



Formulation, *In-vitro* Evaluations and Skin Irritation Study of Losartan Potassium Transdermal Patches

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Abstract

Losartan potassium is a well known orally active non-peptide angiotensin II receptor antagonist. Losartan potassium and its principle active metabolites block the vasoconstrictor and aldosterone secreting effect of angiotensin II by selectively blocking the binding of angiotensin II to AT₁ receptors. The drug is reported to promote the decrease in ventricular hypertrophy, salt and water excretion and vascular smooth muscle relaxation. Present investigation was aimed at the formulation of transdermal therapeutic system of losartan potassium for effective control over hypertension since the drug shows considerable first pass metabolism when administered through oral route. Blends of hydrophobic and hydrophilic polymers like ethyl cellulose with polyvinyl pyrrolidone and ethyl cellulose with hydroxypropyl methyl cellulose were used in the formulation of the medicated films. Films were prepared using dibutyl phthalate as plasticizer with eighteen different combinations of these three polymers by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane. Several physicochemical parameters like moisture content, moisture uptake, thickness, film folding endurance, tensile strength, skin irritation and surface morphology of the films were studied. For all the formulations, skin permeation of the loaded drug through albino mice skin was studied using Keshary-Chien diffusion cell. Formulations containing higher proportion of hydrophilic polymers blended with lower proportions of hydrophobic polymer were found less consistent in comparison to the patches comprised of higher proportion of hydrophobic polymer.

Keywords: Ethyl cellulose; Hydroxypropyl methyl cellulose; Losartan potassium; Polyvinyl pyrrolidone.

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1. Introduction

Of late, transdermal route has become one of the most successful innovative research areas in drug delivery, with around 40% of the

drug candidate products being under the clinical evaluation related to transdermal or dermal systems. The technology has a proven record of FDA approval since the first transdermal patch containing scopolamine was approved in 1981. Statistics reveal a market of \$ 12.7 billion in the year 2005 which is expected to increase to \$ 21.5 billion

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in 2010 and \$ 31.5 billion in the year 2015 [1]. Transdermal patches provide an alternate route of drug delivery avoiding the hepatic first pass effect [2, 3]. It also improves patient compliance and confirms the safety and efficacy of the drug [4]. Losartan potassium (LP) is the drug of choice for sustained release formulation since it has a low terminal elimination half life of about 1.5 to 2 h, which requires frequent dosing necessary to maintain the therapeutic blood level for long term treatment. LP shows considerable first pass metabolism in the liver and thereby has poor bioavailability (25-35%) when administered orally. Molecular weight (422.91) of LP again indicates its suitability for administration by the transdermal route. LP containing transdermal films were prepared using two combinations of the three polymers namely ethyl cellulose (EC) with polyvinyl pyrrolidone (PVP) and ethyl cellulose with hydroxypropyl methyl cellulose (HPMC) in different proportions by solvent evaporation technique. Polyvinyl alcohol (4%, w/v) was used to prepare the backing membrane and dibutyl phthalate (30%, w/w) was added as plasticizer. Concentration of drug was maintained at 20% (w/w) for all the formulations. The physicochemical parameters like moisture content, moisture uptake, thickness, film folding endurance, tensile strength, skin irritation and surface morphology were studied. For all the formulations, skin permeation of the drug through albino mice skin was studied using Keshary-Chien (KC) diffusion cell [5].

2. Materials and methods

2.1. Materials

Losartan potassium was obtained from Alkem Pvt. Ltd., Mumbai as a generous gift sample. Ethyl cellulose (EC), polyvinyl pyrrolidone (PVP K30), hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA) and dibutyl phthalate were procured from S.D. Fine Chem. Ltd., Mumbai. All

other chemicals and solvent used were of analytical grade.

2.2. Preparation of transdermal patch

Matrix type transdermal patches containing losartan potassium were prepared using different ratios of EC with PVP and EC with HPMC (Table 1) by solvent evaporation technique in cylindrical both side opened glass mould of 3 cm of diameter. The bottom of the mould was wrapped with aluminum foil on which the backing membrane was cast by pouring 4 % w/v PVA solution followed by drying at 60 °C for 6 h. Then the two pair of polymers for each combination was weighed in requisite ratio and was dissolved in ethanol. Dibutyl phthalate 30% (w/w) of polymer composition and the drug 20% (w/w) of the total weight of polymer were added to the homogeneous dispersion by slow stirring with a mechanical stirrer. The uniform dispersion (2 ml each) was cast on the PVA backing membrane cast earlier and dried at 40 °C for 6 h. After drying they were kept in desiccators for further study [6, 7].

2.3. Evaluation of transdermal patches

2.3.1. Moisture content

The films were weighed individually and kept in a desiccator containing 10 g of calcium chloride as desiccant at 37 °C for 24 h. The films were weighed individually again and again until it showed a constant weight. The final weight was noted when there was no further change in the weight of individual film. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight [8].

2.3.2. Moisture uptake

The films were weighed accurately and placed in a desiccator where a humidity condition (84%) was maintained by using saturated solution of sodium chloride. The films were taken out periodically and weighed for a period of 72 h. The percentage of

Table 1. Formulation design and study of various physical parameters of the films containing EC and PVP.

Sl. No	Formulation code	Ratio of polymers (EC:PVP)	Thickness (cm)	Mean folding endurance n = 5 (\pm SD)	Mean tensile strength n = 3 (\pm SD)	Skin irritation (gm/cm ²)
1	TDS-1	1:1	0.00168	> 200	241	—
2	TDS-2	1:3	0.00170	>200	239	—
3	TDS-3	1:5	0.00189	>200	234	—
4	TDS-4	1:7	0.00182	>200	229	—
5	TDS-5	1:9	0.00192	>200	218	—
6	TDS-6	9:1	0.00201	<183	273	—
7	TDS-7	7:1	0.00199	>200	266	—
8	TDS-8	5:1	0.00178	>200	251	—
9	TDS-9	3:1	0.00172	>200	244	—

n = number of repeated observation; SD= standard deviation; (-) = indicates no erythema

moisture absorption was calculated as the difference between final and initial weight of the films with respect to initial weight [9, 10].

2.3.3. Thickness

Micrometer with least count of 0-0.01 mm was used to measure the thicknesses of the prepared patches. The thickness was measured at five different points of individual film and the average of five readings with the standard deviation and standard error from the mean was calculated and recorded [11, 12].

2.3.4. Folding endurance

Folding endurance was measured manually for the prepared films. The films were repeatedly folded at the same place till it broke. The number of times the film could be

folded at the same place without breaking gave the value of folding endurance [13].

2.3.5. Tensile strength

The tensile strength measurement was made using an instrument assembled in the laboratory and following the method used by RV Kulkarni *et al.* [14]. The films were fixed individually to the assembly and the required weights to break the films were noted.

2.3.6. Skin irritation

Skin irritation test was performed on male healthy rabbits weighing between 2-3.5 kg. Adhesive tape USP was used as control patch. The transdermal films of 6.1544 cm² were used as test samples. The study was conducted on unbraided skin of rabbits; the control patch was placed on left dorsal surface of the rabbits,

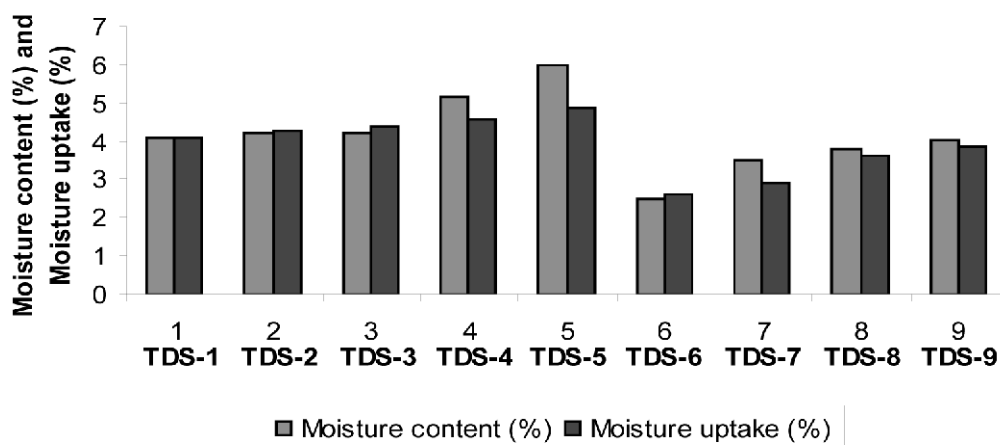


Figure 1. The percentage of moisture content and moisture uptake data of the patches composed of EC and PVP (TDS1 to TDS9).

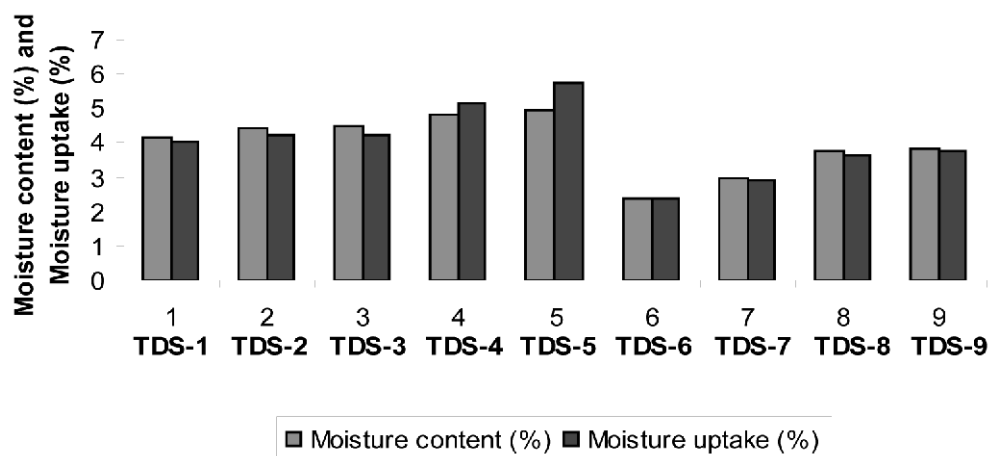


Figure 2. The percentage of moisture content and moisture uptake data of the patches composed of EC and HPMC (TDS1 to TDS9).

whereas test formulations were placed on identical side of the right dorsal surface of the rabbits. The patches were removed after 24 h with the help of an alcohol swab and skin was examined for any erythema and or oedema [15, 16].

2.3.7. Scanning electron microscopy

The surface morphologies of the transdermal patches were investigated by using a JEOL-JSM 6360 scanning electron microscope (SEM) at 7 kV. Prior to examination, samples were gold coated to make them electrically conductive [17].

2.3.8. Skin permeation study

In vitro skin permeation study was performed taking albino rat skin. Young albino rat weighed between (200-250 g) were taken

and sacrificed by excess chloroform inhalation. The abdominal hairs were removed and the abdominal skin was carefully separated from the body, with the dermis part remaining intact. Subcutaneous tissues were surgically removed. The inner part of the skin was washed with distilled water thoroughly to separate the adhering fat. The skin, so obtained, was examined microscopically for the presence of any possible damage. The full thickness skin thus obtained was kept in normal saline solution and stored at 4 ± 1 °C until used for the experiment.

The drug permeation from the transdermal patches through the skin was determined using modified Keshary-Chien diffusion cell. The contents of the donor and receptor compartments were separated by placing the excised skin in between two compartments.

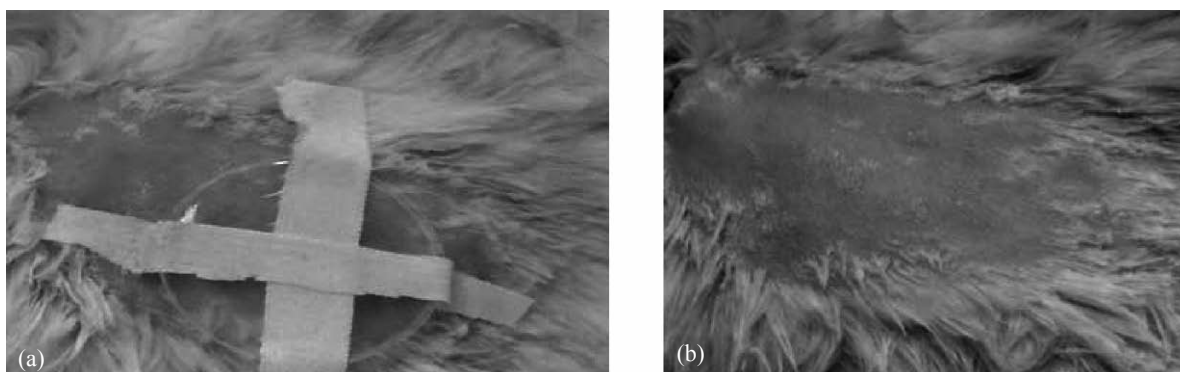


Figure 3. Photographs of skin irritation test: a) application of adhesive tape as control, b) application of films containing drug.

Table 2. Formulation design and study of various physical parameters of the films containing ethyl cellulose and HPMC.

Sl. No	Formulation code	Ratio of polymers (EC:PVP)	Thickness (cm)	Mean folding endurance n = 5 (\pm SD)	Mean tensile strength n = 3 (\pm SD)	Skin irritation (gm/cm ²)
1	TTS-1	1:1	0.00172	>200	278	—
2	TTS-2	1:3	0.00174	>200	274	—
3	TTS-3	1:5	0.00178	>200	269	—
4	TTS-4	1:7	0.00117	>200	261	—
5	TTS-5	1:9	0.00153	>200	253	—
6	TTS-6	9:1	0.00199	<171	304	—
7	TTS-7	7:1	0.00204	>197	297	—
8	TTS-8	5:1	0.00170	>200	288	—
9	TTS-9	3:1	0.00176	>200	281	—

n = number of repeated observation; SD= standard deviation; (-) = indicates no erythema

The skin was mounted in such a way that the stratum corneum side of the skin continuously remained in an intimate contact with the transdermal patch in the donor compartment. The receptor compartment contained 100 ml distilled water where the temperature was maintained at 37 ± 2 °C. The content of the diffusion cell was stirred using a teflon coated bead at a constant speed (100 rpm). Samples (1 ml) were withdrawn and replaced with fresh solvent to maintain the sink condition at predetermined time intervals of 1 h and the study was carried out up to 36 h. The samples were analyzed for drug content using UV-visible spectrophotometer at the λ max of 204.05 nm [18].

3. Results

In the present study, transdermal patches of losartan potassium were prepared as monolithic matrices by solvent evaporation technique employing glass moulds. Patches were prepared using various polymers like EC with PVP and EC with HPMC in different proportions. Various physicochemical parameters of the formulations and the release characteristics of the contained drug were studied.

Moisture content and moisture uptake (Figures 1 and 2) phenomenon of the formulations exhibited that with the increase in the concentration of hydrophilic polymer (PVP and HPMC), both the percentage moisture content and the percentage moisture uptake were increased. The thicknesses of

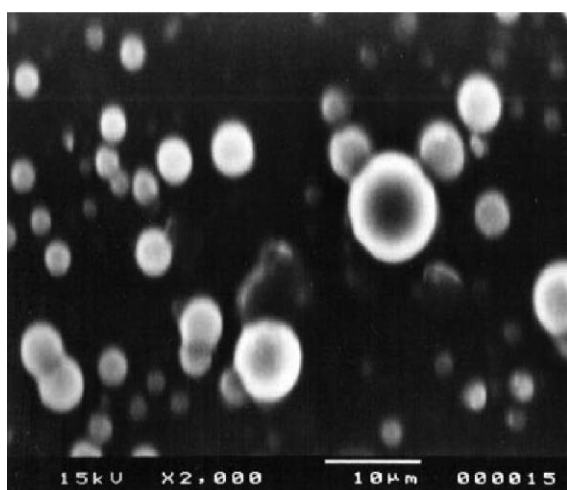


Figure 4. SEM photograph of drug loaded transdermal patch containing EC and PVP.

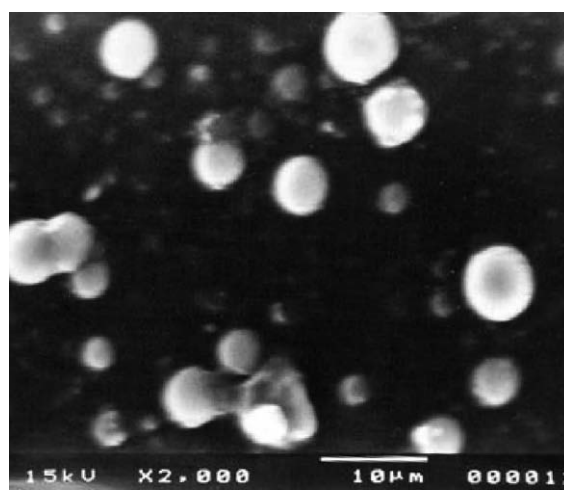


Figure 5. SEM photograph of drug loaded transdermal patch containing EC and HPMC.

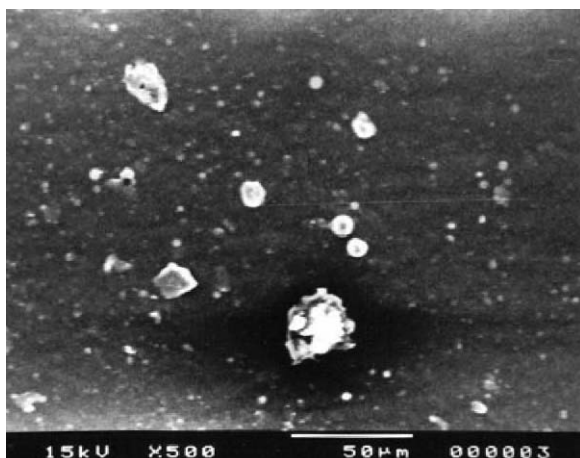


Figure 6. SEM photograph of exhausted film of EC and PVP after skin permeation study.

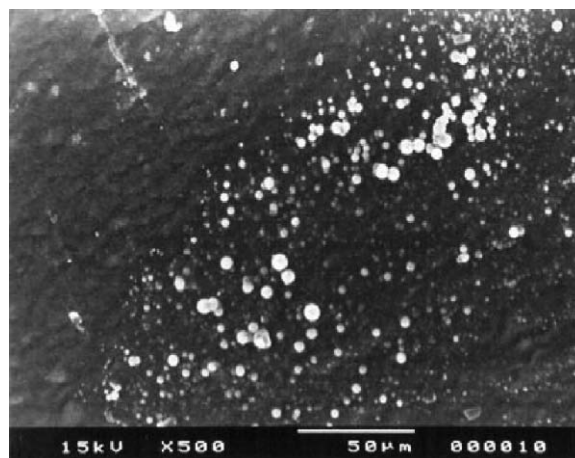


Figure 7. SEM photograph of exhausted film of EC and HPMC after skin permeation study.

the patches prepared with EC and PVP were found in between 0.00199 cm to 0.00201 cm (Table 2) and thicknesses of the patches prepared with EC and HPMC were found in between 0.00117 cm to 0.00204 cm (Table 2). The folding endurance values of all the patches were found satisfactory (Table 1 and table 2). The tensile strength of the patches prepared with EC and PVP in different proportions were found in between 273 gm/cm² to 218 gm/cm², which were 304

gm/cm² to 253 gm/cm² for the patches composed of EC and HPMC (Tables 1 and 2). The results of skin irritation study revealed that the formulations have produced no erythema or oedema (Tables 1 and 2, Figure 3). The scanning electron microscopic examination was carried out for drug loaded patches at pre- and post-skin permeation study (Figure 4, 5, 6 and 7). It was evident from the photographs that superficial film formation was proper. Patches examined after skin

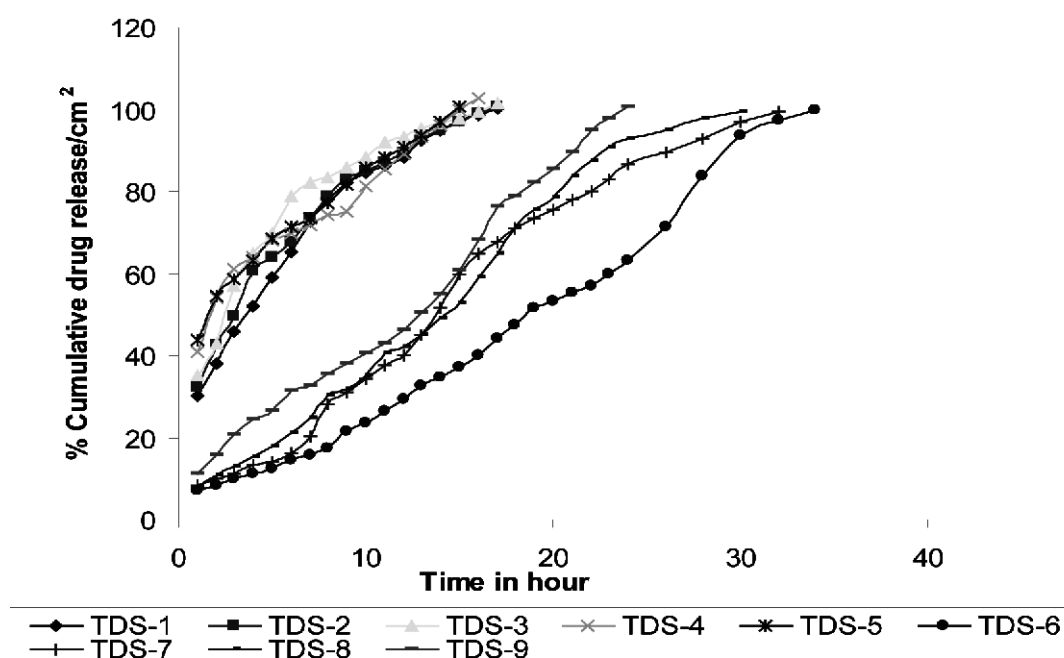


Figure 8. Cumulative drug release/cm² vs time profile of transdermal patches composed of EC and PVP.

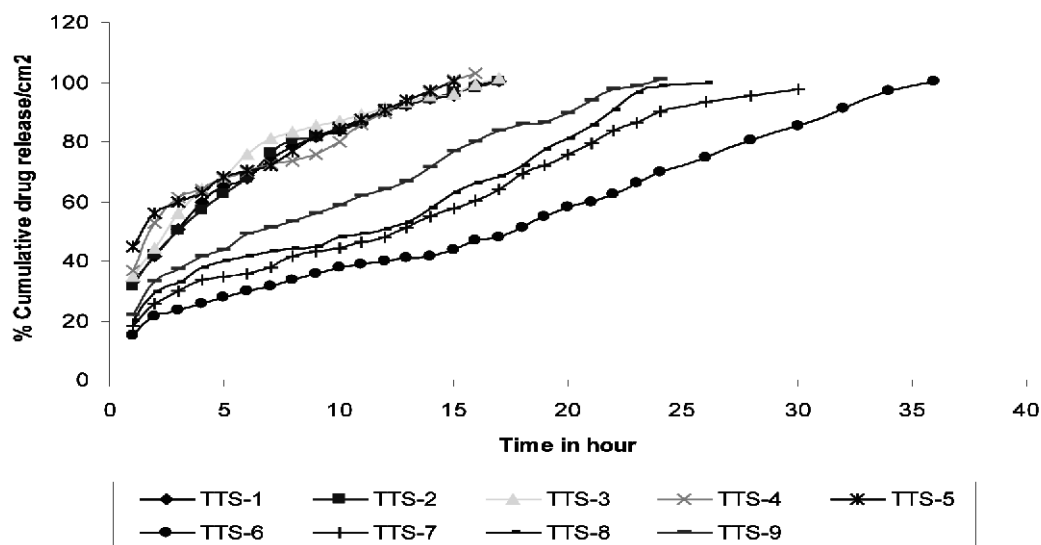


Figure 9. Cumulative drug release/cm² vs time profile of transdermal patches composed of EC and HPMC.

permeation of the loaded drug were appeared with the pores on to the surfaces. The graphical representation of the cumulative percentage of drug permeated as a function of time through the albino mice skin is presented in Figure 8 and Figure 9. It was found that from TDS-6 only 79.74% and from TTS-6 only 76.41% of the loaded drug was permeated in 36 h.

4. Discussion

Transdermal patches composed of highest proportion of hydrophobic polymer (EC) blended with lowest proportion of hydrophilic polymer (PVP and HPMC) were found to have low moisture content. This helps them to remain stable and prevent from being a completely dried and brittle film. Similarly, a low moisture uptake protects the material from microbial contamination and limits the bulkiness of the patches. In this respect, formulations TDS-6 and TTS-6 showed best results amongst all the formulations. Low standard deviation values in the patch thicknesses ensure uniformity of the patches prepared by solvent evaporation technique. Folding endurance values indicated that the patches prepared using dibutyl phthalate in a

concentration of 30% (w/w) of polymer weight were having optimum flexibility and were not brittle. When the tensile strength of the patches was examined, it was observed that with the increase of HPMC and PVP concentrations, the tensile strength of the patches gradually decreased. Skin irritation study indicated that the prepared patches were having no effect of irritation upon administration and is safe for topical application. The scanning electron microscopic photographs of the films were showing the good film formation superficially before skin permeation study. Photographs showing formation of pores onto the surface after skin permeation study was due to the exhaustion of the contained drug. From Figure 8 and Figure 9, it is evident that higher proportions of hydrophilic polymers (PVP and HPMC) in formulations resulted in an enhanced permeation of the contained drug. Whereas permeation of the contained drug was opposed when there was least concentration of hydrophilic polymers blended with highest concentration of hydrophobic polymer (EC). Thus formulations TDS-6 and TTS-6 have shown most delayed permeation amongst all the formulations.

In conclusion, the present investigation has been evidenced that the patches containing higher proportions of hydrophilic polymer blended with lowest proportion of hydrophobic polymer are less consistent in comparison to the patches comprised of higher proportion of hydrophobic polymer blended with lowest proportion of hydrophilic polymer. Transdermal patches TDS-6 and TTS-6 were found to be most promising and capable of delivering the contained drug for more than a day. Authors are hopeful that the present study would certainly contribute to the recent pharmaceutical research activities.

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