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Article

A quantitative study of the influence of coprocessing of binders on the mechanical properties of paracetamol tablets

Abayomi Tolulope Ogunjimi, Gbenga Alebiowu

Department of Pharmaceutics, Faculty of Pharmacy, Obafemi Awolowo University

A 2^3 factorial experimental design has been used to quantitatively study individual and interaction effects of the nature of binder (N), concentration of binder (C) and the applied pressure (P) on two mechanical properties, namely, tensile strength (TS) and brittle fracture index (BFI), of paracetamol tablets. The factorial design was also used to study the quantitative effects of coprocessing of binders on the mechanical properties. The results obtained from this study suggest that the nature (i.e. plastic/elastic) and ratio of binders coprocessed together alter the influence of C and P on TS and BFI.

Uniterms: Coprocessing. Neem gum. Microcrystalline cellulose. Binder. Tensile strength. Brittle fracture index. Paracetamol.

Utilizou-se planejamento experimental fatorial 2^3 para estudar, quantitativamente, os efeitos individuais e de interação da natureza do ligante (N), concentração do ligante (C) e a pressão aplicada (P) em duas propriedades mecânicas, como forças de ruptura (TS) e índice de fragilidade (BFI) de comprimidos de paracetamol. O planejamento fatorial foi, também, empregado para estudar os efeitos quantitativos do coprocessamento de ligantes nas propriedades mecânicas. Os resultados obtidos desse trabalho sugerem que a natureza (plástica/elástica) e a proporção de ligantes coprocessados, juntas, alteram a influência de C e P em TS e em BFI.

Unitermos: Coprocessamento. Goma Neem. Celulose microcristalina. Ligante. Resistência à ruptura. Índice de fragilidade. Paracetamol.

INTRODUCTION

Tablets are the most common dosage form (about 70%) in the market due to their advantages over other dosage forms (Rubinstein, 1988). In the production of tablets, one or more excipients are needed to facilitate the production of good quality tablets particularly for active pharmaceutical ingredients (API) that have little or no directly compressible properties. One of these excipients is a binder e.g. starch which helps to impart cohesion on the powder mix, and hence improve the flow properties of granules and mechanical strength of tablets produced.

The formulator is informed of the suitability of a binder before it is chosen for a tablet formulation, but because no single binder possesses all the attributes of high functionality with superior intrinsic performances, coprocessing is now being carried out by formulators. Coprocessing is the science of particle engineering of individual excipients, combination of two or more conventional excipients (usually with one or more primary functionality which compromises other functionalities) into a single multifunctional/advanced substance of high functionality with superior intrinsic performance – high compatibility, high intrinsic flow, good lubricating efficiency, improved blending properties and good binding properties. The performance of coprocessed excipients exceeds those of conventional ingredients (Nachaegari, Bansal, 2004).

In the present study, Neem gum obtained from the trunk of *Azadirachta indica* A. Juss (Meliaceae) was coprocessed with microcrystalline cellulose at different ratios and evaluated as a binding agent in paracetamol tablet formulations in comparison with neem gum and microcrystalline cellulose used independently as binders. The mechanical properties of tensile strength and brittle

***Correspondence:** G. Alebiowu. Department of Pharmaceutics, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria. E-mail: galebiowu@oauife.edu.ng, galebiowu @rediffmail.com

fracture index were used as assessment parameters while 2^3 factorial was used to analyze the results obtained. Paracetamol powder was used as the model drug because of its poor compression properties; hence it needs a binding agent among other excipients to form satisfactory tablets.

MATERIALS AND METHODS

Materials

The materials used were paracetamol powder BP, microcrystalline cellulose (MCC) (Courtin and Warner, Sussex, England, UK), corn starch, BP (BDH Chemicals Ltd, Poole, UK), Lactose BP (AB Knight and Co., London, UK), 95% ethanol (Sigma-Aldrich Laborchemickalien, GMBH, Seelze, Germany), Neem gum obtained from the incised trunk of *Azadirachta indica* tree at the Obafemi Awolowo University (Ile-Ife, Nigeria) and purified using established methods (Adetogun, Alebiowu, 2007). Briefly, the collected Neem gum was hydrated in a sufficient amount of distilled water for 5 days with intermittent stirring, and extraneous materials were removed by filtering using a Buchner funnel under negative pressure. The gum from the filtered slurry was precipitated with 95% ethanol; the precipitated gum was then filtered, washed several times with acetone and dried in a hot air oven at 30 °C for 96 h before milling and sieving with a mesh No. 60 (250 μm) and then stored in an amber coloured bottle until needed.

Preparation of coprocessed binder

Batches of 200 g each (Table I) containing mixtures of neem gum and MCC at different ratios i.e. 9:1, 7:3, 1:1, 3:7 and 1:9 (Neem gum : MCC) were coprocessed. The neem gum for each batch was dissolved in sufficient quantity of distilled water to form a solution. The MCC which was previously milled and sieved with mesh No. 60 (250 μm) was gradually added to the solution while mixing in a Hobart planetary mixer (Hobart Canada Inc., Don Mills, ON, Canada) to avoid formation of lumps. Mixing was carried out over a period of 15 min and the resulting homogenous paste was dried at 40 °C for 72 h in a hot air oven. The dried mass was then milled and sieved with a mesh No. 60 (250 μm) and stored in an amber coloured screw-capped bottle until needed.

TABLE I - Formulae and codes of coprocessed excipients

Neem Gum : MCC (Ratio)	Batch Codes	200 g batches	
		Neem gum	MCC
9:1	CP1	180 g	20 g
7:3	CP2	140 g	60 g
1:1	CP3	100 g	100 g
3:7	CP4	60 g	140 g
1:9	CP5	20 g	180 g
-	NMG	200 g	-
-	MCC	-	200 g

Preparation of granules

The wet granulation method of massing and screening was employed. Batches (100 g) of a basic formulation of Paracetamol (90% w/w), corn starch (4% w/w), and lactose (6% w/w) were dry mixed for 5 min in a Hobart planetary mixer (Hobart Canada Inc., Don Mills, ON, Canada) and then moistened with appropriate amounts of binding solutions to produce granules containing different concentrations of neem gum, MCC or coprocessed binders. Massing was continued for 5 min and then the wet masses were passed manually through a No. 12 mesh sieve (1400 μm) to granulate the wet masses. The granules were dried in a hot air oven for 24 h at 50 °C and resieved through a No. 16 mesh (1000 μm). The degree of granule mixing was then determined by a spectrophotometric assay of paracetamol at 249 nm and was found to be > 0.95 The moisture content of the formulation, determined with an Ohaus moisture balance (Ohaus Scale Corporation, Pine Brook, USA), was between 0.6 and 2.0% w/w. Particle densities were determined with acetone as the displacement fluid.

Preparation of Tablets

Tablets (550 mg) were prepared from the 250 – 710 μm size fractions of granules by compressing them for 30 s with predetermined loads on a Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, US). Before each compression, the die (12.5 mm diameter) and the flat-faced punches were lubricated with a 2% w/w dispersion of magnesium stearate/talc (1:1) in acetone. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery and hardening and to prevent falsely low-yield values. Their weights (w) and dimensions were then determined within ± 1 mg and 0.01 mm respectively, and their relative densities (D) were calculated by using the following equation.

$$D = {}^{w}\!/\!_{V_t \rho_s} \qquad (1)$$

where V_t is the volume (cm^3) of tablet and ρ_s is the particle density (gcm^{-3}) of the solid material.

Determination of Mechanical Properties

The tensile strength (T) of the normal tablets and apparent tensile strength (T_o) of those containing a hole were determined at room temperature by diametral compression with a Monsanto hardness tester and by applying the Fell and Newton equation (Fell and Newton, 1970) i.e.,

$$T = {}^{2F}/_{\pi dt} \quad (2)$$

where T or (T_o) is the tensile strength of the tablet (MNm^{-2}), F is the load (MN) needed to cause a fracture, d is the tablet diameter (m), and t is the tablet thickness (m). Results were taken only from tablets which split clearly into two halves without any sign of laminating. All measurements were made in triplicate or more, and the results given are means of several determinations. The brittle fracture index (BFI) of the tablet was calculated by using the equation devised by Hiestand *et al.* (1977) i.e.

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

EXPERIMENTAL DESIGN

To study the effect of the nature of the binding agent (denoted by N), concentration of the binding agent (denoted by C), applied pressure (denoted by P) on tensile strength and brittle fracture of Paracetamol tablets made from each of the binding agents, experiments were performed in a factorial design involving the application of simple statistics (Woolfall, 1964, Alebiowu and Ojeleye, 2007). The basis of the experimental design was that each of the three variables was used at a "high" level (denoted by the subscript H) and a "low" level (denoted by the subscript L). The number of experiments in the design was 2^3 (i.e. 8). Using the above nomenclature, the various interacting combinations among the variables used in the design were:

$N_LC_LP_L$ $N_LC_HP_L$ $N_LC_HP_H$ $N_LC_LP_H$
$N_HC_LP_L$ $N_HC_HP_L$ $N_HC_HP_H$ $N_HC_LP_H$

N_L represent the nature of the binding agent (CP1, CP2, CP3, CP4, CP5, and MCC) and N_H represent the nature of the binding agent (NMG, MCC); MCC represents high only when in combination with CP1, CP2, CP3, CP4 and CP5. C_L is the binding agent concentration (1% w/w), C_H is the binding agent concentration (5% w/w), P_L is the applied pressure (95.88 MNm^{-2}) and P_H is the applied pressure (159.81 MNm^{-2})

By grouping the results from different combinations into a number of sets (Table II), it was possible to assess the effects that each of the three variables had separately on the tensile strength and brittle fracture index values of the tablets and also to determine whether the variables were interacting or acting independently of each other. The effect of increasing N from its "low" level to its "high" level on the tensile strength and brittle fracture index values were found by summing up all the tensile strength or brittle fracture index values of the samples containing high levels of N, and subtracting the sum of the results of the samples containing low levels of N:

$$¼[(N_HC_LP_L+N_HC_HP_L+N_HC_HP_H+N_HC_LP_H) - (N_LC_LP_L + N_LC_HP_L + N_LC_HP_H + N_LC_LP_H)]$$

The effect of the concentration of binding agent (C) and applied pressure (P) were calculated using a similar expression.

To determine if there was any interaction between any two variables, the results of the combination in which they appeared together at either "low" or "high" levels were summed and the sum of other combinations was subtracted from this to obtain the interaction coefficient. For example, for N and C, we have:

$$¼[(N_LC_LP_L + N_HC_HP_L + N_HC_HP_H + N_LC_LP_H) - (N_HC_LP_L+N_LC_HP_L + N_LC_HP_H+ N_HC_LP_H)]$$

A result of zero indicates no interaction, but if the interaction coefficient is significantly far from zero, then the two variables are interacting with each other. The extent of difference from zero is a measure of the magnitude of interaction (Woolfall, 1964). All measurements were made in triplicate, and the results given are the mean of triplicate determinations. These results were subjected to analysis of variance (ANOVA) at a 5% confidence level, and were significantly different from zero.

RESULTS AND DISCUSSION

Table II shows the values of tensile strength and brittle fracture index of Paracetamol tablets for each of the combinations. These values were used to calculate the independent and interaction coefficient values using relevant expressions and these are presented in Tables III and IV which were further used in determining the rankings in Tables V and VI.

There were positive influences on the tensile strength while the brittle fracture index values of the Paracetamol tablets had both positive and negative influences. A positive influence indicates that a particular parameter

TABLE II - Values of tensile strength and brittle fracture index of paracetamol tablets for factorial experimental design

Variables and combination codes	Tensile strength (MNm^{-2})	Brittle fracture index
(i) *Employing NMG and CP1*		
$N_LC_LP_L$	0.274	0.202
$N_LC_LP_H$	0.502	0.063
$N_LC_HP_L$	0.666	0.213
$N_LC_HP_H$	1.21	0.232
$N_HC_LP_L$	0.45	0.386
$N_HC_LP_H$	0.773	0.29
$N_HC_HP_L$	0.65	0.251
$N_HC_HP_H$	1.235	0.471
(ii) *Employing NMG and CP2*		
$N_LC_LP_L$	0.354	0.132
$N_LC_LP_H$	0.702	0.293
$N_LC_HP_L$	0.588	0.233
$N_LC_HP_H$	1.031	0.124
$N_HC_LP_L$	0.45	0.386
$N_HC_LP_H$	0.773	0.29
$N_HC_HP_L$	0.65	0.251
$N_HC_HP_H$	1.235	0.471
(iii) *Employing NMG and CP3*		
$N_LC_LP_L$	0.372	0.155
$N_LC_LP_H$	0.65	0.221
$N_LC_HP_L$	0.622	0.506
$N_LC_HP_H$	0.985	0.046
$N_HC_LP_L$	0.45	0.386
$N_HC_LP_H$	0.773	0.29
$N_HC_HP_L$	0.65	0.251
$N_HC_HP_H$	1.235	0.471
(iv) *Employing NMG and CP4*		
$N_LC_LP_L$	0.218	0.365
$N_LC_LP_H$	0.53	0.347
$N_LC_HP_L$	0.353	0.149
$N_LC_HP_H$	0.693	0.173
$N_HC_LP_L$	0.45	0.386
$N_HC_LP_H$	0.773	0.29
$N_HC_HP_L$	0.65	0.251
$N_HC_HP_H$	1.235	0.471
(v) *Employing NMG and CP5*		
$N_LC_LP_L$	0.346	1.031
$N_LC_LP_H$	0.593	0.243
$N_LC_HP_L$	0.32	0.347
$N_LC_HP_H$	0.554	0.039
$N_HC_LP_L$	0.45	0.386
$N_HC_LP_H$	0.773	0.29
$N_HC_HP_L$	0.65	0.251
$N_HC_HP_H$	1.235	0.471
vi) *Employing NMG and MCC*		
$N_LC_LP_L$	0.336	0.866
$N_LC_LP_H$	0.491	0.502
$N_LC_HP_L$	0.223	0.378
$N_LC_HP_H$	0.42	0.109
$N_HC_LP_L$	0.45	0.386
$N_HC_LP_H$	0.773	0.29
$N_HC_HP_L$	0.65	0.251
$N_HC_HP_H$	1.235	0.471
vii) *Employing MCC and CP1*		
$N_LC_LP_L$	0.274	0.202
$N_LC_LP_H$	0.502	0.063
$N_LC_HP_L$	0.666	0.213
$N_LC_HP_H$	1.21	0.232
$N_HC_LP_L$	0.336	0.866
$N_HC_LP_H$	0.491	0.502
$N_HC_HP_L$	0.233	0.378
$N_HC_HP_H$	0.42	0.109
viii) *Employing MCC and CP2*		
$N_LC_LP_L$	0.354	0.132
$N_LC_LP_H$	0.702	0.293
$N_LC_HP_L$	0.588	0.233
$N_LC_HP_H$	1.031	0.124
$N_HC_LP_L$	0.336	0.866
$N_HC_LP_H$	0.491	0.502
$N_HC_HP_L$	0.233	0.378
$N_HC_HP_H$	0.42	0.109
ix) *Employing MCC and CP3*		
$N_LC_LP_L$	0.372	0.155
$N_LC_LP_H$	0.65	0.221
$N_LC_HP_L$	0.622	0.506
$N_LC_HP_H$	0.985	0.046
$N_HC_LP_L$	0.336	0.866
$N_HC_LP_H$	0.491	0.502
$N_HC_HP_L$	0.233	0.378
$N_HC_HP_H$	0.42	0.109
x) *Employing MCC and CP4*		
$N_LC_LP_L$	0.218	0.365
$N_LC_LP_H$	0.53	0.347
$N_LC_HP_L$	0.353	0.149
$N_LC_HP_H$	0.693	0.173
$N_HC_LP_L$	0.336	0.866
$N_HC_LP_H$	0.491	0.502
$N_HC_HP_L$	0.233	0.378
$N_HC_HP_H$	0.42	0.109
xi) *Employing MCC and CP5*		
$N_LC_LP_L$	0.346	1.031
$N_LC_LP_H$	0.593	0.243
$N_LC_HP_L$	0.32	0.347
$N_LC_HP_H$	0.554	0.039
$N_HC_LP_L$	0.336	0.866
$N_HC_LP_H$	0.491	0.502
$N_HC_HP_L$	0.233	0.378
$N_HC_HP_H$	0.42	0.109

TABLE III - Quantitative effect of nature of binder (N), concentration of binder (C) and applied pressure (P) on the tensile strength and brittle fracture index values of paracetamol tablets

Independent coefficient		
Variables	Tensile strength	BFI
(i) *Employing NMG and CP1*		
N	0.114	0.172
C	0.440	0.056
P	0.42	0.001
(ii) *Employing NMG and CP2*		
N	0.108	0.154
C	0.306	0.055
P	0.424	0.044
(iii) *Employing NMG and CP3*		
N	0.119	0.117
C	0.311	0.055
P	0.387	-0.067
(iv) *Employing NMG and CP4*		
N	0.328	0.091
C	0.240	-0.086
P	0.390	0.032
(v) *Employing NMG and CP5*		
N	0.323	-0.153
C	0.149	-0.213
P	0.347	-0.243
vi) *Employing NMG and MCC*		
N	0.409	-0.114
C	0.119	-0.208
P	0.315	-0.127
vii) *Employing MCC and CP1*		
N	-0.293	0.286
C	0.231	-0.175
P	0.278	-0.188
viii) *Employing MCC and CP2*		
N	-0.298	0.268
C	0.161	-0.237
P	0.283	-0.145
ix) *Employing MCC and CP3*		
N	-0.287	0.231
C	0.102	-0.176
P	0.245	-0.256
x) *Employing MCC and CP4*		
N	-0.078	0.205
C	0.031	-0.317
P	0.248	-0.156
xi) *Employing MCC and CP5*		
N	-0.083	0.048
C	-0.059	-0.442
P	0.205	-0.432

TABLE IV - Quantitative effect of nature of binder (N), concentration (C) and applied pressure (P) on the tensile strength and brittle fracture index values of paracetamol tablets.

Interaction coefficient		
Variables	Tensile strength	BFI
(i) *Employing NMG and CP1*		
N-C	-0.109	-0.033
N-P	0.034	0.061
C-P	0.144	0.118
(ii) *Employing NMG and CP2*		
N-C	0.024	0.028
N-P	0.029	0.018
C-P	0.089	0.011
(iii) *Employing NMG and CP3*		
N-C	0.019	-0.032
N-P	0.066	0.129
C-P	0.086	-0.052
(iv) *Employing NMG and CP4*		
N-C	0.091	0.109
N-P	0.064	0.029
C-P	0.072	0.089
(v) *Employing NMG and CP5*		
N-C	0.181	0.233
N-P	0.106	0.305
C-P	0.062	0.199
vi) *Employing NMG and MCC*		
N-C	0.211	0.231
N-P	0.139	0.189
C-P	0.076	0.102
vii) *Employing MCC and CP1*		
N-C	-0.318	-0.265
N-P	-0.107	-0.128
C-P	0.087	0.063
viii) *Employing MCC and CP2*		
N-C	-0.184	-0.203
N-P	-0.112	-0.171
C-P	0.031	-0.043
ix) *Employing MCC and CP3*		
N-C	-0.189	-0.264
N-P	-0.074	-0.059
C-P	0.029	-0.107
x) *Employing MCC and CP4*		
N-C	-0.118	-0.122
N-P	-0.077	-0.159
C-P	0.015	0.034
xi) *Employing MCC and CP5*		
N-C	-0.027	0.002
N-P	-0.034	0.115
C-P	0.005	0.143

TABLE V - Rankings obtained for the independent coefficient effects on the TS and BFI of tablets

Formulation	Independent rankings	
	TS	BFI
With NMG as high level		
NMG/CP1	C > P >> N	N > C >> P
NMG/CP2	P > C > N	N >> C > P
NMG/CP3	P > C > N	N >> P > C
NMG/CP4	P > N > C	N > C > P
NMG/CP5	P > N > C	P > C > N
NMG/MCC	N > P > C	C > P > N
With MCC as high level		
MCC/CP1	N > P > C	N > P > C
MCC/CP2	N > P > C	N > C > P
MCC/CP3	N > P > C	P > N > C
MCC/CP4	P > N > C	N > C > P
MCC/CP5	P > N > C	C > P > N

TABLE VI - Rankings obtained for the interaction variables on the TS and BFI of tablets

Formulation	Interaction rankings	
	TS	BFI
With NMG as high level		
NMG/CP1	C-P > N-C > N-P	C-P > N-P > N-C
NMG/CP2	C-P > N-P > N-C	N-C > N-P > C-P
NMG/CP3	C-P > N-P > N-C	N-P > C-P > N-C
NMG/CP4	N-C > C-P > N-P	N-C > C-P > N-P
NMG/CP5	N-C > N-P > C-P	N-P > N-C > C-P
NMG/MCC	N-C > N-P > C-P	N-C > N-P > C-P
With MCC as high level		
MCC/CP1	N-C > C-P > N-P	N-C > C-P > N-P
MCC/CP2	N-C > N-P > C-P	N-C > N-P > C-P
MCC/CP3	N-C > N-P > C-P	N-C > C-P > N-P
MCC/CP4	N-C > N-P > C-P	C-P > N-C > N-P
MCC/CP5	N-P > N-C > C-P	C-P > N-P > N-C

increased, whereas a negative influence indicates that the value of the parameter decreased.

Individual coefficient

NMG as high level of binder

For NMG/CP combinations, the two common rankings obtained (Table V) for the TS were P > C > N and P > N > C. The particular ranking obtained depends on the ratio of NMG present in the coprocessed binder. In the case of NMG/CP1, where the amount of NMG in the coprocessed binder is 90% w/w, the ranking obtained was C > P > N where this implies that C had more influence on the TS. This could be due to the high NMG present in the combination which would allow for more particle – particle interaction due to the similarity in the particles (NMG present), and cohesive forces taking place between the similar NMG particles which were more predominant than adhesive forces in the coprocessed binder. For NMG/CP2 and NMG/CP3 combinations, the ranking was P > C > N, implying that P had more influence on the TS than other parameters. This was probably due to the reduction in NMG concentration in the coprocessed binders. The reduction in NMG concentration allowed for more adhesive forces to predominate, hence, pressure would be necessary to effect more particle – particle interaction of the granulation due to creation of more binding surfaces caused by breakage of granules (Alebiowu, Ojeleye, 2007). On the other hand, the ranking obtained for NMG/CP4 and NMG/CP5 combination binders was P > N > C. In these binders, the MCC concentration is much higher than that of NMG. The ranking obtained was due to the elastic nature of MCC which, not only require a higher P for more effective bond formation and stronger tablets, but also undermine the influence that C would have had on the tablets. For NMG/MCC combinations, the rank order for the TS was N > P > C. this implies that NMG is a stronger binder than MCC probably due to the plastic nature of gum. It then suggests that the nature of binders used in combination as binder in a tablet formulation would have more influence on the TS than P and C used for the tablet production. The BFI obtained for this binder combination implies that the concentration of binder had more influence on the BFI than P and N (Tables III and V). This was because a higher concentration of binder will lead to the formation of additional bonds due to the increase in the area of contact between particles when binders are forced into interparticular spaces. These additional bonds will assist in reducing the expansion of the tablets on ejection hence, preventing the capping and lamination tendency of the tablets (Kachrimanis *et al.*, 2003; Wu *et al.*, 2005).

The general ranking of the BFI for the NMG/CP combinations was N > C > P. This implies that the N of binders in combination would have more influence on the capping or lamination tendency of the tablets than other parameters i.e. C and P used in this study. The results presented in Table V show that the grade or level of the influence of the parameter studied depends on the concentration of the two binders coprocessed together. The higher influence of N could be due to the elastic or plastic nature

of the binders coprocessed together. With the higher concentration of NMG (plastic material) in the coprocessed binder, the influence of N was more noticeable (Tables III and V), but with increase in MCC (elastic material) concentration, the influence of N becomes reduced. This suggests that in combination or in coprocessing of binders for use in production of tablets, the plasticity of the binders should be given top priority in order to assist in reducing the brittle fracture propensity of the tablets produced.

MCC as high level of binder

For the TS, the general ranking obtained was N > P > C for MCC/CP1, MCC/CP2 and MCC/CP3 (Table V). This suggests the nature of the binder had a greater effect than other parameters on the TS. This could be due to the elastic nature of MCC which would allow or give space for the formation of weak bonds. This was reflected in the negative values obtained for the TS (Table III) suggesting that the N led to a reduction in the TS. For the P to have a higher ranking than C implies that a higher P would be needed to enhance more particle – particle contact in order to ensure bond formation. For MCC/CP4 and MCC/CP5 combinations, the ranking was P > N > C. This ranking could have resulted from the nature of the binders in combination i.e. a higher percentage of MCC was in the combination (Table I). A higher P would be needed for more effective bond formation to undermine the negative influence the N would have on the tablets TS (Table III).

The BFI results obtained generally suggest that the N had more influence on the lamination or capping tendency of the tablets produced. The N generally gave positive values (Table III) where this could be due to the elastic nature of MCC which was at a higher concentration in the combinations. These positive values implied that the N would enhance the tendency of the tablets to cap or laminate.

Interaction Coefficient

NMG as high level of binder

The interaction effects (Tables IV and VI) indicate the influence of the variables in combination. The rankings of interaction effects are shown in Table VI and indicate that the N, C and P interact with each other to influence the TS and BFI of the Paracetamol tablets. The results showed that the rankings were affected by the concentration of NMG in the coprocessed binders. For NMG/CP1, NMG/CP2 and NMG/CP3 combinations, having higher concentration of NMG in the coprocessed binder, the general ranking for TS was C - P > N - P > N - C, suggesting that N had the most independent effect on the TS of the Paracetamol tablets. It also suggested that a change in the binder concentration would have considerable influence on the consequent effects of the pressure on the TS of the tablets. For NMG/CP4, NMG/CP5 and NMG/MCC combinations having increased concentration of MCC in the combinations, the general ranking for TS was N - C > N -P > C - P, suggesting that P had the most independent effect on the TS of the paracetamol tablets. It also suggested that a change in the nature of the binder also changes its concentration effects on TS parameter.

There was no general ranking obtained for the BFI but the most common ranking was N - C > N - P > C-P irrespective of the concentration of NMG or MCC in the combination but the interaction of N with C or with P generally had the highest ranking. Also the N have considerable influence on the effects compared to the concentration of binder on the TS parameter.

MCC as high level

The general ranking for the TS obtained was N-C > N-P > C-P, suggesting that P had the most independent effect on the TS of the paracetamol tablets. It also implies that the nature of the binding agent has a greater influence on the effect than the concentration of the binder, on the TS of the tablets. The ranking obtained for formulations containing binders with MCC as high level is similar to formulations containing NMG/CP4 and NMG/CP5 and NMG/MCC. These rankings could be due to the level of MCC in the combinations. Since MCC is an elastic material it would have a negative influence on the binding activity of the coprocessed binders, hence facilitating the manifestation of the independent effect of P so as to ensure particle-particle interaction that will lead to formation of stable tablets.

Considering the BFI, no particular trend was observed in the general ranking (Table VI) although the ranking N - C > C - P > N - P was obtained for two binder concentrations. It is evident that N - C interaction generally had the highest ranking suggesting that P had the most independent effect on the BFI. It also shows N can have a considerable influence on the effect of C on the BFI of the tablets. This could be due to the same reasons given above for the TS of the tablets.

CONCLUSION

The results of the present study suggest that coprocessing Neem gum and MCC at different proportions can create binders that produce tablets of the same basic formulation but having different mechanical properties. It also suggests that the nature i.e. the plasticity or elasticity,

of the materials coprocessed determines the properties of the coprocessed binder obtained, and hence influences the independent and interaction coefficients of the variables examined on the mechanical properties of the tablets.

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