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Effective and Controlled Transdermal Delivery of Metoprolol Tartarate

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The present work comprises the formulation and evaluation of metoprolol tartarate transdermal drug delivery system for controlled release of drug for extended period of time. Eudragit RL and hydroxypropylmethylcellulose were used for fabrication of the matrix diffusion controlled transdermal drug delivery system. These transdermal drug delivery systems were characterized for their thickness, tensile strength and drug content. Then they were characterized for *in vitro* release kinetics and drug skin permeation studies. The system comprising of Eudragit RL:hydroxypropylmethylcellulose in 40:60 ratio exhibited drug skin permeation 87.5 μg/h/cm². This transdermal system was evaluated for its *in vivo* performance studies and compared its drug plasma profile with those obtained with oral multiple doses administered of conventional tablets of metoprolol tartarate. The transdermal drug delivery system exhibited better and constant drug plasma profile for 24 h as compared to oral administration.

Metoprolol, a β1-selective adrenergic blocking agent, has become well established as a first choice of drugs in the treatment of mild to moderate hypertension and stable angina and is beneficial in post-infarction patients[1]. However, metoprolol is reported to be subjected to extensive hepatic first pass metabolism following oral administration and has a short biological half-life[2]. Therefore, it is aimed to develop transdermal drug delivery system (TDDS) of metoprolol.

Transdermal delivery of metoprolol tartarate avoids the first pass effect and provides greater and more prolonged levels of unchanged metoprolol compared to the oral regime and overcome the problems associated with oral administration of drugs. In addition, patient compliance, convenience of application and removal, reduced frequencies of drug dosing are some more advantages with TDDS[3-8].

In present study, matrix diffusion controlled transdermal drug delivery system was designed and developed for extended delivery of metoprolol using various combinations of hydrophilic and lyophilic polymers. A number of transdermal drug delivery systems of various drugs are reported in the literature but the matrix diffusion controlled transdermal drug delivery system was selected because of ease of fabrication[9-12].

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MATERIALS AND METHODS

Metoprolol tartarate was generously supplied by Concept Pharmaceuticals Ltd., Aurangabad. Eudragit RL was procured from Rohm Pharma, West Germany. Hydroxypropylmethylcellulose was procured from Warner Hindustan Ltd., Hyderabad. Dibutylphthalate was purchased from Sigma Chemical Company, USA. All solvents and other chemicals used were of analytical grade.

Fabrication of transdermal drug delivery system:

The drug reservoir matrix was first casted on a mercury substrate using the method reported by Iyer and Vasavada[13]. Various combinations of Eudragit RL and hydroxypropylmethylcellulose (10% w/v) containing

metoprolol tartarate (5% w/w based on total polymer weight) and 10% w/w (based on total polymer weight) dibutylphthalate as plasticizer were used to cast the drug reservoir matrix films. The solvent evaporation was controlled by an inverted glass funnel of a suitable diameter. After complete evaporation of the solvent at (35±2°), the film was removed from the glass rings and stored at controlled humidity (RH 58%) and temperature (25±2°). Then, one of the surfaces of the drug reservoir film was moistened with its corresponding solvent and a slightly oversized aluminium foil was pressed against it. The film was then allowed to dry in air for 24 h and inspected for complete sealing between the two layers. The aluminium foil was used as a backing membrane. Another surface of the polymeric reservoir film was sprayed with 5% w/v (based on total polymer weight) solution of polyisobutylene (low molecular weight), which was used as adhesive layer. The drug bearing polymeric matrix films was evaluated for their physio-chemical characterization viz. film thickness, tensile strength and drug content.

Characterization of transdermal drug delivery system:

The prepared films were characterized for thickness, tensile strength and drug content. The thickness of the film specimens was measured using a meter gauge (Mercer, USA). The tensile strength (TS) of films was determined using the method reported by Seth *et al.*[14]. The drug reservoir film was fixed to the assembly, the weights required to break the film was noted and simultaneously film elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the drug reservoir film using the formula derived by Allen *et al.*[15], TS=(Break force/axb)x(1+L/l), where, a, b and L are the width, thickness and length of the film and l is the elongation of film at break point. The film thickness and tensile strength was recorded in Table 1.

Drug content was determined by weighing the prepared film (1 cm^2) and dissolving in the respective solvents. The drug concentration noted in Table 1 was determined using HPLC method reported by Hermansson and co-workers[16]

***In vitro* drug release studies:**

The matrix diffusion controlled transdermal drug delivery system of metoprolol tartarate was studied for their *in vitro* drug release to observe the kinetics of drug release from the formulations to the skin. The *in vitro* drug release studies were performed using Franz diffusion cell. The saline phosphate buffer of pH 4.5 containing 20% PEG 400 was used as diffusion medium because the pH of the skin (stratum corneum) is relatively acidic (pH 4.5-5.5) as compared to the dermal side.

TABLE 1: CHARACTERIZATION OF METOPROLOL TARTARATE POLYMERIC FILMS

Polymer film	Film thickness (mm)	Tensile strength kg/cm^2	Drug content (%)/cm^2
Mm RL 10	0.040	2.16	98.9
Mm RL HPMC 82	0.040	2.60	98.9
Mm RL HPMC 64	0.038	2.74	99.0
Mm RL HPMC 46	0.036	2.84	98.9
Mm HPMC 10	0.037	1.42	98.7

Where Mm RL HPMC represents matrix diffusion controlled transdermal of metoprolol tartarate bearing Eudragit RL and hydroxypropyl methylcellulose in the ratio (100:0, 80:20, 60:40, 40:60, 0:100)

***In vitro* drug skin permeation:**

Skin Preparation : Full thickness pig skin was excised from the side of pigs, aged 1-2 w. The subcutaneous fat, tissue, blood vessel and epidermal hairs were carefully removed. The skin was free of obvious holes or defects and was cleaned with normal saline and finally sterile water. It was then blotted dry, wrapped in aluminium foil and stored at –20° before use. To perform the *in vitro* skin permeation experiment, the skin was thawed at room temperature and cut up into 3.5x3.5 cm pieces[17-18].

To assess the skin permeation of metoprolol tartarate from the transdermal drug delivery system bearing metoprolol tartarate, pigskin was sandwiched between the receptor compartment and donor compartment of Franz diffusion cell (1cm^2, Crown Glass Company, NY) in such a way that the stratum corneum side facing upward to the donor compartment and dermal side faced downwards to the receptor compartment. The receptor compartment contained saline phosphate buffer pH 7.4, containing 20% w/v PEG 400 and maintained at 37±1° by a circulating water bath, stirring at 60 rpm. The donor compartment was exposed to ambient temperature (31±1°). A unit of TDDS was placed on the skin, with the drug-releasing surface in close contact with the stratum corneum. Sample of 1ml was withdrawn at frequent intervals for 24 h and replaced immediately with an equal volume of saline phosphate buffer pH 7.4 containing 20% w/v PEG 400. The samples were as-

sayed for metoprolol using HPLC method[16].

In vivo drug skin permeation:

On the basis of *in vitro* drug-skin permeation study, the product Mm RL HPMC 46 was selected for *in vivo* performance studies because it showed drug skin permeation rate nearly equal to the required drug influx rate (87.5 μg/cm²/h) calculated using drug pharmacokinetic parameters.

Selection of animals:

The study protocol approved by the Institutional Animal Ethics Committee, Dr. Hari Singh Gour Vishwavidyalaya, Sagar, and was based on two-way crossover design. Twelve New Zealand rabbits (2.5-2.9 kg, either sex) were chosen for present study. The first set of animals were administered 25 mg metoprolol tartarate (Betaloc^R, AstraZeneca Pharma Ltd, Bangalore) at every six h interval, while the remaining animals were applied TDDS (25 mg/10 cm²), respectively with their adhesive surface to clean inner pinna (ear) skin of rabbit for 24 h period.

Sampling:

After the application or administration of the product, the blood samples were withdrawn from a Teflon-coated indwelling catheter, which had been inserted in the marginal ear vein of the animals. The blood samples (1 ml) collected at 0, 1, 4, 6, 8, 12, 14, 16, 18, 20, 24 and 28 h respectively, were extracted and centrifuged. The organic layer separated and evaporated under a gentle stream of nitrogen at 35°. The residue was reconstituted with mobile phase and an aliquot injected into the HPLC. The HPLC system consisted of 100x3.2 10μm μ Bondapak C18 column, fluorescence detector, F ex 193 em (no cut-off filter), mobile phase composed of MeCN:phosphate buffer (pH-3.0) 30:70. Linearity was evaluated over metoprolol concentration range 10 to 500 ng/ml in plasma, with a minimum detection limit of 0.5 ng/ml[16].

RESULTS AND DISCUSSION

The matrix diffusion controlled transdermal drug delivery system bearing metoprolol tartarate was fabricated using various concentration ratios of Eudragit RS and hydroxypropylmethylcellulose. It is observed that the tensile strength increases from 2.60 kg/cm² to 2.84 kg/cm² as on increasing the concentration of hydroxypropylmethylcellulose (20% to 80%). The drug was uniformly distributed in the polymer films and drug content was found to be 98.9% to 99.4% per cm² in the transdermal drug delivery system.

The transdermal systems of metoprolol tartarate were studied to establish the *in vitro* release kinetics of the drug from the formulations to the skin. The release kinetics was established by determining the diffusional release exponent from the plot of log of cumulative drug release *vs.* log time. The slopes of the straight lines were recorded as values of diffusional release exponent (η)[19]. The slope of diffusional release exponent (η) for matrix diffusion controlled transdermal drug delivery system bearing metoprolol tartarate and consisting of various polymeric combinations with Eudragit RL and hydroxypropylmethylcellulose was calculated to be 0.47 to 0.5 which is very near to 0.5 indicating Fickian diffusion pattern (Square root time dependent of solute release)[19]. Therefore a linear relationship was observed with cumulative drug release *vs.* square root time (fig. 1). The slope of the linear portion of the graph was used to calculate the drug release rate. An initial rapid release was observed in matrix controlled drug delivery systems, which could be accounted for direct exposure of matrix diffusion system to diffusion media and quick release of drug present at the surface[20].

The *in vitro* drug skin permeation studies of the various fabricated transdermal drug delivery systems revealed that on increasing the concentration of the hydrophilic polymer hydroxypropylmethylcellulose from 20% to 80% in the transdermal system, the drug permeation was found to be increased from 77.9 μg/cm²/h to 88.0 μg/h/cm². The enhanced drug skin permeation on incorporation of

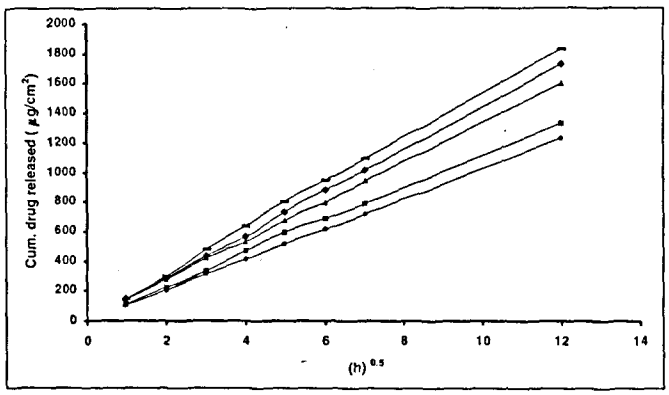

Fig. 1: *In vitro* metoprolol tartarate release profile of matrix diffusion controlled TDDS.

***In vitro* metoprolol tartarate release profile from various combinations of Eudragit RL and hydroxypropylmethylcellulose, RL 10 (-● -), HPMC 10 (-■-), RL HPMC 82 (-▲ -), RL HPMC 64 (-◆-), RL HPMC 46 (- ▬ -)**

hydroxypropyl methylcellulose is due to faster release of the drug from the patch and less partitioning of the drug with the particular polymer combination.

The kinetics of drug permeation through the skin was established by calculating the value of diffusional release exponent from the plot between log cumulative drug permeated *vs.* log time, which is found to be one, indicating that the drug permeation across the skin is following zero order kinetics. Hence a linear relationship was obtained between the cumulative amount of drug (metoprolol tartarate) permeated through the skin and hence a linear relationship was obtained after a lag time of 30-60 min in every case, which could be accounted for time taken by the drug to diffuse across the skin. The slope of linear portion of the graph was used to calculate skin permeability rate (fig. 2).

The system Mm RL HPMC 46 which shows *in vitro* drug skin permeation approximately equal to the required drug influx rate to achieve effective plasma concentration was selected for the *in vivo* performance studies. The *in vivo* performance studies indicates that an effective Metoprolol plasma concentration (~29.0±0.14 ng/ml) can be achieved by the transdermal drug delivery system bearing 25 mg metoprolol tartarate within 6 h which was maintained to 24 h while on oral admininstration of 25 mg/kg metoprolol tartarate at every six hours could achieve (~22.5±0.11 ng/ml) drug plasma concentration (fig. 3).

Moreover, the improved performance of the designed TDDS of metoprolol is also reflected by area under the curve

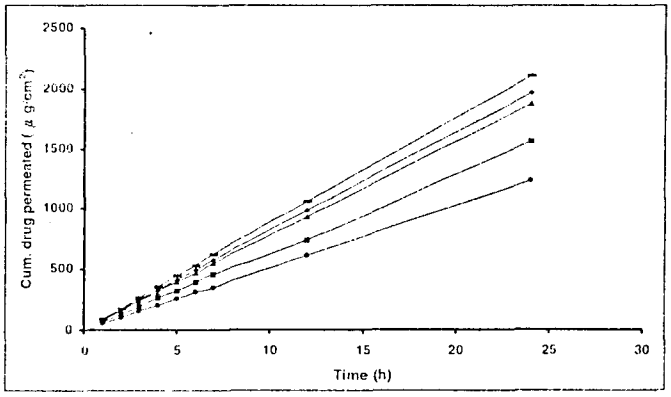

Fig. 2: *In vitro* metoprolol tartarate skin permeation profile of matrix diffusion controlled TDDS.

***In vitro* metoprolol tartarate skin permeation profile from various combinations of Eudragit RL and hydroxypropyl methylcellulose, RL 10 (-●-), HPMC 10 (-■-), RL HPMC 82 (-▲-), RL HPMC 64 (-◆-), RL HPMC 46 (-—-).**

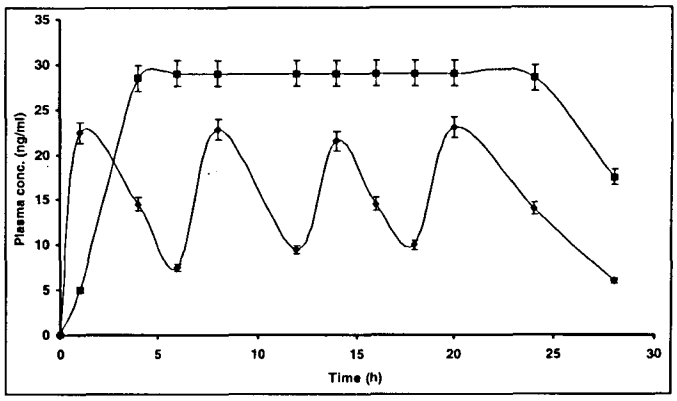

Fig. 3: Plasma level of metoprolol tartarate after oral administration and TDDS application in rabbits.

Data are represented as mean±SD, (n=6). Oral administration (-◆-) TDDS (-■-)

measurement. The most effective *in vivo* performance was recorded for Eudragit RL HPMC 46 (AUC_{0-28} 723 ng.h/ml $^{-1}$) which was better than oral administered conventional doses at every six hours. (AUC_{0-28} 372 ng.h/ml $^{-1}$) as no trough and peaks in drug plasma level was recorded with TDDS It is important to note that area under the curves for transdermal treatment was obtained after the application of 25 mg metoprolol, whereas on oral administration, the AUC was obtained after 25 mg/kg metoprolol tartarate at every six hours i.e. 100 mg.

Thus metoprolol tartarate could be delivered effectively through skin using its transdermal drug delivery system and an effective steady state plasma concentration could be maintained for extended period of time. Using transdermal drug delivery system, the drug doses could be reduced to one fourth.

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