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Research Article

Heckel and Kawakita Analyses of Granules of the Crude Leaves Extract of *Vernonia galamensis* Prepared using Selected Diluents and Maize starch Mucilage Binder

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Abstract

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. Efforts 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". The purpose of this study was to select suitable efflorescent pharmaceutical diluents namely; Aerosil® 200, Avicel® PH 101 and calcium phosphate for the tablet formulation of the deliquescent crude extract of *Vernonia galamensis* and to use the Heckel and Kawakita equations to investigate the compressibility of the granules prepared using maize starch mucilage as binder. The Kawakita model provided an excellent fit having higher R^2 values than the Heckel model and very low P_K values (indicating good fluidity) for all the different formulations and is therefore preferred in explaining the compressibility of granules of the extract. The ranking for good compressibility based on the diluent type was as follows; aerosil® 200 > Avicel® PH 101 > calcium phosphate.

Key words: Compressibility, Heckel, Kawakita, diluents.

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

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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] 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[3].

The aim of this study was to use the Heckel and Kawakita equations to investigate the consolidation behavior of granules of the dry crude leaf extract of *Vernonia galamensis* (EVG) prepared using three different diluents namely; Aerosil® 200 (AR), Avicel® PH 101 (AV) and calcium phosphate (CP) in the tablet formulation of the extract. The EVG is highly hydroscopic and deliquescent and is stored over silica gel in a desiccator. Efforts 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". In the attempt to check the deliquescent characteristics of the extract, efflorescent diluents were selected for this formulation process.

The Heckel equation has by far been the most popular in recent years among pharmaceutical scientists, and many apparent yield pressure values ('in-die", P_y) and mean yield pressure values ('out-of-die') of active substances and tableting excipients have been published[4]. The model has often been applied to study powder mixtures and to evaluate granule manufacture. Of recent, scientists have also made attempts to use the Heckel relation for predicting powder characteristics of active crude plant extracts[2].

But despite the versatility of the Heckel equation, drawbacks and limitations to its use have been reported[3]. Some scientists have used more than one equation to try to eliminate the shortcomings of the other[5.6]. Hence, in this study, both Heckel and Kawakita plots have been used to assess the compression characteristics of EVG in combination with the three efflorescent diluents; AR, CP and AV.

Heckel Analysis: - The plots constructed according to the Heckel equation[7] were used to characterize the consolidation behavior of the formulations:

$$\text{Ln}\,[1/(1-D)] = KP + A \qquad (1)$$

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, 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, *PY,* is usually calculated as the reciprocal of the linear portion of the slope of the Heckel plot. The relative density D_A was calculated from the intercept, *A*, using the equation:

$$D_A = 1 – e^{–A}. \quad (2)$$

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

Kawakita Analysis: - The Kawakita equation[8] describes the relationship between the volume reduction of powder column and the applied pressure;

$$C = [V_o – V/ V_o] = [abP/1 + bP] \quad (4)$$

Where, C, is degree of volume reduction, V_o is Initial volume, V is volume of powder column under the applied pressure P. a, b are constants characteristic to powder being compressed. The equation above can be re arranged in linear form as:

$$P/C = P/a + 1/ab \quad (5)$$

From the graphical presentation of P/C versus P, the constants maybe evaluated. The constant “a”, is given as a reciprocal of the slope from the linear portion of the plot and equivalent to the value of C at infinitely high pressures. 1/ab is the intercept. a, gives an indication of the maximum volume reduction available and is considered to describe the compressibility of a powder, while b is considered to describe an inclination toward volume reduction. However, the actual physical meaning of the constants a and b have been in question[9]. Consequently, Kawakita in 1983 have applied another equation in describing the volume reduction on tapping and vibrating processes, where the pressure P, is replaced by the tapping number, N[10]

$$N/C = [(1/a) N ¸ 1/ab] \quad (6)$$

Where, N is the tapping number, C is the degree of volume reduction and a and b are constants .C in equation vi is given by;

$$C = [V_o – V_N] ¸ V_o \quad (7)$$

Where V_o is the initial apparent volume and V_N, the volume at tapping number N. The constants of Kawakita equation can be used to estimate the flow and cohesiveness properties of powders. Constant “a”, describes the compressibility and constant “1/b” describes cohesive properties of powders or the fastness of how the final packing stage is achieved[9].

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[10]. 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 Maize starch (MS) 5% w/v 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

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.

(b). Angle of repose: The static angle of repose, a, was measured according to the fixed funnel and free standing cone method. 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:

$$\text{Tan a} = 2h/D \qquad (1)$$

©. *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:-

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

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

iv). Preparation of compacts

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.

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. granule size, moisture content

RESULTS AND DISCUSSIONS

Three types of powder compression behavior have been identified based on the Heckel's equation, namely type A, B and C[12]. Figure 1 depicts the Heckel plots obtained for the granulations formulated with AR, AV and CP as diluents and MS at 5% w/v concentration as binder. All the plots exhibited relatively linear and near parallel relationships at all applied pressures, where increase compression pressure significantly increase the relative density of the compacts. This implies that the plots are indicative of type-A materials and that all the granules principally undergo deformation by plastic flow[13].

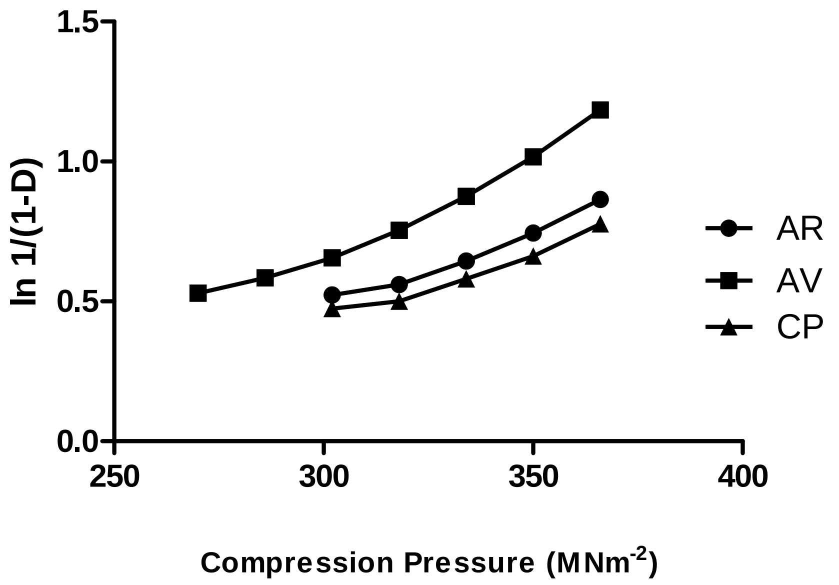

Fig. 1: Heckel plots for EVG compacts produced using selected diluents and MS (5%w/v) as binder. Points refer to mean ± SD values (*n* = 3)

Table 1: Mean granule size and Heckel constants for different formulations

Diluent	Binder (MS) (%)	Py (MNm-2)	A	D_A	D_o	D_B	R^2
AR	5.0	198.26±1.70	-1.04±0.01	-1.82	0.29±0.07	-2.10	0.998
AV	5.0	122.13±2.40	-1.85±0.01	-5.37	0.25±0.04	-5.63	0.998
CP	5.0	163.13±2.10	-1.22±0.02	-2.40	0.46±0.01	-2.86	0.995

AR = Aerosil® 200, AV = Avicel® PH 101 and CP = calcium phosphate.

Results were expressed as mean ± SD of three runs.

The observed deformation characteristics (plastic flow) for all samples used may be due to the extreme hygroscopic and deliquescent nature of the extract. This is because earlier report had indicated that the deformation characteristics for all samples of the extremely hygroscopic and deliquescent chondroitin sulfate were by plastic flow[14]. The increase in slope at higher pressure indicates an increase in the rate of densification as the void spaces between particles decrease. Figure 1 also shows that the EVG/AV compacts were compressed at higher relative densities than those of EVG/AR and EVG/CP.

The tendency of the material to deform either by plastic flow or fragmentation is described by the yield pressure P_y, which is an important indication of granule compressibility. A faster degree of plastic deformation is reflected by a low P_y value (steep slope) in a general sense. Table 1 show that formulations made with AV as diluent gave lower P_y values than those with either AR or CP, indicating that granules of the former deformed plastically at lower pressures than those of the later ones. But negative intercepts were observed in all the different formulations using the selected efflorescent diluents. This negative values of intercepts may be due to the intrinsic characteristics of the extract; being deliquescent in nature. The negative intercepts gave rise to negative values of both D_A and D_B by calculation. Given some more thoughts to this; 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[9].

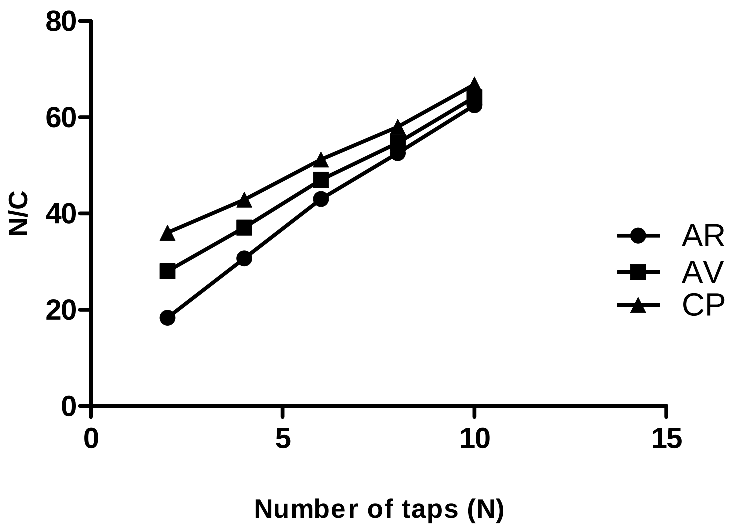

Fig. 2: Kawakita plots for EVG compacts produced using selected diluents and MS (5%w/v) used as binder. Points refer to mean ± SD values (*n* = 3)

This means that for any situation where zero values of D_A and D_B *are* obtained, it would mean that there is no densification at zero and low pressure and no particle rearrangement phase or granule fragmentation at all. But in this situation where negative values (less than zero values) of the D_A and D_B were obtained, it is impracticable to explain the degree of densification at zero and low pressures and the particle rearrangement phase or the extent of granule fragmentation by the use of the Heckel equation. This is a limitation of the equation in this study.

Figure 2 shows the kawakita plots for *Vernonia galamensis* tablet formulations containing selected diluents and MS as binder, where a fairly linear relationship between N/C and N is obtained at all compression pressures used with correlation coefficient ≥ 0.99 for all the formulations, and hence, the equation can be used to predict the densification mechanisms of the *Vernonia galamensis* formulations better than the Heckel equation where negative intercepts were observed.

Table 2: Kawakita constants for different formulations of Vernonia galamensis using maize starch (5%w/v) as binder

Diluent type	1/a	a	Di (1-a)	1/ab	P_k (1/b)	R^2
AR	6.150±0.1	0.163	0.837	6.100±0.1	0.992	1.000
AV	5.250±0.1	0.190	0.610	15.70±0.1	2.990	0.999
CP	3.775±0.1	0.265	0.735	28.05±0.1	7.430	0.998

AR = Aerosil® 200, AV = Avicel® PH 101 and CP = calcium phosphate.
Results were expressed as mean ± SD of three runs.

Values of 1/b and 1/ab were obtained from the slope and intercept of the plots respectively. The tapping experiments were performed on all samples and a and 1/b were evaluated. It was observed from Table 2 (which shows the Kawakita constants) that values of ‘a’ were smaller in the formulations with AR than in the formulation with CP and AV implying that the fluidity of the AR is better. This falls in line with the work of Emeje[9] that the smaller the values of ‘a’, the better the fluidity. The value of P_K for formulations with calcium phosphate is highest implying that the cohesiveness of the granules would be higher than others. The low value of P_K in other formulations is indicative of the reduction in cohesion. A low value of P_K is indicative of materials that are soft and that readily deform plastically under pressure[9].

Conclusion

Two models namely; Heckel and Kawakita models were fitted to the pressure-density-volume data. The Kawakita model provided an excellent fit having higher R^2 values than the Heckel model and very low P_K values for all the EVG formulations. Although the Heckel model also presented acceptably high R^2 values, the negative values of D_A and D_B made it difficult to practically explain the degree of densification at zero and low pressures and the particle rearrangement phase and extent of granule fragmentation. We can therefore conclude that the Kawakita model is preferred in explaining the compressional characteristics of granules of *Vernonia galamensis* prepared using AR, AV or CP as diluent and MS mucilage as binder.

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REFERENCES

1. Allagh TS, Ameh GO and Okafor IS. Formulation and evaluation of the physicochemical properties of *Ageratum conyzoides (Fam asteraceae)* granules and tablets. Nig. J. Pharm. Sc. 2009; 8: 18-25.
2. Isimi CY, Nasipuri RN, Ojile JB, Ibrahim YKE and Emeje M. Effects of the diluent type on the compressional characteristics of the mixed stem bark extract of *Anogeissus leiocarpus* and *Prosopis africana* tablet formulation. Acta. Pharm. 2003; 53: 49–56.
3. Ilic I, Kasa P, Dreu R, Pintye-Hodi K and Sircic S. The compressibility and compactibility of different types lactose. Drug. Dev. Ind. Pharm. 2009; 35: 1271-1280.
4. Sonnergaard JM. A critical evaluation of the Heckel equation. Int. J. Pharm. 1999; 193: 63-71.
5. Krycer I, Pope DG and JA Hersey. The interpretation of powder compaction data – a critical review. Drug. Dev. Ind. Pharm. 198; 28: 307-342.
6. Comoglu T. An overview of compaction equations. J. Fac. Pharm. 2007; 36: 123-133.
7. Heckel W. Density-pressure relationship in powder compaction, Trans Metall. Soc. AIME 1961; 221: 671–675.

8. Kawakita K and Ludde KH. Some considerations on powder compression equations, Powder Technol. 1970/1971; 4: 61.
9. Alderborn G and C Nystrom. Studies on direct compression of tablets. IV. The effect of particle size on the mechanical strength of tablets. Acta Pharm Suecica. 1982;19: 381–390.
10. Emeje M, Isimi C and Kunle O. Effect of *Grewia* gum on the mechanical properties of paracetamol tablet formulations. Afr. J. Pharm. Pharmacol. 2008; 2: 2001-2006.
11. Gunsel WC, Kanin JL. The Theory and Practice of Industrial Pharmacy. Henry Kimpton Publishers, London, 1976, 321-358.
12. Hersey JA and Rees JE. Deformation of Particles During Briquetting, in Proceedings of the 2nd Particle Size Analysis Conference, Bradford, September 1970, Society for Analytical Chemistry, Bradford, 1970, 33.
13. York P and Pilpel N. The tensile strength and compression behavior of lactose, four fatty acids and their mixtures in relation to tableting. J. Pharm. Pharmacol. 1973; 25: 1–11.
14. Ebube NK, Mark W and Hahm H. Preformulation studies and characterization of proposed chondroprotective agents: Glucosamine Hcl and chondroitin sulfate. Pharm. Dev. Tech. 2002; 7: 457-469.