Original Research Article

Investigation of the *ex vivo* and *in vivo* iontophoretic delivery of aceclofenac from topical gels in Albino rats

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Abstract

Introduction: Iontophoresis was used to enhance the delivery of aceclofenac (ACF) from topical gels formulated with various polymers for the purpose of relieving pain and inflammation. **Materials and Methods:** Gels were formulated from hydroxypropyl methyl cellulose (HPMC), carbopol 934P, and sodium carboxymethyl cellulose (NaCMC). The formulations were evaluated for cathodal iontophoretic delivery of ACF through excised rat abdominal skin at three levels of current density of 0.5, 0.6 and 0.7 mA/cm^2. The *in vivo* effectiveness of the drug delivered passively as well as under the influence of iontophoresis at pH 7.4 at a current density of 0.5 mA/cm^2 was also investigated using male Albino rats with carrageenan induced paw edema. **Results and Discussion:** In the *ex vivo* studies, though it was clear that iontophoresis significantly increased drug permeation through the excised skin from all formulations; the percentage drug permeated from HPMC gels was superior to that from carbopol 934P or NaCMC gels but increased with an increase in the current density only for the former. The steady state flux, permeability coefficient, enhancement factor were significantly greater from HPMC gels than from the gels of the ionic polymers due to the interference of competitive ions. With iontophoresis, the carrageenan induced paw edema was significantly reduced by 61.53% ($P < 0.01$) for HPMC gels as compared to the control although passive permeation without iontophoresis showed a 54.6% reduction ($P < 0.05$) at the end of 4 h. **Conclusion:** The results of the study indicate that ACF could be administered topically by using iontophoresis from a suitably formulated gel for effective control of pain and inflammation.

Key words: Aceclofenac, drug permeation, gels, iontophoresis

INTRODUCTION

Most of the Non Steroidal Anti Inflammatory Drugs (NSAIDs) are available in the form of tablet and capsules to treat inflammatory diseases such as rheumatoid arthritis; however, the disadvantage of administering these drugs orally are that the higher doses are required, with frequent dosing for prolonged periods, which give rise to adverse effects such as gastric irritation, vomiting, diarrhea, vomiting, gastric ulcer while parenteral administration can be painful at the site of inflammation.[1]

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Aceclofenac (ACF) is an NSAID which acts by blocking the action of an enzyme cyclo-oxygenase in the body which is involved in the production of prostaglandins which mediate pain, swelling, and inflammation. ACF is often used in the treatment of rheumatoid arthritis to control the pain and inflammation. In the treatment of arthritis, quicker permeation or availability of the drug at the inflamed site is desirable, which may not be feasible with conventional topical gels or creams containing NSAIDS due to poor drug permeation. Gels are more popular among users because of their soothing effects and water washable characteristics; However, the efficacy of these dermatological preparations may be improved by using them in conjunction with iontophoresis.[2]

Iontophoresis is electrically assisted transdermal delivery, which is defined as the migration of ions when low level electrical current is passed through a formulation containing ionized species across the skin.[3] The advantage of this technique is that it provides the usual benefits of transdermal delivery besides controlling the delivery of the drug in a pulsatile fashion by controlling the current input at a pre-determined rate.[4]

Iontophoresis is a localized, non-invasive, convenient and rapid method of delivering ionized medication into the skin. It provides

advantages such as easier termination of therapy inhibit hepatic "first pass" metabolism, inhibit gastrointestinal degradation, avoidance of inconvenience such as risks of infection, inflammation and fibrosis associated with parenteral drug delivery and prevention of variation in the absorption seen with oral administration. Besides these, it also reduces the chance of dosing variation compared to transdermal and topical preparation and improve bioavailability.[5]

According to literature, drug candidates for transdermal delivery should have a molecular weight (MW) around 200-500 Da. ACF, having a MW of around 354.19 fits into the category. Though, ACF is poorly water soluble, its solubility increases dramatically in phosphate buffers of pH 6.8 and above. It has been reported that the solubility of ACF in pH 7.4 is 5.786 mg/ml.[6] ACF (pKa 4.7) at pH 7.4 acquires a negative charge due to ionization of its carboxyl group, which reduces its natural affinity towards the skin due to decreased partition coefficient. Thus, conventional gels of ACF at neutral pH will be expected to show reduced permeation due to increased ionization at this pH. Other authors have claimed that ACF permeated to extent of less than 40% from the gel in 6 h through rat abdominal skin in passive studies.[7,8]

However, under the influence of iontophoresis, this increased ionization and greater repulsion could result in increased permeation. Since the isoelectric point of the skin varies from 3 to 4 at physiological pH, the volume flow will be directed towards the cathode electrode.

Thus, this investigation aims to optimize the therapeutic effects of ACF in the treatment of pain and inflammation by iontophoretic delivery from optimized gel based formulations as a better alternative to the topical use of conventional gels.

The specific objectives of this study were to formulate gels using the sodium carboxymethyl cellulose (NaCMC), Carbopol and hydroxypropyl methyl cellulose (HPMC) K4M evaluate the gels for their physicochemical properties, study the effect of current density using iontophoresis on *in vitro* and *ex vivo* permeation; and examine the effect of iontophoresis on carrageenan induced paw edema in Albino rats.

MATERIALS AND METHODS

Materials

ACF was obtained from Coral laboratories Pvt Ltd., Dehradun. Polymers HPMC was purchased from Central Drug House CDH Laboratory Reagent, New Delhi, and Sodium carboxymethyl cellulose (NaCMC) and Carbopol-934 were procured from Loba Chemie Pvt. Ltd., Mumbai. All other chemicals and solvents were of analytical grade.

Methods

Preparation of ACF gel

ACF gels (1.5%) were prepared by using the polymers such as NaCMC, Carbopol and HPMC (K4M) in various combinations as indicated in Table 1.

Gel formulations of NaCMC and HPMC (G1 and G3) were formulated by dispersing the gums gently in a mixture of propylene glycol and a portion of distilled water. Propylene glycol is used as humectant and also serves as permeation enhancer. ACF was dissolved in alcohol, and the solution was added to NaCMC and HPMC dispersion under continuous stirring for 2 h and adjusted to the required weight with phosphate buffer of pH 7.4. Carbopol gel, G2 was prepared in a similar manner except that the carbopol 934 dispersion was neutralized with triethanolamine before incorporating the drug solution. The pH was adjusted to 7.4 and made up to the required weight with buffer. The gels were allowed to stand for at least 48 h at room temperature for de-aeration and further swelling before they were used for the study.

Evaluation of gels for drug release and permeation

Ex vivo permeation studies using rat abdominal skin

Preparation of rat abdominal skin

All experiments were conducted according to the protocol approved by the Animal Ethics Committee (AEC), protocol number: K.S Hegde Medical Academy KSHEMA/AEC/25/2011. The experiment was conducted according to the guidelines of Committee for the purpose of control and supervision of the experiment on animal.

The male Albino rats weighing 150-200 g were sacrificed by cervical dislocation. The hair on the skin in the abdominal region was removed using the depilatories without altering skin properties. The fresh abdominal skin was excised and separated from the underlying tissue. The excised skin was cleared of its subcutaneous fatty substance and immediately stored at −30°C until use.[9] This step maintained integrity and viability of the skin. For the permeation study, the skin was allowed to thaw at room temperature and mounted on the diffusion cell.

Ex vivo drug permeation study without iontophoresis (passive study)

The *ex vivo* passive permeation profiles of ACF from the prepared gels (G1, G2, and G3) were determined using modified Franz diffusion cell of cross sectional area of 4.84 cm^2. The excised rat abdominal skin (*ex vivo*) was mounted between the donor compartment and receptor compartment of the diffusion cell with the epidermal side facing upwards in the donor cell. The receptor compartment of the diffusion cell was filled with 200 mL of phosphate buffer of pH 7.4, which

Table 1: Composition of topical gels of ACF

Ingredients (g)	Formulation code		
	G1	G2	G3
NaCMC	0.50	-	-
Carbopol	-	0.375	-
HPMC K4M	-	-	0.50
ACF	0.375	0.375	0.375
Propylene glycol	1.25	1.25	1.25
Triethananolamine	-	q.s.	-
Phosphate buffer of pH 7.4	25	25	25

NaCMC: Sodium carboxymethyl cellulose, ACF: Aceclofenac, HPMC: Hydroxypropyl methyl cellulose

was constantly and continuously stirred by a magnetic bead at 50 rpm.[10,11] Skin was kept for hydration about 1 h before use by equilibration with the drug release medium. A quantity of gel equivalent to 25 mg of ACF was applied on the epidermal surface of the skin in the donor compartment. The whole assembly was maintained at 37 ± 0.5°C. Aliquots of dissolution medium were withdrawn at 1 h time interval while replacing the same amount with the fresh medium, and the duration of the study was 8 h. Samples were assayed spectrophotometrically at 274.5 nm for ACF content.

Ex vivo drug permeation study with iontophoresis

For this study, we have used the Dual Channel Pocket Transcutaneous Electrical Nerve Stimulation TENS Iontophoretic instrument (Heera Surgicals, Mumbai) operated by 7.5 volts with a 500 mA A.C. adaptor with two copper electrodes.

The same assembly as described above was used. The cathode was placed on the epidermal surface in the donor compartment and taped in place with adhesive tape, and the anode was introduced into the receptor compartment. The study was carried out for three different current densities, 0.5, 0.6, and 0.7 mA/cm^2 which were applied for a period of 1.5 h.[10,11] At different time intervals, samples were collected and the ACF content was determined spectrophotometrically.

Data analysis

From the permeation studies, the steady state flux of ACF was calculated from the slope of the linear portion of the plot of the cumulative amount permeated against time.

Permeability coefficient was calculated using the formula, $K_p = J_{ss}/C_d$

Where K_p represents permeability coefficient, J_{ss} is the steady-state flux and C_d is the concentration of drug in donor compartment.

Flux enhancement was calculated by dividing iontophoretic steady state flux by the corresponding passive steady state flux.

The fraction change in steady-state flux is used to determine the increase in flux of the drug across the membrane as a result of applied iontophoresis when compared to passive diffusion. This parameter was determined using the following equation:[12,13]

$$\text{Fraction Change in the flux} = \frac{\text{Iontophoretic flux - Passive flux}}{\text{Iontophoretic flux}}$$

In vivo study on carrageenan induced paw edema rats with and without iontophoresis

Methodology

For this study, male Albino Wistar rats of body weight 150-200 g were used.

The abdominal hairs of rats were removed by electrical clippers. All the rats used in the study were anesthetized by ketamine (80 mg/kg, i.p.). The rats were divided into three groups of six each.

- Group 1: Control, carrageenan paw edema induced only
- Group 2: Passive, treated with gel formulation and carrageenan paw edema induced, no iontophoresis
- Group 3: Iontophoresis treated with gel and carrageenan paw edema induced.

In Group 1, carrageenan (1% w/v solution and 0.1 mL) was injected into the plantar region of the left paw. And the volume of paw was measured at different time intervals up to 4 h using a digital plethysmograph (Almeno 2390-5, Paw volume meter).

In Group 2, the gels (G3 equivalent to 6 mg of ACF) were applied to the abdominal skin of the rats. After 1.5 h, the carrageenan (1% w/v solution and 0.1 mL) was injected into the plantar region of the left paw. The volume of the paw was measured using a digital plethysmograph up to 4 h at different time intervals after the injection.

In Group 3, the gels (G3 equivalent to 6 mg of ACF) were applied to the abdominal region ($n = 6$). The drug containing gel was placed beneath the cathode, and to complete the electrical circuit, a conductivity gel was applied beneath the anode, which also helped to inhibit the skin irritation. A current density of 0.5 mA/cm^2 was selected because at this density no damage to the skin or irritation was reported.[14] The direct current was applied for 1.5 h and then the electrodes were removed from the skin and carrageenan solution was immediately injected into the plantar region of the left paw. The volume of the paw was measured using a digital plethysmograph up to 4 h at different time intervals after carrageenan was injected.

The inhibition of inflammation was calculated using the following formula:[14,15]

Percentage inhibition = $100\ (1 - V_t/V_c)$,

where "V_c" represents edema volume in control and "V_t", edema volume in the group treated with test.

Statistical analysis

Statistical analysis was carried out using the one-way ANOVA. The data obtained from *ex vivo* studies and the effect of iontophoresis on paw edema induced rats was separately evaluated by one-way ANOVA followed by Dunnett's test using the software, Graph Pad Prism v 5.01. At 95% and 99% confidence intervals, P values less than 0.05 and 0.01 were considered to be significant.

Ex vivo–in vivo correlation

A plot of *ex vivo* percentage drug permeated was plotted against the *in vivo* percentage inhibition in paw edema and the regression coefficients were obtained.

RESULTS AND DISCUSSION

In this study, three types of polymer gels were prepared using the NaCMC, carbopol, and HPMC. Carbopol was chosen because of its high stability, compatibility, and low toxicity. They form a clear film, which exhibits tack-free adhesion, excellent substantively and moisture resistance. HPMC reduced the surface tension of water and interfacial tension of aqueous systems, which may allow good wetting and spreading of drug on the skin surface and result in the higher permeability of drugs.

Ex vivo permeation study using rat abdominal skin

The passive diffusion study revealed that the release of ACF from each of the three gel formulations was not very different from each other and the maximum percentage permeated at the end of 8 h did not exceed 56%. Since ACF has a pKa of 4.7 and the pH of the gel base is about 7.4, most of the drug would be ionised and therefore, will have lower partition coefficient. The unionised species of the drug at this pH would have permeated the skin via the trans-cellular pathway as it is more lipophilic; However, this form of the drug is present to a lesser extent at the pH of 7.4 and therefore, permeation through the skin was poor. Permeation profile of ACF from gels during passive permeation studies are shown in Figures 1-3.

However, when iontophoresis was applied there was a significant increase in the percentage drug permeated from all formulations.

Effect of iontophoresis

The direct application of electric current (0.5, 0.6 and 0.7 mA/cm^2) with a continuous mode increased the ACF penetration because the molecule was found to penetrate fast enough due to electrochemical polarization in the skin. Figures 1-3 show the effect of iontophoresis which enhanced the amount of ACF permeating through the skin. There was a significant increase in the amount of the drug ($P < 0.01$) that was transferred to the receptor compartment from all gels when iontophoresis was used because the current acts as the driving force for the movement of ions across the skin. This effect is evident from the observed values of percentage drug permeated at the end of 8 h as shown in Table 2. in addition, presence of 'negative carboxyl ion' in the ACF at pH 7.4 also contributes to high conductivity during cathodal iontophoresis; transport of the drug was mainly due to electrostatic repulsion by the respective electrode and lesser by convective solvent flow process. Thus, there is a linear relationship between current density and the flux of a permeating ion.

It has been reported that application of current for prolonged periods lead to the evolution of heat energy, which can make the skin lipids more fluid and thus change the integrity of the skin structure, consequently permeability of the skin would be altered. This explains the increased permeability coefficient of drug during iontophoresis compared to the corresponding values for passive diffusion.[16,17] It is also likely that the electro-osmotic volume flow increases with an increase in current density, which leads to increase in the flux of the drug.[18]

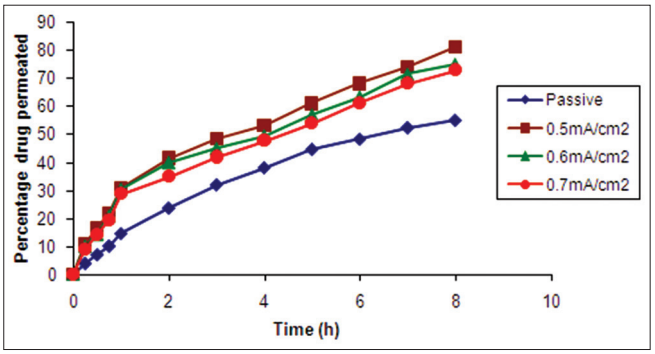

Figure 1: *Ex vivo* permeation profiles of aceclofenac from gel (G1) at pH 7.4

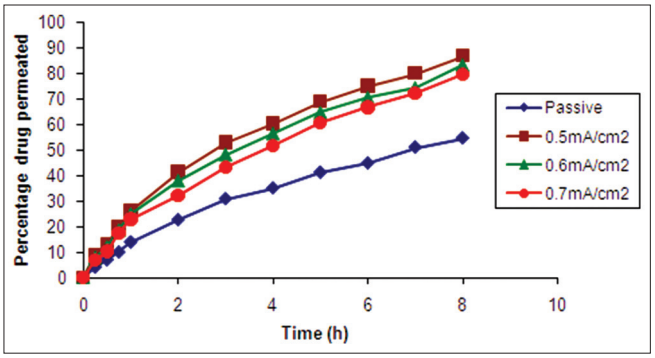

Figure 2: *Ex vivo* permeation profiles of aceclofenac from gel (G2) at pH 7.4

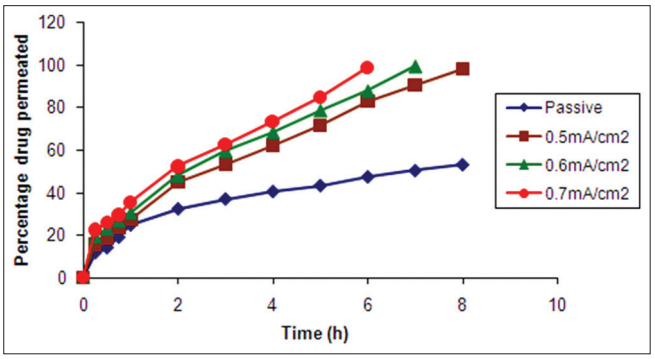

Figure 3: *Ex vivo* permeation profiles of aceclofenac from gel (G3) at pH 7.4

Table 2: Comparison of cumulative percentage drug permeated from gels at different current density

Current density (mA/cm^2)	Cumulative percentage drug permeated at the end of 8 h		
	G1	G2	G3
0	62.3471	57.6846	71.5085
0.5	94.4507	84.1676	99.632
0.6	90.3454	79.7233	98.2308*
0.7	87.3726	74.3226	94.1905*

*The data of G3 were taken at 7 h and 6 h

Drug permeation from G3 appears to increase with an increase in the current density from the beginning but decreased in case of G1 and G2. Thus, an increase in current density beyond 0.5 mA/cm^2 did not increase drug permeation from gels of ionisable polymers such as NaCMC or carbopol but did increase substantially from gels of non-ionisable polymers such as HPMC as can be seen in Table 2. This is because the latter polymers contributed ions that interfered with the flux of the ionized drug in a competitive manner. In the case of G1 and G2, the use of continuous current iontophoresis caused a skin polarization potential to develop that eventually decreased the magnitude of the effective current.

The calculated values of change in the flux of ACF through the skin are shown in Table 3. The results indicate that after applying current there was marked change in the drug permeation from all formulations since there was an increase in the flux at the end of 8 h compared to the values obtained after 2 h. it was observed that flux was twice at the end of 8 h but decreased in the case of ionic polymer (G1 and G2).

The calculated values of permeability coefficient, fraction change in the steady-state flux and enhancement factor for iontophoretic transport of ACF for different current density are shown in Table 4. The data clearly show that at pH 7.4 the flux is increased during iontophoresis from all formulations. Higher flux was observed in HPMC gel with 2-3 fold increase with an increase in current density but decreased in NaCMC and Carbopol containing gel due to ionic nature of polymers. The values of fraction change in the steady-state flux for ACF during iontophoresis are related to their corresponding degrees of ionization of ACF. It was also observed that the permeability coefficient of ACF was increased by applying current when compared to the control. In the presence of current, the cumulative drug transport increased linearly.

Table 3: Comparison of calculated flux of ACF from gels at 2 h and 8 h

Current density (mA/cm^2)	Time interval (h)	Flux (μmol/cm^2)		
		G1	G2	G3
0	2	3.4306	3.2883	4.7222
	8	7.9834	8.0845	7.7535
0.5	2	6.0433	4.9999	6.541
	8	11.8246	12.6232	14.2636
0.6	2	4.8057	4.5115	6.9548
	8	11.0463	12.0911	14.4493*
0.7	2	4.2228	4.6824	7.6184
	8	10.5986	11.5953	14.3789*

*The data of G3 for 0.6 mA/cm2 and 0.7 mA/cm^2 were taken at 7 h and 6 h respectively, ACF: Aceclofenac

Effect of polymers

There was quite a difference in ACF permeation profile by changing the hydro gel polymer. It is observed that for formulation G3 prepared from HPMC, there was a marked increase in permeation and flux of ACF under iontophoresis from passive permeation values than from gels with the ionic polymers, NaCMC and carbopol (G1 and G2). This difference was not so marked for formulation G1 and G2 even though the overall permeation at the end of 8 h is less than G3. As described earlier, as the current density is increased from 0.5 mA/cm^2 to 0.7 mA/cm^2 for G3, the iontophoretic flux increased which may be attributed to increase in the repulsion between similarly charged ions; However, the flux decreased when ionic polymeric gel is used, and therefore lower iontophoretic (cathodal) flux was observed at 0.6 mA/cm^2 and 0.7 mA/cm^2 due to the effect of the co-ion. The drug permeation profile from G3 as shown in Figure 3 indicates an initial burst release in the first hour, which increased with an increase in current density with 35% released at a current density of 0.7 mA/cm^2. Such a burst release was not evident for G1 or G2. This could be attributed to the diffusion of the drug to the surface of the gel during its storage period resulting in a higher concentration here than in the bulk, thereby resulting in a burst release. Though, this phenomenon could have occurred in all the gels, the initial rapid release was apparent for G3 since the interfering polymer anions in G1 and G2 could have suppressed this effect in the latter.

The permeability of cathodal iontophoresis of ACF from Carbopol gel was low which may be due to the anionic polymers carrying a part of current and hence that only a small fraction of current was actually conducted by the ionized ACF. This low permeation was also observed for cathodal iontophoresis from

Table 4: Effect of ITS on the steady state flux, permeability coefficient, enhancement factor and fraction change in flux

Formulation code	Current density (mA/cm^2)	Steady state flux J_{ss} (μmol/cm^2/h)	Permeability coefficient (cm/h)	Enhancement factor	Fraction change in flux
G1	0.0	1.0426±0.0707	0.0147	-	-
	0.5	1.3133±0.0236	0.0186	1.2627±0.0729	0.2062±0.0472
	0.6	1.2303±0.0318	0.0174	1.1847±0.1064	0.1511±0.0798
	0.7	1.1963±0.0395	0.0169	1.1523±0.1105	0.1265±0.0875
G2	0.0	0.9866±0.0295	0.0139	-	-
	0.5	1.5393±0.0997	0.0218	1.5630±0.1486	0.3564±0.0598
	0.6	1.4483±0.0971	0.0205	1.4707±0.1429	0.3158±0.0660
	0.7	1.3796±0.0863	0.0195	1.3974±0.0465	0.2838±0.0242
G3	0.0	0.8263±0.0349	0.0117	-	-
	0.5	1.6453±0.0919	0.0233	1.9965±0.1929	0.4958±0.0504
	0.6	1.9213±0.0640	0.0272	2.3257±0.0261	0.5699±0.0048
	0.7	2.2576±0.0779	0.0319	2.7377±0.2049	0.6333±0.0273

ITS: Iontophoresis

Table 5: Comparison of inhibitory effect of ACF in carrageenan induced paw edema in rats

Group	Increase in edema volume (mL) (% inhibition in paw edema)			
	60 min	120 min	180 min	240 min
Group 1 (control)	0.2667±0.0049	0.3833±0.0030	0.4167±0.0166	0.4333±0.0021
Group 2-gel (6 mg)	0.2017±0.0040 (24.38)*	0.2567±0.0049 (33.03)**	0.2133±0.0049 (48.82)**	0.1967±0.0049 (54.61)*
Group 3-gel (6 mg)+ITS	0.1550±0.0042 (41.89)**	0.2183±0.003 (43.05)*	0.1883±0.0040 (54.82)**	0.1667±0.0042 (61.53)**

Each value is mean±SEM, *N*=6 rats, *Significantly different compared to control (*P*<0.05), **Significantly different compared to control (*P*<0.01), One-way ANOVA followed by Dunnett's multiple comparison tests, ITS: Iontophoresis, ACF: Aceclofenac

NaCMC in which Na + act as the competitive ion. Thus, ionisable polymers may present a problem in iontophoretic drug delivery.

Viscosity of gels can also be a deciding factor in drug releases both passive as well as under the influence of iontophoresis. Consequently drug permeation from G2 was less than G3 due to greater viscosity of carbopol gels.

In vivo study on paw edema induced rats with and without iontophoresis

On the basis of results from *ex vivo* permeation studies, G3 was selected for the *in vivo* study since it demonstrated higher permeation values compared to G1 and G3 within the short period when current was applied compared to passive permeation.

It was observed that there was significant inflammation after 1 h of carrageenan administration, and maximum inflammation was seen at 4 h. The gel was administered at a dose level of 30 mg/kg and was kept constant for the current density level tested. In this *in vivo* study the effect of iontophoresis (0.5 mA/cm^2) on the drug permeation was investigated. Here, propylene glycol present in the gel may act as permeation enhancer since it is capable of disrupting intercellular lipid organization and had a synergistic permeation effect on iontophoresis. Experiments were performed on G3 at constant current density of 0.5 mA/cm^2 for 1.5 h. The values of inhibition in paw edema for iontophoretic and passive delivery are compared in Table 5.

The mean paw volume in the rat was found to decrease in a linear fashion when the current was applied. The percentage reduction in paw edema volume was significantly less in Group 3 when iontophoresis was applied than in Group 1 or Group 2. The detected inhibitions in paw edema without iontophoresis and with iontophoresis were 54.61% ($P < 0.05$) and 61.53% ($P < 0.01$) respectively as compared to the control group at the end of 4 h. These values indicate that the significant increase in the amount of ACF permeated by direct current of 0.5 mA/cm^2 application and the drug delivered was proportional to the applied current and duration of iontophoresis.

Further, it can be concluded that the application of iontophoresis has markedly increased the release and permeation of the drug from the gel since the percentage reduction in paw edema volume were significant ($P < 0.05$) as compared to the control group.

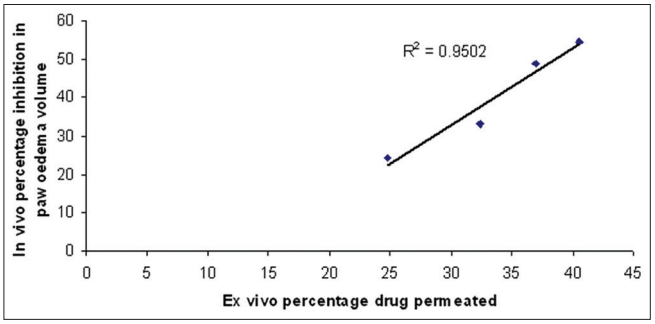

Figure 4: *Ex vivo–in vivo* correlation of passive permeation of aceclofenac from G3

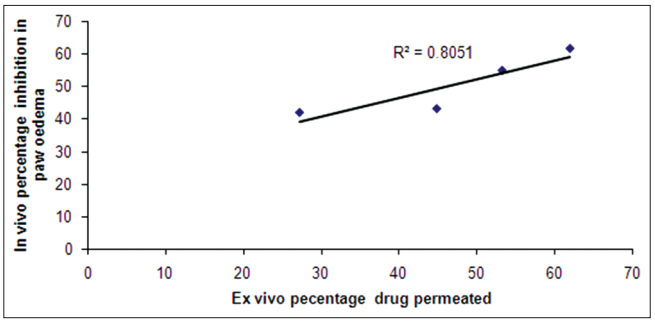

Figure 5: *Ex vivo–in vivo* correlation of iontophoretic permeation of aceclofenac from G3 at current density of 0.5 mA/cm^2

EVIVC

A plot of *ex vivo* percentage drug permeated was plotted against the *in vivo* percentage inhibition in carrageenan induced paw edema and the regression coefficients obtained for passive and iontophoretic permeation as shown in Figures 4 and 5.

It was observed that R^2 value for the correlation was 0.9502 for the passive process and 0.805 for the iontophoretic permeation at 0.5 mA/cm^2.

CONCLUSION

This investigation has demonstrated that with the application of cathodal iontophoresis, the transdermal delivery of ACF from gels could be enhanced. Thus, the efficacy of ACF in reducing pain and inflammation was improved when this mode of treatment is applied as compared to conventional gels. However, the principle drawback of gels is that they may not be suitable for prolonged administration of drugs since they do not remain on the skin for sufficient time and require re-application. They are

also messy and tend to stick to clothing and patient compliance may be lesser.

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