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ARTICLE

Effect of Isopropyl Myristate and Oleic Acid as the Penetration Enhancer on Meloxicam Transdermal Patch: Characteristics and *In-Vitro* Diffusion

Nining Nining [1], Anisa Amalia [1], Novrina Maharani [1], and Siti Robiatul Adawiyah[1]

[1] Department of Pharmaceutical Technology, Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. Hamka, Jakarta 13460, Indonesia

* Correspondence author: anisa.amalia@uhamka.ac.id e-mail (Anisa Amalia); Scopus ID 57193826772

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ABSTRACT

The transdermal drug delivery system (TDDS) delivers meloxicam (MX) that can reduce the adverse effects of orally administered MX with a chemical enhancer. Chemical penetration enhancers interact with skin components to enhance drug molecule flux. This study examines how isopropyl myristate (IPM) and oleic acid (OA), as penetration enhancers, affect the characteristics of transdermal patches and MX diffusion in-vitro. Patches with IPM (1-10% b/b) or OA (5-20% b/b) were prepared, and their characteristics were compared with patches without enhancers. The patches' physical appearance, weight variance, thickness, folding endurance, and pH were all evaluated. For drug-carrier compatibility in the solid dispersion, FTIR investigations were carried out; the Franz diffusion cell was utilized to examine in vitro diffusion characteristics. Patch characteristics obtained were weight variance of 482±2.78 to 541±1.49 mg; thickness 0.85±0.02 to 0.94±0.01 mm; drug content 99.1±1.2 to 99.7±0.6%, folding endurance >300, pH 5.22±0.02 to 5.45±0.02. The release from IPM-MX and OA-MX patches showed the highest flux, at 95.57±0.50% and 96.53±0.26%, respectively. Higuchi release profiles were revealed in all formulations (F1–F7). The data suggest that OA can be applied as a penetration enhancer for transdermal administration of MX through matrix-type patches. The most effective enhancer was OA, which had an excellent diffusion flux of 90.06±0.24 g/cm^{2}h and an enhancement ratio of 1.08.

Keywords: Controlled release formulation; Kinetics; Chemical penetration enhancer; Anti-Inflammatory agents; Drug delivery systems.

1. Introduction

Meloxicam (MX), an oxicam derivative, is a selective inhibitor of cyclooxygenase-2 (COX-2) and a nonsteroidal anti-inflammatory drug (NSAID) [1]. The MX dosage can be delivered at only 7.5 mg daily in the long-term treatment of ankylosing spondylitis and rheumatoid arthritis in the elderly [2]. However, MX's gastrointestinal adverse drug reaction profile was reported to be similar to other NSAIDs [1]. The molecular weight of MX, 4-hydroxy-2 methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine3-carboxamide-1,1-dioxide, is

351.4 [3], coefficient partition (log P) 3.43 [4], pKa_1 = 1.1 (hydroxyl group) and pKa_2 = 4.2 (thiazole group), and a half-life of 15-20 hours [2]–[6]. MX, like other NSAIDs, is practically insoluble in water, and solubility in solutions of pH 1.2 or 4.0 is low, ca. 0.6 g/mL [3], [5], [6]. Solid dispersions formation can increase the solubility of MX and its bioavailability [7], [8].

A transdermal drug delivery system (TDDS) delivers MX that can reduce the adverse effects of orally administered MX. Skin delivery of NSAIDs effectively avoids GI adverse effects, improves patient compliance, and remains safe [9]–[12]. Because of its minimal tissue toxicity, MX can be administered to the skin and mucosa [13]. Other advantages of TDDS are to avoid hepatic metabolism, release drugs for a long time, and provide convenience in drug administration and drug discontinuation in the event of toxicity [14], [15]. However, drug delivery is limited because drug molecules must pass through the stratum corneum barrier sequentially to penetrate deeper layers of the skin [16]. Chemical penetration enhancers interact with skin components to enhance drug molecule flux [17].

The advantages of using chemical penetration enhancers over physical penetration enhancers include design flexibility, simplicity of application, patient compliance, the ability to self-administer and extend medication release through patches, and their inclusion into low-cost and accessible formulas [18]. Esters and fatty acid groups were utilized as chemical penetration enhancers in this research. Isopropyl myristate (IPM), an ester penetration enhancer, is the most common and widely used in commercial products [19]. The mechanism of action is to integrate the lipid layer to increase the fluidity of the skin, soften the rigid skin structure, and increase the diffusion coefficient and drug permeation [18], [20]. Oleic acid (OA) is a fatty acid group that can increase drug penetration by producing a permeable defect in SC lipids due to oleic acid's cis double bond. That enables it to deliquesce itself rather than disperse uniformly in natural skin fats [18], [19], [21]–[23].

In this study, we developed the MX transdermal patch for better anti-inflammatory management therapy. Furthermore, this study assists in determining the penetration-enhancing effect of the patch matrix on the in vitro drug release. A patch matrix composed of hydrophilic and hydrophobic polymers was used to create a system to control and maintain drug release [24], [25].

Experimental

2.1. Materials

MX was purchased from Apex Healthcare Ltd. (India); IPM (BASF, Germany); ethyl cellulose/ EC (Asha Cellulose (I) PVT. LTD., India); HPMC 60SH-10000 (Shin-Etsu, Japan); glycerine (Wilmar Nabati, Indonesia); PEG 6000 (Pan Asia Chemical, Taiwan); and OA (Avantor). All of the other substances utilized were from the pharmaceutical grade.

2.2. Solid dispersion (SD) preparation

PEG 6000 was melted at 70 ± 5˚C and mixed with MX (ratio 8:1). The mixture was rapidly cooled in an ice bath. Then, the solid dispersion was stored for 24 hours in a desiccator at room temperature and sieved through mesh 80 [26].

2.3. SD characterization

SD characterization includes FTIR and MX contents. The FTIR (Agilent Technologies Carry 630) test was carried out by inserting SD into the sample holder and then compressing it. The spectrum was analyzed in the 4000-650 cm^{-1} wavenumber range [27]. MX contents were determined spectrophotometrically following Jafar et al. (2010) method with modifications. MX and SD were carefully weighed and mixed in pH 7.4 phosphate buffer, followed by 5 min of sonication until dissolved. MX contents were measured at a wavelength of 362 nm using UV-Vis spectrophotometry (Shimadzu UV-1900) [7].

2.4. Preparation of Transdermal Patch

Meloxicam transdermal patch formula can be seen in Table 1. Transdermal patches were prepared by solvent evaporation technique where EC dissolves with EtOH, and HPMC dissolves with MeOH. The two polymer solutions were mixed and stirred until homogeneous. Glycerine and enhancer were added and stirred into the polymer mixture. Lastly, SDMX was added and stirred until homogeneous. Afterward, the mixture was poured into the mold provided and dried at room temperature for two days. After drying, the patches were cut into 10 cm^2 squares, covered in aluminum foil, and kept in a desiccator [28].

Table 1: MX Transdermal Patch Formula

Materials	Formula (% b/b)						
	1	2	3	4	5	6	7
SD*	13,75	13,75	13,75	13,75	13,75	13,75	13,75
EC	27	27	27	27	27	27	27
HPMC	12	12	12	12	12	12	12
IPM	-	1	5	10	-	-	-
OA	-	-	-	-	5	10	20
Glycerine	28	28	28	28	28	28	28
Solvents** ad	100	100	100	100	100	100	100

* Equivalent to 7.5 mg of meloxicam per patch
** MeOH: EtOH ratio of 1: 2

2.5. Transdermal Patch Characterization

2.5.1. Visual observation and pH testing

Visual observations include shape, odor, surface conditions, and color. The pH test was conducted by soaking a patch with 10 mL of distilled water for 2-h. Three times measurements were taken with a calibrated pH meter (Hanna) [29].

2.5.2. Determination of drug content

The determination followed the method of Mahajan et al. (2018) with modifications. Patch size 10 cm^2 was dissolved in EtOH and stirred with a magnetic stirrer for 60 min. The solution was filtered into a 50 mL volumetric flask with EtOH as solvent. Next, the solution was pipetted 1 mL and adjusted into a 10 mL measuring flask. Furthermore, a UV-Vis spectrophotometer (Shimadzu UV-1900) was used to measure absorbance at a wavelength of 363 nm [28].

2.5.3. Patch thickness and weight uniformity

The thickness test was carried out in triplicate by measuring a patch at three points using a screw micrometer (Tricle Brand). The weight uniformity test was carried out in triplicate by weighing ten randomly selected patches. The weighing process was done with an analytical balance (Ohaus). The measurement data has calculated the average and standard deviation [28].

2.5.4. Folding endurance

Folding endurance testing was carried out by repeatedly folding the patch at the same spot until damage occurred. The procedure was repeated three times, and the number of folds completed was recorded as the folding endurance value [28].

2.6. Drug Release Studies

2.6.1. Membrane impregnation time optimization

Synthetic nitrocellulose membrane (MF-Millipore Merck, 0.22 m) was impregnated with Spangler's solution. The solution was prepared by melting a mixture of 5% stearic acid, 5% cholesterol, 5% squalene, 10% palmitic acid, 10% liquid paraffin, 15% oleic acid, 15% coconut oils, 15% white vaseline, and 20% olive oil. The membrane was immersed in the

solution for 10, 30, 45, and 60 min, and then the percentage increase in membrane weight after impregnation was calculated. The time the membrane reaches a constant weight was set as the optimum time [30].

2.6.2. In-vitro diffusion studies

This test used a Franz diffusion cell (PermeGear, Inc. Hellertown, AP, USA). A synthetic membrane divided the cylinder into two compartments, the donor compartment and the receptor compartment. The receptor compartment was kept at 37 ± 0.5°C. Diffusion media in a 15 mL phosphate buffer pH 7.4 solution stirred with a magnetic stirrer. A sample port was located next to the receptor compartment [31]. Diffusion was performed for 8-h, and 1 mL of receptor solution was taken at 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480-min intervals for spectrophotometric measurement. Following the sampling, the same volume of receptor solution was introduced to the receptor compartment. The concentration of substances released was determined by sample analysis [32].

2.6.3. Drug release kinetics

The kinetic model was developed after calculating the MX release mechanism from the patch. The acquired concentration was placed into the equation to calculate the value rate and the diffusion model. The regression line equation for every diffusion rate kinetics model was adopted by determining the linearity connection of the data. The diffusion rate kinetics models involved:

Zero-order kinetics showed a zero-order linearity relationship between the time and diffused MX concentration data.

$$W = K_1 t \ldots (a)$$

where W is drug release at t time, and K_1 is a rate constant at zero-order kinetics release.

First-order kinetics: first-order linearity relationship is shown between time and *ln* of diffused MX concentration data.

$$\ln (100 - W) = \ln 100 - K_2 t \ldots (b)$$

Higuchi kinetics: Higuchi linearity relationship is presented between the diffused MX concentration data on the square root of time.

$$W = K_3 t^{1/2} \ldots (c)$$

where W is drug release at t time, and K_3 is a rate constant at Higuchi dissolution

Korsmeyer-Peppas kinetics: linearity relationship is presented between *ln* data of diffused MX concentration on *ln* of time.

$$M_t/M_\infty = K_4 t^n \ldots (d)$$

where M_t/M represents the function of the released drug, while K_4 represents the kinetic constant that represents the structural and geometrical properties of the device, and n represents the drug release, as diffusion exponent. This model has been used to illustrate various drug release mechanisms or n values. When $n = 0.45$, the drug release mechanism is Fickian diffusion, it is non-Fickian if the value of n is higher than 0.45. When the n number equals 0.89, the conventional zero-order release or case II transport is used; when the n value is higher than 0.89, the super case II transport is used.

The determination of diffusion rate kinetics can be seen from the value of r obtained from the linear regression equation. The release kinetics is based on the r-value, which is closest to 1, and the value of the diffusion rate is the slope value (b) in the linear regression equation [25], [33], [34].

3. Results and Discussion

3.1. Meloxicam Solid Dispersion Preparation

Solid dispersions were prepared by fusing MX and PEG 6000. Hydrophilic carriers in solid dispersions have been widely reported to increase the solubility and dissolution of MX [26], [35]; PEG 6000 is an amorphous polymer carrier that produces a second-class solid

dispersion type [36]. The composition of the solid dispersion of MX-PEG 6000 with a ratio of 1:8 is known to have no chemical interactions. It can increase the solubility of MX and good release profile [26]. The melting method was carried out by directly heating the physical mixture between the drug and carrier until it melts at a temperature above its melting point. The advantage of this method is a simple and economical process [36]. The solid dispersion was in the form of yellow powder with a yield of 81.12%. MX content was determined spectrophotometrically with a phosphate buffer with pH 7.4 and a maximum wavelength of 362 nm. The linear regression equation for the calibration curve obtained is y=0.0207x+0.0106, with a value of r=0.9993. The MX content in SD was 10.91 ± 0.08%.

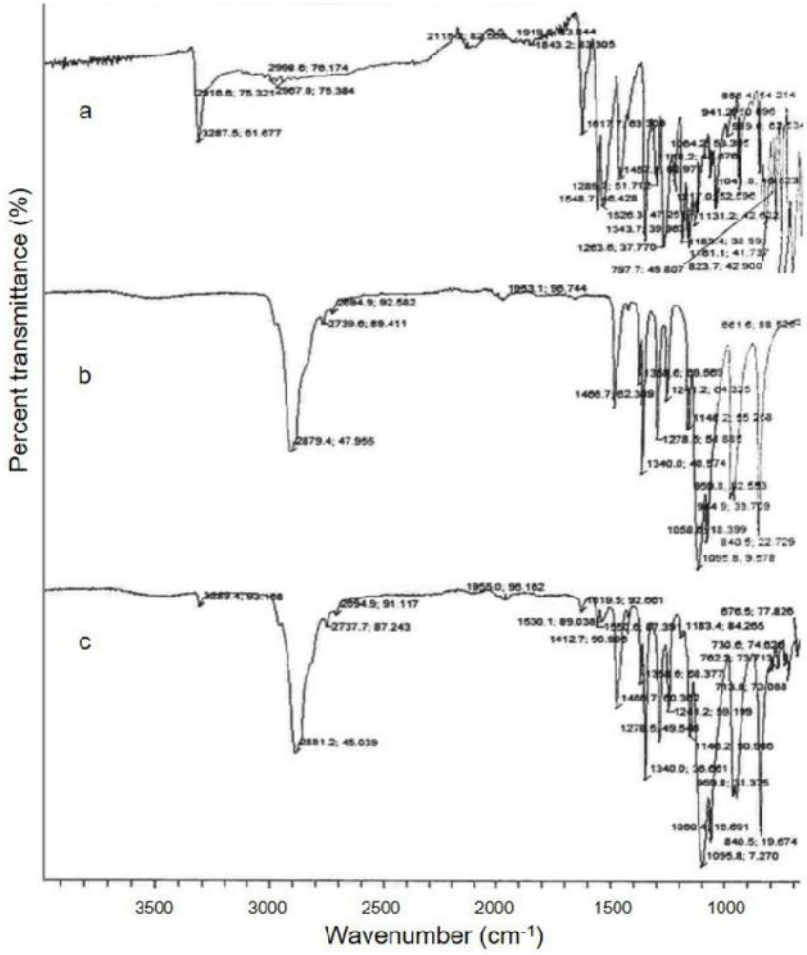

Figure 1: FTIR test results (a) MX (b) PEG 6000 (c) SD

Figure 1 presents the FTIR spectra of solid dispersions and their single compounds. Spectrum 1c shows that the MX crystals appear trapped in the carrier particles. The functional group peaks observed in 1c are similar to 1b with the addition of several peaks whose intensity decreased, namely N-H at 3289.4 cm^{-1}; C=O at 1619.5 cm^{-1}; N at 1530.1 cm^{-1} and 1550.6 cm^{-1}; and S=O at 1183 cm^{-1}. This observation indicates the possibility of hydrogen bonding through the N-H, C=O, C=N, and S=O groups in the MX and PEG 6000 hydroxyl

groups reported in other studies [27]. Several fingerprint peaks in 762.2 to 676.5 cm^{-1} with decreased intensity compared to spectrum 1a with unchanged peak characteristics, suggesting that even though the drug molecule and polymer form hydrogen bonds, the overall group on the drug molecule does not change. Moreover, other studies reported that there is no interaction between carrier and drug where no overlap or merge of spectral peaks was identified [26], [35].

3.2. Transdermal Patch Characteristics

Organoleptically, the patch is rectangular and odorless with a dry, uncracked, flat surface condition with a yellow color scattered throughout the surface (Figure 2). The yellow color appears from the MX content and indicates the homogeneity of the MX dispersion in the patch.

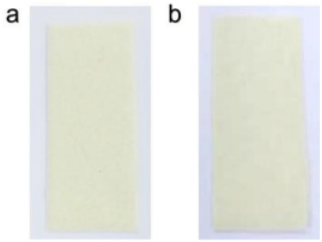

Figure 2: Visual observation (a) IPM-MX patch and (b) OA-MX patch

The MX patches characterize, and the outcomes are presented in Table 2. The mean weights of F1-7 ranged from 482±2.78 mg to 541±1.49 mg, and the percent drug content ranged from 99.1±1.2 to 99.7±0.6%. The results of the various formula's specific weights are similar to drug content with a 90-110% specific range. The similarity in weight and content uniformity indicates that the preparation method is efficient in producing patches with low variations in drug content and can be utilized to generate an MX matrix-type patch commercially.

Table 2: MX matrix-type patch characterization

Formula	Mean ± SD (n=3)				
	Drug content (%)	Thickness (mm)	Weight (mg)	Folding endurance	pH
1	99.5±0.8	0.85±0.02	482±2.78	>300	5.45±0.02
2	99.6±0.6	0.88±0.01	488±4.48	>300	5.38±0.01
3	99.5±0.2	0.90±0.02	504±3.54	>300	5.33±0.02
4	99.6±0.2	0.92±0.02	521±2.58	>300	5.29±0.02
5	99.4±0.2	0.86±0.02	508±2.28	>300	5.41±0.02
6	99.1±1.2	0.90±0.03	523±2.85	>300	5.31±0.01
7	99.7±0.6	0.94±0.01	541±1.49	>300	5.22±0.02

Patch thickness ranged from 0.85±0.02 mm to 0.94±0.01 mm. The increase in patch weight and thickness (F2-F4 for an IPM-MX patch; F5-F7 for an OA-MX patch) could be seen with increasing enhancer concentration. It may be because the EC used as the polymer matrix has low water permeability properties that prevent the evaporation of water and other volatile compounds, thereby retaining significant mass [28]. In determining the concentration of MX in the patch, the measurement of the MX maximum absorption in 96% ethanol solvent was carried out at a wavelength of 363 nm, the same as in other studies [37]. The standard curve linear regression equation obtained is y=0.045x-0.0008 with a value of r=0.9998.

As a mechanical evaluation, folding endurance was performed manually to determine patch plasticity. The folding endurance value is calculated by the number of times the film can be folded in the exact location without breaking. The results showed that the patch had a folding endurance value of more than 300 folds, with the patch being in a good condition, not

damaged, and not cracked. Thus, using glycerine as a plasticizer provides good flexibility to the patch.

Patch pH ranged from 5.22±0.02 to 5.45±0.02. The patch pH value was compatible with the skin pH value of about 5.4-6.9 and it is appropriate for topically administered [38]. Furthermore, considering that MX has a $pKa_1 = 1.1$ and $pKa_2 = 4.2$ [2], [5], the drug is not ionized at this pH, making it optimal for penetration into the stratum corneum [38]. Table 2 shows the decrease in pH from F2-F4 and F5-F7 when the enhancer concentration increased; F4 and F7, Through the highest concentration of enhancers, gave the lowest pH values. It was because of acidic IPM and OA.

3.3. MX Release Diffusion Rate

The *in-vitro* drug that released assays from topical preparations was carried out to characterize the final product's performance as a quality assessment method and justify post-approval alterations and scale-up [31], [39]. Vertical diffusion cells are an in vitro test model for predicting bioavailability and bioequivalence by measuring drug release from semisolid and transdermal dosage forms [9,22–24]. This release test can use synthetic membranes, such as nitrocellulose. Its membrane is less hydrophobic [31], so it needs immersion with a spangler solution. The membrane impregnation time optimizes by immersing the membrane in a spangler solution—optimum time selection based on the membrane's weight that has the smallest weight increase [30]. The optimum result of membrane impregnation is at 10 min.

A diffusion test was performed using a Franz diffusion cell with a nitrocellulose membrane with a pore diameter of 0.22 m impregnated with Spangler's solution. The receptor compartment is filled with a pII 7.4 phosphate buffer solution, which serves as a substitute for simulating the pH conditions of the body's biological fluids. The cumulative amount of diffused MX increased steadily and gradually over time (Figure 3).

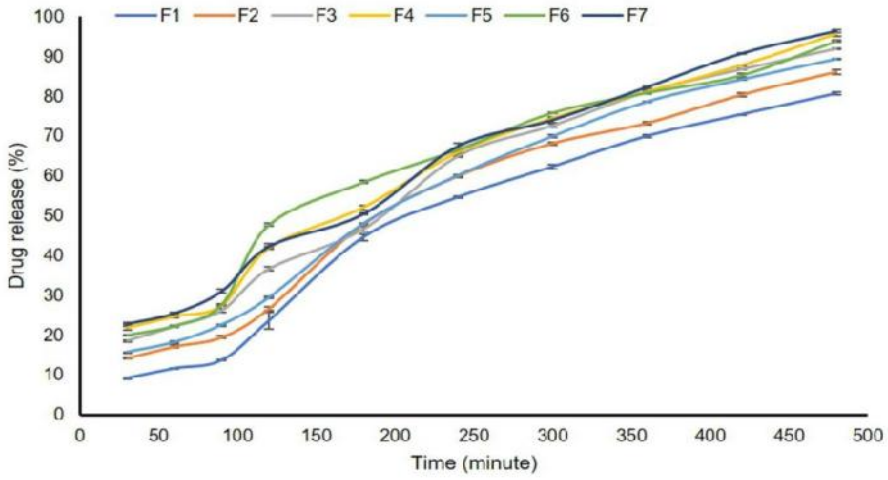

Figure 3: MX release profile in vitro from transdermal patches

In the presence of IPM (F2-F4) and OA (F5-F7) in the patch, when compared to the control formula (F1), MX diffusion was significantly increased. When IPM and OA were added, a synergistic effect of MX diffusion from the patch through the membrane was observed. Various investigators have described the mechanism of drug release from the polymer matrix [29,40,41]. Incorporating EC and HPMC polymers in the patch matrix is expected to provide controlled drug release by EC hydrophobicity.

The cumulative MX diffused from the IPM-MX patch at 8-h was 86.12±0.65% at F2, 92.03±0.08% at F3, and 95.57±0.50% at F4, respectively. Meanwhile, the cumulative amount of MX diffused from the OA-MX patch at 8-h was 89.26±0.04% at F5, 93.48±0.17% at F6, and 96.53±0.26% at F7, respectively. The ranking order of the effects of increasing MX diffusion from the patch is F7 > F4 > F6 > F3 > F5 > F2 > F1. F7, containing the highest OA, showed maximum diffusion at 8-h with the most considerable flux of 90.06±0.24 g/cm^{2}h with an increased ratio of 1.08. As a penetration enhancer, OA can be an effective method for lowering the skin's barrier function. Many NSAIDs are shown to enhance percutaneous absorption by adding OA [22]. OA interacts with stratum corneum lipids and alters their structure, increasing fluidity as a reaction of flux [19], [22]. The reaction of OA with lipids in stratum corneum reduces the lipid glass transition and promotes drug penetration; it also lowers the lipid viscosity of the superficial layer [42]. Touitou et al. investigated the morphology of epidermal Langerhans cells in response to several penetration enhancers. They concluded that OA significantly impacts skin morphology, increasing penetration throughout the skin [43].

Table 3: Model fitting of MX patch release profile

Mathematical models	F1	F2	F3	F4	F5	F6	F7
Zero-order							
r^2	0.9786	0.9802	0.9868	0.9873	0.9861	0.971	0.9604
k_o (h^{-1})	0.0008	0.0008	0.0008	0.0008	0.0032	0.0008	0.0008
First order							
r^2	0.9233	0.9247	0.9529	0.9506	0.9492	0.9717	0.9584
k_1 (h^{-1})	0.0049	0.0042	0.0036	0.0034	0.0004	0.0033	0.0033
Higuchi model							
r^2	0.9878	0.9866	0.9910	0.9919	0.9899	0.9901	0.9924
k_H ($h^{-1/2}$)	0.0230	0.0232	0.0233	0.0236	0.0030	0.0231	0.0239
Korsmeyer-Peppas							
r^2	0.9773	0.9766	0.9855	0.9804	0.9819	0.9778	0.9843
K_{kp} (h^{-n})	0.0016	0.0042	0.0080	0.0113	0.7182	0.6230	0.5779

The controlled system's drug release method is either entirely erosion-controlled or diffusion-controlled. In many circumstances, both methods can lead to release. Table 3 summarizes the findings of the kinetic analysis of the released drug for first order, zero order, the Higuchi model, and the Korsmeyer-Peppas model. The correlation coefficients for each model were generated and compared to the data release for each formula. The kinetic research findings imply the mechanism of drug release from the developed transdermal patch. All formulas show the Higuchi release profile (correlation coefficient R=0.9866-0.9924). It indicates that drug release from the matrix is driven by the square root of time and Fickian diffusion. Time influences drug release indicating that the longer the period, the slower the drug is released. It was due to the longer drug diffusion distance. The Higuchi model describes the drug solubility of several pharmaceutical preparations with a modified release, such as transdermal drug delivery systems and water-soluble matrix tablets [44], [45]. The Higuchi rate constant (k_H) increases with the incorporation of IPM and OA.

4. Conclusions

Based on the results of the study, it can be concluded that the use of IPM and OA as penetration enhancers is able to produce transdermal patches with physical properties that meet the requirements and increase the percent diffused and diffusion rate values of MX. The

data suggest that OA can be applied as a penetration enhancer for transdermal administration of MX through matrix-type patches. The most effective enhancer was OA, which had the most excellent diffusion flux of 90.06±0.24 g/cm^{2}h and an enhancement ratio of 1.08.

5. Conflicts of Interest

There are no declared conflicts.

6. Acknowledgments

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