THE EFFECT OF ALMOND OIL ON THE PERMEABILITY OF KETOPROFEN HYDROGEL

ZAHRAA ALAA HASAN1, JINAN MUHAMMED MUHSIN ALMOUSAWEY2, HAMID SADEQ KHALEEL ALGHURABI3

Department of Pharmaceutics, College of Pharmacy, University of Kerbala, Kerbala City, Iraq.
Email: zahraa.hasan@uokerbala.edu.iq

ABSTRACT

Objective: The object of this study is to formulate ketoprofen hydrogels and to evaluate their permeability following the incorporation of almond oil as a penetration enhancer.

Methods: Five formulas (F2-F6) of ketoprofen hydrogels were formulated with the employment of carbopol 940 and triethanolamine. A gradual increase in the amount of almond oil was used in each formula. In vitro penetration and release kinetic study was conducted for all the formulations and compared with the control formula (F1) which was prepared without the incorporation of almond oil.

Results: There was a strong positive correlation between % of incorporated almond oil and the % of drug released when the samples were compared with F1 that was formulated without almond oil. After 24 h, 90% of medication was penetrated from ketoprofen hydrogel formulation (F6), which had 5% almond oil.

Conclusion: Almond oil has successfully worked as a natural penetration enhancer when five ketoprofen hydrogel formulations were prepared and evaluated.

Keywords: Hydrogel, Almond oil, Ketoprofen

INTRODUCTION

Topical dosage forms of non-steroidal anti-inflammatory drugs (NSAIDs) were formulated to avoid their systemic effects [1]. The outer layer of the skin is called the epidermis and it has a superficial layer known as the stratum corneum which is the main barrier to drug. Topical medication could be absorbed when they reach blood vessels which are located in the second layer of the skin that is called the dermis [2, 3]. Low plasma drug concentrations were achieved with topical NSAIDs when compared with their plasma concentrations following oral administration due to low drug permeability [4, 5].

Therefore, various penetration enhancers were studied to improve drug diffusivity by minimizing the resistance of the stratum corneum. The concentration of penetration enhancer varies with the medication and it should be studied carefully since high concentrations could react with the medication causing side effects [6, 7].

Fatty acid containing almond oil is studied in this research as a penetration enhancer since it has the ability to fluidize lipids within the stratum corneum. Additionally, almond oil could work as an emollient agent. Hence, the absorption of applied medications could be improved [8, 9]. Hydrogels, prepared from synthetic or natural polymers, were prepared to deliver topically administered medications. Carbopol polymers were used to ensure a controlled and prolonged dermato logical delivery system due to their high rheological properties. Good buffering capacity could be achieved with carbopol based hydrogels [10, 11].

According to the biopharmaceutical classification system (BCS), ketoprofen (a NSAID) is an example of Class II drugs which have good solubility but poor permeability [12]. Hence, ketoprofen was selected to be formulated as a topical hydrogel where a natural penetration enhancer was used. Ketoprofen was an appropriate candidate for transdermal delivery owing to its adequate aqueous solubility when compared to other NSAIDs [3, 13]. The chemical structure of ketoprofen is given in fig. 1 below.

This study is aimed to formulate a topical hydrogel of ketoprofen that rapidly penetrates the skin with the employment of almond oil as a natural penetration enhancer.

MATERIALS AND METHODS

Materials

Ketoprofen was purchased from Yarrow Chem Products, Mumbai, India. Carbopol 940 was from Sigma Chemicals, USA. Almond oil was purchased from Hemani live natural, Pakistan. Potassium dihydrogen phosphate and ethanol were from Merck, Germany. Sodium hydroxide was from Himedia, India. Triethanolamine (TEA) was from Merck, Germany. Deionized water was obtained from Iranian Parenteral and Pharmaceutical Company, Iran. Chemicals used were of analytical grade.

Apparatus

UV-Visible Spectrophotometer was from SPUV-26, Germany. The ultrasonic cleaning machine was from scientific Labo, Italy. Sartorius balance used was from Denver Instrument, Germany. Microfilters were from China. The pH-meter was from Hanna Instrument, Italy. Synthetic membrane was purchased from Merck Millipore, Germany. Electrical melting point apparatus was from Barloworld Scientific, UK. Glass Petri dishes were from Wings, U.K.

Methods

Capillary tube method was used in the measurement of the ketoprofen melting point. One end of the tube was dipped in ketoprofen powder and placed inside the electrical melting point apparatus while the second end was closed [15].

A solution of 15 µg/ml of ketoprofen at pH = 7.4 was noted, then it was examined by a UV-Visible spectrophotometer from (200-400)
nm, and the $\lambda_{\text{max}}$ was recorded. The $\lambda_{\text{max}}$ of ketoprofen is shown in fig. 2 [16].

Calibration curve of ketoprofen (pH = 7.4) was constructed by preparing serial dilutions of the drug from a stock solution (40 $\mu$g/ml). Samples were analysed spectrophotometrically at the detected $\lambda_{\text{max}}$ of ketoprofen. The determined absorbance was recorded and plotted versus the concentration ($\mu$g/ml). Calibration curve of ketoprofen is shown in fig. 3 [17].

Ketoprofen hydrogel was developed by dissolving 0.5 g carbopol 940 in 35 ml deionized water and was agitated with the help of magnetic stirrer until a homogeneous dispersion was obtained. In another step, 0.5 g ketoprofen was mixed in 3 ml 96% ethanol and sonicated to get a solution of the complete dissolved drug. The drug solution was added individually to each formula of carbopol 940 dispersion in a drop-wise method with the use of a syringe and the solution was stirred continuously. Almond oil (the selected enhancer) was added in different concentrations to 5 different formulas in which one is being a blank without enhancer and the other formulas having different concentrations of the enhancer as 1%, 2%, 3%, 4% and 5% respectively as described below in table 1. A solution of 1 ml of TEA drop wise was added and stirred well for all formulas. The final volume was completed up to 50 ml by adding a sufficient quantity of deionized water and mixed until a homogenous transparent gel was obtained [18].

### Table 1: The proposed formulations of 1% (w/v) ketoprofen topical hydrogels

| Formula No. | Ketoprofen (%w/v) | Carbopol 940 (%) | TEA (ml) | Ethanol 96% (ml) | Almond oil (%) | Deionized water up to 50 ml |
|-------------|-------------------|------------------|----------|-----------------|----------------|-----------------------------|
| F1          | 1%                | 2%               | 0.5      | 3               | 0%             | up to 50 ml                |
| F2          | 1%                | 2%               | 0.5      | 3               | 1%             | up to 50 ml                |
| F3          | 1%                | 2%               | 0.5      | 3               | 2%             | up to 50 ml                |
| F4          | 1%                | 2%               | 0.5      | 3               | 3%             | up to 50 ml                |
| F5          | 1%                | 2%               | 0.5      | 3               | 4%             | up to 50 ml                |
| F6          | 1%                | 2%               | 0.5      | 3               | 5%             | up to 50 ml                |

RESULTS AND DISCUSSION

Visual examination was used to detect the organoleptic properties of ketoprofen hydrogels such as the colour, phase separation, liquefaction and homogeneity at various periods interval such as 1st, 2nd, 5th, 10th, 20th, 30th, and 50th day [19]. The results for organoleptic properties were documented in table 2.

A pH-meter was used to determine the pH value of ketoprofen hydrogels. The pH measurements were studied at zero time and after 1, 5, 10, 20, 30, 40, and 50 days of preparation [20]. The measured pH values of the prepared ketoprofen hydrogels were documented in table 3.

A skin irritation test of ketoprofen hydrogels was performed on human volunteers to find out any irritation problems that could affect the appropriateness of its usage. Approximately 1 g from each prepared formula was topically applied on the hand of three volunteers near their wrists to an area of 25 cm². The skin was observed for any redness, irritation or lesion as reported in table 2 [20].

The in vitro drug penetration of the prepared ketoprofen formulas was investigated by utilizing an assembled Franz diffusion cells. The prepared cells had diffusional surface areas of 0.8 cm² and receptor cells with volume of 5 ml. The receptor compartment was filled with phosphate buffer solution at pH = 7.4. The synthetic membrane was fixed between the donor and receptor compartments of Franz diffusion cells [21].

Approximately 1 g of ketoprofen gel was placed in the donor compartment directly on the synthetic membrane. The temperature of the cell was maintained at 37 °C by surrounding water in a beaker and the medium was stirred by magnetic stirrer at 100 rotations per minute (r. p. m). Samples of 2 ml were collected from the receptor compartment through a microfilter (0.45 µm) at determined intervals and replaced with equal volumes of fresh buffer solution to keep the volume constant. The amount of ketoprofen in the samples was analyzed by a UV-Visible Spectrophotometer at 260 nm. Fig. 4 shows the release profile of the prepared formulas for 24 h (h).
A statistical analysis was computed to observe the correlation between % almond oil used in each formula and % drug released from the prepared ketoprofen hydrogel formulas at a constant time in minutes (min).

The measured melting point of ketoprofen powder was 94 °C which is within the reported range of 94 °C to 96 °C [22]. This value could confirm the purity of the used powder.

The results for the UV scan of ketoprofen at pH = 7.4 showed a peak at 260 nm which was regarded as the $\lambda_{\text{max}}$ as shown in fig. 2. This result is similar to the documented scan [23]. The documented $\lambda_{\text{max}}$ referred in the quantitative study of ketoprofen.

The homogeneity of the formulations was good and there were no visual clots or any other particles in the hydrogels and the gels were transparent. It could be concluded from table 2 that the organoleptic properties of all the prepared hydrogels were generally accepted due to the absence of liquefaction and phase separation. The results of skin irritation test proved the safety of the prepared formulations.

The measured pH values of the prepared ketoprofen hydrogel formulas for the determined period of study were documented in table 3. The pH change was minimized over the study period which could be attributed to the effect of TEA to neutralize the pH of the prepared formulations [24]. Since the pH of the developed hydrogel formulations was in good range; there was no skin irritation or oedema.

Within the first 24 h, only 40 % drug was penetrated across the synthetic membrane into the receptor solvent from the blank formula which contained ketoprofen without the penetration enhancer (almond oil). However, an increase in the percent drug penetration was documented when incorporating almond oil in ketoprofen formulas. There was a strong positive correlation ($r = 0.9433$) between % of almond oil and the % of the drug penetrated when the samples were compared. The values for the % drug penetrations were documented in table 4 while fig 4 demonstrates the release profile of the prepared ketoprofen hydrogel formulations for 24 h which was assigned as % drug released within time in hours.
CONCLUSION
In the present study, six ketoprofen hydrogel formulations were suggested and prepared with the employment of carbopol 940 and triethanolamine. Formulations F2 to F6 were prepared with the use of different percentages of almond oil which was selected as a natural penetration enhancer and F1 was prepared free of almond oil to compare it with the other formulations. Ketoprofen hydrogel formulations (F2 to F6) showed an enhancement in their skin permeation when compared with the blank formula (F1). The increase in the % drug penetrated was directly proportional with the increase in the % of incorporated almond oil in which there was a strong positive correlation between the two variables.

FUNDING
Nil

AUTHORS CONTRIBUTIONS
All the authors have contributed equally.

CONFLICT OF INTERESTS
Declared none

REFERENCES
1. Abdulhasan M, Assali M, Jaradat N, Tarayra R, Hamdan A, Ardah R, et al. Synthesis and formulation of ibuprofen pro-drug for enhanced transdermal absorption. Int J Pharm Pharm Sci 2014;7:352-4.
2. Chajyana W, Phongpradist R, Leelsornpipit P, Anuchapreeda S. Microemulsion-based hydrogel for topical delivery of indomethacin. Int J Pharm Pharm Sci 2014;7:213-9.
3. Alkilani AZ, McCruden MTC, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics 2015;7:93-80.
4. Morgan CJ, Renwick AG, Friedmann PS. The role of stratum corneum and dermal microvascular perfusion in penetration and tissue levels of water-soluble drugs investigated by microdialysis. Br J Dermatol 2003;148:43-43.
5. Mills PC, Magnusson BM, Cross SE. Penetration of a topical nonsteroidal anti-inflammatory drug into local tissues and synovial fluid of dogs. Am J Vet Res 2005;66:1128-32.
6. Valenta C, Anner BG. The use of polymers for dermal and transdermal delivery. Eur J Pharm Biopharm 2004;58:279-89.
7. Williams AC, Barry BW. Penetration enhancers. Adv Drug Delivery Rev 2004;56:603-18.
8. Herman A, Herman AP. Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review. J Pharm Pharmacol 2015;67:473-85.
9. Fox LT, Gerber M, Plessis JD, Hamman JH. Transdermal drug delivery enhancement by compounds of natural origin. Molecules 2011;16:10507-40.
10. Sarkhejia N, Baldaniya L. Hydrogel: a versatile drug delivery carrier systems. Int J Pharm Sci Nanotechnol 2012;5:3745-56.
11. Liu W, Hu M, Liu W, Xue C, Xu H, Yang X. Investigation of the carbopol gel of solid lipid nanoparticles for the transdermal iontophoretic delivery of triamcinolone acetate. Int J Pharm 2008;364:135-41.
12. Lei J, Zhou Y, Xie D, Zhang Y. Mechanistic insights into a classic wonder drug-aspirin. J Am Chem Soc 2015;137:70-3.
13. Vane J, Bakhle Y, Botting R. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol 1998;38:97-120.
14. Nakada N, Shimohara H, Murata A, Kiri K, Managaki S, Sato N, et al. Removal of selected pharmaceuticals and personal care products (PPCPs) and endocrine-disrupting chemicals (EDCs)
during sand filtration and ozonation at a municipal sewage treatment plant. Water Res 2007;41:4373-82.

15. Tiţa B, Fuliaş A, Bandur G, Marian E, Tiţa D. Compatibility study between ketoprofen and pharmaceutical excipients used in solid dosage forms. J Pharm Biomed Anal 2011;56:221-7.

16. Hussain A, Bhardwaj N. Analytical method development and validation of newly synthesized ester prodrugs of aceclofenac. IJPPR 2015;3:52-7.

17. Anandakumar K, Jayamariappan M. Absorption correction method for the simultaneous estimation of amlodipine besylate, valsartan and hydrochlorothiazide in bulk and in combined tablet dosage form. Int J Pharm Pharm Sci 2011;3:23-7.

18. Khamkar J, Prabhavalkar K, Malya R. Development of a microemulsion gel comprising of Etodolac. World J Pharm Pharm Sci 2015;4:141-63.

19. Esposito CL, Kirilov P, Roullin VG. Organogels, promising drug delivery systems: an update of state-of-the-art and recent applications. J Controlled Release 2018;271:1-20.

20. Swarbrick J, Boylan J.C. editors. Encyclopedia of Pharmaceutical Technology. USA: CRC Press; 2000.

21. Ho HO, Huang FC, Sokoloski TD, Sheu MT. The influence of cosolvents on the in-vitro percutaneous penetration of diclofenac sodium from a gel system. JPP 1994;46:636-42.

22. Garala KC, Patel JM, Dhingani AP, Dharamsi AT. Quality by design (QbD) approach for developing agglomerates containing racecadotril and loperamide hydrochloride by crystallo-co-agglomeration. Powder Technol 2013;247:128-46.

23. Wang HY, Zhang WW, Wang N, Li C, Li K, Yu XQ. Biocatalytic synthesis and in vitro release of biodegradable linear polyesters with pendant ketoprofen. Biomacromolecules 2010;11:3290-3.

24. Yadav SK, Mehra MK, Tiwari A, Shukla A. Emulgel: a new approach for enhanced topical drug delivery. Int J Curr Pharm Res 2016;9:15-9.