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Determination of Aspirin Stability in oil in Water Emulsion prepared using different oils and Gums.

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ABSTRACT

The poor stability of aspirin in aqueous medium is a major drawback in the formulation of aspirin in liquid dosage form. This study is aimed at formulating stable oil preparation of aspirin with okra (*Abelmoschus esculentus* L) mucilage as emulsifying agent. The emulsion was formulated by dispersing the aspirin in the oily phase which was then dispersed in the aqueous continuous phase. The specific density, pH, organoleptic properties and aspirin content of the emulsions were evaluated. The effect of the okra mucilage was compared to acacia which serve as a standard natural emulsifying agent. Emulsions of acacia gave pH of 3.18, 3.31, and 3.35 compared to those of okra mucilage (O.M) with pH of 3.11, 3.10 and 3.06. The percentage content and stability were better in olive oil emulsion compared to emulsions made of palm oil and shea butter. The organoleptic properties of the formulations varied with the viscosity of the oils. This study showed that aspirin and okra mucilage have good compatibility with olive oil, which can serve as a means of formulating aspirin emulsion to enhance compliance in children. O.M can be useful in formulating stable emulsions when combine with other natural emulsifiers in small quantities.

Keywords: Aspirin, Emulsion, Oils, Okra mucilage.

INTRODUCTION

Aspirin exhibits unique combination of effects such as anti-inflammatory, anti-pyretic and analgesic. It is the most popular and effective non-prescription analgesic drug. However, aspirin ingestion can cause severe gastrointestinal bleeding in users, especially, in patients with gastrointestinal lesions (Holt, 1959; Arnold and Gartner, 1976; Huang *et al*, 2011; Cryer and Mahaffey, 2014). Studies have shown that aspirin, when given orally in a liquid form or when given intravenously, produces no occult bleeding (Wessi *et al* 1961; Mitchell *et al*, 2004; Anglolillo *et al*, 2019). On the other hand, aspirin tablets cause gastric bleeding particularly when tablets disintegrate slowly and remain in the stomach as large tablet fragments. These results suggest that gastric irritation by aspirin may be greatly reduced by reducing the particle size of the drug. The reduction of the drug particle size in the gastrointestinal fluid may be best achieved by using a liquid dosage form. Hence, many attempts have been made to formulate a stable aspirin solution to reduce this undesirable side effect (Tomski and Waller, 1940; Farges, 1964; Onah, 2004). The preparation of a stable liquid formulation of aspirin has been a classical pharmaceutical problem because of the instability of aspirin in various solvents. In aqueous solutions or in solvents containing moisture, aspirin is notoriously unstable (Avbunudiogba *et al*, 2012; Avbunudiogba *et al*, 2013). The degradation has been known to be due to the hydrolysis of aspirin into salicylic acid and acetic acid (Eichel and Massmann, 1987; Avbunudiogba *et al*, 2013). Studies showed that the hydrolysis follows first order kinetics and is subject to acid and base catalysis (Onah, 2004). Due to the rapid hydrolysis of aspirin in aqueous media, the attempts of liquid formulation of aspirin have been limited to the use of some non-aqueous solvents such as propylene glycol, ethyl alcohol, glycerol, and polyethylene glycol. The hydrolysis of aspirin in aqueous solvent tends to make it difficult in formulating it in liquid dosage form, hence is majorly formulated into tablets. In the past, attempts were made to solubilize acetylsalicylic acid or to convert it to a liquid preparation in order to render acetylsalicylic acid formulations more palatable. This is particularly important for those people who find it difficult to swallow tablets. Furthermore, the administration of acetylsalicylic acid in pediatric practice is often difficult when tablets have to be sectioned in halves or quarters in order to provide the proper dosage of the drug for children

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Thus, a need has existed for stable liquid preparations of acetylsalicylic acid for the accurate and convenient administration of the drug. Due to the limitation of formulating aspirin into aqueous formulation, oil-in-water emulsion formulation will tend to minimize the degradation process of aspirin; to enhance stability in liquid dosage form using okra mucilage as the emulgent. Okra gum has been evaluated as binder in paracetamol tablets formulations. Formulations containing okra gum as binder have been reported to show a faster onset of disintegration and higher amount of plastic deformation than those containing gelatin (Emeje *et al*, 2007). The mucilage of *Abelmoschus esculentus* has been used as pharmaceutical adjuvant and as a suspending agent and in other pharmaceutical applications as a gelling, emulsifying or disintegrating agent. The okra mucilage was found to be a superior suspending agent than tragacanth and is comparable to sodium carboxyl methyl cellulose (CMC) (Ravi *et al*, 2009). A study of the formulation, development, and evaluation of injectable aspirin revealed that aspirin can be successfully formulated into stable parenteral formulation. The solubility study suggested that aspirin exhibited poor aqueous solubility but showed appreciable solubility in non-aqueous solvent (Patel *et al*, 2013). The objective of the present study was to investigate the effect of formulating emulsions of acetylsalicylic acid (aspirin) using oils of different viscosities as well as okra (*Abelmoschus esculentus* Linn) mucilage as emulgent on stability of acetylsalicylic acid in the oil-in-water emulsion.

MATERIALS AND METHODS

Materials: Okra fruits (pods), palm oil, shear butter and olive oil were purchased from a local market in Delta State, Nigeria. Aspirin powder, Phenolphthalein, sodium hydroxide pellets (NaOH), concentrated hydrochloric acid were products of BDH chemicals, England. All other chemicals used were of analytical grade and used without further purification.

Methods

Extraction of okra gum: The seeds of fresh okra pods were removed prior to extraction; since they do not contain mucilage. A sample of okra pods (500 g) were weighed and sliced. This was homogenized with 100 mL of distilled water and centrifuged for 15 min. The clear viscous solution was decanted and heated for 5 min at 70 ± 0.5^{o}C to inactivate enzymes and re-centrifuged. The cream-coloured viscous solution was preserved in a container.

Preparation of palm oil and olive oil emulsions of aspirin: All the emulsions were prepared according to the formula in **Table 1**.

Table 1: Formulae for preparation of the different batches of emulsion

Codes / Constituents	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11
Aspirin (g)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Palm oil (mL)	-	-	-	-	-	-	30	30	30	-	-
Olive oil (mL)	30	30	30	30	30	30	-	-	-	-	-
Shea butter (mL)	-	-	-	-	-	-	-	-	-	30	30
Okra mucilage (mL)	20	30	50	60	20	-	60	-	20	60	
Acacia (g)	-	-	-	-	-	7.5	-	7.5	-	-	7.5
Tragacanth (g)	-	-	-	-	1.5	-	-	-	1.5	-	-
Water to	100	100	100	100	100	100	100	100	100	100	100

A sample of aspirin crystals (1.5 g) was powdered in a clean dried mortal and triturated with 30 mL of palm oil. A sample of okra mucilage (50 mL) and distilled water were mixed separately, then triturated with the oil to form concentrated primary emulsion which was transferred to a volumetric flask and made up to 100 mL volume with distilled water with vigorous shaking. The same procedure for palm oil was carried out for olive oil and other sets of emulsions were prepared using acacia and tragacanth as the emulgents. For acacia and tragacanth/okra gum, primary emulsions were formed with ratio 4:2:1 (oil: water: acacia) and 1.5% aspirin, respectively.

Preparation of shea butter emulsion: Aspirin crystals (1.5 g) was powdered in a clean dried mortar and triturated quickly with 30 g shea butter already melted. A sample of okra mucilage (50 mL) was mixed with 30 mL of warm water and added to the shea butter and triturated to form concentrated primary emulsion which was then transferred to a volumetric flask and made up to 100 mL volume with water while shaking vigorously and the container was

sealed. Acacia and tragacanth/okra were also used in place of okra.

Assay of Emulsions: A sample of the prepared emulsion (33.3 mL), which is equivalent to 0.5 g of aspirin was measured into a 250 mL conical flask and 50 mL of 0.5 N NaOH was added and heated for 5 min in a water bath; 2 drops of phenolphthalein test solution was added and titrated with 0.5 N hydrochloric acid. This was done for all the different emulsions prepared, (back titration - A). Blank titration of the above procedure was carried out using pure oils of palm oil, olive oil and shear butter without the drug (B). Total amount of NaOH used by aspirin equals: Titer value of blank (B) - titre value of back titration (A). Assay of aspirin was determined by hydrolysis with known quantity of 0.5 N NaOH solution and back titration of the excess amount with 0.5 N hydrochloric acid. Each milliliter of 0.5 N NaOH is equivalent to 45.04 mg of aspirin (BP, 2012).

$$Content\ of\ aspirin\ (\%) = (B - A) * N * 45.04 * \frac{100}{C} * 0.5 \ldots . (1)$$

Where B - A = amount of NaOH used up by the aspirin; N = normality of NaOH and C = weight of aspirin taken in milligram.

Test for stability of aspirin emulsion: The following tests were carried out to evaluate the stability of the prepared emulsion: Organoleptic property, pH, Specific density, effect of storage at ambient temperature (28 to 35°C) and assay (% content)

(i) Organoleptic property: A six-man panel assessed the taste, colour, odour and texture of the emulsions. A chart indicating codes ranging from 1 to 4 were scored. Where 1 represented a negative extreme and 4 was the positive extreme. Any four out of the six persons agreeing to a point obtained positive results.

(ii) pH test: A pH meter (Jenway, Germany) was used to measure the pH of the different emulsions prepared, a phosphate buffer was used to calibrate the equipment at room temperature before measurement was taken.

(iii) Specific density: Syringes of 10 mL were used to carry out the determination. This was done by weighing the syringe first, and 10 mL of water was withdrawn with the syringe and weighed, after which the water was expelled from the syringe. Then 10 mL of the emulsion was then withdrawn and weighed. The weight of syringe was subtracted from the values of water and emulsion respectively.

$$Specific\ density\ of\ emulsion = \frac{Weight\ of\ emulsion}{Weight\ of\ equal\ volume\ of\ water} \ldots . (2)$$

(iv) Effect of ambient temperature and humidity: The different emulsions were allowed to stand on a table, away from sunlight for a period of 90 days at room temperature to evaluate their stability.

RESULTS AND DISCUSSION

The extraction yield of okra gum was 29.24% w/w. Organoleptic properties of emulsions formed from different emulsifying agents such as okra mucilage, acacia powder and combination of tragacanth and okra in different oils (olive oil, palm oil, shea butter) are shown in **Table 2**.

Table 2: Organoleptic properties of various emulsions

	O. M	A. G	O. T
TASTE			
Olive oil	Slightly pungent	Slightly pungent	Slightly pungent
Palm oil	Mild, savory	Mild, savory	Mild, savory
Shea butter	Neutral	Neutral	Neutral
ODOUR			
Olive oil	Distinct smell of olive oil	Distinct smell of olive oil	Distinctive smell of olive oil
Palm oil	Distinct smell of palm oil	Distinct smell of palm oil	Distinctive smell of palm oil
Shea butter	Nutty	Nutty	Nutty
COLOUR			
Olive oil	Creamy	Creamy	Creamy
Palm oil	Yellow	Yellow	Yellow
Shea butter	Creamy	Creamy	Creamy
TEXTURE			
Olive oil	Smooth	Smooth	Coarse
Palm oil	Smooth	Smooth	Coarse
Shea butter	Smooth	Smooth	Coarse

pH of buffer = 7.01 at temperature of 27.4^{o}C; O.M = okra mucilage; A.G = acacia gum; O.T = Okra mucilage and tragacanth powder.

The active drug had no distinctive effect on the organoleptic properties of the formulations since acetylsalicylic acid is an odourless and tasteless crystalline drug. The colours of the emulsions were characteristic of the different oils used in their formulation. Emulsion prepared with palm oil gave yellow colour, shea butter and olive oil emulsions had creamy colourations. The tastes of the formulations were characteristics of the different vegetable oils used in the formulation. Emulsion made of olive oil had a slightly pungent taste, palm oil emulsion had a mild to savory taste like the taste of palm oil and those of shea butter were neutral. Emulsions of O.M were mucilaginous in taste compared to those of acacia emulsion. The odours of the different emulsions were characteristic of the oils used in the formulation. The textures of the emulsions made of O.M were finer compared to those of acacia emulsion. The pH of the stable emulsion of acacia (3.18) was slightly higher than that of the emulsion of okra mucilage (3.11) in olive oil but the difference was not significant ($p > 0.05$). In palm oil, acacia emulsion also had a higher pH of 3.31 compared to 3.10 of O.M emulsion. In shea butter, acacia emulsion is with pH of 3.35 while O.M emulsion has pH of 3.06. The pH of the emulsion was due to the acidic nature of acetylsalicylic acid. pH influences the type of emulsion formed. Acidic emulsion (low pH) generally produces o/w emulsion (Strassner, 1968). Acidic drugs are best absorbed in acidic medium of stomach with low pH where ionization is low (Venkateswarlu, 2010). The specific densities of acacia emulsions in olive oil, palm oil and shea butter which are 0.62, 0.64 and 0.63 respectively were higher than the specific densities of O.M emulsions which are 0.62, 0.61, and 0.62. The specific densities of the formulations deviated from the specific density of the oils and water (0.91 - 0.99) used. This indicates the presence of other additives like the emulsifying agents. Specific density is important in determining the influence of additives used in a material, which might affect the performance and stability of the material (Ezeuko *et al*, 2018). Specific density is important to identify the purity of a drug, since each of the constituents has a distinct specific density. Results of stability study are shown in **Table 3**; emulsions formed from acacia or okra mucilage separately, from the different oils were unstable. The ones formed from okra mucilage combined with tragacanth in olive oil and palm oil were stable, but that of shea butter solidified giving an unstable preparation. Emulsion of O.M in olive oil encountered creaming at a faster rate (within minutes). There was phase separation but easy re-dispersion. Emulsion of O.M made of palm oil showed phase separation when observed for 24 hours. On re-dispersion, there was a complete and irreversible separation of the oils from the aqueous phase containing the mucilage. Emulsions of acacia and O.M made of shea butter were unstable because the shea butter solidifies at room temperature. Emulsion may show phase separation but should be easily re-dispersed on shaking. Though, creaming is usually seen as undesirable because it causes difficulty in storage and handling, but it can be useful

Table 3: Results of stability study of the various emulsions

Formulations	Oily constituents	pH	Specific density	% content
Olive oil				
LOM	20%	2.86	0.61	19.84
	30%	2.85	0.61	64.92
	50%	3.11	0.61	88.00
	60%	3.09	0.62	90.13
LOT	20% O.M/1.5% trag	3.11	0.62	95.02
LAG	Acacia gum	3.18	0.61	93.09
Palm oil				
PAG	Acacia gum	3.31	0.64	27.05
POT	20% O. /1.5% trag	3.10	0.62	87.17
POM	60% O.M	3.10	0.61	36.07
Shea butter				
SAG	Acacia	3.55	0.63	91.54
SOM	60% O.M	3.06	0.6156	78.45

KEY: LOM - Olive oil emulsion of okra mucilage
LOT - Olive oil emulsion of okra mucilage and tragacanth powder.
LAG - Olive oil emulsion of acacia powder.
PAG - Palm oil emulsion of acacia powder.
POT - Palm oil emulsion of okra mucilage and tragacanth powder.
POM - Palm oil emulsion of okra mucilage.
SAG - Shea butter emulsion of acacia powder.
SOM - Shea butter emulsion of okra mucilage

in special cases, especially where it is desirable to concentrate an emulsion (Khan *et al*, 2011). A creamed emulsion increases the likelihood of coalescence due to close proximity of the globules in the cream, it also increases the tendency of an emulsion to inversion. Creaming is not a serious problem, because it can be overcome by simply shaking the emulsion but it is undesirable because it might cause the patient to take incorrect dose if not properly shaken. Emulsions of O.M and acacia in olive oil and palm oil showed less viscosity, resulting in unstable formulations that showed phase separation on standing. Tragacanth was used to enhance the viscosity of the emulsions made of O.M and acacia gum, and was found to be more viscous, forming a stable emulsion. Viscosity of a formulation is its resistance to flow. Substances with high viscosities flow with difficulty, while substances with low viscosities flow and spread quickly. Increase in viscosity is important for the even dispersion of the aspirin throughout the emulsion for accurate dosing. Percentage content values of aspirin (**Table 3**) in some of the emulsions passed the BP specification value of aspirin dosage form (95.0 -105.0%). The deviations observed in some of the formulations might have resulted from: Hydrolysis of the acetylsalicylic acid to acetic acid and salicylic acid in the presence of water (Eichel and Massmann, 1987; Avbunudiogba *et al*, 2013).In olive oil emulsion, the larger the amount of water, the lower the % content as seen in 20% O.M the % content is 19.84%; 60% O.M, the % content is 90.13% and 93.09% when formulated with 7.5% acacia. In palm oil emulsion, the value was lower with 60% O.M, having 36.07% and acacia emulsion 27.05%. This reduction might be due to the presence of stearate in varying amount in these oils. Degradation of aspirin in tablet is increased in the presence of stearates when used as lubricants (PC, 1979). Formulations of O.M, A.G in shea butter, the % contents were 78.45% and 91.54% respectively. Olive oil contains more oleic acid (monosaturated) and less linoleic and linolenic acids (polysaturated) than other vegetable oils. This render olive oil more resistant to oxidation, because generally, the greater the number of double bonds in the fatty acids, the more unstable and easily broken down by heat, light and other factors in these oils.

CONCLUSION

Okra gum (like most naturally occurring gum/emulgent) cannot form stable emulsion when used alone. However, it can form stable emulsion when combined with other gums. Okra gum stabilizing ability is comparable to that of tragacanth. This research work showed that olive oil formed a more stable emulsion of aspirin with okra mucilage than palm oil and shea butter with easy redispersibility. Aspirin will have better stability in oils with little or no stearate since degradation of aspirin is enhanced in the presence of stearates.

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