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Evaluation of the Emulsifying Property of *Detarium Microcarpum* Gum in Ibuprofen Emulsion Formulations

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ABSTRACT

An emulsion is a mixture of two or more immiscible liquids that adopt a macroscopic homogeneous aspect and a microscopic heterogeneous one under specific transforming processes. In an emulsion, one liquid is dispersed in the other and an emulsifying agent is usually added to stabilize it i.e., to prevent the immiscible layers of the mixtures from separating. In this study, the emulsifying property of *Detarium microcarpum* gum (DMG) in ibuprofen emulsion formulations was evaluated. DMG was obtained from the seeds of the plant through acetone precipitation of the filtrate obtained from distilled water maceration of powdered *Detarium microcarpum* seeds. Six Ibuprofen emulsions were formed using tragacanth, DMG or a combination the two as the emulsifying agent. Some of the formulations contained methyl paraben, propyl paraben, vanilla and tartrazine. Physicochemical properties such as pH, viscosity and the type of the emulsions, were evaluated. The pH of the emulsions ranged from 4.5 to 4.8 on the first day and 4.0 to 5.6 on day 15. The viscosity at 28ºC ranged from 1200 to 5400 mPas on day 0 and 1370 to 5400 mPas on day 15. The emulsions were of the oil-in-water type and they exhibit shear thinning behaviour. DMG was used to prepare ibuprofen emulsions with good physicochemical properties that were comparable to those produced using tragacanth as the emulsifying agent.

KEYWORDS: Detarium *microcarpum* gum, tragacanth, emulsion, emulsifying agent, ibuprofen, viscosity

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INTRODUCTION

Ibuprofen is a drug that is utilized in the management and treatment of inflammatory diseases, rheumatoid disorders, mild to moderate pain, fever, dysmenorrhea, and osteoarthritis. It is also available as an over-the-counter medication for pain, usually mild. It belongs to the class of anti-inflammatory drugs called non-steroidal anti-inflammatory drug (NSAID) and it is available as a non-prescription drug for treatment of mild pain[1, 2]. Ibuprofen used at a low dose is equally efficacious as aspirin and paracetamol in treating pain and other over the counter needs[3]. It is a non-selective inhibitor of cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2)[4]. Ibuprofen is nearly insoluble in water and its formulation as emulsion will improve its solubility and bioavailability[5].

An emulsion is a two-phase system composed of two immiscible liquids, in which the dispersed phase is finely and uniformly dispersed as globules throughout the continuous phase[6]. Macroscopically, emulsion appears homogeneous but microscopically they appear heterogeneous[7]. Emulsions are prepared to enhance drug solubility, drug stability, drug action, taste, and appearance[6]. Emulsions are classified into oil-in-water, water-in-oil or multiple emulsion such as oil-in-water-oil and water-in-oil-in-water[4, 8]. Emulsions are thermodynamically unstable systems, therefore, emulsifying agents are often included in their preparations to stabilize them[9, 10]. The emulsion is stabilized by the formation of a thin

film of the emulsifying agent around the globules of dispersed phase[11]. Emulsifying agents have hydrophilic and lipophilic portions in a molecule, therefore, they are amphiphilic molecules[10]. The inclusion of an emulsifying agent or agents is necessary to facilitate actual emulsification during manufacture and also to ensure emulsion stability during the shelf life of the product. Emulsifiers maintain the stability of the emulsions by forming barriers around the dispersed droplets, which prevent them from coalescing. The mechanism of barrier formation is determined by the properties of the emulsifier and includes electrostatic repulsion, creation of a 'bound' water layer, and steric hindrance[12]. A stable emulsion is one in which there is a uniform distribution of the dispersed globules throughout the continuous phase[13]. Regardless of its morphology and target use, one of the main challenges faced by the emulsion formulator is to preserve the physical stability of the emulsified system. Instability in emulsions include creaming, droplet aggregation (or flocculation), Ostwald ripening, and droplet coalescence[14, 15].

Emulsifying agents are classified into synthetic and semisynthetic surface active agents, naturally occurring materials and their derivatives and finely divided solids. Synthetic and semisynthetic surface active agents can be grouped into anionic, cationic, non-ionic and amphoteric surfactants based on their ionization in aqueous solutions. Naturally occurring materials and their derivatives include polysaccharides, semisynthetic polysaccharides and sterol-containing substances. Finely divided solids include montmorillonite clays (such as bentonite and aluminium magnesium silicate) and colloidal silicon dioxide[8].

Polysaccharides are abundant biopolymers and widespread in food colloids. Because they are large molecules, their adsorption is a much slower process than for smaller surface-active agents. However, given the proper conditions that make it possible to get them all at the interface, they may provide superior stability against aggregation due to a strong steric repulsion with mainly entropic contributions[15]. Polysaccharides acts as emulsifying agent for oil-in-water emulsions by forming a strong multimolecular film round each oil globule and thus coalescence is retarded by the presence of hydrophilic barrier between the oil and water phases. Examples include acacia, pectins, galactomannans, and modified starches and celluloses[8, 16, 17].

Detarium microcarpum gum (DMG) is a polysaccharide extracted from *Detarium microcarpum*, Guill. and Perr. (Fam. Fabaceae) seeds[5]. *Detarium microcarpum* plant is indigenous to Africa. It grows in the wild in many countries in Africa, especially in savannah regions. Its leaves and fruits are usually utilized as food and as folk medicine[18]. The French call *Detarium microcarpum* tree petit détar, the English call it sweet detar, sweet dattock or tallow tree, while the Igbo people of South East, Nigeria call it ofo[19]. It exhibits peculiar characteristic behaviour in hot water, showing various degrees of the viscoelastic properties. It has been reported to contain a high concentration of water-soluble non-starch polysaccharide, which is mainly xyloglucan[20]. *Detarium microcarpum* seeds are produced in large quantity in some parts of Nigeria, though they only serve as soup thickeners. The inadequate utilization of the seeds drives the quest for alternative ways of using it especially as pharmaceutical raw material or excipients[5]. Some studies were carried out on the use of *Detarium microcarpum* gum as pharmaceutical excipient such as suspending agent in the formulation of Ibuprofen suspensions[5], as the matrix polymer in sustained release matrix tablets of metformin[20] and mucoadhesive polymer in mucoadhesive albendazole tablets[19].

Investigation into cheaper sources of emulsifying agents could greatly reduce the cost to pharmaceutical industries. This study was done to assess the emulsifying property of *Detarium microcarpum* gum in ibuprofen emulsion formulations.

MATERIALS AND METHODS

Materials

Ibuprofen (Kores Chemical, India), arachis oil, *Detarium microcarpum gum*, tragacanth, glycerol (Merck Schuchardt, Germany), methyl paraben (Central Drug House, India), propyl paraben (Kermel, India), Tartrazine (BDH, England) and vanilla flavor (Merck Schuchardt, Germany).

Extraction of *Detarium microcarpum* gum (DMG)

The method of Okafo *et al*[5] was used. Dried *Detarium microcarpum* seeds were pulverized into powder using a manual blender. A 150 g quantity of the powder was macerated with 1.5 L of distilled water for 24 h. A 300 µm sieve was used to filter it and the filtrate (800 ml) was precipitated with equal volumes of acetone. The crude gum was filtered and 100 ml of acetone was used to wash it twice. It was filtered and dried in an oven at 40°C for 6 h. The gum was kept in a tightly closed container till needed.

Evaluation of DMG

Flow rate and angle of repose

The retort stands with a funnel clamped 7cm above a flat surface was used. Twenty grams (20 g) of the gum was poured into the funnel with its orifice closed. The orifice was opened to enable the granules flow onto a flat surface to form a heap. The time it took for the granules to flow out entirely from the funnel was noted. The diameter and height of the cone formed were measured. The flow rate and angle of repose were calculated using equation 1 and 2 respectively[21].

$$Flow\ rate = \frac{Weight\ of\ gum\ (g)}{Time\ (s)} \qquad 1$$

$$Tan\ \theta = \frac{2h}{d} \qquad 2$$

Where θ = angle of repose, h = height of cone and d = diameter of the cone

Bulk density

Twenty grams (20 g) of DMG was poured into a 100 ml graduated cylinder and the occupied volume (bulk volume) was noted. Equation 3 was used to calculate the bulk density[22].

$$Bulk\ density = \frac{weight\ of\ gum\ (g)}{bulk\ volume\ (ml)} \quad 3$$

Tapped density

The graduated cylinder that contained the gum was tapped 100 times from a height of 20 mm and the occupied volume (tapped volume) was noted. Equation 4 was used to calculate the tapped density[22].

$$Tapped\ density = \frac{weight\ of\ gum\ (g)}{Tapped\ volume\ (ml)} \quad 4$$

Carr's index

This was derived using equation 5:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}}\ X\ 100 \quad 5$$

Hausner ratio

This was derived using equation 6

$$Hausner\ ratio = \frac{\text{Tapped density}}{\text{bulk density}} \quad 6$$

Preparation of ibuprofen emulsion using *Detarium microcarpum* gum

Six ibuprofen emulsion formulations were prepared by wet gum method according to the formula in Table 1. A primary emulsion was prepared using oil:water:gum ratio of 4:2:1. The required quantities of ibuprofen, glycerol, methyl paraben, propyl paraben, vanilla, tartrazine and more distilled water were properly mixed in a mortar with the respective primary emulsions. The emulsions were poured into respective calibrated bottles and the volumes made up to 50 ml mark with distilled water. They were shaken properly and labelled.

Table 1. Composition of ibuprofen formulations EM1-EM6

Ingredients	EM 1	EM2	EM3	EM 4	EM 5	EM 6
Ibuprofen (g)	1	1	1	1	1	1
Arachis oil (ml)	12	12	12	12	12	12
Detarium microcarpum gum (g)			1.5	3	3	3
Tragacanth (g)		3	1.5			
Glycerol (ml)	2.5	2.5	2.5	2.5	2.5	2.5
Methyl paraben (g)					0.05	0.05
Propyl paraben (g)					0.02	0.02
Vanilla flavor						QS
Tartrazine						QS
Distilled water (ml) to	50	50	50	50	50	50

Physical appearance

Organoleptic properties like colour, taste and odour were observed. Phase separation of the emulsion was assessed by visual observation[23].

Physiochemical properties

These include pH and viscosity.

Determination of pH of the emulsions

The pH value of the emulsions was determined using a digital pH-meter (Hanna pH-meter, India) [24, 25].

Determination of viscosity of the emulsions

The viscosity of the emulsions was measured at a temperature of 28ºC using spindle 3 of a Brookfield viscometer (NDJ-5S Digital viscometer, Shanai Nirun Intelligent Technology Co. Ltd. China) at 6, 12, 30 and 60 rpm[26, 27].

Microbial growth

This was determined by checking the pH on the first and final day of the research. Presence of bacteria causes change in pH in the aqueous phase[8].

Determination of emulsion type

The dilution test and dye test methods were used to evaluate the emulsion type. For the dilution test, 0.1 g of the emulsion was transferred respectively into three different beakers. A 2, 5 and 10 ml quantity of distilled water was transferred into the respective beakers and mixed properly with the emulsions. The appearance of the diluted emulsions were observed and recorded. For the dye test, sample of the respective emulsions were mixed with scarlet red dye and viewed using a light microscope[6, 26].

RESULTS AND DISCUSSION

Characterization of *Detarium microcarpum* Gum

The gum has poor flow property as shown by the result on Table 2

Table 2. Micromeritics of *Detarium microcarpum* Gum

Bulk Density	Tapped Density	Carr's index	Hausner ratio
0.29 mg/mL	0.47mg/mL	38.29%	1.62

Evaluation of Ibuprofen Emulsion

Physicochemical Properties of Emulsion

***Organoleptic Properties*:** Microbial contamination of emulsions can produce adverse changes in their physicochemical properties such as production of gas, colour and odour changes, hydrolysis of fats and and breaking of the emulsion[8]. The odour, colour and physical appearance of the emulsions are shown in Table 3. The odours of emulsion formulations EM 1 to EM 5 were characteristic, but emulsion formulation EM 6 had a pleasant odor as a result of the vanilla flavour that was added. EM1 had a clear coloration, EM 2 had a creamy coloration, EM3-EM5 had brown coloration as a result of the addition of DMG. EM6 had a deep orange coloration, as a result of the addition of tartrazine, a colouring agent. The colours of formulations EM1 and EM2 changed from colourless and cream respectively to light brown after four weeks of storage. This may be due to microbial degradation of the products. The formulations were stable except EM2 that creamed but was easily overcome by shaking the bottle lightly. This is undesirable because it might lead to the patient not taking the right dose, if not shaken properly.

Table 3: Organoleptic properties of ibuprofen emulsion formulations EM1 to EM6 on day 0 and day 28

Formulations	Day 0			Day 28		
	Odor	**Color**	**Appearance**	**Odor**	**Colour**	**Appearance**
EM1	Characteristic smell of arachis oil	Colourless	Good	Characteristic smell of arachis oil	Light brown	Good
EM2	Characteristic smell of arachis oil	Cream	Fair	Characteristic smell of arachis oil	Light brown	Fair
EM3	Characteristic smell of arachis oil	Light brown	Good	Characteristic smell of arachis oil	Light brown	Good
EM4	Characteristic smell of arachis oil	Light brown	Good	Characteristic smell of arachis oil	Light brown	Good
EM5	Characteristic smell of arachis oil	Light brown	Good	Characteristic smell of arachis oil	Light Brown	Good
EM6	Pleasant smell of vanilla	Orange	Good	Pleasant smell of vanilla	Orange	Good

pH: As shown in Figure 1, the pH of the emulsions ranged from 4.5 to 5.9. Ibuprofen is an acidic drug and from the pH is can be seen and observed that the drug's acidic pH had a direct effect on the formulations. The pH changed slightly in EM3, and EM4, significantly in EM1 and EM2 and was stable in EM5 and EM6 after 14 days. This showed that EM5 and EM6 were the most stable. This is likely due to the addition of methyl paraben and propyl paraben, which deterred their degradation by microbial organisms, leading to stability of the emulsions at room temperature. Microbial contamination of emulsions can affect their physicochemical properties adversely, causing pH changes in the aqueous phase and breaking of the emulsion[8]. It was also observed that the emulsions prepared with DMG were more stable than those prepared without DMG.

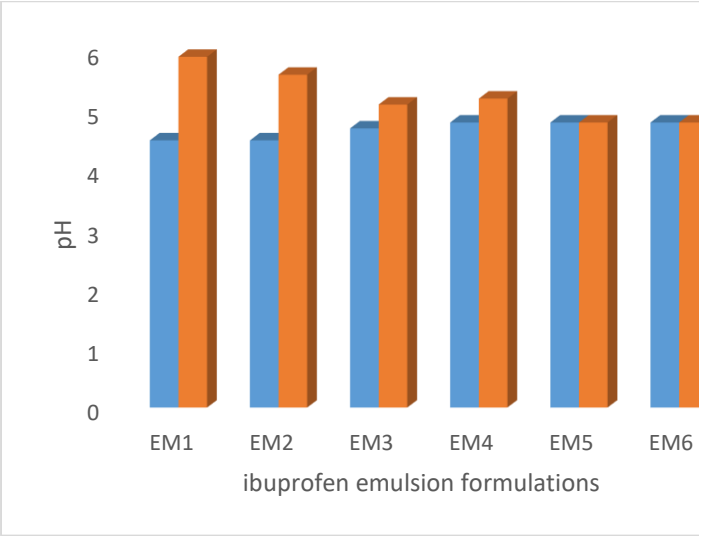

Figure 1: pH of ibuprofen emulsion formulations on day 0 and day 14

Emulsion type: The dilution of the emulsions with distilled water did not produce any physical instability, therefore the emulsions were O/W in nature. Dilution test is based on the solubility of continuous phase of emulsion. Water is used to dilute oil-in-water emulsion while oil is used to dilute water-in-oil emulsion[26, 28]. The dye-solubility test also confirmed that the emulsions are oil-in-water. The oil globules (dispersed phase) were coloured red and the continuous phase (water) were colourless when emulsion samples were viewed using a microscope. Water-soluble dyes dissolve in the aqueous phase and oil soluble dyes dissolve in the oil phase[26, 29].

Viscosity: The emulsions' viscosity was between 1300 and 2200 mPas on day 0. EM3 to EM6 maintained the same viscosity after 2 weeks of storage, while EM1 to EM2 changed slightly in viscosity.

Viscosity curves (Figures 3) indicate that the formulations are shear thinning, i.e. their viscosity decrease with increasing shear stress. There was a decrease in viscosity shown across all the formulations. This is as a result of the nature of the formulations being gums and mucilages. Gums and mucilages decrease in viscosity upon storage[30, 31]. Although there was decrease, it was slight and not significant in formulation EM5 and EM6. It was very evident and significant in EM1 and EM2, while moderate in EM3 and EM4.

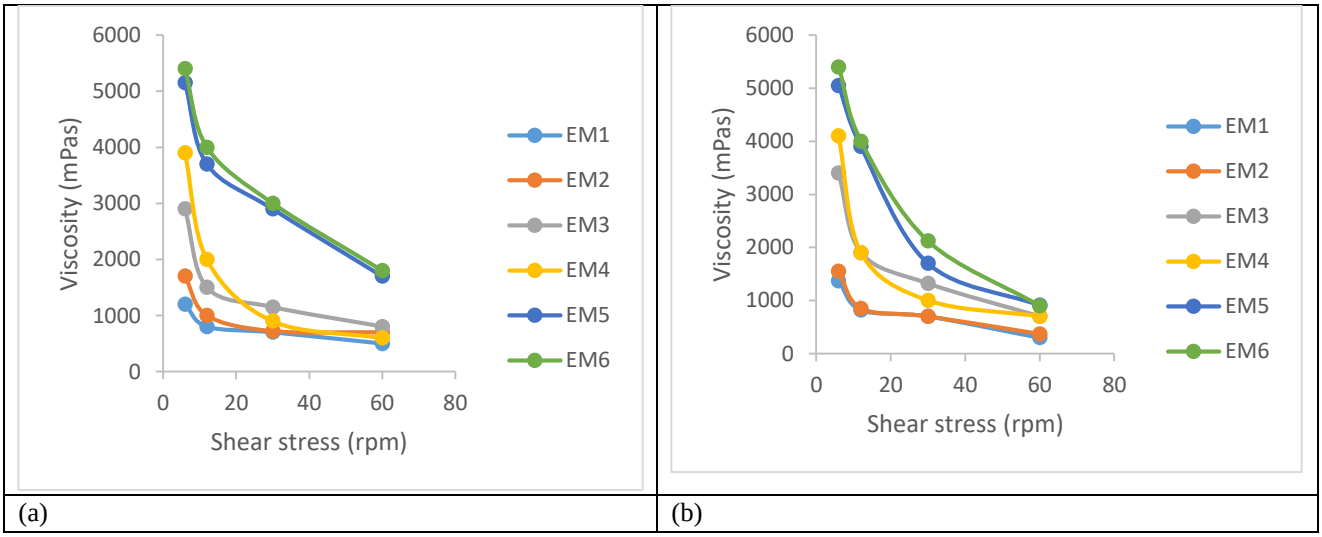

Figure 2: Viscosity curve of ibuprofen emulsion formulation EM1 to EM6 on day 0 and day 14

CONCLUSION

This research work has shown that *Detarium microcarpum* gum can be used successfully as an emulsifying agent in the formulation of ibuprofen emulsion. Ibuprofen emulsions prepared using *Detarium microcarpum* gum were more stable than those prepared using tragacanth gum.

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