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Use of anhydrous calcium phosphate and selected binders in the tablet formulation of a deliquescent crude plant extract: *Vernonia galamensis* (Asteraceae)

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ABSTRACT

In this study, the effect of anhydrous calcium phosphate, an efflorescent pharmaceutical powder of reduced moisture content, ideal for moisture-sensitive materials; and the comparative binding effects of maize starch, polyvinylpyrrolidone and gelatin were investigated in the tablet formulation of the deliquescent crude extract of the leaves of *Vernonia galamensis* (Asteraceae). Materials used include; anhydrous calcium phosphate (BDH chemicals Ltd. Poole, England), maize starch and gelatin (May and Baker, Germany). Granule and tablet analyses were carried out according to standard procedures in the BP 2007. Preparations of the binders at varying concentrations of 2.5, 5.0 and 7.5% w/v were used to produce the granules by wet granulation method and compressed into tablets at 26.25KN. The mechanical strengths and drug release properties of the designed tablets were assessed using the crushing strength-friability, disintegration time ratio (CSFR:DT) and dissolution rate. An increase in binder concentration led to an increase in crushing strength, decrease in friability and increase in disintegration time of the tablets. Anhydrous calcium phosphate used as diluent along with polyvinylpyrrolidone as binder produced the best quality tablets in terms of the CSFR: DT ratio and dissolution rate as compared to the diluent used with maize starch and gelatin as binders.

Keywords: Calcium phosphate, binders, crushing strength, diluents, dissolution.

INTRODUCTION

There is need for continued research into medicinal plants, especially those that are used in traditional medicine across the developing countries of Africa, Asia and South America. Leaves of *Vernonia galamensis* (Asteraceae) have been used in the decoction form for ages in the treatment of diabetes mellitus in folk medicine (Autamashih *et al*, 2011). The crude extract of the leaves have been found to be highly hygroscopic and deliquescent and efforts to use the common diluents such as lactose, maize starch and magnesium carbonate for tablet formulation of the deliquescent crude extract have been futile as very poor quality tablets with many defects especially 'sticking' and 'picking' were produced (Autamashih *et al*, 2011). But because deliquescent materials are highly hydrophilic and absorbed moisture from the atmosphere becoming fluid (Encyclopedia Britannica, 2010), it became quite scientific to look for a suitable efflorescent diluent. This is due to the knowledge that efflorescent materials are hydrophobic in nature and expel water, the aqueous tension of their hydrate being greater than the partial pressure of the water vapor in the air (Encyclopedia Britannica, 2010). It was hoped that the tendency of the deliquescent material to absorb moisture will be counteracted by the ability of the efflorescent

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material to expel all moisture.

In this study, the effect of anhydrous calcium phosphate (CP), an efflorescent pharmaceutical powder used as diluent; and the comparative effects of three standard binders namely maize starch (MS), polyvinylpyrrolidone (PVP) and gelatin (GLT) were investigated in the tablet formulation of the deliquescent crude extract. Anhydrous calcium phosphate is dibasic calcium phosphate (usually found as the dihydrate, with the chemical formula of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) that is converted to the anhydrous form. It is practically insoluble in water, with a solubility of 0.02 g per 100 mL at 25 °C.

MATERIALS AND METHODS

Materials

These include powders of Gelatin and Maize starch (May and Baker, Germany), anhydrous calcium phosphate, Talc and Magnesium Stearate powders (BDH chemicals Ltd. Poole, England), Polyvinylpyrrolidone (Aldrich Chemical company, USA) and the leaves of *Vernonia galamensis* (collected from the natural habitat of Ahmadu Bello University, Zaria, Nigeria and identified in the herbarium unit of the Department of Biological Sciences of the University where a sample was deposited with a voucher specimen number 994).

Methods

i). Preparation of the extract

Leaves of *Vernonia galamensis* were washed, air dried, milled to a coarse powder (particle size ≤ 1000 μm) and macerated in distilled water for 24 h at room temperature and the liquid extract filtered through a calico cloth and concentrated to a ratio of 5:1 using a rotary evaporator. The concentrated filtrate was then transferred into a tray and dried in an oven at 40 °C, pulverized using a mortar and pestle and then passed through a 150 μm sieve.

ii). Preparation of granules

The wet granulation method of massing and screening was used. Appropriate quantities of the dry extract and the diluent ratio 1:1.4 were mixed in a mortar for 5 minutes. Disintegrant (maize starch, 6.8% w/w) was added and mixing continued for another 5 minutes. A liquid binder prepared using selected concentrations (2.5, 5.0 and 7.5% w/v) of Maize Starch mucilage, polyvinylpyrrolidone or gelatin powder was added in 1-mL portions and mixed with a pestle. The moistened mass was forced through a 1000 μm sieve, dried at 40 °C for 2 h to give a moisture content of 4% – 6%, determined on an Ultra X moisture balance (August Gronert Co., Germany). The granules were again passed through a 1000 μm screen to break up agglomerates.

iii). Granule Analysis

(a). *Moisture content analysis*: The method adopted was that specified in the B.P 2007. One gram (1 g) of the sample was transferred into each of several petri dishes and then dried in an oven (Gallenkamp size 3 BS, 2648 Heusentamm, Germany) at 105°C until a constant weight was obtained. The moisture content

was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage. The data presented here is for triplicate determinations.

(b). *Angle of repose*: The static angle of repose, α , was measured according to the fixed funnel and free standing cone method (BP 2007). A funnel was clamped with its tip 2cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the equation:

$$\tan \alpha = r/h \quad (1)$$

Where 'a' is the angle of repose, and 'r' and 'h' are the radius and height of the powder heap respectively

(c). *Bulk density, Tapped density, Hausner's ratio and Carr's index of compressibility*: Thirty gram (30 g) quantity each of the granules was carefully poured through a short stem glass funnel in a 100ml measuring cylinder and the volume, V_0 , occupied by the granules without tapping was noted. After 100 taps on the table, the occupied volume V_{100} was read. The bulk and tap densities were calculated as the ratio of weight to volume (V_0 and V_{100} respectively). Carr's index and Hausner's ratio were calculated using the following equations:-

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (2)$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (3)$$

iv). Preparation and analysis of tablets

Tablets equivalent to 300mg of granules were produced by compressing the granules for 60 s at 26.25 KN (303 MNm⁻²) using a single punch tablet machine (Tianxiang and Chentai Pharmaceutical Machinery Co Ltd, Shanghai, China) fitted with 10.5 mm flat punch and die set. After ejection, the tablets were stored over silica gel in a desiccator for 24 h to allow for elastic recovery and hardening.

Analysis of tablet. – This was done as follows:

- *Tablet diameter and thickness*;- the tablet diameter (D) and thickness (d) were determined to the nearest 0.01 mm with a Mitutoyo model IDC-1012 EB micrometer gauge (Mitutoyo Corporation, Japan).
- *Crushing Strength*;- the tablet diametral crushing strength was determined using the Erweka GmbH model MT 306404 tablet hardness tester. The mean of six readings was taken.
- *Friability*;- ten (10) tablets were subjected to abrasion in a Roche friabilator at 25 rpm for four minutes. The weight of the tablets before and after friabilation was taken. The percentage weight loss was calculated from which percentage friability was determined. The mean of three readings was determined and where capping or fracture of tablets occurred, friability was not determined.

- **Disintegration**;- the disintegration times of the tablets were determined according to standard specifications (BP 2007), using the Erweka disintegration tester (Erweka ZT 71, Germany). Distilled water thermostatically maintained at 37 °C was used as the disintegration medium. Six tablets were placed in the tubes of the tester, of which the lower end is fitted with a gauze disc made of rustproof wire. The disintegration apparatus was calibrated to operate at thirty cycles per min. For each batch of tablets the experiment was repeated to yield three sets of readings.
- **Dissolution Rate**;- this was carried out in accordance with the USP XXIII basket method using the Erweka GmbH model dissolution tester, Type DT 80100328, Germany. Tablets were placed in the medium and the stirrer rotated at 50 rpm in 900 mL of distilled water, maintained at 37 ± 0.5 °C. At ten minutes intervals, samples of the dissolution medium were withdrawn with a syringe filtered through a filter paper of 0.2 µm pore size. Equivalent amount of sample volume withdrawn was replaced with the dissolution medium. Drug content determination was done by measuring absorbance at 216 nm wavelength. The dissolution was carried out on three tablets from each formulation. A calibration curve of concentration versus absorbance values was plotted using various concentrations of the crude extract (0.2 to 1% w/v). The absorbance values were determined using the UV/Visible spectrophotometer ((Jenway 6405, Dunmow, Essex. UK. S/No. 2028)) at a fixed wavelength of 216 nm. The dissolution times of tablets from the various formulations were determined by extrapolation of the absorbance readings from the calibration curve.

Stability test

EVG tablets were stored at a temperature of 30 ± 2 °C and relative humidity of 75 ± 5 % for a period of twelve (12) months. The mechanical and release properties of the tablets were assessed as earlier described.

Data analysis

The graphs were plotted and data analyzed using GraphPad Prism® version 5.03 software. The data used to plot the graphs were the mean of three readings ± SD.

RESULTS AND DISCUSSIONS

Table 1 presents the granule properties; mean granule size, moisture content, bulk and tapped densities, angle of repose, flow rate and Carr's index of compressibility of *V. galamensis* granules produced using anhydrous calcium phosphate as diluent and selected binders (MS, PVP, GLT) at varying concentrations of 2.5, 5.0 and 7.5% w/v. For all binder types, moisture content was generally found to increase as the binder concentration was increased. This agrees with earlier observations (Sebhatu *et al*, 1997). Formulations using GLT as binder were especially observed to have highest moisture content (Table 2), and this could mean that there are larger pore sizes which may trap water and result in high moisture contents (Oyi *et al*, 2009).

For good flow of granules, the British Pharmacopoeia (10) specifies bulk density values < 1.2, Hausner's ratios < 1.25, angle of repose < 50°, Carr's index > 5 < 16. Based on these specifications, all values for our granule analysis were within acceptable range (Table 1).

Table 2 presents the tablet properties; tablet thickness, crushing strength, friability, disintegration time and the crushing strength-friability, disintegration time ratio (CSFR:DT) of *V. galamensis* granules and tablets produced using the efflorescent hydrophobic fumed silica as diluent and selected binders (MS, PVP, GLT) at varying concentrations of 2.5, 5.0 and 7.5% w/v. All the tablet formulations show increase in disintegration time as the concentration of binder increases. This directly agrees with the findings of Tahir *et al*, 2010. PVP shows fastest dispersion time. This may probably be due to formation of a denser capillary network structure resulting from the use of the PVP (Tahir *et al*, 2010).

Kuntz *et al*, (2011) observed that increase in granule size leads to increase crushing strength of tablets as a result of increased surface irregularity of the larger granules which leads to an increased number of binding surface areas. It was difficult to ascertain this hypothesis in our study. Instead, what we observed was close to a reverse hypothesis (Tables 1 and 2). The effect of binder type could be explained as the reason for the discrepancies. For example in our study, PVP was found to have lower binding effect (formulations containing it have lower crushing strength and shorter disintegration time values) than GLT and MS agreeing

Table 1: Properties of granules of the leaves extract of *V. galamensis* prepared using selected binders (MS, PVP and GLT) and anhydrous calcium phosphate as diluent.

Binder	Binder Conc. (% w/v)	Mean Granule size (µm)	Moisture Content (% w/v)	Bulk Density (gm/ml)	Tap Density (gm/ml)	Angle of Repose (°)	Flow Rate (g/s)	Hausner's Ratio	Carr's Index (%)
MS		497±1.0	8.50±0.1	0.78±0.03	0.95±0.02	20.3±0.5	4.33±0.3	1.21±0.1	15.38±0.3
PVP	2.5	640±2.5	7.00±0.1	0.65±0.01	0.70±0.01	26.6±0.4	1.46±0.1	1.08±0.2	7.69±0.2
GLT		618±5.2	9.50±0.1	0.68±0.03	0.76±0.04	27.6±0.5	1.46±0.1	1.12±0.2	11.11±0.4
MS		746±1.5	9.50±0.1	0.78±0.04	0.93±0.03	27.8±0.4	5.33±0.1	1.19±0.2	16.00±0.4
PVP	5.0	638±3.2	8.50±0.1	0.78±0.02	0.88±0.01	27.6±0.3	3.03±0.1	1.13±0.1	11.78±0.7
GLT		435±3.2	11.00±0.1	0.61±0.02	0.71±0.04	24.9±0.4	6.94±0.1	1.16±0.1	15.10±0.5
MS		722±2.7	13.00±0.2	0.70±0.04	0.81±0.03	25.3±0.3	5.49±0.3	1.16±0.5	12.50±0.5
PVP	7.5	683±3.2	9.50±0.1	0.89±0.02	0.93±0.02	23.7±0.3	5.08±0.1	1.04±0.1	3.61±0.7
GLT		557±5.9	13.00±0.2	0.60±0.02	0.69±0.03	26.6±0.6	6.90±0.1	1.15±0.1	14.30±0.6

MS = Maize starch, PVP = Polyvinylpyrrolidone, GLT = Gelatin. Results were expressed as mean ± SD of three runs and at 95% confidence level, p values ≤ 0.05 were considered significant.

directly with the findings of Varshosaz *et al*, 1997. So the use of a binder of lower binding capacity will result to low crushing strength, regardless of granule size. We also observed an increase in crushing strength with increase binder concentration (Table 2), agreeing with the findings of Chowhan, (2006). This is in order because binders are added during granulation to provide the cohesive binding of particles and to ensure that granules and tablets can be formed with the required mechanical strength (Cunnigham and Scattergood, 2001). So an increase in binder concentration will result in an increase of crushing strength. Binders however, form films on the surface of the granules; therefore if added at too high a concentration, the films can form viscous gels on the granule surface and may retard dissolution (Cunnigham and Scattergood, 2001).

Table 2: Properties of tablets of the leaves extract of *V. galamensis* prepared using selected binders (MS, PVP and GLT) and anhydrous calcium phosphate as diluent.

Binder (% w/v)	Binder Conc.	Tablet Thickness (mm)	CS (kgf)	FR (%)	CS/FR	DT (min)	CSFR/DT
MS		3.84±0.1	3.7±0.2	0.02±0.003	185	5.57±0.1	33.21
PVP	2.5	3.46±0.1	3.2±0.1	0.02±0.004	160	3.00±0.1	53.33
GLT		3.39±0.1	3.9±0.4	0.01±0.001	390	5.57±0.2	70.02
MS		3.77±0.1	4.0±0.4	0.01±0.004	400	5.75±0.2	69.57
PVP	5.0	3.42±0.1	4.1±0.4	0.01±0.003	410	3.43±0.2	119.53
GLT		3.33±0.1	4.2±0.2	0.01±0.003	420	5.65±0.2	74.34
MS		3.73±0.1	4.1±0.03	0.01±0.007	410	5.95±0.2	68.91
PVP	7.5	3.26±0.1	4.4±0.02	0.01±0.006	440	3.95±0.5	111.93
GLT		3.32±0.1	4.8±0.02	0.01±0.005	480	6.46±0.2	74.30

MS = Maize starch, PVP = Polyvinylpyrrolidone, GLT = Gelatin. Results were expressed as mean ± SD of three runs and at 95% confidence level, p values ≤ 0.05 were considered the limit of significant

The British Pharmacopoeia (BP, 2007) specifies crushing strength values ≥ 4 kgf and ≤ 15 kgf, friability < 10%, and disintegration time ≤ 15 min for uncoated tablets. Results in Table 3 show that values for all the batches fall within the standard specification signifying the success achieved in using the efflorescent anhydrous calcium phosphate in the tablet formulation of the deliquescent EVG. Crushing strength-friability ratio (CSFR) which is the quotient of the crushing strength (CS) value divided by the friability (FR) value, has been the index used as a measure of mechanical strength of tablets. But the CSFR:DT ratio which is a later index has been suggested as being better for measuring tablet quality. This is because in addition to measuring tablet strength (crushing) and weakness (friability), it simultaneously evaluates all negative effects of these parameters on disintegration time. Higher values of the CSFR:DT indicate a better balance between binding and disintegration properties (Alebiowu and Itiola, 2003). It was clearly observed that the plots of CSFR:DT versus percentage concentration of binder for all the formulations

recorded peak CSFR:DT values at the 5% w/v concentrations (Figure 1). This indicate that 5% w/v concentration of binders might be the optimum to be used in the tablet formulation of the deliquescent EVG. Based on the effects of the three binders used (MS, PVP and GLT), on the various formulations, the order of CSFR:DT in ranking was as follows; PVP > GLT > MS (Figure 1). Indicating that formulations made with PVP as binder were of higher quality than those made with GLT and MS. Interestingly, the order of dissolution rate in ranking was also found to be the same with that of the CSFR:DT based on the effects of the three binders used as follows; PVP > MS > GLT (Figure 2), also indicating that formulations made with PVP as binder are of higher quality in terms of dissolution rate than formulations made with GLT or MS.

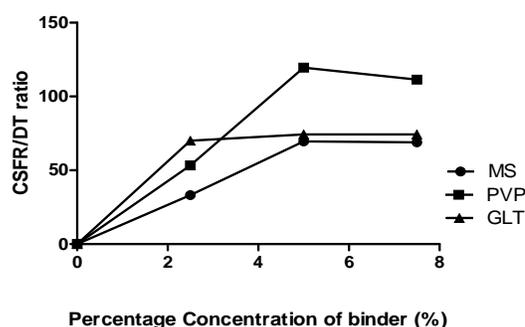


Fig.1: Crushing strength-friability, disintegration time (CSFR/DT) ratio Vs percentage concentration of selected binders [maize starch (MS), polyvinylpyrrolidone (PVP) and gelatin (GLT)] for *Vernonia galamensis* tablets prepared using anhydrous calcium phosphate as diluents.

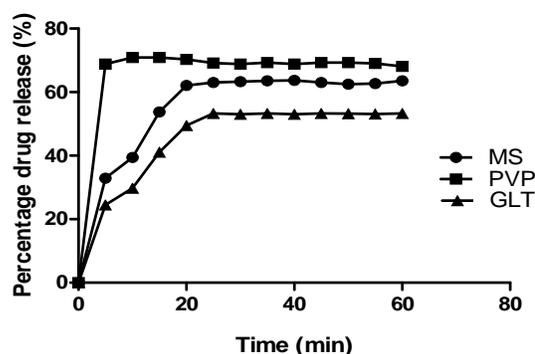


Fig. 2: Percentage drug release Vs time of *Vernonia galamensis* tablet formulations prepared using calcium phosphate and selected binders [maize starch (MS), polyvinylpyrrolidone (PVP) and gelatin (GLT)].

In addition, the British Pharmacopoeia (BP 2007) specifies that (for optimum absorption and pharmacological activity), conventional tablets should release 70% of active components within 45 min. according to our study, only tablet formulations produced using PVP as binder meets this specification, releasing 70% active components in less than 10 min (Figure 2). Drug release properties of tablets were characterized by the disintegration and dissolution times. The result of spectrophotometric analysis shows that the EVG exhibited a

principal absorption maximum at 216 nm typical for saponin alkaloids with a diene chromophore (Schmidt *et al.*, 1980). Thus the calibration curve to assess the release properties of the tablets were determined at a wavelength of 216 nm and the linear regression equation for the plot of absorbance versus concentration was obtained as $y = 0.1734x - 0.0043$, indicating a negative intercept, likely to be due to the deliquescent characteristics of the extract. The amount of drug (crude saponin alkaloid) released was plotted against time and the representative plots for tablets containing CP as diluent and MS, PVP and GLT as binders are depicted in figure 2.

CONCLUSION

Due to the deliquescent property of the extract, the type and concentration of excipients employed for tablet formulation need to be carefully chosen to enable the production of suitable tablets that will conform to current Good Manufacturing Practice (GMP). We can conclude from this study that good quality tablets of the deliquescent EVG (especially in terms of the CSFR:DT and dissolution rate), can be formulated using the efflorescent anhydrous calcium phosphate as diluent and a carefully selected binder; PVP at 5% w/v concentration.

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