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TRANSDERMAL PATCHES OF VALSARTAN: FORMULATION AND EVALUATION

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ABSTRACT

Transdermal drug delivery system has been seen a veritable explosion in the past decades. In the present scenario, very few transdermal patches are available. Matrix-diffusion type transdermal film of valsartan was designed with various concentration of HPMC (k4M, K15M, K100M). Valsartan is a nonpeptide angiotensin II AT_1 receptor antagonist and very well-tolerating hypertension by specifically blocking the action of angiotensin-II on the angiotensin Type-1 receptor. The drug has 23% bioavailability with biological half life of 7.5h. The result of the formulation E was showing weight variation(0.0519 ± 0.0004), percentage moisture absorption (3.45 ± 1.08), percentage moisture loss (4.8 ± 1.14), water vapour transmission rate (0.46 ± 0.015g/hr/cm^2), thickness (0.056 ± 0.005mm), Folding endurance (1033.67 ± 7.094), tensile strength (0.379 ± 0.006 kg/mm^2). In vitro release studies showed zero-order release from all the patches. The permeation was studies were carried out for 24h showing release up to 39%. Stability studies are carried out for 7 weeks and indicates that drug remain stable for that period and primary irritation studies indicated that the transdermal patches are non irritant

KEYWORDS: Transdermal patches, Valsartan, HPMC, Hypertension.

1.1 INTRODUCTION

Skin, the largest organ of the body, is composed of several layers: the stratum corneum (uppermost layer), the viable epidermis, the dermis, and the lower layers of adipose tissue. An average square centimeter of skin contains 10 hair follicles, 15 sebaceous glands, 12 nerves, 100 sweat glands, 360 cm of nerves, and three blood vessels. The skin forms an

attractive and accessible route of delivery for systemic drugs because of the problems associated with other methods of administration, such as oral and parenteral. However, few drugs are able to passively diffuse across the uppermost layer of the skin, the stratum corneum, as a result of its effective barrier properties. The stratum corneum, or horny layer, consists of flat, roughly hexagonally shaped, partly overlapping cells, with a thickness of approximately 0.3 mm and a diameter of approximately 30 mm (Asbill and Michnaik, 2000; Hadgraft, 2004; El Maghraby et al., 2008 and Darlenski, 2009). Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications and offers many advantages over other traditional routes of administration (Benson, 2005 and El Maghraby et al., 2008). The advantages of TDD have included the: therapeutic benefits such as sustained delivery of drugs to provide a steady plasma profile, particularly for drugs with short half-lives, and hence reduced systemic side effects; reducing the typical dosing schedule to once daily or even once weekly, hence generating the potential for improved patient compliance; and avoidance of the first-pass metabolism effect for drugs with poor oral bioavailability (Thomas and Finnin, 2004). Valsartan is rapidly absorbed following oral administration, with a low bioavailability of about 23%. It is not significantly metabolized and is excreted mainly via the bile as unchanged drug (86%). The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. It is highly bound to serum proteins (95%), mainly serum albumin. It has low molecular weight (435.5) and melting point (116–117°C) with a favourable log partition coefficient (4.5) and mean biological half life (7.5 hours). All the above characteristics make valsartan a good candidate for transdermal delivery (Rizwan et al., 2008 and Moffat, 2006).

1.2 MATERIALS AND METHODS

Gift sample of Valsartan was provided (Torrent Pharmaceuticals, Baddi) and Hydroxypropylmethylcellulose (HPMC: K4M, K15M and K100M) (Colorcon, Mumbai). All other reagents/solvents used in this study are of analytical grade (Sigma Aldrich, Delhi).

1.3 Preparation of Transdermal Patches

Transdermal films containing Valsartan were prepared by solvent casting technique employing mercury as substrate. Overall nine formulations were formulated using different ratios of three HPMC grades i.e. HPMC K4M, HPMC K15M and HPMC K100M.

In initial study, only drug containing formulations were prepared. Glycerine was incorporated

at concentration of 150% w/w, as plasticizer. The formulations are designated as A, B, C, D, E, F, G and H. The detailed compositions of the patches are given in table 1.

1.3.1 Preparation of casting solution

The casting solutions were prepared by dissolving appropriate polymers, plasticizer in suitable vehicle using magnetic stirrer. The mixture was stirred continuously in such a manner that evaporation of solvent was minimum. The drug was added slowly to the solution and dissolved by continuous stirring for 30 minutes.

1.3.2 Casting of matrices

For the formulation of films, mercury was used as the backing membrane. Mercury was spread uniformly on glass petridish. The mould was kept on a table with smooth horizontal surface. About 4.5 ml of the solution was poured on the mercury (10.74 cm^2). The rate of evaporation was controlled by inverting the funnel over the mould. After 4 hours, the dried patches were cut into 2.5 cm diameter, wrapped in aluminium foil and stored over fused calcium chloride in a desiccator at room temperature for further use.

1.4 Physicochemical Properties of the Patches

The patches were evaluated for the following physicochemical properties.

1.4.1 Weight variation

Uniformity of weight was determined by weighing five matrices of each formulation. After each film unit was weighed individually on a digital balance, the average weight of film was taken as the weight of the film (Samanta et al., 2003).

1.4.2 Percentage Moisture Absorption

The films were weighed accurately and placed in the dessicator containing 100 ml of saturated solution of aluminum chloride, which maintains 79.50% RH. After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula (Kusum Devi et al., 2003).

Percentage moisture absorption

$$\frac{\text{Final weight-Initial weight}}{\text{Initial weight}} \times 100$$

1.4.3 Percentage Moisture Loss

The films were weighed accurately and kept in a dessicator containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula (Kusum Devi et al., 2003).

Percentage moisture loss

$$\frac{\text{Final weight-Initial weight}}{\text{Initial weight}} \times 100$$

1.4.4 Water Vapour Transmission Rate

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1 g anhydrous calcium chloride was placed in the cells and the respective polymer film was fixed over the brim. The cells were accurately weighed and kept in a closed dessicator containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48, and, 72 h of storage. The amount of water vapour transmitted was calculated using the formula (Kusum Devi et al., 2003).

$$\text{Water vapour transmission rate} = \frac{\text{Final weight-Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

1.4.5 Thickness

The thickness of the patch was measured at five different points using a screw gauge (Mitutoyo Japan) and average thickness recorded (Kusum Devi et al., 2003).

1.4.6 Folding Endurance

The folding endurance is expressed as the number of folds or number of times the film is folded at the same place either to break the film or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. The number of times the film can be folded at the same place without breaking gives the value of folding endurance (Kusum Devi et al., 2003).

1.4.7 Content Uniformity

A film was cut into small pieces and put in 100ml buffer (pH 7.4). This was shaken on mechanical shaker for 2 hr to get a homogeneous solution and filtered. The resulting

solutions were quantitatively transferred to volumetric flasks, and appropriate dilutions were made with pH 7.4 Phosphate buffer. The resulting solutions were filtered and analyzed for Drug content at 210 nm in UV spectrophotometer. The average reading of three patches was taken as the content of drug in one patch (Kusum Devi et al., 2003).

1.4.8 In Vitro Permeation Study

For the study of in vitro release patterns from the prepared TDDS formulation, a Franz diffusion cell was used. The films were placed in between the donor and donor receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment. The receptor compartment was filled with phosphate buffer and stirred with magnetic bead and the temperature was controlled at 37 ± 1^0C. A sample of 5 ml was withdrawn at predetermined intervals, being replenished by equal volumes of the elution medium. This was carried out for a period of 24 hr. The drug concentration in the aliquot was determined spectrophotometrically and was calculated with the help of standard calibration curve (Samanta et al., 2003).

1.4.9 Primary Skin Irritation Studies

The patches were tested for their potential to cause skin irritation/sensitization in healthy albino rats of 200-220gms. The skin from the back of each rat was depilated 24 hours prior to the application of the patch. The dorsal surface of the rats was cleared and hair was removed by hair removing cream. The skin was cleared with rectified spirit. The patches were placed over the skin with the help of adhesive tape. They were removed after 24 hour exposure. Upon removal of patches, the resulting reaction was evaluated according to US-FDA grading scale (Gattani et al., 2006).

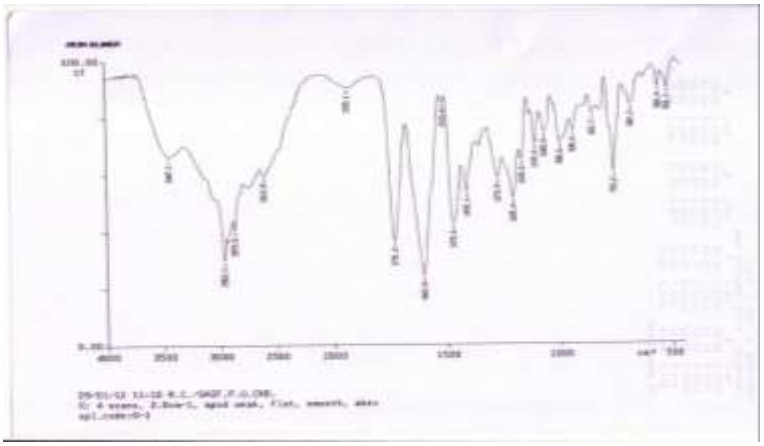
1.4.10 Stability Studies

The formulation E were sealed in aluminium foils and stability studies was conducted at different temperature and humidity conditions for 7 weeks at freezing temperature (4^0C), room temperature and 40^0C ± 75% RH (Saxena et al., 2006).

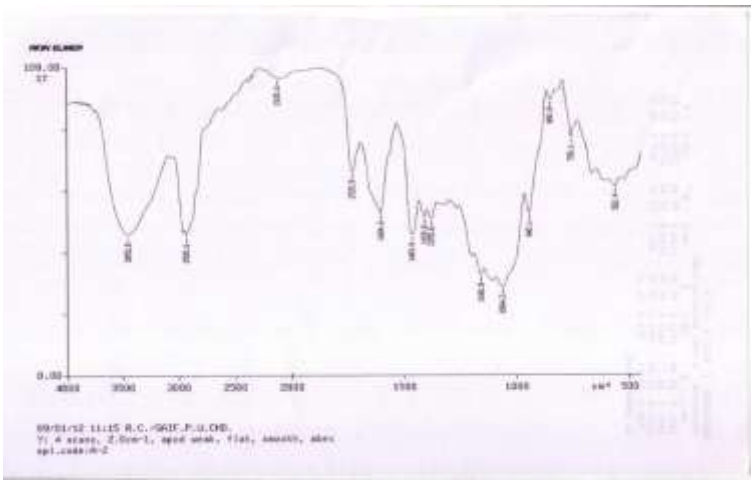
1.5 Compatibility Studies of Drug and Polymers by FT-IR

FT-IR (Perkin Elmer IR spectrometer 4000-400 (V_{max} in cm^{-1}) spectra of Valsartan, Hydroxypropylmethylcellulose (HPMC K4M, K15M and K100M). Fifty milligrams of sample and 150mg of KBr was taken in a mortar and triturated. The triturated sample was

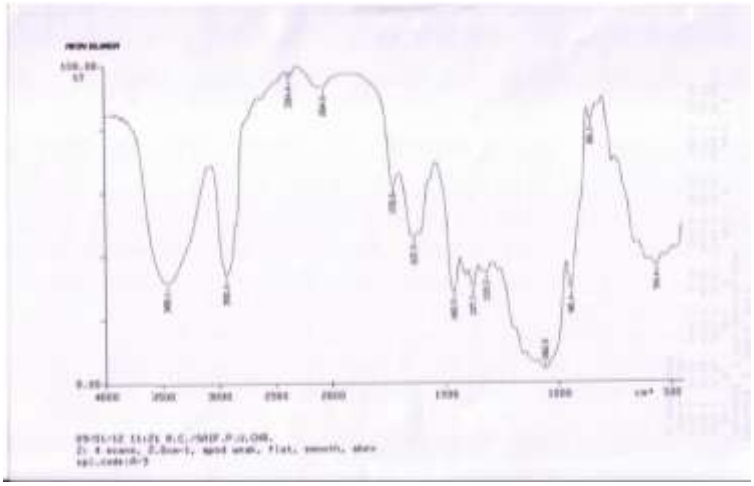
kept in a holder and scanned between 400 and 4000 cm^{-1}.



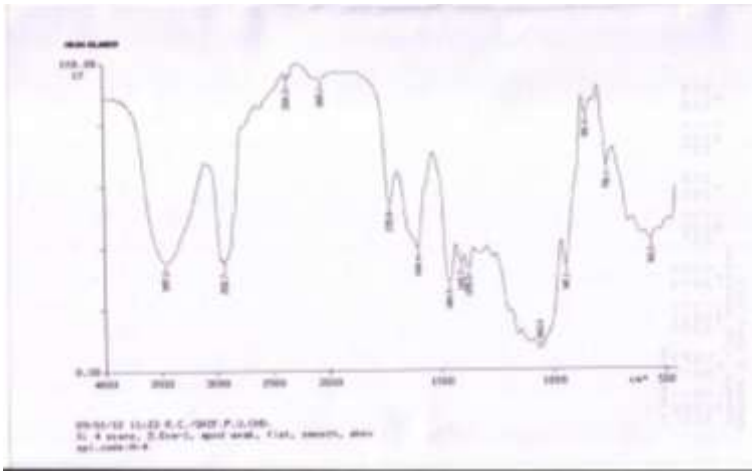
IR Studies of Pure Drug Valsartan.



IR Studies of Drug with HPMC K4M.



IR Studies of Drug with HPMC K15M.



IR Studies of Drug with HPMC K100M.

1.6 RESULTS AND DISCUSSION

The transdermal patches of Valsartan was formulated using the HPMC as a polymer and also act as a rate controlling membrane. The prepared patches were characterized for physicochemical properties, *in vitro* permeation profile using nitrocellulose membrane and skin irritation studies.

The physicochemical properties of Valsartan transdermal patches are shown in table 2. The weight variation shown by patch (0.0519 ± 0.0004), percentage moisture absorption (3.45 ± 1.08), percentage moisture loss (4.8 ± 1.14), the patch formulated with HPMC alone shown water vapour transmission rate of (0.46 ± 0.015g/hr/cm^2), thickness varied from (0.056 ± 0.005mm), Folding endurance was (it measures the ability of patch to withstand rupture) (1033.67 ± 7.094), tensile strength (0.379 ± 0.006 kg/mm^2) and transdermal patches consisting of the HPMC the release profile of films were shown to be, reaching 39% from the formulation E after 24 h as shown in table 3. The figure 1 showing the release of drug from all the formulations. All the formulations showed the zero order release. No erythema or odema was observed on the skin after the application of the patch for 24h. The patches were subjected to stability studies at three extreme temperatures after that drug content and changes in physical appearance especially the colour and visibility were noticed and results are shown in table 4.

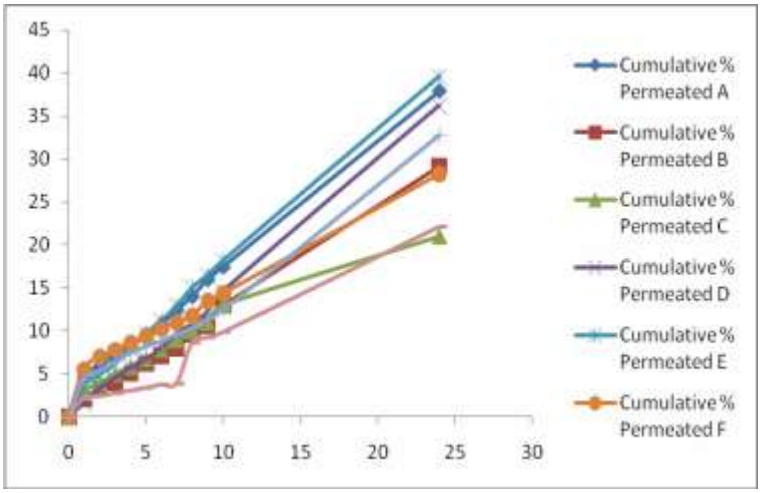


Fig. 1: Plot of Cumulative Percent Permeated Versus Time for Formulations A-H.

Table 1: Composition of Transdermal Patches.

S.No.	Formulation	Code	Composition (drug: polymer)	icizerGlycerin (% w/w)*	Casting solvent (2:2:1)
1	HPMCK4M	A	1:1	150	Chloroform: Dichloromethane: Ethanol
2	HPMCK4M	B	1:1.5	150	Chloroform: Dichloromethane: Ethanol
3	HPMCK4M	C	1:2	150	Chloroform: Dichloromethane: Ethanol
4	HPMCK15M	D	1:1	150	Chloroform: Dichloromethane: Ethanol
5	HPMCK15M	E	1:1.5	150	Chloroform: Dichloromethane: Ethanol
6	HPMCK15M	F	1:2	150	Chloroform: Dichloromethane: Ethanol
7	HPMCK100M	G	1:1	150	Chloroform: Dichloromethane: Ethanol
8	HPMCK100M	H	1:1.5	150	Chloroform: Dichloromethane: Ethanol

- %w/w of the polymer.

Table 2: Showing Different Evaluation Parameters.

Formulation Code	Weight variation (mg)	% Moisture Absorption	% Moisture Loss	WVTR (g/hr/cm2)	Thickness (mm)	Folding endurance	Content Uniformity
A	0.0532±0.0004	18.30 ± 2.83	11.96 ± 0.18	0.547 ± 0.019	0.092 ± 0.002	884.33 ± 8.020	18.05 □ 0.05
B	0.0584±0.0005	5.29 ± 0.825	4.77 ± 0.93	0.537 ± 0.304	0.065 ± 0.004	946 ± 6.55	17.88 □ 0.096
C	0.0642±0.004	9.58 ± 2.07	8.61 ± 0.54	0.776 ± 0.575	0.068 ± 0.002	977.33 ± 7.023	17.37 □ 0.045
D	0.0426±0.0005	11.30 ± 1.67	6.55 ± 0.22	0.5 ± 0.16	0.043 ± 0.001	942.33 ± 6.89	17.66 □ 0.051
E	0.0519±0.0004	3.45 ± 1.08	4.8 ± 1.14	0.46 ± 0.015	0.056 ± 0.005	1033.67 ± 7.094	18.15 □ 0.07
F	0.0598±0.0003	13.46 ± 1.54	4.90 ± 0.70	0.338 ± 0.010	0.078 ± 0.005	1185 ± 12.53	17.98 □ 0.065
G	0.0428±0.0002	18.05 ± 1.39	11.80 ± 0.75	0.354 ± 0.010	0.0492 ± 0.002	1145 ± 11	18.16 □ 0.105
H	0.0505±0.0003	9.71 ± 2.16	14.73 ± 1.81	0.462 ± 0.464	0.051 ± 0.003	1227.33 ± 7.505	18.09 □ 0.05

Table 3: Showing in vitro release of drug.

Time	Cumulative % Permeated A	Cumulative % Permeated B	Cumulative % Permeated C	Cumulative % Permeated D	Cumulative % Permeated E	Cumulative % Permeated F	Cumulative % Permeated G	Cumulative % Permeated H
0	0.0000	0	0.0000	0	0.0000	0.0000	0.0000	0.0000
1	4.8321	2.0929	3.0138	1.6367	3.6271	5.5723	4.3697	2.1897
2	5.8912	3.2051	3.9211	3.3489	4.8811	6.9943	5.3735	2.4573
3	7.1640	4.0046	4.9825	4.5305	6.1818	7.8228	6.4153	2.7910
4	8.3101	5.0746	5.8481	5.7575	7.9037	8.6748	7.4365	3.0762
5	9.5826	6.1866	6.7432	6.7267	9.6910	9.3734	8.1992	3.4276
6	10.8114	7.1000	7.9053	8.0292	11.1692	10.2047	8.8650	3.7892
7	12.4282	8.0434	8.9901	9.6803	12.8813	10.9976	9.6041	3.9257
8	14.0144	9.6183	9.9918	10.7856	15.0240	11.7492	10.3608	8.5923
9	16.0017	10.6517	11.0231	12.2242	16.4924	13.5189	11.3700	9.2949
10	17.4481	12.9180	13.0333	14.6177	18.1854	14.4090	12.4672	9.8974
24	37.8611	29.1071	21.0533	36.1996	39.5887	28.2878	25.8132	22.1668

Table 4: Stability studies showing drug content.

Time in weeks	Drug content at freezing temperature	Drug content at room temperature	Drug content at accelerated temperature
0	18.11	18.16	18.14
1	18.07	18.12	18.09
3	18.02	18.07	18.01
7	17.91	17.96	17.89

1.7 REFERENCES

1. Asbill, C.S., Michniak, B. B., Percutaneous penetration enhancers: local versus transdermal activity. *PSTT*., 2000; 3(1): 36-41.
2. Benson, H.A.E., Transdermal Drug Delivery: Penetration Enhancement Techniques. *Current Drug Del.* 2005; 2: 23-33.
3. Darlenski, R., Sassning, S., Tsankov, N., Fluhr, J.W., 2009. Non-invasive in vivo methods for investigation of the skin barrier physical properties. *Euro J Pharm Sci.* in press.
4. El Maghraby, G.M., Barry, B.W., Williams, A.C., Liposomes and skin: From drug delivery to model membranes. *Euro J Pharm Sci*, 2008; 34: 203–222.
5. Gattani, S.G., Gaud, R.S., Chaturvedi, S.C., Formulation and evaluation of transdermal films of ondansetron hydrochloride. *Indian Drugs*., 2006; 43: 245-251.
6. Hadgraft, J., Skin Deep. *Euro J Pharm and Biopharm*., 2004; 58: 291–299.
7. Kusum Devi, V., Saisivam, S., Maria, G.R., Deepti, P.U., Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. *Drug Dev Ind Pharm*., 2003; 29: 495-503.
8. Moffat, A. C., Clark's analysis of drugs and poisons. London: Pharmaceutical Press. Samanta, M.K., Dube, R., Suresh, B., 2003. Transdermal drug delivery system of haloperidol to overcome self-induced extrapyramidal syndrome. *Drug Dev Ind Pharm*., 2006; 29: 405-415.
9. Saxena, M., Mutalik, S., Reddy, M.S., Formulation and evaluation of transdermal patches of metoclopramide hydrochloride. *Indian Drugs*., 2006; 43: 740-745.
10. Thomas, B.J., Finnin, B.C.,. The transdermal revolution. *Drug Deliv Tech.*, 2004; 16: 697- 703.