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FORMULATION AND EVALUATION OF TRANSDERMAL GEL OF LORNOXICAM AND ITS DELIVERY BY PASSIVE AND IONTOPHORESIS METHOD: A COMPARATIVE STUDY

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ABSTRACT: The objective of present study was to develop Lornoxicam transdermal gel and its iontophoretic delivery to enhance its permeation for systemic effect and to avoid its side effects. Lornoxicam is a COX-1 and COX-2 inhibitor used in the treatment of inflammation, pain, edema and rheumatoid arthritis. Transdermal gel of Lornoxicam was formulated using triethanolamine as solvent, carbopol 934P as gel base and enhancement in its permeation by iontophoresis was investigated. Formulated gel was evaluated for pH, viscosity, spreadability, drug content and gel strength. Permeation study was carried out using cellophane membrane for 6 hours. Anti-inflammatory activity of Lornoxicam gel was studied in albino rats by carrageenan induced paw edema method in which Lornoxicam was delivered through rat's skin by passive delivery and iontophoretic delivery. Iontophoretic delivery of formulation F1 showed edema inhibition up to 62% whereas passive delivery of F1 showed 22% of edema inhibition in 1 to 6 hours. Edema inhibited by iontophoretic delivery was around 2.5 fold than compared to that of passive delivery; hence iontophoretic delivery was superior over passive delivery. In present study physiochemically stable Lornoxicam gel was formulated which could deliver significant amount of drug across the skin and elicit the anti-inflammatory activity.

INTRODUCTION: Lornoxicam is a potent non-steroidal anti-inflammatory drug (NSAIDs), used for the variety of inflammatory conditions such as inflammation, pain, edema, rheumatoid arthritis and so on. Its half-life is 3 to 5 hr and peak plasma concentration is attained within 2.5 hr. Lornoxicam is ten times more potent than other oxicam derivatives. Its daily dose is 8-16 mg taken before meal but dose above 8 mg should be divided into two or more doses.

The mechanism of action Lornoxicam is primarily due to inhibition of prostaglandin synthesis through the inhibition of cyclooxygenase (COX-1 and COX-2) enzymes. Like other NSAIDs, common side effect of Lornoxicam is gastrointestinal irritation. Thus the delivery of the Lornoxicam through the skin for the treatment of inflammation is desirable^{1,2}.

Transdermal drug delivery systems are designed to deliver a therapeutically effective amount of drug across a patient's skin for prolonged period of time³. In the present scenario around 40% of the drug candidate products under clinical evaluation are related to transdermal system. Transdermal delivery of drugs promises many advantages over oral or intravenous administration, such as a better

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control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism, reduced side effects, longer duration of action resulting in a reduction in dosing frequency and also improved bioavailability. However, drugs should possess several physico-chemical prerequisites such as shorter half-life, small molecular size, low dose etc. to be a suitable candidate for transdermal drug delivery system due to formidable barrier action of keratinized cells present in stratum corneum of skin⁴.

Many physical approaches have been applied to increase the efficacy of the drug to transfer across the intact skin which expands the range of drugs delivered⁵. These involves physical methods, based on strategies like increasing skin permeability and providing driving force acting on the drug which can bypass stratum corneum^{6, 7}. Physical transport system have achieved huge success in increasing the transdermal transport, which would improve the efficacy, safety and convenience of use and open up the benefits of the transdermal drug delivery technology to a much broader range of therapeutic areas⁸.

In order to increase therapeutic efficiency and efficacy of topically applied drug, it is necessary to employ physical enhancers i.e. iontophoresis⁹. Iontophoresis is the novel process of enhancing the permeation of topically applied therapeutic agents through the skin by the application of electric current. The drug is applied under an electrode of the same charge as the drug, and an indifferent counter electrode is positioned elsewhere on the body.

The active electrode effectively repels the active substance and forces it into the skin¹⁰. Increase in drug penetration across the skin by iontophoresis can be due to following mechanisms: (a) the present mechanism proposes that the drug is forced across the skin by simple electronic repulsion of similar charges. (b) The second explanation suggests that the electric current enhances the permeation by inhibiting the skin's ability to perform its protective barrier function. (c) The third mechanism states that iontophoresis causes water, a very effective penetration enhancer, to enter the stratum corneum by electrosmosis³. Iontophoresis

is gaining the wide popularity in the area of pain relief as it provides a non-invasive means of systemic administration of minute amount of drug¹¹.

In this study, an attempt has been made to enhance the permeation of Lornoxicam gel by using physical enhancers (iontophoresis) and to study the topical delivery of Lornoxicam through the rat's skin.

MATERIALS AND METHODS:

Materials:

Lornoxicam was provided by Naprod Life Science Pvt. Ltd (India), Carbopol 934P, Triethanolamine, Tween, Span, Ethanol (S.D fine chemicals Pvt. Ltd, Mumbai, India). Iontophoretic device integrated with metal electrodes used as cathode and anode. Reverse osmosis (RO) water was used for preparing all the solutions and samples.

Animals:

Approximately 180-200g of male albino rats was used. All the animals were properly fed and housed as per guidelines of Institutional Animal Ethics Committee (IAEC). All the experimental procedure and protocol used in this study were reviewed and approved (SACCP/IAEC/24/2013-14) by IAEC of Sri Adichunchanagiri College of Pharmacy, B.G Nagara-571448, Karnataka constituted under Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Ethical guidelines were strictly followed during all the experiment period.

Electrodes assembly for iontophoresis:

Simple iontophoretic device was made with the voltage control system that consists of two electrodes. Electrodes were connected with the copper wire at the end i.e. square sized metal with 2cm² area which acts as electrodes. Electrodes connected with the copper wire were connected to the respective charges in the adaptor as required. The adaptor with the voltage control provided the ease to change the voltage during iontophoresis process.

Solubility studies:

The solubility of Lornoxicam was determined in distilled water, pH 6.8 phosphate buffer, chloroform and 5% triethanolamine solution in

water by shake flask method. Briefly, an excess amount of Lornoxicam was added to each vial containing 10 ml of selected solubilizer. The mixtures were subjected to the mechanical agitation for 48 hr in isothermal shaker at 25°C ±1°C followed by the filtration through Watmann's filter paper prior to UV⁹.

FT-IR interaction studies:

Infrared spectroscopy was conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm⁻¹. FTIR studies were carried on pure drug and its physical mixture of drug to confirm the compatibility of the drug with other excipients used for the preparation of gel formulation¹².

Diffraction scanning calorimetry (DSC):

Thermal properties of the pure Lornoxicam and its physical mixtures were analyzed by Shimadzu DSC-60, Shimadzu Limited Japan. The samples were heated in a thermally sealed aluminum pans. Heat runs for each sample were set from 25 to 350°C at a heating rate of 10°C/min, using nitrogen as blanket gas¹². The 3gm of sample was used for the analysis.

Composition of gels:

Lornoxicam 0.2% containing gel formulation was prepared (Table 1). Carbopol 934P was used as gel base and it is slowly dispersed into distilled water and allowed to swell for 24 hours. Lornoxicam solution was prepared by dissolving in 5% triethanolamine and the solution was slowly dispersed into gel base with continuous mixing (about 10 min). Finally a preservative was added in the above gel base.

TABLE 1: COMPOSITION OF LORNOXICAM GEL FORMULATION

Sl. No	Ingredients	F1
1.	LRN (mg)	200
2.	Carbopol 934 (%)	1
3.	Triethanolamine (5%) (ml)	10
4.	Ethanol (ml)	1
5.	Methyl paraben (% w/v)	0.15
6.	Propyl paraben (% w/v)	0.02
7.	Distilled Water (QS)	100 ml

LRN is Lornoxicam, TEM is Triethanolamine, MP is Methyl paraben and PP is Propyl paraben

Evaluation of Lornoxicam gel:

pH:

pH of Lornoxicam gels were determined by using a calibrated pH meter (Equiptronics). The readings were taken for average of two samples. The pH meter was calibrated before each use with standard 4, 7 and 9.2 pH buffer solutions¹³.

Drug content:

Drug content analysis was determined by dissolving 1g of gel in 100ml of phosphate buffer pH 6.8: methanol (50:50). Then 1ml of this solution was transferred to the 10ml volumetric flask and final volume was made by same solutions. Finally absorbance of prepared solution was measured at 380nm using UV visible spectrophotometer. The percentage drug content is calculated¹⁴.

Viscosity and rheological studies:

Brookfield digital viscometer (Model LVDV-E, USA) was used for the determination of viscosity and rheological properties of Lornoxicam gel using spindle no T-96. The viscosity of gel was measured at different angular velocities at a temperature of 25°C. A typical run comprised changing of the angular velocity from 0.5 to 2.5 rpm¹³. The averages of three readings were used to calculate the viscosity.

Spreadability:

For the determination of spreadability, excess of sample was applied between the two glass slides and was compressed to uniform thickness by placing 1000 gm weight for 5 min. Weight (50 gm) was added to the pan. The time required separating the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spreadability (S).

$$\text{Spreadability (g.cm/s) (S)} = M \times L / T$$

Where M = weight tide to upper slide, L = length moved on the glass slide, T = time taken¹⁴.

Determination of gel strength:

A TA-XT2i (Stable microsystems, Ltd. UK) Texture analyser is used. The experiment was done by placing the gels in standard beaker below the probe. In this an analytical probe is then immersed into the sample. The Texture Analyser was set to the 'gelling strength test' mode or compression

mode with a test-speed of 1.0 mm/s. An acquisition rate of 50 points per seconds and a trigger force of 5 gm were selected. An aluminium probe of 7.6 cm diameter was used for all the samples. The study was carried out at room temperature. The force required to penetrate the gel was measured as gel strength in terms of gm¹³.

In-vitro diffusion study:

The experiments were conducted in Franz diffusion cells with donor compartment and a receiver compartment. A suitable size of pre-treated cellophane membrane was mounted in between donor and receptor cells of the Franz diffusion cells (locally fabricated). The receiver contains 15 ml phosphate buffer solution (PBS), PBS pH 6.8 was constantly stirred by magnetic stirrer at 150 rpm and was maintained at a temperature of $37 \pm 1^\circ\text{C}$ throughout the experiments. A formulation that is drug equivalent to 2 mg Lornoxicam was applied homogeneously in the donor compartments; 1ml samples were withdrawn from receiver at predetermined time intervals over 6 hours and immediately replaced with an equal volume of fresh PBS. Samples were assayed for drug content spectrophotometrically at 380 nm. Sink condition was maintained throughout the experiments¹⁴.

In-vivo anti-inflammatory activity:

Anti-inflammatory effect of topically applied Lornoxicam gel was determined in male albino rats (180-200g, 8-10 weeks) by carrageenan induced paw oedema method. For this purpose, rats were divided into two groups (n=3): **group 1**-normal control receiving 1% (w/v) carrageenan saline, **group 2**-Lornoxicam gel (F1). Briefly, 30 min after formulation application (0.25 g), rats of both treated groups were challenged by a subcutaneous injection of a 1% (w/v) solution of carrageenan in saline (0.1 ml) into plantar site of right hind paw. Then the volume of paw was measured in plethysmograph immediately after injection and considered as zero hour volume. Then after volume was taken at 0.5, 1, 2, 3, 4, 5, 6 hrs and the percentage inhibition of edema is calculated by following formula.

$$\text{Percent reduction of edema} = \frac{C-T}{C} \times 100$$

Where, C= mean volume of edema for control, T= mean volume of edema for treated group¹⁵.

Anti-inflammatory activity using iontophoretic delivery:

For this study, rats were divided into two groups (n=3) and abdominal part of the rats was shaved with area of 2cm² to apply the gel. **Group-1** normal control receiving 1% (w/v) carrageenan saline, **group-2** received Lornoxicam gel (F1) with anodal iontophoresis with 3V current for ten minutes. Briefly, 30 min after formulation application (0.25 g), rats of both treated groups were challenged by a subcutaneous injection of a 1% (w/v) solution of carrageenan in saline (0.1 ml) into plantar site of right hind paw. Then the volume of paw was measured in plethysmograph immediately after injection and considered as zero hour volume. Then after volume was taken at 0.5, 1, 2, 3, 4, 5, 6hrs and the percentage inhibition of edema was calculated and compared with that of anti-inflammatory activity showed by gel without iontophoretic delivery¹⁵.

Drug release kinetics:

To understand the drug release kinetics of the Lornoxicam gel formulation, the drug release data were treated with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to Korsmeyer-Peppas equation $M_t / M_a = Kt^n$, where ' M_t / M_a ' is fraction of drug released at time ' t ', ' K ' is kinetic constant and ' n ' is release exponent which characterized the drug release mechanism. If the value of ' n ' is less than 0.45 then it is considered as Fickian release, values more than 0.45 and less than 0.89 is considered as anomalous (non-Fickian) transport and finally ' n ' value greater than 0.89 follows super case-II release mechanism¹⁵.

Stability study:

Stability study of optimized formulation was carried out at 25°C/60% and 40°C/75% RH for a period of three months. During stability study *in-situ* gel was analysed for pH, viscosity, drug content and *in-vitro* drug release¹⁴.

RESULTS AND DISCUSSIONS:

Solubility:

Lornoxicam (LRN) is poorly soluble in water (0.0385±0.02 mg/ml). Among the different solubilizer screened LRN exhibited the highest solubility in 5% triethanolamine (42.5±0.01

mg/ml). Solubility of LRN in chloroform and PBS pH 6.8 was 0.25 ± 0.2 and 0.15 ± 0.2 mg/ml respectively. Hence 5% triethanolamine is selected for the formulation of LRN gel.

FT-IR interaction studies:

From the FT-IR studies, all the characteristic peaks of Lornoxicam were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. The spectra were recorded over the wave number range 4000-400 cm^{-1} . The FT-IR spectrum of Lornoxicam showed a

characteristic peak at $3,065 \text{ cm}^{-1}$ corresponding to NH stretching vibration. Intense absorption peak was found at $1,733 \text{ cm}^{-1}$ due to the stretching vibration of the C=O group in the primary amide. The stretching vibrations of the S=O group appeared at $1,034 \text{ cm}^{-1}$. C-Cl bending vibration at 948 cm^{-1} which indicates groups is match with structure of drug and confirms the purity of the drug. There is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients (**Fig. 1** and **Fig.2**).

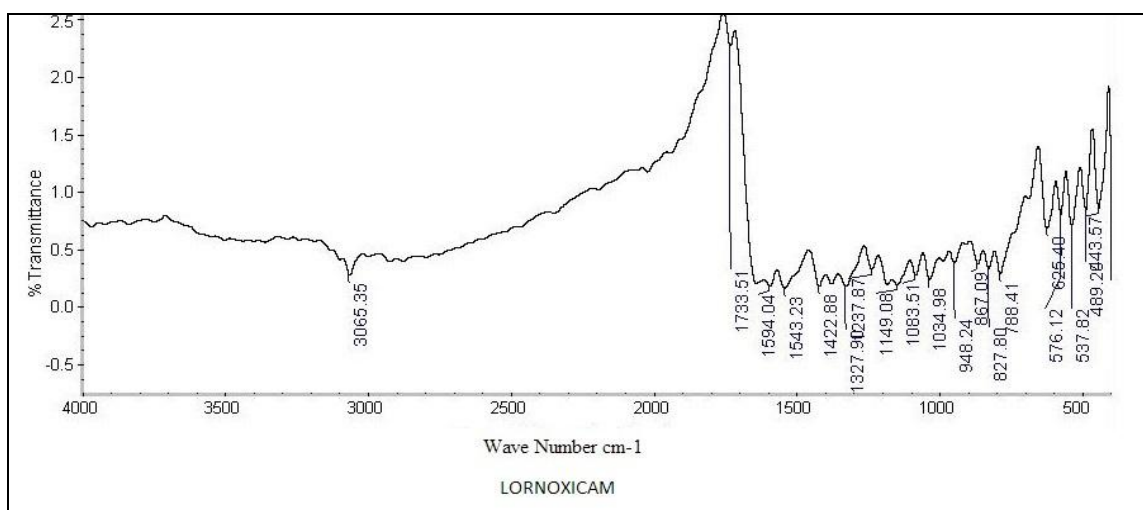


FIG. 1: FT-IR OF PURE LORNOXICAM

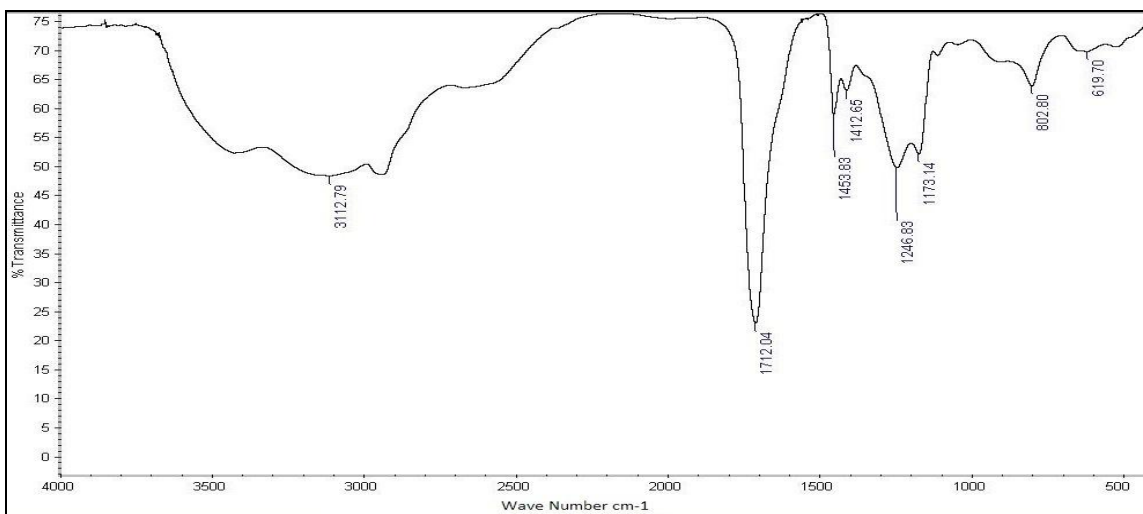


FIG. 2: FT-IR OF LORNOXICAM AND CARBOPOL

DSC studies:

The DSC thermogram of Lornoxicam was typical of a crystalline substance, exhibiting a sharp exothermic peak at 223.66°C corresponding to its melting and decomposition. The thermogram of Lornoxicam with excipients showed the existence of the drug exothermic peak at 239.07°C . This

showed not much shift in the exothermic peak of pure drug which indicates absence of interactions between Lornoxicam and other excipients. The DSC thermogram of pure drug, its physical mixture and formulation are shown in the **Fig.3** and **Fig. 4**.

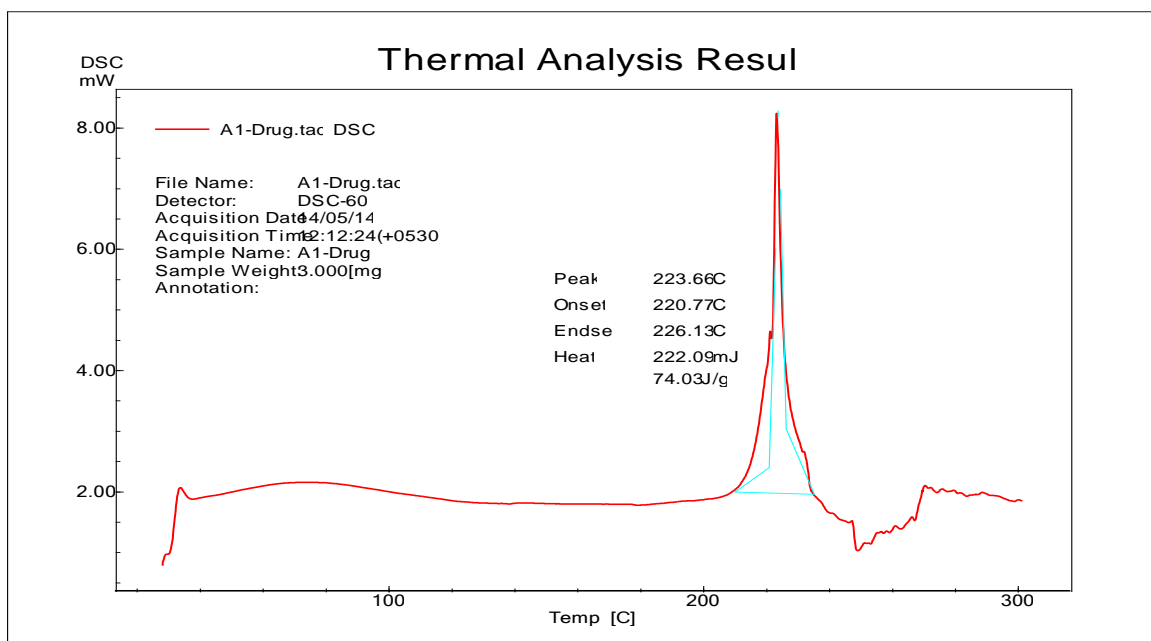


FIG. 3: DSC THERMOGRAM OF LORNOXICAM PURE DRUG

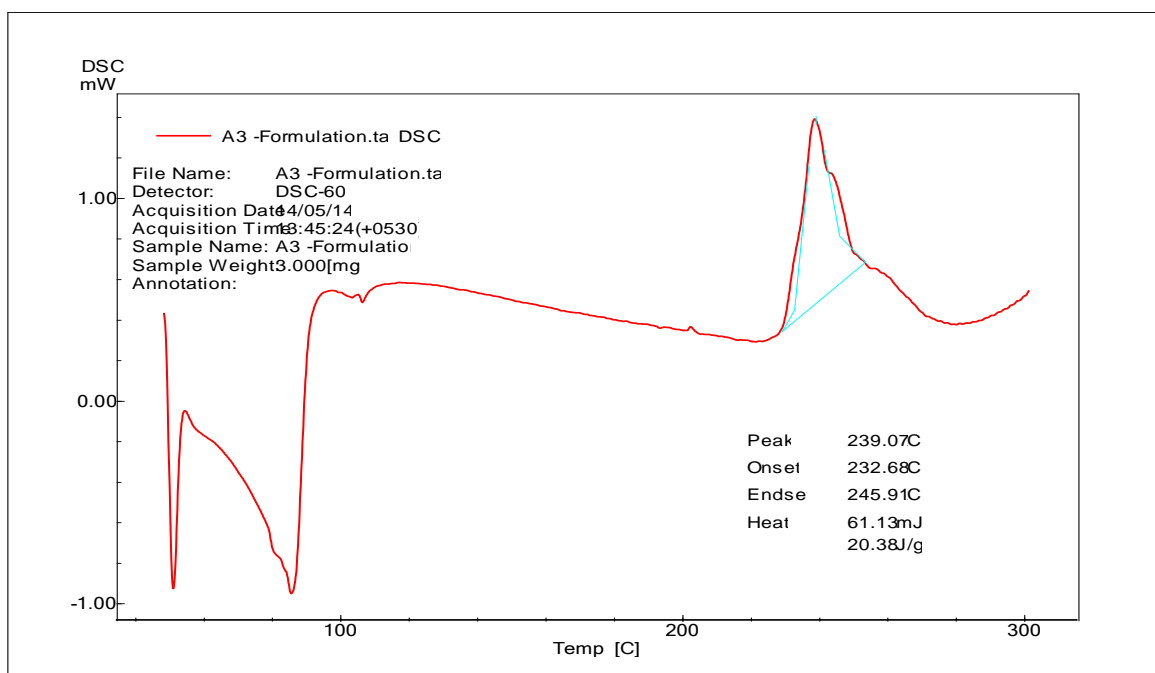


FIG. 4: DSC THERMOGRAM OF LORNOXICAM GEL FORMULATION

Evaluation of Lornoxicam gel:

Carbopol (1% w/w) was used for the preparation of gel on the basis of optimum viscosity and spreadability because at 0.5% w/w it produced gel with fluid consistency and above 1.5% it produced a gel with high viscosity and low spreadability.

pH:

The pH of Lornoxicam gels were determined by using a calibrated pH meter (equiptronics) and pH of the gel was found to be 6.8 ± 0.4 (n=3), which is

required pH for transdermal drug application (Table 2).

Drug content:

The drug content of Lornoxicam gel was found to be $97.07 \pm 0.1\%$, results complies with official pharmacopeia (Table 2).

Viscosity and rheological studies:

The viscosity of LRN gels were shown in Table 3 and rheological property was shown in Fig. 5.

Rheological studies showed that the viscosity of the formulations decreases with increase in share rate, which indicates the characteristics of pseudo-

plastic flow or non-Newtonian flow (shear thinning).

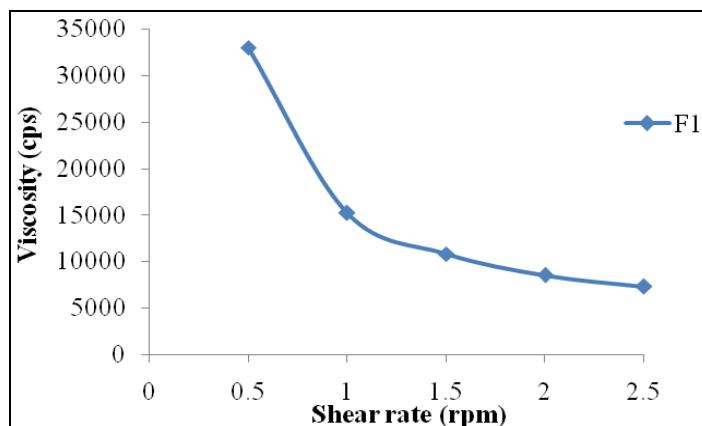


FIG. 5: RHEOLOGICAL PROPERTIES OF LORNOXICAM GEL FORMULATION

Spreadability:

The spreadability of the gels was found to be 7.00g.cm/sec, which is indicative of good spreadability. The obtained results showed that gel gets evenly spread after application (Table 2).

TABLE 2: CHARACTERISTICS OF LORNOXICAM GEL FORMULATION

Formulation Code	pH	Spreadability g.cm/s	Gel strength g/sec	Drug content (%v/w)
F1	6.5	7.00	203.33	93.81±0.058

Gel strength:

The gel strength of the Lornoxicam gels formulations were determined by using texture analyser (TA.XT2i, Stable micro systems, Ltd. UK) and gel strength of gel is tabulated in Table 2.

In-vitro diffusion studies:

From the *in-vitro* studies it's found that the percentage of Lornoxicam released after 6 hr was 42% i.e. drug is released in sustain manner for prolonged period of time (Fig.6).

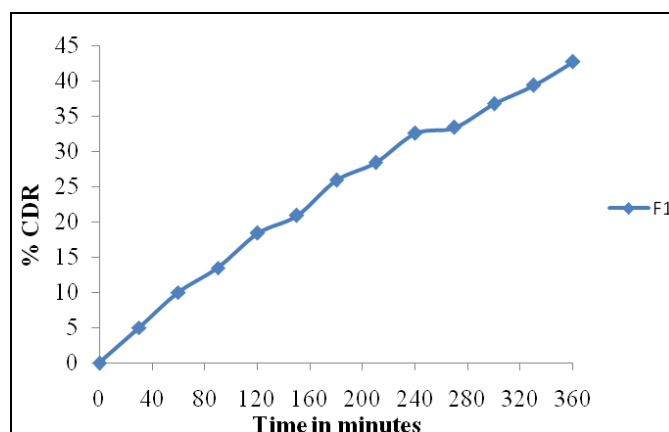


FIG. 6: IN-VITRO RELEASE STUDIES OF LORNOXICAM GEL FORMULATION

In-vivo anti-inflammatory activity:

In anti-inflammatory activity test using carrageenan induced paw oedema method gel formulation, F1 exhibited anti-inflammatory activity up to 6 hours (Fig.7) and peak activity was observed between 2–6 hours. Percentage oedema inhibition produced by the application of gel F1 was 9-22% between 1-6 hours. The result confirmed the fact that significant

amount of Lornoxicam was delivered from the gel to induce the anti-inflammatory effect (Fig.7).

In-vivo anti-inflammatory activity using iontophoresis:

In anti-inflammatory activity test using iontophoretic delivery of gel formulation F1 exhibited anti-inflammatory activity up to 6 hr.

Initially percentage oedema inhibited by both methods was less but with increase in time maximum inhibition was observed. The peak activity was observed between 2-6 hr. Percentage oedema inhibition produced by gel F1 was 22-62% between 1-6 hours which was about 2.5 fold more

than that of passive delivery of formulation. The activity of F1 with iontophoresis was found to be more, which might be due to modification of the stratum corneum as well as driving force of current across the skin (Fig.7).

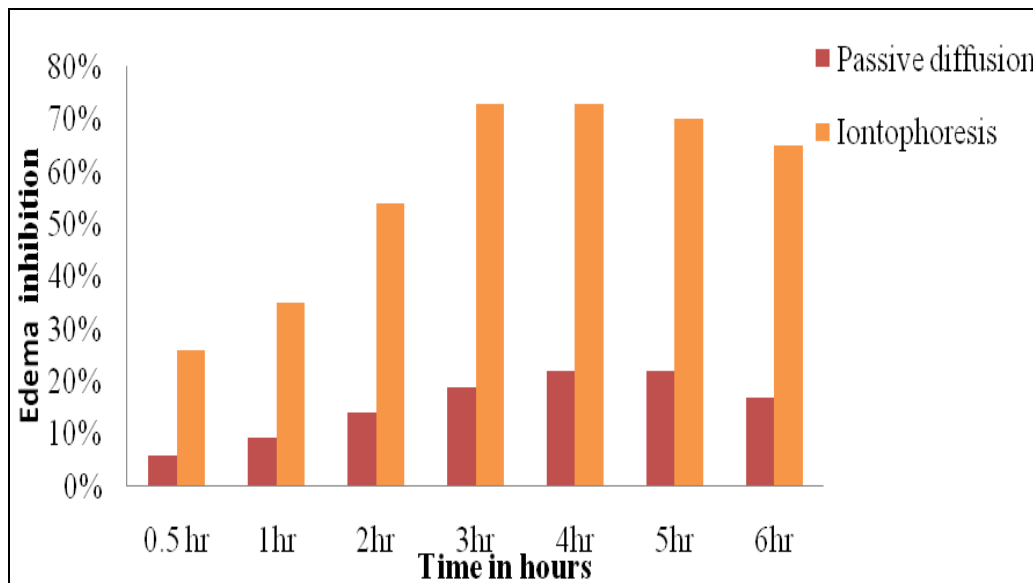


FIG. 7: COMPARATIVE PERCENTAGE INHIBITION OF PAW OEDEMA BY PASSIVE DIFFUSION AND IONTOPHORESIS

Anti-inflammatory activity study using 1.5V and 3.0V:

From the anti-inflammatory activity studies using iontophoresis i.e. 1.5V and 3.0V, it was observed that in both voltage formulations F1 exhibited anti-inflammatory activity at up to 6 hr. Gel formulation exhibited higher activity when the voltage applied was higher i.e. 3.0V and the percentage edema inhibition was found to be 26%-73% within 0.5 to

6 hr and percentage edema inhibition was decreased when 1.5V current was applied. Due to increased current volts (3V) the activity enhanced as compared to that of iontophoresis done with 1.5V but it seems that the activity became stagnant after 3rd hour to 5th hr and decreased (Table 4). This indicates that increase in current strength increases the drug transport but becomes stagnant at certain point and decreases thereafter.

TABLE 4: COMPARISON OF PERCENTAGE INHIBITION OF PAW OEDEMA USING IONTOPHORESIS (1.5V AND 3.0V)

Voltage applied	Percentage inhibition of paw oedema by iontophoresis						
	Time in hours						
	0.5	1	2	3	4	5	6
1.5V	24	30	47	63	68	61	58
3.0V	26	35	54	73	73	70	65

Drug release kinetics:

From the kinetic studies, the examination of correlation coefficient ‘r’ indicated that the drug release followed diffusion controlled mechanism through first order kinetics. It was found that the value of ‘r’ for first order was 0.996 which is near to 1 when compared to zero order Higuchi square root model. Further, to understand the drug release mechanism, the data were fitted into

Korsmeyer/Peppas exponential model $M_t / M_a = Kt^n$. Where M_t / M_a is the fraction of drug released after time ‘t’ and ‘k’ is kinetic constant and ‘n’ release exponent which characterizes the drug transport mechanism. The value for ‘n’ was found to be 1.132 indicating gel follows Super Case II release mechanism (Table 5).

TABLE 5: RELEASE EXPONENT VALUES AND RATE CONSTANT VALUES FOR LORNOXICAM GEL

Formulation Code	Kinetic models				
	Zero order	First order	Higuchi	Korsmeyer peppas	
	R ²	R ²	R ²	R ²	n
F1	0.986	0.996	0.962	0.686	1.132

Stability studies:

The results of stability studies revealed that there was no change visual appearance, spreadability, and gel strength. All the formulation has shown slight changes in pH and viscosity which was in acceptable limits (± 0.5). Study of the drug content, *in-vitro* drug release, viscosity and pH revealed that there were no definite changes observed that justify drug degradation.

CONCLUSION: Above investigation presents physiochemically stable topical gel of Lornoxicam which would minimise oral side effects of Lornoxicam and deliver significant amount of drug across skin. From anti-inflammatory activity studies it is concluded that the iontophoretic delivery of Lornoxicam is far effective than passive delivery. Iontophoresis (physical method) can inhibit the large extent of inflammation in short period of time when compared to passive delivery.

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