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Physical and Chemical Permeation Enhancers in Transdermal Delivery of Terbutaline Sulphate

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INTRODUCTION

Terbutaline sulphate (TS) is a drug widely used for the treatment of acute and chronic bronchitis patients; it has an elimination half-life of about 5.5 hours [1]. The objective of this study was to design controlled release matrix type transdermal delivery systems of TS using hydroxypropyl methylcellulose. Because of the low permeability of the drug, enhancers had to be used in the formulations. Preliminary studies on magnetophoresis and the factors that influence the magnetophoretic permeation of TS are reported elsewhere [2,3]. This study analyzed the practical application of magnetophoresis for TS transdermal delivery.

MATERIALS AND METHODS

Hydroxypropyl methyl cellulose (HPMC; 15 cps at 1% wt/vol in water), polyisobutylene (E-Merck, Mumbai, India), isopropyl myristate (IPM), Tween 80, and sodium lauryl sulphate (SLS) were obtained from S.D. Fine Chemicals, Mumbai, India.

Systematic investigations were undertaken to optimize the concentration of polymer, plasticizer, volume of casting solution, drying temperature, and drying period to prepare films of uniform thickness. Two grams of HPMC, 0.8 g of polyethylene glycol (PEG) 400 (40% wt/wt of polymer concentration), and 4 g of IPM (4% wt/vol) were dispersed uniformly in 50 mL of distilled water and then agitated for 30 minutes. Next, 96 mg of TS was dissolved in this solution and the volume was diluted with distilled water to 100 mL. Five milliliters of the solution was casted into an aluminium foil cup of 12 cm^2 area and dried at 50ºC for 8 hours (hence the film contained 0.4 mg/cm^2 TS). Three milliliters of adhesive polyisobutylene solution (50% wt/vol in acetone) was poured onto the dried film, and the solvent was evaporated to provide a thin uniform layer of adhesive on the film. The film (F1) was cut into 10 cm^2 pieces for further evaluation.

Design of magnetic transdermal systems

The film (F2) was formulated by the same technique without incorporating IPM. A flat circular permanent magnet (2 mm thickness and 10 cm^2 area) of field strength 1 x 10^{-4} Tesla (T) was sandwiched between the aluminium foil backing membrane and the polymeric film.

In vitro diffusion studies of transdermal films

The in vitro diffusion studies were carried out in a modified Keshary-Chien diffusion cell (**Figure 1**) using distilled water as the receptor medium. Fresh human cadaver skin epithelium, which was excised from the chest portion and isolated by trypsin digestion, was used as the barrier [4]. The area of skin exposed to the formulations was 10 cm^2. The agitation speed of 50 rpm was maintained using a mechanical propeller stirrer inserted through an additional side port for uniform distribution of temperature and the diffused drug throughout the distribution medium. The temperature was maintained at 37 ± 1ºC. The samples were withdrawn from the receptor compartment (25 mL) at hourly intervals and analyzed spectrophotometrically for the drug [5].

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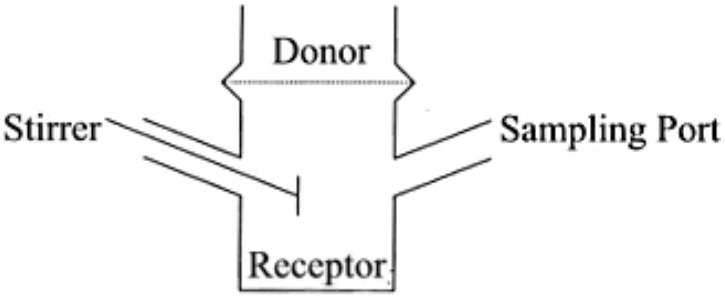

Figure 1. Schematic diagram of modified Keshary-Chien diffusion apparatus.

Pharmacodynamic studies in conscious guinea pigs

Six 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 Si electronic nebulizer (ATMOS Medical equipment GmbH & Co, Lenzrkirch, Germanay, compressed air flow 15 L/min, particle spectrum of 0.5-5 microns). 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 [6]. Guinea pigs removed from the chamber at this time were allowed to recover and breath normally. The transdermal system was then applied on the dorsal portion of the guinea pigs' backs after shaving the hairs without affecting the intactness of the skin layers. The system was tightly secured using a nonirritant adhesive tape. PCT was reassessed at hourly intervals up to 12 hours and at 18, 24, and 36 hours.

Pharmacokinetic studies in human volunteers

The study, which was approved by the ethics committee, was conducted at Bowring and Lady Curzon Hospital, Bangalore. Six healthy 50 to 70 kg volunteers 20 to 30 years of age of both sexes were recruited. The nature and purpose of the study were explained to them. An informed written consent was obtained. The subjects were withheld from any drugs or alcohol for 1-week before the study 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 look for any sign of irritation at the application site. Blood samples were collected from the subjects' cubital vein of the forearm via a hypodermic syringe (rinsed with diluted heparin) at 1, 2, 4, 8, 12, and 24 hours.

Blood samples were immediately centrifuged at 5000 rpm and plasma was separated and kept in the refrigerator until analysis was carried out within 2 hours. The drug was extracted and analyzed by gas liquid chromatography [7].

An analysis of variance test with a 95% confidence interval was used to determine the statistical differences between the pharmacokinetic parameters; $P < .05$ was considered significant.

Stability studies

The formulations were stored at 27ºC, 35ºC, 45ºC, and 60ºC for 3 months [8]. The samples were withdrawn every week, and the amount of intact drug remaining was estimated.

RESULTS AND DISCUSSION

The films were completely formed after 8 hours when dried at 50ºC. Films dried above 50ºC were found to be brittle and of nonuniform thickness. This may be because of the solvent's rapid rate of evaporation, which led to shrinkage of the films. The concentration of the polymer was found to have a direct influence on the thickness and tensile strength of the films as well. Film tensile strength and percent of elongation grew up to 50% wt/wt with the increased concentration of the plasticizer and remained invariably constant above this concentration. The films formed by casting solution (5 mL/12 cm^2) of 2% wt/vol polymer and 40% wt/wt (of polymer) PEG 400 were found to yield reproducible and uniform film properties. The peel strength [9] of the films coated with the polyisobutylene adhesive solution (3 mL/12 cm^2) was appreciable at 50% wt/vol concentration. The films formed with the casting solution containing 4% wt/vol of IPM did not significantly vary in their properties from the one formed without IPM. The properties of matrix film formulation are given in **Table 1**.

Table 1. Properties of HPMC Transdermal Matrix Films (n = 6)

Thickness µm	Water Vapor Permeability g/cm^2 (24 h)	Tensile Strength dynes/cm^2	Elongation (%)	Peel Strength kg/m^2
72 ± 4.2	8.6 ± 0.8 × 10-4	11.85 ± 0.9 × 107	2.0 ± 0.6	26.66 ± 1.23

At lower doses such as 1 to 3 mg, a lag period of 1 to 2 hours was observed in the in vitro release profile. The desired minimum flux (Desired flux = clearance rate of 15 L/hr × minimum effective concentration of 3 ng/mL/ patch area of 10 cm^2) for TS is 4.5 µg/h/cm^2, which could not be achieved at a dose of 4 mg/patch. This necessitated the incorporation of enhancers in the formulation. The enhancers chosen for the study were IPM, Tween 80, and SLS. The efficacy of enhancers was determined by carrying out permeability studies in the presence of different concentrations of enhancers from the saturated solution of drug across human cadaver skin epithelium. The permeability was significantly enhanced by IPM. Enhancement resulting from the presence of SLS and Tween 80 was negligible, possibly a result of the property of IPM to favor the partitioning of the drug in the IPM; therefore, IPM was used as an enhancer in the formulation.

The transdermal formulations containing various concentrations of IPM were subjected for in vitro diffusion studies, and the one prepared with the casting solution containing 4% wt/vol IPM resulted in an in vitro flux of 5.10 ± 0.21 µg/h/cm^2 (**Figure 2**). A comparable diffusion flux of 5.26 ± 0.31 µg/h/cm^2 was obtained from the transdermal systems when backed with a magnet of strength 1×10^{-4} T (F2). The presence of magnets on permeation of the drug was found to be similar to that of IPM. The drug is a diamagnetic substance, which tends to escape from the applied magnetic field. The drug experiences a driving force to diffuse across the barrier [10]. The possibility of magnetic field influence leading to some temporary change in the physicochemical nature of the skin constituents favoring the diffusant flow could be another reason.

The average PCT of guinea pigs (n = 6) was found to be 137.56 ± 7.18 seconds. On application of the patch, the animals' PCT increased significantly after 6 hours (F1 316 ± 20.8 seconds and F2 189.25 ± 26.64 seconds), lasting for 36 hours (**Figure 3**). Whereas with F3, which lacked the enhancers, the increase in PCT (176.66 ± 16.08 seconds) was observed for only 12 hours.

Figure 2 In vitro release profile of transdermal formulations

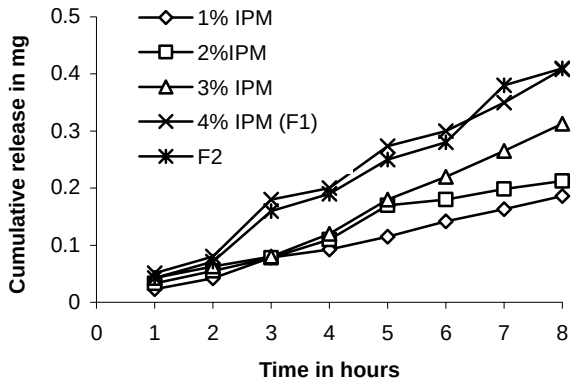

Figure 2. *In vitro* release profile of transdermal formulations.

Both F1 and F2 maintained appreciable blood levels of drug for a prolonged period. Measurable plasma concentrations were attained within 4 hours and the elimination half-life of the drug was significantly prolonged when compared to oral administration (5.5 hours) up to 18.2 hours (F1) and up to 16.7 hours (F2). The pharmacokinetic values of F1 and F2 are summarized in **Table 2**; the profiles are shown in **Figure 4**. An insignificant statistical variation of the parameters at the 5% level of significance between the groups (F1 and F2) and within the groups supports the in vivo efficacy of the applied magnetic field on par with the enhancer IPM. The volunteers did not show any skin reaction up to 1 week after removal of the patch.

Both formulations exhibited good stability at all storage conditions. The films were dipped in about 5 mL of distilled water for 4 hours, and the water was transferred to a separating funnel. The interfering impurities were extracted with 6 portions of chloroform mixture. The solvent was evaporated to a dry residue in a rotary flash evaporator (Superfit continental Pvt. Ltd, Mumbai, India). The infrared spectra of this residue, when compared with that of the reference standard drug, confirmed that the the molecule in the drug delivery system was intact.

Table 2: Mean Pharmacokinetic Parameters of Terbutaline Sulphate Transdermal Formulations (n = 6)

Parameters	F1	F2	F - Value
C_{max} (ng/mL)	4.6 ± 1.3	6.7 ± 1.4	3.02
T_{max} (hours)	5.3 ± 2.1	6.7 ± 2.1	1.8
AUC 0-24(ng/mL/h)	86.4 ± 8.7	122.1 ± 20.0	4.86
AUC total	145.6 ± 27.3	195.4 ± 65.2	4.84
AUMC0-24(ng/ml/h^2)	872.9 ± 103.8	1215.7 ± 284.3	4.70
AUMC total	2748.5 ± 1327.7	4621.9 ± 2871.1	2.24
MRT (h)	19.1 ± 6.8	23.7 ± 7.6	0.19
Kel (h^{-1})	0.04 ± 0.02	0.04 ± 0.02	0.13
Elimination T1/2 (hours)	18.2 ± 10.0	16.7 ± 6.7	0.38
Cl(L/h)	8.5 ± 1.7	6.3 ± 1.8	4.45

Figure 4 Mean plasma level/time profiles of terbutline sulphate from transdermal formulations

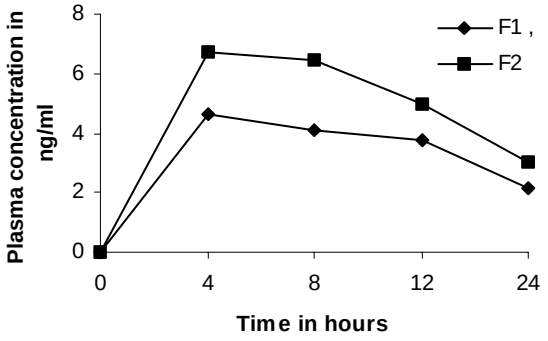

Figure 4. Mean plasma level/time profiles of terbutaline sulphate from transdermal formulations.

Figure 3 Pharmacodynamic studies in guinea pigs

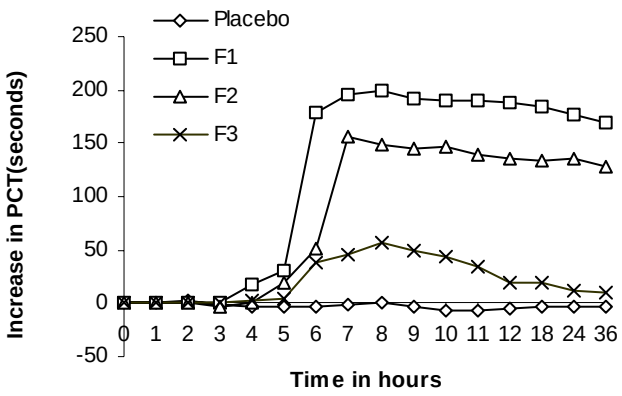

Figure 3. Pharmacodynamic studies in guinea pigs.

CONCLUSIONS

The efficacy of a magnetic field to act as a permeation enhancer was demonstrated. Because in vitro and in vivo performance of F1 and F2 were comparable, the substitution of chemical enhancers by magnetic field in transdermal delivery systems appears to be possible.

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