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In vitro permeation studies of Indapamide from transdermal films

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ABSTRACT

The aim of the present work was to develop and evaluate a transdermal bioadhesive transdermal film containing indapamide. Indapamide is a long-acting hypertensive with both diuretic and vasodilative actions and is defined by the 1999 WHO/ISH Hypertension Guidelines as a first-line drug for the treatment of hypertension. Transdermal films were prepared by dissolving in water Eudragit RS100, lauric acid, adipic acid, polyvinyl alcohol, sorbitol and indapamide. The resultant mixture was spread on siliconized paper and dried. The in-vitro permeation experiments were performed in Franz-diffusion cell using freshly excised rat skin for 12 h. The permeation results of indapamide form 2 mg/ml and 5mg/ml solutions in phosphate buffer (pH 7.4) showed significant permeation behaviour. The in vitro permeation results of transdermal films showed good permeation characteristics across the skin, with linear release from film F3. The Eudragit RS 100 and polyvinyl acetate in 1:2 proportions proved to be better composition for preparation of transdermal film which can be a promising and innovative therapeutic system for indapamide.

Keywords: Transdermal film, Indapamide, Eudragit RS100, polyvinyl alcohol.

INTRODUCTION

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Transdermal patches are innovative drug delivery systems intended for skin application to achieve a systemic effect. Among the different types of systems, the drug-in-adhesive products in which drug is included in the adhesive layer contacting the skin are commonly used, being thin and comfortable to wear. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a timed-released dose of medication through the skin to treat systemic conditions. Since fron last two decades, transdermal delivery systems are avaible commercially offering variety of significant clinical benefits over other drug delivery

systems. These systems provides controlled release of the drug and produces steady-level profile leading to reduced systemic side effects and sometimes improved efficacy. In addition these dosage forms are user's friendly, convenient, painless and offers multi-day dosing which leads to improved patient compliance.

Indapamide is a long-acting hypertensive with both diuretic and vasodilative actions and clinically used as a first-line drug for the treatment of hypertension. Indapamideis a non-thiazide indole derivative of chlorosulphonamide, which has an anti-hypertensive action causing a drop in systolic, diastolic and mean blood pressure. This work was undertaken to investigate indapamide transport from the transdermal film and to determine whether therapeutically relevant delivery rates could be achieved from transdermal delivery system to maintain suitable plasma drug levels for increased therapeutic efficacy.

MATERIAL AND METHODS

Indapamide was received as gift from, India. Eudragit RS100 was received as a generous gift samples from Arihant Trading Corp. Mumbai. Polyvinyl acetate, glycerol, sorbitol, lauric acid and adipic acid were purchased from S. D. Fine Chemicals, Mumbai and the double distilled water was used throughout the study.

Preparation of transdermal patch of indapamide

The Eudragit RS100 (20% w/w), lauric acid (10% w/w) and adipic acid (2% w/w) were added to hot purified water. The mixture was stirred by maintaining the temperature at 80 ^{0}C until the clear solution was formed. The solution was cooled down to 60 ^{0}C and glycerol (2% w/w) was added. The solution then cooled to room temperature. Indapamide
dissolved in methanol along with sorbitol was added to polyvinyl acetate solution, which is prepared in water and then to Eudragit E200 solution.
The resultant mixture was stirred for 24 h and then laminated on silicone membrane having thickness 0.25 mm and oven dried at 45 ^{0}C for 1 h. The solvent evaporation technique used for preparation of Metoclopramide hydrochloride: fulvic acid Complex in 1:1 molar ratio. The circular film of 25 mm diameter was cut from each film.

Table: 1 Composition of transdermal film of Indapamide

Component (% w/w)	Formulation					
	F1	F2	F3	F4	F5	F6
Eudragit RS 100	10.0	15.0	20.0	20.0	15.0	10.0
Polyvinyl acetate	30.0	35.0	40.0	40.0	35.0	30.0
Lauric acid	10.0	10.0	10.0	10.0	10.0	10.0
Adipic acid	2.0	2.0	2.0	2.0	2.0	2.0
Glycerol	1.0	1.0	1.0	1.0	1.0	1.0
Sorbitol	2.0	2.0	2.0	2.0	2.0	2.0
Methanol	3.0	3.0	3.0	3.0	3.0	3.0
Water	42.0	32.0	22.0	22.0	32.0	42.0

Characterization of film

Each circular film of 25 mm diameter was evaluated for weight. The transdermal films were dissolved in 50 ml of purified water under sonication for 2 h. The solutions obtained were analyzed by HPLC in order to determine the amount of indapamide contained in the film. The results were expressed as both µg of indapamide per cm^2 and percentage of indapamide.

Indapamide analysis

Indapamide analysis was performed by HPLC (Young Lin Aceme 9000) equipped with UV detector and Hypersil column (5 um 200mm x 4.6 mm) was used. A mixture of methanol, distilled water and acetic acid (45:55:0.1 v/v/v) was used as a mobile phase. The column was maintained at 40 ^{0}C and the flow rate was 1 ml/min while the UV detector was set at 240 nm. The retention time in the assay was found to be 4.05 and 5.95 min for internal standard and indapamide respectively. The methanolic solution of acetaniline was used as an internal standard.

***In vitro* skin permeation experiments**

In vitro skin permeation experiments were performed using a vertical Franz diffusion cell whose diffusion area was 0.72 cm^2, and hairless rat skin. The abdominal skin of male Wister rat was excised and subcutaneous fat and other extraneous tissue were trimmed. The skin was mounted on the Franz diffusion cells with stratum corneun facing the donor compartment. The receptor compartment was filled with phosphate buffer (pH 7.4) whose temperature was maintained at 37± 0.5^{0}C. At predetermined time intervals the receptor solution was sampled and analyzed by HPLC for the determination of drug content. The permeation profiles were then fitted to the following equation to calculate the cumulative amount of drug permeated per unit area.

$$Q = (Kh)\, C_v\, [D/H^2 t\text{-}1/6\text{-}2/\pi^2 \textstyle\sum^{n}_{n=1}(-1)^2/n^2 \exp(-D\, n^2\, \pi^2 t/H^2)$$

Where Q is the cumulative amount of drug permeated per unit area at time t, C_v is the concentration of drug in transdermal film, K is the stratum cormeum/film partition coefficient, D the diffusion coefficient and H the diffusion path length. The results were expressed as the mean±SEM and the statistical difference was determined by student's t-test.

Table 2: Result of in vitro permeation studies of Indapamide through rat skin

Time (h)	Indapamide permeated through excised rat skin (µg/cm^2)					
	F1	F2	F3	F4	F5	F6
0	00	00	00	00	00	00
1.0	90.24	84.0	57.00	63.0	71.0	90.0
2.0	155.0	161.0	115.0	139.0	120.0	140.0
4.0	200.0	199.0	171.0	198.0	179.0	211.0
6.0	266.0	286.0	229.0	255.0	233.0	278.0
8.0	317.0	341.0	287.0	296.0	278.0	324.0
10.0	380.0	394.0	345.0	347.0	320.0	379.0
12.0	415.0	410	408.0	391.0	384.0	400.0

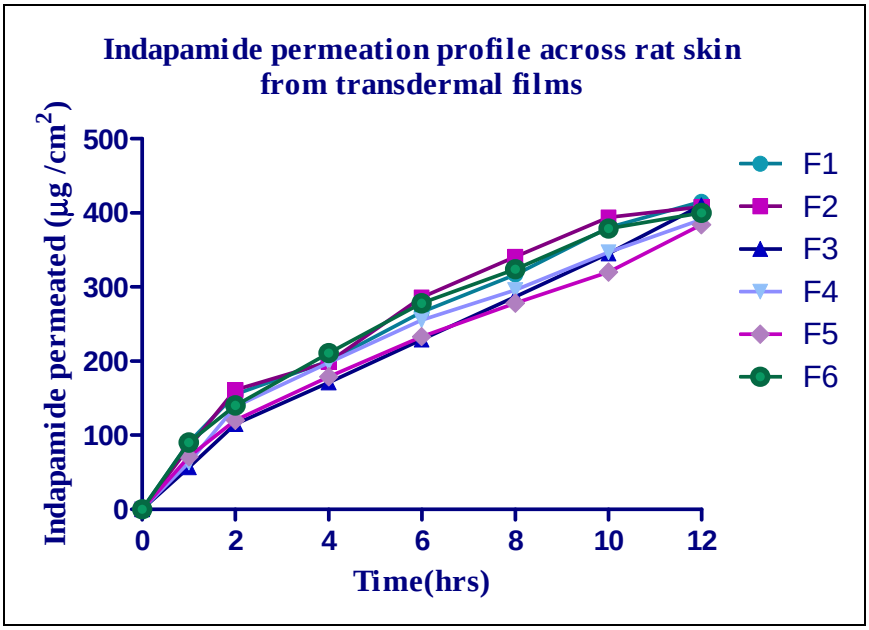

Fig. 1: Indapamide permeation profile across excised rat skin from transdermal film.

RESULT AND DISCUSSION

Freshly excised male Wister brat skin was used as a animal model skin for *in vitro* permeation experiments. Initially the skin permeation of indapamide was studied from aqueous solutions to characterize the permeation properties of the drug. In fact till date no official record of permeation data is available. Indapamide water solutions 2 mg.ml and 5 mg/ml prepared in phosphate buffer (pH 7.4) by using methanol as a co-solvent showed significant drug permeation through rat skin with very short lag time. The permeation flux calculated as the slop of the regression line in the interval 1-12 h, resulted 15.3 ± 2.6 and 38.15 ± 0.08 $\mu g cm^{2} h^{-1}$ for 2 and 5 mg/ml respectively.

Fig.1 reports permeation profile of indapamide from prepared transdermal film formulations resulted in linear with the square root of time, suggesting a matrix-type control of drug delivery by the transdermal film. It was also observed that there is a steady and continuous permeation of indapamide from all films indicating that indapamide was dissolved in adhesive with uniform distribution. The cumulative drug permeated from formulation F1 and F2 was higher but the permeation from formulation F3 resulted in linear release. A t-test showed that the difference was statistically significant ($p<0.05$). These results indicated that Eudragit RS 100 and polyvinyl acetate at a proportion of 1:2 will be suitable for the development of transdermal drug delivery systems for indapamide.

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