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Comparative study of the Functionality of Povidone, Gelatin and Corn Starch on M*oringa oleifera* Leaf Granule and Capsule formulations

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ABSTRACT

This research was aimed to study the functionalities of gelatin (G), polyvinylpyrrolidone (P), and corn starch BP (CS) on the wet granulation of *M. oleifera* leaf powder. Granules of the leaf powder were formulated using the binders at various concentrations: 1.0, 3.0 and 5.0% w/w (G and P); 5.0, 7.5 and 10.0% w/w (CS); and CS at 10.0% w/w and 12.5% w/w as disintegrant. The micromeritic and pharmaceutical qualities of the granules and leaf powder were studied. Results revealed that, the mean particle diameter for the non-granulated leave powder (MOP) was 192 µm, while those of the granules ranged between 194 µm and 275 µm. The particle densities ranged from 1.12 g/ml to 1.36 g/ml with significant difference ($p < 0.05$). The poorest flow characteristics were observed in MOP. Granule friability ranged from 0.20% to 10.83%; while disintegration time ranged from 17.74 ± 2.244 min to 55.06 ± 1.288 min. Capsule disintegration time ranged from 10.59 ± 3.062 min to 22.75 ± 0.412 min. The release profile for the capsules within 30 min depicted about 100%, 70%, 70% and 60% release of the herbal principles by MOP, granules formulated with povidone or gelatine at 1% w/w, or corn starch BP at 5% w/w respectively. Granules formulated with gelatin 1% w/w as binder and cornstarch BP 10% w/w as disintegrant displayed the best micromeritic and acceptable pharmaceutical qualities and are suggested to be given choice consideration in the formulation of *M. oleifera* granules.

Keywords: *Moringa oleifera*, binder functionality, granules, pharmaceutical quality.

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INTRODUCTION

Moringa oleifera Lam. family Moringaceae, commonly referred to as horseradish tree, drumstick tree and mother's best friend, is a small fast-growing ornamental tree whose origin has been traced to India. Different parts of the plant are consumed as food in many cultures and the nutritional contents of the plant have been reported[1]. The root, bark, pods and leaves of this tree are used in traditional medicine for the treatment of various human ailments such as headaches, worms, diarrhoea, stomach ulcers, skin conditions, anaemia, infections, fevers, urinary problems, liver and spleen problems, arthritis and rheumatism [2, 3, 4, 5, 6, 7, 8, 9]. Various parts of this plant have therefore been presented in different dosage forms (external and oral) for the treatment or management of both human and veterinary ailments [10, 11, 12]. However, the presentations of most of these dosage forms may not enable easy scale up processes in the pharmaceutical industries and this entails obvious disadvantages for large scale production of this miracle product. All *Moringa oleifera* leaf powder dosage forms, except one (from Genius Nature Herbs Private Ltd) [13] are presented as bulk powders or divided powers in capsules that are manually filled [14, 15].

Granulation may be defined as a size enlargement process which converts fine or coarse particles into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity. There are many other reasons for granulation such as: increasing the bulk density of a product; facilitating metering or volumetric dispensing; controlling the rate of drug release; decrease dust generation and reduce employee exposure to drug product; improving product appearance [16]. Granulation of powders improves their compressibility and compactibility, promotes a better handling as a consequence of a higher control over the product's bulk density (even for high drug contents), narrows the size distribution of the particles produced and provides a better control of the drug's content uniformity at low drug concentrations [17, 18].

The science and technology of small particles was given the name Micromeritics by Dalla Valle in 1948 [18]. Information describing materials characterization, particle size, surface properties, porosity, and pore structure is essential to a great many technologies and industries. The potential for applications of these characterization techniques, derived from an immeasurable diversity of materials and their uses, may itself be unlimited. In the area of tablet and capsule manufacture, control of particle size is essential in achieving the necessary flow properties and proper mixing of granules and powders [19]. Excipients influence the micromeritics of herbal as well as synthetic active pharmaceutical ingredient powder mixtures or granules in diverse ways. In wet and dry

granulation processes, binder type and concentration influence the micromeritic properties of granules and therefore the quality of tablets or capsules produced with the granules. In tablet production, press speed requires powders to be very fluid, a property commonly referred to as product flowability. Good flow characteristics are necessary because the mechanical action of the tablet press requires a volume of fill. The volume of fill represents the actual tablet weight. A tablet press does not weigh the precise amount of powder for each tablet. To achieve consistent tablet weights, the formula must be designed to flow consistently and to fill volumetrically. The powders in a formula must therefore possess a consistent particle-size distribution and density to attain proper flow and achieve volume of fill (i.e., tablet weight). In other words, the powders must flow consistently to attain consistent results [18]. Furthermore, in automated capsule filling processes, excellent flow properties are primary to ensuring uniformity of dose since the principle of volume of fill is also applicable. These requirements inform the current study to investigate the best binder and disintegrant combination for the formulation of *Moringa oleifera* granules whose qualities meet compendial standards.

MATERIALS AND METHODS

Materials

Moringa oleifera leaves were collected in Oyo, Oyo State, Nigeria. The leaves were authenticated by Dr (Miss) R.A. Lawal of Lagos State University, Lagos. Excipients used included corn starch BP (Sigma–Aldrich, USA)– as binder and disintegrant, polyvinylpyrrolidone (PVP K15) (Fluka, USA) – binder, gelatin [gel strength (Bloom): 160] (Fluka Germany) – binder, xylene of specific gravity, 0.879 g/ml (Sigma – Aldrich, Germany). Other reagents are of analytical grade.

Methods

Preparation of *Moringa oleifera* leaves powder

The leaves were shade dried for two weeks and then pulverised using a blender. Thereafter, the powder was sieved using sieve of aperture size 150 µm and the resulting powder stored in air tight container.

Determination of average moisture loss on drying

The method described in BP 2009[19], was adopted with slight modification. One gram of the *Moringa oleifera* leave powder was weighed in tarred petri dish. The petri dish with its content was placed in an oven (Lab. Oven Model No. DHG –9101. 1SA, Ceword Medical Equipment, England) and dried at 105^{o}C for 3 h. Thereafter, the petri dish with content was cooled in a

desiccator over anhydrous silica gel and reweighed. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage. Triplicate determinations were made and the means of the values reported.

Preparation of granules

Eighteen (18) batches of a basic formulation of *Moringa oleifera* powder (15 g), and corn starch B.P. as disintegrant (10.0% or 12.5% w/w with respect to the weight of herbal drug powder and binder where applicable) were dry – mixed for 10 minutes in a planetary mixer (Model A120, Hobart Manufacturing CO, UK), moistened with the appropriate amount of binder solution (gelatin, PVP) or mucilage (corn starch BP) prepared according to the methods reported by previous researchers [20, 21], except that the volume of the solutions or mucilage was maintained at 7.5 ml equivalent to 1.0, 3.0, 5.0% w/w (gelatin, PVP) or 5.0, 7.5, 10.0% w/w (corn starch BP) in the final granules. Wet massing was carried out with mortar and pestle for 10 min. The homogeneous wet mass was then screened through a 1400µm sieve and the wet granules dried in a hot air oven (Lab. Oven Model No. DHG –9101. 1SA, Ceword Medical Equipment, England) at 50^{o}C for 2 h. Thereafter, the dried granules were screened through a 600 µm sieve in order to generate uniformly sized granules[22] and stored in air tight containers over silica gel before subsequent tests were conducted on them.

Particle size analysis of leaf powder/granules

Each sieve was tarred to the nearest 0.001 g. Thereafter, 10 g of non-granulated *Moringa oleifera* leaf powder or the granules was carefully loaded on the coarsest sieve of the assembled stack (1000µm to 150µm) and the lid was replaced. The nest was subjected to mechanical vibration using the Shaker (AS 400 Retsch, Germany) for 25 min at 5 min interval per shaking session. Thereafter, the sieves were carefully separated and each sieve was carefully reweighed with its content. The weights of powder retained on each sieve and the collecting pan were determined by difference. The values were used to calculate the percent of sample retained on each sieve [23, 24, 25, 26] and the average diameter of the particles (d_{av}) using the formula [27]:

$$d_{av} = \frac{\sum(\%\ \text{retained} \times \text{mean aperture size})}{100} \quad \ldots (1)$$

Determination of powder / granule particle density

Xylene was used as the displacement fluid. The pycnometer, very clean and dry, was weighed and its weight recorded. It was filled with xylene, the counterpoise replaced, and the excess fluid carefully and completely wiped off. The bottle with its content was weighed and the weight recorded. The pycnometer was then emptied, washed thoroughly with soapy water, rinsed with

acetone, and dried very well in the hot air oven at 40°C. The dry pycnometer was reweighed to check if there was difference between the new dry weight and the initial one. Thereafter, some quantity of leaf powder/granules being examined was introduced very carefully into the dry pycnometer, the counterpoise was replaced and the bottle with its content weighed. The weight of the powder/granules was therefore determined by difference. A little xylene was introduced into the pycnometer and the bottle shaken carefully to displace the air bubbles entrapped by the powder/granule particles. Finally, the bottle was filled with xylene, its counterpoise replaced, and the excess fluid wiped off thoroughly. The bottle with its contents was again weighed and the reading recorded. This procedure was carried out thrice for each batch of powder/granules and the mean value used in calculating the particle density (ρ_s) using the equation below:

$$\rho_s = \left[\frac{w}{(a + w) - b}\right] S_g \quad \ldots \quad (2)$$

where w is powder/granule weight; S_g is the specific gravity of xylene; a is the weight of pycnometer + xylene, and b is the weight of pycnometer + xylene + granules [28].

Determination of bulk, tapped and relative densities, bulkiness and porosity of powder / granule bed

The bulk density of each powder / granule sample was determined by pouring 10 g (M) of the powder into a 50 ml glass measuring cylinder and the bulk volume (V_o) determined. The bulk density (D_b) was then calculated from the relationship:

$$D_b = \frac{M}{V_0} \quad \ldots \quad (3)$$

Triplicate determinations were made and the mean values reported [28].

The tapped density of each powder was determined using Stampf Volumeter (model STAV 2003, JEF Germany). The ten grams (M) of each powder/granules sample after the bulk density determination was subjected to 250 taps mechanically and the volume V_{250} of the powder column determined and applied to evaluate tapped density (D_t) using the relationship:

$$D_t = \frac{M}{V_{250}} \quad \ldots \quad (4)$$

Triplicate determinations were made and the mean values reported [28].

Relative density and porosity of powder / granules bed after 250 taps were determined using the equations 5 and 6 respectively:

$$RD = \frac{TD_{250}}{\rho_s} \quad \ldots (5)$$

$$\varepsilon = 1 - RD \quad ... (6)$$

where RD = relative density, ρ_s = particle density, ε = porosity.

Determination of Angle of repose

The static angle of repose, θ, was measured according to the BP (2005) fixed funnel and free standing cone method. A glass funnel was clamped with its tip of diameter 1 cm at a given height (h = 1.5 cm) above a graph paper placed on a flat surface. Ten gram of powder/granules sample was carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The diameter (d) of the base of the cone was measured. This procedure was repeated three times for each powder/granules batch and the means were used to calculate the angle of repose for each powder/granule sample using the formula:

$$\tan\theta = \frac{2h}{d} \quad ... (7)$$

Hausner's Ratio (HR)

This was calculated using the formula:

$$HR = \frac{D_t}{D_b} \quad ... \quad (8)$$

where D_t = Tapped density; D_b = Bulk density

Carr's Index (compressibility Index – CI)

This was calculated using the formula:

$$CI = \frac{D_t - D_b}{D_t} \times \frac{100}{1} \quad ... \quad (9)$$

Determination of granule friability

Each batch of granules was pass through a 600 µm sieve and 5 g of granules retained on the sieve was subject to friability test in a friabilator (Copley/Erweka GmbH Type: TAR 20 Heusenstamm Germany). The apparatus was operated at 25 revolutions per minute for 5 min. Thereafter, the granules were carefully collected and passed through 600 µm sieve, weight of granules retained was determined and granule friability evaluated using the formula:

$$\text{Friability} = \frac{W_i - W_f}{W_i} \times \frac{100}{1} \quad ... (10)$$

where W_i = initial weight of granules before test; W_f = final weigh of granules after test

Determination of granule disintegration time

A sieve cloth of aperture size less than 150 µm was used to cover the outer surface of the disintegration test basket rack assembly of the disintegration tester (Manesty, Model: MK 4, UK). Three hundred and fifty milligrams (350 mg) of granules from each batch was weighed and

quantitatively transferred into each of the six hollow tubes of the basket assembly. The test was conducted with 800 ml of water maintained at 37±0.5^{0}C until all the granules had disintegrated and passed through the sieve cloth. The time taken for the granules in each tube to do this was noted and the mean ± standard deviation was evaluated and reported.

Filling of capsule shells

For each batch, an amount of granules containing 350 mg of *M. oleifera* leaf powder was manually filled into capsule shells (size 2). Similarly, 350 mg of ungranulated leaf powder was manually filled into separate capsule shells (size 2). Twenty (20) capsules were filled for each batch of granules or ungranulated leaf powder.

Disintegration test for capsules

The disintegration times of the capsules were determined in distilled water at 37±0.5^o C using the disintegration tester (Manesty, Model: MK 4, UK). Six capsules, each containing 350 mg of M. oleifera granules were selected at random from each batch. One capsule was placed in each cylindrical tube of the tester and the machine was operated until all the capsules disintegrated. The results reported are the means ± standard deviation.

Determination of wavelength of maximum absorption (λ_{max}) of *M. oleifera* leaf extract

Five hundred milligrams (500 mg) of the leaf powder was extracted by shaking with 50 ml of methanol using the Vortex Vibrator (Vortex Genie 2 scientific industries Inc Bohemia NY, Model C. 560 E) for 30 min. Thereafter, the mixture was filtered using Whatman No 1 filter paper and the resulting filtrate was made up to 100 ml with 0.1 N HCl. The final solution was subsequently scanned between 200 nm and 800 nm using 0.1 N HCl as blank in the UV-Visible spectrophotometer (Jenway 6405, England) [29]. The identified wavelength of peak absorbance (250 nm) was then employed in the following tests:

Preparation of calibration curve for *M. oleifera* leaf extract

Ten grams (10 g) of M. oleifera leaf powder was dispersed in 200 ml of methanol and shaken for 1 h using the vibrator. The mixture was filtered using Whatman no 1 filter paper, and the resulting filtrate concentrated by using a rotary evaporator (Model R 201B Jiangsu Zhengi, China) operated at 75^{0}C. The concentrate was subsequently evaporated to dryness over a water bath (Karl Kolb D-6072 Dreieich, West Germany) regulated at 60^{0}C. The resulting powder was then stored in a desiccator over fused $CaCl_2$ for 48 h before use. One hundred milligrams (100 mg) of the dried extract was dissolved with 10 ml of methanol and made up to 100 ml with 0.1 N HCl. Serial dilutions were then carried out from this stock solution to prepare 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml, 14 µg/ml, 16 µg/ml, 18 µg/ml, and 20 µg/ml solutions of

the extract. The absorbance values of these solutions were determined at 250 nm using 0.1 N HCl as blank in the UV-Visible spectrophotometer (UV– 160A Shimadzu Corporation Japan) [30].

Dissolution test on *M. oleifera* capsules

The dissolution test was carried out using the USP XXIII basket method (Erweka Germany Type: DT 80) operated at 50 rpm for 30 min in 900 ml of 0.1N HCl maintained at 37 ± 0.5^{o} C (USP, 2004). At 5 min intervals, 5 ml of dissolution fluid was withdrawn and replaced with 5 ml of fresh 0.1N HCl. Each withdrawn sample was filtered and the amount of drug released determined using the UV–Visible spectrophotometer (UV– 160A Shimadzu Corporation Japan), at 250 nm with 0.1N HCl as blank and applying the calibration curve equation: y = 0.0074 *x* + 0.0249.

Statistical analysis

One way ANOVA (Excel 2007) was applied and $p < 0.05$ indicated statistically significant difference between the values analyzed.

RESULTS AND DISCUSSION

The average moisture loss on drying for the powdered *Moringa oleifera* leaves was 7.93± 0.142%. This value is less than the officially allowed maximum[19] and the low value of moisture content could prevent bacterial, fungal or yeast growth. Table 1, shows some of the micromeritic properties of the granules and powdered leaf. The mean particle diameter for the ungranulated leave powder (MOP) was 192 µm, while those of the granules ranged between 194 µm (CS10CS12.5 – granules containing starch mucilage 10% w/w and starch powder 12.5% w/w as binder and disintegrant respectively) and 275 µm (P3CS10 – granules containing polyvinylpyrrolidone 3% w/w and starch powder 10% w/w as binder and disintegrant respectively). Factors that contribute to granule size and characteristics include- nature of powder mix, binder type and concentration, amount of granulating fluid, type and quantity of intra-granular disintegrant, extent of kneading, aperture sizes of sieves used in wet and dry screening, etc. With exception of binder type and concentration, and disintegrant concentration, the other parameters were constant for all the granules. It is obvious from Table 1 that there is no relationship between binder type or concentration, or disintegrant concentration and mean particle diameter of the granules. This may be attributed to the nature of the drug (ordinary milled and sieved leaf powder, which is neither amorphous nor crystalline), thus the physical interaction (wetting and nucleation; consolidation and growth; and breakage and attrition) between the leaf powder and the excipients during wet massing with pestle was not affected in a

precise manner during the granulation process. The particle densities of MOP and the granules ranged from 1.12 g/ml to 1.36 g/ml. The particle densities of all the granules were higher than that of *M. oleifera* leaf powder and this is explained by the densification that accompanies granulation[17]. These values ordinarily may seem not to vary greatly, but on the application of one way ANOVA, significant differences ($p < 0.05$) were found to exist between the particle densities of MOP and those of granules formulated with either gelatin or corn starch BP; but none existed between the values for MOP and granules formulated with polyvinylpyrrolidone. This implies that gelatin and corn starch BP imparted better densification on the *M. oleifera* powder during the granulation process than did polyvinylpyrrolidone. Previous worker [31] had shown that majority of APIs must be densified before manufacturing the final dosage form so that sufficiently high doses can be administered in a reasonably sized dosage form. This finding suggests that gelatin and corn starch BP are better binders for the densification of *M. oleifera* powder than polyvinylpyrrolidone. The relative densities of powdered pharmaceutical materials generally increase as the materials are processed into solid dosage forms. The higher the relative density of a powder bed, the lower its porosity and the better its packability. Furthermore, bulkiness, which is the inverse of bulk density, is a very important characterization property of powders, because it makes direct impression on the packaging and shipping cost of powders[31]. MOP has high porosity and bulkiness in comparison to some of the granulated products especially G1CS10 (Table 1). The latter possessed the least porosity (best packability) and bulkiness (most economic packaging and shipping cost) among all the granulated products. These two properties suggest that G1CS10 granules will require a smaller sized capsule shell for encapsulation purpose, or give smaller sized tablets when compacted (these will enhance patients' compliance) and cost less during shipping in comparison to the other granulated products or MOP.

The flowability of a powder is an important property influencing several drug manufacturing steps. Flowability is affected by the physical properties of the powder, such as particle size and shape, the loading experienced by particles (gravity, interaction with air flow and container etc.), the current state of the powder (i.e. tap, free flowing etc.) and the processing environment (e.g. humidity). Particles larger than 250 μm usually flow freely while those below 100 μm are generally cohesive and prone to flowability problems [32]. The particle size distribution (PSD) of a powder defines the relative amounts of particles present, sorted according to size. The flow properties of particulate solids are also known to depend on the size distribution of particles[33, 34]. The PSD of MOP is bimodal with the higher mode appearing below particle size of less than 500

µm. The second mode was at about 500 µm size and the proportion of particles whose sizes are greater than 500 µm is much lesser than those with sizes ≤ 500 µm (Figure 1 - 6). The granules of G1CS10, CS5CS10 (Figure. 2), G3CS10, P3CS10 (Figure.3), P5CS10, G1CS12.5, CS5CS12.5, P3CS12.5, CS7.5CS12.5, and G5CS12.5 (Figures. 3, 4, 5, 6), all displayed bimodal PSD. Among all these, CS5CS10 possessed the greatest percentage of granules with particle sizes > 500 µm. Although P3CS10 granules possessed the highest mean particle size (275 µm), the proportion of its granules with particle sizes < 500 µm is higher than those of CS5CS10 whose mean particle size is 255 µm (Table 1). All the granules with unimodal PSDs, P1CS10 (Figure. 1), CS7.5CS10 (Figure. 2), G5CS10, CS10CS10 (Figure. 3), P1CS12.5 (Figure. 4), G3CS12.5 (Figure. 5), P5CS12.5 (Figure. 6), had larger proportions of granules with particle sizes less than 500 µm.

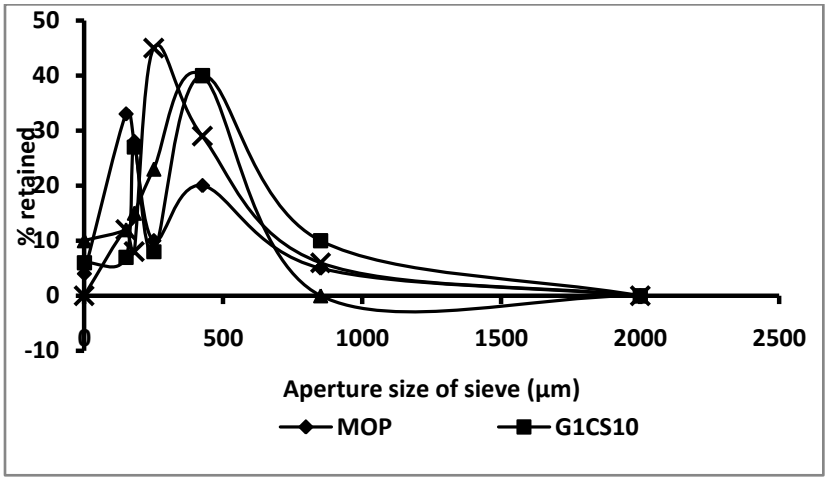

Figure. 1: Particle size distribution of M. oleifera leaf powder/ granules (MOP, G1CS10, P1CS10,CS5CS10)

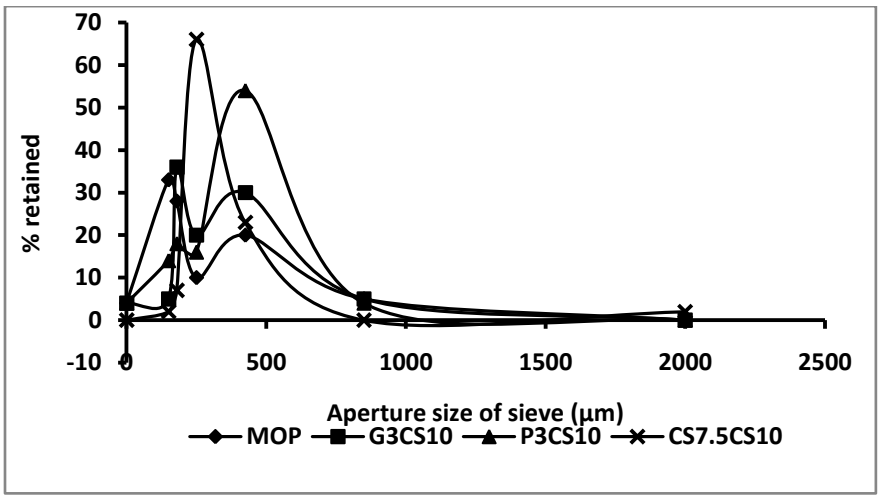

Figure. 2: Particle size distribution of M. oleifera leaf powder/ granules (MOP, G3CS10, P3CS10,CS7.5CS10

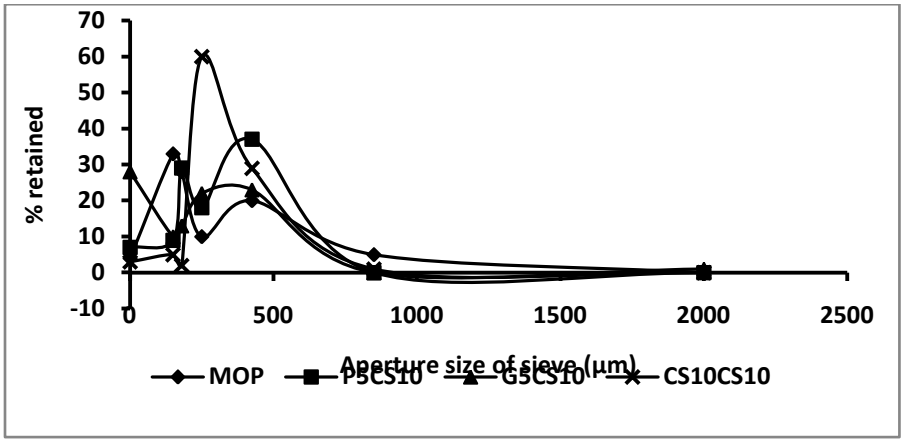

Figure. 3: Particle size distribution of M. oleifera leaf powder/ granules (MOP, G5CS10, P5CS10,CS10CS10

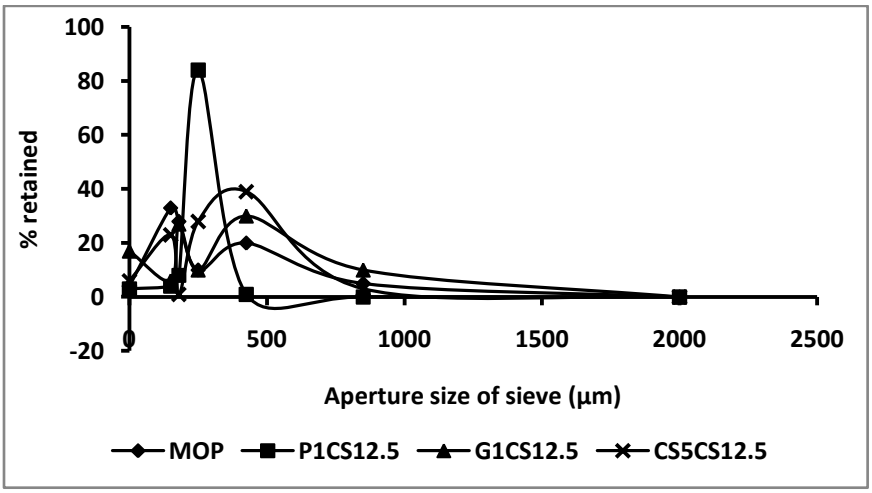

Figure. 4: Particle size distribution of M. oleifera leaf powder/ granules (MOP, P1CS12.5, G1CS12.5, CS5CS12.5)

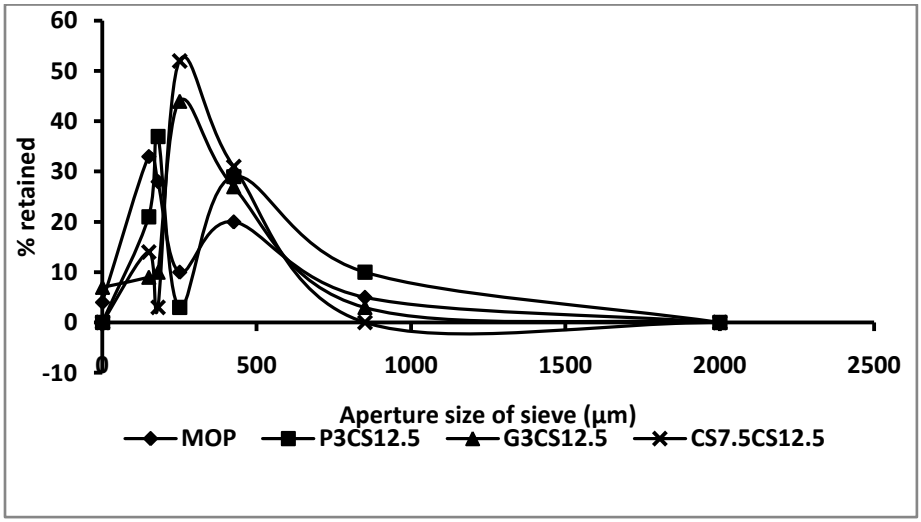

Figure. 5: Particle size distribution of M. oleifera leaf powder/ granules (MOP, P3CS12.5,G3CS12.5, CS7.5CS12.5)

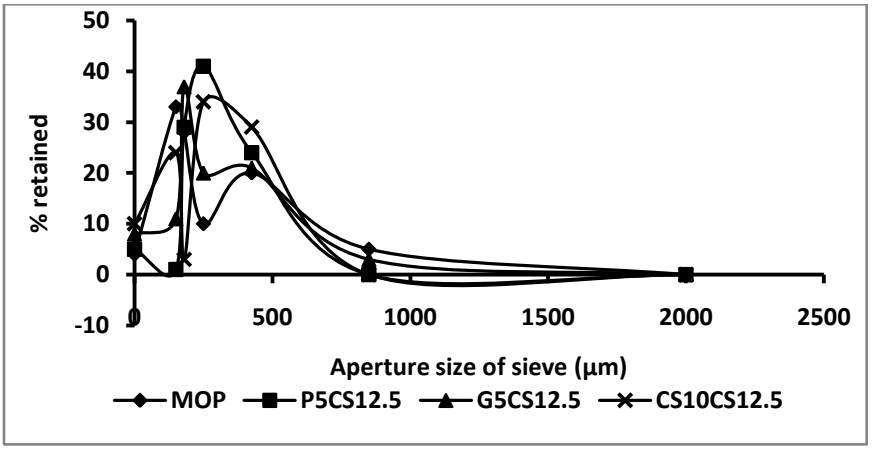

Figure. 6: Particle size distribution of M. oleifera leaf powder/ granules (MOP, P5CS12.5,G5CS12.5, CS10CS12.5)

These PSDs influenced the flow properties of the various granule batches and is evident in Table 1. MOP particles displayed the lowest flowability in comparison to all the granule batches as expected. Flowability is actually dependent on the attraction between particles, including friction and adhesion. Inter-particle friction mostly depends on the characteristics of outer surface of particles, which is in turn determined by the ingredient of the wall material and the preparation method to form the particles. Generally speaking, smoother surface results in smaller friction, while inter-particle adhesion is caused by intermolecular forces, such as van der Waals forces, local chemical bonds, electrostatic charges, and bridging forces. Apart from chemical compositions, particle size and size distribution are other two very important factors to determine particle flow property. Particle size influences contact area greatly. For bigger particles, gravity is generally greater than inter-particle adhesive force, making the flow easier. The relation between particle gravity and inter-particle adhesive forces and its influence on the particle flowability have been elucidated [35, 36]. Small quantity of fine particles in larger particles would lead to good powder flowability because of their lubricating ability. Too many small granules would however increase the contact area, just as a broad particle size span will make the contact area larger and the flow more difficult. Wide particle distribution, including broad bimodal pattern, has been shown to do harm to the flow properties of pharmaceutical powders[37]. Tapping experiments usually give results that differ from those of free fall. This is traceable to the denser packing resulting from reorientation of particles during tapping and the filling of the spaces between larger particles by smaller ones. This is obvious in the values of Carr's index and Hausner's ratio (Table 1). Although MOP consistently possessed the highest values for both indices, except for G5CS10 and P1CS12.5, there is no significant difference ($p > 0.05$) between

MOP Carr's and Hausner's indices and those of other granule batches. It therefore implies that for the granules resulting from this study, flow rate and angle of repose determinations gave a more reliable indication of their flow properties.

The determination of friability/attrition of granules reveals information about their stability and behaviour under mechanical stress. Granule friability test estimated the ability of the granules to withstand abrasion especially during automated encapsulation processes or flow from the hopper to the die during tableting. Granule friability was inversely related to binder concentration and ranged from 0.20% (G5CS12.5) to 10.83% (P1CS12.5) (Table 2). Generally, granules formulated with gelatin as binder were the least friable while those containing povidone were the most friable. Granule friability has been used to estimate granule strength[38]. The resistance to abrasion exhibited by the granules may serve as an index of the bonding strength between the binding agents and the other powders in the formulations. At the drying stage, migration of the binders from the interior of the granules to the periphery has been reported[39], thereby providing resistance to abrasion/attrition during subsequent operations. It therefore follows that gelatin imparted the greatest bonding strength and thus the highest ability to resist abrasion to the *M. oleifera* granules than povidone or corn starch BP. This is reflected in the disintegration test results, which ranged from 17.74 ± 2.244 min (P1CS12.5) to 55.06 ± 1.288) min (G5CS12.5). This test evaluated the time taken by the granules to break down to the primary powder size (< 150 µm). Granules containing gelatin had the longest disintegration times, while povidone containing ones displayed the lowest disintegration times (Table 2). Apart from granule strength, another factor that must have contributed to the observed difference is the solubility of the various binders in the dissolution medium. Povidone which is the most soluble binder among them delayed granule disintegration the least while gelatin the least soluble at 37^0C delayed disintegration time the most (Table 2).

Capsule disintegration time ranged from 10.59 ± 3.062 min (CS10CS12.5) to 22.75 ± 0.412 min (CS7.5CS12.5) (Table 2). It is evident from Table 2 that capsule disintegration times were not influenced by the formulae of the capsule contents, but rather the components of the capsule shell. It is however noteworthy that all the capsules disintegrated within the compendial requirement for capsules, i.e. ≤ 30 min [40].

The amounts of herbal principles released by the various capsule formulations were monitored for 30 min and the results revealed that whereas capsules containing ungranulated leaf powder (MOP) released more than 100% within 30 min, capsules containing granules formulated with povidone (P1CS10), gelatin (G1CS10) and corn starch BP (CS5CS10) released 70%, 70% and

60% respectively (Figure. 7). When the concentrations of povidone and gelatin were increased to 3% w/w and that of corn starch BP to 7.5% w/w, there was obvious reduction in the amount of herbal principles released (Figure 8 and 9), however, these formulations also possessed obvious advantages with respect to the other physical qualities of the granules (Tables 1 and 2). The effect of disintegrant concentration on the amount of herbal principles released was compared using P1CS10/P1CS12.5, G1CS10/G1CS12.5, P5CS10/P5CS12.5, CS5CS10/CS5CS12.5 and G5CS10/G5CS12.5 (Figure. 10, 11, 12). Within 10 min, P1CS12.5 released about 70% of the herbal principles while the amount released by P1CS10 was about 45% (Figure. 10). This observation is attributable to the granules' higher affinity for dissolution medium as disintegrant concentration was increased from 10% w/w to 12.5% w/w. Water uptake by granules depends on the hydrophilicity of the drug /excipient. For starch functioning as a disintegrant, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary and helps in disintegration by creating a hydrophilic network around the drug particles[41]. In the case of G1CS10/G1CS12.5, the amount of herbal principles released was virtually similar, which implies that disintegrant increase from 10% to 12.5% did not cause appreciable change in the release profile of the granules (Figure. 10). From Figure 10, it is also evident that P1CS10, P1CS12.5, G1CS10 and G1CS12.5 formulations met the official requirement for dissolution test of conventional capsules (USP, 2009), which is a cumulative release of at least 70% of the drug within 30 min.

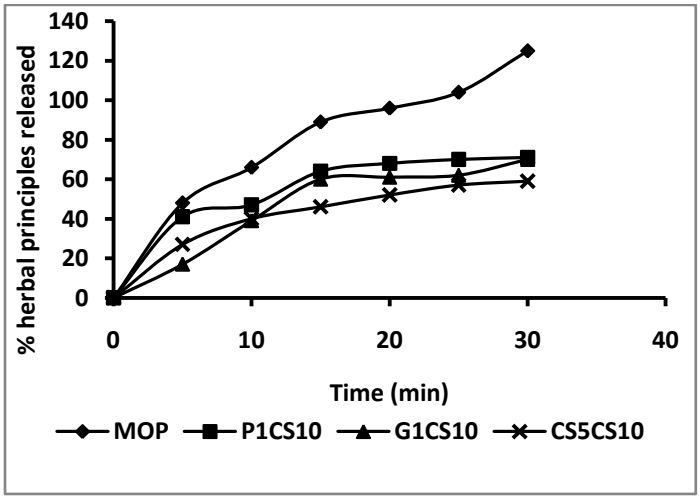

Figure. 7: Dissolution profile of *M. oleifera* leaf powder/granules (MOP, P1CS10, G1CS10, CS5CS10

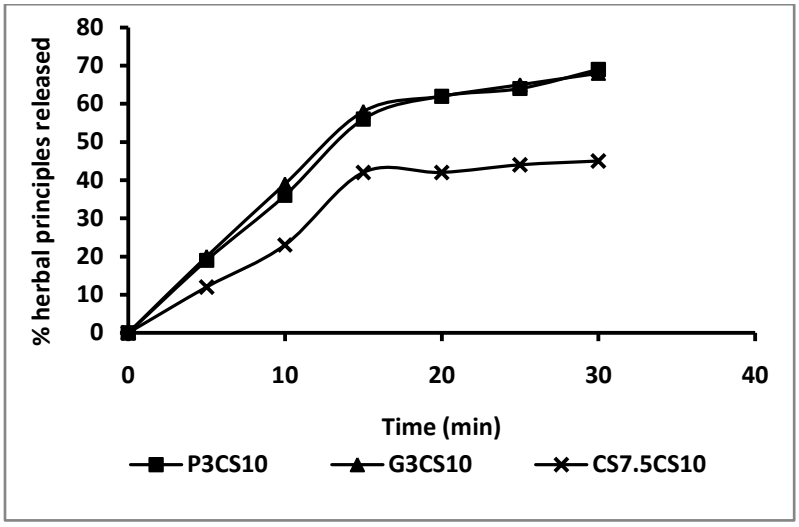

Figure. 8 : Dissolution profile of *M. oleifera* leaf granules (P3CS10, G3CS10, CS7.5CS10

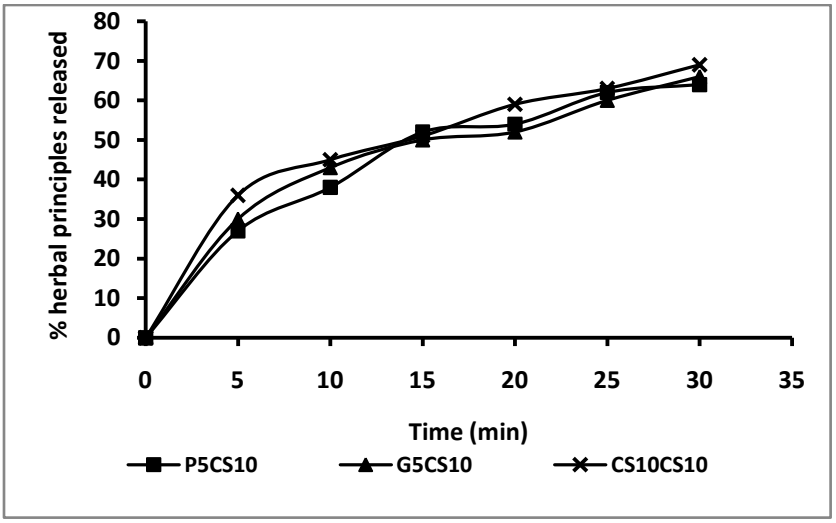

Figure 9 : Dissolution profile of *M. oleifera* leaf granules (P5CS10, G5CS10, CS10CS10)

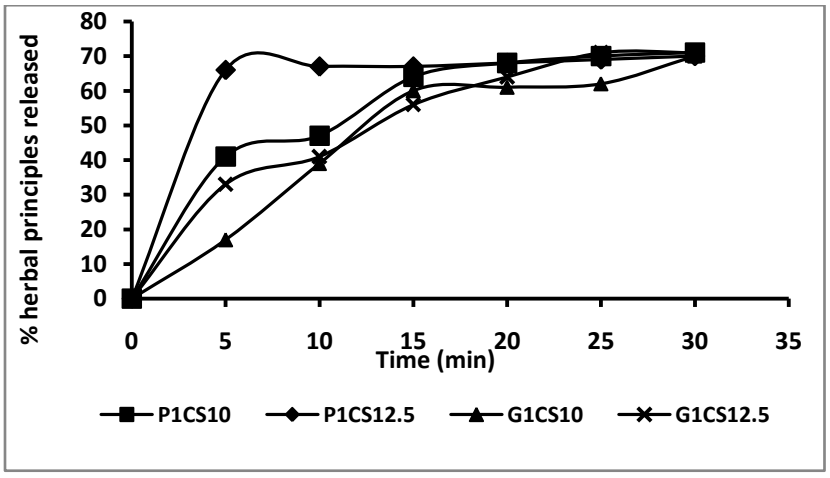

Figure 10 : Dissolution profile of *M. oleifera* leaf granules (P1CS10, P1CS12.5, G1CS10, G1CS12.5

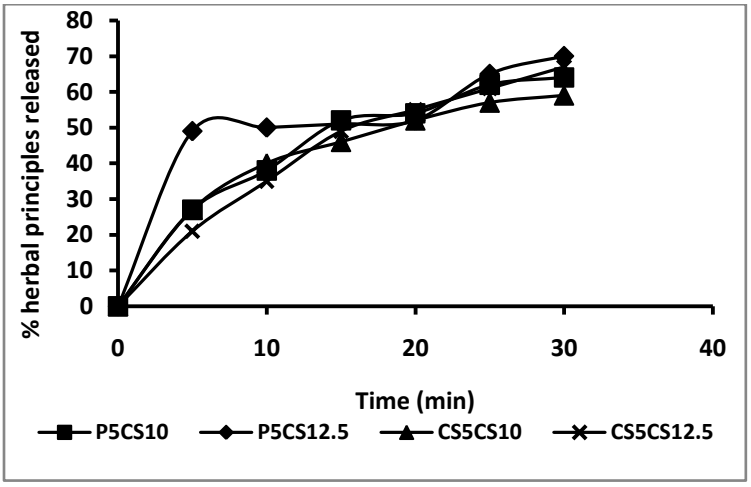

Figure. 11 : Dissolution profile of *M. oleifera* leaf granules (P5CS10, P5CS12.5, CS5CS10, CS5CS12.5)

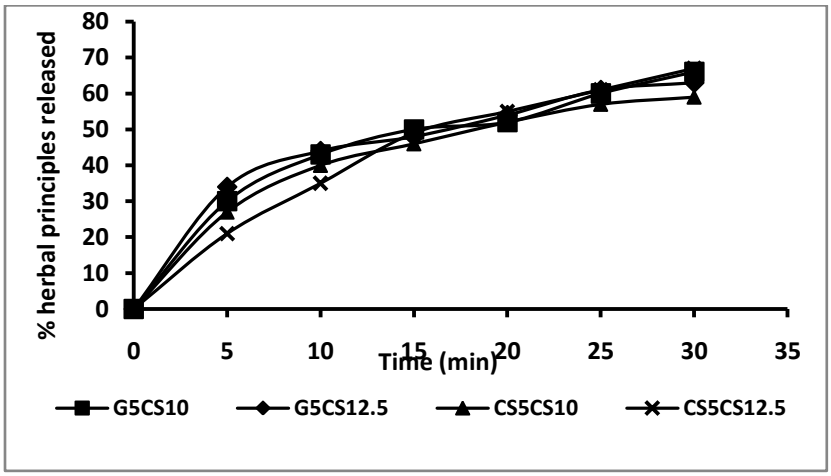

Figure 12: Dissolution profile of *M. oleifera* leaf granules (P5CS10, P5CS12.5, CS5CS10, CS5CS12.5

At higher binder concentration (5% w/w), only formulations containing povidone and the disintegrant at 12.5% w/w released up to 70% of the herbal principle in 30 min (Figure. 11 and 12). Furthermore, when other quality control test results are considered in conjunction with those of dissolution test, formulations containing gelatin as binder at 1% w/w and corn starch BP as disintegrant at 10% w/w possessed the best granule characteristics (least bulkiness- i.e. best packability, good flow, good friability, good disintegration and acceptable dissolution profile). Granules formulated with povidone as binder at 1% w/w and corn starch BP as disintegrant at 10% w/w also displayed good flow and dissolution characteristics, but their bulkiness and friability values were high (Tables 1 and 2). Finally, bringing economy into consideration, formulating *Moringa oleifera* leaf granules with gelatin as binder at 1% w/w and corn starch BP as disintegrant at 10% w/w proved to be the best combination of the excipients from this study.

Table 1: Some micromeritic properties of M. oleifera leaf powder and granules

Batch	Mean particle size (µm)	Particle density (g/ml)	Bulk density (g/ml)	Tapped density (g/ml)	Bulkiness (ml/g)	Hausner's ratio	Carr's index (%)	Angle of repose (°)	Flow rate (g/s)
MOP	192	1.12±0.007	0.32	0.45	3.12	1.41	28.89	40.20	0.50
G1CS10	265	1.28±0.061	0.53	0.68	1.90	1.28	22.21	40.20	1.66
G3CS10	239	1.29±0.060	0.45	0.58	2.21	1.26	21.21	25.60	1.85
G5CS10	269	1.29±0.046	0.48	0.58	2.07	1.19	16.13	31.90	1.27
G1CS12.5	235	1.32±0.069	0.43	0.55	2.31	1.28	21.87	37.60	1.28
G3CS12.5	228	1.32±0.079	0.42	0.55	2.36	1.29	22.86	33.50	1.41
G5CS12.5	202	1.33±0.089	0.42	0.55	2.41	1.32	24.32	37.10	1.81
P1CS10	198	1.16±0.038	0.43	0.53	2.34	1.25	20.00	35.90	0.94
P3CS10	275	1.29±0.329	0.43	0.53	2.35	1.25	20.00	36.70	1.69
P5CS10	218	1.14±0.046	0.41	0.53	2.41	1.27	21.85	32.40	1.62
P1CS12.5	200	1.21±0.138	0.45	0.53	2.23	1.17	15.14	31.20	1.91
P3CS12.5	245	1.25±0.089	0.33	0.42	2.99	1.28	22.55	28.90	1.74
P5CS12.5	217	1.31±0.057	0.40	0.53	2.49	1.33	25.00	36.20	1.81
CS5CS10	255	1.36±0.046	0.36	0.48	2.77	1.33	24.98	36.30	4.42
CS7.5CS10	261	1.36±0.077	0.34	0.45	2.93	1.33	24.98	38.10	2.25
CS10CS10	240	1.34±0.033	0.33	0.46	2.99	1.37	27.45	34.50	2.41
CS5CS12.5	230	1.30±0.055	0.37	0.48	2.71	1.30	23.39	38.40	2.30
CS7.5CS12.5	232	1.33±0.060	0.36	0.48	2.78	1.34	25.53	33.10	2.60
CS10CS12.5	194	1.33±0.070	0.38	0.49	2.63	1.29	22.74	32.40	3.16

MOP- *M. oleifera* leaf powder; G1CS10, G3CS10, G5CS10- granules formulated with gelatin 1.0, 3.0, 5.0% w/w as binders and corn starch 10%w/w as disintegrant; G1CS12.5, G3CS12.5, G5CS12.5- granules formulated with gelatin 1.0, 3.0, 5.0% w/w as binder and corn starch 12.5%w/w as disintegrant; P1CS10, P3CS10, P5CS10- granules formulated with polyvinylpyrrolidone 1.0, 3.0, 5.0% w/w as binder and corn starch 10%w/w as disintegrant; P1CS12.5, P3CS12.5, P5CS12.5- granules formulated with polyvinylpyrrolidone 1.0, 3.0, 5.0% w/w as binder and corn starch 12.5%w/w as disintegrant; CS5CS10, CS7.5CS10, CS10CS10- granules formulated with corn starch mucilage 5.0, 7.5, 10.0% w/w as binder and corn starch 10%w/w as disintegrant; CS5CS12.5, CS7.5CS12.5, CS10CS12.5- granules formulated with corn starch mucilage 5.0, 7.5, 10.0% w/w as binder and corn starch 12.5%w/w as disintegrant.

MOP- *M. oleifera* leaf powder; G1CS10, G3CS10, G5CS10- granules formulated with gelatin 1.0, 3.0, 5.0% w/w as binders and corn starch 10%w/w as disintegrant; G1CS12.5, G3CS12.5, G5CS12.5- granules formulated with gelatin 1.0, 3.0, 5.0% w/w as binder and corn starch 12.5% w/w as disintegrant; P1CS10, P3CS10, P5CS10- granules formulated with polyvinylpyrrolidone 1.0, 3.0, 5.0% w/w as binder and corn starch 10%w/w as disintegrant; P1CS12.5, P3CS12.5, P5CS12.5- granules formulated with polyvinylpyrrolidone 1.0, 3.0, 5.0% w/w as binder and corn

Table 2: Some pharmaceutical qualities of *M. oleifera* granules and capsules

Batch	Friability of Granules (%)	Disintegration Time of Granules (min)	Disintegration Time of Capsules (min)
G1CS10	5.28	31.12 ± 5.079	12.62 ± 1.327
G3CS10	5.08	33.28 ± 5.038	14.95 ± 5.397
G5CS10	4.02	36.18 ± 3.887	17.86 ± 3.254
G1CS12.5	2.76	41.08 ± 2.995	16.96 ± 2.390
G3CS12.5	1.05	49.59 ± 2.374	17.81 ± 1.602
G5CS12.5	0.20	55.06 ± 1.288	16.58 ± 3.165
P1CS10	10.61	18.49 ± 5.107	15.88 ± 0.671
P3CS10	9.97	19.03 ± 9.771	17.38 ± 2.803
P5CS10	9.41	23.52 ± 10.635	12.93 ± 1.971
P1CS12.5	10.83	17.74 ± 2.244	14.08 ± 1.695
P3CS12.5	9.77	23.50 ± 4.135	10.95 ± 3.062
P5CS12.5	7.59	31.33 ± 3.560	14.25 ± 1.669
CS5CS10	7.37	25.62 ± 2.012	14.34 ± 3.253
CS7.5CS10	6.71	29.73 ± 3.387	22.75 ± 0.412
CS10CS10	5.30	30.23 ± 4.817	15.62 ± 1.604
CS5CS12.5	8.48	26.90 ± 4.543	22.26 ± 1.520
CS7.5CS12.5	6.91	29.18 ± 4.251	18.93 ± 1.379
CS10CS12.5	3.99	38.58 ± 5.212	10.59 ± 1.668

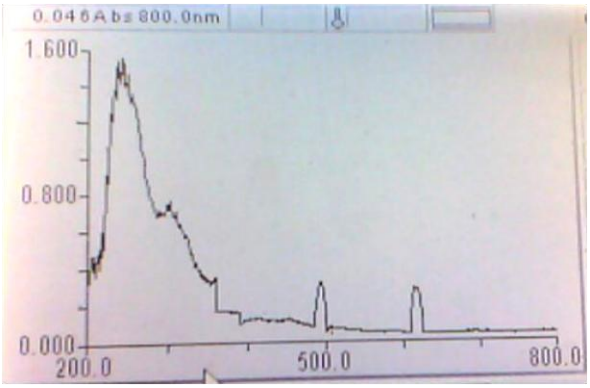

Figure13 *: M. oleifera* herbal principles spectrum in 0.1N HCl

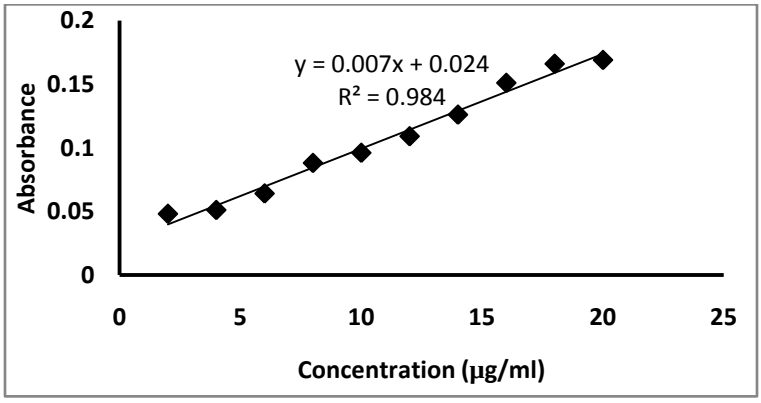

Figure.14 : Calibration curve for herbal principles in *M. oleifera* leaf powder

starch 12.5%w/w as disintegrant; CS5CS10, CS7.5CS10, CS10CS10- granules formulated with corn starch mucilage 5.0, 7.5, 10.0% w/w as binder and corn starch 10%w/w as disintegrant; CS5CS12.5, CS7.5CS12.5, CS10CS12.5- granules formulated with corn starch mucilage 5.0, 7.5, 10.0% w/w as binder and corn starch 12.5%w/w as disintegrant.

CONCLUSION

The formulation of pharmaceutical powders into granules is an established process of improving the quality of oral solid dosage forms. Recent developments show that herbal products are becoming highly preferred to synthetic drugs, hence the obvious popularity of *M. oleifera* products. This study revealed that granulated *M. oleifera* products possessed much better pharmaceutical qualities than ungranulated ones. In addition, albeit all the granulated products have similar micromeritic properties, granules formulated with gelatin at 1% w/w and corn starch BP at 10% w/w as binder and disintegrant respectively, displayed the best packability, good dissolution profile and may be the most economic choice. This binder-disintegrant combination is therefore suggested to be given a positive consideration as a workable drug/excipients combination for the formulation of good quality *M. oleifera* granules.

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