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Research Article

MECHANICAL AND RELEASE PROPERTIES OF *VERNONIA GALAMENSIS* TABLET FORMULATIONS PREPARED USING GELATIN AS BINDER

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ABSTRACT
The purpose of this study was to formulate the crude aqueous leaf extract of *Vernonia galamensis* (used in folk medicine for the treatment of diabetes mellitus) into conventional tablets using three selected efflorescent diluents namely Aerosil® 200, Avicel® PH 101 and calcium phosphate, due to the deliquescent nature of the extract. Attempted use of ordinary diluents for the tablet formulation had resulted to tablets defects. The crushing strength, friability, disintegration and dissolution times of tablets were determined using the methods specified in BP 2007. The rank order of crushing strength - friability, disintegration time ratio (CSFR:DT) and dissolution rate values using gelatin as binder in terms of the three efflorescent diluents used was; calcium phosphate > Avicel® PH 101 > Aerosil® 200. Results indicate that good quality tablets of the deliquescent crude extract of *Vernonia galamensis* could be produced using the three selected efflorescent diluents with gelatin as binder but tablets produced using calcium phosphate as diluent were of best quality.
Key words*:* Gelatin, crushing strength, disintegration, dissolution, tensile strength.

INTRODUCTION

Traditional herbalists have revealed the folkloric use of the dried powdered leaves of *Vernonia galamensis* (Asteraceae) in the treatment of diabetes mellitus. But because folkloric medicines have no standard dose or acceptable method of formulation[1], there is the need to standardize and formulate them in conformity with current Good Manufacturing Practice (GMP). Some researchers have chosen the tablet over other dosage forms for the formulation of medicinal plant extracts[2,3], due to the advantages of the former. Most plant extracts are hygroscopic and susceptibility to microbial degradation, so the choice of a suitable pharmaceutical dosage form that will conform to GMP cannot be overemphasized. Tablets are by far the most frequently used dosage form for all active medicinal ingredients; they have advantages for both manufacturer and user. Ease of administration, convenience of administration, and accurate dosing make tablets a versatile and popular dosage form[4].

The aim of this study was to formulate the dry crude leaves extract of *Vernonia galamensis* (EVG) into tablets in accordance with current GMP. The EVG is highly hydroscopic and deliquescent and is stored over silica gel in a desiccator. The use of common diluents like lactose, maize starch and magnesium carbonate for the formulation produced tablet with defects especially 'sticking' and 'picking' due to the deliquescent nature of the extract. But of paramount importance in this study was the use of gelatin an officially approved pharmaceutical binder, and carefully selected efflorescent diluents for tablet formulation of the extract. The mechanical strengths of tablets were assessed using the crushing strength-friability, disintegration time ratio (CSFR:DT) and tensile strength.

Tensile strength (TS) is a method of measuring the mechanical strength of tablets. It is the force required to break a tablet in a diametral compression test. It is calculated from the equation:

$$TS = 2CS/\pi Dd$$

where CS is the crushing strength which is the force required to break the tablet, D and d are the diameter and thickness respectively[5]. Various factors e.g. test conditions, deformation properties of the material, adhesion conditions between compact and its support and tablet shape may influence the measurement of the tensile strength.

MATERIALS AND METHODS

Leaves of *Vernonia galamensis* were collected from the natural habitat of plant within Ahmadu Bello University,

Zaria, Nigeria and was identified in the herbarium unit of the Biological Sciences Department the University (voucher specimen number 994) where a sample has been deposited. The leaves were washed, air dried, milled to a coarse (1000 µm) powder 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. The dried extract was pulverized using a mortar and pestle and passed through a 150 µm sieve and kept in an airtight desiccator.

Preparation of Binder. –The required amount of gelatin (GLT) powder to make 2.5, 5.0, and 7.5% w/v was suspended in cold water and allowed to hydrate. The suspension was then warmed on a water bath until a flowable material was obtained. To avoid gelling, the suspension was kept warmed during use.

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 min. Disintegrant (maize starch, 6.8% w/w) was added and mixing continued for another 5 min. The liquid binder was added to the powder mix in 2-mL portions and mixed with a pestle. The moistened mass was forced through a 1000 µm sieve, dried at 60 °C for 1 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.

Particle Size Classification of Granules: - 50 g of the granules was placed on a stack of seven sieves of descending mesh sizes of 1000 µm, 850 µm, 710 µm, 600 µm, 500 µm, 250 µm and 150 µm. The sieves were vibrated on a sieve shaker (Retsch GmbH, No. 223110019, Type AS 200, Haan, Germany) for 15min. Thereafter the granules retained on the sieves were divided into three groups as follows; >710 < 1000 µm, >500 < 710 µm and >150 < 500 µm, and weighed on a toploading balance.

Preparation of Tablets. – The tablet formula was designed by varying the types and quantities of the excipients with the ultimate view of obtaining tablets of highest quality (Table 1). 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 10.5mm flat punch and die set. Before each compression, the die (10.5 mm in diameter) and the flat-faced punches were lubricated with a 1% (*m/v*) dispersion of magnesium stearate in ethanol. After ejection, the tablets were stored over silica gel in a desiccator for 24 h to allow for elastic recovery and hardening[3].

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 4 min. 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 the BP 2007 specifications using the Erweka disintegration tester (Erweka ZT 71, Germany). Distilled water thermostatically maintained at 37 ^{o}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 using 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 10 min intervals, samples of the dissolution medium were withdrawn with a syringe filtered through a filter paper of 0.2 um 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

Vernonia galamensis 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

Table 2 presents the values of mean granule size, moisture content, crushing strength (CS), friability (FR), disintegration time (DT) and crushing strength-friability, disintegration time ratio (CSFR:DT) of *V. galamensis* tablets produced using selected diluents Aerosil® 200 (AR), Avicel® PH (AV) 101 and calcium phosphate (CP) in combination with selected concentrations of GLT (2.5 %, 5.0 % and 7.5 % w/v) as binder. On a general note, the rank orders of CSFR:DT values for the three diluents, using GLT as binder at 2.5 %, 5.0 % and 7.5 % were similar and as follows; AV > CP > AR. This was further simplified in figure 1 where the rank order of CSFR:DT was vividly seen to be; AV > CP > AR with the highest values of CSFR:DT obtained at 5 % w/v concentration of the binder.

Figure 2 depicts the tensile strength (TS) - pressure profile of EVG compacts formulated using CP as diluent and GLT as binder. All the granules exhibited significant sensitivity to changes in the compaction force. TS increased up to 290 MNm^{-2} for the whole granule size range, thereafter, further increase in compaction force results in a decrease in the compact TS.

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[6]. Thus the calibration curve to assess the release properties of the tablets were determine at a wavelength of 216 nm and the linear regression equation for the plot of absorbance versus concentration was given as $y = 0.1734x - 0.0043$. The amount of drug (saponin alkaloid) released was plotted against time and the representative plots for tablets containing AV, CP and AR as diluents and GLT as binder were presented (Figure 1). The rank order for both disintegration time (Table 2) and dissolution time (Figure 3) were found to be the same as follows CP < AV < AR.

DISCUSSION

Previous studies have observed that increase in granule size leads to increase crushing strength of tablets and that this is as a result of increased surface irregularity of the larger granules, leading to an increased number of binding surface areas[7]. It was difficult to ascertain this fact in our study. On the contrary, we observed almost a complete reverse of that hypothesis. The effect of binder type could be explained as the reason for the discrepancies. For example gelatin and maize starch have been found to have higher binding effects than polyvinylpyrrolidone[8]. So if a binder of lower binding capacity is used, the crushing strength will be low, regardless of granule size.

Moisture content was found to increase as the binder concentration was increased, with a corresponding increase in crushing strength (Table 2). This is in agreement with previous study which revealed that increased binder concentration usually result in increase moisture content and increased tablet tensile strength[9].

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[3]. But the CSFR:DT which is a later index, is the quotient of the CSFR value divided by the disintegration time (DT) value, and 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[10]. The higher CSFR:DT and dissolution rate values obtained for tablets produced using CP and AV as diluents as presented in Table 2 and figure 3 respectively, could be explained by the presence of crystalline components in the CP and AV since crystals would normally disintegrate more easily in water than amorphous materials. CP and AV contain crystalline components while AR is completely amorphous[11]. Comparing CP and AV however, tablet formulations with CP have higher CSFR:DT and dissolution rate values than those with AV (Figs. 4-6). This could be as a result of a decrease surface irregularity, leading to decrease number of binding surface areas for binders in CP[2].

It was also generally observed that for all three diluents used, increase in binder concentration lead to increase crushing strength, decrease friability and increase disintegration time of tablets (Table 2). This exactly follows the trend observed by Oyi *et al*[12], and it implies that in situations where high bond strength is desired

especially in chewable tablets and lozenges, higher binder concentrations can be used.

The TS of tablets formulated with CP/PVP increased with increase in granule particle size. This means stronger bonds were formed within the particles as the particle size increased. The stronger bonds in the larger particles could be a result of an increased surface irregularity, leading to an increased number of binding surface areas[2]. The stronger larger particles definitely required higher force to consolidate, dissipating energy and resulting in increase temperature. As the tablet temperature rises, stress relaxation and plasticity increases while elasticity decreases and strong compacts are formed[13,14]. This agrees with previous works which revealed that compression of material at elevated temperature with increase in ductility should result in stronger compacts[15].

The tensile strengths for the EVG/CP tablets increased with increasing compaction force to their peaks levels at 290 MNm–2 compaction force for the whole granule size range. Thereafter, further increase in compaction force resulted in a decrease in the tablet tensile strengths. This can be ascribed to the possibility of the work associated with compaction above 290 MNm^{-2} being recovered during elastic relaxation, which results in a weakening of the tablet structure[16]. This also agrees with previous works which revealed that plastic deformation is believed to create the greatest number of clean surfaces and that because plastic deformation is a time dependent process, higher rate of force application should lead to the formation of less new clean surfaces and thus resulting in weaker tablets[17,18].

CONCLUSION

The dried EVG as prepared from the laboratory is highly hygroscopic and deliquescent and is permanently stored in a desiccator. Efforts in trying to use the usual common pharmaceutical diluents such as lactose, maize starch (MS) or magnesium carbonate for tablet formulation of the deliquescent plant extract proved abortive as the resulting powder mixture or granules quickly absorbed moisture and become sticky. The major problems encountered with the tableting process were; (i) difficulty in feeding the die, the granules being sticky, and (ii) 'tablet defects' especially 'sticking' and 'picking'. But understanding the definition of deliquescent materials as those materials that are highly hydrophilic and absorbed moisture from the atmosphere becoming fluid, it was quite scientific and wise to look for efflorescent diluents. This is simply 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[19]. A balance was believed to be achieved along the line where the tendency of the deliquescent material to absorb moisture was counteracted by the ability of the efflorescent material to expel all moisture.

In terms of mechanical strength therefore, our study revealed that good quality tablets of EVG could be produced using the efflorescent diluents; AR, AV and CP, regardless of binder type. When we included dissolution test results however, we were able to conclude that using GLT as binder, the best quality tablets of EVG could be produced when using CP as diluent compressed at 290 MNm^{-2}.

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Table 1: Tablet formula for respective batches

Material	Quantity per tablet (mg)
Dried Aqueous Extract	115
Diluents (aerosil® 200, avicel® PH 101, calcium phosphate)	155
Endodisintegrant (Maize starch 6.8%w/w)	20.4
Binder (Gelatin - 2.5, 5.0, and 7.5% w/w)	Qs
Talc (3.0%w/w)	9.0
Magnesium Stearate I (0.2%w/w)	0.6
Theoretical tablet weight	**300 ± 7.5**

Table 2: Values of granule size, moisture content and crushing strength-friability, disintegration time (CSFR/DT) ratio values for V. galamensis granules and tablets prepared using selected concentrations of gelatin (GLT) as binder.

Diluent	GLT (% w/v)	Mean Granule size (um)	Moisture Content (% w/w)	CS (kgf)	FR (%)	DT (min)	CSFR/DT
AR	2.5	267±1.2	8.5±0.1	4.4±0.04	0.02±0.001	12.03±0.31	18.29
AR	5.0	418±5.2	9,0±0.1	5.3±0.05	0.01±0.003	12.54±0.22	42.26
AR	7.5	466±1.3	10.0±0.1	6.2±0.02	0.01±0.005	14.72±0.21	42.12
AV	2.5	298±1.7	8.5±0.1	8.6±0.02	0.02±0.005	8.12±0.12	52.96
AV	5.0	439±4.1	9.5±0.1	9.0±0.03	0.01±0.003	9.48±0.18	94.94
AV	7.5	362±1.2	12.0±0.1	9.8±0.01	0.01±0.002	10.33±0.12	94.87
CP	2.5	618±.2.1	9.5±0.1	3.9±0.01	0.02±0.003	5.57±0.22	70.02
CP	5.0	435±7.2	11,0±0.1	4.2±0.04	0.01±0.001	5.65±0.18	74.34
CP	7.5	557±2.3	13.0±0.1	4.8±0.02	0.01±0.003	6.46±0.16	74.30

AR = aerosil® 200, AV = avicel® PH 101, CP = calcium phosphate

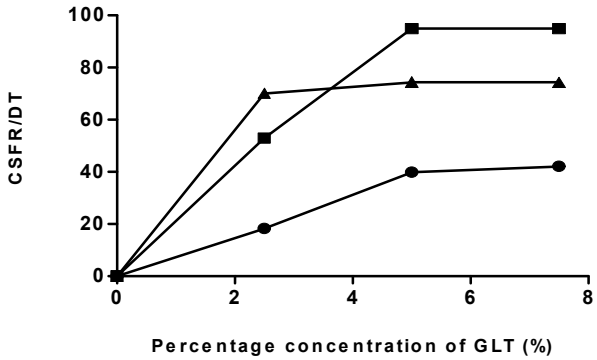

Fig. 1: CSFR/DT ratio Vs Percentage Concentration of Gelatin (GLT) used in the formulation of tablets of *Vernonia galamensis* leaf extract using selected Diluents

Aerosil Avicel Calcium phosphate

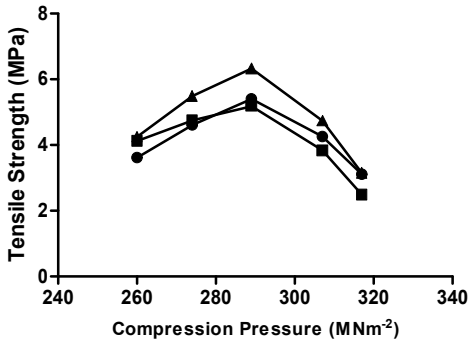

Fig. 2: Tensile Strength Vs Compression Pressure for tablets prepared using Cacium phosphate as Diluent and Gelatin (GLT) 5%w/v as Binder

>150<500 >500<710 >710<1000

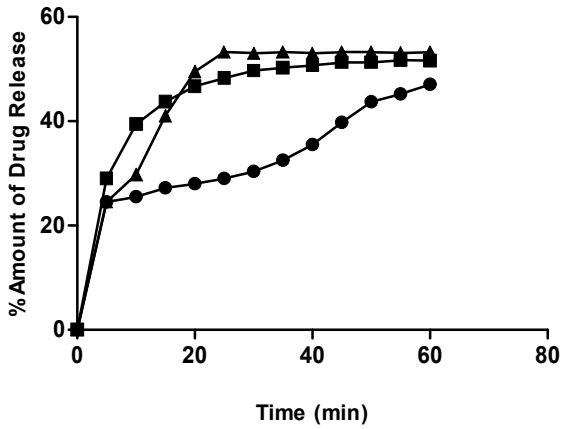

Fig. 3: Percentage amount of drug release Vs Time of *Vernonia galamensis* tablets produced using selected diluents and gelatin (GLT) as Binder

Aerosil Avicel Calcium phosphate

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