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DEVELOPMENT AND EVALUATION OF TRANSDERMAL SALBUTAMOL DELIVERING SYSTEMS

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ABSTRACT

The transdermal drug delivery systems based on polymeric pseudolatex and matrix diffusion controlled systems for salbutamol were prepared and compared for *in vitro* skin permeation profile and *in vivo* performances. Poly (isobutylene) was used as release controlling polymer in both the systems. *In vitro* skin permeation was studied using the human cadavar skin in franz diffusion cell. Permeation rate constants for matrix diffusion controlled system and pseudolatices were 10.625 and 13.750 mcg/hr/cm^2 respectively. The prepared transdermal systems were tested on human volunteers having chronic reversible airways obstruction and compared with oral treatments (Asthaline). The *in vivo* drug plasma profiles following transdermal and oral treatments reveal that although peak plasma level by oral administration was higher in comparison with the transdermal treatments, troughs and peaks were discernible at dosing times. In the case of transdermal treatments, constant drug plasma and FEV_1 levels were recorded indicating controlled and systemic delivery of drug spaced over 30 hours.

Among the prepared transdermal drug delivery systems, pseudolatices demonstrated better drug plasma profile, maintained at relatively higher level and flatter in appearance. The relative performance of the systems was noted to reflect in AUC and FEV_1.

INTRODUCTION

Transdermal application of drugs have attracted pharmaceutical scientist and acquired considerable importance during last few years. The release of active ingredient from these systems and the permeation through the skin are governed by the law of passive diffusion.

The ability of transdermally delivered drug to produce an efficacious systemic level of a medicament and the advantages associated with this mode of systemic delivery system have stimulated the development of several experimental and commercially available reservoir systems. These reservoirs are matrix diffusion controlled, membrane permeation controlled, microsealed, and pseudolatices (1-5). The polymeric matrix is an "open cell molecular sponge" which contains a drug in a dispersed or dissolved state. Recently, a pseudolatex based transdermal system has been developed for lidocaine and ephedrine (5-6). Pseudolatices are a new class of polymeric colloidal dispersions which produce highly substantive, clear and virtually invisible polymeric films on their application to the skin.

Salbutamol is a semi-selective $beta_2$-agonist commonly used as a bronchodilator for the treatment of chronic obstructive airways disease. It is generally accepted that the optimal method of administration of a sympathomimetic drug is by inhalation from a pressurised aerosol or drug powder device (7). The recommended dose of salbutamol for oral administration is 4 mg 3-4 times daily for adults. In order to achieve an optimal clinical effect it is most important that the drug should be taken regularly at every 6-8 hours. For better patient compliance and to reduce the

proportion of missed doses. The controlled release preparation of salbutamol has been devised to provide linear release of the drug based on osmotic pressure mediated delivery principle (8). The salbutamol is metabolised by hepatic pass effect in the liver, and as a result, about half of the administered dose is recovered in the urine as an inactive sulphate metabolite (9). Green and Sapra (10) and Jain et al. (11) reported that salbutamol is significantly absorbed through skin on topical application. Therefore, the designing of transdermal drug delivery systems are realised to exclude hepatic first pass metabolism and to control the delivery of drug to the systemic circulation.

The present study was undertaken to design and assess the in vitro and in vivo performances of matrix diffusion controlled and pseudolatex based transdermal drug delivery systems of salbutamol. The in vivo performance of these systems was compared with orally administered salbutamol.

MATERIALS AND METHODS

Materials

Salbutamol (Ranbaxy Laboratories, Delhi, India), Poly (isobutylene), (medium molecular weight, Aldrich Chemical Co. Inc. Milwaukee WIS 53233 USA), Tween 80 [Polyoxyethylene-(80)- Sorbitan monooleate, Kochlight Chemical Lab. England]. Dibutyl-phthalate (Sigma Chemical Co., St. Louis, USA), liquid paraffin (Loba Chemie Ind. Co. Bombay) other chemicals and reagents were used as obtained.

Determination of Partition Coefficient

The partition coefficient of salbutamol was determined between n-octanol and saline phosphate buffer of pH 7.4 (12). A 0.01% solution of drug (standard) was prepared in organic phase and 20 ml aliquots pipetted into each of four 100 ml glass stoppered conical flasks. 20 ml of Buffer (pH 7.4) was added to each flasks which were corked and agitated at 37^{o} for 8 h. After

separation, the concentration of drug in aqueous phase was determined spectrophotometrically by the method reported by Shigbal and Joshi (13).

Preparation of Matrix Diffusion Patch

Matrix diffusion patches containing salbutamol were prepared on mercury substrate by the method reported by Iyer and Vasavada (14) for film casting. The polymeric solution of 5.0 w/w poly (isobutylene) of medium molecular weight containing 5% w/w mineral oil and 2% w/w salbutamol (based on total polymer weight) in chloroform was used for casting of drug reservoir film. Five millilitre of drug-polymer solution was poured into glass ring (10 cm^2) on a mercury substrate. The films were removed from these glass rings after complete evaporation of solvent and stored at controlled humidity (R.H. 58%) and temperature (28 ± 1^oC).

The surfaces of drug polymeric films formed were moistened with chloroform to seal an oversized aluminum foil over it to serve as backing membrane. The films were allowed to dry in air for 24 hours and inspected for complete sealing.

Preparation of Pseudolatices :

The salbutamol-poly (isobutylene) pseudolatices were prepared by a solvent evaporation method (5). The drug, polymer and mineral oil solution in chloroform of the same composition as used in the preparation of matrix diffusion patch was emulsifiedd with an aqueous solution of surfactant (Tween-80, 10% w/w based on total polymer weight). The organic solvent and water fraction (30-40%) were removed by evaporation at 50^oC under constant stirring. The pseudolatices were stored at a constant humidity (R.H. 58%) and temperature (28 ± 2^oC).

Determination of Drug Concentration

The salbutamol content in both the formulations was determined spectrophotometrically (13). A sample of dried product was weighed (100-200 mg) and dissolved in 10 ml chloroform and the drug was extracted with distilled water (20 ml). The aqueous

phase was separated and after appropriate dilution with distilled water the color was finally developed using p-nitroaniline, sodium nitrite and sodium hydroxide solution as reported by Shigbal and Joshi (13). Absorbance was measured at 485 nm using a Shimadzu double beam uv 150-02 spectrophotometer.

In-vitro Skin Permeation Studies

The in-vitro skin permeation studies were undertaken in order to quantitate the in-vitro availability of the salbutamol from the prepared transdermal systems using a franz diffusion cell (Crown Glass Co. New Jersey, USA). The full thickness (undermatized) cadavar skin (55 yrs, male, mastoid prominence region) was so mounted on the diffusion cell that stratum corneum faced the donor compartment.

The preparation was applied directly to the stratum corneum in the donar compartment of the diffusion cell. The receiver compartment of the diffusion cell contained saline phosphate buffer pH 7.4. In this system, sink condition was simulated by controlling the rceiver compartment temperature at $37\pm1^{O}C$ while allowing the donar compartment to be exposed to the ambient temperature ($28^{O}C$).

Samples (0.5 ml) from the receiver compartment were withdrawn periodically for 32 hours and replaced with an equal volume of fresh saline phosphate buffer (SPB) pH 7.4. The salbutamol concentrations were determined spectrophotometrically (13).

In-vivo Performance

The in-vivo performance of matrix diffusion transdermal drug delivery system and pseudolatices of salbutamol was evaluated by periodic measuring of salbutamol concentration in blood vis-a-vis the forced expiratory volume (FEV_1) and these were compared with an orally given conventional tablet of salbutamol (Asthaline^{R}, 4 mg salbutamol tablet, Cipla Laboratories, India).

Subjects : The study was undertaken on 12 human volunteers (male) with chronic reversible airways obstruction. The average height,

weight and age were 167.5 cm (165-170 cm), 60 kg (55-65 kg) and 50 year (40-60 years) respectively. The consent was given by all the volunteers prior to their participation in the study.

Study design : The study was of a randomized three-way cross-over design. All volunteers entered the study simultaneously. The volunteers were devided into three groups. The first group received Asthaline^{R} (4 mg salbutamol conventional tablet, Cipla Laboratories India) orally at every six hours intervals. The volunteers of second group received a matrix diffusion controlled transdermal drug delivery system (MDC-TDDS) and third group volunteers received the pseudolatex based transdermal drug delivery system (PS-TDDS). Both transdermal systems contain 5 mg salbutamol and were applied topically on a cleaned 10 cm^2 area of the mastoid prominence (near intra-auricular region). After a gap of fifteen days a randomized three way cross over study was performed by exchanging the subjects of different groups for the application of salbutamol transdermal preparations and oral administration of the conventional tablet.

Sampling : Following the application of transdermal systems and oral administration of Asthaline^{R} tablets, the blood samples were collected from each subjects at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28 and 32 hours and the plasma was separated by centrifugation and stored frozen till subsequently assayed.

Simultaneously the forced expiratory volume (FEV_1) was measured in a manner described by Walker and co-workers (15). The salbutamol concentration was determined by high performance liquid chromatography described by Hutchings and co-workers (16) using Shimadzu model LC-3A high performance liquid chromatograph equipped with a fluorescence spectromonitor (Shimadzu model RF 530).

RESULTS AND DISCUSSION

The partition coefficient of salbutamol between n-octanol and saline phosphate buffer pH 7.4 was determined to be 0.84,

which is very near to the partition coefficient for an ideal drug for transdermal permeation (17). It is reported that compounds with higher partition coefficient do not penetrate from the stratum corneum layer to water rich dermal tissues (18). Therefore, the drug should have the lipophilicity that facilitates across skin permeability via stratum corneum layer.

Matrix diffusion controlled transdermal drug delivery system (MDC-TDDS) and pseudolatex based transdermal drug delivery system (PS-TDDS) were prepared using poly (isobutylene), medium molecular weight. They were studied for their in-vitro skin permeation. The skin permeation study was performed using human cadaver skin in franz diffusion cell. It was observed that the skin permeation of the drug from cadavar skin follows zero-order kinetics as shown in Fig. 1. The skin permeation rate for drug from pseudolatices was comparatively higher than determined after the application of MDC-TDDS (i.e. 13.750 and 10.625 mcg/hr/cm^2 respectively). The higher permeation rate of salbutamol from pseudolatices could be ascribed to the uniform and fine dispersion of the drug in coalesced structure of the pseudolatices. Moreover, the use of a surfactant in the pseudolatices may also enhance the drug penetration through skin as discussed by Buyukyaylaci et al. (5).

In-vivo performance of transdermal products were compared with orally administered conventional tablets (Asthaline^R). The drug plasma level as well as forced expiratory volume (FEV_1) were measured in asthmatic patient. The mean salbutamol plasma concentrations as a function of time for both transdermal drug delivery systems and orally administered conventional tablets are shown in Figure 2. The plasma concentration of salbutamol gradually increased and reached an average steady state level of approximately 9.626 ± 0.625 ng/ml within 6 hrs and 11.25 ± 1.00 ng/ml within 5 hrs for MDC-TDDS and PS-TDDS respectively (Table 1). The average plasma concentration of salbutamol remained constant for 24 hours and declined gradually on removal of the transdermal

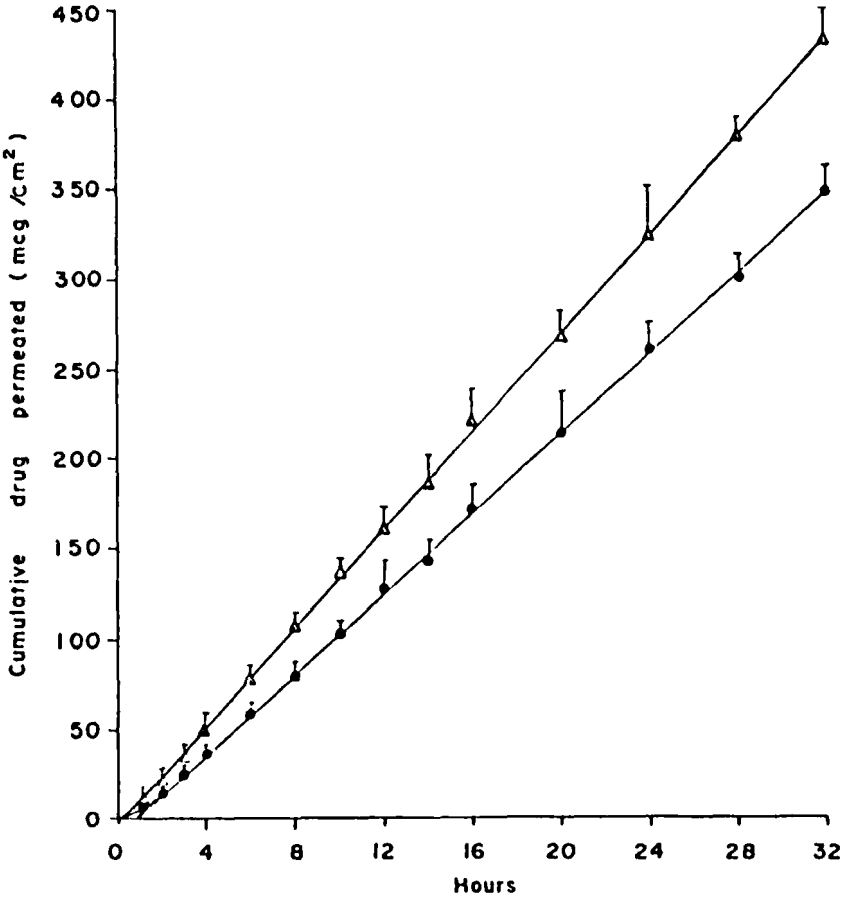

Figure 1

In vitro drug permeation profiles of salbutamol from matrix diffusion controlled and pseudolatex based transdermal drug delivery systems through human cadavar skin. (Bar indicates +SD (one side deviation). (●) Matrix diffusion controlled TDDS, (▲) Pseudolatex based TDDS.

preparation (after 24 hours). However, in case of oral administration of salbutamol conventional tablet Asthaline^{R}, the peak plasma concentration of salbutamol was reached to 14.5 ± 1.25 ng/ml within 3 hours and declined rapidly. On multiple dosing of Asthaline^{R} (i.e. 4 mg at 6 hours intervals) the drug profile assumed a shape of troughs and peaks (Figure 2).

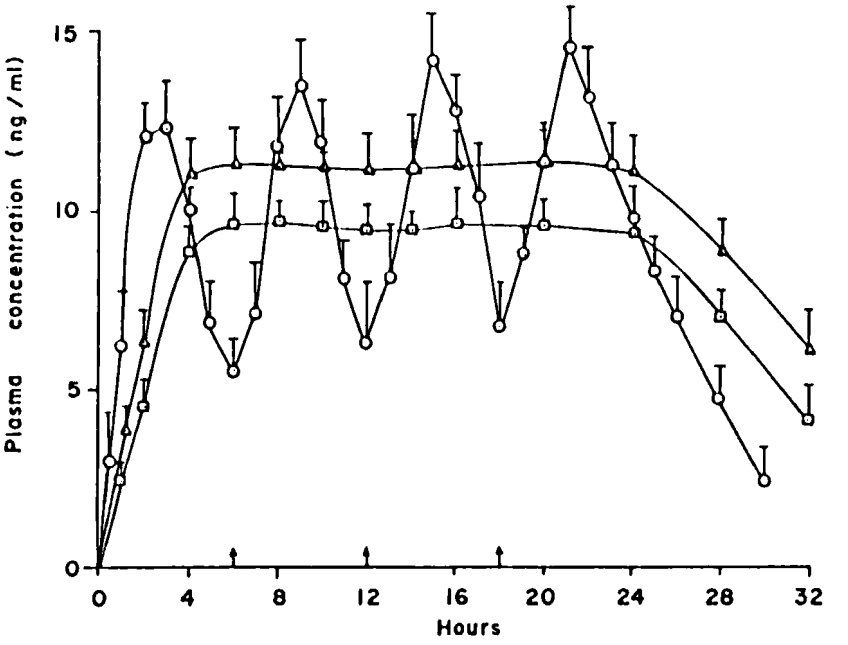

Figure 2

Drug plasma profiles of salbutamol following oral administration of conventional tablet and TDD preparation application. (●) Oral conventional tablet administration; (□) Matrix diffusion controlled TDDS and (△) Pseudolatex based TDDS. Bar indicates +SD (one side deviation).

TABLE 1

Pharmacokinetic parameters of salbutamol delivering systems

System	t_p hr	C_p ng/ml	$AUC_{0\rightarrow 30}$ ng.hr/ml
1. Oral administered conventional tablet Asthaline®	3.0	14.500 ± 1.250	238.3125 ± 35.75
2. MDC-TDDS	6.0	9.625 ± 0.625	263.3750 ± 19.60
3. PS-TDDS	5.0	11.250 ± 1.000	316.0625 ± 26.06

t_p = time required to reach peak plasma concentration;
C_p = peak plasma concentration of drug;
AUC = Area under the curve;
MDC-TDDS = Matrix diffusion controlled transdermal drug delivery system;
PS-TDDS = Pseudolatex based transdermal drug delivery system.

The peak plasma drug concentration was significantly higher in subjects given orally salbutamol conventional tablet (Asthaline), as compared to the transdermal application of pseudolatices of salbutamol ($p < 0.05$ ANOVA). The fluctuation in plasma salbutamol level was less with transdermal drug delivery systems indicating significantly flatter profile for the transdermal drug delivery systems ($p < 0.05$ ANOVA). Less fluctuation in drug plasma level may presumably be ascribed to controlled release of salbutamol from transdermal drug delivery system and the device rather than skin which could act as a rate controlling membrane. This ensures a more consistent and evenly divided bioavailability of the drug, thus avoiding side effects due to elevated drug levels associated with conventional salbutamol oral therapy. The fluctuations recorded with oral administration of Asthaline^{R} could be ascribed to the gastric emptying and gastrointestinal absorption etiology of individual subjects (19,20).

Similarly, the maximum increase in FEV_1 72 to 84 per cent over resting FEV_1 in all the subjects was recorded (Fig. 3). The maximum increase in FEV_1 was noted at 3 hours after oral dose. The recorded response could be correlated with the peak plasma drug concentration (18). A decrease in FEV_1 between 4 to 6 hours followed by an increase on second dose administration was noted. In case of transdermal drug delivery system application, the maximum increase in FEV_1 was observed to be 75 ± 6 per cent for MDC-TDDS and 80 ± 5 per cent for PS-TDDS. Maximum FEV_1 was recorded at 8 hours and 6 hours following the application of MDC-TDDS and PS-TDDS respectively and remained nearly constant over a period of 24 hours. The FEV_1 decreased gradually on removal of transdermal drug delivery system after 24 hours, while the plasma concentration dropped rapidly. This could be attributed to the controlled release of the drug from the transdermal drug delivery system and constant skin permeation throughout the period of its applications which could have maintained the steady level of salbutamol in blood.

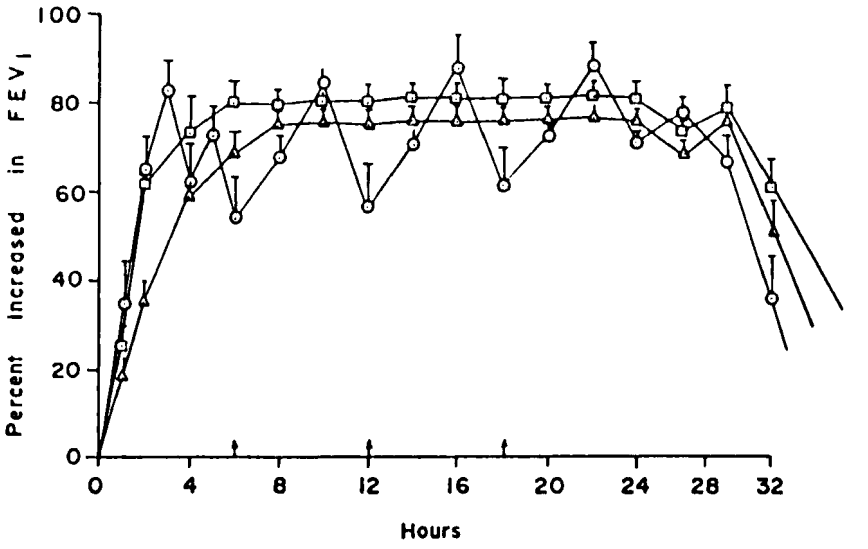

Figure 3

Percent increase in FEV_1 vs time plot following oral administration of conventional tablet and TDD preparation application. (●) Oral conventional tablet administration; (▲) Matrix diffusion controlled TDDS; and (□) Pseudolatex based TDDS. Bar indicates +SD (one side deviation).

The improved performance of the designed transdermal drug delivery systems of salbutamol was established (Table 1). The areas under the curves ($AUC_{0\rightarrow 30}$) calculated for the three treatments are indicative of the relative availability of the drug. The most effective in-vivo performance was recorded for the PS-TDDS ($AUC_{0\rightarrow 30}$: 316.0625 ± 26.06 ng.hr/ml). The MDC-TDDS ($AUC_{0\rightarrow 30}$: 263.3750 ± 19.60 ng.hr/ml) was better than the oral treatment with conventional tablet ($AUC_{0\rightarrow 30}$: 238.3125 ± 35.75 ng.hr/ml) as no troughs and peaks in drug plasma levels were recorded. It is also important to mention that the AUC for transdermal treatments are obtained after the application of 5 mg of salbutamol, whereas in the case of conventional tablet, the recorded AUC value is obtained after oral administration of 16 mg

salbutamol (4 mg administered orally four times). This may be attributed to the poor systemic availability of the drug which is reported to be 30% weight fraction of the oral administered dose (21).

CONCLUSIONS

It is concluded that transdermal drug delivery system of salbutamol can be prepared using poly (isobutylene) containing 2% (w/w based on total polymer weight) salbutamol. The total amount of salbutamol contained in the transdermal drug delivery system was 5 mg. The in-vivo performance of these systems is significantly improved as compared to the plasma profiles resulted from oral administration of 16 mg salbutamol, which may be attributed to the poor systemic availability of the drug from oral administration. Furthermore, it was noted that an enhanced absorption of drug was obtained from pseudolatices as compared to matrix diffusion controlled transdermal drug delivery system though both were of the same polymeric composition.

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