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RESEARCH PAPER

# Formulation and Evaluation of Controlled-Release Transdermal Patches of Theophylline–Salbutamol Sulfate

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## ABSTRACT

*Transdermal formulations containing theophylline and salbutamol sulfate (SS) were formulated using hydroxypropylmethylcellulose. Theophylline was loaded by adsorption with the aid of the coadsorbate sodium chloride. The formulations were subjected to in vitro release studies, and the dose of salbutamol and theophylline was optimized to yield the desired flux. The films were uniform and* $93 \pm 5.4$ *μm thick. The in vitro fluxes of theophylline and salbutamol sulfate from the formulation were* $1.22 \pm 0.4$ *mg/h/cm*$^2$ *and* $13.36 \pm 1.02$ *μg/h/cm*$^2$*, respectively. The formulation was subjected to pharmacodynamic studies in guinea pigs. The preconvulsive time (PCT) of guinea pigs increased significantly after 4 h, and the same was observed even after 24 h. Pharmacokinetic studies were carried out in healthy human volunteers. Theophylline was analyzed in saliva, and salbutamol was analyzed in the blood plasma. The* $T_{max}$ *of the drugs was 3 h, and appreciable concentrations of the drugs above their MEC could be analyzed even after 12 h. The elimination half-life of the drugs was significantly prolonged compared to that for tablets. There were no signs of erythema or edema in the volunteers during observation for a period of 7 days.*

## INTRODUCTION

Theophylline is useful for treatment of asthma in only a fairly narrow plasma concentration range. Patients with a peak level exceeding 20 μg/ml experience toxic concentrations as serious as convulsions, yet asthmatics with a mean steady-state concentration less than 5 μg/ml may obtain little protection from the risk of an attack. Theophylline is also a commonly used drug for the treatment or



prevention of recurrent apnea of premature infants. Theophylline kinetics vary greatly among individuals on oral administration, and several gastric disturbances are also reported (1). Salbutamol sulfate (SS) and theophylline are administered in combination by oral route to obtain a synergistic activity of the drugs. Dosage forms with this combination were reported to perform better than a single drug in most patients. But, controlled-release formulations with both drugs in a single formulation are available only as oral dosage forms.

Treatment of ailments using transdermal formulations is effectively in vogue and is known to have several advantages over oral dosage forms. The present work was an attempt to incorporate two drugs in the transdermal formulation and to monitor the release of the drugs to maintain therapeutic levels. Hence, theophylline and salbutamol sulfate were selected as they undergo first-pass metabolism on oral administration and have short elimination half-lives. The dose of theophylline is high for incorporation into a transdermal delivery system. One of the objectives of the study was to overcome the problem of loading high doses of theophylline into the polymeric matrix.

## EXPERIMENTAL

### Materials

Hydroxypropylmethylcellulose (HPMC; 15 cps at 1% w/v in distilled water), polyisobutylene (E-Merck, India), SS, theophylline (Astra-IDL, Ltd., Bangalore), polyethylene glycol (PEG400), and sodium chloride (AR) (S.D. Fine Chemicals, Bombay, India) were used.

### Adsorption of Theophylline on Hydroxypropylmethylcellulose

Adsorption studies were carried out, and the experimental variables were optimized to achieve maximum adsorption of theophylline on the polymer. The influence of the presence of an electrolyte on the extent of adsorption was determined using sodium chloride in different concentrations. Theophylline-adsorbed polymer was prepared by placing a known weight of the polymer (200–225 μm range) in contact with the saturated solution of the drug (in 96% v/v ethanol) containing 0.1% w/v sodium chloride for a period of 5 h. The polymer was then removed by filtration and dried under vacuum at low temperature.

### Formulation of Transdermal Films of Theophylline and Salbutamol Sulfate

The drug-adsorbed polymer equivalent to 150 mg of theophylline was weighed and dissolved in about 10 ml of water to which 40% w/w (of polymer concentration) PEG400 and 2.5 mg SS were added, and the mix was stirred at a low speed. This solution was cast onto aluminum foil cups with a 10 $cm^2$ area and dried at room temperature. We poured 5 ml of polyisobutylene solution (50% w/v in acetone) on the dried film surface, and the solvent was evaporated to form a thin layer of adhesive on the films.

### In Vitro Diffusion Studies

The in vitro diffusion studies were carried out using a modified Keshary-Chien diffusion cell. Distilled water was the receptor medium, and epithelium of fresh human cadaver skin excised from the chest and isolated by the trypsin digestion method was utilized as the barrier (2). The agitation speed of 50 rpm and a temperature of $37^\circ C \pm 1^\circ C$ were maintained. The area of skin exposed to the formulations was 10 $cm^2$. The samples were withdrawn from the receptor compartment at hourly intervals and analyzed for the drugs spectrophotometrically (3).

### Pharmacodynamic Studies in Conscious Guinea Pigs

Female guinea pigs (200–300 g) were placed in a histamine chamber and challenged with a histamine aerosol generated from a 500 μg/ml solution of histamine hydrochloride using an Atmolette silicon electronic nebulizer (compressed airflow 15 L/min, particle spectrum 0.5–5 μm). The duration of exposure to the aerosol resulting in respiratory distress (deep abdominal respiration and cessation of breathing occurring before asphyxial convulsions) and the preconvulsive time (PCT) were recorded (4). Guinea pigs removed from the chamber at this time were allowed to recover and breathe normally. The transdermal system was applied to the same animals on the dorsal portion of their backs after shaving the hairs without affecting the intactness of the skin layers. The system was tightly secured

using a nonirritating adhesive tape, and PCT was reassessed at hourly intervals up to 12 h and at 18, 24, and 36 h.

### Pharmacokinetic Studies in Healthy Human Volunteers

The study, which was approved by the ethics committee, was conducted at Bowring and Lady Curzon Hospital, Bangalore, India. Six healthy volunteers of either sex, weighing 50–70 kg and 20–30 years old, were recruited, and the nature and purpose of the study were explained to them. An informed written consent was obtained. The subjects were withheld from any drug or alcohol for a 1-week period.

The transdermal patch was applied to the anterior surface of the forearm near the elbow. The volunteers were instructed not to remove the patch, but to observe for any sign of irritation at the application site. Blood samples were collected from the cubital vein of the forearm via a hypodermic syringe (rinsed with diluted heparin) at 4, 8, 12, and 24 h.

Blood samples were withdrawn from the cubital vein of the forearm with the help of a hypodermic disposable syringe (rinsed with diluted heparin) every 3 h up to the 12th hour. Blood samples were immediately centrifuged at 5000 rpm, and plasma was separated and kept in the refrigerator until analysis was carried out. We also collected 3 ml of saliva from the same subjects at the same time intervals. Theophylline was extracted from the saliva with 10 ml of organic solvent (ether-dichloromethane-isopropanol, 6:4:1). The aqueous phase was frozen, and the supernatant was decanted. The organic phase was then evaporated, and the residue was dissolved in deionized water for estimation. SS was extracted by the method reported by Gokhale et al. (5) and estimated by a reverse-phase high-performance liquid chromatographic (HPLC) method (Hewlett Packard, Inertsil ODS column 150 mm × 4.6 mm internal diameter, mobile phase of methanol:water:acetic acid 50:50:1) with ultraviolet (UV) detection at 280 nm (6).

Analysis of variance and a 95% confidence interval were used to measure the statistical differences between the pharmacokinetic parameters, and $P < .05$ was considered significant.

## RESULTS AND DISCUSSION

The desired in vitro fluxes for theophylline and salbutamol sulfate are 1.17 mg/h/cm$^2$ and 18.36 μg/h/cm$^2$, respectively. To achieve this flux, the concentration of theophylline to be incorporated in the matrix is high. The maximum dose of theophylline that could be incorporated in a film with a 10 cm$^2$ area prepared by the casting technique (10 ml of solution containing 1% w/v of HPMC and 40% w/w of PEG400) was found to be as low as 55 mg. Several attempts to increase the solubility of drug in the matrix (such as cosolvency, complexation with cyclodextrin) could not increase solubility to a greater extent. A report of loading theophylline into a hydrogel disk from its saturated solution has been reported (7). Hence, systematic investigation was undertaken to study the adsorption pattern of the drug on the polymer, and variables were considered for maximizing the drug load.

The data of the adsorption studies were found to best fit with the Freundlich relationship (8). The $K$ values indicate the amount of drug adsorbed per unit weight of adsorbent for a unit drug concentration. The slope constant $n$ represents the amount of drug adsorbed for a given change in drug concentration. The relationship represents a logarithmic proportionality between the amount adsorbed and the concentration of the solute. A linear regression was performed to frame an equation.

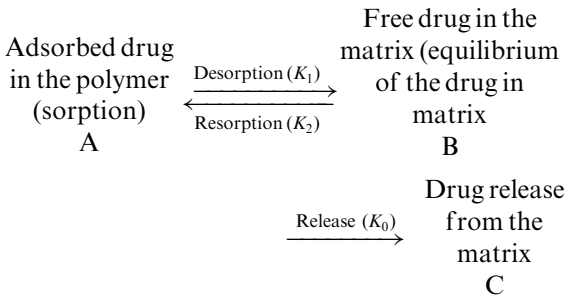
$$(1/n)K \log (x/m) = 0.878 \log (\text{Equilibrium concentration}) + 0.091$$

The presence of electrolyte in smaller concentration influenced the $x/m$ factor to a greater extent. At 0.1% w/v sodium chloride concentration, the $x/m$ factor increased to 738.27 mg. Further increase in the concentration of sodium chloride led to a decrease in the adsorption of the drug.

Theophylline is weakly acidic in nature, with a p$K_a$ value of 8.7. Most of the drug is in the un-ionized form at the pH of its solution; hence, it was assumed that the adsorption onto HPMC might be absolutely physical. The adsorption of the drug is enhanced by the presence of electrolyte, which acts as a coadsorbate with ions that adsorb onto the polymeric surface, thus imparting a charge. This phenomenon may cause static forces to aid better adsorption of the drug. The assumption was further supported by a decrease in the pH of

the alcoholic solution of theophylline in the presence of sodium chloride. This is due to the interaction of theophylline with the sodium ions to liberate the free proton, thus acidifying the solution (pH reduced from 6.7 to 6.2).

The release of adsorbed theophylline from polymeric films may be assumed to occur in the following manner (9):




The rate of desorption is $-dA/dt = K_1[A]$. The rate of change of equilibrium concentration of the drug in the polymeric matrix is $d[B]/dt = K_1[A] - K_0[B]$. The rate of release of the drug is $d[C]/dt = K_0[B]$.

The rate of accumulation of the desorbed drug in the polymer matrix is faster than the release of drug from the device; hence, the apparent release kinetics of drug are zero order.

The films were uniform in appearance and thickness. The film properties (given in Table 1) did not change on incorporation of 2.5 mg/patch SS (optimized dose after several trials with varying doses to achieve desired flux). Theophylline and SS flux from the formulation was $1.22 \pm 0.4$ mg/h/cm$^2$ and $13.36 \pm 1.02$ μg/h/cm$^2$.

The average PCT of guinea pigs was found to be $137.56 \pm 7.18$ s ($n = 6$, SD). On application of the patch, the PCT of the animals increased significantly after 4 h, further increased after 7 h, and was observed even after 24 h (Fig. 1).

The pharmacokinetic parameters of drugs in healthy human volunteers are summarized in Table 2. Mean plasma concentration-time profiles for each drug can be seen in Figs. 2 and 3. A measurable

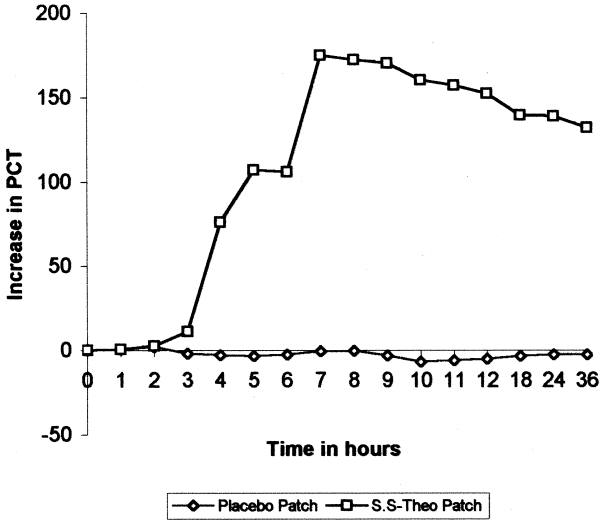



**Figure 1.** Pharmacodynamic studies of SS-theophylline transdermal patch in guinea pigs.

***Table 2***

*Pharmacokinetic Parameters of Theophylline and Salbutamol Sulfate (SS) on Application of Transdermal Patch in Healthy Human Volunteers (Mean of* $n = 6 \pm SD$*)*

| Parameters | Salbutamol Sulfate | Theophylline |
|---|---|---|
| $C_{max}$[a] | $10.46 \pm 3.40$ | $4.47 \pm 1.00$ |
| $T_{max}$ (h) | 3 | 3 |
| $AUC_{0-12}$[b] | $82.67 \pm 48.12$ | $38.50 \pm 10.22$ |
| AUC total[b] | $100.92 \pm 52.67$ | $78.53 \pm 39.96$ |
| $AUMC_{0-12}$[c] | $437.98 \pm 91.96$ | $222.47 \pm 66.74$ |
| $AUMC_{total}$[c] | $1334.99 \pm 1838.88$ | $1281.61 \pm 1043.58$ |
| MRT (h) | $13.23 \pm 7.14$ | $16.32 \pm 4.74$ |
| $K_{el}$ ($h^{-1}$) | $0.1472 \pm 0.07$ | $0.063 \pm 0.02$ |
| $T_{1/2}$ (h) | $4.71 \pm 6.61$ | $10.99 \pm 3.86$ |
| Cl (L/h) | $15.78 \pm 5.16$ | $1.864 \pm 0.69$ |

[a]ng/ml for SS and mcg/ml for theophylline.
[b]ng/ml·h for SS and mcg/ml·h for theophylline.
[c]ng/ml·h$^2$ for SS and mcg/ml·h$^2$ for theophylline.

***Table 1***

*Properties of Hydroxypropylmethylcelluose (HPMC) Transdermal Matrix Films (Mean of* $n = 6 \pm SD$*)*

| Thickness (μm) | Water Vapor Permeability (g/cm$^2$) (24 h) | Tensile Strength (dynes/cm$^2$) | % Elongation | Peel Strength (kg/m$^2$) |
|---|---|---|---|---|
| $93 \pm 5.4$ | $6.7 \pm 0.7 \times 10^{-4}$ | $9.86 \pm 0.9 \times 10^7$ | $1.5 \pm 0.4$ | $29.46 \pm 1.86$ |

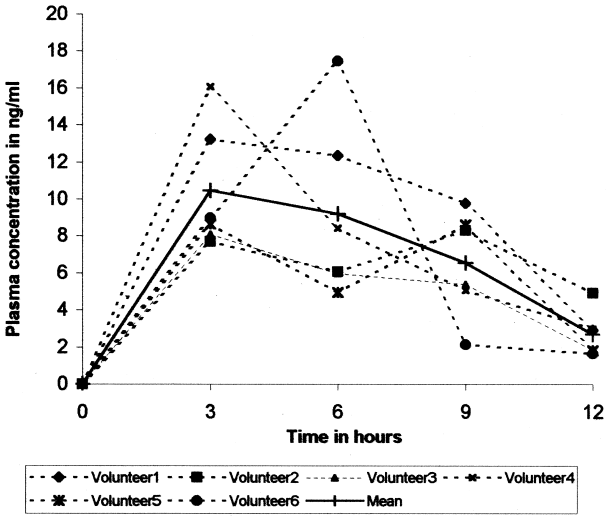



**Figure 2.** Pharmacokinetic profile of salbutamol sulfate in healthy human volunteers.

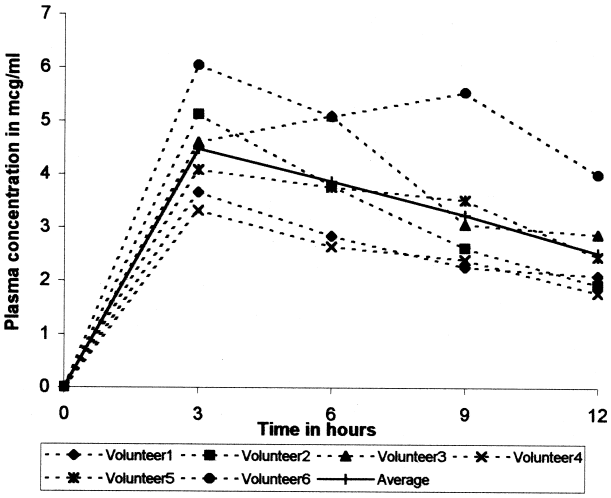



**Figure 3.** Pharmacokinetic profile of theophylline in healthy human volunteers.

concentration of salbutamol in plasma could be achieved after 3 h. The mean peak plasma concentration (10.46 ng/ml) was lower from the transdermal patch when compared to the conventional 4 mg salbutamol tablet (18 ng/ml). The elimination half-life of the drugs was prolonged, and the clearance was decreased significantly compared to that reported for an oral dosage form (10–13). A steady-state salbutamol concentration of 5.3 to 6.8 ng/ml was maintained for a longer duration. It can be safely assumed that the concentration of drugs even after 12 h was appreciably above the MEC as the plasma concentration of theophylline is double the salivary concentration at any point in time (14). The mean residence time of theophylline was $16.32 \pm 4.74$ h, and that of SS was $13.23 \pm 7.14$ h. The variation within the group was insignificant. The volunteers did not show any signs of edema or erythema or any kind of skin reactions on observation for a period of 7 days.

The transdermal drug delivery of these drugs has a distinct advantage over the conventional dosage form and also over sustained-release tablets in that it bypasses first-pass metabolism. Unlike the oral dosages, there is no drastic increase in peak plasma concentration and fluctuation in concentration. A smooth and narrow steady-state profile was observed in the case of transdermal delivery, which would also reduce the severity of the side effects.

## CONCLUSIONS

It is evident from the results that the formulation of the transdermal drug delivery system for simultaneous delivery of theophylline and salbutamol sulfate is feasible, and the system is capable of maintaining the therapeutic level of the drugs in the blood.

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