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Formulation and Evaluation of Diclofenac Potassium Transdermal Gel

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ABSTRACT

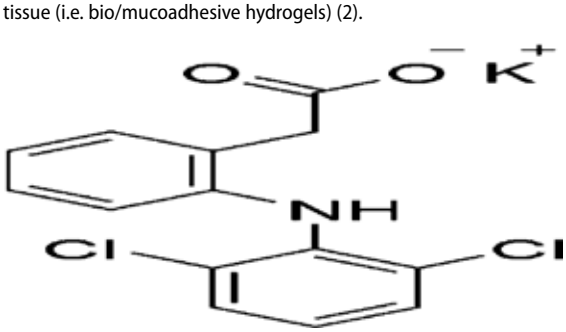
Diclofenac potassium is a non-steroidal anti-inflammatory drug (NSAID) of the phenylacetic acid group which showed remarkable anti-inflammatory effect than the traditional Diclofenac sodium that is found on the market. The oral use of Diclofenac potassium is not recommended as it has many side effects. The present study was designed to formulate and evaluate different formulae of transdermal gel containing Diclofenac potassium. The gel was formulated by using different polymers as HPMC, CMC, Carbopol940, HPMC & CMC mixture and HPMC & Carbopol940 mixture with and without penetration enhancers as propylene glycol and ethanol. Drug-excipients compatibility studies were confirmed by carrying out FT-IR, DSC and XRD. Ten prepared different formulae were characterized physically in terms of colour, homogeneity, texture, pH, spreadability, drug content and rheological properties. In-vitro drug permeation study through cellulose membrane in phosphate buffer solution pH 7.4, were performed. The rheological behavior of the prepared formulae showed shear-thinning flow indicating structural breakdown of the existing intermolecular interactions between polymeric chains. In addition, evaluation of the anti-inflammatory activity of Diclofenac potassium from selected formulae was done using Rat Paw Edema method. The results of in vitro permeation studies showed that the highest values was obtained fromF2 (95.78 % of drug permeated after 24 hr.). Also F2 showed the highest anti-inflammatory activity (63.5% percent edema inhibition after 8 hrs.) in comparison with the results of the marketed formulation Olfen® gel (1% of Diclofenac sodium) (21.2% percent edema inhibition after 8 hrs).

KEYWORDS : Diclofenac potassium, Transdermal gel, Penetration enhancers, HPMC, CMC and Carbopol940

Introduction

Transdermal gel preparations are intended for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. Transdermal gel reduces the adverse drug reaction associated with oral formulations. Transdermal application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compare to creams and ointments (1).

Also, gel vehicles containing therapeutic agents are especially useful for application to mucous membranes and ulcerated or burned tissues, because their high water content reduces irritancy. Furthermore, gels are easily removed by gentle rinsing or natural flushing with body fluids, reducing the propensity for the mechanical abrasion and are capable to adhere to biological tissues or the mucous layer of the tissue (i.e. bio/mucoadhesive hydrogels) (2).



The chemical structure of Diclofenac potassium

Diclofenac potassium (DP), 2-[(2, 6-dichlorophenyl) amino]-benzeneacetic acid, is an acid phenyl acetic derivative with anti-inflammatory, analgesic and anti-thermal properties. It inhibits the enzyme cyclooxygenase and there by inhibits the synthesis of Prostaglandins (PGs). It is used as non-steroidal analgesic, antipyretic and anti-inflammatory drug (3). Also, it is indicated for rheumatoid arthritis, degenerative joint disease, chronic pain associated with cancer and kidney stones and endodontic procedures (4).

The aim of this work is to formulate and evaluate transdermal gel containing Diclofenac potassium using different types of gelling agents. In addition, to improve the anti-inflammatory activity of Diclofenac through using different penetration enhancers and also, exclude the adverse effects of dose dumping which often occurred after oral or parenteral Diclofenac delivery.

Materials and methods

Materials

Diclofenac potassium pure sample was kindly supplied by Delta pharma (Egypt). Hydroxy propyl methyl cellulose (HPMC) powder low viscosity (6000) was purchased from Sigma Chemical Co. (USP). Carboxy methyl cellulose (CMC), Carbopol 940 (CP940) and triethanolamine (TEA) was kindly supplied by Delta pharma (Egypt). Propylene glycol (PG) and ethanol was kindly supplied by Delta pharma (Egypt). Disodium hydrogen phosphate, potassium dihydrogen phosphate were purchased from El –Nasr Pharmaceutical Co. (Egypt). Cellulose membrane, molecular weight cut -off 10 000 (Arthur H. Thomas Co., Philadelphia, Pa, USA) was purchased from Sigma Chemical Co. (USP).

Methods

Drug-Excipients Compatibility Studies

Fourier transform Infrared spectroscopy (FTIR)

Samples of 1-2 mg of drug (Diclofenac potassium), each polymer

and physical mixtures of drug with the investigated polymer (1:1 w/w) prepared by simple and perfect mixing were mixed with KBr (IR grade) compressed into discs in the compression unit under vaccum and scanned from 4000 – 400 cm^{-1} with an empty pellet holder as a reference. FTIR spectrum for the above samples were obtained on Fourier Transform Infrared spectroscope (FTIR), Shimadzu Corporation, Model – 8400 S (5).

Differential scanning calorimetry (DSC)
Samples of drug (Diclofenac potassium), each polymer and physical mixtures of drug with the investigated polymer (1:1 w/w) were prepared by simple and perfect mixing. Approximately 10 mg of samples were weighed, hermetically sealed in the aluminum pans and were measured with a Shimadzu, model DSC-50. The DSC thermogram were obtained over a temperature range of 30-450 °C with a thermal analyzer equipped with advanced computer software program at a scanning rate of 10 °C / min and nitrogen gas of purge of 30 ml / min. The instrument was calibrated with pure indium as a reference (6).

X-ray diffraction analysis (XRD)
Samples of 10 mg of drug (Diclofenac potassium), each polymer and physical mixtures of drug with the investigated polymer (1:1 w/w) prepared by simple and perfect mixing were subjected to powder X-ray diffraction (XRD). XRD measurements were made using Philips diffractometer. The X-ray generator was operated at 40kV and 50mA, musing the CuKα line at 1.54056 A° as the radiation source. Each powdered specimen was packed in a specimen holder made of glass. In setting up the specimen and apparatus, co-planarity of the specimen surface with the specimen holder surface, and the setting of the specimen holder at the position of symmetric reflection geometry were ensured. The powders were passed through a 100 mesh sieve and were placed into the sample holder by the side drift technique. The holder consisted of a central cavity. In order to prepare a sample for analysis, a glass slide was clipped to the top face of the sample holder so as to form a wall. The powder sample was filled into the holder, gently tapped and used for XRD measurement. Ten milligram of each sample was scanned at 25°C from 10° to 70° (2 θ) and in step size of 0.020 and count time of 2.00 s, using an automatic divergence slit assembly and a proportional detector. Relative intensities were read from the strip charts and corrected to fixed slit values (7).

Preparation of Diclofenac potassium transdermal gels:
The composition of Diclofenac potassium transdermal gel formulae are shown in table 1. Polyacrylic acid polymer (Carbopol 940), cellulose polymers (HPMC, CMC) gel were prepared by dispersing the calculated amount of polymer in calculated amount of warm water with constant stirring using magnetic stirrer at a moderate speed. The pH of Carbopol gel was adjusted using TEA. Diclofenac potassium (1% w/w) and penetration enhancers, at the corresponding concentration, were added from the beginning during the preparation of the gel bases. Finally, the prepared gels were packed in wide mouth glass jar covered with screw capped plastic lid after covering the mouth lid with an aluminum foil and were kept in dark and cool place (8). All prepared gel formulations contain 10 mg Diclofenac potassium / 1g gel.

Evaluation of the prepared Diclofenac potassium transdermal gels:

Physical Examination:
The prepared gel formulations were inspected visually for their colour, homogeneity and texture. Results are shown in table (2).

Determination of the pH of prepared gels:
The pH of each base was determined using a pH meter (410A, ORION). Solution containing 1 g of each base in 30 ml of distilled water was prepared and the pH was measured (9). Results are shown in table (2).

Spreadability:
The spreadability of the prepared gels was determined by pressing 0.1g gel between two squared slides each of 5 mm sides and left for about 5 minutes where no more spreading was expected (10). Diameters of spread circles were measured in cm and were taken as comparative values for spreadability. The results obtained were the average of three determinations. Results are shown in table (2).

Determination of drug content in prepared gels:
A specified quantity (100 mg) of developed gel was taken and dissolved in 100ml of phosphate buffer pH 7.4. The volumetric flask containing gel solution was stirred on magnetic stirrer for three hours in order to get absolute solubility of drug. This solution was filtered through a Millipore filter (0.45µm) and estimated spectrophotometrically at 276nm using phosphate buffer pH 7.4 as blank .The concentration of the drug in the sample was calculated using the slope and the intercept obtained from the standard curve of Diclofenac potassium in phosphate buffer of pH 7.4 (11, 12).The results are shown in table (2).

Rheological studies on the formulated gels:
The viscosity of the medicated gel bases containing 1% Diclofenac potassium were determined using a programmable viscometer (Brookfield's apparatus, Inc. DV-II + Pro Viscometer).The measurement of the viscosity was done on each base at room temperature with one minute time interval. The measurement was done using one of two spindle (SC4 21 and SC4 29), and then certain amount of the base was placed inside the sample holder. The viscometer was adjusted to start at certain r.p.m and the speed gradually increased by constant rate at certain time interval and the speed was then reduced gradually with the same rate as increasing one till we reached the starting r.p.m. The rheological parameters (viscosity, shear rate and shear stress) were directly obtained (13). A complete rheogram was obtained by plotting the shear rate as a function of shear stress. The data obtained were graphically illustrated in figures (4-8).

***In vitro* permeation study of the prepared Diclofenac potassium gels through cellulose membrane:**
The outer tube of a plastic syringe, 10 ml capacity, was cut smooth to whole diameter near the nozzle and is used as donor compartment. Accurately weighed 1 gm. of each of the different bases containing 1% Diclofenac potassium was introduced into the tube at the cut end and leveled with a stainless steel spatula. Cellulose membrane (molecular weight cut - off 10 000), previously soaked for 24 hours in the phosphate buffer solution pH 7.4, was then stretched around the cut end touching the base, with effective permeation area of 3.14 cm^2. The membrane was fixed around the tube with rubber band and its edges were sealed with an adhesive tape. The whole tube was hanged into a 100 ml glass beaker (as receptor compartment) containing 50 ml of phosphate buffer solution pH 7.4 at 37°C , so that the cut end of the tube, covered with cellulose membrane, is in the center of the liquid. The phosphate buffer solution pH 7.4 in the receptor compartment was stirred at 100 r.p.m. throughout the time of the diffusion studies. At specified time intervals for 24 hr., 0.7 ml samples were withdrawn from the receptor compartment. The drug was determined spectrophotometrically at λmax 276 nm. Each sample withdrawn was replaced by an equal volume of the phosphate buffer solution pH 7.4 (13). Sink condition was maintained throughout the experiment. The results obtained for prepared gel formulae are graphically illustrated in figure (9).

***In vitro* permeation parameters of Diclofenac potassium across cellulose membrane:**
The permeation parameters of Diclofenac potassium as steady state flux (Js), permeability coefficient (K_p) through cellulose membrane, Diffusion coefficient (D) within the cellulose membrane and lag time (t_L) were calculated from the penetration data. The steady state flux (Js) of Diclofenac potassium was calculated from the slope of the portion of the amount permeated through unit area of the cellulose membrane versus time plot (14).

The permeability coefficients through the cellulose membrane and lag time which is the x-intercept of the extrapolated linear portion of the amount of drug permeated through unit area of the cellulose membrane were calculated according to the following equations (15, 16).

$Js = K_p C_d$
$K_p = Js/C_d$

$t_L = H^2/6D$

Where:

Js is the steady state skin flux (μg/cm^2.hour).
K_p is the permeability coefficient (cm/hour).
C_d is the initial drug concentration in the donor compartment
D is the diffusion coefficient (cm^2/hour)
H is the thickness of the cellulose membrane (0.009 cm)
t_L is the lag time (hour)

To evaluate the promoting activity of each penetration enhancer an enhancement ratio (ER), was defined as the relationship between the flux from certain gel and that from the control one, was calculated according to the following formula:

$$E.R. = \frac{\text{Kp in presence of enhancer}}{\text{Kp in absence of enhancer}}$$

Results are shown in table (3).

Kinetic data analysis:
The kinetic parameters for all in-vitro release study of Diclofenac potassium were determined using specific computer programme and were analyzed in order to explain the mechanism of drug release.

Semi-empirical Peppas Equation

$Mt/M\infty = Kt^n$
Where, $Mt/M\infty$ is the fraction of drug release at time t, K is the diffusion rate constant depending upon structural and geometric characteristics of the drug/polymer system, n is diffusional exponent used to characterize the transport mechanism and $M\infty$ is the amount of drug incorporated in the gel. The value of K and n were estimated by linear regression of Log $Mt/M\infty$ on Log t where Log K is the intercept and n is the slope of the straight line (17). Results are shown in table (4).

Anti-inflammatory activity:
The study was conducted according to the Helsinki agreement protocol and the requirements of the ethical committee of Faculty of Pharmacy at Cairo University in Egypt. Anti-inflammatory effect of Diclofenac potassium gels was determined by the carrageenan induced rat paw edema method. Three gel formulae (F2, F4, F8) that gave the best in vitro permeation results were chosen. In addition, the anti-inflammatory activity of Diclofenac potassium gels was compared with the same gel formulae without penetration enhancers and with 1% of Diclofenac sodium gel commercially available in the market namely Olfen gel as no topical formulation of Diclofenac potassium is available on the market.

Adult male albino rats, weighting (180±20 g), were used in this study; they were housed in groups and allowed free access to food and water prior to the experiments. The animals were divided into 8 groups, each consisting of six animals as follows:

- Group1: control group, animals were received carrageenan (as 1% concentration) only.
- Group 2: animals were treated with 1% Diclofenac potassium gel using HPMC 4%.
- Group 3: animals were treated with F2 (1% Diclofenac potassium gel using HPMC 4% containing 5% propylene glycol and 5% ethanol).
- Group 4: animals were treated with 1% Diclofenac potassium gel using CMC 2%.
- Group 5: animals were treated with F4 (1% Diclofenac potassium gel using CMC 2% containing 5% propylene glycol and 5% ethanol).
- Group 6: animals were treated with 1% Diclofenac potassium gel using HPMC 2% and CMC 2% mixture.
- Group 7: animals were treated with F8 (1% Diclofenac potassium gel using HPMC 2% and CMC 2% mixture containing 5% propylene glycol and 5% ethanol).
- Group 8: Standard group animals were treated with marketed formulation of Diclofenac sodium (1%) (Olfen gel).

Certain amount of the investigated gels (0.5 g) containing 5 mg of Diclofenac potassium were applied to the plantar surface of the left hind paw by gently rubbing 50 times with the index finger. The area of application was occluded with bandages and it was left in place for two hours. The dressing was then removed and the gel remaining on the surface of the skin was wiped off with a piece of cotton. Acute inflammation (paw oedema) was induced in rats by injection of 0.1ml of 1% Carrageenan solution in normal saline sub-cutaneously into sub- plantar region of the left hind paw, two hours after topical administration of the drug (18, 19). The thickness of the injected paw was measured immediately after carrageenan injection and after 1, 2, 4, 6, 8 and 24 hours using dial micrometer model 120-1206.

The percentage swelling of oedema at each time intervals was determined according to the equation (18):

Percent swelling = (V-Vi/Vi) × 100

Where:

V is the paw thickness 1, 2, 4, 6, 8, 24 h after the carrageenan injec tion.
Vi is the initial paw thickness.

The percentage inhibition of oedema at each time intervals was determined according to the equation (18):

Percent inhibition = [1-percent swelling of drug-treated group/percent swelling of control group] × 100
Results are shown in tables (5-7)

Results and discussion:

Drug-Excipients Compatibility Studies

Fourier transform Infrared spectroscopy (FTIR)
An IR spectrum of Diclofenac potassium alone is characterized by the absorption bands at 3251.98 cm^{-1} at high frequency, most probably attributed to N-H stretching band of secondary amine group, at 3022.8 cm^{-1} denoting C-H stretching vibration of pyrimidine ring. At low frequencies the bands at 1573.91 cm^{-1} and 1273.02 cm^{-1} indicating C=O stretching vibration of the carboxyl ion. Also the band at 744.52 cm^{-1} is attributed to C-Cl stretching. These results are in a good agreement with finding of (20, 21, 22).

Differential scanning calorimetry (DSC)
The DSC thermograms of Diclofenac potassium is characterized by an exothermic peak at 294°C with a corresponding enthalpy change (ΔH) of 81.1 *J* and another sharp exothermic peak at 303.35°C with a corresponding enthalpy change (ΔH) of 54.69 *J* due to its decomposition with no apparent endothermic melting. It has been previously reported that above 300°C, Diclofenac potassium decomposes in the range of 290 ± 350°C with a possible decarboxylation of the diclofenac anion (23, 24). The exothermic, sharp melting peak showed that Diclofenac potassium used was pure and crystalline, as this is comparable to the melting point reported for diclofenac in (25).

X-ray Diffraction (XRD)
X-ray diffraction pattern for pure powdered Diclofenac potassium alone shows sharp peaks reflecting its crystalline nature this in accordance with (24).

It was found that there was no change in the position of the char-

acteristic peaks and also no significant reduction in the crystallinity of Diclofenac potassium in all the physical mixtures with the used polymers which indicates that there was no interaction between Diclofenac potassium and all polymers used in the preparation of gel formulations.

Physical Examination:
It is clearly evident that, all the prepared Diclofenac potassium gel formulae were transparent and white colour with a smooth and homogenous appearance.

Determination of pH:
We can notice from table (2) that, pH values of all the formulations are found to be between 4.9±0.01 and 7.11±0.02, which indicate suitability of the formulations for application on the skin. It was found that this pH range was considered acceptable to avoid any irritation upon application to the skin (26).

Spreadability:
Spreadability of the topically applied formulation is an important property considering patient compliance. Results of spreadability test are shown in table (2). It is clear that all the prepared gel formulae of Diclofenac potassium gave acceptable spreadability range with diameters between 5.5±0.012 to 6.67±0.021 which indicates good spreadability. This is in agreement with finding of (27). Also, it should be mentioned that the addition of propylene glycol to most prepared formulae improved the physical characteristics concerning spreadability, consistency and skin feel (28).

Determination of drug content:
The actual drug content was determined for each gel formula and results are shown in table (2). The determined drug content values were ranged from 98.33±0.95 to 101±0.153%. All the gels show acceptable range of drug content and low standard deviations of results. It indicates that the drug is uniformly distributed in the gel formulation.

Rheololgical properties measurement:
The rheological property determination of all formulations was shown in figures (4-8). These figures showed the rheogram of gel formulations through plotting the shearing stress versus the shearing rate.

It was found that Carbopol based formulations possessed considerably higher viscosities than other cellulose based formulations. This effect may be attributed to the higher hygroscopicity of cellulose derivatives as gelling agent compared with Carbopol (29). So that, the type and the concentration of the base used play an important role in the topical preparation design since it affects the viscosity of the gels. Meanwhile, incorporation of penetration enhancers namely, propylene glycol and ethanol for different types of gelling agent gave marketed effect in the consistency of the resulted base as a more viscous gel is obtained (30).

The variation in viscosity may attributed to variation in shape and dimensions of crystallites of different polymers and their ordering in the three dimensional structures within the resulting network where the liquid phase is held by adsorption capillarity and molecular interaction mechanisms (31,32).

It was clear from figures (4-8) that all the prepared formulae exhibited shear thinning pseudoplastic flow; indicating the disarranged viscosity (the slope of the curve) of the system decreases with increase in shear rate. As the shear stress is increased, the normally molecules of the gelling material are caused to align their long axes in the direction of flow. Such orientation reduces the internal resistance of the material and hence decreases the viscosity (33). The figures also show that gel formulations possessed thixotropic behavior, where the down curve was displaced with regard to the up curve, showing at any rate of shear on the down curve a lower shear stress than it had on the up curve. Thixotropy, or time dependent flow, occurs because the gel requires a finite time to rebuild its original structure that breaks down during continuous shear measurements (29, 34).

It is noteworthy that thixotropy is a desirable characteristic in pharmaceutical preparations, both in engineering design and consumer application, in order to deliver an initially thick product as a thinner, easily spreadable material. This is in agreement with (9, 33).

***In Vitro* permeation study of the prepared Diclofenac potassium gels through cellulose membrane:**
The In-Vitro permeation profile of Diclofenac potassium transdermal gel formulae was represented in Fig. (9). It was observed that the release of the drug from different gel formulations can be ranked based on the percent of drug released and permeated through cellulose membrane after 24 hours in the following descending order: F2 (95.78%) > F8 (90.5%) > F4 (89.69%) > F1 (81.25%) > F7 (80.22%) > F3 (70.89%) > F10 (65.66%) > F9 (50.23%) > F5 (49.67%) > F6 (40.99%). It was seen that the maximum drug released and permeated was obtained when HPMC was used as a base with propylene glycol and ethanol as penetration enhancers F2 (95.78%) while the minimum drug released obtained when Carbopol was used as a base without any penetration enhancer F6 (40.99%). This result may be attributed to the physical structure of the polymer network and shape of three dimensions structure of the polymer. In addition, the result may be also due to higher viscosity of the Carbopol gel compared to other gelling agent. These results are in agreement with (33, 35).

By an overview on the release data of Diclofenac potassium from the different gels it is obvious that the addition of propylene glycol as penetration enhancer into different polymer bases result in enhancing drug release data. This was related to the high solubility of propylene glycol which might have increased the solubility of the drug and hence partition coefficient of the drug between the gel and skin barrier, which in turn increased the penetration rate of drug (36). The same was found by (37) who stated that propylene glycol has been the most commonly used excipients in topically applied dosage forms.

Kinetic data analysis:
Table (4) shows the kinetic analysis of the *in-vitro* permeation data of Diclofenac potassium from the different investigated formulae. If n is equal to one the release is zero order or Case II transport, and n > 1 for Super Case II transport. If n is equal to 0.5 the release is best explained by Fickian diffusion and if $0.5 < n < 1$ then the release is through anomalous diffusion or non-Fickian diffusion transport. In this model a plot of % drug released versus log time is linear diffusion rate constant. Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion (38).

Anti-inflammatory activity:
Table (5) shows the mean thickness in paw edema in control and treated groups after treatment with different Diclofenac potassium formulations at different time intervals and the market gel group. While, table (6) shows the percent swelling of oedema and table (7) shows the percent oedema inhibition by application of different Diclofenac potassium gel formulations.

It was observed that the groups 2, 4 and 6 without penetration enhancers produced maximum percent edema inhibition after 4 hrs (45.3%, 46% and 43.4%) respectively and then the effect was reduced gradually with time up to 24 hrs (22.9%, 21.6% and 22.5%) respectively, while groups 3, 5 and 7 related to F2, F4 and F8 respectively with penetration enhancers enhanced drug permeation and produced maximum percent edema inhibition after 8 hrs (63.5%, 60.5% and 63%) respectively and continued for 24 hrs (49.9%, 45.7% and 47.9%) respectively. This indicates that the prepared formulations with penetration enhancers exhibited a better efficacy than the standard preparation without penetration enhancers. In addition, the market gel group produced maximum percent edema inhibition after 4 hrs (31.2%) and then the effect was reduced gradually with time up to 24 hrs (18.8%). These results are in accordance with those of (39).

The remarkable anti-inflammatory effect of Diclofenac potassium than Diclofenac sodium (market gel) could be due to the intercellular pathway that does not contain potassium. Therefore, this could have influence on deriving Diclofenac potassium faster than Diclofenac sodium in passive permeation way. The fact that, Diclofenac potassium is more water soluble than Diclofenac sodium, which when reach the dermis with pH value 7.5 it dissolves faster than Diclofenac sodium forming ion pairs which is more extractable by lipid tissues. The hydration condition of living skin could have role in affecting permea-

tion (40). This finding is in a good agreement with (41).

Conclusion

On the basis of the previous findings we can concluded that Diclofenac potassium was successfully incorporated into the different transdermal gel preparations. From among all the developed formulation the formula F2 shows good spreadability, viscosity, drug permeation and anti-inflammatory activity. Therefore, it was concluded that our formulae could be very promising transdermal alternative as an anti-inflammatory preparation.

Declaration of interest:

The authors have none.

Table (1): Shows Composition of Diclofenac potassium Transdermal gels (% w/w)

Formulae Code	Diclofenac potassium	HPMC	CMC	Carbopol 940	Propylene Glycol	Ethanol	Distilled water to
F1	1	4					100
F2		4			5	5	
F3			2				
F4			2		5	5	
F5				1			
F6				1	5	5	
F7		2	1				
F8		2	1		5	5	
F9		2		0.5			
F10		2		0.5	5	5	

Table (2): Physical characters of prepared Diclofenac potassium gel formulae

Formulae Code	Colour	Homogenity	Texture	pH ±SD	Drug Content ±SD	Spreadability ±SD
F1	Transparent	Homogenous	Smooth	6.75±0.08	100.46±0.451	5.767±0.09
F2	Transparent			6.247±0.03	101±0.153	5.5±0.012
F3	Transparent			7.11±0.02	99.2±0.413	6.67±0.021
F4	Transparent			6.413±0.01	100.2±0.500	6.56±0.08
F5	White			4.9±0.01	100.5±0.68	5.8±0.078
F6	White			5.693±0.11	98.33±0.95	5.75±0.056
F7	Transparent			6.547±0.01	100.2±0.69	5.67±0.054
F8	Transparent			6.412±0.05	98.68±0.32	5.56±0.087
F9	White			5.6±0.06	99.9±0.356	6.5±0.054
F10	White			5.332±0.07	100.45±0.123	6.5±0.115

Table (3): Shows permeation parameters of Diclofenac potassium from its gel formulae through cellulose membrane into phosphate buffer pH 7.4

Formulae	Steady-state flux (Js) ($\mu g.cm^{-2}.hr^{-1}$)	Lag time (t_L) (hr)	Permeability coefficient (Kp) ($cm.hr^{-1}$)	Diffusion coefficient (D) ($cm^2.hr^{-1}$)	Partition coefficient (K)	r	Enhancement ratio (ER)
F1	164.25	2.562	0.0164	5.152	283.73	0.9823	___
F2	219.25	1.096	0.0219	1.2404	162.05	0.9896	1.334
F3	112.925	3.324	0.0112	3.971	253.09	0.9546	___
F4	202.5875	0.560	0.0202	2.353	76.61	0.9945	1.794
F5	112.2	3.094	0.0112	4.267	234.05	0.9929	___
F6	176.875	3.666	0.0176	3.601	437.19	0.9851	1.576
F7	131.875	2.425	0.0131	5.443	215.64	0.9979	___
F8	192.075	0.610	0.0192	2.161	79.09	0.9692	1.456
F9	131.15	3.062	0.0131	4.311	270.74	0.8942	___
F10	155.125	1.151	0.0155	1.146	120.42	0.9403	1.1828

Table (4): Shows Kinetic analysis for the *in vitro* release of Diclofenac potassium from different gel bases according to Krosmeyer – Peppas equation

Formulae	r	n	K	Mechanism of transport
F1	0.95487002	0.55109344	0.0083389	Non Fickian
F2	0.95658564	0.56414374	0.00836517	Non Fickian
F3	0.97868829	0.51041545	0.00811644	Non Fickian
F4	0.97567423	0.50330989	0.01091362	Non Fickian
F5	0.97022829	1.03959677	0.00010535	Super case II
F6	0.94217562	0.96358686	0.00020635	Non Fickian
F7	0.97715438	0.63638536	0.00407186	Non Fickian
F8	0.97901541	0.5751857	0.00692312	Non Fickian
F9	0.97252259	1.0974417	9.1741	Super case II
F10	0.9588134	0.59272185	0.00373529	Non Fickian

Table (5): Mean hind paw oedema thickness after application of different Diclofenac potassium gel formulations

Time (hrs) / Group no	Mean hind paw oedema thickness (cm) ± S.D.					
	1	2	4	6	8	24
1 (control)	0.551±0.022	0.701±0.012	0.823±0.036	0.766±0.019	0.681±0.015	0.491±0.034
2	0.475±0.031	0.499±0.041	0.450±0.026	0.469±0.039	0.502±0.052	0.379±0.016
3	0.439±0.011	0.425±0.028	0.410±0.068	0.319±0.047	0.249±0.031	0.246±0.087
4	0.480±0.056	0.475±0.021	0.445±0.053	0.499±0.071	0.509±0.041	0.385±0.006
5	0.445±0.014	0.459±0.018	0.415±0.067	0.326±0.013	0.269±0.045	0.267±0.019
6	0.470±0.023	0.475±0.061	0.466±0.052	0.476±0.014	0.486±0.036	0.381±0.067
7	0.446±0.044	0.435±0.033	0.409±0.043	0.322±0.021	0.252±0.036	0.256±0.033
8 (market)	0.486±0.029	0.537±0.066	0.566±0.032	0.545±0.016	0.536±0.020	0.399±0.014

Table (6): Percent swelling of oedema by application of different Diclofenac potassium gel formulations

Time (hrs) / Group no	Percent swelling of oedema					
	1	2	4	6	8	24
1 (control)	31.1	66.9	95.9	82.38	62.14	17
2	26.94	47.63	52.48	50.41	45.79	13.11
3	24.8	40.54	47.78	34.27	22.68	8.5
4	27.16	45.29	51.81	53.62	46.41	13.32
5	25.17	43.81	48.35	35.09	24.54	9.23
6	26.57	45.29	54.30	51.15	44.30	13.7
7	25.23	41.47	47.59	34.59	22.99	8.85
8 (market)	27.50	51.24	66.01	58.57	48.98	13.80

Table (7): Percent oedema inhibition by application of different Diclofenac potassium gel formulations

Time (hrs) / Group no	Percent inhibition of oedema					
	1	2	4	6	8	24
1 (control)	0	0	0	0	0	0
2	13.6	28.8	45.3	38.8	26.3	22.9
3	20.4	39.4	50.2	58.4	63.5	49.9
4	12.9	32.3	46	34.9	25.3	21.6
5	19.3	34.5	49.6	57.4	60.5	45.7
6	14.8	32.3	43.4	37.9	28.7	22.5
7	19.1	38	50.4	58	63	47.9
8 (market)	11.8	23.4	31.2	28.9	21.2	18.8

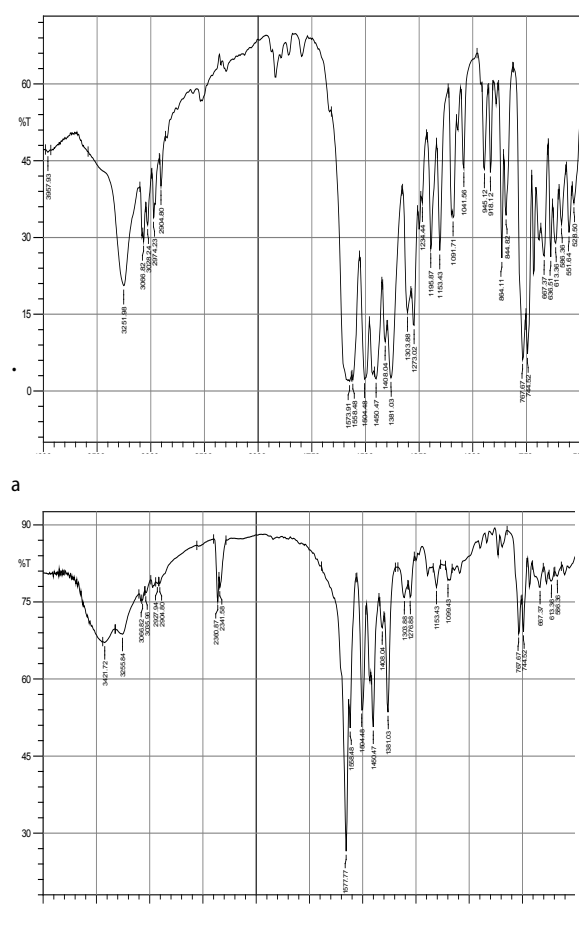


Figure (1): FTIR spectra of (a) Diclofenac potassium and

(b) Diclofenac potassium - CMC physical mixture (1:1 w/w)

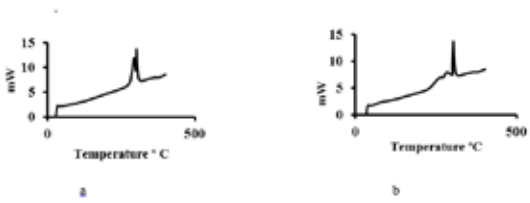


Figure (2): DSC thermograms of (a) Diclofenac potassium and (b) Diclofenac potassium - HPMC physical mixture (1:1 w/w)

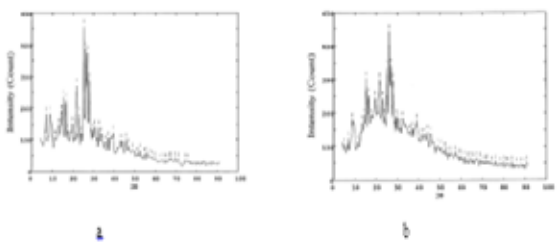


Figure (3): X-ray diffraction patterns of a) Diclofenac potassium and (b) Diclofenac potassium – Carbopol 940 physical mixture (1:1 w/w)

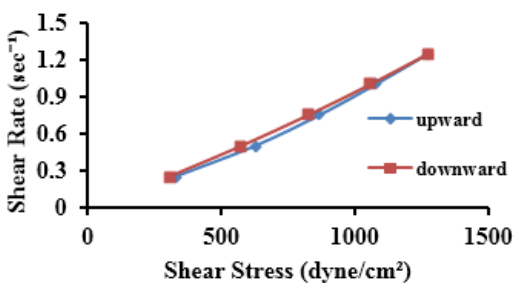


Figure (4): Rheogram of Formula (2) (HPMC gel base)

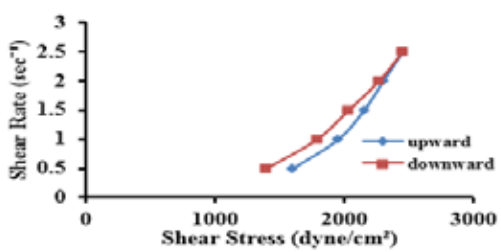


Figure (5): Rheogram of Formula (4) (CMC gel base)

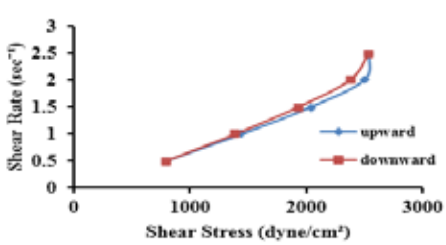


Figure (6): Rheogram of Formula (6) (Carbopol 940 gel base)

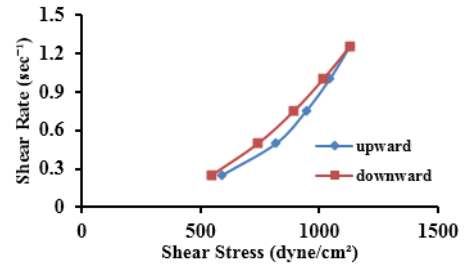


Figure (7): Rheogram of Formula (8) (HPMC & CMC mixture gel base)

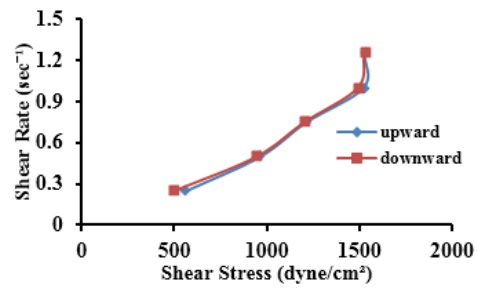


Figure (8): Rheogram of Formula (10) (HPMC & Carbopol mixture gel base)

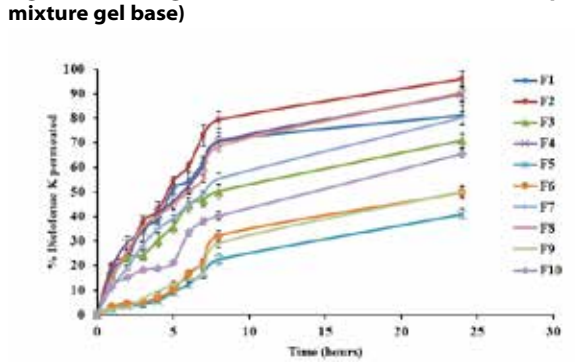


Figure (9): Shows *In vitro* permeation of Diclofenac potassium from its gel formulae through cellulose membrane into phosphate buffer pH 7.4

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