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Research Article

Evaluation of physicochemical, in vivo analgesic and anti-inflammatory activities of *Brachystegia eurycoma* gum-based naproxen loaded niosomal gels

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Abstract

Protracted oral Naproxen administration for acute and chronic conditions, such as rheumatoid arthritis treatment, may cause peptic ulcers. The topical application of Naproxen will circumvent this effect. This research aims to assess the physicochemical, anti-inflammatory and analgesic properties of Naproxen-loaded niosomal gels formulated using *Brachystegia eurycoma* gum (BEG) as the gelling polymer. BEG was isolated by acetone precipitation of filtrate produced by cold maceration of *Brachystegia eurycoma* seeds powder. Naproxen and BEG compatibility was evaluated using Fourier transform infrared FTIR) spectroscopy. Naproxen-loaded niosomes were produced with cholesterol, surfactant (tween 80) and water using a modified ethanol injection method. The formulated niosomes were incorporated into either BEG (5, 7.5 or 10%) or HPMC (1.5, 5%) gel base to produce the respective Naproxen-loaded niosomal gels. The niosomal gels were assessed for their physicochemical, anti-inflammatory and analgesic properties using a commercially available gel as a positive control. There was no incompatibility between BEG and Naproxen. The formulated gels' pH ranged from 6.4 to 7.3, while the viscosity ranged from 1476.2 to 2980 mPas. The formulated gels had good extrudability and spreadability compared to the commercially available gel (1%). *In-vivo* studies using white albino rats showed that gels from the optimized formulation (F1) had comparable anti-inflammatory (26.5% inhibition) and analgesic properties to the commercially available gel (31.3% inhibition). Naproxen-loaded niosomal gels having good physicochemical, analgesic and anti-inflammatory properties were successfully formulated using BEG as a gelling agent.

Keywords: *Brachystegia eurycoma* gum; niosome; analgesic; anti-inflammatory; gels

Introduction

Niosome is a drug delivery system composed of an active pharmaceutical ingredient (API) enclosed in a vesicle using a non-ionic surfactant [1]. Niosomes are bilayer vesicles that consist of non-ionic surfactants and cholesterol. Niosomes are usually barely toxic due to their non-ionic nature [2]. They are produced by self-associating cholesterol and non-ionic surfactant after hydration in the aqueous phase [3,4]. They resemble liposomes, but unlike liposomes that contain phospholipids, they contain non-ionic surfactants [5]. Niosomes prepared using different kinds of non-ionic surfactants have been shown to enable the entrapment of many drugs with a wide range of solubility [3]. In the preparation of niosomes, the vesicular layer is formed by non-ionic surfactants, while cholesterol and the charged molecules (dicetyl phosphate) are the additives. The rigidity of the bilayer is enhanced by the presence of the steroidal system (cholesterol), which is also a vital component of the cell membrane. The bilayer fluidity and permeability are influenced by cholesterol in the membrane. This carrier system shields the incorporated drug molecules from untimely degradation and inactivation because of undesirable immunological and pharmacological effects [5]. Niosomes can deliver hydrophilic as well as hydrophobic types of drugs. Hydrophilic drugs are usu-ally encapsulated in the inner aqueous core or adsorbed on the bilayer surfaces, while lipophilic substances are entrapped by their partitioning into

the lipophilic domain of the bilayers [4,6]. The drug delivery performance of niosomes can be improved by varying and optimizing the composition, size, number of lamellae, and surface charge of niosomes [3]. The size of niosomes ranges from 10 to 1000 nm [7]. They are grouped into small unilamellar vesicles (10 nm-100 nm), large unilamellar vesicles (100 nm-500 nm), and multilamellar vesicles (0.5 μm-10 μm) [4].

Unlike liposomes, niosomes are chemically stable. They are biocompatible, biodegradable, perishable and nonimmunogenic. They are low cost, low toxicity, and easy to handle and store materials [1,3,7]. They are used for sustained, controlled and targeted drug delivery [7,8]. Niosomes have some demerits that may reduce their shelf life, including physical and chemical instability, aggregation, a fusion of vesicles, and leaking or hydrolysis of the encapsulated drug [6]. The polydispersity index value of less than 0.3 indicates a homogenous system [1]. Niosomes are identified as an excellent vehicle for delivering anti-fungal drugs topically. These systems can solubilise poorly soluble drugs, thereby providing high local concentration as a depot in sustaining drug release when used for topical delivery [1]. Niosomes have various applications concerning drug delivery to oral, parenteral, and transdermal delivery routes. Many niosomal preparations were patented for dermal applications. Preparations of niosomes are used in treating skin ailments like psoriasis, vitiligo, inflammation, alopecia, and other cosmetic complications [1]. Niosomes can be administered via different routes, oral, parenteral, and topical, and using different dos-age forms such as powders, suspensions, and semisolids, enhancing the oral bioavailability of drugs that are poorly soluble and also enhancing the permeability of drugs via the skin when applied topically [6]. Various researchers have prepared niosomes that contain nonsteroidal anti-inflammatory drugs (NSAIDs). Drugs for topical applications are recommendable for long-term use of NSAIDs, especially in rheumatic symptoms treatment. The effectiveness of topical NSAIDs depends largely on their ability to permeate across the skin [6].

Brachystegia eurycoma belongs to Caesalpiniaceae, phylum spermatophyte, and order Fabaceae. *Brachystegia eurycoma* seed flour gels when dispersed in water. When used in making soups, it yields a product with a gummy texture that makes it desirable for eating garri and pounded yam. It is called achi by the Igbo people of Nigeria. Other peoples in Nigeria such as the Yoruba, the Ijaw, the Edo call it akalado or eku, akpakpa or apaupan and okwen respectively. BEG compares creditably with gums used commercially in the food industry [9]. BEG has a pH of 5.5 at 28ºC. It is brown, has a bland taste and has a coca-like smell. It is insoluble in acetone, ethanol and chloroform but soluble in hot water, forming a cloudy dispersion. It has moisture sorption and loss at 1.22 gm and 16% drying values, respectively [10]. The cloudy dispersion (mucilage) formed due to the dispersion of BEG in hot water could be used as a binder or suspending agent. BEG has been used as suspending agent in metronidazole suspensions [11], as a hydrophilic polymer matrix for sustained released diclofenac [9] and as a swellable polymer for gastro retentive metronidazole tablets [12]. BEG was co-processed with an egg albumen mixture and used to formulate sustained-release metronidazole tablets [13].

Inflammation is a body response to cell and tissue injuries affected by various factors, including microbial infection and chemical, thermal, and mechanical inducers. This triggers the healing phase by expunging the harmful agents around tissue debris. Inflammation-related disorders are marked by pain, reddish colour and inflamed tissues. Drugs that are used for inflammation are grouped into steroidal anti-inflammatory drugs (SAID) and non-steroidal anti-inflammatory drugs (NSAID) [14,15]. Anti-inflammatory drugs are divided into agents that prevent or decrease inflammation produced by the interactions between physical damage, infection, heat and antigen-antibody. When steroidal and non-steroidal anti-inflammatory medications are used as long-term treatment, they may cause significant side effects, such as gastrointestinal and peptic ulcer bleeding [14,15].

Naproxen is an NSAID that is utilized in the management of inflammation and pain associated with arthritis. Its absorption from the gastrointestinal tract after it is administered orally is very rapid. Its half-life is about 12 h, and it has a mean oral bioavailability from the tablet of 95% when compared to the oral solution [16]. Naproxen causes gastrointestinal disorders like gastrointestinal irritation when administered peroral. The topical administration of the drug may surmount these potential untoward effects. Skin is one of the most easily reached organs in the human body for administering drugs

topically. It is the major route for topical drug delivery systems [17]. Naproxen has been formulated as emulgel for topical use [18,19] and as a topical *in situ* gel model [20]. This research was performed to formulate a naproxen-loaded niosome, incorporate it into *Brachstegia eurycoma* gum gel base, and evaluate the physicochemical, in vivo analgesic and anti-inflammatory activities of naproxen loaded niosomal gels.

Materials and Method

Materials

Naproxen was received as a gift from Swiss Pharma Nigeria Ltd, Tween 80 (JHD, China), Benzoic acid (CDH, China), HPMC (Shangi Chem, China), Cholesterol (MOLY CHEM, China), Polyethylene glycol 200 (Qualikems, India).

Extration of *Brachystegia eurycoma* gum

The procedure of Okafo et al. [9,12] was used. The fresh seeds of *Brachystgsia eurycoma* were bought from Abraka Main Market, Abraka, Delta State, Nigeria. The seeds were washed to remove all debris. The seeds were then sliced into smaller fragments and dried at room temperature (28ºC) for 72 h. The dried seeds were pulverized into powder, and 100 gm of the powdered *Brachystegia eurycoma* was macerated with 500 ml of distilled water for 24 h. It was filtered using a muslin cloth, and the filtrate (575 ml) was precipitated with 600 ml of acetone. The crude gum was washed twice with 100 ml of acetone and dried in a hot air oven for 6 h at 40°C. The dried gum was ground to powder using an electric grinder (Vitamix Blender, Ohio, USA.) and stored in an airtight container.

Preparation of niosomes

A modification of the ethanol injection method was used [21,22]. Two different ratios of cholesterol and Tween 80 (1:1 and 1:2) were used, and the ratio that produced the nano-sized niosomes (1:2) was used to prepare the niosome. A 0.3 gm quantity of cholesterol was mixed properly with 0.6 gm (0.54 ml) of Tween 80 (ratio 1:2) using a magnetic stirrer to produce the oil phase. The water phase was produced by dispersing 0.3 gm of naproxen powder in 300 ml of distilled water. The water phase was transferred into the oil phase drop-wise, and the mixture was continuously stirred using a magnetic stirrer with a hotplate heated to 60°C for 30 min. The formed niosome was stored in an airtight container.

Preparation of naproxen niosomal gel

The naproxen-loaded niosomal gel was prepared using the formula in Table 1 [23]. A 0.1 gm quantity of the naproxen-loaded niosome was transferred into a beaker and stirred using a magnetic stirrer. A 5 gm quantity of BEG was dispersed in the niosome and heated to 40°C with stirring until gel was formed. A 0.1 gm quantity of benzoic acid was dissolved in 10 ml (11.24 gm) of polyethylene glycol and added to the beaker with proper stirring. The other formulations were produced accordingly, but those that contained HPMC were prepared at room temperature. The prepared gels were transferred into their respective cream jars and labelled appropriately.

Table 1. Composition of naproxen-loaded niosomal gels.

Formulation	F1	F2	F3	F4	F5
Naproxen-loaded niosome (gm)	0.1	0.1	0.1	0.1	0.1
Brachystegia eurycoma gum (gm)	5	7.5	10	-	-
HPMC (gm)	-	-	-	1.5	5
Polyethylene glycol (gm)	11.24	11.24	11.24	11.24	11.24
Benzoic acid (gm)	0.1	0.1	0.1	0.1	0.1
Water to (gm)	100	100	100	100	100

Evaluation of BEG

Flow rate and angle of repose

A 10 gm of BEG was weighed and transferred into a glass funnel 5 cm above a flat surface, plugged at the orifice. The plug was removed from the orifice of the funnel, and the time taken for the powder to

flow completely through the orifice was recorded. The height and the diameter of the cone formed by the powder were measured and recorded. The flow rate was calculated using Equation 1.

$$Flow\ rate\ = \frac{weight\ of\ powder\ (g)}{Time\ of\ flow\ (s)} \ldots (1)$$

The angle of repose (θ)was calculated using Equation 2.

$$\text{Tan } \theta = h/r \quad \ldots (2)$$

Angle of repose (θ) = tan-1h/r

Where h = height of powder heap, r = radius of circular base.

Bulk and tapped densities

A 5.0 gm quantity of BEG was poured into a 10 ml graduated measuring cylinder, and the volume occupied (bulk volume) was recorded. The cylinder was mechanically tapped for hundred times, and the new volume occupied (tapped volume) was recorded. These were done three times. The bulk and tapped densities were calculated using Equations 3 and 4, respectively.

$$\text{Bulk density} = \frac{\text{mass (g)}}{\text{Bulk volume (ml)}} \quad \ldots (3)$$

$$\text{Tapped density} = \frac{\text{mass (g)}}{\text{Tapped volume (ml)}} \quad \ldots (4)$$

Carr's index

Carr's density was calculated using Equation 5.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad \ldots (5)$$

Hausner ratio

Hausner ratio was calculated using Equation 6.

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density} \quad \ldots (6)$$

Viscosity

The viscosity of BEG (1%) was determined using a Brookfield viscometer (NDJ -5S Digital viscometer, Shangai Nirun Intelligent Technology Co. Ltd, China) using spindle 3. The measurement was started at 6 rpm and increased until it reached 30 rpm [24,25].

Drug/excipient compatibility

The Fourier transform infrared (FTIR) spectrum of naproxen and that of naproxen and BEG were performed using the potassium bromide disc method. The spectra were recorded by scanning using the transmittance mode in the wavelength region of 650 to 4000 cm^{-1} in an FTIR Spectrophotometer (Agilent Technologies, Malaysia) [26].

Evaluation of the naproxen-loaded niosome

Determination of particle size and polydispersity index

Naproxen-loaded niosome sample prepared using Tween (80) and Cholesterol in the ratio of 2:1, respectively, was analyzed using a Zetasizer (Malvern Instruments, UK) to determine the particle size and polydispersity index (PDI) using the dynamic light scattering (DLS) technique with an angle of 90 degree at the ambient temperature (25°C). The process was repeated thrice at room temperature (25°C) without dilution [27,28].

Physicochemical evaluation of naproxen-loaded niosomal gel

Opacity

It was visually inspected under black and white background [29].

Homogeneity

The homogeneity of the niosomal gel was evaluated by visual inspection [24] and by pressing a small quantity of the gel between the index finger and the thumb.

Spreadability

A 0.25 gm quantity of the niosomal gel was placed on a glass slide, and the circle's diameter formed by the gel was recorded. An upper glass slide was used to cover the lower slide, and a 300 gm weight was placed on top of the slide for 5 min. The new diameter of the circle produced by the gel was recorded. Spreadability was calculated from the difference between the two diameters [25].

Extrudability

A 10 ml quantity of the niosomal gel was filled in a 10 ml syringe clamped to a retort stand. A 0.6 kg weight was placed on the free end of the plunger, and the amount of the niosomal gel extruded was recorded.

pH

The niosomal gel (0.1gm) was dispersed evenly in distilled water (10 ml) for 2 h using a magnetic stirrer. The pH of the dispersion was measured using a digital pH meter (Hanna Instruments, China) [30].

Viscosity

The viscosity for formulations F1-F4 was evaluated at 25ºC using spindle 3 of a Brookfield viscometer rotated at 6, 12, 30 and 60 rpm [25]. Formulation F5 was excluded because it was highly viscous (like a solid).

In vivo studies

Ethical approval (REC/FBMS/DELSU/21/97) for the in vivo anti-inflammatory, analgesic and skin irritation studies was obtained from the Ethical Committee of the Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria. Formulation (F1) was evaluated for in vivo anti-inflammatory, analgesic and skin irritation activities. Formulation F1 was selected because it had comparable physicochemical properties to others, but it was formulated with the least quantity of BEG.

Anti-inflammatory test

A slight modification of the methods used by Simanjuntak *et al.* [31], Muhwana *et al.* [32], and Djunarko *et al.* [15] was used for the anti-inflammatory study. The percentage inhibition of carrageenan-induced inflammation by the formulation F1 and marketed diclofenac gel (Drugfield, Nigeria) was determined. Fifteen Wistar rats divided into 3 groups were used for the study. The first group, the negative control group, received 0.1 gm of carrageenan. The second group also received 0.1 gm of carrageenan 30 min after applying the commercially available diclofenac gel. The third group received 0.1 gm of carrageenan 30 min after applying formulation F1. The first measurement of the paw size was taken after one hour and subsequently hourly for three consecutive hours using a Vernier calliper.

Analgesic test

The analgesic test was done using the hot plate method [33,34]. Fifteen albino rats were weighed (210 - 230 gm). They were divided into three groups: negative control, positive control, and test groups. The negative control group did not receive any treatment. At the same time, the commercially available gel and formulation F1 were applied on the dorsal surface of the paws of the rats in the positive control group and test group, respectively. After 30 min, they were placed on the hot plate, and the time it took the rats to respond to the thermal stimulus was noted, and the average was computed.

Skin irritation test

The furs on the dorsal surface of three Wistar rats were shaved to expose the skin. A 0.25 gm quantity of formulation F1 was applied to the exposed skin surface. After 24 h exposure, the niosomal gel was removed, and the sites were properly examined for signs of irritation (erythema and oedema) [34-37].

Statistical analysis

The research was conducted in triplicates for the validity of data analysis, and they were shown as mean ± SD. The analysis was done using Microsoft Excel.

Results and Discussion

Following extraction with acetone, the percentage of BEG that could be recovered from 100 grams of powdered *Brachystegia eurycoma* was determined to be 37.61% w/w.

Evaluation of BEG

Organoleptic properties of BEG

The gum was light brown, odourless and had a bland taste. There was no phase separation after three months of stability study at 40ºC for all the formulations except for formulation F2. This may be due to formulation issues rather than physicochemical activity because formulations with lower (F1) and higher (F3) concentrations of BEG were stable.

Physicochemical properties of BEG

The percentage yield, flow rate, bulk density, tapped density, Carr's index, Hausner ratio, pH and viscosity of the gum are shown in Table 2. The pH of the isolated BEG (6.1) was higher than what was reported by Olubunmi and Oremeyi (pH of 5.5) [10]. This may be due to the difference in the source of Brachystegia eurycoma seeds and the isolation method.

Table 2. Physicochemical properties of BEG.

Parameters	Results
Percentage yield (%)	37.6
pH	6.1
Flow rate (g/s)	2.40 ± 0.17
Angle of repose (º)	20.36 ± 1. 00
Tapped density (g/ml)	0.73 ± 0.05
Bulk density (g/m)	0.63 ± 0.01
Hausner's ratio	1.16 ± 0.06
Carr's Index	12.8 ± 1.33

Evaluation of naproxen-loaded niosomal gels

The opacity, pH, viscosity, spreadability, homogeneity and extrudability of the niosomal gels are shown in Table 3.

Table 3. Physicochemical properties of the naproxen-loaded niosomal gels.

Formulation	Opacity	Homogeneity	Spreadability (g/cm)	Extrudability (%)	pH	Viscosity at 30 rpm (mPas)
F1	Opaque	Good	5.43 ± 0.03	100	6.4	2327.1
F2	Opaque	Good	4.93 ± 0.02	100	7.1	1476.2
F3	Opaque	Good	4.93 ± 0.02	74	6.8	2864.6
F4	Translucent	Good	3.97 ± 0.00	100	7.3	3290.9
F5	Translucent	Good	2.97 ± 0.01	26.7	6.8	-
Commercially available gel	Translucent	Good	5.25 ± 0.02	100	7.2	2670.0

Opacity

Formulations F1, F2, and F3 gels were opaque and creamy in colour, which could be attributed to the natural gum colour (BEG). In contrast, formulations F4 and F5, which contained HPMC and the commercially available gel, were translucent.

Homogeneity

Formulations F1-F5, including the commercially available gel, all showed good homogeneity. No lumps or grit was felt when the gel was felt between the thumb and the index finger. They all had a smooth texture. The homogeneity and appealing appearance of pharmaceutical formulations indicates physical and chemical stability [38].

Spreadability

Formulations F1, F2 and F3 had good spreadability comparable to that of the commercially available gel, but F4 and F5 exhibited low spreadability. Their low spreadability may be due to the high viscosity of the gel formed by HPMC, the polymer used in their formulation. The ability of a gel to spread evenly on the skin surface is its spreadability. It is a vital requirement for uniformity and ease of application of skin formulations. It also plays a key role from the patient's compliance point of view. It is salient because the therapeutic effectiveness of the applied gel depends on the extent of its spread on the skin [25,39]. Application of the gel to the skin is more comfortable if the base spreads easily, manifesting maximum "slip" and "drag" [39].

Extrudability

As shown in Table 3, formulations F1, F2 and F4 showed excellent extrudability (100%) comparable to that of the commercially available gel but formulations F3 and F5 showed lower extrudability values (74% and 26.7%). Among the gel formulations prepared with BEG, formulation F3 had the highest polymer concentration (10%), while for those prepared\ with HPMC, F5 had a higher concentration than F4. Extrudability is an empirical test used to evaluate the force required for a gel to be extruded or expelled from the tube. It is a salient way to assess the easiness of the gel to expel from the tube [39]. Good extrudability is an ideal property of a gel, and it shows the ease with which the gel is forced out from the tube upon slight pressure application. The larger the quantity of gel extruded, the better the extrudability [40].

pH

As shown in Table 3, the pH of the niosomal gels ranged from 6.4 to 7.3, which is within or close to the normal skin pH range (4-7). The results suggest the gel may be applied to the skin without irritating it [41,42]. Formulations F2 and F4 have the same pH as a commercially available gel (7.2).

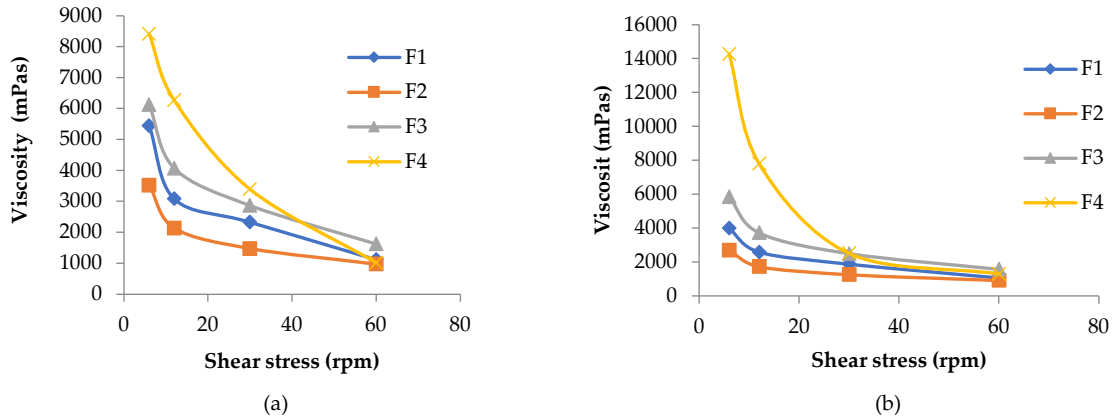


Figure 1. Viscosity curves for naproxen-loaded niosomal gels at (A) 0 week and (B) after 4 weeks.

Viscosity

The consistency of any semisolid formulation is dependent on its viscosity. Preparations with relatively low viscosity flow easily from the surface, while those with high viscosity have spreading issues [43]. The viscosity at 28ºC of the niosomal gel formulations (F1- F4) using spindle 3 at 30 rpm ranged from 1476.2 - 3980.0 mPas while that of the commercially available gel was 2670.0 mPas (Table 3). The viscosity was comparable to that of the commercially available gel except for formulation F2

(7.5% BEG), which showed an unusually lower value (1476.2 mPas). Figure 1 shows that all gels exhibited shear thinning behaviour, as their viscosity decreases with increasing shear stress [25]. There was no significant change in viscosity after three months of stability study at 40ºC.

Particle size analysis and polydispersity index

The zeta sizer results in Figures 2 and 3 showed that the niosome formed with Tween 80: cholesterol (2:1) had a mean particle diameter of 61.59 nm and PDI of 0.292. This showed that the niosome was within the nano range. The PDI value showed that the niosome had a narrow particle size distribution.

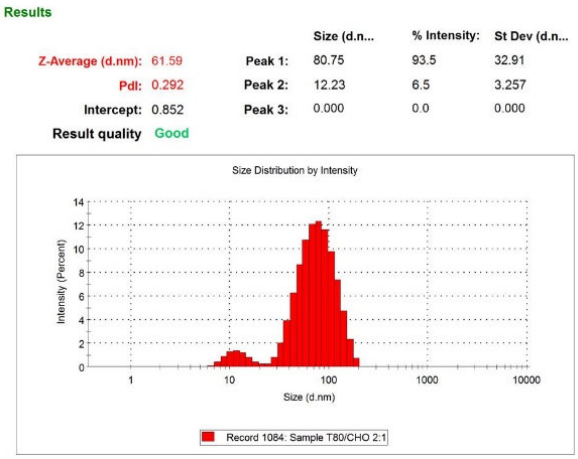


Figure 2. Particle size distribution by intensity for naproxen-loaded niosome containing Tween 80: cholesterol (2:1).

In-vivo Anti-Inflammatory Studies

Induction of inflammation with carrageenan is a useful acute test commonly used as a vital model in assessing the anti-inflammatory activity of drugs. The induction of inflammation with carrageenan is biphasic; the release of histamine, serotonin and kinins occurs in the first hour as the first phase, whereas the second phase occurs in the second to a third hour with the release of prostaglandins and lysosome enzymes [44-46]. From the percentage inhibition of inflammation results shown in Figure 4, the optimized gel formulation (F1) had comparable activity (26.5%) to that of the standard gel (31.3%) after 3 h. This agrees with the result of an in vivo anti-inflammatory study of aceclofenac by Godbole et al., which reported that percentage inhibition of inflammation increased from the first hour to the third hour and that the %inhibition increase with time was comparable to that of the commercial available diclofenac gel [35].

Analgesic test

NSAIDs act by cyclooxygenase (COX) enzyme inhibition, resulting in decreased prostaglandins production and reduced nociceptive signal transduction. Topical analgesics act by decreasing transduction (NSAIDs) or transmission (local anaesthetics) of nociceptive signals [47]. This is manifested in the form of an increase in response time to a thermal stimulus. Figure 5 revealed that the formulated gel, F1 has the comparable analgesic property to the commercially available gel (diclofenac gel). There was an increment in response time, 2.65 min for F1 and 2.75 min for commercially available gel, compared with negative control (1.6 min). Khullar et al. also reported a hike in lapse time for mefenamic acid formulations, comparable with diclofenac sodium gel (commercially available preparation) [48]. The response time decreases with time, hours after application of the gels (from 2.65 min, one hour after application to 2.10 min, two hours after application of formulation F1).

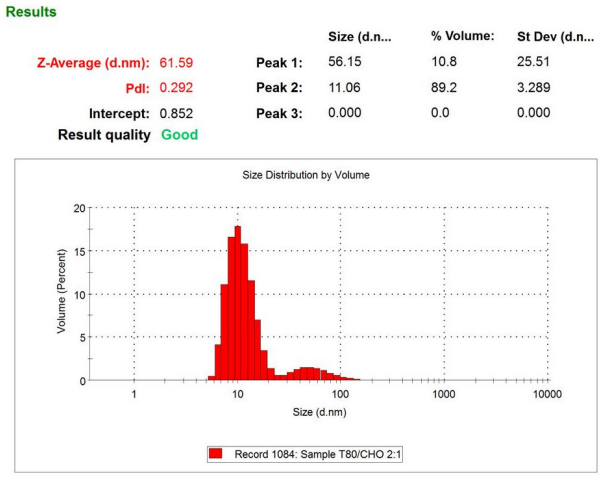


Figure 3. Particle size distribution by volume for naproxen-loaded niosome containing Tween 80: cholesterol (2:1).

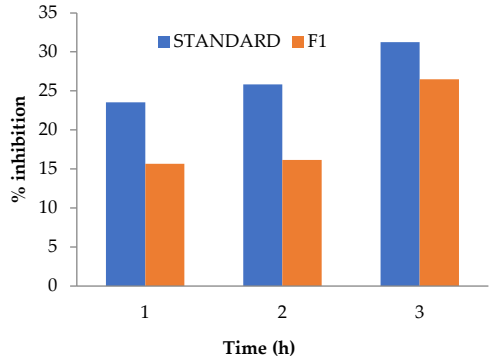


Figure 4. Percentage inhibition of inflammation studies for standard (diclofenac gel) and test (F1) groups.

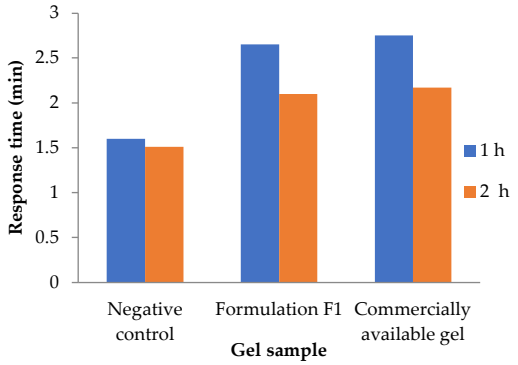
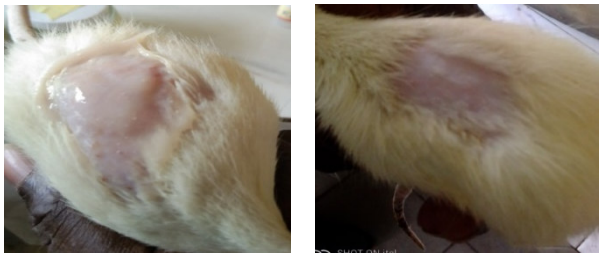


Figure 5. The response time to heat of Wistar rats, after 1 h (blue) and 2 h (red) of application of gels from the negative control, standard (commercially available product) and test groups (Formulation F1).

Skin irritation studies

Skin irritation is marked by undesirable skin changes, such as colour change and change in skin morphology within 24 h of application of a topical preparation [48]. The absence of erythema, oedema or inflammation, as shown in Figure 6, indicates that the prepared naproxen-loaded niosomal gel causes no skin irritation in the test rats. Therefore, the gel can be safely applied to the skin. This result was comparable to that obtained by Reddy et al., where the application of selected gel formulations did not produce redness of skin and skin irritation on the skin of test rats and was found to be safe when topically applied [19]. It also agreed with the result obtained from the study of mefenamic acid emulgel by Khullar et al. They reported that no allergic symptoms such as inflammation, redness, or irritation were observed 24 h after applying the emulgel to test rats [48].

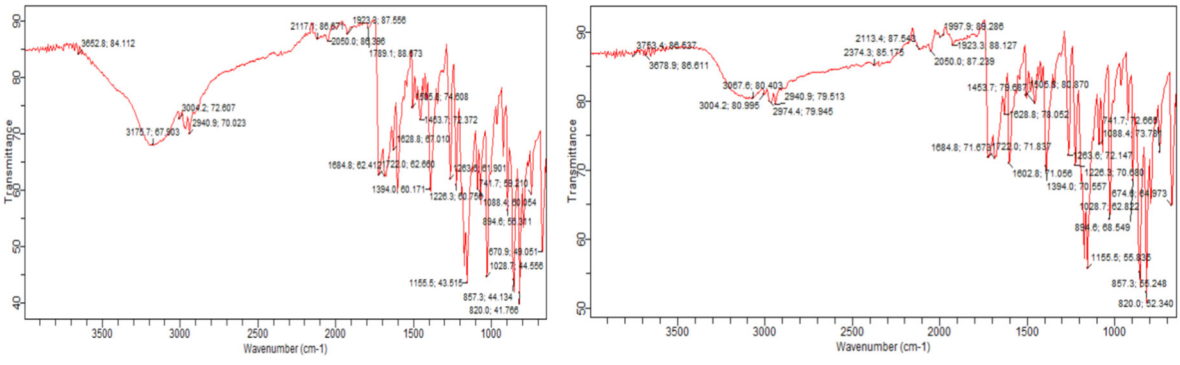


(a) (b)

Figure 6. Wistar rat 24 h after application of (a) formulation F1 and (b) commercially available diclofenac gel.

Drug/excipient compatibility

As shown in Figures 7a and 7b, the characteristic peaks for naproxen were present in both spectra. This shows that there was no interaction between naproxen and BEG. The peak for C=C-C stretch of the aromatic ring (1615-1580 cm^{-1}), was present at 1602.8 cm^{-1} and 1594.0 cm^{-1} in the naproxen and naproxen + BEG spectra respectively. The alkyl C-O of ether (1150-1050 cm^{-1}), was present at 1088.4 cm^{-1} and 1088.4 cm^{-1} in the naproxen and naproxen + BEG spectra respectively. The peak for O-H stretch of the carboxyl group (3550-2400 cm^{-1}) was present at 3067.6 cm^{-1} ad 3175. 7 cm^{-1} in the naproxen and naproxen + BEG spectra respectively [26,49].



(a) (b)

Figure 7. FTIR spectra of (a) naproxen and (b) naproxen + BEG.

Conclusion

This study confirmed that naproxen could be loaded into niosomes using Tween 80 and cholesterol (2:1). Brachystegia eurycoma gum (BEG) could be used as gel-base to provide stability for the prepared niosomes and as a vehicle for their use as topical preparations. Naproxen-loaded niosomal gel with good physicochemical properties was successfully formulated using BEG as the gelling polymer. The gels formulated using BEG as the gelling polymer exhibited good physicochemical properties comparable to those prepared using HPMC, a standard polymer. The formulated naproxen-loaded niosomal gels have good anti-inflammatory and analgesic properties comparable to the commercially available diclofenac gel. The formulated gels were safe to apply topically because they did not cause skin irritation when applied to rats' skin.

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Authors contribution

Each of the authors contributed substantially.

Declaration of interest

The authors declare no conflict of interest.

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