Original Article

Compressional characteristics and drug release profile of tablets of the crude leaves extract of *Vernonia galamensis*

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Tablet formulation of the crude aqueous extract of the leaves of *Vernonia galamensis* (Asteraceae), used for the treatment of diabetes in folk medicine was carried out using the wet granulation method. The dried extract is deliquescent in nature; therefore, efflorescent diluents were carefully selected for the formulation. The purpose of this study was to establish suitable diluents for the formulation of *Vernonia galamensis* tablets and to study the compressional characteristics and drug release profile. The efflorescent diluents were; calcium phosphate (Hopkins and Williams, UK), Aerosil® 200 (GmbH, Meggle, Germany) and Avicel® PH 101 (FMC Corporation, USA). The dissolution times of tablets were determined as specified in BP 2007. Heckel analysis was used for compaction studies, tensile strength for mechanical strength and dissolution time for drug release studies. GraphPad Prism® version 5.03 software was used for statistical analysis. Negative intercepts were a major limitation to the use of Heckel analysis, but good quality tablets of the deliquescent crude extract of *Vernonia galamensis* (Asteraceae) with acceptable release profile could be formulated using calcium phosphate as diluent and polyvinylpyrrolidone (5%, w/v) as binder at a compression pressure of 290 MNm^{-2}.

Key words: Compressibility, dissolution, Heckel equation

INTRODUCTION

Oral communication with traditional herbalists in northern Nigeria revealed the folk use of the dried powdered leaves of *Vernonia galamensis* (Asteraceae) in the treatment of diabetes mellitus. But folkloric medicines generally have no standard dose or acceptable method of formulation.[1] In this study therefore, efforts were made to formulate tablets of the crude extract of *Vernonia galamensis* (EVG) and investigate the compressional characteristics and release profile. Tablets are by far the most popular and versatile dosage form due to their advantages for both manufacturer and user which include durability, convenience of administration and accurate dosing.[2]

MATERIALS AND METHODS

Materials

Polyvinylpyrrolidone (PVP) was obtained from Aldrich Chemical company, USA; Calcium phosphate and Magnesium stearate from Hopkins and Williams, UK; Aerosil® 200 (AR) from GmbH, Meggle, Germany and Avicel® PH 101 (AV) from FMC Corporation, USA

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Methods

Preparation of the extract: - Leaves of *Vernonia galamensis* were plugged from the stem, washed with distilled water, dried in open air and milled to a coarse (1000 μm) powder. The powder was then soaked 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 60°C until dry. The dry extract was pulverized using a mortar and pestle and then passed through a 150 μm sieve.

Preparation of granules and particle size classification: These were done according to the methods adopted by Isimi *et al*.[3]

Preparation and analysis of compacts: Compacts equivalent to 300 mg of granules were produced by compressing the granules for 60s at various compression pressures 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

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over silica gel in a desiccator for 24 h to allow for elastic recovery and hardening preventing false low-yield values.[4] Dimensions of the compacts were determined to the nearest 0.01 mm with a Mitutoyo model IDC-1012 EB micrometer gauge (Mitutoyo Corporation, Japan).

Heckel analysis: The Heckel equation is written as follows:[5]

$$\ln[1/(1 - D)]=KP + A, \quad (1)$$

where D is the ratio of the density of the powder mass at pressure P to the density of the powder mixture (i.e. relative density). K is the slope of the straight portion of the graph, reflects the reduction in porosity or the resistance to volume reduction of granules and A is a constant. The yield pressure, P_Y, is usually calculated as the reciprocal of the linear portion of the slope of the Heckel plot. The relative density D_A is calculated from the intercept, A, using the equation:[6]

$$D_A=1 - e^{-A}. \quad (2)$$

Here D_B is the relative density during the rearrangement phase is calculated from the difference between D_A and D_O (relative density of the granules at nil pressure).

Tensile Strength: This is a non-compendial method of measuring the mechanical strength of tablets. It is the force required to break a tablet in a diametral compression test. The tensile strength (TS) was calculated from the equation:

$$TS=2CS/\pi Dd, \quad (3)$$

where CS is the crushing strength which is the force required to break the tablet, D and d are the diameter and thickness, respectively.[7]

Data analysis: The graphs were plotted and analyzed using the non linear regression of XY analyses in the GraphPad Prism® version 5.03 software. The data used to plot the graphs were the mean of three readings±SD.

RESULTS AND DISCUSSION

Based on the Heckel's equation, three types of powder compression behaviour have been identified, namely type A, B and C.[8,9] Figures 1–3 depict the Heckel plots obtained for granules formulated using EVG/AR, EVG/AV and EVG/CP combinations with various concentrations of PVP (2.5, 5.0 or 7.5%) as binder. Relatively parallel relationships were observed with the plots at all applied pressures which is more indicative of type-A materials. This implies that the granules containing these combinations at all concentrations of the PVP principally undergo plastic deformation.[9]

The observed deformation characteristics (plastic flow) for all samples used, may have to do with the deliquescent property of the extract. Ebube *et al*, reported the deformation characteristics for all samples of the extremely hygroscopic and deliquescent chondroitin sulfate used in their study to be by plastic flow.[10] The increase in slope at higher pressure indicates an increase in the rate of densification as the void spaces between particles decrease. Figure 4 shows that the EVG/AV/PVP compacts were compressed at higher relative densities than those of EVG/AR/PVP and EVG/CP/PVP. The rank order for densification depending on the diluent type was as follows; EVG/AV/PVP>EVG/AR/PVP>EVG/CP/PVP.

P_y which is the yield pressure is an important indication of granule compressibility and it describes the tendency of the material to deform either by plastic flow or fragmentation.[11] A faster degree of plastic deformation is reflected by a low P_y value (steep slope) in a general sense.[12] A low P_y value, however, need not necessarily reflect that the compact has an acceptable tensile strength.[13] Table 1 show that for all

Table 1: Mean granule size, moisture content, compressibility and Heckel constants for different formulations

Diluent	Binder (PVP) (%)	Mean granule size (µm)	Moisture content (%)	Carr's index (%)	*Py* (MNm^{-2})	*A*	D_A	D_o	D_B
AR		250±1.2	1.5±0.1	11.6±0.2	416.7±1.50	−0.18±0.01	−0.20	0.28±0.04	−0.48
AV	2.5	500±3.5	2.0±0.1	12.9±0.1	188.7±2.70	−0.92±0.02	−1.51	0.24±0.08	−1.75
CP		1000±1.7	2.5±0.1	7.7±0.3	178.6±2.90	−1.19±0.02	−2.29	0.31±0.02	−2.60
AR		250±1.7	2.0±0.1	18.4±0.2	454.6±1.70	−0.22±0.01	−0.20	0.20±0.07	−0.01
AV	5.0	500±3.2	1.5±0.1	16.7±0.1	293.6±2.40	−0.35±0.01	−0.42	0.24±0.04	−0.66
CP		1000±1.4	1.5±0.1	11.8±0.1	181.8±2.10	−1.22±0.02	−2.40	0.35±0.01	−2.75
AR		250±1.3	5.0±0.1	12.2±0.1	769.2±1.30	−0.00±0.01	−0.00	0.22±0.03	−0.22
AV	7.5	500±3.8	2.0±0.1	16.1±0.1	769.2±1.90	0.18±0.01	−0.16	0.18±0.04	−0.02
CP		1000±1.1	2.5±0.1	3.6±0.3	227.3±2.30	−0.90±0.01	−1.46	0.41±0.02	−1.88

AR – Aerosil® 200; AV – Avicel® PH 101; CP – Calcium phosphate; PVP – Polyvinylpyrrolidone. Results were expressed as mean±SD of three runs

diluents used (AR, AV and CP), P_y values were observed to increase as the binder concentration was increased from 2.5% to 7.5%. Formulations made with CP as diluent gave lower P_y values than those with either AR or AV at all binder concentrations, indicating that granules of the former deformed plastically at lower pressures than those of the later ones.

Negative intercepts were observed in almost all the formulations. This may have to do with the intrinsic characteristics of the extract; being deliquescent in nature. As a result of the negative intercepts, negative values of both D_A and D_B were also obtained by calculation. Mathematically, the negative values can easily be explained as follows; from Table 1, granules formulated with AR as diluent had the highest D_A and D_B values while those formulated with CP as diluent had the lowest D_A and D_B values; the rank order of the D_A and D_B values for all the three diluents used at all the binder concentrations (2.5, 5.0 or 7.5%) were AR>AV>CP. But considering this issue more critically, the mathematical explanation above have no sense of practical application because D_A represents the total degree of densification at zero and low pressures and D_B represents the particle rearrangement phase in the early compression stages which also indicate the extent of granule fragmentation.[14] This means that, if for instance we have a situation where zero values of D_A and D_B are obtained, the explanation would be that there is no densification at zero and low pressure and no particle rearrangement or granule fragmentation at all. But in this situation where negative values of the D_A and D_B were obtained, how does anyone explain the degree of densification at zero and low pressures and the particle rearrangement phase or the extent of granule fragmentation? Certainly, this is another limitation of the Heckel equation yet to be reported. Few researchers have also reported negative intercepts while using the Heckel equation,[2,15,16] but none tangibly explained the implication of having the resulting negative values of D_A and D_B or clearly observed that the negative values were an added limitation of the Heckel equation. Other limitations of the Heckel equation have been enumerated by Sonnergaard.[17]

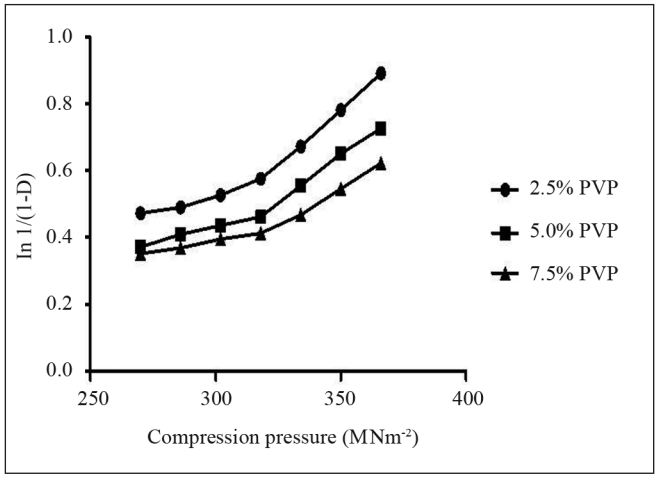

Figure 1: Heckel plots for EVG/AR compacts using selected concentrations of PVP as binder

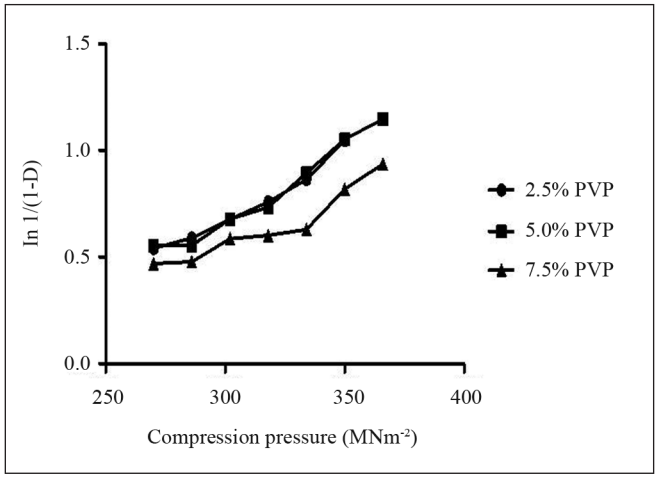

Figure 2: Heckel plots for EVG/AV compacts using selected concentrations of PVP as binder

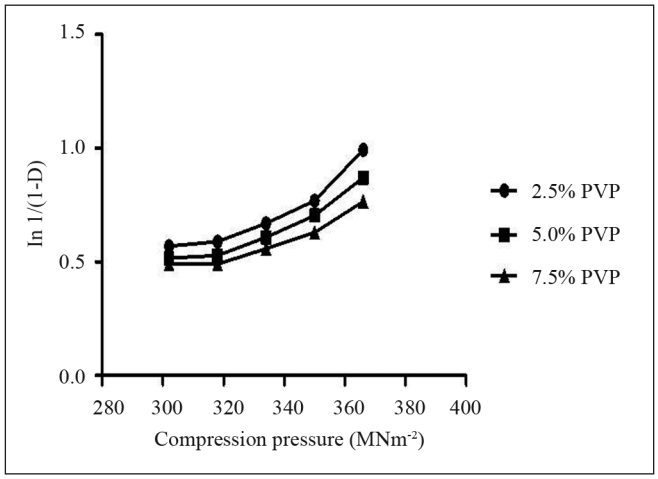

Figure 3: Heckel plots for EVG/CP compacts using selected concentrations of PVP as binder

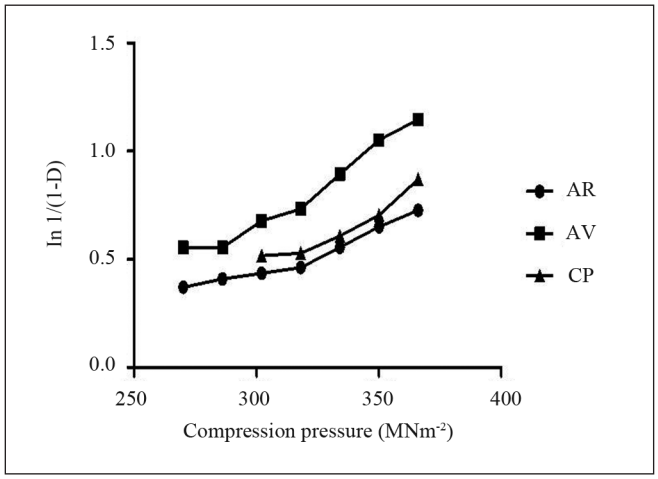

Figure 4: Heckel plots for EVG/CP compacts using selected concentrations of PVP as binder

Moisture content was found to increase as the binder concentration was increased. This agrees with previous work which showed that increased binder concentration and moisture content usually result in increased tablet tensile strength.[18] Also D_0 values for granules formulated with CP were found to increase as binder concentration was increased and this may be attributed to the differences in particle size and shape.[19] D_B increased with an increase in binder concentration for granules formulated with AV as diluent, while there was a decrease in D_B values with an increase in binder concentration for granules formulated with CP. D_B values for formulations with AR increased as binder concentration was increased from 2.5% to 5.0%, and then decreased as the binder concentration was increased to 7.5. Granules prepared using PVP 5% (w/v) showed better compressibility (Carr's index) than those prepared using either the 2.5% (w/v) or 7.5% (w/v) concentrations of PVP [Table 1].

Figures 5–7 depict the pressure-tensile strength profile of compacts formulated using EVG/AR/PVP, EVG/AV/PVP and EVG/CP/PVP combinations respectively. All the granules exhibited significant sensitivity to changes in the compaction force. For EVG/AR/PVP and EVG/AV/PVP compacts [Figures 5 and 6], the tensile strength for all the granule size ranges showed slight decreased with an increase in compaction pressure from 260 to 290 MNm^{-2} followed by an increase to 320 MNm^{-2}, whereas for the EVG/CP/PVP compacts, the tensile strength increased up to 290 MNm^{-2} (except for the >150<500 μm size range which slightly increased) followed by a sharp decrease for all the granule size ranges. This can be ascribed to the possibility of the work associated with compaction above 290 MNm^{-2} being recovered during elastic relaxation, which resulted in a weakening of the tablet structure.[20]

Figure 8 presents the results of the dissolution profile of formulations with the three diluents (AR, AV and CP). The rank order for dissolution rate is as follows; CP>AR>AV. For formulations with CP, 70% of the extract was released

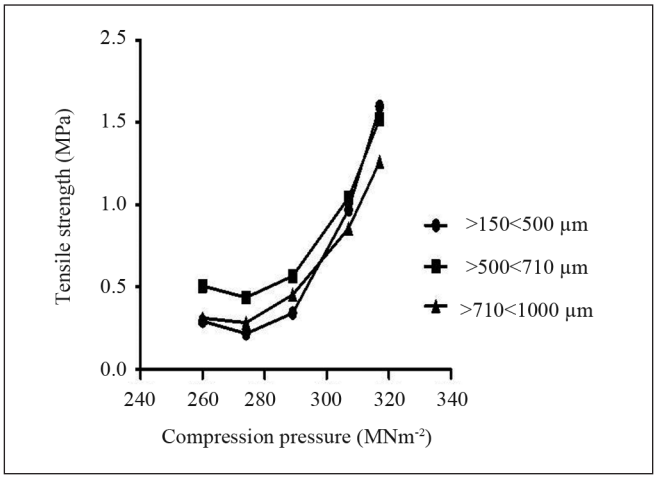

Figure 5: Tensile strength vs compression pressure for tablets produced using AR as diluent and PVP (5%, w/v) as binder

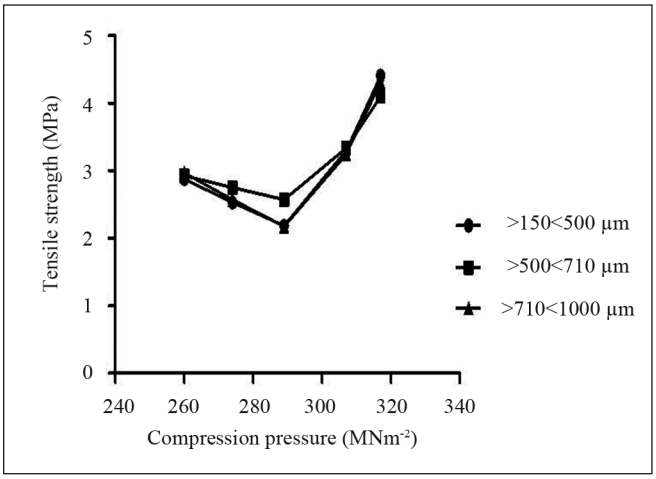

Figure 6: Tensile strength vs compression pressure for tablets produced using AV as diluent and PVP (5%, w/v) as binder

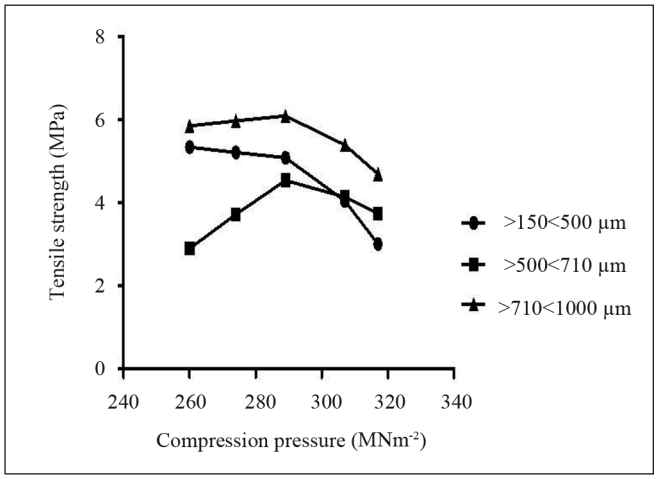

Figure 7: Tensile strength vs compression pressure for tablets produced using CP as diluent and PVP (5%, w/v) as binder

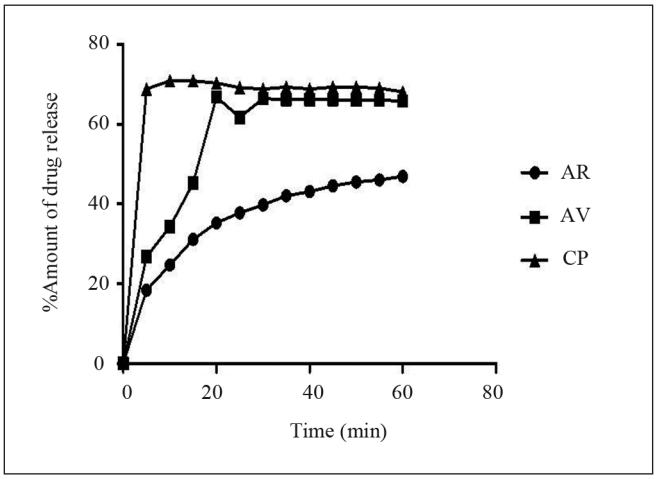

Figure 8: Percentage amount of drug release vs time for EVG tablets produced with selected diluents (AR, AV and CP) using PVP (5%, w/v) as binder

within 10 minutes. This conforms to BP 2007 standard, which specifies that uncoated tablets should release 70% or more of active ingredients within 45 minutes. Formulations with AR and AV failed to meet the standard.

CONCLUSIONS

Negative intercepts gotten while applying the Heckel analysis on the dry deliquescent crude extract of *Vernonia galamensis* is another major limitation to the use of the equation. Examination of the compressibility profile suggests the optimum compression pressure of 290 MNm^{-2} for formulations using CP as diluent, whereas both compaction and compressibility profiles of the extract were greatly affected by the diluent type. Only formulations with CP as diluent met the BP 2007 standard for dissolution rate implying that good quality tablets of the crude extract could be produced using CP as diluent and PVP as binder at 5% (w/v) concentration.

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