

RESEARCH

Open Access



Enhanced anti-inflammatory and ulcerogenicity of Ibuprofen microsphere formulations using Irvingia wombolu fat (IRW) and moringa oil (MO) as co-lipids

Thaddeus H. Gugu^{1*}, Geraldine C. Agu², Emmanuel M. Uronnachi³ and Salome A. Chime²

Abstract

Ibuprofen is a member of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAIDs) with anti-inflammatory, analgesic, and antipyretic activities used to relieve a variety of pains. The objective of this study was to formulate, characterize and evaluate the in vitro and in vivo properties of ibuprofen formulated as solid lipid microspheres (SLMs) for enhanced delivery. The mixtures of *Irvingia wombolu* fat (IRW) and moringa oil (MO) each with Phospholipon[®] 90G (PL90G) at the ratio of 2:1 w/w were prepared by fusion, characterized and used to prepare SLMs. The SLMs were thereafter evaluated using the following parameters: particle size and morphology, stability, and encapsulation efficiency EE (%). In vitro release was carried out in phosphate buffer (pH 7.4). The ibuprofen based SLMs were also evaluated for anti-inflammatory and anti-ulcer effects using animal models. The pH showed significant increase after two months of formulation with a maximum value of 6.4 while the EE obtained were 95.6, 89.4 and 61.6% for SLMs formulated with lipid matrix of Phospholipon[®] 90G (1% and 2%), and MO (1%) respectively. The in vitro release showed maximum release of 87.8 and 98.97% of the two different lipid-based formulations while anti-inflammatory effect was up to 89.90% after 5 h of inducing inflammation. The SLMs did not show any lesion thus conferring gastroprotection on the formulations. The SLMs exhibited good anti-inflammatory property with gastro-protective action.

Keywords Ibuprofen, Lipid-microspheres, Anti-inflammation, Ulcerogenicity, Bioavailability

Introduction

Ibuprofen is a propionic acid class of nonsteroidal anti-inflammatory drugs simply called NSAIDs with anti-inflammatory, analgesic, and antipyretic activities. It is used in the management of a wide range of different pains

such as muscular pain and rheumatic pain [1]. Also, ibuprofen is one the leading NSAIDs used in certain illnesses like headaches, cold, backache, dysmenorrhoea, migraine neuralgia, arthritis, fever and other flu symptoms [2]. Recent research has shown that NSAIDs such as ibuprofen and others have a potential effect in the treatment of Alzheimer's disease [3]. The wound healing properties of ibuprofen and its side effects, as well as its efficacy have been extensively investigated [4, 5]. It undergoes rapid bio-transformation with a serum half-life of about 1.5 to 2 h thus leading to a short duration of action. Like other NSAIDs, it causes gastric irritation which in most cases, led to gastrointestinal damage [6]. In order to overcome this limitation, ibuprofen-loaded lipid microspheres were

*Correspondence:

Thaddeus H. Gugu
thaddeus.gugu@unn.edu.ng

¹ Drug Delivery Unit, Department of Pharmaceutical Microbiology and Biotechnology, University of Nigeria, Nsukka, Enugu State, Nigeria

² Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka, Enugu State, Nigeria

³ Department of Pharmaceutics and Pharmaceutical Technology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

considered to improve solubility and mucosa absorption for maximum biodistribution and bioavailability into the systemic circulation while offering reduced inflammation and gastric irritation. Lipid microspheres, also known as lipospheres, are regarded as drug carrier systems consisting of water and lipids dispersions to form a solid-based system with a particle size range of 0.01 to 100 μm . They possess a hydrophobic lipid core stabilized by layers of phospholipid molecules around their surface. The active drugs are usually dispersed in the lipid matrix which form the internal core to enhance solubility [7], and subsequently increase plasma concentration thus improving bioavailability. Lipid-based systems are widely used in drug delivery. They enhance the bioavailability and therapeutic index of many compounds, especially poorly water-soluble drugs. They are a commercially viable approach in formulating pharmaceutical dosage forms for different routes of administration such as parenteral, oral or topical delivery [8]. Solid lipid lipospheres have earlier been investigated as a system for oral drug delivery of insulin using a methacrylic acid-based microparticulate hydrogel formulation [9]. Similarly, previous researchers have reported the delivery of ibuprofen using synthetic lipid materials [10]. *Irvingia wombolu* (Irvingiaceae) is a tropical African tree that grows in local settings across West and Central Africa and is used extensively as fruit and a thickener in food preparations [11]. *Irvingia wombolu* fat is a natural fat extracted from the kernel seeds of *Irvingia wombolu* which has been used in cosmetics and also, as a potential lipid carrier in drug delivery [12]. Moringa oil on the other hand, is also a natural oil extracted from the *Moringa oleifera* Linn. (Moringaceae) plant spread across the tropical and subtropical regions of the globe, especially the India subcontinent where it is mostly used in diet for its medicinal value [13]. The moringa seed is reported to contain up to 47% oil which is rich in oleic acids and other monounsaturated fatty acids [14]. The substitution of synthetic lipids with natural product materials such as *Irvingia wombolu* fat and moringa oil as co-lipids is an alternative worth exploring to reduce the toxicities or incompatibilities that may be associated with synthetic materials.

Solid lipid particles combine several advantages and avoid the disadvantages of other colloidal carriers. They provide a condition for drug targeting and controlled drug release and also, protect the loaded active compounds against enzymatic or chemical degradation and gastric irritation [15]. The solid matrix is made up of physiologically compatible lipids which allow hydrophilic or hydrophobic drugs to be incorporated and form a vesicular core [16, 17]. These lipid-based particulate drug carriers exist as nano-carriers, microparticulate and colloidal carriers [18]. Non-steroidal anti-inflammatory

drugs (NSAIDs) today, have been considered for delivery in nano- or micro-sized particles for solubility enhancement and gastroprotection using lipid matrixes to reduce/prevent a rise in gastric intestinal tract (GIT) disorders such as ulcerative lesions, colitis and colon polyps which may be aggravated by the direct contact of these agents with the lining tissues of the GIT [19]. This research seeks to optimize the delivery of ibuprofen to enhance solubility, biodistribution and bioavailability with natural based lipid carrier systems for patient compliance and limited GIT mucosal cell injury. Ibuprofen was formulated into lyophilized and reconstitutable parenteral powder as ibuprofen solid lipid microspheres (Ib-SLMs). The consideration of dry *micro* and *nano* crystalline powder formulation of these poorly water-soluble drugs, has over the years proven to be more efficient in systemic drug delivery and bioavailability for a quicker onset of action [20–22].

Materials and methodology

Materials

The following materials were used for the study. Ibuprofen (Juhel Pharmaceutical Ltd, Nigeria), mixtures of *Irvingia wombolu* fat (IRW) and moringa oil (MO) gotten from Natural product unit, Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria Nsukka. All other chemicals and reagents used were of analytical grade.

Formulation composition

The percentage composition of the formulations is expressed in Table 1.

Methodology

Formulation of lipid matrix

Mixtures of *Irvingia wombolu* fat (IRW) with moringa oil (MO) (Natural product unit, department of Pharmaceutical and medicinal chemistry, University of Nigeria Nsukka with Phospholipon® 90G (Phospholipid GmbH, Koln, Germany) (2:1 w/w) respectively, were prepared by fusion. The varying lipids as presented in the table above were weighed out using an analytical weighing balance (Adventurer, Ohaus, China), melted together and stirred at a temperature of 70 °C using a magnetic stirrer (SR1 UM 52188, Remi Equipments, India), until a completely homogenous and transparent white mixture was obtained. The homogenous mixture was stirred at room temperature until solidification to obtain the solid lipid matrix [23].

Preparation and lyophilization of Ib-SLMs

The ibuprofen-loaded lipid microspheres were prepared using the melt homogenization technique [17],

Table 1 Percentage ratio of raw materials in formulations

Batch code	Lipid* matrix (%)	Ibuprofen (%)	Soluplus® (%)	Sorbitol (%)	Sorbic acid (%)	Distilled water qs (%)
A1	5	1	2	4	0.05	100
A2	5	1.5	2	4	0.05	100
A3	5	2	2	4	0.05	100
A4	5	0	2	4	0.05	100
B1	5	1	1	4	0.05	100
B2	5	1.5	1	4	0.05	100
B3	5	2	1	4	0.05	100
B4	5	0	1	4	0.05	100

Key: *Contains lipid matrix combinations in the ratio of 2:1: A1-A3 contains *Irvingia wombolu* fat (IRW) and Moringa oil (MO) respectively; B1-B3 contain *Irvingia wombolu* fat and Phospholipon® 90G (PL90G) respectively

following the formula in Table 1 above. In each case, 5 g of the lipid matrix (LM) was melted using Ultra-Turrax homogenizer (T25 Basic Digital, Ika, Staufen, Germany) at 70 °C and an appropriate amount of Ibuprofen was incorporated into the melted lipid. Also, sorbitol (Wharfedale Laboratories, Otley, West Yorkshire) was dissolved in hot distilled water at the same temperature with the lipid melt together with Soluplus® (BASF corporation, USA) to obtain an aqueous phase. The hot aqueous phase was poured into the lipid melt and immediately subjected to high shear homogenization with Ultra-Turrax at 5000 rpm for 10 min. An o/w emulsion was obtained by phase inversion. All batches of the formulation were lyophilized using a freeze-dryer (Amsco/Finn-Aqua_Lyovac GTZ, Hürth, Germany) to obtain the resultant solid particles for further characterization and analysis.

Percentage yield The percentage yield (% w/w) of the resultant solid lipid-microspheres prepared was determined to obtain the extent of the miscibility and homogenization of the mixture using equation 1.

$$\text{Percentage recovery (\%)} = \frac{W_1}{W_2 + W_3} \times 100 \quad (1)$$

Where w_1 is weight of SLMs formulated (g), w_2 is the weight of drug added (g) and w_3 is the weight of raw materials {lipid, sorbitol, sorbic acid and soluplus® (g)}.

Time-dependent pH stability studies The pH of both the lyophilized and un-lyophilized formulations was studied in a time-dependent manner: 24 h, 1 week, 2 weeks, 3 weeks, 1 month, and 2 months using a pH meter (pH ep® Hanna instrument, Padova, Italy) to check the stability of the formulations [24]. The pH meter was first calibrated with standard pH solutions of pH 4, 7 and 10.

Afterwards, the pH of the dispersions was determined by inserting the electrode of the instrument into the dispersion of the formulation.

Particle size and morphology analysis The bottles containing the different batches of the formulations were shaken vigorously and were syringed out using a 5 ml syringe. Two drops of the different formulations were dispensed on a clean slide, covered with a cover slip and examined under a binocular microscope attached with a motic image analyzer at a magnification of X 400. For the lyophilized lipid-microspheres, about 200 mg of the lipid-microspheres from each batch was dispersed in a small amount of water and placed on a slide, covered with a cover slip and also examined under a binocular microscope at a magnification of X 400.

Drug content determination Quantities of lipid microspheres equivalent to 0.1 g of ibuprofen were weighed out and placed in a 100 ml volumetric flask. The flask was made to the volume with phosphate buffer and heated at 70 °C with intermittent shaking until the lipid microspheres completely melted. The dispersion was cooled at room temperature and filtered through filter paper. Ibuprofen content of appropriate dilutions were analyzed spectrophotometrically using UV spectrophotometer (Spectrum laboratory, The Netherlands) at a predetermined wavelength at 287 nm. This was repeated three times for all the batches. The drug concentrations were calculated with reference to a Beer's plot.

Entrapment efficiency (EE %) of Ib-SLMs The quantities of the drug theoretically contained in the lipid-microspheres were compared with the quantity actually

obtained from the drug content studies. This was calculated using the Eq. (2).

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug (Ib) remaining in SLMs}}{\text{Total amount of drug (Ib) added into the SLMs}} \times 100 \quad (2)$$

Loading capacity (LC) Loading capacity (LC) expresses the ratio between the entrapped active pharmaceutical ingredient (API) and the total weight of the lipids [25]. LC was determined using the relationship.

$$\text{Loading capacity (\%)} = \frac{\text{Amount of entrapped drug (Ib) in SLMs}}{\text{Total weight of SLMs}} \times 100 \quad (3)$$

In vitro release studies Beer's plot was obtained for ibuprofen in phosphate buffer (pH 7.4) at a concentration range 0.1–1.0 mg% at a pre-determined wavelength of 287 nm. The in vitro release kinetics was determined following an established protocol in dissolution medium consisting of 250 ml of freshly prepared medium, phosphate buffer (pH 7.4) maintained at 37 ± 1 °C [26]. The polycarbonate dialysis membrane (MWCO 6000–8000, Spectrum Labs, Breda, the Netherlands) selected was pre-treated by soaking in the dissolution medium for 24 h prior to use. A quantity of the lipid particles equivalent to 0.1 g of ibuprofen was weighed from each batch and placed in a polycarbonate dialysis membrane containing 2 ml of the dissolution medium, securely tied with a thermo-resistant thread and placed in the appropriate chamber on the magnetic stirrer (SR1 UM 52188, Remi Equipment Mumbai, India) as release apparatus. The paddle was rotated at 100 rpm, and at pre-determined timed intervals, 5 mL portions of the dissolution medium was withdrawn, appropriately diluted and analyzed for drug content in a spectrophotometer. The volume of the dissolution medium was kept constant by replacing it with 5 mL of fresh medium after each withdrawal to maintain sink condition. The amount of drug released at each time interval was determined with reference to Beer's plot.

Anti-inflammatory studies The anti-inflammatory activity of the ibuprofen loaded lipid microspheres was carried out using the rat paw oedema test [27]. All the protocols were approved and carried out in accordance with guidelines and regulations of the Animal Ethics Committee, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka with ethical approval number of UNN/FPS/20/0025a. The experimental animals were procured from the animal facility of the Department of Veterinary Medicine, University of Nigeria, Nsukka and allowed access to water. The phlegmatic agent employed

in the study was fresh undiluted egg albumin. Adult Wistar rats of either sex (96–150 g) were divided into four experimental groups of three rats per group. The ani-

mals were fasted and deprived of water for 12 h before the experiment. The deprivation of water was to ensure uniform hydration and to minimize variability in oedematous response [28]. The ibuprofen-loaded lipid-microspheres of the different batches (A1 and B1) equivalent to 6 mg/kg body weight was administered orally to the rats. The reference group (positive control) received 6 mg/kg of the pure sample of ibuprofen, while the control group (negative control) received normal saline. Thirty minutes' post-treatment, oedema was induced by the injection of 0.1 ml fresh undiluted egg-albumin into the sub plantar region of the right hind paw of the rats. The volumes of distilled water displaced by treated right hind paw of the rats were measured using a plethysmometer before injection, and at 0.5, 1, 2, 3, 4, 5 and 6 h after egg albumin injection. The average oedema at every interval was assessed in terms of difference in volume displacement ($V_t - V_o$), while percent inhibition of oedema was calculated using the equation below [29].

$$\text{Percentage oedema inhibition (I)} = \frac{(dt)}{(dc)} \times 100 \quad (4)$$

Where dt is the difference in paw volume of the animals treated with drug-treated group and dc is the difference in paw volume in control group, while I stand for inflammatory inhibition.

Ulcerogenicity studies The ulcerogenicity of ibuprofen-loaded lipid-microspheres was determined using the gastric mucosa irritation animal model method as described in earlier studies [30]. The studies were carried out on healthy Wistar rats (96 – 150 g). The animals were divided into four experimental groups of three animals per group. The control group received normal saline while the reference group received 6 mg/kg of pure sample of ibuprofen orally. The animals were fasted for 8 h prior to administering a single dose of either the control or the test compounds, given free access to food and water, and sacrificed 17 h later by ether anaesthesia. The gastric mucosa of the rats was examined under a microscope using a X 4 binocular magnifier. The lesions were counted and divided into large (greater than 2 mm in diameter), small (1–2 mm) and punctiform (less than 1 mm). For each stomach, the severity of mucosal

damage was assessed according to the following scoring system [31]; 0 – no lesions or one puntiform lesion; 1 – two to five puntiform lesions; 2 – one to five small ulcers; 3 – more than five small ulcers or one large ulcer; and 4 – more than one large ulcer. All the experimental methods were reported in accordance with the ARRIVE guidelines.

Results and discussion

Percentage yield

The result of percentage recovery of the lipid microspheres as seen in the Fig. 1 showed a good yield of the formulations for both loaded and unloaded lipid-microspheres (batch A1-A4 and B1-B4). There was a high percentage recovery ranging from 57 – 96%.

Time-dependent pH stability studies

The result of pH stability of the un-lyophilized lipid microspheres as shown in Table 2, showed that after

2 months, all the batches formulated with the lipid matrix of *Irvingia wombolu* fat and moringa oil (batches A1-A4) had a pH in the range of 5.0 ± 0.04 to 7.2 ± 0.02 and the batches formulated with *Irvingia wombolu* fat and Phospholipon® 90G (batches B1-B4) had a pH of 4.8 ± 0.01 to 6.0 ± 0.05 . Changes in pH of the unlyophilized formulations may be due to degradation of excipients. Lyophilizing the formulation and the possible inclusion of a buffer may be used to maintain the pH.

The pH profile of lyophilized lipid microspheres dispersion

The result of the pH stability after lyophilizing the lipid-microspheres dispersion as shown in Table 3, show the pH to be in the range of 6.0 ± 0.05 to 6.4 ± 0.03 . This is within the pH range of the pure ibuprofen which is 6.2 ± 0.03 . A prior stable drug may be affected by degradation of excipients with storage through generation of an unfavourable pH (increase or decrease) or reactive species for the drug. However, the slight increase in the pH values in most lipid-microspheres formulation was

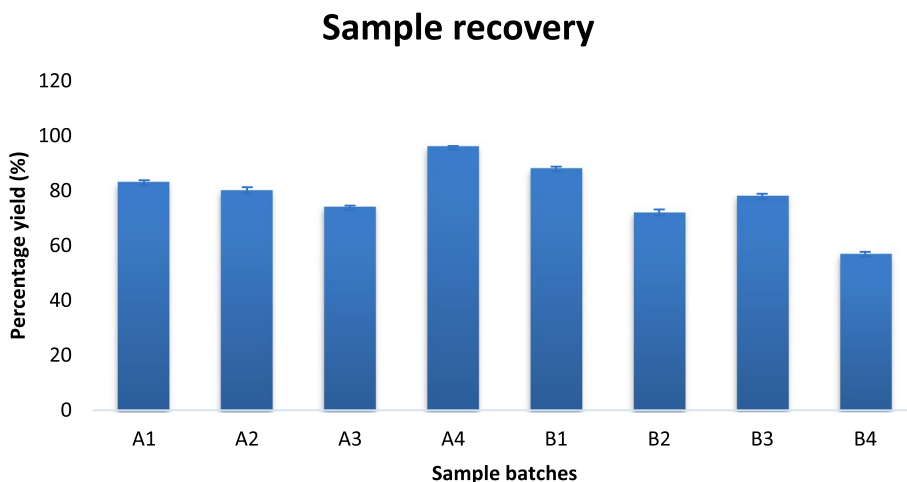


Fig. 1 Percentage recovery of lipid microspheres; A1-A3 contains LM *Irvingia wombolu* fat and moringa oil, B1-B3 contains LM *Irvingia wombolu* fat and Phospholipon® 90G and different concentrations of ibuprofen while batches A4 and B4 contain no API, (n = 3)

Table 2 pH result before lyophilization

Batch codes	1 day	1 week	2 weeks	3 weeks	1 month	2 months
A1	5.3 ± 1.2	5.6 ± 1.3	5.6 ± 1.3	6.2 ± 0.03	6.2 ± 0.03	6.1 ± 0.03
A2	5.2 ± 2.0	5.5 ± 1.2	5.4 ± 1.0	5.8 ± 0.4	6.0 ± 0.05	6.0 ± 0.05
A3	5.0 ± 0.8	5.4 ± 1.0	5.3 ± 1.2	6.3 ± 0.04	6.4 ± 0.03	6.0 ± 0.05
A4	5.4 ± 1.3	5.7 ± 1.2	5.4 ± 1.5	7.2 ± 0.03	7.0 ± 0.01	6.3 ± 0.1.2
B1	5.1 ± 1.0	5.1 ± 1.0	5.0 ± 1.2	5.4 ± 1.4	5.5 ± 1.2	5.6 ± 1.3
B2	5.0 ± 0.4	4.9 ± 0.6	4.8 ± 1.3	5.2 ± 1.3	5.4 ± 1.0	5.0 ± 1.5
B3	5.0 ± 0.4	5.0 ± 0.4	4.9 ± 2.2	5.6 ± 1.2	5.7 ± 1.0	5.5 ± 1.3
B4	5.3 ± 1.2	5.2 ± 1.0	5.1 ± 1.0	5.7 ± 1.2	5.8 ± 0.4	6.0 ± 0.05

Key: A1-A3 contains LM *Irvingia wombolu* fat and moringa oil, B1-B3 contains LM *Irvingia wombolu* fat and Phospholipon® 90G and different concentrations of ibuprofen while batches A4 and B4 contain no API, (n = 3). Results presented as mean ± SD

Table 3 The pH result after lyophilized lipid microspheres dispersion

Batch code	pH value
A1	6.4±0.21
A2	6.4±0.13
A3	6.2±0.21
A4	6.4±0.22
B1	6.0±0.16
B2	6.2±0.31
B3	6.0±0.15
B4	6.2±0.27
C	6.2±0.13

Key: A1-A3 contains LM *Irvingia wombolu* fat and moringa oil, B1-B3 contains LM *Irvingia wombolu* fat and Phospholipon® 90G and different concentrations of ibuprofen while batches A4 and B4 contain no API, Batch C is the pure sample of ibuprofen, (n=3). Results presented as mean ± SD

not attributed to drug degradation since there was an increase in the pH of the unloaded lipid-microspheres.

Differential scanning calorimetry (DSC)

The DSC thermograms in Figs. 2 and 3 show a sharp endothermic point at 77.1°C which is in agreement with the melting point of ibuprofen with the range of 75 to 78°C as contained in British Pharmacopeia (BP),

therefore indicating presence of pure crystalline ibuprofen. The lipid matrix employed in the formulation of lipid-microspheres, when scanned with the DSC traced various peaks due to the lipid content of the matrices which contains fatty acids and steroids of different endothermic peak points and functions as a structural components of cell membranes [32, 33]. The lipid-microspheres containing lipid matrix in Fig. 2b, c and d of *Irvingia wombolu* fat and moringa oil gave a lower enthalpy at 41.4 °C.

Particle size

Particle size distributions were extrapolated and calculated in Table 4. The lipid-microspheres formulated with the highest concentration of ibuprofen (2%) in batch A3 and B3 showed highest mean particle size in each batch with 23.97 ± 0.20 and 19.74 ± 0.21 µm respectively.

Figure 4 showed the photomicrograph of the unlyophilized lipid microspheres with different sizes. The various sizes and morphologies could possibly be as a result of shear force applied during formulation as earlier reported [34], this subsequently enhanced the breakdown of larger particles into smaller sizes. Furthermore, the nature of lipids used in formulations could have affected sizes obtained [35]. Batch A formulated with the lipid

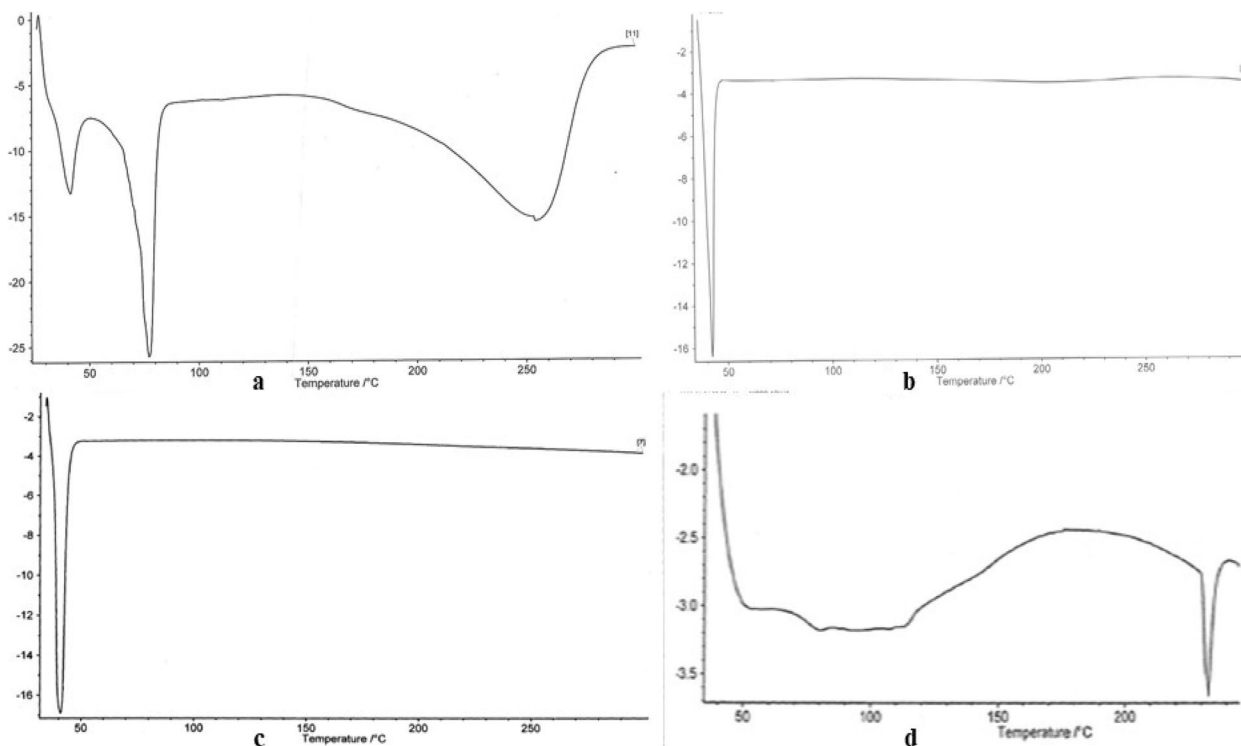


Fig. 2 The DCS thermograms: a. Ibuprofen drug, b. *Irvingia wombolu* fat, c. Moringa oil, d. Phospholipon® 90G

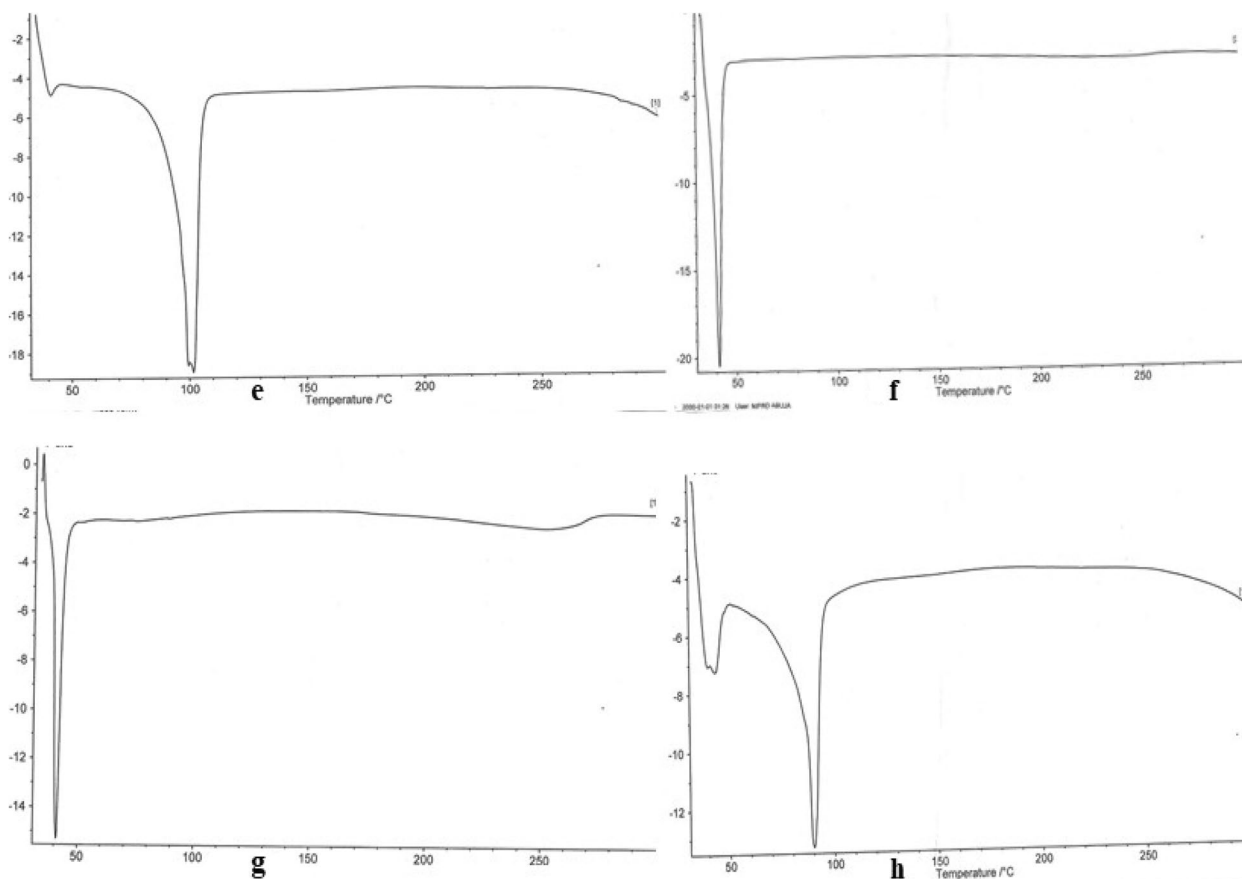


Fig. 3 The DCS thermograms: **e** Lipid matrix *Irvingia wombolu* fat and phospholipon® 90, **f** Lipid matrix *Irvingia wombolu* fat and moringa oil, **g** 1% ibuprofen loaded liposphere containing lipid matrix *Irvingia wombolu* fat and moringa oil, **h** 1% ibuprofen-loaded liposphere containing lipid matrix *Irvingia wombolu* fat and phospholipon® 90G

Table 4 Particle size analysis of lipid microspheres

Batch code	Particle size (µm)	
	Before lyophilization (µm ± SD)	After lyophilization (µm ± SD)
A1(a)	22.56 ± 0.39	21.15 ± 0.99
A2(b)	18.33 ± 0.67	9.85 ± 0.99
A3(c)	23.97 ± 0.20	25.38 ± 0.39
A4(d)	19.74 ± 0.19	18.33 ± 0.10
B1(e)	16.92 ± 0.19	25.38 ± 0.40
B2(f)	16.92 ± 0.19	36.66 ± 0.58
B3(g)	19.74 ± 0.21	18.33 ± 0.21
B4(h)	16.92 ± 0.19	18.33 ± 0.10

Key: A1-A3 contains Lipid matrix, *Irvingia wombolu* fat and moringa oil, B1-B3 contain LM *Irvingia wombolu* fat and Phospholipon® 90G and different concentrations of ibuprofen while batches A4 and B4 contain no API, (n = 3). Results presented as mean ± SD

matrix of *Irvingia wombolu* fat and moringa oil, showed a higher mean particle size ranging from 18.33 ± 0.67—23.97 ± 0.20 µm than batch B which was formulated with

Irvingia wombolu fat and Phospholipon® 90G with particle size ranging from 16.92 ± 0.19—19.74 ± 0.21 µm.

Entrapment efficiency (EE%) and loading capacity (LC)

The result in Table 5 represents the EE % and the LC of various batches of ibuprofen-loaded lipid-microspheres. The EE% showed that the lipid-microspheres loaded with 1% ibuprofen (batches A1 and B1) had highest EE% of 89 and 95% respectively. Also, the loading capacity obtained for ibuprofen-loaded lipid-microspheres ranged from 8.94 – 12.88 g/100 g lipid for A batches, and 9.56 – 12.32 g/100 g lipid for B batches. Batches A3 and B3 with 2% ibuprofen gave the highest LC for each batch, 12.88 and 12.32 respectively.

In vitro release profile of ibuprofen lipid-microspheres in phosphate buffer

The result of in vitro release showed in Figs. 5 and 6 indicated that the release kinetics of ibuprofen in phosphate buffer exhibited a very good release of ibuprofen in all batches ranging from 49—90.1% after 12 h.

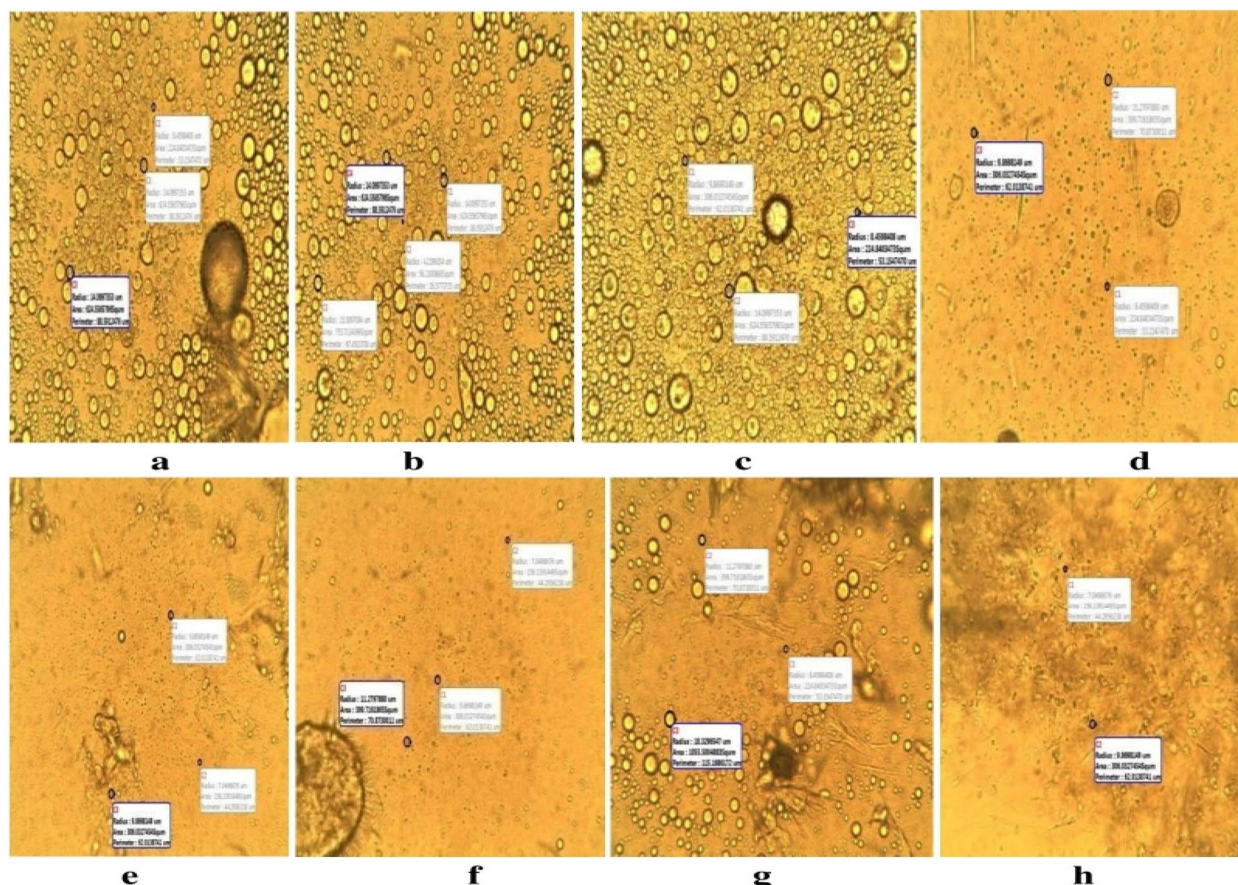


Fig. 4 Photomicrographs of liposphere before lyophilization: (a) 1% ibuprofen lipid microspheres with IRW and MO, (b) 1.5% ibuprofen lipid-microspheres with IRW and MO, (c) 2% ibuprofen with IRW and MO, (d) bland lipid-microspheres with IRW and MO, (e) 1% ibuprofen lipid-microspheres with IRW and PL90G, (f) 1.5% ibuprofen lipid-microspheres with IRW and PL90G, (g) 2% ibuprofen lipid-microspheres with IRW and PL90G, (h) bland ibuprofen lipid-microspheres with IRW and PL90G, IRW = *Irvingia wombolu* fat, MO = moringa oil, PL90G = Phospholipon® 90G

Table 5 The Entrapment efficiency and loading capacity

Batch code	EE (%)	LC
A1	89	8 ± 0.94
A2	81	11 ± 0.93
A3	32	12 ± 0.88
B1	95	9 ± 0.56
B2	91	10 ± 0.52
B3	61	12 ± 0.32

Key: batch A1, A2 and A3 contains LM *Irvingia wombolu* fat and moringa oil loaded with 1, 1.5 and 2% of ibuprofen respectively, batch B1, B2 and B3 contains LM *Irvingia wombolu* fat and Phospholipon® 90G loaded with 1, 1.5 and 2% of ibuprofen respectively, (n = 3 ± 5D)

In formulation A, batch A1 which was loaded with 1% ibuprofen, gave the highest release of 87.8% at 12 h, while batch A3 containing 2% of ibuprofen gave the least release of 50% at 12 h. Similarly, batch B1 loaded with 1% Ibuprofen, gave the highest release of 98.97% at 12 h while batch B3 containing 2% of ibuprofen gave

the least release of 49% at 12 h. However, the formulation with the lipid matrix of *Irvingia wombolu* fat and Phospholipon® 90G (batch B) showed a relatively higher drug release than the formulation with *Irvingia wombolu* fat and moringa oil (batch A). The release of the commercial ibuprofen (Brufen®) used as the reference gave its highest release of 98.87% at 12 h.

Anti-inflammatory properties of lipid-microspheres

The results of percentage inflammatory inhibition of ibuprofen-loaded microspheres in Fig. 7 showed that at 0.5 h, the lipid-microspheres least inhibited the size of the oedematous inflammation with 10.97 and 29.10%. Batch A showed good percentage inhibition when compared with the positive control (ibuprofen pure sample) of 37.89% oedema inhibition within the same 0.5 h. The Batch B1 formulated with *Irvingia wombolu* fat and Phospholipon® 90G gave 76.90% oedema inhibition at 6 h while batch A1 formulated with *Irvingia wombolu* fat and moringa oil 89.90% oedema inhibition at 6 h,

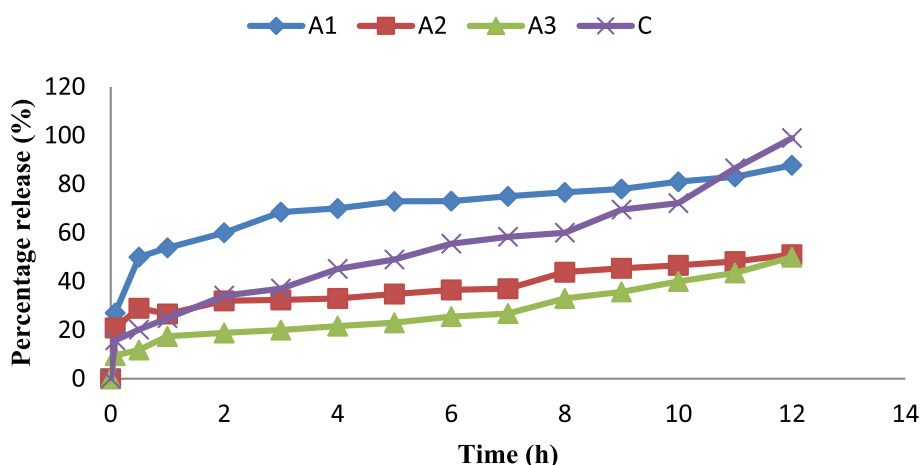


Fig. 5 The in vitro release profile of ibuprofen of the liposphere formulated. A1-A3 contains LM *Irvingia wombolu* fat and moringa oil with different concentrations of ibuprofen and C is pure sample of ibuprofen, (n=3)

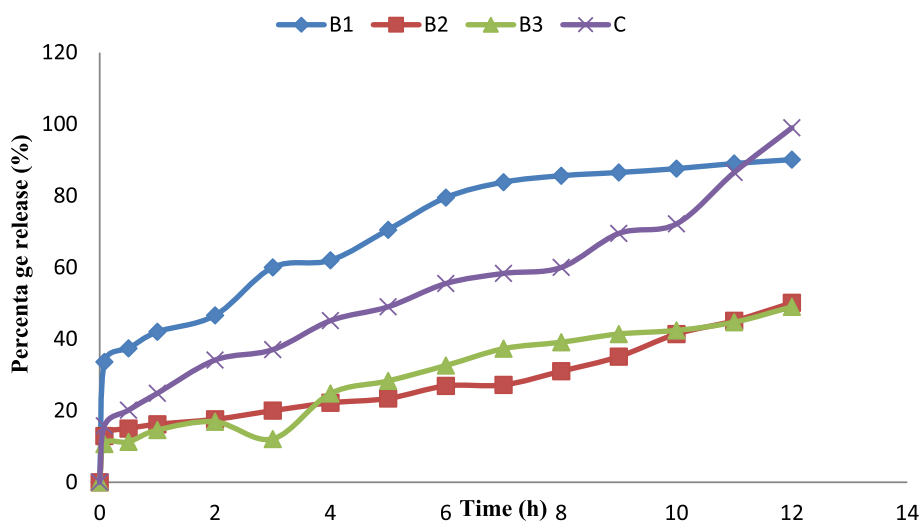


Fig. 6 The in vitro release profile of ibuprofen of the lipid-microspheres formulated. B1-B3 contain LM *Irvingia wombolu* fat and phospholipon® 90G with different concentrations of ibuprofen and C is pure sample of ibuprofen, (n=3)

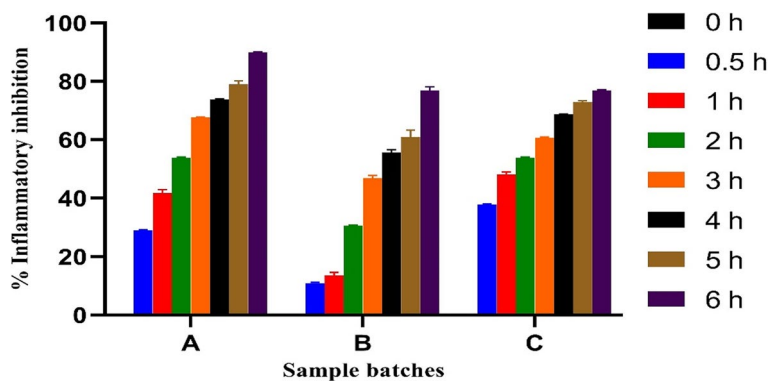


Fig. 7 Anti-inflammatory properties of ibuprofen-loaded lipid-microspheres

comparable with the reference drug which had 76.90% oedema inhibition at 6 h. This may be due to an improved oral bioavailability through an enhanced lipids solubility in agreement with an earlier report [36].

Ulcerogenic properties of the lipid microspheres

The result of percentage ulcer inhibition, showed that the formulation exhibited good gastro-protective properties in addition to its sustained release properties, the ulcer inhibition in Table 6 showed 85 and 72% respectively for the batch B1 and A1 when compared with the positive and negative control.

Discussions

The increased values of the percentage recovery of the lipid microspheres formulated indicates that the formulation technique adopted was reliable and can be reproducible. The change in pH of the unlyophilized lipid microspheres may be due to hydrolytic degradation of some excipients used, hence, suggesting the need to lyophilize the formulation and the possible inclusion of a buffer to maintain the pH. The use of natural oils and fats has been reported in some nanostructured lipid carrier (NLC) formulations majorly in transdermal applications [37]. Lipid drug conjugates are generally used to carry lyophobic drug molecules [38]. These insoluble drug-lipid conjugates had reported better delivery when prepared by its salt formation or through homogenized covalent linkage of the drug and lipids [39]. This suggests less crystallinity and possible retention of an entrapped drug over time. The DSC of the different lipids *Irvingia wombolu* fat, moringa oil and Phospholipon® 90G show endothermic peaks at different temperatures thus signifying the thermal behavior of each excipient used in the formulation process. The thermograms of ibuprofen-loaded lipid-microspheres containing *Irvingia wombolu* fat, moringa oil and phospholipon® 90G in Figs. 5 and 8, show sharp endothermic peaks of ibuprofen corresponding to its crystallinity and melting point as observed

in lipid matrices [40]. The varied fatty acids contents of these lipids may have interacted in such a manner as to partly disorder the crystal arrangement of individual lipids. This means that the lipid matrices as shown in Figs. 5 and 8 generated imperfect matrices due to distortion of crystal arrangement of individual lipids after melting and solidification, which may have created numerous spaces for drug localization. However, a minor shift in transition temperature as observed would occur in addition to change in enthalpy of the transition based on the thermotropic behaviour of lipid mixtures [41]. Furthermore, the sharp endothermic peak of Ibuprofen attests to the crystallinity and purity of the drug.

The particle size and distribution could be due to active drug entrapment and encapsulation property. Combination of non-biodegradable natural lipid matrix has shown advantages in drug delivery systems of poorly soluble drugs leading to its bioavailability, prolonged shelf-life, stability and non-toxic properties [22]. The lipid-microspheres formulated with the highest concentration of ibuprofen (2%) in batch A3 and B3 showed the highest mean particle size, this suggests a concentration dependent increase in particle size and reflects the influence of drug concentration on the size of microspheres. The pH and ionic charge of the drugs affect the particle size distribution and kinetics of the lipospheres by the drug ratio to lipid matrix in the formulation [42, 43]. The different particle sizes of lyophilized lipid-microspheres formulated with the lipid matrix *Irvingia wombolu* fat and Phospholipon® 90G (batch B) had a lower particle size than batch A which was formulated with *Irvingia wombolu* fat and moringa oil. These were also at variance within the unlyophilized batch formulations. Therefore, this particle diameter and distribution may result from the following factors; excipients, degree of homogenization, internal force, rate of particle size growth, crystalline habit of the particle size. The mean particle diameter of lipid-microspheres affects the bioavailability of formulated drug and also determines the site of administration of drug formulations. The small particle size of lipid-microspheres (<20 µm) can be well tolerated by single cell contact, large particle sizes (>50 µm) are much more reactive due to attractive forces [44].

The increased entrapment efficiency, could be due to an increased surface area of the drug in the medium against saturation effect as reported in drug solubility properties [45], and consequently help to reduce the drug loading concentration with maximum effect and mask toxicity [25]. The batches loaded with 2% ibuprofen (batches A3 and B3) and 1.5% ibuprofen (batches A2 and B2) had the least EE%. This may have arisen from saturation solubility of the lipids thus preventing further entrapment of

Table 6 Results of ulcerogenic properties of ibuprofen-loaded microspheres

Group	Ulcer score	Ulcer inhibition (%)	Ulcer diameter (mm)
A1	1.03±0.8	72	Lesion < 1
B1	0.99±1.5	85	Lesion < 1
C (reference)	5.04±1.0	10	Lesion ≥ 2
D (control)	0.00±0.00	100	No lesion

Key: A1 and B1 are 1% ibuprofen-loaded lipid-microspheres, C is pure sample of ibuprofen, D is control (normal saline) (n = 3 ± SD)

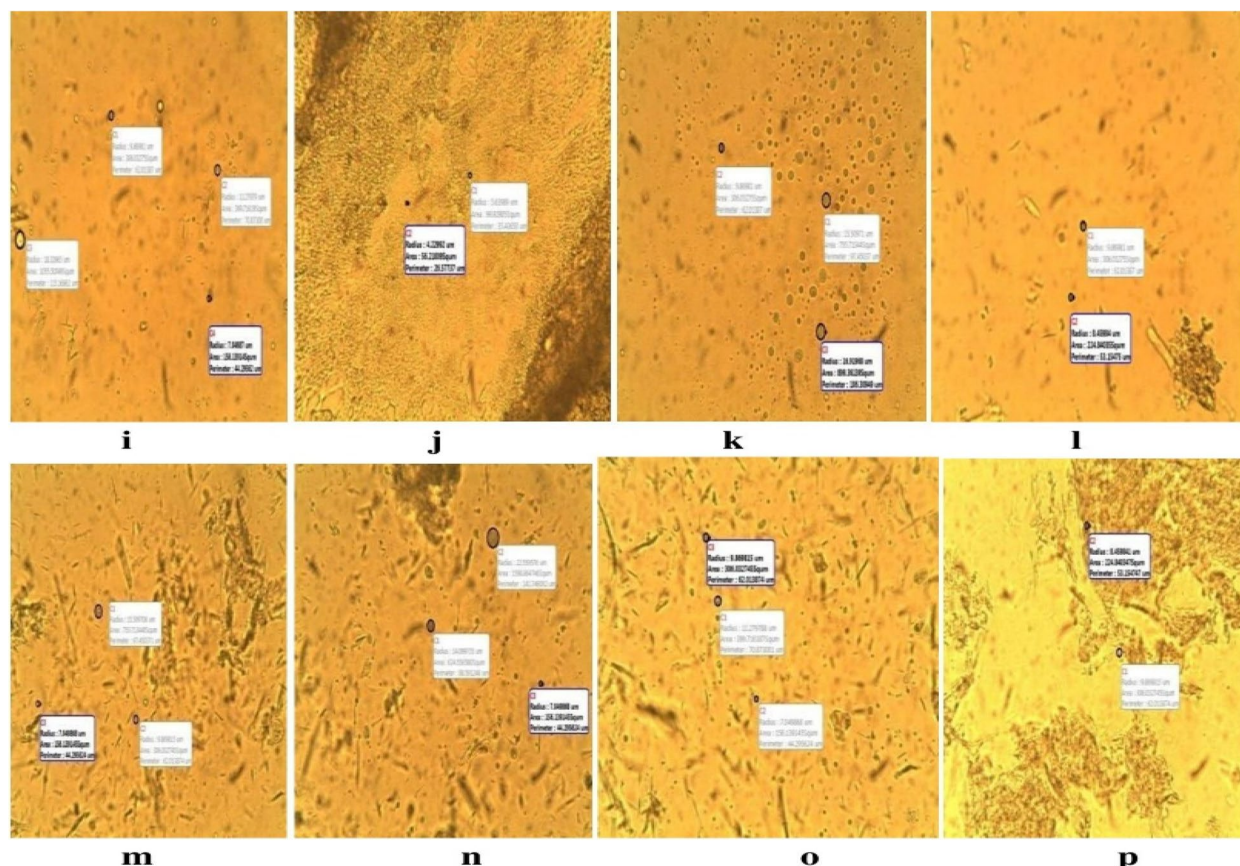


Fig. 8 Photomicrographs of lipid-microspheres after lyophilization: (i) 1% ibuprofen lipid microspheres with IRW and MO, (j) 1.5% ibuprofen lipid-microspheres with IRW and MO, (k) 2% ibuprofen with IRW and MO, (l) bland lipid-microspheres with IRW and MO, (m) 1% ibuprofen lipid-microspheres with IRW and PL90G, (n) 1.5% ibuprofen lipid-microspheres with IRW and PL90G, (o) 2% ibuprofen lipid-microspheres with IRW and PL90G, (p) bland ibuprofen lipid-microspheres with IRW and PL90G, IRW = *Irvingia wombolu* fat, MO = moringa oil, PL90G = Phospholipon® 90G

higher drug concentrations (beyond 1%). However, LC increased with increase in drug loading. The ability of the lipid-microspheres to accommodate active molecules is an important property which could be expressed by the entrapment efficiency and loading capacity.

The *in vitro* release profile of ibuprofen formulated lipid-microspheres followed first order kinetics. The release of the drug for up to 12 h ensured the possibility of a sustained effect for a longer period and ruled out the possibility of immediate release and dose dumping. Previous studies have shown that there was a burst release from ibuprofen microspheres when evaluated *in vitro* [46, 47]. This, was attributed to the possibility of the presence of the unloaded drug on the surface of the microspheres. Our formulation, therefore, was able to overcome this issue. In line with earlier reports, ibuprofen lipid-based formulations have shown good sustained release property which could increase its therapeutic effect [48, 49]. The batches of ibuprofen-loaded microspheres formulated with natural oil and fat, showed good

anti-inflammatory properties with up to 100% inflammatory inhibition. The inflammatory inhibitions are a confirmation of the ability of ibuprofen as an NSAID to suppress the cascade of physiological and immunological processes caused by mediators and cytokines which can lead to inflammation [50, 51]. The ulcerogenic properties and inhibition potentials of the ibuprofen-loaded microspheres as shown in Table 6, indicate the advantage of these natural lipid matrices for oral drug administration. The batch (B1) formulated with the lipid matrix consisting of *Irvingia wombolu* fat and Phospholipon® 90G showed higher ulcer-inhibition than the batch formulated with *Irvingia wombolu* fat and moringa oil. However, it was observed that the formulations, when administered, had less ulcerogenic effect in comparison with the pure sample of ibuprofen and the negative control. This indicated that formulation of the microparticle reduces the ulcerogenicity of ibuprofen thus providing a better and protective carrier for its delivery. Previous works support this finding [52].

Conclusion

Ibuprofen-loaded lipid-microspheres were formulated with lipid matrices consisting of *Irvingia wombolu* fat with moringa oil and *Irvingia wombolu* fat with Phospholipon® 90G in the ratio of 2:1 respectively to enhance solubility and bioavailability. In vitro studies carried out showed that ibuprofen-loaded lipid-microspheres exhibited good physicochemical properties and a sustained release property for once daily administration. The formulated lipid-microspheres exhibited good anti-inflammatory properties when compared with the commercial dosage form of ibuprofen in addition to inhibition of the ulcerative effect of ibuprofen. Ibuprofen-loaded lipid-microspheres have advantages over the commercial formulations of ibuprofen which include: low cost of ingredients, low cost of technologies involved in the production (equipment and labour requirement for the production of lipid dosage forms are minimal), little or no ulcerogenicity and better control of inflammation due to an enhanced absorption of drugs from the lipids. The delivery performance of these lipids makes them a better and viable option for the oral delivery of ibuprofen to reduce dosing frequency, enhance its bioavailability and therapeutic effect.

Acknowledgements

We acknowledge and thank the University of Nigeria, Nsukka, for the provision of a well-equipped laboratory and a conducive environment for the study.

Author's contributions

S.A. Chime conceptualized and supervised the work. S.A. Chime and T.H. Gugu design of methodology; C.G. Agu and T.H. Gugu conducted experiments and investigation process. T.H. Gugu and E.M. Uronnachi analyzed data and drafted the manuscript. All authors contributed personal resources for the research.

Funding

No fund was secured for this research work.

Availability of data and materials

We declare that all data generated in the course of this research have been properly presented in the manuscript.

Declarations

Ethics approval and consent to participate

All the protocols were approved and carried out in accordance with guidelines and regulations of the Animal Ethics Committee, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka with ethical approval number of UNN/FPS/20/0025a.

Consent for publication

Not applicable.

Competing interests

This research was done in maximum understanding of all the authors and have declared no conflict of interest in the course of the development of the manuscript.

Received: 2 March 2023 Accepted: 13 June 2023

Published online: 19 July 2023

References

1. Ngo VTH and Bajaj T, Ibuprofen, in StatPearls. 2022, StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).
2. Brunton L, Chabner B, Knollman B. Goodman and Gilman's The Pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2010.
3. Rivers-Auty J, Mather AE, Peters R, Lawrence CB, Brough D. Anti-inflammatory in Alzheimer's disease-potential therapy or spurious correlate? *Brain Commun.* 2020;2(2):fcaa109.
4. Jørgensen B, Friis GJ, Gottrup F. Pain and quality of life for patients with venous leg ulcers: proof of concept of the efficacy of Biatain-Ibu, a new pain reducing wound dressing. *Wound Repair Regen.* 2006;14(3):233–9.
5. Ofek L, Goder D, Zilberman M. Formulation-Properties of Novel Ibuprofen-Loaded Soy Protein Wound Dressings. *Recent Progress in Materials.* 2019;01(04):004.
6. Ghlichloo I and Gerriets V, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), in StatPearls. 2022, StatPearls Publishing
7. Banerjee S, Pillai J. Solid lipid matrix mediated nanoarchitectonics for improved oral bioavailability of drugs. *Expert Opin Drug Metab Toxicol.* 2019;15(6):499–515.
8. Nanjwade BK, Patel DJ, Udhani RA, Manvi FV. Functions of lipids for enhancement of oral bioavailability of poorly water-soluble drugs. *Sci Pharm.* 2011;79(4):705–27.
9. Kumar A, Lahiri SS, Singh H. Development of PEGDMA: MAA based hydrogel microparticles for oral insulin delivery. *Int J Pharm.* 2006;323(1–2):117–24.
10. Momoh M, Kenechukwu F, Gwarzo M, Builders P. Formulation and Evaluation of Ibuprofen Loaded Lipospheres for Effective Oral Drug Delivery. *Dhaka University Journal of Pharmaceutical Sciences.* 2015;14(1):17–27.
11. Matsinkou R, Ngondi J, Kuate D, Mbofung C, and Oben J. Antioxidant and anti-hyperglycemic potential of pulp extracts of *Irvingia wombolu* fruits. *Biology and Medicine*, 2012. 4: p. 10+.
12. Onyishi IV, Chime SA, Attama AA. Evaluation of excipient potentials of *Irvingia wombolu* fats and Moringa oil in rifampicin-loaded lipospheres: in vitro-in vivo characterisation. *Journal of Drug Delivery Science and Technology.* 2014;24(4):404–12.
13. Alam D, Singh MP, and Singh A, Wound healing potential of some medicinal plants. *International Journal of Pharmaceutical Sciences Review and Research*, 2011. 9.
14. Eugenia Nonye O, Okeke CC. Determination of antioxidant of Moringa oleifera seed oil and its use in the production of a body cream. *Asian J Plant Sci Res.* 2013;3:1–4.
15. Hu FQ, Yuan H, Zhang HH, Fang M. Preparation of solid lipid nanoparticles with clobetasol propionate by a novel solvent diffusion method in aqueous system and physicochemical characterization. *Int J Pharm.* 2002;239(1–2):121–8.
16. Lippacher A, Müller RH, Mäder K. Preparation of semisolid drug carriers for topical application based on solid lipid nanoparticles. *Int J Pharm.* 2001;214(1–2):9–12.
17. Jaspert S, Bertholet P, Piel G, Dogné JM, Delattre L, Evrard B. Solid lipid microparticles as a sustained release system for pulmonary drug delivery. *Eur J Pharm Biopharm.* 2007;65(1):47–56.
18. Pardeshi C, Rajput P, Belgamwar V, Tekade A, Patil G, Chaudhary K, Sonje A. Solid lipid based nanocarriers: an overview. *Acta Pharm.* 2012;62(4):433–72.
19. Ahmed OAA, Fahmy UA, Bakhaidar R, El-Moselhy MA, Alfaleh MA, Ahmed AF, Hammad ASA, Aldawsari H, Alhakamy NA. Pumpkin Oil-Based Nanostructured Lipid Carrier System for Ant ulcer Effect in NSAID-Induced Gastric Ulcer Model in Rats. *Int J Nanomedicine.* 2020;15:2529–39.
20. Gigliobianco MR, Casadidio C, Censi R, Di Martino P. Nanocrystals of Poorly Soluble Drugs: Drug Bioavailability and Physicochemical Stability. 2018;10(3):134.
21. Misra SK and Pathak K, Chapter 10 - Drug nanocrystals as drug delivery systems, in *Industrial Applications of Nanocrystals*, S. Mallakpour and C.M. Hussain, Editors. 2022, Elsevier. p. 153–178.
22. Bhalani DV, Nutan B, Kumar A, Singh Chandan AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. 2022;10(9):2055.
23. Chime SA, Attama AA, Onunkwo GJJoDDS, and Technology, Sustained release indomethacin-loaded solid lipid microparticles based on

- solidified reverse micellar solution (SRMS): in vitro and in vivo evaluation. 2012. 22: p. 485–492.
24. Umeyor EC, Kenechukwu FC, Ogbonna JD, Chime SA, Attama A. Preparation of novel solid lipid nanoparticles loaded with gentamicin and its evaluation in vitro and in vivo. *J Microencapsul.* 2012;29(3):296–307.
 25. Attama AA, Okafor CE, Builders PF, Okorie O. Formulation and in vitro evaluation of a PEGylated microscopic lipospheres delivery system for ceftriaxone sodium. *Drug Deliv.* 2009;16(8):448–57.
 26. Abobakr FE, Fayez SM, Elwazzan VS, Sakran W. Effect of Different Nail Penetration Enhancers in Solid Lipid Nanoparticles Containing Terbinafine Hydrochloride for Treatment of Onychomycosis. *AAPS PharmSciTech.* 2021;22(1):33.
 27. Lalan BK, Hiray RS, and Ghongane BB, Evaluation of Analgesic and Anti-Inflammatory Activity of Extract of *Holoptelea Integrifolia* and *Argyrea Speciosa* in Animal Models. *J Clin Diagn Res.* 2015. 9(7): p. Ff01–4.
 28. Anosike CA, Obidoa O, Ezeanyiika LUS, and Nwuba MMJAJBR, Anti-inflammatory and anti-ulcerogenic activity of the ethanol extract of ginger (*Zingiber officinale*). 2009. 3: p. 379–384.
 29. Karim N, Khan I, Khan W, Khan I, Khan A, Halim SA, Khan H, Hussain J, and Al-Harrasi A, Anti-nociceptive and Anti-inflammatory Activities of Asparosin A Involve Selective Cyclooxygenase 2 and Inflammatory Cytokines Inhibition: An in-vitro, in-vivo, and in-silico Approach. 2019. 10.
 30. Gugu TH, Chime SA, Attama AA. Solid lipid microparticles: An approach for improving oral bioavailability of aspirin. *Asian J Pharm Sci.* 2015;10(5):425–32.
 31. Chung MC, dos Santos JL, Oliveira EV, Blau L, Menegon RF, Peccinini RG. Synthesis, ex vivo and in vitro hydrolysis study of an indoline derivative designed as an anti-inflammatory with reduced gastric ulceration properties. *Molecules.* 2009;14(9):3187–97.
 32. Fahy E, Subramaniam S, Murphy RC, Nishijima M, Raetz CR, Shimizu T, Spener F, van Meer G, Wakelam MJ, and Dennis EA, Update of the LIPID MAPS comprehensive classification system for lipids. *J Lipid Res.* 2009. 50 Suppl(Suppl): p. S9–14.
 33. Subramaniam S, Fahy E, Gupta S, Sud M, Byrnes RW, Cotter D, Dinasarapu AR, Maurya MR. Bioinformatics and systems biology of the lipidome. *Chem Rev.* 2011;111(10):6452–90.
 34. Garud A, Singh D, Garud N. Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications. *International Current Pharmaceutical Journal.* 2012;1(11):384–93.
 35. Ong SG, Ming LC, Lee KS, and Yuen KH, Influence of the Encapsulation Efficiency and Size of Liposome on the Oral Bioavailability of Griseofulvin-Loaded Liposomes. *Pharmaceutics.* 2016. 8(3).
 36. Audu MM, Achile PA, and Amaechi AAJPJoZ, Phospholipon 90G based SLMs loaded with ibuprofen: an oral antiinflammatory and gastrointestinal sparing evaluation in rats. 2012. 44: p. 1657–1664.
 37. Puglia C, Blasi P, Rizza L, Schoubben A, Bonina F, Rossi C, Ricci M. Lipid nanoparticles for prolonged topical delivery: an in vitro and in vivo investigation. *Int J Pharm.* 2008;357(1–2):295–304.
 38. Anthony AA, Mumuni AM, and Philip FB, Lipid Nanoparticulate Drug Delivery Systems: A Revolution in Dosage Form Design and Development, in *Recent Advances in Novel Drug Carrier Systems*, S. Ali Demir, Editor. 2012, IntechOpen: Rijeka. p. Ch. 5.
 39. Wissing SA, Kayser O, Müller RH. Solid lipid nanoparticles for parenteral drug delivery. *Adv Drug Deliv Rev.* 2004;56(9):1257–72.
 40. Abdul W, Pre-formulation investigation and in vitro evaluation of directly compressed ibuprofen-ethocel oral controlled release matrix tablets: A kinetic approach. *African Journal of Pharmacy and Pharmacology.* 2011. 5(19).
 41. Popova AV, Hinch DK. Thermotropic phase behavior and headgroup interactions of the nonbilayer lipids phosphatidylethanolamine and monogalactosyldiacylglycerol in the dry state. *BMC Biophys.* 2011;4(1):11.
 42. Shaker S, Gardouh AR, Ghorab MM. Factors affecting liposomes particle size prepared by ethanol injection method. *Res Pharm Sci.* 2017;12(5):346–52.
 43. Scherphof GL, Velinova M, Kamps J, Donga J, van der Want H, Kuipers F, Havekes L, Daemen T. Modulation of pharmacokinetic behavior of liposomes. *Adv Drug Deliv Rev.* 1997;24(2):179–91.
 44. Chime SA, Attama AA, Builders PF, Onunkwo GC. Sustained-release diclofenac potassium-loaded solid lipid microparticle based on solidified reverse micellar solution: in vitro and in vivo evaluation. *J Microencapsul.* 2013;30(4):335–45.
 45. AshokKumar J, Ramkanth, Prabu L, and Gopal. Enhancement of Saturation Solubility and In Vitro Dissolution of Carvedilol Nanoparticles by High Pressure Homogenization Technique. 2015.
 46. Bolourtchian N, Karimi K, Aboofazeli R. Preparation and characterization of ibuprofen microspheres. *J Microencapsul.* 2005;22(5):529–38.
 47. Mady O. Ibuprofen encapsulation by eudragit RS100 as microspheres: preparation and drug release. *MOJ Bioequiv Availab.* 2017;4(1):193–9.
 48. Al-Thamarani S, Gardouh A. Enhanced oral bioavailability and gastroprotective effect of ibuprofen through mixed polymer–lipid nanoparticles. *Ther Deliv.* 2021;12(5):363–74.
 49. Almeida H, Amaral MH, Lobão P. Comparative study of sustained-release lipid microparticles and solid dispersions containing ibuprofen. *Braz J Pharm Sci.* 2012;48(3):529–36.
 50. Megha KB, Joseph X, Akhil V, Mohanan PV. Cascade of immune mechanism and consequences of inflammatory disorders. *Phytomedicine.* 2021;91: 153712.
 51. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. *Front Immunol.* 2018;9:586.
 52. Shinde AJ, Patil NC. DESIGN AND DEVELOPMENT OF NANOSTRUCTURED LIPID CARRIER CONTAINING TRIAMCINOLONE ACETONIDE. *Int J Pharm Pharm Sci.* 2019;11(12):26–35.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

