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INVESTIGATION OF *CHRYSOPHYLLUM AFRICANUM* (SAPOTACEAE) SEED GUM POTENTIAL AS A BINDER IN METRONIDAZOLE TABLET FORMULATION

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ABSTRACT

Background and aim: *Chrysophyllum africanum* (Sapotaceae) seed gum was investigated as a potential binder in metronidazole tablet formulation and to compare same with existing standard binders so as to determine its binding efficiency in the dosage form.

Methods: The seed gum was extracted and phytochemical parameters determined. Polyvinylpyrollidone BP, Acacia gum BP and *C. africanum* gum mucilage at concentrations of 2.5, 5, 7.5 and 10%w/v each were used to wet granulate the metronidazole/excipient powder blend, and formulated to contain 400 mg main ingredient per tablet. The physicochemical properties (angle of repose, flow rate, bulk and tapped densities, Haunser's ratio and compressibility index) of the granules were also determined. Granules were compressed using Manesty single punch tableting machine at 30 N/m^2 compression pressure, and the physicochemical properties of the tablets (hardness, friability, weight uniformity, disintegration time) assessed.

Results and Discussion: Phytochemical screening showed the presence of polysaccharides, and absence of alkaloids, tannins, flavonoids, glycosides, saponins, anthraquinones and terpenoids. The physicochemical properties of the granules were within standard limits for good flowability and compressibility, as revealed by weight uniformity values for all types and concentrations of binders (ranged from 0.5093 mg to 0.5310mg for Acacia, 0.5022mg to 0.5104mg for PVP, and 0.5045mg to 0.5197 mg for CAG respectively. Results for hardness test showed a range of 3.20 – 6.20 kgf for Acacia, 3.85 – 6.75 kgf for PVP, and 3.60 – 6.90 kgf for CAG. Generally, the tablet hardness and disintegration time increased with increased binder concentration.

Conclusion: *C. africanum* seed gum had a comparable good binding property at concentrations of 5 – 10%w/v to those of acacia and polyvinylpyrrolidone BP powders. It can therefore be used as a substitute in the formulation of metronidazole tablets to reduce the unit cost of production of the dosage form thus enhancing affordability and patient compliance.

Keywords: *Chrysophyllum africanum*, seed gum, binder, polyvinylpyrolidone, Metronidazole tablet.

INTRODUCTION

The creation and manufacture of pharmaceutical dosage forms have been the centre of pharmacy practice for the past thousand years. Tablets are solid dosage forms produced by the compaction of powders or granules using relatively high pressures from punches within a confined space known as die in a tableting machine. They are the most popular and versatile dosage forms in pharmaceutical care services and can be designed to achieve diverse drug delivery systems [1,2]. Binders are one of the main ingredients required in tablet formulation, as they impact cohesiveness on the powders thereby improving their flow and compaction properties. Effectiveness of these binders can be better at high concentrations while some achieve same values at low concentrations. Metronidazole is a synthetic antibiotic derived from azomycin, a nitroimidazole produced by the genera *Actinobacteria* and *Proteobacteria*. The compound has been found to be effective against *Trichomonas vaginlis*, dysentery and liver abscess produced by the intestinal protozoan parasite, *Entamoeba histolytica*. It has also been found to be efficacious against *Giardia lamblia*, another intestinal parasite that causes malabsorption and epigastric pain [3].

Chrysophyllum africanum, known as Africa star apple is indigenous to Africa. In Nigeria, it is widely spread in lowland tropical rain forest, fruiting in July and ripens between December and March [4]. Typical of agricultural produce in Africa, poor storage of *C. africanum* fruits leads to wastage that is obvious on inspection of refuse dump sites and markets during the ripening season of the fruits. The fruit apart from its food and nutraceutical properties, may be harnessed for pharmaceutical excipient purposes by indigenous industries to further improve its economic value, encourage large scale cultivation and reduce unemployment [5].

Gums and mucilages are the most commonly available plant ingredients with a wide range of applications in pharmaceutical and cosmetic industries. They are being used as pharmaceutical excipients due to their abundance in nature, biocompatibility, safety and economic factors [6]. Owing to similarity in composition, they yield a mixture of sugars and uronic acid on hydrolysis. Being hydrophilic in nature, they combine with water to form viscous solutions or gels having different properties [7]. Gums are colloidal in nature, contain high amounts of sugar (and are closely allied to pectin) which render them soluble in water either completely or to form gels, but they are insoluble in alcohol and ether. The polymeric nature of gums permits their use in the formulation of delay released dosage forms within certain concentration range as reported by Okoye and Ndiwe [5], hence improving patient's compliance.

MATERIALS AND METHODS

Materials

Materials used include: Metronidazole powder BP, Acacia gum BP, Polyvinyl pyrrolidone BP powder and Talc powder BP (all of CDH Vardaan, Daryagan, New Delhi, India). Others include lactose BP powder (Danone® Germany), Ethanol (Analar® BDH Limited Poole, England) Hydrochloric acid (Analar® BDH Limited Poole, England). These chemicals were supplied by Sonitex Nigeria Limited. Benin City, Edo State, Nigeria. *Chrysophyllum africanum* fruits were purchased from a local market at Okada, Edo State, Nigeria. The fruits were

authenticated in the herbarium of University of Benin by Professor MaConald Idu (Taxonomist) with herbarium number UNB/56/04.

Equipment

Single Punch Tableting Machine (Manesty, England), Tablet friabilator (FTA-024 Technmel, USA), Monsanto hardness Tester (Monsanto Chemical Company, USA, Disintegration Test Apparatus (Type HUANHSIN 910-21824), USP Dissolution Apparatus (Paddle 11), UV-visible spectrophotometer (Labtect® Microprocessor UV-VIS Double Beam, AVI-2802) were used.

Preparation of seeds

Seeds were removed from *C. africanum* fruits, air-dried in the sun for 7 days, mechanically cracked using a nutcracker for the mesocarp to be removed. Resultant mesocarps were further air-dried for 5 days, followed by oven-drying at 80^{o}C for 8 hours.

Gum extraction and purification

Gum extraction was accomplished using the method of Okoye and Ndiwe [5] with slight modifications. Dried mesocarps (400 mg) were milled using a locally fabricated milling machine and 250 mg weighed and converted into a slurry by adding distilled water up to 2500 ml mark in a stainless steel container and allowed to stand for 24 hours with intermittent stirring. Mixture was strained using a muslin cloth and mucilage precipitated by mixing with three times its volume of ethanol. Suspension of precipitated gum was centrifuged at 3000 rpm for 15 minutes and gum harvested after decanting the supernatant. The latter was soaked in the precipitating anti-solvent (ethanol) for 8 hours to remove entrapped water. Product was air-dried, heated in hot air oven at 60^{o}C for 1 hour, cooled, milled into fine powder and stored in a desiccator for further use.

Phytochemical screening of gum

Phytochemical tests were carried out to determine the presence of basic phytometabolites and reducing sugars according to Okoye and Ndiwe [5].

Preparation of metronidazole granules

The wet granulation method [8] was employed to produce 12 batches of granules each suitable for preparing 50 tablets using *C. africanum* gum (CAG), polyvinylpyrrolidone (PVP) and acacia gum mucilage respectively as binders at 2.5, 5, 7.5 and 10% $^{w}/_{v}$. Each batch consisting of10 g (400 mg main ingredient per tablet) of metronidazole powder, lactose and corn starch powders of adequate amounts were sieved and dry mixed using a spatula in a porcelain mortar. Powder was then moistened with each of the binder mucilages using a volume equivalent to concentration of 2.5, 5, 7.5 and 10% w/v mixture kneaded with a spatula to form a damp mass which was screened using a sieve of aperture size BSS7 and dried in the oven at 60^{o}C for 30 minutes. Dried granules were further sieved with sieve of aperture size BSS10, packed in airtight containers over silica gel for further analysis.

Determination of physicochemical properties of metronidazole granules

For this purpose, granules were evaluated for angle of repose, flow rate, bulk and tapped densities, Hausner's ratio and Carr's index.

Angle of repose (^{o}) $tan\theta = \frac{h}{r}$ ----------=1

Where h, is the height of the cone formed, and r, the radius of the base of the cone.

Flow rate. This was determined using the Erweka Granules Flow Tester. Fifty grams of the granules were weighed into funnel and allowed to flow through the orifice of the equipment. The time taken for the granules to pass through was noted and the rate of flow per second was calculated from the formula:

$$\text{Flow rate (g/sec)} = \frac{weight\ of\ granule\ (g)}{Time\ of\ flow\ (\text{sec})} - 2$$

Bulk and tapped densities. Granules (50 g, Wo) were carefully placed in a measuring cylinder and the bulk volume occupied by each of the batch samples without tapping was noted. Bulk density was calculated according to the equation below. The bottom of the cylinder was tapped 100 times on a table top until no change in volume was observed. Tapped volume occupied was noted. Tapped density was calculated as the ratio of weight of granules to the tapped volume.

$$\text{Bulk density} = \frac{weight\ of\ granule\ (g)}{Bulk\ volume}\ (\text{g/cm}^3) \text{ ---------- 3}$$

$$\text{Tapped density} = \frac{weight\ of\ granule\ (g)}{Tapped\ volume\ (cm^3)}\ (\text{g/cm}^3) \text{ ---------- --4}$$

Hausner's ratio and Carr's index. This was calculated as the ratio of tapped density to bulk density of the samples.

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density} \text{ --- 5}$$

Carr's (compressibility) index (%)

$$= \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times \frac{100}{1} \text{ --------6}$$

Compression of granules into metronidazole tablets

Bulk granules were treated with 0.5% w/w each of talc and magnesium stearate acting as glidant and lubricant respectively in a tumbling mixer for 5 minutes. Granules were compressed into metronidazole (200 mg) tablets with a compression weight of 340 ± 5 mg using a Manesty Single Punch tableting machine, at 30 N/m^2 compression pressure. Compressed tablets were dusted and stored in air-tight glass bottles for 24 hours at room temperature for further evaluation.

Evaluation of the physicochemical properties of metronidazole tablets

Tablets were evaluated for weight uniformity, crushing strength, friability, disintegration time, binder efficiency and dissolution profile.

Weight uniformity test. The BP (2004) method was used. Twenty tablets were randomly selected from each batch, weighed individually and collectively and mean weight recorded. Percent coefficient of the tablet weight variation was calculated as follows:

$$\text{Percent (\%) variation} = \frac{standard\ deviation}{Mean\ weight} \times \frac{100}{1} \text{ ---------- 7}$$

Hardness test. Crushing strength of six tablets randomly selected from each batch was determined using the jaws of Monsanto Hardness Tester and the mean calculated.

Friability test. Ten tablets were randomly selected and their weights recorded. Tablets were placed in the Erweka Tablet Friability Tester and set to rotate at 25 rpm for 4 minutes. Tablets were collected, dusted and re-weighed. The difference in weight was determined and the loss expressed as percentage.

Disintegration test. Six tablets were selected randomly for each batch. Disintegration time

for each batch was determined using the Erweka disintegration apparatus. Distilled water 700 ml was used as the medium, maintained at 37 ± 1°C. One tablet was placed in each of the six tubes of the assemblage. The time taken for each individual tablet to break, and the particles pass through the wire mesh was recorded. Average time for six tablets was taken as the disintegration time of the batch.

Statistical Analysis The statistical analysis of the generated data was done by one-way Analysis of Variance of the means (ANOVA) at the 5% significance level using Microsoft 2008 excel package.

RESULTS AND DISCUSSION

Physicochemical properties of *C. africanum* seed gum

Results of the physicochemical properties are presented in the Table 1.

Table 1**:** Physicochemical and organoleptic properties of C. *africanum* gum

Parameter	Result
Percentage Yield	15.81%($^{w}/_{w}$)
Organoleptic properties	
Colour	Light Brown
Odour	Odourless
Taste	Bland
Solubility	
Water	Slightly Soluble
Acetone	Insoluble
Ethanol	Insoluble
Chloroform	Insoluble

The ability of excipients to provide their intended functions and for the drug to be pharmacologically active throughout its shelf life must be established. The information obtained should justify the choice, concentration and characteristics that may influence the final product [8b]. Gum from the seeds of *C. africanum* was studied to determine its usefulness and applicability. Yield obtained (15.81%) was compared with that of similar gum precipitated with ethanol and acetone reported by Okoye and Ndiwe [4], 12 and 19.63%, and Ologunagba *et al*. [9], 15.43 and 17.35%. It has been observed that extraction yield from crude plant material sources (natural gums) vary depending on the environmental conditions (e.g, soil type, climate, plant age), gum source (seed or bark) and extraction methods/techniques [10,11]. The organoleptics as observed in the Table 1 agreed with previously documented observations [5, 12].

Phytochemical screening of *Chrysophyllum africanum* seed gum

From the results of the phytochemical screening, the gum contained entirely polysaccharides. Other known basic phytometabolites like alkaloids, anthraquinones, tannins, flavonoids, glycosides and saponins were absent.

Controlled hydrolysis and detection of polysaccharides in the hydrolysate carried out by modifying the method adopted by Okafor *et al*. [13] indicated that the gum contains polysaccharides which is the major component of pharmaceutical gums [8, 14].

Physicochemical properties of Metronidazole granules

Table 2 showed the results of the physicochemical properties of metronidazole

granules and indicate that the granules had good flow and compressibility properties.

Table 2: Physicochemical properties of metronidazole granules

Binder concentration	**Angle of Repose (º)**	**Bulk Density(g/cm^3)**	**Tapped Density (g/cm^3)**	**Bulkiness (g/cc)**	**Compressibility Index (%)**	**Hausner's Ratio**	**Flow rate (g/secs)**
2.5% Acacia	26.98	0.555	0.714	1.802	22.27	1.29	0.625
5% Acacia	27.85	0.526	0.612	1.901	13.77	1.16	0.571
7.5% Acacia	28.44	0.493	0.541	2.028	8.87	1.12	0.556
10% Acacia	35.42	0.503	0.588	2.000	14.97	1.18	0.450
2.5% PVP	24.78	0.455	0.571	2.200	20.32	1.25	0.911
5% PVP	25.11	0.476	0.541	2.100	12.01	1.14	0.712
7.5% PVP	30.96	0.435	0.513	2.300	15.20	1.18	0.425
10% PVP	34.09	0.426	0.488	2.350	12.70	1.15	0.531
2.5% CAG	26.21	0.465	0.571	2.150	18.55	1.23	0.833
5% CAG	30.84	0.408	0.513	2.451	20.47	1.26	0.625
7.5% CAG	31.72	0.47	0.555	2.150	16.21	1.19	0.83
10% CAG	33.21	0.47	0.625	2.100	23.84	1.31	1.25

Table 3. Mean and Standard deviation for physicochemical properties of metronidazole granules

Parameters	**Acacia binder**	**PVP binder**	**CAG binder**
Angle of repose (^{0})	29.673 ± 3.878	28.735 ±4.560	30.495 ± 3.024
Bulk density (g/cm^3)	0.519 ± 0.028	0.448 ± 0.028	0.453 ± 0.030
Tapped density(g/cm^3)	0.613 ± 0.073	0.528 ± 0.036	0.566 ± 0.046
Bulkiness (g/cc)	1.933 ± 0.103	2.238 ± 0.111	2.213 ± 0.161
Compressibility index	14.972 ± 5.536	15.058 ± 3.766	19.768 ± 3.226
Hausner's ratio	1.183 ± 0.073	1.184 ± 0.052	1.248 ± 0.051
Flow rate (g/secs)	0.551 ± 0.073	0.635 ± 0.220	0.884 ± 0.263

Physicochemical properties of metronidazole tablets

The results of the physicochemical properties are as summarised in Table 4.

Table 4. Physicochemical properties of metronidazole tablets

Binder Concentration	Weight uniformity test (mg)	Variation of Tablets (%)	Friability test (%)	Hardness test (kg/cm^3)	Disintegration test (minutes)	Binder Efficiency
2.5% Acacia	0.560 ±0.036	6.43	2.87	1.67	1.01	0.576
5% Acacia	0.490 ±0.031	6.33	4.18	0.83	1.36	0.146
7.5% Acacia	0.509 ±0.041	8.05	1.54	1.33	2.13	0.432
10% Acacia	0.523 ±0.038	7.18	0.39	1.50	7.15	0.538
2.5% PVP	0.509 ±0.048	9.44	18.79	3.17	0.37	0.456
5% PVP	0.502 ±0.035	6.97	2.40	3.50	0.50	2.911
7.5% PVP	0.490 ±0.052	10.62	0.83	4.67	5.40	0.104
10% PVP	0.447 ±0.051	11.42	0.43	5.52	8.10	1.581
2.5% CAG	0.449 ±0.061	13.59	78.87	0.57	0.29	0.025
5% CAG	0.467 ±0.042	8.99	38.28	6.73	0.34	0.515
7.5% CAG	0.482 ±0.035	7.26	37.58	0.52	0.33	0.040
10% CAG	0.520 ±0.050	9.62	0.99	1.04	0.43	2.349

Crushing strength/hardness test is an inprocess means of assessing the ability of tablets to withstand pressure or stress of handling during packaging and transportation such as breakage, chipping and crumbling; yet not so hard as to delay disintegration [15]. The greater the compression pressure applied, the harder the tablet [16]. The BP [17] recommends a crushing strength of 4 - 8 kgf (49.0333 – 78.4532 N); and a minimum of 4 kgf. Allen *et al*., [18], also reported that for mechanical strength of a tablet to be satisfactory, the minimum required should

be 4 kgf. The result showed that the hardness of the tablets increased with increase in binder concentration. Disintegration time is a rate limiting step in drug absorption and the type and concentration of excipients may influence disintegration and consequently bioavailability of drugs. Results obtained herein showed that disintegration time values differed significantly between binders at the same concentration, but there was no significant difference between different concentrations of a binder at $p < 0.05$. Binder efficiency measures the interaction between tablet hardness, friability and disintegration time. A high binder efficiency implies that tablets formulated with that concentration of binder, possesses excellent hardness, low friability (< 1%) and short disintegration time [19,20]. The results showed that the different tablets formulated from the various batches had good binder efficiency. Natural polysaccharides are widely used in the pharmaceutical and food industry as excellent arid additives due to their low toxicity, biodegradable availability and low cost. They are used to modify the release of drug thereby, influencing the absorption and subsequent bioavailability of the incorporated drug. Furthermore, they act as vehicles which transport the incorporated drug to the site of absorption and are expected to guarantee the stability of the drug, the precision and accuracy of the dosage, and also improve on the organoleptic properties of the drugs where necessary in order to enhance patient adherence.

CONCLUSION

At a concentration of 10% w/v of *C. africanum* seed gum, the values of tablet properties obtained were within the acceptable standard limits. Hence, *C. africanum* seed gum (CAG) had good binding properties when compared with the polyvinylpyrrolidone (PVP) and can be used as an acceptable substitute in the formulation of metronidazole. Further studies should be carried out to fully characterize the gum and assess it as binder at higher concentrations other than the concentration already studied. Attempt should also be made to bleach the gum for aesthetic gains.

Conflict of interest: The Authors hereby declare that there is no conflict of interest in this research.

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