

# Preliminary research on ibuprofen self-emulsifying formulation

Zwanden Sule YAHAYA <sup>1\*</sup> , Fatima Shuaibu KURFI <sup>1</sup> , Danjuma MALLAM <sup>2</sup> , Rukayat Bukola OLOYEDE <sup>3</sup> , Olutayo Ademola ADELEYE <sup>4</sup> , Gideon Owoicho OKPANACHI <sup>5</sup> 

<sup>1</sup> Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Nigeria.

<sup>2</sup> Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Nigeria.

<sup>3</sup> Department of Pharmaceutical and Medical Chemistry, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Nigeria.

<sup>4</sup> Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Federal University Oye Ekiti, Nigeria.

<sup>5</sup> Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Gombe State University, Gombe, Nigeria.

\* Corresponding Author. E-mail: pharmzwanzy@gmail.com (Z.S.Y); Tel. +234-80-60235790.

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**ABSTRACT:** Ibuprofen is an important and commonly used nonsteroidal anti-inflammatory medication (NSAID). Its medicinal potentials are however severely hindered due to its poor water solubility and low oral absorption. A self-nano emulsifying drug delivery system (SNEDDS) is a lipid formulation that takes advantage of the solubilizing capacity of a mixture of oil, surfactant, and cosurfactant to improve intestinal permeability. The aim of this study is to develop SNEDDS of ibuprofen employing both labrafac CC and a natural lipophile (N-L) (vegetable oil) from pressed sesame seeds to improve the anti-inflammatory activity of ibuprofen. The formulation was stable against phase separation and drug precipitation, exhibited rapid emulsification within 5 s to yield an emulsion with a mean droplet size of 27.23 nm and showed a significant ( $p = 0.000$ ) increase in anti-inflammatory properties compare to the aqueous suspension of the standard drug and each treatment agent across the test period. Overall, SNEDDS of ibuprofen with desirable physicochemical properties and improved anti-inflammatory activities were successfully developed using an un-refined lipophile obtained from pressed sesame seed.

**KEYWORDS:** Self-emulsification; nano; bioavailability; ibuprofen; anti-inflammatory.

## 1. INTRODUCTION

Poorly water-soluble drugs continually remain a challenging class of pharmacological substances, despite their importance in the treatment of a wide range of illnesses. Oral administration of such drugs is frequently associated with limited bioavailability and significant intra- and inter-subject variation [1,2]. To address these issues, a variety of formulation options, such as salt formation, amorphous solid dispersions, inclusion complex formation, solubilization in surfactant micelles, micronization, utilization of permeation enhancers, lipid-based formulations, complexation with hydrophilic polymers and supersaturable systems have all been explored [3]. A Self-nano emulsifying drug delivery system (SNEDDS) is an oral lipid dosage form. It's a combination involving oils, surfactants and cosurfactants/cosolvents that can form fine oil in water (o/w) emulsions (with droplet diameter under 50 nm) after dilution with the aqueous phase and moderately agitated [4,5]. By providing a large interfacial area for drug partitioning between the oil and the gastrointestinal tract (GIT) fluid, SNEDDS promotes medication dissolution [6]. Other advantages of SNEDDS include the ability to by-pass the hepatic first-pass effect, ease of manufacture, long life span, enhancement of the intestinal absorption, promoting medication uptake via lymphatic channels in the intestine and suppression of the P-glycoprotein (P-gp) efflux [7,8]. The main step in the formulation of SNEDDS is the choice of lipidic and emulsifying agents capable of solubilizing the drug at the therapeutic concentration needed. To make a lipid carrier, you can choose from a variety of vehicles. Although Pharmacopoeial vegetable oils are widely preferred, indigenous natural vegetable oils are satisfactory and comparable with commercial

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triglycerides and modified oils. Natural vegetable oils also have the added advantages of being physiologically biocompatible, nutritionally acceptable, non-toxic, economically affordable and commercially available [9,10].

Ibuprofen is an important and commonly used nonsteroidal anti-inflammatory drug (NSAID). It is a nonselective cyclooxygenase (COX)-inhibitor largely used to treat mild to moderate pain from headaches, migraines, dysmenorrhea, dental pain and postoperative pain, as well as rheumatoid arthritis, spondylitis soft tissue problems and osteoarthritis. Ibuprofen also has antipyretic qualities and is one of the safest NSAIDs in the market [11]. The aim of this study is to develop SNEDDS of ibuprofen employing both labrafac CC and a natural lipophile (N-L) (crude oil) from pressed sesame seeds to improve the anti-inflammatory activity of ibuprofen.

## 2. RESULTS

### 2.1. Loading efficiency, emulsification time, drug precipitation, phase separation, droplet size, and polydispersity index

Formulation A had a loading efficiency of 94.6 % and Formulation B had a loading efficiency of 95.2%; none of the formulations exhibited drug precipitation or phase separation. Graphical representations of the mean droplet size and polydispersity index (PDI) of formulations A and B are shown in Figures 1 and 2. The mean droplet sizes of formulations A and B are 52.03 nm and 27.23 nm, respectively, while the PDIs are 0.212 and 0.078.

Formulation B was chosen as the optimal batch for *in vivo* anti-inflammatory testing because it had a lower mean droplet size and polydispersity index, as well as a faster emulsification time of 5 s compared to 7 s for formulation A.

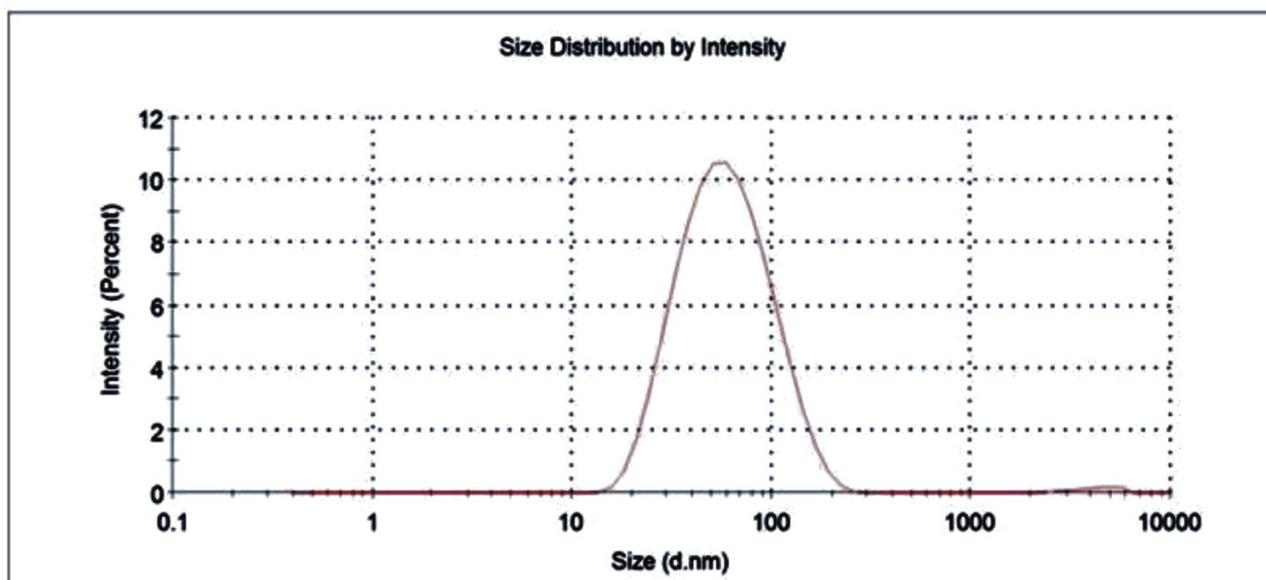


Figure 1. Graphical presentation of globule size of formulation A

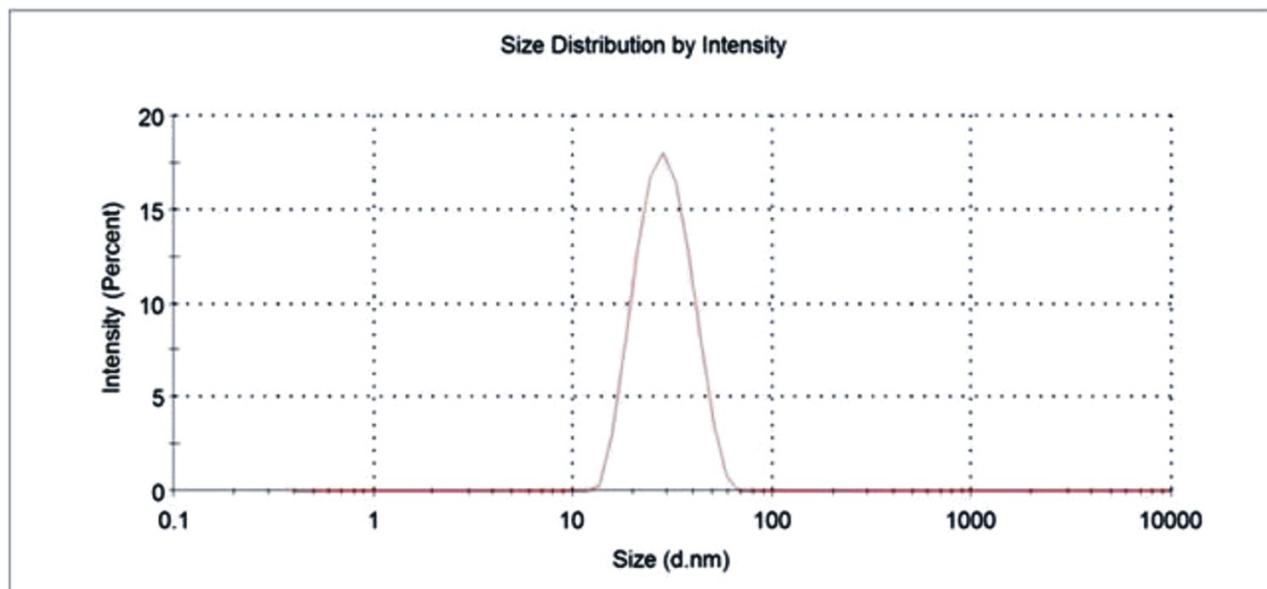


Figure 2. Graphical presentation of globule size of formulation B

### 2.2. Fourier Transform Infrared Spectroscopy (FTIR) analysis of optimized ibuprofen SNEDDS

The superimposed FT-IR spectra of standard ibuprofen and the optimized formulation are shown in Figure 3. The characteristic FT-IR peaks occurred at 2000-1667  $\text{cm}^{-1}$  indicating aromatic overtones 1690-1760  $\text{cm}^{-1}$  due to C=O stretching and 2500-3000  $\text{cm}^{-1}$  indicating OH stretching.

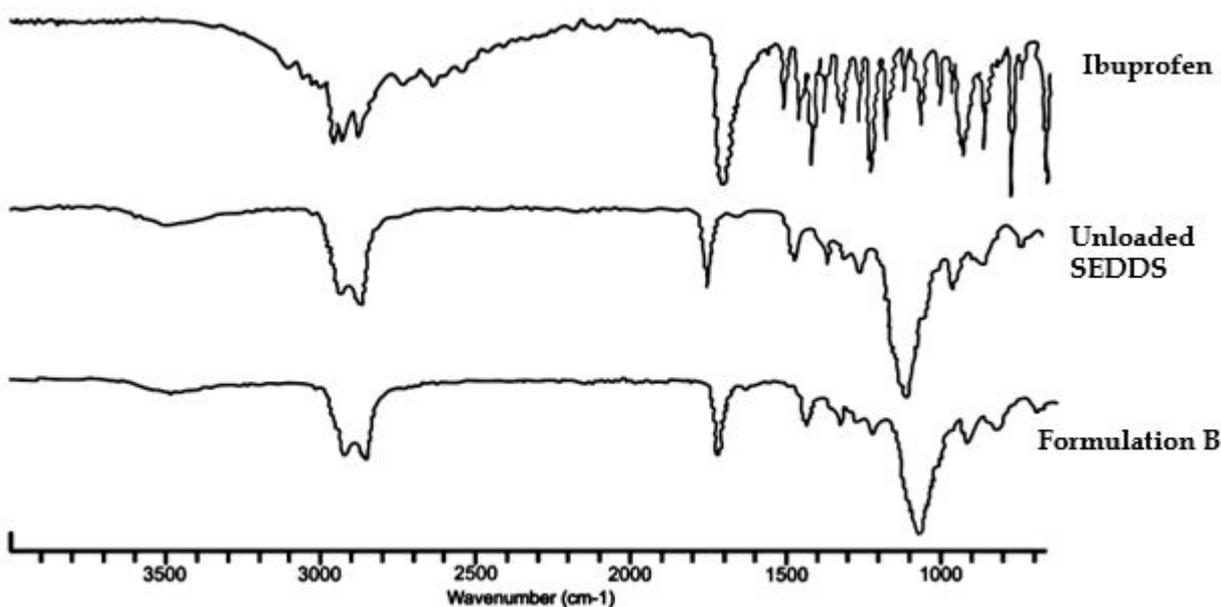


Figure 3. Superimposed FT-IR spectra of the optimized formulation, pure ibuprofen and the unloaded SNEDDS

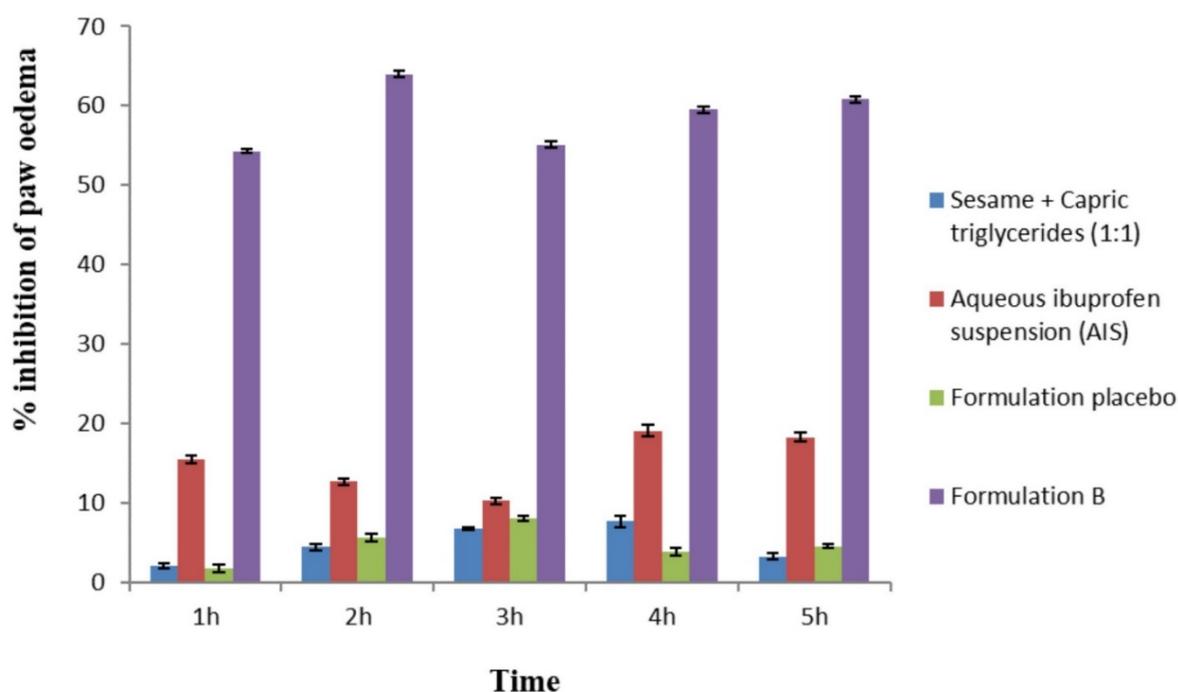
### 2.3. Anti-inflammatory activity of the optimized ibuprofen-SNEDDS formulation

The induction of acute inflammation resulted in a significant increase in paw thickness, beginning 1 hour after an intra-plantar injection of carrageenan and spiking 3 hours later as shown in Table 1. The anti-inflammatory characteristics of several ibuprofen formulations in terms of paw edema inhibition are depicted in Figure 4. The results showed that formulation B suppressed paw edema significantly more ( $p = 0.000$ ) than the aqueous suspension of ibuprofen all through, from the first to the fifth hour. The paw oedema suppression

by the different treatment agents was in the following order; Formulation B > Aqueous ibuprofen suspension (AIS) > unloaded SNEDDS (Formulation placebo) > Sesame + Capric triglycerides (1:1) > 0.9% normal saline.

**Table 1.** Mean paw size of test animal

Treatment	Mean increase in paw oedema (mm) ( $\pm$ SD)				
	1 h	2 h	3 h	4 h	5 h
Control (0.9% normal saline)	3.87 $\pm$ 0.03	6.45 $\pm$ 0.01	7.75 $\pm$ 0.06	7.13 $\pm$ 0.01	6.30 $\pm$ 0.03
Sesame + Capric triglycerides (1:1)	3.79 $\pm$ 0.05	6.16 $\pm$ 0.03	7.22 $\pm$ 0.03	6.58 $\pm$ 0.05	6.09 $\pm$ 0.02
Aqueous ibuprofen suspension (AIS)	3.27 $\pm$ 0.01	5.63 $\pm$ 0.05	6.95 $\pm$ 0.05	5.77 $\pm$ 0.04	5.15 $\pm$ 0.06
Formulation placebo (unloaded SNEDDS)	3.80 $\pm$ 0.02	6.08 $\pm$ 0.07	7.12 $\pm$ 0.07	6.85 $\pm$ 0.03	6.01 $\pm$ 0.03
Formulation B	1.77 $\pm$ 0.04	2.32 $\pm$ 0.03	3.48 $\pm$ 0.01	2.89 $\pm$ 0.02	2.47 $\pm$ 0.02



**Figure 4.** Percentage inhibitions of carrageenan-induced paw oedema by different ibuprofen formulations

### 3. DISCUSSION

Only extremely specific combinations of oil and surfactant - cosurfactant mix could lead to effective self-emulsification systems, as evidenced by the surfactant concentration, the oil/surfactant ratio, and the type of the oil/surfactant combination [12]. The dispersion of the formulation in an aqueous medium within a short time is a crucial criterion for evaluating emulsification efficacy [13]. Both formulations spontaneously emulsified in less than 8 s to give fine oil-in-water emulsions. This suggests that the formulation will rapidly disperse in the GI fluid *in vivo* under the action of the stomach and intestine's digestive motility, forming fine oil-in-water emulsions. The medication was well contained within the oil droplets, as evidenced by the excellent loading efficiency of the formulations. After dilution and centrifugation, both formulations exhibited stability against both phase separation and drug precipitation, indicating high stability. Creaming, cracking, and precipitation all pose serious challenges to the stability of emulsions, hence resistance to these challenges is a desired feature [14].

The distribution of droplet sizes after self-emulsification is an important feature to consider when evaluating a self-emulsifying drug delivery system. It demonstrates the emulsion's quality. Smaller droplet

sizes suggest a more efficient emulsification system, as well as the creation of a much more robust surfactant coat at the oil-water interface, which helps to stabilize the oil droplets [12]. Oils with shorter chain triglycerides (e.g., labrafac CC) have a low viscosity, which is proven to enhance emulsification spontaneity and thus emulsification efficiency, which does have a positive impact on emulsion droplet size [5,6]. As a result, formulation B (containing a mixture of labrafac CC and N-L as the oily phase) produced an emulsion with smaller mean droplet size and PDI compared to formulation A, whose oily phase is 100% N-L (consisting of long-chain triglycerides). Drug absorption is thought to be influenced by droplet size; the smaller the droplet, the greater the interfacial surface area for drug absorption [15]. The polydispersity index measures the degree of homogeneity in droplet size inside a formulation. A low PDI value indicates a monodisperse system with a narrow size range.

Carrageenan injections into the hind paw generated considerable oedema that peaked at 3 hours. The paw oedema volume of the group treated with Formulation B was in each case significantly ( $p = 0.000$ ) lower compared to the groups treated with other agents from the first to the fifth hour. After 5 hours, Formulation B and the aqueous ibuprofen suspension both reduced the paw oedema by 51 % and 16 %, respectively. Formulation B exhibited a 3.0-fold increase in oedema inhibition compared to ibuprofen aqueous suspension. The increased anti-inflammatory action of Formulation B is not unrelated to its ability to keep the drug in solution and present it to the GIT, bypassing the dissolution stage in favor of a fast liquid-liquid partitioning process between the solubilized reservoir and the drug in free solution. Also, SNEDDS by their lipid content can stimulate lymphatic transport thereby avoiding first-pass metabolism [1]. Most lipid substances and their metabolites possess the ability to initiate changes in the GIT that favour drug absorption, e.g., the "ileal brake," which lowers small intestine motility and hence increases the time available for digestion and absorption, is known to be activated by lipids [16]. Furthermore, it has been shown that lipids, surfactants, and cosurfactants promote intestinal permeability by opening tight junctions, inhibiting efflux transporters, and boosting transcellular permeability and membrane solubilization [4,16]. SNEDDS emulsify into nanodroplets which encapsulate the drug solution in an oil droplet thereby shielding it from the degradation effect of stomach acid [17]. The superior anti-inflammatory activity exhibited by formulation B is most likely the consequence of a combination of these activities.

#### 4. CONCLUSION

In this study, ibuprofen-loaded SNEDDS was formulated and evaluated for anti-inflammatory activity. The formulation was stable against phase separation and drug precipitation, exhibited rapid emulsification within 5 s to yield an emulsion with a mean droplet size of 27.23 nm, and a significantly ( $p = 0.00$ ) higher anti-inflammatory action compares to the aqueous suspension of the standard drug and each treatment agent across the test period. The utilization of the natural lipophile will minimize the usage and overdependence on costly commercial triglycerides, with the additional advantages of requiring fewer processing steps, physiologically biocompatible, nutritionally acceptable, and economically affordable lipidic carrier in the formulation of a self-emulsifying drug delivery system.

#### 5. MATERIALS AND METHODS

##### 5.1. Preparation of ibuprofen-loaded SNEDDS

The phase behaviour and diagram have been examined and previously reported [18]. From the phase diagram investigation, the various quantities of oil, surfactant, and co-surfactant (shown in Table 2) were selected and combined to form the SNEDDS. The maximum amount of ibuprofen that could dissolve in the SNEDDS was determined by adding increasing amounts of ibuprofen to 1 g quantities of SNEDDS and vigorously agitated at 50°C for 30 minutes. Informed by the results of the solubility test, 400 mg of ibuprofen was dissolved in the chosen SNEDDS at  $50 \pm 5$  °C with constant agitation for 30 min in a water bath. The formulations were stored in glass vials at room temperature ( $28 \pm 2$ °C) for future research.

**Table 2.** Composition of SNEDDS

Components	Composition (mg)	
	A	B
N - L	264	-
N - L + labrafac CC (1:1)	-	240
Kolliphor HS - 15	400	424
PEG - 400	136	136
Total	800	800

## 5.2. Loading efficiency of ibuprofen-SNEDDS

Each formulation was diluted in 0.1N NaOH and passed through a Whatman filter paper no. 41. After that, the filtrate was diluted and spectrophotometrically analyzed for drug content at  $\lambda_{max}$  of 221 nm as described by Obitte et al, [19].

## 5.3. Assessment of ibuprofen-SNEDDS emulsification time

One (1) mL of each formulation was added to 250 mL distilled water in a beaker, which was kept at  $37 \pm 2$  °C with constant stirring at 50 rpm. The time it took to achieved a completely uniform cloudy/turbid dispersion was recorded as the emulsification time [19].

## 5.4. Determination of droplet size and polydispersity index of ibuprofen-SNEDDS

After diluting each formulation 100 fold with distilled water and gently agitated, the droplet size and polydispersity index (PDI) of each formulation were determined by dynamic light scattering technique using Malvern Zetasizer ZS90 (M/s Malvern Instruments, Worcestershire, UK).

## 5.5. Determination of phase separation and drug precipitation

One (1) mL of each formulation was diluted to 50 mL with distilled water and stored for a period of 24 h at room temperature ( $28 \pm 2$  °C), and observed afterward for precipitation and phase separation as described by Obitte et al, [10, 20].

## 5.6. Centrifugation studies

One (1) mL of each formulation was diluted 100 times with distilled water, then 5 mL was poured into a test tube and spun for 5 minutes at 4,000 rpm in a laboratory centrifuge. The samples were then examined for physical instability, such as drug precipitation and phase separation as described by Obitte et al, [13].

## 5.7. Fourier Transform Infrared Spectroscopy analysis of optimized ibuprofen-SNEDDS

The Fourier Transform Infrared Spectroscopy (FTIR) spectra of the ibuprofen powder, unloaded SNEDDS and the optimized formulation were recorded over the range 650 - 4,000  $\text{cm}^{-1}$  wavenumber using FT-IR spectrometer (Agilent technologies Cary 630) under dry air at room temperature.

## 5.8. Anti-inflammatory activity of the optimized ibuprofen-SNEDDS formulation

The Ahmadu Bello University Committee on Animal Use and Care approved (Approval number ABUCAUC/2018/017) the protocol. Winter et al, [21] rat's paw oedema test method was used to examine the anti-inflammatory activity of the optimized formulation (Formulation B). From the animal house facility of the Department of Pharmacology and Toxicology, twenty-five (25) mature Wistar rats of either sex (weighing 180 to 200 g) were obtained and randomly categorized into five (5) groups ( $n = 5$  per group) and allowed to adapt to the environment for eight days before the experiment began. They were fed rat pellets (Vital feeds Limited, Ibadan, Nigeria) and water *ad libitum* during the adaptation phase. For 12 h, the rats were fasted and denied water before the beginning of the experiment to achieve consistent hydration and decrease variability in oedematous response. Oral gavage was used to administer the various treatments to the various groups of animals shown in Table 1. Oedema was induced 30 min after treatment by injecting a 1% suspension of carrageenan in 0.9% sterile saline solution into the sub plantar tissue of each rat's left hind paw. After injecting the carrageenan, the paw thickness was measured using a Vernier caliper at 0, 1, 2, 3, 4, 5, and 6 h. Equation 1 was used to determine the percentage inhibition of paw oedema [22]. At the completion of the study, the animals were not euthanized but return back to a section of the animal house.

$$\text{Inhibition (\%)} = \left[ 1 - \left( \frac{Et}{Ec} \right) \right] \times 100 \quad \dots 1$$

Et = average oedema of the treated group

Ec = average oedema of the control group

## 5.9. Statistical analysis

The findings from the different tests were expressed as mean  $\pm$  standard deviation (SD). Data were analyzed by one-way analysis of variance (ANOVA) followed by Bonferroni *post hoc* test for multiple comparisons using SPSS 23 software (SPSS, Chicago, IL, USA). Results were considered significant at  $p < 0.05$ .

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