BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e21131

Article

Development and optimization of metoclopramide containing polymeric patches: impact of permeation enhancers

Zunaira Sarwar[1], Muhammad Farooq*[1], Sherjeel Adnan[1], Muhammad Umer Saleem[1], Zeeshan Masood[1], Asif Mahmood[2]

[1]Faculty of Pharmacy, The University of Lahore, Lahore, Pakistan,
[2]Department of science, University of Chakwal, Chakwal, Pakistan

The study is aimed to develop a monolithic controlled matrix transdermal patches containing Metoclopramide as a model drug by solvent casting method. Eudragit L100, Polyvinylpyrrolidone K-30, and Methylcellulose were used in different ratios and Polyethylene glycol 400 added as a plasticizer. Resulting patches were evaluated for their physicochemical characters like organoleptic characters, weight variation, folding endurance, thickness, swelling index, flatness, drug content, swelling index, percentage erosion, moisture content, water vapor transmission rate and moisture uptake. Formed patches were also evaluated through Fourier transform spectroscopy (FT-IR), X-ray diffraction (XRD), Differential Scanning calorimetry (DSC) and Scanning Electron Microscopy (SEM). Results of SEM unveiled smooth surface of drug-loaded patches. *In-vitro* dissolution studies were conducted by using dissolution medium phosphate buffer saline pH 7.4. Effect of natural permeation enhancers was elucidated on two optimized formulations (Z4 and Z9). Different concentrations (5%- 10 %) of permeation enhancers i.e. Olive oil, Castor oil and Eucalyptus oil were evaluated on Franz diffusion cell using excised abdominal rat skin. Z4-O2 (Olive oil 10%) had enhanced sustain effect and flux value (310.72) close to the desired flux value. Z4-O2 followed Higuchi release model (R^2= 0.9833) with non-fickian diffusion release mechanism (n=0.612).

Keywords: Matrix transdermal patch. Metoclopramide. Eudragit L100. Essential oil. Permeation enhancer. Flux.

INTRODUCTION

Transdermal drug delivery system (TDDS) is a unique dosage form that delivers a drug into systemic circulation through skin. Drug released from TDDS is absorbed through the stratum corneum, epidermis and dermis into blood circulation. An ideal TDDS facilitates transport of optimum drug contents through skin layers into systemic circulation (Allen, Ansel,2013). Major advantages of the Transdermal drug delivery system are that they are non-invasive in nature so painless, therapy can easily be stopped if some side effects occur and it bypasses hepatic circulation thus increased quantity of drug is available in plasma and blood. Molecular weight, chemical functionality and glass transition temperature of polymer should be that drug diffuses properly released from the transdermal system.

The chemical structure of essential oils as enhancers affects drug permeation process through skin. Usually, transdermal penetration of hydrophilic drugs were better enhanced by terpenes with polar functional groups, while the absorption of lipophilic drugs was more enhanced by hydrocarbon terpenes (Williams, Barry, 1991). Mechanisms of action of active compounds derived from essential oils were primarily based on interaction with intercellular lipids and changing the structure of the barrier to increase drug diffusivity. A possible mechanism for the enhancement action of *d*-limonene and ethanol through rat skin, it was considered that *d*-limonene penetrated the skin under coexistence with ethanol and could modify diffusivity through changing the structure

***Correspondence:** M. Farooq. Faculty of Pharmacy. The University of Lahore. Lahore, Pakistan. Phone: +923346901320. E-mail: muhammad.farooq@pharm.uol.edu.pk. https://orcid.org/0000-0001-6389-2286

of the stratum corneum layer (Williams, Barry, 1991). Therefore essential oils were ideal over conventionally used synthetics enhancers as safe permeation enhancers to promote the percutaneous absorption of many drugs from topical dosage form into lower skin layers (Miguel, 2010).

Metoclopramide is benzamide dopamine-receptor antagonist as antiemetic drug that listed in WHO essential model lists. It is mostly prescribed in pregnancy, cancer therapy and migraine to treat nausea and vomiting. The half-life and bioavailability of Metoclopramide are 3 to 4 hr and 35-100%, respectively. Because of its short half-life, 10-15mg dose of Metoclopramide administered three or four times a day. Metoclopramide is variable due to hepatic first-pass metabolism and oral dosage forms often vomited out before systemic absorption. Rectal and parenteral administration routes both outcome in low patient compliance. Thus, Metoclopramide transdermal delivery appears to be an attractive and effective alternative route (Aktar *et al*., 2014). The objective of this study was to develop a matrix transdermal film of metoclopramide by employing hydrophilic (Polyvinylpyrrolidone K-30 and Methylcellulose) and hydrophobic polymers (Eudragit L100) in conjugation with essential oils (olive oil, castor oil and eucalyptus oil) as permeation enhancer in a different ratio.

MATERIAL AND METHODS

Material

Metoclopramide (CSH Pharmaceuticals), Eudragit L-100 (Merck, Germany), Polyvinylpyrrolidone K-30 (PVP K-30) (Merck, Germany), Methocel (Merck, Germany), Methanol (BDH, England), Chloroform (Aldrich Chemical Co Ltd), Polyvinyl Alcohol (PVA) (Merck, Germany), Polyethylene glycol (PEG-400) (Merck, Germany), Olive Oil (Merck, Germany), Castor Oil (Merck, Germany), Eucalyptus Oil (Merck, Germany), Sodium Chloride (Merck, Germany), Potassium chloride (Merck, Germany), Potassium dihydrogen phosphate (Merck, Germany), Disodium hydrogen phosphate (Merck, Germany), Sodium hydroxide (Riedel-de Haen), Calcium Chloride ((Uni-chem, Serbia), Hydrochloric Acid (BDH, England).

Preparation of Matrix Transdermal Patch of Metoclopramide without permeation enhancer

To prepare backing membrane PVA (4%) solution was prepared by dissolving weighed quantity of PVA in distilled water (80 ^{o}C) on circulating water bath (Jisico, Korea). Afterwards, PVA solution was transferred to hot plate magnetic stirrer (Jisico J-HSD 180, Korea) and stirring was performed at 500 rpm for 2 hrs. Resultant solution was carefully poured in petri dish.

A precisely weighed amount of Polyvinylpyrrolidone K-30 (PVP K-30), Eudragit L100 (E L-100) and Methylcellulose was dissolved in 10 ml mixture of Chloroform and Methanol (5:5) (Table I) and the solution was mixed for about 30 minutes on a hot plate stirrer at 200 rpm at 32°C then weighed amount of Metoclopramide was added to solution and mixed for another 30 minutes. After complete solubilization, air bubbles were removed by casting solution in a sonicator (Supersonic X3, AFD instrument, Lahore, Pakistan) for 30 min. After sonication, formulations were poured in Petri dishes containing baking membrane. Inverted funnel is placed on Petri dishes to control the evaporation of organic solvent at room temperature for 24 hours (Shabbir *et al*., 2016).

Preparation of Matrix Transdermal Patch of Metoclopramide with permeation enhancer

Optimized patches were prepared by keeping the ratio of polymer constant and varying concentrations of different permeation enhancers. To prepare matrix transdermal patches containing permeation enhancer accurately weighed amount of polymers were added in the 10ml of the organic solvent (Table I) and were mixed on hot plate magnetic stirrer for about 30 min at 200 rpm. To the resultant polymer solution plasticizer propylene glycol 400 (PEG-400) and stirring was continued for further 30mins. Finally, permeation enhancers were added in different strengths i.e. 5% and 10%. Resultant blend after sonication was transferred into petri dish containing backing membrane. The organic solvent was evaporated by inverting funnel on the petri dish at room temperature for 24 hours (Guru *et al*., 2010).

Table I - Formulation of matrix transdermal patches containing Metoclopramide (10mg) and polyethylene glycol (45% w/w).

Formulation	Eudragit L-100 (mg)	PVP K-30 (mg)	Methylcellulose (mg)	Chloroform : Methanol (ml)	Permeation enhancer
Z1	500	-	-	5:5	-
Z2	400	100	-	5:5	-
Z3	300	200	-	5:5	-
Z4	200	300	-	5:5	-
Z5	100	400	-	5:5	-
Z6	-	500	-	5:5	-
Z7	400	-	100	0:10	-
Z8	300	-	200	0:10	-
Z9	200	-	300	0:10	-
Z10	100	-	400	0:10	-
Z11	-	-	500	0:10	-
Z4-O1	200	300	-	5:5	Olive oil (5%)
Z4-O2	200	300	-	5:5	Olive oil (10%)
Z4-C1	200	300	-	5:5	Castor oil (5%)
Z4-C2	200	300	-	5:5	Castor oil (10%)
Z4-E1	200	300	-	5:5	Eucalyptus oil (5%)
Z4-E2	200	300	-	5:5	Eucalyptus oil (10%)
Z9-O1	200	-	300	0:10	Olive oil (5%)
Z9-O2	200	-	300	0:10	Olive oil (10%)
Z9-C1	200	-	300	0:10	Castor oil (5%)
Z9-C2	200	-	300	0:10	Castor oil (10%)
Z9-E1	200	-	300	0:10	Eucalyptus oil (5%)
Z9-E2	200	-	300	0:10	Eucalyptus oil (10%)

Physicochemical evaluation of Metoclopramide matrix transdermal patch

Organoleptic characters

Transdermal patches were evaluated in terms of patch color, level of transparency, the flexibility of patch, homogeneity and glossiness. Patches that contain desirable characters were given (+++) and formulation that contains the least desired or negative characters was given (---) (Can *et al.*,2013).

Weight variation

Three patches from each formulation were chosen to determine variation in weight. Selected transdermal patches were dried previously at 60 °C in the oven for 4 h before weighing. The Individual weigh of the patch was carried out on digital weighing balance (DV215 CD, Ohaus, New Jersey, USA). The average weight and standard deviation were calculated from individual weight using SPSS (Fatima *et al.*, 2017).

Thickness

Patch thickness was measured using a digital Vernier caliper (SH-0281, Zhejiang, China). Three patches from each formulation were selected randomly for thickness measurement. Thickness was observed from the center and edges of patch. The average thickness and standard deviations were calculated using SPSS (Nussinovitch *et al.*, 2008).

Folding Endurance

Folding endurance was calculated by frequently folding the transdermal patch until it broke. The 2x2 cm piece was cut from center and edge of patch. The value of folding endurance was denoted by the number of times a patch was folded. Average values and standard deviation were calculated using SPSS (Garala, Shinde, Shah, 2009).

Flatness

Flatness of patches was evaluated by cutting a strip of 4cm length from center and each side. Change in length of strips was noted after cutting. If the length of strips was unchanged then it was confirmed that there was no constriction and 100% flatness. Percentage flatness was evaluated by the following formula (Shabbir *et al.*, 2016).

$$Percentage\ constriction = \frac{Initial\ length - Final\ length}{Initial\ length} \times 100$$

Percentage moisture uptake (PMU)

To determine moisture uptake (%), a 2×2 cm piece from each patch was taken after cutting and it was precisely weighed on a digital weighing balance. It was placed on perforated plate of desiccator at 25 °C. It was removed from desiccator periodically and any change in weight was recorded. After achieving constant weight, patch was exposed to 200 ml saturated solution of potassium chloride for 84% relative humidity (RH) (Bagyalakshmi *et al.*, 2007). Percentage moisture content was calculated by the following equation:

$$Percentage\ moisture\ uptake = \frac{Final\ weight - Initial\ weight}{Final\ weight} \times 100$$

Water vapor transmission rate (WVTR)

A piece of 1×1cm of known weigh was cut from the transdermal patch. This piece was fixed on the brim in a glass vial of 5 ml and 1gm of potassium chloride was added. The vial was weighed individually and exposed to 200ml saturated solution of potassium chloride that provides 84% relative humidity in a desiccator at 25 °C. Vial was weighed again at an interval of 24 hours for 5 days. The water vapor transmission rate was calculated by the following formula (Shabbir *et al.*, 2016).

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

Swelling index and percentage erosion

A piece of 1×1cm was cut from each patch and dried at 40 ± 2 °C overnight. Patches were fixed on glass coverslips and weighed on a digital weighing balance. Patches were transferred to appropriate label Petri dishes, distilled water was poured into the petri dish so that films were sunk in distilled water. After 5,10 and 30 mins the coverslips were removed from the petri dish and blotted with tissue paper to remove excess water and weighed immediately. If patch showed any signs of fragmentation or it began to dissolve, discontinue the process. The swelling index was calculated by the following equation (Pichayakorn *et al*., 2012).

$$Swelling\ Index = \frac{W_2 - W_1}{W_1}$$

Where W_1: weight before swelling, W_2: weight after time't' after swelling.

Percentage of drug content

Percentage drug content was determined by cutting a film of 2×2 cm from each patch and dissolved in 100 ml of phosphate buffer saline pH 7.4 on hot plate magnetic stirrer for 12 h at 32°C. After 12 hours, the solution was sonicated for about 30 minutes in a sonicator. 5ml of sample was taken with the help of a syringe filter. The filtrate was diluted with an equal volume of phosphate buffer saline pH 7.4 and analyzed on UV spectrophotometer at 273nm. The quantity of drug was measured by the calibration curve method (Cilurzo *et al*., 2014).

Scanning Electron Microscopy (SEM)

The surface morphology of drug-loaded transdermal matrix patches was examined by an electron microscope (JSM 7500 Joel, Japan) using 0.5–1 Kv. A small portion of patch was placed on a gold stub and observed under different magnification powers.

Drug excipients interaction studies

Fourier transforms infrared (FTIR) analysis

Fourier transforms infrared (FTIR) spectroscopy analysis was done to determine any structural changes that occur during the time of preparation between drug and polymer. The analysis was performed on Fourier transform infrared Spectrophotometer (Agilent Technologies Cary 660, USA). The infrared spectra of drug, excipients and formulations were recorded ranging from 4000 cm^{-1} to 500 cm^{-1}.

X-ray diffraction analysis (XRD)

XRD analysis was performed to evaluate the crystalline and amorphous nature of drug, excipients and drug-loaded transdermal matrix patches. D8 Discover (Bruker, Germany) was used to record X-ray diffractogram with a scanning range of (2θ) = 4° - 80° at a scanning rate of 1°/min.

Differential scanning calorimetry (DSC)

Thermal behavior of drug, excipients and drug-loaded patches were examined by performing DSC analysis to evaluate any possible interactions (DSC4000; Perkin Elmer, USA). Accurately weighed samples were heated at a rate of 10 °C/min over a range of 0 to 300 °C in the presence of an inert nitrogen atmosphere.

***In vitro* dissolution studies of Metoclopramide transdermal patches**

Metoclopramide release from matrix type transdermal patches (2×2 cm size) was conducted in USP apparatus II (Curio 2020+, Lahore, Pakistan) by using 500ml phosphate buffer saline pH 7.4 dissolution medium to maintain sink conditions. The paddle was rotated at 50 rpm and the temperature of apparatus was maintained at 37±1 °C (Limpongsa, Umprayn, 2008). After a specific time interval of 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h. 5ml of the sample was withdrawn using syringe filter 0.10µm pore size and replaced by an

equal volume of fresh phosphate buffer saline pH 7.4. The sample was diluted with 5ml of the phosphate buffer saline pH 7.4 and analyzed using a spectrophotometer at 273nm for the absorption. The test was run in triplicate and average reading was taken.

Ex vivo skin permeation studies

Preparation of rat skin

The rat was euthanized with written permission from the Animal Ethics Committee, The University of Lahore, under reference number IAEC-2015-12. To perform ex vivo skin permeation studies skin of the ventral side of male albino rat (weighing 200-250 grams) was used. The hair of rat was removed with the help of an electric shaver. Rat was euthanized by cervical dislocation and skin region was obtained. For the preparation of epidermis, the removed skin was soaked in water at 60 °C for about a minute that will loosen up fats. Subdermal tissues of the epidermis were removed with the help of scalpel and forceps. The remaining fats on the skin were removed by wiping the skin with cotton soaked in isopropyl alcohol (IPA) for 1 minute. The skin obtained was kept in a normal saline solution in a refrigerator and used within a week. Before usage, skin was allowed to come at 25 ºC for at least 10 hours and equilibrated in phosphate buffer saline pH 7.4 for 1 h (Jamakandi *et al.*, 2014).

Ex vivo skin permeation

Ex vivo skin permeation of metoclopramide transdermal patches was done in Franz diffusion cell having a diffusion area of 1.2cm^2. The volume of the receptor compartment was filled with 10ml of phosphate buffer saline pH 7.4. Then rat skin was mounted in such a way that the dermal layer of skin was facing the donor compartment while the deeper layer of skin facing receptor compartment. A patch was applied onto Franz's cell in such a way that the backing membrane was facing away from dermal side of skin. The temperature was controlled on a water bath at 32 ± 2 °C by a water circulation jacket surrounding the cell body (Allena *et al.*, 2012). Samples were withdrawn from the receptor compartment with the help of LP needle. 1 ml sample was obtained after a specific time interval of 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12th h and the volume of receptor compartment was replaced with an equal volume of fresh phosphate buffer saline pH 7.4.

Data Analysis

Kinetic modeling on drug release from matrix type Metoclopramide transdermal patches

In vitro dissolution study and ex vivo permeation study was further analyzed by model-dependent approaches by applying data in the following models:

$$Q_\circ = \frac{A}{T}$$

$$Q_1 = \frac{2.3 \log(\frac{A_\circ}{A})}{t}$$

$$Q_H = \frac{C}{\sqrt{t}}$$

$$Q_k = \frac{M_t / M_a}{t^n}$$

$$Q_w = Q_\circ\left[1 - e^{-k(t-T)}\right]$$

Where $Q_\circ$ is the zero-order rate constant expressed in units of concentration/time and t is the time. A is the amount of drug released in time t, $A_\circ$ is the initial concentration of drug and Q_1 is first-order constant. Q_H is the Higuchi dissolution constant. Q_w is the amount of drug dissolved as a function of time. $M_\circ$ is the original mass of film and M is the mass of film at time t. M_t/M_a is the fraction of the drug release at time t and *n* is the release exponent as an indication of drug release mechanism. T accounts for lag time measured in dissolution process (Shoaib *et al.*, 2006).

Data analysis for ex vivo permeation studies

The ex-vivo data obtained was also analyzed for the cumulative amount of drug that is permeated through skin, drug flux, permeability coefficient and

enhancement ratio. Cumulative amounts of drug permeated in µg/cm^2 were plotted against time and drug flux in µg/cm^2/hr at steady state was calculated by dividing the slope of linear portion of curve by area of the exposed skin surface. The permeability coefficient was derived by dividing the flux obtained by the initial drug load (Shankar, 2010).

$$J_{ss} = P_s C_d = \frac{K \times D_{ss}\, C_d}{L}$$

$$\text{Extraction ratio} = \frac{\text{Drug permeability coefficient after enhancer treatment}}{\text{Drug permeability coefficient before enhancer treatment}}$$

Where, J_{ss}: Steady-state flux, C_d: Concentration of drug in donor compartment, D_{ss}: Apparent diffusivity through the skin, P_s: Permeability coefficient, K: Partition coefficient, L: Thickness of skin.

RESULT AND DISCUSSION

Physicochemical evaluation of matrix transdermal patch of Metoclopramide without permeation enhancer.

Organoleptic evaluation

Organoleptic properties of patches including patch color, glossiness, transparency, flexibility, smoothness of patch and homogeneity. All formulation of Metoclopramide transdermal patches were tested for organoleptic properties and it was seen that formulations were clear and colorless in appearance while Z6 showed opaque appearance. The main reason for colorless and opaque patches was that when Eudragit L100 and methylcellulose were dissolved in methanol and chloroform they yield a colorless solution, while when Polyvinylpyrrolidone and methylcellulose were dissolved in water they form a milky solution (Snejdrova, Dittrich, 2012). Formulations that contained Eudragit L100 in increased quantity, all parameters were in an excessive number of desired characters as compared to other formulations that contain less amount of Eudragit L100 (Ammar *et al.*, 2006). Smoothness and flexibility to patches was imparted by PEG400. Moreover, PEG 400 is also responsible for polymer elongation by weakening polymer interaction. As a result, patch cracking was markedly reduced (Prabhu, Shah, Gundad, 2011).

Weight Variation

To assess weight variation, three patches from each formulation were randomly selected and weighed on an analytical weighing balance. Mean and standard deviation was also calculated for transdermal patches. Variation in weight of patches were recorded between 1.2041 ± 0.0190 to 1.2683 ± 0.0268 mg (Table II). A small value of standard deviation shows that weight variation in the transdermal patch is minimal and patches are reproducible (Kumar, Jain, Nayak, 2012).

Thickness

Thickness of Metoclopramide transdermal patches ranges from 0.050262 ± 2.20 x 10^{-5} to 0.050498 ± 7.35 x 10^{-5} mm. Thickness of all Metoclopramide transdermal patches is shown in Table II. Small variation in thickness infer that patches have uniformity in thickness and the process is reproducible (Patel, Patel, Patel, 2012).

Folding Endurance

Folding endurance from formulations Z1 to Z11 was less than 100 with one exception in formulation ZS-6A, where the value of folding endurance was greater than 120 which was due to increased concentration of Polyvinylpyrrolidone (Table II). An increase in folding endurance was due to presence of both hydrophilic polymers in the formulations. Backing membrane and presence of PEG 400 as plasticizer also play in increasing the integrity of formulation (Sathali, Mageshkumar, 2013).

Flatness

Formulation Z4, Z5, Z6 and Z11 revealed signs of constriction and Z6 offered minimum flatness (Table II).

All the above formulations have a high concentration of Polyvinylpyrrolidone that caused constriction. Remaining formulations did not show any sign of constriction and were 100% flat. Uniformity in flatness indicates that transdermal patch prepared by solvent casting method is reproducible and maintains a satisfactory smooth surface (Guru *et al.*, 2010).

Percentage Moisture Uptake

It is used to calculate the maximum quantity of moisture a patch can retain when it is presented to increased conditions of humidity. The percentage moisture uptake of Metoclopramide patches was in range of 2.12% to 19.31% (Table II). Optimum percentage of moisture uptake in the case of transdermal patches is 15%, any percentage above that increased the bulkiness in transdermal patch and cause discomfort. Results indicate that when concentrations of Polyvinylpyrrolidone and methylcellulose were increased, the capacity of transdermal film to uptake moisture was also increased. Eudragit L100 is a hydrophobic nature, which restricts the moisture uptake due to the presence of a quaternary ammonium group present in the molecular structure. So transdermal patches that have a high concentration of Eudragit L100 in their formulations have less affinity to absorb moisture (Ubaidulla *et al.*, 2007). PEG 400 makes polymeric network less dense by increasing the mobility of the polymer chain in matrix system. Water molecules absorption increased the formation of pores that enhance porosity (Nussinovitch *et al.*, 2008).

Water vapor transmission rate (WVTR)

Water vapor transmission rate was estimated to understand the movement of vapors from a patch, per unit area per unit time, to make sure that patch will remain stable during its storage. Formulation Z10 has the maximum water vapor transmission rate of 25.4 x 10^{-4} g/cm^2, while formulation Z1 has the lowest water vapor transmission rate of 9.54 x 10^{-4} g/cm^2 (Table III) (Shabbir *et al.*, 2016). The low amount of WVTR emphasized the long-term stability and storage of formulation. Formulations containing high concentrations of Eudragit L100 has reduced WVTR.

Table II. Physicochemical evaluation of matrix transdermal formulations of Metoclopramide.

Formulation	Weight variation ± S.D. (mg)	Thickness ± S.D. (mm)	Folding endurance	Flatness ± S.D. (%)	Moisture uptake (%)
Z1	1.2683 ± 0.0268	0.050279 ± 2.83 x 10^{-5}	<100	100 ± 0	2.12
Z2	1.2360 ± 0.0102	0.050262 ± 2.20 x 10^{-5}	<100	100 ± 0	4.86
Z3	1.2372 ± 0.0231	0.050271 ± 2.68 x 10^{-5}	<100	100 ± 0	8.40
Z4	1.2241± 0.0101	0.050375 ± 8.79 x 10^{-5}	<100	99.54 ± 0.48	11.70
Z5	1.2436 ± 0.0329	0.050498 ± 7.35 x 10^{-5}	<100	98.64 ± 0.50	13.21
Z6	1.2192 ± 0.0204	0.050454 ± 3.51 x 10^{-5}	>150	97.39 ± 0.35	19.31
Z7	1.2041± 0.0190	0.050357 ± 1.33 x 10^{-5}	<100	100 ± 0	7.46
Z8	1.2426 ± 0.0140	0.050387 ± 1.50 x 10^{-5}	<100	100 ± 0	8.91
Z9	1.2180 ± 0.0102	0.050372 ± 5.10 x 10^{-5}	<100	100 ± 0	13.41
Z10	1.2390 ± 0.0074	0.05034 ± 1.60 x 10^{-5}	<100	100 ± 0	15.18
Z11	1.2256 ± 0.0175	0.050447 ± 2.08 x 10^{-5}	>150	97 ± 0	10.63

Swelling index and percentage erosion studies

Swelling index varied from 0.92 to 1.56 and percentage weight increase due to swelling increase from 92.50%, to 156.4% (Table III). Formulation Z10 showed maximum swelling index and percentage weight increase due to swelling. The percentage erosion varies from 4.71% to 24.19% in Z1 to Z10 while formulations Z5, Z6 and Z11 were disintegrated and converted into gel after about 10 minutes. Results revealed that formulations containing a high amount of hydrophilic polymers (Methylcellulose, PVP K-30) exhibited increased swelling behavior of films and disintegrated in short life span as compared to formulation having higher content of Eudragit L100 due to low quaternary ammonia group that reduces hydration and permeability of medium. The hydration of polymeric film in matrix patch leads to a higher swelling index due to the formation of empty structure and spaces (Mishra, Kumar, Kothiyal, 2012; Srikanth, Raja, 2013).

Percentage of drug content

Drug content (%) are shown in Table III. The minimum value of drug content was seen in formulation Z8 that was 98.30 ± 0.045 %. The highest percentage of drug content was seen in formulations Z4, Z5 and Z10 that was 100.38 ± 0.0167%, 100.12 ± 0.0214% and 100.22 ± 0.0278%, respectively. Drug content analysis showed uniform distribution of drug throughout polymeric matrix.

Table III. Results of swelling index, percentage erosion, water vapor transmission rate and drug content matrix transdermal patch of Metoclopramide.

Formulation	Swelling Index ± (SD)	Percentage Erosion (%)	WVTR (g/m2.hr)	Drug content (%) ± S.D.
Z1	0.92 ± 0.0250	4.71 ± 0.212	9.54 x 10^{-4}	99.79 ± 0.017
Z2	1.24 ± 0.0458	8.42 ± 0.233	21.4 x 10^{-4}	99.28 ± 0.026
Z3	1.52 ± 0.0741	13.06 ± 0.274	19.2 x 10^{-4}	98.46 ± 0.032
Z4	1.85 ± 0.0854	17.71 ± 0.698	15.8 x 10^{-4}	100.38 ± 0.01
Z5	Disintegrated after 10 min		10.25 x 10^{-4}	100.12 ± 0.02
Z6	Disintegrated after 10 min		24.14 x 10^{-4}	99.97 ± 0.029
Z7	1.07 ± 0.0478	9.03 ± 0.306	19.5 x 10^{-4}	98.83 ± 0.043
Z8	1.12 ± 0.0358	10.97 ± 0.549	18.5 x 10^{-4}	98.30 ± 0.045
Z9	1.22 ± 0.0650	16.27 ± 0.404	15.6 x 10^{-4}	98.80 ± 0.062
Z10	1.56 ± 0.0414	24.19 ± 0.763	24.4 x 10^{-4}	100.22 ± 0.02
Z11	Disintegrated after 10 min		12.6 x 10^{-4}	98.31 ± 0.035

Scanning Electron Microscopy (SEM)

The surface morphology of optimized formulations exposed homogeneous dispersion of drug in transdermal matrix patches. The optimized formulations showed formation of irregular shape pores in patches that were due to the blend of Eudragit L100, PVP K30 and methylcellulose. These pores in formulation enhanced the permeation of drug without affecting other parts of patch. The finding of SEM micrographs of polymeric blend patches was in according with the results of Rauf et al 2018 where transdermal patches contain surface pores (Figure 1 A and B) (Akram *et al.*, 2018).

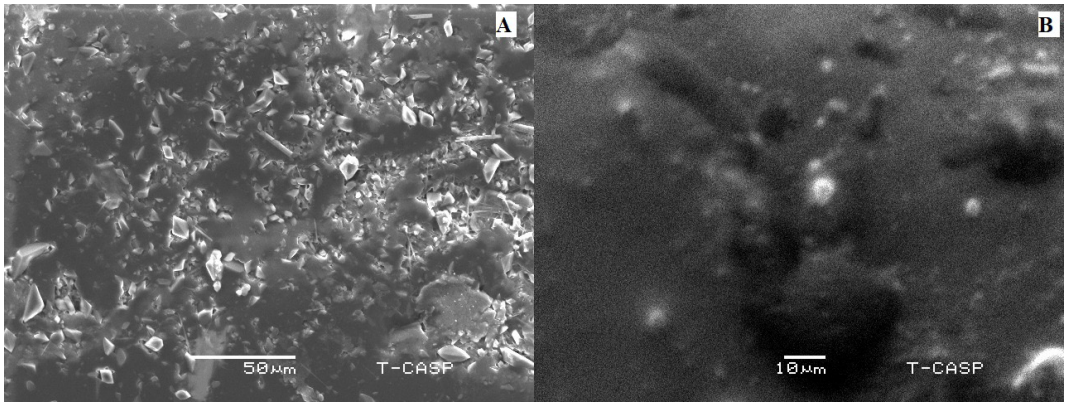

FIGURE 1 - Scanning electron microscopy micrograph of optimized transdermal patches Z4 (A) and Z9 (B).

FTIR analysis

Fourier transform infrared (FTIR) spectroscopy was used to find any incompatibility between drug and polymers. Pure dug showed prominent peaks at 3397cm^{-1} due to O-H stretching of strong alcohol bond, N-H stretching of aliphatic amine at 3200cm^{-1} and O-H stretching of carboxylic group at 2647cm^{-1}, respectively. The peaks at 1635cm^{-1} and 1594cm^{-1} were attributed to S=O stretching of sulfate and N-H stretching of nitro compounds, respectively. Other characteristic peaks were observed at 835 cm^{-1} and 678 cm^{-1} that were due to C-Cl stretching of alkyl halide group and C-Br stretching of halo compounds (Figure 2A) (Mushtaq, Fazal, Niaz, 2020). Eudragit L100 revealed characteristic peaks at 3417 cm^{-1}, 2830 cm^{-1} and 2194 cm^{-1} that attributed to C=O stretching, C-H stretching and carbonyl vibrations of ester group (Figure 2B). Methylcellulose exhibited peaks at 1058 cm^{-1}, 1650 cm^{-1} and 2900 cm^{-1} that corresponds to C-H stretching of CH2 and CH_3 groups (Figure 2B). FTIR spectrum of PVP-K30 absorptions band of carbonyl group at 1650 cm^{-1} and broad peak at 3440 cm^{-1} explains moisture presence that confirmed hygroscopic nature PVP-K30. FTIR spectra of formulations Z4, Z9, Z4-O2 and Z4-E2 indicated prominent metoclopramide peaks that were observed at 3397cm^{-1}, 3200cm^{-1}, 2647cm^{-1} 1635cm^{-}1, 1594cm^{-1}, 835 cm^{-1} and 678 cm^{-1} due to their respective functional groups of alcohol, aliphatic amine, carboxylic, sulfate and alkyl halide (Figure 2 D, E, F and G) . FTIR spectra of drug and formulations concluded that there were no intermolecular forces developed between drug and excipients.

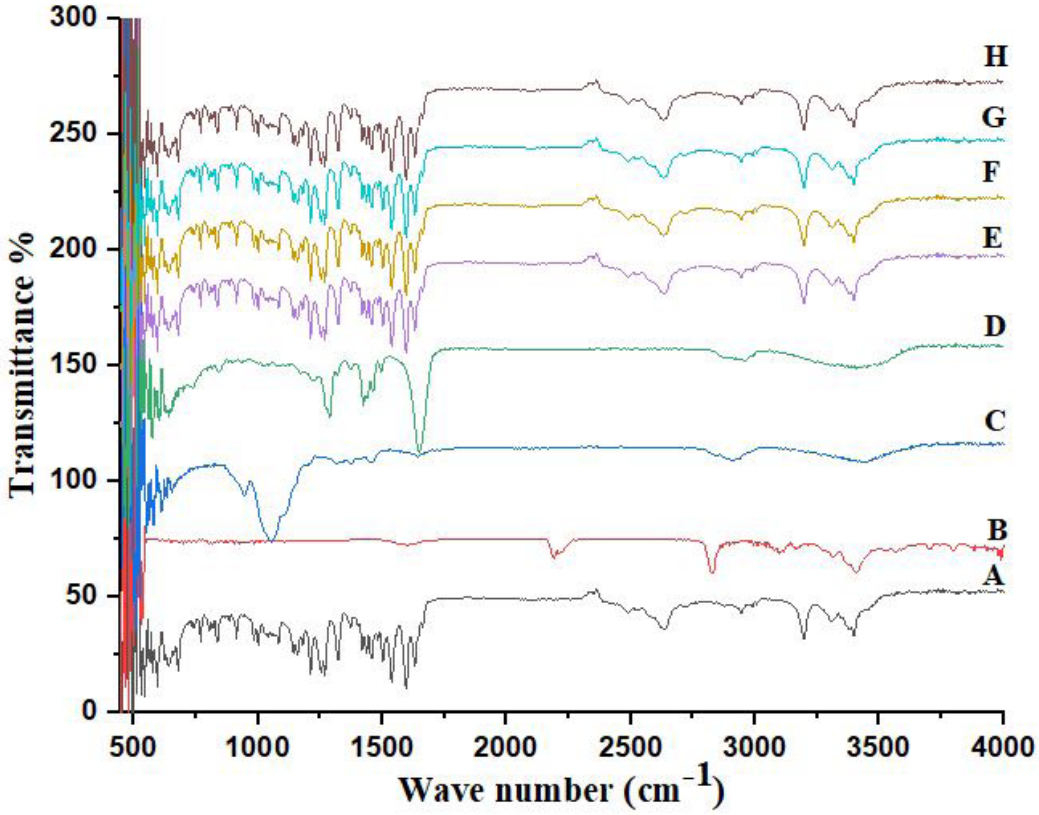

FIGURE 2 - FTIR spectra of Metoclopramide (A), Eudragit L100 (B), Methylcellulose (C), Polyvinylpyrrolidone K30 (D), formulations Z4 (E), Z9 (F), Z4-O2 (G) and Z4-E2 (H).

X-ray diffraction analysis (XRD)

X-ray diffraction studies of drug, polymers and drug-loaded patches were performed to determine the crystalline or amorphous nature. The pure drug showed XRD intense peaks at diffraction angle 2(θ) with their respective counts of 6° (81), 8° (40), 23.1° (49), 25.4° (93) and 26.4° (108) (Figure 3 A) (Nugraha, Uekusa, 2018). Eudragit L100 and PVP-K30 indicated low-intensity peaks at diffraction angle 2(θ) with counts of 11° (79), 13.5° (104) and 10° (70), 20° (72), respectively (Figure 3 B and C). Methylcellulose expressed low-intensity peaks at diffraction angle 2(θ) with counts of 10.7° (89) and 15.5° (92) (Figure 3 D). Drug loaded matrix patches diffractogram presented the reduction of a sharp and intense peak at diffraction angle 2(θ) with count of 7.5° (50) which confirmed the increase amorphous behavior and molecular dispersion of drug in polymeric films (Figure 3 E, F, G and H). Eudragit L100 is amorphous form due to the presence of a bulky side group and lack of comprehensive stereoregularity. The pure drug peaks were intense and sharp in diffractogram but, the physical mixture of drug and polymers confirmed loss of sharpness in peaks of drug due to decrease in crystallinity.

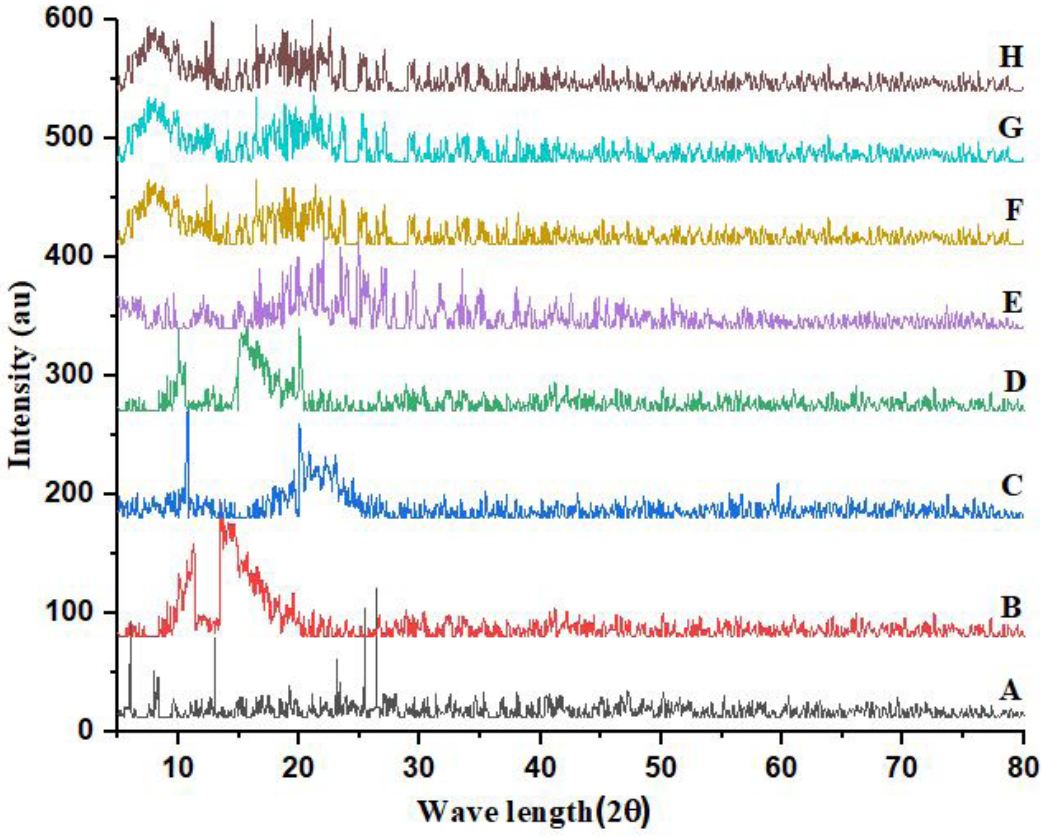

FIGURE 3 - X-ray diffractogram of Metoclopramide (A), Eudragit L100 (B), Polyvinylpyrrolidone K30 (C), Methylcellulose (D), formulations Z4 (E), Z9 (F), Z4-O2 (G) and Z4-E2 (H).

Differential scanning calorimetry (DSC)

The DSC thermogram of pure dug showed two melting endothermic peaks at 86 °C and 195 °C, respectively (Figure 4A). The first endotherm peaks at 86°C corresponds to the formation of anhydrous polymorph. This form was resulted due to removal of water from crystal lattice decomposition of Metoclopramide hydrochloride followed by melting and recrystallization by structural rearrangement. Second endothermic peaks at 195 °C attributes to the melting point of metoclopramide, which represents the crystalline behavior (Nugraha, Uekusa, 2018). There was a slight shift in the first endothermic peak while sending endothermic peaks was in formulations (Figure 4E). It was evident that crystalline nature of drug changed into amorphous nature with polymeric content throughout heating procedure of DSC. Results revealed that no extra peak was observed in a phase transition that indicated no drug-polymer interaction.

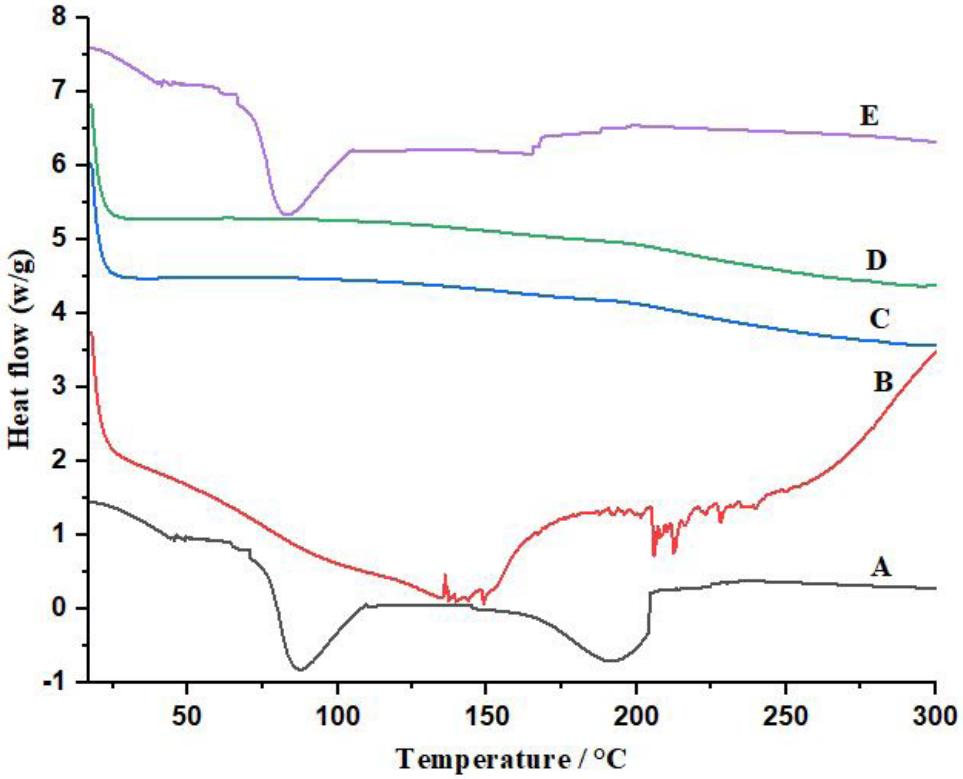

FIGURE 4 - DSC thermograms of Metoclopramide (A), Eudragit L100 (B), Polyvinylpyrrolidone K30 (C), Methylcellulose (D) and Z4 (E).

In-vitro drug release studies

Metoclopramide release from formulations (Z1 – Z6) containing Eudragit L-100 and PVP K-30 ranged from 34.86% to 60.4%, respectively. Formulation Z6 presented optimum drug release i.e. 60.4% because of higher contents of hydrophilic polymer PVP K-30. On the other hand, formulation Z1 presented lowest metoclopramide release i.e. 34.86% because of higher contents of hydrophobic polymer Eudragit L-100. Findings of release studies confirmed that controlled release behavior was associated with contents of hydrophobic polymer.

Formulations (Z7 – Z11) containing Eudragit L-100 and methylcellulose exhibited metoclopramide release 42.10% - 97.71%, respectively. Results are presented in Figure 5. Maximum release of metoclopramide was governed by formulation (Z11) containing highest concentration of methylcellulose in the absence of Eudragit L-100. In contrast to this, Metoclopramide release was compromised (42.10%) in formulation (Z7) having higher contents of Eudragit L-100.

Kinetic models were applied on release data of formulations Z5, Z7, Z8, Z9 and Z10, the best-fitted model was Higuchi release model with regression coefficient (R^2) value of 0.9898, 0.9889, 0.9991, 0.9935, 0.9880, 0.9830 and 0.9730, respectively (Table IV). The best fit model for the formulations Z1, Z2, Z3, Z4, Z6 and Z11 was Zero order because it had the maximum value of regression coefficient (R^2) of 0.9921, 0.9944, 0.9893, 0.9914 0.9974 and 0.9601, respectively. Value of release exponent '*n*' was in the range of 0.699 - 0.935 that shows the drug released from transdermal patch formulations followed non-fickian diffusion with anomalous release while Z9 and Z10 followed fickian diffusion (Costa, Lobo, 2001). Shape of the dissolution curve (β) was also calculated in Weibull model. If β =1 then shape of release curve is exactly same as an exponential profile. If β is higher than 1 then shape of curve is sigmoidal with a turning point. If β is lower than 1 then shape of release curve is steeper when β=1 (Dash *et al.*, 2010). Results indicate that shape of curve in case of Z2 and Z3 is somewhat steeper because value of 'β' is less than

1, While shape of release curve in all other formulations is sigmoidal in shape as value of 'β' is greater than 1.

It was confirmed that initial burst release of drug from the patch formulation especially in Z11, Z5 and Z6 which was due to presence of a hydrophilic polymer whereas, in Z2, Z3 and Z4, drug is released in a more controlled and sustained manner (Padmaja *et al.*, 2018). It was seen that when hydrophilic polymer and hydrophobic polymer were combined that increased release rate of drug due to insoluble film formation. The main reason is formation of pores by the gelation of the hydrophilic part of polymer combination, which results in increased drug release (Shivalingam *et al.*, 2015).

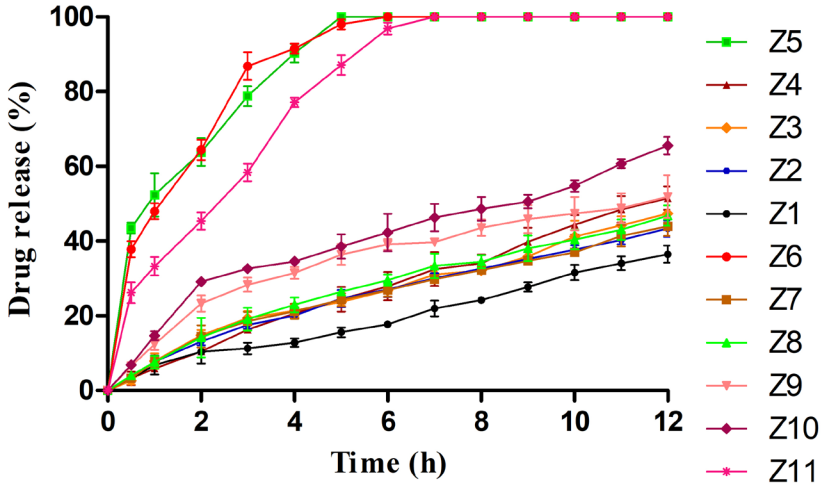

FIGURE 5 - *In vitro* dissolution profiles of Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z7, Z8 Z9, Z10 and Z11 (n=3).

Table IV. Kinetic modeling of release data (Z1-Z11)

Formulation	Zero order	First order	Higuchi	Krosmeyer-Peppas		Weibull	
	R^2	R^2	R^2	R^2	n	R^2	β
Z1	0.9921	0.9818	0.8931	0.9947	0.917	0.9920	1.030
Z2	0.9944	0.9822	0.8807	0.9980	0.699	0.9988	0.814
Z3	0.9893	0.9825	0.9397	0.9912	0.751	0.9889	0.875
Z4	0.9914	0.9799	0.8761	0.9919	0.964	0.9857	1.149
Z5	0.9837	0.9690	0.9914	0.9981	0.825	0.9991	1.010
Z6	0.9974	0.9877	0.8886	0.9990	0.935	0.9966	1.186
Z7	0.8544	0.9255	0.9846	0.9921	0.577	0.9935	0.673
Z8	0.8569	0.9261	0.9791	0.9874	0.583	0.9880	0.682
Z9	0.6444	0.8105	0.9710	0.9757	0.449	0.9823	0.554
Z10	0.6196	0.7946	0.9615	0.9693	0.435	0.9743	0.544
Z11	0.9601	0.9525	0.9240	0.9862	0.777	0.9900	1.524

Ex-vivo skin permeation studies

Ex-vivo skin permeation studies of optimized formulations (Z4 and Z9) without permeation enhancer

Skin permeation studies were performed on optimized formulations Z4 and Z9, these formulations were selected after *in vitro* dissolution studies. Formulation Z4 had released about 2060.13 μg/cm^2 after 12 hours from the initial drug concentration of 10000 μg/cm^2 and followed Higuchi model with R^2 value of 0.9914. The cumulative amount of drug permeated from formulation Z9 was 2244.96 μg/cm^2 from the initial concentration of 10000 μg/cm^2 (Costa, Lobo, 2001). The flux of both formulations Z4 and Z9 was 125.98 μg/cm^{2}hr and 144.49 μg/cm^{2}hr. Formulation Z9 has slightly increased flux, although contains same quantity of hydrophilic polymer, because of high hydrophilicity of methylcellulose as compared to Polyvinylpyrrolidone (Patel *et al*., 2009). There was the movement of drug from the skin over 12 hours but formulations failed to achieve the desired sustained action. Therefore, it was necessary to add a permeation enhancer to increase the flux and improve transport of drug.

Ex-vivo skin permeation studies of metoclopramide transdermal patches with Olive oil as a permeation enhancer

It was evident that when concentration of olive oil in formulation was used at 5% and 10%, the cumulative amount of the drug permeated was also increased (Figure 4). When olive oil was used as a permeation enhancer in Z4-O1 (5%) and Z4-O2 (10%), drug permeation was increased to that was 3180.13 μg/cm^2 (31.8%) and 4744.27 μg/cm^2 (47.4%), respectively (Table IV). Similarly in formulations Z9-O1 (5%) and Z9-02 (10%), total cumulative drug release increased to 2622.89 μg/cm^2 (26.2%) and 3373.2 μg/cm^2 (33.7%) respectively (Table IV). Formulations Z4-O1 and Z4-O2 both best fitted in Higuchi release model with R^2 values of 0.9802 and 0.9833, respectively which signifies diffusion-controlled release (Siepmann, Peppas, 2012). On the other hand, formulations Z9-O1 and Z9-O2 followed zero order model with R^2 values of 0.9959 and 0.9964 respectively (Table IV). Values of 'n' of these formulations were ranges from 0.612 to 0.813, which indicated the non-fickian diffusion. The shapes of the release curves were steeper as signified by their values in Weibull's model (Mutalik, Udupa, 2005). Olive oil increases the drug diffusivity by altering the stratum corneum that acts as a barrier. Similar results were achieved in literature when the penetration of flurbiprofen through skin was increased by increasing concentration of olive oil. In another literature, the penetration of drug from topical gel was increased from 20% to 48% with the addition of olive oil (Hussain *et al*., 2012).

Ex-vivo skin permeation studies of metoclopramide transdermal patches with Castor oil as a permeation enhancer

As the amount of castor oil increased (5% and 10%), the amount of drug permeated increased from 2060.13 μg/cm^2 (Z4) to 4093.11 μg/cm^2 (Z4-C1) and 44724.2μg/cm^2 (Z4-C2), respectively (Figure 4). While in formulations Z9-C1, Z9-C2 and showed an increase in drug permeation from 2244.96 μg/cm^2 (Z9) to 2890.48 μg/cm^2 (Z9-C1) and 3729.10 μg/cm^2 (Z9-C2) (Table IV). The R^2 value Z4-C1, Z4-C2 and Z9-C1 followed Higuchi release, which exhibited diffusion controlled drug release. The value of 'n' ranges from 0.667 to 0.825 which exhibited non-fickian diffusion with polymer relaxation and case II transport (Shoaib *et al*., 2006). The curve of release profile was steep when compared with β=1. While formulation Z9-C2 followed zero order release with R^2 value of 0.9964 and release mechanism was non-fickian diffusion with super case II transport. The value of β (1.016) showed that the shape of release curve was sigmoidal with a turning point (Table IV).

Ex-vivo skin permeation studies of metoclopramide transdermal patches with Eucalyptus oil as permeation enhancer

The data of the cumulative amount of drug permeated through matrix patches containing Eucalyptus oil as permeation enhancer is given Figure 3. It was evident that when concentration of eucalyptus oil in formulation was

used at 5% and 10%, the cumulative amount of the drug that permeated was also increased. The study depicts that drug permeated through skin increased from 2060.13 µg/cm^2 to 3563.58 - 4691.86 µg/cm^2 in formulations Z4-E1 and Z4-E2 that was about 2.17 folds increase. Whereas in Formulations Z9-E1 and Z9-E2 showed increase in drug permeation from 2244.96 µg/cm^2 to 3368.27 µg/cm^2 and 4647.58 µg/cm^2, respectively (Figure 6) (Hussain *et al.*, 2012). Presence of oil (olive oil, castor oil eucalyptus oil) with the drug promotes transport of drug across membrane by altering the integrity of skin barrier. Permeation flux was promoted due to marked increase in fluidity of membrane by penetration of oil into the intracellular lipid phase of membrane. (Shams *et al.*, 2010).

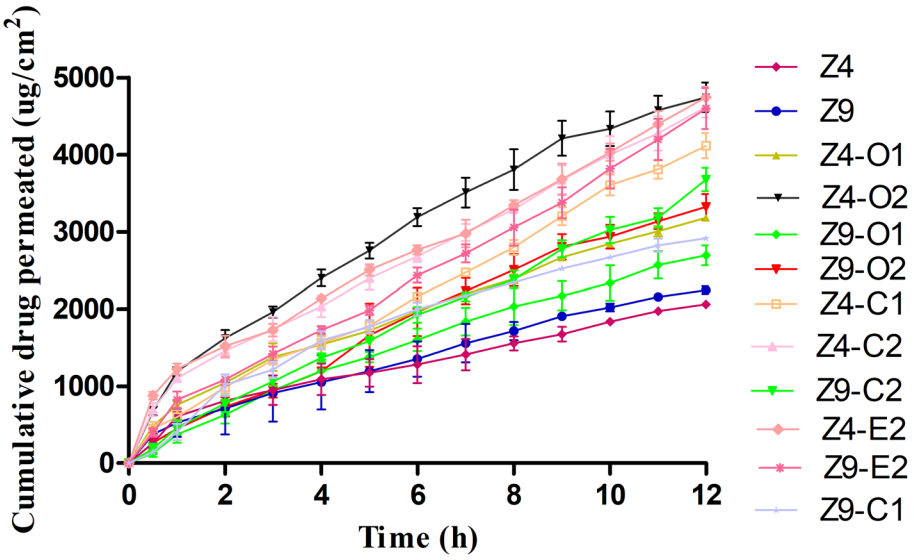

FIGURE 6 - Ex *vivo* cumulative drug release from transdermal patches containing permeation enhancers (n=3).

Comparison of enhancement ratio (ER) of transdermal patches of Metoclopramide containing permeation enhancers

Minimum ER was seen in formulation Z9-O1 containing Eudragit L100 and Methylcellulose with 5% olive oil while maximum ER was seen in Z4-O2 with 10% olive oil (Table V). The presence of hydrophilic compounds along with the highest concentration of enhancers used in skin treatment produces major enhancement (Hussain *et al.*, 2012). In case of olive oil, ER increased in the following order: Z9-O1< Z4-O1< Z9-O2< Z4-O2 with value of 1.26, 1.60, 1.62 and 2.46 respectively. In case of castor oil, the ER increased in the following order: Z9-C1< Z9-C2< Z4-C1< Z4-C2 with value of 1.40, 1.71, 2.17 and 2.27 respectively. In case of eucalyptus oil, the ER increased in the following order: Z9- E1< Z9-E2< Z4-E1< Z4-E2 with value of 1.57, 1.97, 2.97 and 2.37 respectively.

Table V - Slope, flux, permeability coefficient and enhancement ratio (ER) of Metoclopramide matrix patch.

Formulation	Slope	Flux ($\mu g/cm^2hr$)	Permeability coefficient (cm/hr)	Extraction ratio (ER)
Z4	151.17	125.98	0.0151	-
Z9	173.39	144.49	0.0173	-
Z4-O1	241.97	201.64	0.0241	1.60
Z4-O2	372.87	310.72	0.0372	2.46
Z4-C1	328.35	273.62	0.0328	2.17
Z4-C2	343.55	286.29	0.0343	2.27
Z4-E1	298.30	248.59	0.0314	1.97
Z4-E2	358.46	298.71	0.0362	2.37
Z9-O1	219.74	183.11	0.0219	1.26
Z9-O2	280.54	233.78	0.0280	1.62
Z9-C1	241.85	201.54	0.0241	1.40
Z9-C2	293.70	244.75	0.0293	1.71
Z9-E1	273.75	228.13	0.0298	1.57
Z9-E2	343.24	286.03	0.0369	1.97

CONCLUSION

Based on this study, it was concluded that drug release rate increase by the addition of hydrophilic polymer in hydrophobic matrix formulation. The organoleptic evaluation results showed that formulations with hydrophobic polymer content had the highest characteristic of organoleptic properties. Values of the swelling index, percentage weight gain due to swelling, moisture content, moisture uptake and water vapor transmission rate were higher for those formulations that have high concentrations of hydrophilic polymer. SEM analysis revealed that all formulations were smooth in surface. FTIR, XRD and DSC spectra specified the absence of any physical interaction between drug, polymers and excipients. The blend of Eudragit L100, PVP K-30, PEG (45%w/w) and olive oil can be used to enhance the permeation of Metoclopramide from matrix transdermal formulation. The present study can be useful for future bioequivalence and in vivo pharmacokinetics studies for a better conclusion.

REFERENCES

Allen L, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems: Lippincott Williams & Wilkins; 2013.

Allena RT, Yadav HK, Sandina S, Prasad MSC. Preparation and evaluation of transdermal patches of metformin hydrochloride using natural polymer for sustained release. Int J Pharm Pharm Sci. 2012;4(3):297-305.

Ammar H, Ghorab M, El-Nahhas S, Kamel R. Design of a transdermal delivery system for aspirin as an antithrombotic drug. Int J Pharm. 2006;327(1):81-8.

Aktar B, Erdal MS, Sagirli O, Güngör S, Özsoy Y. Optimization of biopolymer based transdermal films of metoclopramide as an alternative delivery approach. Polymers. 2014;6(5):1350-65.

Akram MR, Ahmad M, Abrar A, Sarfraz RM, Mahmood A. Formulation design and development of matrix diffusion controlled transdermal drug delivery of glimepiride. Drug Des Dev Ther. 2018;12:349-64.

Bagyalakshmi J, Vamsikrishna RP, Manavalan R, Ravi TK, Manna PK. Formulation development and in vitro and in vivo

evaluation of membrane-moderated transdermal systems of ampicillin sodium in ethanol: pH 4.7 buffer solvent system. AAPS PharmSciTech. 2007;8(1):E50-E5.

Can AS, Erdal MS, Güngör S, Özsoy Y. Optimization and characterization of chitosan films for transdermal delivery of ondansetron. Molecules. 2013;18(5):5455-71.

Cilurzo F, Minghetti P, Gennari CG, Casiraghi A, Selmin F, Montanari L, et al. Formulation study of a patch containing propranolol by design of experiments. Drug Dev Ind Pharm. 2014;40(1):17-22.

Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-33.

Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67(3):217-23.

Fatima RA, Muhammad HS, Rabia IY, Syed AA, Muhammad SI, Lubna B, et al. Design, development, and optimization of Dexibuprofen micro emulsion based transdermal reservoir patches for controlled drug delivery. J Biomed Res Int. 2017;2017:1-15. doi.org/10.1155/2017/4654958.

Guru S, Biplab DK, Nagarajan K, Sujit D, Kumar Vijaya S, Dinesh V, et al. Effect of various permeation enhancers on propranolol hydrochloride formulated patches. Int J Pharm Pharm Sci. 2010;2(2):21-31.

Garala KC, Shinde AJ, Shah PH. Formulation and in-vitro characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. Int J Pharm Pharm Sci. 2009;1(1):108-20.

Hussain A, Khan GM, Jan SU, Shah SU, Shah K, Akhlaq M, et al. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as enhancer. Pak J Pharm Sci. 2012;25(2):365-9.

Jamakandi V, Mulla J, Vinay B, Shivakumar H. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian J Pharm. 2014;3(1):59-65.

Kumar SR, Jain A, Nayak S. Development and Evaluation of Transdermal patches of Colchicine. Pharm Lett. 2012;4(1):330-43.

Limpongsa E, Umprayn K. Preparation and evaluation of diltiazem hydrochloride diffusion-controlled transdermal delivery system. AAPS PharmSciTech. 2008;9(2):464-70.

Miguel MG. Antioxidant and anti-inflammatory activities of essential oils: a short review. Molecules. 2010;15(12):9252-87.

Mishra S, Kumar G, Kothiyal P. Formulation and evaluation of buccal patches of simvastatin by using different polymers. Pharma Innovation. 2012;1(7):87-92.

Mushtaq M, Fazal N, Niaz A. Formulation and Evaluation of Fast-disintegrating Tablets of Flurbiprofen and Metoclopramide. J Pharm Innovation. 2020;16(11):419-438.

Mutalik S, Udupa N. Formulation development, in vitro and in vivo evaluation of membrane controlled transdermal systems of glibenclamide. J Pharm Pharm Sci. 2005;8(1):26-38.

Nugraha YP, Uekusa H. Suppressed hydration in metoclopramide hydrochloride by salt cocrystallisation. J Cryst Eng Comm. 2018;20(19):2653-62.

Nussinovitch A, Gal A, Padula C, Santi P. Physical characterization of a new skin bioadhesive film. AAPS PharmSciTech. 2008;9(2):458-63.

Padmaja B, Ramakrishna R, Harikishan S, Sunitha T. formulation development and evaluation of clopidogrel bisulfate transdermal patches. Int J Pharm Sci Res. 2018;9(1):250-255.

Patel KN, Patel HK, Patel VA. Formulation and characterization of drug in adhesive transdermal patches of diclofenac acid. Int J Pharm Pharm Sci. 2012;4(1):296-9.

Patel DP, Setty CM, Mistry GN, Patel SL, Patel TJ, Mistry PC, et al. Development and evaluation of ethyl cellulose-based transdermal films of furosemide for improved in vitro skin permeation. AAPS PharmSciTech. 2009;10(2):437-42.

Pichayakorn W, Suksaeree J, Boonme P, Amnuaikit T, Taweepreda W, Ritthidej GC, et al. Nicotine transdermal patches using polymeric natural rubber as the matrix controlling system: Effect of polymer and plasticizer blends. J Membr Sci. 2012;411:81-90.

Prabhu P, Shah S, Gundad S. Formulation development and investigation of domperidone transdermal patches. Int J Pharm Invest. 2011;1(4):240.

Sathali AAH, Mageshkumar L. Studies on the Development of Transdermal Patches of Nisoldipine. J Curr Chem Pharm Sci. 2013;3(2):146-160.

Shabbir M, Ali S, Farooq M, Adnan S, Yousaf M, Idrees A, et al. Formulation factors affecting In Vitro and Ex Vivo permeation of bisoprolol fumarate from a matrix transdermal patch. Adv Poly Tech. 2016;35(3):237-47.

Shankar M. Development and evaluation of aceclofenac transdermal patches using hydrophilic and hydrophobic polymers. J Global Pharm Tech. 2010;2(4):102-109.

Shams MS, Alam MI, Ali A, Sultana Y, Aqil M. Pharmacodynamics of a losartan transdermal system for the treatment of hypertension. Drug Dev Ind Pharm. 2010;36(4):385-92.

Shoaib MH, Tazeen J, Merchant HA, Yousuf RI. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. Pak J Pharm Sci. 2006;19(2):119-24.

Snejdrova E, Dittrich M. Pharmaceutically used plasticizers. Recent advances in plasticizers: InTech; 2012.

Srikanth P, Raja SW. Design and invitro rvaluation of diclofenac-paracetamol dual release transdermal patch. Int J Pharm Ther. 2013;4(2):127-33.

Shivalingam M, Vineela A, Vaishnavi K, Sunanda C, Prince VA, Jyotsna S, et al. Formulation and evaluation of pantaprazole transdermal patches for enhanced therapeutic efficacy. Int J Pharm Biomed Res. 2015;2015:ID 201511.

Siepmann J, Peppas N. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Del Rev. 2012;64:163-74. https://doi.org/10.1016/j.addr.2012.09.028

Williams AC, Barry BW. Terpenes and the lipid–protein–partitioning theory of skin penetration enhancement. Pharm Res. 1991;8(1):17-24.

Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on in vitro and in vivo characteristics. AAPS PharmSciTech. 2007;8(1):E13-E20.

Received for publication on 04th March 2021
Accepted for publication on 19th October 2021