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Development and *In Vitro* Evaluation of Transdermal Matrix Films of Metoprolol Tartrate

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The transdermal matrix films of metoprolol tartrate (MT) were prepared by casting on mercury substrate employing different ratios of polymers, ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP), using dibutyl phthalate (DBT) as a plasticizer. Four formulations were prepared. Formulations MF-1, MF-2, MF-3 and MF-4 were composed of EC and PVP in the following ratios: 4.5 : 0.5, 4 : 1, 3 : 2 and 2 : 3 respectively. The formulations were subjected to various physical characterization studies namely, thickness, weight variation, drug content, moisture uptake, *in vitro* drug release and *in vitro* skin permeation. The *in vitro* permeation studies were carried out across excised porcine ear skin using Franz diffusion cell. Cumulative amounts of the drug released in 24 hours from the four formulations were 69.58%, 96.13%, 98.85% and 99.60%, respectively. Corresponding values for the cumulated amounts of drug permeated across the porcine skin for the above matrix films were 124.38, 153.22, 156.46 and 163.25 $\mu g/cm^2$ respectively. By fitting the data into zero order, first order and Higuchi model, it was concluded that drug release from matrix films followed Higuchi model ($r^2=0.9147$–0.9823), and the mechanism of release was diffusion mediated. Based on the physical evaluation, *in vitro* drug release & permeation characteristics, it was concluded that for potential therapeutic use, monolithic drug matrix films MF-3, composed of EC: PVP (3 : 2), may be suitable for the development of a transdermal drug delivery system of MT.

Key words——matrix film; transdermal drug delivery; metoprolol tartrate; porcine skin; hypertension

INTRODUCTION

The formulations for skin are of two types depending on the target site of action of the incorporated drug(s). One exhibits systemic effects after the drug uptake from the cutaneous microvasculature network and the other shows local effects in the skin. The pharmacological effects of the former formulations are influenced by the penetration of drug molecules through stratum corneum.[1–4] The development of technology for transdermal delivery of a drug at a predetermined rate into systemic circulation has become popular for various reasons such as avoidance of first pass effect, enhanced efficacy and improved patient compliance. The release of drugs through polymer films is dependent on properties of the polymers and plasticizers.[5,6] The study of *in vitro* drug permeation kinetics through a model skin is important in evaluation of a transdermal drug delivery system and it is also valuable for studying the rate and mechanism of percutaneous absorption of drugs.

Metoprolol tartrate is used as a β-adrenoreceptor blocker. It has a mean plasma half life of 4 hours. Only 40% of the orally administered drug reaches the systemic circulation due to hepatic first pass metabolism. The short plasma half life makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long term treatment of hypertension.[7–10] The objective of the present study was to develop and evaluate different transdermal polymeric matrix films of EC and PVP containing metoprolol tartrate to avoid the hepatic first-pass effect and improve therapeutic efficacy of the drug. For *in vitro* permeation studies excised pig ear skin was used as a model.[11,12] An attempt was made to find out a combination of polymers EC and PVP to formulate transdermal matrix films with good physical characteristics as well as *in vitro* drug release and permeation properties.

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MATERIALS AND METHODS

Materials Metoprolol tartrate (Astra Zeneca, India), Ethyl cellulose (S. D. fine chemicals, Mumbai), Polyvinyl pyrrolidone K-30 (Himedia Labs, Mumbai), Dibutyl phthalate (Qualigen fine chemicals, Mumbai) were used. All reagents and solvents were of analytically graded and used as received.

Compatibility Studies The compatibility studies were carried in order to find out possible interaction between MT and the formulation ingredients. Briefly, 50 mg of drug along with the same amount of formulation additives were placed into separate stoppered volumetric flasks and the volume was made up to 50 ml with phosphate buffered saline pH 7.4 (PBS). The solutions were kept at room temperature for 24 hours with intermittent shaking. At the end of the interaction period, the samples were taken and after suitable dilutions analyzed for drug content at 223 nm using a UV spectrophotometer (Perkin Elmer, model EZ 301). A change in the absorption peak or a shift in the wavelength of absorption was considered as an interaction.

Preparation of Monolithic Drug Loaded Films Four polymeric matrix films were prepared by casting on mercury surface.[13] Briefly, the polymer solution (10% w/v) was prepared in chloroform by dissolving EC and PVP (ratios 4.5 : 0.5, 4 : 1, 3 : 2 and 2 : 3 corresponding to formulations MF-1, MF-2, MF-3 and MF-4 respectively) along with plasticizer DBP (15% w/w of the polymer weight) and the drug MT (30% w/w of polymer weight) (Table 1). The ingredients were dissolved by stirring for 30 min using a magnetic stirrer bar. The homogenous polymer solution was poured into glass rings placed on the surface of mercury kept in a Petri dish. The solvent was allowed to evaporate at room temperature and evaporation was controlled by placing an inverted funnel over the Petri dish. A locally fabricated patch die was used to cut out matrix films of desired size from the cast film. The films were stored in desiccators until used for physical characterization and permeation studies.

Physical Evaluation of Matrix Films The monolithic matrix films of the drug were evaluated for the following physical characteristics.

Thickness The thickness of a matrix film was measured at four points using a thickness gauge employed for plastic films (Prolific Engineers, NOIDA, India). For each formulation three randomly selected films were used.

Table 1. Composition of Metoprolol Tartrate Matrix Films

Ingredients	Matrix film composition			
	MF-1	MF-2	MF-3	MF-4
EC: PVP	4.5 : 0.5	4 : 1	3 : 2	2 : 3
DBP (w/w)	15%	15%	15%	15%
MT (w/w)	30%	30%	30%	30%

EC, ethyl cellulose; PVP, polyvinyl pyrrolidone; DBP, dibutyl phthalate; MT, metoprolol tartrate.

Weight variation Six films from each formulation batch were cut out using a patch die of 1.5 cm diameter, weighed individually and the average weight was calculated to find out the percent weight variation.

Drug content A matrix film of the size specified above was cut into small pieces using a sharp blade and transferred into USP dissolution apparatus vessel containing 900 ml of phosphate buffered saline pH 7.4 and stirred with paddle (50 rpm) at 37±0.5°C for two hours to ensure complete dissolution/release of the drug into the buffer. The solution was analyzed for drug content at 223 nm using UV spectrophotometer. The samples were taken until the absorbance readings became constant (about 3 hours). The drug content of the matrix film was calculated with the help of a standard curve. All the experiments were carried out in triplicate.

Moisture uptake The matrix film of the size specified above was accurately weighed, wrapped in aluminium foil and placed in desiccators containing a saturated solution of aluminium chloride (79.05% RH). After three day, the film was taken out and weighed again. The percent moisture uptake was calculated from the difference between the initial and final weights. All the experiments were carried out in triplicate. The results of all the above matrix film evaluations are shown in Table 2.

Flatness The constriction of a film strip cut out from a drug loaded matrix film is an indicator of its flatness. Briefly, longitudinal strips (1.5×0.75 cm length) were cut out from the prepared medicated matrix films. The initial length of each strip was measured, and then they were kept at room temperature for 30 min. The variation in the length due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero

Table 2. Physical Evaluation Results of Metoprolol Tartrate Matrix Films

Formulations	Composition	Thickness[a] (mm)	Weight[b] (g)	Drug[a,♯] Recovery (%)	Moisture[a] Uptake (%)
MF-1	EC: PVP (4.5 : 0.5)	0.211 (±0.003)	0.2801 (±0.0007)	98.77 (±0.74)	4.18 (±3.31)
MF-2	EC: PVP (4 : 1)	0.216 (±0.005)	0.2848 (±0.0007)	98.93 (±1.00)	9.02 (±0.061)
MF-3	EC: PVP (3 : 2)	0.230 (±0.002)	0.2972 (±0.0019)	99.74 (±0.28)	10.00 (±0.006)
MF-4	EC: PVP (2 : 3)	0.227 (±0.002)	0.3055 (±0.0036)	99.77 (±0.28)	13.12 (±0.22)

a Data represent mean±S.D. (n=3).
b Data represent mean±S.D. (n=6).
♯ Drug content of matrix films=49.4 mg.

Table 3. Determination of Flatness of Different Formulations

S no.	Formulation	EC: PVP	Film length*	Constriction in film	Flatness
1.	MF-1	4.5 : 0.5	1.5 cm	0	100%
2.	MF-2	4 : 1	1.5 cm	0	100%
3.	MF-3	3 : 2	1.5 cm	0	100%
4.	MF-4	2 : 3	1.5 cm	0	100%

* The film strip width was 0.75 cm.
Data represent mean of three observations.

percent constriction was considered to be equal to hundred percent flatness. The experiments were carried out in triplicate (Table 3).

$$\text{Constriction}(\%) = [(L_1 - L_2)/L_1] \times 100$$

where, L_1 is initial length and L_2 is final length of the strip.

***In Vitro* Drug Release Studies** A modified paddle over disc USP dissolution apparatus was used in these studies.[14] A transdermal matrix film was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml of phosphate buffered saline of pH 7.4. The apparatus was equilibrated to 37±0.5℃ and the stirrer paddle speed was set at 50 rpm. The samples were withdrawn at appropriate time intervals and analyzed at 223 nm using a spectrophotometer. The amount of drug released was calculated from the standard curve. All the experiments were carried out in triplicate.

***In Vitro* Skin Permeation Studies** The transdermal permeation studies were carried out using a modified Franz diffusion cell taking porcine skin as an *in vitro* model.[15] The porcine skin from pinna was procured from a local slaughter house. The skin samples were clipped, excised, cleaned with phosphate buffered saline and mounted on the diffusion cell with the stratum corneum side facing the donor compartment.[16] The receptor compartment was filled with PBS at 37±0.5℃. The matrix film was cut out, measured and placed on the skin. The donor compartment was covered with a sheet of aluminium foil and wrapped with a piece of stretchable plastic film to prevent evaporation/drying. At predetermined time intervals, samples were withdrawn from the receptor compartment and the cell was refilled with an equal amount of fresh pre-warmed buffer solution. After suitable dilutions the samples were analyzed at 223 nm by a spectrophotometer. All the experiments were carried out in triplicate.

Statistical Analysis The results were expressed as arithmetic mean±S.D. The statistical analysis was performed using Student's paired t-test. The data was considered significant at $p<0.05$.

RESULTS AND DISCUSSION

Matrix type transdermal films containing metoprolol tartrate with different ratios of polymers, ethyl cellulose and polyvinyl pyrrolidone, were prepared and evaluated for various physical and permeation

characteristics. The possible interaction between drug and the additives was studied by carefully designed compatibility studies. There was no interaction between the drug and polymers and plasticizers as evident from the absence of any difference in the ultraviolet absorption values at 223 nm between the pure drug solution and the drug solutions containing additives. The results of the physical evaluation of matrix films are shown in Table 2. The thickness and weight of matrix films were found to be uniform, which is indicated by low standard deviation values among different batches. This suggests an even distribution of the drug and the polymers in the matrix film cast over the mercury surface. Good uniformity in the drug content among the batches was observed for all the formulations and the percent drug recovery ranged from 98.77±0.74% for formulation MF-1 to 99.77±0.28% for formulation MF-4 (Table 2). The moisture uptake was found to increase slightly with increasing concentration of the hydrophilic polymer PVP in the films. The moisture present in the matrix films helps in maintaining suppleness thus preventing drying and brittleness. Furthermore, a low moisture uptake protects the films from microbial contamination as well as bulkiness of the transdermal patches. Due to moisture uptake from the atmosphere, significant changes in properties like increased total porosity, pore diameter and reduced crushing strength has been reported for matrix films containing hydrophilic polymers.[17] The flatness studies conducted on the matrix films did not show any constriction as indicated by 100% flatness for all the formulations (Table 3). Therefore the films are expected to maintain a smooth surface when applied onto skin. The drug content studies indicate that the drug was homogeneously dispersed in the matrix films (Table 2). The release of a drug from matrix films is controlled by physico-chemical properties of the drug and the polymers used. In this study, the polymeric films of different combinations of EC and PVP released variable amounts of metoprolol tartrate. The cumulative amount of drug released in 24 hours was the highest at 99.60±0.52% from formulation MF-4, containing EC and PVP in 2 : 3 ratios (Table 4 and Fig. 1). Furthermore, the cumulative amount of drug permeated across porcine skin was also found to be the highest for the formulation MF-4, with a 24 hour flux value being 163.25±4.21 $\mu g/cm^2$ (Table 4 and Fig. 2). However, the matrix films MF-4 were found to be too soft and slightly unmanageable. Moreover, there was no significant difference observed between the three formulations MF-2, MF-3 and MF-4 in terms of the amount of drug released as well as the amount permeated through skin *in vitro*. Therefore,

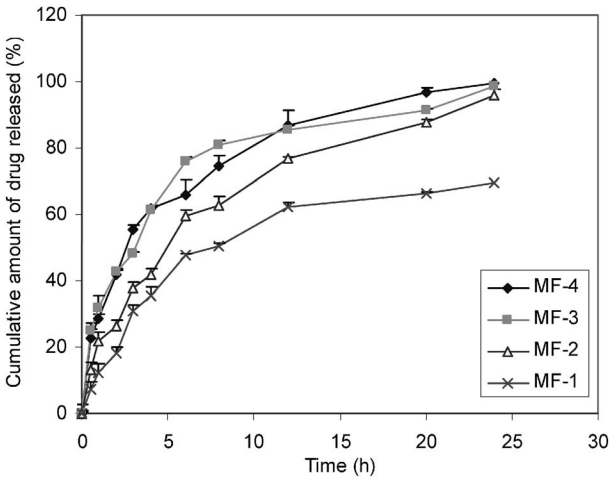

Fig. 1. *In Vitro* Release Profiles of Metoprolol Tartrate from Matrix Films MF-1, MF-2, MF-3 and MF-4
Each data point represents mean±S.D. value ($n=3$).

Table 4. *In Vitro* Drug Release and Skin Permeation Profiles of Metoprolol Tartrate Matrix Films

In Vitro Parameters	Formulation code (EC: PVP ratio)			
	MF-1 EC: PVP (4.5 : 0.5)	MF-2 EC: PVP (4 : 1)	MF-3 EC: PVP (3 : 2)	MF-4 EC: PVP (2 : 3)
Cumulative amount of drug released in 24 hours (%)[a]	69.58 (±0.50)	96.13 (±1.97)	98.85 (±1.27)	99.60 (±0.5)
Cumulative amount of drug Permeated in 24 hours ($\mu g/cm^2/h$)[a]	124.38 (±3.47)	153.22 (±5.33)	156.46 (±4.28)	163.25 (±4.12)
Transdermal flux ($\mu g/cm^2/h$)[a]	5.34 (±0.15)	6.58 (±0.11)	6.41 (±0.19)	6.58 (±0.21)

[a] Results represent mean of triplicate observations.

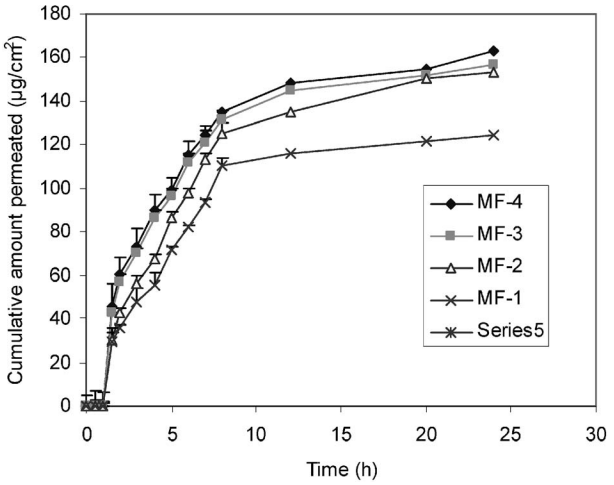

Fig. 2. *In Vitro* Permeation Profiles of Metoprolol Tartrate from Matrix Films MF-1, MF-2, MF-3 and MF-4
Each data point represents mean±S.D. value ($n=3$).

based on better physical characteristics, we selected formulation MF 3 containing EC and PVP in 3 : 2 ratio as the optimized formulation for further studies.[18]

The release of a drug from a transdermal drug delivery system occurs by diffusion, which involves transport of a drug from the polymer matrix into the *in vitro* study medium depending on concentration.[19,20] As the gradient varies, the drug is released and the distance for diffusion becomes increasingly greater. This could be an explanation why the drug diffuses comparatively at a slower rate as the distance for diffusion increases.[21] Initially a rapid drug release and permeation were observed, which gradually approached plateau values (Figs. 1 and 2), thus confirming the controlled release behavior of the matrix formulations. The initial quick migration of the drug towards the matrix surface would help achieve the therapeutic plasma concentration of the drug and the relatively constant release later on would then provide a sustained and controlled release of the drug.

Release Mechanism Investigation The dissolution studies were performed using the USP paddle-over-disc method (50 rpm). The objective was to estimate, characterize and rationalize the drug release from matrix films. The *in vitro* dissolution profiles are often used as surrogates, indicating how a drug will behave *in vivo*. The quantitative analysis of the values obtained in dissolution tests is easier when mathematical equations that express the dissolution results as a function of some of the dosage form characteristics are used. Drug dissolution from solid dosage forms has been described by kinetic models such as zero order, first order, Higuchi, Peppas and Hixon-Crowell.[22] However, the Higuchi model remains one of the most popular mathematical models that have been employed for studying the drug release mechanisms from polymeric films.[23–25] This model is applicable when diffusion is primary drug release controlling mechanism. Peppas[26] introduced the power law equation $M_t/M\infty = kt^n$ to explain the drug release by coupling Fickian and non-Fickian mechanisms. The value of exponent n was used to characterize different release mechanisms. ($n=0.5$, for Fickian diffusion; $0.5 \langle n \rangle 1.0$ or $n=1.0$ or higher, for non-Fickian diffusion). The value of n can be calculated from the slope of $\ln M_t/M\infty$ *vs* $\ln t$. This model is generally used to analyze the drug release from polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.[27]

In order to propose a release mechanism, MT release data was fitted to zero-order, first-order and the Higuchi empiric mathematical model. The *in vitro* drug release profiles did not fit into the zero-order kinetics ($r^2=0.7112$–0.8600) or first-order kinetics ($r^2=0.2965$–0.4448). However, the drug release was found to follow Higuchian kinetics, as the correlation coefficient (r^2 value) was the highest for this model ($r^2=0.9147$–9823), indicating that the drug release was governed by a Fickian diffusion mechanism. Water soluble drugs are released from the polymer matrix primarily by diffusion, while poorly water-soluble drugs are released predominantly by erosion mechanism.[28,29] The equations for the mathematical models employed in our study along with the results are shown in Table 5. The results suggest that PVP, being a hydrophilic polymer, has a major influence on drug release, permeation and physical characteristics of the films, as evidenced by an increase in the amount of drug release and permeation, with increase in the proportion of PVP in formulations MF-1 to MF-4. Thus, based on physical attributes of matrix films and satisfactory release and permeation profiles, formulation MF-3 (EC : PVP, 3 : 2) was selected for development of a transdermal drug delivery system for metoprolol tartrate.

Current models for transdermal delivery assume that the drug diffusivity in the membrane remains constant during transport *i.e.*, the membrane is un-

Table 5. Release Kinetics of Matrix Films of Metoprolol Tartrate

Batch	Zero-order $f_t=k_0 t$		First-order $\ln f_t=k_1 t$		Higuchi $f_t=k_H (t)^{1/2}$	
	k_0	r^2	k_1	r^2	k_H	r^2
MF-1	2.7051	0.794	0.1048	0.4448	15.572	0.9485
MF-2	3.5814	0.86	0.103	0.415	20.159	0.9823
MF-3	3.2599	0.7112	0.0875	0.2965	19.472	0.9197
MF-4	3.4216	0.7605	0.0905	0.3147	20.096	0.9456

Where f_t is the fraction of drug released in time t; k_0, k_1 and k_H are the rate constants for zero-order, first-order and Higuchian release, respectively; r^2 is the coefficient of correlation for each model.

affected by the formulation. However, the aim of a transdermal formulation is to maximize delivery, either by occluding the skin or by releasing the vehicle components that enhance drug penetration. Thus, the membrane is being changed by the formulation. Therefore, a possible advance will be the development of mathematical models that incorporate time-dependent diffusivity that reflect the effect of formulation on the membrane barrier, without compromising the assumption that the membrane remains basically unmodified during the passing of the permeant, diffusion coefficient remaining constant.[30]

CONCLUSION

On the basis of the *in vitro* evaluations of the matrix film formulations, it can be reasonably concluded that metoprolol tartrate can be formulated into transdermal polymeric matrix films for development of a transdermal drug delivery system. The formulation MF-3 (EC : PVP, 3 : 2) was found to be the best one and it may be employed for further pharmacokinetic and pharmacodynamic studies in suitable animal models and human beings.

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