

EVALUATION OF CISSUS GUM AS BINDER IN A PARACETAMOL TABLET FORMULATION

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Abstract

The paper present a study regarding the binding properties of Cissus gum, obtained from *Cissus populnea* (Vitaceae), in paracetamol tablet formulations in comparison with official gelatin. Compressional properties were analyzed using density measurements and compression equations of Heckel. The mechanical properties of the tablets were assessed using the crushing strength and friability of the tablets, while drug release properties were assessed using disintegration and dissolution times.

Formulations containing Cissus gum exhibited faster onset and higher amount of plastic deformation during compression when compared with those of gelatin. The crushing strength, disintegration and dissolution times of the tablets increased with binder concentration while friability values decreased. Cissus gum tablets presented faster disintegration and higher crushing strength-friability ratio (CSFR) values than those containing gelatin. The dissolution profiles of formulations containing the two binders showed similarity factors above 50. Cissus gum would be a better alternative to gelatin in producing uncoated tablets for which the fast release is essential.

Rezumat

Articolul prezintă un studiu privind proprietățile gumei Cissus, obținute din specia *Cissus populnea* (Vitaceae), utilizată ca liant în formularea comprimatelor cu paracetamol. Studiul a fost efectuat comparativ cu gelatina. Au fost studiate proprietățile mecanice de compactare și de eliberare a substanței active pentru cele două formulări.

Rezultatele obținute confirmă faptul că guma Cissus ar putea fi o alternativă mai bună a gelatinei, ca liant în formulările tabletelor cu eliberare rapidă.

Keywords: Cissus gum, gelatin, binding agent, Heckel equation, mechanical properties, similarity factor

Introduction

Binders are agents used in the pharmaceutical industry to impart cohesive properties to the powdered material during the production of tablets. Several gums, e.g. xanthan, karaya and guar have been evaluated as binders in the formulation of tablets and have been found to be of interest because they produce tablets of various mechanical and release properties depending on the intended use [1,2]. Natural gums are among the most

popular hydrophilic polymers because of their cost-effectiveness, lack of toxicity and regulatory acceptance. Cissus gum is a natural non-ionic polysaccharide obtained from the incised sliced stem of *Cissus polpunea* Guill. & Perr. (*Vitaceae*). The gum is a natural, biosynthetic, edible substance consisting of glucose, mannose, and glucuronic acid, being used locally as thickener in foods. Ibrahim and Dawes [3] have previously investigated *C. polpunea* gum in the formulation of theophiline sustained release tablet but no work has been reported on the compression, mechanical and release properties of conventional tablets incorporating *C. polpunea* gum as binder.

The Heckel equation is based on the assumption that powder compression follows first-order kinetics, with the interparticulate pores as the reactant and the densification of the powder bed as the product [4]:

$$\ln \left[\frac{1}{1-D} \right] = K \cdot P + A \quad (1)$$

where D is the relative density of a powder compact at pressure P . Constant K is a measure of the plasticity of a compressed material. A is related to the die filling and particle rearrangement before deformation and bonding of the discrete particles [5]. Hence the mechanism of bonding in a powder compact can be elucidated using a Heckel plot.

The relative density (D_A), which represents the total degree of packing at zero and low pressures, can be calculated from the value of A , using the equation:

$$D_A = 1 - e^{-A} \quad (2)$$

The initial rearrangement phase of densification as a result of die filling is obtained from the ratio of the loose density to the particle density, and is the relative density (D_O) of the powder bed at the point when the applied pressure equals zero, while the phase of rearrangement of particles during the initial stages of compression is described as D_B . The extent of rearrangement phase depends on the theoretical point of densification at which deformation of particles begins.

$$\text{Thus, } D_B = D_A - D_O \quad (3)$$

The Heckel plot thus allows for the elucidation of bonding mechanism.

The present study was designed to evaluate the effects of Cissus gum as a binder in a paracetamol tablet formulation in comparison to official gelatin British Pharmacopoeia (BP) grade. Paracetamol was a good choice

of active drug for the binder study because of its poor tableting properties and fragmentation properties.

Materials and methods

Materials

Paracetamol powder, gelatin BP (BDH, England), lactose BP (DVM Veghel, Holland) were used as supplied. Cissus gum was obtained from the incised stem of *Cissus populnea*, by a method similar to that previously reported [2].

Preparation of granules

250g batches of a basic formulation comprising of paracetamol (60%w/w), lactose (30% w/w) and corn - starch (10% w/w) were dry mixed for five minutes in a Kenwood planetary mixer. The mixture was then moistened with the appropriate amount of pastes of the binding agent (Cissus gum or gelatin) to produce masses containing 1.0, 2.0, 3.0 and 4.0%w/w of the binders.

Massing was continued for about five minutes and the wet masses were granulated by passing them manually through a No. 12 mesh sieve (1,400 μ m). The granules were dried in a hot air oven for 24hours at 60°C and then re-sieved through a No. 16 mesh sieve (1,000 μ m), before storage in air - tight containers. The granule particle density was determined by the pycnometer method using xylene as the displacement fluid.

Determination of pre-compression density

The bulk density for each formulation at zero pressure (loose density) was determined by pouring the granules into a 50mL glass measuring cylinder with a diameter of 24mm through a funnel at an angle of 45°. Determinations were made in triplicate. The relative density D_o of each formulation was obtained from the ratio of the loose density to its particle density.

Preparation of tablets

Tablets were prepared using a Carver hydraulic press (Model C, Carver Inc, Menomonee Falls, Wisconsin, U. S. A), fitted with a pressure gauge reading up to 2.5 metric tones. Tablets of 400mg weight were prepared from granules of size fraction 500 - 1,000 μ m using a 10.5mm diameter die and flat faced lower and upper punches. The tools were lubricated by brushing with 2% w/v dispersion of magnesium stearate in

ethanol - ether (1:1) mixture before compression. The tablets were stored over silica gel for 24hr to allow for elastic recovery and hardening before tablet properties were determined.

Tablet weights (w) were accurately determined at room temperature to within $\pm 1\text{mg}$ while the diameter and thickness of the tablets were accurately measured to within $\pm 0.01\text{mm}$. The relative density D, of the tablets was calculated using the equation:

$$D = \frac{w}{V_t \cdot \rho_s} \quad (4)$$

where V_t is the volume of tablet (cm^3) and ρ_s is the particle density of the solid material (g/cm^3).

Friability and Crushing strength tests

The friability of the tablets was determined using the Veego tablet friability apparatus (Veego Scientific Devices, Mumbai, India) at a speed of 25rpm for 4minutes. The diametrical crushing strength of ten tablets per batch was determined using the Erweka TBH 28 hardness tester (Apparatebau, GMBH, Germany). The crushing strength results were accepted only if the samples split cleanly into two halves.

Disintegration test

Tablet disintegration time was determined in distilled water at $37^\circ \pm 0.5^\circ\text{C}$ using the Apex disintegration testing Apparatus (Apex Construction Ltd; Northfleet Gravesent and Dartford, Kent, U.K). Determinations were performed in triplicate.

Dissolution test

The dissolution rate of the tablets was determined using the Rotating Basket (USP Apparatus I) method. Each tablet was placed in a cylindrical basket of stainless wire mesh attached to a variable speed drive mechanism and suspended in a glass vessel containing 900mL of distilled water kept at $37^\circ\text{C} \pm 0.5^\circ\text{C}$.

The apparatus was set to rotate at 100rpm and was started simultaneously with a stop clock. 5mL samples of the dissolution medium was removed at designated time intervals and replaced with an equal volume of fresh sample of dissolution medium. The absorbance of the removed samples was measured using a UV spectrophotometer (SP6-450 UV/VIS spectrophotometer, Pye Unicam, Middlesex, England), from which the concentration of drug dissolved was calculated.

Data analysis

The similarities between two dissolution profiles were assessed by a pair-wise model independent procedure such as similarity factor (f_2) [6]:

$$f_2 = 50 \operatorname{Log} \left\{ \left[1 + \frac{1}{n \sum_{n=1}^n (R_t - T_t)^2} \right]^{-0.5} \times 100 \right\} \quad (5)$$

where n is the number of pull points, w_t is an optional weight factor, R_t is the reference profile at time point t , and T_t is the test profile at the same time point; the value of f_2 should be between 50 and 100. An f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases.

Statistical analysis was performed to compare the effect of Cissus gum and gelatin on tablet properties using the t -test. At 95% confidence interval, p value lower than or equal to 0.05 was considered the limit of significance.

Results and discussion

Figure 1 shows representative Heckel plots for paracetamol formulations containing 3%w/w binder. The mean yield pressure, P_y , was calculated from the regions of the plots showing linearity with correlation coefficient of ≥ 0.99 for all formulations. The intercept, A , represented the point at which a coherent or intact tablet was just formed during compression and was determined from the extrapolation of the region used for the determination of P_y . The values of D_A and D_B were calculated from equations 2 and 3 respectively. The values of P_y , D_0 , D_A , and D_B for the formulations are presented in table I.

Table I

Parameters obtained from density measurements and Heckel plots					
	Binder conc. (% w/w)	D_0	P_y (MN/m ²)	D_A	D_B
Gelatin	0.0	0.237	476.91	0.775	0.538
	1.0	0.372	263.16	0.875	0.552
	2.0	0.329	256.41	0.861	0.550
	3.0	0.311	208.33	0.850	0.521
	4.0	0.271	147.06	0.823	0.503
Cissus gum	1.0	0.336	526.32	0.859	0.610
	2.0	0.249	400.00	0.828	0.581
	3.0	0.240	384.62	0.821	0.572
	4.0	0.155	270.27	0.765	0.523

where D_0 – the relative density of the powder bed at the point when the applied pressure equals zero; P_y – mean yield pressure; D_A – the relative density that represents the total degree of packing at zero and low pressures; D_B – the phase of rearrangement of the particles during the initial stages of compression.

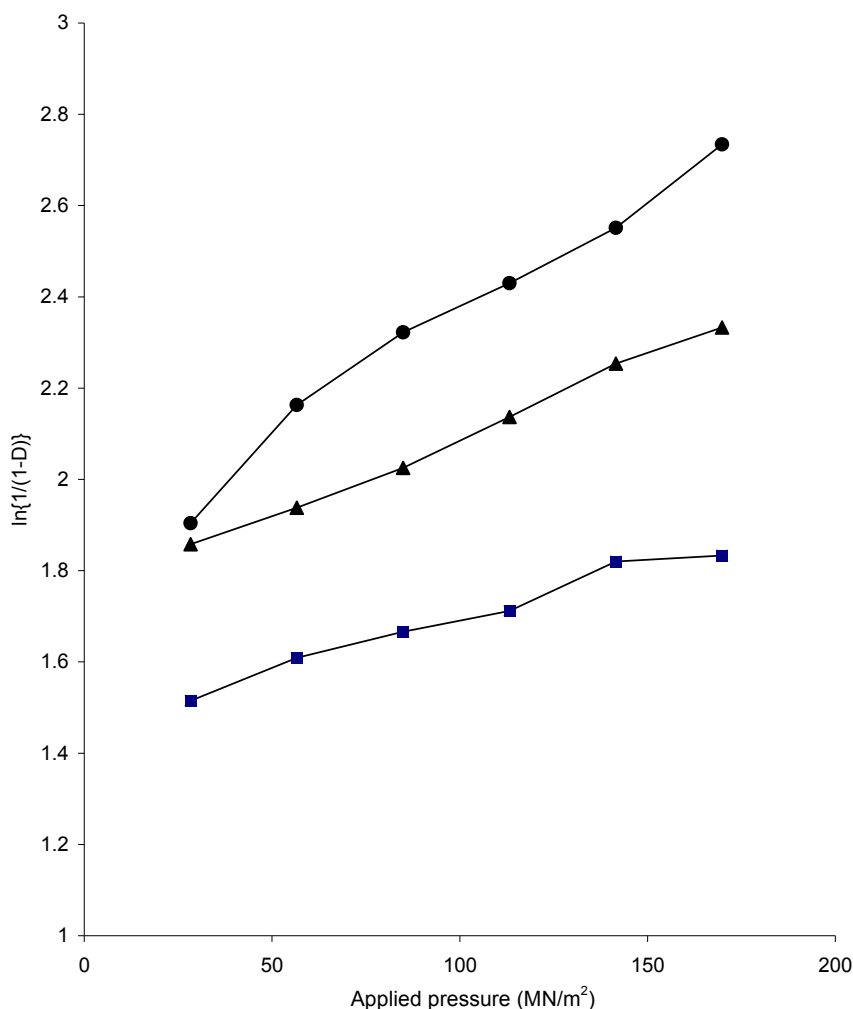


Figure 1

Heckel plots for paracetamol tablets containing 0.0%w/w binding agent ■, 3%w/w Gelatin ●, and 3.0%w/w Cissus gum ▲

The values of D_0 decreased with the binder concentration, implying that the initial packing of the formulation as a result of die filling decreased with the increase in binder content. Formulations incorporating gelatin had higher values indicating that formulations containing gelatin exhibited a higher degree of packing in the die as a result of die filling than formulations containing Cissus gum.

The mean yield pressure P_y is inversely related to the ability of a material to deform plastically when compressed [7, 8]. The values of P_y

decreased with the increase in binder concentration, with formulations containing Cissus gum having higher values compared to gelatin. This implies that the onset of plastic deformation in the formulations containing gelatin was faster than those containing Cissus gum.

The D_A values, which represent the total degree of packing at zero and low pressures, decreased as the binder concentration increased. Formulations containing Cissus gum showed the lowest D_A values while those containing gelatin exhibited the highest values.

The D_B value represents the particle rearrangement phase in the early compression stages and tends to indicate the extent of particle or granule fragmentation, although fragmentation has been observed to occur concurrently with plastic and elastic deformation of constituent particles. The D_B value also decreased with an increase in binder content with formulations containing Cissus gum showing the highest values and those containing gelatin exhibiting the lowest values. This result indicates that granule fragmentation decreased with an increase in binder concentration. Furthermore, the values of D_B which were higher than those of D_O showed that granule fragmentation and the subsequent filling of void spaces between particles occurred extensively at low pressures. However, there was no significant difference ($p > 0.05$) in the values obtained for all the parameters observed.

The mechanical properties of the paracetamol tablet formulations were assessed by the crushing strength (CS), friability (F) and the crushing strength-friability ratio (CSFR). While the crushing strength indicates the strength of the tablet, friability values provide a measure of tablet weakness. The friability test for tablets is designed to evaluate the ability of the tablets to withstand abrasion on packaging, transportation and handling in general [10]. Although there are no official monograph specifications on the allowed limits of friability of different tablets, the test is included in the British Pharmacopoeia. By convention, tablets that lose not more than 1% of their weight in the test for friability are considered acceptable. Figure 2 shows representative plots of the friability versus relative density for paracetamol tablets containing binders at a concentration of 3.0%w/w. It can be observed that there is a decrease in friability with the increasing binder concentration, with the highest friability obtained in formulations with no binder and gelatin-containing tablets least friable. This relationship has been previously noted and can be attributed to the increase in the potential of the powder particles to bond together as the relative density increased, thus producing stronger tablets with decreased friability [9, 10].

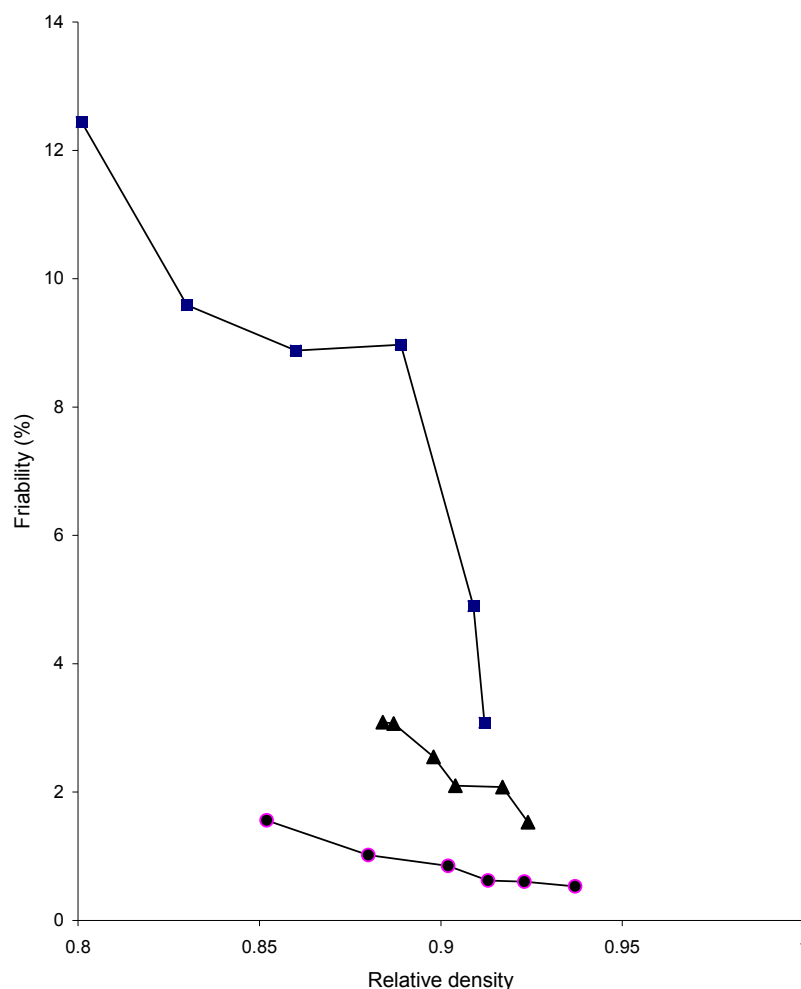


Figure 2.

Plots of friability versus relative density for paracetamol tablets containing 0.0%w/w binding agent ■, 3.0%w/w Gelatin ●, and 3.0% w/w Cissus gum ▲.

There is no official requirement for crushing strength due to the fact that strength requirements for a given formulation will depend on the end use of the tablet [7], tablets are generally required to have a friability value less than 1%. Table II presents the values of crushing strength and friability for all formulations at a relative density of 0.90, which is normal for commercial tablets. An increase in crushing strength was registered, with the corresponding decrease in friability values with binder concentration for

all formulations. It evaluates the resistance of the tablet to chipping, abrasion or breakage under the conditions of storage, transportation and handling [10]. Although, there are no official specifications for the crushing strength of tablets, however the resistance to crushing of the tablets is included as a tablet evaluation test in the British Pharmacopoeia [11]. It is accepted by convention that oral tablets should ideally have crushing strength values of between 4kg (39.2N) and 10 kg (98.0N) [10]. However, excessively hard tablets may not disintegrate in the required time to meet the dissolution specifications [12]. Table II shows the crushing strength values tablets at different binder concentrations.

The crushing strength-friability ratio (CSFR) also provides a parameter for measuring tablet strength [9]. Generally, the higher the CSFR value, the stronger the tablet [13]. Table II shows an increase in CSFR values with the increase in binder concentration, with tablets containing gelatin showing significantly ($p < 0.05$) higher values than those containing Cissus gum.

Table II

Values of Crushing Strength, Friability and Crushing Strength-Friability Ratio (CSFR) for Paracetamol tablets at a Relative Density 0.90

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

The disintegration time values for the tablets at the relative density of 0.90 are presented in table II. An increase was observed in the disintegration time with the increase in binder concentration for all formulations, although there were no significant ($p > 0.05$) differences in disintegration time between the formulations. Representative plots of the formulations at 3.0%w/w binder concentration are given in figure 3. The increase in relative density is generally a consequence of decreased porosity, leading to a decrease in water penetration into tablets and hence decrease in disintegration time. Formulations containing Cissus gum had lower disintegration times compared to those containing gelatin as binder. This is

probably due to the formation of more solid bridges in the latter and consequent less penetration of fluid by capillary action [14].

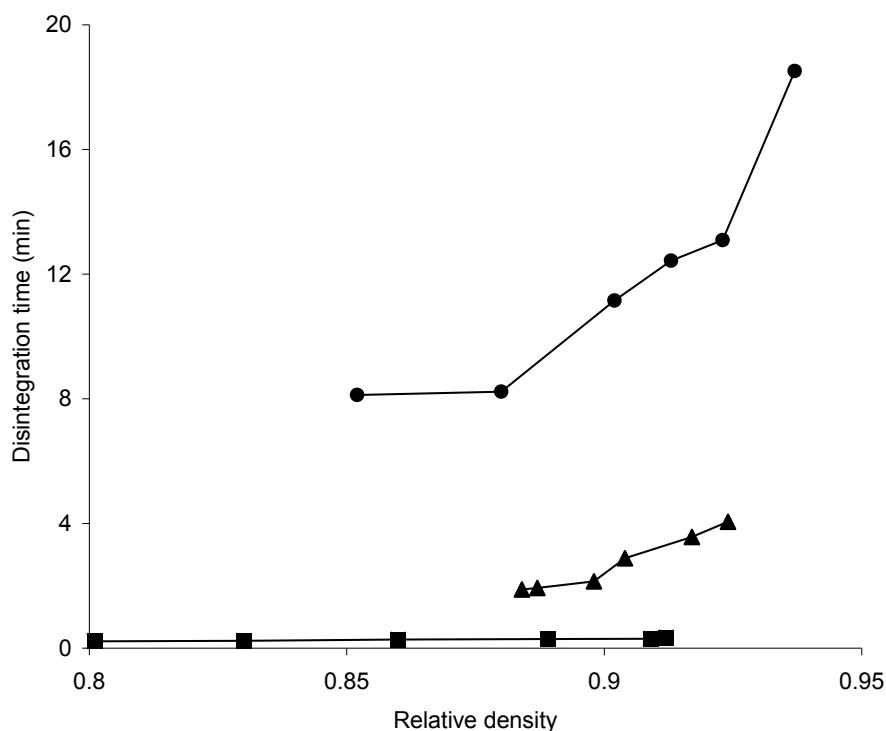


Figure 3.

Representative plots of disintegration time (min) versus relative density for paracetamol tablets containing 0.0%w/w binding agent ■, 3.0%w/w Gelatin ●, and 3.0% w/w Cissus gum ▲.

Figure 4 shows representative plots of the amount of paracetamol released against time for tablets containing 3% w/w binder. The values of t_{80} (time taken for 80% of the drug to be released) and the difference and similarity factors were calculated. These values for tablets containing Cissus gum tablets at a relative density of 0.90 are presented in table III. The t_{80} values were found to be binder concentration dependent. The similarity factor values for the Cissus gum tablet formulations when compared with tablets containing equal concentration of gelatin as binder were all above 50 [15, 16]. The f_2 for tablets containing 2% w/w of either binder was the highest, rendering the most similar formulations [17].

Table III
Time for 80% drug release (t_{80}), f_2 for paracetamol tablet formulations containing Cissus gum and corresponding gelatin as reference

	Binder conc. (% w/w)	t_{80} (min)	f_2
Cissus gum	1.0	4.6	63
	2.0	4.3	88
	3.0	4.6	84
	4.0	6.3	60

where f_2 – similarity factor

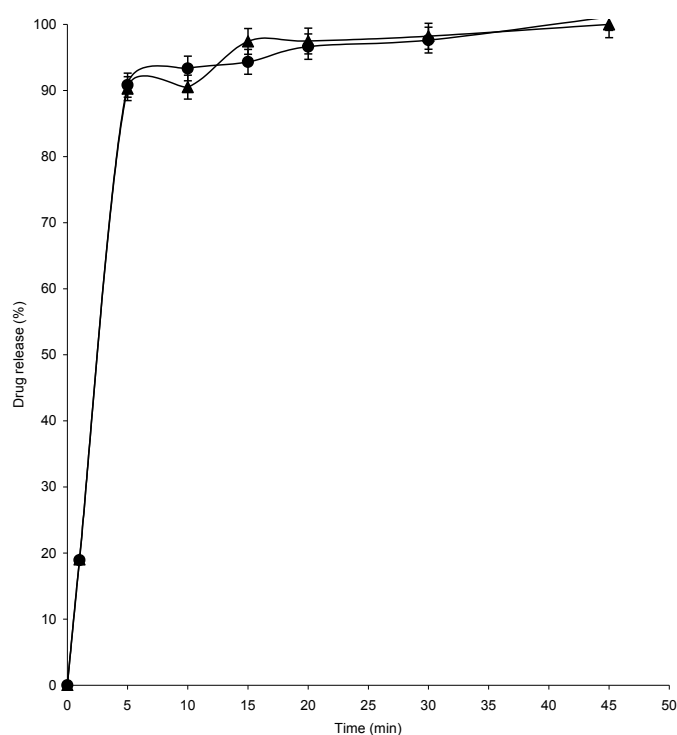


Figure 4.
Dissolution profiles of paracetamol tablets containing 3.0%w/w Gelatin ●, and 3.0% w/w Cissus gum ▲.

Conclusions

The results suggest that *Cissus* gum will be a binder of choice when the requirements are moderate mechanical strength and fast disintegration and drug release.

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Manuscript received: September 28th 2009