



Preliminary Evaluation of *Delonix regia* Seed Gum as a Suspending Agent in a Liquid Oral Dosage Form

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ABSTRACT

The study focused on the extraction and utilization of *Delonix regia* seed gum as a suspending agent in amoxicillin dry granules for reconstitution. The seeds were dehulled, defatted with diethyl ether and the gum extracted from its aqueous dispersion by antisolvent precipitation method. *Delonix regia* gum (DRG), sodium carboxymethyl cellulose (CMC) and hydroxylpropylmethyl cellulose at 0.50, 0.75 and 1.00% (with or without NaCl at 0.02% or 0.04%) were separately used to formulate amoxicillin granules. The granules were reconstituted and characterized using standard protocols for suspension dosage forms. Results revealed that at similar concentrations, products viscosities were: CMC>HPMC>DRG; and pourability: DRG>HPMC>CMC. At 1.00%, DRG gave the best product and flocculation with NaCl was better at 0.02%. The order of degree of flocculation at 1.00% suspending and 0.02% NaCl was DRG>HPMC>CMC, while at 0.04% NaCl, it was CMC>HPMC>DRG. Ease of redispersion for DRG products was significantly better ($p<0.05$) than those of CMC, HPMC and two popular commercial products in Nigeria. Particle shapes and interaction with the excipients as revealed by photomicrographs illuminated some of the observed properties of the products, in that the ones whose particles were planar or acicular shaped had significantly higher ($p<0.05$) degree of flocculation than products containing mostly circular particles. In conclusion, the qualities of products formulated with DRG compared very well and for redispersibility is significantly better ($p<0.05$) than products formulated with standard suspending agents and the two popular commercial products in Nigeria markets.

Keywords: *Delonix regia*, suspending agent, amoxicillin suspension, HPMC, CMC.

INTRODUCTION

The search for suitable ingredients for the formulation of human and veterinary dosage forms is one that may continue as long as medical practice involves the use of medicaments to treat or manage diseases. Just as there is need to develop new active ingredients, so also is the need to find new excipients or modify existing ones in order to improve their functionality or reduce the cost of production. The research into and 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.^[1]

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Majority of non-active ingredients, otherwise known as excipients are of natural origin. Some of these have been extensively studied and fully standardized while very many have not been investigated appreciably. *Delonix regia* (Bojer ex Hook) Raf seed gum belongs to the latter group. *Delonix regia* is a species of flowering plant in the family: leguminosae, sub family: Fabaceae. It is native to Madagascar but its seeds have travelled the world and the species is now common through the tropical cities. It is noted for its fern-like leaves and flamboyant display of flowers. In many tropical parts of the world it is grown as an ornamental tree and in English it is given the name Royal Poinciana or Flamboyant.^[2] *Delonix regia* is a very distinctive tree with large, bright red flowers. The genus name is derived from the Greek words *delos* (meaning conspicuous), and *onyx*, meaning claw, referring to the appearance of the spectacular flowers.^[3] *Delonix regia* seed gum contains galactomannan-type polysaccharides that are similar to those of guar gum and locust bean gum.^[4] The few branched regions present in the seed gum consist of α -D-

mannose (1 → 4) linkages and α-D-galactose (1 → 6) branches. Its mannose and galactose proportions are similar to those of guar gum but differ in terms of the OH bond position in the main chain. The gum has α-D-mannose while guar gum has β-D mannose. [5] The physicochemical properties of *Delonix regia* seed gum had been reported previously. [2, 6] The gum has been applied as a binder in paracetamol tablet; [6] and other workers have evaluated its usability in sustained release tablet dosage form [7] and microencapsulation of bioactive natural products. [8-9]

A pharmaceutical suspension is a coarse dispersion in which the internal phase is dispersed uniformly throughout the external phase. The internal phase consists of insoluble solid particles dispersed uniformly throughout the suspending vehicle with the aid of single or combination of suspending agents. The external phase (suspending medium) is generally aqueous, but in some instance, may be an organic or oily liquid for non oral use. Formulating a good suspension dosage form involves careful choice of various ingredients especially the suspending agent because it holds the key to countering the common challenges that encumber such dosage forms during use and storage. Some of the challenges include rapid sedimentation, caking, crystal growth, Ostwald ripening, irredispersability and bad pourability. The ability of a suspending agent to forestall these challenges is a characteristic worth investigating. In the present study therefore, *Delonix regia* seed gum's ability to function as a suspending agent in amoxicillin suspension is deemed relevant to its eventual acceptance as a pharmaceutical excipient.

MATERIALS AND METHODS

Delonix regia seeds were harvested from flamboyant tree at All Saints Cathedral Onitsha, Nigeria and authenticated by Mr Patrick Obi of the pharmacognosy department, Madonna University Elele, and given the Voucher number: MU/PHGSV/12/005. Diethyl ether (JHD India), Ethanol (JHD India), amoxicillin trihydrate powder (KDL Biotech Limited Maharashtra India), Potassium sorbate (Sinoright Int. Ltd China), Sodium chloride (Zigma-Aldrich, Germany), Hydroxypropylmethyl cellulose (Fluka, USA), Sodium carboxymethyl cellulose (Fluka, USA), amoxicillin 125 mg suspension (Amoxil® GSK, England; TEVA®, UK). Other reagents were of analytical grade and water was distilled.

Extraction of gum from *Delonix regia* seeds

The seeds were soaked in hot water (70°C) for 1 h and left to stand as the water cooled for another 11 h, after which the seed coats were removed. Thereafter, the seeds were sundried and milled with a kitchen blender (Philips Model HR 1731/6), and the resulting powder was weighed (Mettler Toledo B154, Switzerland). Three hundred and fifty grams (350 g) of the powder was soaked with 1 L of diethyl ether for 24 h in a Winchester bottle with intermittent shaking. After 24 h, the slurry was filtered using a 100% cotton white cloth. The residue was washed several times with hot water until no oily smear remained on it. It was then poured into an open mouthed container and soaked with 500 ml of distilled water at room temperature (32°C) for 12 h. After 12 h the slurry was filtered with the cotton cloth and 400 ml of the filtrate was mixed with 800 ml of ethanol, in order to precipitate the gum. The mixture was allowed to settle and the supernatant was decanted leaving the gum, which was re-soaked in ethanol for 18 h, air dried for 72 h and oven dried

at 60°C for 1 h. The dried gum (DRG) was milled with mortar and pestle, packed in airtight container over silica gel.

Formulation of amoxicillin trihydrate granules

The granules were formulated according to the design shown in Table 1. Amoxicillin trihydrate powder (14.35 g) was intimately mixed with the relevant amount of suspending agent (DRG, HPMC, or CMC), potassium sorbate (KS) and NaCl (where necessary) in a porcelain mortar using a stainless steel spatula. The mixture was moistened with 1.50 ml of distilled water at 32°C and kneaded with pestle to form a homogeneous mass, which was screened through sieve of aperture size 850µm and dried at 50°C for 1 h. The resulting granules were dry screened with sieve of aperture size 600µm and re-dried at 50°C for 1 h. The granules were transferred to a desiccator and allowed to cool down over silica gel. Thereafter they were packed in airtight amber coloured glass bottles. One batch (AMX0) of granules was formulated without any suspending agent or NaCl, to serve as reference in the evaluation of the other batches.

Reconstitution of the granules

In order to evaluate the qualities of the products as suspension dosage form, relevant amounts of granules to make 100 ml suspension from each batch (e.g. 3.51 g of granules from batch DRG.5S2) were reconstituted with sufficient volume of water to make 100 ml suspension and shaken vigorously to ensure formation of a homogeneous dispersion.

Evaluation of the quality of the suspension

Sedimentation volume (F) and degree of flocculation (β)

The reconstituted suspension was thoroughly mixed and left to stand in a 100 ml measuring cylinder and the volume of sediment read on daily basis for the first 7 days and then weekly for the next 4 weeks. The sedimentation volume was calculated using equation 1:

$$F = \frac{V_u}{V_o} \dots (1)$$

Where V_u is ultimate volume, V_o is original volume.

The degree of flocculation was evaluated using the relationship:

$$\beta = \frac{F}{F_\infty} \dots (2)$$

Where F_∞ is the sedimentation volume of batch AMX0 (suspension formulated without suspending or flocculating agent). [10]

Flow rate

The time required for 25 ml of each suspension sample to flow through a 25 ml pipette was determined and the flow rate (ml per sec) was calculated using equation 2: [11]

$$\text{Flow rate} = \frac{\text{Volume of suspension sample (ml)}}{\text{Flow time (s)}} \dots (3)$$

Viscosity

The viscosity of the amoxicillin suspension with different suspending agents was determined using a digital viscometer (Shangi and Nirun intelligent, China). Their viscosities were measured using spindle number three at 12 rpm.

Redispersibility

After recording sedimentation volume for 5 weeks, the suspensions were subjected to redispersibility test. This was conducted by firmly sealing the mouth of the measuring cylinder and turning the cylinder through 180°. The number of times the cylinder was turned in order to effect complete redispersion of the sediment was recorded as a measure of the product's redispersibility value. [11]

Table 1: Formula for the preparation of amoxicillin suspension

BATCH	Amount of ingredients for 500 ml suspension					
	API (g)	DRG (%)	HPMC (%)	NaCMC (%)	KS (%)	NaCl (%)
AMX0	14.35	-	-	-	0.12	-
DRG.5	14.35	0.50	-	-	0.12	-
DRG.75	14.35	0.75	-	-	0.12	-
DRG1	14.35	1.00	-	-	0.12	-
DRG.5S2	14.35	0.50	-	-	0.12	0.02
DRG.75S2	14.35	0.75	-	-	0.12	0.02
DRG1S2	14.35	1.00	-	-	0.12	0.02
DRG.5S4	14.35	0.50	-	-	0.12	0.04
DRG.75S4	14.35	0.75	-	-	0.12	0.04
DRG1S4	14.35	1.00	-	-	0.12	0.04
HPMC.5	14.35	-	0.50	-	0.12	-
HPMC.75	14.35	-	0.75	-	0.12	-
HPMC1	14.35	-	1.00	-	0.12	-
HPMC.5S2	14.35	-	0.50	-	0.12	0.02
HPMC.75S2	14.35	-	0.75	-	0.12	0.02
HPMC1S2	14.35	-	1.00	-	0.12	0.02
HPMC.5S4	14.35	-	0.50	-	0.12	0.04
HPMC.75S4	14.35	-	0.75	-	0.12	0.04
HPMC1S4	14.35	-	1.00	-	0.12	0.04
CMC.5	14.35	-	-	0.50	0.12	-
CMC.75	14.35	-	-	0.75	0.12	-
CMC1	14.35	-	-	1.00	0.12	-
CMC.5S2	14.35	-	-	0.50	0.12	0.02
CMC.75S2	14.35	-	-	0.75	0.12	0.02
CMC1S2	14.35	-	-	1.00	0.12	0.02
CMC.5S4	14.35	-	-	0.50	0.12	0.04
CMC.75S4	14.35	-	-	0.75	0.12	0.04
CMC1S4	14.35	-	-	1.00	0.12	0.04

DRG – *Delonix regia* gum; KS – potassium sorbate**Table 2: Some physical properties of reconstituted amoxicillin suspension dosage forms**

Batch	Flow rate (ml/s)	Viscosity (Centipoise)	% Decrease in Viscosity with NaCl addition	Redispersibility No	Degree of flocculation
AMX0	0.45±0.03	1438±8.89	-	5.67±0.88	-
DRG.5	0.43±0.02	1442±4.10	-	1.00±0.00	2.33
DRG.75	0.33±0.03	1473±10.14	-	2.33±0.33	2.67
DRG1	0.25±0.03	1488±5.04	-	3.67±0.33	3.67
DRG.5S2	0.82±0.05	1319±10.59	8.50	1.00±0.00	2.67
DRG.75S2	0.53±0.02	1349±3.18	8.40	2.67±0.33	3.33
DRG1S2	0.45±0.02	1397±9.13	6.10	3.00±0.00	3.83
DRG.5S4	2.57±0.12	1195±3.48	17.13	1.00±0.00	2.00
DRG.75S4	1.59±0.07	1322±11.79	10.25	1.67±0.33	2.00
DRG1S4	1.28±0.05	1333±6.93	10.42	2.00±0.00	2.00
HPMC.5	0.15±0.02	1481±5.00	-	5.67±0.33	2.00
HPMC.75	0.12±0.02	1501±5.55	-	6.67±0.33	2.33
HPMC1	0.09±0.01	1506±7.37	-	7.33±0.88	3.33
HPMC.5S2	0.41±0.03	1314±3.21	11.28	3.67±0.33	1.83
HPMC.75S2	0.39±0.05	1386±3.48	7.66	5.00±0.00	2.33
HPMC1S2	0.31±0.03	1483±4.04	1.55	6.33±0.33	2.67
HPMC.5S4	0.83±0.06	1196±4.41	19.24	4.67±0.88	2.00
HPMC.75S4	0.61±0.03	1341±2.91	10.66	5.33±0.88	2.67
HPMC1S4	0.45±0.05	1427±7.69	5.25	7.00±0.58	3.00
CMC.5	0.08±0.01	1595±17.68	-	7.33±0.33	1.67
CMC.75	0.05±0.01	1643±15.72	-	8.33±0.33	1.67
CMC1	0.04±0.00	1700±7.84	-	10.67±0.33	1.83
CMC.5S2	0.33±0.05	1352±6.89	15.23	6.33±0.33	1.00
CMC.75S2	0.24±0.02	1482±8.82	9.80	8.00±0.58	1.00
CMC1S2	0.15±0.02	1565±11.78	7.91	9.33±0.33	1.33
CMC.5S4	0.45±0.03	1328±7.84	16.74	5.33±0.33	3.00
CMC.75S4	0.34±0.02	1358±6.17	16.74	7.00±0.00	3.33
CMC1S4	0.34±0.04	1469±7.31	13.59	8.67±0.67	4.00
Amoxil (GSK)	0.34±0.04	1372±9.53	-	7.67±0.88	5.83
Amoxicillin (Teva)	0.27±0.03	1383±11.85	-	8.00±0.00	6.17

Photomicroscopy of the suspension

A drop of the suspension was smeared on a microscope slide and viewed at x 40 magnification on the Nikon eclipse microscope (model ME 600, Nikon, Melville, NY, USA) fitted with Link system software. The live image was captured on the computer LCD.

Statistical analyses

All the evaluation tests for the products were conducted in triplicates and the results reported were means ± standard

deviation computed with Excel 2007. The results were further subjected to analysis of variance using ANOVA single factor package in Excel 2007.

RESULTS AND DISCUSSION

The yield of gum from *Delonix regia* seeds after the purification process was 16.69±0.52%. Table 2 shows some of the physical properties of the reconstituted amoxicillin suspension. The flow rate of the various batches decreased

with increase in the concentration of the suspending agents, and may be explained by the increase in the viscosities of the products. At similar concentrations, products formulated with sodium carboxymethyl cellulose had the highest viscosity values, while the ones formulated with *Delonix regia* gum had the least and these were clearly translated to their flow rates (Table 2). Higher suspension viscosity tends to slow down the rate of particle sedimentation in accordance to Stokes law but may not prevent the incidence of caking when the particles eventually sediment. This informs the use of electrolytes to cause flocculation of the suspended particles via the reduction of the zeta potential of the system. Addition of sodium chloride as flocculating agent decreased viscosity and invariably increased flow rate. Percentage reduction in viscosities of the products upon NaCl addition was most pronounced in products formulated with CMC while the ones formulated with HPMC were most resistant to it (Table 2). It has been generally reported that presence of electrolytes in polymer dispersions reduces viscosity due to interruption of polymer framework, [12-14] however, the higher lability of CMC to this effect in comparison to DRG or HPMC as a suspending agent in the present study is not immediately explainable, unless it is tied to the reasoning that in the aqueous environment, the dissociated sodium ion from CMC may also contribute to the disentanglement of the polymer framework. Generally, the differences between the viscosities of the formulated products are significant ($p < 0.05$) and so are the ones between them and those of the commercial products. It is however noteworthy that the viscosities of products formulated with DRG enabled pourability and hindered spillage from the container, except for the ones containing NaCl at 0.04%, as is evident from their flow rates (Table 2).

Sedimentation volume is a pointer to flocculation/deflocculation in a suspension dosage form. The effects of type and concentration of suspending agent and concentration of flocculating agent (NaCl) on sedimentation volume of the products are depicted in Figs. 1-3. Sedimentation volume was potentiated by increase in concentration of the suspending agents and the order of the potentiation with respect to type of suspending agent is DRG>HPMC>CMC (Fig. 1).

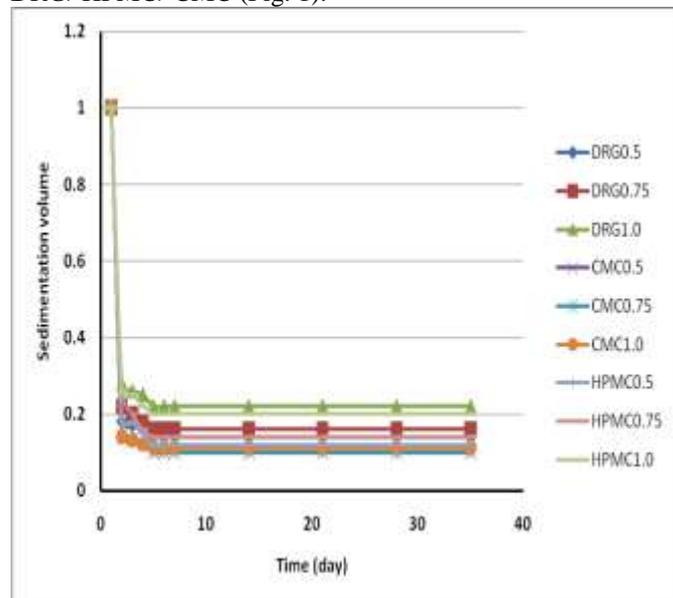


Fig. 1: Effect of type/concentration of suspendants on sedimentation volumes of products

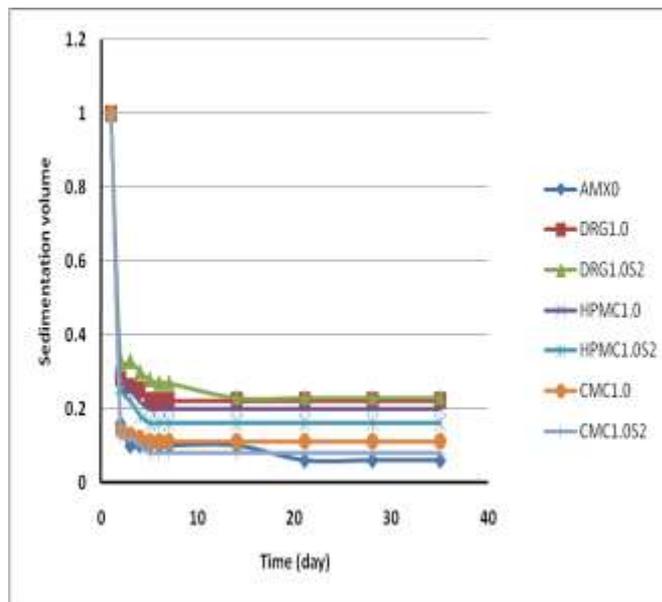


Fig. 2: Effect of absence/presence of NaCl on sedimentation volumes of products

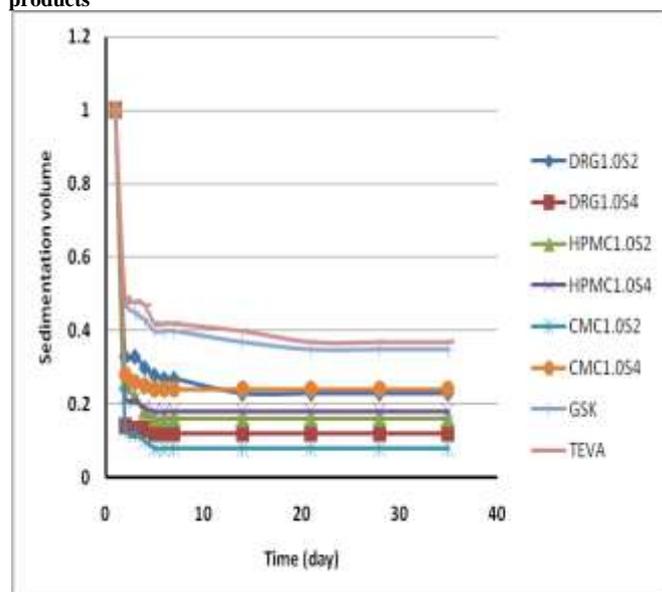


Fig. 3: Effect of NaCl concentration on sedimentation volume of products

The effect of concentration of the suspending agents on sedimentation volume may be attributed to the reported linear relationship between their concentration and viscosity of their aqueous dispersions [15] in conjunction with Stokes law, which reveals an inverse relationship between sedimentation rate and the viscosity of the dispersion medium. [16] The effect of type of agent on this parameter however cannot be explained by viscosity only since the viscosities of products formulated with DRG are less than those of products containing either HPMC or CMC. It is possible that since DRG is a natural polymeric material some of its metallic contents might be involved in some level of flocculation with the suspended drug particles. Fig. 1 also shows that at 1.00% DRG imparted the highest sedimentation volume, so it was selected for the flocculation test using NaCl. The effect of flocculating with NaCl at 0.02% on sedimentation volume of products is shown on Fig. 2. It is apparent from the figure that at 1.0% of DRG, HPMC, or CMC, and 0.02% NaCl, that the order of potentiation of sedimentation volume still remained DRG>HPMC>CMC.

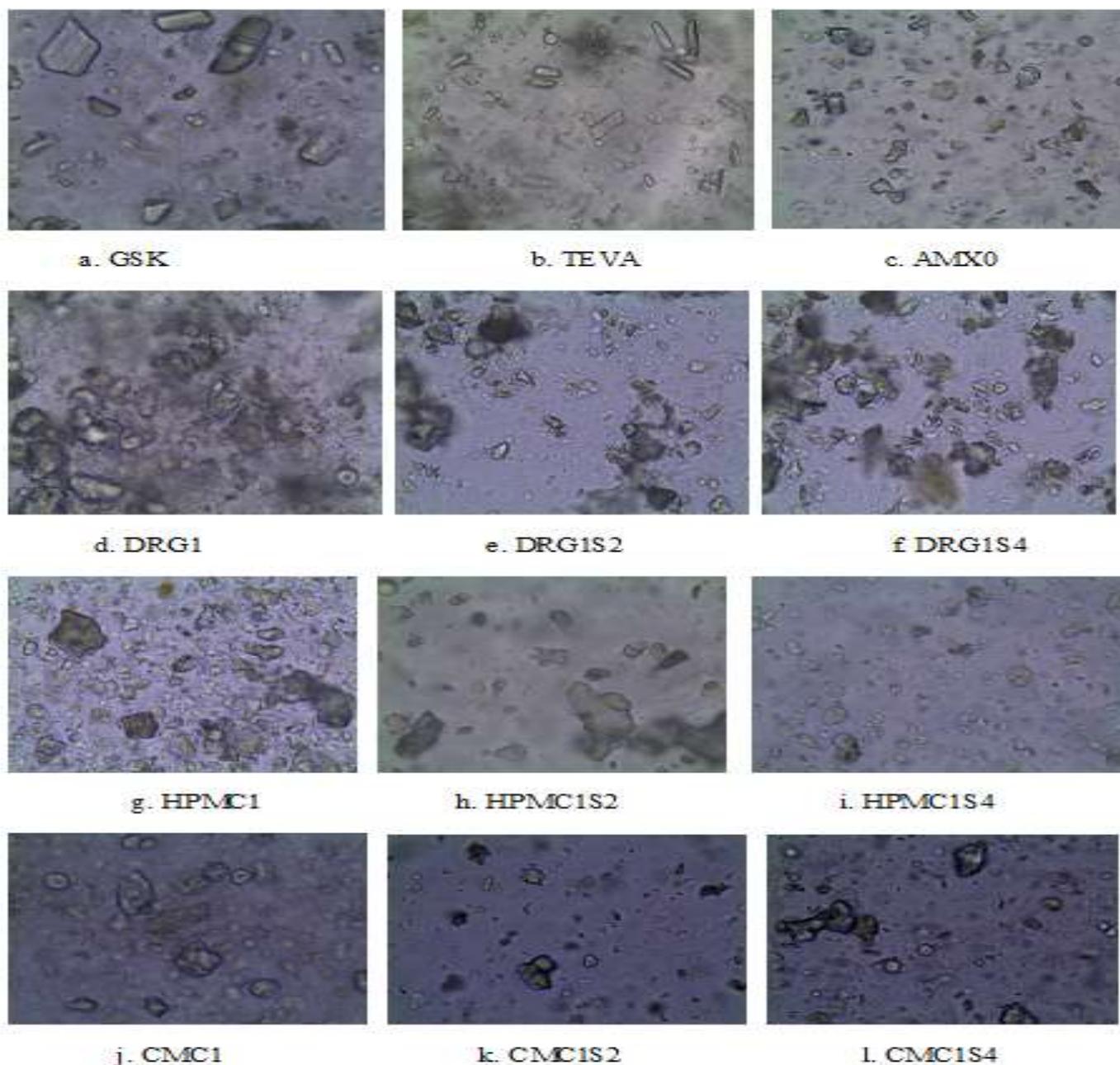


Fig. 4: Photomicrographs of commercial amoxicillin suspension (a and b) and test products (c to l).

At polymers and NaCl concentrations of 1.0% and 0.04% respectively, sedimentation volume was of the order CMC>HPMC>DRG (Fig. 3). The sedimentation volumes of the Innovator (GSK) and generic (TEVA) were higher than those of DRG, HPMC and CMC (Fig. 3). When translated to degree of flocculation, the order was very obvious: TEVA>GSK>CMC1S4>DRG1S2>HPMC1S4 (Table 2). The decrease in sedimentation volume and degree of flocculation with increase in NaCl concentration in suspensions containing DRG may be attributed to the higher interaction between the drug particles and the electrolyte thereby leading to the reduction in bridge formation between floccules.^[11] In contrast, increase in electrolyte concentration potentiated both parameters in products containing CMC and this observation cannot be accounted for by viscosity increase (Table 2). It was observed above that percentage reduction in viscosity with increase in NaCl concentration was highest in CMC containing products, so the higher degree of flocculation at 0.04% of NaCl may be pinned to

greater reduction in zeta potential on the surface of the dispersed particles with decrease in the viscosity of the dispersion medium.

The redispersibility number for the products is shown in Table 2. The order of increasing redispersibility number of some selected products is as follows: DRG1S2<DRG1<HPMC1S4<HPMC1<GSK<TEVA<CMC1S4. The ease of redispersion of a suspension dosage form gives insight into the structure and strength of the sediment formed. Easily redispersed sediment is likely loose structured in comparison to less loose structured sediment which demands more shaking to effect its redispersion. Ease of suspension redispersion is a desirable attribute of a well formulated product because it ensures uniformity of dosage units. It is worthy of note from this study that DRG at 1.0% concentration, and also in combination with 0.02% NaCl gave flocculated products that were most easily redispersed even in comparison to very popular commercial products.

The photomicrographs of some of the products are displayed in Fig. 4. The particles shapes of GSK, TEVA and the test amoxicillin are planar, acicular and mixed circular and planar respectively (Fig. 4 a, b and c). Incorporation of suspending agents caused dense coating of the drug particles by the polymeric materials (Fig. 4 d, g and j). On the addition of NaCl at 0.02%, the dense coatings thinned out as a result of viscosity reduction, but “string” formation between adjacent particles is visible in DRG1S2 (Fig. 4 e). This explains the increased sedimentation volume of this product since the “stringed” particles settled to occupy higher volumes than the “unstringed” ones. For HPMC1S2 and CMC1S2, the thinning out of the suspending agent upon addition of NaCl was very obvious (Fig. 4 h and k) but “string” formation was absent. At NaCl concentration of 0.04% however, the “stringing” effect was very visible in CMC1S4, minimal in HPMC1S4 and very clear thinning out occurred in DRG1S4. These effects explain the measurable increase in sedimentation volume of CMC1S4, decrease in DRG1S4 and minimal improvement in that of HPMC1S4. For GSK and TEVA, the ingredients and the formulation methods employed in their production are the exclusive knowledge of their manufacturers. Nevertheless, from the shapes of their crystals, their relatively higher degrees of flocculation may be related to the architecture of their sediments. Acicular and planar particles settle mainly without forming dense packing due to the spaces between the particles. And if their particle size distributions are narrow there may be very few smaller particles to fill the spaces. The shapes may also explain the contrast between the degrees of flocculation and the ease of redispersion of the commercial products. This is because being acicular or planar, upon sedimentation the first few layers may most likely have particles lying flat on their surfaces or sides rather than erect or at an angle. This settling behaviour may enhance adhesion between the particles and the container thereby requiring longer agitation to effect redispersion unlike in the test products in which there are mainly circular and some planar shaped particles.

Delonix regia seed gum from this study has demonstrated remarkable ability to function as a suspending agent in liquid dosage forms. The qualities of products formulated with it compared very well and for redispersibility is significantly better ($p < 0.05$) than products formulated with standard suspending agents and the two popular commercial products in Nigeria markets. It is worthwhile to further exploit this seed bearing in mind that its other products (oil and roughage) may be useful as fuel and animal feed.

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