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EVALUATION OF THE QUANTITATIVE EFFECTS OF VARIABLES ON A PARACETAMOL TABLET FORMULATION PREPARED WITH GUM AS BINDING AGENT

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ABSTRACT
The individual and interaction effects of gum – binder type (B), binder concentration (C), as well as the relative density (D) of a paracetamol tablet prepared with *Delonix regia* seed gum (DRSG), acacia gum BP (ACG) and tragacanth gum BP (TRG) on the mechanical {tensile strength (TS) and brittle fracture index (BF)} and disintegration {disintegration time (DT) and crushing strength–friability/disintegration time ratio (CSFR/DT)} properties of the tablets were studied using a 2^3 factorial experimental design. For the TRG/ACG and DRSG/ACG, the individual effects of the variables presented a rank order of D>C>B on the two mechanical properties studied, while a rank order of B>C>D was obtained for the studied disintegration properties. However, considering the TRG/DRSG combination, effect of C was more on the DT (C>D>B), whereas D had more effect on the CSFR/DT (D>C>B). Generally, the interaction between B and C was more on TS and DT than on BFI and CSFR/DT, while a similar result was observed for B and D on BFI and CSFR/DT than on TS and DT. This implies that the B is a very important variable to be considered when combining binders in a formulation.

Keywords: *Delonix regia seed gum; gum–binder; tensile strength; brittle fracture index; disintegration time; crushing strength–friability disintegration time ratio.*

INTRODUCTION

Gums are polysaccharide complexes that have found diverse application in pharmacy in the formulation of dosage forms as suspending agents for indiffusible materials, as emulsifying agents, as viscosity imparting agents, and as binders in solid dosage.[1] In pharmaceutical solid dosage formulation they provide adequate mechanical properties by promoting the bonding properties existing between the different components of a powder mix in a formulation.[2] The ability of gums to promote bonding between powder particles also have a profound effect on the disintegration properties of tablets.[3, 4] The mechanical and disintegrant properties of a tablet have been found to be influenced by the type of gum – binder, the concentration of the gum – binder and the relative density of the tablet.[5]

The factorial experimental design is a useful mathematical tool that permits the quantitative evaluation of the effects of individual factors and the interactions between these factors with a view to providing quantitative estimates of the various responses from the experimental design. This present work employs the 2^3 factorial analysis to measure the quantitative effects of the type of gum–binder (B), concentration of gum–binder (C) and the relative density (D) of the tablets on the mechanical {tensile strength (TS) brittle fracture index (BFI)} and disintegration {disintegration time (DT) crushing strength–friability/disintegration time ratio (CSFR/DT)} properties of the tablets.

Paracetamol, an analgesic and antipyretic agent was chosen for the present work due to its poor compression properties, and as a result would require a binding agent to form good quality tablet.

EXPERIMENTAL

Materials

The materials used were corn starch BP (BDH Chemicals Ltd., Poole, U.K), Lactose (AB Knight and Co., London, UK), Paracetamol powder BP (Gawo Pharmaceuticals Ltd., Lagos, Nigeria), tragacanth powder BP (Kimpton Brothers Ltd., London, U.K.), acacia gum (Hopkin and Williams Chadwell, Heath Essex, England), *Delonix regia* seed gum extracted from the seed of unripe but matured pods of *Delonix regia* (Bojer ex Hook) Raf. Family Fabaceae as described[6] in our laboratory, and ethanol 99.8% (Sigma-Aldrich Laborchemikalien GmbH, D-30926 Seelze, Germany).

Preparation of granules

Batches (300 g) of a basic paracetamol – lactose formulation (84.75: 15.25 $\%^{w}/_{w}$) were dry-mixed for 5 min in a planetary mixer (Hobart model N – 50 planetary mixer, Hobart, Canada, Inc.,). The mixture was moistened with sufficient quantity of distilled water or appropriate amounts of gum mucilage to produce

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granules containing various concentrations of gum. Massing continued for 5 min, the wet masses were granulated manually by passing them through a 16 – mesh sieve (1000 ìm), dried in a hot air oven for 18 h at 50 ^{0}C, and re – sieved through a 16 – mesh sieve (1000 ìm). The granules were stored in airtight containers before use. The granular density of each batch was determined by the pycnometer method with acetone as the displacement fluid. This same procedure was repeated for batches containing tragacanth and acacia gum – binder.

Preparation of tablets

Tablets (590 mg) were prepared from the granules by compressing them using a 12.5 mm die and flat faced punches for 30 s with pre – determined loads on a model C, hydraulic hand press (Carver Inc., Menomonee Falls, WI). Tablets with a hole (1.5 mm diameter) at their center were made using an upper punch with a hole and a lower punch with a pin.[7] After ejection, the tablets were stored in a desiccator for 24 h to allow for elastic recovery and hardening in order to prevent false low – yield values. The tablets' weights and dimensions were determined to within ±1 mg and 0.01 mm respectively, and their relative densities (*D*) were calculated using the equation:

$$D = m / V_t ñ_s \quad (1).$$

where V_t is the volume (cm^3) of the tablet volume (including the hole when present) and $ñ_s$ is the particle density of the solid material. The volume reduction, which increased with increase in compression pressure led to variable relative density.

Determination of mechanical properties of the tablets

The tensile strengths (*T*) of the normal tablets and apparent tensile strength (T_0) of those containing a hole were determined at room temperature by diametral compression[8] using a Monsanto hardness tester and by applying the equation:

$$T \text{ (or } T_0) = 2F/ðdt \quad (2).$$

where *T* (or T_0) is the tensile strength of the tablet (MNm^{-2}), *F* is the load (MN) needed to cause fracture, *d* is the tablet diameter (M) and *t* is the thickness (m). Results were taken from tablets that split clearly into two halves without any sign of lamination. All results were expressed as mean of triplicate determinations.

The *BFI* of the tablets were calculated using the following equation:

$$BFI = 0.5 (T/T_0 – 1) \quad (3).$$

Friability test

This was determined using an Erweka friabilator (Erweka Apparatebau, Offenbauch / Main Germany). Ten weighed tablets were placed inside the drum and allowed to tumble for four minutes at a speed of 25 r.p.m. the tablets were then weighed and the loss in weight expressed as a percentage of the initial weight. Determinations were done in triplicate.

Crushing strength

The load required to break the tablet (crushing strength) at room temperature into two equal halves was determined by the application of a diametrical force using the Monsanto hardness tester (Monsanto Chemical, USA). Tablets with signs of lamination or capping were excluded. Results are expressed as mean of three determinations.

Disintegration test

Tablet disintegration time (*DT*) was determined in distilled water at 37±0.5 ^{o}C in a BP Manesty (Manesty Machines, UK) disintegration test unit. Tablets were placed on the wire mesh just above the surface of the distilled water in the tube and the apparatus was started simultaneously with a stop clock. The time taken for each tablet to disintegrate and all the granules to go through the wire mesh was recorded at each relative density and the results were expressed as mean of three determinations.

Experimental design

To study the effect of the type of gum as a binding agent (B), its concentration (C) and relative density (D) of the tablet on tensile strength (TS), brittle fracture index (BFI), disintegration time (DT) and crushing strength-friability/disintegration time ratio (CSFR/DT) of paracetamol tablets, experiments were performed in a factorial design that involved the application of simple statistics.[9 10] In this factorial design, formulations were only mathematically combined. The basis of the experimental design was that each of the three variables was utilized at a "high" level (denoted by subscript H) and a "low" level (denoted by subscript L). The number of experiments in the design was 2^3, *i.e.*, 8. Using the above nomenclature, the various combinations between the variables used in the design were:

$B_LC_LD_L$, $B_LC_LD_H$, $B_LC_HD_L$, $B_LC_HD_H$,
$B_HC_HD_H$, $B_HC_HD_L$, $B_HC_LD_H$, $B_HC_LD_L$

where B_L is the type of gum binding agent DRSG or ACG when used in combination with TRG and B_H represent the type of gum binding agent TRG or DRSG when used in combination with ACG. The choice of B_L or B_H was based on results obtained from the laboratory. C_L represents the concentration of the gum binding agent (2 % $^w/_w$), C_H – concentration of the gum binding agent (5 % $^w/_w$), D_L – tablet relative density of 0.80; D_H – tablet relative density of 0.90. By grouping the results from the combinations into a number of sets, it was possible to assess the effects that each of the three variables (B, C or D) separately had on the mechanical/ disintegration properties of the tablets and determine whether the variables were interacting or acting

independently of each other. The effects of increasing B, from its 'low' level to its 'high' level, on the mechanical/disintegration parameters were found by summing up all the mechanical (TS or BFI) or disintegration (DT or CSFR/DT) parameter results of samples containing 'high' levels of B and subtracting the sum of the results of samples containing 'low' levels of B. That is:

$$¼ \{(B_HC_HD_H + B_HC_HD_L + B_HC_LD_H + B_HC_LD_L) – (B_LC_LD_L + B_LC_LD_H + B_LC_HD_L + B_LC_HD_H)\}$$

The effects of the concentration of binding agent, C, and relative density of binding agent, D, were calculated similarly. To determine whether there was any interaction between any two variables, the results of the combinations in which they appeared together at either 'high' or 'low' levels were summed up and the sum of other combinations was subtracted to obtain the interaction coefficient. For example, for B and C, we have:

$$¼\{(B_LC_LD_L + B_LC_LD_H + B_LC_HD_L + B_LC_HD_H) – (B_HC_HD_H + B_HC_HD_L + B_HC_LD_H + B_HC_LD_L)$$

A zero result indicates no interaction, but if the interaction coefficient was significantly removed from zero, then the two variables concerned were interacting with each other. The extent of removal from zero is a measure of the magnitude of interaction.[10, 11] All measurements were made in triplicate and the results given are the mean values. These results were subjected to the analysis of variance (ANOVA) at a 5 % probability level and found to be significantly different from zero.

RESULTS AND DISCUSSION

Table 1 shows the value of tensile strength, brittle fracture index, disintegration time and crushing strength-friability/disintegration time ratio of paracetamol tablets for the different combinations. The values were used to calculate the independent and interaction coefficient values using the relevant expressions as presented in Tables 2 and 3. There were both positive and negative influences on the properties of the tablets tested. Positive influence indicates that a particular property has increased while a negative influence indicates that the value of the property has decreased.

Individual effects

This involves the effects that gum-binder type (B), concentration of binder (C) and relative density (D) of tablet would have on the tensile strength, brittle fracture index, disintegration time and the crushing-strength-friability/disintegration time ratio of the tablets. Results and rankings of the variables are shown in Tables 2 and 4 respectively.

In considering the combinations i.e. TRG/DRSG, TRG/ACG and DRSG/ACG, the ranking obtained for all on TS and BFI was D>C>B. The fact that D exhibited the

Table 1: *Characteristics of paracetamol tablets for factorial experimental design*

	Variables and combination codes	TS (MN^{-2})	BFI	DT (min)	CSFR/DT
Employing TRG and DRSG as binder	$B_L C_L D_L$	1.729	0.987	17.532	0.064
	$B_L C_L D_H$	2.890	0.487	58.229	0.321
	$B_L C_H D_H$	3.330	0.226	97.028	0.821
	$B_L C_H D_L$	2.045	0.233	84.159	0.105
	$B_H C_L D_L$	1.647	1.432	32.014	0.263
	$B_H C_L D_H$	2.686	0.612	66.247	0.561
	$B_H C_H D_H$	3.403	0.239	98.678	1.134
	$B_H C_H D_L$	2.195	0.924	73.050	0.348
Employing TRG and ACG as binder	$B_L C_L D_L$	1.326	1.777	5.891	1.263
	$B_L C_L D_H$	2.148	0.471	27.063	1.284
	$B_L C_H D_H$	3.110	0.206	47.287	1.333
	$B_L C_H D_L$	2.028	0.890	7.864	1.196
	$B_H C_L D_L$	1.647	1.432	32.014	0.263
	$B_H C_L D_H$	2.686	0.612	66.247	0.561
	$B_H C_H D_H$	3.403	0.239	98.678	1.134
	$B_H C_H D_L$	2.195	0.924	73.050	0.348
Employing DRSG and ACG as binder	$B_L C_L D_L$	1.326	1.777	5.891	1.263
	$B_L C_L D_H$	2.148	0.471	27.063	1.284
	$B_L C_H D_H$	3.110	0.206	47.287	1.333
	$B_L C_H D_L$	2.028	0.890	7.864	1.196
	$B_H C_L D_L$	1.729	0.987	17.532	0.064
	$B_H C_L D_H$	2.890	0.487	58.229	0.321
	$B_H C_H D_H$	3.330	0.226	97.028	0.821
	$B_H C_H D_L$	2.045	0.233	84.159	0.105

tensile strength (TS), brittle fracture index (BFI), disintegration time (DT) and crushing-strength-friability disintegration time ratio (CSFR/DT)

Table 2: *Individual effects of variables on paracetamol tablet.*

Variables	Independent			
Coefficient	TS(MN^{-2})	BFI	DT	CSFR/DT
Employing TRG and DRSG				
B	-0.016	0.316	3.260	0.248
C	0.505	-0.474	44.723	0.300
D	1.173	-0.503	28.357	0.514
Employing TRG and ACG				
B	0.330	-0.034	45.471	-0.693
C	0.732	-0.508	23.916	0.160
D	1.038	-0.874	30.114	0.310
Employing DRSG and ACG				
B	0.346	-0.353	42.211	-0.941
C	0.605	-0.542	31.906	0.131
D	1.087	-0.624	28.540	0.283

gum-binders type (B), concentration of binder (C) and relative density (D)

Table 3: *Interacting effects of variables on paracetamol tablet.*

Variables	Interaction Coefficient			
	TS (MNm^{-2})	BFI	DT (min)	CSFR/DT
Employing TRG and DRSG				
Effect of B and C	0.127	0.034	-7.990	0.029
Effect of B and D	-0.050	-0.250	1.574	0.028
Effect of C and D	0.073	0.157	-9.108	0.237
Employing TRG and ACG				
Effect of B and C	-0.100	0.068	12.817	0.169
Effect of B and D	0.086	0.121	-0.183	0.231
Effect of C and D	0.107	0.189	2.412	0.151
Employing DRSG and ACG				
Effect of B and C	-0.227	0.034	20.807	0.140
Effect of B and D	0.135	0.371	-1.757	0.204
Effect of C and D	0.096	0.279	-2.394	0.144

highest individual effect on both parameters suggests the importance of D in the formulation of strong and stable tablets. It could also explain why granulation is used for the production of tablets[12], because at higher relative densities more granules would be broken. This would lead to more bonding surfaces, hence more particle–particle interactions[13] with a resulting increase in bond strength. Increase in D would lead to a higher reduction in the amount of air present in the die, and in the tablet produced. Hence, a reduction (negative value) observed in the BFI (Table 2), since excessive amount of air present in a tablet would lead to capping and lamination caused by expansion[14, 15] due to elastic recovery of the tablet after ejection from the die. The influence that D had on TS and BFI also suggests that for gum/gum combinations as in the case of the experiment, a high D would be required to form stable compacts. The effect that D had over C could be due to the fact that though, a higher binder concentration will ensure the formation of stronger granules, only a higher D would bring the granules together for more particle–particle interaction. For the TRG/DRSG combination, it is seen (Table 2) that B caused a reduction (negative value obtained) on the TS and a decrease (positive value obtained) on the BFI. These observations suggest that gum/gum combination for a formulation may not enhance the mechanical properties of a tablet, and that TRG may not be a stronger binder than DRSG.

In considering the combinations on DT and CSFR/DT, the general ranking (Table 4) was B>D>C, but when TRG/DRSG combination was considered, for DT it was C>D>B while for CSFR/DT it was D>C>B. This ranking for DT in TRG/DRSG combination could have arisen from the negative influence (i.e. a reduction) that B had on the TS hence the C would play a prominent role since a tablet needs to disintegrate into granules before deaggregating to fine particles. The ranking obtained for this combination on CSFR/DT implies that D had a higher influence on the CSFR/DT than C and B. the importance of D in ensuring more particle–particle interaction in the die leading to formation of strong solid bonds could be responsible for the higher influence of D.

The general ranking of B>D>C obtained in TRG/ACG and DRSG/ACG combinations on the DT and CSFR/DT implied that the binder type had more influence on the two parameters, and suggests that TRG and DRSG are stronger binders than ACG. The result for these two combinations (Table 2) further revealed that though B had more influence, it would lead to a reduction in the balance between the binding and disintegration properties of the paracetamol tablet produced. This is because of the negative value of B on the CSFR/DT. Also, as shown in Table 2, D facilitates a better balance between binding and disintegrant properties more than other variables studied in this work. This could be due to the effect of D in enhancing more particle–particle interaction.

Interaction effect

The interaction effect values (Table 3) indicates the effect of the variables in combination. The rankings of interaction effects are also seen in Table 4. The ranking of the interaction effects on the TS and DT shows that the interaction between B and C were generally the highest, and those between B and D the lowest. This suggests that a change in the type of gum – binder would have considerable influence on the activity that C will have on the TS and DT and that D is the most independent variable acting on TS and DT. Thus, the type of gum used as a binder is important in formulation studies. The results (Table 3) further showed that combination of gum binders though may lead to an increase in TS, it does not necessarily lead to increase in DT, and vice–versa.

In considering the BFI and CSFR/DT it is seen (Table 4) that the interaction between B and D were generally the highest while those between B and C the lowest. This suggests that a change in the gum binder type would have considerable influence on the activity that D will have on the tablets produced. It also implies that the most independent variable is the C of the binder used. The result further showed that though there may be a reduction in DT (Table 3), this may not necessarily transfer to an improved balance in the binding and disintegrant properties i.e. CSFR/DT. The variables would be affected by gum–binders in combination.

Table 4: *Rankings obtained for the coefficient effects on paracetamol tablet characteristics.*

Formulation	TS (MNm^{-2})	BFI	DT (min)	CSFR/DT
		Independent coefficient		
Employing TRG/DRSG.	D > C > B	D > C > B	C > D > B	D > C > B
Employing TRG/ACG.	D > C > B	D > C > B	B > D > C	B > D > C
Employing DRSG/ACG.	D > C > B	D > C > B	B > C > D	B > D > C
		Interaction coefficient		
Employing TRG/DRSG.	B-C >> C-D > B-D	B-D >> C-D >> B-C	C-D > B-C > B-D	C-D >> B-C > B-C
Employing TRG/ACG.	C-D > B-C > B-D	C-D > B-D > B-C	B-C >> C-D > B-D	B-D > B-C > C-D
Employing DRSG/ACG.	B-C > B-D > C-D	B-D > C-D >> B-C	B-C >> C-D > B-D	B-D > C-D > B-C

CONCLUSION

The results of this work have shown that an increase in D of a tablet would have more influence on the production of tablets with low lamination and/or capping tendencies than B, particularly, when considering changing from a weak gum – binder (DRSG or ACG) to a stronger gum – binder (TRG or DRSG). The variable B would have a greater influence on the production of tablets with optimal DT and CSFR/DT, if a change from a weaker gum – binder (ACG) to a stronger gum - binder (TRG or DRSG) is considered. However, C and D would have greater effect on DT and CSFR/DT when changing from DRSG to TRG. The study also showed that B has considerable influence on the interactions between the variables (B, C, or D). Therefore, with the factorial design analysis, it is possible to quantitatively predict the possible effects that the combination of gum – binder whatsoever would have on the property(s) of a tablet, and hence would be a useful tool in decision making in tablet formulation at the industrial level.

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