Research Article

Valuation ofAfrican Breadfruit Seed Oil as Lipid Phase of Self-Emulsifying Drug Delivery System for Improved Gastrointestinal Fluid Solubility of Ibuprofen: Design And Evaluation

ABSTRACT

Introduction: Rain forest vegetations all over the world produce large quantity of economically important seed oils which, in most developing countries are utilized only as food condiments but hardly employed in pharmaceutical formulations.

Objectives: The purpose of this work was to formulate ibuprofen-loaded self-emulsifying drug delivery system for the enhancement of the gastrointestinal fluid solubility of this poorly water soluble drug.

Methods:The breadfruit seed oil was extracted by the soxhlet extraction technique and characterized for various physicochemical propertiesincluding acid, iodine, peroxide, saponification values and organoleptic properties. The super saturation solubility process, water titration studies and pseudo ternary phase diagrams were used to select and quantify the components of the emulsion systems. The liquid self-emulsifying drug delivery systems were converted to solid forms by adsorption onto a blend of miceocrystalline cellulose and Aerosil-200 powders. The resulting wet mass was dried and processed for encapsulation. **Results:**The percentage yield of the oil fromthe extraction process was 20.68 % while the acid, iodine, and saponification values were, 4.12 ± 1.24, 21.91 ± 0.88, and 302.45 ± 1.22 respectively. The ibuprofen exhibited higher solubility in the hydrolysed oil than in the crude form. Fourier transform infrared analysis did not reveal existence of component incompatibility. The optimized liquid and solid emulsions exhibited standard characteristics that were compatible toprevious literature reports. The formulations also exhibited superior drug release properties overtwo control samples. It was concluded that the

Conclusion: Breadfruit seed oil has the potential to function as the lipid component of ibuprofen-loaded self-emulsifying drug delivery system formulated to enhance the aqueous solubility of the drug.

Key words: Breadfruit seed oil, self-emulsifying drug delivery systems, ibuprofen,lipid phase, pseudo ternary phase.Surfactant mix.

1. INTRODUCTION

Good solubility in the gastrointestinal fluid is a prerequisite for optimum absorption of drugs administered via the oral route[1]. Poorly water soluble drugs (PWSD) face the challenge of poor absorption and low bioavailability when delivered through the gastrointestinal route. Formulation of such drugs as conventional dosage forms is also associated with incidences of inter and intra patient pharmacokinetic variability, greater susceptibility to first pass metabolism, food effects and degradative actions ofgastrointestinal enzymes and other bioactive chemicals, present in the gastrointestinal tract. A lot of formulation strategies have been developed to overcome these challenges and enhance the systemic delivery of poorly water soluble drugs. Among these strategies are: particle size reduction achieved by micronization, nano-suspension approach, high pressure homogenization and precipitation methods[2].Other strategies include amorphosization through solid dispersion, spray drying,hot melt extrusion and inclusion complexes such as cyclodextrins as well as by use of lipid based formulations like self-emulsifying drug delivery systems (SEDDS) [3, 4].

Among these strategies, the SEDDS have become very attractive because of their, simplicity, relative biocompatibility, safety profiles, low energy requirement for preparation and versatility in dosage form designs[5,]. SEDDS are also the preferred formulation choice for poorly soluble, low dose and low melting point drugs because of the low requirement of heat for their preparation. Theynot only overcome the problem of poor drug solubility but also ensures uniform distribution of active ingredients within the dosage form.

A self emulsifying drug delivery system has been described as, an isotropic physical mixture of oil(s), surfactant(s) and co-surfactant(s) in which a pharmaceutical active ingredient had been dissolved and which when introduced into an aqueous medium under gentle agitation undergoes spontaneous self emulsification to form stable oil - in-water (o/w) emulsion.[6]. Gupta et al. [7] proposed the lipid formulation classification system (LFCS) which associated the specific type of emulsion formed from a self-emulsification process with the type and proportion of the formulation excipients. Imdad and Reddy[8] highlighted the critical role of component selection and their proportions, formulation environment and the specificity of these factors on the spontaneity, type and quality of emulsion formed. One of the major advantages of SEDDS over other novel delivery systems is their ability to deliver drugs to the absorption sites in solubilised forms.

Literature review has revealed previous successfulattempts at using many plant oils including oilive, castor palm kernel, coconut seed oils and palm oils as the lipid phase of SEDDS[9, 10, 11].

Ibuprofen is a pharmacologically active compound with the IUPAC chemical name, 2-(4-Isobutylphenyl) propanoic acid. It is a non steroidal anti-inflammatory drug (NSAID) used for the management of pains, fever and manyinflammatory conditions. Pharmacokinetically, it is a member of group II of the biopharmaceutics classification system (BCS). Members of this group are known to be poorly water soluble but highly membrane permeable and solubility has been identified as their absorption rate limiting step. Improving the aqueous solubility of ibuprofen via SEDDS has the potential to enhance its gastrointestinal absorption and systemic bioavailabilty.

Breadfruit oil is a natural vegetable oil obtained from the seeds of African breadfruit plant (*Treculia africana Dence*). Such oils are widely used in pharmaceutical and food formulations because of their safety profiles, biocompartibility, biodegradability and low immunogenicity. The major draw back to the use of natural vegetable oil for such purposes is their poor solvent capacity for many drugs, storage instability and poor extractive yields.In the current work, the oil was hydrolysed to overcome the reported limitations and improve its solvency for the model drug.

2. MATERIALS AND METHODS

2.1. Materials

Three matured African breadfruit (TreculiaAfricana Dence) heads were purchased from a local market in ObolloAfor, Udenu Local Government Area of Enugu State, Nigeria. The fruit was identified and issued reference number PCG/PMI/401/2022 by Mr. Patrick Ozioko of the Department of Pharmacognosy, Enugu State University of Science and Technology, Enugu State who also deposited a voucher specime in the faculty herbarium. Ibuprofen was a product of Hetero Drugs, Hyderabad, while Cremophor EL, Tween-20, Tween-80, polyethylene glycol 400 (PEG-400) and propylene glycol (PG) were products of BASF (Mumbai). Microcrystalline cellulose (MCC), Aerosil-200 and empty hard gelatin capsule shells were obtained from Global Pharmaceutical Pvt. Ltd. Islamabad, Pakistan. Ethanol and n-haxane were products of Sigma Aldrich, USA. The commercial ibuprofen capsules were obtained from Nichben Pharm Ind. Ltd Awo-Ommama, Imo State, Nigeria. All other reagents and chemicals were of analytical grades and were used as obtained except otherwise specified

2.2. Extraction of breadfruit oil

The oil extractions were carried out in batches using a soxhlet extractor (ST 243 Soxtec^{TM} Denmark) in accordance with the Association of Official Analytical Chemist[11]. procedure using n-hexane as the extraction solvent. In brief, 250 ml of the n-hexane was used to extract oil from 200g of dry powdered seeds by boiling the solvent under reflux for 2 h and then recovering the oil by rotary evaporation (Hei-Vap Core, Heidolph Instruments, Gmb Germany). The percentage yield of oil was calculated using equation 1

$$\text{Yeild} = \frac{\text{Weight of oil}}{\text{Weight of ponder}} \times 100\% \quad \text{----------eqn 1.}$$

2.3. Degumming of oil

A modified version of the method reported by Mounts[12]was employed for the degumming of the oil. Briefly, a 5 %w/w oil in hot water (80 ^{o}C) mixture prepared in a glass flask was shaken (Flask shaker-FS,1 Stuart^{R} Germany) for 50 min. The hot mixture was placed in a separating funnel and allowed to stand for 2h. The water layer containing dissolved phospholipids was carefully removed while the oil portions were recovered.

2.4. Neutralization of oil

The method of Jahani et al.[13] was used to neutralize free fatty acid in the oil. Thirty gram (30 g) quantity of the degummed oil was placed in a beaker and heated to 80°C. Forty millilitres of a 0.1M sodium hydroxide (NaOH) was added and the mixture stirred to homogeneity. To this mixture was added, sodium chloride equivalent to 10 % of the weight of the oil and then stirred. The mixture was transferred into a separating funnel and allowed to stand for 1h to enable the formed soap separate from the oil. The neutralized oil was then drawn off into another beaker.

2.5. Bleaching and deodorization of the oil

The oil was bleached and deodorized using activated charcoal as reported in Obite et al. [14]. A 2 %w/w mixture of activated charcoal and oil was heated in a beaker at 90 °C for one hour. Thereafter the mixture was vacuum-filtered using a Burkner's funnel.

2.6. Hydrolysis of the breadfruit oil.

Hydrolysis of the breadfruit oil was necessary to break the long fatty acid chains into smaller chains with the aim of increasing its drug solubilising capacity. C. rugosa lipase was used to catalyze the hydrolytic reaction. As reported by Serri et al.[15] three gram (3 g) weight of the oil and 30 mL of iso-octane were placed in a 250 mL capacity stopper conical flask. Thereafter, 30 mL of phosphate buffer (pH 7.5) was introduced into the flask to produce oil to phosphate buffer solution ratio of 1:1. Two separate layers were obtained. The enzymatic

reaction was induced by introducing a 0.3 g lipase (C. rugosa) into the mixture under a temperature of 45 ^{o}C and orbital shaker (Certomat, B. Braun) speed of 200 rpm for 1h after which the oil phase was decanted.

2.7. Characterization of extracted breadfruit oil

The recovered oil was characterized for various oil parameters including; acid, iodine, peroxide and saponification values.

2.7a. Determination of the acid values of breadfruit oil

Acid value is the number of milligrams of potassium hydroxide (KOH) required to neutralize 1 g of an oil. The acid value was determined using the AOCS [16] method. Ten grams of the oil was placed in a 250 mL capacity conical flask. Hundred milliliters (100 mL) of neutral ethyl alcohol was then added and the mixture heated to boiling. The resulting solution was titrated with 0.1N KOH under constant shaking and employing two drops of phenolphthalein as indicator until a persistent pink color that lasted for 2 min was obtained. The acid value (AV) was calculated using equation 2.

AV = 0.56 x No of ml of 0.1N KOH ----------.eqn 2

2.7b. Determination of the saponification value of bread fruit seed oil

The saponification value was obtained using sample titration method. Herein, a 2.0 g quantity of the oil was placed in a conical flask containing 30 mL of ethanolic KOH and then heated gently (reflux condenser) for 30 min at which point saponification was completed indicated by the absence of oil matter and appearance of clear solution. After sample has cooled, 1.0 mL of phenolphthalein indicator was added and solution titrated with 0.1M HCl until a pink color appeared. The above procedure was carried out for a blank solution using same quantity of KOH solution but without the oil. The saponification value was calculated using equation 3

Saponification Value $=\frac{56.1N(Vo-Vi)}{M}$---------- eqn 3.

Where; V_O = volume of solution used for blank titration, V_I = volume of solution used for test titration, N = actual normality of the HCl used and M = mass of sample used.

2.7c. Determination of iodine value of extracted oil

The modified AOCS [9] method described in Nkpa et al. [17] was adopted for the iodine value determination. Briefly described, 0.4g of the oil was weighed into a conical flask containing 20 mL of carbon tetra chloride as solvent. Twenty five millilitres (25 mL) of Dam's reagent was added to the flask using a safety pipette in a fume chamber. A stopper was then inserted and the content of the flask vigorously swirled. The flask was then placed in a dark cupboard for 2.5 h. At the end of this period, 20 mL of a 10 % aqueous potassium iodide and 125 mL of distilled water were added to the mixture. The resulting mixture was titrated with 0.1M sodium-thiosulphate solution until the yellow colour of the mixture disappeared. Three

drops of 1 % aqueous starch solution indicator was added and the titration continued by adding the sodium thiosulphate drop wise until blue coloration disappeared following vigorous shaking. This procedure was repeated in a blank (without oil) titration. The iodine value (IV) was calculated using equation 4.

$$IV = \frac{12.69C \times (V1 - V2)}{M} \quad \text{---------- eqn 4}$$

where C = molar concentration of sodium thiosulphate used, V_1 = volume of sodium thiosulphate used for blank, V_2 = volume of sodium thiosulphate used for determination and M = mass of oil sample in grams.

2.7d. Determination of peroxide value

The peroxide value was determined by the method described in Amri et al.[18]. In brief, a mixture of the oil and chloroform/acetic acid (1.0:1.5 v/v) was incubated with a solution of potassium iodide (KI) in a dark cupboard for 5 min. Twenty five millilitres (25 mL) of distilled/deionized water and 500 μl of Amidon 1% were added and the liberated iodine was titrated with sodium thiosulfate $Na_2S_2O_3$ (0.01N). The peroxide value described as milliequivalence of active oxygen per kilogram of oil was calculated using equation 5.

$$PV = \frac{Sx\ Nx\ 103}{W} \quad \text{---------- eqn 5}$$

Where; S = mL of sodium thiosulphate, N = normality of sodium thiosulphate and W =weight of oil in grams

2.7e. Investigation of the fatty acid profile of the breadfruit oil

The degummed oil was analyzed for fatty acid composition by the gas chromatography - mass spectroscopy technique using Agilent Technologies equipment (7890A GC and 5977B MSD). The mass spectroscope capillary standard non polar column, dimension was 30 M while the film thickness was 0.25 µm and flow rate of the mobile phase (carrier gas: HE) was set at 1.0 mL/min. In the gas chromatography part, temperature program (oven temperature) was 40 ^{o} C raised to 250 ^{o} C at 5 ^{o} C/min and injection volume of 1 µL. Samples dissolved in methanol were run full scan at a range of 40.650 m/z and the results compared using Nist mass spectral library search program.

2.8. Drug and excipient compatibility study – Fourier transform infrared spectroscopy

Samples of the pure ibuprofen and the ibuprofen-loaded SEDDS dissolved in dichloromethane solution were scanned in an FTIR equipment (Agilent Technologies USA). A thin film smear of the samples were made on a NaCl crystal cell and sandwiched with a second cell. This was then placed in the sample holder of the equipment and sample scanned from 4000 to 400 cm^{-1}.

2.9.Construction of pseudo-ternary phase diagrams.

Pseudo-ternary phase diagrams (PTPD) were constructed to provide visual schematic representation of the effects of different proportions of formulation components on the in-vitro formation and stability of self-emulsifying systems and as such provide basis for the selection and quantification of the components. Data for the construction of the PTPD was generated using the water titration technique.[19]while the plotting was performed with the aid of Sigma Plot 14 software. To generate data for the plot, five sets of surfactant and co-surfactant mixtures (Tween 80 and PEG) in different weight ratios of 1:1, 1:2, 1:3, 3:1, 2:1 were prepared. Each of the above Smix and the bread fruit oil were also mixed together in the following Smix to oil ratios; 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. To each of the resulting mixtures was added double distilled water in a drop wise manner from a 1 mL capacity syringe with gentle shaking and with the temperature maintained at 37 ± 2 ^{o}C. The quantity of water required to cause spontaneous formation of clear, transparent, translucent, cloudy or milky mixture was noted. The quantity of the three components required for the formation of SEDDS were optimized by feeding the percentage weight proportions of the three components (oil, Smix and water) as obtained into the Sigma Plot 14 software and identifying maximum emulsification regions from the resulting pseudoternary diagrams.

2.10. Formulation of drug-free liquid SEDDS

On the bases of the observed regions of self emulsification on the pseudoternary phase diagrams, six trial drug free SEDDS (DFS) formulations were prepared. The selected formulation were from the Smix ratios of 1:1, 2:1, 3:1, 1:2, 1:3 and 2:3. Appropriately calculated and weighed quantities of the oil and the Smix were blended together in a 50 ml capacity round bottomed flask placed in a water bath heating at temperature of 37 ± 2 ^{o}C. The mixture was gradually added to double distilled water heated to the same temperature with gentle stirring until the emulsion was formed.

2.11. Thermodynamic Stability Studies of drug-loaded SEDDS.

Six drug-free formulations namely DFS 01, DFS 02, DFS 03, DFS 04, DFS 05 and DFS 06 were subjected to the standard thermodynamic stability studies to evaluate their capacity to remain stable under various stress conditions including, heating, cooling, centrifugation and cyclic freeze - thaw exposures [19]

2.11a. Heating-cooling cycle .

Five milliliters (5 mL) of each of the formulations was separately placed in an appropriately labeled test tube. The samples were subjected to 6 cycles of alternating refrigerator temperatures of 4 and 45 ^{o}Cwith storage at each temperature for 48 h. At the completion of

the sixth cycle, the samples were examined for phase separation or other signs of instability. The samples that remained stable at this stage were subjected to the centrifugation test.

2.11b. Centrifugation test

The test tubes were placed in a centrifuge (CentriTemp. Shimadzu Corporation, Japan) and operated at 3500 rpm for 30 min. The centrifuged samples were kept at ambient temperature for 15 h and thereafter observed. The formulations that did not show any phase separation were taken for freeze - thaw stress test.

2.11c. Freeze-thaw cycle test

Selected samples were alternately, for three cycles, placed in a freezer temperature of -21 ^{o}C and +25 ^{o}C with storage at each temperature for 48 h. Samples that remained stable at this stage were considered as having passed the thermodynamic stability test.

2.12. Preparation of drug-loaded liquid self-emulsifying drug delivery systems

Four selected drug-free formulations DFS 08 (Smix-2:1), DFS 10 (Smix-3:1), DFS 16 (Smix-3:2 and DFS 04 (Smix 1:2)) which remained stable at the end of the thermodynamic stability tests were loaded with pre-calculated quantities of ibuprofen and re-designated as ILS 01, ILS 02, ILS 03 and ILS 04 respectively. The optimized weights of the oil and Smix were blended together by manual stirring in a beaker over a water bath at 37 ± 2 ^{O}C to form a clear homogenous mixture. The drug was gradually added with gentle stirring and the mixture further blended using a vortex mixer, (Mixex 5000SP, VaxasEquipments Mumbai) for 2 h.

2.13. Preparation and encapsulation of solidSEDDS

2.13a. Processing of dry SEDDS granules by adsorption method

The anhydrous portion (without the distilled water) of the liquid SEDDS was converted to solid SEDDS granules by mixing appropriate portion with a predetermined quantity of a blend of equal proportion ofAerosil 200 and microcrystalline cellulose (MCC) powders. This powder combination has been shown to exhibit high drug adsorption capacity of up to 95 % [20, 21].The resulting wet mass was screened through N0 60 sieve, oven dries at 45 ^{o}C to moisture content of 1 % and then re-screened through No 80 sieve to produce fine dry SEDDS granules.

2.13b.Encapsulation of solid SEDDS granules

Weighed quantity of granules equivalent to 200 mg of the ibuprofen was manually filled into empty hard gelatin capsules shells (No 4)

2.14. Characterization of drug-free liquid SEDDS

2.14a. Phase Separation Test

Two separate 1 mL portion of each optimized formulation was diluted with manual shaking to 10 mL and 100 mL respectively with distilled water at 25 ^{0}C. Both preparations were allowed to stand for 24 h and then observed for phase separation.

2.15. Characterization of drug loaded SEDDS.

2.15a. Robustness to dilution and pH

Three separate 10ml samples of ILS 01, ILS 02, ILS 03 and ILS 04 were each diluted separately and shaken with excess (200 ml) volume of water, standard phosphate buffer (pH 6.8) and 0.1N HCl. The dilutions were stored for 12 h under ambient temperature and thereafter observed. Any sample that yielded no precipitate and/or phase separation in all the three media was considered as being robust to both pH and dilution [22, 23].

2.15b. Determination of percentage transmittance

One milliliter (1 ml) of the four drug-loaded SEDDS was added to 100ml of double distilled water and the transmittance read from a UV spectrophotometer (JENWAY 7305, Germany) at 640 nm using the distilled water as blank.

2.15c Determination of Cloud Point

The cloud point values of the drug – loaded SEDDSs were determined as follows: Each formulation was diluted with water in the ratio of 1 : 100 and placed in a water bath followed by gradual increase in temperature (2 °C/min) from 25 to 100 °C [24].Cloud point was regarded as the temperature at which there was a sudden appearance of cloudiness observable visually [25].

2.15d. Determination of pH

The pH of a 2 ml aliquot of each preparation was determined in triplicate runs using a digital pH meter (Mettler Tonado, PCE – 224HTE, China).

2.15e. Determination of the viscosity of the liquid SEDDS

Brookfield viscometer, (Visco - CPE40; Brookfield Engineering Laboratories, Inc, Middleboro) was used to determine the viscosity of different formulations at ambient temperature using the equipment standard procedure.

2.15f. Determination of droplet sizes, zeta potential and polydispersity index

A laser light diffraction Zetasizer (Model ZEN3600, Malvern, United Kingdom) was used to determine the droplet sizes, polydispersity indices (PDI) and the zeta potential (ζ) of the various formulations. One milliliter (1 ml) of each product was put in a volumetric flask and diluted to 1000 ml with double distilled water. Samples of each diluted formulation were taken in cuvettes for the determination of relevant parameters with light scattering monitored at 25°C at angle 90°.

2.15g. Assay of liquid SEDDS for drug content.

A quantity of the liquid SEDDS equivalent to 200 mg of ibuprofen was weighed out and placed in a volumetric flask containing 10 mL of 0.1 M NaOH (1 mg/ml) and thoroughly shaken. A 2.5 ml volume of the solution was withdrawn and diluted to 1000 ml with methanol. The absorbance of this final solution was read on a uv spectrophotometer (JENWAY 7305, Germany) at a wavelength of 640 nm.

2.16. Evaluation of solid SEDDS capsules.

2.16a. Friability test

A single drum friabilitor (Erweka; 50254 Germany) was used to study the friability of the encapsulated SEDDS using the USP standard procedure. The percentage friability was calculated according to equation 6.

$$\% \text{ friability} = \frac{W0 - Wt}{W0} \text{x } 100 \quad \text{---------- eqn. 6}$$

where, Wo is the initial total weight of six capsules before the test, and Wt is the total weight of the same six capsules after the test

2.16b. Disintegration time test

The USP [28]official procedure was also used to perform the capsule disintegration test. Distilled water maintained at a temperature of 37+2 ^{o}C was used as the disintegration fluid.

2.17c. Capsule weight uniformity test

The mean weight of 20 randomly selected capsules was determined. Each of the capsules was then weighed separately and the percentage weight deviation from the calculated mean for the 20 capsules was determined. The obtained data was analyzed and compared to official specifications.

2.17d. Drug release studies

In-vitro dissolution rate of raw ibuprofen, formulated liquid SEDDS, encapsulated solid SEDDS and commercial samples of ibuprofen capsules were studied separately in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) using the USP apparatus II equipment, (metrolab H44 - 6) with the paddle rotating at 50 rpm. The volumes and temperatures of the dissolution media were maintained at 900 mL and 37±0.5^{o}C respectively. For each study, one capsule or quantity of powder or liquid SEDDS equivalent to 200 mg of ibuprofen was placed inside the dissolution flask containing the appropriate medium under paddle rotation. A 5 mL aliquot of the test media was withdrawn after 5 min and subsequently at 10 min intervals for spectrophotometric analysis. The withdrawn portion was filtered, diluted and the absorbance determined at 640 nm. The 5ml aliquot withdrawn was immediately replaced with equivalent volume of fresh medium to maintain sink conditions. The

calculated mean cumulative percentage quantity of drugs released was plotted against time.

2.18. Statistical analysis

Triplicate data obtained from the various tests were expressed as mean ± standard deviation and statistically significant differences were determined at $p < 0.05$ using one-way analysis of variance (ANOVA) in GraphPad Prism version 7.0 software.

3. RESULTS

3.1. Extractive yield, purification and fatty acid composition of the breadfruit oil

The percentage yield of oil by the breadfruit seeds was 24.54 %. The purifications of the oil involving water-based degumming and heat-bleaching using activated charcoal resulted in a reduction in viscosity from 37.45 ± 23 to 31.45 ± 0.68 $_{C}$P and in the brightening of the color from dull dark yellow to bright yellow. Gas chromatography-mass spectroscopic (GCMS) analysis of the oil revealed the presence of eight fatty acids and a lot of aldehydes, ketones among others. The GCMS spectra of the two most prominent fatty acids are shown as figures 1 and 2.. About eighty four other spectra representing various compounds were obtained.

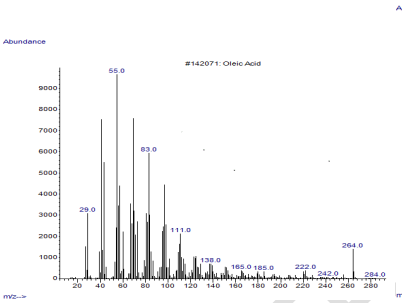

Fig. 1:GCMS spectra of linoleic acid

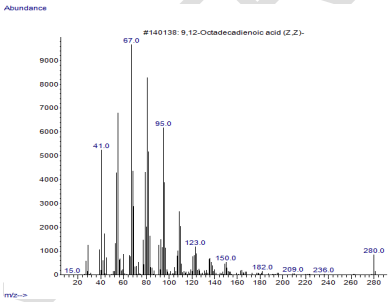

Fig. 2:GCMS spectra of oleic acid

3.2. Characterization of oil

The iodine and peroxide values of the oil were 17.50 ± 0.05 and 4.20 ± 0.08 meqO_2/kg respectively. The saponification value was 236.46 ± 0.02 while the acid value was 3.4 ± 0.33% (value = mean ± S.D)

The solubility of ibuprofen in the breadfruit oil, soy-bean oil, some selected surfactants and two co-surfactants. The drug was practically insoluble in water and the crude breadfruit oil. It however, exhibited improved solubility in the hydrolysed form of the oil. Tween 80 exhibited the highest solvent capacity of 197. 17±1,25 followed by polyethylene glycol 400 and then Kolliphore where ibuprofen had solubility of 112.68 ± 1.81. The solubilizing capacity of other tested components were, in order of decreasing values, Tween 20 > propylene glycol > soy-bean >hydrolysed breadfruit oil.

3.3. Fourier transform infrared (FTIR) analysis.

Fourier transform infra red (FTIR) spectroscopy was conducted for the optimized batch to elucidate the molecular bonding characteristics of the sample and identify any spectral discrepancy arising from interaction between ibuprofen and the excipients used in formulating the SEDDS. The FTIR spectra of pure ibuprofen and the ibuprofen-loaded SEDDS are shown as figure 4 (A & B).

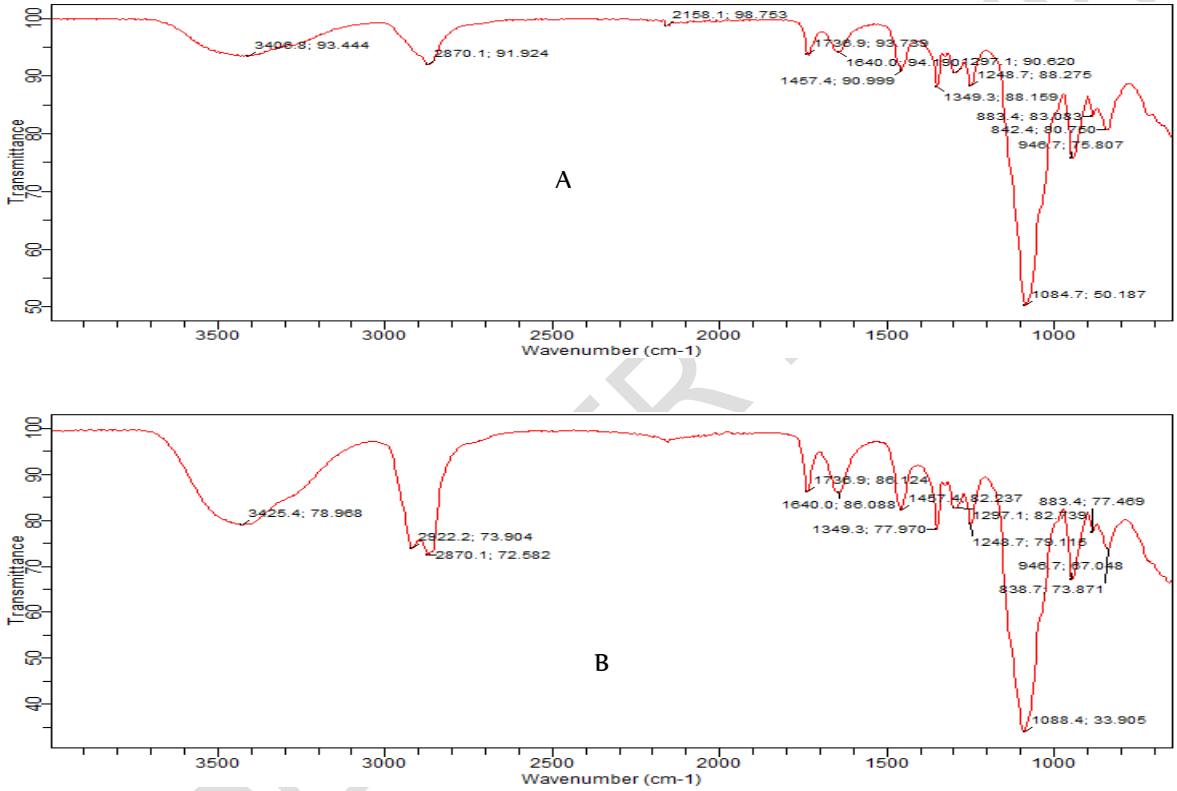

Fig. 3: FTIR spectra of; A – pure ibuprofen and B – ibuprofen-loaded SEDDS

3.4. Construction of pseudoternary phase diagrams.

Data from the water titration processes were fed into SigmeaPlot-14 software. Figure 5 shows the phase diagrams generated for three selected Smix ratios. Component proportions for final formulations were determined from the observed regions of self-emulsification in the phase diagrams. It was observed that the formulation with Smix ratio of 3:1 had the largest region of self-emulsification followed by Smix ratio 2:1. The Smix 3:1 also exhibited better and fastest ease of self-emulsification.

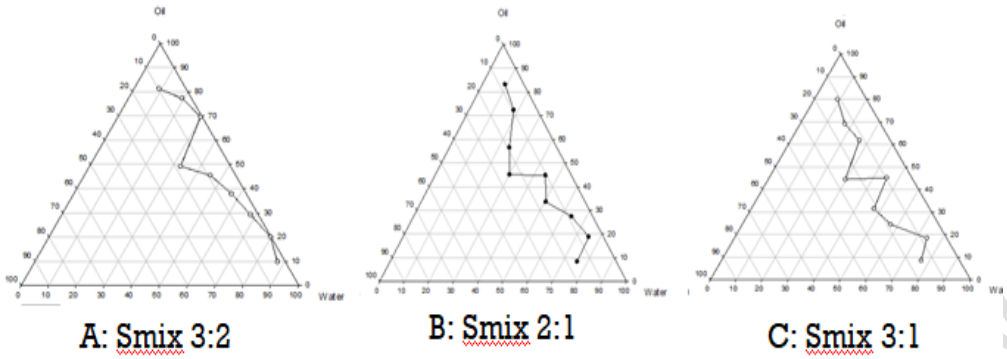

Fig. 4 (A, B. C): Pseudoternary phase diagrams of three formulations.

3.5. Formulation of drug – free SEDDS

The SEDDS formulation components and their percentage proportions for six batches are presented on table 1. Formulations DFS 02, 03 and 06 yielded clear transparent emulsions while DFS 01 and 05 were milky emulsion. Formulation DFS04 had a translucent appearance.

Table 1: Formulary for preparation of various batches of drug-free SEDDS

	Formulation/Smix ratio					
	DFS 01	DFS 02	DFS03	DFS04	DFS 05	DFS 06
Component (%)	(1:1)	(2:1)	(3:1)	(1:2)	(1:3)	(3:2)
Breadfruit oil	24.24	18.08	19.31	20.31	36.32	18.37
Smix (Tween 80 & PEG	56.58	72.34	77.30	76.40	54.50	73.46
Distilled water	19.18	9.58	3.39	3.29	9.18	8.17
Appearance	milky	clear	clear	transluscnt	milky	clear

3.6. Thermodynamic stability tests of drug - free SEDDS.

The results of the thermodynamic stability studies of the various drug-free SEDDS are shown on table 2. All the tested formulations passed the stage one (heating& cooling cycle) while only formulation DFS 05 failed the centrifugation test and was as such discontinued in the tests. Formulations DFS 02, 03, 04 and 06 passed the final freeze-thaw cycle tests.

Table 2: Results of thermodynamic statbility studies

Batch Codes	Heating & cooling cycle	Centrifugation test	Freeze - Thaw cycle test	Final Appearance
DFS 01 (Smx 1:1)	Pass	Pass	Fail	2 phases
DFS 02 (Smx 2:1)	Pass	Pass	Pass	Transparent

DFS 03 (Smx 3:1)	Pass	Pass	Pass	Transparent
DFS 04 (Smx 1:2)	Pass	Pass	Pass	Transluscent
DFS 05 (Smx 1:3)	Pass	Fail	N/A	2 phases
DFS 06 (Smx 3:2)	Pass	Pass	Pass	Transparent

Key: DFS: Drug – free SEDDS

3.7. Preparation of drug loaded self-emulsifying drug delivery systems

Four drug – free formulations that passed the thermodynamic stability tests were loaded with calculated quantities of ibuprofen and re-designated as ILS 01, ILS 02, ILS 03 and ILS 04. Their corresponding formulation components are shown in table 3.

Table 3: Formulations of ibuprofen - loaded SEDDS

	Formulation codes and Smix ratios			
Components (% w/w) (excipients only)	ILS 01 (Smix 2:1)	ILS 02 (Smix 3:1)	ILS 03 (Smix 3:2)	ILS 04 (Smix 1:2)
Bread fruit oil	18.08	19.31	8.37	20.31
Tween 80/PEG 400	72.34	77.30	73.46	764.40
Distilled water	9.58	3.39	8.17	3.29
Ibuprofen, add	30.00 g	30.00 g	30.00 g	30.00 g

Visual examination showed that upon incorporation of the ibuprofen, formulations ILS 01 and ILS 02 retained their transparency while ILS 03 and 04 showed some slight cloudy appearance. There was however no noticeable precipitation or phase separation even after standing for 96 h.

Fig 5: A – processed breadfruit seeds, B - formulated breadfruit oil-based liquid and encapsulated solid SEDDS

3.8. Characterization of drug loaded liquid and solid SEDDS

3.8a. Robustness to dilution and pH

Robustness test was used to investigate the effect of dilution and change in pH on the stability of the formulations. All the formulations retained their appearance, colour, homogeneity and non precipitation after being diluted with 500 ml each of double distilled water, 0.1N HCl and phosphate buffer pH 7.2.

3.8b. Physicochemical parameters of drug – loaded SEDDS

Table 4 shows some physicochemical parameters of the various SEDDS formulations.

Table 4: Physicochemical parameters of four SDDS formulations

Code	pH	Viscosity (cPs	% Transmittance	Cloud point (^{o}C)	ZP (mV)	Droplet size (nm)	PDI
ILS 01	7.8 ± .67	31.19 ± 07	99.75 ± 24	87 ± 3.11	-54.04 ± .014	69.59 ± 0 .81	0.237
ILS 02	7.4 ± 76	29.57 ± 25	98.96 ± 54	79 ± 7.42	-29.11 ± .311	72.04 ± 0 .35	0.228
ILS 03	7.7 ± 63	21.34 ± 41	90.96 ± 71	76 ± 6.29	-32.67 ± .852	452.66 ± 0.22	0.447
ILS 04	7.4 ± 78	28.83 ± 19	72.96 ± 36	75 ± 9.24	-37.73 ± 687	1412.14 ± .05	0.77 5

n = 3 ± SE

The viscosities of the four formulations were in the range of 21.34 ± 41 to 31.19 ± 07 cPs while their cloud points ranged from 75 ± 9.24 - 87 ± 3.11 ^{o}C.The mean droplet size distribution of the various formulations are also shown on table 6 and presented in a system generated normal distribution curve as shown in figures 7and 8. All the investigated formulations exhibited negative zeta potentials ranging from -54.04 ± .014 to -29.11 ± .311 mV. The PDI of all the formulations were below 1 (one).

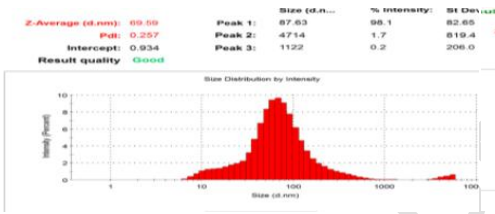

Fig. 6: Droplet size distribution of ILS 01

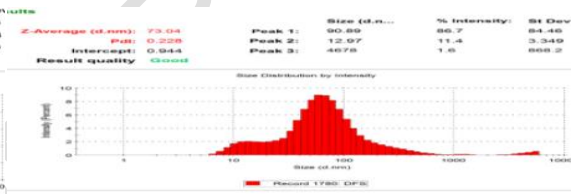

Fig. 7: Droplet size distribution of ILS 02 01

3.9. Characterization of Solid SEDDS capsules

Solid SEDDS capsules of four batches prepared as describes in chapter two were characterized for uniformity of capsule weight, percentage friability, drug contents and release profiles.

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3.9a. Physicochemical characteristics of encapsulated solid SEDDS

Some of the physicochemical characteristics of the SEDDS capsules are presented on table 5.

Table 5: Physicochemical characterization of solid SEDDS capsules

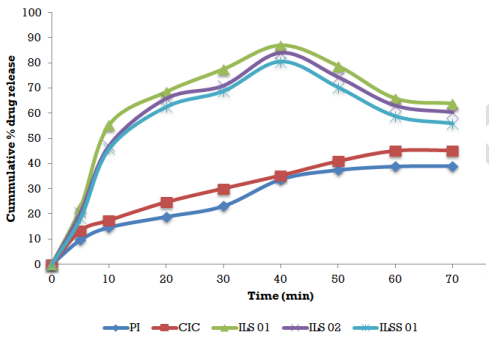
Solid SEDDS formulation	Weight uniformity	% Friability	D.T (min)	Drug content (%), n = 2 ± SE
ILSS 01	Pass	0.55	6	88.46 ± 0.32
ILSS 02	Pass	0.62	7	81.27 ± 0.76
ILSS 03	Pass	0.73	5	87.61 ± 0.64
ILSS 04	Pass	0.74	4	80.17 ± 0.16

Key: D.T = Disintegration time

All the capsule formulations conformed to the USP [28] official specifications for weight uniformity, percentage friability (< 1 %) and disintegration time (≤ 15 min). The percentage drug contents for the four batches were close to the lower limits of the official specification of 85 – 115 % of label weight.

3.10. Invitro drug dissolution studies

Figures 8 and 9 represent the dissolution profiles of the various SEDDS formulations, commercial samples and the raw samples of ibuprofen. The studies were carried out in phosphate buffer (pH 7.2) and 0.1N HCl, (pH 1.2) to simulate both the intestinal and the gastric fluid pH.



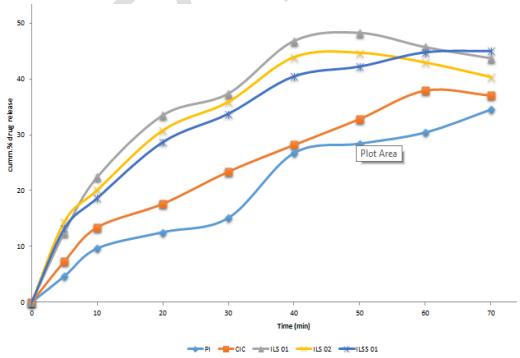


Fig. 8: Release profiles in Phosphate buffer **Fig. 9:** Releases profiles in 0.1N HCl

Fig. 8 and 9 show the in-vitro release profiles of ibuprofen from different formulations into the phosphate buffer (pH 7.2) and the 0.1N HCl (pH 1.2). It was observed from the two figures that the SEDDS formulations exhibited faster (p< 0.5) initial drug releases than the raw and commercial samples. This may be an indication that the SEDDS actually enhanced the solubility of the ibuprofen. Formulation ILS 02 (Smix 3:1 in Smix : oil, 9:1) exhibited the overall highest releases than other formulations.Raw samples of ibuprofen did not release up to 50 % of its contents within 70 minutes of the study.

3.11. Drug release half life

Drug release half-life ($t_{½}$) was considered as the time at which the formulation released 50 % of its determined drug content. The $t_{1/2}$ for some formulations in the two selected media are shown as table 6.

Table 6 : Drug release half life ($t_{1/2}$) of ibuprofen of various formulations

	$t_{1/2}$ (min)					
	Dissolution media	Commercial capsule	ILS 01	ILS 02	ILSS 01	ILSS 02
Phosphate buffer	nil	nil	24	27	34	32
0.1N HCl (pH 1.2)	nil	nil	37	40	50	52

The raw ibuprofen powder and the commercial ibuprofen capsules did not release up to 50 % of their content within the 70 min of the test. For all the SEDDS formulations, the $t_{1/2}$ in the phosphate buffer were less than in the0.1N HCl (pH 1.2).

3.12. Calculation of drug release similarity factors

Similarity factor (f_s) is a mathematical model that compares the release profiles of different formulations. The release profiles of the optimized solid SEDDS (ILSS 01) was compared to that of the commercial brand by computing their similarity factor (f_2) using equation 7 as proposed by Moore et al.[26].

$f_2 = 50 \times \log\{[1+ (1/n)\Sigma t=_1^n (Rt-Tt)^2]^{-0.5} \times 100\}$ ---------- eqn. 7

where, n is the number of dissolution test sampling time points, Rt is the dissolution value of the reference batch at time point t, and Tt is the dissolution value of the test batch at same time. The calculated $f_2$are presented on table 7.

Table 7: Similarity factors of some SEDDS formulations versus commercial sample.

Formulation pair	f_2	Inference
Ibuprofen-loaded liquid SEDDS (ILS 02) and commercial Ibuprofen capsule	18	dissimilar
Ibuprofen-loaded solid SEDDS (ILSS 02) and commercial Ibuprofen capsule	29	dissimilar

4. DISCUSSION

4.1. Extractive yield and purification of oil

The oil yield of 24.54 %was comparable to the 20.68 % obtained in a previous study.[11]The improvement was thought to be due to the adoption of longer extraction period. Similarly, the changes arising from water degumming and bleaching was attributed to the removal of phospholipids and other mucilaginous substances from the oil. [27].Apart from giving unattractive appearance, such substances cause darkening, unpleasant odour and flavour and reduce the rate of transesterification reactions in the oil [28].The brighter colour of the oil after bleaching is likely due to adsorption of natural colouring pigments by the activated charcoal.

4.2. Characterization of oil

Iodine value is an oil parameter that indicates the degree of unsaturation of the oil fatty acids and also a measure of the oil stability and resistance to oxidation [29]. The value for the test oil was relatively high and attributable to the presence of unsaturated fatty acids [30].Our GCMS analysis revealed that breadfruit oil contains many unsaturated long chain fatty acids like oleic acid, linoleic acid and palmitic acid.[11]Peroxide value is an oil parameter for predicting to what extent the oil had undergone deterioration during processing or storage and its tendency to become rancid upon further storage. Values in the range of 20 -40 meqO_2/kg is suggestive of the likelihood of rancidity.[17]The low value of our sample makes it suitable for both industrial and domestic uses. The value is also comparable to that of linseed and sunflower with PV of 11.28 and 12.87 meqO_2/kg respectively [31, 32]obtained in previous studies. Saponification value (SV) is a measure of the relative molecular mass of the fatty acid in the oil. [33].The current oil has SV of 236.46 ± 0.02 which was an indication of the presence of high molecular weight fatty acids. The identified fatty acids in the breadfruit oil have high molecular weights.

Similarly, the acid value (AV) of oil is the weight of potassium hydroxide (KOH) in milligram (mg) required to neutralize the organic acids present in 1g of oil or fat. Low free acid content is desirable for edible oils[34].The current breadfruit oil with acid value of 3.4 ± 0.33% may be adjudged as good for the intended formulation with regard to its edibility.

4.3. FTIR Studies

Examination of the FTIR spectra showed that bands occurred within the mid infra red spectrum (400 – 4000 cm^{-1}) with majority of the peaks within both the single (2500 - 4000 cm^{-1}) and the double (1500- 2000 cm^{-1}) bond regions. No peak occurred within the triple bond zone (2000 -2500 cm^{-1}) confirming the absence of triple bonds in the ibuprofen structure. The appearance of peaks in the range of 1510 – 1420 cm^{-1} and 1850 -1650 cm^{-1} in both spectra are typical of the aromatic ring and C=O stretch bands respectively of the ibuprofen molecule Exact peaks at 2870 cm^{-1}obtainable in both the pure ibuprofen and ibuprofen-loaded SEDDS are characteristic of C-H stretch [35, **36**].Only minor shifts were observed for most spectral bands. These shifts mat be explained by the fact that the ibuprofen in the SEDDS formulation was in asolubilised state. These features suggest that no molecular alteration from chemical interaction between the drug and the excipients occurred in the SEDDS.

4.4. Thermodynamic stability studies

It was observed that batches DFS 02, 03, 04 and 06 maintained their transparency and non precipitation at the end of the three stages of the thermodynamic stability tests. Formulations containing higher proportion of co-surfactant than surfactant in the Smix did not pass the

final stages of the tests. This also emphasizes the critical role of surfactants in the formation and stability of emulsions. “Surfactants stabilize emulsions by establishing a single layer around the emulsion droplets, lowering interfacial energy, and preventing coalescence [37]. The emulsions that passed the final stage of the test are likely to remain stable under storage and handling which are generally less stressful than the thermodynamic conditions.

4.5. Robustness to dilution and pH

The selected formulations retained their integrity after being diluted with large volume of various media of varying pH values. This suggested that the SEDDS will likely maintain their homogeneity and the drug will remain solubilized in both the gastric and intestinal fluids. This is desirable since the major advantage of SEDDS over other novel solubility enhancement formulations is its ability to retain and present the drug to the absorption sites in solubilized state thereby overcoming the poor aqueous solubility of the cargo drug.

4.6. Characterization of the physicochemical properties of the formulated SEDDS

Various standard tests were conducted to determine the pH, viscosity, transmittance, cloud point, zeta potential, droplet sizes and the polydispersity indices (PDI) of the various formulations.

The pH values were within the neutral range of 7.4 ± 76 - 7.8 ± .67. The product will need no pH adjustment before being used. The viscosity of liquid SEDDS affects its gastrointestinal spreadability and drug releases within the stomach. Highly viscous preparation may exhibit poor spread and drug release within the GIT. Such preparation may also be unpalatable to patients and difficult to dose out from containers. The viscosities of the four formulations which rangedfrom 21.34 ± 41 to 31.19 ± 07 cPs will pose no such problems.Given the cloud point obtained, it may be concluded that the product with clear appearance will remain so during normal handling and storage conditions since their cloud points values are higher than normal storage temperatures.

4.7.Droplet size, polydispersity index and zeta potential.

A lot of pharmacokinetic characteristics of drug-loaded SEDDS like drug solubility, drug release rate, membrane adhesion and permeation as well as cellular internalization and circulatory half-life are influenced by the droplet sizes [38]. The results obtained indicated that formulations ILS 01and ILS 02 were in the nano size range while ILS 03 and ILS 04 fell within the micro size range. Nano emulsions have droplet sizes in the range of 1 – 100 nm[39].

PDI has a dimensionless scale ranging from 0 to 1. Values less than 0.05 are exhibited by systems with highly mono-size disperse phase while values above 0.7 are seen in systems with broad particle size distribution range [40].The net negative values of the zeta potential

presuppose that the system would experience inter-droplet repulsion and minimal tendency for coalescence. It has been postulated that most conventional self-emulsifying systems containing non ionic lipids have negative charges due to the presence of fattyacids.[24] In the case of the current formulations, free fatty acids may originate from the breadfruit oil.

4.8. Dissolution studies

For all the formulations and other samples, drug releases were higher in the phosphate buffer than in the 0.1N HCl ($p< 0.5$) suggesting that release was pH dependent. This is likely due to the lipophilicity (pKa 4.52) of ibuprofen. Formulation ILS 02 (Smix 3:1 in Smix : oil, 9:1) exhibited the overall highest drug releases than other formulations. The releases from the liquid SEDDS were higher than from their solid equivalents, ($p < 0.5$) It may be reasoned that the solid microcrystalline cellulose and Aerosil-200 blend used as solid adsorbent, in addition to its intended role as solid carrier acted as matrix barrier to the transport of the SEDDS into the dissolution medium. This observation is in tandem with report of Friedman and Nylund [41].Drug releases from the raw samples and commercial capsules into both media were relatively poor hence, the desirability of SEDDS formulation.

The similarity factor ($f_{2)}$ obtained suggested that the dissolution profiles of the formulated SEDDSs and those of the commercial capsules were not identical. For two release curves to be considered similar, the calculated f_2 value must be greater than 50 % [42, 43].

5. CONCLUSION

Ibuprofen-loaded self-emulsifying drug delivery systems based on breadfruit oil has been successfully formulated. The model oil showed good edible feature and physicochemical characteristics that supported its use. The oil, however exhibited poor solvent capacity for ibuprofen, a feature that was attributed to the presence of long chain unsaturated fatty acids in the oil. The optimized formulations exhibited basic physicochemical attributes that were consistent with standard SEDDS formulations and in tandem with reviewed previous works. A major observation of the work was that the concentration of surfactant influenced the quality and performance as well as the spontaneity of emulsions formation. The optimized SEDDS was formulated withsurfactant to co-surfactant mix ratio of 3:1 in a surfactant mix (Smix) to breadfruit oil ratio of 9:1. The formulation enhanced the in-vitro solubility of ibuprofen in simulated intestinal fluid with likelihood of similar in-vivo performance. The low solubility of ibuprofen in the oil was a major challenge that necessitated the use of high proportion of surfactants. Future works in this area may explore formulation and processing techniques that would improve the solubility of ibuprofen in the oil. The results obtained strongly suggest that the intestinal fluid solubility of ibuprofen can be enhanced by formulating it as a self-emulsifying drug delivery system employing breadfruit oil as the lipid component of theformulation.

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