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Design and Evaluation of Nifedipine Transdermal Patches

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In the present investigation we prepared drug free polymeric films of ethyl cellulose (EC), to explore their suitability for transdermal application as the rate controlling membrane. Castor oil, glycerol was incorporated at a concentration of 30%w/w, 40%w/w of dry polymer, as plasticizer. The dry free films were evaluated for various physicochemical characters. The permeability characteristics of free films was studied using nifedipine as model drug. Drug was incorporated in 4% hydroxy propylmethylcellulose gel. The backing membrane was a non permeable aluminium foil laminated with polyethylene. Skin irritation study for the transdermal patches were assessed and were found to be free of irritation. An enhancement technique for drug permeation and *in vivo* pharmacological studies were also carried out. From this study it was concluded that faster release was observed from ethyl cellulose patches containing glycerol as plasticizer.

More recent approach to drug delivery is to deliver the drug into systemic circulation at a predetermined rate which is known as controlled release drug delivery system. Such systems helped to overcome the side effects associated with conventional systems of medication, which require multi-dose therapy[1]. The development of technology for release of drug at controlled rate into systemic circulation using skin as port of entry has become popular for various reasons[2]. The transdermal entry of a drug into systemic circulation at a desired rate can be achieved by using a suitable rate controlling membrane and drug reservoir[3]. The permeability of drugs through polymeric free films is dependent on characteristics of the polymer[4,5], casting solvent[6] and plasticizer used[7].

Nifedipine, a potent drug which is widely used for the treatment of hypertension[8]. Although it is well absorbed from the gastrointestinal tract, it's bioavailability is low due to extensive first pass metabolism. The suitability of nifedipine with respect to dose, solubility, molecular weight to get incorporated into a reservoir type, transdermal delivery system prompted the selection of drug nifedipine for the study. Molecular weight of nifedipine is 346.34[9], which is in the prescribed range of transdermal drug selection (100-800). Moreover it is easy to incorporate low dosage of drugs into transdermal therapeutic system. The above mentioned factors made this drug a suitable candidate for administration by transdermal route.

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MATERIALS AND METHODS

Nifedipine was a gift sample from Tablets India (P) Ltd, Chennai. EC with an ethoxyl content of 47.5–53.5% by weight and a viscosity of 14 cp in a 5% w/w 80:20 toluene:ethanol solution at 25° was procured from (S. D. Fine Chemicals Ltd., Boisar). Chloroform and glycerol was obtained from Loba Chemicals, Mumbai. Dialysis membrane (cut off 12,000) was purchased from the Sigma Chemicals Co., St. Louis, USA. All other ingredients were of analytical

grade and were used as procured.

Preparation of free films:

Free films of EC were prepared by casting on glass plate method[10]. A 3% w/v polymer solution was prepared using chloroform as solvent. Then two different plasticizer in two different concentration castor oil (30%, 40% w/w of dry polymer) and glycerol (30%, 40% w/w of dry polymer) were incorporated. Five millilitre of polymer solution was poured into the glass plate of size 5x5 cm. The solvent was allowed to evaporate at a controlled rate by placing an inverted funnel over the glass plate. After 24 h the dry film were removed from the glass plate and stored in a desiccator until use.

Physicochemical evaluation:

The free films prepared were evaluated for physical appearance, weight variation, uniformity of thickness, folding endurance, percentage moisture absorption, percentage moisture loss, and water vapour transmission rate.

Folding endurance[11]:

The folding endurance was measured manually for the prepared films. A strip of flim (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the flim could be folded at the same place without breaking gave the exact value of folding endurance.

Percentage moisture absorption:

The moisture absorption studies (MA) of various films were studied at 63% relative humidity. The film of known thickness was fixed over the edge of the glass vial containing 3 g of fused calcium chloride as desiccant by using an adhesive. Then the vial was weighed and kept in a desiccator maintained at 63% relative humidity. The vial was taken out periodically and weighed for a period of 72 h. The experiment was performed in triplicate and the average values were calculated by the method previously reported by Utzemi *et al.*[12].

Percentage moisture loss:

The film of known thickness was fixed over the edge of the glass vial using an adhesive. Then the vial was weighed and kept in a desiccator containing 10 g of calcium chloride as desiccant. The vial was taken out periodically and weighed for a period of 72 h and the values were calculated using the method reported by Bruno and John[13].

Water vapour transmission rate:

The film was fixed over the edge of the glass vial containing 3 g of fused calcium chloride as a desiccant by using an adhesive. Then the vial was placed in a desiccator containing saturated solution of potassium chloride. The vial was taken out periodically and weighed for a period of 72 h. The experiment was performed in triplicate and the average values were calculated by the method of Ragavendra *et al.*[14].

Preparation of transdermal gel:

The polymer (quantity of polymer with the drug and other ingredients were specified in Table 1 was taken in a beaker and water was added. This was allowed to soak for about 24 h and then glycerol was added and mixed well. Finally the required amount of drug along with other additives was added. Polymeric solution was stirred with the help of mechanical stirrer for 30 min in order to get homogenous dispersion of the drug in the gel.

Preparation of transdermal patches:

Aluminium foil was used as backing membrane and EC was used as the rate controlling membrane for the transdermal patches. Transdermal patches of nifedipine were prepared by sandwitching the gel containing 160 mg equivalent of drug in between two membranes. The rate controlling membrane was placed over the gel and it was fixed by applying chloroform on the edges of the controlling membrane.

***In vitro* release:**

The *in vitro* release was carried out with the dialysis membrane. It was washed in running water for 3 h in order to remove glycerin which was included as humectant in the membrane. Then the membrane was soaked in 90% alcohol for 24 h. For the removal of sulphur from the membrane, it was treated with 0.3% w/v sodium sulphide at 80° for 2 min. The membrane was washed with warm water 60° for 2 min

TABLE 1: COMPOSITION OF NIFEDIPINE GEL.

Ingredients	Amount
Hydroxy Propyl Methyl Cellulose	0.4 g
Glycerol	1 g
Methyl Paraben	20 mg
Propyl Paraben	20 mg
Nifedipine	400 mg
Distilled Water	Up to 10 g

Nifedipine was incorporated in 4% HPMC gel

followed by acidification with 0.2% v/v solution of sulphuric acid and rinsed with hot water to remove the acid.

The diffusion cell was fabricated with the help of a small funnel. The donor compartment was a funnel of diameter 4.5 cm. The transdermal patch of area 12 cm^2 was placed on the dialysis membrane, which was then tied to the diffusion cell. This diffusion cell was immersed in a beaker (receptor compartment) containing 100 ml of phosphate buffer of pH 7.4 with methanol 20% v/v as diffusion media. The receptor compartment was stirred by using a magnetic stirrer at 100 rpm and the whole assembly was maintained at 37±1°. The amount of drug released was determined by withdrawing 5 ml of samples at specific time intervals up to 24 h. The volume withdrawn was replaced with equal volume of fresh and pre-warmed (37 °) phosphate buffer media containing methanol. The absorbance of the withdrawn sample was measured after suitable dilution at 238 nm to estimate nifedipine. The experiment was carried out in triplicate and average values were reported.

In vitro skin permeation studies[15]:

Male Wistar rats weighing between 130–160 g and free from any visible sign of disease were selected for the *in vitro* studies. The hair on abdominal region was removed using a depilatory preparation one day prior to experiment. On the day of experiment, animals were sacrificed by cervical dislocation and the abdominal skin was excised. The fatty material adhered to the dermis was carefully peeled off. Freshly excised rat skin of thickness (2 mm) was mounted on the donor compartment. Among the four patches, transdermal patch containing 40% glycerol as plasticizer was placed. The permeation study was carried out in the similar manner as that of *in vitro* studies.

Permeation enhancement studies[16]:

Permeation enhancement study was performed as described by Huang *et al.* The freshly excised rat skin was treated on the stratum corneum side with volatile oil for a time period of 30 min. Then the respective volatile oil was removed and then the transdermal patch containing 40 % glycerol as plasticizer was placed and the permeation of the drug through the treated skin was studied. The same procedure was repeated with different volatile oils.

Skin irritation test[17]:

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on 8 healthy rabbits weighing 1.3 to 1.5 kg. Drug free polymeric films of diameter 4.1 cm containing glycerol as plasticizer were used as control. The dorsal surface of rabbits was cleared well and the hair was removed by using a depilatory preparation. The skin was cleared with rectified spirit. Transdermal patches containing nifedipine (6.4 mg equivalent) in HPMC gel were placed over the skin with the help of adhesive tape. The films and patches were removed after 24 h and the skin was examined for erythema. All the experimental protocols involving laboratory animals were approved by the IAEC.

In vivo release studies:

In vivo release studies were carried out using male rabbits (*Orytolagus cunniculus*) for transdermal patch containing 40% glycerol as plasticizer and for the patch obeying zero order release profile. Four rabbits weighing 1.5 kg were selected and the dorsal surface was cleaned and hair was removed. The dose of nifedipine was calculated according to the body weight. Transdermal patch containing gel equal to 6.4 mg of nifedipine, which is in turn equivalent to 240 mg nifedipine for human use, was selected for *in vivo* studies. Transdermal patch of 4.1 cm were placed and immediately occluded with an adhesive tape. Blood samples (0.5 ml) were withdrawn from the marginal ear vein into heparinized glass vessels at 0, 2, 4.8, 16 and 24 h.

The plasma was separated immediately by centrifugation at 2000 rpm for 10 min and stored in the refrigerator until analysis. The absorbance of the solution was measured at 238 nm against a blank. The method was validated for accuracy, precision and interference. The experiments were carried out in triplicate (n=3). From the results obtained, the relative error and co efficient of variation were found to be 1.25% and 1.6%, respectively.

RESULTS AND DISCUSSION

Ethyl cellulose used for the fabrication had a good film forming property. Prepared films were thin, flexible, smooth and transparent. The method of casting the film on the glass plate was found to be satisfactory. The physicochemical evaluation data for drug free films was presented in Table 2. The physicochemical evaluation study reveals that there were no physical changes like appearance, colour and flexibility when the films stored at room temperature. The weight of films containing castor oil as plasticizer was more than that of glycerol containing films. It may be due to the higher viscosity[18] of the castor oil containing polymer solution (Table 2). The thickness was found to be high with the films prepared with castor oil as plasticizer. As the

TABLE 2: COMPOSITION AND PHYSICOCHEMICAL EVALUATION OF PREPARED RATE CONTROLLING MEMBRANE.

RCM	PC	Plasticizer concentration	Weight of RCM** (mg)	T* (μ)	FE**	PMA	PML	WVT g / cm/ h
R1	3% E.C.	30%Castor oil	330	340	>268	4.173	0.281	$0.332x10^{-3}$
R2	3% E.C.	40%Castor oil	345	355	>277	4.073	0.182	$0.362x10^{-3}$
R3	3%E.C.	30%Glycerol	300	310	<231	4.826	0.523	$1.53x10^{-3}$
R4	3%E.C.	40%Glycerol	310	320	<242	6.336	0.914	$1.46x10^{-3}$

RCM denotes the rate controlling membrane, PC indicates polymer concentration, T represents thickness, FE denotes folding endurance, PMA and PML represents percentage moisture absorption and percentage moisture loss. WVT indicates water vapour transmission rate. ** Average of five determinations. * Average of three determinations.

proportion of castor oil was increased, the thickness was also increased (Table 2).

The thickness was found to be less with the films prepared with glycerol even though moisture absorption and moisture loss is high (Table 2). The folding endurance was measured manually, films were folded 250 times and if the films show any cracks it was taken as end point. The folding endurance was better in castor oil containing films when compared with glycerol containing films. Water vapour transmission through films determines the permeability characters of the films.

The water vapour transmission, percentage moisture absorption, percentage moisture loss was found to be least with the films containing castor oil 30%, 40% w/w of dry polymer as plasticizer. This can be explained on the basis of affinity of the film towards water, which is in the following order glycerol > castor oil (more lipophillic) (Table 2). Drug diffusion study of free films with respect to nifedipine through dialysis membrane indicates that the film is permeable to drugs.

Membrane permeation controlled transdermal patches have an advantage regarding the stability of nifedipine, which is a light sensitive drug, may be protected in the reservoirs covered by the membrane. The results of the *in vitro* release study from different transdermal patches across the dialysis membrane are depicted in fig. 1. The release pattern was found to be faster through the patches containing glycerol as plasticizer than the patches containing castor oil as plasticizer (fig. 1). Moreover as the percentage of plasticizer was increased, the drug release was found to be increased (fig. 1). These two observations may be reasoned out as follows; 1) faster release from EC patches containing glycerol as plasticizer may be correlated with the thickness of the film, high water vapour transmission rate. The thickness of the film was found to be less in case of film prepared with glycerol as plasticizer (Table 2).

As the thickness of the film was decreased, an increase in permeation of drug was observed, may be due to decrease in path length to the movement of the drug, as it is inversely proportional to diffusion rate. 2) Glycerol being a better plasticizer increases the flexibility and permeability of the film and 3) The presence of hydrophilic plasticizer

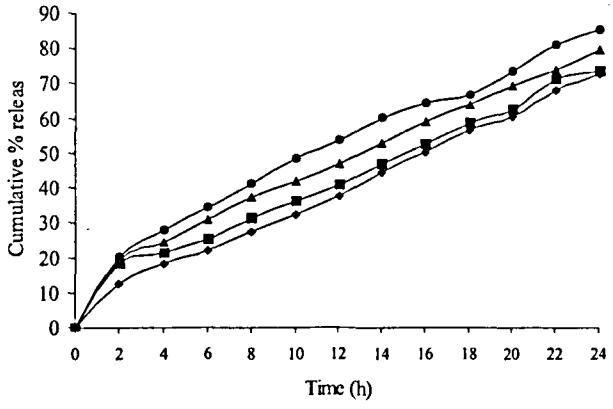

Fig. 1:Comparative *in vitro* release profile of nifedipine from transdermal patches.

(-♦-) release of nifedipine through R_1 (EC membrane containing 30% castor oil as plasticizer). (-▫-) release through R_2 (EC membrane containing 40% castor oil as plasticizer). (-▲-) release through R_3 (EC membrane containing 30% glycerol as plasticizer). (-●-) release through R_4 (EC membrane containing 40% glycerol as plasticizer).

may enhance the partitioning of water insoluble nifedipine .

The drug diffusion from transdermal patch containing 40% glycerol as plasticizer follows zero order release pattern, which is presented in (fig. 2). The regression value was found to be 0.9814. This shows that controlled transdermal permeation of nifedipine is possible with the prepared formulation.

The *in vitro* permeation of the drug through the rat skin was slightly lesser than artificial membrane. Hence newer technique such as volatile treatment was employed. Volatile oils brought dramatic change in the drug permeation through rat skin. Permeation brought about by volatile oil treatment was in the following order, no treatment<lemon oil<clove oil<eucalyptus oil<winter green oil (fig. 3).

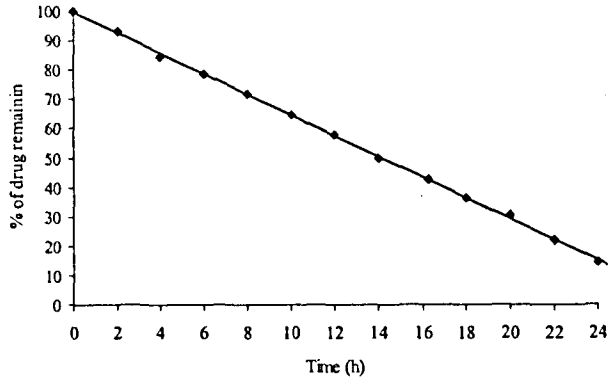

Fig. 2: Zero order release pattern of nifedipine from transdermal patch.

(-♦-) Rate controlling ethyl cellulose membrane containing 40% glycerol as plasticizer

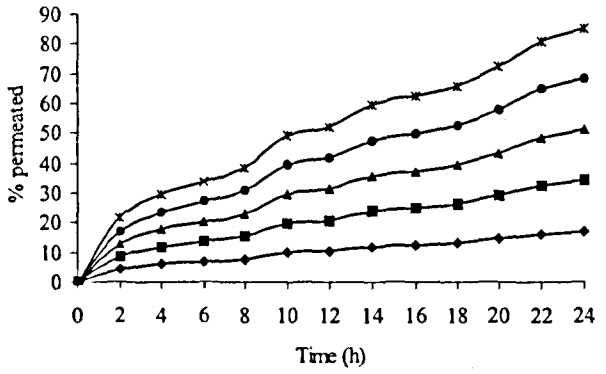

Fig. 3: Comparative effect of volatile oil treatment on the permeation of nifedipine through rat abdominal skin.

(-♦-) indicates no treatment. (-■-) represents treatment with lemon oil. (-▲-) represents treatment with clove oil.(-●-) denotes treatment with eucalyptus oil. (-x-) denotes treatment with wintergreen oil.

Winter green oil resulted in maximum drug permeation enhancement. Nearly 5 fold increase was observed (fig. 3). Next to that a 3, 4 fold increase was obtained after treatment with clove oil and eucalyptus oil respectively. After treatment the drug permeation from transdermal patches containing 40% glycerol as plasticizer showed perfect positive correlation. When the regression analysis was carried out the correlation value was found to be 0.9858. It shows that the artificial membrane simulates skin impermeability characteristics to a greater extent and can be used in *in vitro* permeation studies. A primary skin irritation test on rabbits after the application of transdermal patches a slight erythema was observed which is similar to that of solvent control.

The *in vivo* drug release studies in rabbits revealed that *in vivo* controlled delivery of nifedipine is possible with the patches. Even though the drug release was slow during the initial hours (up to 4 h) from the EC patches containing 40 % glycerol as plasticizer, the maximum percentage release was attained within 24 h. Moreover the drug release was satisfactory and it extended up to 24 h (fig. 4). The delivery system was found to release 82.6% of loaded drug at the end of 24 h.

In summary drug free films of ethyl cellulose contain-

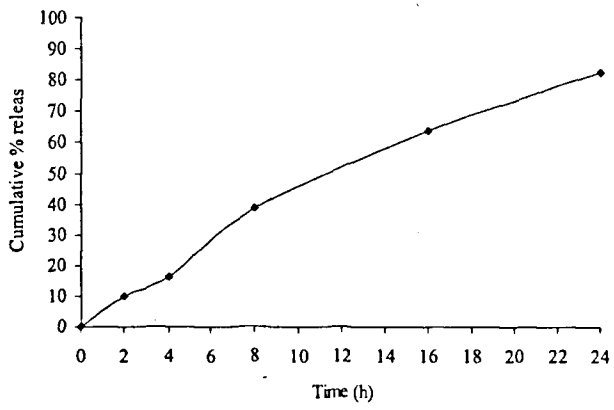

Fig. 4: *In vivo* drug release profile from nifedipine transdermal patch.

(-♦-) Rate controlling ethyl cellulose membrane containing 40% glycerol as plasticizer.

ing glycerol as plasticizer can be used as rate controlling membrane. Moreover, the drug diffusion was extended over a longer period of time at a controlled rate. The drug permeation through excised rat skin was enhanced after volatile oil treatment. The primary irritation studies shows no erythema indicating the formulated transdermal patches are safer for use. The *in vitro* and *in vivo* results of the study show the feasibility of formulating rate controlled transdermal drug delivery system for nifedipine in order to achieve improved bioavailability.

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