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COMMUNICATION

Characterization of Khaya Gum as a Binder in a Paracetamol Tablet Formulation

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ABSTRACT

The influence of khaya gum, a binding agent obtained from Khaya grandifolia *(Meliaceae family), on the bulk, compressional, and tabletting characteristics of a paracetamol tablet formulation was studied in comparison with the effects of two standard binders: polyvinylpyrrolidone (PVP; molecular weight 40,000) and gelatin. The relative ability of khaya gum to destroy any residual microbial contamination in the binder or in the formulation during tabletting was also studied using* Bacillus subtilis *spores as a model.*

Formulations containing khaya gum exhibited more densification than formulations containing PVP and gelatin during die filling, but less densification due to rearrangement at low pressures. The mean yield pressure of the formulation particles obtained from Heckel plots, and another pressure term, also inversely related to plasticity, obtained from Kawakita plots, showed dependence on the nature and concentration of the binder, with formulations containing khaya gum exhibiting the lowest and highest values respectively. The values of the pressure terms suggest that the yield pressure relates to the onset of plastic deformation during compression, while the Kawakita pressure relates to the total amount of plastic deformation occurring during the compression process.

Tablets made from formulations containing khaya gum had the lowest tensile strength values but also the lowest tendency to laminate or cap, as indicated by their lowest brittleness. All the tablets had friability values $< 1\%$ at higher concentrations of the three binders. In addition, khaya gum demonstrated

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a comparable ability to destroy microorganisms in the formulation during tabletting as the two binders.

The characterization of the formulations suggests that khaya gum can be developed into a commercial binding agent for particular tablets.

INTRODUCTION

A binding agent is required to impart the structural strength required during the processing, handling, and packaging of tablets. Various parameters can be useful in the characterization of the binding properties of binders. The most valuable are the compression and tabletting parameters. The Heckel and Kawakita equations have proved useful in characterizing the compression properties of pharmaceutical powders and formulations (1–3), while the tabletting properties can be characterized using the tensile strength (T), a measure of bond strength, and the brittle fracture index (BFI), a measure of the brittleness of tablets.

Khaya gum is obtained from the incised trunk of the tree *Khaya grandifolia* (Meliaceae family). It is known to contain highly branched polysaccharides consisting of D-galactose, L-rhamnose, D-galacturonic acid, and 4-0-methyl-D-glucoronic acid (4), and it has been shown to possess tablet binding properties (5,6). These binding properties have been shown to compare favorably with those of standard binders (7).

Raw materials, especially from natural origins, have been shown to be a source of heavy microbial contamination in tablets, and this would raise questions about the propensity of contamination of tablet formulations from khaya gum itself, from the microbial load it would incur from the source. The compression of tablet formulations is known to effect some level of microbial destruction, but this depends on the compression pressure employed, the properties of the contaminating microorganisms, and the properties of the formulation involved (8–11).

In the present work, khaya gum has been characterized as a binding agent in a paracetamol tablet formulation in comparison with two standard binding agents: polyvinylpyrrolidone (PVP; molecular weight 40,000) and gelatin, using the compression equations of Heckel and Kawakita, and the tensile strength, brittle fracture index, and friability values of tablets as assessment parameters. The relative ability of the gum to destroy any residual microbial contamination in the binder or in the formulation during tabletting was also studied using *Bacillus subtilis* spores as a model.

The Heckel equation is widely used for relating the relative density, D, of a powder bed during compression to the applied pressure, P. It is written as:

$$\ln[1/(1-D)] = KP + A \tag{1}$$

where the slope of the straight line portion, K, is the reciprocal of the mean yield pressure, P_y, of the material. From the value of the intercept, A, the relative density, D_A, can be calculated using the following equation (12):

$$D_A = 1 - e^{-A} \tag{2}$$

The relative density of the powder at the point when the applied pressure equals zero, D_0, is used to describe the initial rearrangement phase of densification as a result of die filling. The relative density, D_B, describes the phase of rearrangement at low pressures and is the difference between D_A and D_0:

$$D_B = D_A - D_0 \tag{3}$$

The Kawakita equation is used to study powder compression using the degree of volume reduction (C) and is written as:

$$C = (V_0 - V_p)/V_0 = abP/(1 + bP) \tag{4}$$

The equation, in practice, can be rearranged to give:

$$P/C = P/a + 1/ab \tag{5}$$

V_0 is the initial bulk volume of the powder and V_P is the bulk volume after compression. The constant a is equal to the minimum porosity of the material before compression, while the constant b is related to the plasticity of the material. The reciprocal of b gives a pressure term P_k, which is the pressure required to reduce the powder bed by 50% (13,14).

The BFI was devised by Hiestand et al. (15) and is obtained by comparing the tensile strength of tablets having a hole at their center with the tensile strength of tablets with no hole, both at the same relative density (15,16). A low value of BFI is desirable for the minimization of lamination and capping during tablet production. On the other hand, the desirable effect on tensile strength depends largely on the intended use of the tablets (17).

Paracetamol was chosen for the study because of its poor compression properties, thus requiring a binder among other excipients to form satisfactorily strong tablets. The spore-forming bacterium *B. subtilis* was chosen as the contaminating microorganism because of its resistance to destruction by physical and chemical agents.

MATERIALS AND METHODS

Materials

The materials used in this work were paracetamol BP and corn starch BP (BDH Chemicals Ltd., Poole, UK), lactose (DMV Veghel, Netherlands), gelatin BP (Hopkin&Williams, Chadwell Heath, Essex, UK), PVP (MW 40,000; Aldrich Chemicals Co. Ltd., Gillingham, Dorset, UK), and khaya gum (from *K. grandifolia*, Botanical Gardens, University of Ibadan, Ibadan, Nigeria).

The khaya gum was hydrated in double-strength chloroform water for 5 days with intermittent stirring, and extraneous materials were removed by straining through a calico cloth. The gum was precipitated from solution using absolute ethanol. The precipitated gum was filtered, washed with diethyl ether, and then dried in a hot air oven at 40°C (18).

Preparation of Binder Solutions and Mucilages

Binder solutions of PVP and gelatin were prepared in glass beakers by dissolving the required quantity of the binder in 35 mL of distilled water while stirring, in the cold (PVP) or with warming on a water bath (gelatin). On the other hand, binder mucilages of khaya gum were prepared by slowly adding 40 mL of boiling water to the required quantity of the binder in a glass beaker with continuous stirring to produce a mucilage.

Preparation of Granules

Batches (250 g) of a basic formulation of paracetamol (83% w/w), lactose (10% w/w), and corn starch (7% w/w) were dry-mixed for 5 min in a Kenwood planetary mixer and then moistened with either 31 mL of distilled water, or appropriate amounts of aqueous solutions (PVP or gelatin), or mucilages (khaya gum) to produce granules containing different concentrations of the binders. Massing was continued for 5 min and the wet masses were granulated by passing them manually through a number 12 mesh sieve (1400 μm), dried in a hot air oven for 18 hr at 50°C, and then resieved through a number 16 mesh sieve (1000 μm). The degree of mixing of the granules was determined by spectrophotometric assay of paracetamol at 249 nm (BP, 1980) and was found to be >0.95. The moisture content of the formulation as determined with an Ohaus moisture balance (Ohaus Scale Corporation, USA) was between 1.1% and 1.8% w/w. Particle densities were determined by the pycnometer method with xylene as the displacement fluid.

Determination of Precompression Density

The bulk density of each formulation at zero pressure (loose density) was determined by pouring the powder at an angle of 45° through a funnel into a glass measuring cylinder with a diameter of 21 mm and a volume of 50 mL (19,20). Determinations were done in triplicate. The relative density, D_0, of each formulation was obtained from the ratio of its loose density to its particle density.

Preparation of Inoculum

An overnight culture of 18 hr was prepared from *B. subtilis* (laboratory stock culture obtained from the Department of Veterinary Microbiology and Parasitology, University of Ibadan) in nutrient broth. One milliliter of the overnight culture was placed in 9 mL of peptone water or sterile distilled water. Two milliliter volumes were then placed in sterile glass mortars, covered, and allowed to dry at 37°C for 48 hr.

Contamination of Granules

Six-gram quantities of 500–1000 μm size fraction of the prepared paracetamol granules were gently

mixed in the contaminated glass mortars by the method of increasing quantities (8) established in preliminary experiments to give an even dispersion of the contaminating microorganism with the granules. Viable counts were approximately 10^8 colony-forming units per gram (cfu/g). Viable count tests were also carried out on the uncontaminated granules as control.

Preparation of Tablets

Contaminated granules as well as uncontaminated granules in 500 mg quantities were compressed for 1 min with predetermined pressures using a Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, WI) fitted with a pressure gauge reading up to 2.5 metric tonnes. Before each compression, the die (10.5 mm diameter) and the flat-faced punches were lubricated with a 2% w/v dispersion of magnesium stearate in ethanol-ether (1 : 1). Tablets with a hole at their center were made using an upper punch with a hole through the center and a lower punch fitted with a pin (16). After ejection, the tablets were stored over silica gel for 24 hr to allow for elastic recovery and hardening. Their weights (w) and dimensions were then determined to within ± 1 mg and 0.01 mm respectively, and their relative densities (D) were calculated using the equation:

$$D = w/V_t \rho_s \tag{6}$$

where V_t is the volume (cm^3) of the tablet (including the hole when present) and ρ_s is the particle density (g/cm^3) of the solid material. Heckel plots of $\ln[1/(1-D)]$ vs. applied pressure (P) and Kawakita plots of P/C vs. P were constructed for all formulations.

Testing

The tensile strengths, T, of the normal tablets and T_0, of those containing a hole were determined at room temperature by diametral compression (21) using a PTB 301 hardness tester (Pharmatest, Switzerland) and applying the equation:

$$T = \frac{2P}{\pi d t} \tag{7}$$

where T (or T_0) is the tensile strength of the tablet (MN/m^2), P is the load needed to cause fracture (MN), d is the tablet diameter (m), and t is the tablet thickness (m). Results were taken only from tablets which split cleanly into two halves without any sign of lamination. All measurements were made in triplicate and the results given are the means of several determinations. The BFI of the tablets were then calculated using the equation:

$$\text{BFI} = 0.5[(T/T_0) - 1] \tag{8}$$

The percentage friability, F, of the normal tablets was determined using a Roche Friabilator operated at 25 rpm for 4 min. Ten tablets were used at each mean relative density for a test. Determinations were made in triplicate.

Determination of Viability

Contaminated or uncontaminated tablets in 1 g quantities were disintegrated in 9 mL of distilled water. Serial dilutions were made and viability assessed using the pour plate method, with plates incubated at 37°C for 24 hr. Survival, estimated as the mean of triplicate or more determinations, was expressed for the contaminated formulations as a percentage relative to uncompressed control contaminated granules.

RESULTS AND DISCUSSION

Figure 1 shows representative Heckel plots for paracetamol formulations containing 3% w/w binder. Two phases of compression are discernable, with the first phase having correlation coefficient for linearity between 0.920 and 0.980, and the second phase commencing approximately between 85 and 110 MN/m^2, and showing higher correlation coefficient for linearity of >0.990 for all formulations.

The mean yield pressure values for the paracetamol formulations were calculated from the slope of the second compression region of the Heckel plots, and the intercept, A, was determined from the extrapolation of the region. The values of D_A and D_B were calculated from Eqs. (2) and (3) respectively. Values of P_y, D_0, D_A, and D_B for all formulations are presented in Table 1. Values of D_0 for the formulations increased with increase in binder concentration, with formulations containing khaya gum generally having comparable values to those of the standard binders. This implies that the initial packing of the formulation in the die as a result of die filling increased with increase in binder content.

The relative density, D_B, describes the phase of rearrangement of particles during the initial stages of compression. The extent of the rearrangement phase depends on the theoretical point of densification at which deformation of particles begins. The D_B values decreased with increase in binder concentration, with formulations containing khaya gum generally having lower values than formulations containing PVP and gelatin. The values of D_B are also higher than the values of D_0, probably as a result of fragmentation of granules and subsequent filling of void spaces between the particles at low pressures (16).

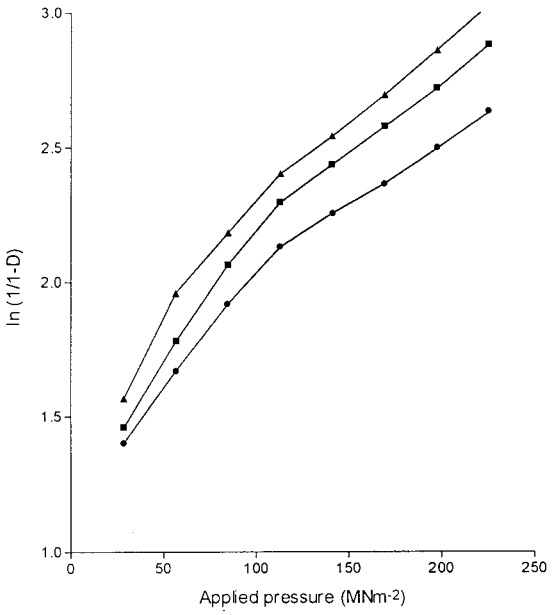

Figure 1. Heckel plots for paracetamol formulations containing 3% w/w binder. Khaya gum ■; PVP ▲; gelatin ●.

D_A represents the total degree of packing achieved at zero and low pressures as a result of rearrangement processes before an appreciable amount of interparticulate bonding takes place (20). The value of D_A was found to decrease with increase in binder concentration. Furthermore, formulations containing khaya gum generally exhibited slightly lower D_A values than formulations containing PVP and gelatin. Higher values of D_A indicate softer and more readily compressible granules.

The values of P_y for the formulation decreased with increase in binder concentration, implying that the onset of plastic deformation in the formulation occurred at lower pressures with increase in binder content. Formulations containing khaya gum generally exhibited the lowest P_y values, while those containing gelatin exhibited the highest P_y values. This implies that khaya gum would induce faster

Table 1

Parameters Derived from Heckel and Kawakita Plots for Paracetamol Tablet Formulations

Binder	Binder Concentration (% w/w)	Heckel Plots				Kawakita Plots	
		D_0	P_y	D_A	D_B	$D_I\,(1-a)$	P_k
	0.00	0.209	270.3	0.787	0.578	0.329	5.329
Khaya gum	0.50	0.267	242.8	0.795	0.526	0.327	5.217
	1.00	0.269	229.8	0.792	0.523	0.313	5.015
	2.00	0.272	179.9	0.790	0.516	0.310	4.978
	3.00	0.279	168.0	0.788	0.509	0.301	4.957
	4.00	0.282	158.5	0.786	0.505	0.294	4.908
PVP	0.50	0.245	274.5	0.821	0.576	0.305	5.181
	1.00	0.250	253.2	0.820	0.570	0.300	4.373
	2.00	0.258	198.3	0.813	0.555	0.291	3.860
	3.00	0.260	171.9	0.809	0.549	0.285	3.639
	4.00	0.267	156.9	0.805	0.538	0.284	3.144
Gelatin	0.50	0.259	353.9	0.829	0.570	0.331	5.389
	1.00	0.263	291.6	0.818	0.555	0.324	5.255
	2.00	0.269	261.2	0.815	0.546	0.299	5.135
	3.00	0.276	236.3	0.809	0.533	0.293	4.697
	4.00	0.291	183.1	0.779	0.488	0.281	4.587

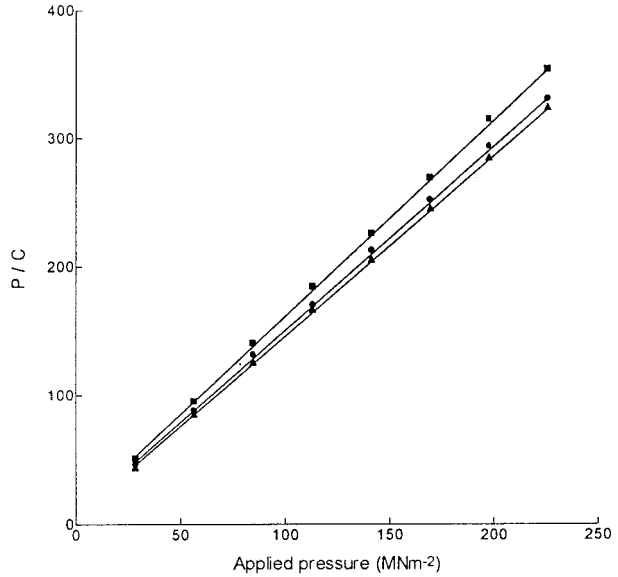

Figure 2. Kawakita plots for paracetamol formulations containing 3% w/w binder. Khaya gum ■; PVP ▲; gelatin ●.

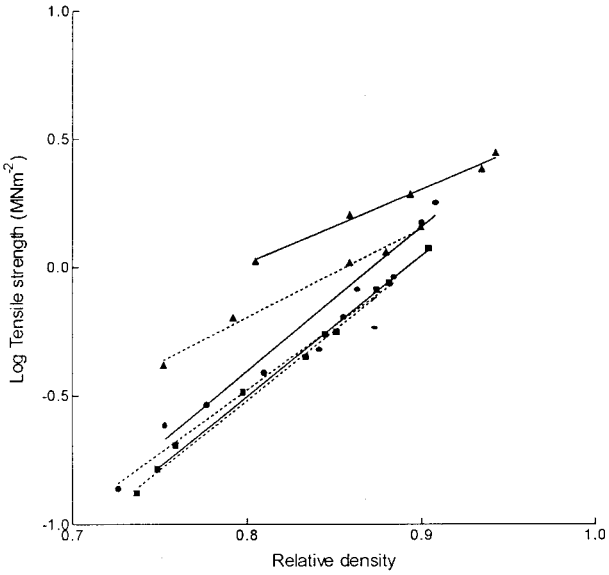

Figure 3. Log tensile strength vs. relative density for paracetamol tablets containing 3% w/w binder with (-----) and without (——) a hole at their center. Khaya gum ■; PVP ▲; gelatin ●.

onset of plastic flow in the formulation than PVP and gelatin.

Figure 2 shows representative Kawakita plots for paracetamol formulations containing 3% w/w of the binders. A linear relationship was obtained at all compression pressures employed with correlation coefficient of 0.999 for all formulations. The constants a and b were obtained from the slope and intercept of the plots respectively. The value of a is equal to the minimum porosity of the powder bed prior to compression, while b is related to the plasticity of the material (14). Values of $1-a$ give the initial relative density of the formulations, D_I, while P_k values were obtained from the reciprocal of the values of b.

The values of P_k, which represent the pressure required to reduce the powder bed by 50% (13,14), are presented in Table 1. Values of P_k for the formulations containing PVP were lower, especially at high concentrations of binder, than those of formulations containing khaya gum and gelatin which have more comparable P_k values.

D_I represents the packed initial relative density of the formulation with the application of small pressure or tapping (7). The values of D_I are seen to decrease with increase in binder concentration, with formulations containing khaya gum generally exhibiting the highest values and those containing PVP the lowest values.

Representative plots of T vs. relative density for tablets made from formulations containing 3% w/w binders are presented in Fig. 3. Values of T and BFI for all the formulations at relative density 0.90, which is representative of commercial paracetamol tablets, are presented in Table 2. It can be seen that T increased with increase in binder concentration, while the BFI decreased. This indicates that the presence of a binder at interparticulate junctions facilitates plastic deformation for the relief of localized stresses (16). Tablets containing PVP exhibited the highest BFI values, while those containing khaya gum had the lowest values. The results indicate that khaya gum produced paracetamol tablets with the lowest bond strength but also with the lowest brittleness. Thus khaya gum could be more useful as a binder than PVP and gelatin when problems of lamination and capping are of more concern than bond strength.

Representative plots of F vs. relative density for tablets made from formulations containing 3% w/w binders are presented in Fig. 4. Values of F for all the formulations at relative density of 0.90 are included in Table 2. It can be seen that the value of

Table 2

Tensile Strength (MN/m^2), BFI, Friability (F) Values, and Percentage Survival of B. subtilis *Spores for Paracetamol Tablets at* $D = 0.90$

Binder	Binder Concentration (% w/w)	T (MN/m^2)	BFI	F (%)	Percentage Survival of *B. subtilis* Spores
	0.00	0.612	0.450	3.92	7.50
Khaya gum	0.50	0.734	0.063	2.91	3.35
	1.00	0.771	0.057	1.37	3.00
	2.00	1.000	0.048	1.24	2.51
	3.00	1.147	0.040	0.85	1.39
	4.00	1.180	0.036	0.65	0.96
PVP	0.50	1.433	0.294	1.53	6.04
	1.00	1.433	0.266	0.91	3.87
	2.00	1.945	0.246	0.82	2.75
	3.00	2.023	0.232	0.71	1.91
	4.00	2.382	0.227	0.61	0.88
Gelatin	0.50	0.870	0.204	2.23	11.04
	1.00	1.265	0.203	1.92	4.83
	2.00	1.360	0.200	0.84	3.85
	3.00	1.438	0.176	0.58	2.84
	4.00	1.494	0.143	0.51	1.14

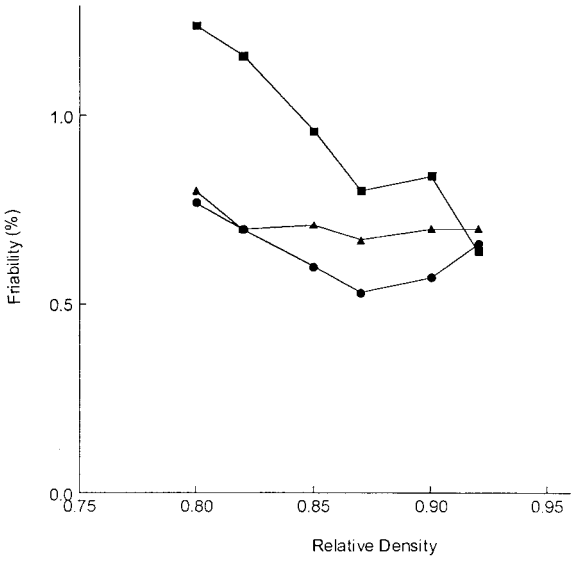

Figure 4. Friability (%) vs. relative density for paracetamol tablets containing 3% w/w of binder. Khaya gum ■; PVP ▲; gelatin ●.

F decreased with increase in binder concentration. Conventional compressed tablets which lose less than 1% of their weight during the friability test are generally considered acceptable (22). Table 2 shows that all the paracetamol tablets generally had friability values $< 1\%$ at higher concentrations of the binders. This suggests that at certain concentrations khaya gum should be able to provide adequate protection for the tablets against abrasive motions during handling.

The results of the tests on the uncontaminated granules of the formulations showed no growth or negligible growth of less than 10^2 cfu/g spores. No growth was observed from any of the formulations after the uncontaminated granules were compressed, even at the lowest relative density (0.77). Thus, it can be inferred that survival of organisms after compression was mainly from the deliberate contamination of the granules.

Representative plots of log% survival of *B. subtilis* spores in the contaminated formulations after compression vs. relative density are shown in Fig. 5 for formulations containing 0.5% w/w of the binders. Values of percentage survival for all formulations at relative density 0.90 are given in Table 2. Except at the lowest binder concentration, very high reduction in *B. subtilis* spores' viability of over 90% was generally achieved in the formulations. As the relative density of the tablet increases, more solid bonds are formed between the particles, leading to an increase in bond strength and hence an increase

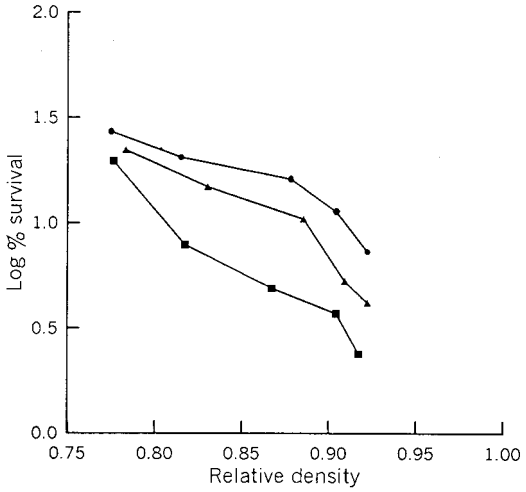

Figure 5. Log % survival vs. relative density for paracetamol formulations containing 0.5% w/w binder. Khaya gum ■; PVP ▲; gelatin ●.

in localized heat and shearing forces on the microorganisms with a consequent reduction in their survival. It can also be seen that in all cases, the percentage survival of *B. subtilis* spores decreased with increase in binder concentration in the formulation. In addition, khaya gum demonstrated a comparable ability to destroy microorganisms in the formulation during tabletting as the two standard binders. It can also be seen from Table 2 that the higher the binder concentration, the higher the tensile strength of the tablets, and the lower the percentage survival of *B. subtilis* spores during compression.

CONCLUSION

The characterization of the formulation suggests that khaya gum would be useful as a commercial binding agent for particular tablet formulations.

REFERENCES

1. Heckel, R.W. Density–Pressure Relationships in Powder Compaction. Trans. Metall. Soc. AIME **1961**, *221*, 671–675.
2. Heckel, R.W. An Analysis of Powder Compaction Phenomena. Trans. Metall. Soc. AIME **1961**, *221*, 1001–1008.
3. Kawakita, K.; Ludde, K.H. Some Considerations on Powder Compression Equations. Powder Technol. **1970/71**, *4*, 61–68.
4. Aspinal, G.O.; Bhattacharjee, A.K. Plant Gums of the Genus Khaya. Part IV. J. Chem. Soc. C **1970**, 365–369.
5. Adeyemo, O.A.; Itiola, O.A. Effects of Khaya Gum and Gelatin on the Compressional Characteristics of a Griseofulvin Tablet Formulation. J. West Afr. Pharm. **1993**, *7*, 27s–29s.
6. Odeku, O.A.; Itiola, O.A. Effects of Interacting Variables on the Friability and Disintegration of Griseofulvin Tablets. Nig. J. Sci. **1996**, *30*, 205–212.
7. Odeku, O.A.; Itiola, O.A. Evaluation of Khaya Gum as a Binder in a Paracetamol Tablet Formulation. Pharm. Pharmacol. Commun. **1998**, *4*, 183–188.
8. Plumpton, E.J.; Gilbert, P.; Fell, J.T. Effect of Spatial Distribution of Contaminating Microorganisms within Tablet Formulation on Subsequent Inactivation Through Compaction. Int. J. Pharm. **1986**, *30*, 237–240.
9. Plumpton, E.J.; Gilbert, P.; Fell, J.T. The Survival of Microorganisms During Tabletting. Int. J. Pharm. **1986**, *30*, 241–246.
10. Blair, T.C.; Buckton, G.; Bloomfield, S. On the Mechanism of Kill of Microbial Contaminants During Tablet Compression. Int. J. Pharm. **1991**, *72*, 111–115.
11. Odeku, O.A.; Itiola, O.A.; Odelola, H.A. Evaluation of the Destructive Effect of Khaya Gum on *B. subtilis* Spores During Tabletting. Phytother. Res. **1999**, *13*, 296–299.
12. Humbert-Droz, P.; Gurny, R.; Mordier, D.; Doelker, E. Densification Behaviour of Drugs Presenting Availabilty Problems. Int. J. Pharm. Tech, Prod. Manuf. **1983**, *4*, 29–35.
13. Shivanand, P.; Sprockel, O.L. Compaction Behaviour of Cellulose Polymers. Powder Technol. **1992**, *69*, 177–184.
14. Lin, C.; Cham, T. Compression Behaviour and Tensile Strength of Heat-Treated Polyethylene Glycols. Int. J. Pharm. **1995**, *118*, 169–179.
15. Hiestand, E.N.; Wells, J.E.; Poet, C.B.; Ochs, J.F. Physical Processes of Tabletting. J. Pharm. Sci. **1977**, *66*, 510–519.
16. Itiola, O.A.; Pilpel, N. Tabletting Characteristics of Metronidazole Formulations. Int. J. Pharm. **1986**, *31*, 99–105.
17. Itiola, O.A.; Pilpel, N. Formulation Effects on the Mechanical Properties of Metronidazole Tablets. J. Pharm. Pharmacol. **1991**, *43*, 145–147.
18. Tyler, V.E.; Brady, L.R.; Robbers, J.E. In *Pharmacognosy*, 8th Ed.; Lea & Febiger: Philadelphia. 1981; 21–54.

19. Paronen, P.; Juslin, M. Compressional Characteristics of Four Starches. J. Pharm. Pharmacol. **1983**, *35*, 627–635.
20. Itiola, O.A. Compressional Characteristics of Three Starches and the Mechanical Properties of Their Tablets. Pharm. World J. **1991**, *8* (3), 91–94.
21. Fell, J.T.; Newton, J.M. Determination of Tablet Strength by Diametral Compression Test. J. Pharm. Sci. **1970**, *59*, 688–691.
22. Banker, G.S.; Anderson, N.R. Tablets. In *The Theory and Practice of Industrial Pharmacy*, 3rd Ed.; Lachman, L., Lieberman, H.A., Kanig, J.L., Eds.; Lea&Febiger: Philadelphia, 1986; 297–303.