

Compressional Physics of Binary Mixture of Dried *Andrographis paniculata* and *Moringa oleifera* Leaves

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Abstract

Traditionally, the leafy part of *Andrographis paniculata* and *Moringa oleifera* have been widely reported to manage hypertension. Investigation of its pharmacological actions justifies its use. As part of formulation studies to standardize them, this study focused on their compaction and compression properties. Compacts equivalent to 250 mg of *A. paniculata* and *M. oleifera* were produced by compressing powders and granules at various compression pressure. Results show that *M. oleifera* met the WHO limit for ash values. Relative density values for granulated batches were higher, while their moisture content values were lower when compared to those of direct compression. The result from Heckel plots shows that batches deform mainly by plastic flow. For Kawakita plots, values of 1/b show that batches containing microcrystalline cellulose were less cohesive. The plot of tensile strength signifies that granulated batches achieved maximum crushing strength faster at low pressure. Formulations containing maize starch were shown to have higher percent porosity, and granulated batches gave higher values for apparent density-pressure relationship and lower friability values. Tablets produced by the wet granulation method showed better compression and compaction properties than those formulated by direct compression.

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INTRODUCTION

The use of herbs for medicinal, nutritional, and economic benefits is increasing globally because they are easier to obtain, more affordable, and often exhibit minor side effects than conventional medicines. Formulating them into suitable dosage forms will not only increase their acceptability but will also improve their stability. Hence, a proper understanding of how herbal powders behave during compaction and compression is necessary to overcome dosage form and dosing challenges^{1,2}.

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, the convenience of administration, and accurate dosing make it a versatile and popular dosage form³. The ability to predict the mechano-structural attributes of tablets based on their raw material properties and process parameters is challenging due to poor understanding of the complex nature of the powder compaction process linked to parameters like

deformation behavior, particle size and shape, compression stress, particle rearrangement, as well as elastic and plastic deformation of single particles and particle fragmentation⁴. This calls for a systematic and thorough characterization of raw materials' compression and compaction behavior as a prerequisite for a rationally based formulation and process development.

The ability of a powder bed to produce a strong tablet mechanically is called compactibility, while compressibility has to do with how a powder bed is compressed and consequently reduces volume⁵. Compaction and compression play a key role in manufacturing tablets, granules, and powder handling. The study of powder technology has continued to evolve by the need of the herbal industries⁶.

Andrographis paniculata (Figure 1) is an ancient oriental and ayurvedic plant belonging to the Angiosperm division, Dicotyledon class, Gamopetalae subclass, Bicarpellatae series, Personales order, Acanthaceae family, Acanthoideae subfamily, Justiciae tribe, Andrographideae subtribe, and has about 40 different species⁷. It is an annual, branched, and erect plant of about 1 m high indigenous to the Indian peninsula, Sri Lanka, and cuts across Southeast Asia's different regions⁸. The leaves/aerial part treats colic pain, loss of appetite, hepatitis, tuberculosis, cough, mouth ulcer, bronchitis, diarrhea, pyrexia, hypertension, diabetes, cancer, and urinary tract infection^{9,10}. Studies have shown that *A. paniculata* could reduce angiotensin-converting enzymes and reactive oxygen species activities in spontaneously hypertensive rats¹¹. In isolated rats, it has been shown to decrease coronary perfusion pressure. The crude extract was able to induce dramatic hypotensive effects and inhibit the influx of Ca_2^+ through receptor and voltage-gated Ca_2^+ channels in hypertensive rats¹². Aside from its anti-inflammatory and anti-oxidant activities, *A. paniculata* could also inhibit the activation of NF κ B¹³.

When compared to propranolol, its anti-hypertensive activity was shown to be higher in cats¹⁴. The ethanolic herb extract of *A. paniculata* induced hypertensive activity in phenylephrine-induced hypertensive rats¹⁵.



Figure 1. *Andrographis paniculata* plant

Moringa oleifera (Figure 2) belongs to the Magnoliophyte division, Magnoliopsida class, Capparales order, and Moringaceae family, having up to 13 species from tropical and subtropical climates¹⁶. It is native to Africa and Asia. A perennial plant with about 15 m height has a diameter of about 40 cm¹⁷. The leafy part has been demonstrated to have antihypertensive, anti-diabetic, anti-malarial, and anti-typhoid properties¹⁸. The methanolic and ethyl acetate extracts decreased systolic blood pressure in nitro-arginine methyl ester-induced hypertensive mice¹⁹. The leaf of *M. oleifera* reduced systolic and diastolic pressure in hypertensive males aged between 35-50 years²⁰. The aqueous extract of *M. oleifera* reduced intraocular and blood pressure of normotensive adults after 60 minutes of administration²¹.



Figure 2. *Moringa oleifera* plant

In an effort to standardize herbal anti-asthmatic agent (AA1), the effects of some channeling agents on the compaction properties of the mixed stem bark extract of *Anogeissus leiocarpus* and *Prosopis africana* were evaluated using the Heckel equation. None of the channeling agents used were seen to alter their compaction properties significantly²². In another study, Heckel, Kawakita, and Walker's model were proven suitable while discussing the properties of the freeze-dried herbal extract from *A. paniculata*, *Eurycoma longifolia*, and *Orthosiphon stamineus*²³. In a similar work²⁴, compressional properties of three selected Malaysian herbs (*E. longifolia*, *Ficus deltoidea*, and *Morinda citrifolia*) were evaluated using microcrystalline cellulose as a binder. *Moringa oleifera* and spirulina complex were successfully co-formulated to produce a nutraceutical tablet using the direct compression method²⁵. The micromeritics of the polyherbal dispersible tablet for managing kidney disorders in geriatric patients has been proven to have good flow properties²⁶.

This study discussed the properties of such herbal extract powder from *A. paniculata* and *M. oleifera*. It focused on the characterization of compaction and compression of a binary mixture of *A. paniculata* and *M. oleifera* leaf powder as part of formulation studies to standardize them since most work conducted on these herbs are limited to their chemical and medicinal properties. This will help determine the technical feasibility and economic viability of producing solid oral dosage forms of these herbs via direct compression or wet granulation methods. Both plants have been widely reported in managing hypertension traditionally. Administration of two or more complementary antihypertensive in fixed doses is always linked to greater efficacy with reduced dose-dependent side effects and adverse reactions when compared to monotherapy^{27,28}. When smaller doses of medicines with a different mechanism of action are

combined, a synergistic effect is achieved, patient convenience and compliance is enhanced, the response rate is improved, dosing becomes more appropriate, alteration in pharmacokinetic becomes favorable, and the cost is reduced²⁷⁻²⁹.

MATERIALS AND METHODS

Materials

Andrographis paniculata and *M. oleifera* leaves were collected from the National Institute for Pharmaceutical Research and Development (NIPRD) botanical garden. Identification and authentication of the plants were done by Mr. Akeem Lateef of the Herbarium unit of the Institute and given voucher numbers NIPRD/H/7263 and NIPRD/H/7265 for *A. paniculata* and *M. oleifera*, respectively. They were washed with distilled water, oven-dried at 40°C for six hours, and milled to a coarse powder. This was passed through a 150 µm sieve, transferred into a plastic container, and stored in a desiccator containing silica gel for further analysis. Instruments and other materials used include Tableting machine-94305 (Manesty, China), Stampfvolumeter-STAV 2003 (Engelsmann, Germany), digital moisture analyzer (Ohaus, US), micrometer screw gauge-IDC-1012EB (Mitutoyo, Japan), analytical weighing balance-AB54 (Mettler Toledo, Switzerland), tablet hardness tester-D6072 (Erweka, Germany), friabilator-TA (Erweka, Germany), magnesium stearate, and talc (BDH, UK).

Methods

Determination of ash values

Total ash, water-soluble ash, and acid-insoluble ash to establish the quality and purity of the powdered plant materials were determined by the methods reported from previous research³⁰.

Granulation

Four batches of the powdered materials were prepared by either direct or wet granulation methods. For the batch mixture of *A. paniculata* and *M. oleifera* powders containing maize starch as binder and disintegrant (ABMP), 125 mg of *A. paniculata* and 125 mg of *M. oleifera* were mixed to give a homogenous mixture to be compressed directly using 5 and 10% maize starch as binder and disintegrant. The mixture of *A. paniculata* and *M. oleifera* powders containing microcrystalline cellulose (MCC) starch as binder and disintegrant (ABMCP) was the same as ABMP, but MCC was incorporated in place of maize starch as binder and disintegrant. For the granulated mixture of *A. paniculata* and *M. oleifera* powders containing maize as binder and disintegrant (ABMG), the mixture of the ingredients was the same as that of ABMP but was wetted with a prepared maize starch mucilage and the wet mass forced through a 599 μm screen granulating sieve. The granules were oven-dried at 40°C for an hour. The dried granules were again passed through a 599 μm screen to break up agglomerates. The batch granulated mixture of *A. paniculata* and *M. oleifera* powders containing MCC as binder and disintegrant (ABMCG) was the same as ABMG with MCC substituted for maize starch.

Determination of flow properties and densities

Bulk density (BD) was determined by placing 20 g of powdered sample into a weighed 50 mL graduated measuring cylinder. For tapped density (TD), a measuring cylinder filled with powdered material was tapped until a constant volume was reached using a tapped density machine. True density (TrD) was determined by a method described elsewhere using liquid paraffin as the displacement fluid²². Relative density (RD) of the materials was determined using the ratio of tapped density to particle density. The angle of repose (AR) was determined based on the fixed funnel

and free-standing cone method. Hausner ratio (HR) was calculated as the ratio of tapped density to bulk density; while Carr index (CI) was evaluated using the difference between bulk density and tapped density to the ratio of tapped density; and porosity (P) was determined as the ratio of void volume (VV) to BD, where VV is the difference between TrD and BD. The moisture content was determined using a digital moisture analyzer set at 105°C. All measurements were in triplicates and presented as mean and standard deviations.

Compaction

Compacts equivalent to 250 mg of samples *A. paniculata* and *M. oleifera* were produced by compressing powders and granules for 60 seconds at various compression pressure with the aid of a Manesty tableting machine, with the basic components of tablets were presented in **Table I**. The uniaxial die was attached to the upper moving crosshead of the machine. Compression was made by lubricating the die and punches with 1% w/v dispersion of magnesium stearate in chloroform at room temperature with a relative humidity of about 75%. Fifty tablets were compressed at each pressure. The compressed tablets were wrapped in a polythene bag and stored in a desiccator containing silica gel for 24 hours to allow elastic recovery and hardening. The tablets' diameter, height, mass, and volume were measured using a micrometer screw gauge to obtain the density before and after compression to observe for signs of plastic recovery, hardening, and to prevent false low-yield values. Weight variation was determined using the analytical weighing balance, and the crushing strength was evaluated using a tablet hardness tester. This information was used to determine values for tensile strength (**Equation 1**) and data for validation of Heckel and Kawakita models. Friability was determined using a friabilator, set at 25 rpm for 4 minutes.

Table I. Basic tablet component

Ingredients	Weight (mg)
<i>Andrographis paniculata</i>	125
<i>Moringa oleifera</i>	125
Binder	12.5
Disintegrant	25
Magnesium stearate	1
Talc	0.5
Total	289

$$TS = 2CS/\pi dt \quad [1]$$

TS: tensile strength; CS: crushing strength (kgF); d: diameter of the tablet (mm); t: thickness of the tablet (mm)

Model

Heckel model expresses the volume of reduction mechanism under compression force by relating the relative density of the powder bed during compression to the applied pressure. This model assumes that powder compression obeys first-order kinetics with interparticle pores as the reactants and densification of the powder as the product³¹, as represented in [Equation 2](#).

$$\ln \left[\frac{1}{1-D} \right] = KP + A \quad [2]$$

Plotting a graph of $\ln [1/(1 - D)]$ against the applied pressure P, values of K and A could be obtained from the slope and intercept, respectively. The slope of the straight-line plot K was the reciprocal of the material's mean yield pressure (P_y). The relative density (D_A) could be obtained from intercept A ([Equation 3](#)):

$$D_A = 1 - e^{-A} \quad [3]$$

The relative density of the material when the pressure was zero (D_0) was the initial rearrangement of densification due to die filling. The relative density (D_b) was the phase rearrangement at low pressure, and it was the difference between D_A and D_0 ([Equation 4](#)):

$$D_b = D_A - D_0 \quad [4]$$

Based on the deformation properties described by Heckel, materials were type A if a linear relationship was observed at all the applied pressures indicating densification only by plastic deformation. If a linear one follows an initial curved region, it implies type B. For type

C, an initial steep linear region becomes superimposed and flattened at increased pressure³².

Kawakita model has received considerable attention in powder compaction, relating the volume of reduction of the powder column to the number of taps, as represented in [Equation 5](#).

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \quad [5]$$

In which a and b were constants; a: describing the degree of volume reduction at the limit of tapping and was called compactibility; while $1/b$ was considered a constant relating to cohesion and was called cohesiveness. Numerical values for constants a and $1/b$ were obtained from the slope of plots of N/C versus the number of taps N ³³.

RESULTS AND DISCUSSION

Ash values

Ashing determines the purity and quality of powdered material by measuring the total amount of inorganic components of material after ignition or complete oxidation. It indicates the types/concentration of minerals, taste, appearance, texture, and stability of material related to the safety of the material. From our study, *M. oleifera* met World Health Organization (WHO) specifications, as shown in [Table II](#). The presence of impurities could make a sample not meet specifications for ash values.

Table II. Ash values

Samples	Total ash (%w/w)	Water-soluble ash (% w/w)	Acid-insoluble ash (%w/w)
<i>A. paniculata</i>	9.27±0.04	6.83±0.02	1.60±0.02
<i>M. oleifera</i>	5.56±0.03	4.73±0.02	0.43±0.02
<i>A. paniculata</i> + <i>M. oleifera</i>	12.27±0.01	10.63±0.06	1.54±0.02
WHO Limits	<8.0	-	<1.0

Flow properties

The flow properties of the samples were presented in [Table III](#). Suitable flow property was necessary to ensure

proper die fill during compression. The powders exhibited poor flow ($AR > 50^\circ$), while the granules demonstrated reasonable flow potentials ($AR < 35^\circ$). This underscores the cohesive nature of the powders. The flow rate of the powders and those of the granules were seen to be significantly different. These differences in values favor the granules over the powders in tableting. High moisture content, many fines, and electrostatic charges can cause a powder not to have a good flow behavior^{34,35}.

Bulk and tapped density relationships are another way to index flowability. Batches containing maize starch as binder and disintegrant were seen to have higher bulk densities than those with MCC. This may be due to the cohesive nature of maize starch. Similarly, increased tapped density for all batches implies better compactibility due to applied pressure³⁶.

Hausner ratio relates bulk density to tapped density³⁷. All batches have values greater than 1.2 except ABMCG, indicating poor flow attributes. Carr index value for ABMG shows good flow property while others have fair flow properties. However, CI being a one-point determination may not always predict the ease or speed with which the powder or granules consolidate, as some materials with high CI will consolidate rapidly in the tableting machine die cavity³⁸. The true density of a material can relate the tableting profile of a material to the interparticle bonding strength. However, similarity in true density does not necessarily mean similarity in tableting. An increase in granule filling density impacts tableting and compactibility and limits the ability to achieve tablets of adequate mechanical strength³⁹. This is why the batches produced through direct compression in this study did not have adequate mechanical stability, as seen in the friability test.

Moisture content, a key determining factor in tablet stability, was seen to be lower in granulated batches and

relatively higher in those of direct compression. This explains why the granulated batches had a better flow⁴⁰. Moisture plays a key role in interparticle bond formation by increasing the tensile strength of the powder bed and decreasing density variation within the tablet. Moisture increases plastic deformation, decreases elastic properties of materials, and reduces ejection force⁴¹.

Table III. Flow properties

Batch	MC (%)	BD(g/cm ³)	TD(g/cm ³)	TrD(g/cm ³)	RD(g/cm ³)	FR(g/sec)	AR (°)	HR	CI (%)
ABMP	5.3±0.2	0.27±0.1	0.36±0.3	0.49±0.2	0.55±0.3	0.13±0.1	53.13	1.33	25
ABMG	3.7±0.2	0.31±0.1	0.35±0.2	0.39±0.1	0.79±0.3	0.46±0.1	33.45	1.13	11
ABMCP	4.8±0.1	0.26±0.1	0.35±0.2	0.48±0.1	0.54±0.1	0.13±0.3	52.90	1.36	26
ABMCG	3.5±0.2	0.27±0.1	0.32±0.2	0.35±0.1	0.77±0.1	0.28±0.2	34.08	1.19	16

Values were expressed as mean±SD of n=6 where applicable.

Compaction and compression properties

The slopes for the Heckel plot (Figure 3) increased proportionally for all the formulations as the compression pressure increased. This shows that the densification rate of the batches reduces with an increase in the force of compression⁴⁰. As compression progresses, the linearity obtained shows that plastic deformation occurs. The lack of a discernible initial curved region shows different fragmentation stages; hence, the batches were deformed mainly by plastic flow⁴². Our work also revealed that the compaction behavior of ABMCG was characterized by a lower degree of plastic deformation when compared to ABMG, and this may be as a result of the brittle nature of MCC, which increases hardness and makes it more resistant to plastic deformation. Hence, a higher yield was required to initiate deformation.

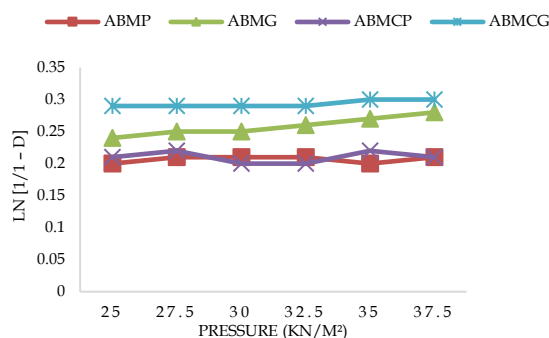


Figure 3. Heckel plots for compacts produced

Values of D_0 obtained for all batches show weak electrostatic forces preventing the packaging of particles in the recompression stage^{40,43}. Slightly higher values of D_0 for granulated batches imply that the degree of initial packing in the die due to die filling is greater than those of direct compression (Table IV). The excipient type did not significantly affect the degree of packing, as no trend was observed. A higher value of D_A for powders indicates a greater degree of fragmentation. When pressure is low, the large materials are fractured into small ones, further enhancing rearrangement. The larger the slopes, the greater the degree of plasticity of materials. Powders were more resistant to movement once the initial packing phase had been completed. This could be due to high cohesive forces, likely due to their amorphous nature⁴⁴. D_B explains the particle rearrangement phase in the consolidation process of the batches. Values of D_B were higher than those of D_0 , and this indicates the presence of fragmentation of granules at the applied pressures⁴³.

Table IV. Heckel and Kawakita parameters

Batch	P_y	D_A	D_0	D_B	a	$1/b$
ABMP	1666.7	0.81	0.27	0.54	2.26	0.01
ABMG	129.9	0.80	0.31	0.49	2.68	0.01
ABMCP	20.6	1.00	0.26	0.74	4.76	0.003
ABMCG	434.8	0.75	0.27	0.48	4.46	0.007

P_y : mean yield pressure values of the formulations; D_A : the total degree of densification occurring at the initial stages of compressions; D_B : phase of particle rearrangement in the early compression stages; D_0 = degree of initial packing of the granules in the die as a result of filling; a : degree of volume reduction at the limit of tapping (compactibility); b : cohesiveness of the material

The mean yield to pressure, P_y shows value in the following order: $ABMCP < ABMG < ABMCG < ABMP$. The results of this research were in line with the results of Haruna *et al.*⁵, who co-processed MCC with crospovidone for direct compression to yield an excipient with a lower degree of plastic deformation. High values of P_y represent brittle materials, while low values imply that the materials underwent plastic deformation readily⁴⁵.

The meager value of ABMCP may result from MCC being a material that forms extremes of the deformation spectrum. Compaction of the materials at higher pressures may extend powder densification, lowering the slope gradient, hence the increase in mean yield pressure values³⁰. Wide variations in P_y values across batches may be due to many factors such as the type of experiment, speed of compaction, compaction pressure, error in true density, the effect of regression coefficient on the gradient of the slope and particle size; these all affect derived values, and there is no standardization being set on these^{46,47}.

For the Kawakita plot as presented in Figure 4, the inverse relationship of the slope implies that the value of a decreases with an increase in slope values leading to better material compressibility. In other words, the smaller the values of a , the better the fluidity of the material⁴⁶. Higher values of a for batches containing MCC correlate with its tendency to form poor compacts. Similarly, the value of $1/b$ shows that batches with MCC are soft and can readily deform under pressure plastically. These findings imply that the interparticle force favoring compression was more petite and hence will probably result in the production of more friable tablets⁴⁷.

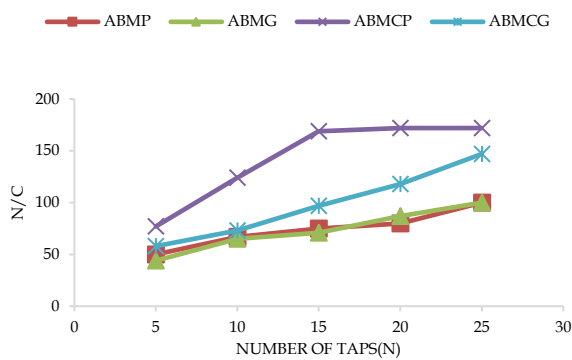


Figure 4. Kawakita plots for compacts produced

For the plot of tensile strength against pressure (Figure 5), granulated batches showed a similar trend of compression characteristics. Granulated batches achieved maximum crushing strength faster at low pressure than direct compression. It shows that granules can build a compact with higher strength than direct compression formulation. Due to reduced compressibility and compactibility, tablets of lower tensile strength were obtained with granulated batches. Tablets with relatively higher tensile strength were obtained with ABMCP because of MCC's good binding and tableting ability profile linked with its tendency to undergo plastic deformation during compression⁴⁸.

Furthermore, particle size and shape have been shown to influence the contact surface area of the powder, which can influence the tablet's tensile strength⁴⁹. Studies have shown that poly formulations have lower tensile strength than mono formulations due to adding one powder to another, which contaminates its particle surface and thereby decreases bonding among them^{46,47}. Crushing strength seems to remain constant for granules irrespective of compression pressure, and this could be a hint for capping tendency as the pressure of compression increases. Variable internal tensions are generated, manifesting differently when crushing strength is evaluated. Generally, the tensile strength of all compacts was independent of the type of excipient used⁴⁹.

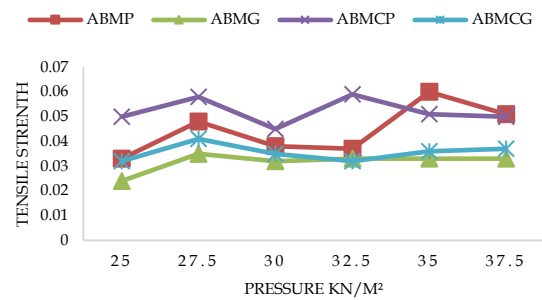


Figure 5. Effect of compression pressure on tensile strength of compacts

Our study's plot of porosity against pressure shows an inverse relationship (Figure 6). As the pressure of compression increases, percent porosity decreases. This underscores previous works⁵. When pressure is applied during compression of the powdered material, the voids or pores present within particles are removed, reducing the porosity of the given powder material¹⁴. Formulations containing maize starch were shown to have higher porosity than those containing MCC. This relationship also portrays a good picture of the compression properties of the formulations.

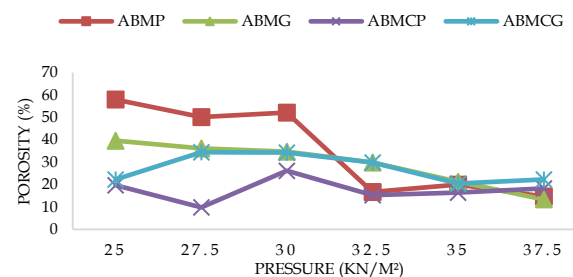


Figure 6. Effect of compression pressure on porosity of compacts

The relationship between apparent density versus pressure is linear, with granules having higher values than powder formulations (Figure 7). As the density increases, applied pressure increases. When a material undergoes compression at a given pressure, the air present among the powder particle is partially removed, and the particle becomes compact and closer to each other, thereby decreasing the bulk volume of the material⁴⁹.

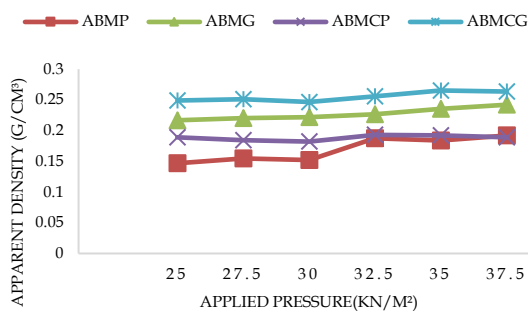


Figure 7. Effect of applied pressure on apparent density of the compacts

Friability is a compendium mechanical test with a specification of not more than 1%. It is a surface deformation that is enhanced by the morphology of the tablet. The tablet should withstand attrition in a pack owing to partial powdering, chipping, or fragmentation during handling and transportation. Tablets with rough surfaces will be more friable than those with smooth surfaces. Moisture content, type, and concentration of excipients used could all affect friability⁴⁹. Batches containing MCC granules had a better friability result, indicating mechanical stability, while batches for direct compressions did not meet specifications, as shown in

Figure 8.

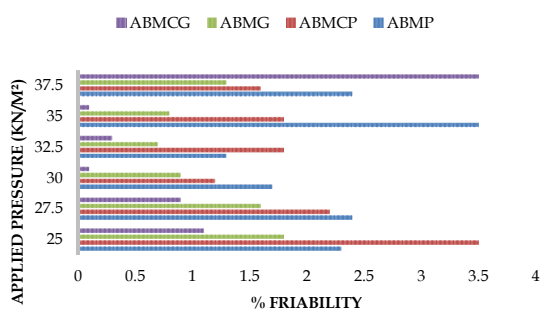


Figure 8. %friability at different pressures

CONCLUSION

Wet granulation and direct compression method were utilized to formulate AP and MO leaf powder tablets. Although formulations were significantly different based on the type of excipients used, formulations from wet

granulation showed better compression and compaction behavior. Fluctuations in plots could be as a result of several factors such as variations in size distributions and shape of the particles, nature of the API, the extent of particle rearrangement and fragmentation of the granules and powders, resistance of granules to densification, as well as type of bonding that exist between API and excipients. Optimization of process parameters such as granulation, moisture content, and compressional force can help achieve ideal biopharmaceutical properties in the tablet.

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AUTHORS' CONTRIBUTION

All authors have an equal contribution in carrying out this study.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest whatsoever regarding this work.

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