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Assessment of compressional, mechanical and release properties of *Terminalia randii* gum in paracetamol tablet formulation

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ABSTRACT

Paracetamol tablets were formulated with *Terminalia randii* gum as a binder at varying concentrations (1-10%, w/w) and the compressional characteristics was compared with polyvinyl pyrrolidone (PVP). The compressional properties were evaluated using density measurements, Heckel and Kawakita equations. The mechanical properties were evaluated using friability, crushing strength, and crushing strength-friability ratio (CSFR), while the release properties were studied using disintegration time, dissolution time and Kitazawa equations. Formulations containing *Terminalia* gum showed faster onset of plastic deformation with a lower total amount of plastic deformation. The crushing strength and release properties of the formulations increased, while friability decreased, with increase in binder concentration. Formulations containing PVP had better mechanical properties as seen in the high CSFR values. Formulations produced with *Terminalia* gum produced tablets with slower dissolution. This study shows that the onset of plastic deformation was faster, but the total amount of plastic deformation was lower in formulations containing *Terminalia* gum.

Keywords: *Terminalia randii* gum, compressional characteristics, Heckel equation, Kawakita equation

INTRODUCTION

A powdered drug or active pharmaceutical ingredient cannot be made into a tablet without the use of excipients such as binders, diluents, disintegrants, gli-

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dants and lubricants. Binders are known to promote bonding between the particles of a powder and other excipients in the powder mixture, hence improving the mechanical properties of the tablet [1,2]. Binders can be classified as natural or synthetic/semisynthetic polymers. Some natural polymers that have been used as binders are *Cedrela odorata* [2], *Eucalyptus tereticornis* [3], *Albizia zygia* [4], while xanthan gum [5], and hydroxyl methyl cellulose [6] are synthetic/semisynthetic polymers used as binders. Compressibility and compactibility of binders are some of the physicochemical properties which bear direct relationship to the tableting performance of a particulate solid [7]. Decrease in volume of a powder under pressure is known as compressibility, while the compression of a powdered material into a tablet of specified strength is known as compactibility and this influences bioavailability. Various mathematical equations such as Heckel, Kawakita, Leuenberger and Gurnham equations have been used in studying the compression and compaction of powders and tablets [7-10]. In Heckel's equation, the applied pressure is related to the relative density of powder during compression, the Kawakita's equation relates degree of volume reduction of powders to applied pressure during compression and Leuenberger's equation relates deformation hardness of powders during compression to applied pressure.

Terminalia gum is exudate obtained by cutting the trunk of *Terminalia randii*. This gum has been characterised and assessed as a binder, disintegrant, and in oral film formulation [11-13]. However, when *Terminalia* was characterised, the compressional characteristics was not evaluated. Hence, in this study, the compressional characteristics and release properties of *Terminalia* gum as a binder in paracetamol tablet formulation in comparison with PVP was evaluated.

METHODOLOGY

Materials

The materials used were paracetamol powder BP, corn starch (S.D Fine chemicals Ltd, Mumbai, India) polyvinylpyrrolidone USP K29/32 (molecular weight: 58,000) (ISP Technologies, Inc Wayne, USA), lactose monohydrate (Ind-Swift Labs Ltd, Parwanoo, India), magnesium stearate (Loba Chemie Pvt Ltd, Mumbai, India), Talc ((Loba Chemie Pvt Ltd, Mumbai, India), *Terminalia* plant was collected from Olabisi Onabanjo University Ago-Iwoye and authenticated at the Forest Research Institute of Nigeria, Ibadan with a Voucher number FHL NO 107917.

Collection and extraction of terminalia gum

Terminalia gum was obtained from the incised trunk of *Terminalia randii (Family Combretaceae)*. The trunk of the tree was incised, and the gum exu-

date was allowed to dry and then hand-picked from the trees. The dried gum was washed and dried in hot air oven at 40 ºC and then crushed with a pestle and mortar to break up the gum. The gum was hydrated in double strength chloroform water for 5 days while stirring intermittently. The mucilage obtained was strained through a clean calico cloth and the gum obtained was precipitated with 95%, v/v ethanol. The precipitated gum was filtered, washed with diethyl-ether, and then dried in hot air oven. The dried gum was pulverized and passed through a number 60 mesh sieve (250 μm) [11].

Preparation of granules

A 250 g quantity of basic formulation containing paracetamol (60%, w/w), lactose (30%, w/w) and corn starch (10%, w/w), was dry mixed for 5 minutes in a planetary mixer (Model A120, Hobart Manufacturing Co, U.K) and moistened with water or appropriate amount of aqueous solution of PVP or mucilage of *Terminalia* gum (1-10%, w/w) to produce granules containing different concentrations of the binders. Massing was continued for 5 minutes, 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 16 hours at 60 ºC and then resieved through a number 16 mesh sieve (1000 μm) and then stored in air tight container.

Granule size distribution

The size distribution of the granules was determined by sieve analysis method (British standard 1460). A stack of sieves of the following sizes: 16 mesh (1000 μm), 22 mesh (710 μm), 30 mesh (500 μm), 44 mesh (355 μm), 60 mesh (250 μm), mesh (150 μm) and the receiver were arranged in descending order of aperture size with the receiver at the bottom. 200 g quantity of granules was placed on the uppermost sieve, the cover was firmly placed, and the stack of sieves was shaken for 10 minutes using a mechanical shaker. The quantity of granules retained on each sieve was carefully weighed; the cumulative percentage oversize was calculated and the mean granule size which corresponds to the sieve size (μm) at 50% cumulative weight percentage oversize was calculated. The granules of size 500 - 1000 μm were collected and stored in an air tight container.

Determination of particle density

The particle density of granules was determined by the liquid pycnometer method using xylene as the displacement fluid. An empty 50 mL pycnometer bottle was weighed (w), then filled to the brim overflowing with xylene and the excess wiped off. The bottle with the xylene was weighed again (w_1). A 2 g

weight of the sample was weighed (w_3) and quantitatively transferred into the pycnometer bottle. The excess xylene was wiped off and the bottle weighed again (w_4). The particle density was calculated from the equation [5].

$$P_t = \frac{W_2 W_3}{50(W_3 - W_4 + W_2 + W)} \quad (1)$$

Determination of bulk (loose) density

The bulk density [3] was determined by weighing 30 g (W) of terminalia gum into a 50 mL measuring cylinder of internal diameter 21 mm. The height, h (cm) of the powder bed and internal radius, r (cm) of the measuring cylinder were used to compute the loose bulk volume, $V_{O.}$

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

The value obtained was used to calculate the loose bulk density

$$P_o = \frac{W}{V_o} \quad (3)$$

Preparation of Tablets

500 mg of granules was compressed with predetermined load at a dwell time of 30 seconds on a Carver hydraulic press (Model C, Carver Inc. Wisconsin, USA), using a 10.5 mm die and flat faced punches lubricated with a 1% dispersion of magnesium stearate in acetone prior to compression. After ejection, the tablets were stored over silica gel for 24 hours to allow for elastic recovery and hardening. The weights (w) and dimensions of the tablets were measured to within ± 1 mg and ± 0.01 mm respectively, and their relative density D was calculated using the equation [2]:

$$D = \frac{W}{V_{tPs}} \quad (4)$$

Where is the volume, cm^3, of the tablet and , is the particle density, gcm^{-3}, of the granules.

Compression Properties

The Heckel and Kawakita equations were used to determine the compressional characteristics [3, 14]. The Heckel equation relates the relative density of a powder bed D to the compressional pressure P. The equation is written as:

$$In \frac{1}{1-D} = KP + A \ldots\ldots \quad (5)$$

A plot of against pressure P was constructed to obtain a linear graph with slope K, which is the reciprocal of the mean yield pressure P_y, of the material and intercept A, which is used to calculate the relative density D_A using the equation:

$$D_A = 1 - e^{-A} \quad \text{.....} \quad (6)$$

The relative density of powder bed when applied pressure is zero D_O, is the initial rearrangement phase of densification as a result of the die filling. The relative density of powder at low pressure, D_B, describes the phase of rearrangement of particles during initial stages of compression and it is the difference between D_A and D_O:

$$D_B = D_A - D_o \quad \text{.....} \quad (7)$$

The Kawakita equation [15] was used to evaluate powder compression using the degree of volume reduction C and applied pressure. The equation is expressed as:

$$C = \frac{V_o - V_p}{V_o} = \frac{abP}{1 + bp} \quad \text{.....} \quad (8)$$

The equation is simplified to give:

$$\frac{p}{c} = \frac{p}{a} + \frac{1}{ab} \quad \text{.....} \quad (9)$$

V_O is the initial volume of powder bed before compression; V_p is the volume after compression. The constant a is the minimum porosity before compression, while reciprocal of constant b, gives a pressure term P_K, which is the pressure required to reduce the powder bed by 50% [16-18].

Determination of mechanical properties

The friability test was carried out on a friabilitor (MAC, Macro Scientific Works, New Delhi India). Ten tablets were selected at random, weighed together using an electronic balance and then placed in the friabilitor. The machine was operated at 25 revolutions per minute for 4 minutes. The tablets were dusted and reweighed and the percentage loss was calculated. Determinations were done in triplicate.

The crushing strength of the tablets was determined using a Monsanto hardness tester (MAC, Macro Scientific Works, New Delhi, India). Tablet was placed between spindle and anvil of the tester and the calibrated length adjusted to zero. The knob was then screwed to apply a diametric compression force on the

tablet and the position on the calibrated length at which the tablet broke into two halves was recorded. Six tablets were used for each batch and the results are given as the mean and SD.

Determination of release properties

The disintegration test was carried out in 900 mL of distilled water at 37 ºC ± 0.5 ºC using a Mac disintegration test apparatus (Macro Scientific Works, New Delhi, India) (USP/NF2007). Six tablets from each batch were placed in the cylindrical tubes of the basket. The time taken for the tablets to break up into particles and pass through the mesh was recorded and the mean disintegration time was calculated.

Calibration Plot

Stock solution of pure paracetamol was prepared and scanned on a UV spectrophotometer (Genesys 6, Thermospectronic, USA) at a wavelength range of 200 - 400 nm. The wavelength of 243 nm was obtained for maximum absorbance. Different concentrations of the paracetamol solution were prepared from the stock solution by dilution and their absorbance taken. A plot of absorbance against concentration was plotted to obtain the calibration plot that was used in calculating the concentration of paracetamol released from each formulation.

Dissolution test

The *in vitro* dissolution test was carried out in 900 mL 0.1 M HCL maintained at a constant temperature of 37 °C ± 0.5 °C using a USP Type 2 dissolution apparatus (Labindia Dissolution test apparatus DISSO 2000) rotated at 50 rpm. The pre-weighed tablet was then introduced into the dissolution medium and at different time intervals; 5 mL sample was withdrawn and replaced with 5 mL of fresh medium. The samples were analyzed using a UV spectrophotometer (Genesys 6, Thermospectronic, USA) at a wavelength of 243 nm. All determinations were made in triplicate.

Dissolution rate constant

The plot of Kitazawa *et al.* [19] was used to determine the dissolution rate constant. Employing Noyes and Whitney equation, the values of was plotted against time (t) [20]. Two straight lines of slope k_1 and k_2 were obtained from the plot and the time (t_1) at which the lines intercept was determined.

Statistical analysis

Statistical analysis was carried out using analysis of variance with computer software GraphPad Prism® 4 (GraphPad Software Inc. San Diego, USA).

RESULTS AND DISCUSSION

Compression properties

Increase in binder concentration caused an increase in mean granule size (Table 1). This was in agreement with the work of other researchers [3, 21]. This could be due to increase in bond strength between particles as there would be more binder due to increment in concentration [22]. The type of binding agent also affected the granule size. The granule size of formulations comprising *Terminalia* gum were significantly ($p<0.001$) lower than those comprising PVP. Granule size is important in tableting as it is known to affect flow rate, which may invariably affect tablet weight uniformity. Increase in binder concentration caused a decrease in particle density, while there was increase in relative and loose bulk densities. Granule density has been shown to influence the compression properties of the granules [23]. High compressive loads are required for dense hard granules to produce a strong compact which are less friable. The relative density of the powder bed at the point when the pressure applied is zero (D_0) depicts the initial rearrangement phase of densification after die filling. Increasing binder concentration caused a significant ($p<0.0001$) increase in D_0 values as shown in Table 1. This is an indication that the initial packing due to die filling increased with increment in binder. Formulations containing *Terminalia* gum exhibited significantly lower ($p<0.001$) extent of packing in the die due to die filling than formulations comprising PVP.

The relative density of the tablets at various applied pressures was used for the Heckel plot by plotting Ln (1/1-D) against applied pressure. A representative Heckel plot at 5%, w/w binder concentration is shown in figure 1. Each plot shows two compression phases, with the second phase starting at 42.42 MNm^{-2} up to 169.68 MNm^{-2}, and the formulations having high correlation coefficient for linearity of >0.985. The values for mean yield pressure, P_y, relative densities D_A and D_B, and relative density due to die filling, D_O, for formulations are presented in Table 2. There was decrease in the value of P_y as the binder concentration increased. Low value of P_y, is an indication of fast onset of plastic deformation [8, 24]. Formulations comprising *Terminalia* gum generally exhibited lower P_y values indicating the beginning plastic deformation at a fast rate when compared with formulations comprising PVP. The relative density D_B, which depicts the rearrangement phase of particles at the beginning of compression, increased with increasing binder concentration. These values were observed to be greater than the values of D_o probably due to breaking up of granules at low pressures thereby filling up void spaces between particles [25]. The values of D_B were generally higher for PVP formulations than for *Terminalia* gum

formulations. This implies that there were more fragmentation and rearrangement of PVP formulation granules than *Terminalia* granules at low pressures. Increasing binder concentration increased the values of $D_{A.}$ Lower D_A values were observed in formulations containing *Terminalia* gum in comparison to those formulations containing PVP. The higher the values of $D_{A,}$ the higher the extent of packing at zero and low pressures.

Table 1. Values of mean granule size, and densities of the formulation

Binder type	Binder Concentration (%w/w)	Mean granule size (µm)	Particle density (gcm^{-3})	Loose bulk density (gcm^{-3})	Relative density D_0 (gcm^{-3})
	0.00	115.00±5.00	1.532±0.033	0.405±0.006	0.264±0.008
PVP	1.00	300.00±2.65	1.450±0.100	0.454±0.017	0.313±0.003
	2.00	350.00±3.00	1.441±0.004	0.462±0.004	0.321±0.003
	3.00	670.00±1.00	1.428±0.013	0.469±0.006	0.328±0.002
	5.00	700.33±2.52	1.419±0.002	0.475±0.011	0.335±0.005
	10.00	739.67±1.53	1.396±0.006	0.477±0.018	0.342±0.007
Terminalia	1.00	112.00±2.00	1.498±0.021	0.411±0.018	0.274±0.005
	2.00	140.00±1.00	1.444±0.032	0.417±0.007	0.289±0.001
	3.00	359.67±3.79	1.432±0.120	0.424±0.007	0.296±0.003
	5.00	460.00±2.65	1.430±0.080	0.425±0.017	0.297±0.003
	10.00	605.33±2.08	1.397±0.075	0.434±0.014	0.311±0.014

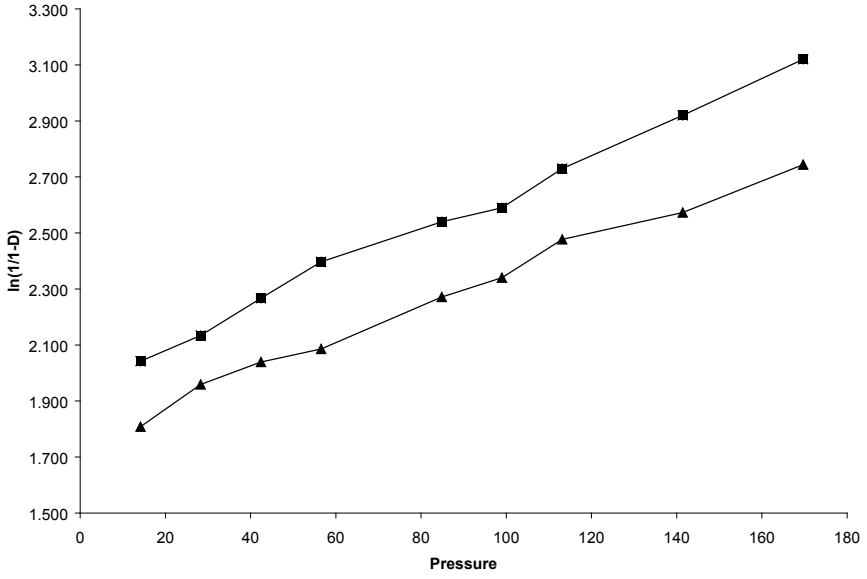

Figure 1. Heckel plots for paracetamol tablets containing 5% w/w binders terminalia gum ▲, PVP ■

A representative Kawakita plot of the formulations at 5%, w/w binder concentration is shown in figure 2. A correlation coefficient > 0.999 was obtained for all formulations at all compressional pressures. The slope and intercept gave values of a, and ab respectively. The initial relative density D_i, was obtained as 1 – a, from the values of a. From the reciprocal of b values, P_K values were obtained. The values of D_i and P_K are presented in Table 2. The values D_i reduced generally with increase in binder content for the formulations and it is generally greater than the values of D_o. The difference in values of D_o and D_i could be due largely to the fact that D_o depicts the loose initial relative density of the formulations due to die filling, D_i depicts the initial packed relative density of the formulations with the application of small pressure or tapping of the formulations [4].

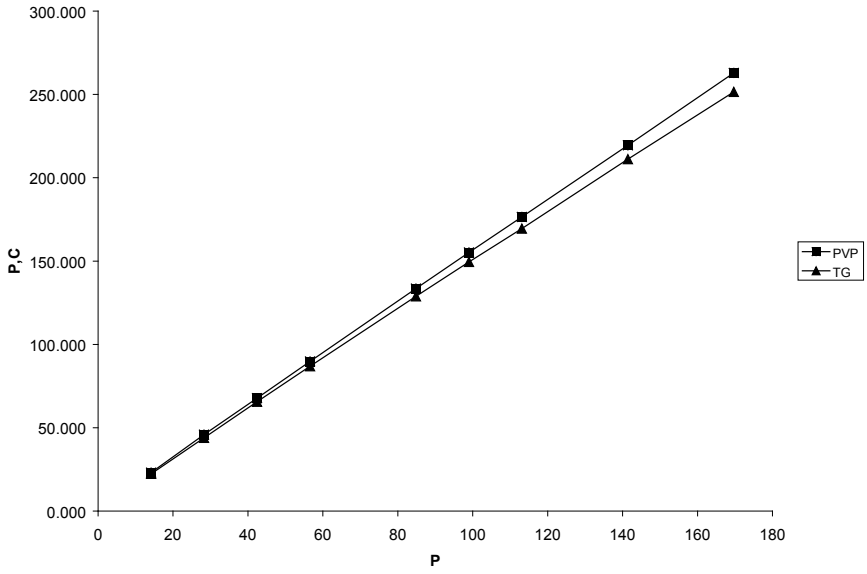

Figure 2. Kawakita plots for paracetamol tablets containing 5% w/w binder

Table 2. Parameters obtained from Heckel and Kawakita plots

Binder type	Binder concentration (%w/w)	P_Y	D_A	D_B	D_i (1-a)	P_K
	0.00	204.08	0.768	0.504	0.529	5.643
PVP	1.00	208.33	0.832	0.519	0.504	3.712
	2.00	196.08	0.846	0.525	0.465	2.999
	3.00	188.68	0.854	0.526	0.436	2.140
	5.00	151.52	0.863	0.528	0.372	1.681
	10.00	151.52	0.871	0.529	0.346	1.553
Terminalia	1.00	217.39	0.778	0.504	0.485	3.772
	2.00	181.82	0.806	0.517	0.386	2.480
	3.00	178.57	0.827	0.531	0.362	2.113
	5.00	175.44	0.833	0.536	0.321	1.912
	10.00	147.06	0.824	0.513	0.315	1.882

Low P_K values are an indication of materials that are soft and easily deform plastically under pressure. The reduction in P_K values with increase in binder content is an indication that increment in binder concentration leads to softness and capability of formulations to deform plastically under pressure. P_K values of formulations comprising PVP were generally lesser than those of formulations comprising *Terminalia* gum. This indicates that formulations containing PVP are softer than those containing *Terminalia* gum and they would readily undergo plastic deformation.

Mechanical properties of tablets

The crushing strength and friability of the tablets were evaluated and their values at 0.9 relative densities which represent those of commercial tablets are presented in Table 3. Crushing strength (CS) is an estimate of tablet strength while friability (FR) is an estimate of tablet weakness [26]. The crushing strength increased significantly ($p<0.0001$) with increment in relative density of the paracetamol formulations and binder concentrations. This may be due to a reduction in porosity resulting in an increment in the number of points in contact thus leading to an increment in the formation of solid interparticle bonds [22, 27] and also during compression, the heat produced caused melting of binding agents which solidifies on cooling to form strong bonds between the particles. The crushing strength of formulations containing *Terminalia* gum was significantly low ($p<0.001$) at low concentrations (1-3%, w/w), but at higher concentrations (5% - 10%, w/w), there was no significant difference ($p>0.05$) in the crushing strength. At 5% - 10%, w/w concentrations it was observed that the friability of paracetamol formulations containing *Terminalia* binder was significantly higher ($p<0.01$) than that of formulations containing PVP. This shows that having a high crushing strength does not necessarily mean that a tablet would be strong enough for transportation and handling by patients. This was also confirmed by the low crushing strength-friability ratio (CSFR) that was obtained for formulations containing *Terminalia* binder. CSFR is a parameter that is also used in measuring the mechanical strength of tablets. High CSFR value is an indication of strong tablets since it harmonizes the tablet weakness and strength [28].,

Table 3. Mechanical properties of Paracetamol tablets at relative density 0.9 gcm^{-3}

Binder type	Binder Concentration (%w/w)	Crushing strength (N)	Friability (%)	CSFR
	0.00	54.88±4.14	3.5±0.08	15.68
PVP	1.00	102.10±2.67	0.84±0.00	121.55
	2.00	109.40±5.42	0.80±0.00	136.75
	3.00	111.50±1.52	0.72±0.02	154.86
	5.00	115.70±1.34	0.56±0.00	206.61
	10.00	119.50±2.62	0.51±0.00	234.31
Terminalia	1.00	74.40±1.61	1.55±0.02	48.00
	2.00	85.20±1.12	1.10±0.00	77.45
	3.00	102.00±3.98	0.84±0.01	121.43
	5.00	117.60±2.44	0.73±0.00	161.10
	10.00	120.50±1.52	0.72±0.00	167.36

Release properties of tablets

Disintegration time of the tablets increased ($p<0.0001$) with increment in binderconcentration (Table 4). This increase could have been due to formation of solid bonds formed by binders during compression [3]. The relative density of the tablets was directly proportional to the dsintegration of the tablets, and this was in agreement with the work of other researchers [3, 29, 30]. It was observed that the disintegration of paracetamol formulations containing *Terminalia* gum binder, which incidentally gave lower CSFR values were higher than that of formulations containing PVP. The disintegration time of the tablet is influenced by the ease of fluid penetration into the tablet. This may be due to the swelling of *Terminalia* gum on contact with water, thus forming a gelatinous viscous barrier between the granules and the water, which reduced the penetration of fluid into the interstitial void spaces thus prolonging the disintegration time of the tablet [12]. All the formulations disintegrated within the 15 minutes specified for uncoated tablets in the Pharmacopeia [31]. All the tablets released more than 70% of their paracetamol content within 30 minutes of dissolution (Figure 3).

Table 4. Release properties of Paracetamol tablets at relative density of 0.9

Binder	Binder Concentration (%w/w)	Disintegration time (mins)	t_{50} (mins)	t_{80} (mins)	t_1 (mins)	k_1	k_2
	0.00	0.60±0.00	1.65±0.03	3.01±0.02	1.50±0.04	0.18±0.01	0.83±0.01
PVP	1.00	0.75±0.01	3.20±0.01	6.80±0.03	4.00±0.06	0.60±0.00	1.10±0.01
	2.00	1.10±0.00	3.21±0.01	8.00±0.21	8.50±0.32	0.52±0.00	1.21±0.00
	3.00	1.15±0.03	3.40±0.03	8.40±0.05	9.28±0.04	0.22±0.00	1.85±0.00
	5.00	1.55±0.02	3.42±0.11	8.42±0.02	9.40±0.01	0.42±0.00	1.67±0.02
	10.00	4.52±0.01	3.60±0.06	9.20±0.42	12.00±0.11	0.24±0.00	2.10±0.00
Terminalia	1.00	0.88±0.00	5.25±0.02	7.40±0.11	5.53±0.11	0.25±0.00	1.17±0.01
	2.00	0.95±0.01	5.60±0.12	7.62±0.04	5.57±0.02	0.24±0.00	1.24±0.00
	3.00	1.18±0.04	8.20±0.04	12.00±0.01	6.50±0.07	0.22±0.00	0.86±0.00
	5.00	5.25±0.00	10.00±0.13	18.20±0.15	6.75±0.15	0.29±0.00	1.05±0.00
	10.00	6.48±0.00	11.00±0.23	18.50±0.08	17.90±0.27	0.59±0.01	2.88±0.01

This shows that all the tablets passed the dissolution test as specified by the British Pharmacopoeia [31]. The parameters t_{50} and t_{80} (time at which 50% and 80% of the drug were released respectively), k_1, k_2 and t_1 obtained from the Kitazawa plot (Figure 4) are presented in Table 5. The values of k_1, k_2 and t_1 were seen to increase with increasing binder concentration. k_2 was observed to be generally higher than k_1, indicating an initial release rate of the drug from the disintegrating tablet followed by a higher release rate after time t_1. Thus, t_1 can be taken to coincide with the point at which there was complete tablet disintegration which now leads to increase in surface area and release rate of the drug. The fragmentation of tablets caused a change in surface area, and this could be attributed to change from k_1 to k_2 at time t_1 [25, 32]. The disintegration time values were seen to be lower than the corresponding t_1 values and this could be attributed to the greater agitation employed in the disintegration test than in the dissolution test [25].

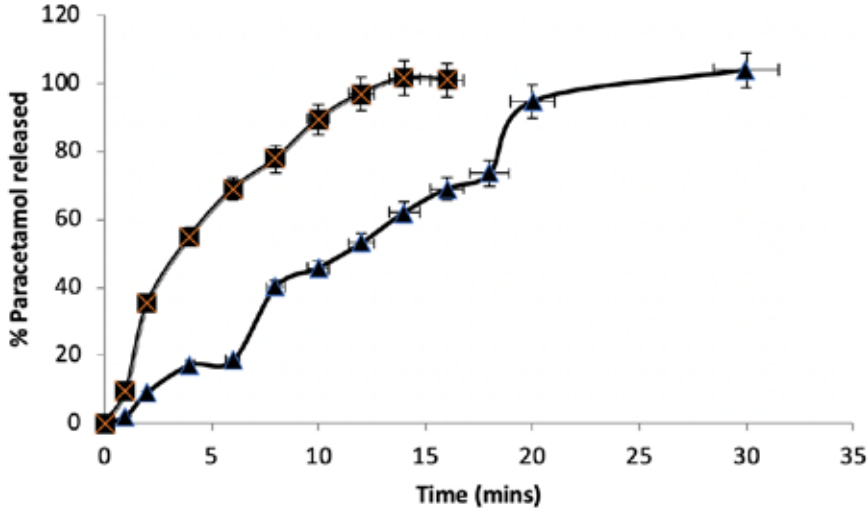

Figure 3. Plots of percentage paracetamol released against time for tablets formulated with 5%, w/w of gums as binders *Terminalia;* ▲, PVP ■ (Mean ± SE, n =3)

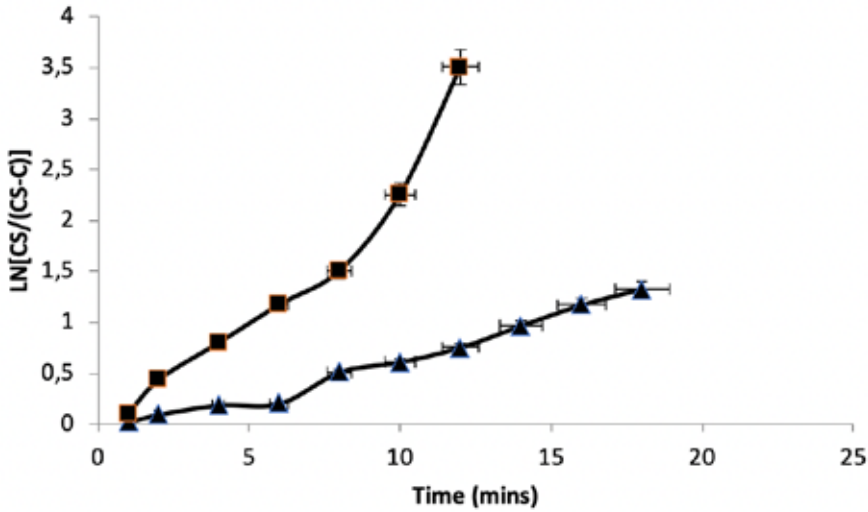

Figure 4. ln [CS / (CS-C)] versus time for paracetamol tablets containing 5%, w/w binders: *Terminalia*; ▲, PVP ■ (Mean ± SE, n =3)

CONFLICT OF INTEREST

The authors declare that they don't have any conflict of interest.

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AUTHORS' CONTRIBUTIONS

Design: Oluyemisi Bamiro

Collection of data: Oluyemisi Bamiro, Olutayo Adeleye, Lateef Bakre

Analysis of data: Oluyemisi Bamiro, Olutayo Adeleye, Lateef Bakre

Drafting of manuscript: Oluyemisi Bamiro

Critical Revision of manuscript: Oluyemisi Bamiro, Olutayo Adeleye, Lateef Bakre

Statistical analysis: Oluyemisi Bamiro, Olutayo Adeleye, Lateef Bakre

Technical or financial support: Oluyemisi Bamiro, Olutayo Adeleye, Lateef Bakre

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