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Formulation and Evaluation of Etoricoxib Topical Gel using Different Gelling Agent and Different Penetration Enhancer

Dinesh Chandra*[1], Sarvesh Kumar Singh[1], Jayant Kumar Maurya [1], Santosh Singh[1], Vikash Mishra[1], Ravi Rai[2]

1. Kamla Nehru Institute of Management and Technology, Sultanpur, India.

2. M.I.T, meerut, India.

ABSTRACT

The present investigation has been undertaken with aim to formulation and evaluation of etoricoxib gel with different gelling agent and different penetration enhancer. Etoricoxib is highly selective cyclooxygenase-2 (COX-2) inhibitor. In this present study gel with carbopol, HPMC and Na-CMC as gelling agent prepared with different penetration enhancer like propyl glycol, oleic acid. Menthol oil. Formulation were evaluated for pH, stability study, spreadibilty, extrudabilty, bioadhesive (ex-vivo), skin irritation, viscosity, appearance and In-vitro drug diffusion. The formulation of Etoricoxib topical gel was prepared using carbopol, HPMC and Na-cmc in three batches A, B and C. With the consideration of all formulation characteristic and parameter we selected batch-A formulation for further study of anti-inflammatory and anti-analgesic activity. It was concluded that the Etoricoxib gel formulation containing carbopol with increase concentration of propyl glycol 10% and 2% oleic acid (OA) was suitable for topical application and it shows comparable result with market product and shows much better result of formulation, anti-inflammatory and anti-analgesic activity.

Keywords: Etoricoxib, topical gel, Carbopol, HPMC, Sodium CMC, Propyl glycol, Oleic acid, Anti-inflammatory activity, Anti-analgesic activity.

*Corresponding Author Email: Hii.sarvesh@gmail.com

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INTRODUCTION

The transdermal drug delivery system are self contained, discrete dosage forms which when applied to intact skin deliver the through the skin at a controlled rate to the systemic circulation[1].

The success of transdermal delivery depends on the ability of the drug to permeate the skin in sufficient quantities to achieve its desired therapeutic effects. The skin is very effective as a selective penetration barrier. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum provides the gretest resistance to penetration and it is the rate-limiting step in percutaneous absorbtion[2].

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes leading to a need for high and /or frequent dosing, which can be both cost prohibitive and inconvenient[3].

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficiency and safety of drugs by more precise, spatial and temporal placement within the body thereby reducing both size and number of doses. One of the methods most often utilized has been transdermal delivery. This delivery transports therapeutic substances through the skin for systemic effect.

Gel are transparent to opaque semisolids containing a high ratio of solvent to gelling agent merge or entangle to form a three-dimensional colloidal network structure. This network limits fluid flow by entrapment and immobilization of the solvent molecules. The network structure is also responsible for a gel resistance to deformation and therefore, its viscoelastic properties. Gel tend to be smooth, elegant, non greasy and produce cooling effect and utilize better drug release as compared to other semi-solid formulation[4,5].

The use of non-steroidal anti-inflammatory drug is well recognized for regional inflammatory disorders such as muscle pain, osteoarhtritis and rheumatoid arthritis[6,7].

Etoricoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and antipyretic activities. It is potent, highly selective Etoricoxib, which is described chemically as 5-chloro-6'-methyl-3-[4-(methylsulfonyl) phenyl]-2, 3'-bipyridine. However its use has been associated with a number of gastrointestinal disorders. These potential side effects may be overcome by the topical administration of the drug[8,9].

In the present study, topical gel formulations of etoricoxib were prepared using HPMC, Na-

CMC, Na-alginate and carbopol 934 as gel forming polymers. After *in vitro* evaluation of gel formulations permeation of etoricoxib was evaluated.

MATERIALS AND METHOD

Etoricoxib was gifted sample from sun pharma Pvt. Ltd.,Sikkim, Carbapol 934, Na-alginate, HPMC, Na-CMC, propylene glycol, oleic acid, methyl paraben, propyl paraben, triethanolamine from S.D Fine. chem. Pvt. Limited, Mumbai.

Experimental Animal

Adult wistar albino rats, weighing (150-200g) were procured from Institutional of Health and Biologicals. The animals were feed a normal laboratory pellet diet and water *adlibitum*. They were housed in colony cages under standard laboratory conditions (12:12h light and day cycle, temperature at 25±2°C and relative humidity at 55±10%). The ethical clearance was obtained from Institutional Animal Ethics Committee (CPCSEA NO.711/02/a/CPCSEA).

Method

The specific amount of drug was dissolved in preweighed amount of ethanol to preweighed amount of permeation enhancer was added. And after the resulting solution appropriate amount of polymer and other excipients (methyl paraben and propyl paraben) was added slowly and kept under constant stirring until clear gel was formed. Etoricoxib gel formulations were prepared using different concentration of Carbapol 934, Na-alginate, HPMC, Na-CMC were prepared with different concentration of permeation enhancers like, menthol oil, oleic acid. pH of the gel was brought to skin pH by TEA (triethnolamine).

Table-1 Composition of Etoricoxib gel Formulation

Ingredients %W/W	Batch A			Batch B			Batch C		
	A_1	A_2	A_3	B_1	B_2	B_3	C_1	C_2	C_3
Etoricoxib	1	1	1	1	1	1	1	1	1
Carbapol 934	2	2	2	-	-	-	-	-	-
HPMC	-	-	-	2	2	2	-	-	-
Na-CMC	-	-	-	-	-	-	2	2	2
Propyl glycol	2.5	5	10	2.0	2.5	5	2.0	2.5	5
Oliec acid	2	2	2	2	2	2	2	2	2
Methyl paraben	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Propyl paraben	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Triethnolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Hydro alc. vehicle	90	90	90	90	90	90	90	90	90

EVALUATION

Appearance

Colour is important for patient compliance. The prepared gels were inspected visually for clarity, colour and presence of any particle.

pH

The pH of gel was determined using digital pH meter. 2gm Etoricoxib gel was stirred in distilled water till a uniform suspension is formed. The volume was made up to 40 ml and pH of the solution was measured.

Viscosity

Viscosity of the gel was determined by using (LV) Brookfield viscometer (Dial type). As the system is non-Newtonian spindle no. 4 is used. Viscosity was measured for the fixed number of time 2 min for 0.3 rpm.

Skin irritation[10]

Ten healthy male and female volunteers were selected for skin irritation testing. 100 mg gel was applied on area of 2 cm for 6 hours, on the interior surface of upper arm and covered with cotton bandage. After 6 hr the sites were cleaned with acetone and readings was made according to the scale given by Draize.

No irritation: 0

Slight irritation: 1, Irritation: 2

Spreadability[11,12,13,14,15]

Spreadability of formulations was determined by an apparatus suggested by Multimer45, which was fabricated itself in laboratory and used for slide fixed on wooded block and upper slide with one end tide to glass slide and other end tied with other end tied to weight pan. An excess of gel (2 – 5 gm) was placed in between two glass slides and then 1000 gm weight was placed on slides for 5 min to compress the sample to a uniform thickness. Weight (80 gm) was added to pan. The time (seconds) required to separate the two slides, was taken as a measure of spreadability.

It was calculated using formula,

$$S = M. L / T$$

Where, S = spreadability

M = weight tied to upper slide

L = length of glass slide

T = time taken Shorter time interval, to cover distance of 6.5 cm, indicates better spreadability.

Extrudability[16,17] **–**

In this test, sample is extruded from the tube by usual procedure. A closed collapsible tube containing gel was passed firmly at crimpened end. When the cap was removed, gel extrudes until pressure was dissipates. The weight in grams required to extrude 0.5 cm ribbon of gel in 10

seconds was determined. The results for each formulation were recorded as extrusion pressure in grams.

Drug Content[18,19]

1gm gel was dissolved with little amount of methanol in a 100 ml volumetric flask and mixture was shaken till solution was affected. The volume was made up to 100 ml with methanol. The solution was filtered through Whatman filter paper (No. 41). Further dilute 5ml to 50 ml with methanol. The absorbance of the solution was measured at 238 nm (systronics pc based double beam spectrophotometer 2202) against reagent blank.

***In Vitro* Drug Diffusion Study [20]:**

All formulations were subjected to in vitro diffusion through cellulose membrane by using Keshary- Chein type cell. The receptor compartment was filled with saline phosphate buffer pH 7.4 and methanol (90:10) and kept at 32 + 0.5°C and stirred with the help of magnetic stirrer. Methanol (10%) was added to maintained sink condition. About 200 – 300 mg of gel was placed on the cellulose membrane. 1ml of sample was withdrawn from the receptor compartment at 1, 2, 3, 4, 5, 6, 7, 8 hour and replaced with same volume of medium. All samples were diluted up to 10 ml with medium and analyzed for Etoricoxib content spectrophotometrically (systronics pc based double beam spectrophotometer 2202) at wavelength 238 nm.

Ex–Vivo Bioadhesive Strength Measurement Of Etoricoxib Gel[21,22]:

Fresh goat hairless skin was obtained from a local slaughter – house and used within 2 hours of slaughter. The skin was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with 0.1 N NaoH. The modified Patel et al (2007) method was used for the measurement of bioadhesive strength. The fresh skin was cut into pieces and washed with 0.1 N NaoH. Two pieces of skin were tied to the two glass slide separately from that one glass slide was fixed on the wooden piece and other piece was tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left – hand pan. 1 gm of topical gel was placed between these two slides containing hairless skin pieces, and extra weight from the left pan was removed to sandwich the two pieces of skin and some pressure was applied to remove the presence of air. The balance was kept in this position for 5 minutes. Weight was added slowly at 200 mg/ min to the left – hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the gel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength was calculated by using following:

Bioadhesive Strength = Weight required (g) / Area (cm2)

Assessment of Anti-Inflammatory Activity [23,24,25,26]**:**

Anti-inflammatory activity was evaluated by inducing paw oedema using carrageenan in rats. Rats were deprived of food overnight and treated topically on the dorsal part of the hind paw with the 55 mg/kg Etoricoxib gel (A_1, A_2, A_3, positive control (pure etoricoxib 10mg/kg and control) 60 min before 0.1 mL 1% carrageenan in isotonic saline was injected sub-plantar into the left hind paw. The contralateral paw was injected with 0.1 mL saline and used as a control. The volume difference between the carrageenan and saline injected paws was used to evaluate the inflammatory response. Paw volume (V) was measured by water plethysmometer immediately before and 1, 2, 3, 4, and 5 h after the injection of carrageenan into the plantar region of the left hind paw (n = 5 for each group). The percent inhibition of oedema induced by carrageenan was calculated for each group using following equation:

$$\text{Inhibition of oedema (\%)} = V_{\text{control}} - V_{\text{treated}} / V_{\text{control}} \times 100$$

Hot plate test[23,24,25,26]:

Rats were placed on an aluminum hot plate kept at a temperature of 62 ±0.5 ◦C for a maximum time of 30 s. The temperature of the plate was monitored at all times. For each set of experiments, 50 mg/kg of Etoricoxib gel (A_1, A_2, and A_3), positive control (containing 10mg/kg pure Etoricoxib) and control were applied to an area of approximately 4 cm on the dorsal skin. The reaction time was determined when animals licked their fore and hind paws and jumped before and 15, 30, 45, 60, 90, and 120 min after the topical application of each formulation (n = 5 for each group). After each measurement, the plate was wiped with a damp cloth to remove traces of urine and faeces.

Stability Study

Selected formulations (A_1, A_2, A_3, B_1, B_2, B_3, C_1, C_2 and C_3) which showed comparatively better results were subjected to stability

study. Formulations were stored at room temperature for two months. Physical evaluation of the samples stability carried out by visual inspection. Stability was evaluated by pH measurements and spectrophotometric analysis of the drug content.

RESULTS AND DISCUSSION

All the formulations of etoricoxib(Table-1) were good homogenesity and showed no clogging and lumps which indicate good texture of system. pH of hydrogels was around the neutral pH and in the range of 6.8-7.1. All gel formulations showed not any skin irritation on intact skin. Therefore, indicating skin acceptability of these gel formulations for topical application. The

description of appearance has been provided in Table-02. Viscosity is an important parameter for characterizing the gels as it affects the spreadibility, extrudability and release of the drug. The ranges of viscosities of formulations were between 24000-32250 cps (Table -2). Easy spreadability is one of the most important characteristics of any topical preparation as far as patient compliance is concerned. Gel is considered to be good if it takes minimum time to spread on the surface. Among the various gels studied A batch of etoricoxib gel has better spreadability and drug release. The values of spreadability indicate that the gel is easily spreadable by small amount of shear. Extrusion of gel from the tube is important during application and for the patient compliance. The values of extrudability of different formulations were ranges in between 475-612 (Table-3). Drug content uniformity of all gel formulations was observed and A batch shows the 99.5% drug content (Table-3). Maximum drug diffusion was observed from A batch of etoricoxib gel as compare to marketed gel. On the base of different evaluation parameters made on all formulations, batch A declared as an optimized batch. The cumulative drug release profile of different formulation ranges from 49 to 83 percentage in 8 hours when compared to marketed formulation having 75 percentage in 8 hours. With consideration of all formulation characteristic and parameter we selected Batch-A formulation for further study of anti-inflammatory and analgesic activity.

Table-2 Evaluation of appearance, pH, Skin irritation, Viscosity of different batch of Etoricoxib gel formulation

Batch	Formulation	Appearance	pH	Skin irritation	Viscosity(cp)
	A_1	Cream	6.9	0	26000
	A_2	Cream	7.0	0	25000
Batch A	A_3	Cream	7.1	0	27000
	B_1	White	6.7	0	21000
	B_2	White	6.9	0	22170
Batch B	B_3	White	6.8	0	20720
	C_1	White	6.9	0	22250
	C_2	White	6.8	0	23750
Batch C	C_3	White	6.9	0	22000
	Market gel	Cream	7.0	0	25950

Table-3 Evaluation of Spreadibilty, Extrudabilty, bioadhesive strength & drug content of different batch of etoricoxib gel formulation

	Formulation	Time (sec)	Spreadability (g.cm/sec)	Extrudability (Wt. req. in g)	Bioadhesive Strength (g/cm)	Drug Content%
Batch A	A_1	11	53	612	1.19	99.2
	A_2	11	53	570	1.28	99.5
	A_3	12	48.5	563	1.75	98.7

	B_1	13	44	556	1.06	96.5
Batch	B_2	14	41	563	1.14	97.8
B	B_3	15	39	554	1.11	98.9
	C_1	13	43	475	1.19	98.4
	C_2	15	38	498	1.20	97.5
Batch	C_3	16	35	504	1.07	98.6
C	Market gel	10	65	560	1.13	97

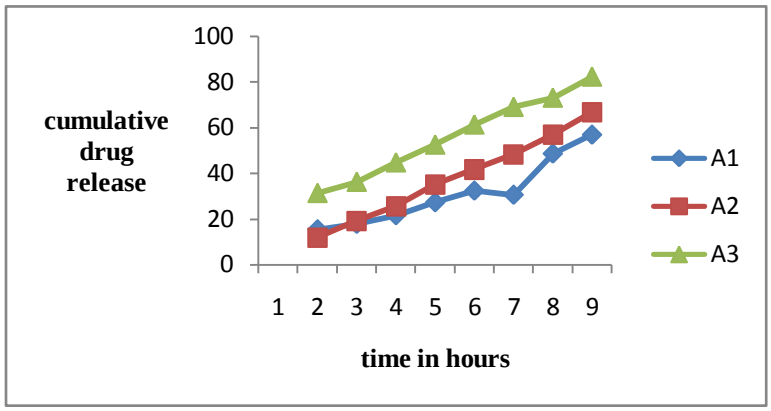

Figure-1. Drug release profile of etoricoxib gel with Carbopol

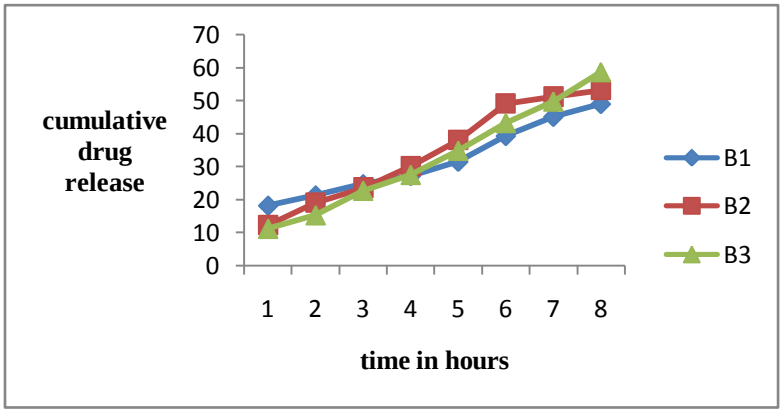

Figure-2. Drug release profile of etoricoxib gel with HPMC

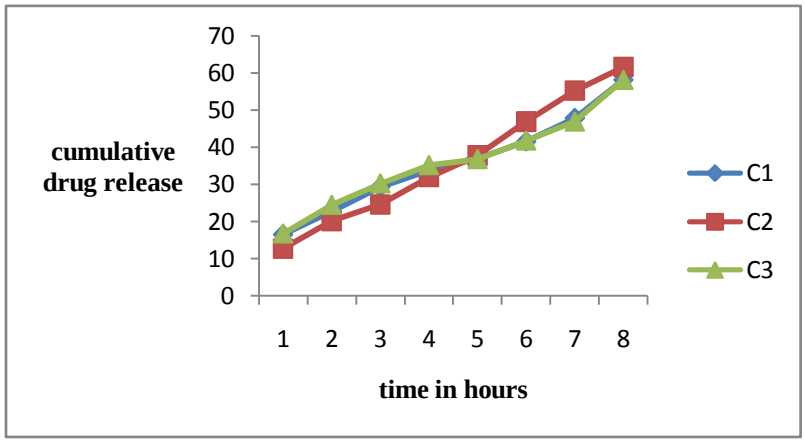

Figure-3. Drug release profile of etoricoxib gel with Na-CMC

Table-4 Cumulative % drug release profile of etoricoxib gel

Time(hrs)	A_1	A_2	A_3	B_1	B_2	B_3	C_1	C_2	C_3	Market Gel
0	00	00	00	00	00	00	00	00	00	00
1	15.4	11.8	31.3	18.2	12.3	11.3	16.5	12.80	16.8	22.4
2	17.8	19.06	36.2	21.3	19	15.4	22.8	20.21	24.5	27
3	21.6	25.43	44.7	24.7	23.6	22.8	29.3	24.70	30.3	33.2
4	27.3	35.21	52.5	27.2	30.01	27.6	33.7	32.00	35.2	46.9
5	32.4	41.70	61.3	31.5	38.09	34.9	36.9	37.80	36.80	51.8
6	30.6	48.34	69.02	39.3	49.06	43.3	41.5	46.90	41.80	60.5
7	48.7	57.1	73.07	45.1	51.07	49.8	47.8	55.30	46.9	67.7
8	57	66.8	82.3	49	53.1	58.7	58.1	61.60	58.1	74.1

Table-5 Anti-Inflammatory Activity

	0	1hr	2hr	3hr	4hr	5hr
Control	00	0.32±0.001	0.41±0.001	0.63±0.003	0.69±0.007	0.64±0.004
PositiveControl	00	0.19±0.002	0.21±0.001	0.23±0.004	0.29±0.002	0.27±0.002
A_1	00	0.21±0.001	0.24±0.002	0.27±0.008	0.26±0.004	0.24±0.002
A_2	00	0.23±0.005	0.23±0.002	0.24±0.003	0.23±0.003	0.23±0.004
A_3	00	0.21±0.003	0.23±0.003	0.24±0.002	0.24±0.003	0.23±0.002

Anti-inflammatory Effect

The carrageenan-induced oedema test was used to examine the in-vivo effects of the developed Etoricoxib gel formulations. Intraplantar injection of carrageenan caused a time-dependent paw oedema in the rat, whereas the saline injection did not cause swelling. The application of the formulations (Positive control, A_1, A_2, and A_3) inhibited paw swelling. The maximum percent inhibition for A_1 was observed at 4 h which was 59.40% , likewise, A_2 and A_3 was observed at 3 h which was found to be 58.91% and 58.91% respectively(Table-6).

Table-6 Percentage Anti-Inflammatory activity by inhibition of odema

	1hr	2hr	3hr	4hr	5hr
Positive control	36.22%	44.49%	60.3%	55.12%	54.91%
A_1	30.33%	39.84%	54.23%	59.40%	59.52%
A_2	33.28%	42.16%	58.91%	63.69%	61.06%
A_3	33.28%	42.16%	58.91%	62.27%	61.06%

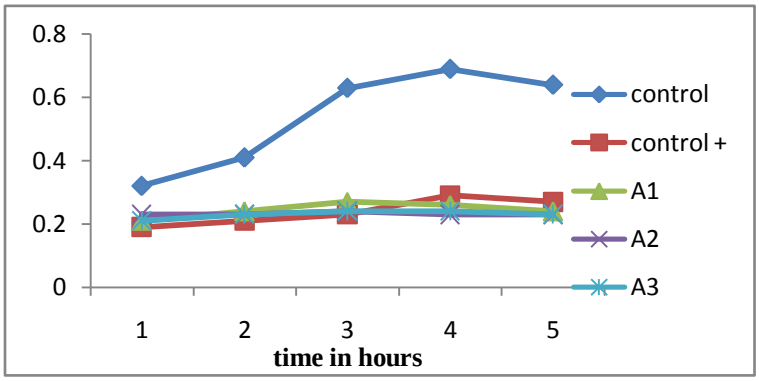

Figure-4. Inflammatory activity

Carrageenan administration into the rat hind paw produced a significant inflammation associated with hyperalgesia, as shown by decreased rat paw withdrawal latency in response to a thermal stimulus. Previously it has been reported that the formulations having a better drug release profile will have the strongest acute anti-inflammatory activity. Similarly, the results of this study demonstrated that the A_1, A_2 and A_3 having better cumulative % of drug release (99.2, 99.5 and 98.7 respectively) possessed the strongest anti-inflammatory activity.

In order to have a better comparison between the anti inflammatory activity of Etoricoxib pure (positive control) and Etoricoxib gel (A_1, A_2 and A_3), evaluation was made on the basis of their ability to inhibit the oedema produced in hind paw of rats after challenging with the carrageenan. In control group, the increase in paw volume was (0.31±0.001) ml at first hour. With time, the increase in paw volume increased up to 3th hour and then decreased, following administration of pure Etoricoxib at a dose of 10mg/kg body weight. On the other hand, the increase in paw volume following administration of Etoricoxib gel (A_1, A_2, and A_3) was slightly higher than that produced by the pure drug. However, the change in paw volume with time followed the same pattern. Pure Etoricoxib inhibits the paw oedema volume but to a lesser extent, on the other hand the inhibitory or anti-inflammatory effect produced by Etoricoxib loaded gel was found over a long period of time. From these observations it can be concluded that oleic acid is a bioavailability enhancing agent as it enhances bioavailability of Etoricoxib.

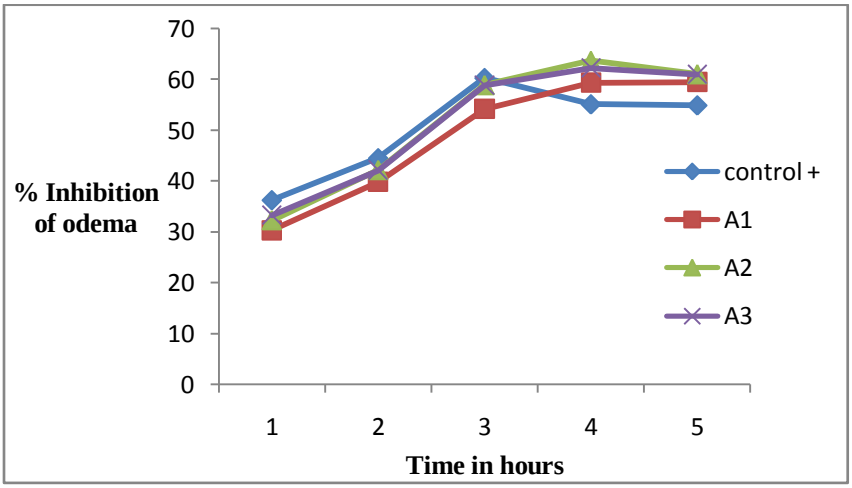

Figure-5. Percentage inhibition of odema

Hot plate test

In the hot plate test, the maximum analgesic response of A_1 was determined to be 8.4 ± 0.25 at 90 min. Likewise in A_2 was determine to be 9.0±0.26 at 45 and 60 min and in A_3 was at 45 min was to be 9.0±0.37 (Table-7).

Table-7 Analgesic Activity by hot plate experiment

	0min	15min	30min	45min	60min	90min	120min
Control	4.8±0.27	5.2±0.47	5.0±0.39	4.9±0.27	4.0±0.22	3.6±0.27	4.2±0.20
Positive Control	5.0±0.40	8.6±0.27	9.6±0.27	9.2±0.34	8.0±0.39	7.6±0.27	6.2±0.34
A_1	4.6±0.27	6.4±0.42	7.0±0.27	8.2±0.34	8.4±0.39	8.6±0.27	7.4±0.39
A_2	4.9±0.42	5.6±0.42	7.9±0.27	9.0±0.26	9.0±0.39	8.0±0.39	6.9±0.26
A_3	5.0±0.22	7.0±0.39	7.6±0.27	9.0±0.37	7.6±0.27	7.9±0.42	6.2±0.56

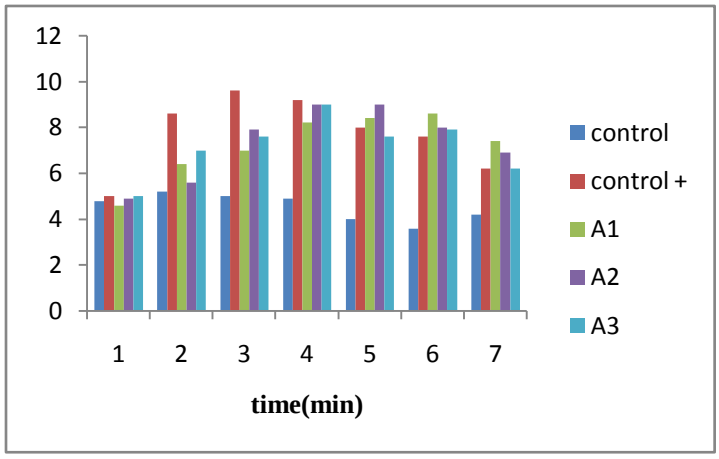

Figure-6. Hot plate method- assessment of analgesic activity

Stability studies

Stability studies at ambient room conditions for 2 months. After 2 months, gels did not show any change in physical appearance or drug content. It indicates that the drug was stable in gels even after two months of short term storage.

Results indicated that the carbopol gels show higher release of the drug compared to other gelling agents. Therefore, it can be concluded that carbopol is a potential gelling agent for Etoricoxib gels.

CONCLUSION

Etoricoxib is a non steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. It is potent, highly selective cyclooxygenase-2 (cox-2) inhibitor. To overcome the side effects associated with oral etoricoxib therapy and to have the benefits associated with topical therapy; etoricoxib topical gels are prepared in this study. From the above results it can be concluded that the etoricoxib gel formulation containing carbapol with increase concentration of propyle glycol upto 10% with 2% oleic acid was suitable for topical application and it shows comparable results with marketed product. It shows much better result of formulation, anti-inflammatory and anti-analgesic profile. It can also play a vital role in efficient drug delivery of drug like various anti-inflammatory and anti-analgesic agents.

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