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Original Article

THE EFFECT OF ALMOND OIL ON THE PERMEABILITY OF KETOPROFEN HYDROGEL

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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

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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 dermatological 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.

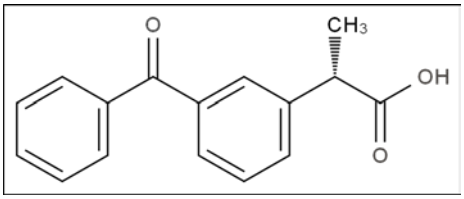

Fig. 1: The chemical structure of ketoprofen [14]

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 di-hydrogen 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. Sartorious 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 λ_{max} was recorded. The λ_{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 µg/ml). Samples were analysed spectrophotometrically at the detected λ_{max} of ketoprofen. The determined absorbance was recorded and plotted versus the concentration (µg/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
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 days [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 d 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 cm^2. 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 cm^2 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).

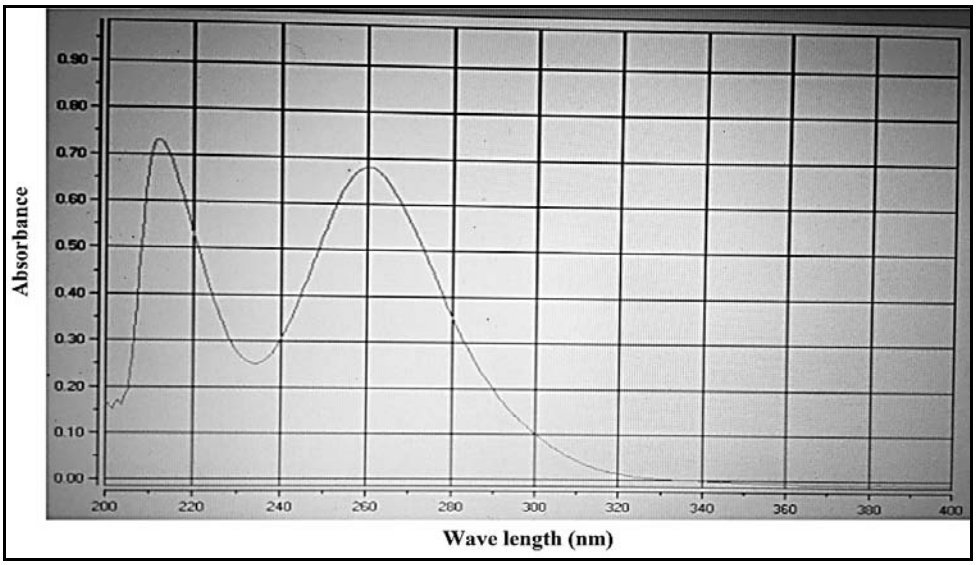

Fig. 2: UV scan of ketoprofen (15µg/ml) within the range (200-400) nm (pH = 7.4) showing λ_{max} at 260 nm, the calibration curve of ketoprofen in phosphate buffer (pH = 7.4) is shown in fig. 3. Beer-Lambert`s law was obeyed since a straight line with high regression coefficient (R^2 = 0.9909) was obtained by plotting the absorbance (nm) versus the concentration (µg/ml)

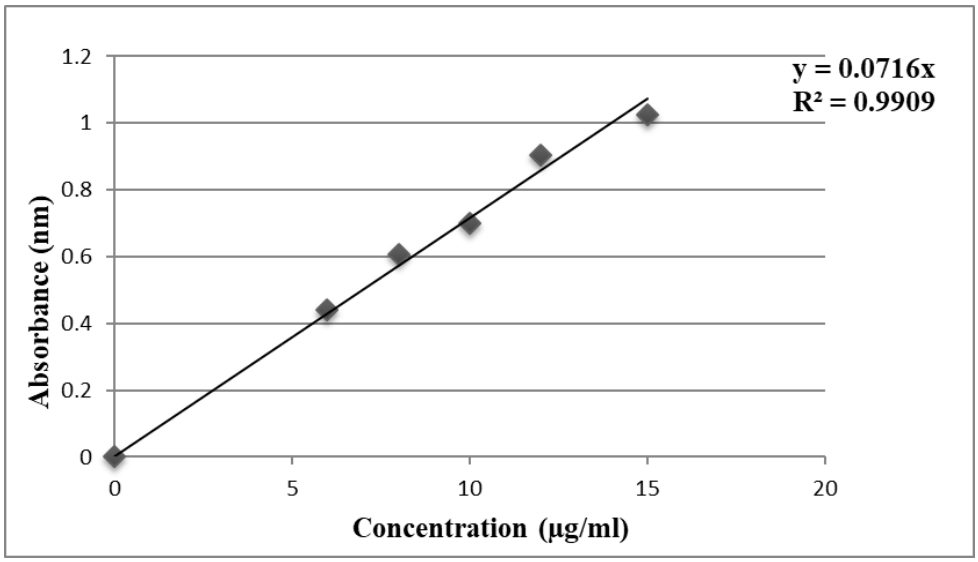

Fig. 3: Calibration curve of ketoprofen in phosphate buffer (pH = 7.4) at λ_{max} of 260 nm

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 λ_{max} as shown in fig. 2. This result is similar to the documented scan [23]. The documented λ_{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.

Table 2: The results for organoleptic properties and skin irritation test of the prepared ketoprofen hydrogels

Parameters	Formulas					
	F1	F2	F3	F4	F5	F6
Colour	Clear	Clear	Clear	Clear	Clear	Clear
Liquefaction	No	No	No	No	No	No
Phase separation	No	No	No	No	No	No
Skin irritation	No	No	No	No	No	No

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.

Table 3: The pH values of the prepared ketoprofen hydrogel formulas

Time (day)	pH value					
	F1	F2	F3	F4	F5	F6
0	5.4	6.0	6.0	6.4	6.5	6.8
1	5.5	6.2	6.1	6.5	6.5	6.9
5	5.5	6.3	6.3	6.6	6.7	6.7
10	5.7	6.2	6.3	6.5	6.8	6.8
20	5.9	6.3	6.4	6.4	6.8	6.8
30	6.0	6.5	6.6	6.6	6.9	6.9
50	6.1	6.4	6.7	6.8	6.8	6.9

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.

Table 4: Percentage ketoprofen penetrated from the prepared hydrogels within time*

Formula	Time (h)						
	1	2	3	4	5	8	24
F1	2%±0.12	5%±0.09	6%±0.11	8%±0.21	9%±0.17	12%±0.13	40%±0.12
F2	6%±0.26	10%±0.15	15%±0.14	19%±0.26	21%±0.11	30%±0.22	65%±0.23
F3	8%±0.19	10%±0.23	18%±0.16	23%±0.12	24%±0.19	43%±0.15	72%±0.09
F4	9%±0.12	15%±0.14	22%±0.21	25%±0.16	26%±0.18	55%±0.21	76%±0.18
F5	11%±0.14	16%±0.09	22%±0.12	27%±0.13	30%±0.15	62%±0.16	84%±0.13
F6	15%±0.11	18%±0.13	25%±0.22	30%±0.17	35%±0.23	69%±0.10	90%±0.19

* Results are expressed as a mean±SD, n=3.

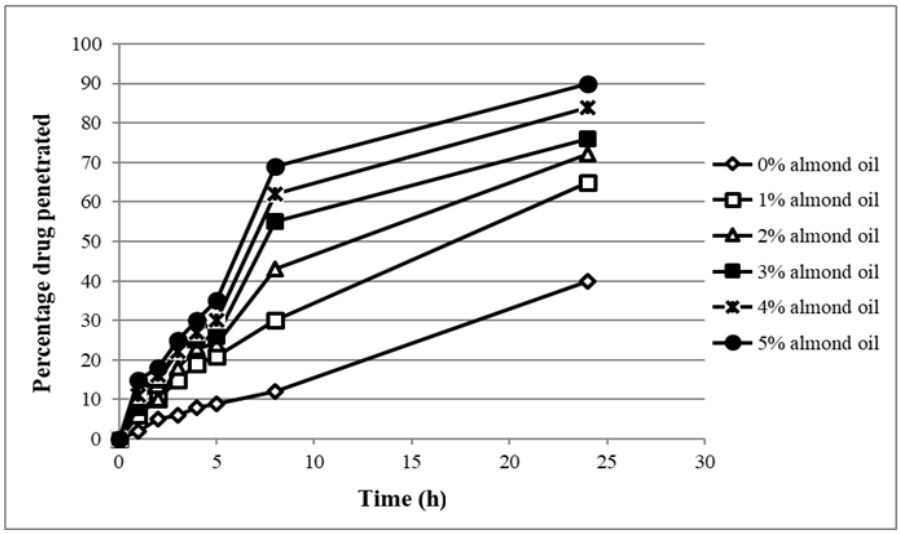

Fig. 4: The percentage ketoprofen release curves of the prepared ketoprofen formulations within the specified study time in a phosphate buffer at pH = 7.4

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.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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