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DEVELOPMENT, CHARACTERIZATION, AND INVESTIGATION OF ANTI-INFLAMMATORY POTENTIAL OF LUMIRACOXIB TOPICAL GEL

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Abstract

This research introduces the development of controlled release lumiracoxib gels that are effective when applied topically. The study examines the potential of these gels as carriers for delivering lumiracoxib. The in-vitro drug release pattern of all formulations demonstrated diffusion-controlled release following a zero-order pattern. Additionally, all formulations were determined to be compatible with the skin and stable according to the ICH guidelines. The optimized lumiracoxib gel exhibited a significant reduction in paw edema, reaching up to 79.51% after 6 hours. However, it was observed to have no significant effect on inhibiting 5-lipoxygenase, even with higher doses. Based on the findings, the lumiracoxib gel containing 0.5 g of Carbopol was identified as the optimized formulation for treating local inflammation.

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Introduction

In the context of delivering drugs topically, a formulation containing the drug is directly applied to the skin to target the cutaneous symptoms of a systemic condition[1,2]. This route of administration offers advantages such as bypassing first-pass effects[3], reducing gastrointestinal irritation, preventing metabolic degradation associated with oral intake, having a less greasy texture, and facilitating easy removal from the skin[4]. To overcome these drawbacks, the use of gel formulations has been proposed as a solution for topical drug delivery. These gels consist of gelling agents that, when dispersed in a suitable solvent, merge or entangle to create a three-dimensional colloidal network structure. This structure effectively restricts the flow of fluid by trapping and immobilizing solvent molecules[5].

NSAID exert their effects by disrupting the cyclooxygenase and lipoxygenase pathways, both of which play crucial roles in inflammatory disorders. The conversion of arachidonic acid (AA) to prostaglandins (PGs) is facilitated by cyclooxygenase (COX-1 and COX-2) [6,7]. COX-1 is present in most tissues and maintains normal bodily functions[8], while COX-2 is responsible for generating PGs during an inflammatory response[9]. On the other hand, the lipoxygenase pathway involves the conversion of arachidonic acid into leukotrienes (LTs) by the enzyme 5-lipoxygenase. This enzymatic transformation contributes to the development of chronic inflammatory conditions[10]. Lumiracoxib, known as {2-[(2-chloro-6-fluorophenyl)amino]-5-methylphenyl}acetic acid, possesses anti-inflammatory, analgesic, and antipyretic properties[11, 12]. However, the oral administration of COX-2 inhibitors, including lumiracoxib, is associated with increased risks of cardiovascular complications and potentially life-threatening gastrointestinal bleeding[13]. This research focuses on exploring the topical application of lumiracoxib (depicted in Figure 1) through the development of various polymeric gels. Additionally, the study investigates the ability of these gels to inhibit both the COX and LOX pathways.

Experimental Section

Analytical-grade chemicals were employed in the study without any additional purification. Double distilled water was utilized for UV analysis and in vitro release investigations.

Preparation of Gels

Polymeric dispersion techniques were employed to prepare a range of gel formulations[14]. The required quantity of the drug was dissolved in propylene glycol, followed by the addition of a hydroalcoholic vehicle in a ratio of 2:1. The resulting solution was then utilized to disperse non-toxic gelling agents, namely MC, Carbopol 934, and HPMC, at varying concentrations (0.5 g, 1 g, and 2 g) to obtain different homogeneous gels. Additionally, penetration enhancers and other excipients such as methyl paraben and propyl paraben were incorporated while maintaining continuous stirring. The pH of all formulations was adjusted to match the skin's pH by adding TEM. Any trapped air bubbles were eliminated by placing the gels in a vacuum oven (Model: Acm-22068-I, Acmas, India) for a duration of 2 hours.

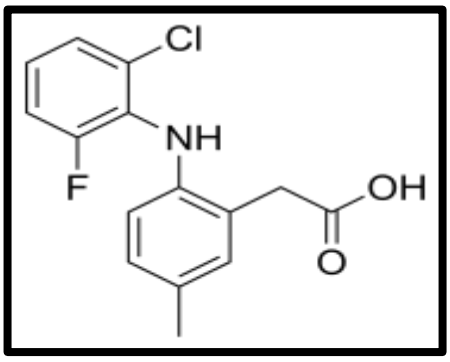

Fig 01: Lumiracoxib

Evaluation of Gels

The physical characteristics of the formulated gels were assessed through visual examination to determine their

appearance, presence of any blockages, and sudden changes in viscosity[15]. A smear of the gels was prepared on a glass slide and observed under a microscope to identify the presence of any blockages. The formulations were applied to the skin, and their sensory properties were evaluated using psychorheological techniques. The drug content was quantified spectrophotometrically following a previously described procedure[14]. In this method, a sample of the formulation (0.5 g) was diluted with a 1% w/v solution of sodium lauryl sulphate (SLS) and thoroughly dissolved by shaking. The resulting solution was then filtered using a Whatman filter paper (No.1). The filtrate was analyzed spectrophotometrically at a wavelength of 239 nm (lmax). Viscosity measurements were performed at room temperature (RT) using a programmable cone and plate rheometer (Model: DV-III ULTRA, Brookfield Engineering Lab; Inc; Middleboro, USA) equipped with a Cp-52 cone spindle. The pH of the formulations was determined using a pH meter (Model: 7007, Digisun electronics, Hyderabad, India)[17].

Spreadability

A custom apparatus was constructed to evaluate the spreadability of the formulated gels. The apparatus consisted of a wooden block with a pulley attached at one end. A ground glass slide was securely positioned on the block, and an excess amount of the formulated gel (2 g) was placed on it. Another glass slide with the same dimensions as the fixed ground slide, equipped with a hook, was used to sandwich the gel. A weight of 1 kg was placed on top of the two slides for a few minutes to eliminate trapped air and create a uniform gel film between the slides. Any excess gel from the edges was carefully removed. The hook on the sandwiched slides was connected to the pulley, and a weight was added to it. The time taken for the top slide to travel a distance of 7.5 cm was recorded.[18]

In vitro Drug Diffusion Studies

The drug diffusion rate from various gel formulations was investigated using a modified Keishery Chein Cell. A cellophane membrane (MWCO 12-14 kD, HIMEDIA, Mumbai, India) was employed as a barrier in the diffusion cell[19,20]. The diffusion cell, along with the diffusion membrane (with an effective surface area of 3.8 cm^2), was assembled on a magnetic stirrer. This membrane acted as a separator between the donor and receptor compartments. The receptor compartment contained a 1% w/v aqueous solution of SLS as the diffusion medium, which was maintained at a temperature of 32±2°C for 30 minutes to establish equilibrium. In the donor compartment, 1 g of the gel was placed on the membrane.

At predetermined intervals, a 5 ml sample was withdrawn from the receptor compartment for duration of 6 hours. The withdrawn sample was replaced with an equal volume of fresh medium. The absorbance of these samples was measured spectrophotometrically at a wavelength of 239 nm using a UV-VIS double beam spectrophotometer (Model: Shimadzu-1700, Shimadzu Corp., Japan). The cumulative release (%) of lumiracoxib from the different gel formulations was calculated based on these measurements.

Skin Compatibility Studies[21]

The study protocols were authorized by the Institutional Animal Ethical Committee to ensure ethical considerations. Male albino rats with an average body weight of 200-250 g were allocated into three groups, each consisting of five animals. Group I was designated as the control group, while Group II and III were considered as the test groups. Prior to the application of gel formulations, the ventral surface of the rats was depilated. The gel formulations were administered twice daily for a duration of one week. Throughout the study period, the animals were closely monitored for the presence of any allergic reactions or manifestations.

Stability Studies

The study was conducted following the established procedure outlined in previous reports[22]. All formulations underwent a cyclic temperature exposure regime, involving five cycles ranging from -5°C to 25°C, with each cycle lasting 24 hours. The gels were subjected to assessment for physical stability and syneresis22. Additionally, in accordance with the guidelines set by the International Conference on Harmonisation (ICH), a three-month stability analysis was performed. The gels were subjected to varying temperatures (25±2°C to 40±2°C) and relative humidity (75±5% RH) during this period. Monthly evaluations were conducted to gather data on drug content, viscosity, pH, and in vitro diffusion.

Cycloxygenase-2 Inhibition Study

This study aimed to evaluate the anti-inflammatory activity of the formulated gels due to the involvement of the COX-2 enzyme in the production of PGs, which contribute to inflammation.[23,24] To achieve this, albino rats weighing between 200 and 250 g were divided into two groups, each comprising six animals. In order to induce edema, a 1% w/v carrageenan solution (0.1 ml) was injected into the plantar surface of the hind paw. The paw volume was measured by immersing it in a mercury column plethysmometer. The optimized gel formulation was then applied with gentle rubbing. By comparing the paw edema with the change in the height of the mercury column between the control and test groups, the anti-inflammatory effect was assessed. Paw volume measurements were taken at hourly intervals for a duration of six hours over the course of seven days. The control group rats received only the gel base without the inclusion of the drug, following the same method of application. The inhibition percentage of edema was calculated using the formula: (Vc - Vt / Vc) x 100, where Vc represents the average paw volume in the control group and Vt represents the average paw volume in the drug-treated group.

Results and Discussion

Lumiracoxib topical gels were developed using different gelling agents, namely MC, Carbopol 934, and HPMC, to achieve the desired consistency and aesthetic appeal. Propylene glycol (PG) was employed as a solvent and humectant to facilitate drug solubility in the formulation and prevent gel drying. The hydroalcoholic vehicle (2:1) served as a crucial component in the formulation as it promoted hydration of the gelling agents, thereby contributing to gel structure formation and stability. It also played a significant role in the gelation process. The alcohol component in the formulation also acted as a co-solvent for the drug. The inclusion of high concentrations of alcohol led to a decrease in the viscosity of the formulated gels, potentially due to the disruption of cross-linking between the polymer molecules. The stratum corneum, being the outermost layer of the skin, serves as a major barrier for the topical delivery of drugs. Menthol was incorporated in the formulation to modify the properties of this barrier and enhance drug delivery through the skin by increasing both the drug concentration and diffusion rate. Menthol possesses hydrogen bonding functional groups and is a lipophilic terpene, making it particularly effective in facilitating drug penetration through both the lipid and pore pathways.

Menthol imparts a refreshing sensation upon application of the formulated gel to the skin[25,26]. Methyl and propyl paraben, widely recognized preservatives, were incorporated into the formulation to prevent microbial growth. Various gel formulations were developed utilizing different concentrations (0.5, 1, and 2 g) of MC (A1, A2, and A3), Carbopol 934 (B1, B2, and B3), and HPMC (C1, C2, and C3) to optimize the gel formulation based on its consistency and in vitro drug release, as outlined in Table 1. The formulated gels exhibited no signs of clogging or

unexpected viscosity alterations. The post-application sensory experience of all gels was perceived as smooth and comfortable. The MC and Carbopol 934-based lumiracoxib gels appeared transparent, while the HPMC gel had a whitish appearance, potentially due to the HPMC's high cross-linking property. The drug content of the formulated gels indicated minimal variation. As viscosity is inversely related to in vitro drug release, any changes in viscosity can potentially diminish the product's effectiveness.[27-53]

The viscosity of the formulations is influenced by factors such as polymer concentration, molecular weight, and degree of cross-linking. The gels formulated with Carbopol 934 exhibited higher viscosities compared to MC and HPMC gels, as indicated in Table 2. This can be attributed to the higher molecular weight of Carbopol 934 and its greater degree of cross-linking, which restricts the flow of the liquid. It was observed that the viscosities of the gels were compatible with the skin's pH, minimizing the likelihood of skin irritation. Achieving the desired therapeutic effect at the affected area necessitates the spreadability of the gel to that specific localized site. The spreadability of the gel depends on its viscosity, which ranged from 19.41 ± 0.14 to 28.75.94 ± 0.04 gcm/s for all formulations (Table 2). Comparative analysis of the cumulative drug release (%) over a 6-hour study from various gels (Table 2) revealed an inverse relationship between in vitro drug release and polymer concentration. Water and propylene glycol hydrate the stratum corneum, facilitating the opening of channels through which the drug can penetrate into deeper layers of the skin. The evaporation of alcohol on the skin surface increases the concentration of the drug on the skin, creating a concentration gradient that serves as the driving force for drug penetration.

In addition, alcohol is known to fluidize the skin surface, enhancing the permeation of the drug. However, the concentration of alcohol used must be limited as an excessive amount can harm the skin. The Carbopol 934 gels exhibited higher rates of drug release compared to the gels formulated with MC and HPMC. The drug release kinetics from the gels (Table 2) indicated that all formulations followed zero-order kinetics, as evidenced by the R2 values ranging from 0.9763 to 0.9796. The mechanism of drug release was determined to be diffusion-controlled based on Higuchi data, which suggests that the rate-limiting step in drug permeation is diffusion. Among all the batches, formulation B1 (0.5 g, Carbopol 934) met all the essential criteria as an optimized formulation (Table 2), demonstrating desirable in vitro release (14.46 ± 0.06%), viscosity (2244.9 ± 0.04 cpc), and spreadability (28.53 ± 0.06 gcm/s). All the gels were composed of pharmaceutically approved excipients in appropriate quantities, ensuring non-immunogenicity and biocompatibility. Nevertheless, there is still a possibility of allergic manifestations occurring after application to the skin.

Therefore, the skin compatibility study revealed some initial behavioral changes in rats after the first application, which could be attributed to the cooling effect of menthol and alcohol. However, with subsequent applications, the rats exhibited tolerance to these effects. No allergic manifestations were observed during the 7-day study period. In the stability study, the formulated gels were exposed to cyclic temperature conditions (25°C and -5°C) and showed no changes in their physical stability.. Furthermore, all formulations passed the stability tests in accordance with the ICH guidelines for a period of three months. There were no significant changes observed in drug content, viscosity, pH, and in vitro drug release (Table 3), indicating the stability of the formulated gels.

The optimized gel formulation (B1) demonstrated significant anti-inflammatory potential, as shown in Table 4. It exhibited

a maximum inhibition of rat paw edema of up to 79.01%, which aligns with the reported values. This indicates that the optimized formulation (B1) possesses potent topical activity in inhibiting edema. The in vitro 5-lipoxygenase inhibition by the optimized lumiracoxib gel was assessed using increasing dosages.

Conclusions:

Topical administration of lumiracoxib offers a safer alternative to oral delivery, as it minimizes the risk of severe side effects such as gastric bleeding. In this study, various gels of lumiracoxib were formulated using methyl cellulose, carbopol, and HPMC as gelling agents. Among these formulations, the carbopol gel exhibited remarkable efficacy against COX-2, making it a promising candidate for the treatment of local inflammation. Further research in this direction is warranted and holds potential for addressing local inflammatory conditions in a targeted and attentive manner.

Table 1: Formulation table for lumiracoxib gels

Ingredients in gm	Formulation Code								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
Methyl Cellulose	0.5	01	02	-	-	-	-	-	-
Carbapol 934	-	-	-	0.5	01	02			
HPMC	-	-	-	-	-	-	0.5	01	02

Every formulation code has: lumiracoxib, 0.5 g; mentha oil, 1 g; prostaglandin (PG), 5 g; methyl paraben, 0.32; propyl paraben, 0.62; triethanolamine (TEM), Q.S and hydroalcoholic vehicle (2:1), Q.S. to 50 g

Table 2—Evaluation parameters of lumiracoxib gels [values are represented as Mean±SD, (n=3)]

Formulation Code	Drug Content %	Viscosity CPS	pH	Spreadability gcm/s	Drug release in 6 hr % Q	Cumulative drug release in 6h % Q/A	First Order R^2	Zero Order R^2	Higuchi Model R^2
A1	98.80± 0.35	1157.2 ± 0.08	6.98±0.15	19.41 ± 0.14	52.61 ± 0.04	15.01 ± 0.03	0.9653	0.9763	0 .9685
A2	98.61± 0.32	2985.4 ± 0.03	6.87±0.03	32.47 ± 0.13	40.29 ± 0.13	11.89 ± 0.05	0.9556	0.9765	0 .9675
A3	99.42± 0.54	4134.3 ± 0.06	6.89±0.13	34.02 ±0.03	32.52 ± 0.21	9.66 ± 0.02	0.9861	0.9752	0 .9745
B1	98.93± 0.53	2244.9 ± 0.04	7.00±0.11	28.53 ±0.06	57.73 ± 0.09	14.46 ± 0.06	0.973	0.9779	0 .9684
B2	98.66± 0.44	3253.4 ± 0.01	6.88±0.04	35.68 ±0.43	33.73 ± 0.03	9.17 ± 0.04	0.9553	0.9738	0.9646
B3	98.82± 0.11	4633.3 ± 0.13	6.92±0.05	36.94 ±0.09	29.32 ± 0.24	7.35 ± 0.05	0.9345	0.9769	0.9612
C1	98.57± 0.54	1365.4 ± 0.04	7.00±0.07	20.88 ±0.12	51.46 ± 0.73	12.37 ± 0.04	0.985	0.9786	0.9805
C2	99.95± 0.72	1924.5 ± 0.08	6.80±0.12	21.42 ±0.42	47.58 ± 0.06	13.25 ± 0.02	0.9661	0.9719	0.9483
C3	98.81± 0.82	2895.6 ± 0.24	7.02±0.01	28.75 ±0.04	44.67 ± 0.54	12.49 ± 0.01	0.9642	0.9796	0.9505

Table 3—Stability studies data [values are represented as Mean±SD, (n=3)]

Formulation code	Drug content %	Viscosity cps	pH	Cumulative drug release in 6 h, % Q/A
A1	99.74 ± 0.36	1131.9 ± 0.03	6.42 ± 0.03	14.20 ± 0.02
A2	99.43 ± 0.32	2934.5 ± 0.02	6.63 ± 0.09	10.70 ± 0.03
A3	98.34 ± 0.23	4122.7 ± 0.08	6.72 ± 0.11	9.12 ± 0.08
B1	98.14 ± 0.37	2222.5 ± 0.07	6.49 ± 0.12	16.32 ± 0.02
B2	99.22 ± 0.38	3218.1 ± 0.03	6.37 ± 0.08	10.21 ± 0.03
B3	97.90 ± 0.34	4545.2 ± 0.09	6.66 ± 0.04	8.90 ± 0.09
C1	98.31 ± 0.14	1333.3 ± 0.03	6.74 ± 0.11	13.97 ± 0.06
C2	97.40 ± 0.09	1924.5 ± 0.05	6.81 ± 0.07	13.31 ± 0.05
C3	98.77 ± 0.91	2826.4 ± 0.13	6.86 ± 0.10	12.20 ± 0.07

Table 4—Anti-inflammatory study of lumiracoxib Gel (B1)

Group	Time (hr)	Mean paw oedema volume	Inhibition of oedema (%)
Control	1	0.199	-
	2	0.238	-
	3	0.297	-
	4	0.344	-
	5	0.408	-
	6	0.438	-
Test	1	0.139	21.70
	2	0.139	42.44
	3	0.121	57.14
	4	0.112	68.44
	5	0.104	74.01
	6	0.102	79.02

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