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Full Length Research Paper

Impact of Starch Gel on Granule and Tablet Characteristics of the Potent Herbal Extract AM-1

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The ability to convert potent herbal medicines into robust tablet will require a good understanding of certain critical factors such as effect of binder concentration on granule particles and tablets properties. In this study, granules of AM-1, a prototype herbal extract has been produced by the wet granulation process of massing and screening using different concentrations of maize starch gel as binder. The effect of the binder concentrations and granule particles' size on the granules' flow and moisture uptake characteristics as well as, their effect on the friability and tensile strength of tablets produced with the granules were investigated. The AM-1 granules prepared with the different concentrations of maize starch gel as binder were of variable particulate dimensions. The particle size and size distribution of the granules showed a remarkable binder concentration sensitivity with a shift to larger particles with increasing binder concentrations. The flow of the granules as determined by evaluating their angle of repose and Carr compressibility indices showed enhanced flow relative to the unformulated AM-1. At simulated tropical humidity and temperature conditions, the AM-1 granules exhibited binder concentration sensitivity to moisture uptake. There was also a reduction in the moisture uptake ability of the granulated AM-1 relative to the ungranulated sample. The tensile strength and friability of the AM-1 tablets showed binder concentration and granule particle size sensitivity: the duo increased with increase in binder concentrations as swell as particle size. This study has shown the effects of granulation as well as starch gel concentration on some critical formulation properties of an herbal extract AM-1, obtained by freeze drying the aqueous decoction of a powdered root material.

Key words: Herbal extract AM-1, starch gel, binder concentration, granule properties, tablet properties.

INTRODUCTION

There has been renewed interest in the use of natural products as medicines, especially those from plant origin. This is because of their multifunctionality and diverse applications, potency, efficacy and low side effects (Wang and Jiao, 2000). These are among the reasons for the global shift towards natural therapies (Iwu et al., 1997; Raghavendra et al., 2009). In Africa, herbal medicines have continued to play a key role in primary health care delivery with about 80% of the people depending either wholly or partly on herbal medicines (Farooqi et al., 1998). In many developed countries and urban Africa, it serves mainly as an alternative or complimentary medicine. One of the special roles of herbal medicines in Africa is in their efficacy in the management of the many endemic diseases. They have proved especially useful in the management of malaria, which remains a priority disease of Africa because of its enormous economic importance. Their effectiveness and contributions to primary health care is shown by the reduction in excessive mortality, morbidity and disability due to the numerous endemic diseases especially in rural Africa (Briskin, 2000; Okigbo and Mmeka, 2006). Despite the presence of a large variety of plants with confirmed useful pharmacological activity, health benefits and long history of use for the treatment of known ailments and maintenance of health, the place of herbal medicine in the official health care system in Africa continues to face immense challenges (Okigbo and Mmeka, 2006). These include the problems of appropriate standardization, quality control and presentation in appropriate and

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Table 1. Formula for preparation of AM1 granules.

Material	5% Binder (mg)	7.5% Binder (mg)	10% Binder (mg)
AM1	200	200	200
Binder	22.5	22.5	30
Disintegrant	30	30	30
Diluents (lactose)	55	47.5	40
Total weight	300	300	300

acceptable dosage forms. The commonest dosage presentation of most native herbal preparations is as liquids derived from infusions and decoctions (Raghavendra et al., 2009) with the associated problem of large dose volumes, clumsy packaging and poor stability (Okunlola et al., 2007). Solid preparations on the other hand have higher stability, easier to standardize and test for quality which adds to increase their therapeutic acceptance, efficacy and product value (Runha et al., 2001). Tablets are simple and convenient dosage forms that enable accurate tamper proof doses to be delivered. The formulation of herbal medicines into robust tablet presentation is challenging due to the inherent poor tabletting properties of most herbal extracts and powdered plant parts, and limited information on relevant physico-technical properties of these crude drugs in relation to the commonly used excipients (Palma et al., 2002). A wide range of excipients with different functional application are employed in the formulation of tablets. Maize starch is among the widely used excipients in tablets formulation, it is so employed especially because of its multifunctionality and cheapness. The dry maize search is used as disintigrant and diluents while the paste obtained after gelatinization is an effective binder in formulation of granules using the wet granulation process.

AM-1 is a freeze dried decoction of the powdered root of a shrub that grows locally within northern Nigeria. Its anti-malarial potential has been established in our laboratories and is currently undergoing further studies towards its development into a standardized phyto-medicine. Factors such as granulation technique and binder type and concentration have been found to affect the formulation of tablets (Okunlola and Odeku, 2009). Only little information is available on the effect of these factors on the formulation of herbal extracts into granules and tablets. The aim of this study therefore is to establish the effects of wet granulation, maize starch gel as binder and binder concentration variation on some critical granule and tablet properties of an herbal extract using AM-1 and maize starch gel as the prototype herbal extract and binder respectively.

MATERIALS AND METHODS

The materials used were maize starch, sodium chloride and magnesium stearate, ethanol (Sigma–Aldrich Chemie, Germany) and lactose (Hopkin and William, Switzerland). AM-I was produced by freeze drying decoctions of the dried powdered root material using standardized methods in the laboratories of National Institute for Pharmaceutical Research and Development (NIPRD).

Preparation of granules

Quantities of AM-1 (<250 µm), maize starch and lactose, pre dried at 50°C in a hot air oven (Unitemp drying cabinet, Great Britain) for 2 h. The formulation formula stating the amount of ingredient per tablets is presented on Table 1. Quantities of the pre-dried AM-1, maize starch and lactose required to prepare for 50 tablets were mixed for 10 min in a tumbler mixer (JEL-Karl Kolb, Germany).The powder mix was granulated using the massing and screening method (Kunle et al., 2003; Ibezim et al., 2008) . Different concentrations (5, 7.5 and 10% w/w) of maize starch gel were used as the binder and incorporated as 10% w/v gel (Table 1). The wet mass was screened through a granulating sieve (1.6 mm) size and dried in a hot air oven at 50°C for 1 h. The granules were again passed through the sieve and dried at 50°C for another 1 h. The dry granules were stored in an air tight container until used.

Granule size analysis

A set of four sieves (150, 500, 710 and 1000 µm mesh sizes) were arranged in descending order and mounted on a sieve shaker (Retsch As200, Germany). 100 g of each granulation was placed on the top sieve and shaken for 10 min at a vibration interval of 15 rpm/s. The weight of the particles retained in each sieve were determined with an analytical balance (Mettler Toledo, USA), these were then stored in air tight containers for further evaluation. The percentage cumulative over size was determined in relation to particle size. The mean particle size of the granules was taken as 50% cumulative oversize (Builders et al., 2005).

Particle properties

The angle of repose of the granule samples were determined by measuring the internal angle between the surface of the heap of granules obtained when 30 g of granules were 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 1 (Builders et al., 2005). The bulk and tapped densities of 30 g of the granules were measured in a 50 ml graduated measuring cylinder as a measure of densification of the powders. The tapped volume of the granules was then determined using a Stampfvolumeter (STAV 2003 JEF, Germany) until the volume was constant. The compressibility indices of the various granules were determined with the data obtained for the bulk and tapped densities using Equations 2 (Well, 2003; Builders et al., 2005).

$$\text{Angle of repose (Tan } \theta) = \frac{\text{Height of cone}}{\text{Radius of cone (r)}} \quad (1)$$

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad (2)$$

Moisture uptake

Equal quantities of the granulates were placed in 100 ml Petri dishes in an activated desiccating chamber at 25°C for one week to remove any residual moisture. The moisture sorption isotherms of these were then determined by the gravimetric method (Beristain et al., 2006) using an analytical balance (Mettler Toledo, USA). 1 g quantity of each granule sample was then placed in an aluminum foil and put in a hermetically sealed glass chamber containing saturated sodium chloride solution (75% RH) and maintained at 27°C. The samples were weighed at 1 h intervals until equilibrium was attained. The percentage moisture uptake (% MU) at different time (t) was calculated using Equation 3 (Lin and Chen, 2005).

$$\%MU = \frac{M_t}{M_d} \times 100 \quad (3)$$

Where M_t is the amount of moisture uptake at time t and M_d is the dry weight of the material. The profile of percentage weight gain vs. time was then evaluated for each sample.

Compression of granules

Compacts of 300 mg were made from granules of different particle sizes using a single punch power driven tablet press (Shanghai Tianxiang and Chentai Pharmaceutical Machinery Co Ltd, China) at a compression pressure of 27.5 KN. Before each compression, the die was lubricated with a 2% w/v dispersion of magnesium stearate in ethanol. Fifty tablets were made for each sample.

Tensile strength

The hardness of the tablets was determined by diametral compression using a hardness tester (Karl Kolb, Erweka Germany) (Odeku et al., 2005). The dimensions of each tablet were determined using a micrometer gauge (Mitutoyo, Japan) and their tensile strength then evaluated using Equation (4) (Hiestand et al., 1997).

$$\text{Tensile strength} = \frac{2F}{dt} \quad (4)$$

Where F is the load in KN applied to cause diametral fracture of the tablets, while d and t are tablets diameter and thickness respectively.

Friability

The friability of the tablets was assessed using a Roche friability tester (Copley/Erweka, Germany). The machine was set at 25 rpm and allowed to run for 4 min. Six tablets of each sample were selected at random and assessed. The friability (f), was then determined using Equation (5).

$$f = 100.\ (1 - w_o/w) \quad (5)$$

Where w_o is the weight of six tablets before the abrasive test and w is the weight of the tablets after the test.

Data and statistical analysis

All experiments were performed in replicates of three for validity of statistical analysis. Results were expressed as mean and percentage ± standard deviation. Student t-tests were performed on the data sets generated using SPSS software. Differences were considered significant for p values <0.05.

RESULTS AND DISCUSSION

Particle size analysis

The cumulative distributions of the AM-1 granules produced by wet granulation process (Table1), using different concentrations of maize starch gel as binder are shown in Figure 1. The particle size and size distributions of the various granules of the formulated AM-1 varied with variation in the binder concentrations (Figure 1). The formulated AM-1 granules showed decreasing amount of granular fines (150 m) and a higher amount of coarse granules with increasing concentrations of the starch paste due to increasing interparticulate bonding. The average particle size of the AM-1 granules generally increased with increasing concentrations of the starch gel used as binder (Figure 2).

Granule flow property

The flow properties of the AM-1 formulated granules were determined by indirect methods by evaluating the angle of repose and compressibility indices. The flow- ability of the granules as assessed by the angle of repose is based on the cohesion between the particles with value of less than 25° is indicative of very- good flow whereas values equal or greater than 25° and less than 50° is good and 50° is poor. Assessing with the Carr's compressibility indices, values below 15% represent good flow and 15 to 25% is fair while values above 25% is indicative of poor flow (Well, 2003). The angle of repose and the Carr's compressibility indices of the three granulations prepared with the different concentrations of the maize starch gel as binder and their differentiated size particles are presented in Table 2.

The flow qualities of the unformulated AM-1 and the three formulation granulations as determined by angle of repose corroborate the assessment with Carr's compressibility index. The angle of repose and Carr's compressibility index of AM-1 were 47±4° and 21±3% respectively. Thus, the various granulations and their different sifted components all had very good flow properties as compared to that of the unformulated AM-1

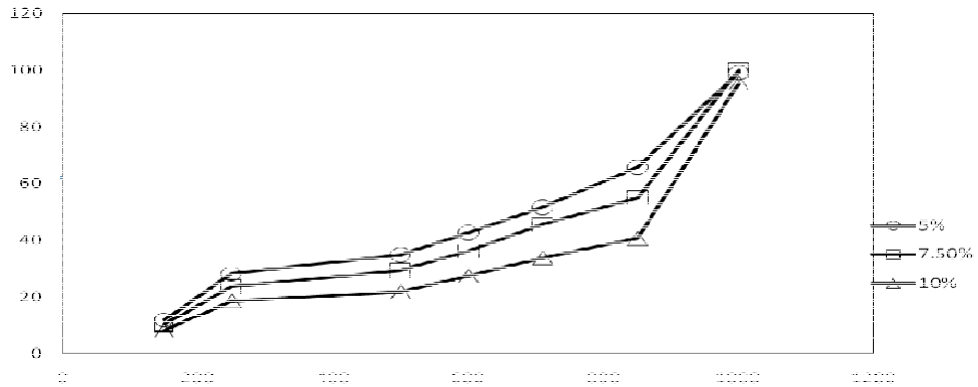

Figure 1. Cumulative frequency of granules particle size of AM 1 granules.

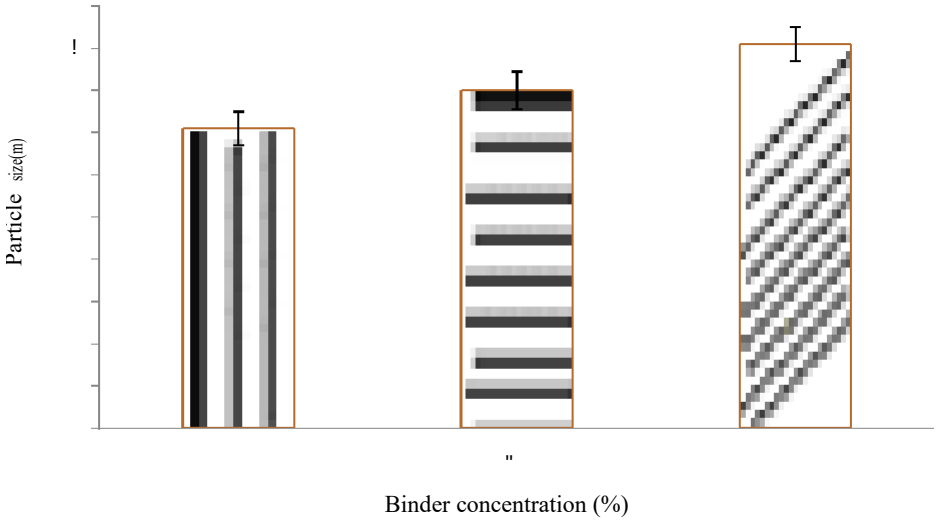

Figure 2. Average particle size of granules prepared with 5,7.5 and 10% maize.

Table 2. Effect of binder concentrations and particle size on the compressibility index and angle of repose on AM1 and AM1 formulation granules.

Particle size (m)	Compressibility index			Angle of repose (°)		
<250	13.21±0.9	11.00±1.1	11.00±0.7	26.6±0.9	26.6±0.7	21.8±1.1
<500	11.35±1.1	10.26±0.9	10.33±1.1	21.8±0.4	26.6±1.1	26.6±0.9
<710	12 ±1.0	13.70±1.2	11.79±0.9	26.6±1.2	21.8±0.6	21.8±1.0
<1000	12 ±0.92	11.55±0.9	13.79±1.3	21.8±0.5	26.6±0.9	26.6±1.0
Mix	10 ±0.98	10.92±1.2	12.94±1.3	26.6±1.1	20.8±0.9	26.6±0.4

(Table 2) (Wells, 2003; Builders et al., 2010). This could be due to a number of factors which includes: a near spherical shape of the granules, the presence of fines in the multipartculate structure of the granulations which could improve the flow of granules by filling voids especially between the large particles thereby decreasing surface roughness.The poor flow of the unformulated AM-1 could be attributed to factors which may include: stickiness of the powder on exposure to atmospheric air, rough surface structure and a uniform particle size of the

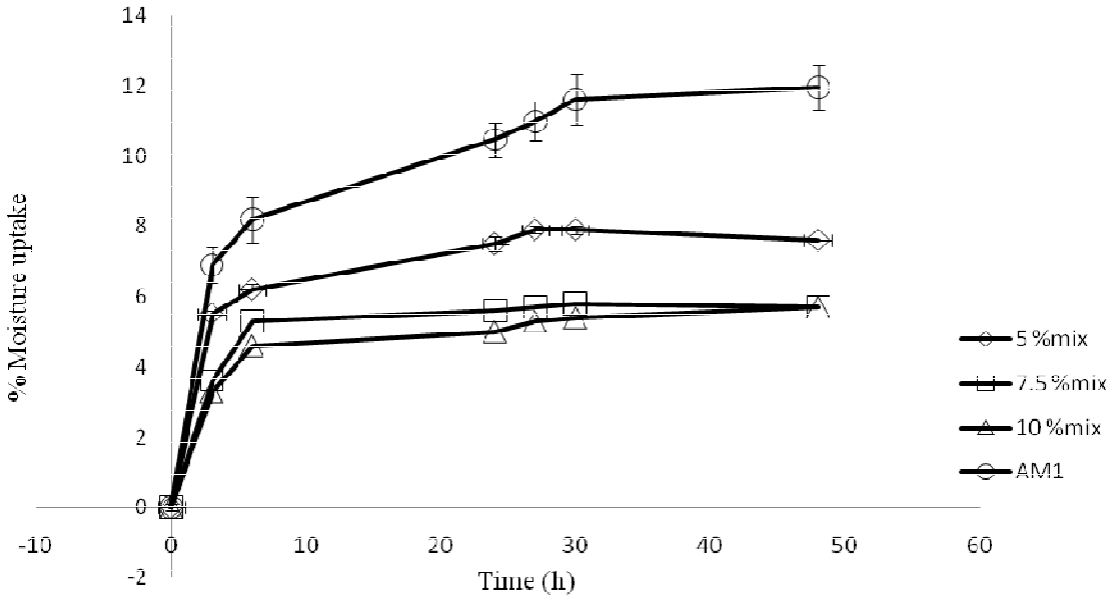

Figure 3. Moisture uptake profile for AM1powder and AM1 formulation granules prepared with 5, 7. 5 and 10% starch gel as binder.

fine powder (150 µm). The flow of the three granulations showed only slight sensitivity to binder concentration and granules' particle sizes as there were only small changes with variation in binder concentration and particle sizes (Table 2). The values of the angle of repose and compressibility indices for the fines (150 µm) and the largest particle granules (1000 µm) showed relatively higher values. This may be related to the higher interparticulate friction (angle of repose) and a lower aptitude of the materials to diminish in volume when tapped (compressibility index) (Marshall, 1987).

Granule moisture uptake profile

The moisture uptake profiles of the formulated and unformulated AM-1 particles are presented in Figure 3. The moisture uptake profile of the unformulated AM-1 powder and its granulations has been evaluated to establish the effects of granulation and variation in binder concentration on the moisture uptake characteristics of the freeze dried herbal extract, AM- 1. The assessment of the moisture uptake characteristic becomes imperative due to the critical effect of this parameter on the mixing, flow, compaction, dissolution, stability, product packaging and storage of pharmaceutical solids (Kontny and Zografi, 1995; Hancock and Zografi, 1997; Mangel, 2000). Apart from accelerating the rate of decomposition of bioactive components especially by hydrolysis, moisture also facilitates the reactive degradation between the active agent and excipient, and excipient and excipient, thereby affecting the shelf life and quality of the final product. Most powdered plant extracts obtained by concentrating the aqueous extracts of the plant material are often hydroscopic and will absorb large quantities of water when exposed to normal tropical humidity conditions. Thus, moisture presents a critical challenge not only on the processes involved during the formulation of herbal extracts or plant drug materials but also accelerates the physical as well as the chemical degradation hence, the need for a thorough understanding of the effect of moisture uptake on the extract and extract formulations. Thus, the assessment of the AM-1 and its formulated granules in controlled tropical temperature and humidity conditions.

The unformulated AM-1 powder showed higher moisture uptake sensitivity relative to the granulated formulation (Figure 3). The higher moisture uptake of unformulated AM-1 could be attributed to a higher affinity of the AM-1 to water molecules. Because AM-1 is a freeze dried decoction, this makes it freely soluble in water a property that could be related to the presence of numerous sites (functional groups) that enables it to form hydrogen bonds with water molecules. Another contributing factor to the higher moisture uptake potential of AM-1 is its relatively small particle size which is responsible for the relatively larger surface area available for interaction with moisture. The moisture sorption sensitivity of the particles in relation to their binder concentrations was significant. The moisture uptake potential of the granulates prepared with the different binder concentrations generally decreased with increasing binder concentrations (Figure 4). This could be attributed to a higher degree of intermolecular crosslinking between the particles of AM- 1 and the maize starch gel during the granulation process that reduced the available free sites

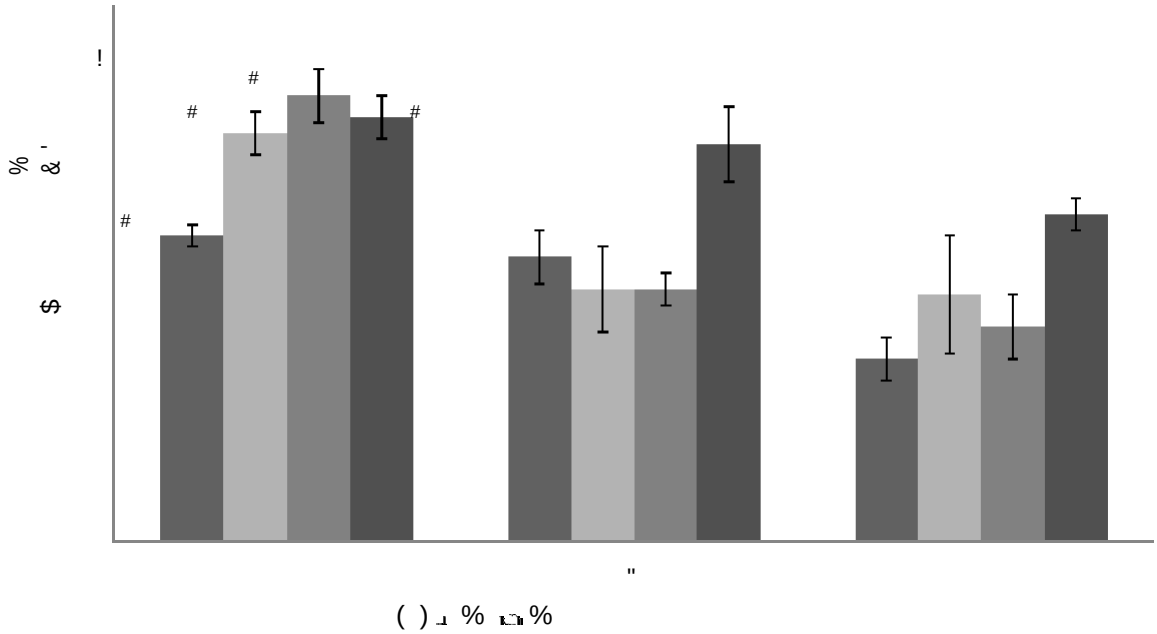

Figure 4. Moisture sorption characteristics of different AM-1 granules particles size prepared with different binders concentrations.

for interaction with water molecule (Zografi and Kontny, 1986). Increase in binder concentration also resulted in the cumulatively larger sized granules which correlate with a reduction in surface area available for interaction with water molecules.

Tablet friability

An important innovation in orthodox herbal medicine dosage formulation is the ability to present the medicines in forms that are convenient for both administration and handling. Oral tablets remain the most convenient dosage forms and the presentation of herbal medicines as effective tablets that meet all relevant quality stan-dards remains a challenge in the development of herbal medicines. When tablets are poorly formulated handling conditions such as friction and shock may cause tablets to chip, cap or break. An acceptable herbal tablet must meet the prescribed standards for tablet friability. Values of between 0.8 and 1.0% are the acceptable upper limit for tablets friability. The friability of AM-1 tablets prepared with 0, 5, 7.5 and 10%w/w starch gel as binder were 15±0.5, 1.6±0.1, 0 and 0% respectively. Tablets prepared using 0 and 5% maize starch as binder failed the friability assessment as their friability 15±0.5, 1.6±0.1 respectively were higher than 1%, the highest acceptable limit. The resistance of AM-1 tablets to surface abrasion was thus binder concentration sensitive with a critical binder concentration above which the tablets friable friability is diminished. The AM-1 tablets prepared without binder (0% w/w starch gel) were highly friable, more friable than tablets prepared with 5% w/w maize starch gel as binder. The tablets prepared with 7.5 and 10% w/w starch gel as binder were not friable (Table 3).

The effect of particle size on the tablets friability is also presented in Table 3. Apart from the tablets prepared with granules with particles sizes below 250 m using the 5% w/w of starch gel as binder which gave a friability of 1.6±0.01, the friability of all the tablets prepared with the various differentiated particle size granules using the 5, 7.5 and 10% w/w starch gel as binder were all below the lower acceptable limits for tablets friability (Table 3).

Tablets tensile strength

Tablets tensile strength is a non-compendia method of measuring the mechanical strength of tablets and can be used to predict comparative tablet bond strength, capping and lamination tendency. It is the force required to break a tablet by a diametral compression process. The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage are dependent on the tensile strength. The effect of binder concentration on tensile strength of AM-1 tablets is presented in Figure 5.The tensile strength of the tablets increased with increase in the starch gel concentration. The AM- 1 tablets thus, showed a significant sensitivity ($P < 0.05$) to binder concentration. The increased tensile strength of the AM-1 tablets could be attributed to the presence of binder as well as the

Table 3. Effect of binder concentrations and particle size on the tensile strength of AM-1 formulation granules.

Particle size (m)	Tablet tensile strength			Tablets friability		
	5%	7.5%	10%	5%	7.5%	10%
<250	0.11±0.01	0.11±0.01	0.1±0.01	1.6±0.01	0	0
<500	0.14±0.01	0.13±0.01	0.12±0.01	0	0	0
<710	0.16 ±0.02	0.14±0.01	0.14±0.01	0	0	0
<100	0.16±0.01	0.15±0.01	0.16±0.01	0	0	0
	0. 15±0.01	0.18 ±0.01	0.16±0.02	0	0	0

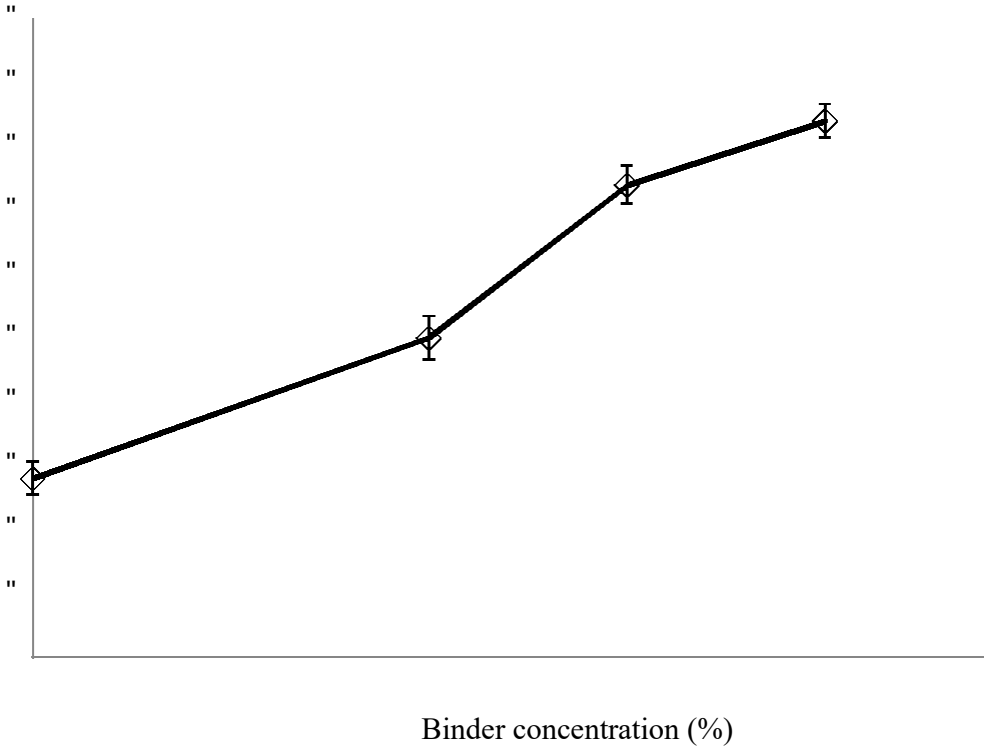

Figure 5. Effect of binder concentration on the tensile strength of AM1 tablets.

granulation process (Eichie et al., 2008). When the AM-1 granules were differentiated into different particle sizes there was a low sensitivity and poor correlation of the tablets' tensile strength to binder concentration (Table 3 and Figure 6).

Conclusion

The effect of starch gel binder concentration on some critical granule and tablet properties of AM-1, a potent herbal extract has been determined. Granulation of AM-1 with the different concentrations of maize starch gel as binder produced multi-particulate granules. The particle size, particle size distribution and moisture uptake of the AM- 1 granules were binder concentration dependent. The average particle size of the granules increased with increase in binder concentration and particle moisture uptake decreased with increase in binder concentration. The mechanical properties of the tablets as assessed by tensile strength and friability also showed binder concentration and granule particle size sensitivity increasing with increase in binder concentration as well as particle size. The study has shown that granulation and binder concentration controlled the particle size, size distribution, moisture uptake, flow properties as well as the friability and tensile strength of the tablet of the freeze dried herbal extract AM-1. Thus, the granulation of freeze dried herbal extracts using different binder concentrations can be used to control critical formulation parameters that

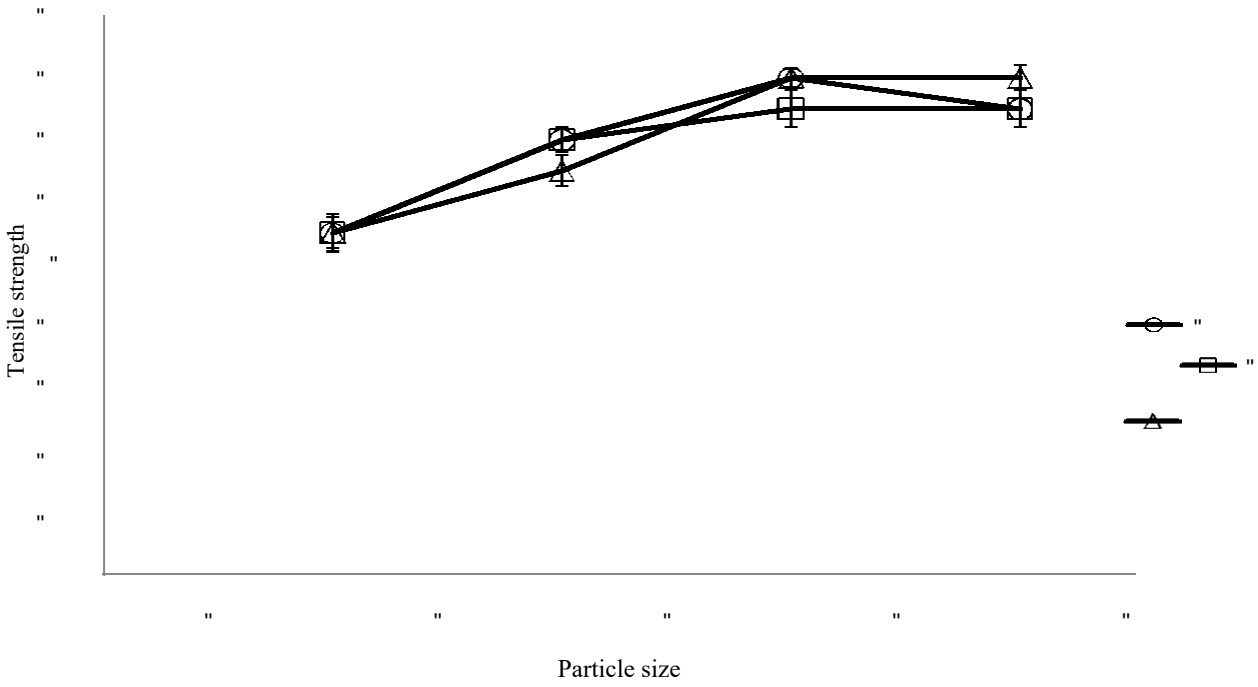

Figure 6. Effect of particle size on tensile strength of tablets.

can ensure the production of a robust tablet.

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