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Matrix type transdermal drug delivery systems of metoprolol tartrate: *In vitro* characterization

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The monolithic matrix type transdermal drug delivery system of metoprolol tartrate were prepared by the film casting on a mercury substrate and characterised *in vitro* by drug release studies, skin permeation studies and drug-excipients interaction analysis. Four formulations were developed, which differed in the ratio of matrix-forming polymers. Formulations MT-1, MT-2, MT-3 and MT-4 were composed of Eudragit RL-100 and polyvinyl pyrrolidone K-30 with the following ratios: 2:8, 4:6, 6:4 and 8:2, respectively. All the four formulations carried 10% (*m/m*) of metoprolol tartrate, 5% (*m/m*) of PEG-400 and 5% (*m/m*) of dimethyl sulfoxide in isopropyl alcohol: dichloromethane (40:60). Cumulative amounts of the drug released in 48 hours from the four formulations were 61.5, 75.4, 84.3 and 94.5%, respectively. The corresponding values for cumulative amounts of the permeated drug for the said formulations were 53.5, 62.5, 69.8 and 78.2%. On the basis of *in vitro* drug release and skin permeation performance, formulation MT-4 was found to be better than the other three formulations and it was selected as the optimized formulation.

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Transdermal delivery has many advantages over conventional modes of drug administration; it thus avoids hepatic first pass metabolism and improves patient compliance (1). Intensive research has shown that transdermal route is a potential mode of delivery of lipophilic drugs in systemic circulation (2). Matrix-based transdermal formulations have been developed for a number of drugs such as nitroglycerin (3), ephedrine (4), ketoprofen (5), propranolol (6) and estradiol (7).

Metoprolol tartrate is a drug used in the treatment of mild to moderate essential hypertension. It acts by blocking the β_1 adrenoreceptors and is almost completely absorbed (95%) after oral administration, although the systemic bioavailability varies widely owing to extensive presystemic metabolism (40–60%). Peak plasma concentrations are

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achived after 2–3 hours. The plasma half-life is about four hours (8), which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long--term treatment. Therefore, MT is an ideal drug candidate for transdermal drug delivery.

EXPERIMENTAL

Metoprolol tartrate, MT (courtesy ASTR-IDL, India), Eudragit-RL 100 (Pharmax India), polyvinyl pyrrolidone, PVP K-30 (Dabur, India), liquid mercury (S.D.S., India), polyethylene glycol PEG-400 (CDH, India), dimethyl sulfoxide, DMSO (S.D. fine chemicals, India), isopropyl alcohol, IPA, and dichloromethane, DCM (E. Merck, India), disodium hydrogen phosphate (Loba Chemie, India), sodium dihydrogen phosphate (BDH, India), sodium chloride (E. Merck, India) and methanol (S.D. fine chemicals, India) were used. All solvents were of analytical or HPLC grade.

Fabrication of patches

The polymeric solution (10%, *m/V*) was prepared by dissolving Eudragit RL 100 and PVP K-30 (ratios 2:8, 4:6, 6:4 and 8:2 in formulations MT-1, MT-2, MT-3 and MT-4 respectively), along with 10% (*m/m*) of MT, 5% (*m/m*) of plasticizer PEG-400 and 5% (*m/m*) of penetration enhancer DMSO (based on total polymer mass) in a mixture of IPA and DCM (40:60). The solution was poured into a glass ring of 6.06 cm diameter placed on the surface of liquid mercury kept in a Petri dish). The solvent was allowed to evaporate under ambient conditions (temperature 32 °C and r.h. 45%) for 24 hours (the solvent got completely evaporated in 24 hours whereas PEG-400 and DSMO remained in the drug--polymer matrix). Aluminium foil was used as backing film and wax paper as released liner (which could be removed before patch application on the skin). The polymer matrix was found to be self sticking due to the presence of Eudragit polymers along with plasticizer. The patches were cut with a circular metallic die of 2.93 cm internal diameter to give an area of 6.74 cm^2 and stored in an airtight container under ambient conditions for 7 days prior to use.

Evaluation of patches

In vitro *drug release studies*. – A modified paddle over disc assembly (USP 23, Apparatus 5), was used for assessment of the release of the drug from the patches (9). The transdermal drug delivery system (TDDS) was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 mL isotonic phosphate buffer (IPB) of pH 7.4, which was composed of 0.16% (*m/V*) sodium dihydrogen phosphate, 0.76% (*m/V*) disodium hydrogen phosphate and 0.44% (*M/V*) sodium chloride. The apparatus was equilibrated to 32 ± 0.5 °C and operated at 50 rpm. The samples (5-mL aliquots) were withdrawn at appropriate time intervals up to 48 hours and analysed at 243 nm (Beckman DU-64 spectrophotometer, USA).

In vitro *skin permeation studies*. – A cell fabricated on the lines of the Franz (10) diffusion cell with a diffusional area of 6.74 cm^2 was used. The skin was removed from the abdominal portion of an albino rat after killing the animal. The hair and fat were re-

moved after treating the skin with 0.32 mol L^{-1} ammonia solution for 35 minutes (11). The stratum corneum side of the skin was kept in intimate contact with the release surface of the TDDS (kept in the donor cell). The receiver phase was 50 mL IPB of pH 7.4 stirred at 500 rpm on a magnetic stirrer. The whole assembly was kept in an oven preset at 32 ± 0.5 °C. The skin was allowed to stabilize till zero UV absorbance was observed before mounting the TDDS in the donor cell. The amount of drug permeated was determined by removing 100 μL samples at appropriate time intervals up to 48 hours. The volume was replenished with an equal quantity of pre-warmed receiver solution. Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm^{-2}) *vs.* time in hours (12) and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^{-2}).

Interaction studies. – Interaction studies were conducted on the medicated TDDS formulations by comparing them with the pure drug and placebo formulations on the basis of assay, UV, IR and TLC analyses. *Assay.* – The TDDS was dissolved in isopropanol and the drug content was determined by UV spectrophotometry. *UV Analysis:* – The isopropanolic solutions of the pure drug, medicated and placebo formulations were filtred through Whatman filter paper no. 42 and scanned spectrophotometrically between 200–400 nm. *IR analysis.* – The IR absorption spectra of the pure, medicated and placebo formulations were taken in the range of 400–4000 cm^{-1} using the potassium bromide disc method (Hitachi-270-30 IR spectrophotometer, Japan). *TLC studies.* – TLC analysis was conducted according to the method reported by Bhushan *et al*. (13) using the silica gel plate with acetonitrile/methanol (80:20 *V/V*) as mobile phase. Iodine vapours were used as visualizing agent.

Stability studies. – Stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines (14) by storing the TDDS samples at 40 ± 0.5 °C and 75 ± 5% r.h. for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyzed for drug content by HPLC (Waters, USA). The chromatographic conditions were as follows: column Lichrospher RP-18.5 μm (125×4 mm); mobile phase: methanol/0.01 mol L^{-1} disodium hydrogen phosphate (60:40); flow rate: 1.5 mL min^{-1}; injection volume: 20 mL; detector: UV, 254 nm; Retention time: 5.5 min.

RESULTS AND DISCUSSION

The monolithic matrix type TDDSs of MT were prepared and characterized on the basis of *in vitro* drug release, skin permeation, interaction and stability studies. The polymers did not interfere with the UV spectrophotometric method used for the analysis as they showed λ_{max} other than observed for the drug. The cumulative amount of drug released in 48 hours was found to be the highest (94.5 ± 2.4%) from formulation MT-4 carrying Eudragit RL-100 and PVP K-30 in 8:2 ratio (Table I, Fig 1). The cumulative amount of drug permeated was again maximum for formulation MT-4 with a value of 78.2 ± 2.8% (Table I, Fig. 2), the permeability coefficient being 0.018 cm h^{-1} (Table I). Formulation MT-4 was selected as the optimized formulation. The results suggest that Eudragit RL 100, being a freely permeable polymer has the major influence on drug release and permeation, as observed by the increase in the amount of drug released and permeation with the incerease in the quantity of Eudragit RL 100 in formulations MT-1 to MT-4. Ini-

Table I. In vitro *drug release and skin permeation of the developed transdermal drug delivery system of metoprolol tartrate*

In vitro parameter	Formulation (Eudragit RL 100/PVP K-30 ratio)			
	MT-1 (2:8)	MT-2 (4:6)	MT-3 (6:4)	MT-4 (8:2)
Cumulative amount of drug released in 48 hours (%)[a]	61.5 (± 1.1)	75.4 (± 1.0)	84.3 (± 2.3)	94.5 (± 2.4)
Cumulative amount of drug permeated in 48 hours (%)[a]	53.5 (± 1.7)	62.5 (± 1.6)	69.8 (± 2.0)	78.2 (± 2.8)
Permeability coefficient (cm $h^{-1} \times 10^2$)[a]	1.2 (± 0.1)	1.2 (± 0.1)	1.5 (± 0.03)	1.8 (± 0.1)

[a] Results are the mean of triplicate observations, SEM values are given in parentheses.

tial rapid release and permeation were observed, gradually approaching constant values for the rest of the time (Figs. 1 and 2), thus conforming to the controlled released behaviour of the formulations. The initial quick release (burst effect) would be beneficial since it would help achieve the therapeutic plasma concentration of the drug in minimum time and the constant release later on would then provide a sustained and controlled released of the drug. Burst effect might be due to the initial migration of the drug towards the surface of the matrix. Linear curves were obtained on plotting the graphs for cumulative % of drug released *vs.* square root of time suggesting the Higuchian matrix diffusion mechanism of drug release from the TDDS formulations. Also, lower RSD values were obtained for zero-order release rate constants compared to the first-order release rate constants indicating a zero-order release pattern from the formulations (Table IV).

Interaction studies were carried out to ascertain any interaction of the drug with the excipients used in the preparation of TDDSs. Therefore, medicated and placebo formulations along with the pure drug sample were subjected to assay, UV, IR, and TLC analyses. Small variations of R_f values of MT as a pure drug and in medicated formulations

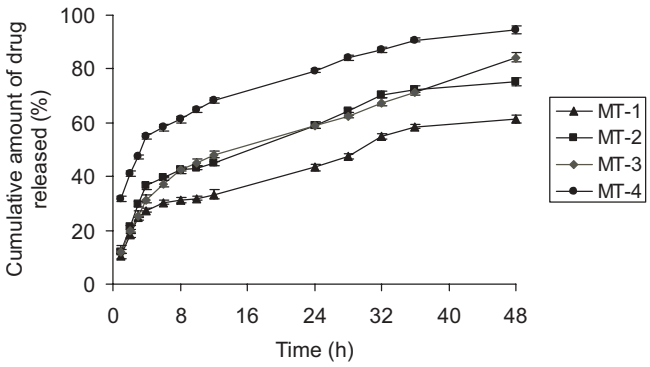

Fig 1. *In vitro* release profiles of metoprolol tartrate from TDDS formulations MT-1, MT-2, MT-3 and MT-4 carrying Eudragit RL 100 and PVP K-30 in 2:8, 4:6, 6:4, 8:2 ratios, respectively. Each point represents the mean ± SEM value (n = 3).

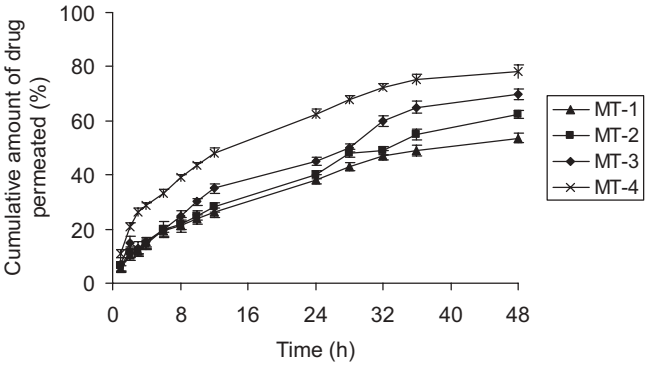

Fig 2. *In vitro* skin permeation profiles of metoprolol tartrate from TDDS formulations MT-1, MT-2, MT-3 and MT-4 carrying Eudragit RL 100 and PVP K-30 in 2:8, 4:6, 6:4, 8:2 ratios, respectively. Each point represents the mean ± SEM value (n = 3).

are evident from Table II. The UV absorption maxima for the pure drug and the medicated formulations was found to be at 243 nm. In analyses of the IR spectra of the pure drug and the medicated formulations, a slight difference was observed in the absorption peak pattern. This might be due to some chemical interaction between the drug and the polymers but this does not seem to affect the drug release from the formulations. The UV and IR spectra of the placebo formulations gave entirely different absorption profiles

Table II. TLC results of the pure drug sample and transdermal formulations of metoprolol tartrate

Sample	R_f value[a]	SEM
Pure drug	0.23	0.02
Formulation MT-1	0.28	0.02
Formulation MT-2	0.24	0.05
Formulation MT-3	0.27	0.08
Formulation MT-4	0.22	0.04

[a] Results are the mean of triplicate observations.

Table III. Assay results of medicated transdermal formulations of metoprolol tartrate

Formulation	Drug loaded (%)[a]	Drug recovered (%)[a]
MT-1	100.0	97.5 (± 1.2)
MT-2	100.0	98.2 (± 1.5)
MT-3	100.0	98.7 (± 0.8)
MT-4	100.0	99.1 (± 0.5)

[a] Results are the mean of triplicate observations, SEM values are given in parentheses.

from those of the pure drug and medicated formulations. On performing the assay, as much as 99.1% of the drug was recovered from the optimized formulation (Table III). The results indicate that the drug remained intact in TDDS and that there was negligible chemical interaction between the drug and the excipients therein.

Table IV. Release rate constants for transdermal formulations of metoprolol tartrate

Formulation	Zero-order rate constant k_0[a]		First-order rate constant k_1 (h^{-1})[a]	
	Mean	RSD (%)	Mean	RSD (%)
MT-1	0.07	46.4	5.75	68.8
MT-2	0.11	53.8	7.13	79.2
MT-3	0.08	33.6	5.92	65.8
MT-4	0.06	41.6	4.63	66.6

[a] $n = 3$

A very low degradation rate constant ($k = 1.7\times10^{-4}$ day^{-1}) was observed on performing the stability studies according to ICH guidelines and a shelf-life of two years could be assigned to the TDDS.

CONCLUSIONS

On the basis of the *in vitro* characterization it was concluded that MT could be administered transdermally through the matrix type TDDS developed in our laboratory. The drug remained intact and stable in the TDDS during storage, with no significant chemical interaction between the drug and the excipients. Further work is under way to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamic studies on human beings.

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S A Ž E T A K

Matriksni transdermalni terapijski sustavi metoprolol tartarata: *In vivo* karakterizacija

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Monolitni transdermalni matriksni terapijski sustavi metoprolol tartarata pripravljeni su u obliku filmova na živinom supstratu. *In vitro* je praćeno oslobađanje ljekovite tvari, permeacija kroz kožu i interakcije ljekovite i pomoćnih tvari. Načinjena su četiri pripravka s različitim udjelom polimera. Pripravci MT-1, MT-2, MT-3 i MT-4 su pripravljeni s Eudragit RL-100 i polivinil pirolidonom K-30 u sljedećim omjerima: 2:8, 4:6, 6:4, odnosno 8:2. Svi pripravci sadržavali su 10% (*m/m*) metoprolol tartarata, 5% (*m/m*) PEG-400 i 5% (*m/m*) dimetil sulfoksida u smjesi izopropanola i diklorometana (40:60). Iz pripravaka je tijekom 48 h ukupno bilo oslobođeno 61,5, 75,4, 84,3 i 94,5% ljekovite tvari. Odgovarajuće vrijednosti ukupno apsorbirane ljekovite tvari iz navedenih pripravka bilo je 53,5, 62,5, 69,8 i 78,2%. Na temelju *in vitro* oslobađanja i apsorpcije kroz kožu, pripravak MT-4 pokazao se boljim od ostalih pripravaka i izabran je kao optimalan.