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Compressional, mechanical and release properties of a novel gum in paracetamol tablet formulations

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ABSTRACT

The binding properties of Eucalyptus gum obtained from the incised trunk of *Eucalyptus tereticornis*, were evaluated in paracetamol tablet formulations, in comparison with that of Gelatin B.P. In so doing, the compression properties were analyzed using density measurements and the compression equations of Heckel, Kawakita and Gurham. In our work, the mechanical properties of the tablets were assessed using the crushing strength and friability of the tablets, while the drug release properties of the tablets were assessed using disintegration and dissolution times. The results of the study reveal that tablet formulations incorporating Eucalyptus gum as binder, exhibited faster onset and higher amount of plastic deformation during compression than those containing gelatin. What is more, the Gurnham equation could be used as a substitute for the Kawakita equation in describing the compression properties of pharmaceutical tablets. Furthermore, the crushing strength, disintegration and dissolution times of the tablets increased with binder concentration, while friability values decreased. We noted that no significant differences in properties exist between formulations derived from the two binders ($p > 0.05$) exist. While tablets incorporating gelatin exhibited higher values for mechanical properties, Eucalyptus gum tablets had better balance between mechanical and release properties - as seen from the CSFR/D_t values. Tablets of good mechanical and release properties were prepared using Eucalyptus gum as a binder, and, therefore, it could serve as an alternative binder in producing tablets with good mechanical strength and fast drug release.

INTRODUCTION

Most drug powders cannot be made into satisfactory tablets without the incorporation of excipients. These adjuvants impart necessary compressive and flow characteristics to the active ingredient, and commonly used excipients include binders, diluents, glidants, lubricants and disintegrants. Binders generally act by promoting the bonding properties through increasing plasticity, between the different components of the powder mixture, and, hence, provide satisfactory mechanical properties to granule and tablet formulations [21]. Powders and granules are bound together in either the direct compression and wet granulation processes, respectively.

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Development and evaluation of new excipients for use as binding agents in tablet formulations is of continued interest. Different binding agents, having varying characteristics, can be used to obtain tablets with particular mechanical strength and drug release properties [12]. The application of gums from various sources, as pharmaceutical excipients, has gained attention in recent times. These gums generally are polysaccharides obtained from woody and non-woody plant parts. Plant gums are used as binders, suspending agents and sustained released polymers for the formulation of pharmaceutical dosage forms [2,8,22].

The compaction behavior of powders and formulations are assessed using compaction parameters such as measurement of ejection forces, die wall friction, axial to radial load transmission, compressibility, and deformation characteristics. The mathematical equations of Heckel, Kawakita and Gurnham [28,29,32] are used in studying the powder

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behaviour during compression and in assessing tablet properties. The Kitazawa equation is used to analyze the release characteristics of tablet formulations.

Eucalyptus gum is obtained from the incised trunk of the *Eucalyptus tereticornis* tree (*Myrtaceae*). The species, native to Australia, has a wide distribution, occurring over the widest range of latitudes of any Eucalyptus species. The gum is normally secreted honey coloured, but, however, hardens on exposure to air, changing in colour to dark-brown/ black nodules which tear upon aging. Many plant gums have been investigated as binders, among these, for example, okra gum [23], *Delonix regia* seed gum [4] Cissus gum [3], and Cedrela gum [29]. However, the gum extract of the *Eucalyptus tereticornis* tree has not been investigated for its potential binding properties in pharmaceutical tablet formulations. Thus, the compressive, mechanical, and release properties of tablet formulations incorporating the gum obtained from the incised trunk of the *Eucalyptus tereticornis* tree was investigated in this study. Subsequently, the derived formulations were compared with those containing Gelatin BP. Paracetamol, which is poorly compressible, was used as model drug.

MATERIALS AND METHODS

Materials

The materials used were Paracetamol B.P. (BDH Chemicals Ltd, Poole, UK), Corn starch B.P.(BDH Chemicals Ltd, Poole, UK), Lactose B.P. (DVM, Veghel, Holland), Eucalyptus gum from the incised trunk of *Eucalyptus tereticornis* (*Myrtaceae*) (University of Ibadan Botanical Garden), Gelatin B.P. (Hopkins and Williams, Chadwell Health, Essex, UK). All other materials used were of Analar grade.

METHODS

Extraction of the gum

The *Eucalyptus tereticornis* tree source was incised, and the exudates were allowed to harden. After this, it was collected and dried in an oven at 50°C for about 10 hours. The gum was then pulverized after drying with an Osterizer blender (Model 857, Willamette Industries, Bowling Green, Kentucky, USA) to produce a powdered form of the gum. The powder gum was subsequently hydrated in double strength chloroform water for 5 days, while stirred intermittently. The mucilage obtained was strained through a clean piece of calico cloth to remove extraneous materials and undissolved gum. The pure gum was then precipitated from the solution with 96% ethanol. Following this, the precipitated gum was filtered and washed with diethyl ether and dried in a hot air oven at 50°C.

Preparation of Powder formulations

The basic formulation of paracetamol was made thus:

Paracetamol	70% w/w
Lactose	20% w/w
Corn starch	10% w/w.

The ingredients were dry mixed in a Kenwood planetary mixer for 5 minutes.

Preparation of granules

Batches (100g) of the basic formulation were moistened with distilled water or an appropriate volume of binding solutions to produce granules containing different concentrations of either Eucalyptus gum or gelatin as binders. Massing was continued for 5 minutes, and the wet masses were granulated by passing them manually through a mesh 12 sieve (1400 μm), then dried in a hot air oven for about 4 hours at 50°C. The dried granules were subsequently sieved through a mesh 16 sieve (1000 μm) and then stored in airtight containers.

Table 1. Formulation components and binder concentration

Formulation	Components	Binder/concentration
PO	Basic formulation	water
PG 1	Basic formulation + Binder	Gelatin 1.0%
PG 2	Basic formulation + Binder	Gelatin 2.0%
PG 3	Basic formulation + Binder	Gelatin 3.0%
PG 4	Basic formulation + Binder	Gelatin 4.0%
PE 1	Basic formulation + Binder	Eucalyptus gum 1.0%
PE 2	Basic formulation + Binder	Eucalyptus gum 2.0%
PE 3	Basic formulation + Binder	Eucalyptus gum 3.0%
PE 4	Basic formulation + Binder	Eucalyptus gum 4.0%

Density Measurements

Determination of particle density

Particle density of samples was determined by the pycnometer method, with xylene (a non-solvent) as the displacement fluid.

Determination of Loose bulk density (LBD)

The bulk density of each sample at zero pressure (loose density) ρ_o was ascertained by pouring a known weight of the sample at an angle of 45° through a funnel, into a glass cylinder with a diameter of 24 mm and a volume of 50 mL. Determination was made in triplicate. Bulk density values were generated by using the following equation:

$$LBD = w/\pi r^2 h \quad (1)$$

where:
w = weight of sample in the cylinder (g)
r = radius of the cylinder (cm)
h = height of the sample in the cylinder (cm)

Determination of relative density of tablets

The weights and dimensions of the tablets were accurately determined to within ±1.00 mg and ±0.01 mm, using an electronic balance and a micrometer screw gauge, respectively. The relative densities of the tablets, D, were calculated using the equation below:

$$D = w/\pi r^2 h\rho_t \quad (2)$$

where:
w = weight of the tablet (mg)
r = radius of the tablet (m)
h = thickness of tablet (m)
ρ_t = particle density

Compression properties

The Heckel equation is widely used to determine the relative density, D, of a powder bed during compression [1,9]. Heckel plots of ln [1/1 – D] against the applied pressure (P) (MN^{-2}) were constructed for the different formulations. Values of K and A were obtained from the slope and intercept, respectively. The yield pressure P_y, is the reciprocal of the slope. The equation is written as follows:

$$Ln[1/(1-D)] = KP + A \quad (3)$$

The slope of the straight line plot, K is the reciprocal of the mean yield pressure, P_y of the material. The relative density, D, can be obtained from the intercept, A:

$$D_a = 1\text{-}e^{-A} \quad (4)$$

The relative density of the material when the pressure is zero is D_o, which is the initial rearrangement of densification due to die filling. The relative density, $D_{b,}$ is the phase rearrangement at low pressure, and it is the difference between D_a and D_o:

$$D_b = D_a - D_o \quad (5)$$

The Kawakita [24] equation had been used to evaluate powder compression using the degree of volume reduction, C [1,5]. The equation describes the relationship between the volume reduction of the powder column and the applied pressure:

$$C = (V_o - V/V_o) = (abP/1 + bP) \quad (6)$$

In practice, the equation can re-arranged thus:

$$P/C = P/a + 1/ab \quad (7)$$

Where Vo is the initial bulk density of powder, Vp is the bulk density after compression. Constant a is the minimum porosity of the material before compression, and b gives the pressure term Pk, which is the pressure required to reduce the powder bed by 50% [7,24].

Friability

The friability of the tablets was determined using a friabilator (Erweka Apparatebau GMBH Germany) in which 10 tablets were weighed and subjected to a controlled series of falling and rotation for 4 minutes at 25 revolutions per minutes. The tablets were then cleaned to remove dust and fragments, and were weighed again. The percentage loss then was calculated and recorded.

$$\% \text{ Friability} = X/X_0 \times 100$$

X = Weight of dust and particles from tablets, $X = X_1 - X_0$
X_o = Initial weight of tablets
X_1 = Weight of tablets after rotation.

Crushing strength of tablets

The crushing strength of tablets was determined at room temperature by diametrical compression [10,15], using a tablet hardness tester (DBK INSTRUMENT, MUMBAI-400060, Model:EH01). The tablet was placed between the platen of the tester, and the adjustable knob was screwed until contact was made with the tablet. Enough pressure was subsequently applied to cause tablet breakage. The crushing strength was read on the tester. Results were taken only from tablets which split cleanly into two halves without any sign of lamination. All measurements were made in quadruplicate.

Disintegration time

The disintegration times of the tablets were determined individually at 37.0 ± 0.5°C, using a disintegrating tester (Model MK4, Manesty Machines, England). The tablets were placed on the wire mesh just above the surface of the water in the tube, and the apparatus was started simultaneously with a stop clock. The tablets were kept in contact with the distilled water contained in the tube. The time taken for all the tablets to disintegrate and go through the wire mesh was recorded.

Dissolution rate

The dissolution rates were determined at a temperature of 37 ± 0.5°C, in 0.1M hydrochloric acid. Stirring was at a rate of 50 revolutions per minute, using a Spafil dissolution rate tester (Transicon Engeen PVT Ltd, Singapore). Samples (5 mL) of the dissolution medium were removed every 5 minutes and replaced with an equal volume of 0.1M HCL at the same temperature. The absorbance of the removed samples was measured, and the total concentration of drug in each sample was determined using a UV-VIS spectrophotometer (Unicam 8620, Unicam Ltd,U.K).

Dissolution rate constant

The plot of Kitazawa et al. [25] was used to determine the dissolution rate constant. Using the integrated form of the Noyes and Whitney [27] equation, values of $\ln\{C_s/(C_s\text{-}C_t)\}$ were plotted against time (t). From the plots, two straight lines of slope k_1 and k_2 were obtained. The time at which the lines intersect (t_1) was determined.

Statistical analysis

Paired t-test and A One-way ANOVA with Dunnett's post test was performed using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

RESULTS

The values of the mean granule size ($\overline{G}$), loose bulk density (ρ) and relative density (D_o) for the paracetamol formulations, are presented in Table 2. The parameters obtained from the density measurements, and the Heckel, Kawakita and Gurnham plots at relative density of 0.9, are given in Table 3. Values of Crushing Strength, Friability, Crushing Strength-Friability Ratio (CSFR), Disintegration time (D_t) and CSFR/D_t for paracetamol tablets at relative density 0.90, are presented in Table 4.

Heckel, Kawakita and Gurnham plots for paracetamol tablet formulation containing Gelatin and Eucalyptus gum

Table 2. The values of mean granule size, loose bulk density (ρ) and relative density (do) for paracetamol formulations

Sample code	Mean granule size ($\overline{G}$) (μm)	Loose bulk density(ρ_o) (gcm^{-3})	Particle density (ρ_t) (gcm^{-3})	Relative density (P_o/ρ_t)
P – 0	370	0.370	0.689	0.415
PG – 1	455	0.400	0.688	0.581
PG – 2	500	0.435	0.686	0.634
PG – 3	630	0.440	0.685	0.642
PG – 4	710	0.488	0.670	0.728
PE – 1	480	0.435	0.680	0.640
PE – 2	498	0.444	0.676	0.659
PE – 3	600	0.453	0.665	0.681
PE – 4	700	0.480	0.663	0.724

Table 3. Parameters obtained from Density Measurements, Heckel, Kawakita and Gurnham Plots

Formulation	Concentration (%w/w)	D_o (gcm^{-3})	D_a (gcm^{-3})	D_b (gcm^{-3})	D_i (gcm^{-3})	P_y (MN/m^2)	P_k (MN/m^2)	c
	0.0	0.415	0.563	0.148	0.333	411.5	0.336	0.861
Gelatin	1.0	0.581	0.700	0.119	2.932	424.1	0.369	0.927
	2.0	0.634	0.734	0.100	2.475	625.0	0.427	0.957
	3.5	0.642	0.700	0.058	2.463	800.0	0.391	0.997
	4.0	0.728	0.758	0.030	1.645	1240.0	0.392	0.992
Eucalyptus gum	1.0	0.640	0.653	0.013	2.551	1360.0	0.347	0.933
	2.0	0.659	0.675	0.016	2.564	860.0	0.354	0.934
	3.5	0.681	0.685	0.004	2.551	819.0	0.337	0.965
	4.0	0.724	0.754	0.030	2.487	415.0	0.395	1.001

Table 4. Values of Crushing Strength, Friability, Crushing Strength-Friability Ratio (CSFR), Disintegration time (Dt) and CSFR/Dt for Paracetamol tablets at Relative Density 0.90

	Binder conc. (%w/w)	Crushing strength	Friability (%)	CSFR	Disintegration time (min)	CSFR/Dt
	0.00	7.07±0.43	4.9±0.33	1.44	3.40±1.32	0.424
Gelatin	1.00	14.70±1.21	2.56±0.97	5.74	6.78±1.76	0.847
	2.00	15.09±1.34	1.09±0.21	13.84	12.30±2.26	1.125
	3.00	16.46±2.11	0.85±0.11	19.36	12.60±1.89	1.537
	4.00	16.27±1.75	0.53±0.45	30.69	22.80±2.39	1.346
Eucalyptus	1.00	9.41±0.37	4.06±1.12	2.32	1.37±1.32	1.693
	2.00	12.64±1.98	2.32±0.34	5.45	2.30±1.87	2.370
	3.00	13.13±0.45	2.10±1.01	6.25	3.40±1.15	1.838
	4.00	14.60±1.15	1.55±0.23	12.69	5.80±1.22	2.188

as binders are presented in Figures 1, 2 and 3, respectively, while parameters obtained from the plots are presented in Table 3. Figure 4 presents the dissolution profile of the tablet formulations incorporating the binders, while the dissolution characteristics of paracetamol tablets at different relative densities are shown in Table 5. A representative plot from the Kitazawa equation is presented in Figure 5.

Table 5. Dissolution characteristics of Paracetamol tablets containing no binder, 3.0% w/w gelatin and Eucalyptus gum at different relative densities

Sample code	Relative density	$t_{50\%}$(min)	$t_{90\%}$ (min)	t_1(min)	k_1	k_2
P - 0	0.76	5.81	18.63	2.07	0.165	0.295
	0.79	7.27	19.15	1.77	0.127	0.132
	0.81	8.74	22.55	1.85	0.120	0.220
	0.84	10.75	25.15	3.12	0.094	0.203
	0.87	12.89	28.21	8.96	0.126	0.780
PG - 3.0	0.79	9.56	19.46	5.38	0.200	0.989
	0.83	11.45	21.12	5.96	0.510	0.737
	0.84	13.05	23.69	6.09	0.145	0.785
	0.85	15.85	27.47	8.29	0.120	0.853
	0.90	19.07	33.83	8.75	0.089	0.662
PE - 3.0	0.79	8.78	24.68	2.5	0.120	0.285
	0.82	10.10	22.72	3.27	0.120	0.359
	0.86	12.29	24.44	3.5	0.110	0.354
	0.88	16.43	28.84	5.21	0.072	0.346
	0.91	18.38	32.13	7.89	0.090	0.600

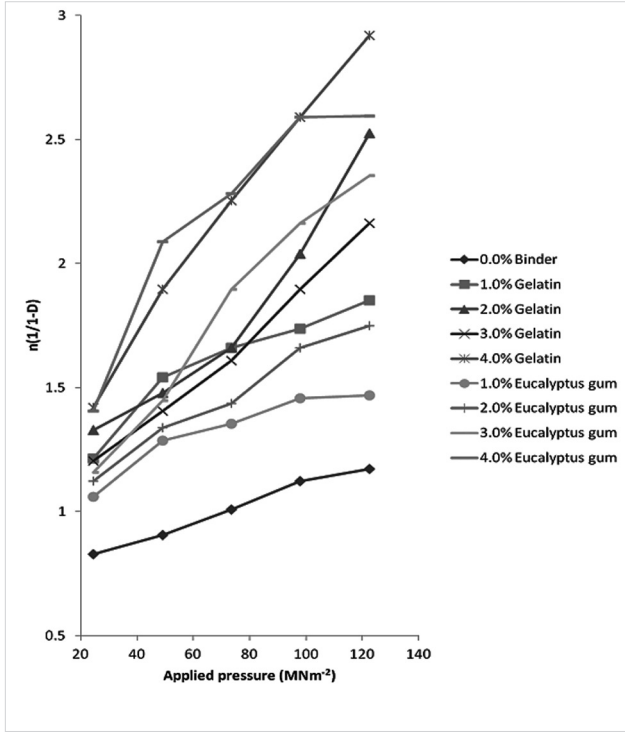

Figure 1. Heckel Plots for paracetamol tablet formulations incorporating gelatin and Eucalyptus gum as binders

DISCUSSION

Values of mean granule size ($\overline{G}$) were obtained from the plots of cumulative weight percentage oversize versus granule size, and were presented in Table 3. An increase in $\overline{G}$, with increase in binder concentration, was observed for all formulations. This agrees with the works of Luangtana-Ana and Fell [26], as well as Ayorinde and Itiola [10]. The nature of binder was also seen to affect the granule size, as formulations containing gelatin produced larger granules than those

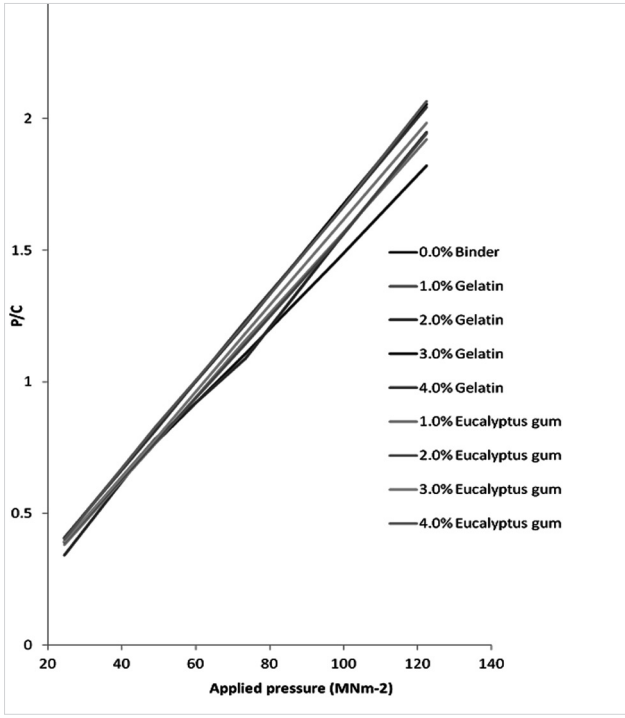

Figure 2. Kawakita Plots for paracetamol tablet formulations incorporation Gelatin or Eucalyptus gum as binders, at different concentrations

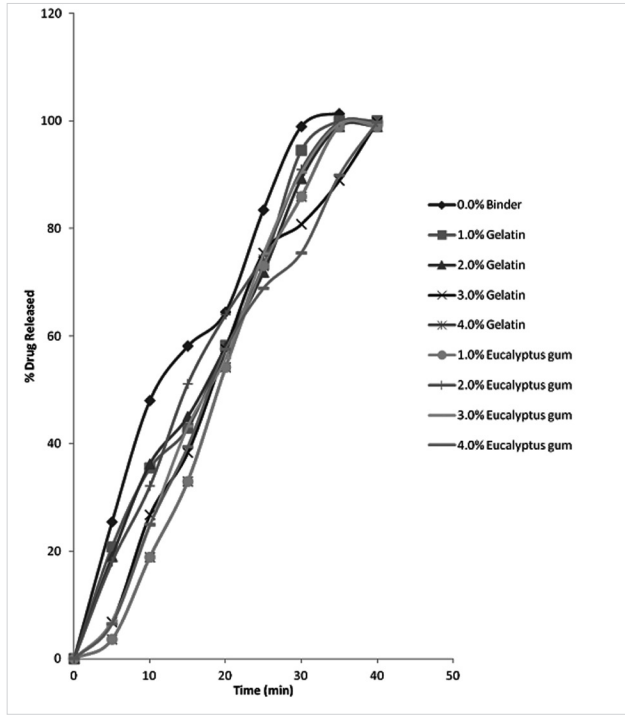

Figure 4. Plots of percentage drug release versus time, for paracetamol tablet formulations incorporating gelatin or Eucalyptus gum as binders

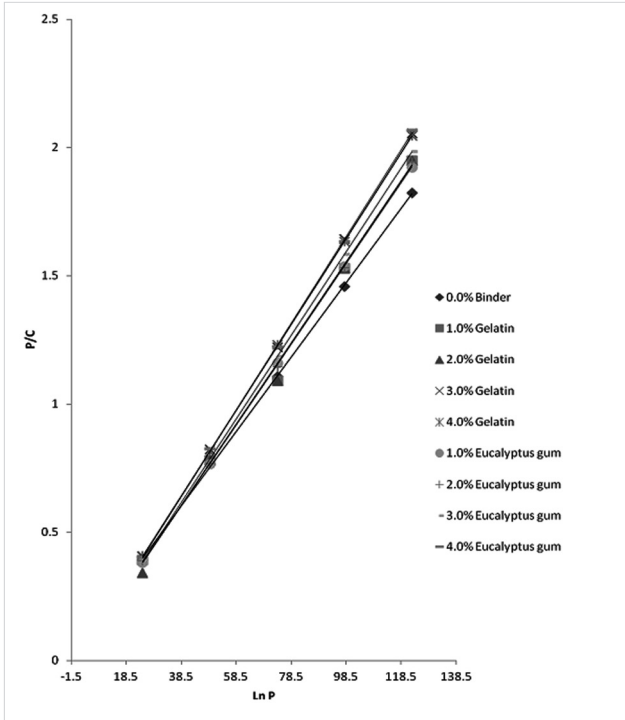

Figure 3. Gurnham plots for paracetamol tablet formulations incorporating gelatin or Eucalyptus gum as binders, at different concentration

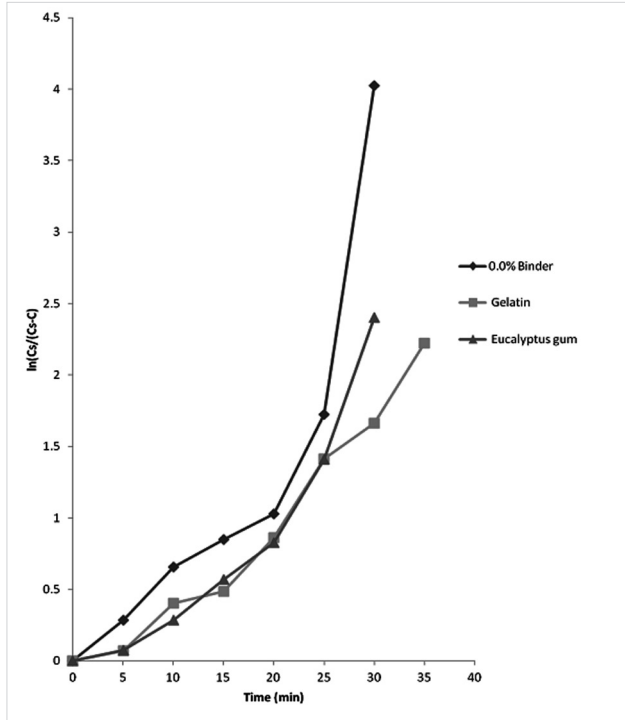

Figure 5. Representative Kitazawa plots for paracetamol formulations containing 3.0%w/w binder

of Eucalyptus gum. This might be due to the differences in the mechanisms and rate by which the materials take up water. The mean granule size ($\bar{G}$) is of importance in tablet formulation; granule size distribution usually affects the flowability, compression characteristics, and tablet properties (such as weight variation and mechanical strength) [20]. It could also provide useful information in binder selection, as well as in choosing the optimum concentration of binder to be employed in pharmaceutical preparations.

Generally, an increase in concentration of Eucalyptus gum and gelatin resulted in granules with lower bulk densities. A similar result was reported by Upradashta et al. [31] for chlorpheniramine maleate granules prepared with various concentrations of chitosan as binder. This effect presumably

resulted from the larger voids associated with larger size of granules. Our work found that the bulk density was generally lower for granule fractions containing a binder, when compared with granules containing no binder. Of note, the percentage of fines in granules prepared with Eucalyptus gum was less than that of granules prepared with gelatin. This is attributable to an absence of a binder bridge and/or interparticulate interaction between materials and binder, which resulted in high bulk density. The particle density values are shown in Table 3. This effect decreased with increase in binder concentration. This is due to the fact that binders are softer than the other powder materials in the basic formulation. In our work, 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 D_o values obtained from the ratio of loose bulk density to the particle density, are, as shown in Table 4, seen to increase as binder concentration increased. This implies that the degree of initial packing in the die, as a result of the die filling, is higher for formulation containing high concentration of binder. Our work reveals that formulations containing Gelatin gum showed higher D_o values relative to those containing Eucalyptus gum. It should be explained that the values of K and A were, respectively, obtained from the slopes and intercepts of the plots of $\ln(1/1 - D)$ against applied pressure. Moreover, the relative densities D_a and D_b were obtained from equations 4 and 5, respectively.

The curve experienced at low compression pressures (initial phase of compression cycle) indicates rearrangement and particle fragmentation [5,29]. As compression progresses, the higher linearity obtained indicates that plastic deformation is taking place [16]. High linearity, with correlation coefficients generally greater than 0.95, were obtained at the second phase of the plots, which generally commenced at the applied pressure of 0.75 metric tonnes. Such high linearity is often experienced with comparatively soft materials that undergo plastic deformation while retaining different degrees of porosity, depending on the initial packing arrangement in the die.

The constant A represents the degree of packing achieved at low pressures as a result of rearrangement processes during die filling, before appreciable amount of interparticulate bonding takes place. This is primarily a function of particle size and shape [7,18]. The low values of A observed in this study indicates that the granules are generally soft and readily compressible. It was also observed that A values decreased ($p > 0.05$) as binder concentration increased, suggesting that the binders further improved the compressibility of the materials.

The total relative pre-compression density, D_b, derived from the values of A (equations 4 and 5), is the total degree of packing, and is obtained from D_o (the degree of packing at zero pressure) and D_b differences. That higher D_a values were observed in formulations containing gelatin showed that they were more readily compressible than those containing the experimental gum. Formulations containing gelatin were also found to exhibit higher values of D_b than those containing Eucalyptus gum, suggesting more fragmentation of its granules.

The mean yield pressure, P_y is an inverse plasticity parameter, and it determines the onset of plastic deformation in materials. The P_y values for the paracetamol tablet formulations were obtained from the slope of the second compression region of the Heckel plots. In our work, the P_y values were observed to decrease with increased concentration of binder. This indicates that formulations with high concentrations of binder deformed plastically at relatively low pressure. However, formulations containing Eucalyptus gum showed lower P_y values than those containing gelatin, suggesting that Eucalyptus gum would induce faster onset of plastic flow. With plastic deformation process being time dependent, [30], the rate of deformation could be more important than the total plastic flow for the production of tablets without capping or lamination problems. The rate of deformation could also be very important for tabletting considerations, bearing in mind that most machines have short dwell or compression time.

Kawakita plots for paracetamol formulations (Figure 2) show a linear relationship at all compression pressures that were employed with a correlation coefficient of 0.999 for all formulations. In our work, values of a and b were obtained from the slope and intercept of the Kawakita plots, respectively. The initial relative density of the formulation, D_i was given by the values of (1-a), while P_k values was obtained from the reciprocal of b values. The D_i and P_k values are presented in Table 5.

The D_i values were observed to increase, with increase in binder concentration. These values were also lower than the values of D_o (Table 5). Bearing in mind that the methods of determination involved have their limitations [19], the differences in the values of D_i and D_o describe the loose initial relative density of the formulation due to die filling, while the D_i values alone, provide a measure of the packed initial relative density of the formulations with the application of small pressure. Formulations containing gelatin exhibited higher values of D_i than those of Eucalyptus gum at all concentrations.

Another inverse plasticity parameter, P_k is obtained from the Kawakita plots. P_k determines the total amount of plasticity of materials. Low values of P_k indicate materials that are soft and that are readily deform plastically under pressure. It was observed from Table 5 that P_k values for the formulations decreased with increased binder concentration, indicating that the binders increased the softness of the formulations and their ability to deform plastically. Our work saw that the values of P_k for formulations containing Eucalyptus gum are lower than those containing Gelatin. The differences in P_k and P_y values for the two binders (Eucalyptus gum and gelatin) could be due to the fact that the P_y values relate essentially to the onset of plastic deformation during compression, while the P_k values appear to relate to the amount of plastic deformation occurring during compression [1,5].

In our study, the plots of ln P against porosity using the Gurnham equation gave a linear relationship at all stages of compression (Fig. 3), and the regression coefficient values for the compression stages were >0.920 for all formulations. As can be seen, the c values obtained for formulations containing Eucalyptus gum and Gelatin were not significantly different, and both increased with binder concentration,

with the experimental gum showing better compressibility. Previous studies have used the Gurnham equation to characterize crystalline pharmaceutical powders [32] and tablet formulations [29]. The latter study observed a limitation in the application of the equation to some plasto-elastic materials at high compression pressures. However, the results obtained from our study showed that the equation can be substituted for the Kawakita equation at all compression pressures used. What is more, it gives a better picture of the compression properties of the formulations.

As can be seen in our work, there was a generally decrease in friability with increase in concentration of binder (Table 4). Of note, the friability values for tablets produced with Eucalyptus gum were generally higher than those containing gelatin. This increase in friability observed in the tablets produced using Eucalyptus gum could be due to a lesser measure of interparticulate bond strength imparted by the gum on the particles of the paracetamol tablets [10]. Of note, a general decrease in friability is also observed with increasing pressure.

Crushing strength is used to determine the physical strength of a tablet. Increasing binder concentration resulted in an increase in the crushing strength of tablets. However, the paracetamol tablets produced with gelatin had a much higher crushing strength than those produced with Eucalyptus gum. This is likely due to the greater measure of interparticulate bond strength imparted by the polymer on the particles of the paracetamol tablet formulations. It was also observed that crushing strength increased with binder concentration. The increase in crushing strength or hardness can also adduced to the fact that the concentration of the binder determines the amount and extent of solid bonding that takes place between the particles.

A parameter for measuring tablet strength is the crushing strength-friability ratio (CSFR) [5]. High CSFR values general indicate strong tablets. The CSFR values for the paracetamol formulations are presented in Table 4. Tablets incorporating gelatin showed higher CSFR values for each binder concentration and an increase in CSFR with amount of binder used. However, there were no significant differences in the values obtained.

The disintegration times of the paracetamol tablets are given in Table 4. The BP 2010, specifies 15 minutes for uncoated tablets. The inability of tablets to disintegrate within this time limit is an indication that the drug may show poor release *in vivo*. Hence, the tablet may not be broken down to facilitate release of content into the system, and this has a direct effect on the dissolution and bioavailability of the drug. All the tablets, except those containing 4% w/w gelatin, passed the disintegration test, and there was a general increase in disintegration time and dissolution times ($t_{50\%}$ and $t_{90\%}$) with increase in relative density and binder concentration. The increase in disintegration time with increase in relative density is similar to the results obtained by other workers [13,31,33].

The presence of a binder in a formulation leads to formulation of solid bonds between particles, and, hence, an increase in disintegration time indicates difficulty in the breaking of those bonds. Ferrari et al. [14], in their studies on bonding and disintegrating properties of pharmaceutical materials, suggested that the disintegrating media employed in the disintegration test are capable of weakening the intermolecular bonds. It was concluded that water promotes the loosening of the structure and a certain degree of pore enlargement. The penetration of liquid into the capillaries of tablets has been shown to be necessary for the process of disintegration and dissolution [6,20]. However, the disintegration of tablets is not only due to capillarity, but can be explained by pore widening, as well as the swelling of the powder bed [11]. The disintegration phenomenon itself, has been the object of extensive investigation. As an outcome of these studies; two principal mechanisms of disintegration have been proposed [17]. One mechanism refers to the swelling of disintegrants. This purportedly results in the development of a swelling force. The other mechanism refers to the annihilation of intermolecular bonds. This supposedly results in the development of a repulsive force. According to research upon both proposed mechanisms, the development of a disintegration force is needed to produce disintegration, while the swelling mechanism has proved to be capable of producing a force [11]. In our work, the results of in vitro dissolution shows that all the tablets released >70% of paracetamol within 30 minutes, and, as such, passed the British Pharmacopoeia standard for dissolution tests for uncoated tablets. From the values obtained in Table 5 for $t_{50\%}$, $t_{90\%}$, t_1, k_1 and k_2 for all samples at different relative densities, it was seen that the values of D_t, $t_{50\%}$, $t_{90\%}$ and t_1 all increased with binder concentration, whereas the values of k_1 and k_2 decreased. It was also observed that the t_1 values were greater than the D_t values. This can probably be ascribed to the greater agitation used in the disintegration test than in the dissolution test. Table 5 shows k_1 to be lower than k_2, implying that the dissolution rate of the drug was faster after t_1. It would appear that changes in the surface area of the dissolving particles brought about by the disintegration and de-aggregation of the tablets were manifested in the substantial increase in dissolution rate after t_1 [24]. As is evident in our results, values of t_1, k_1 and k_2 for formulations containing gelatin were higher than for formulations containing Eucalyptus gum as binder.

CONCLUSIONS

The mean yield pressure (P_y) and the inverse measure of plasticity (P_k), for the paracetamol formulations depended on the nature and concentration of the binding agent employed. Formulations containing Eucalyptus gum were more plastic and compressible than those containing gelatin. Increasing the concentration of binder increased the mechanical properties of tablets. Tablets incorporating the gum disintegrated faster, but the release profiles of paracetamol from formulations containing Eucalyptus gum and gelatin were similar. Thus, Eucalyptus gum could be useful as an alternative binding agent to gelatin in producing pharmaceutical tablets with good mechanical strength and fast drug release.

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