

Formulation And Evaluation Of Controlled Release Transdermal Patches Of Theophylline - Salbutamol Sulphate

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Citation

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Abstract

Transdermal formulations containing theophylline and salbutamol sulphate were formulated using hydroxy propyl methyl cellulose. Theophylline was loaded by adsorption with the aid of co-adsorbate, sodium chloride. The formulations were subjected to in vitro release studies and the dose of salbutamol and theophylline were optimized to yield the desired flux. The films were uniform and of 200 ± 40 micron thickness. The in vitro flux of theophylline and salbutamol sulphate from the formulation was 1.22 ± 0.4 mg/hr/sq.cm and 13.36 ± 1.02 mcg/hr/sq.cm respectively. The formulation was subjected for pharmacodynamic studies in guinea pigs. The PCT of guinea pigs increased significantly after 4th hour the same was observed even after 24 hours. Pharmacokinetic studies were carried out in healthy human volunteers. Theophylline was analyzed in saliva and salbutamol in the blood plasma. The T_{max} of the drugs was 3 hours and appreciable concentrations of the drugs above their MEC could be analysed even after 12 hours. The half-lives of the drugs were significantly prolonged compared to tablets. There was no signs of erythema or oedema in volunteers on 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 20mcg/ml experience toxic concentrations as serious as convulsions, yet asthmatics with a mean steady state concentration less than 5 mcg/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 sulphate and theophylline are administered in combination by oral route to effect the synergistic activity of drugs. The dosage forms with this combination were reported to be performing better than a single drug in most of the 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 known to have several advantages over the oral dosage forms. The present work is an attempt to incorporate two drugs in the transdermal formulation and to monitor the release of the drugs to maintain the

therapeutic levels. Hence theophylline and salbutamol sulphate were selected, as they undergo first pass metabolism and have short half-lives. The dose of theophylline is quite high for incorporation into a transdermal delivery. To overcome the problem loading high doses of theophylline into the polymeric matrix was also one of the objectives of the study.

MATERIALS AND METHODS

Hydroxy propyl methyl cellulose (15 cps at 1%w/v in distilled water), polyisobutylene (E-Merck, India), salbutamol sulphate and theophylline (Astra- IDL Ltd , Bangalore), Polyethylene glycol (PEG-400) and sodium chloride (A.R) (S.D fine chemicals, Bombay) were obtained.

ADSORPTION OF THEOPHYLLINE ON HPMC

Adsorption studies were carried out and the experimental variables were optimized to achieve maximum adsorption of theophylline on the polymer. The influence of presence of electrolyte on extent of adsorption was determined using sodium chloride in different concentrations. Theophylline adsorbed polymer was prepared by placing a known weight of the polymer (200-225micrometer 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 about 5 hours. The polymer was then removed by filtration and dried under vacuum at low temperature.

FORMULATION OF TRANSDERMAL FILMS OF THEOPHYLLINE AND SALBUTAMOL SULPHATE

The drug adsorbed polymers equivalent to 150 mg of theophylline was weighed and dissolved in about 10 ml of water to which 40%w/w (of polymer concentration) PEG-400 & 2.5mg S.S was added stirred at a low speed and the polymeric solution was casted on to aluminium foil cups of area 10 sq.cm and dried at room temperature. 5 ml polyisobutylene. Solution (50%w/v in acetone) was poured onto the dried film surface and the solvent was evaporated to form a thin layer of adhesive on the films.

DIFFUSION STUDIES

The in vitro diffusion studies were carried out using a modified Keshary-Chein diffusion cell. The agitation speed of 50 rpm and a temperature of $37 \pm 1^\circ\text{C}$ maintained. Distilled water was used as the receptor medium and epithelium of the fresh human cadaver excised from the chest portion, isolated by trypsin digestion method was utilized as the barrier [2]. The samples were withdrawn from the receptor compartment at hourly interval and analyzed for the drugs spectrophotometrically [3].

PHARMACODYNAMIC STUDIES IN CONSCIOUS GUINEA PIGS [4]

Female guinea pigs (200-300g) were placed in histamine chamber and challenged with a histamine aerosol generated from a 500mcg/ml solution of histamine hydrochloride using Atmolette Si electronic nebulizer (compressed air flow 15L/min, particle spectrum of 0.5-5 microns). The duration of the period of exposure to the aerosol resulting in respiratory distress, the preconvulsive time (PCT) was recorded. The first sign of respiratory distress was taken as deep abdominal respiration. Guinea pigs were removed from the chamber at this time were fully recovered within 5-10 min. Animals were then applied with transdermal system on its dorsal back portion after shaving the hairs without affecting the intactness of the skin layers. The system was tightly secured and PCT was reassessed at different time intervals up to 36 hours.

PHARMACOKINETIC STUDIES IN HEALTHY HUMAN VOLUNTEERS.

The study was conducted at Bowring and Lady Curzon

Hospital, Ministry of health, Govt of Karnataka, Bangalore, after the approval of the ethics committee. Six healthy human volunteers of either sex aged between 20-30 years and weighing about 50-70 Kg were recruited. The nature and purpose of the study were fully explained to them and an informed written consent was obtained from each subject before study. They were asked to abstain from any drug or alcohol for 1 week and were deprived of food for 12 hour prior to the study. The transdermal patch was applied onto the anterior surface of the forearm near the elbow. The volunteers were instructed not to remove the patch and also to observe for any sign of irritation at the site of application. Blood and salivary samples were collected from the cubital vein of the forearm with the help of hypodermic disposable syringe (rinsed with diluted heparin) at every 3 hours interval upto 12th hour. Blood samples were immediately centrifuged at 5000 rpm and plasma was separated and kept in the refrigerator until analysis was carried out.

Theophylline was extracted from 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 deionised water for estimation. Salbutamol sulphate was extracted by the method reported by Rajeev Gokhale [5] and estimated by reverse phase HPLC method using analyzed for the drug content by reverse phase HPLC (Hewlett Packard, Inertsil ODS column 150mm X4.6mm internal diameter, mobile phase methanol: water: acetic acid (50:50:1)) with U.V detection at 280nm [6].

Analysis of variance with 95% confidence interval were used to measure the statistical differences between the pharmacokinetic parameters and $P < 0.05$ was considered significant.

RESULTS AND DISCUSSION

The desired in vitro flux for theophylline and salbutamol sulphate is 1.17mg/hr/sq.cm and 18.36mcg/hr/sq.cm. To achieve this flux the concentration of theophylline to be incorporated in the matrix is high. The maximum dose of theophylline which could be incorporated in a film of 10sq.cm area prepared by casting technique (10 ml of solution containing 1%w/v of HPMC and 40% w/w of PEG-400) was found to be as low as 55mg. Several attempts to increase the solubility of drug in the matrix such as cosolvency, complexation with cyclodextrin could not increase the drug load to the desired extent. A report of loading theophylline into hydrogel disk form its saturated

solution is already reported [7]. Hence systematic investigations were 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 was found to best fit with 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.

Figure 1

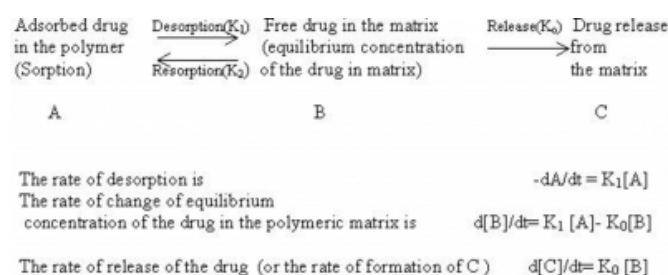
$$\log(x/m)^{(1/n)} = \frac{K}{0.878} \log X + 0.091$$

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 shot up to 738.27 mg. Increase in the concentration of sodium chloride lead to decrease in the adsorption of the drug.

Theophylline is weakly acidic in nature with a pKa value of 8.7. Hence most of the drug is in the unionised form at the pH of its solution and hence it was assumed that the adsorption on to HPMC might be absolutely physical. The adsorption of the drug is enhanced by the presence of electrolyte, which acts as a co-adsorbate. This may be due to the adsorption of the ions onto the polymeric surface thus imparting a charge. The assumption was further supported by decrease in the pH of the alcoholic solution of theophylline in presence sodium chloride which 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 be in the following manner [9].

Figure 2

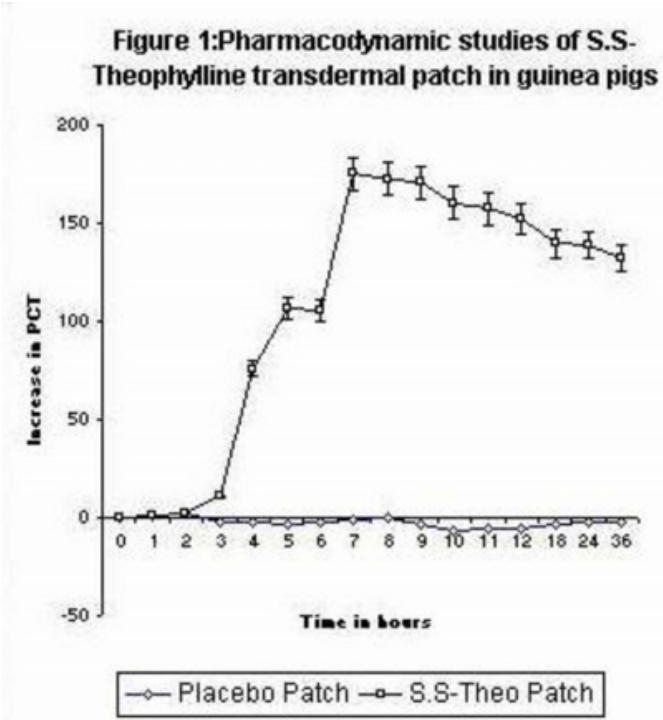


The rate of accumulation of the desorbed drug in the polymer matrix is faster initially than the release of drug from the device and hence the apparent release kinetics of drug is zero order but on depletion of the bound drug in the later stages the release attains an exponential pattern.

The films were uniform and of 200±40 micron thickness. The film properties did not change on incorporation of salbutamol sulphate at a dose of 2.5mg/patch (dose was optimized after evaluation of formulations with different doses of salbutamol sulphate). Theophylline and salbutamol sulphate flux from the formulation was 1.22±0.4 mg/hr/sq.cm and 13.36± 1.02 mcg/hr/sq.cm.

The average PCT of guinea pigs was found to be 137.56 ±7.18 s (n=6, s.d). On application of the patch, the PCT of the animals increased significantly after 4th hour and further increased after 7th hour and the activity was observed even after 24 hours (Figure 1).

Figure 3



The Pharmacokinetic parameters of drugs in healthy human volunteers are summarized in table 1. Mean plasma concentration –time profiles for each drug can be seen in Figure 2 and 3.

Figure 4

Table 1: Pharmacokinetic parameters of theophylline and salbutamol sulphate on application of transdermal patch in healthy human volunteers (mean of $n=6 \pm s.d$)

PARAMETERS	Salbutamol sulphate	Theophylline
C max **	10.46±3.40	4.47
T max (h)	3	3
AUC ₀₋₂₄ *	82.67±48.12	38.50±10.22
AUC _{total} *	100.92±52.67	78.53±39.96
AUMC ₀₋₂₄ *	485.04±98.96	242.58±70.67
AUMC _{total} *	1382.04±1833.49	1301.72±1046.61
MRT (h)	13.69±7.0	16.58±4.67
K _{el} (h ⁻¹)	0.1472±0.067	0.063±0.024
T _{1/2} (h)	4.71±6.61	10.99±3.86
Cl (L/h)	15.78±5.16	1.864±0.69

** ng/ml for salbutamol sulphate and mcg/ml for theophylline

* ng/ml.h for salbutamol sulphate and mcg/ml.h for theophylline

Figure 5

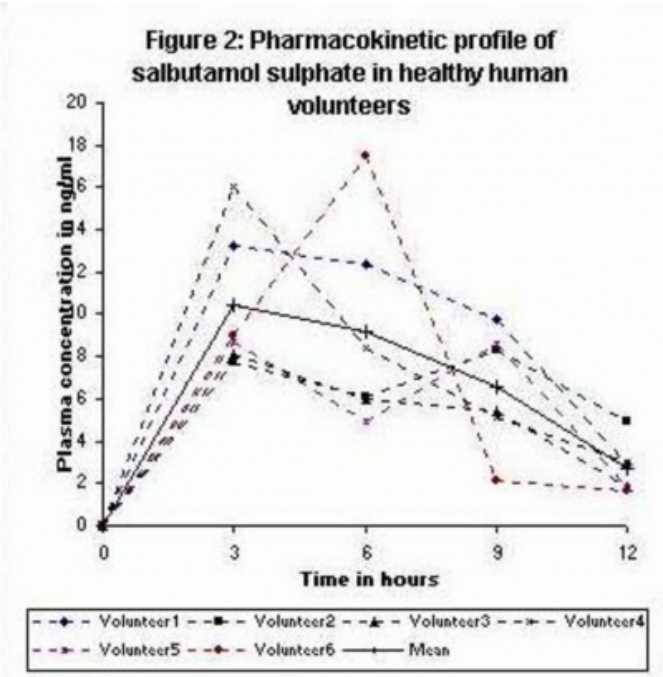
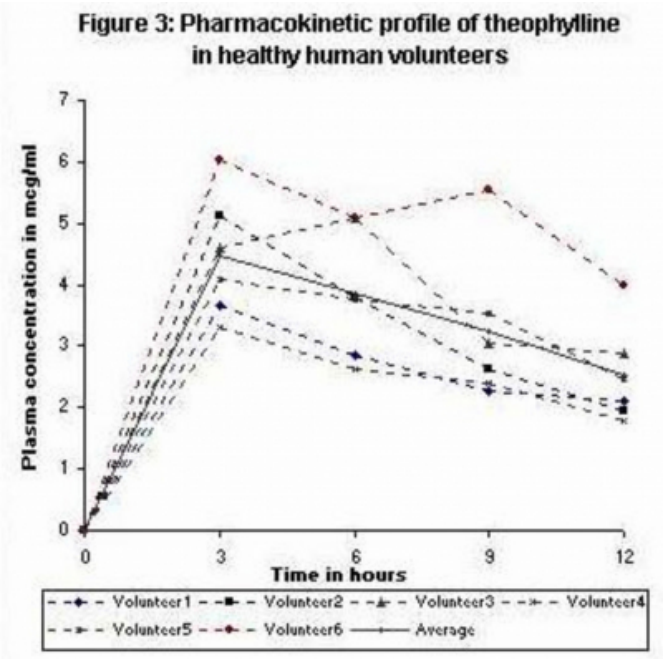


Figure 6



Measurable concentration of salbutamol sulphate in plasma could be achieved after 3 hours. Half-lives of the drugs was prolonged and the clearance was decreased significantly compared to that reported for an oral dosage form [10,11,12,13]. It can be safely assumed that concentration of drugs even after 12 hours was appreciably above MEC, as the plasma concentration of theophylline is double the salivary

concentration at any point of time on single dose administration [14]. The mean residence time of theophylline was 16.58 ± 4.67 hours and that of salbutamol sulphate was 13.69 ± 7.0 hours. The variation within the group was insignificant. The volunteers did not show any signs of oedema or erythema or any kind of skin reactions on observation for a period of 7 days.

CONCLUSIONS

It is evident from the results that the formulation of transdermal drug delivery system for simultaneous delivery of theophylline and salbutamol sulphate is feasible and the system is capable of maintaining the therapeutic levels of the drugs in the blood. The in vivo evaluation proved our assumptions of desorption -release to be practical than just hypothetical.

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