Research Article

FORMULATION DEVELOPMENT AND COMPARATIVE EVALUATION OF ACETAMINOPHEN SUSPENSION USING POLYSACCARIDE DERIVED FROM SEED COTYLEDONS OF IRVINGIA *WOMBOLU.*

Onyishi V.I.*, Chime S.A, Odika F.C., Obitte N.C
Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka 410001, Nigeria.
***Corresponding author's E-mail:** docikeonyishi@gmail.com

Accepted on: 10-08-2012; **Finalized on:** 31-10-2012.

ABSTRACT

The aim of the study was to formulate acetaminophen paediatric suspension using gum from *Irvingia wombolu* as suspending agent. Gum extracts from *Irvingia wombolu* seed cotyledons was used at concentrations of 1.6 and 3 % in acetaminophen paediatric suspension. The suspending properties of *Irvingia wombolu* gum were compared to the properties of its mixtures with acacia and sodium carboxymethyl cellulose (SCMC). The phytochemical analysis of *Irvingia wombolu* gum and the effects of aging on the viscosity of the suspension formulations were studied. From the results, phytochemical analysis showed that the gum contains alkaloids, flavonoids, saponin, tannins and glycosides. The rheological properties of the suspensions showed that the viscosity of the suspensions were stable and did not show significant reduction over time ($p < 0.05$). The results of sedimentation volume of suspension showed that batch K formulated with *Irvingia wombolu* gum alone exhibited high stability and hence showed low sedimentation rate over time. Suspensions formulated with *Irvingia wombolu* gum exhibited properties comparable to those formulations containing mixtures of the three suspending agents ($p < 0.05$). Therefore, *Irvingia wombolu* gum can be used alone or with mixtures of acacia and SCMC as suspending agents in acetaminophen suspension for paediatrics.

Keywords: *Irvingia wombolu*, acetaminophen, paediatric suspension, gums.

INTRODUCTION

Gums from plants are mainly long chain, straight or branched chain polysaccharides that contain hydroxyl groups which bond to water molecules. They are generally non-toxic and widely available, hence the continued interest[1]. The widening availability of natural gums with specific characteristics offers flexibility of application with respect to improving the bioavailability of drugs and manipulating their release profile[2]. The research into the use of natural materials in pharmaceutical formulations, particularly in developing countries will continue to be relevant because of local accessibility, natural abundance, cost effectiveness, and eco-friendliness compared to synthetic and semi-synthetic excipients[3]. Also the use of synthetic polymer matrix materials often goes along with detrimental effects on incorporated drug during manufacturing of formulations or during the erosion of the polymers after application[4]. Some natural polymers have found uses as suspending agents[5-9], as binders and sustained-release matrix in tablet formulations, as film coating agent, thickeners in cosmetics, and in food [3].

Irvingia wombolu commonly called bush mango/wild mango, or dika nut, is an edible Africa indigenous fruit tree that produces edible fruits and seeds [10-11]. *Irvingia* belongs to the family Irvingiacea. In Nigeria, the kernels are used as a condiment and are highly valued for their food thickening properties in preparing "ogbono" or draw soup[12-13]. Pharmaceutical suspensions are liquid dosage forms that often require the addition of suspending agents in order to stabilize their system[14]. These suspending agent increase ease of redispersibility, enhance pourability and prevent compact cake formation.

Suspending agents are grouped into three classes: synthetic, semi synthetic and the natural polysaccharides, in which class Acacia, tragacanth and *Irvingia wombolu* gum belong to the later class[14-15]. In a pharmaceutical suspension, a suspending agent helps the drug stay suspended thereby reducing caking at the bottom of the preparation. Consistency of the solute throughout the suspending medium is facilitated with the drug or solute staying suspended in the continuous phase[3]. As a suspension is energetically unstable, the particles that have settled tend to interact to form a cake or hard crystalline network. It is required that suspensions are formulated such that caking is minimized and so that the particles that have settled may be readily redispersed upon shaking[3].

Majority of the medications used in paediatric patients are not labeled for paediatric use. As a result, there is a lack of dosage formulations appropriate for use in paediatric patients, and clinicians often have to rely on adult formulations such as tablets and capsules. However, infants are either not willing or unable to swallow these dosage forms[16]. Furthermore, these dosage forms do not provide adequate flexibility in dosing for the paediatric patient. Most medications used in paediatric patients are dosed based on their body weight or body surface area. Oral liquid formulations are, therefore, preferred due to their flexibility in dosing[17]. The aim of this work is to formulate acetaminophen paediatric suspension using a new gum extracted from edible *Irvingia wombolu* as suspending agent and to compare the suspending properties of this gum with other suspending agents in acetaminophen paediatric suspension.

MATERIALS AND METHODS

Materials

Sodium carboxymethylcellulose, acacia, acetone (BDH, England), Magnesium stearate, acetaminophen (May and Baker, England), distilled water (Lion water, Nsukka, Nigeria). *Irvingia wombulu* seed gum was obtained from a batch processed in our laboratory. All other reagents and solvents were analytical grade and were used as supplied.

Extraction of *Irvingia wombolu* gum

Irvingia wombolu nuts were purchased from a village market near Nsukka, Enugu State, Nigeria in the month of June, 2010. The plant material was authenticated by Mr. A.O. Ozioko, a consultant taxonomist with the International Center for Ethnomedicine and Drug Development (InterCEDD) Nsukka. The voucher specimen of the plant studied was kept in the herbarium of the Department of Pharmacognosy and Environmental Medicines, University of Nigeria, Nsukka. *Irvingia wombolu* seeds were milled using an equipment of hammer mill type and soaked in water containing 1 % sodium metabisulphite for about twelve hours, it was then filtered and the gum was precipitated using acetone. The precipitated gum was dried for two hours in a tray dryer (Manesty Ltd, Liverpool, England) at 40^{o}C. The dried gum was milled in an end runner mill (Pascal engineering co Ltd, England) and finally passed through 55 mm sieve (Turgens & Co., Germany).

Phytochemical Screening

Phytochemical tests were carried out on the powdered gum for the presence of alkaloids, tannins, saponins, flavonoids, resins, oils, steroids, glycosides, terpenoids, acid compounds, carbohydrates, reducing sugars and proteins. The tests were carried out using standard procedures of analysis as described elsewhere [18-20].

Rheological properties of *I. wombolu* gum

A 3 %w/v of *I. wombolu* gum was prepared and the viscosities were determined at temperatures of 25, 40, 80, 60 and 100 ^{o}C respectively [21].

Solubility

The solubility of the *Irvingia wombolu* gum was tested in water (cold and hot), n-hexane, petroleum ether, chloroform, ethyl ether, acetone, ethanol and methanol.

pH stability test

The pH of 0.2, 1.6 and 3 %w/v dispersion of the gums were determined in time dependent manner from day one to seven days using a pH meter (Suntex TS-2, Taiwan).

Formulation of acetaminophen suspension

Suspensions containing 2.5 %w/v of acetaminophen were prepared (table 1), using 1.6 and 3.0 % of *Irvingia wombolu*, and acacia respectively and 0.1, 0.3 and 0.5 % of SCMC as suspending agents. Tween® 80 was used as the wetting agent. Mucilages of the suspending agent were prepared by hydration using part of the vehicle. The solid components of the formulation were finely triturated with the aid of mortar and pestle with water containing the wetting agent. The slurry of the suspending agents was added to the drug and triturated until homogeneous slurry was obtained. Methyl paraben (0.02 %) was used as the preservative and citric acid (0.5 %) was used as a synergist and a sequestering agent. Each preparation was transferred into a 100 ml beaker and made up to volume with the remaining vehicle used to rinse the mortar.

Evaluation of acetaminophen suspension

Sedimentation volume

The sedimentation volume of acetaminophen suspensions was determined by measuring the volume of the sediments in the suspension placed in 100 ml measuring cylinders. The sedimentation volume was recorded daily for 7 days. The sedimentation volume (F) was calculated using the formula:

F = Vu /Vo - ---------- (1)

Table 1: Composition of paracetamol suspension

Batch	Paracetamol (%)	*I. wombolu* (%)	Acacia (%)	SCMC (%)	Tween® 80 (%)	Citric acid (%)	Methyl paraben (%)	Purified water qs (ml)
A	2.5	1.6	1.6	0.3	0.8	0.5	0.02	60.0
B	2.5	3.0	3.0	0.5	1.5	0.5	0.02	60.0
C	2.5	1.6	1.6	0.3	0.8	0.5	0.02	60.0
D	2.5	1.6	1.6	0.3	0.8	0.5	0.02	60.0
E	2.5	3.0	-	3.0	0.1	0.5	0.02	60.0
F	2.5	3.0	3.0	0.5	0.1	0.5	0.02	60.0
G	2.5	1.6	1.6	0.3	0.8	0.5	0.02	60.0
H	2.5	3.0	3.0	0.5	0.1	0.5	0.02	60.0
I	2.5	3.0	3.0	0.1	0.1	0.5	0.02	60.0
J	2.5	1.6	1.6	0.3	0.8	0.5	0.02	60.0
K	2.5	3.0	-	-	1.5	0.5	0.02	60.0
L	2.5	3.0	3.0	0.5	1.5	0.5	0.02	60.0

SCMC: sodim carboxymethyl cellulose

Evaluation of acetaminophen suspension

Sedimentation volume

The sedimentation volume of acetaminophen suspensions was determined by measuring the volume of the sediments in the suspension placed in 100 ml measuring cylinders. The sedimentation volume was recorded daily for 7 days. The sedimentation volume (F) was calculated using the formula:

F = Vu /Vo - ---------- (1)

Where, Vu = height of sediment at a given time and Vo = original volume of sediment before settling occurred. From the values of F obtained, graphs of sedimentation volume (Vu/Vo) against time were plotted, from which sedimentation rate was calculated [14].

Rheological measurements

The viscosity of each batch of the suspension was determined using a viscometer (Universal torsion viscometer (Gallenkamp, England). Also the effect of aging on the viscosity of the suspension was determined by recording the viscosity at time intervals from 1 day to 30 days.

RESULTS AND DISCUSSION

Phytochemical constituents of gum

Phytochemical analysis (table 2) of *I. wombolu* gum revealed the presence of alkaloids, saponins, tannins, flavonoids and glycosides in substantial quantities. Reducing sugars was however, not found in the gum. The medicinal plants that are moderately rich in alkaloids and tannins have potential health promoting effects[22-23]. Similarly, saponins have anti-carcinogenic properties and other health benefits. Alshawsh *et al*., reported that tannins may have anti-plasmodial activity[24]. The stem bark of the plant also contains glycosides. Cardiac glycosides treat heart problems that may result from severe malaria attack. Phytochemicals are non-nutritive plant chemicals that have protective or disease preventive properties. Plants produce these chemicals substances to protect themselves, and they are also believed to protect humans against certain diseases[25].

Table 2: Results of the Phytochemical screening of *Irvingia wombolu* seed gum

Phytochemical constituents Analysed	Remarks*
Alkaloids	+
Saponins	+
Reducing sugars	-
Tannins	+
Glycosides	+
Flavonoids	+

*- Absent, + present

Solubility

Irvingia wombolu gum was soluble in hot and cold water (0.1 %w/v). However, the gum was insoluble in n-hexane, petroleum ether, chloroform, ethyl ether, acetone, ethanol and methanol.

Rheological properties of gum

The effect of temperature on the viscosity of *I. wombolu* gum is shown in table 3. From the results, increase in temperature increased the viscosity of the gum. Therefore, suspension formulations containing this gum can withstand fluctuations in temperature and very high temperatures unlike most suspending agents which lose their suspending properties with increase in temperature.

Table 3: Effect of Temperature on 3 % dispersion of the gum

Viscosity (cp)	Temperature (°C)
1200.00	25
1300.00	40
1350.00	60
1400.00	80
1500.00	100

The pH stability of gum slurry

The pH stability studies of the slurry of *I. wombolu* gum are shown in Fig.1. The gum dispersion exhibited acidic pH which decreased significantly with time ($p < 0.05$). The decrease in pH showed that the formulation would need a buffer to keep the suspension containing this gum as suspending agent more stable in order to maintain the pH. Hence, citric acid was added to the formulations of acetaminophen suspension in order to maintain the pH. Reduction in pH may also be due to microbial activity, therefore the suspension of the acetaminophen formulated with this gum should contain a preservative, hence the inclusion of methyl paraben to the formulations.

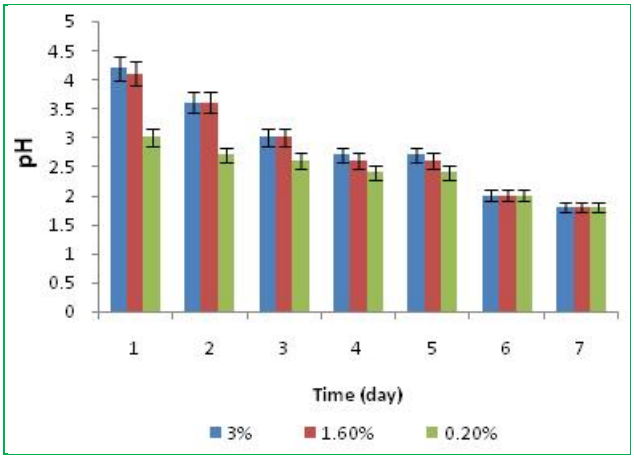

Figure 1: The pH stability of *Irvingia wombolu* gum dispersion over time

Rheological properties of suspension

Sedimentation volume

The results of the suspending properties of acetaminophen suspension are presented in Fig. 2. From the results, suspensions formulated with combinations of *Irvingia wombolu* (3 %), acacia (3 %) and SCMC (0.5)

(batches B, F, H, I and L) exhibited lower settling rate than formulations containing lower amounts of suspending agents. Also batch K formulated with *I. wombolu* gum alone had low settling and hence exhibited good property as a suspending agent. Increase in the amount of Tween® 80 (wetting agent) also increased the stability of the suspensions as shown in Fig. 2. This may be as a result of increase in wetting of the hydrophobic particles by this agent. Suspension with a large negative slope will settle very fast and will pose the problem of inaccurate dose withdrawal[26]. Therefore, batch F is the most stable formulation, followed by batch K and batch L in that order. *I. wombolu* gum can be used as suspending agent alone in acetaminophen suspension; also it can be used in combination with acacia and SCMC.

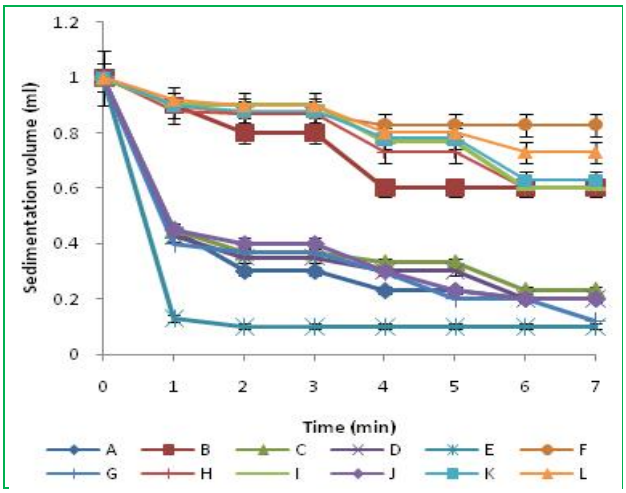

Figure 2: Sedimentation volume of acetaminophen suspension formulated with *I. wombolu* (K) and combinations of *I. wombolu* (3 %), acacia (3 %) and SCMC (0.5 %) (Batches B, F, H, I and L); and 1.6% of *I. wombolu,* acacia and SCMC (0.3 %) (A, C, D, G and J); batch E was formulated with *I. wombolu* and SCMC.

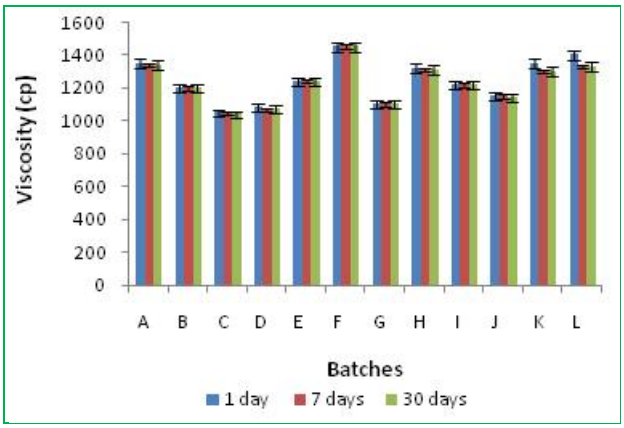

Figure 3: Effect of aging on the viscosity of acetaminophen suspension formulated with *I. wombolu* (K) and combinations of *I. wombolu* (3 %), acacia (3 %) and SCMC (0.5 %) (Batches B, F, H, I and L); and 1.6% of *I. wombolu,* acacia and SCMC (0.3 %) (A, C, D, G and J); batch E was formulated with *I. wombolu* and SCMC.

Effect of aging on viscosity

The results of the viscosity of acetaminophen suspensions formulated with *I. wombolu* gum and blends of *I. wombolu*, acacia and SCMC are shown in Fig. 3. From the results, most of the formulations were stable from day 1 to 30 days, however, a few formulations showed slight reduction in viscosity with time as shown in Fig. 3. The decrease in viscosity may be due to an increase in the mean particle size of dispersed phase (crystal growth) which led to a fall in viscosity due to structural breakdown of the suspending agent used.

CONCLUSION

Acetaminophen paediatric suspensions were formulated with *I. wombolu* gum and mixtures of *I. wombolu* gum, acacia and SCMC. The properties of the suspensions studied showed that *I. wombolu* gum can be used alone or with mixtures of acacia and SCMC as suspending agents in acetaminophen suspension for paediatrics. *I. wombolu* gum has advantage of local accessibility, natural abundance, cost effectiveness, and eco-friendliness compared to synthetic and semi-synthetic excipients.

REFERENCES

1. Emeje M, Isimi C and Kunle O. Effect of *Grewia* gum on the mechanical properties of paracetamol tablet formulations. Afr. J. of Pharm. Pharmacol. 2, 2008, 001-006.
2. Momoh MA, Onunkwo GC, Chime SA and Akpabio EI. Comparative Evaluation of Detarium Microcarpium Seed Gum as a Potential Polymer for Film Coating of Normal Release Tablets. Drug Invention Today. 3(9), 2011, 206-210.
3. Ogaji JI and Hoag SW. Effect of *Grewia* gum as a suspending agent on ibuprofen paediatric formulation. AAPS Pharm. Sci. Tech. 12(2), 2011, 507-513.
4. Reithmeier HJ, Herrmann and Gopferich A. Development and characterisation of lipid microparticles as a drug carrier for somatostatin Int. J. Pharm. 218,2001, 133 – 143.
5. Alhamami OMO. The effects of some physico-chemical factors and pharmaceutical excipients on the bioavailability of nitrofurantoin oily and aqueous suspensions in rats. Drug Dev. Ind. Pharm. 28, 2002, 305–16.
6. Bommireddi A, Li LC. Stephens D, Robinson D, Ginsburg E. Particle size determination of a flocculated suspension using a light-scattering particle size analyzer. Drug Dev. Ind. Pharm. 24:1998; 1089–93.
7. Femi-Oyewo MN, Adedokun MO, Olusoga TO. Evaluation of the suspending properties of Albizia zygia gum on sulphadimidine suspension. Trop. J. Pharm. Res. 3:2004; 279–84.
8. Johnston D, Gray MR, Reed CS, Bonner FW, Anderson NH. A comparative evaluation of five common suspending agents used in drug safety studies. Drug Dev. Ind. Pharm. 16: 1990; 1893–909.
9. Nayak AK. Evaluation of Spinach oleracea L. leaves mucilage as an innovative suspending agent. J. Advan. Pharm. Tech. Res. 1(3):2010; 338 – 341.
10. Atanngana AR, Ukafor V, Anegbeh PO, Asaah E, Tchoundjeu Z, Usoro C, Fondoun JM, Ndoumbe M, Leakey RRB. Domestication of Irvingia gabonensis: 2. The selection of multiple traits for potential cultivars from Cameroon and Nigeria. Agroforestry Syst. 55: 2002; 221- 229.
11. Harris DJ. A revision of the Irvingiacea in Africa. Bulletin du Jardin Botanique National de Belgique. 65 (1-2):1996; 55-64.
12. Fajimi O, Sarumi MB, Olayode MN, Gamra EO, Sanusi SI. *In vitro* propagation of *Irvingia gabonensis.* Afr. J. Biotech. 6 (8):2007; 976-978.
13. Ndjouenekeu R, Goycoolea FM, Morris ER, Akingbala JO. Rheology of Okra (Hibiscus esculentus) and dika nut (Irvingia gabonensis) polysaccharides. Carbonhydrate Polymer 29:1996; 263-269.

14. Mahmud HS, Oyi AR, Allagh TS and Gwarzo MS. Evaluation of the Suspending Property of *Khaya snegalensis* Gum in Co-Trimoxazole Suspensions. Res. J. App. Sci. Eng. Techn. 2(1):201; 50-55.

15. Mbang NF, Musiliu OA and Taiwo OO. Evaluation of the suspending properties of *Albizia zygia* gum on sulphadimidine suspension. Trop. J. Pharm. Res. 3 (1):2004; 279-284.

16. Mennella J, Beauchamp G. Optimizing oral medications for children. Clin Ther. 30:2008; 2120–32.

17. Harborne JB. Phytochemistry. Academic Press, London 1993; p. 89-131.

18. Sofowora H. Screening Plants for Bioactive Agents In: Medicinal Plants and Traditional Medicine in Africa, Spectrum Books Ltd., Sunshine House, Ibadan. Nigeria 2nd Edn. 1993, p. 134-156.

19. Trease GE and Evans WC. Pharmacology. 15thg Edn. Saunders Publishers, London 2002; p. 42-44, 221-393.

20. Onyechi JO. Introductory formulation Science 2. Global Publishers Nig. Ltd. Nsukka 2008; 25-30.

21. Ikewuchi CC and Ikewuchi JC. Chemical profile of *Pleurotus tuberregium* (Fr) Sing's Sclerotia. The Pacific J. Sci. Tech. 10(1):2008; 28-30.

22. Jigam AA, Helmina O, Dauda BEN, Okogun JO. Polygalloyltannin isolated from the root of *Acacia nilotica* Del. (Leguminoseae) is effective against *Plasmodium berghei* in mice. J Med. Plants Res. 4(12):2010; 1169 – 1175.

23. Olajide Olajide OA, Awe SO, Makinde JM, Ekhelar AI. Studies on the anti-inflammatory, antipyretic and analgesic properties of *Alstonia boonei* stembark. J. Ethnopharmacol. 71(1-2):2000; 179-86.

24. Edeoga HO, Okwu DE, Mbaebie BO. Phytochemical Constiuents of some Nigerian medicinal plants. Afri. J. Biotechnol. 4 (7):2005; 685-688.

25. Ofoefule SI. A text book of pharmaceutical technology and industrial pharmacy. Samakin (Nig.) Enterprises 2002; 129-155.

****