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Original Research Article

Evaluation of diclofenac emulgel prepared with sesame oil as a lipophilic carrier

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Abstract

Purpose: *To investigate the suitability of sesame oil as an oily phase for diclofenac emulgel formulation.*
Methods: *Different batches of emulgel comprising different proportions of oils (sesame oil and/or Labrafac CC), surfactants (Tween-80 and/or cremophor EL-30), and gelling agents (xanthan gum or gelatin) were prepared. The formulations were evaluated for rheology, syneresis, Fourier transform infrared (FTIR) spectroscopy, spreadability, extrudability, and anti-inflammatory activity.*
Results: *Product characteristics of batches A2, A4, and A6 were not consistent with those of emulgels. Because Batch A1 showed characteristics that were the most stable, such as no pH changes, non-statistically significant changes (p = 1.000) in the viscosity results, and least spectrum changes following FTIR investigation, it was selected as the best batch. It showed similar anti-inflammatory activity when compared with commercially available diclofenac emulgel, giving a 50 % higher anti-inflammatory effect than aqueous diclofenac dispersion.*
Conclusion: *Sesame oil is a potential lipophilic component in emulgel formulations for topical delivery of hydrophobic drugs.*

Keywords: *Diclofenac, Emulgel, Ant-inflammatory, Sesame oil*

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INTRODUCTION

Gels are semisolid systems composed of the dispersion of smaller or large molecules in an aqueous liquid medium that has been made jellylike by the addition of a gelling agent [1]. Gels are ideal carriers for water–soluble medications due to their high-water content. They are smooth, and elegant, and provide cooling effects as a result of water evaporation they may also dry out to form films [2]. An emulgel is an emulsion that has been jellified by the formation of a gelled structure in the continuous phase as a result of the application of gelling agents to immobilize the emulsion's external phase. The external liquid phase

becomes more viscous as it changes from a liquid to a jelly-like form. This restricts movement in the internal phase and stops the dispersed liquid-phase droplets from coagulating [3]. In comparison to the emulsion, the product has greater thermodynamic stability [3]. Emulgels for dermatological usage offer a number of advantageous qualities, including thixotropy, ease of spreading, ease of removal, greaselessness, ease of spreading, ease of removal, emollience, bio-friendliness, pleasing appearance, and long shelf life. Emulgel's mucoadhesive feature allows it to prolong the duration that medication is in contact with the skin [4].

The emulsion-based gel is a method for incorporating and delivering a hydrophobic bioactive moiety with increased solubility and skin penetration [5]. Since emulgels are emulsion-based gels, the primary requirement for their development includes the selection of an oil phase, an emulsifier, and a gelling agent. Lipids of both synthetic and natural origin have generally been investigated for use in creating formulations for food, cosmetics, and pharmaceutical industries. The anticipated physical qualities of the finished product play a major role in determining the lipid phase. Moreover, the oil utilized may have therapeutic benefits depending on its source.

Sesame oil is obtained from the ripe seeds of *Sesamum indicum* Linne´ (Fam. Pedaliaceae) [6]. The oil has been reported to possess anti-inflammatory and a host of other therapeutic properties [7]. Previous research shows that self-emulsifying formulations made with oil from pressed sesame seeds as the oil phase exhibited favorable physicochemical characteristics [8,9]. Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) and a sparingly soluble phenylacetic acid derivative used to treat pain and inflammation in a variety of conditions [10]. This study aimed to investigate the suitability of sesame oil as the oil phase for diclofenac emulgel formulation.

EXPERIMENTAL

Materials

Diclofenac sodium (Pal Pharmaceutical Ltd, Kano, Nigeria), Voltaren emulgel (Novartis Pharma AG batch no. BLB02915, 03/2021 – 03/2024), caprylic/capric glycerides (GTCC) (Gattefosse, Lyon, France), Cremophor EL-35 (BASF, Mumbai, India), Tween 80 (Shanghai Sungo Technology Chemical, Shangai, China), Propylene glycol, Methyl parabens (BDH Chemicals Ltd, Poole Dorset, England), Xanthan gum (Central Drug House India), Gelatin powder (Loba Chemie Laboratory Reagents and Fine Chemicals Ltd, India), ethanol and menthol (BDH Chemicals Ltd, Poole, Dorset, England). Distilled water and sesame oil were obtained from a batch processed in Pharmaceutics laboratory, Kaduna State University, Kaduna, Nigeria.

Preparation of diclofenac emulgel

The gel was produced by dispersing the gelling agent (xanthan gum or gelatin powder) in hot distilled water while shaking continuously at 60 rpm with a mechanical stirrer (Remi motor stirrer, elektrotechnik Ltd, India) to produce a mixture with a homogenous consistency. The aqueous phase of the emulsion was made by combining distilled water, a solution of diclofenac in ethanol, methyl parabens in propylene glycol, and an ethanolic solution of menthol. The oily phase of the emulsion was made by dissolving surfactant (Tween 80 and/or Cremophor EL-35) in the oil (sesame oil and/or Caprylic/Capric glycerides (GTCC). Both the oily and aqueous phases were heated to a temperature of 70 to 80 ^{o}C before the oily phase was added drop-wise to the aqueous phase and continuously stirred for 30 min until it was cooled to room temperature. The resulting emulsion was mixed with the gel in a 1:1 ratio at 60 rpm for 30 min [11]. The formulations made are shown in Table 1.

Table 1: Diclofenac emulgel formulations' quantitative compositions (% w/w)

Ingredient	A1	A2	A3	A4	A5	A6
Diclofenac	0.5	0.5	0.5	0.5	0.5	0.5
Xanthan gum	12.5	-	12.5	-	12.5	-
Gelatin powder	-	12.5	-	12.5	-	12.5
Sesame oil	2.00	2.00	1.00	1.00	1.00	1.00
GTCC	-	-	1.00	1.00	1.00	1.00
Tween-80	0.50	0.50	0.50	0.50	0.25	0.25
Cremophor EL-35	-	-	-	-	0.25	0.25
Propylene glycol	0.65	0.65	0.65	0.65	0.65	0.65
Ethanol	0.63	0.63	0.63	0.63	0.63	0.63
Methyl parabens	0.01	0.01	0.01	0.01	0.01	0.01
Methanol	1.25	1.25	1.25	1.25	1.25	1.25
Purified water	25.0	25.0	25.0	25.0	25.0	25.0

Organoleptic properties assessment

Visual inspection such as colour, odour, appearance, consistency, after-feel, and phase separation was carried out and repeated after 5 months of storage.

Rheological evaluation

A rotary viscometer (NDJ-SS Digital viscometer, SearchTech, instrument, London, United Kingdom) was used to measure the viscosity of the formulated emulgels at a spindle speed of 30 rpm using rotor no. 2. The measurements were taken at ambient temperature (28 ± 2 ^{o}C). The viscometer values were taken when it was observed to be stable for 2 - 3 sec. This was repeated on the samples after 5 months of storage.

Syneresis measurement

Exactly 3 g of the formulated emulgel was transferred into a perforated-bottom cylindrical plastic tube with a foil paper covering. The tube and its contents were centrifuged for 15 min. Then the weight of the tube and the separated liquid were measured, and the percentage syneresis was calculated using Eq 1 [12].

Syneresis (%) = $(W_L/W_T)100$ …….. (1)

where W_L is the weight of liquid separated from the emulgel and W_T is the total weight of emulgel before centrifugation.

pH determination

The pH of emulgels produced was measured in triplicate with a digital pH meter. This was accomplished by immersing a glass electrode in the emulgel for 1 min and recording the pH. This was repeated on the same samples after 5 months of storage.

Compatibility test

Characteristics of the formulations were investigated by obtaining Fourier Transform Infrared (FTIR) spectra of freshly prepared and 5-month-old formulations. The spectra were taken in 4000 to 650 cm^{-1} range.

Optimization criteria and further evaluation

Preliminary evaluation of the three batches found that A1 had the most stable properties (less significant change in pH and viscosity, and it contained all the bands of diclofenac IR spectra), and therefore it was chosen as the optimized batch.

Spreadability measurement

In each case, the optimized formulation and marketed emulgel were sandwiched between two glass slides, then a 200 g weight was added on top and left for about 10 seconds. This measurement was carried out in triplicate. The area of spread was calculated using Eq 2 [13].

Area = length x breadth …….. (2)

Extrudability measurement

The amount of emulgel (cm^2) that could be extruded from a collapsible tube using a 400 g weight was determined using Eq 3 [13].

Extrudability = (W/A) …… (3)

Where W is applied weight to extrude emulgel from tube in grams and A is the area in cm^2

Anti-inflammatory assessment

The anti-inflammatory properties of formulations were assessed using the method described by Yahaya *et al* [9]. Ahmadu Bello University Zaria Committee on Animal Use and Care approved all experimental protocols (approval no. ABUCAUC/2018/017), which also followed international guidelines for animal studies. This study employed five groups of five animals each (mature Wistar rats of either sex weighing 180 to 200 g). For Group I, Group II, Group III, Group IV, and Group V, respectively, 0.9% w/v normal saline, 1% aqueous diclofenac dispersion, formulated diclofenac emulgel (1 %), and the marketed emulgel (1 %), were applied to the subplantar surface of the left hind paw of each rat. Thirty minutes post-treatment, a subplantar injection of 0.1 mL of fresh, undiluted egg albumin was used to induce edema in the subplantar region of the left hind paw of each rat. The paw diameter was measured with the aid of a Vernier caliper 1, 2, 3, 4, and 5 h after the injection of the egg albumin. The percentage inhibition of paw edema was calculated using Eq 4.

Inhibition (I) = {1-(Et/Ec)} …….. (4)

Et = Average edema of the group

Ec = Average edema of the control group

Statistical analysis

The statistical analysis was carried out using SPSS software, version 23 (IBM Inc., Chicago, Illinois, USA. Mean comparisons between the means of multiple groups were performed using one-way ANOVA and Bonferroni post hoc test.

The results were considered significant at $p < 0.05$.

RESULTS

Organoleptic, rheological, syneresis, pH, and compatibility

Emulgel formulations were off-white, viscous, soft, cream-like, and opaque, with a smooth, homogeneous, and glossy appearance as shown in Figure 1. The syneresis, viscosity, and pH of batches A1, A3, and A5 when freshly prepared and after 5 months of storage at ambient temperature (28 ± 2 ^{o}C) are presented in Table 2. Batch A5 had the highest viscosity. The pH results were between 7.0 and 8.2. The FTIR spectra of the pure drug (diclofenac), batches A1, A3, and A5, shortly after they were prepared and after five months of room temperature storage (28 ± 2 ^{o}C) are shown in Figure 2. The FTIR spectrum of diclofenac revealed peaks at 3213.0 cm-1 (NH stretching of the secondary amine), 1572.9 cm^{-1} (-C=O stretching of the carboxyl ion), 1498.4 and 1453.7 cm^{-1} (-C=C aromatic ring stretch), 1304.6 cm^{-1} and 1390.3 cm^{-1} (C-N), -C-Cl stretching at 1088.4 and 745.58 cm^{-1} for meta substituted benzene.

Anti-inflammatory properties

Intra-plantar injection of egg albumin into the rats' hind paws elicited a significant inflammatory reaction, resulting in paw edema. All groups began to display noticeable changes in gross morphology of their paws one hour after the egg albumin injection, including redness and swelling. Swelling in the paws peaked at 3 hours, following which it began to decrease (Table 3). The results of anti-inflammatory studies are shown in Figure 3.

DISCUSSION

A diclofenac emulgel will allow for easy application and provide an effective means of delivering the drug directly to the site of pain or inflammation. Understanding the physicochemical properties of diclofenac emulgel can provide valuable insights into its efficacy. All of the batches (A2, A4, and A6) in which gelatin was employed as the gelling agent failed to yield a product with characteristics consistent with those of emulgels and were thus discarded, showing that the gelling agent is incompatible with the oils, surfactant, and co-surfactant used.

Figure 1: A photograph showing the physical appearance of the formulation

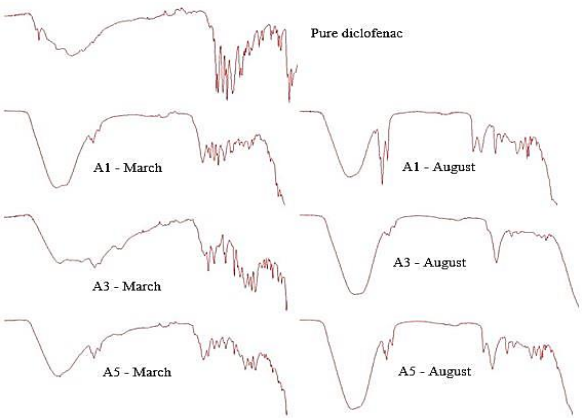

Figure 2: Fourier-transform infrared spectra of diclofenac, freshly prepared and 5-month-old Batch A1, A3, and A5

Table 2: Some physicochemical characteristics of batches A1, A3, and A5 when freshly prepared and after 5 months of storage at ambient temperature (28 ± 2 ^{o}C)

Test	Formulation	Freshly prepared	5-month old formulation	*P*-value
Viscosity (mPa.s)	A1	208.2±0.65	208.3±0.32	1.000
	A3	208.3±0.58	208.8±0.45	0.001*
	A5	208.6±0.38	208.1±0.87	0.001*
Syneresis (%)	A1	23.3±3.21	30.7±2.56	0.000*
	A3	26.7±1.94	49.7±4.12	0.000*
	A5	33.0±3.65	35.7±3.97	0.000*
pH	A1	8.2±0.39	8.2±0.68	1.000
	A3	8.4±0.73	7.4±0.44	0.088
	A5	7.9±0.55	7.0±0.47	0.232

*Significant mean difference at a 5 % level (i.e. $p < 0.05$)

Table 3: Increase in rats' paws 1 to 6 hours after egg albumin injection (mm) (Mean ± SD)

Treatment	1h	2h	3h	4h	5h	6h
Control	2.78±0.92	2.87±0.85	3.11±0.51	2.15±0.53	1.39±0.36	1.32±0.52
Aqueous diclofenac dispersion	2.52±0.89	2.54±0.33	2.78±0.92	1.87±0.35	1.21±0.02	0.98±0.60
Emulgel base (placebo)	2.67±0.15	2.70±0.41	3.02±0.90	2.09±1.02	1.33±0.20	1.11±0.64
Formulated diclofenac emulgel	2.26±0.53	2.34±0.13	2.59±1.05	1.47±0.53	1.08±0.53	0.65±0.24
Marketed emulgel	1.87±1.15	2.06±0.93	2.55±0.05	1.17±0.37	0.95±0.29	0.38±0.29

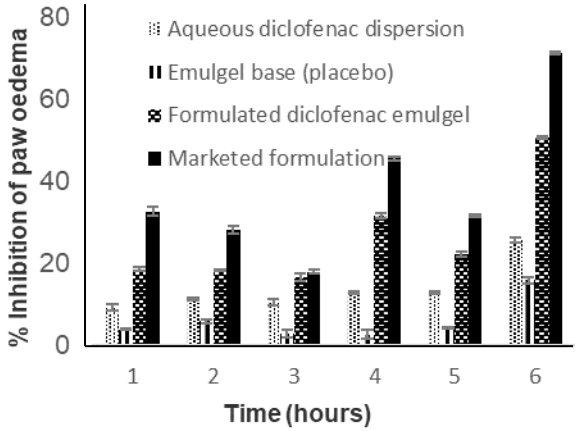

Figure 3: The percentage inhibition of edema in rats' paws by the various preparations 1 to 6 hours after egg albumin injection

However, successful emulgel formation was achieved with batches A1 (containing xanthan gum, sesame oil, and tween-80), A3 (containing xanthan gum, sesame oil, and GTCC), and A5 (containing xanthan gum, sesame oil, GTCC, and tween-80+cremophor EL-35). The results obtained revealed that batch A1 was the most stable. The obtained results indicate that using sesame oils as a lipophilic carrier in emulgel formulation will be obtained when it is combined with tween-80 as the surfactant and xanthan gum as the gelling agent. These results corroborate other authors' observations that an oil/surfactant pair and ratio, surfactant/co-surfactant pair, and concentration are important determinants of the phase properties exhibited by a system [14].

Soft, smooth, off-white emulgels with a homogeneous and glossy appearance were formulated. The acceptance of a product and ultimately its marketing success are positively impacted by elegance and aesthetic appeal [13]. The removal or expulsion of a liquid from a gel is known as syneresis [15]. The gel system of an emulgel periodically shrinks after standing; this phenomenon, known as syneresis, can cause a small quantity of liquid to be squeezed out of a product, thereby depriving it of its visual appeal. Syneresis measurement serves as a means of assessing liquid leakage from products [15]. There was a significant ($p < 0.05$) increase in syneresis results of all 3 batches after 5 months of storage. Syneresis can be minimized or prevented through measures such as packaging design to conceal the area where syneresis may emerge, keeping the product at a stable temperature as much as possible, and preventing external pressure [15]. Generally, batches viscosities were within the same range (208.1 – 208.6 mPa.s). After storage for 5 months, there was a significant change in viscosity for all the batches except batch A1. Temperature fluctuations may cause changes in viscosity. In addition to temperature fluctuations, additional factors that affect a liquid's viscosity include molecule bond strength, solution concentration, molecular size, weight, pressure, and presence of other chemicals. Variations in the viscosity of a product over time may also indicate structural instability in the system [16]. The viscous, creamy, and smooth texture of the formulations will allow for easy and convenient dermal application. The pH of batch A1 remained unchanged after 5 months of storage, however, batches A3 and A5 had slight pH changes. According to Khan *et al* [11], a decline in pH over time may be due either to the migration of water (pH 5 - 7) from the internal phase to the external phase or the generation of extremely acidic by-products from any of the oil constituents. Changes in the pH of a product could thus be attributed to product instability.

The observed FT-IR results for diclofenac were well corroborated by published data [10]. These bands were all present in the IR spectra of batch A1. However, changes in the FTIR spectra of batches A2 and A3 were observed after 5 months of storage, ranging from the wavelength of the NH and C-Cl stretching shifting to a lower frequency, while the wavelength of the C=O stretching of the carboxyl ion shifted to a higher frequency (from 1572.9 to 1584.1 and 1580.4 cm^{-1}, respectively). There was a disappearance of the -C=C aromatic ring stretch (in batch A3) and the meta-substituted benzene (in batch A5). Peak emergence, disappearance, and/or shifting are typically the outcomes of chemical alteration caused by chemical interaction or degradation [17]. Spreadability and extrudability are two important properties of semisolid formulations such as emulgels, ointments, and gels. Spreadability is the ease with which a semisolid formulation spread over a surface [13].

Extrudability, on the other hand, is the force necessary to push or expel a semisolid formulation from a tube or container [13]. Both are usually desired in semisolids because they are essential in deciding how simple it is to remove and apply semisolids products. The optimized and market formulations both had the same extrudability (800 g/cm^2), however, spreadability of the optimal formulation was higher (13.8 cm^2) than the marketed formulation (12.25 cm^2). This means that optimized formulation will spread quickly. The produced emulgels must have good spreadability to be suitable for topical administration since the spreading of the gel aids in uniform application of the product to the skin. Additionally, it is believed that this has a significant impact on how well patients comply with their treatment [18].

The inhibition of paw swelling by the different preparations was in the following order: marketed formulation > formulated diclofenac emulgel > aqueous diclofenac dispersion > emulgel base (placebo) treated groups. There was no statistically significant difference in edema suppression between the formulated emulgel and the marketed formulation from the first to the sixth hour. The percentage inhibition of paw edema achieved in the group treated with the formulated diclofenac emulgel was about 50 % higher than the inhibition obtained with the aqueous diclofenac dispersion. After 6 h, there was a 15 % suppression of edema by the emulgel base (placebo); this could be attributed to sesame oil's anti-inflammatory properties, which have been described in the literature [7]. A possible synergistic effect between sesame oil and diclofenac as well as the ability of the emulgel technique to promote efficient and prolonged access of the product to the skin and facilitate penetration and delivery of the drug may be the reason the optimized formulation has a greater anti-inflammatory effect than the aqueous diclofenac dispersion.

CONCLUSION

The formulation exhibits good physicochemical properties and *in vivo* anti-inflammatory activity. Its spreadability and extrudability characteristics are comparable with those of a commercially available emulgel. It inhibits paw edema 50 % more effectively than aqueous diclofenac dispersion. Therefore, sesame oil-based emulgel is a promising topical formulation for the delivery of diclofenac.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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