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THE AFRICAN BAOBAB SEED OIL AND ITS POTENTIAL FOR SOLUBILISING POORLY SOLUBLE DRUGS

A. D. Aberimah, R. Johnson *, M. T. Bayor, N. Kuntworbe and F. W. A. Owusu

Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

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Correspondence to Author:
Raphael Johnson

Ph.D., Senior Lecturer, Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

E-mail: ralph355@yahoo.com

ABSTRACT: Most lipids used in solubilizing poorly soluble drugs are synthetic or semi-synthetic. In this study, the African Baobab seed oil (natural oil) was investigated for its potential in solubilizing poorly soluble drugs in a microemulsion formulation. Oil was extracted from untreated seeds by hydraulic pressing. Physicochemical characteristics of the oil were determined. The solubility of Furosemide, Griseofulvin, Ibuprofen, and Mebendazole was determined in the seed oil, surfactants, and co-surfactants. The miscibility of the oil, surfactants, and co-surfactants was assessed. A ternary phase diagram was developed to determine the microemulsion zone. Formulations of drug incorporated microemulsions were prepared using the seed oil. The microemulsions were characterized by droplet size, pH, transmittance, *in-vitro* drug release, and stability. The oil from the seeds was golden yellow in appearance. It was free from disease-causing pathogens. Analysis of the oil constants revealed that the oil was good for use as a pharmaceutical excipient. Optimised composition of 15% oil, 75% surfactant and 10% water formed a clear and stable microemulsion which solubilised Furosemide (30 mg/ml), Griseofulvin (30 mg/ml), Ibuprofen (450 mg/ml) and Mebendazole (25 mg/ml). Percentage cumulative drug releases of 68.81 ± 1.21, 68.86 ± 7.16, 77.70 ± 0.68 and 55.64 ± 0.17% for Furosemide, Griseofulvin, Ibuprofen, and Mebendazole, respectively were obtained over a four-hour dissolution study using phosphate buffer pH 6.8, showing a retarded release of the drugs from the microemulsion. The extracted oil is suitable for use in a microemulsion formulation for the solubilization and delivery of poorly soluble drugs.

INTRODUCTION: Lipids in the form of mono and di-glycerides as well as pure triglyceride oils are important components in oral drug delivery systems such as liposomes, solid lipid nanoparticles, and microemulsions. These systems are carriers for the delivery of both lipophilic and hydrophilic drugs.

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They are considered to be biocompatible, biodegradable, stable, and cost-effective to manufacture. Microemulsions are defined as colloidal, optically isotropic, transparent, or slightly opalescent formulations, consisting of an oil, surfactant, co-surfactant and water [1, 2].

Microemulsions have several advantages, such as ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading and enhanced penetration through the biological membranes, which increases bioavailability and less individual variability in drug pharmacokinetics [3, 4, 5].

These advantages make microemulsions attractive drug delivery systems. The majority of the oils used in microemulsion formulations are either synthetic or semi-synthetic. Oils from natural sources such as olive, raspberry, coconut, sesame, castor, and peanut oils have been investigated in various oral drug delivery systems [6]. Oil from the seeds of *Adansonia digitata*, L. Malvaceae (African baobab tree) has been found to possess similar constituents as those above, but its application in drug formulations is not fully exploited. The Baobab tree is found in many African countries and is common in Northern Ghana. Traditionally, indigenous people have, for centuries, employed the baobab tree and its seed oil in the preparation of food, cosmetics and for therapeutic purposes in various concoctions. In combination with other herbs, the oil is used to treat conditions such as cough, fever, worm infestations, dandruff, muscle spasms, and several other therapies [7]. The high amounts of oleic and linoleic acids of the Baobab oil, determined as mono-unsaturated and poly-unsaturated fatty acids, have an oil stability index as per literature reports similar to olive oil used in pharmacy [8, 9, 10, 11].

The oil is reported by Vertuani *et al*., to have a variable shelf life between 2-5yrs, which will prevent early deterioration of formulations. Aside from unsaturated fatty acids, the presence of sterols in the oil enhances its antioxidant activities [12]. Vitamins including those of A, C, D, E, and Kare are documented to be present in this oil [13]. These constituents will inure to the benefit of the oil as a pharmaceutical excipient.

Poorly soluble drugs of Biopharmaceutics Classification System (BCS), classes II and IV have low bioavailability, nonlinear pharmaco-kinetics and high variability when administered by the oral route. Lipid formulation systems have become the recommended approach to improve the absorption of these classes of drugs. This study sought to investigate the use of the oil from the seeds of *Adansonia digitata* as an excipient in the formulation of microemulsions; and its subsequent use as a vehicle for the solubilization and delivery of poorly soluble drugs.

MATERIALS AND METHODS: Seeds of *Adansonia digitata* (African Baobab tree) were purchased from the Bolgatanga market in the Upper East region of Ghana in December 2017. It was authenticated by the Herbal Medicine Department of the Faculty of Pharmacy and Pharmaceutical Sciences in Ghana. Ernest Chemist Pharmaceuticals Limited, Ghana donated pure powder samples of Furosemide and Griseofulvin. Ibuprofen and Mebendazole were a gift from Trade Winds Pharmaceuticals Limited, Ghana. Tween 20, Tween 80, Propylene glycol, Dipotassium hydrogen phosphate, and Potassium dihydrogen phosphate were purchased from UK Chemicals Limited, Kumasi. Transcutol®, Labrasol®, Labrafil® M 2125 CS, Labrafil® M 1944 CS and Labrasol® ALF were received as gift samples from GATTEFOSSE Company in France. Cetrimide agar, Bismuth sulphite agar, Nutrient Agar, MacConkey agar, Sabouraud agar, and Mannitol salt agar were purchased from Oman chemicals Limited, Accra in Ghana. All other reagents were of analytical grade.

Oil Extraction from Dried Seeds of the African Baobab Tree: Seeds of *Adansonia digitata* (family Malvaceae) were poured into a drum of water in order to separate out any unwanted floating materials. Twenty-five (25 kg) of seeds were crushed in the milling compartment of the oil extractor (IO 67 Bonagro screw press, China). The crushed seed materials were slightly sprinkled with water and left overnight to help softened the hard coat of the seeds. The seeds were cold-pressed to obtain the oil. The extracted oil was left overnight for clarification, then filtered and bottled.

Determination of Moisture Content of the African Baobab Seed Oil: The moisture content of the baobab oil was determined using the American Oil Chemists' Society (AOCS) method Ca 2c-25 (2009) [14].

The oil was accurately weighed (5 g) into a previously dried and weighed dish. The dish was placed in a thermostatically controlled oven at 105°C for 5 hours. The dish was then removed and placed in desiccators to cool to room temperature, after which it was re-weighed. A triplicate determination was done. The moisture content was calculated using the relationship below

$$\text{Moisture content (\%)} = (W1\text{-}W2 \times 100) / W1$$

Where: W1 = weight (g) of sample before drying, W2 = weight (g) of sample after drying

Determination of Free fatty acid value of the African Baobab Seed Oil (FFA): The free fatty acid was determined using the American Oil Chemists' Society (AOCS) method Ca 5a-40 (2009) [15].

Oil was weighed (5 g) into a 250 ml Erlenmeyer flask with a stopper and mixed thoroughly with 50 ml of ethanol. Two drops of phenolphthalein indicator solution were added to the mixture, which was then titrated against 0.1 N sodium hydroxide solution. The endpoint of the titration was indicated by a pink colour. The procedure was repeated two more times. The FFA was determined using the relationship below.

FFA (%) = (Vol. of NaOH(ml) × normality of NaOH × 28.2) / (Weight of sample (g))

Determination of Acid Value (AV) of the African Baobab Seed Oil: Acid value of the Baobab oil under study was determined utilizing method of the American Oil Chemists' Society (AOCS) method Ca 5a-40 (2009) [15].

The oil (5.0 g) was placed in a conical flask and mixed with 25 ml of absolute alcohol. Three (3) drops of phenolphthalein were added as an indicator to the solution. This was heated while shaking in a water bath for 10 min. The solution was then titrated against 0.1 N KOH until a pink colour appeared at the endpoint. The experiment was conducted in triplicate. The acid value was calculated using the relationship below;

AV (mg/g) = (Vol. of KOH × N (KOH) × 56) / (Weight of sample)

Determination of Iodine Value (IV) of the African Baobab Seed Oil: The iodine number was determined using AOAC method 993.2 (1999) [16].

One (1) g of the oil was weighed into a 250 ml flask and mixed with 10 ml of chloroform and 30 ml of Hanus solution. The flask was closed with a parafilm and carefully shaken for 30 minutes. The solution was then mixed with 10 ml of 15% potassium iodide solution, covered, and shaken again. The solution was diluted with 100 ml of distilled water and titrated against 0.1 N sodium thiosulfate until a yellow colour was formed. Three (3) drops of the starch solution were then added and the titration was continued until the blue colour disappeared. Blank determinations were carried out by repeating the procedure without a sample. The procedure was repeated two more times. The iodine value was determined using the equation below.

Iodine Value = ((B-S) × N of $Na_2S_20_3$ × 0.127 (g/m_{eq}) × 100) / (Gram of sample)

S = Volume (ml) of $Na_2S_2O_3$ at endpoint of sample determination
B = Volume (ml) of $Na_2S_2O_3$ at endpoint of the blank determination.

Determination of Peroxide Value of the African Baobab Seed Oil: The peroxide value was determined using the AOAC method 965.33 (2002) [17].

The sample (5.0 g) was weighed into a 250 mL glass stoppered Erlenmeyer flask and mixed thoroughly with 30 mL of acetic acid - chloroform mixture (480 mL Acetic Acid and 320 mL Chloroform) and 0.5 ml of saturated potassium iodide solution. The mixture was diluted with 30 ml deionized water and titrated against 0.1 N sodium thiosulfate using starch as an indicator until a blue-grey colour disappeared in the aqueous layer. The experiment was performed in triplicate. The peroxide value was calculated using the formula below.

Peroxide Value = ((Vs-Vb) × N of $Na_2S_20_3$ × 1000) / (Gram of sample)

Vs = Volume (ml) of $Na_2S_2O_3$ at end point of sample determination
Vb= Volume (ml) of $Na_2S_2O_3$ at end point of the blank determination.

Determination of Saponification Value (S v) of the African Baobab Seed Oil: The Saponification value was determined using AOAC method 933.08 (1999) [18].

The saponification number was determined by weighing 5 g of the oil into a 250 ml conical flask along with 25mL of 0.5 N potassium hydroxide prepared in an ethanol solution. The conical flask was fitted with a reflux condenser placed in a boiling water bath for 1 hour. Three (3) drops of

phenolphthalein were added while the solution was still hot. The solution was titrated against 0.5 N HCl. The experiment was repeated two more times. The saponification number was determined using the equation below.

Saponification value = Vs = Volume (ml) of $Na_2S_2O_3$ at end point of sample determination

Vb= Volume (ml) of $Na_2S_2O_3$ at endpoint of the blank determination. (56.1 (B-S) × N of HCl) / (Gram of sample)

S = ml of hydrochloric acid at endpoint of sample
B = ml of hydrochloric acid at an endpoint using 25 ml of KOH as blank

Determination of Density of the African Baobab Seed Oil: The density of the oil was determined using a relative density bottle (R.D). The weight of the empty density bottle was determined. Water was filled into the density bottle and the weight was determined and recorded. The water was poured away and the bottle dried thoroughly. The bottle was then filled with the oil, weighed, and the weight recorded.

The relative density was determined using the equation below:

$$\text{Relative Density} = W_3\text{-}W_1 / W_2\text{-}W_1$$

W_1 = Weight of empty R.D. bottle
W_2 = Weight of R.D bottle with water
W_3 = Weight of R.D. bottle with oil sample

Determination of Viscosity of the African Baobab Seed Oil: The viscosity of the oil sample relative to that of distilled water (1.0020 cP) was determined using a Ubbelohde viscosity tube. The bigger lower arm bulb of the viscosity tube was filled with distilled water to the etched mark. The distilled water was then drawn up to fill the upper etched mark of the smaller bulb using pipette filler.

When the pipette filler was released, the time taken for the water to drop to the lower etched mark was recorded. The procedure was repeated with the oil sample, and the oil viscosity was determined using the equation below. The experiment was done in triplicate

$$V = D_s \times t_s \times 1.0020cP / D_w \times t_w$$

D_s = density of sample
t_s = time taken for the sample to flow through the Ubbelohde viscosity tube.
D_w = density of water
t_w = time taken for the water to flow through the Ubbelohde viscosity tube

Determination of Microbial Quality of Extracted Baobab Oil: In determining the microbial quality of the extracted Baobab oil, 1.0 ml of the oil was added to previously sterilized MacConkey agar. The inoculated agar was incubated at 37°C for 48 hours. The growth of organisms on the media indicated the presence of *E. coli*. The procedure was repeated for the other media, where Mannitol salt agar was used for the growth of *Staphylococcus aureus*, Cetrimide agar for *Pseudomonas* spp., Bismuth Sulphite agar for *Salmonella* spp., Sabouraud agar for Fungi and Nutrient agar for viable aerobes. However, for the fungal determination, incubation was done at 25°C for five (5) days.

Determination of Solubility of Drugs in the Excipients: For Ibuprofen, an excess amount of the drug powder was added to 1ml baobab oil (or surfactant or co-surfactant) in a test tube and kept in a shaking water bath (Fisher scientific DMS 360.LE115RG, UK) set at 50 revolutions per minute (rpm) and 37°C for 24 hours.

After 24 hours, the test tube was centrifuged (Wagtech international; C 257-120, UK) for 10 minutes at 1000 rpm to separate undissolved Ibuprofen from the supernatant. The latter was decanted into a 10 ml volumetric flask and made up to volume with the 0.1M sodium hydroxide (NaOH) solution. Using a blank solution, the absorbance of the test solution was read at a wavelength of 265nm after appropriate dilutions using a UV-Vis spectrophotometer (Jenway 7315 UK). This was repeated with two more samples. The amount of ibuprofen was calculated with the help of a calibration curve.

The same procedure was used in the determination of Furosemide at a wavelength of 272nm. For Griseofulvin, 0.1M ethanolic acid was used and at 294 nm. The solubility of Mebendazole was determined using methanol-water in 4:1 proportions and at 288nm.

Miscibility of Surfactants and Co-surfactants with the Baobab Seed Oil: Two (2) ml of the surfactants and co-surfactants (Table 5) were mixed with 2ml oil in 5ml test tubes. After shaking each thoroughly for about a minute, these were placed in test tube rack for about 24 h before visual observation for any phase separation.

Formulation of African Baobab Seed Oil Microemulsions and Construction of Ternary Phase Diagram: The composition of oil and surfactant used was based on the Lipid Formulation Classification system (LFCS), Type IIIB where the maximum amounts of oil required is 20% w/w [19, 20, 21, 22]. The seed oil, Labrasol ALF, and water (100 %w/w) were mixed in a transparent glass tube. With the aid of a magnetic stirrer, the mixture was stirred for five (5) minutes and the self-emulsifying properties of the mixture were visually observed. Emulsions that were clear and transparent, with required droplet size were considered appropriate. Different compositions **Table 7** were tried and a ternary phase diagram was constructed.

Formulation of Drug Containing Microemulsions: Baobab seed oil (15%), 75% Labrasol ALF and 10% water was considered the optimized formulation. The oil, Labrasol ALF, and water (Total = 4g) were added and magnetically stirred for 5 min to mix. An excess amount of drug (Furosemide, Griseofulvin, Ibuprofen or Mebendazole) was added to the mixture and sonicated for 30 minutes at 25°C. The mixture was centrifuged at 1000 rpm, 25℃ for 10 minutes. The supernatant was kept in glass vials protected from light. The mixture was allowed to equilibrate at ambient temperature for 24 hours and examined for signs of phase separation and precipitation prior to drug content, droplet size and transmittance analysis.

Droplet Size of Microemulsions: A quantity of 100µl of the mixture (blanks and drug containing microemulsions) was added in drops to 100ml of distilled water under moderate magnetic stirring for 5 min. One (1) ml of the mixture was taken and measured [23]. The size measurements were conducted by dynamic light scattering using the Malvern zetasizer, Nano-ZS (Zetasizer Nano ZS, Malvern Instruments, England), and data analyzed with Zetasizer software V 6.20. Measurements were done in triplicate. The Z-average and polydispersity index (PDI) were recorded.

pH of the Microemulsions: The blank microemulsion as well as that containing Ibuprofen, Furosemide, Griseofulvin and Mebendazole had the pH determined at 25℃ using a pH meter (HI 2210 HANNA instrument). All measurements were carried out in triplicate.

Percentage Transmittance of Microemulsions: Blank (1 ml) as well as drug containing microemulsions was pipetted into a 1cm path-length cuvette and their percentage transmittance determined using UV-Vis spectrophotometry at a wavelength of 475 nm. The experiment was performed in triplicate.

Drug Content in Microemulsion: Microemulsion (1 ml) was pipetted into a 10 ml volumetric flask and made up to volume with the 0.1M sodium hydroxide (NaOH) solution. Using a blank solution, the absorbance of the test solution was read at a wavelength of 265nm after appropriate dilution using a UV-Vis spectrophotometer. This was repeated with two more samples. The amount of ibuprofen was calculated with the help of a calibration curve.

The same procedure was used in the determination of Furosemide at a wavelength of 272nm. For Griseofulvin, 0.1M ethanolic acid was used and at a wavelength 294 nm. The solubility of Mebendazole was determined using methanol-water in 4:1 proportions and at 288 nm.

In-vitro **Drug Release Studies:** The USP Apparatus 2 (Erweka GmbH DT6, Germany) was used for the drug release studies with phosphate buffer solution (pH 6.8) as the medium. 900 ml of the phosphate buffer was placed in each of the six vessels of the apparatus, and the temperature equilibrated to 37 ± 0.5℃. The paddle speed was maintained at 50 revolutions per minute. Ibuprofen microemulsion (5 ml) was loaded into a SpectraPor® Float-A-LyzerG2 dialysis tube (MWCO 0.1 – 0.5 kD). This was vertically suspended in the dissolution medium. At pre-determined time intervals of 20, 40, 60, 80, 100, 120, 180, and 240 minutes, 5ml of the medium was withdrawn and replaced with an equal volume of dissolution medium. The drawn aliquot was filtered, and the filtrate made up to 10 ml with the dissolution medium in a volumetric flask. The

absorbance of the diluted filtrate was determined at 265 nm using the UV-VIS spectrophotometer. The cumulative percentage of Ibuprofen released was plotted as a function of time.

The procedure was repeated for Furosemide (272 nm), Griseofulvin (294 nm), and Mebendazole (288 nm) microemulsions.

Statistical Analysis: The data were analyzed using GraphPad Prism software (GraphPad Prism, Version 8 for Windows, San Diego, CA, USA). P values of < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION: The majority of baobab oil in literature are extracted using organic solvents such as chloroform, n-hexane, and acetone [9, 24, 25, 26, 27]. However, extraction by cold pressure preserves at best the physicochemical and bioactive properties of the extracted oils [25]. Thus, the baobab seed oil in this work was extracted by the cold pressing method.The extracted baobab seed oil had a mild and characteristic aroma (nutty) with a golden yellow colour. These characteristics conformed to literature [12]. The extracted oil is shown in **Fig. 1**.

FIG. 1: THE EXTRACTED BAOBAB SEED OIL

Quality Assessment of the Baobab Oil: For oil to be used in the food, cosmetics, and pharmaceutical industry, it must meet certain defined specifications. The oil should also be stable and free from pathogenic organisms. The parameters that were assessed are listed in **Table 1**. Of pharmaceutical importance are the saponification value, peroxide value, acid value, iodine value, and free fatty acids.

TABLE 1: THE ANALYSIS OF OIL CONSTANTS OBTAINED FROM THE BAOBAB SEEDS (n=3)

Test	Mean ± SD	Reference Standard
Moisture (%)	0.054 ± 0.01	APCC-0.1-0.5%
Protein (%)	1.43 ± 0.13	
Free Fatty Acid (%)	0.864 ± 0.24	Codex Alimentarius-< 4mg
Refractive Index	1.4667 at 27.3℃	
Acid Value (mg/g)	1.1042 ± 0.01	Codex Alimentarius-< 4mg
Density (g/ml)	0.9117	
Peroxide Value (Meq/kg)	6.25 ± 0.45	IOC-< 20meq/kg
Saponification Value (mg/g)	224.8 ± 9.53	
Iodine Value (g/100g)	14.38 ± 0.17	
Boiling point	36.3℃	
pH	4.3	
Viscosity	7.31mp	

*results are mean ± standard deviation

The saponification value is a measure of the average molecular weight (or chain length) of all the fatty acids present in the oil as triglycerides. The higher the saponification value, the lower the average chain length of fatty acids, and *vice-versa*. Practically, fats or oils with high saponification value (such as coconut and palm oil) are more suitable for soap making. The saponification value of the oil was obtained as 224.8±9.53 mg/g. This value is slightly lower than that obtained by Cissé *et. al*. (233.587±0.478) [25]. The oil is thus comparable to coconut oil (242-263), palm oil (200-205), and palm kernel oil (240-257) used for domestic and industrial purposes [28].

Detection of peroxide gives the initial evidence of rancidity in unsaturated fats and oils. It is useful for assessing the extent to which spoilage has advanced. The double bonds found in fats and oils play a role in autoxidation. Oils with a high degree of unsaturation are most susceptible to autoxidation. The peroxide value requirement by the Codex Alimentarius and the International oil company (IOC) should be less than 20 meq/Kg. Based on the

value obtained, the extracted oil is not rancid and therefore could last for an appreciable period.

Iodine value is used as a measure of the degree of unsaturation of oils and fats. The results are normally expressed as the number of grams of iodine absorbed by 100 g of oil or fat. Iodine numbers are often used to determine the amount of unsaturation in fats, oils and waxes. In fatty acids, unsaturation occurs mainly as doubles bonds which are very reactive towards halogens, the iodine in this case. Thus, the higher the iodine value, the more unsaturationis present in the fat. The value obtained for the extracted oil was 14.38±0.17 g/100g. This value is far less than that obtained by Cissé and colleagues (99.113±0.528 mg/100g) [25]. The oil in this case contains less double bonds and hence not too prone to oxidative hydrolysis. This quality is confirmed by the value of the free fatty acids. In terms of oil quality, the free fatty acid value of oil is an important qualitative parameter. The acid content of edible fats is given by the quantity of free fatty acids deriving from the hydrolytic rancidity of triglycerides. The lower the free fatty acid value, the less rancid the oil. The IOC requires the free fatty acid value to be less than 4 mg. The baobab seed oil therefore meets the requirement. All the oil constants assessed were comparatively lower than those obtained by Cissé *et al*.

Oils for pharmaceutical use should be free from disease causing pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi* and Fungi. There was no growth in any of the media to suggest the presence of pathogens **Table 2**. This results show that the extracted oil is safe for human consumption. Analyses of the oil constants and the microbial assessment revealed that the oil is suitable to be used as a pharmaceutical excipient.

TABLE 2: MICROBIAL QUALITY ASSESSMENT OF OIL FROM UNTREATED SEEDS OF BAOBAB

Selective medium	Results	Inference
Mannitol Salt Agar	No growth observed	*Staph. aureus* absent
Nutrient Agar	No growth observed	No viable aerobic count
Cetrimide Agar	No growth observed	*Pseudomonas spp.* Absent
Bismuth Sulphite Agar	No black colonies observed	*Salmonella spp.* Absent
Sabouraud Agar	No growth observed	Fungi Absent
MacConkey Agar	No growth observed	*Escherichia coli* Absent

Selection of Excipients for the Microemulsion: The choice of excipients for the formulation of microemulsions depends on the solubility of the active pharmaceutical ingredient in the excipient as well as the miscibility of the various components. The results of the solubility of the drugs (Furosemide, Griseofulvin, Ibuprofen and Mebendazole) in the extracted oil, surfactants and co-surfactants are shown in **Table 3**. Ibuprofen was highly soluble in all the excipients with the exception of the baobab oil. Furosemide was highly soluble in Transcutol® and Labrasol® ALF while both Griseofulvin and Mebendazole were appreciably soluble in Labrasol® ALF.

TABLE 3: SOLUBILITY OF APIs IN SOME SURFACTANTS AND CO-SURFACTANTS (mg/ml) (n=3)

Drugs Excipients	Ibuprofen	Furosemide	Griseofulvin	Mebendazole
Baobab oil	250.83±63.48	7.17±3.68	4.97±1.64	2.7±1.08
Transcutol®	Highly soluble	Highly soluble	61.57 ± 7.27	12.51 ± 8.1
Labrasol	Highly soluble	18.61 ± 1.28	31.12 ± 7.42	11.94 ± 1.14
Propylene glycol	Highly soluble	6.32 ± 2.17	19.51 ± 4.04	3.85 ± 0.16
Tween 80	Highly soluble	5.32 ± 1.75	28.83 ± 3.96	3.13 ± 0.99
Tween 20	Highly soluble	0.52 ± 0.04	33.70 ± 6.97	6.45 ± 0.14
Labrasol® ALF	Highly soluble	Highly soluble	925.3 ± 29.67	59.4 ± 18.8
Labrafil® M 2125CS	Highly soluble	42 ±5.67	23± 8.75	4.7 ±1.45
Labrafil® M 1944CS	Highly soluble	329.6 ± 6.87	60 ± 12.76	18.1 ± 4.9

*results are mean ± standard deviation

In the formulation of microemulsions, solubility alone cannot be the criterion for selecting the excipients. Miscibility of the selected components is also important. The baobab oil was miscible with Labrasol® ALF (caprylocaproylmacrogol-8 glycerides EP), Labrafil® M 2125CS (Linoleoyl

macrogol-6 glycerides EP) and Labrafil®M 1944CS (Oleoyl macrogol-6 glycerides EP). These surfactants are oily in nature even though they are soluble in water. The hydrophobic portions of the surfactants are similar in nature to the triglycerides in the baobab oil hence their miscibility. Labrifil®M 2125CS and Labrafil® M 1944CS emulsify in aqueous medium to form coarse emulsions and not microemulsions. Thus, even though they were miscible with the baobab oil and the drugs had appreciable solubility in them, the Labrasol® ALF was selected as the surfactant for the preparation of the microemulsions.

Ternary Phase Diagram: The construction of a phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed and the ratios thereof. A ternary phase diagram of oil, surfactant, and water without the drug (blank) was thus prepared by considering the droplet size of the resulting mixture. Microemulsion delivery systems produce transparent and isotropic mixtures with droplet sizes less than 300 nm [29]. Type IIIB microemulsion of the Lipid Formulation Classification System (LFCS), an oil-in-water emulsion, was aimed at this work. In this type, a maximum of 20% oil component is permitted. Some of the ratios of the components of the microemulsions investigated are shown in **Table 4,** with the developed ternary phase diagram shown in **Fig. 2**.

TABLE 4: PERCENTAGE TRANSMITTANCE (475nm), DROPLET SIZE AND POLYDISPERSITY INDEX OF BLANK MICROEMULSIONS (n=3)

Composition Water/oil/surfactant	ID	% Transmittance	Droplet size (nm)	Polydispersity index (PDI)
5/10/85	A	68.97±0.20	174.6±4.2	0.301±0.017
5/15/80	B	66.99±0.15	237.5±2.6	0.504±0.020
5/25/70	C	63.09±0.03	203.8±1.2	0.480±0.018
5/20/75	D	62.09±0.17	224.3±9.7	0.528±0.120
6/16/78	E	64.69±0.20	297.2±3.2	0.510±0.113
10/5/85	F	71.72±0.60	203.4±1.1	0.401±0.103
10/15/75	G	66.11±0.06	278.1±3.8	0.523±0.012
15/10/75	H	68.48±1.00	282.3±4.4	0.540±0.011
8/27/65	I	60.12±0.80	237.4±12.4	0.570±0.022

*results are mean ± standard deviation

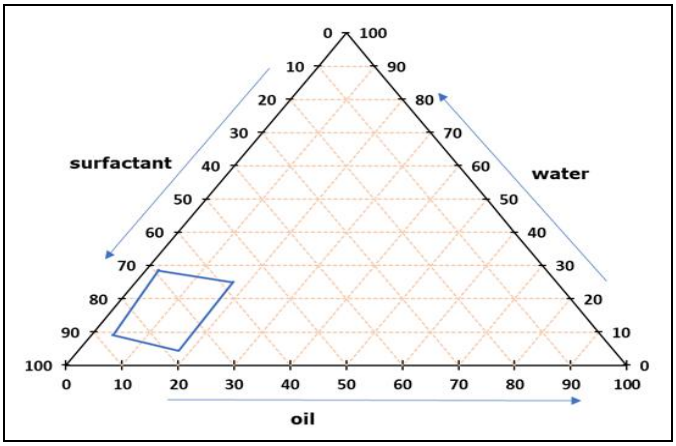

FIG. 2: TERNARY PHASE DIAGRAM OF WATER, BAOBAB SEED OIL AND LABRASOL® ALF (SURFACTANT)

The amount of light that passes through a medium without reflection, refraction, and diffraction depicts its transparency. Thus, the transmittance of the blank microemulsions was assessed. The higher the transmittance, the clearer, and more transparent the microemulsion. There was no correlation between the ratio of components and the droplet size but generally, the smaller the size, the smaller the polydispersity index. However, amount of oil beyond 20% produced droplets that were beyond the required size range (data not shown). It was the objective of this work to incorporate as much oil as possible to achieve the desired product. All the products in **Table 4** had the desired droplet size of less than 300 nm. However, it was observed that an increase in the amount of oil decreased the percentage transmittance and hence reduced transparency. This may be due to the increased hydrophobic constituents in the mixture. Compositions A, B, F, G and H had comparatively high percentage transmittance. Out of them, B and G contained the highest amount of oil. Excipients used for the delivery of drugs as well as formulated products should not be toxic systemically and to tissues of the body. The excipients used are generally regarded as safe (GRAS) by the U.S. FDA and have been included in a great number of

formulations for various routes of administration [30]. Surfactants have been used extensively as drug solubilizers by either a direct co-solvent effect or by uptake into micelles [31]. Strickley concluded that the commonly used surfactants such as cremorphors, polysorbates, Labrafils, *d*-α-tocopherol polyethylene glycol 1000 succinate (TPGS), and Span 20 are proven worthwhile, but they have limitations. It is, however, known in the literature that some of them have haemolytic effect and causes gastric irritation [32]. It is therefore paramount that the amount of surfactant is reduced to the barest minimum. A high amount of oil required for adequate solubilization of the APIs for optimal microemulsion formulation is obtainable in compositions B and G. The high amount of surfactant used with the attendant anticipated gastric irritation is a hindrance for the selection of B, though the transmittance is similar to that of composition G. Emulsification efficiency for the optimal formulation is most appropriate with composition G. This composition does have, not only droplet size within the acceptable nanometric range but also a high percentage transmittance and comparatively low surfactant involvement. This necessitated the choice of composition G for further work which was scaled up to 10 ml for the API-microemulsion formulations.

Formulation of API-microemulsions: The maximum equilibrium amount of a drug in a formulation is of utmost importance since it dictates the maximum dose that can be incorporated in a unit dosage form [33]. The most important parameter was the amount of the active pharmaceutical ingredient (API) that could be incorporated into the microemulsion. Furosemide (antidiuretic), Griseofulvin (antifungal), Ibuprofen (a non-steroidal anti-inflammatory agent) and Mebendazole (antihelminthic) which are poor water-soluble drugs, were incorporated into the blank microemulsion containing 15% baobab oil, 75% Labrasol® ALF, and 10% water.

The role of surfactants in emulsions is to reduce the interfacial tension (between oil and water) and adjust the spontaneous curvature of the interface so as to enhance the dispersion process and provide a flexible film that can easily cover the lipid core [6]. The amount of each drug that was solubilized, droplet size, polydispersity index, pH, percentage transmittance, and the effect of dilution are indicated in **Table 5**. Labrasol® ALF is obtained by the polyglycolysis of medium-chain triglycerides from coconut oil and PEG 400 and has been used to formulate 20 mg of the sparingly water-soluble piroxicam (Piroflam-Li) [33]. This drug belongs to the same class as Ibuprofen. The baobab oil microemulsion was able to solubilize 450±12 mg/ml of Ibuprofen. Hauss in his review on oral lipid-based formulations, stated that the total daily drug dose administered from simple solutions to multi-excipient drug delivery systems ranges from less than 0.25 µg to greater than 2000 mg. The amount of drug contained in a unit dose capsule product ranges from 0.25 µg to 500 mg, and for oral solution products, from 1 µg/ml to 100 mg/ml[34]. This indicates that the solubilized amounts of Ibuprofen, Furosemide (30±6mg/ml), Griseofulvin (30±7 mg/ml), and Mebendazole (25±3 mg/ml) are appreciable **Table 5**.

TABLE 5: PARAMETERS ASSESSED FOR THE FORMULATED API-MICROEMULSIONS AT ROOM TEMPERATURE (n=3)

Drug product	Amount of drug solubilised (mg/ml)	% Transmittance	Droplet size (nm)	Polydispersity index (PDI)	pH	Dilution effect (10X)
Blank (10/15/75)		66.11±0.06	203.4±2.3	0.414±0.008	5.8±0.2	No phase seperation
Ibuprofen	450±12	68.42±0.01	190.2±12	0.430±0.004	4.3±0.1	No phase seperation
Furosemide	30±6	68.71±0.03	198.8±2.4	0.440±0.075	4.0±0.5	No phase seperation
Griseofulvin	30±7	68.60±0.06	198.6±1.8	0.399±0.005	4.7±0.8	No phase seperation
Mebendazole	25±3	64.58±0.01	350.5±3.6	0.510±0.017	4.5±0.1	No phase seperation

*results are mean±standard deviation

There was a slight reduction in the droplet size for Ibuprofen, Furosemide, and Griseofulvin compared to the blank. This observation could be a result of molecular interactions of the drugs with the formulation excipients. However, the droplet size of the mebendazole microemulsion was significantly higher. The higher the droplet size, the greater the polydispersity index signifying a greater variability in droplet sizes. The higher the droplet size, the lower the percentage transmittance and

hence the decrease in transparency. All the formulations had a lower pH compared to the blank. No phase separation was observed when the microemulsions were diluted ten-fold **Table 5**.

Stability of API-microemulsions: The stability of the drug formulated microemulsions was assessed at room temperature and 40 °C for a period of four months. The outcome is given in **Tables 6** and **7**.

TABLE 6: STABILITY ASSESSMENT OF API–MICROEMULSIONS AFTER FOUR MONTHS OF STORAGE AT ROOM TEMPERATURE (n=3)

Drug product	Amount of drug solubilised (mg/ml)	% Transmittance	Droplet size (nm)	Polydispersity index (PDI)	pH	Dilution effect (10X)
Blank (10/15/75)		66.11±0.06	203.4±2.3	0.432±0.006	5.6±0.1	No phase seperation
Ibuprofen	453±8.0	68.42±0.03	188.2±2.4	0.379±0.081	4.1±0.1	No phase seperation
Furosemide	32±3.0	68.71±0.01	196.8±2.2	0.400±0.162	4.3±0.5	No phase seperation
Griseofulvin	29±5.0	68.60±0.01	198.2±1.2	0.403±0.201	4.9±0.5	No phase seperation
Mebendazole	26±3.0	64.58±0.03	350.8±4.6	0.622±0.141	4.4±0.3	No phase seperation

*results are mean ± standard deviation

TABLE 7: STABILITY ASSESSMENT OF API-MICROEMULSIONS AFTER FOUR MONTHS OF STORAGE AT 40°C (n=3)

Drug product	Amount of drug solubilised (mg/ml)	% Transmittance	Droplet size (nm)	Polydispersity index (PDI)	pH	Dilution effect (10X)
Blank (10/15/75)		68.05±0.03	280.0±2.0	0.440±0.006	6.1±0.1	No phase seperation
Ibuprofen	455±6	69.02±0.01	187.2±0.4	0.410±0.010	4.9±0.1	No phase seperation
Furosemide	31±4	68.80±0.03	201.8±2.8	0.511±0.190	4.5±0.3	No phase seperation
Griseofulvin	28±2	68.60±0.02	188.2±1.1	0.408±0.002	5.8±0.6	No phase seperation
Mebendazole	26±6	64.60±0.01	355.8±2.2	0.612±0.133	5.7±0.2	No phase seperation

*results are mean ± standard deviation

Though slight changes in all assessed parameters of API incorporated microemulsions occurred, particularly at 40°C storage, instability could not be visually observed in the formulations. It was observed that the droplet sizes did not change significantly ($p>0.05$) to affect formulation transparency. There was a significant change ($p<0.05$) in pH between storage at room temperature and 40°C for the blank, Griseofulvin, and Mebendazole microemulsions. There was also no phase separation and precipitation, even though there were slight changes in the transmittance values. Upon dilution with excess water, there were no phase separation and precipitation of the drugs from the microemulsions. These proved that the microemulsions were very stable at the storage temperatures.

Release of Drugs from Microemulsions: The *in-vitro* release of drugs from the microemulsion formulations was conducted using phosphate buffer (pH 6.8) as a medium which mimicks the intestinal system as the site of absorption of most substances due to its large surface area. The British Pharmacopoeia dissolution standard requires that not less than 70% of immediate-release (I R) drugs should be released in 45 minutes of study [35]. The United States Pharmacopoeia standard recommends that in 30 minutes of the dissolution process, not less than 80% release of drug should be achieved from such I R compounds [36]. The results of the release studies are shown in **Fig. 3**.

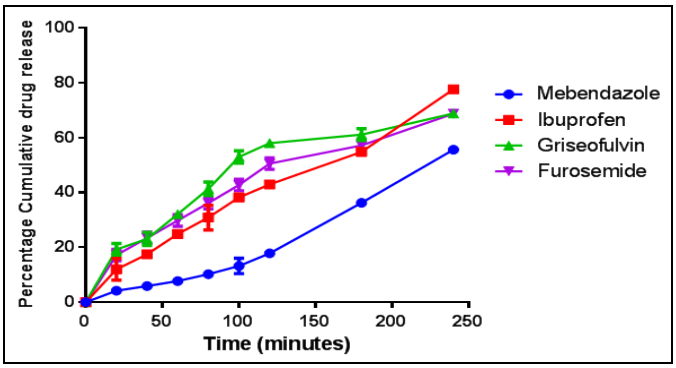

FIG. 3: PERCENTAGE CUMULATIVE RELEASE OF FUROSEMIDE, GRISEOFULVIN, IBUPROFEN AND MEBENDAZOLE FROM THE MICROEMULSIONS

Only 17% of Ibuprofen, 23.5% of Furosemide, 23% of Griseofulvin and 5.9% of Mebendazole were analyzed to have dissolved after 45 minutes of the dissolution study. This is clearly well below standard requirement by both the BP and USP specifications for immediate-release products. Over the study time period of four (4) hours, Ibuprofen showed the highest percentage cumulative release from the microemulsion. Griseofulvin and Furosemide had almost the same percentage

cumulative releases within the four hour study. The release characteristics of these APIs from the microemulsions suggest a retarded dissolution characteristics **Fig. 3**.

Contrary to the observation in this study, Ibuprofen dissolution of more than 90% in 30 minutes (satisfying immediate release mode in accordance with USP standard) was achieved in a similar work using phosphate buffer (pH 7.4) [37]. The Ibuprofen-developed SEDDS in that work employed an alternative oil phase (Labrafac). This oil is mainly composed of a mixture of medium chain triglycerides which favours complete solubilization of the API. The prolonged release characteristics (77% in 4 hours) noticed with the baobab oil matrix could emanate from the presence of a large proportion of saturated medium chain fatty acids which could not support the immediate release of the drug. The dissolution of Ibuprofen is also pH dependent since it is a weak acid. Another research conducted a dissolution study of Ibuprofen from liquid SMEDDS using a phosphate buffer of pH 7.2 and achieved 80% release within 30 minutes of the dissolution process [38]. Thus, the pH of 6.8 did not provide the required release of Ibuprofen from the prepared microemulsion.

In a dissolution study on the release rate of Griseofulvin from nanocrystal formulation, drug release of over 80% in 90 minutes was observed in 4% sodium lauryl sulphate solution [39]. A cumulative release of 68.86% of Griseofulvin was observed in 4 hours for the prepared microemulsion in this study using phosphate buffer (pH 6.8). The type and pH of the medium and droplet or particle size affect the dissolution characteristics of drugs. Thus, sodium lauryl sulphate, a surface-active agent, enhanced the dissolution of the Griseofulvin from the nanocrystals.

Another study determined the dissolution profile of Furosemide from prepared SNEDDS using oleic acid as the oil phase, tween 80, and propylene glycol (PG) as surfactant and co-surfactant, respectively. A 100% release of Furosemide was observed in 120 minutes [40]. It is noted that the outcome of that work was consistent with a research report which asserted that oleic acid has a high capacity and large dissolution propensity for dissolution of Furosemide from SNEDDS formulation [41]. A cumulative Furosemide release of 68% in 240 minutes was analyzed in this baobab oil study. The components of an emulsified system contribute to the release pattern of drugs from such systems. Propylene glycol is a hydrophilic cosurfactant that aids the solubilization of poorly soluble compounds. Thus, its inclusion contributed immensely to the total release of 100 % in 2 hours as compared to the release of 68 % in 4 hours. Additionally, the comparatively lower droplet size of the SNEDDS (88.9 ± 4.9 nm) in that report enhanced the high dissolution rate compared to the microemulsion (198.8 ± 2.4 nm) under study.

On enhancing the bioavailability of Mebendazole, pH is a major contributing factor. Findings from a conducted dissolution study in a buffer of pH 2.5 saw a significant enhancement of dissolution of Mebendazole of about 93% as compared to the release of a marketed Mebendazole formulation prepared in distilled water [42]. The prepared Mebendazole microemulsion showed a cumulative release of 55% in the phosphate buffer of pH of 6.8 in the 4 hour period of study. The pH of the medium is seen to significantly influence the dissolution characteristics of the drug.

The release characteristics of the four drugs from the microemulsions were evaluated statistically as shown in **Fig. 4**.

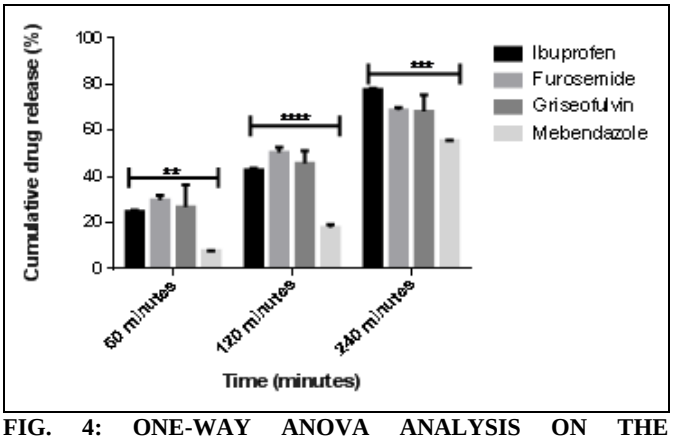

FIG. 4: ONE-WAY ANOVA ANALYSIS ON THE CUMULATIVE DRUG RELEASE OF THE APIs AT DIFFERENT TIME POINTS (60,120 AND 240 MINUTES). VALUES ARE MEAN ±SD. ****P< 0.0001,* P≤0.001,** P≤0.01**

Ibuprofen, Mebendazole and Griseofulvin belong to class II of the BCS. Comparatively, there was a significant difference between their cumulative release profiles after 4 hours **Fig. 4**. This could stem from their different physicochemical

properties and varying interactions with the components of the matrix of the microemulsion. Frusemide, belonging to BCS class IV has the most difficult aqueous solubility, and thus its cumulative release was also significantly different (P<0.0001) from the other three APIs.

CONCLUSION: The oil was successfully extracted from the Baobab seeds by cold pressing. Microbial quality assessment of the oil indicated it was free from pathogens and hence safe for human consumption. Analysis of the oil constants revealed that the oil was fit to be used as a pharmaceutical excipient for the formulation of microemulsion. The formulated baobab seed oil microemulsion showed good potential as a vehicle for solubilizing and delivery of poorly water-soluble drugs, such as Furosemide, Griseofulvin, Ibuprofen and Mebendazole.

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