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Gum from the bark of *Anogeissius leiocarpus* as a potential pharmaceutical raw material – granule properties

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Abstract

With the continuous effort to discover and produce cheap but high quality excipients for drug production *Anogeissius leiocarpus* gum (ALG), a brownish exudate obtained from the bark of *Anogeissius leiocarpus* a commonly occurring tree in Nigeria has been investigated for its potential as a binder in tablet formulation, by studying the properties of metronidazole granules prepared with it as binder. The properties of the resulting granules were compared with those of corn starch and poly vinyl pyrolidone (PVP) at various concentration levels. The granule elegance, mean particle size and particle size distribution, bulk, tapped and true densities, friability, angle of repose and compressibility (Carr's index) were determined and used to assess the gum relative to PVP and corn starch in granule formulation. Results of the various studies showed that lower concentrations of ALG produced granules that were quite comparable to those prepared with corn starch and PVP. However, higher concentrations of ALG produced granules that were comparatively different from those of corn starch and PVP. The optimal binding concentration of ALG lies within the concentration range of 1 – 3 % $^{w}/_{v}$. *Anogeissius leiocarpus* was found to have good binding potential for the formulation of Metronidazole granules.

Keywords: *Anogeissius leiocarpus gum* (ALG); Corn starch; PVP; Metronidazole; Granule properties.

Introduction

Anogeissius leiocarpus (D. C.) Guil. & Perv family Combretaceae is a tree that occurs widely in the savannah areas from the driest region to the borders of the forest zone and is abundant in Nigeria. The different parts of the plant have various uses in folklore medicine (Keay, 1989). The gum is of very good viscosity and useable as a substitute for, or adulterant of gum Arabic. It can be used in pharmacy as an emulsifying agent (Oliver, 1990). The plant has found wide use among Nigerian herbalists and its infusion or decoction is used as cough medicines, while pulped roots are applied to wounds and ulcers. The decoction of the leaf is used in washing and fumigation. The leaf decoction is used in Nigeria to treat malaria (Bhat *et al.*, 1990). The bark is generally grey, scaly and exudes a sparingly water-soluble, brown gum called "marike" in Hausa.

Gums because of their high viscosity are important pharmaceutical excipients and are very useful in drug formulation as binders in tableting as well as emulsifying and suspending agents in liquid formulations. Several workers (Nasipuri *et al.*, 1996; Kunle *et al.*, 1998; Isimi *et al.*, 2000) in an effort to

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develop new and less expensive local sources of binders have investigated various materials. Most of these materials, however, are also used as food sources. Thus making economic feasibility of their use in the production of pharmaceuticals doubtful. *Anogeissius leiocarpus* bark, which yields the gum, is not generally viewed as being of any economic value and should be a cheap alternative binder in drug formulations.

Binders are the inert glue that holds powders together to form granules which are compressed to form tablets (Aulton, 1988). Binders impart cohesiveness, improve the flowing qualities of powders by forming granules of desired hardness and size and ensure that integrity of granules are maintained and tablets remain intact after compression (Aulton, 1988; Lieberman *et al.*, 1989). The ease of compression as well as elegance of tablets is related to the quality of binder employed in the granulation process (Lieberman *et al.*, 1989). Binders used in wet granulation usually improve dissolution rate of poorly soluble drugs by imparting hydrophilic properties to the granules (Nasipuri and Akala, 1986). They may also alter the effects elicited by a drug (Esezobo, 1986). There is, therefore, the need to properly investigate the properties of a binder before using it in the formulation of pharmaceuticals.

The aim of this study is to investigate the potential of ALG as a binder in tablet formulation by studying the properties of metronidazole granules prepared with it as a binder. These properties will be compared to granules produced with PVP and corn starch as binders.

Experimental

Materials: Lactos, PVP and Corn Starch BP (all from Sigma, Italy) metronidazole (obtained from NIPCO Pharm. Abuja.), acetone (BDH, England), ALG obtained in NIPRD lab as described below, were used.

Purification of gum: The method of Mital and Adotey (1970) was used for purification with some modification. The dried exudate (gum) from the bark of the tree was collected and dissolved in warm distilled water to make a solution, which was passed through a fine muslin cloth to remove solid impurities such as insects and sand. The solution was then precipitated with large volumes of acetone. The precipitate was dissolved in water and again precipitated with acetone. The precipitated gum was collected by filtration using the fine muslin cloth and dried in a hot air oven at 45 ^{0}C. The dried flakes were then pulverized and passed through a no 25 mesh sieve and stored in a dry screw capped bottle until used.

Preparation of metronidazole granules: Granules were formulated according to the method of Nasipuri (1979). 40 g batch of a basic formulation of metronidazole (40%), lactose (40%) and corn starch (20%) as internal disintergrant were mixed for 5 min. in a Kenwood planetary mixer (Type 4142, Japan) and then mixed with equal volume of a predetermined amount of aqueous dispersion of the binding agents (corn starch or PVP at 5%, 7.5% and 10 % $^{w}/_{v}$ concentration levels) or ALG (at 1, 2, 3, 5, 7.5 and 10 % $^{w}/_{v}$ concentration levels) were then added with further mixing. The wet mass was passed through a no 10 mesh sieve and dried at 50 ^{o} for 30 min, after which it was again passed through a no 16 mesh and finally dried at 60 ^{o} for 1 h and stored until used.

Physical characteristics

Appearance: The elegance of the various batches of metronidazole granules was comparatively determined by visual observation. The hardness of the different batches of granules was also determined by pressing the granules between the thumb and the forefinger.

Bulk and tapped densities: 30g of each granulation were poured into a 100ml calibrated glass cylinder through a short-stemmed glass funnel the volume occupied by the granule was noted. The cylinder was then subjected to 250 taps using a stampvolumeter (model stav 2003 J. Engelmann Ag, Germany) the final volume noted, from the values obtained the bulk and tapped densities were calculated.

True density: The weight of pycnometer filled with xylene was determined and 1 g of granules was transferred into the xylene filled pycnometer and the weight determined. The true density was then calculated (BP, 1998). The various densities were used to calculate the compressibility index of the granules.

Granule friability: Only granules retained on sieve no 18 were used for this test. 10 g of the granules of the different batches were subjected to friability test at 25 rpm for 4 minutes using an Erweka double drum friability tester (Copley Tar Erweka, Germany). The granules were then sieved through the same sieve and the weight of granules retained determined. This was expressed as a percentage of the initial weight.

Angle of repose: The angle of repose was determined by measuring the angle formed by the heap of the granules obtained when 30g of each granulation was allowed to flow through a glass funnel (orifice diameter 2 cm) clamped 10 cm above a flat surface. The angle of repose was calculated using the equation below (Aulton, 1988; Lachman *et al.*, 1987).

$\tan \theta$ = Height of cone (h)/ Radius of cone (r)   Eq. 1

Granule size analysis: Eight sieves of the following sizes: 75, 90, 150, 250, 500, 710 and 1000μm were arranged in descending order and 50g from each granulation of each batch was placed on the top sieve and shaken on a sieve shaker (Endecotts, UK) for 15 minutes. The mass of granules retained on each sieve was determined and the percentage of cumulative over size plotted against the sieve size. The mean size of the granules was taken as a 50% cumulative oversize.

Results and Discussion

Based on colour brightness metronidazole granules prepared with PVP were more elegant than those prepared with corn starch and ALG as binder. At low concentrations of ALG (1, 2 and 3 $\%^{w}/_{v}$) the granules formed were comparable to those of corn starch. However at higher concentrations of ALG (5, 7.5, and 10 $\%^{w}/_{w}$), granules produced were grey in colour. It was observed that increasing the concentration of ALG resulted in a progressive diminishing of the whiteness (colour elegance) of the granules this could be due to the light brown colour of the gum. The granules formulated with the various concentrations of ALG were found to be harder than those formulated with PVP. The granules formulated with 3 % $^{w}/_{v}$ ALG were comparatively very harder and coarse.

The values of bulk and tapped densities of the batches of metronidazole granules produced with ALG mucilage were similar to those obtained for corn starch and higher than those of PVP (Table 1). The bulk and tapped densities of the various batches of the granules produced with the different binders generally increased with increase in concentration. This observed increase in the two parameters (bulk and tapped densities) with increasing concentration of binder may be because, at the various binder concentrations employed for the granulation produced granules with large particle size and very small amount of fines Fig.1 and 2 so that there were large granules that resulted in increase in weight per - unit volume (Oladimeji *et al.*, 1998; Naspuri 1975). Higher concentration of binders was generally observed to produce coarser and harder granules with low amount of fines.

The true densities for all the granules prepared with various concentrations of binders were found to increase with increase in binder concentration. This might have resulted from the packing of more particles into the granule due to increased densification due to increased binding power of the particles by the higher concentrations of the binders. The values of the true densities of the granules prepared with ALG are more similar to those of corn starch than those formulated with PVP (Table 1). The values were higher than those for the PVP granules with the density of the 3 % ALG granules for example being almost equal to the granules prepared with 10 % $^{w}/_{v}$ PVP.

Table 1. Some physicochemical properties of metronidazole granules formulated with ALG, Corn starch and PVP as binders.

Binder	Concentration (% w/v)	Bulk density (g/ml)	Tapped Density (g/ml)	True Density (g/ml)	Friability (% $^{w}/_{w}$)	Angle of Repose	Compressibility (Carr's index)	Mean granules size (μm)
Corn starch	5	0.5000	0.5357	1.3484	3.40	17. 38	10.01	680
	7.5	0.5085	0.5556	1.3484	2.60	18.38	11.60	680
	10	0.5100	0.5769	1.3698	1.60	20.22	11.86	705
PVP	5	0.4000	0.5000	1.3012	6.60	15. 33	9.60	580
	7.5	0.4286	0.4688	1.3075	5.40	16. 55	8.56	600
	10	0.4412	0.4615	1.3121	4.80	16. 69	4.40	660
ALG	1	0.4688	0.5172	1.2881	6.60	16.42	9.36	668
	2	0.4890	0.5357	1.3076	2.40	18.37	8.19	680
	3	0.4918	0.5357	1.3277	2.00	20.00	10.36	690
	5	0.5000	0.5455	1.3484	1.20	25.42	21.66	700
	7.5	0.5000	0.5660	1.3484	0.80	36.82	23.33	710
	10	0.5000	0.5769	1.3698	0.80	48.70	28.33	740

Fig. 1 Comparative particle distribution of metronidazole granules formulated with equiconcentration of ALG, Corn starch and PVP as binder

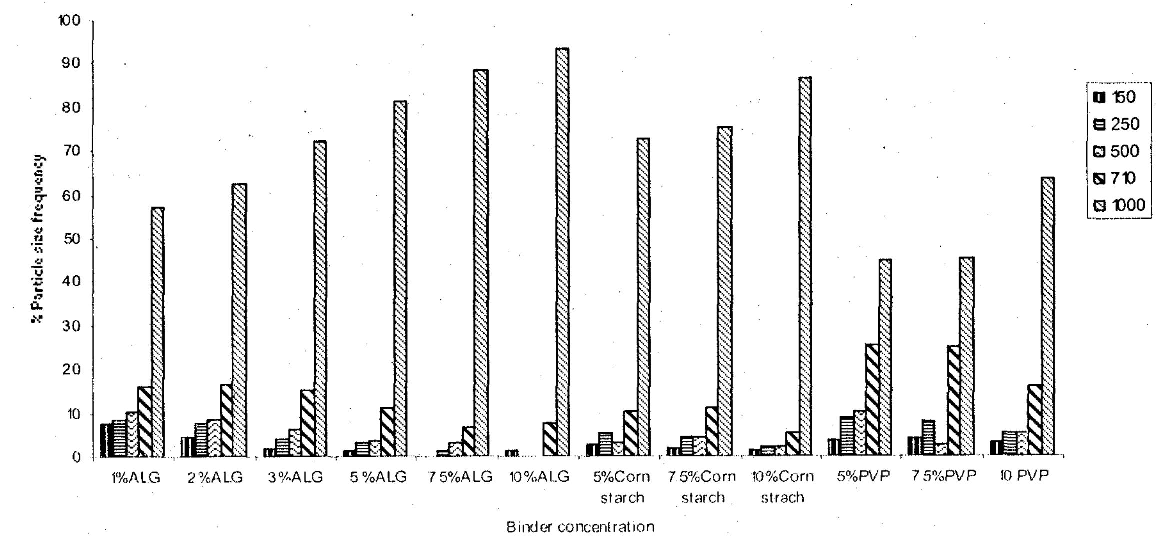

Fig. 2 Particle size and particle size distribution of metronidazole granules formulated with 1, 2 and 3 %w/v ALG and 5, 7.5 and 10 %w/v of corn starch and PVP used as binders.

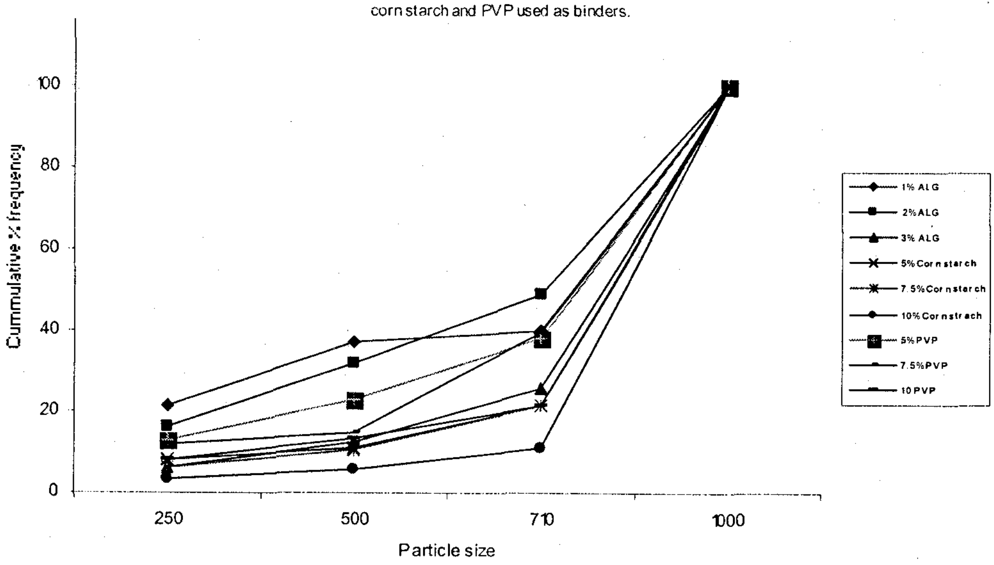

Fig.3 Particle size and particle size distribution of metronidazole granules formulated with equal volume and concentrations of ALG, Corn starch and PVP used as binder .

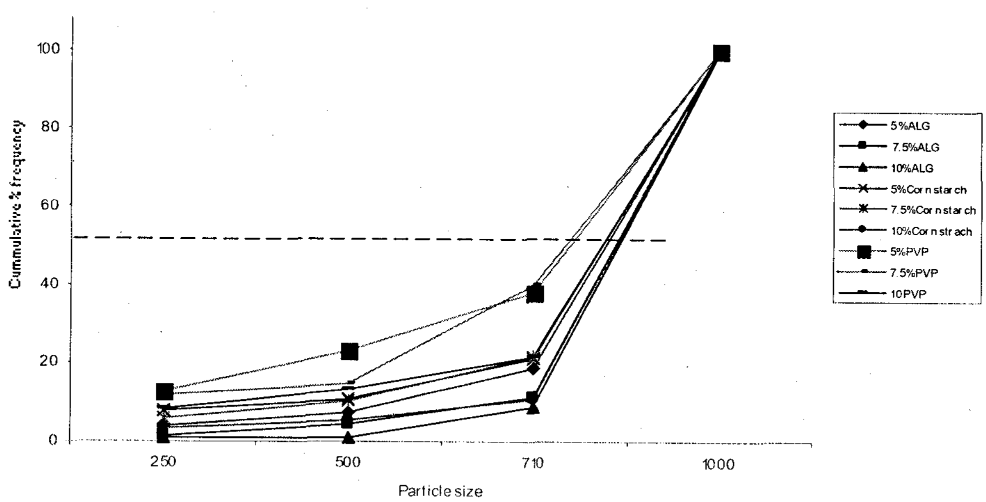

Fig. 1 shows the particle size distribution of the metronidazole granules formulated with ALG, corn starch and PVP at the various binder concentrations. The larger sized granules (500, 710 and 1000 μm) were predominant in all the formulations. The mean particle size of the granules with the various binders and at various concentrations increased with increasing binder concentrations and highest for granules formulated with 10 % $^{w}/_{v}$ ALG (Fig. 2 and 3). At equal binder concentrations, the metronidazole granules formulated with ALG contained granules with higher amount of the larger particle. The particle size distribution of the granules formulated with 3 and 5 % $^{w}/_{v}$ ALG as binder closely resembled those produced with 7.5 and 10 % $^{w}/_{v}$ Corn starch while those 1 and 2 % $^{w}/_{v}$ ALG was similar to that of 7.5 and 10 % $^{w}/_{v}$ PVP. All the formulations, however, contained variable amount of fines (> 250 µm), the amount of fines increased with decreasing binder concentrations and was least for granules formulated with 7.5 and 10 % $^{w}/_{v}$ ALG (Fig. 1).

Granules prepared with ALG were significantly more resistant to friability than those of corn starch and PVP when equal volumes of binders at same concentration were evaluated (Table 1). The results of the simple hardness test performed are also similar to those of the friability test. The granules prepared with 1 %$^{w}/_{v}$ ALG had a relatively high friability, similar to that obtained with 5 %$^{w}/_{v}$ PVP (Table 1). That the friability of all the binders investigated decreased with increase in concentration is not unexpected since granules are expected to be harder as the concentration of binder is increased (Oladimeji *et al.*, 1998). The comparatively lower friability obtained for granules prepared with ALG indicates that it has a higher binder effect than either of the two other binders as earlier observed due the bond strengthening effect of particles within the granules (Nasipuri and Akala, 1986).

The flow of granules is the paramount attributes of granulation. Flow properties of granules are very important in tablet formulation because rapid and reproducible flow of granules is essential if tablet weight and dose uniformity are to be maintained in a batch (Lachman, *et al.*, 1987). The angles of repose and compressibility index are simple indicative parameters by which flow of granular materials can be sassed (Lachman *et al.* 1987). The angle of repose is primarily a function of surface roughness, which is characteristic of the internal friction or cohesion of the granules while compressibility. As expected the angle of repose increased with increased binder concentration for all the different batches of granules studied (Table1). The relatively higher value obtained for the granules prepared with ALG mucilage is most likely due to their large particle size resulting in lower inter particulate friction.

The values of the angle of repose obtained for granules formulated with ALG gum at lower concentration (1, 2 and 3 %$^{w}/_{v}$) were similar to those obtained for corn starch and higher than for PVP granulations (Table 1). The angle of repose of the various granulations increased with binder concentration which is similar to the result for other formulations as observed by Oladimeji *et al.* (1981). As a general rule powders with angle of repose greater than 50^{o} have unsatisfactory flow where as those with angle of repose close to 25^{o} would be expected to have a good flow property (Aulton, 1988). Thus the granules formulated with ALG have angles of repose approaching 50^{o} as the gum concentration increased 10 %$^{w}/_{v}$. This observation could be due to the progressive increase in particle size and coarseness of the granules that probably resulted in increased cohesive force between the granule particles.

The compressibility index (I) (or Carr's index) is another simple method by which the flow of granules or powders could be assessed. The empirical values of (I) can be obtained by mathematical manipulation of the bulk and tapped densities of the granules (Aulton, 1988; Lachman *et al.* 1987). The various batches of metronidazole granules formulated with different concentrations of ALG as binders exhibited results similar to those obtained by the angle of repose experiment. The values of (I) for metronidazole granules formulated with (1, 2 and 3% $^{w}/_{v}$) ALG as binder were found to be similar to those obtained for corn starch but, values of (I) for granules formulated with PVP were lower than those of corn and ALG (Table 1). However all these values were below 15 % which is indicative of excellent flow (Aulton, 1988; Lachman *et al.* 1987) however granules formulated with 5, 7.5 and 10 % $^{w}/_{v}$ ALG concentrations had values of (I) greater than 25% (Table 1). Aulton (1988) regards values of (I) 5 – 15% as (excellent flow), 12 – 16% (Good flow) 18 - 21% (Fair or passable flow), 23 – 35% (Poor flow), 33 – 38 % (Very poor flow) and greater than 40% (Extremely poor flow). Thus all the batches of metronidazole granules prepared with the low concentrations of the gum as binders will be expected to be free flowing, while granules prepared with high gum concentrations is expected to have progressively poor flow.

The results obtained from the various parameters evaluated indicate that metronidazole granules formulated with ALG at low concentration (1, 2 and 3 % $^{w}/_{v}$) exhibited some favorable physicochemical properties closer to those formulated with corn starch than those formulated with PVP. Further studies are being carried out to determine the suitability of the granules in tablets production.

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