (5 %) and oleic acid (5%). The FTIR and DSC thermogram shows that the sample drug metoprolol tartrate is the original standard drug. The physical characteristics data of metoprolol tartrate on solubility and partition coefficient and literature shows that the drug has a biological half life of 4 h. Hence a good candidate drug for transdermal delivery. The solubility of metoprolol tartrate in different solvents was found to be in the given order-distilled

TABLE-5

Drug with different enhancers	Steady state flux* J_{SS} ($\mu g/cm^2/h$)	Permeability coefficient* K_p (cm/h)	Enhancement factor*	Lag time* (h)	Diffusion coefficient* D (cm^2/h)
Control	1.1984	0.2996	-	1.68	6.03×10^{-4}
SLS (5 %)	1.4183	0.3545	1.183	1.79	5.66×10^{-4}
DMSO (5 %)	2.3778	0.5944	1.984	2.31	4.386×10^{-4}
Oleic acid (5 %)	1.9797	0.4949	1.651	2.11	4.80×10^{-4}

*Study conducted in triplicate.

water > phosphate buffer saline 7.4 > ethanol > methanol > chloroform > acetone. The partition coefficient (log K) of metoprolol tartrate is around 1.9 which shows the suitability of metoprolol tartrate for tdds. Melting point obtained by DSC and capillary method were found to be 125.29 and 125.66 ºC, respectively corroborates with the literature value (122.3 ºC). *In vitro* release study in phosphate buffer saline of pH 7.4 across porcine skin showed that, the drug could permeate through the skin, when in solution. Hence transdermal formulations can be developed. *In vitro* permeation studies of these preparations were conducted in triplicate, to understand the flux of drug, permeability rate and enhancement ratio. Diffusivity and log time were also derived. Our findings suggest that 5 % DMSO, 5 % SLS and 5 % oleic acid are useful for enhancing the transdermal absorption of metoprolol tartrate across porcine skin. Among the penetration enhancers tested 5 % DMSO showed the highest enhancing effect (1.984 fold) but 5 % oleic acid and 5 % SLS also produced a significant increase in permeation. The results provide useful information for the development of a transdermal formulation for use in humans.

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