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EVALUATION OF NAPROXEN-LOADED EMULGELS FORMULATED USING *MORINGA OLEIFERA* SEED OIL

OKAFO SE*, ALALOR CA, ISRAEL NC AND AGBAMU E

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Delta State University, Abraka, Nigeria

***Corresponding Author: Dr. Okafo Sinodukoo Eziuzo: E Mail: okafose@delsu.edu.ng**

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ABSTRACT

Naproxen is a potent non-steroidal anti-inflammatory drug but it is insoluble in water. Formulation of naproxen as emulgel improves its solubility. The aim of the study was to formulate and evaluate naproxen-loaded emulgels produced using *Moringa oleifera* seeds oil.

Moringa oleifera seeds were dried, ground and the oil extracted with petroleum ether using a Soxhlet extractor. The oil was concentrated using a rotary evaporator. Emulsion was formed by mixing the oil and the aqueous phase at 70°C. The aqueous phase was composed of tween 80, methyl paraben, propylene glycol and naproxen. Sodium carboxymethylcellulose was dispersed in warm water and stirred to form gel. The emulsion was gradually added to the sodium carboxymethylcellulose gel base to produce the emulgel. The emulgels were evaluated for physicochemical, analgesic and anti-inflammatory properties.

The prepared naproxen emulgels were white to creamy white and opaque in appearance. The pH of emulgels ranged from 5.00±0.04 to 5.85±0.01. The emulgels have good spreadability, extrudability, homogeneity and did not cause skin irritation. They showed good analgesic and anti-inflammatory activities.

The study showed that Moringa seed oil could be used to produce naproxen-loaded emulgels with acceptable physicochemical, analgesic and anti-inflammatory properties.

Keywords: Emulgel, naproxen, *Moringa oleifera*, spreadability, analgesic, anti-inflammatory

INTRODUCTION

Topical administration of drug is a localized system of drug delivery through vagina, eyes, rectum and the skin. The skin is the most salient route for topical administration of drug and it can be reached easily **[1]**. Topical/transdermal drug delivery is a good replacement for oral and parenteral routes which are conventional routes. Topical delivery is non-invasive and it bypasses first pass metabolism. There is reduction in drug toxicity/side effects and improvement in patient compliance **[2]**. Topical delivery involves the direct application of a medication containing active pharmaceutical ingredient(s) to skin to cure skin disorders or the skin manifestation of general disease with the intention of restricting the pharmacological or other effects of the medication to the periphery of skin or within the skin. Semisolid dosage forms in frequent use include gels, creams and ointments **[3]**.

Gels are two-component semisolid systems rich in liquid. Continuous structures that provide them with solid-like properties are usually present **[4]**. Gels are semi-solid masses formed in certain concentrations by dispersions of lyophilic colloids, particularly when the colloidal material's solubility is reduced by change in temperature **[5]**. There is usually an involvement of a high degree of physical or sometimes chemical cross-linking **[6, 7]**. They are a comparatively newer group of drug delivery systems produced by entrapment of huge quantity of aqueous or hydroalcoholic liquid in a complex colloidal solid particles mesh, usually consisting of inorganic substances or organic polymers **[8, 9]**. Emulgel is a dosage form produced as a result of mixing both oil-in-water or water-in-oil type emulsion and a gel base or gelling agent together **[3, 10, 11]**. The conversion of the classical emulsion into an emulgel is brought about by the effect of the gelling agent in the water phase. Emulgels are known as hydrogels that contain randomly distributed oil micro droplets. Emulsified gel is better and stable means of delivery of hydrophobic or poorly water soluble drugs **[9, 12]**. Emulgels are highly accepted by patients because of their good attributes like being thixotropic and greaseless. They have good spreadability, ease of removal and are emollient. They are non-staining, transparent, stable, bio-friendly and have attractive appearance **[3, 10, 13]**.

Naproxen is chemically 2-(6-methoxynaphthalen-2-yl) propanoic acid. It is a white or almost white, crystalline powder that is practically insoluble in water but soluble in alcohol and in methanol **[14]**. It is

a non-steroidal anti-inflammatory drug (NSAID) that is utilized in the treatment of inflammations, rheumatoid arthritis, ankylosing spondylitis, musculoskeletal disorders and gout **[15]**. It works by inhibiting both the COX-1 and COX-2 enzymes **[16]**.

Moringa oleifera is a small to medium-sized, evergreen or deciduous tree native. In English it is called drumstick tree and Ben tree. It is native to northern India, Nepal and Pakistan. It is however, now found in different countries worldwide both cultivated and in the wilds. Its edible fruits, leaves, flowers, roots, and seed oil are very valuable and they are extensively applied in traditional medicine throughout its native and introduced ranges **[17, 18]**.

M. oleifera seeds are globular, about 1 cm in diameter. Oil makes up about 36.7% of the weight of the seed. Solvent extraction method usually using n-hexane is utilized in the extracted of oil from the seeds. Cold press extraction method produces lower yields. Actually, only 69% (on average) of the oil content of the seeds can be extracted by cold press **[19, 20]**. Among rural dwellers, the edible oil is extracted by boiling de-husked seeds with water, and collecting the oil from the surface of the water **[19]**. The oil is liquid at room temperature and golden yellow in colour. The density and refractive index of the oil remain the same irrespective of the extraction method **[21]**. Moringa plants abound in various parts of Nigeria both cultivated and in the wild. Various parts of the plant are consumed as food or used as herbal medicines but it is not utilized commercially. The aim of this study was to formulate and evaluate naproxen-loaded emulgel produced using oil extracted from *Moringa oleifera* seeds.

MATERIALS AND METHODS

Materials:

Naproxen (Divi's Laboratories Ltd, India) was a gift from Swiss Pharma Nig. Ltd, 5 Dopemu Road, Agege, Lagos, Nigeria, Propylene glycol (BDH, Poole, England), ethanol (Guangdong Guanghua Sci – Tech. Co. Ltd, Shantou, Guangdong, China), sodium carboxymethylcellulose, Tween 80 (Guangdong Guanghua Sci – Tech. Co. Ltd, Shantou, Guangdong, China), petroleum ether (BDH, Poole, England). All other chemicals and reagents used were of analytical grade.

Extraction of Moringa oil from *Moringa oleifera* seeds

Fresh seeds of *Moringa oleifera* were bought from Abraka market, Delta State, Nigeria, and authenticated by Dr. Akinnibosun Henry Adewale, of the Department of Plant Biology

and Biotechnology, Faculty of Life Sciences, University of Benin, Benin City, Nigeria. It was assigned voucher number UBH-M340. The outer coverings were removed and the seeds ground into powder using a manual grinding mill (Corona mill, China). Four hundred grams of the powdered *Moringa oleifera* seeds was extracted with petroleum ether using a Soxhlet extractor. The extract was concentrated using a rotary evaporator at 60 °C. The extracted oil was exposed to ensure complete evaporation of petroleum ether. It was kept in an airtight container.

Characterization of *Moringa oleifera* seed oil:

Determination of relative density: Analysis was done by direct reading in glass hydrometer (pycnometer) at 25°C.

Determination of refractive index: This was performed using a refractometer (ABBE model) as described by a previous researcher **[21]**. Refractive index is specific for oils, within certain limits. It is related to the extent of binding/bonding saturation, but it is affected by other factors such as free fatty acids content, oxidation, and thermal treatment.

Determination of pH: This was done using a model HI 2211 pH/ORP meter (Hanna Instruments, India) at 25 ± 2°C.

Determination of viscosity: This was evaluated at 25 ± 2°C using Brookfield viscometer at 100 rpm (spindle 4) **[22]**.

Preparation of naproxen-loaded emulgel:

The emulgel was prepared using a slightly modified method of Khullar *et al* **[8]** according to the formula on **Table 1**. Tween 80 was dissolved in distilled water to form the aqueous phase. Methyl paraben was added to the aqueous phase except in formulations BF4, BF5 and BF7, where it was dissolved in propylene glycol before it was added to the aqueous phase. Naproxen was dissolved in ethanol and transferred into the aqueous phase. They were mixed properly using a magnetic stirrer with hot plate. Moringa oil was the oily phase. The aqueous and oily phases were heated to 70^{o}C separately. The oily phase was transferred into the aqueous phase and the mixture was stirred continuously until it cooled to room temperature. Sodium carboxymethylcellulose (NaCMC), a gelling agent was dispersed in warm water in a beaker and stirred using magnetic stirrer at a moderate speed to form gel. The emulsion formed was added to the NaCMC gel and stirred gently to produce the emulgel.

Table 1: Composition of the naproxen-loaded emulgel

Ingredients	BF1	BF2	BF3	BF4	BF5	BF6	BF7
Moringa oil (ml)	6	6	6	6	6	-	-
Arachis oil (ml)	-	-	-	-	-	6	6
Tween 80 (ml)	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Methyl paraben (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Naproxen (g)	2	2	2	2	2	2	2
Ethanol (ml)	8	8	8	8	8	8	8
Sodium carboxymethyl cellulose (g)	1	1.5	2	2	2	2	2
Propylene glycol (ml)	-	-	-	10	15	-	10
Distilled water to (g)	100	100	100	100	100	100	100

Evaluation of the Emulgels:

Physical appearance: The emulgels were examined visually for their color, consistency and homogeneity. Homogeneity was also checked by feeling the sample of the emulgel between the thumb and the index finger.

pH determination: The pH of 1% aqueous solution of the emulgels was measured using a model HI 2211 pH/ORP meter (Hanna Instruments) **[23]**.

Drug Content: Five milliliter (5 ml) of the emulgel (equivalent of 100 mg of naproxen) was measured and transferred into 100 ml beaker containing 20 ml of phosphate buffer pH 7.4. It was dissolved and transferred into 100 ml volumetric flask. Additional quantity of the phosphate buffer was used to adjust the volume to 100 ml mark. It was shaken properly and filtered using a 0.45 µm Whatmann filter paper. The filtrate was diluted to 10 µg/ml and analyzed using a UV spectrophotometer at 230.4 nm. The drug concentration was calculated from calibration curve plotted using the absorbance values obtained from the analysis of know concentrations of the pure naproxen samples.

Ease of removal: A small sample of the formulated emulgel was rubbed on the skin. It was washed off using flowing water from a running tap **[24]**. The ease with which the emulgel was washed off was noted.

Determination of emulsion type: This was done using the dilution test **[25]** and dye test **[26]** methods. For the dilution test, 0.1 g sample was transferred into three respective beakers. A 2, 5 and 10 ml quantity of distilled water was added to the respective samples and mixed properly. The new nature of the emulgel was noted. For the dye test, sample of the emulgel was mixed with scarlet red dye and viewed using a light microscope.

Spreadability: A 0.1 g sample of the emulgel was placed in between two glass slides and the diameter of circle (D_1) formed was recorded. A 300 g weight was placed on top of the slides for 5 min and the diameter of the new circle formed (D_2) was recorded

[27-29]. Spreadability was calculated using equation 1.

$$\%\ \boldsymbol{Spreadability} = \frac{(\boldsymbol{D_2 - D_1})}{D_2}\ \boldsymbol{X\ 100} \quad . \ . \ . \ . \ \boldsymbol{1}$$

Extrudability: Collapsible tube was filled with a known weight of naproxen-loaded emulgels (W_1). A 900 g weight was placed on the tube for 1 min and the weight of extruded emulgel (W_2) was recorded **[30]**. The extrudability was calculated using equation 2.

$$\boldsymbol{Extrudability} = \frac{\boldsymbol{W_2}}{\boldsymbol{W_1}}\ \boldsymbol{X\ 100} \quad . \ . \ . \ . \ \boldsymbol{2}$$

Viscosity: The viscosity of the various naproxen-loaded emulgels was evaluated at 25 °C using spindle 3 of a Brookfield viscometer (Brookfield DV-E viscometer) at 6, 12, 30 and 60 rpm.

Anti-inflammatory Study

Ethical clearance was received from the Research and ethical committee of the Faculty of Basic Medical Sciences of Delta State University, Abraka, Nigeria [Resolution no: REC/FBMS/DELSU/19/54] before the research commenced.

White albino Wistar rats were utilized for the *in vivo* anti-inflammatory study. Twenty rats were shared into four groups i.e. the Control, Standard, Test 1 and Test 2 with each group containing 5 animals.

GROUP I (Control Group): Carragenan (1%) was administered in the plantar surface of rat.

GROUP II (Standard group): Topical marketed diclofenac gel + Carragenan.

GROUP III (Test Group 1): Formulation BF4+Carragenan

GROUP IV (Test Group 2): Formulation BF5+Carragenan

The left hind paw of the rats was given subplantar injection of 1% Carragenan to induce oedema. The test formulations (BF4 and BF5) and Standard (diclofenac gel) were rubbed 30 min after administration of carrageenan. The paw volume was measured at intervals of 1, 2 and 3 hours by water displacement method using Plethysmometer **[31; 3]**.

The percentage inhibition of paw oedema in drug treated groups was compared with control group and calculated using equation 3.

$$\%\ \boldsymbol{Inhibition} = \frac{(\boldsymbol{Vc - Vt})}{\boldsymbol{Vc}}\ \boldsymbol{x\ 100} \quad . \ . \ . \ . \ \boldsymbol{3}$$

Vc = inflammatory increase in paw volume of control group

Vt = inflammatory increase in paw volume in (drug + Carragenan) treated animals [31].

In vivo analgesic activity

The in vivo analgesic study was conducted using hot plate method. Twenty Wistar rats were shared into four groups of five animals. The time it took the rat to react to the effects of the heat from the hot plate (latency period) was recorded **[8]**.

Group 1 (Control Group): No topical treatment was given

Group 2 (Standard Group): The rats were treated with diclofenac gel

Group 3 (Test Group 1): The rats were treated with test formulation BF4

Group 4 (Test Group 2): The rats were treated with test formulation BF5

Skin irritation test: This test was conducted on male Wistar rats. The Wistar rats were grouped into four groups, namely, control, standard, test group 1 and test group 2. The hair in the dorsal region of the rats were shaved a day before the commencement of the study. A standard irritant, 0.8% of Formalin was applied to the standard group after 24 h of shaving the skin of the rats. Formulations BF5 and BF7 were applied to test group 1 and 2 respectively. Nothing was applied to the control group. The rats were observed for any irritation such as erythema or oedema at the end of 24 h **[3; 25]**.

Accelerated stability studies: Emulgels from formulations BF4 and BF5 were kept at 40^{o}C and were evaluated based on viscosity, homogeneity and colour changes once every month for 3 months.

Data analysis:

The experiments were done in triplicates for validity of statistical analysis and were expressed as mean ± SD. Statistical analysis was done using Microsoft Excel and IBM SPSS statistics 23 software. Differences between means were determined with one way analysis of variance (ANOVA) at a level of significance of $P < 0.05$.

RESULTS AND DISCUSSION

Physicochemical characteristics of *Moringa oleifera* oil:

The results on **Table 2** showed the physicochemical characteristics of extracted *Moringa oleifera* seed oil. Density of the moringa seed oil was observed to be 0.86 g/mL; specific gravity of the extracted oil was observed to be 0.86 which shows that it is less dense than water. Refractive index of the oil measured in an ABBE refractometer at a temperature of 28.5 °C was observed to be 1.4595.

Physicochemical characteristics of the emulgels:

Physical appearance: Naproxen emulgel from all the formulations were opaque in nature. Formulations BF1 and BF2 were flowable and creamy white in colour. BF3 to BF5 were creamy white viscous gels while BF6 and BF7 were white viscous gels **(Table 3)**. White gels are cosmetically appealing to patients and this may result in increased patient compliance and ultimately therapeutic effect. The emulgels showed good homogeneity **(Table 3)**. No palpable mass

was felt when sample of the emulgel was placed between the thumb and the index finger. Also on visual inspection the emulgel seemed to be homogeneous.

pH: The pH of emulgels prepared using moringa seed oil ranged from 5.61 ± 0.04 to 5.85 ± 0.01 while those prepared using arachis oil ranged from 5.00 ± 0.04 to 5.10 ± 0.07 **(Table 3)**. The pH of naproxen emulgel from all the formulations (5.0 ± 0.04 to 5.85 ± 0.01) was within the normal skin pH range (4 to 6) **[32]**. Highly acidic or alkaline pH may irritate skin. The pH obtained for the prepared naproxen emulgels was similar to that obtained by Chavda and Rupapara **[23]**. It was however, lower than that reported by some researchers **[33]** from naproxen topical gel (6.8±0.2). Another researcher **[34]**, reported that the pH of naproxen proniosomal gel was between 6.4 to 7.5 and this was higher than the pH obtained in this present study. The difference in the pH may be due to variation in the types and quantities of excipients used in the different formulations. Variation in the pH has been shown to play a role in the pathogenesis of skin diseases like irritant contact dermatitis and atopic dermatitis. Maintaining the skin's pH factor helps maintain a proper balance of the "acid mantle" which aids in protecting the body from bacteria and helps prevent moisture loss **[32]**.

Drug content: The drug content of the prepared emulgels ranged from 97.54% to 98.89% **(Table 4)** and they were all within the allowed limit.

Ease of removal: All the emulgel formulations were easily washed off using running tap water **(Table 4)**. Oil-in-water creams or emulgels have water as their continuous phase and therefore, they are easily diluted and washed off with water.

Emulgel type: The dilution test showed that all the emulgel formulations are of the oil-in-water type **(Table 4)**. Dilution test is based on the solubility of continuous phase of emulsion. Water is used to dilute oil-in-water emulsion while oil is used to dilute water-in-oil emulsion **[25]**. The dye-solubility test also confirmed that the emulgels are oil-in-water **(Table 4)**. The oil globules (dispersed phase) were coloured red and the continuous phase (water) were colourless when emulgel samples were viewed using a microscope. Water-soluble dyes will dissolve in the aqueous phase and oil soluble dyes will dissolve in the oil phase **[25, 35]**.

Spreadability: The results on **Table 4** showed that the emulgels spread easily by little amount of shear. The spreadability ranged from 71.01 ± 2.49 to 85.67 ± 1.03%.

Good spreadability is a desirable quality for emulgels. It shows the degree of spread or the area where the gel readily spreads to when it is applied to the affected part. The spread of an applied gel dictates its therapeutic efficacy. Good spreadability is an ideal quality of a topical application that enables it to achieve uniform application to the skin **[29, 36]**. The spreadability values obtained signified that the emulgels were easily spreadable by small amount of shear (71.01 ± 2.49 to 85.67 ± 1.03). Good spreadability is a vital factor in patient compliance to treatment schedule **[36]**.

Extrudability: As shown on Table 4, the extrudability of the emulgels from the different formulations ranged from 25.57 ± 5.2 to 92.89 ± 10.2%. Extrudability is a measure of ease of expulsion of an emulgel from its container. It shows how easy or difficult it is, to press out an emulgel from its container for application to the skin. Extrudability of an emulgel is dependent on its viscosity. Emulgels with high viscosity have low extrudability and vice versa. However, emulgels that exhibit shear thinning may have low extrudability at low shear but higher extrudability when the shear is increased. Extrusion of an emulgel from its tube is important during application and for the patient compliance **[9]**.The extrudability of the emulgels ranged from 25.57 ± 5.2 to 92.89 ± 10.2 and was found to be satisfactory.

Viscosity: As shown in **Figure 1**, viscosity of the emulgels ranged from 3500 to 65000 mPas, with formulation BF7 been the most viscous and formulation BF1 having the lowest viscosity. Viscosity of the emulgels ranged from 270 to 9980 mPas. The viscosity of formulation BF1 (1% NaCMC) was the least, 270 mPas, followed by BF2 (1.5% NaCMC), 840 mPas. The viscosity of formulations BF3 to BF7 that contained 2% NaCMC ranged from 3800 to 9980 mPas. It shows that greater the concentration of the gelling agent (NaCMC), the greater the viscosity. They displayed shear thinning behaviour because their viscosity decreased with increasing rate of shear. This behaviour is preferred due to its low flow resistance when applied at high shear conditions. This pseudoplastic behaviour is of great advantage because high spreadability occurs when certain force is applied due to the decrease in viscosity, while the emulgel is retained at the site of application when not sheared **[36]**.

Viscosity of the emulgel affects its spreadability and extrudability. There is an inverse relationship viscosity and the two parameters. Increase in viscosity results in decrease in the spreadability and

extrudability of the emulgel. Reduction in viscosity leads to decrease in resistance to flow and deformation. The spreading of formulation on skin and its extrusion from tubes are flow and deformation processes **[9, 37]**. Viscosity of emulgel plays a major role in the control of drug permeation through the skin and the effectiveness of an anti-inflammatory and analgesic preparation depends on it **[36]**.

Anti-inflammatory studies: As shown in **Figure 2**, the % inhibition of inflammatory activity by the formulations and standard emulgels ranged from 8.25 to 26.80%. The % inhibition by the formulated gels was less than that of the standard gel. This may be because they are not of equivalent concentration. % inhibition by formulation BF5 (10.31%) was higher than that of BF4 (8.25 %) and this may be due to the presence of propylene glycol (penetration enhancer) in formulation BF5.

Analgesic studies: The response time for the rats when placed on the hotplate 30 and 60 minutes after application of the emulgels was for the negative control (1.53±0.42 and 1.43±0.04 s), formulation BF4 (2.61±0.10 and 2.27±0.16 s) and BF5 (2.60±0.21 and 2.40±0.14 s) respectively. There was significant difference ($p > 0.05$) between the lapse or response time of the rats used as negative control and those that were applied with either formulation BF4 or BF5. This shows that the prepared emulgels have analgesic property but not as good as the standard at the concentration used. There was no significant difference ($p > 0.05$) between lapse or response time of the rats 30 min after application of formulation BF4 and BF5.

Skin irritation: The animals used in the skin irritation test are shown on **Figure 3**. There was no skin erythema or swelling in any of the rats used, therefore no skin irritation.

The emulgels prepared from moringa seed oil and arachis oil showed no obvious skin irritation such as erythema or oedema on the male albino Wistar rats' skin after 24 hours of application. This shows that the emulgels will be safe when applied topically.

Table 2: Physicochemical characteristics of *M. oleifera* oil

Parameters	Values
Density (g/mL)	**0.86**
Specific gravity	**0.86**
Refractive index (28.5 °C)	**1.4595**

Table 3: Physicochemical properties of the emulgels

Batch	Colour	Consistency	Appearance	pH	Homogeneity
BF1	Creamy white	Flowable	Opaque	5.61±0.04	Good
BF2	Creamy white	Flowable	Opaque	5.81±0.07	Good
BF3	Creamy white	Gel	Opaque	5.85±0.01	Good
BF4	Creamy white	Gel	Opaque	5.82±0.02	Good
BF5	Creamy white	Gel	Opaque	5.81±0.04	Good
BF6	White	Gel	Opaque	5.10±0.07	Good
BF7	White	Gel	Opaque	5.00±0.04	Good

Table 4: Physicochemical properties of the emulgels (continued)

Batch	Emulsion type	Extrudability ± S.D (%)	Spreadability ± S.D (%)	Drug content (%)	Ease of removal
BF1	O/W	99.89 ± 0.3	85.67 ± 1.03	97.54	Very easy
BF2	O/W	91.85 ± 3.7	74.39 ± 2.71	97.89	Very easy
BF3	O/W	77.15 ± 1.5	80.39 ± 0.38	98.77	Easy
BF4	O/W	84.85 ± 4.3	79.17 ± 0.00	98.81	Easy
BF5	O/W	84.98 ± 4.9	75.00 ± 0.00	98.84	Easy
BF6	O/W	40.00 ± 4.6	79.87 ± 2.02	97.99	Easy
BF7	O/W	61.90 ± 7.7	71.01 ± 2.49	98.89	Easy

Key: O/W = oil-in-water; S.D = standard deviation, n = 3

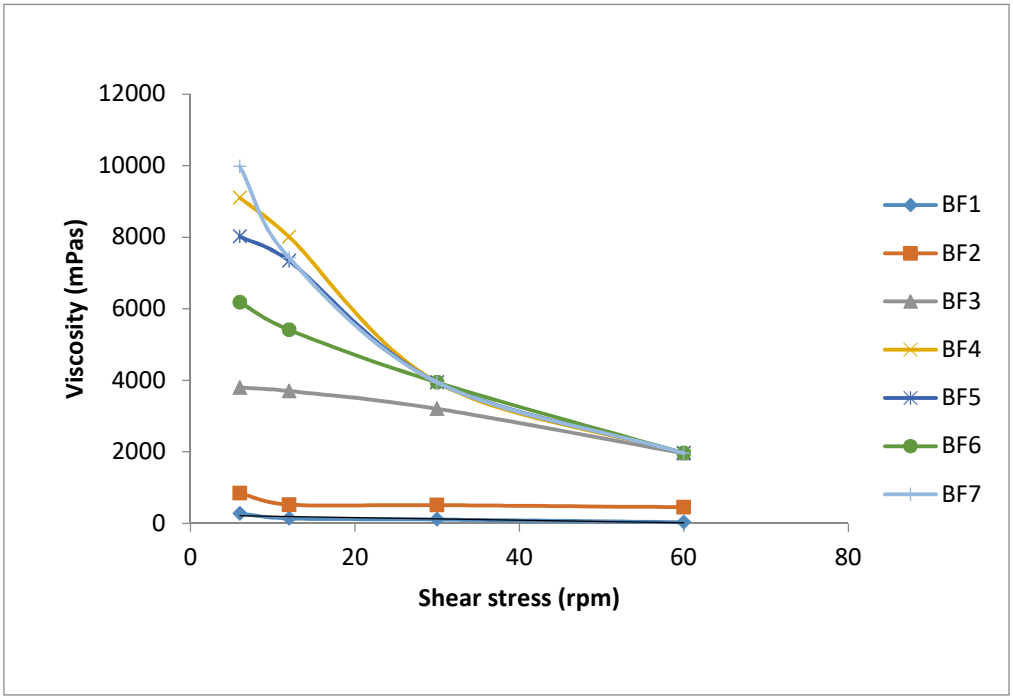


Figure 1: Viscosity curve of the naproxen-loaded emulgels

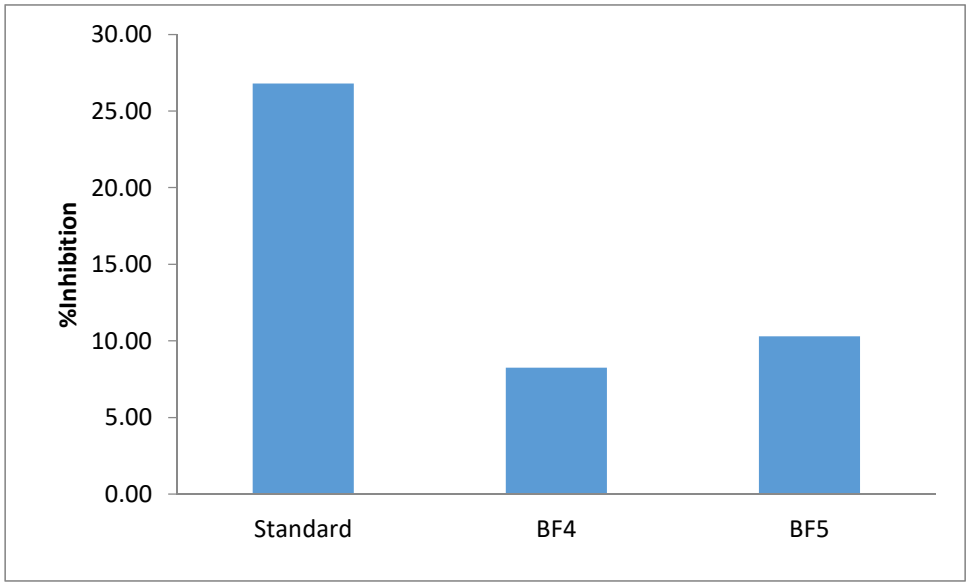
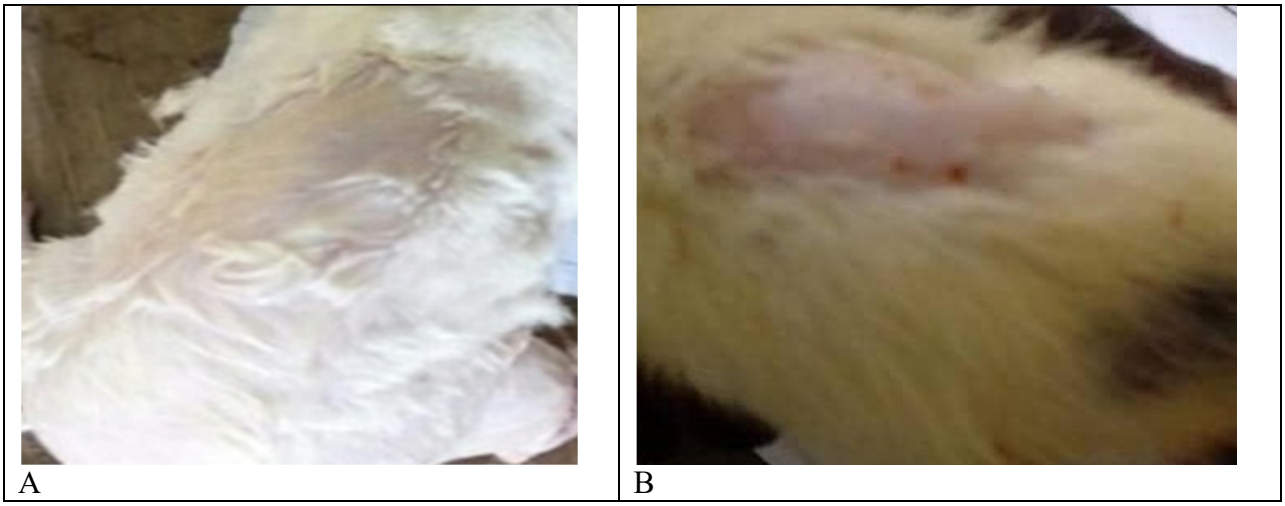


Figure 2: % inhibition of the inflammatory effect by standard, formulations BF4 and BF5



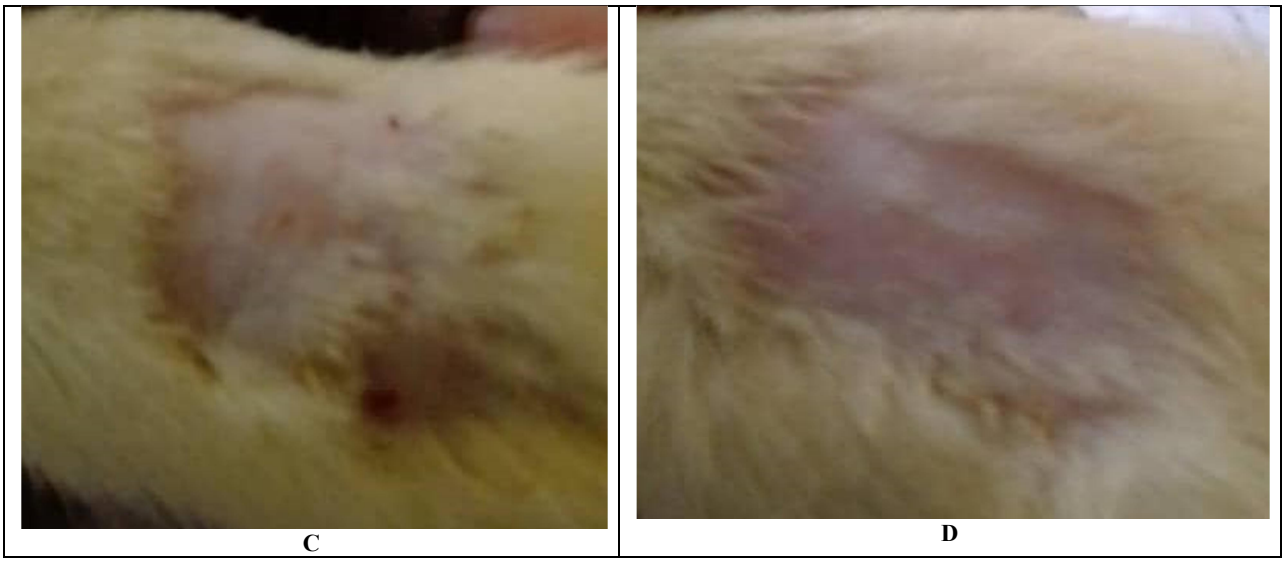


Figure 3: Skin irritation test
Key: A = control group (0.8% formalin); B = standard group; C = test group 1(BF4); D = test group 2 (BF5)

Stability: None of the prepared gels showed change in colour, homogeneity or viscosity three months after storage at 40^{o}C. The viscosities for the optimized formulation (BF5) after 0, 1, 2 and 3 months of stability studies were 8020, 8017, 8015 and 8010. This showed that there was no significant change in viscosity ($p > 0.05$).

CONCLUSION

Moringa seeds oil and arachis oil were successfully used to formulate naproxen-loaded emulgels. The naproxen emulgels formulated with *Moringa* seeds oil showed acceptable physicochemical properties such as acceptable colour, consistency, spreadability, extrudability, viscosity and pH value comparable to those prepared using arachis oil. The emulgels prepared using moringa seeds oil also showed good analgesic and anti-inflammatory activities.

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