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EFFECTS OF EXCIPIENTS AND FORMULATION TYPES ON COMPRESSIONAL PROPERTIES OF DICLOFENAC

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Abstract: Different models used to characterize powders have not been extended to granule behavior in tablet technology. Hence, Kawakaita equation and tapping experiments were used to compare the effect of different excipients on the properties of powders and granules in diclofenac formulations containing corn starch (DCS), lactose (DL) and dicalcium phosphate (DDCP). The binding properties of Albizia gum from *Albizia zygia* tree were also compared with those of gelatin in the granule formulations. Diclofenac (powder and granule) formulations were characterized for particle size and particle size distribution. Volume reduction was done by subjecting materials to N number of taps. Values of maximum volume reduction (*a* 'determined') and index of compressibility (*b*) were obtained from the plots of N/C against powder volume reduction with tapping (C). Another value for *a* (*a*' calculated) were obtained from Kawakita equations. The individual and interaction effects of type of diluent (X_1) and formulation (X_2) on the characteristics of powder and granule were determined, using a 2^2 factorial experimental design. The mean granule size increased with binder concentration, larger granules were obtained with Albizia gum than gelatin in the formulations. In DCS, *a* was lower in granules, granules had higher values of *a* than powders in DDCP ($p < 0.05$). There were no significant differences in the values of *a*' for granule and powder formulations. Diclofenac had higher compressibility index (*b*) with the excipients. Generally, *b* was higher in granules than in powder formulations ($p < 0.05$). The factorial analysis indicates no significant differences in the contribution of formulation type to the compression properties. Granules and powders can be characterized using the same parameters. Albizia gum was shown to confer good flow and compression properties in diclofenac formulations.

Keywords: drug formulations, compression properties, diclofenac, Albizia gum

Powders and granules are used in the production of solid dosage forms such as tablets and capsules. Several works have been done to study the properties of powders and how these properties influence drug production (1-3). Factors such as packing and cohesive properties, size and shape of powders have been found to be relevant during powder mixing, hopper and capsule filling (4). Powders and powder mixtures have been characterized by different models such as parameters obtained from tapping experiment, Heckel and Kawakita equations, and angle of internal flow (θ) which is obtained from the plot of porosity (E) against number of taps (N) (4-6). It is essential to consider these parameters in granules and their influence on granule behavior. It is also important to determine the extent of interaction between these parameters and compare them with the characterizations obtained for powders. This will serve to establish the use of these parameters in tablet operations involving granules.

Pharmaceutical granules typically have a size range of 0.2–0.4 mm, prepared from powdered ingredients. After granulation, granule could be packed (when used as a dosage form) or mixed with other excipients and used for tablet compaction or capsule filling (7). Albizia gum is a gummy exudate from the trunk of *Albizia zygia* tree (family Leguminosae). Ayorinde et al. (7) showed that Albizia gum is capable of imparting high plasticity, producing tablets of satisfactory mechanical strength and reduction of viability of microbial contaminant. Hence, this study seeks to investigate the effect of Albizia gum on compression characteristics, and to compare the packing, cohesive and compression properties in powder and granule formulations. The work also determines the influence of individual and interacting variables on powder and granule characteristics.

The aim of this work is to compare the packing, cohesive and compression properties in powder

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and granule formulations. Comparative studies will be done on the binding properties of gelatin and Albizia gum and the influence of individual and interacting variables in powder and granule formulations will also be determined.

MATERIALS AND METHODS

The materials used were diclofenac (Unique Chemicals, Gujarat, India.), corn starch, dicalcium phosphate (DCP), lactose (Sam Pharmaceuticals, Ilorin, Nigeria), gelatin BP (Hopkins and Williams, Chadwell Health, Essex, UK), Albizia gum (from *Albizia zygia* tree, Botanical Gardens, University of Ibadan). All reagents used were of Analar grade.

Table 1. Formulations and proportions of their constituents.

Formulation	Constituents/Proportion
DCS	Diclofenac (50%) + Corn starch (50%)
DL	Diclofenac (50%) + Lactose (50%)
DDCP	Diclofenac (50%) + DCP (50%)

Characterization of materials

The particle shape and size distributions of the formulations were determined by optical microscopy on 500 particles for each material. Paraffin oil was used for DDCP and DL while ethanol was used for DCS. Also, the particle densities of the formulations were determined by the pycnometer method with xylene (a non-solvent) as the displacement fluid.

Preparation of granules

Two hundred fifty gram batches of diclofenac formulations containing diclofenac (50% w/w) and the excipients were prepared by mixing the powders in the proportions stated in Table 1. Each formulation batch was dry-mixed for 5 min in a Kenwood planetary mixer and then moistened with either 30 mL of distilled water or appropriate quantities of mucilage of *Albizia zygia* gum, to give 1% or 4% w/w of the gum and gelatin in the final granule formulation. Massing was continued for 5 min and the wet masses were granulated by passing them manually through a number 12 mesh sieve (1400 μm). The granules produced were dried in a hot air oven for 18 h at 50°C and thereafter re-sieved through a

Table 2. Values of mean particle size, mean granule size, loose bulk density, particle density and relative density for the powder and granule formulations.

Material	Binder /Concentration	Mean particle size (mm)	Mean granule size (mm)	Loose bulk density (g/cm^3)	Particle density (g/cm^3)	Relative density at zero pressure
DCS powder	No binder	6.05	-	0.297	1.456	0.204
DL powder	No binder	5.00	-	0.353	1.429	0.247
DDCP powder	No binder	4.40	-	0.398	2.166	0.184
DCS granule	No binder	8.00	6.05	0.345	1.454	0.237
DCS granule	Gelatin, 1%		6.50	0.308	1.455	0.212
DCS granule	Gelatin, 4%		7.10	0.340	1.454	0.234
DCS granule	Albizia, 1%		8.00	0.345	1.454	0.237
DCS granule	Albizia 4%		8.50	0.372	1.453	0.256
DL granule	No binder	6.80	5.00	0.353	1.489	0.237
DL granule	Gelatin, 1%		5.65	0.359	1.489	0.241
DL granule	Gelatin, 4%		6.30	0.363	1.487	0.244
DL granule	Albizia, 1%		6.80	0.389	1.486	0.262
DL granule	Albizia, 4%		7.30	0.456	1.484	0.307
DDCP granule	No binder	6.10	4.00	0.398	2.166	0.184
DDCP granule	Gelatin, 1%		4.80	0.430	2.165	0.199
DDCP granule	Gelatin, 4%		5.60	0.433	2.164	0.200
DDCP granule	Albizia, 1%		6.10	0.480	2.163	0.222
DDCP granule	Albizia, 4%		6.50	0.505	2.160	0.234

number 16 mesh sieve (100 µm). The granules were stored in air tight containers.

Determination of volume and density parameters

In determining the initial bulk volume, V_o, 20 g from each of the formulations was poured into a 50 mL glass measuring cylinder at an angle of 45° and the volume of the untapped bulk was determined. The material was then subjected to various (N) numbers of taps in the cylinder according to British Standard 1460 (38 taps/min) and the volume reduction (C) was taken. This was continued until the maximum possible relative decrease in the initial bulk volume due to tapping was reached. Values of tapped volume (V_N) for the formulations were determined at intervals of 25 taps. Densities were calculated using the weight of the powders. Determinations were done in quadruplicates, using the following equations:

$$V_o = \pi r^2 h \quad (2)$$

$$V_N = \pi r^2 h \quad (3)$$

$$D = W/ \pi r^2 h \quad (4)$$

where D is the density of material, W is the weight of material in the measuring cylinder, r is radius of the measuring cylinder and h, the height of powder in the measuring cylinder (cm).

Maximum volume reduction

The values of maximum volume reduction, *a* (*a* determined) and index of compressibility *b*, were obtained respectively from the values of the reciprocal of slope and intercepts of the plots of N/C *versus* N. Another values for the degree of volume reduction of the materials were also obtained (*a*' calculated) using Kawakita equations (6).

Porosity

The porosity, E (Table 3) of the individual excipients and diclofenac formulations, was calculated using the equation:

$$E = 1 - D_r \quad (5)$$

The values of K (Table 3) for the excipients and diclofenac formulations were obtained from the equation:

$$K = E^2 - N/ 1 - E \quad (6)$$

Angle of internal flow

Plots of K *versus* N were made and the values of K_o were obtained from the intercepts of the plots.

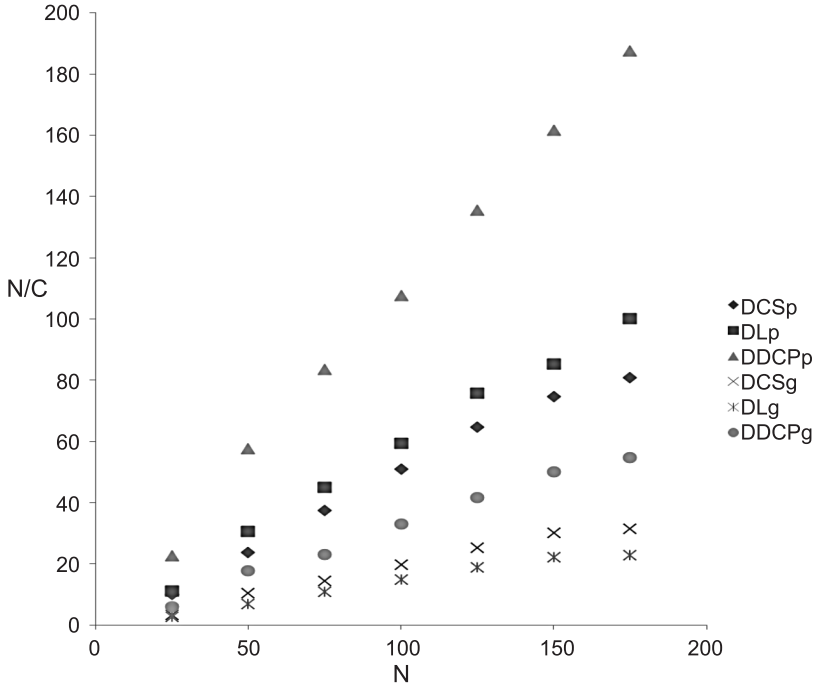

Figure 1. Plots of N/C against N for the formulations

Table 3a. Values of bulk volume, volume reduction, compressibility index and angle of internal flow for the formulations.

Material	Volume at zero pressure (cm^3), V_o	*a* (determined)	*a*' (calculated)	*b*	θ
DCS powder	16.628	79.441	0.761	0.010	7.020
DL powder	12.471	60.290	0.722	0.005	5.128
DDCP powder	12.021	65.520	0.786	0.007	2.938
DCS granule (No binder)	1.347	62.559	0.761	0.011	15.200
DL granule (No binder)	1.133	61.816	0.727	0.007	18.810
DDCP granule (No binder)	0.930	92.950	0.790	0.008	5.370

*b value for diclofenac = 0.007

Table 3b. Values of bulk volume and volume reduction for the granule formulations.

Formulation	Binder/Concentration	Volume at zero pressure (cm^3), V_o	*a*' (calculated)
DCS granule	No binder	1.347	0.761
DCS granule	Albizia gum, 1%	1.159	0.725
DCS granule	Albizia gum, 4%	1.075	0.707
DCS granule	Gelatin, 1%	1.297	0.753
DCS granule	Gelatin, 4%	1.176	0.730
DL granule	No binder	1.133	0.727
DL granule	Albizia gum, 1%	1.028	0.699
DL granule	Albizia gum, 4%	0.877	0.651
DL granule	Gelatin, 1%	1.114	0.723
DL granule	Gelatin, 4%	1.102	0.722
DDCP granule	No binder	1.005	0.790
DDCP granule	Albizia gum, 1%	0.833	0.751
DDCP granule	Albizia gum, 4%	0.792	0.739
DDCP granule	Gelatin, 1%	0.930	0.774
DDCP granule	Gelatin, 4%	0.924	0.776

Further plots of $K - K_o$ were then made against N, the slopes of which gave values of tan θ. The angles of internal flow of the materials were obtained from the inverse of tan θ.

Factorial experimental design

In order to determine the individual and interaction effects of type of diluents (X_1) and formulation type (X_2) on the packing and cohesive properties of diclofenac formulations, a factorial experimental design was used. This has been found in previous works to be useful in determining the effect of various formulation factors on the properties of drug formulations (3, 7). The basis of the design was that each of the variables was utilized at a 'high' level (denoted by +1) and a 'low' level (denoted by -1). Table 3 summarizes the range of the two independent process parameters. A 2^2 full factorial design was + used as a research methodology that required preparation of four batches (Table 4). The use of the experimental design enables the identification of the individual influences of the process parameters and their interaction using a suitable statistical tool (Minitab©, 15.1.1.0).

RESULTS

Size distribution

The particle sizes of the powder and granule formulations are shown in Table 2. Granules were bigger in sizes than powder formulations. Significant differences were obtained in formulations containing different excipients, binders and binder concentrations.

Densities

Values of loose bulk density, particle density and relative density are given in Table 2. DDCP had the highest bulk density. Bulk density was found to be higher in formulations containing binder than those without a binder. Particle density decreased with an increase in binder concentration.

Volume reduction (*a*) and compressibility index (*b*)

Tables 3a and b show the values of *a* determined, *a* calculated and compressibility index. Figure 1 is the plot of N/C against N, the slope of which gave the value of *a* determined. The values of *a* calculated were generally lower than *a* determined in all the formulations. However, the values varied with excipient and formulation type. Formulations containing plastically deforming corn starch had the highest values of compressibility index.

Angle of internal flow

Tables 3a and b also shows the values of angle of internal flow. DCP appeared to be the least cohesive material and imparted the best flow properties among the excipients. Figure 2 shows the plots of

Table 4. Independent process parameters and their levels.

Independent Process Parameters	Associated variable	Lower level (Coded -1)	Upper level (Coded +1)
Diluent type	X_1	DCS	DDCP
Formulation type	X_2	Powder	Granule

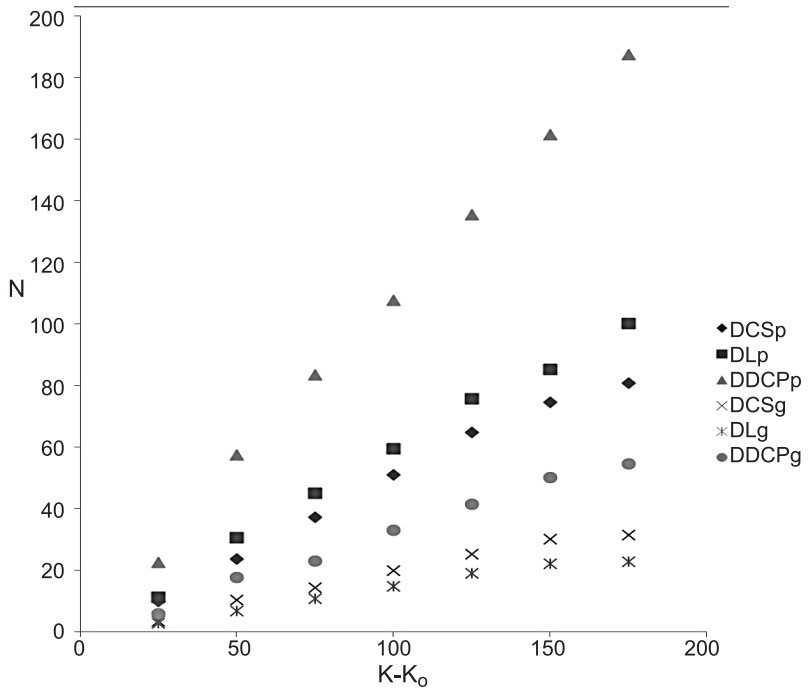

Figure 2. Plots of N/C against K - K_o

Table 5. Values of *a*, *a'*, *b* and θ for the powder binary mixtures for the factorial experimental design.

Batch no.	Diluent type	Formulation type	*a*	*a'*	*b*	θ
1	-1	-1	79.441	0.761	0.010	7.020
2	+1	-1	65.520	0.786	0.007	2.938
3	-1	+1	62.559	0.761	0.011	15.200
4	+1	+1	92.950	0.790	0.008	5.370

Key: -1: Low values; +1: High values

Table 6. Summary of the individual and interaction coefficients of the variables on the Percentage maximum volume reduction due to tapping 'a' and angle of internal flow 'θ'

Factor	Coefficient	*a*	*a'*	*b*	θ
X_1	Effect p-value	8.235 0.660	0.027 0.005	-0.003 0.051	-6.956 0.245
X_2	Effect p-value	5.274 0.782	0.002 0.926	0.001 0.684	5.306 0.424
X_1X_2	Effect	22.156	0.002	0.000	-2.874

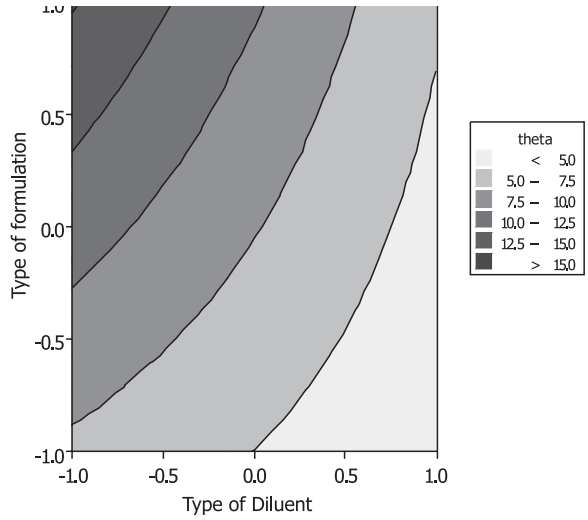

Figure 3. Contour plot of effect of formulation type and type of excipient on angle of internal flow, θ

$K - K_0$ against N. Slopes of the plots gave the values of θ, from which the angle of internal flow was determined.

Factorial experiments

Results of the factorial experiments are presented in Tables 4–6. Figure 3 shows the contour plots of effects of formulation and excipient on the angle of internal flow.

DISCUSSION

Size distribution

The rank order of the particle sizes is DCS granule > DL granule > DDCP granule > DCS powder > DL powder > DDCP powder (Table 2). The granules were found to have higher values of mean particle size than powder formulations ($p < 0.05$). This accounts for why granules are generally better

flowing than powders, as granulation has been shown to improve the flow properties of powder mix. Formulations containing corn starch had the largest particles while those containing DCP had the smallest. This is significant as it has been reported that even small differences in the particle size can have a strong effect on flow property (8). Formulations containing corn starch are therefore expected to have the least cohesiveness and best flow property, which suggests DCS to be the most plastic formulation as there is likely to be higher closer repacking of the particles than in other formulations.

The mean granule size (G) values for the materials were obtained from the plot of cumulative weight (%) oversize *versus* granule size and presented in Table 2. The mean granule size of the materials generally increased with an increase in binder concentration. This is expected as increasing binder concentration makes available more binder per bond. A general increase in granule diameter of glass spheres with an increase in binder concentration had been reported (9). Also, Alebiowu & Femi-Oyewo (10) observed a general increase in the granule size of *Datura metel* granules with an increase in binder concentration.

The nature of excipient and binder used in diclofenac formulation was found to affect the granule size. The ranking of mean granule size among diclofenac formulations was DCS > DL > DDCP. Mean granule size value was also found to be higher in formulations containing Albizia gum than those containing gelatin. This suggests that higher strengthening of bonds occurred in formulations containing Albizia gum as a binder.

Loose bulk density (ρ_o)

The values of loose bulk density (Table 2) were found to be higher in formulations with binder than those without binder. Also, as the concentration of binder increased, the loose bulk density values increased. This is attributable to the fact that binder increases both the intra- and interparticle interactions among materials. The values were found to be higher in formulations containing Albizia gum than those containing gelatin ($p < 0.05$). This suggests that Albizia gum imparted a higher degree of initial packing to diclofenac formulations than gelatin.

Among diclofenac formulations, the trend of loose bulk density was DDCP > DL > DCS. This is probably due to the fact that the small particle size of DCP filled up the void spaces in the formulation mixture, thus reducing porosity and increasing densification. High bulk density has also been reported for DCP by Zhang et al. (11). Therefore, the increased cohesive force associated with small particle size of DCP was probably responsible for the increased densification observed.

Particle density

Particle density (ρ_t), may influence the compression properties of the granules. Dense, hard granules may require higher compressive loads to produce a cohesive compact but are usually less friable. The values of the particle density of formulations (Table 2) decreased with an increase in binder concentration and formulations containing no binder had higher values than those containing binders ($p > 0.05$), also, there was no significant difference in the particle density of formulations containing gelatin and Albizia gum as binder. DDCP had the highest particle density value; the ranking among the formulations was DDCP > DL > DCS ($p < 0.05$). Flowability is typically determined by powder properties which include density; high particle density favors free flow. The result suggests that dicalcium phosphate had greater effect than both corn starch and lactose on the particle density of diclofenac and that the presence of DCP will improve diclofenac flow properties better than corn starch and lactose. A previous study has also shown DCP to have excellent flow property (11) despite smaller particle size.

Relative density at zero pressure (D_o)

The relative density of the powder bed at the point when the applied pressure equals zero (D_o) is used to describe the initial rearrangement phase of densification as a result of die filling. The values of D_o (Table 2) were found to be higher in formulations containing Albizia gum than those containing gelatin and as the concentration of binder increased in the formulations, the values of D_o also increased. This indicates that the initial packing in the die as a result of die filling is higher in formulations containing Albizia gum and increased with increase in binder content.

The values of loose bulk density, mean granule density, particle density and relative density were found to be higher in granule than powder formulations (Table 2). This is attributable to the presence of binders in the granules.

Maximum volume reduction (*a* determined and *a'* calculated)

In all the formulations, the tapped volume and porosity values decreased with increasing number of taps. In addition to particle shape and size, packing of powders is affected significantly by electrostatic forces between the powder particles and pressure

applications (in the form of tapping). Tapping leads to a decrease in volume which results in higher bulk density and relative density. This decrease in volume continued with increasing number of taps until a constant volume which is considered the minimum volume (tapped volume) was attained. This volume is however of limited accuracy because further tapping after the minimum volume is reached can result in increased volume of the powder. A more reasonable accuracy is obtainable from the slope of the plot of N/C *versus* N (Fig. 1) (4).

The values of maximum volume reduction (*a* determined and *a'* calculated) for powder and granule (containing no binder) formulations are presented in Table 3a while Table 3b shows the values for granule formulations containing different binders at varying concentrations. DCS had lower values of *a* in granules than powders ($p < 0.05$). DDCP granules had significantly higher value of *a* than powders, while the values were almost similar in DL powders and granules. There was no significant difference in the values of *a'* in powder and granule (containing no binder) formulations. Formulations containing corn starch powder had the highest values of *a* (79.44%), compared with 66.29% for DL powder and 65.52% for DDCP powder. A different trend was however observed in the formulation granules; DCP granules gave the highest value of *a* (92.95%), while DCS and DL granules, respectively, had 62.56 and 61.82%.

The process of volume reduction of powders is dependent on particle properties such as shape and size and the degree of interparticulate friction. It should however be noted that it is not readily possible to quantify the relative contributions of each of these properties to the volume reduction ability of the powder (4, 12). Thus, it would appear that under the applied pressure of tapping which would overcome to a large extent, the electrostatic forces of attraction between the particles of the powders (13), the spherical shaped and smaller particle sized powders would promote closer packing of its particles than irregularly shaped particles. Podczeck and Sharma (14) reported that the size distribution of particles is another factor that influences the packing of powders. The finer the particles of each component of a binary mixture, the larger the value of volume reduction and the more closely packed the particles are. This was found to be true for the formulation granules, in which the formulations containing dicalcium phosphate (DDCP) had the highest values of *a* and *a'*, followed by DCS, with DL having the least value. This probably accounts for the reason why granules generally produce satisfactory strong tablets with low tendency to cap or laminate. Anomaly was however observed for the powder formulation, in which formulations containing the coarse corn starch gave the highest value of *a*. This anomaly may be due to changes that occur in the packing arrangement of the powder on application of small pressure (or tapping). These structural changes are opposed by the intermolecular forces which are not yet exceeded by the small pressure occasioned by tapping.

The values of *a'* calculated from Kawakita equation were found to be lower than *a* determined from the slopes of the plots of N/C *versus* C for granule and powder formulations. The Kawakita function gave a more linear relationship with high values of slope of generally not less than 0.999. This high linearity agrees with the previous work (4, 14) that Kawakita equation is more reliable than tapping experiment in determining volume reduction. Thus, in granules also, volume reduction is not absolutely dependent on reaching the minimum bulk volume as the volume may start to increase after some time.

Index of compressibility (*b*)

The values of the index of compressibility, *b*, are also presented in Tables 3a and 3b. The *b* value for diclofenac was determined to be 0.007. The values of *b* for the formulations (both powders and granules) were higher than that of the drug alone. This is indicative of the need for these excipients in order to improve the compressibility of diclofenac in formulations, since materials tend to be more compressible as the value of *b* increases. Also, the values of *b* obtained for diclofenac formulations containing corn starch (both powders and granules) were approximately intermediate between those of the drug and excipients. This further shows that corn starch imparted an improved compressibility on diclofenac, which is attributable to the higher plasticity of corn starch. However, for formulations containing lactose and DCP, the values of *b* were not intermediate between those of the drug and excipients, and similar extents of variations were obtained for powders and granules. This anomaly for DL and DDCP could also be ascribed to changes that occur in the packing arrangement of the powder particles. Varthalis and Pilpel (15) reported that some properties of powder mixtures exhibit anomalous behaviors, and from the above observations, index of compressibility may be one of such powder properties.

In general, the values of *b* were found to be higher in formulations containing plastically deforming corn starch than fracturing DCP and in

granule than in powder formulations. This shows that granules exhibit better compressibility than powders and are likely to produce tablets of better mechanical properties.

Angle of internal flow (θ)

The values of the angle of internal flow, θ are presented in Table 3a. These values were obtained from the slopes of the plots of $K - K_o$ *versus* N (Fig. 2). The plots gave high linearity with correlation coefficients of generally greater than 0.999 for all the materials.

The higher the value of θ, the higher the cohesiveness and the poorer the flow properties of the material. The rank order among the powder formulations was DCS > DL > DDCP. This suggests that DDCP powder is the least cohesive material with the best flow properties. Based on particle size, it would be expected that DCS (containing corn starch) should have the least value of θ and the best flow property contrary to the observed trend. This observation could be described as a powder anomaly, which occurred in the individual excipients. This anomaly was also observed in the granules, but to a smaller extent. The values of θ for the granules were found to be generally smaller than those of the powders. This shows that granules possess better flow properties than the powdered materials. This is expected, as one of the reasons for granulation is to improve the flow properties of powders (16, 17).

Generally, the flow properties of powders are very important in their handling and processing, and it is affected by the packing arrangement of the powder particles. This will in turn affect the properties of tablets and capsules that are prepared from such powders. It is therefore necessary to determine the proportion of diluents that will be needed to improve the flowability of the powder. The occurrence of anomalies in the flow properties of powder mixtures is likely to have consequences in several areas of pharmaceutical practice such as die filling of powders and granules, and uniformity of doses.

Factorial experimental design

A factorial experimental design was used to study the influence of type of diluents and formulation type on *a, a', b* and θ of the powders and granules. The experimental design of the independent process parameters and the levels used is presented in Table 4. The values of the quantitative effect of the variables, the nature and concentration of diluent, are presented in Table 5, while the summary of the individual and interaction coefficients are given in Table 6.

The effect of a change in the type of diluent was observed to be positive for both *a* and *a'* indicating that changing from the 'low' level (DCP) to the 'high' level (DDCP) led to an increase in the values of these parameters, i.e., the maximum volume reduction due to tapping 'a', both calculated and determined. While this effect was to be observed to be insignificant for *a,* it was significant for *a'* ($p < 0.05$). However, this change in diluent type led to a negative but insignificant effect on the values of *b* and θ.

The change in formulation type from 'low' (powder) to the 'high' level (granule) was positive but insignificant for all parameters measured, indicating that the granule formulations caused an increase in volume reduction, compressibility and angle of internal flow for the formulations investigated. In studying the effect of interactions between the diluent type (X_1), and formulation type (X_2), the interaction $X_1 X_2$ on the *a, a'* and *b* was positive indicating that the effects of the two variables influenced each other, while that on the angle of internal flow θ, was negative (Fig. 3).

CONCLUSION

The same parameters could be used to characterize powders and granules used in tablet formulation processes. Granule formulations containing Albizia gum as binder had better volume reduction and flow properties with improved compressibility than those containing gelatin. Extent of plasticity of the excipient in the formulation had a positive effect on both determined and calculated volume reduction parameters.

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