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Effect of Permeation Enhancer and Iontophoresis on Permeation of Atenolol from Transdermal Gels

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Transdermal free films of atenolol were made using sodium CMC as polymeric matrix and porpylene glycol as the plasticizer. DMSO, PEG 400, Tween 20, Pluronic F127 and Brij 35 were used as permeation enhancers. The drug free films were evaluated for various mechanical properties. The drug diffusion studies were carried out using Keshary-Chein cell. A comparison of various permeation enhancers on permeation rate of atenolol was made. The effect of iontophoresis on permeation of atenolol was studied. Iontophoresis increased the permeation rate of the drug to a greater extent compared to the permeation enhancers.

Transdermal drug delivery at a controlled rate is proclaimed as effective route of administration. The success of a transdermal drug delivery system (TDDS) will depend on the ability of the drug to penetrate the stratum corenum at a rate sufficient to achieve concentration in the systemic circulation, necessary for the desired therapeutic effect. However, the practical application of TDDS has always been challenged by the formidable barrier properties of stratum corneum. One of the approaches to overcome this problem is administration of skin permeation enhancer[1-3]. The permeation of ionizable as well as non-ionizable drugs can be improved by the application of current (iontophoresis) across suitable elecrode terminals.[4-6]

Atenolol is a β_1-selective antagonist that is devoid of intrinsic sympathomimetic activity. It is a drug used in all grades of hypertension in early management of acute myocardial infection and can control both supra ventricular and ventricular arrhythmias. It is hydrophilic in nature. Atenolol is incompletely absorbed from GIT and has a half-life of 6.1 h[7]. Therefore, this drug was used as a model to study the permeability characters.

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The present investigation was carried out to study the influence of various permeation enhancers and the effect of iontophoresis on the permeability of atenolol from transdermal film through rat abdominal skin.

EXPERIMENTAL

Atenolol was obtained as a gift sample from Eros Pharma Pvt. Ltd., Bangalore. Propylene glycol was obtained from Loba Chemicals and Alu poly from Jagdale Scientific Research Foundation, Bangalore. All the other chemicals used were of analytical grade.

Preparation of free films of Atenolol:

The casting solution was prepared by dissolving polymer (sodium CMC 4%) and plasticizer (propylene glycol 30% of the polymer) in distilled water by heating on a water bath for 30 min to effect complete solution. Atenolol (1%) and pemeation enhancers (10%) were added to the polymer solution and dissolved by stirring at 500 rpm for 30 min. Aluminium foil (Alu poly) laminated with polyethylene was used as inert support casting the film. A foil cup (5 cm diameter) was prepared by pressing the foil between 2 plastic cups. About 3 ml of the solution was pipetted into the cup. This was dried at 50° for 10 h and the film with 3 cm^2 diameter was cut and taken for

TABLE 1 : FORMULATION AND PHYSICO-CHEMICAL PARAMETERS

Batch No.	Permeation Enhancer	Thickness (μ)	Weight (mg)	Folding Endurance
1.	—	113	88	>150
2.	DMSO	118	109	>150
3.	PEG-400	122	130	>150
4.	Tween-20	115	85	>150
5.	Pluronic F127	135	129	>150
6.	Brij - 35	150	141	>150

in vitro release studies. The formulation details and physiochemical characters of the films are shown in Table 1.

In vitro release studies:

In vitro evaluation was carried out using the Keshary-Chein cell[8]. Freshly excised rat abdominal skin was mounted between the donor and the receptor comartment of the diffusion cell. 0.2% W/V Phosphate buffer (pH 4.5) was used as the receptor fluid. The donor compartment was exposed to atmospheric conditions. Aliquots of the receptor fluid was drawn out every hour and replaced with fresh receptor fluid. The drug permeated was estimated at 224 nm spectrophotometrically[9]. The diffusion rate and permeability co-efficient was calculated and reported in Table 2.

Permeation enhancement studies:

Result obtained in the *in vitro* experiment indicated that although the drug permeates across the rat skin, the amount of drug permeated was not satisfactory. Modification were therefore effected by casting the free films using various permeation enhancers namely DMSO, PEG 400, Tween 20, Pluronic F 127 and Brij 35. The films were then evaluated for the release of the drug for 10 h. The results obtained are presented in Fig.1.

Effect of iontophoresis on permeation enhancement:

Freshly excised rat abdominal skin was sandwiched between the two compartment of the permeation cell. The donor compartment and the receptor compartment were filled with 10 ml of 0.2% W/V phosphate buffer (pH 4.5). The transdermal film (plain atenolol film) was placed in the donor compartment. A platinum wire electrode was placed in the receiver side, which served as the cathode, and another wire electrode was placed in the donor side, which served as the anode. Current was passed through the electrode by creating a potential difference between the two electrode of a required voltage (2.5 v). Every hour aliquots of the receptor fluid was drawn out and replaced with fresh receptor fluid. The drug permeation was estimated at 224 nm spectrophotometrically for 10 h and shown in Fig. 1.

TABLE 2 : DIFFUSION AND PERMEABILITY CO-EFFICIENT OF FORMULATIONS

Sl No.	Permeation Enhancer	Film Thickness mm	Diffusion Rate Co-efficient μg/cm²h	Permeation Rate co-efficient μg/cm²hr	Tensile Strength Kg.cm²
1.	NIL	56.9 ± 3.2	4.2 ± 0.6	1.1 ± 0.2	52.4 ± 1.2
2.	Brij - 35	52.8 ± 2.6	7.9 ± 0.8	2.4 ± 0.46	48.6 ± 2.8
3.	Pluronic- F 127	20.9 ± 3.8	10.2 ± 0.3	4.2 ± 0.6	50.9 ± 2.1
4.	Tween - 20	25.4 ± 2.4	12.5 ± 0.2	6.5 ± 1.8	38.2 ± 2.4
5.	PEG - 400	46.2 ± 4.2	17.5 ± 0.3	12.9 ± 0.25	50.4 ± 4.2
6.	DMSO	20.4 ± 1.4	20.2 ± 0.2	19.2 ± 2.2	64.8 ± 2.4

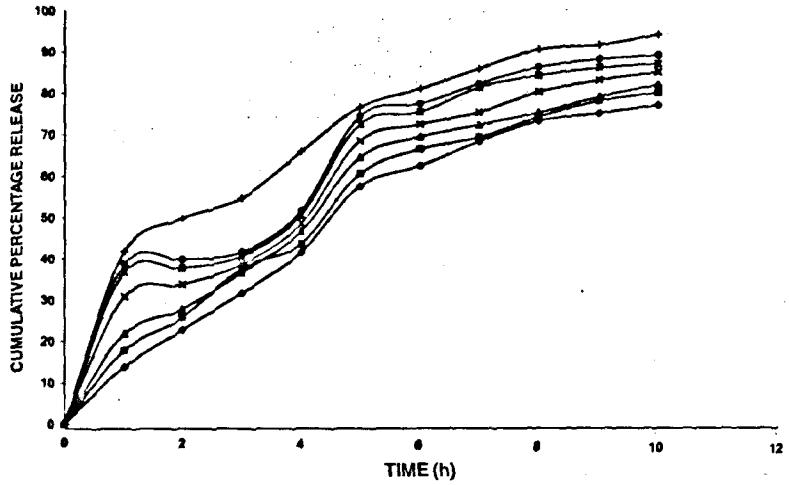

Fig. 1: Effect of permeation enhancers and iontophoresis

Effect permeation enhancers and iontophoresis was studied by determining rate of release of atenolol from transdermal films (+) Iontophoresis (•) Brij 35, (✳) Pluronic f-127, (x) Tween 20, (▲) PEG 400, (■) DMSO, (◆) Plain

RESULTS AND DISCUSSION

Since atenolol is incompletely absorbed from GIT transdermal film of atenolol were prepared. The physicochemical factors were found to be satisfactory. The permeation enhancers used increased the permeation of the drug and they can be arranged in the following increasing order according to their permeation rate. Brij 35> Pluronic F127> Tween 20> PEG 400> DMSO. The increased permeation rate in all these may be due to surfactant action.

Iontophoresis increased the permeation rate of the drug to a greater extent compared to the permeation enhancers. This may be due to increased membrane permeability and altered tissue extensibility. So it is evident that permeation could be improved using iontophoresis with the addition of few efficient permeation enhancers.

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