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TRANSDERMAL FILMS OF EPHEDRINE

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ABSTRACT

Ephedrine, often used in the treatment of asthma, is a good candidate for development of its transdermal therapeutic system. This investigation reports the design of polymeric matrix type transdermal films of ephedrine and its hydrochloride salt. The films possessing appropriate physico-chemical qualities were tested for *in vitro* and *in vivo* drug diffusion pattern, stability and skin irritation. The films were found to be free from skin irritation and stable at room temperature but adversely affected by extremes of humidity or high temperature. Both systems gave adequate release of drug and diffusion through skin into systemic circulation when tested on human volunteers.

INTRODUCTION

Transdermal drug delivery systems provide a means to prolong and sustain drug action and reduce undesirable effects. In addition, they are easy to use and easily retracted in case of development of untoward effects. Transdermal therapeutic systems for Scopolamine[1], Nitroglycerin[2], Clonidine[3], etc. have already been marketed and have shown wide acceptability. Such systems are also being developed for Estradiol, Isosorbide dinitrate, Indomethacin, etc[4].

Ephedrine is a good candidate for administration as transdermal therapeutic system. Its high permeation through skin is recently recognised[5]. Further, it is employed in the treatment of asthma, a condition which needs controlled drug administration for round the clock therapy, thereby avoiding nocturnal and early morning attacks, common with the ailment.

The present investigation is limited to the design of matrix type transdermal films of ephedrine and ephedrine hydrochloride which could form the basis for the development of a controlled release transdermal patch.

Polymers are found to play an important role in the design of such films. Amongst the different polymers investigated by us, a combination of polyvinyl alcohol and polyvinyl pyrrolidone with glycerol as plasticizer provided suitable lattice structure and satisfactory *in vitro* drug release and diffusion. The films were

tested for skin irritation, stability to different conditions of storage and *in vivo* permeation through skin of human volunteers.

EXPERIMENTAL

MATERIALS :

Ephedrine hydrochloride-IP, Glycerol-IP, Ammonium Chloride-IP, Ephedrine Base-USP, Polyvinyl alcohol-USP, Polyvinyl pyrrolidone-USP. All other reagents used were of AnalaR grade.

METHODS :

I. Casting of Films :

Polyvinyl alcohol (15 g) and Polyvinyl pyrrolidone (8 g) were dissolved in 60 ml of water by heating on a water bath at 90°C. Glycerol (15 g) and Ephedrine or Ephedrine Hydrochloride (4 g) were added and mixed to form a uniform mixture. The clear solution was poured into glass plates with suitably raised edges and heated in a hot air oven at 37°±1°C for 10 hours in case of Ephedrine and 60°±1°C for 6 hours in case of Ephedrine Hydrochloride. The films were then removed, packed in an aluminum foil covering and stored in a 58% Rh chamber [at room temperature (27°±3°C)]

II. Evaluation of Films :

A. Physico-chemical properties : Uniformity of weight was determined by weighing 20 films of 1 cm^2.

The tensile strength was determined by a method described by Allen *et al*[6].

The moisture absorption/loss of the films was determined at 20% Rh, 58% Rh, 63% Rh, 85% Rh and 93% Rh by a method described by Kaing *et al*[7].

The drug content of the films was determined by measuring the UV absorbance of the drug by the method suggested by Chafetz[8].

B. *In vitro* diffusion studies : Films of Ephedrine and Ephedrine hydrochloride measuring 1 cm^2 area were subjected to *in vitro* diffusion testing using a Keshary Chien diffusion cell[9]. Guinea pig skin was clamped between the donor and recipient compartments. The film was placed in the donor compartment over the skin whereas the recipient compartment contained distilled water at 37°±1°C as medium which was stirred at a high speed by use of a star headed magnet. The amount of drug that diffused through the guinea pig skin was determined by removing 1 ml samples at hourly intervals for 12 hours and then taking a 24 hour sample. The drug was analysed by a method reported by Chafetz[8]. The cumulative amount of drug that penetrated the skin was then calculated.

C. Accelerated stability study : Films containing Ephedrine Hydrochloride were stored at room temperature (27°±3°C), 37°C, 45°C in a 58% Rh chamber. The films were also stored at 20% Rh and 85% Rh at room temperature. Samples of films were withdrawn

at weekly intervals for four weeks and evaluated for their physico-chemical properties and *in vitro* diffusion through guinea pig skin.

D. Primary skin irritation studies : Films of Ephedrine and Ephedrine Hydrochloride were applied to the depilated skin on the back of four albino rabbits and secured using an adhesive tape. A 0.8% aqueous solution of formalin was also applied as a standard irritant. The animals were observed for any sign of erythema or oedema for a period of seven days and scored as reported by Draize *et al*[10].

E. *In vivo* studies : Three healthy human volunteers in the age group of 20-24 and weighing 55-75 kg were included in the study. The volunteers were administered a syrup of ammonium chloirde (1 g dose), the night prior to the trial, one hour prior to application of films and every four hours during the trial. Films of Ephedrine/Ephedrine Hydrochloride of 10 cm^2 area were applied on the wrist of the volunteers and secured with an adhesive tape. Urinary samples were collected prior to application of films and then at 1, 2, 4, 6, 8, 11, 16, 20, and 24 hours post application of films. The amount of drug in the urine samples was analysed by a method suggested by Wallace[11].

RESULTS AND DISCUSSION

The films of both Ephedrine and Ephedrine Hydrochloride showed satisfactory physico-chemical properties. The *in vitro*

drug diffusion rate from the films through the guinea pig skin followed first order kinetics for the period of 24 hours. The films of Ephedrine base showed three to four fold greater diffusion of the drug than that obtained with the films of Ephedrine Hydrochloride (Figure 1).

The *in vitro* drug diffusion profile of films of Ephedrine Hydrochloride stored at various temperatures and humidities for four weeks are shown in Figure 2. The results revealed no significant change in drug diffusion pattern of films stored at room temperature and 37°C for four weeks. Films stored at 85% Rh showed an increase in the amount of drug diffusion while those stored at 20% Rh showed a decrease in diffusion. This could be attributed to the amount of moisture picked up or lost after storage for four weeks at these extreme conditions of humidity. The physico-chemical characteristics of the films are shown in Table I. The results revealed a decrease in the tensile strength of the films stored at 20% Rh. The results of the stability study indicated that the storage of films at higher temperatures and lower humidities should be avoided.

No erythema or oedema was noticed on the skin of the albino rabbits. Thus, the primary skin irritation studies did not reveal any irritation after application of the films for seven days on the skin of rabbits.

In vivo evaluation of the films was done by estimating the excretion of the drug in the urine. The pH of the urine

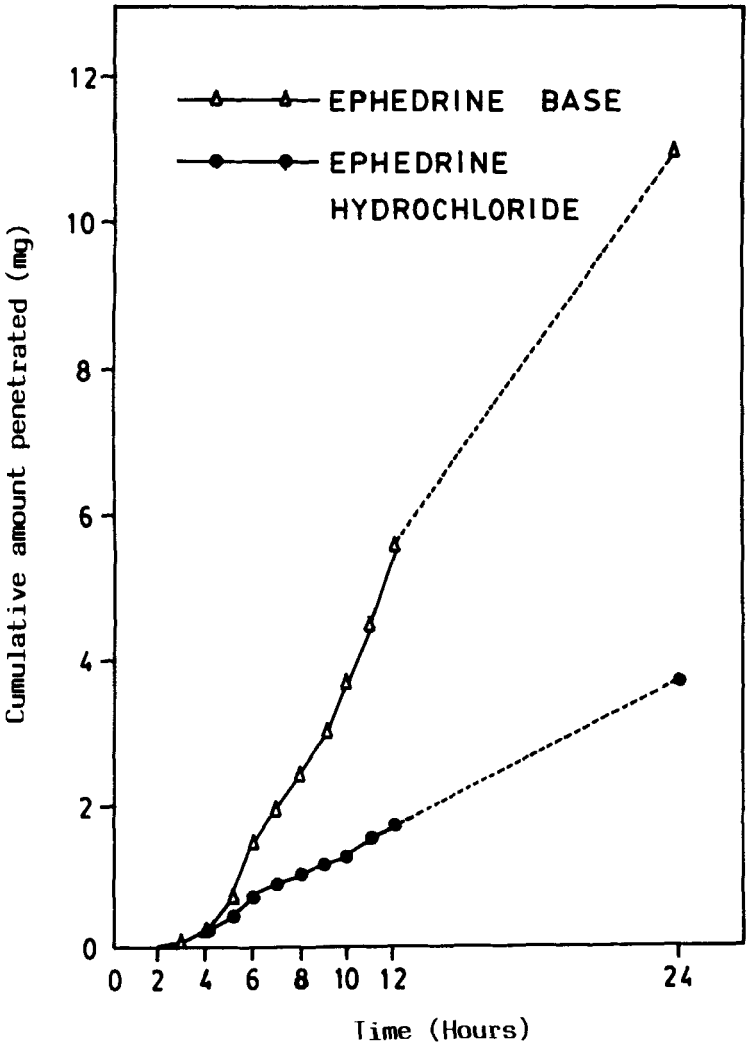

Figure 1

In vitro Diffusion Profiles of 1 cm^2 Films of Ephedrine Base and Ephedrine Hydrochloride Through Guinea Pig Skin

was maintained to less than 5.5 by administration of ammonium chloride as the excretion of Ephedrine is found to be dependent on the pH[12]. The *in vivo* urinary excretion data (Figure 3) revealed a marked three to four fold greater excretion of

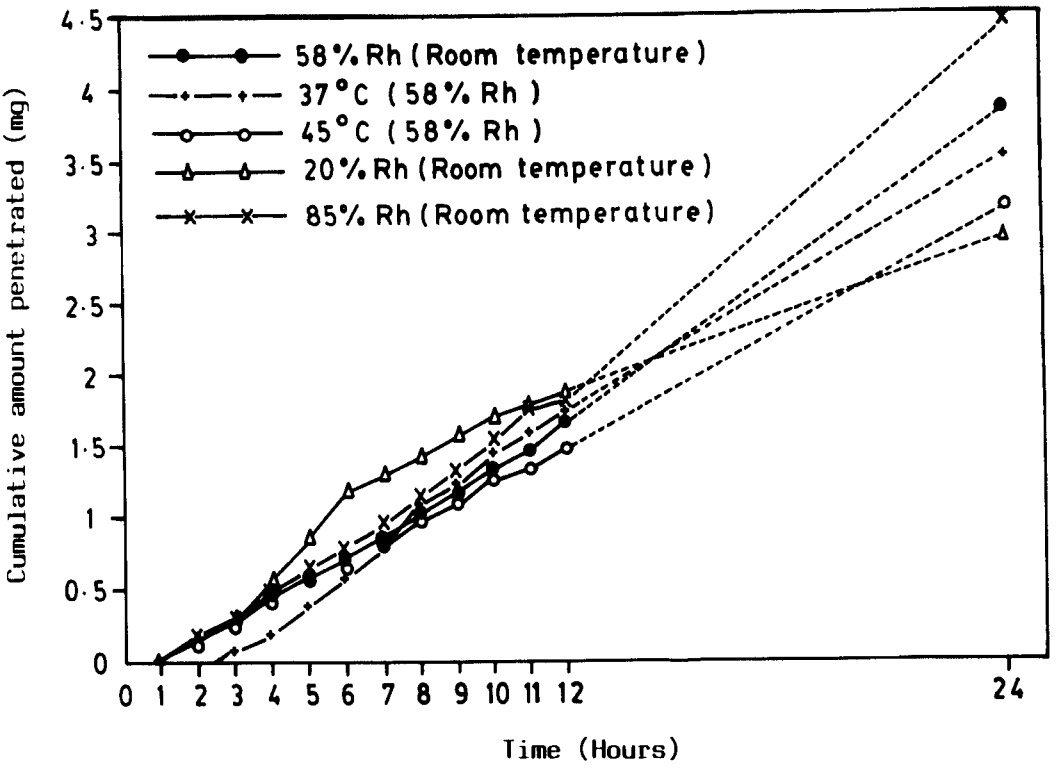

Figure 2

In vitro Diffusion Profiles of Ephedrine Hydrochloride Films Stored at Various Temperatures and Humidities for Four Weeks

Ephedrine base as compared to Ephedrine Hydrochloride. The films of Ephedrine base and Ephedrine Hydrochloride showed a cumulative excretion of 12.2 mg and 4.9 mg respectively after 24 hours when applied as 10 cm^2 patches. Both patches showed a sustained pattern throughout the period of 24 hours. The rate of absorption of the drug from the skin was calculated from the urinary excretion data by the equation suggested by Shaw *et al*[13]. The rate of absorption was 58 mcg/cm^2/hr and 23.6 mcg/cm^2/hr for

TABLE I

Parameters of Ephedrine Hydrochloride Films Stored at Various Temperatures and Humidities for Four Weeks

	Initial Value	37°C	45°C	20% Rh (at RT)	85% Rh (at RT)
Mean per cent deviation from average weight	9.21	9.98	8.76	9.47	9.84
Tensile strength (kg/cm^2)	28.00	23.40	20.40	17.20	25.00
Per cent moisture absorbed/lost	0.28	2.03	2.39	-8.18	7.75
Drug content(mg/cm^2)	20.05	19.75	20.42	19.02	21.37
Cumulative amount penetrated (mg/24 hours)	3.85	3.45	3.12	2.91	4.40

Note : - -ve sign indicates loss of moisture content

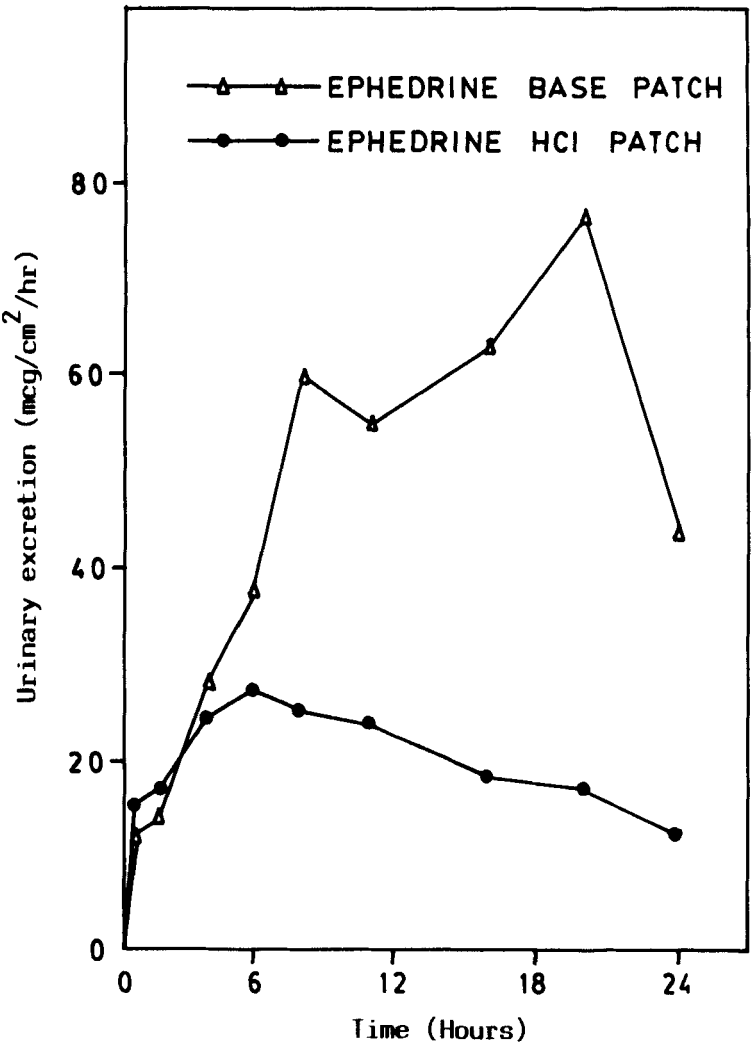

Figure 3

In vivo Urinary Excretion Profiles Obtained After Application of 10 cm^2 Patches of Ephedrine Base and Ephedrine Hydrochloride on Three Human Volunteers

Ephedrine base and Ephedrine Hydrochloride respectively. Keith *et al*[14] have determined that a transdermal therapeutic system of Ephedrine should release 5-30 mg of the drug in 24 hours in order

to achieve adequate blood levels. Films of Ephedrine base measuring 10 cm^2 were capable of providing an adequate diffusion of drug through the skin into the systemic circulation for a period of 24 hours. However, films of Ephedrine Hydrochloride as 10 cm^2 showed a lower diffusion and use of 20 cm^2 patches is required to provide the adequate amount of drug into the systemic circulation.

CONCLUSIONS

The results of this preliminary study indicated that the films of polyvinyl alcohol and polyvinyl pyrrolidone with the plasticizer glycerol could form the basis of a polymeric matrix type transdermal therapeutic system of Ephedrine. Further work needs to be done to establish the usefulness of these films in the treatment of asthma through long term pharmacokinetic and pharmacodynamic studies. Also, a backing membrane and a suitable adhesive need to be prepared and studied in order to design a complete system.

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