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Original Research Article

Development of Diclofenac and Capsaicin Emulgel for the Management of Inflammation in Rheumatoid Arthritis

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ABSTRACT

The topical application of diclofenac for the management of inflammation in rheumatoid arthritis has minimized systemic adverse effect by providing local therapeutic action around the joints. Capsaicin – a naturally occurring compound obtained from plants of the genus Capsicum has anti-inflammatory and analgesic property which when combined with diclofenac may lead to enhanced activity. Therefore, a diclofenac-capsaicin emulgel topical formulation was developed and evaluated for its anti-inflammatory activity. Emulgel formulations containing capsaicin, diclofenac, or diclofenac-capsaicin were prepared and subjected to physicochemical characterization, anti-inflammatory activity, skin irritation test and histopathology study in rats. All the formulations had off-white, smooth texture, and glossy appearance. The pH and viscosities of all formulations ranged from 5.51 - 6.23 and 10452 - 52920 mPa.s respectively. All formulations possessed good spreadability and bioadhesive strength, however, the formulations with smaller amount of the alkyl acrylate polymer (1% Carbopol®) as gelling agent had a better spreadability but lesser bioadhesiveness than those with higher gel content (1.5% Carbopol®). The release of diclofenac from all formulations followed the Higuchi model. The diclofenac-capsaicin formulations containing 0.2 and 0.3% capsaicin respectively had a higher anti-inflammatory effect than the diclofenac formulation ($p<0.05$); the 0.2% formulation had the highest anti-inflammatory effect. The formulations showed no symptoms of allergy nor changes in the microstructure of the skin upon application. The formulations possessed desired physicochemical properties and safety for application to the skin. The spreadability and bioadhesive property of the formulation is dependent on the concentration of carbopol®. The diclofenac-capsaicin emulgel formulation showed improved anti-inflammatory effect when compared with the diclofenac formulation.

Keywords: Inflammation, Rheumatoid arthritis, diclofenac, capsaicin, emulgel formulation

Introduction

Inflammation is a defense mechanism in which the immune cells recognize and remove foreign substances from the body to promote healing and restore homeostasis.[1] Persistent inflammation leads to a plethora of chronic inflammatory disease such as chronic obstructive pulmonary disease, arthritis, diabetes, cardiovascular diseases amongst others. According to the World Health Organization, chronic inflammatory diseases are the greatest threat to human health and the most significant cause of death worldwide; globally, it is estimated that 3 out of 5 deaths recorded are due to chronic inflammatory diseases.[2] They constitute a burden to humans because of life-long debilitating illness, increased mortality and high costs for therapy and care.[3]

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that primarily affects joints leading to swelling and pain.[4] The management of Rheumatoid arthritis is aimed to minimize symptoms such as pain and swelling, prevent bone deformity and maintain day-to-day functioning to improve symptoms and slow the progression of the disease.[4]

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This is primarily achieved with disease-modifying anti-rheumatic drugs, anti-inflammatory and analgesic agents, lifestyles changes, surgery, and alternative medicine.

Over the years, several anti-inflammatory and analgesic drug molecules especially the non-steroidal anti-inflammatory drugs have been used in the management of inflammation and pain in RA. Diclofenac is an NSAID of the phenylacetic acid class with anti-inflammatory, analgesic, and antipyretic properties. The advent of topical formulations of diclofenac enabled local treatment of pain and inflammation while minimizing systemic absorption of diclofenac.[5]

Capsaicin is a naturally occurring alkaloid (8-methyl-N-vanilyl-6-nonenamide) derived from plants of the genus Capsicum e.g *Capsicum annuum* L., *Capsicum frutescens* L., *Capsicum chinense* Jacq. belonging to the family Solanaceae.[6] It is commonly known as chili pepper fruit. It is hydrophobic in nature owing to the presence of a long hydrophobic chain in its chemical structure (Figure 1). It is a colourless, odourless, crystalline compound that has been used for many years for the management of different types of pain.[7] Capsaicin produces its analgesic effect by activation of TRPV-1 (transient receptor potential vanilloid 1). This activation causes an influx of extracellular calcium ions resulting in deterred functionalization of nociceptor terminals.[8] The activation of the TRPV-1 receptor is due to the presence of the vanillyl group present in the chemical structure of Capsaicin.[9] Exposure of the skin and eye to capsaicin can cause irritation, lacrimation and conjunctivitis. It has high oral toxicity and moderate dermal toxicity with LD50 of 47.2 mg/kg and >512 mg/kg in mice respectively.[10] Capsaicin has been formulated as topical preparations at low concentrations (0.025 – 0.1%) for rapid absorption through the skin in humans.[11]

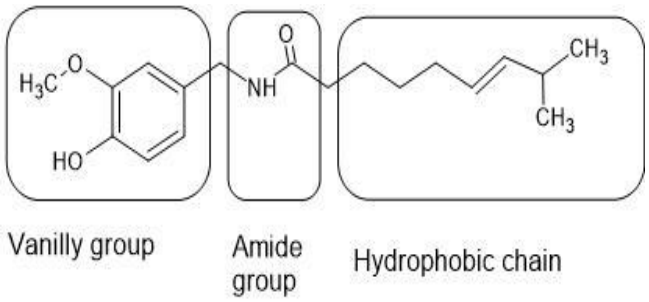

Figure 1: Chemical structure of Capsaicin

Recent advancements in topical delivery systems brought about the advent of emulgel formulations. An emulgel is composed of an emulsion and gel in which the emulsion is incorporated into a water phase containing a gelling agent.[12] They offer an approach for the topical administration of a wide variety of hydrophilic and hydrophobic therapeutic agents. Emugels allow for increased penetration of active pharmaceutical ingredients through the skin, provide an elegant and stable formulations with improved bioavailability, possess drug efficacy at low doses when compared with other conventional semi solid preparation,[13] and are easily removed when required, hence have superior patient acceptability and use.[14]
In this study, the formulation of a combination of diclofenac-capsaicin as an emulgel was explored to minimize the systemic side effects associated with diclofenac as well as enhance its anti-inflammatory activity. Several diclofenac-capsaicin emulgel formulations were prepared, characterized, and subjected to anti-inflammatory activity in *in vivo* rat model.

Materials and Methods

Materials
Diclofenac sodium was obtained as a gift from Swipha, Lagos; Carbopol® 940 was purchased from Shree Chemicals, India; Tween 80, Span 80 and triethanolamine were obtained from Sigma Aldrich (St. Louis, MO, USA); propylene glycol was procured from The Chemicals Company, USA; Ethanol was obtained from Fisher Scientific, UK. Pure Capsaicin extract was sourced from Aramacs Industries, India; pure natural shea butter was purchased from Strange® Industries Ltd, Abuja; methyl paraben and propyl paraben were obtained from Jigchem Universal, India.

Preparation of Diclofenac-Capsaicin Emulgel
Six emulgel formulations (F1- F6) were prepared using varying quantities of ingredients as stated in Table 1. The gel phase of the formulations was prepared by dispersing Carbopol® 940 in 30 mL of water and allowed to soak overnight. The oil phase of the emulsion was prepared by weighing required quantities of pure Capsaicin extract crystals, shea butter, refined palm oil and span 80 into a melting pan. The aqueous phase was prepared by weighing the required quantities of Diclofenac, methyl paraben, propyl paraben, ethanol, propylene glycol and tween 80 into another melting pan. The oil and aqueous phases were heated separately to 70ºC. The oil phase was then added gradually to the aqueous phase with continuous stirring to form an emulsion. The emulsion was added gradually in 5 mL portions into the gel phase with continuous stirring after each addition to form an emulgel. The emulgel was homogenized for 15 min using a magnetic stirrer; triethanolamine was then added to adjust the pH and thicken the emulgel.[15]

Physicochemical Characterization of the Emulgel Formulations
The emulgels were subjected to physical examination, rheology study, determination of pH, particle size, morphology and spreading coefficient, bioadhesive study, Fourier Transform Infrared Spectroscopy (FTIR) and *in vitro* release study.

Physical examination
The prepared emulgel formulations were inspected visually for their colour, appearance and consistency. The formulations were stored at room temperature for six months and re-examined visually for colour, appearance and consistency.

Rheological study
The viscosity of the formulated batches was determined at ambient temperature using a DV-E Digital Viscometer (Mettler-Toledo, Switzerland). The formulation was placed at the bottom of the device with the spindle (Number 4) fully immersed in the formulation. The viscosity of each formulation was measured at 10, 20, 30, 40 and 50 rpm.

pH Measurement
The pH of the emulgels were measured using a Mettler Toledo pH meter (Mettler-Toledo Group, Switzerland). The electrode of the pH meter was immersed in the emulgel samples and the values obtained were recorded.

Microscopic Evaluation
The morphology of the emulgel formulations were examined under a light microscope. A drop of each emulgel formulation was applied on a microscopic slide and covered with a cover slip. It was observed under the microscope and pictures of microscopic features were taken.

Spreading Coefficient
Spreading coefficient was measured based on a slip and drag characteristics of emulgels as described by Khullar *et al*.[15] A ground glass slide was fixed on a wooden block. An excess emulgel of 2g was placed on the ground slide, a second glass slide of the same dimension as the fixed ground slide was placed on the ground slide such that the emulgel preparation is sandwiched between the two slides. The second glass slide is provided with a hole drilled at one end and a rope running through the hole to act as a pulley. Weight of 70g was placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. The diameter to which the gel had spread between the two glass slides was measured using a ruler. The rope was then pulled gradually, and the time (in seconds) required by the top slide to cover 5cm was noted. A shorter interval indicates better spreading coefficient.

Bioadhesive study
The bioadhesive strength of the formulations was determined using a modified two arm balance method as described by Khullar *et al*.[15] An accurately weighed emulgel of 1g was placed between two glass slides containing hairless fresh rat skin pieces previously attached to two pans, some pressure was applied for 5 min to remove the presence of air. Weight was added slowly at 200 mg/min to the left-hand pan until the two glass slides got detached from each other. The weight required to detach the emulgel from the glass surface was obtained and the bioadhesive strength was calculated using equation 1.

$$\text{Biodhesive strength} = \frac{weight\ (g)}{Area\ (cm2)} \quad \text{Equation 1}$$

Fourier Transform Infrared Spectroscopy (FTIR) Studies
The compatibility of the components of the formulation was assessed using FTIR as described by Velmurugan and Ali.[16]

In vitro Release Studies
The *in vitro* drug release studies were carried out on a modified Franz diffusion cell using a synthetic membrane mounted between the donor and receptor compartment of the apparatus. A volume of 25 mL of phosphate buffer (pH 6.8) release medium was transferred into the receptor compartment, the apparatus was placed on a magnetic stirrer and the temperature was maintained at 37^0C $\pm 0.5^0$C. A weight of 0.2g of the formulation was spread across the surface of the membrane in the Franz diffusion cell apparatus, at time intervals of 5, 15, 30, 45, 60 and 120 min, 1 mL sample was withdrawn for analysis and replaced with 1 mL of the release medium to maintain sink condition. A 1 in 10 dilution of the samples in phosphate buffer was carried out, the diluted samples were analyzed spectrophotometrically at 276 nm and the cumulative percentage release of diclofenac was determined.[17] The release data was

fitted into various kinetic models to determine the mechanism of release from the formulation.

In vivo Anti-Inflammatory Activity

Thirty-five male Wistar rats aged 12-13weeks weighing 100-105g were used in the anti-inflammatory activity experiment. The study was carried out in accordance with the Institution guidelines approved by the College of Medicine University of Lagos Heath Research and Ethical Committee CMUL/HREC/10/18/450. The rats were kept in a well aerated cage maintained at a temperature of 30 ± 2 °C, and relative humidity of 45 ± 10% with a 12-hour light/dark cycle. They were fed with mouse cubes and clean drinking water ad libitum. The rats were divided into 7 groups consisting of 5 rats each to make 6 treatment groups and a control group. The diameter of the right hind paws of the rats were measured using a vernier caliper, edema was induced on the right hind paw of all the rats by subplantar injection of 0.1 mL of 1%w/v carrageenan in normal saline. The diameter of the right hind paws of the rats were measured 30 min after the injection. Subsequently, 0.1 g each of emulgel formulations F1-F6 were applied on the right hind paws of the rats except the control group. The diameter of the right hind paws were measured at 30 min interval over a 2 h period and values were recorded.[18,19] The percentage inhibition of edema was calculated using equation 2.

$$Percent\ inhibition = \frac{\text{Paw diameter after carrageenan injection} - \text{paw diameter after particular time}}{Paw\ diameter\ after\ carrageenan\ injection} x\ 100$$

-- Equation 2

Skin Irritation Test (Patch Test)

A set of twelve rats divided into 6 groups were used for this study. The hair on the dorsal side of the rats was removed carefully and the formulations F1-F6 were applied uniformly. Changes in colour and skin morphology were checked for a period of 24 h.

Histopathology of the Skin

Upon conclusion of the skin irritation study, one rat from each of the 6 groups and a rat devoid of treatment (control) was sacrificed by cervical dislocation and the subcutaneous tissue of the application area were obtained for histology. Each specimen was fixed in 10% buffered formalin, treated with alcohol and xylene, and embedded in paraffin wax. Section of blocks of 5 µm were cut and treated with xylene and alcohol. The treated blocks were stained with hematoxylin and eosin (H&E). The sections were rinsed in alcohol, cleared using xylene and examined under the microscope for pathological lesions.[20,21]

Statistical analysis

The data was presented as mean ± standard deviation. Statistical difference between the mean values were determined by one-way analysis of variance (ANOVA). A p value < 0.05 was considered significant.

Table 1: Composition of the different diclofenac-capsaicin emulgel formulation

Ingredients	F1	F2	F3	F4	F5	F6
Diclofenac (g)	-	-	1	1	1	1
Carbopol® 940 (g)	1.50	1.00	1.50	1.50	1.00	1.50
Triethanolamine (mL)	0.10	0.10	0.10	0.10	0.10	0.10
Shea butter (g)	0.50	0.50	0.50	0.25	0.50	0.25
Palm oil (mL)	15.00	15.00	15.00	12.50	15.00	10.00
Tween 80 (mL)	2.50	2.50	2.50	4.00	2.50	4.00
Span 80 (mL)	2.50	2.50	2.50	2.50	2.50	2.50
Pure Capsaicin (g)	0.60	0.40	0.40	0.30	0.20	-
Propylene glycol (mL)	10.00	10.00	10.00	10.00	10.00	10.00
Ethanol (mL)	5.00	5.00	5.00	5.00	5.00	5.00
Methyl paraben (g)	0.02	0.02	0.02	0.02	0.02	0.02
Propyl paraben (g)	0.05	0.05	0.05	0.05	0.05	0.05
Distilled water to (g)	100	100	100	100	100	100

Results and Discussion

Physicochemical Characterization of the Emulgel Formulations

The emulgel formulations were off-white, opaque preparations with smooth texture and glossy appearance (Figure 2).

The viscosity of the prepared formulations at 10rpm ranged from 10452 to 52920 mPa.s as shown in Figure 3. The formulations with diclofenac were more viscous than those containing capsaicin alone. The formulations containing capsaicin alone (F1 and F2) had lower viscosity than those containing capsaicin and diclofenac or diclofenac alone (F3 - F5 and F6), therefore increase in viscosity can be attributed to diclofenac. An increase in viscosity to some extent is desirable among other factors for the development of a stable formulation. The viscosities of diclofenac-capsaicin formulations increased with decreasing concentration of capsaicin in the formulations (F3, F4 and F5). An increase in speed from 10 to 50 rpm caused a decrease in the viscosity of all the formulations (Figure 3), this is an attribute of a non-Newtonian system that is peculiar to topical formulations. Therefore, the amount of shear to be used during preparation of the emulgel should be optimized to produce a product with appropriate and consistent fluidity required for easy application.

The pH, spreadability and bioadhesive strength of the emulgel formulations is represented in Table 2. The pH of the emulgel formulations were in the range of 5.51 – 6.23, all the formulations had a spreadability and bioadhesive strength between 30.12 – 65.38 g.cm/s and 2.20 – 3.10 g/cm^2 respectively. Formulations containing lesser amount of Carbopol® (F2 and F5) had a better spreadability but reduced bioadhesive properties than other formulations with higher amount of the alkyl acrylate polymer. Generally, topical formulations are to be developed to possess similar pH as an intact human skin in the range 4-6 for maintenance of a healthy skin during treatment.[22] The emulgel formulations containing only diclofenac or capsaicin have pH within the stipulated range, however, the formulation containing both diclofenac and capsaicin had a slightly higher pH values (Table 2), the slight deviation observed may be due to the different concentrations of the ingredients of each formulation.

The spreadability and bioadhesive properties of a topical formulation is important in the development of an ideal formulation. The spreadability depicts the ease at which the formulation will spread upon application to the skin to enhance skin penetration while the bioadhesive strength shows the ability of the formulation upon application to adhere to the

epithelial tissues of the skin to promote prolonged drug release.[23,24] A high spreadability coefficient and bioadhesive strength is desirable for topical formulations. All formulations possessed good spreadability and bioadhesive strength (Table 2). It was observed that the spreadability and bioadhesive properties of the formulations prepared was dependent on the concentration of the gelling agent. The formulations (F2 and F5) that had lesser amount of the gelling agent - Carbopol® (1.0%) had better spreadability than the other formulations (F1, F3, F4 and F6) that contained higher amount of the gelling agent (1.5%). However, the formulations with lesser amount of Carbopol® (F2 and F5) had a lower bioadhesive strengths than their corresponding formulations with higher amount (1.5%) of gelling agent (F1 and F4 respectively) (Table 2). Therefore, the amount of gelling agent to be used in the emulgel formulation should allow for easy application and considerable attachment to epithelium. The emulgel formulations contain clusters of granular, spherical, and crystalline particles (Figure 4). The crystallinity was more predominant in formulations F1 and F2 which contained capsaicin alone.

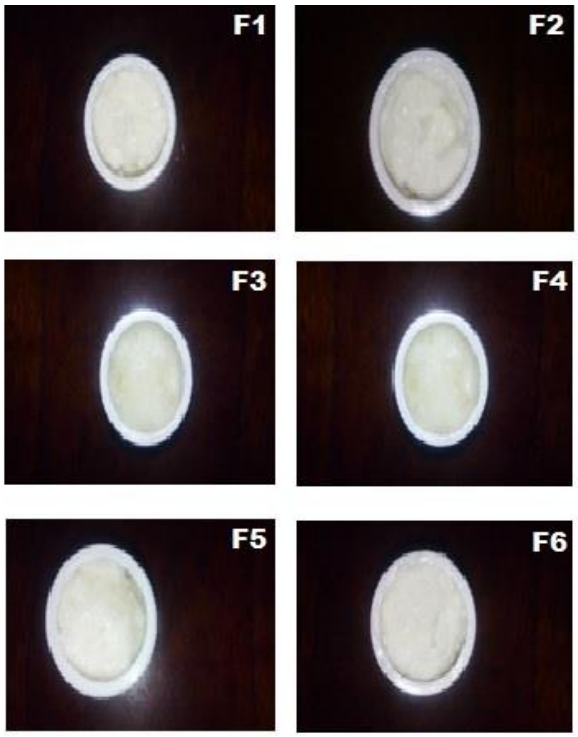

Figure 2: Appearance of formulated emulgels

The FTIR spectra of all formulations represented in Figure 5 showed presence of peaks for the functional groups which are characteristic of both Diclofenac and Capsaicin with no major shift in the peaks. The FTIR study was carried out on the formulations to ascertain the compatibility of the ingredients employed in the development of the formulations. The FTIR data helps to detect interactions between compounds which are presented as a change in the position or disappearance of characteristic peaks of the functional groups of the compounds. The Spectra of all formulations (Figure 5) showed presence of peaks for the functional groups which are characteristic of both diclofenac and capsaicin with no major shift in the peaks. These functional groups include C=O, carbonyl stretching (1650-1750cm^{-1}), C=C (1600-1680cm^{-1}) and N-H, amide group stretching (3300-3500cm^{-1}). A C-C-O and O-C-C, ester stretching (1000-1300cm^{-1}) was also observed which may be due to the possible interaction between the diclofenac at site B (Figure 6) and capsaicin at site C (Figure 6). However, a minor shift was observed at 1200-1400cm^{-1} for C-N group.[25] The FTIR showed no significant chemical interactions between the drug and excipients used.

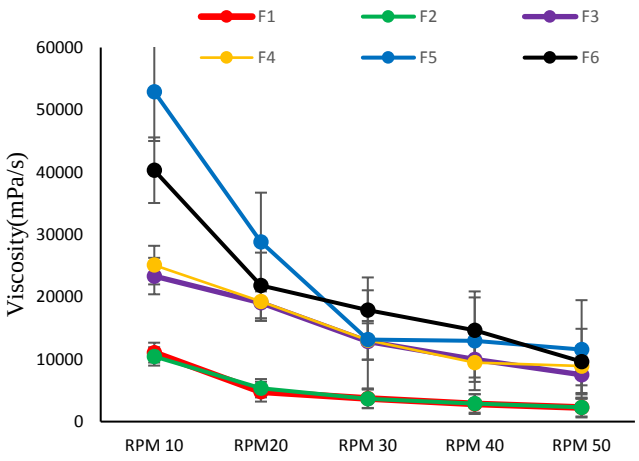

Figure 3: Viscosity of emulgel formulations
Key: F1 – 0.6% capsaicin; F2 – 0.4% capsaicin; F3 – 0.4% capsaicin and 1% diclofenac; F4 – 0.3% capsaicin and 1% diclofenac; F5 – 0.2% capsaicin and 1% diclofenac; F6 – 1% diclofenac

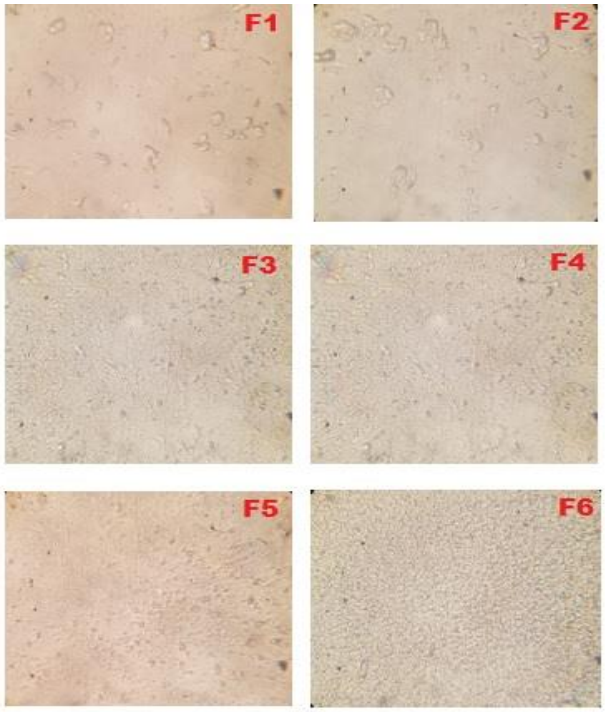

Figure 4: Surface morphology of emulgel formulations, magnification 100X
Key: F1 – 0.6% capsaicin; F2 – 0.4% capsaicin; F3 – 0.4% capsaicin and 1% diclofenac; F4 – 0.3% capsaicin and 1% diclofenac; F5 – 0.2% capsaicin and 1% diclofenac; F6 – 1% diclofenac

The mechanism of diclofenac release from the drug loaded emulgels is shown in Table 3. The release of diclofenac from all formulations followed the Higuchi model (depicted by the highest values of coefficient of correlation R^2) which describes the drug release as a diffusion process based on fickian diffusion drug transport mechanism.

In vivo Evaluation of Anti-Inflammatory Activity of Formulations
The anti-inflammatory activity of the emulgel formulations measured as the percentage inhibition of edema on the inflamed paws of rats over a period of 2 h is shown in Figure 7. At the end of the period of study, the formulations containing capsaicin alone (F1 and F2) and the diclofenac-capsaicin formulation with the highest amount of capsaicin

(F3) had the least anti-inflammatory effect while the diclofenac-capsaicin formulation with the least amount of capsaicin (F5) had the highest anti-inflammatory effect. The formulations of capsaicin and diclofenac (F4 and F5) had a higher anti-inflammatory effect than the formulation containing diclofenac (F6). The anti-inflammatory effect observed in the formulations with diclofenac or diclofenac-capsaicin increased with increase in time up to 2 h. The diclofenac-capsaicin formulations containing 0.2 and 0.3% capsaicin showed higher anti-inflammatory effects when compared with the diclofenac formulation. The anti-inflammatory activity of the emulgel formulations were measured as the percentage inhibition of edema after the induction of inflammation on the paws of rats over a period of 2 h. The improved anti-inflammatory activity observed in the diclofenac-capsaicin combination can be attributed to the complementary inhibition of prostaglandin E2 (PGE2) exhibited by both compounds.[26]

Table 2: The pH, Spreadability and Bioadhesive strength of Emulgel Formulations

Formulation	pH	Spreadability (g.cm/s)	Bioadhesive Strength (g/cm^2)
F1	5.64 ± 0.09	44.65	2.50
F2	5.57 ± 0.09	60.88	2.20
F3	6.09 ± 0.10	36.53	2.20
F4	6.23 ± 0.21	42.62	3.10
F5	6.23 ± 0.12	65.38	2.60
F6	5.51 ± 0.21	30.12	2.80

Key: F1 – 0.6% capsaicin; F2 – 0.4% capsaicin; F3 – 0.4% capsaicin and 1% diclofenac; F4 – 0.3% capsaicin and 1% diclofenac; F5 – 0.2% capsaicin and 1% diclofenac; F6 – 1% diclofenac

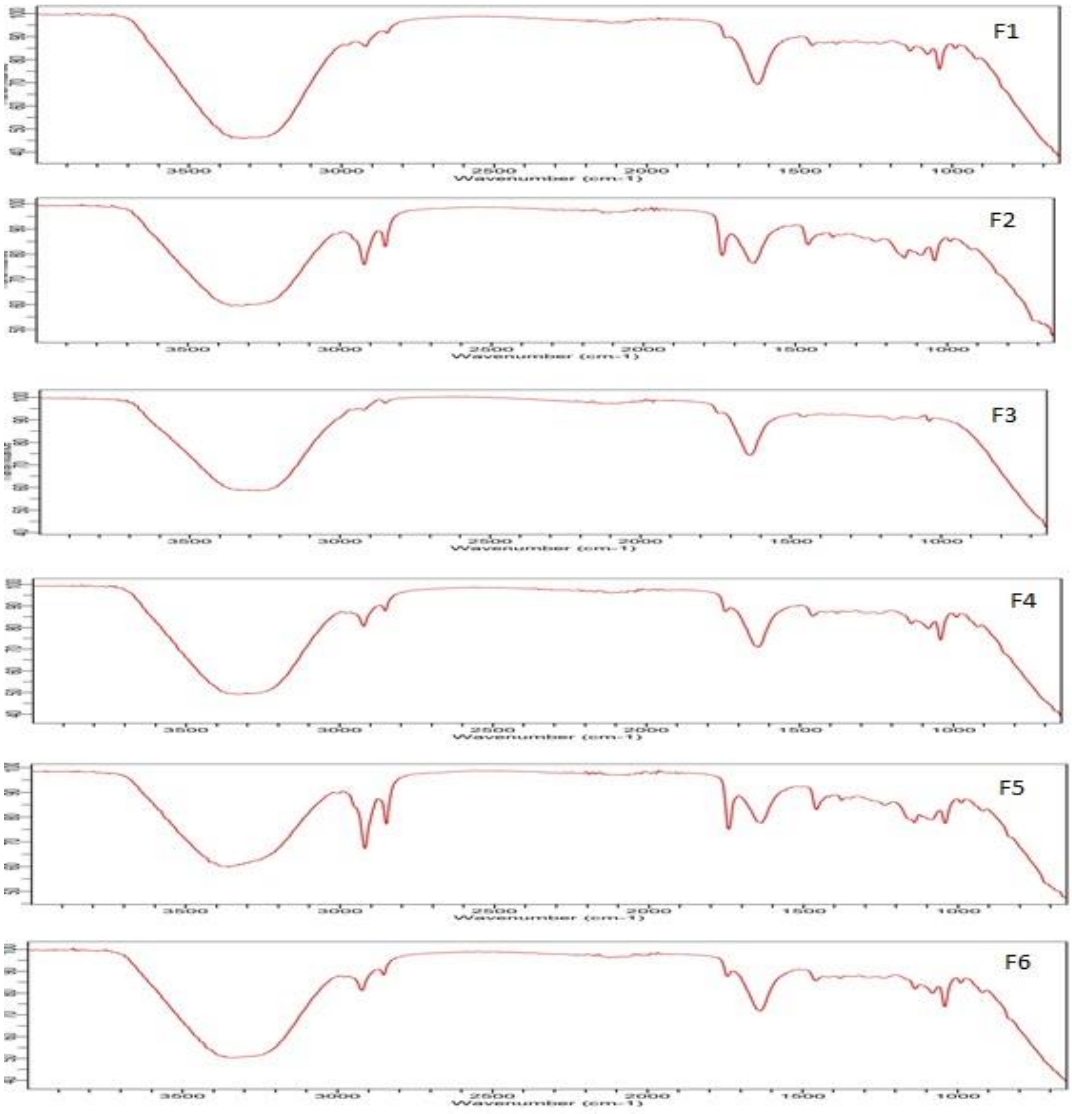

Figure 5: The FTIR spectra of the emulgels formulations
Key: F1 – 0.6% capsaicin; F2 – 0.4% capsaicin; F3 – 0.4% capsaicin and 1% diclofenac; F4 – 0.3% capsaicin and 1% diclofenac; F5 – 0.2% capsaicin and 1% diclofenac; F6 – 1% diclofenac

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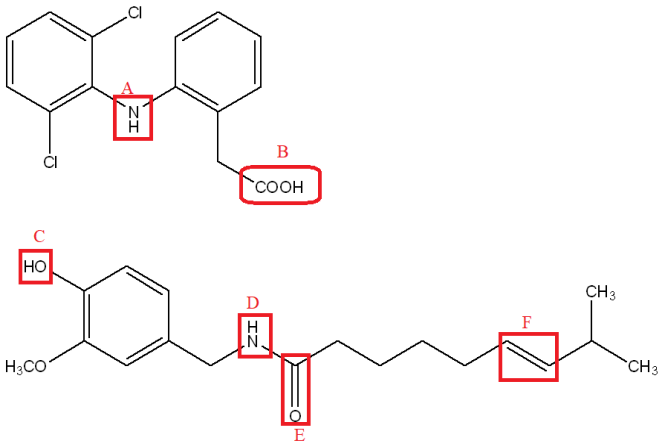

Figure 6: possible reaction site for interaction between diclofenac and capsaicin molecule

Skin Irritation Test and Histopathology of Emulgel Formulations

There were no allergic symptoms such as inflammation, redness, or irritation on the rats' skin after the application of all formulations. The histologic section of the soft tissues in the treated and control group showed overlying skin epidermis with various stratum layers, and dermis with underlying fibro-fatty tissue (Figure 8). There were no areas of inflammation, increased fibrosis or histologic abnormalities observed in the skin tissue following application of the emulgels. The formulations did not affect the microscopic structure of the skin and no pathological changes or damages were found, thus establishing the safety of the prepared formulations.

Conclusion

The combination of diclofenac and capsaicin emulgel formulations demonstrated enhanced anti-inflammatory activity when compared with diclofenac formulations. A higher concentration of alkyl acrylate polymer reduces the spreadability and increases the adhesion of the emulgels to the epithelial tissues of the skin. The diclofenac-capsaicin formulation containing 0.2% capsaicin and 1% Carbopol® possessed desired properties because of its high viscosity, good spreadability and bioadhesive property and ultimately exhibited the most anti-inflammatory effect when compared with the other diclofenac-capsaicin formulations or diclofenac formulations. This formulation can be further investigated for use as a topical medication in the management of inflammation in rheumatoid arthritis.

Table 3: The Mechanism of Release of Diclofenac from the Emulgel

Formulation	Zero Order	First Order	Higuchi	Korsmeyer Peppas	Hixon Crowel
	R^2	R^2	R^2	R^2	R^2
F3	0.7692	0.7756	0.8684	0.6594	0.4570
F4	0.8464	0.8542	0.9790	0.7184	0.4873
F5	0.8166	0.8212	0.9816	0.8295	0.4821
F6	0.7961	0.7989	0.8782	0.8034	0.4878

Key: F1 – 0.6% capsaicin; F2 – 0.4% capsaicin; F3 – 0.4% capsaicin and 1% diclofenac; F4 – 0.3% capsaicin and 1% diclofenac; F5 – 0.2% capsaicin and 1% diclofenac; F6 – 1% diclofenac

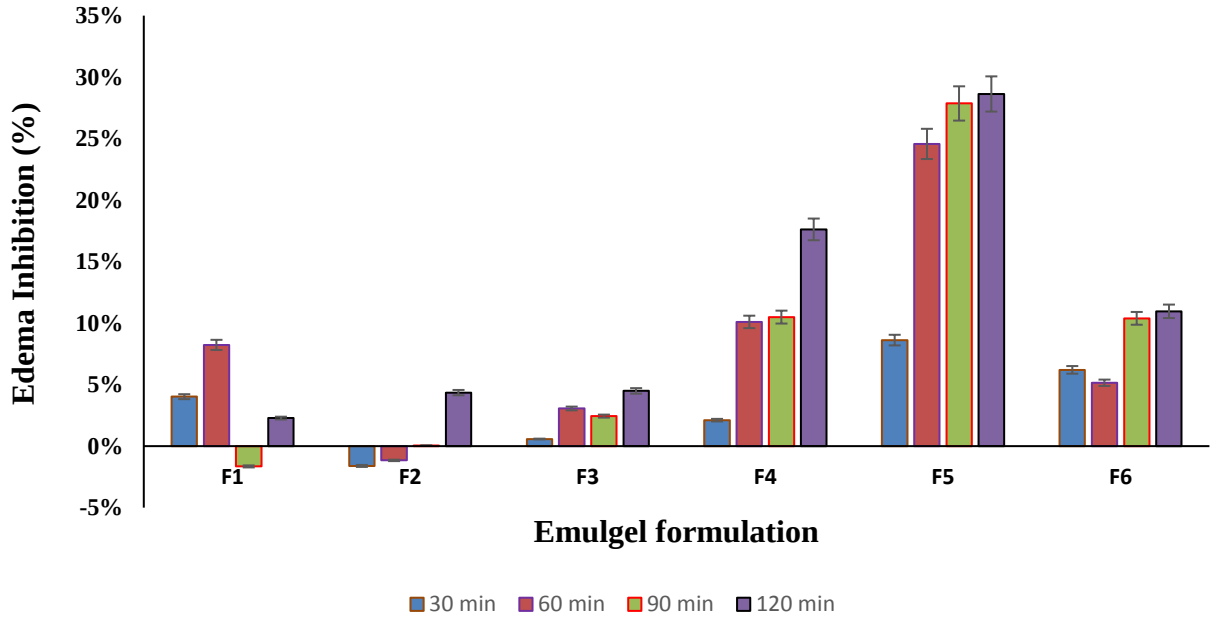

Figure 7: Percentage inhibition of carrageenan induced paw edema in rats after treatment with emulgels.
Key: F1 – 0.6% capsaicin; F2 – 0.4% capsaicin; F3 – 0.4% capsaicin and 1% diclofenac; F4 – 0.3% capsaicin and 1% diclofenac; F5 – 0.2% capsaicin and 1% diclofenac; F6 – 1% diclofenac

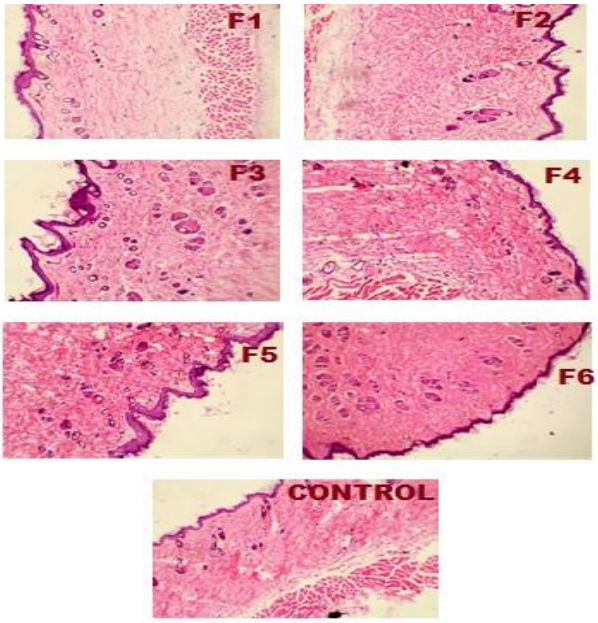

Figure 8: Histopathology observation of the dorsal area of rat skin after application of the emulgels
Key: F1 – 0.6% capsaicin; F2 – 0.4% capsaicin; F3 – 0.4% capsaicin and 1% diclofenac; F4 – 0.3% capsaicin and 1% diclofenac; F5 – 0.2% capsaicin and 1% diclofenac; F6 – 1% diclofenac

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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