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The influence of cissus gum on the mechanical and release properties of paracetamol tablets – a factorial analysis

Adeleye, Adetayo O[1]; Odeniyi, Michael A[1]*; Jaiyeoba, Kolawole T[1]

[1]Department of Pharmaceutics & Industrial Pharmacy, Faculty of Pharmacy,
University of Ibadan, Nigeria.

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ABSTRACT

The quantitative effects of a new gum, used as a binder, on the mechanical and release properties of paracetamol tablet formulations were analyzed in a 2^3 full factorial experiment. Cissus gum extracted from *Cissus populnea* Guill. *&* Perr. (Vitaceae) was compared with official gelatin. The individual and interaction effects of type of binder, concentration of binder and packing fraction on the friability, tensile strength, brittle fracture index, disintegration time and drug release profile of tablets were determined. Changing the binder from gelatin to cissus gum led to an increase in friability and a decrease in tensile strength, brittle fracture index (BFI) and drug release variables. Increasing binder concentration from 2.0w/w to 4.0%w/w, and increasing relative density from 0.80 to 0.90, led to increases in lamination tendency and release rate of the formulations. Tablets containing gelatin had higher tensile strength, lower friability, longer disintegration time and a greater tendency to laminate than those with cissus gum. Hence, care must be taken in choosing a suitable binder for tablet formulations, with respect to their mechanical and release characteristics. The study suggests that cissus gum should be preferred to gelatin in tablet formulations that tend to cap or laminate or in formulations meant for rapid drug release.

Keywords: Cissus gum. Paracetamol. Factorial analysis. Mechanical / release properties.

INTRODUCTION

Binders are agents used to impart cohesiveness to the powdered material during the production of tablets, to ensure that the tablet remains intact after compression, as well as to improve the free flowing quality of the granules (Ibezim et al., 2008). The choice of a particular binding agent depends on the binding force required to form the granules and its compatibility with the other ingredients, particularly the active drug (Gordon et al., 1990). Owing to their physicochemical properties and relative inertness, gums are widely used in tablet formulations, primarily as binders in conventional tablets and matrix formers in sustained and modified-release formulations. Recently, efforts to develop some local gums from various tropical African plant sources as pharmaceutical excipients in tablet formulations have been reported (Kalu et al., 2007; Odeniyi & Jaiyeoba, 2009). Cissus gum is a natural, nonionic polysaccharide derived from the incised sliced stem of the local liane *Cissus polpunea* Guill. *&* Perr. (Vitaceae).

In order to determine the suitability of a particular gum for tablet production, it is necessary to assess the quantitative effects on the mechanical and release properties of the tablet of substituting the gum for the standard binder, as well as of important processing variables. A factorial experimental design has proved useful for such an investigation (Odeniyi & Jaiyeoba, 2004; Adetunji et al., 2007). In factorial experiments, more than one factor is varied at a time in a structured fashion. This approach is very useful in experimental optimization, and is more effective and efficient than the method of varying only one factor at a time. Factorial experiments can be used to explore which factors and levels of those factors will maximize the difference between a control and an effect (Alebiowu & Itiola, 2002; Odeniyi et al., 2008). The basis of the experimental design in this study was that each of three parameters was used at a high level (+1) and a low level (-1). The number of experiments in the design was thus 2^3 (or 8).

The mechanical properties of the tablets were assessed from the tensile strength (T), a measure of their bond strength, and the brittle fracture index (BFI), a measure of their lamination and capping tendency (Hiestand et al., 1977). BFI is determined by comparing the value of T of a tablet with a hole in the center with that of a tablet without a hole, at the same relative density, the hole acting as a built-in stress-concentrating defect. The release properties of the

Corresponding Author: Michael A Odeniyi - Department of Pharmaceutics & Industrial Pharmacy - Faculty of Pharmacy - University of Ibadan - Ibadan - 200284 - Oyo State - Nigeria - phone: +234-8028982268 - e-mail: deleodeniyi@gmail.com

tablets were assessed by observing the times required for disintegration (DT) and for 80% drug release (t_{80}).

In the present study, an investigation was made into the quantitative effects of the type of binder, concentration of binder and packing fraction (P_f) of paracetamol tablets on their mechanical and release properties. Paracetamol was chosen as it has poor tableting properties and hence requires a binder, among other excipients, to form satisfactory tablets.

MATERIALS & METHODS

The materials used were paracetamol powder (Bayer, Germany), gelatin B.P. (BDH, Chemicals Ltd., Poole, U.K.), and lactose B. P. (DVM Veghel, Holland). Cissus gum was obtained from the stem of *Cissus polpunea* Guill. *&* Perr. (Vitaceae). The experimental gum was prepared in our laboratory at the University of Ibadan and the method of preparation and purification of the gum were similar to those previously described (Tavakoli et al., 2004; Kalu et al., 2007). Briefly, the gum was extracted from the incised sliced stem of *Cissus polpunea* by overnight soaking in distilled water, followed by filtration of the viscous solution and precipitation of the extracted gum with acetone.

Preparation of granules

Batches (250g) of a basic formulation comprising paracetamol (60%w/w), lactose (30% w/w) and corn starch (10% w/w) were dry mixed for about five minutes in a Kenwood planetary mixer (Kenwood Electronics UK Ltd, Herts, UK). The mixture was then moistened with appropriate amounts of a paste of the binding agent (*C. polpunea* gum or gelatin), to produce masses containing various concentrations of the binder. Massing was continued for about five minutes and the wet masses were granulated through a No. 12 mesh sieve (1,400µm). The granules were dried in a hot-air oven for 24 hours at 60°C and then resieved through a No. 16 mesh sieve (1,000µm), before storage in airtight containers.

Preparation of tablets

Granules of the size fraction 500-1,000µm were compressed on a Carver hydraulic hand press (Model C, Carver Inc, Menomonee falls, Wisconsin, U. S. A), fitted with a pressure gauge reading up to 2.5 metric tons. 400mg tablets of diameter 10.5mm were pressed in a die-punch assembly. Before each compression, the tools were lubricated by brushing with a 2% w/v dispersion of magnesium stearate in ethanol - ether (1:1).

Tablets were produced with a hole (1.59mm diameter) in the center by using an upper punch with a hole through the centre and a lower punch fitted with a pin. The tablets were accurately weighed at room temperature (25°C) on a PC 400 Mettler balance (Mettler Instruments AG, Zurich), while the diameter and thickness of the tablets were measured to within ± 0.01mm with a micrometer screw gauge (Model 996m/25 capacity, Moore and Wright Ltd, Handsworth Road, Sheffield, UK).

The packing fraction, P_f, of the tablets was calculated from equation (1):

$$P_f = W / \rho_s.v \qquad (1)$$

where W is the weight (g) of the tablet, ρ_s is the solid material density (g/cm^3) and v is the volume of the tablet (cm^3).

Determination of Friability

The percent friability of the tablets was determined with the Veego tablet friability apparatus (Veego Scientific Devices, Mumbai, India) at a speed of 25rpm for 4 minutes. Ten tablets were used for each determination in triplicate

Determination of tensile strength and brittle fracture index

The tensile strength of the normal tablets (T) and apparent tensile strength of those containing a hole (T_o) were determined at room temperature by diametral compression, using an Erweka TBH 28 hardness tester (Apparatebau, GMBH, Germany). Measurements were made in triplicate on individual tablets and the results were accepted only if the samples split clearly into two halves. Equation 2 was used to calculate the tensile strength (MNm^{-2}) (Hiestand et al., 1977; Okor et al., 1998):

$$T \text{ (or } T_o) = 2 F / p\, dt \qquad (2)$$

where F is the load (MN) needed to cause fracture, d the tablet diameter (m), and t, the tablet thickness (m).

The Brittle Fracture Index (BFI) of the tablets was calculated from T and T_o by equation 3:

$$BFI = 0.5\, [(T / T_o)] - 1 \qquad (3)$$

where T and T_o are as defined above (Hiestand et al., 1977; Okor et al., 1998).

Disintegration test

The disintegration times of the tablets were determined in distilled water, at 37 ± 0.5 °C, with the Apex disintegration testing apparatus (Apex Construction Ltd; Northfleet, Gravesend, Dartford, Kent, UK). The time taken for all the tablets to disintegrate and go through the wire mesh was recorded. Determinations were made in triplicate.

Dissolution test

The dissolution rate of the tablets was determined at 37 ± 0.5 °C in 900mL of 0.1 mol L^{-1} HCl, with an Erweka dissolution rate apparatus (Erweka, Germany).

The apparatus was set to rotate at 100rpm and samples of the dissolution medium were removed at designated intervals and replaced with fresh sample of dissolution medium. The absorbance of the removed samples was measured at a wavelength of 243nm (SP6-450 UV/VIS Spectrophotometer, Pye Unicam, Middlesex,

England) and the drug concentration determined from a calibration curve.

Experimental design

In order to determine the individual and interacting effects of the selected formulation factors on the properties of the tablets, a factorial experimental design was used. This has been found very useful in determining the effect of various formulation factors on the characteristics of drug formulations (Khanvilkar et al., 2002; Odeniyi & Jaiyeoba, 2004)

Three independent process parameters, viz. binder type, binder concentration and packing fraction, were chosen at two different levels. These parameter levels are summarized in Table 1. A 2^3 full factorial design was used as the research methodology, which required eight batches to be prepared (Table 2). The sequence of the eight experiments was randomized. The purpose of using a full factorial experimental design was to carry out a complete study of the effects of the process parameters and their interactions, with the aid of a computer and suitable statistical software (Minitab© 14.2).

Table 1. Independent process parameters and their levels

Independent Process parameters	Associated variable	Lower Level (coded -1)	Higher Level (coded +1)
Binder type	X_1	Gelatin	Cissus gum
Binder content	X_2	2% w/w	4%w/w
Packing fraction	X_3	0.80	0.90

Statistical analysis

The effects of the various parameters on the mechanical and release properties of the tablets were compared by Student's *t*-test. At the 95% confidence level, a *p* value lower than or equal to 0.05 was required for significance

RESULTS

Representative plots of percent friability (F), log tensile strength (T), brittle fracture index (BFI) and disintegration time (DT) of the paracetamol tablets against packing fraction are presented in Figures 1 to 4, respectively, and the dissolution profiles in Figure 5. The results of the factorial design experiments are shown in Tables 2 and 3.

Table 2: Factor combinations and values of Friability (F), Tensile strength (T), Brittle fracture index (BFI), Disintegration time (Dt) and Dissolution time (t_{80}) for paracetamol tablets in the factorial experimental design.

Batch No.	Binder type (X_1)	Binder content (X_2)	Packing fraction (X_3)	Friability (%)	Tensile Strength (MNm^{-2})	Brittle Fracture Index	Disintegration Time (min)	t_{80} (mins)
1	-1	-1	-1	3.78	0.803	0.723	5.18	3.1
2	+1	-1	-1	5.20	0.521	0.614	1.21	3.6
3	-1	+1	-1	2.26	1.002	0.316	10.03	3.5
4	+1	+1	-1	3.13	0.678	0.480	2.08	7.2
5	-1	-1	+1	1.18	1.502	0.706	10.27	4.8
6	+1	-1	+1	2.58	1.294	0.595	2.30	4.4
7	-1	+1	+1	0.51	1.659	0.282	17.50	5.1
8	+1	+1	+1	2.04	1.487	0.448	5.80	6.3

Key: -1: Low values / +1: High values

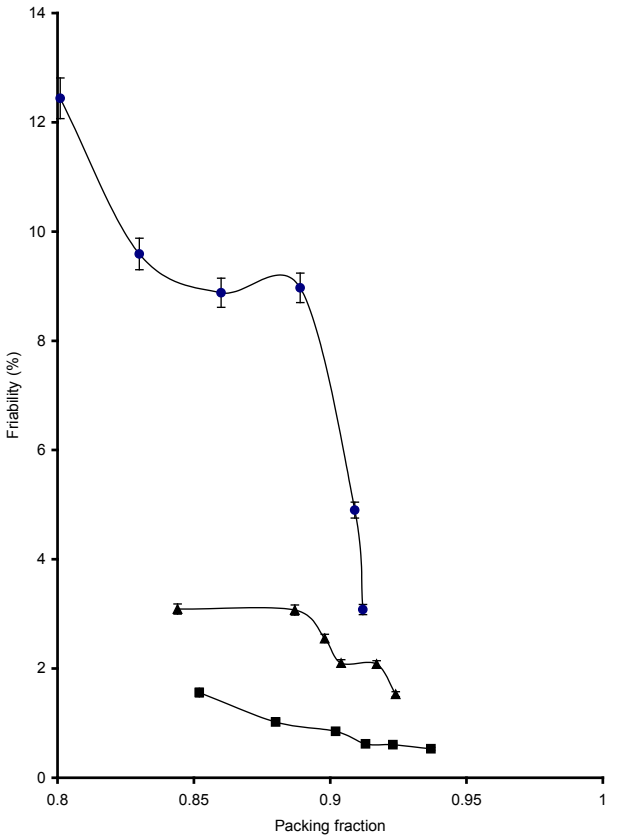

Figure 1. Representative plots of friability versus relative density for paracetamol tablets containing 0.0%w/w binder , ■; 3.0%w/w gelatin, ●; and 3.0% w/w cissus gum▲

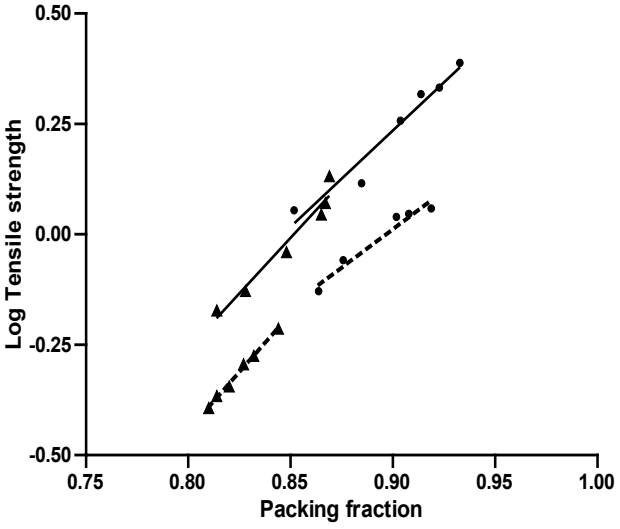

Figure 2: Log Tensile strength(MNm-2) versus packing fraction for paracetamol tablet formulations with (-------) or without(_____) a hole at the center, containing 3.0%w/w gelatin●; and 3.0%w/w cissus gum▲

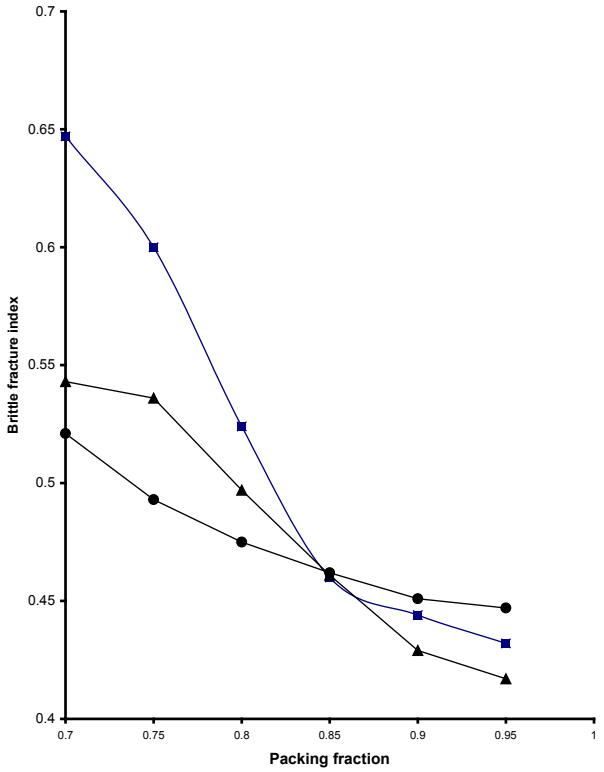

Figure 3: Representative plots of brittle fracture index versus packing fraction for paracetamol tablets containing 0.0%w/w binder, ■; 3.0%w/w gelatin, ●; and 3.0% w/w cissus gum ▲

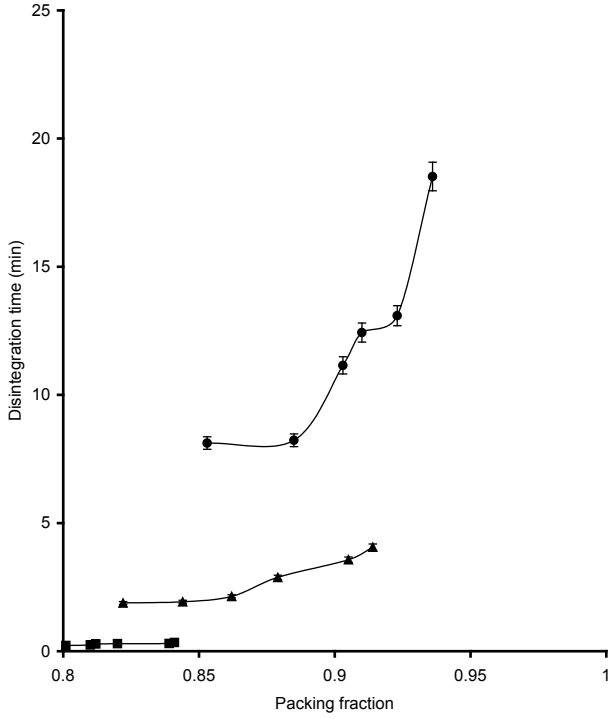

Figure 4. Representative plots of disintegration time (min) versus relative density for paracetamol tablets containing 0.0%w/w binder, ■; 3.0%w/w Gelatin, ●; and 3.0% w/w cissus gum▲

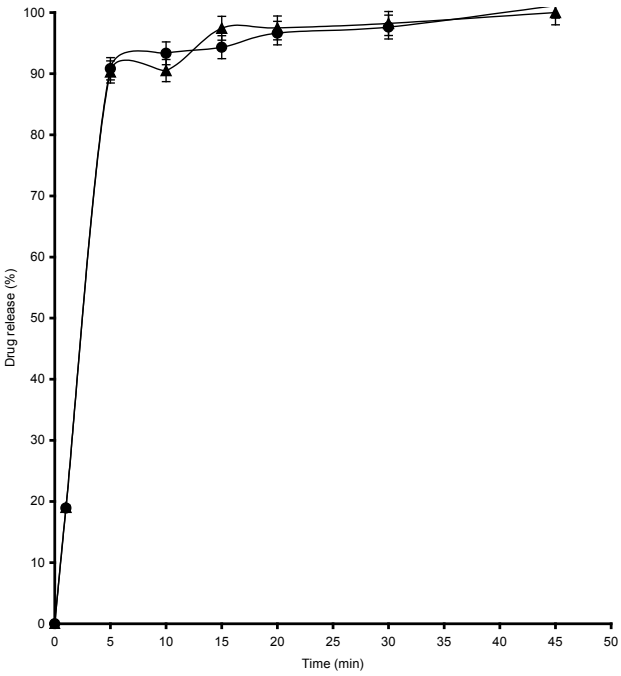

Figure 5. Dissolution profiles of paracetamol tablets containing 3.0%w/w gelatin ●; and 3.0% w/w cissus gum▲

Table 3: Individual coefficients of process parameters for paracetamol tablet properties.

Factor	Coefficient	Friability (%)	Tensile Strength (MNm^{-2})	BFI	Disintegration Time (min)	t_{80} (mins)
X_1	Effect	0.653	-0.123	0.014	-3.949	0.625
	p-value	0.016	0.001	0.710	0.006	0.191
X_2	Effect	-0.600	0.882	-0.139	2.056	0.775
	p-value	0.021	0.004	0.016	0.052	0.123
X_3	Effect	-1.008	0.367	-0.013	2.171	0.400
	p-value	0.003	0.000	0.730	0.045	0.371

DISCUSSION

The results shown in Table 2 provide a clear indication of the qualitative effects of the three parameters - concentration of binder (X_1), binder type (X_2) and packing fraction (X_3) - on the five response variables studied. The independent coefficient values (Table 3) show the individual effects of the parameters studied (factors) on the values of F, T, BFI, DT and 80% dissolution time, t_{80}. The ranking of the individual effects of the factors on friability was $X_3 > X_1 > X_2$; on tensile strength, it was $X_2 > X_3 > X_1$; on BFI, $X_2 > X_1 > X_3$; on DT, $X_1 > X_3 > X_2$, and on t_{80}, $X_2 > X_1 > X_3$. The rankings show the relative magnitudes of the effects of the factors on these variables. A positive effect signifies that the response variable has increased in value or magnitude, while a negative effect shows a decrease.

Packing fraction (X_3) had the largest effect on the friability, F, of the tablets. This effect was negative, showing that changing the packing fraction from the lower (0.8) to the higher value (0.9) caused a decrease in the percent friability of the tablet formulations. This effect was found to be significant ($P < 0.05$) and can be explained by an increase in bond strength and reduction in porosity of the tablets as the packing fraction increased. The effects of the

other two factors on friability, while smaller than that of the packing fraction, were almost equal but opposite, binder type having a positive effect and binder concentration a negative influence. This indicates that using cissus gum as binder yielded tablets that were more friable than those incorporating gelatin. On the other hand, increasing binder concentration from 2.0%w/w to 4.0%w/w caused a reduction in friability.

Binder concentration (X_2) had the greatest effect on the tensile strength of the tablets, showing that the amount of binder incorporated into the formulation is more significant than the type of binder. At higher concentrations, the other two factors were also found to have significantly less influence on tablet strength (Cook & Summer, 1990).

The disintegration time of the tablets was most strongly affected by binder type (X_1). The coefficient was negative, showing that a change of the binder from gelatin to cissus gum caused the tablets to disintegrate faster.

Brittle fracture index (BFI) is a measure of the tendency of the tablet to cap or laminate during decompression. It is measured by comparing the tensile strength (T_o) of a tablet with a central hole with the tensile strength (T) of a normal tablet. The hole is a built-in model defect that simulates the actual voids formed in the tablets (due to air entrapment) during manufacture. The voids or low density regions in a tablet are weak points from which cracks emanate when stress (at the die wall) is applied to the tablet. Tablet formulations with BFI values≥0.5 are prone to brittle fracture (Hiestand, 1977). The influence of X_2 on BFI was negative and the strongest, being the only significant effect on BFI detected ($P<0.05$). This implies that increasing the content of the binder caused a reduction in the brittle fracture propensity of the tablets. This result shows that under the high compressive forces employed in compaction, more gum will facilitate more plastic deformation, to give tablets with reduced capping and lamination tendency. The influence of X_1 on BFI was intermediate and positive (but not significant), suggesting that changing the binder to cissus gum might yield tablets with a higher brittle fracture index. X_3 had the weakest (negative) effect on BFI, suggesting that increasing P_f from 0.80 to 0.90 decreased the brittleness of the tablets due to the formation of harder tablets at higher relative densities.

All the factors had significant effects on DT. From the ranking above, it was observed that X_1 had the greatest (and negative) effect on this variable. In other words, the type of binder had a significant influence on the disintegration of the tablets changing it from gelatin to cissus gum resulted in faster disintegration of the tablets. The effects of both X_2 and X_3 were positive, implying that increasing the binder content or the packing fraction led to longer disintegration times. This effect can be attributed to a decrease in porosity with increasing packing fraction or binder content of the tablets. Increased porosity has been correlated with increased water penetration and a consequent effect on the disintegration time of tablets (Adetunji et al., 2007).

All the factors had a positive effect on t_{80}, which is the time taken for 80% of the drug to be released into solution. This implies that positive changes in any of the factors under study will lead to an increase in the dissolution time. However, none of the effects observed was found to be statistically significant ($P > 0.05$).

The influence of X_2 on t_{80} was higher than those of other variables. This effect was positive and could be attributed to the increased amount of binder in the interparticle spaces forming additional solid bonds due to binder adhesion. The effect of X_3 was the smallest, but showed that an increase in the packing fraction from 0.80 to 0.90 tends to increase the dissolution time. This is probably due to reduction in the capillary space between particles and consequently in water penetration.

The interaction coefficient values shown in Table 4 indicate the effects of the factors in combination. The rankings for the interaction effects on friability were $X_1X_3 > X_2X_3 > X_1X_2$, on tensile strength $X_1X_3 > X_2X_3 = X_1X_2$, on BFI $X_1X_2 > X_2X_3 > X_1X_3$, on DT $X_1X_3 > X_1X_2 > X_2X_3$, and on t_{80} $X_1X_2 > X_1X_3 > X_2X_3$. The results show that interaction between binder type and packing fraction had the highest influence on the mechanical properties of the tablets and disintegration time, while the interaction between binder type and binder concentration had highest influence on drug release.

The rankings show that, in general, the greatest factor-factor interactions occurred between X_1 and X_2. This is probably because the nature of the binder determines its plastoelastic properties and the amount of plastic deformation it will undergo under compression (Juppo, 1996). The higher the binder content (i.e X_2), the more plastic deformation it will manifest. The rankings also show that the packing fraction of tablets generally exhibited the weakest interactions with the other two factors, X_1 and X_2. This implies that X_3 exhibited more independence than the other factors in determining the values of the chosen response variables.

This type of study is very important in that it can expose significant interactions or lack of interaction between formulation factors with respect to the drug under study. Such a study should be a useful aid in choosing the binder, binder content and packing fraction that will be used to produce tablet, in order to achieve desired objectives.

The results suggest that a change of binder from gelatin to *Cissus polpunea* gum would lead to increased friability, while tensile strength, tendency to laminate and the disintegration time of the tablets would decrease. The interaction between binder type and packing fraction of the tablet formulations had the highest effects on the friability, strength and disintegration of the formulations, while the interaction between the nature and content of the gum had the highest effect on the BFI and drug release of the tablets. Hence, care must be taken in choosing a suitable binder for tablet formulations with respect to mechanical and release characteristics. The study suggests that cissus gum should be preferred to gelatin in tablet formulations that exhibit a tendency to cap or laminate or in formulations meant for rapid drug release.

Table 4: Interaction coefficients of process parameters for paracetamol tablet properties.

Factor	Coefficient	Friability (%)	Tensile Strength (MNm^{-2})	BFI	Disintegration Time (min)	t_{80} (mins)
X_1X_2	Effect	-0.052	-0.001	0.069	-0.964	0.600
	p-value	0.832	0.973	0.001	0.359	0.220
X_1X_3	Effect	-0.969	0.028	0.000	-0.969	-0.425
	p-value	0.021	0.212	1.000	0.021	0.280
X_2X_3	Effect	0.626	-0.001	-0.004	0.626	-0.225
	p-value	0.032	0.951	0.084	0.032	0.463

RESUMO

A influência da goma de Cissus nas propriedades mecânicas e de liberação de comprimidos de paracetamol - uma análise fatorial

Os efeitos quantitativos de uma nova goma como agente agregante nas propriedades mecânicas e de liberação de formulações de comprimidos de paracetamol foram avaliados utilizando um modelo fatorial 2^3 experimental. A goma foi obtida de *Cissus populnea* Guill. & Perr. (Vitaceae) e comparada com a gelatina oficial. Os efeitos individuais e de interação do tipo de agregante, concentração de agregante, porcentagem de friabilidade, resistência à tração, índice de fratura e tempo de desintegração e liberação do fármaco dos comprimidos foram determinados. A mudança do agente agregante de gelatina para goma de cissus levou a um aumento da friabilidade e a uma diminuição na resistência à tração, no índice de fratura e nos parâmetros de liberação do fármaco. O aumento da concentração do agregante de 2,0% p/p para 4,0% p/p e da densidade relativa de 0,80 a 0,90 levou a um aumento na tendência de laminação e na taxa de liberação das formulações. Comprimidos contendo gelatina apresentaram maior resistência à tração com menor friabilidade e maior tempo de desintegração e dissolução com maior tendência para laminado, quando comparados com a goma de cissus. Por isso, cuidados devem ser tomados na escolha de um agente agregante para formulações de comprimidos no que diz respeito às características mecânicas e de liberação. O estudo sugere que a goma de cissus pode ser empregada ao invés de gelatina em formulações de comprimidos que apresentam tendência de formar laminado ou decapeamento ou em formulações para liberação controlada de fármacos.

Palavras-chaves: Goma de cissus. Paracetamol. Análise fatorial. Propriedades mecânicas e de liberação.

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