Original article

Design of Transdermal Delivery Patches of Diclofenac Sodium Using Different Concentrations of Hydroxypropyl Methylcellulose and Evaluation on the Physicochemical and Dissolution Profile of the Patches

*Wai Leong Tan, Lee Huang Chia

Faculty of Pharmacy SEGi University, Kota Damansara, Malaysia.

Abstract

Background: Long term use of oral diclofenac sodium is associated with higher risk of adverse effects. Diclofenac sodium which is formulated in transdermal drug delivery system (TDDS) shows a lower rate of non-steroidal anti-inflammatory drugs (NSAIDs) associated adverse effects and at the same time providing sufficient pain relief. **Aim:** The aim of this study was to determine the effect of different concentrations of hydroxypropyl methylcellulose (HPMC) on the physicochemical properties and dissolution profile of diclofenac sodium transdermal patches. **Materials and Methods**: Different formulation of diclofenac sodium transdermal patches had been formulated using the solvent evaporation method. Each of the formulation was evaluated based on the parameters of moisture content, flatness, thickness and folding endurance. A paddle type of dissolution tester was used to investigate the in vitro drug release profile of formulation F1, F3, and F5 of the diclofenac sodium transdermal patches. One-way ANOVA test with post hoc analysis was used to analyse the moisture content, thickness, folding endurance, and dissolution tests. **Results:** The results of the physicochemical tests showed that increase in concentrations of HPMC would increase the moisture content and thickness of the diclofenac sodium transdermal patch. On the other hand, other physicochemical properties such as flatness and folding endurance of the diclofenac sodium transdermal patch were not affected by change in the concentrations of HPMC. Formulations F1, F3 and F5 showed optimum results because these formulations possesses suitable physicochemical characteristics, including moisture content, flatness and folding endurance. The in vitro drug release study revealed that increase in the concentrations of HPMC would increase the time taken for the drug to diffuse out from the polymer matrix of transdermal patch. **Conclusion:** This study showed that change in the concentrations of HPMC would affect the physicochemical properties such

Keywords: Transdermal, Patch, Diclofenac, Hydroxypropyl Methylcellulose, HPMC

Corresponding author:

Tan Wai Leong

Faculty of Pharmacy, SEGi University, Kota Damansara, 47810, Petaling Jaya, Selangor, Malaysia

Email: twleong0605@gmail.com

Introduction

Pain is an unpleasant feeling that causes negative effects in several areas of a person's life, including emotion, thought, normal daily activities and comfort[1]. Nowadays, there is an increase in the popularity of painkiller, such as non-steroidal anti-inflammatory drugs (NSAIDs) secondary to the increasing prevalence of work-related musculoskeletal pain[2]. Oral formulation of NSAIDs such as diclofenac sodium tablet has been regularly prescribed and dispensed to treat mild to moderate musculoskeletal pain and it is proved to be effective in managing such disorder. However, long term use of oral diclofenac sodium is associated with higher risk of adverse effects such as cardiovascular disease, gastrointestinal ulceration and renal dysfunction[3–5]. Hence, topical formulation of diclofenac sodium has been introduced to minimise the adverse effects of the oral diclofenac sodium by maximising the local exposure and decreasing the systemic exposure of diclofenac sodium[6].

Hydroxypropyl methylcellulose (HPMC) is a novel hydrophilic and swellable polymer that is commonly used in TDDS to regulate the drug release kinetics. HPMC is a film forming polymer that possesses few properties such as it acts as a surface active agent, which is capable of adsorbing water and provide lubricity, easy dispersion and soothing feel during its application on the skin. HPMC rarely shows any significant interaction with other excipients or drugs when they are mixed together in the formulation. Moreover, HPMC is also able to produce a uniform film which is light and non greasy[7].

Few studies had been carried out by other researchers to study the formulation of diclofenac transdermal patches. Out of these studies, different types of polymers, including HPMC, had been incorporated together with the diclofenac transdermal patch and all of the polymers showed good compatibility with the drug[8–10]. However, the range of concentrations of HPMC which had been studied by them were narrow, which typically ranged from 1% w/v to 3% w/v. This may restrict one to determine the most suitable concentration of HPMC for the formulation of diclofenac transdermal patch. Hence this research was focused on investigating the effect of different concentrations of HPMC (ranged from 1% to 6% w/v) on the physicochemical properties and dissolution profile of diclofenac transdermal patches.

MATERIALS AND METHOD

Materials and equipment's

List of chemicals

Hydroxypropyl methylcellulose, M.N. 86,000; viscosity 4,000 cP (2% solution), ACROS Organics™, Diclofenac sodium, 98%, ACROS Organics™, and Methanol, Certified AR for analysis that were purchased from Fisher Scientific (Malaysia). 12-Propylene Glycol C.P that was purchased from R&M Chemicals (Malaysia).

List of equipment's

DU ®730 UV-Vis Spectrophotometer (Beckman Coulter), TDT-080L Dissolution Tester (Electrolab), AL204 Analytical Balance (Mettler Toledo), Spectrum 100 FTIR Spectrophotometer (Perkin Elmer), Lambda 25 UV/VIS Spectrophotometer (Perkin Elmer), and Fisherbrand™ Isotemp™ Basic Stirring Hotplate: Model 11-102-505H (Fisher Scientific).

Preparation of transdermal patches

The diclofenac sodium transdermal patch was prepared using solvent casting method that was adapted from the study by Singh and Bali[11]. In brief, specific amount of HPMC powder, propylene glycol and diclofenac sodium powder were dissolved in methanol and mixed homogeneously with magnetic stirrer. 10 mL of the mixture was withdrawn with graduated pipette and transferred into a silicone mould with 7.8 cm length and 5.3 cm width. The silicone mould was placed horizontally on a flat surface and the solution was allowed to dry at the room temperature of 27 $\pm$ 1.5 °C and relative humidity of 65 $\pm$ 2%

for 24 hours. After 24 hours, the transdermal patch was taken out from the mould and cut into smaller size of patches, with length of 4 cm and width of 2 cm. These transdermal patches were wrapped with aluminium foil and stored properly before proceeding to evaluation studies. The above steps were repeated to fabricate the formulations F2, F3, F4, F5, and F6 where each of the formulation contained different concentration of HPMC. The amount of materials used in each formulation was shown in the Table 1.

Table 1: **Formulation of diclofenac sodium transdermal patch**

Formulation	HPMC (% w/v)	Propylene glycol (% w/w)	Diclofenac sodium (mg)	Methanol (mL)
F1	1	30	250	50
F2	2	30	250	50
F3	3	30	250	50
F4	4	30	250	50
F5	5	30	250	50
F6	6	30	250	50

Evaluation of transdermal patch

Physical appearance

All the formulated patches were visually inspected for smoothness, clarity, and colour.

Percentage moisture content

The evaluation study on the moisture content of transdermal patch was based on the method reported by Ubaidulla et al, .[12] The initial weight of a transdermal patch was weighed using an analytical balance and the result was recorded as m_1. Then, the transdermal patch was placed into a desiccator containing active silica gel beads for 24 hours. After 24 hours, the weight of the transdermal patch was measured again using the same analytical balance and the result was recorded as m_2. The moisture content of a transdermal patch was calculated using the formula:

$$\%\ Moisture\ Content = \frac{m_1 - m_2}{m_1} x\ 100\%$$

Where m_1= Initial weight of the patch (g)

m_2= Final weight of the patch (g)

Flatness

The initial length of a transdermal patch was measured and the reading was recorded as l_1. After this, the patch was cut longitudinally into three strips; where one strip from the centre and the remaining two from the side of the patch. The length of the cut strips were measured again and the reading were recorded as l_2 [13]. The following formula was used to calculate the flatness of a diclofenac sodium transdermal patch:

$$\% Constriction = \frac{l_1 - l_2}{l_1} x\ 100\%$$

$$\% Flatness = 100\% - \% Constriction$$

Where l_1= Initial length of the strips (cm)

l_2= Final length of the strips (cm)

Thickness

The thickness of a transdermal patch was measured at three different locations with a micrometer screw gauge, and the mean thickness was calculated for each of the patch[14].

Folding endurance

The folding endurance of a patch was determined by continuously folding at the centre of the patch until it was broken or a crack was shown. The total folding count right before the patch was broke or showed any crack was indicated as folding endurance value[12].

Compatibility study

The compatibility of diclofenac sodium with other excipients was determined through the Fourier Transform Infrared (FTIR) spectroscopic study. Samples of pure diclofenac sodium powder, propylene glycol, HPMC powder, methanol and the mixture of diclofenac sodium, propylene glycol, HPMC and

methanol were prepared and analysed through FTIR spectrophotometer. The infrared spectrum of each of the samples were recorded and compared with each other.

***In vitro* drug release**

Phosphate buffer of pH 7.4 was used as dissolution medium during the dissolution process. Paddle type of dissolution tester was used with each dissolution vessel was filled up with 500 mL of phosphate buffer. The dissolution tester was set at temperature of 32 ± 0.5 °C and rotation speed of 50 rpm[15]. A stainless steel woven wire mesh was used as a sinker to hold the transdermal patch and prevented it from floating during the dissolution process.

The transdermal patch was assembled between the wire mesh and placed at the bottom of the vessels and centred using a glass rod. During the dissolution process, 5 mL of sample was withdrawn at the interval of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 40, 50, 60, 75, 90, 105, 120, 150, and 180 minutes. The drug contents in the withdrawn samples were analysed using ultraviolet-visible (UV-visible) spectrophotometer at maximum wavelength of 277 nm (Figure 1). The *in vitro* drug release study had been done on the formulation F1, F3, and F5. However, formulations F2, F3 and F6 were omitted from drug release assay due to large standard deviation in the physicochemical characteristics, including moisture content, folding endurance and thickness.

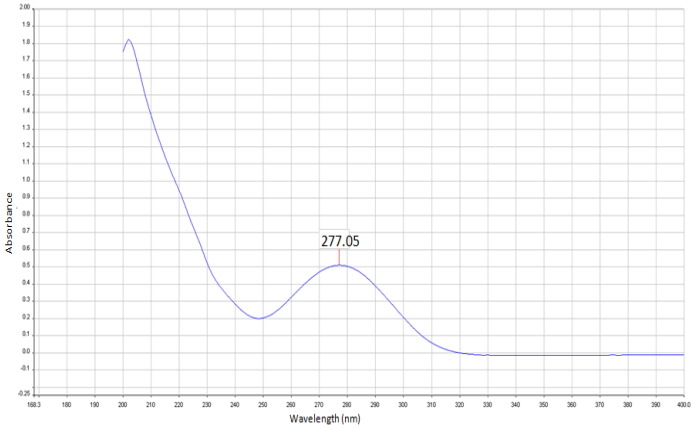


Figure 1: The diclofenac sodium shows the maximum absorbance at wavelength of 277 nm

Statistical analysis

IBM SPSS Statistics version 22 was used to carry out statistical analysis for the evaluation tests in this study. One-way ANOVA test with post hoc analysis was used to analyse the moisture content, thickness, folding endurance, and *in vitro* drug release tests.

RESULTS

Physicochemical properties

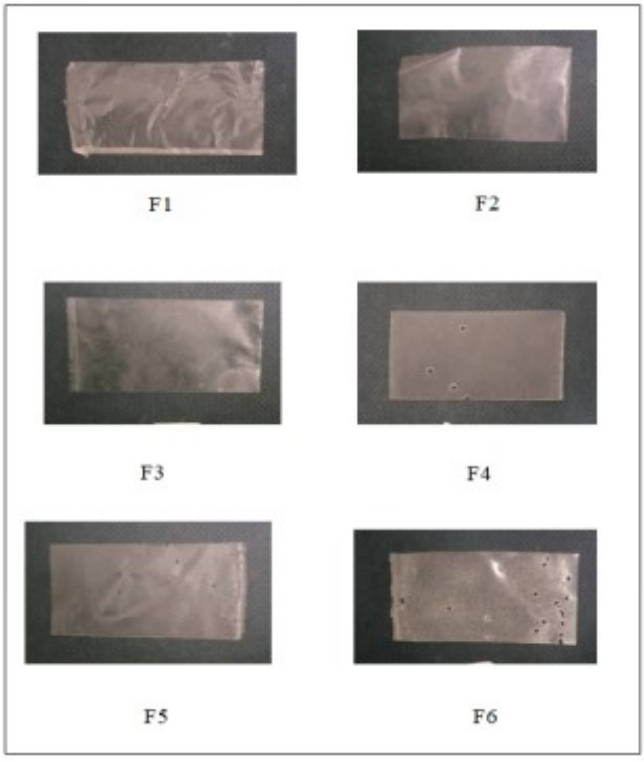


Figure 2: Formulation of diclofenac sodium transdermal patches

Table 2: Physicochemical properties of diclofenac sodium transdermal patches with different concentration of HPMC *Sample size = 3

Formulation	F1	F2	F3	F4	F5	F6
Colour	Colourless	Colourless	Colourless	Colourless	Colourless	Colourless
Clarity	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
Smoothness	Smooth	Smooth	Smooth	Smooth	Smooth	Not smooth
Moisture Content (%)*	2.000 ± 0.630	2.685 ± 0.840	3.505 ± 1.432	3.766 ± 2.196	3.954 ± 0.466	4.577 ± 0.784
Flatness (%)*	100	100	100	100	100	100
Folding Endurance*	150.333 ± 5.508	259.333 ± 29.006	168.667 ± 58.526	370.000 ± 152.355	151.333 ± 37.647	72.000 ± 15.716
Thickness (cm)*	0.0633 ± 0.0173	0.0656 ± 0.0201	0.1167 ± 0.0224	0.1511 ± 0.0196	0.1622 ± 0.0211	0.2311 ± 0.0220

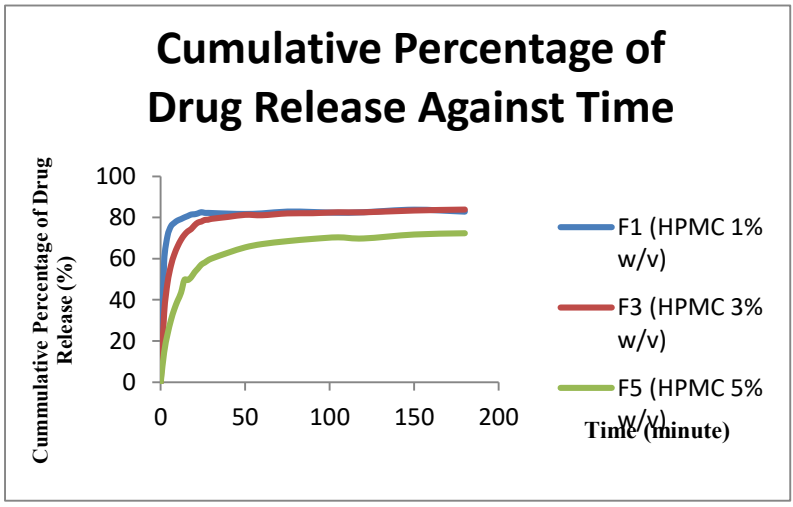
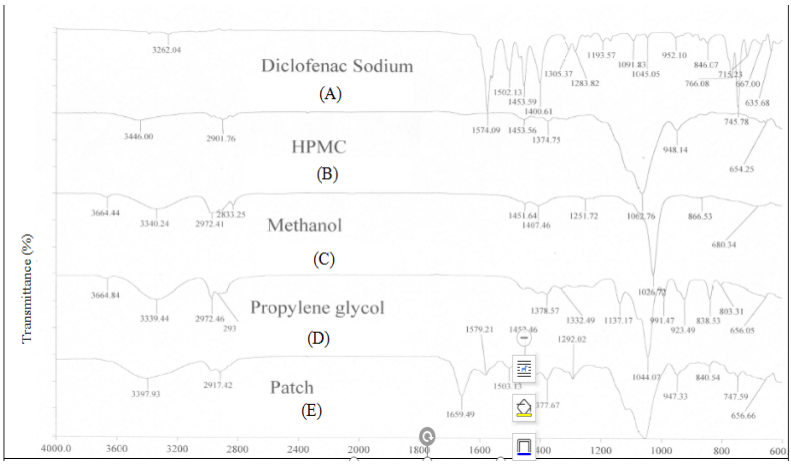


Figure 3: *In vitro* drug release profile of formulation F1, F3, and F5 diclofenac sodium transdermal patch (Graph of cumulative percentage of drug release against time). Sample size= 12

Compatibility study



Wavenumber (cm^{-1})

Figure 4: FTIR spectrum of (A) diclofenac sodium, (B) HPMC, (C) methanol, (D) propylene glycol, (E) mixture of diclofenac sodium and excipient

DISCUSSION

Physical appearance

All the formulations with different concentrations of HPMC were able to form colourless and transparent patches. All patches had smooth appearance except

formulation F6. This might due to solution used in formulation F6 during the solvent casting process was too viscous and led to uneven spread of the solution on the mould. This resulted in non smooth appearance in F6 patches.

Moisture content: The lowest moisture content was observed in formulation F1 and the highest moisture content was observed in formulation F6. Generally, the moisture content of diclofenac sodium transdermal patches increased with the increased of HPMC concentrations. This might be due to the presence of hydroxyl and ether functional group in HPMC, which favoured the hydrogen bonding of water molecules in the environment[16]. There were more sites available for hydrogen bonding within the HPMC molecules with increasing concentrations of the HPMC. Hence, higher the concentration of HPMC, the more water molecules from the environment would be attracted to form hydrogen bond with the polymer, which resulted in higher amount of moisture content in the formulation. Nevertheless, the result of one-way ANOVA test showed that the change in the moisture content due to different amount of HPMC was not significant (p-value > 0.05).

Currently, there was no maximum limit requirement for the moisture content in a transdermal patch. Based on the studies conducted by Ramadan et al.[16], Garala et al.[17], Garud et al.[18], Kumar et al.[19], Thakur et al.[20] , a transdermal patch with moisture content value of less than 5% was considered as low and acceptable. Low moisture content could prevent the patches from breakage or cracking due to the presence of water as natural plasticiser[21]. In addition, the

low moisture content in the transdermal patches increases the stability of the patches and prevents microbial contamination in the formulations[14]. The percentage moisture content of the patches which were fabricated in this research were ranged from 2.000 to 4.577%. Thus the moisture content for all the formulations were considered as low and acceptable.

Flatness: The results of the evaluation test showed that all formulations had 100% flatness. This indicated that all the patches did not exhibit any sign of constriction. Hence, all the patches from the formulations with the concentrations of HPMC ranged from 1% w/v to 6% w/v had smooth and flat surfaces[8]. Moreover, the results also implied that the change in the concentration of HPMC in the formulation would not have any effect on the flatness of the transdermal patches. This experiment was conducted at laboratory with controlled temperature, light and humidity. Factors such as heat, light and humidity have less impact on the stability of the HPMC.

Thickness: Physical evaluation test showed that the thickness of diclofenac sodium transdermal patches would increase with the increase in concentration of HPMC. This phenomenon was also found to be similar with the process of making thin film coating of the tablet, where the increased polymer concentration would increase the thickness of the thin film.[22] From one-way ANOVA test, it is showed that there was a significant difference (p-value < 0.05) between the thickness of transdermal patches of varying concentrations. In the post hoc analysis, the results were significant (p-value < 0.05) for all

formulations except the comparison between the thickness of formulation F1 with F2, and F4 with F5.

The thickness of transdermal patch is important as it determines the rate of drug release from the matrix form of transdermal patch.[23] Referring to the "Guideline of Quality of Transdermal Patch" published by European Medicines Agency, there was no reference value for the thickness of the formulated transdermal patch. The thickness of the patch would be accepted as long as it is justified rationally[24].

The experiment result, showed that the formulated transdermal patches for six formulations had large relative standard deviations (RSDs) (range from 8.994% to 28.863%). The large RSDs for all the formulations indicated that the thickness of the patches were not uniform. This might be due to the unequal distribution of HPMC during the solvent casting process. Furthermore, transdermal patches with non-uniform thickness might affect the overall rate of drug release from the formulation. A study conducted by Imani et al, .[25] showed that the rate of drug release from a TDDS was affected by the thickness of the patch. This phenomenon might be explained by the Fick's law of diffusion:

$$J = \frac{DP}{h} \times C \times A$$

Where D = Diffusion coefficient

J = Flux

P = Partition coefficient of drug

h = Thickness

C = Concentration

A = Surface area

Based on the Fick's law of diffusion, the diffusion of the drug from the polymer would be affected by the thickness of the polymer matrix. A highly varied thickness of a transdermal patch would result in varied drug release in the transdermal patch[26, 27]. Hence all the formulations in this study did not have a satisfactory thickness value. A larger sample size should be included to decrease the standard deviation of this evaluation test.

Folding endurance: A study by Bala and Sharma[28] reported that the folding endurance of a polymeric film increased with the concentrations of polymer. Moreover, B. Vyas et al.[29] proposed that there was a strong correlation between the concentration of HPMC and the folding endurance of the polymeric film.

From the result of one-way ANOVA test of this experiment, change in the concentrations of HPMC in the formulations had a significant effect on the folding endurance (p-value < 0.05). However, the findings in this experiment are not consistent with reported results conducted by other researchers. It was observed that the folding endurance values were not increased according to

the concentration of HPMC added into the formulation. The fluctuation of value might be due to random error, where the force applied to fold a transdermal patch each time was not consistent. This resulted in non-equal force being applied on the folded area and caused the fluctuation on the folding endurance value. Thus, a higher sample size should be included in this evaluation test to minimize such error.

The aim of the folding endurance test was to evaluate ability of the patch to endure with such folding force[30]. When the transdermal patch was applied on the skin, the patch might have been folded when there were body movements. Even though it is one of the important parameters in the evaluation of transdermal patch, there are no guidelines or pharmacopoeia indicated for folding endurance of a transdermal patch, but based on other studies that had been conducted by other researchers, an ideal transdermal patch should have folding endurance of not less than 100[14,31,32]. Referring to the results of this study, all the formulations except formulation F6 exhibited acceptable folding endurance.

Compatibility study: Figure 4 (E) showed the mixture of diclofenac sodium were still preserved, such as –C=O stretch (1659.49 cm^{-1}) and –C–Cl stretch (747.59 cm^{-1}). The peaks at wavenumbers of 3397.93 cm^{-1} and 2917.42 cm^{-1} represented as –O-H stretch and –C-H stretch respectively. The presence of these peaks could be due to the presence of excipients such as HPMC or propylene glycol[33]. Thus, it could be concluded that no new peak was observed

in Figure 4 (E). These indicated that there was no major interaction between the diclofenac sodium with the other excipients[34].

There was a slight change in the FTIR spectrum of mixture of diclofenac sodium and excipients. This could likely be due to formation of hydrogen bond between the drug and excipients. Nonetheless, the *in vitro* drug release profile from the dissolution studies showed that these interaction did not interfere with the release of diclofenac sodium from the HPMC polymer matrix[35].

In vitro drug release study: Formulations F1, F3 and F5 were selected for the *in vitro* drug release study because the formulations possessed acceptable physicochemical characteristics, including moisture content, flatness and folding endurance.

Figure 3 showed that all the formulations had initial burst release of drug from 0 to 10 minutes, followed by a constant drug release from 12 to 180 minutes. Similar results were reported by Vora et al.[36], where HPMC was also used as the polymer in the formulation of transdermal patch in their study. The experiment showed that the initial burst release of drug could be attributed to the hydrophilic properties of the HPMC.

The dissolution study showed that there was significant difference in the percentage cumulative drug release between the formulations with varying concentrations of HPMC. This could refer to the one-way ANOVA test on the cumulative percentage of drug release at different time points. The difference

between the total amount of drug release of diclofenac sodium transdermal patch with varying concentrations of HPMC at each time interval from 2 minutes to 180 minutes were significant (p-value < 0.05).

In the post hoc analysis of one-way ANOVA, from the time interval of 2 to 10 minutes, it showed that the cumulative percentage drug release of F1 was significantly higher than F3 and F5 (p-value < 0.05). When the dissolution process proceeded to the time interval of 12 to 120 minutes, the difference in cumulative percentage drug release between formulations F1 and F3 was not significant (p-value > 0.05) as the drug release rate from both formulations started to reach plateau. Nevertheless, the cumulative percentage drug release of F5 was still significantly lower than F1 and F3 from time interval of 12 to 120 minutes (p-value < 0.05), and the drug release from the formulation F5 did not reach the plateau. At 150 minutes, there was no significant difference in the cumulative percentage drug release between the formulations (p-value > 0.05). Generally, it could be observed that formulation F1 reached the constant drug release first, followed by the F3 and F5. Thus, this indicated that, the higher the concentration of HPMC, the longer the time taken for the cumulative percentage drug release to reach plateau.

The phenomenon in this *in vitro* drug release study could be explained by the properties of HPMC. When the HPMC polymers were hydrated with water, the polymer would start to swell and changed from glassy matrix into gel-like structure. The mechanism of drug release from the HPMC matrix could be

either through drug diffusion or erosion of polymer matrix. However, diclofenac sodium was a water soluble drug, hence it was suggested that diclofenac sodium was released from the HPMC matrix mainly through diffusion method[37,38]. When the concentrations of HPMC increased, there would be increase in the physical cross-linking of the polymer chain, which in turn resulted in the higher chain entanglement in the HPMC matrix. This caused the diffusional pathway to become convoluted and the effective diffusion coefficient of the diclofenac sodium from the polymeric film would be reduced during the dissolution process[39]. Thus, higher the concentration of HPMC, higher the physical cross-linking of the polymer chain, slower diclofenac sodium to be diffused out from the polymer matrix.

CONCLUSION

This *in vitro* drug release study showed that changed in the concentration of HPMC had a significant effect on the percentage cumulative drug release of diclofenac sodium transdermal patch (p-value < 0.05). The higher the concentrations of HPMC, the longer it took for the drug to be released from the diclofenac sodium transdermal patches. This could be attributed to the varying amount of physical cross-linking of the HPMC polymer when different concentrations of HPMC were used in the formulation.

AKNOWLEDGEMENT

The authors would like to thank Mr. Kwong Kee Siong, Ms. Ang Yean Dee, Mr. Mohd Ikmal Hafiz Bin Mahamad Isa, Mr. Loh Xi Rong, and Ms Drena Chua Hui Yi for their assistance during the research study.

References:

1. Pain terms: a list with definitions and notes on usage. Recommended by theIASP Subcommittee on Taxonomy. Pain. 1979 ;6(3):249.

2. Deros BM, Darius DDI, Khamis NK, Mohamad D, Daud SFM, Amdan SM, et al. Prevalence of Work Related Musculoskeletal Disorders Symptoms among Construction Workers: a Case Study in Malaysia. Iran J Public Health. 2014;**43** (3):53–7.

3. Griffin MR. Epidemiology of Nonsteroidal Anti-inflammatory Drug–Associated Gastrointestinal Injury. Am J Med. 1998; 104:23-29 .

4. Huang WF, Hsiao FY, Wen YW, Tsai YW. Cardiovascular events associated with the use of four nonselective NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) versus a cyclooxygenase-2 inhibitor (celecoxib): a population-based analysis in Taiwanese adults. Clin Ther. 2006 ;28(11):1827-36.

5. Gooch K, Culleton BF, Manns BJ, Zhang J, Alfonso H, Tonelli M, et al. NSAID Use and Progression of Chronic Kidney Disease. Am J Med.2007; 120(3):280.e1-280.e7.

6. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. Drugs. 2000; 60(3):555–74.

7. Vijaya R, Pratheeba C, Anuzvi A, Sanoj V, Kumar J. Study of the Hydroxy Propyl Methyl Cellulose (HPMC) Combinations in the Development of Transdermal Film for Amitriptyline HCl and Their in vitro Characterization. International Journal of Pharmaceutical, Chemical, and Biological Sciences. 2015;**5**(3):548–56.

8. Arora P, Mukherjee B. Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. J Pharm Sci. 2002;91(9):2076-89.

9. Modi C. Effect of components (polymer, plasticizer and solvent) as a variable in fabrication of diclofenac transdermal patch. J Pharm Bioallied Sci. 2012 ;**4**:S57–9.

10. Patel KN, Patel HK, Patel VA. Formulation and Characterization of Drug in Adhesive Transdermal Patches of Diclofenac Acid. International Journal of Pharmacy and Pharmaceutical Sciences.

2012;**4**(1):297–9.

11. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J Anal Sci Technol. 2016;**7**(1):25.

12. Ubaidulla U, Reddy MVS, 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 Mar;**8**(1):E13.

13. Vishvesh B. K, Vipul P. P, Sumit M. D. Formulation and evaluation of transdermal patch of Cefdinir with various polymers. The Pharma Innovation Journal. 2015;**4**(6):74–7.

14. Prajapati ST, Patel CG, Patel CN. Formulation and Evaluation of Transdermal Patch of Repaglinide [Internet]. International Scholarly Research Notices. 2011 [cited 2018 Sep 30]. Available from: https://www.hindawi.com/journals/isrn/2011/651909/

15. U.S. Pharmacopoeia. USP 37, NF 32: the United States Pharmacopeia, the National Formulary. United States Pharmacopeial Convention; 2014.

16. Ramadan E, Borg T, Abdelghani GM, Saleh NM. Design and in vivo pharmacokinetic study of a newly developed lamivudine transdermal patch. Future Journal of Pharmaceutical Sciences . 2018

17. Garala KC, Shinde AJ, Shah PH. Formulation and in-vitro characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. International Journal of Pharmacy and Pharmaceutical Science. 2009;**1**(1):108–20.

18. Garud A, Garud N, Namdeo A. Development and Evaluation of Transdermal Patches of Quetiapine fumerate for the treatment of psychosis. International Journal of Drug Delivery. 2013 Mar 17;4(4):470–6.

19. Kumar SS, Behury B, Sachinkumar P. Formulation and evaluation of transdermal patch of stavudine. Dhaka University Journal of Pharmaceutical Sciences. 2013;**12**(1):63–9.

20. Thakur G, Singh A, Singh I. Formulation and evaluation of transdermal composite films of chitosan-montmorillonite for the delivery of curcumin. Int J Pharm Investig. 2016 Mar; **6**(1):23–31.

21. Karbowiak T, Hervet H, Léger L, Champion D, Debeaufort F, Voilley A. Effect of Plasticizers (Water and Glycerol) on the Diffusion of a Small Molecule in Iota-Carrageenan Biopolymer Films for Edible Coating Application. Biomacromolecules. 2006 ; **7**(6):2011–9.

22. Pethrick RA, Rankin KE. Criteria for uniform thin film formation for polymeric materials. Journal of Materials Science: Materials in

Electronics. 1999 Apr 1;**10**(2):141–4.

23. Ruby PK, Pathak SM, Aggarwal D. Critical attributes of transdermal drug delivery system (TDDS) – a generic product development review. Drug Development and Industrial Pharmacy. 2014 Nov 1;**40**(11):1421–8.

24. European Medicines Agency. Guideline on quality of transdermal patches. European Medicine Agency. 2014;1–27.

25. Imani M, Lahooti-Fard F, Taghizadeh SM, Takrousta M. Effect of Adhesive Layer Thickness and Drug Loading on Estradiol Crystallization in a Transdermal Drug Delivery System. AAPS PharmSciTech. 2010 Aug 13;**11**(3):1268–75.

26. Riviere JE, Papich MG. Potential and problems of developing transdermal patches for veterinary applications. Adv Drug Deliv Rev. 2001 Sep 1;**50**(3):175–203.

27. Varma MVS, Kaushal AM, Garg A, Garg S. Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. Am J Drug Deliv. 2004 Mar 1;**2**(1):43–57.

28. Bala R, Sharma S. Formulation optimization and evaluation of fast dissolving film of aprepitant by using design of experiment. Bulletin of

Faculty of Pharmacy, Cairo University [Internet]. 2018 May 7 [cited 2018 Sep 25]; Available from: http://www.sciencedirect.com/science/article/pii/S1110093118300103

29. B. Vyas M, A. Patel C, K. Shah S, Raj A. Design and Development of Fast Disintegrating Film of Quetiapine Fumarate. MIT International Journal of Pharmaceutical Sciences. 2016; **2**(2):24–34.

30. Sarkar G, Saha NR, Roy I, Bhattacharyya A, Bose M, Mishra R, et al. Taro corms mucilage/HPMC based transdermal patch: an efficient device for delivery of diltiazem hydrochloride. Int J Biol Macromol. 2014 May;**66**:158–65.

31. Cherukuri S, Batchu UR, Mandava K, Cherukuri V, Ganapuram KR. Formulation and evaluation of transdermal drug delivery of topiramate. Int J Pharm Investig. 2017;**7**(1):10–7.

32. Kumar M, Trivedi V, Shukla AK, Dev SK. Effect of Polymers on the Physicochemical and Drug Release Properties of Transdermal Patches of Atenolol. International Journal of Applied Pharmaceutics. 2018 Jul 7;**10**(4):68–73.

33. Sigma-Aldrich. IR Spectrum Table & Chart [Internet]. Sigma-Aldrich. 2019 [cited 2019 Apr 29]. Available from: https://www.sigmaaldrich.com/technical-

documents/articles/biology/ir-spectrum-table.html

34. Sarıışık M, Arıcı M, Topbaş Ö, Karavana SY, Öztürk C, Ertan G. Design of orthopedic support material containing diclofenac sodium microparticles: preparation and characterization of microparticles and application to orthopedic support material. Textile Research Journal. 2013 Jun 1;**83**(10):1030–43.

35. Chandak AR, Verma PRP. Design and development of hydroxypropyl methycellulose (HPMC) based polymeric films of methotrexate: physicochemical and pharmacokinetic evaluations. Yakugaku Zasshi. 2008 Jul;1**28**(7):1057–66.

36. Vora N, Lin S, Madan PL. Development and in-vitro evaluation of an optimized carvedilol transdermal therapeutic system using experimental design approach. Asian Journal of Pharmaceutical Sciences. 2013 Feb 1;**8**(1):28–38.

37. Tahara K, Yamamoto K, Nishihata T. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. Journal of Controlled Release. 1995 Jul 1;**35**(1):59–66.

38. Ghori MU, Conway BR. Hydrophilic Matrices for Oral Control Drug Delivery. American Journal of Pharmacological Sciences. 2015 Dec

18;**3**(5):103–9.

39. Mitchell K, Ford JL, Armstrong DJ, Elliott PNC, Rostron C, Hogan JE. The influence of concentration on the release of drugs from gels and matrices containing Methocel®. International Journal of Pharmaceutics. 1993; **100**(1):155–63.