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RESEARCH PAPER

Evaluation of the Effects of Khaya Gum on the Mechanical and Release Properties of Paracetamol Tablets

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ABSTRACT

A study of the comparative effects of khaya gum and two standard binding agents—polyvinylpyrrolidone (PVP) and gelatin—on crushing strength and friability, and the disintegration and dissolution characteristics of paracetamol tablets was made. The crushing strength-friability ratio (CSFR), the disintegration times, D, and the dissolution times t_{50}, t_{90}, and t_1 (derived from the equation of Noyes and Whitney), all increased with an increase in binder concentration; however, the dissolution rate constants, k_1 and k_2, decreased. The ranking for the values of CSFR for tablets containing the different binders was PVP > gelatin > khaya gum. The ranking for D and the dissolution times was gelatin > khaya gum > PVP, whereas the ranking for the dissolution rate constants was PVP > khaya gum > gelatin. There were significant linear correlations between CSFR, D, t_{50}, t_{90}, and t_1 for the tablets. There were also significant correlations between k_1 and D, t_{50}, t_{90}, and t_1, and between k_2 and t_{90}. The results suggest that khaya gum could be useful as an alternative binding agent to produce tablets with particular mechanical strength and drug release profiles.

INTRODUCTION

Pharmaceutical tablets must have the mechanical strength to withstand the rigors of hand involved in manufacture, packaging, transportation, dispensing, and in the hands of the user. They must also, in relevant cases, be able to release the drug content in the gastrointestinal tract for absorption. The mechanical strength of tablets is quantifiable by their crushing strength (CS) and friability (F), whereas their release properties are quantifiable by their disintegration and dissolution profiles.[1] These parameters in turn have been shown to depend considerably on the nature and concentration of the binding agent used in tablet formulation.[2,3]

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A number of binding agents are available for use in tablet formulations. However, different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purposes. Thus, the development of new excipients for potential use as tablet binders continues to be of interest.

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

Recently, Odeku and Itiola[8] investigated the suitability of khaya gum as a binder in a paracetamol tablet formulation in comparison with two standard and widely used binders: polyvinylpyrrolidone (PVP; mol. wt. 40,000) and gelatin BP. The results suggested that khaya gum could be more useful as a binding agent for particular tablet formulations. Further work has shown that khaya gum possesses the ability to destroy microorganisms during tableting in a similar manner to the two standard binders[9] and has also fostered the interest in the gum as a binding agent.

In the present work, further studies have been made to determine the suitability of khaya gum as a binding agent for paracetamol tablets. The effects of khaya gum on CS and F, and the disintegration and dissolution characteristics of paracetamol tablets were investigated, in comparison with the two standard binders. Paracetamol is a sparingly soluble drug with poor compression properties, which requires a binding agent among other excipients to form satisfactorily strong tablets.

MATERIALS AND METHODS

Materials

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

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 then precipitated from solution using absolute ethanol. The precipitated gum was filtered, washed with diethylether, and dried in a hot air oven at 40°C.[10]

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 cold PVP or by warming in a gelatin water bath. 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 and continuously 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 the prepared binder solutions (gelatin or PVP) 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 no. 12 mesh sieve (1,400 μm), dried in a hot air oven for 18 hr at 50°C, and then resieved through a no. 16 mesh sieve (1,000 μm). The moisture content of the granule formulations 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. It was not found possible to satisfactorily incorporate more than 4% w/w of khaya gum as binder in the paracetamol granule formulation.

Degree of Mixing of Granules

The degree of mixing (M) of granules from three different regions of each formulation batch was determined by spectrophotometric assay of paracetamol at 249 nm. The sample size was 180 mg, and determinations were made in quadruplicate. The value of M was calculated using the equation:

$$M = 1 - \sigma/\sigma_o \quad (1)$$

where σ is the standard deviation estimated from the analyzed samples, and σ_o is the standard deviation of the completely unmixed system. That is:

$$\sigma_o = [y(1-y)]^{1/2} \quad (2)$$

where y is the proportion of paracetamol in the granule formulation.

In each case, M was found to be >0.95.

Preparation of Tablets

Quantities (500 mg) of the 500–1,000 μm size fraction of granule formulations were compressed for 1 min with predetermined loads using a Carver hydraulic hand press (model C, Carver, Inc., Menomonee Falls, WI, USA). 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). After ejection, the tablets were stored over silica gel for 24 hr to allow hardening and elastic recovery. Their weights (W) and dimensions were then determined to within ±1 mg and 0.01 mm, respectively, and their packing fractions, P_f, were calculated using the equation:

$$P_f = W/V_t \cdot \rho_s \quad (3)$$

where V_t is the volume of the tablet in cubic centimeters, and ρ_s is the particle density of the solid material in grams-cubic centimeters.

Determination of Tablet CS and F

The load (N) required to diametrically break the tablet was determined at room temperature using a PTB 301 Crushing Strength Tester (Pharmatest, Switzerland). Ten tablets were tested at each mean packing fraction.

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

Disintegration and Dissolution Tests

The disintegration times, D, of the tablets were determined in distilled water at $37 \pm 0.5^{\circ}$C using an Apex disintegration testing apparatus (Apex Construction Ltd., Kent, UK).

The dissolution rates of the tablets were determined at the same temperature in 1 L of 0.1 M HCl using an Erweka dissolution rate machine (Erweka, Germany), with the rotating basket positioned 25 mm above the inside bottom of the round-bottomed flask and operating at 100 rpm to ensure no clogging of the basket by fragments of tablets containing khaya gum. The amount of paracetamol that had dissolved after a certain period was determined spectrophotometrically at 249 nm using a Lambda 3B UV/visible spectrophotometer (Perkin-Elmer, Corp., Norwalk, CT, USA) replacing the sample with an equal volume of 0.1 M HCl at the same temperature to keep the volume of dissolution medium constant during the course of the test.

All determinations were made in sextuplet.

RESULTS AND DISCUSSION

Crushing strength and F are important tests for pharmaceutical tablets that often form part of a manufacturer's own specifications. Friability is especially important because the tablet is likely to be subjected to various abrasive motions during production and subsequent use. There are now requirements for these tests in the British Pharmacopoeia,[11,12] but with no clear limits for acceptance or rejection of tablet batches. In the case of CS, this is probably because the desired strength depends largely on the intended use of the tablets.[13] For F, the reason is probably because the principles of the test are not understood.[14] In general, conventional compressed tablets that lose less than 1% of their weight during the F test are usually considered acceptable.[1] In the present work, values of CS and F for paracetamol tablets were plotted as a function of packing fraction. Representative plots for tablets containing 3% w/w of the binders are given in Figs. 1 and 2, respectively. Values of CS and F for all samples at a selected P_f of 0.90, which is representative of commercial tablets, are presented in Table 1. The values of CS increased, and those of F decreased with increasing binder concentration. It is well known that increasing the concentration of the plastoelastic binding agent leads to an increase in plastic deformation of formulation during compression and consequently to the formation of more solid bonds in the resulting tablets to provide more resistance to tablet fracture and abrasion.[15,16] All paracetamol tablets generally had F values of $<1\%$ 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 values of CS and F provide measures of tablet strength and weakness, respectively. Thus, the CS–F

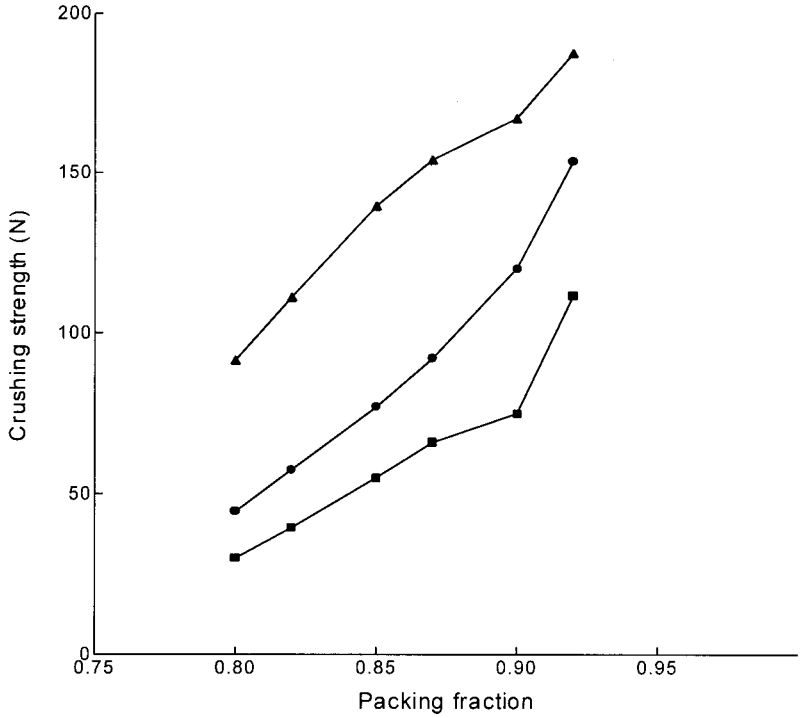

Figure 1. CS (N) vs. packing fraction (P_f) for paracetamol tablets containing 3% w/w of binder. ■, khaya gum; ▲, PVP; ●, gelatin.

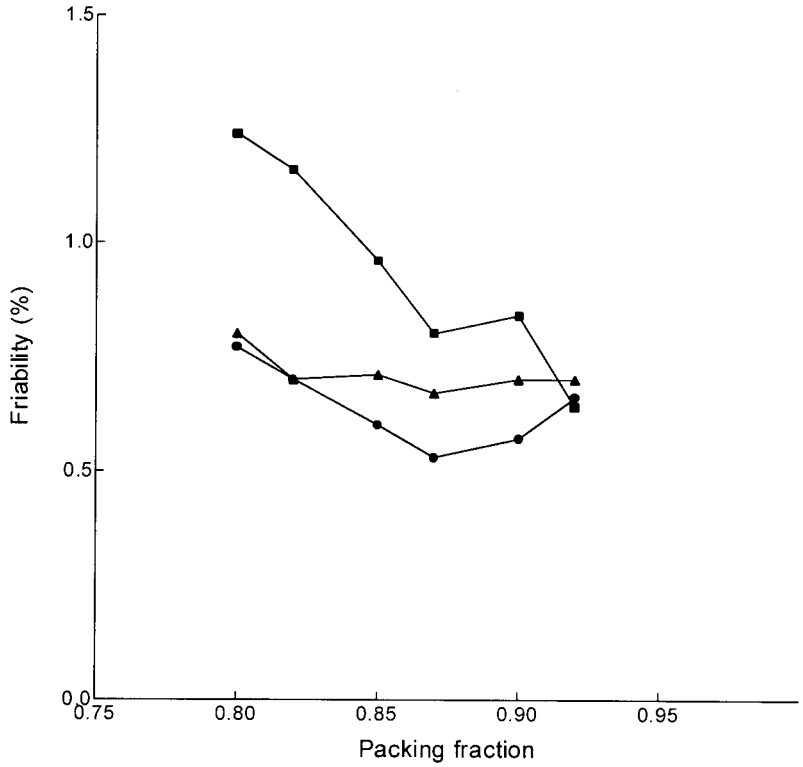

Figure 2. F (%) vs. packing fraction (P_f) for paracetamol tablets containing 3% w/w of binder. ■, khaya gum; ▲, PVP; ●, gelatin.

Table 1. Values of CS, F, and CSFR for paracetamol tablets at packing fraction = 0.90 (±SD).

Binder	Concentration of binder (% w/w)	CS (N)	F (%)	CSFR
	0.00	49.20 (2.58)	3.92 (0.08)	12.55
Khaya gum	0.50	54.88 (2.60)	2.91 (0.08)	18.86
	1.00	60.85 (2.48)	1.37 (0.06)	44.42
	2.00	69.99 (2.04)	1.24 (0.04)	56.44
	3.00	75.08 (1.61)	0.85 (0.02)	88.33
	4.00	95.10 (1.47)	0.65 (0.03)	146.31
PVP	0.50	114.60 (2.24)	1.53 (0.06)	74.90
	1.00	122.30 (2.48)	0.91 (0.06)	134.40
	2.00	146.88 (1.97)	0.82 (0.02)	179.12
	3.00	169.02 (1.56)	0.71 (0.02)	238.06
	4.00	200.38 (1.44)	0.61 (0.03)	328.49
Gelatin	0.50	66.52 (1.34)	2.23 (0.05)	29.83
	1.00	97.88 (1.91)	1.92 (0.04)	50.98
	2.00	111.40 (1.46)	0.84 (0.03)	132.62
	3.00	121.40 (1.53)	0.58 (0.02)	209.31
	4.00	129.36 (1.40)	0.51 (0.03)	253.65

ratio (CSFR) can be used as a measure of the mechanical strength of the paracetamol tablets. The higher the CSFR, the stronger the tablet. The values of CSFR for the tablets were plotted against packing fraction. Typical plots for tablets containing 3% w/w of the binders are presented in Fig. 3. The CSFR values increased with increasing packing fraction. Values of CSFR for the tablets at P_f of 0.90 are included in Table 1. The ranking of CSFR values for tablets containing the different binders was PVP > gelatin > khaya gum.

Values of disintegration time, D, for the tablets were plotted as a function of packing fraction. Representative plots for tablets containing 3% w/w of the binders are given in Fig. 4. The disintegration time of the tablets increased with an increase in packing fraction. Similar observations have been made by other investigators and have been explained in terms of the effect of packing fraction on the specific surface area of the particles and the rate of penetration of liquid into the interior of the tablets.[2,3,17]

Typical dissolution profiles for tablets containing 2% w/w of khaya gum compressed to different packing fractions are shown in Fig. 5. From these, the values of t_{50} and t_{90} (the time required for 50% and 90% of the paracetamol to be dissolved) were calculated.

The integrated form of the equation of Noyes and Whitney[18] is:

$$In[C_s/(C_s - C)] = kt \quad (4)$$

where C_s is the concentration of the solute at saturation, C is the concentration at time t, and k is a dissolution rate constant. Values of $In[C_s/(C_s - C)]$ were plotted vs. t[19] as shown typically in Fig. 6 for tablets containing 3% w/w of the binders. In all cases, two straight regression lines of slopes k_1 and k_2 were obtained. The time at which the lines intersect is denoted t_1.

Values of D, t_{50}, t_{90}, t_1, k_1, and k_2 for all samples at P_f of 0.90 are presented in Table 2. It is seen that the values of D, t_{50}, t_{90}, and t_1 all increased with binder concentration, whereas the values of k_1 and k_2 decreased. The ranking of values of D, t_{50}, t_{90}, and t_1 for tablets containing the different binders was gelatin > khaya gum > PVP. For the dissolution rate constants k_1 and k_2, the ranking was generally PVP > khaya gum > gelatin. Furthermore, values of k_1 for the tablets were less than the values of k_2, with the implication that the dissolution rate of the drug was faster after t_1.

When the rank orders for the three different binders are compared, it is notable that tablets containing khaya gum exhibited the lowest strength, but gave the intermediate rate of release of paracetamol. This type of finding could be important for binder selection. The results suggest that khaya gum can be useful (in particular, tablet formulations) because the rate of drug release can have considerable influence on the bioavailability of a sparingly soluble drug, such as paracetamol.[20,21]

The linear relationships between various measured parameters were analyzed using two-way analysis of variance. Individually, the CS and F values for all tablets containing the different binders

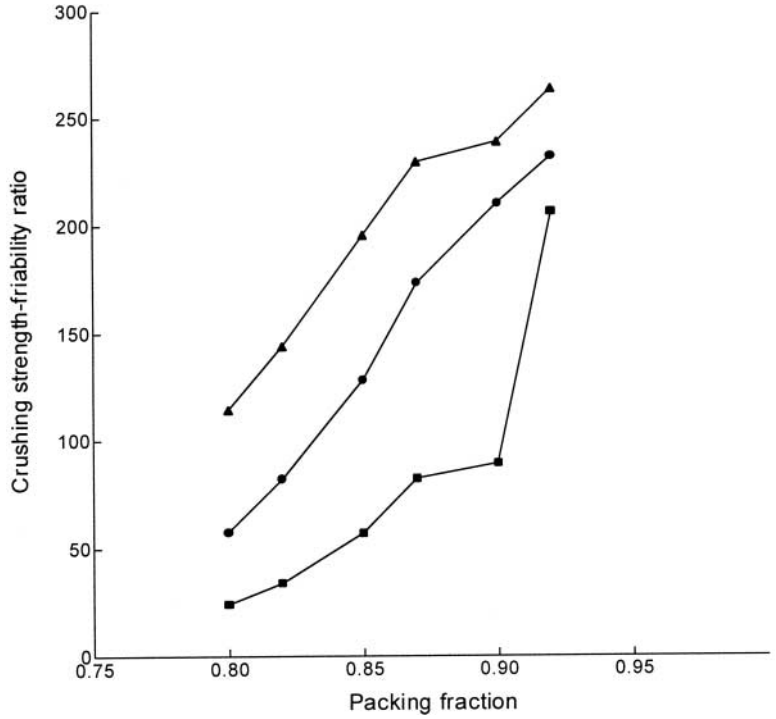

Figure 3. CSFR vs. packing fraction (P_f) for paracetamol tablets containing 3% w/w of binder. ■, khaya gum; ▲, PVP; ●, gelatin.

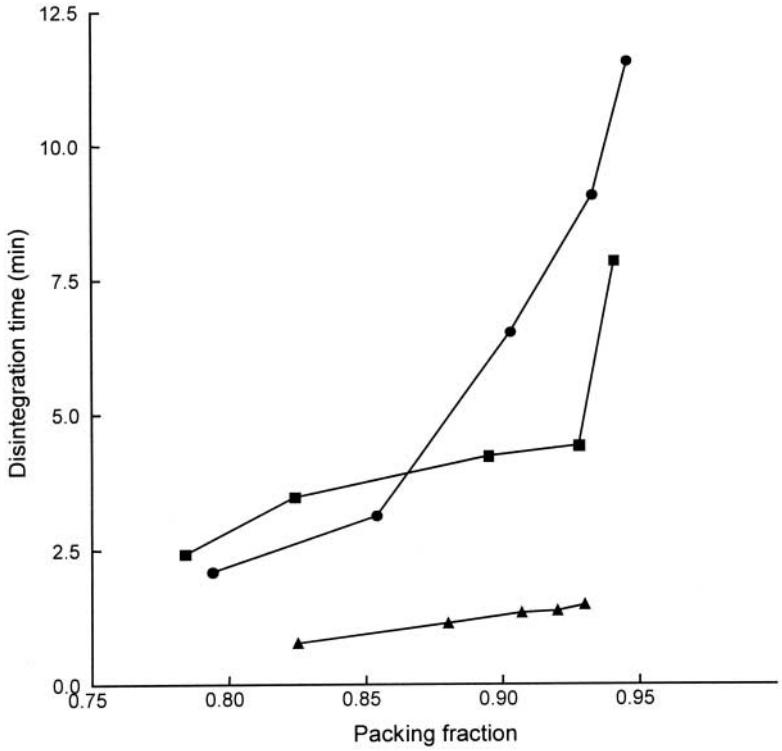

Figure 4. Disintegration time (min) vs. packing fraction (P_f) for paracetamol tablets containing 3% w/w of binder. ■, khaya gum; ▲, PVP; ●, gelatin.

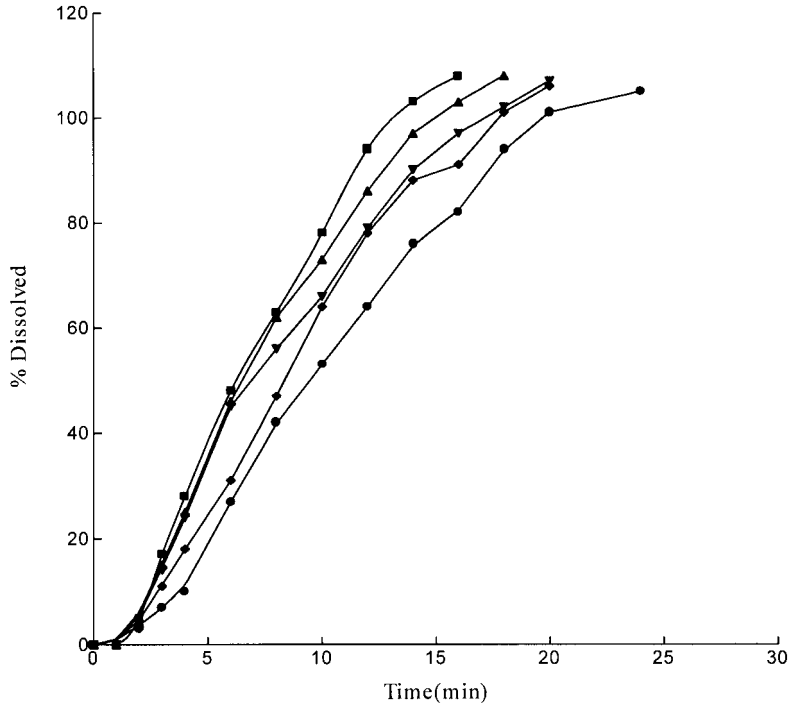

Figure 5. Effect of packing fraction on the dissolution profiles of paracetamol tablets containing 2% w/w of khaya gum. Mean P_f: ■, 0.765; ▲, 0.818; ▼, 0.889; ◇, 0.902; ●, 0.942.

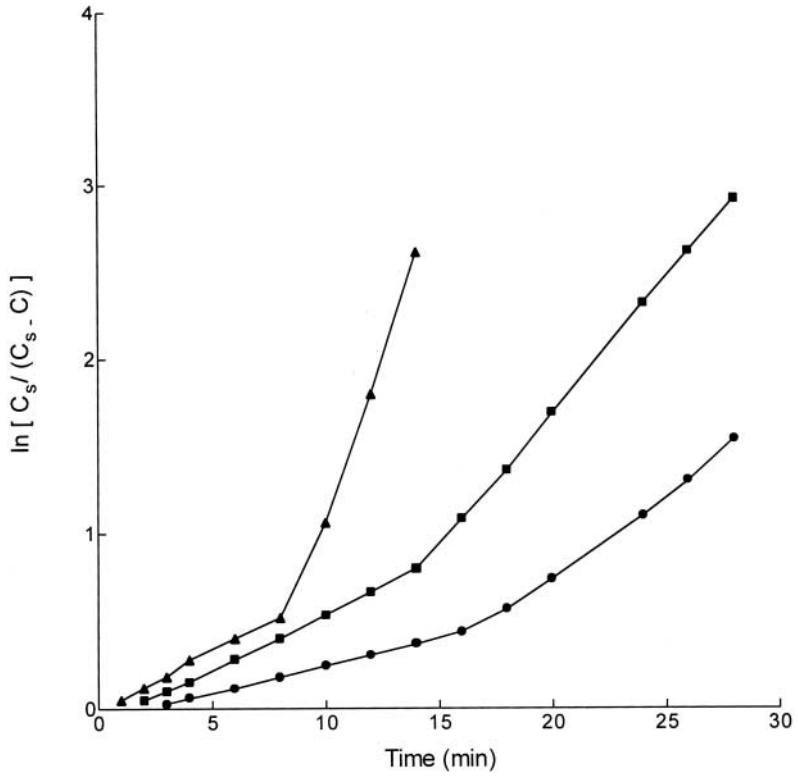

Figure 6. ln $[C_s/(C_s - C)]$ vs. time plots to determine dissolution rate constants for paracetamol tablets containing 3% w/w of binder. ■, khaya gum, $P_f = 0.900$; ▲, PVP, $P_f = 0.894$; ●, gelatin, $P_f = 0.898$.

Table 2. Disintegration and dissolution characteristics of paracetamol tablets at packing fraction = 0.90 (±SD).

Binder	Concentration of binder (% w/w)	D (min)	t_{50} (min)	t_{90} (min)	t_1 (min)	k_1	k_2
	0.00	0.43 (0.03)	3.76 (0.04)	7.82 (0.25)	5.65 (0.12)	0.125 (0.002)	0.927 (0.019)
Khayagum	0.50	0.54 (0.03)	7.93 (0.12)	11.25 (0.26)	8.80 (0.21)	0.086 (0.004)	0.533 (0.015)
	1.00	0.80 (0.03)	8.22 (0.18)	15.96 (0.35)	9.35 (0.23)	0.069 (0.002)	0.283 (0.014)
	2.00	2.02 (0.04)	8.75 (0.20)	16.72 (0.37)	11.65 (0.22)	0.061 (0.004)	0.248 (0.016)
	3.00	4.30 (0.05)	12.10 (0.16)	21.72 (0.35)	14.25 (0.34)	0.056 (0.003)	0.155 (0.012)
	4.00	5.10 (0.04)	13.76 (0.16)	24.12 (0.35)	15.30 (0.28)	0.050 (0.001)	0.135 (0.009)
PVP	0.50	0.57 (0.04)	4.12 (0.27)	8.75 (0.37)	7.05 (0.12)	0.163 (0.005)	0.505 (0.019)
	1.00	0.77 (0.03)	6.63 (0.18)	10.25 (0.36)	7.65 (0.14)	0.099 (0.002)	0.498 (0.008)
	2.00	1.12 (0.07)	9.24 (0.20)	13.45 (0.41)	10.01 (0.21)	0.068 (0.003)	0.445 (0.015)
	3.00	1.25 (0.05)	10.13 (0.19)	14.55 (0.37)	10.58 (0.21)	0.049 (0.004)	0.415 (0.019)
	4.00	1.66 (0.16)	10.36 (0.32)	16.05 (0.54)	11.65 (0.25)	0.041 (0.003)	0.285 (0.013)
Gelatin	0.50	0.64 (0.04)	14.10 (0.64)	20.75 (0.43)	13.70 (0.18)	0.035 (0.001)	0.280 (0.011)
	1.00	1.02 (0.05)	16.45 (0.50)	22.25 (0.46)	13.85 (0.19)	0.032 (0.004)	0.200 (0.008)
	2.00	2.20 (0.08)	17.23 (0.36)	25.45 (0.35)	15.68 (0.19)	0.030 (0.002)	0.181 (0.005)
	3.00	6.31 (0.04)	22.65 (0.56)	35.05 (0.66)	19.22 (0.24)	0.022 (0.003)	0.078 (0.004)
	4.00	10.36 (0.11)	27.93 (0.82)	40.00 (0.74)	23.28 (0.20)	0.018 (0.004)	0.074 (0.003)

generally exhibited poor linear relationships ($p > 0.05$) with all release parameters. This can probably be explained. For example, any surface roughness or damage in tablets would affect the release properties, but this is not usually quantifiable by the F test,[14] and probably not by the CS as well. Itiola and Pilpel[2] observed no significant correlation between the tensile strength and the release properties of metronidazole tablets.

However, the CSFR values appear to be of more relevance in the present consideration, because they gave significant linear relationships with D, t_{50}, t_{90}, and t_1 as shown in Table 3. It seems reasonable to describe the CSFR as a measure of the balance between binding (CS) and disruptive (F) forces in the tablet. It should be noted that, in a similar manner, disintegration of tablets has been described as the net outcome of adhesive and disintegrating forces.[22–24]

Table 3 also shows significant linear correlations between the release parameters themselves. The correlations between D and the dissolution parameters are probably because disintegration of tablets plays a vital role in the dissolution process, since it determines, to a large extent, the area of contact between solid and liquid.[2,17] Tablets containing gelatin generally gave the best correlations.

It can also be seen from Table 3 that the correlation between D and t_1 appears to be best for the tablets. This is probably because similar to D, the change from k_1 to k_2 at time t_1 is attributable to a change in the surface area from breakup of the tablets into fragments.[19] However, it can be seen from Table 2 that the t_1 values were greater than the D values. This can probably be ascribed to the greater agitation used in the disintegration test than the dissolution test.[2]

The dissolution rate constants, k_1 and k_2, did not show significant correlations with some of the other parameters. Although k_1 showed significant ($p < 0.05$) correlations with D, t_{50}, t_{90}, and t_1, it did not generally show a significant correlation with CSFR ($p > 0.05$). On the other hand, k_2 showed a significant ($p < 0.05$) correlation with only t_{90}. This is probably because k_2 represents essentially the period of time during dissolution when the tablet has broken up.

CONCLUSIONS

The results of the present study show the effects of khaya gum on the mechanical properties and release characteristics of the paracetamol tablets studied in comparison with the effects of the standard binders. The binders increase the CSFR of the tablets in the rank order PVP > gelatin > khaya gum, while increasing the disintegration and dissolution times of the tablets in the rank order gelatin > khaya

Table 3. Correlations between various parameters of CSFR, disintegration, and dissolution of paracetamol tablets.

Ordinate	Abscissa	Binder	Equation for best-fitting line	Correlation coefficient (r)	Probability (p)
CSFR	D	Khaya	$CSFR = 22.50 + 13.44$	0.945	< 0.05
		PVP	$CSFR = 24.86D - 7.09$	0.985	< 0.005
		Gelatin	$CSFR = 21.65D + 45.36$	0.947	< 0.05
CSFR	t_{50}	Khaya	$CSFR = 17.96t_{50} - 111.51$	0.960	< 0.01
		PVP	$CSFR = 32.88t_{50} - 75.19$	0.902	< 0.05
		Gelatin	$CSFR = 16.58t_{50} + 190.91$	0.952	< 0.05
CSFR	t_{90}	Khaya	$CSFR = 9.26t_{90} - 95.32$	0.957	< 0.05
		PVP	$CSFR = 30.89t_{90} - 198.57$	0.962	< 0.01
		Gelatin	$CSFR = 11.01t_{90} - 178.57$	0.966	< 0.01
CSFR	t_1	Khaya	$CSFR = 15.93t_1 - 118.25$	0.937	< 0.05
		PVP	$CSFR = 47.34t_1 - 253.49$	0.954	< 0.05
		Gelatin	$CSFR = 22.82t_1 - 256.00$	0.960	< 0.01
t_{50}	D	Khaya	$t_{50} = 1.25D + 6.96$	0.983	< 0.005
		PVP	$t_{50} = 5.79D + 1.88$	0.922	< 0.05
		Gelatin	$t_{50} = 1.33D + 14.20$	0.993	< 0.001
t_{90}	D	Khaya	$t_{90} = 2.36D + 11.94$	0.958	< 0.05
		PVP	$t_{90} = 7.00D + 5.09$	0.981	< 0.005
		Gelatin	$t_{90} = 1.98D + 20.27$	0.987	< 0.005
t_1	D	Khaya	$t_1 = 1.39D + 8.32$	0.994	< 0.005
		PVP	$t_1 = 4.52D + 4.53$	0.990	< 0.005
		Gelatin	$t_1 = 0.98D + 13.12$	0.998	< 0.001
t_{90}	t_{50}	Khaya	$t_{90} = 1.82t_{50} - 0.56$	0.943	< 0.05
		PVP	$t_{90} = 1.10t_{50} + 3.67$	0.973	< 0.01
		Gelatin	$t_{90} = 1.51t_{50} - 1.17$	0.987	< 0.005
t_1	t_{50}	Khaya	$t_1 = 1.06t_{50} + 1.14$	0.960	< 0.001
		PVP	$t_1 = 0.70t_{50} + 3.68$	0.959	< 0.01
		Gelatin	$t_1 = 0.73t_{50} + 2.88$	0.989	< 0.005
t_1	t_{90}	Khaya	$t_1 = 0.55t_{90} + 2.08$	0.958	< 0.05
		PVP	$t_1 = 0.65t_{90} + 1.25$	0.997	< 0.001
		Gelatin	$t_1 = 0.474t_{90} + 3.68$	0.986	< 0.005

gum > PVP. The results suggest that khaya gum could be useful as an alternative binding agent to produce tablets with particular mechanical properties and drug release profiles.

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