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Research Article

EFFECTS OF SELECTED DILUENTS AND MAIZE STARCH MUCILAGE BINDER ON THE TABLETS FORMULATION OF THE CRUDE AQUEOUS EXTRACT OF *VERNONIA GALAMENSIS*

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Abstract

Context: Leaves of *Vernonia galamensis* (Asteraceae) have been used for the treatment of diabetes mellitus in folk medicine in northern Nigeria for ages. The crude extract of the leaves is deliquescent and usually stored in airtight desiccators. Attempts to use common diluents such as lactose, starch, and magnesium carbonate for tablet formulation of the extract produced tablets with defects such as "sticking" and "picking", therefore efflorescent diluents were selected for the formulation. *Aim:* The aim of this study was to establish suitable efflorescent diluents for tablet formulation of the deliquescent crude extract of *Vernonia galamensis* using maize starch mucilage as binder, and to investigate and quantify the mechanical and drug release properties of the tablets. *Methods*: The mechanical properties of the designed tablets were assessed using crushing strength-friability and disintegration time ratio (CSFR:DT), while the drug release properties were evaluated using dissolution time. The crushing strength, friability, disintegration and dissolution times of tablets were determined using the methods specified in BP 2007. *Results:* Using maize starch 2.5%, 5% and 7.5% w/v as binder for the three diluents, the rank order of CSFR:DT was; avicel® PH 101 > calcium phosphate > aerosil® 200. And the rank order of dissolution rate was; calcium phosphate > avicel® PH 101 > aerosil® 200. *Conclusion:* Dissolution rate is a compendial requirement and

therefore a better index than the CSFR:DT, therefore our results indicate that tablet formulations using calcium phosphate as diluent are of best quality.

Key words: binders, crushing strength, diluents, dissolution.

Introduction

Oral communication with traditional herbalists in northern Nigeria revealed the folkloric use of the dried powdered leaves of *Vernonia galamensis* (Asteraceae) in the treatment of diabetes mellitus. But folkloric medicines have no standard dose or acceptable method of formulation [1]. There is therefore the need for standardization and formulation of the medicines 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 current 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 good quality tablets by wet granulation method using the efflorescent diluents; aerosil® 200, avicel® PH 101 and calcium phosphate and maize starch mucilage as binder. The EVG is highly hydroscopic and deliquescent and is stored over silica gel in a desiccator. Attempts to use common diluents such as lactose, starch, and magnesium carbonate for tablet formulation of the extract produced tablets with defects such as “sticking” and “picking”, therefore the efflorescent diluents were selected for the formulation.

Materials and Methods

Materials

These include aerosil® 200 (GmbH, Meggle, Germany), avicel PH-103 (FMC Corporation, USA) calcium phosphate (BDH chemicals Ltd., Poole, England), maize starch (May and Baker, Germany) 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 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.

ii). Preparation of granules

The wet granulation, a versatile process, was employed because of the very high humidity and poor flow property of the extract [5]. Appropriate quantities of the dry extract and 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) mucilage 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.

iii). Granule Analysis

(a). Moisture content analysis

The method specified in the B.P 2004 for acacia as adopted by Shengjum [6] was used. One gram (1.0g) of the sample was transferred into each of several petri dishes and then dried in an oven 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, a, was measured according to the fixed funnel and free standing cone method.[7] 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:

$$\text{Tan } a = 2h/D \quad \text{…….(1)}$$

(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 ratios of weight to volume (V_0 and V_{100} respectively). Carr's index and Hausner's ratio were calculated using the following equations:-

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

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

iv). Preparation and analysis of tablets

The tablet formula was designed by varying the type and quantities of the excipients to obtain 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 10.5 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.

Table 1: Tablet formula for respective batches

Material	Quantity per tablet (mg)
Dried Aqueous Extract	115
Diluent (AR, AV or CP)	155
Endodisintegrant (Maize starch 6.8%w/w)	20.4
Binder (MS 5% w/v)	Qs
Talc (3.0% w/w)	9.0
Magnesium Stearate I (0.2% w/w)	0.6
Theoretical tablet weight	**300 ± 7.5**

Analysis of tablet. – This was done as follows:

i. 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).

ii. 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.

iii. 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.

*iv. Disintegration; T*he disintegration times of the tablets were determined according to standard specifications,[7] 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.

v. 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 0.1 M Hcl, 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 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

EVG 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.

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 2 presents the values of granule size, moisture content, crushing strength, friability, disintegration time and the crushing strength-friability, disintegration time ratio (CSFR:DT) of *V. galamensis* granules and tablets produced using selected diluents (AR, AV and CP) and MS (at varying concentrations of 2.5, 5.0 and 7.5% w/v) mucilage as binder.

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 maize starch (MS) as binder.

Diluent	MS Binder (% w/v)	Mean Granule size (um)	Moisture Content (%)	CS (kgf)	FR (%)	DT (min)	CSFR/DT
AR	2.5	287.9±1.2	1.0±0.1	5.0±0.3	0.02±0.04	10.22±0.2	24.46
	5	276.9±1.0	1.5±0.1	5.4±0.3	0.01±0.05	12.01±0.1	44.96
	7.5	320.6±1.3	3.5±0.1	5.9±0.2	0.01±0.03	13.45±0.1	43.87
	2.5	282.8±1.7	2.5±0.1	5.0±0.3	0.02±0.01	5.80±0.1	68.54

AV	5	305.6±1.5	3.0±0.1	5.4±0.3	0.01±0.02	6.16±0.2	97.95
	7.5	318.3±1.2	5.0±0.1	7.2±0.1	0.01±0.01	7.53±0.1	95.62
	2.5	496.5±.2.1	1.5±0.1	3.7±0.2	0.02±0.03	5.57±0.3	33.21
CP	5	745.6±.2.7	2.5±0.1	4.0±0.1	0.01±0.03	5.75±0.1	69.57
	7.5	722.3±.2.3	4.0±0.1	4.1±0.1	0.01±0.02	5.95±0.2	68.91

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 that increased binder concentration usually result in increase moisture content and increased tablet tensile strength [8]. Previous study had 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 [9]. It was difficult to ascertain this hypothesis in our study. Instead, we observed an increase in crushing strength with increase binder concentration without commensurate increase in granule size except for formulations with AV (Table 2). The effects of diluent type may be explained to be the reason for the deviation. Each diluent has unique characteristics, for example CP and AV contain crystalline components while AR is completely amorphous [10]. The ranking for granule size increase based on diluent type is as follows; CP > AV > AR (Table 2) indicating that tablets produced using AR had the least crushing strength.

The British Pharmacopoeia 2007 specifies crushing strength values ≥ 4 kgf and ≤ 15 kgf, friability < 10%, and disintegration time ≤ 15 min for uncoated tablets.. Results in table 2 show that all the batches passed the crushing strength, friability and disintegration tests as expected of standard uncoated tablets signifying the success achieved in using the selected diluents and MS mucilage binder in the tablet formulation of the deliquescent EVG.

All the tablet formulations show increase in disintegration time as the concentration of binder increases. This is in order because binders are added during granulation to provide the cohesive binding and ensure that granules and tablets can be formed with the required mechanical strength. Similar trend was observed by Tahir [11] where in *in vitro* dispersion time increases as the concentration of binder increases. In our study using MS as binder, CP

shows fastest dispersion time. This may probably be due to formation of dense capillary network structure resulting from the use of the CP.[11]

The ranking for CSFR:DT based on the three different diluents used (Figure 1), at all concentrations of the binder (2.5%, 5.0% and 7.5%) was as follows; AV > CP > AR. 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 [12].

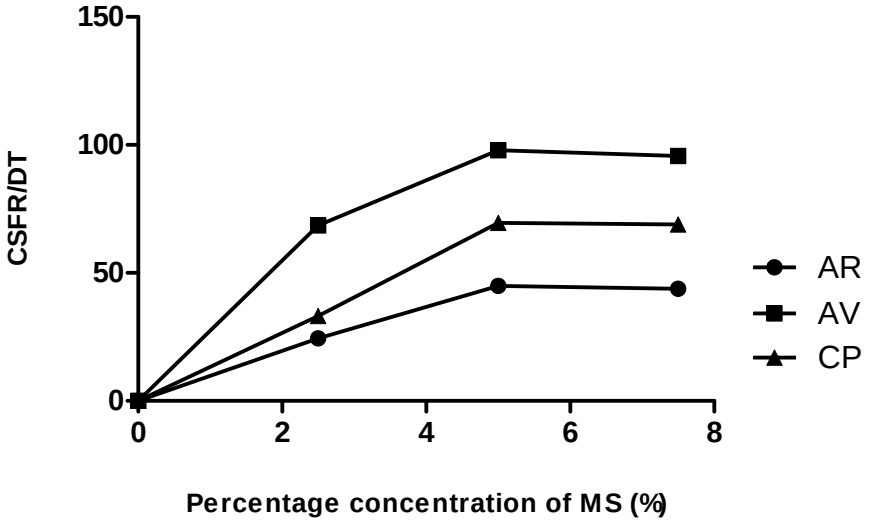

Fig. 1: CSFR/DT ratio Vs Percentage Concentration of MS used in the formulation of tablets of Vernonia galamensis leaf extract using selected Diluents (AR, AV & CP).

Figure 2 presents the dissolution profiles of the EVG tablets produced using different diluents (AR, AV and CP) and MS (5% w/v) as binder. 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 216nm typical for saponin alkaloids with a diene chromophore [13]. Thus the calibration curve to

assess the release properties of the tablets were determine at a wavelength of 216nm 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 MS as binder were presented (Figure 2). The rank order for both disintegration time (Table 2) and dissolution time (Figure 2) were found to be the same as follows CP < AV < AR.

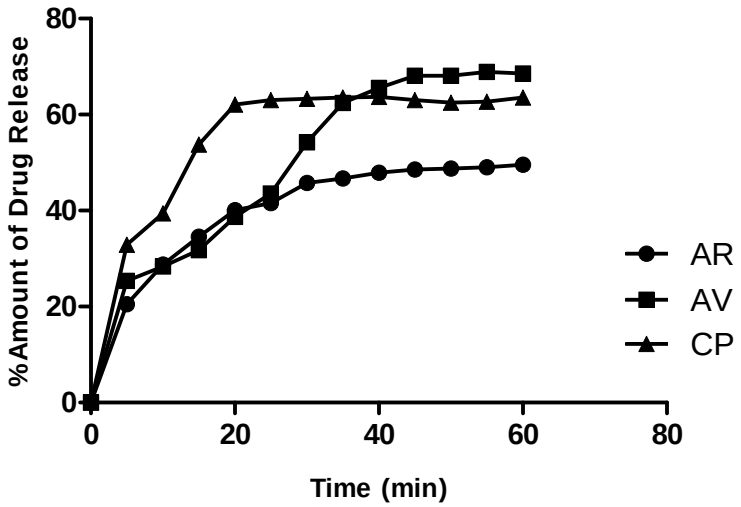

Fig. 2: Plots of Percentage amount of drug release Vs Time of Vernonia galamensis tablets produced using selected diluents (AR, AV & CP) and maize starch (MS) 5%w/v as Binder

Conclusion

Although the ranking for CSFR: DT (Figure 1) based on the three different diluents used, at all concentrations of the binder (2.5%, 5.0% and 7.5%) is; AV > CP > AR which appears to be different from the ranking for dissolution times (Figure 2) which is; CP > AV > AR, the difference in the CSFR: DT values between AV and CP were statistically insignificant ($p>0.05$). This concludes that better quality tablets of *V. galamensis* leaves extract could be produced using CP and AV than using AR as diluent, since the dissolution rate of formulations using AR was significantly lower. However, since dissolution rate is a more important index (being an official requirement) than

the CSFR:DT in the production of tablets, we can conclude that the best quality tablets of *V. galamensis* leaves extract could be produced using CP as diluent.

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