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TRANSDERMAL PERMEATION OF CETIRIZINE DIHYDROCHLORIDE FROM HYDROGEL BASED DRUG DELIVERY SYSTEM

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ABSTRACT

In the present study, hydrogel transdermal patches were evaluated as a transdermal drug delivery system for Cetirizine dihydrochloride. The patches were prepared using polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) as base material with PEG 400 as plasticizer and Ca^{2+} was employed as a crosslinking agent. They were evaluated for swelling properties, water vapor permeability (WVP) and permeation studies through a synthetic membrane to select an optimized formulation for skin permeation studies. The *ex vivo* skin permeability studies were evaluated by Franz diffusion technology with hairless mouse skin as permeability media. Tween 80 was incorporated as a permeation enhancer in M5. Different kinetic models were employed to stimulate the release and penetration pattern of Cetirizine from hydrogel patches in order to investigate the drug transport mechanism. It was observed that drug release from the hydrogel carriers increased with an increase in the amount of polyvinyl pyrrolidone (PVP) due to higher

WVP. Permeation enhancer-loaded patch accelerated the drug release and highest cumulative drug release was obtained at 40% w/w Tween 80 concentrations. The formulation M5-$T80_4$ followed the Weibull model with an anomalous drug release pattern.

Keywords: Cetrizine, hydrogel patch, polyvinyl alcohol, polyvinyl pyrrolidone, flux, enhancement ratio

INTRODUCTION

Transdermal drug delivery system (TDDS) is a self-contained discrete dosage form which delivers the drugs through the skin to systematic circulation at a controlled rate. A transdermal patch is a medicated patch that is applied to the skin to deliver a specific dose of medicine into the blood stream through the skin [1]. It provides various advantages over conventional dosage form in term of avoidance of the first pass metabolism, non-invasive administration, maintenance of stable drug delivery profiles and reduction in dosing frequency [2]. Thus, the main aim of the current paper is the development of biocompatible and composite patches which would provide a sustained release drug profile. The TDS is tailored by polymer based hydrgel system which would form a three-dimentional network capable of imbibing large amount of water in its structure.

Cetitzine dihydrochloride is a second generation H_1 (histamine) antagonist with long acting antihistaminic effect.. The drug has a number of anti-inflammatory and anti-allergic properties that are independent of H_1-blockade activity by mast cell stabilization. The skin has a high concentration of these mast cells which aid in the synthesis of histamines and other mediators. Thus, Cetirizine has been used as the treatment of choice for managing atopic skin conditions and symptoms related to chronic urticaria [3]. The reason for formulating the hydrogel transdermal patch of Cetirizine is attributed to its solubility in water. During the casting process, the drug particles would become situated and entrapped within the polymer matrix. When the drug is added into the casting solution, the cluster of drug molecule would extend from the surface deep into the matrix system and form connected pore spaces. Upon dissolution, the drug would be released from these clusters [4]. The effect of increasing permeation enhancer (Tween 80) concentration with the mixture of polyvinyl alcohol-polyvinyl pyrrolidone as base material were deliberated to examine the skin

permeation of Cetirizine dihydrochloride across the mouse skin.

MATERIAL AND METHOD

Material: Cetirizine dihydrochloride (Purchased from MediSearch Pharma, Lahore, Pakistan); Polyethylene glycol 400 (Merck, Germany); Tween 80 (Daejung, Korea); Polyvinyl alcohol (Merck, Germany); Polyvinyl pyrrolidone (Merck, Germany); Sodium hydroxide (Riedel-de Haen, Germany); Sodium chloride (Merck, Germany); Potassium chloride (Aldrich Chemicals, USA); Potassium dihydrogen phosphate (Fluka, Germany); Disodium hydrogen phosphate (Fluka, Germany); Silica beads (Unichem, India); Calcium chloride (Unichem, India)

Method

Preparation of polymeric dispersion and hydrogel patches of Cetrizine dihydrochloride

For the preparation of the hydrogel patches, polyvinyl alcohol (PVA) dispersion (Table 1) was initially prepared by adding precisely weighed amount of PVA into distilled water as dispersion medium. The powder was sifted into the vortex of the rapidly mechanically stirred water (250 rpm) for 1 hour at 60°C in order to obtain complete hydration of polymer and reaching the maximum clearance. Polyvinyl pyrrolidone (PVP) was then added, under magnetically stirring (250 rpm) to the PVA dispersion. After complete dissolution of PVP (typically in 30 minutes), drug and plasticizer, PEG 400, was added and stirred for a further 30 minutes to obtain homogenous mixture. The polymeric mixture was sonicated to remove air bubbles and poured into petri dishes. The hydrogel patch was obtained by the chemically crooslinking method. The crosslinking was achieved by layering calcium chloride solution (2% w/v) onto the formed patches.

Preparation of polymeric dispersion and hydrogel patches of Cetrizine dihydrochloride with permeation enhancer

For the preparation of hydrogel patches containing permeation enhancers, the same procedure was employed as stated above with slight modification. The permeation enhancer was added in the drug polymeric dispersion and stirred for additional 30 minutes before sonication.

Swelling ratio

The patches were cut into a square of 1×1 cm and they were soaked in distilled water for 60 minutes. After an interval of 10 minutes, the films were taken out, blotted to remove excess of water and weighed on digital analytical weighing balance. The swelling

index and percentage weight increase were estimated as follows

Swelling Index = $(W_2 – W_1) / (W_1)$

Percentage weight increase = $(W_2 – W_1) / (W_1) * 100$

Where, W_1: initial weight before swelling; W_2: weight of the film after time 't' [5].

Water vapor permeability (WVP)

A film of definite dimensions (1×1 cm) was fixed in a vial of 5 ml capacity. Silica beads were added in each vial as a desiccant and weighed individually. The vials were placed in a desiccator containing saturated solutions of potassium chloride (KCl) at 30˚C and weighed after 24 hours. The WVP was calculated by:

$$P = \frac{Q \times d}{A \times T \times S \times (R_1 - R_2)}$$

Where, P: permeability of vapor; Q: amount of vapor absorbed (mg) at time t (h); d: thickness of the film (cm); A: area of the film (cm^2); S: saturated water vapor pressure at test temperature (Pa); R_1: RH in the desiccator (84% RH); R_2: RH inside the vial (0% RH) [6].

Fourier Transmission-Infrared (FTIR)

IR spectra of Cetrizine dihydrochloride, polymers and admixtures disks thereof were prepared manually with potassium bromide (KBr) by press method. The samples were prepared by triturating the ingredient with KBr in glass mortar. The disks were placed in the sample holder of FTIR (Shimadzu, Japan) and the spectrum was scanned over a frequency of 400 to 4000 cm^{-1} [7].

***Ex vivo* permeation studies**

The *ex vivo* permeation studies were conducted through the synthetic membrane (12 hours) and excised skin of mice (14 hours). To select an optimized formulation for examining the effect of permeation enhancer through the skin, the hydrogel patches (M1 to M5) were tested for the permeation of drug through the synthetic membrane having a pore size of 0.45 µm. For the skin permeation studies, the mice were sacrificed by cervical dislocation. The dorsal skin was excised and the adhering fats were removed and wiped with isopropyl alcohol (IPA) swabs. The processed skin was dipped in warm water for about 45-55 seconds and transferred to normal saline solution (0.9%). The skin was refrigerated and used within 72 hours [8].

The skin was allowed to reach room temperature before the experiment and placed in PBS for 1 hour to attain equilibrium. Sections of full-thickness skin of mice were placed into Franz diffusion cells. The hydrogel patch was placed on the synthetic membrane or skin (stratum corneum side) and was fixed with an aid of a

clamp. The receptor fluid (10 ml capacity), containing PBS, was used to provide sink conditions and water was pumped through the outer jacket of the Franz diffusion cell by a pneumatic pump to maintain the temperature at 32±2°C. The receptor fluid was collected in glass vial during a period of 14 hours. All the permeation experiments were repeated thrice and their mean with standard deviation were calculated [6].

According to the concentration of each sample, the cumulative amount of the drug permeated per unit area at time point 'n' (Q, µg/cm^2) was calculated by the following formula:

$Q = C_n \times V + \sum_{i=1}^{n-1} C_i / S$

Where C_n is the drug concentration at a time point 'n'; V is the volume of the receptor cell; C_i is the drug concentration at time point 't'; S is the effective area

The cumulative amount per unit area (Q) of drug permeated through the skin was plotted as a function of time (t, h) and drug flux (J, µg/cm^2. hr) at steady state was estimated by dividing the slope of the curve by the area of skin (1.2 cm^2). The coefficient of permeability (P, cm/hr) was inferred by dividing the flux with an initial drug amount [6]. For the formulation containing permeation enhancers, an enhancement ratio (ER) was calculated by the following equation:

$ER = J_{P.E.} / J_{P.E}$

Where $J_{P.E.}$ is the permeation flux in the presence of a permeation enhancer; J_B is the permeation flux in the absence of permeation enhancer [9].

Mathematic modeling of drug release kinetics

Ex vivo permeation data of skin were further examined by the model dependent methodology.

Zero order equation: $Q_t = Q_0 + K_0t$

First order equation: $\log Q_t = \log Q_0 + K_1t / 2.303$

Higuchi equation: $M_t / M = k_2 \sqrt{t}$

Korsmeyer-Peppas equation: $M_t / M = k_3 t^n$

Weibull Model: $m = 1 – \exp [- (t - T_t)^b / a]$

Hixson Crowell Model: $W_0^{1/3} – W_t^{1/3} = K_st$

Where, Q_t is the amount of drug dissolved after time t; Q_0 is the initial amount of drug in solution; $K_1$is the first order release constant; K_0 is the zero order release constant; M_∞ is the absolute cumulative amount of drug released at infinite time; M_t is the cumulative amount of drug released at time t; k_2 is a constant reflecting the design variable of the system; k_3 is a constant incorporating geometric and structural characteristics of the device; n is the release exponent indicative of drug release

mechanism ; *a*: time scale of the process; T_i is the lag time before dissolution onset; *t* is the time; *m* is the accumulated fraction of drug in solution after time *t*; *b* is the shape of curve; W_0 is the initial amount of drug; W_t is the drug remaining; K_s is a constant incorporating the surface-volume relation (Kondamudi *et al*., 2015).

RESULT AND DISCUSSION

Swelling

When the amount of PVP against PVA was increased, the swelling property of the patches increased as indicated in the surface plot (Figure 1). With an increased PVA concentration, the swelling property was lesser due to the formation of a dense polymeric network. The results reveal that at the higher PVA amount the equilibrium in swelling is attained earlier as compared to the patches containing lesser amounts of PVA. The decrease in swelling ratio is due to much greater density of the gel which would inhibit the diffusion of water molecule into the gel-matrix. Thus, the relaxation of PVA chains becomes difficult and this lead to slower penetration of water molecule into the patch [10]. M6 (PVP alone) swelled the most as compared to the other formulations because of its greater hydrophilic nature. The swelling behavior is an indicative of the relative moisture absorption capacity of polymer and whether the formulation would maintain its integrity after absorption of moisture. The hydration of polymers, used in sustained release application, is an important consideration because it affects the drug release from matrix system. The hydrophilic polymer shows considerable swelling because of the increases surface wettability and consequently increased penetration of water within the matrix patches [11].

Water Vapor Permeability (WVP)

The maximum WVP was observed in M5, whereas minimum WVP was seen in M2 (Figure 2). An increase in WVP was observed with an increase in polyvinyl pyrrolidone (PVP) concentration. This occurs due to the irregular arrangement of polyvinyl pyrrolidone (PVP) molecules present in the amorphous form that causes these molecules to be spaced further apart in comparison to the crystalline form. Hence, the density decreases and the specific volume increases and leads to the absorption of water vapors into these interstices [11]. WVP is a phenomenon which determines the onset of drug release and drug release rate during dissolution [6]. It can be observed from 3-D surface plot (Figure 3) that as the concentration of polyvinyl pyrrolidone (PVP) increased, the WVP improved which

subsequently lead to an increase in the rate of dissolution (t: 24th hour).

FTIR

The FTIR of the drug Cetirizine dihydrochloride (Figure 4.1) had an intense band at 756.10 cm^{-1}, 1055.06 cm^{-1}, 1178.51 cm^{-1} and 1317.38 cm^{-1} that corresponded to the aliphatic chlorocompound, alkyl substituted ether, tertiary amines and carboxylic acid respectively [12].

The FTIR spectra of polyvinyl alcohol (PVA) showed all major peaks (3317 cm^{-1}, 1734.01 cm^{-1}, 1132.21 cm^{-1} and 1076.28 cm^{-1}) related to hydroxyl and acetate groups of polymer [13] as shown in Figure 4.2. The bands at around 3200-3600 cm^{-1} occurs due to the strong hydrogen bonding with water molecules (intermolecular or intramolecular). The peak at 2918.30 cm^{-1} indicate the stretching of alkyl groups and the vibration peak at 1734.01 cm^{-1} is due to the asymmetric stretching of carbonyl (C=O) from the acetate functional group. The band at 1132.21 cm^{-1} arises due to the C-O and C-C stretching. The vibrational peaks at 923.34 cm^{-1} and 864.11 cm^{-1} were attributed to the C-C stretching [14].

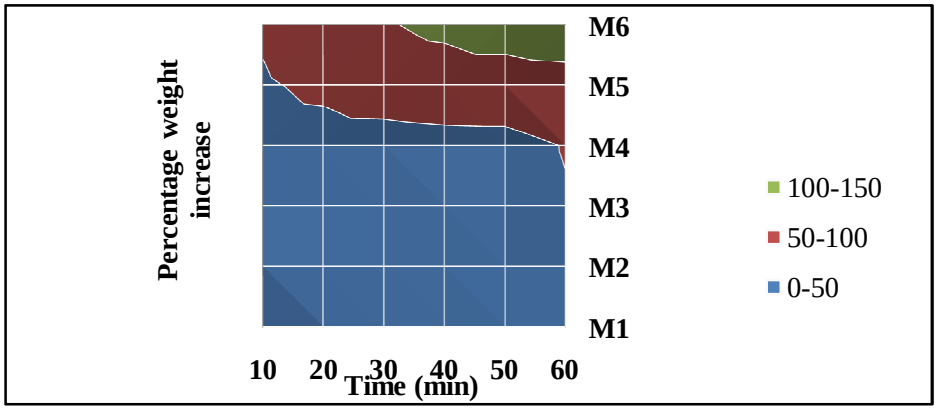

Figure 1: Surface plot of percentage weight increase due to swelling of hydrogel transdermal patch

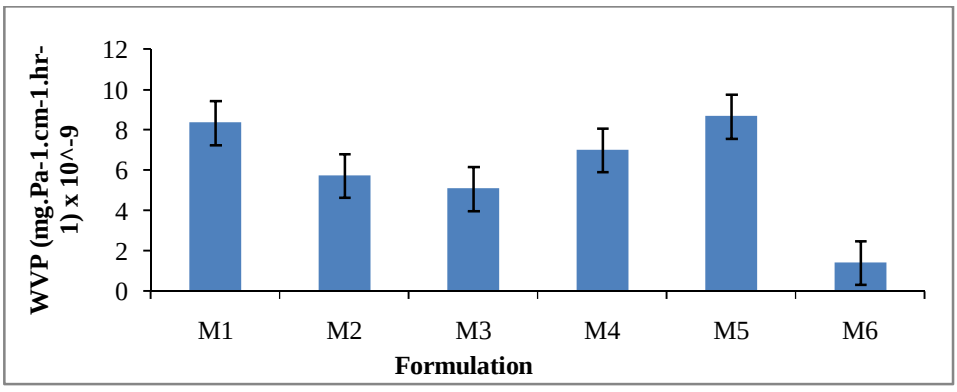

Figure 2: WVP of hydrogel transdermal patch of Cetirizine dihydrochloride

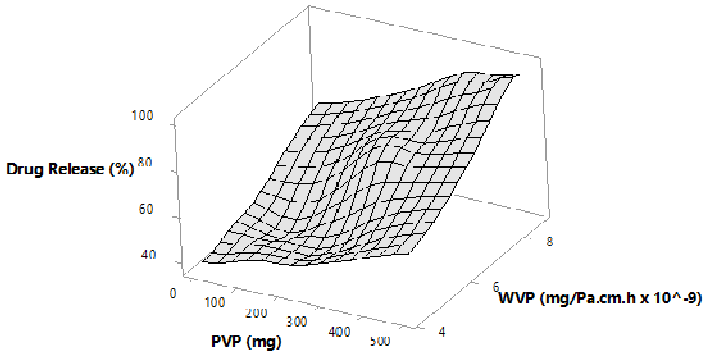

Figure 3: 3D- surface plot indicating the effect on drug release with an increase in PVP concentration and WVP.

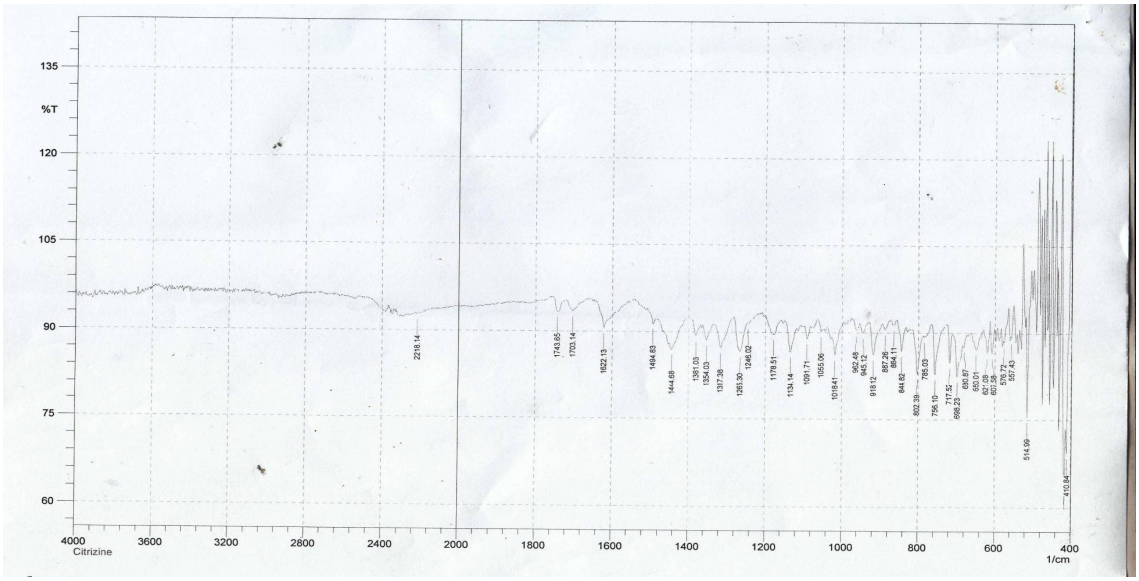

Figure 4.1: FTIR spectra of Cetirzine dihydrochloride

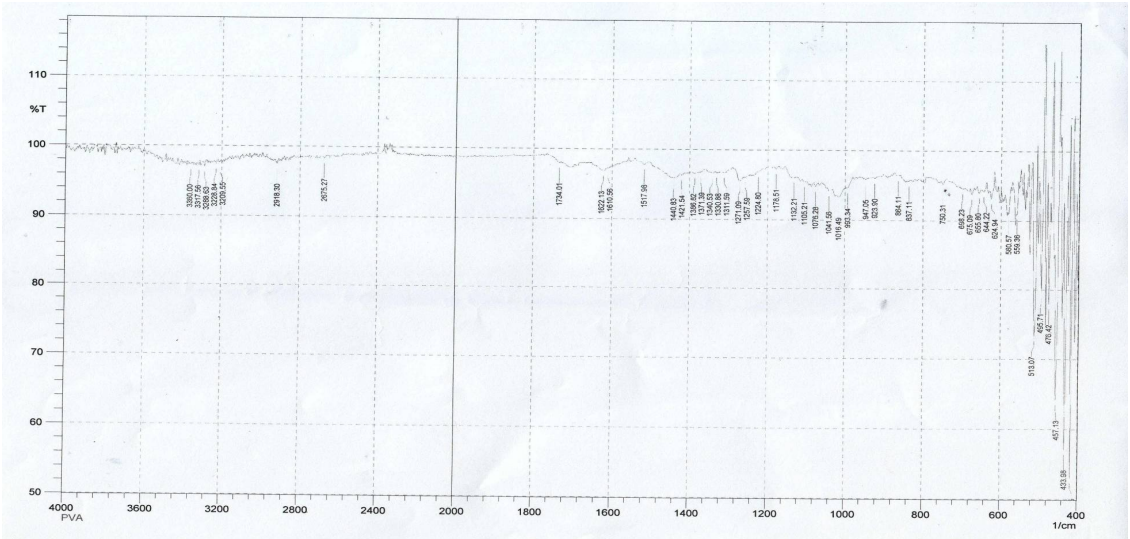

Figure 4.2: FTIR of polyvinyl alcohol (PVA)

The standard peaks for polyvinyl pyrrolidone (PVP) were obtained at 450-550 cm^{-1}, 1440.8 cm^{-1}, 1633.71 cm^{-1} and 3000-3700 cm^{-1} (Figure 4.3). The FTIR bands obtained in the region of 450-550 cm^{-1} are due to the symmetric C-N bending. The peaks in the region 1440.83 cm^{-1} is assigned to group. The band at 1633.71 cm^{-1} is due the presence of a carbonyl group present in polyvinyl pyrrolidone (PVP). Studies suggest that the bands obtained in the region of 3000-3700 cm^{-1} is due to the symmetric stretching vibration of hydrogen water molecules. The appearance of a peak at 1269.30 cm^{-1} is attributed to the bond vibration of the N-H-O complex [15].

The Figure 4.4 shows the FTIR spectrum of the blend of Cetirizine dihydrochloride, polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP). The peak at 3394.72 cm^{-1} arises due to the stretching of the O-H group, whereas a shift in 1645.28 cm^{-1} occurred due to the stretching of C=O group. The bending of the $-CH_2$ causes the peak at 1440.83 cm^{-1} and twisting of the $-CH_2$ group gives band at 1382.96 cm^{-1}. The peak at 1091.71 cm^{-1} indicates the bending of C-H and O-H group [16]. The bands of Cetirizine dihydrochloride were visible at 756.10 cm^{-1}, 1176.58 cm^{-1} and 1317.38 cm^{-1}, which indicated that there was no interaction between the polymers and drug.

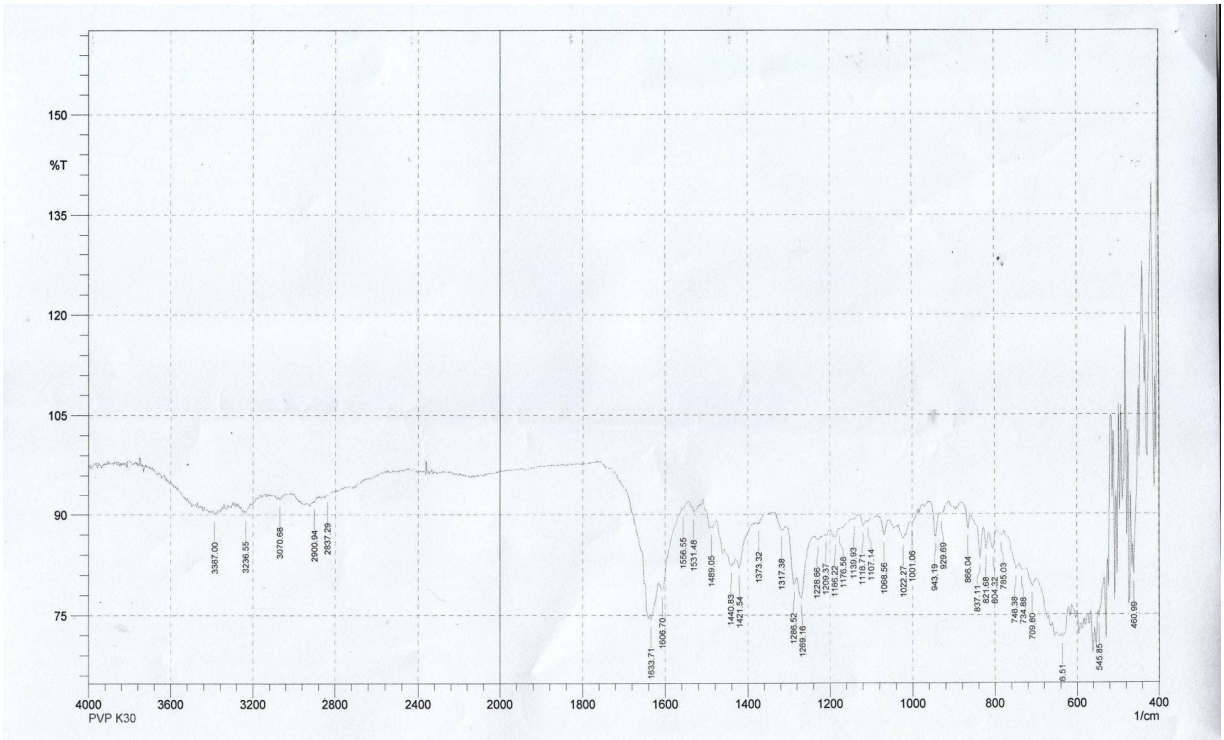

Figure 4.3: FTIR of polyvinyl pyrrolidone (PVP)

***Ex vivo* permeation studies**

Transdermal patches are usually designed to assure a sustained release of drug systematically. Determination of drug release profiles from transdermal patches, although does not represent a measure of bioavailability, it gives considerable information on the drug release characteristics that have a potential to alter the biological performance of the drug released from the dosage form.

***Ex vivo* permeation studies of Cetirizine dihydrochloride through synthetic membrane**

The *ex vivo* permeation studies were examined with reference to the calibration curve of Cetirizine dihydrochloride in PBS (pH 7.4) (Figure 5).

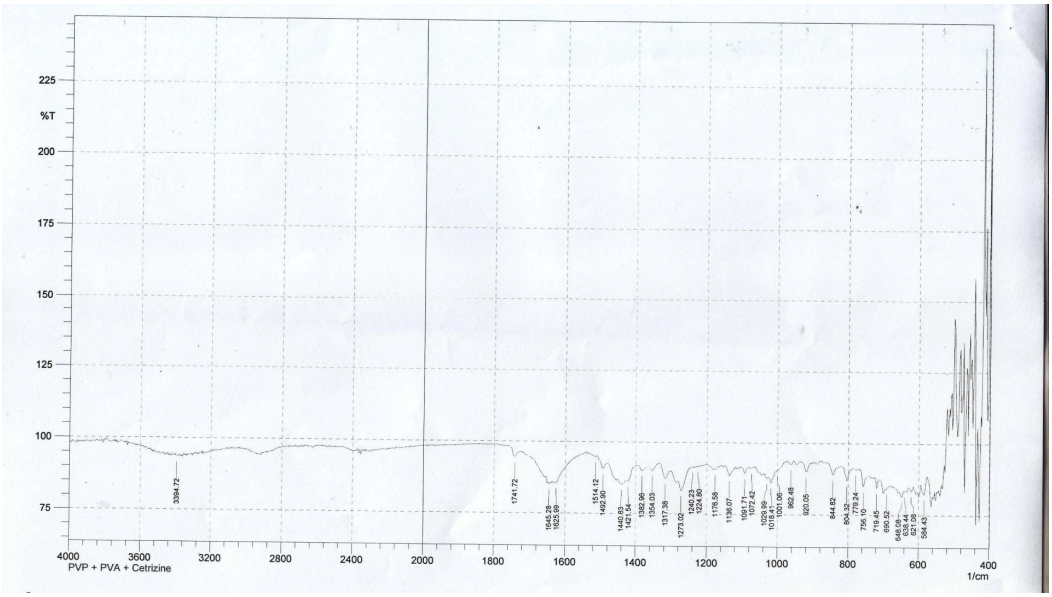

Figure 4.4: FTIR of Cetirizine dihydrochloride, polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP)

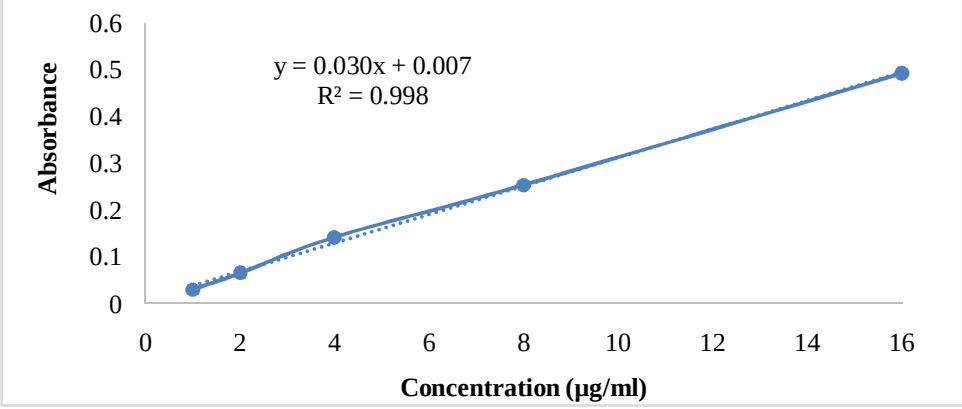

Figure 5: Calibration curve of Cetrizine dihydrochloride in PBS (pH 7.4)

Due to the dense network of polyvinyl alcohol (PVA) matrix [17], only 38.60% of the drug had released from the hydrogel system of M1 (containing polyvinyl alcohol alone). The patch followed the Weibull model with anomalous drug release pattern (Table 2) [18]. Due to the hydrophilic nature of polyvinyl pyrrolidone (PVP), 100% of the drug had released from the patch after 10 hours.

The *ex vivo* permeation study of Cetirizine dihydrochloride containing mixture of polyvinyl alcohol-polyvinyl pyrrolidone signified that the maximum drug release was given by M5 with 94.57% of drug release after 12 hours. The minimum drug release was evident in M2, which had a drug release of 40.27% after 12 hours. As shown in Figure 6, with an increase in polyvinyl alcohol (PVA) concentration, the drug release through the membrane decreased. This was due to the formation of dense networks, which causes a decrease in the drug release rate [17]. An initial rapid release of Cetirizine (burst effect) was evident with an increase in polyvinyl pyrrolidone (PVP) concentration which is because of the rapid dissolution of drug present on the surface of hydrogel patch. The burst effect is an essential component for dermal penetration of drug into the system for loading effect of the drug. Initial release of the drug and subsequent absorption maintains a sufficient concentration gradient of drug which might be required for diffusion of Cetirizine across the skin. Pyrrolidones have been reported in the literature to fluidize the lipids present in the stratum corneum and hence decreasing the barrier properties of the skin [19]. The increase in drug release, with an increase in polyvinyl pyrrolidone (PVP) concentration, is due to the leaching of polymer and formation of pores within the matrix patch. The improvement in drug flux can be accredited to the anti-nucleating effect of polyvinyl pyrrolidone (PVP) that converts the crystalline form of drug into an amorphous form which possesses improved solubility characteristics. The thermodynamic activity of Cetirizine is increased due to this solubility enhancement, which would facilitate the drug permeation through the skin [20].

The formulation M2 and M4 had a good fit in the Weibull model with an anomalous drug release mechanism of the power law (Korsmeyer Peppas model). The relevance of the Weibull function with the power law gives a description of the entire release profile and is an indicative of a combined drug release mechanism [21]. The formulations M3 to M5 better fitted in zero

order kinetics that signified that drug release rate was not dependent on the initial drug concentration [6]. The formulation M6 followed the Higuchi model, i.e. it favors diffusion controlled drug release from the matrix system. As the 'n' value for the formulations was greater than 0.5 and less than 1.0, therefore the release of drug mechanism was anomalous, i.e. an amalgamation of diffusion and swelling [6].

Table 2: Percentage drug release and kinetic models of hydrogel patches through synthetic membrane

Formulation	M1	M2	M3	M4	M5	M6
Drug release (%) after 12 hours	38.60	40.27	43.80	77.84	94.57	100.00
Zero Order	0.9580	0.9726	0.9850	0.9848	0.9971	0.9481
First Order	0.9000	0.9607	0.9755	0.8905	0.9151	0.7890
Higuchi Model	0.9539	0.9636	0.9435	0.9481	0.9324	0.9728
KP Model	0.9555	0.9755	0.9568	0.9911	0.9935	0.9555
n	0.59	0.58	0.64	0.79	0.88	0.71
Weibull Model	0.9645	0.9800	0.9815	0.9874	0.9969	0.9719
b	0.67	0.68	0.78	0.82	0.93	0.74
Hixson-Crowell	0.9224	0.9421	0.9725	0.9828	0.9704	0.9722

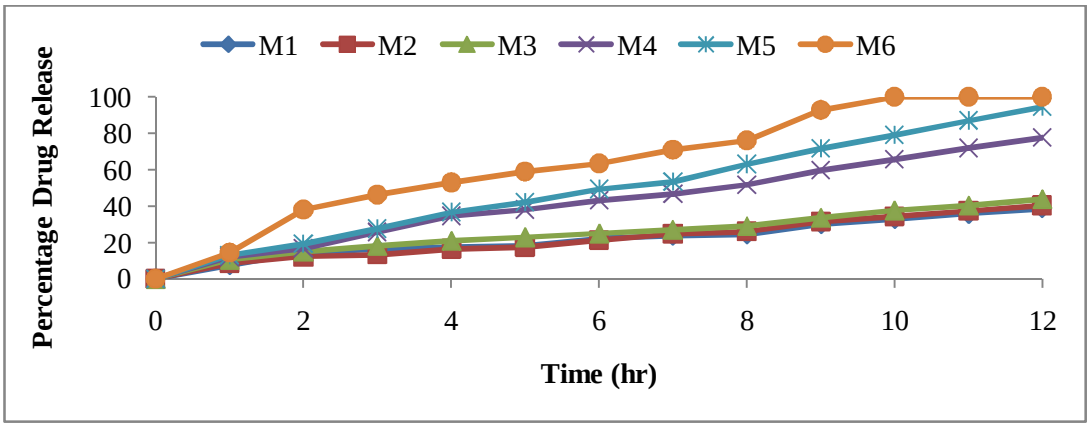

Figure 6: Percentage drug release of Cetrizine dihydrochloride through synthetic membrane

Ex vivo skin permeation studies

The stratum corneum layer of the skin is considered as the primary barrier to transport of drug through the layer with two parallel diffusional pathways; i.e. a pore-pathway and a lipoidal pathway. The ex *vivo* skin permeation data of Cetirizine dihydrochloride were obtained from the Franz diffusion cell by using a two layer physical model; the stratum corneum layer in series with the porous epidermis-dermis layer [22].

The percentage drug release from control patch containing polyvinyl alcohol-polyvinyl pyrrolidone is given in Table 3. The pyrollidones are reported to act as

permeation enhancers by partitioning between the interfacial region, where it intercalates and disrupts the alkyl chain order in the barrier realm of the bilayer layer of the skin [22]. However, only 11.33% of the drug had permeated through the mouse skin after 14 hours of study. Based on these results, it is concluded that at this lower concentration of polyvinyl pyrrolidone (PVP) lipid extraction is of less importance by which it may aid in the absorption of Cetirizine via the lipid pathway. Therefore, a permeation enhancer was required to accelerate the passage of drug through the skin.

Table 3: Percentage drug release, kinetic models, flux, permeability coefficient and enhancement ratio (ER) of hydrogel patches through model skin

Formulation	M5	M5-T80$_1$	M5-T80$_2$	M5-T80$_3$	M5-T80$_4$
Drug release (%) after 14 hours	11.33	15.56	27.21	39.10	59.81
Zero Order	0.9910	0.9880	0.9900	0.9893	0.9896
First Order	0.9122	0.9358	0.9573	0.9331	0.9281
Higuchi Model	0.8803	0.9478	0.9069	0.9491	0.8924
KP Model	0.9810	0.9877	0.9276	0.9875	0.9574
n	1.13	0.70	0.78	0.70	0.99
Weibull Model	0.9951	0.9898	0.9845	0.9900	0.9902
b	1.43	0.80	0.97	0.80	1.31
Hixson-Crowell	0.3751	0.9285	0.9885	0.9886	0.9506
Flux (µg/cm^2 hr^1)	109.97	133.58	246.43	334.66	566.11
Permeability Coffiecient	0.0059	0.0072	0.0132	0.0179	0.0303
ER	--	1.21	2.24	3.04	5.15

The cumulative drug release (µg/cm^2) is demonstrated in Figure 7. As expected, the drug permeation rate through the excised mouse skin was slower than that through the synthetic membrane. The maximum percentage of drug permeated through the rat's skin was in M5-T80$_4$ at 40% w/w concentration, whereas minimum percentage drug release was evident in M5-T80$_1$ at 10% Tween 80 concentration. Only 6.57% of the drug were released from M5-T80$_1$ after 14 hours, i.e. 2419.33 µg/ cm^2 from the initial drug concentration. The highest percentage drug release of 64.34% was observed at 40% w/w concentration with a cumulative drug release of 9300.53 µg/ cm^2 after 14 hours. When the percentage drug release was fitted in different kinetic models, M5-T80$_2$ demonstrated a best fit in zero order kinetics and M5-T80$_1$, M5-T80$_3$ and M5-T80$_4$ had a good fit in Weibull model with an anomalous drug release pattern (Table 3), favoring movement of drug through the hydrogel patch based on diffusion and polymeric erosion [23]. The Weibull function was chosen due to its prior success in modeling

parabolic shaped dissolution curves in M5-$T80_1$, M5-$T80_3$ and M5-$T80_4$. According to the *b* value, a parabolic curve was signified for M5-$T80_1$ and M5-$T80_3$, whereas S-shaped dissolution curve was obtained in M5-$T80_4$ [23]. Tween 80 is a non-ionic surfactant and possess long chain hydrocarbon along with ethyleneoxide. Therefore, it has both hydrophilic and hydrophobic characteristics. This aspect of Tween 80 aids in the partitioning of molecules between lipid membrane (lipophilic) and protein domain (hydrophilic) [24].

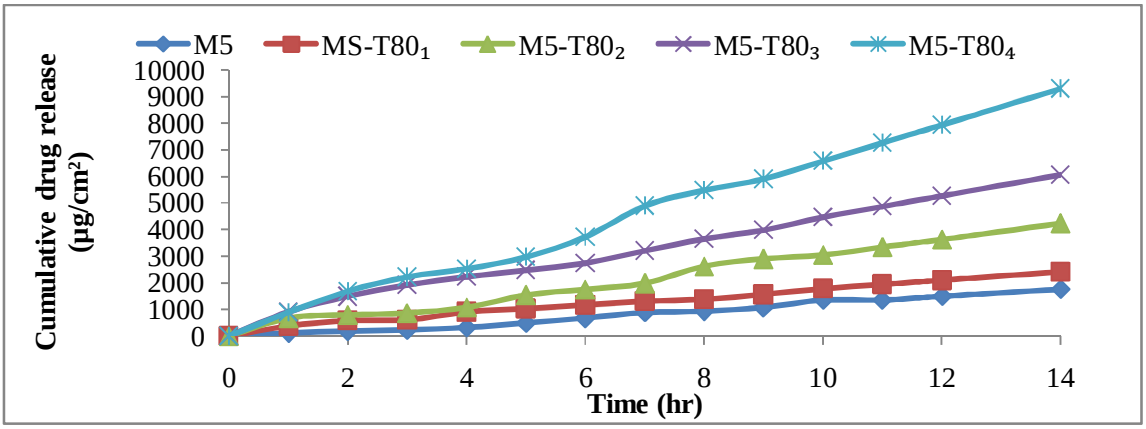

Figure 7: Cumulative drug release of Cetrizine dihydrochloride through model skin

Enhancement ratio (ER) of a hydrogel patch of Cetirizine dihydrochloride with permeation enhancers

The permeability coefficient and enhancement ratio (ER) of different penetration enhancers at a concentration of 10% w/w to 40% w/w are shown in Table 3. The ER ranged from 1.21 to 5.15 for a formulation containing mixture of polyvinyl alcohol-polyvinyl pyrrolidone with Tween 80 as permeation enhancers. The least enhancement ratio (ER) was shown by M5-$T80_1$ at 10% w/w Tween 80 concentration, whereas the maximum effect was shown by M5-$T80_4$ at 40% w/w concentrations. As indicated by the results, there was an increase in drug permeation enhancing ability of the permeation enhancer with an increase in concentration. This may be due to the greater degree of disruption of the stratum corneum that leads to an increase in flux and permeation rate of drug from the skin.

CONCLUSION

The skin permeation studies showed that there was an optimal ratio of film formers that gave the highest permeation rate of Cetirizine dihydrochloride for each permeation enhancer. The preparations, giving the highest drug penetration rate not necessarily coincided with the one giving the

highest release rate, i.e. the skin penetration of Cetrizine is not regulated by the drug release kinetics, but by the effect of permeation enhancers on the skin permeation. Several factors such as the release kinetics and the interaction between enhancers and polymers in the film would influence the enhancing activity. The effects of these factors are dependent on the ratio of film formers and permeation enhancers.

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