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Research Article

Use of avicel® ph-103 and selected binders in the tablet formulation of the deliquescent crude leaves extract of *Vernonia galamensis* (Asteraceae)

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ABSTRACT

A decoction of the leaves of *Vernonia galamensis* (Asteraceae) has been used in folk medicine for the treatment of diabetes mellitus. But because folkloric medicines have no standard dose or acceptable method of formulation, attempts have been made by some scientists to formulate crude plant extracts into tablets. The crude leaves extract of *Vernonia galamensis* is highly hygroscopic and deliquescent and is stored over silica gel crystals in a desiccator. In this study, the effect of a grade of microcrystalline cellulose; avicel PH-103 (FMC Corporation, USA), 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. 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. Granule properties such as angle of repose, moisture content, bulk and tapped densities, Carr's index, and tablet properties such as tablet thickness, friability, disintegration times, and dissolution rates using standard methods were investigated. An increase in binder concentration led to an increase in crushing strength, decrease in friability and increase in disintegration time of the tablets. Formulations using gelatin as binder produced the best quality tablets in terms of the CS/FR ratio, CSFR/DT ratio and dissolution rate. Gelatin can therefore be a useful binding agent in the formulation of the deliquescent crude leaves extract of V. galamensis when the efflorescent fumed silica is used as diluent.

Keywords: Crude extract; binding effect; maize starch; polyvinylpyrrolidone; gelatin.

INTRODUCTION

The decoction of leaves of *Vernonia galamensis* (Asteraceae) have been used in folk medicine for ages in the treatment of diabetes mellitus. This information was revealed through oral communication with traditional herbalists in northern Nigeria during a search for anti-diabetic herbal remedies. But folkloric medicines have no standard dose or acceptable method of formulation, and most plant extracts are hygroscopic and deteriorate quickly (Allagh et al, 2009), therefore there is the need for standardization and formulation into suitable pharmaceutical dosage forms. Tablets are by far the most frequently used dosage form due to their advantages for both manufacturer and user. Ease of administration and accurate dosing make tablets a versatile and popular dosage form (Ilic et al, 2009).

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The crude leaves extract of *Vernonia galamensis* is highly hygroscopic and deliquescent and is stored in airtight containers or over silica gel crystals in a desiccator. Attempts to use the common diluents; lactose, maize starch and magnesium carbonate for tablet formulation of the deliquescent crude extract yielded very poor quality tablets with defects especially 'sticking' and 'picking'. It became necessary to carefully select a suitable diluent of efflorescent nature, so as to counteract the deliquescent characteristic of the extract. In this study, the effect of avicel PH-103 (FMC Corporation, USA), an efflorescent pharmaceutical powder of reduced moisture content, ideal for moisture-sensitive materials (Gohel and Jogani, 2005) was used as diluent and the comparative binding effects of maize starch, polyvinylpyrrolidone and gelatin were investigated in the tablet formulation of the deliquescent crude extract. Avicel PH-103 is a brand name of microcrystalline cellulose (MCC) of special grade. MCC is purified partially depolymerized cellulose, prepared by treating α-cellulose with mineral acids. After purification by filtration and spray-drying, porous microcrystals are obtained (Gohel and Jogani, 2005). MCC occurs as white

odorless, tasteless crystalline composed of porous particles of agglomerate product.

MATERIALS AND METHODS

Materials

These include avicel PH-103 (FMC Corporation, USA), Maize starch and Gelatin (May and Baker, Germany), 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

Preparation of the extract: Leaves of *Vernonia galamensis* were washed, air dried, milled to a coarse powder (particle size ≤ 1000 um) 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.

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 (MS), polyvinylpyrrolidone (PVP) or gelatin (GLT) powder was added in 1-mL portions and mixed with a pestle. The moistened mass was forced through a 1000µm 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.

Granule Analysis and Characterization of Tablets: These were carried out according to the methods adopted by Oyi, et al (2009).

Preparation of tablets: Tablets equivalent to 300mg of granules were produced by compressing the granules for 60 seconds 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 According to the methods adopted by Isimi *et all*, (2003).

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). 0.1M HCl 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 0.1M HCl, 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^{o}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.

Table 1: Properties of granules of the leaves extract of *V. galamensis* prepared using selected binders (MS, PVP and GLT) and avicel PH-103 as diluent

Binder	Binder Conc (% w/v)	Mean Granule size (um)	Moisture Content (%w/w)	Bulk Density (gm/ml)	Tap Density (gm/ml)	Angle of Re-pose(0)	Flow Rate (g/s)	Hausn-er's Ratio	Carr's Index (%)
MS	2.5	283±1.0	7.50±0.1	0.36±0.03	0.40±0.01	20.9±0.9	0.94±0.1	1.11±0.1	12.92±0.2
PVP	2.5	304±4.3	7.50±0.2	0.38±0.03	0.43±0.01	29.1±0.4	1.25±0.1	1.13±0.1	12.89±0.2
GLT	2.5	298±4.2	8.50±0.1	0.33±0.02	0.45±0.02	33.3±0.3	1.10±0.1	1.36±0.2	6.67±0.6
MS	5.0	306±1.5	9.00±0.1	0.38±0.03	0.44±0.04	27.6±0.5	6.95±0.1	1.13±0.1	13.58±0.5
PVP	5.0	446±3.2	7.50±0.1	0.34±0.05	0.41±0.05	31.6±0.3	3.00±0.1	1.21±0.1	16.07±0.4
GLT	5.0	439±5.2	9.50±0.1	0.46±0.01	0.54±0.06	24.4±0.5	5.52±0.1	1.17±0.1	13.90±0.9
MS	7.5	318±.2.7	12.00±0.1	0.32±0.06	0.37±0.03	31.7±0.8	3.82±0.1	1.18±0.2	13.80±0.3
PVP	7.5	380±5.1	9.00±0.2	0.33±0.02	0.39±0.03	28.2±0.6	4.55±0.1	1.13±0.1	16.66±0.1
GLT	7.5	362±3.2	12.00±0.1	0.49±0.0	0.53±0.03	28.0±0.4	5.10±0.1	1.08±0.2	8.50±0.4

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.

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 efflorescent fumed silica 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).

Bulk and tap densities usually provide information on the flowability of powders and granules hence are used to calculate the parameters of Hausner's ratio and Carr's index. The British Pharmacopoeia (BP) 2007 specifies that for good flow, bulk density values should be less than 1.2, values greater than 1.6 give poor flow, but for tap densities, the values depend on number of tapings. In our study, bulk density values for all the formulations were far below 1.2 (Table 1), indicating excellent flow. Hausner's ratio and Carr's index are considered as indirect measurements of flowability (Staniforth, 1996). Hausner's ratios less than 1.25 indicate good flow (BP 2007). For Carr's index, the lower the value the better the flowability, and Carr's index values of 5 to 10, 12 to 16, 18 to 21 and 23 to 28 represent excellent, good, fair and poor flow properties respectively (Carr, 1965). Based on the Hausner's ratio and Carr's index values obtained, our study indicates good and excellent granule flow for all binder types at all the concentrations used. The flow rate and angle of repose are also known to be good measures of flowability and for good flow; powders or granules should flow through the funnel orifice and the angle of repose values should be less than 50^{o}, values greater than 50^{o} give poor flow (BP 2007). Based on these specifications, values of our flow rate and angle of repose fall 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 avicel PH-103 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. Similar trend was observed by Tahir *et al* (2010) where in *in vitro* dispersion time increases as the concentration of binder increases. In our study using avicel PH-103 as diluent MS shows fastest dispersion time. This may probably be due to formation of dense capillary network structure resulting from the use of the MS (Tahir *et al,* 2010).

Kuntz *et al* have 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. The effect of binder type is of paramount importance in explaining this deviation. For example in our study, GLT and MS were found to have higher binding effects (formulations containing these have higher crushing strength and longer disintegration time values) than PVP agreeing directly with the findings of Varshosaz *et al*. So the use of a binder of higher binding capacity will result to higher crushing strength,

Table 2: Properties of tablets of the leaves extract of *V. galamensis* prepared using selected binders (MS, PVP and GLT) and avicel PH-103 as diluent

Binder	Binder Conc. (% w/v)	Tablet Thickness (mm)	Crushing Strength (kgf)	Friability (%)	Crushing Strength/ Friability ratio	Disintegration Time (min)	CSFR /DT
MS	2.5	4.44±0.1	4.4±0.2	0.02±0.002	220	5.80±0.2	68.54
PVP	2.5	4.35±0.1	7.0±0.1	0.02±0.004	350	8.24±0.2	42.48
GLT	2.5	4.17±0.1	8.6±0.4	0.02±0.001	430	8.12±0.2	52.96
MS	5.0	4.18±0.1	5.4±0.4	0.01±0.001	540	6.16±0.2	97.95
PVP	5.0	4.31±0.1	7.8±0.4	0.01±0.003	780	9.47±0.1	82.36
GLT	5.0	4.17±0.1	9.0±0.2	0.01±0.003	900	9.48±0.2	94.94
MS	7.5	4.14±0.1	7.2±0.3	0.01±0.005	720	7.53±0.1	95.62
PVP	7.5	4.12±0.1	8.6±0.2	0.01±0.006	860	10.47±0.3	82.14
GLT	7.5	4.17±0.1	9.8±0.2	0.01±0.005	980	10.33±0.2	94.87

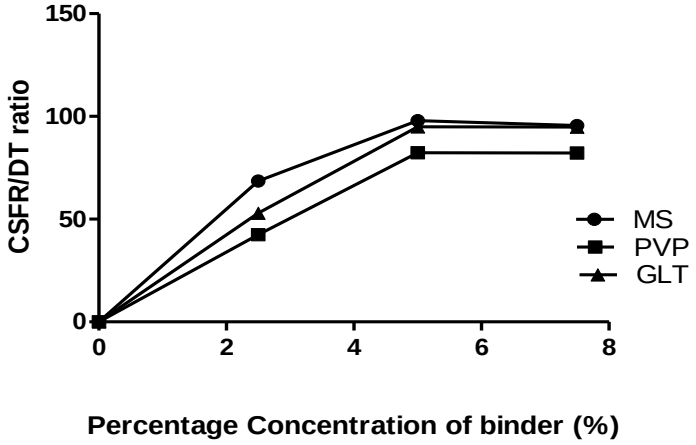

Figure 1: CSFR/DT ratio Vs percentage concentration of selected binders for *Vernonia galamensis* tablets prepared using avicel PH-103 as diluents

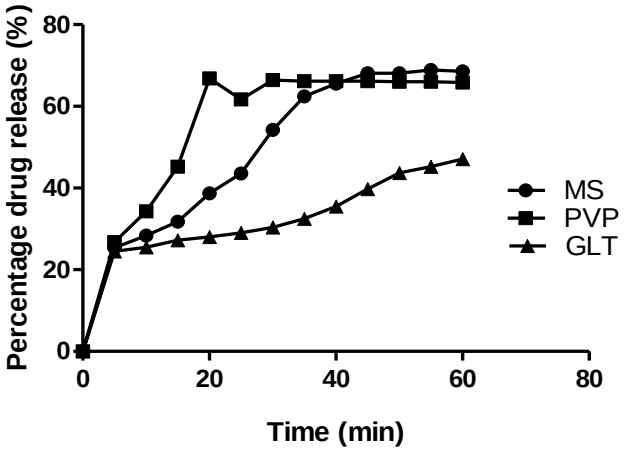

Figure 2: Percentage drug release Vs time of *Vernonia galamensis* tablet formulations prepared using Avicel PH-103 and selected binders

regardless of granule size. We also observed an increase in crushing strength with increase binder concentration (Table 2), agreeing with previous work (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 to an increase in crushing strength. Binders however, form films on the surface of the granules; therefore if added at too great a concentration, the films can form viscous gels on the granule surface and may retard dissolution (Cunnigham and Scattergood, 2001).

The British Pharmacopoeia 2007 specifies the following values for uncoated tablets; crushing strength ≥ 4 kgf and ≤ 15 kgf, friability < 10%, disintegration time ≤ 15 min, and for dissolution time; 70 – 100% of the active ingredients should be released within 45 min. Results in table 5 show that all the batches passed the crushing strength, friability and disintegration tests as expected of standard uncoated tablets.

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 et al, 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 indicates that 5% w/v concentration of binders is the optimum for tablet formulation of the deliquescent EVG. The rank order of CSFR:DT based on the three binders (MS, PVP, GLT) was found to be as follows; MS > GLT >PVP (Figure 1). This indicates that the tablet formulations using MS as binder were of superior quality based on the CSFR:DT. But it should be noted that as mentioned above, all the formulations already passed the crushing strength, friability and disintegration tests as expected of standard uncoated, therefore the CSFR:DT values for all the formulations are acceptable regardless of the rank order. The major factor therefore to be considered will be the dissolution rate. The rank order of dissolution rate for all the formulations based on the three binders (MS, PVP, GLT) was found to be; PVP > MS > GLT (Figure 2), indicating that formulations using PVP as binder were of superior quality. It will be therefore reasonable to select PVP (5% w/v) as binder of choice in the tablet formulation of the deliquescent EVG using avicel PH-103 (FMC Corporation, USA), an efflorescent pharmaceutical powder of reduced moisture content, and ideal for moisture-sensitive materials.

CONCLUSION

The results obtained show that the methods of preparation of the deliquescent EVG tablets need to be carefully selected to ensure the production of tablets with adequate bond strength to withstand the rigors of handling and at the same time release the active compound(s) for biological action. Furthermore the type and concentration of excipients employed need to be carefully chosen to enable the production of suitable tablets that will conform to Good Manufacturing Practice (GMP).

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REFERENCES

Alebiowu G and Itiola OA, Effects of starches on the mechanical properties of paracetamol tablet formulations. II. Sorghum and plantain starches as disintegrants. Acta Pharmaceutica*,* vol. 53, November, 2003 pp. 49-57.

Allagh, TS, Ameh, GO. and Okafor IS, Formulation and evaluation of the physicochemical properties of *Ageratum conyzoides (Fam asteraceae)* granules and tablets. Nigerian Journal of Pharmaceutical Sciences, vol. 8, no. 2, October, 2009 pp 18-25.

Carr RI, Evaluating flow properties of solids, Chem Eng, vol. 72, February, 1965 pp. 163-168.

Chowhan ZT. Role of binders in moisture-induced hardness increase in compressed tablets and its effect on *in vitro* disintegration and dissolution*. J Pharm Sciences,* vol. 69, no. 1, September, 2006 pp. 1-4. DOI: 10.1002/jps.2600690102

Cunnigham C. R. and Scattergood L. K., The effect of Starch 1500® on the stability of aspirin tablets stored under accelerated conditions, AAPS, October, 2001.

Gohel MC and Jogani PD, A review of co-processed direcly compressible excipients. J Pharm Pharmaceut Sci, vol. 8, no. 1, April, 2005 pp. 76-93.

Ilic I, Kasa P, Dreu R, Pintye-Hodi K and Sircic S, The compressibility and compactibility of different types lactose. Drug Development and Industrial Pharmacy, vol. 35, no. 10, May, 2009 pp. 1271-1280.

Kuntz T, Schibert MA and Kleinebudde P, Increase compactibility of acetames after roll compaction. Europian Journal of Pharmaceutics and Biopharmaceutics, vol. 77, no. 1, January, 2011 pp. 164-169.

Oyi AR, Allagh TS, Olayemi OJ. Comparative binding effects of wheat, rice and maize starches in chloroquine phosphate tablet formulations. Res J Appl Sci Eng Technol, vol. 1, no. 2, August, 2009 pp. 131-136

Sebhatu T, Ahlneck C and Alderborn G, The effect of moisture content on the compression and bond-formation properties of amorphous lactose particles, Int J Pharm vol. 146**,** January, 1997 pp. 101-114.

Staniforth JN, Pharmaceutics: The science of dosage form design, 1st Edition, Churchill Livingstone Medical division of Longman group, UK, 1996.

Tahir MA, Awadhesh K, Swati S, Sant S, Sajid MA, Pattnaik GD, Farheen. Optimization of fast disintegrating tablets for diclofenac sodium using isabgol mucilage

as super disintegrants. Int J Pharm Sci, vol. 2, no. 2. May-August, 2010 pp. 496-501.

Varshosaz J, Kennedy RA and Gipps EM, Effect of binder level and granulating liquid on phenylbutazone pellets prepared by extrusion spheronization. Drud Development and Industrial Pharmacy, vol. 23 no. 6, October, 1997 pp. 611-618.