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Original Article

EXCIPIENTS COPROCESSING INFLUENCE ON THE INTERACTING VARIABLES THAT AFFECT THE DISINTEGRATION PROPERTIES OF A PARACETAMOL TABLET FORMULATION

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ABSTRACT

Objective: Neem gum (NMG) was coprocessed with lactose (LTC) at different ratios to produce novel binders.

Methods: The quantitative individual and interaction effects of formulation variables, nature of the coprocessed binders (N), concentration of coprocessed binders (C) and their tablet's relative density (D) on two disintegration properties–disintegration time (DT) and crushing strength-friability/disintegration time (CSFR/DT) ratio–of a Paracetamol tablet formulation was studied using a 2^3 factorial experimental design.

Results: The result showed that changing from neem gum to any of the coprocessed binders decreases the disintegration time of the Paracetamol tablet while an increase in C of the coprocessed binders led to an increase in the CSFR/DT ratio of the Paracetamol tablets. The extent of this decrease in disintegration time or increase in CSFR/DT depends on the proportion of NMG or LTC in the coprocessed binders.

Conclusion: The study concluded that the nature and proportions of individual materials coprocessed together would alter the influence C or D would have on disintegration time and CSFR/DT ratio. It further concludes that a 2^3 factorial analysis could be helpful to formulators in creating a design space for choosing optimal formulation and process variables that would produce desired product qualities.

Keywords: Coprocessing, binder, Neem gum, Disintegration time, Crushing-strength-friability/disintegration-time ratio

INTRODUCTION

Disintegration, the physical process of a tablet breakage is a very important step that determines the fate of a drug medicament in the gastrointestinal tract. Its role is to assist in increasing the area of contact between solid drug compacts, and digestive fluids cannot be overemphasized as it is a rate limiting step in the dissolution of a tablet [1]. Thus, disintegration is a highly required step that facilitates the bioavailability of drug molecules in a formulated tablet. Two properties that could be used to assess the disintegration of a pharmaceutical tablet is the disintegration time (DT) and crushing strength-friability-disintegration time (CSFR/DT) ratio. These disintegration properties of a pharmaceutical tablet are largely dependent on factors such as type, concentration and efficiency of the disintegrants used in formulating the tablet. The CSFR/DT ratio has been suggested to be a better index of evaluating tablet quality as it measures the balance between the binding and disintegrating properties of a tablet. Moreover, in addition to measuring tablet strength (crushing strength) and weakness (friability), it simultaneously evaluates the negative effect of these parameters on disintegration time [2, 3]. The CSFR/DT ratio is generally calculated as (CS/FR)/DT but it is represented in texts as indicated above. In general, high values of CSFR/DT ratio correspond to a better balance between binding and disintegration properties and thus better tablet quality.

Disintegrants play an important role in producing tablets of good quality by influencing the breakage of the tablets. However, binders which are employed in a pharmaceutical tablet formulation to provide adequate mechanical strength promotes bonding between the different components of a powder mix in a formulation [4, 5]. It functions by opposing the disintegration rate of a tablet formulation [6] and in essence oppose the influence of a disintegrant. Thus, it is important that a formulator understands the properties of a binder, with a view to assessing its suitability in a tablet formulation. This is important so as to balance its efficacy and efficiency with other excipients in a formulation so as to produce a tablet with optimum mechanical strength, suitable disintegration and release properties. However, due to the non-existence of a single binder/excipient that possesses the attributes of high functionality and performance, coprocessing is currently employed by formulators to engineer and improve the functionality of excipients without adversely affecting the chemical properties of the coprocessed excipients.

Coprocessing is the science of particle engineering that involves the combination of two or more conventional excipients (which has one or more primary functionality that undermines other required functionalities) into a single multifunctional/advanced material of high functionality with superior performances. The superior performances include high compressibility properties, a high intrinsic flow that could enhance direct compression, good lubricating efficiency, improved mixing properties and optimum binding/release properties. Coprocessing is not a chemical reaction process but produces new materials with performances that exceed those of its primary conventional ingredients. Studies have shown that several coprocessed excipients possess improved properties such as good flowability, compressibility, a hardness that is independent of machine speed [7-11].

Natural polymers have enjoyed popularity in drug delivery because of their availability, affordability, biocompatibility, little or no toxicity and non-irritant nature [12-14]. In a previous study, neem gum and its coprocessed neem gum-lactose binders were compared in terms of their flow and consolidation properties. The study confirmed a favourable change in the structural, flow and consolidation properties of these novel coprocessed binders as compared to their original individual constituents (10).

Thus, this study set to evaluate the influence these coprocessed binders would have on the disintegration of a Paracetamol tablet formulation. It will also evaluate their ability to maintain a balance between the binding and disintegrating properties of a Paracetamol tablet formulation. The evaluation compared the relative quantitative effects of the nature of binder (N), the concentration of binder (C) and relative density of Paracetamol tablets (D) on disintegration time (DT) and crushing strength-friability/ disintegration time (CSFR/DT) ratio of the formulated Paracetamol tablets. Also, the influence of coprocessing and ratio of coprocessed ingredients on the two parameters was evaluated.

MATERIALS AND METHODS

Materials

Materials used were Lactose BP (A B Knight and Co. London, United Kingdom), Paracetamol powder BP (BDH Chemicals Ltd., Poole, UK), Acetone and 99.8 % Ethanol (Sigma-Aldrich Laborchemikalien GMBH, D 30926 Seelze, Germany), Neem gum was obtained from the incised trunk of *Azadirachta indica* tree at the Obafemi Awolowo University, Ile-Ife, Nigeria, and was extracted and purified according to established methods [8, 10].

Methods

Identification, collection and processing of neem gum

Azadirachta indica plant was identified and authenticated at the Obafemi Awolowo University, Ile-Ife, Nigeria campus. The voucher specimen number *FPI 2060* was deposited in the herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria.

The gum collected from the injured trunk of the *Azadirachta indica* tree was hydrated insufficient amount of distilled water with intermittent stirring until all materials have completely dissolved/solubilized, extraneous materials were removed by filtering using a Buchner funnel under negative pressure. The gum from the filtered slurry was precipitated with 99.8 % ethanol; the precipitated gum was filtered, washed several times with acetone and dried in a hot air oven at 30 ^{o}C for 96 h before milling and sieving with a mesh No. 60 (250 µm). The gum was thereafter stored in an amber coloured bottle until needed and labeled 'neem gum'[8, 10].

Acute toxicity testing

The acute toxicity test of *Azadirachta indica* gum was carried out using the Locke's method (15). The toxicity was carried out in two phases using 13 experimental animals (rats). The animals were divided into three groups consisting of three animals per group. In the first phase, neem gum at doses of 10, 100, 1000 mg/kg body weight were administered orally in order to establish the range of doses that could produce toxic effects. The animals were observed for mortality within 24 h of administration. The second phase involved repeating the 1000 mg/kg body weight and new doses of 1600, 2900 and 5000 mg/kg body weight, which were administered orally (n = 1) and were observed for 24 h for mortality. The result obtained was used to determine the LD_{50} of the neem gum [16].

Preparation of coprocessed binders

Batches of 200 g as shown in table 1 containing Neem gum-lactose mixtures at different ratios of 3:1, 1:1 and 1:3 were co-processed respectively according to the methods of Ogunjimi and Alebiowu but with slight modification [8]. Briefly, Neem gum for each batch was dissolved in sufficient quantity of distilled water with continuous stirring to form a little viscous homogeneous solution. Previously milled and sieved (250 µm) lactose based on formulae ratio in table 1 was dispersed in sufficient volume of distilled water under continuous stirring to form a homogenous dispersion. The lactose dispersion was added to the Neem gum solution in a Hobart planetary mixer (Hobart Canada Inc., Don Mills, ON, Canada) under continuous stirring. Mixing was carried out over a period of 15 min to ascertain homogeneity. The homogenous mixture was then dried at 40 ^{o}C for 72 h in a hot air oven. The dried mass was milled, sieved with a mesh No. 60 (250 µm) and stored in an amber coloured screw-capped bottle until needed.

Table 1: Formulae ratios and codes of coprocessed binders

Composition (ratios)		Codes
Neem gum	Lactose	
3	1	NL1
1	1	NL2
1	3	NL3

NL1: Neem gum/lactose (3:1), NL2 Neem gum/lactose (1:1), NL3 Neem gum/lactose (1:3)

Preparation of paracetamol granules

The wet granulation method was employed in making the Paracetamol granules. Basically, 100 g batch of a formulation mixture containing Paracetamol, lactose and rice starch as shown in table 2 were dry-mixed for 5 min in a Hobart planetary mixer (Hobart Canada Inc., Don Mills, ON, Canada). The dry mix was then moistened with the necessary amounts of binder solution/slurry containing different concentrations of either pure Neem gum or coprocessed binders as shown in *table* 2. The little damp mass produced were granulated by passing them manually through a 12–mesh (1400 µ) sieve, dried at 50 ^{o}C and then dry screened through a 16–mesh (1000 µ) sieve. Particle densities were determined using the liquid pycnometer method with acetone as displacement fluid. Recorded values were mean of triplicate determinations.

Table 2: Formulae of tablets prepared*

Ingredients	Batches											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Paracetamol	90	90	90	90	90	90	90	90	90	90	90	90
Lactose	5	3	1	5	3	1	5	3	1	5	3	1
Rice starch	4	4	4	4	4	4	4	4	4	4	4	4
NMG	1	3	5	-	-	-	-	-	-	-	-	-
NL1	-	-	-	1	3	5	-	-	-	-	-	-
NL2	-	-	-	-	-	-	1	3	5	-	-	-
NL3	-	-	-	-	-	-	-	-	-	1	3	5

* The values are expressed as percentages; NMG: Neem gum, NL1: Neem gum/lactose (3:1), NL2 Neem gum/lactose (1:1), NL3 Neem gum/lactose (1:3)

Preparation of tablets

Tablet compacts of weight 555 mg each was prepared from Paracetamol granule fractions within the size range of 250–710 µm by compression on a Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, US) for 30 s at five predetermined compression loads (95.886–159.810 MNm-2). Prior to each compression cycle, the die (12.5 mm diameter) and the flat-faced punches were smeared with a 2 %w/w magnesium stearate/talc (1:1) mixture dispersed in acetone which served as a lubricant. Before tablet evaluations, tablets were stored in airtight containers to allow for elastic recovery and hardening in order to prevent falsely yield low values. The weight (w) of the Paracetamol tablets was determined on a digital Mettler Toledo weighing balance (Model PB153, United States) to within±1 mg while the dimension of each tablet was determined with a micrometer screw gauge to within 0.01 mm and the relative density, RD of the tablets were calculated using equation 1 below;

$$RD = w/V_t\rho_s \ldots\ldots\ldots (1)$$

Where *V*t and ρs are the volume (cm3) of the Paracetamol tablet and particle density of the Paracetamol formulation granular material respectively. According to equation 1, volume reduction in the tablet

compacts which increased with successive increase in compression pressure led to variable relative density.

Determination of tablet crushing strength and friability

The crushing load required to split the Paracetamol tablets diametrically into two equal halves was determined using a digital Erweka hardness tester (G. B. Caleva, Dorset, England) at room temperature excluding tablets showing signs of lamination or capping from the determination of the crushing load. The friability of the tablets was determined using ten (10) tablets at each relative density in a Roche friabilator (Erweka T. A., Düsseldorf, Germany) operated at 25 rpm for 4 min. Determinations were made in triplicate, and the mean values were used.

Determination of disintegration time (DT)

Tablet DT was determined using distilled water at 37±0.5 ^{o}C as disintegration medium in a BP Manesty disintegration test unit (Manesty Machines Ltd., Liverpool, UK). Six Paracetamol tablets were tested at each relative density and the time required for all the tablets to pass through the basket completely was recorded. Determinations were made in triplicate, and the mean values were used.

Experimental design

In order to evaluate the effect of the binder nature (denoted by N), binder concentration (denoted by C), relative density of tablets (denoted by D) on disintegration time and CSFR/DT of Paracetamol tablets made from each of the binding agents, an experimental 2^3 factorial design involving the application of simple statistics was used [17, 18].

The experimental design was such 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 total 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 was represented as shown below:

Table 3: 2^3factorial experimental design

NLCLDL	NHCLDL	NHCHDH	NLCHDH
NLCHDL	NHCHDL	NHCLDH	NLCLDH

NL represents the nature of binder (NL1, NL2, NL3) and NH represents the nature of binder (NMG); CL is 1.0 %^{w}/$_{w}$ and CH is 5 %^{w}/$_{w}$ while DL and DH are tablet relative density of 0.84 and 0.90 respectively.

Thus, by grouping the results of the different combinations into sets (table 4), the possible effects each of the three variables had individually on the disintegration time or CSFR/DT of the tablets were assessed while the design model was also used to evaluate if the variables were interacting or acting independently of each other. For example, in order to evaluate the effect of increasing N from its "low" level to a "high" level on disintegration time or CSFR/DT values, the disintegration time or CSFR/DT average values from all combinations containing low level of N (NL) were subtracted from the disintegration time or CSFR/DT average values obtained from the combinations containing high levels of N (NH) as shown in the expression below.

¼[(NHCLDL + NHCHDL + NHCHDH + NHCLDH)– (NLCLDL + NLCHDL + NLCHDH + NLCLDH)] (2)

The effects of the binder concentration (C) and relative density (D) were calculated based on similar expression as shown above. In this evaluation, a result of zero indicates no influence of that variable while the extent of difference from zero indicates the magnitude and direction of the influence. In order to calculate the interaction coefficient effects between any two variables, the average value obtained from every other combination in the design model was subtracted from the average value of all combinations in the design model where the two variables in evaluation appear together at either "low" or "high" levels. For example, to calculate the interaction coefficient between N and C, the expression below was used.

¼ [(NHCHDL + NHCHDH + NLCLDL + NLCLDH)– (NHCLDL + NLCHDL + NLCHDH + NHCLDH)] (3)

Likewise, a result of zero indicates no interaction; however, a significant difference from zero indicates an interaction between the two variables. The extent of difference from zero represents a measure of the magnitude of interaction [17].

RESULTS AND DISCUSSION

Acute toxicity

The acute toxicity results show that the LD50 of neem gum is higher than 5000 mg/kg, which suggests that neem gum is safe as there were no deaths recorded at this dose (15).

Granule homogeneity

The degree of granule mixing was determined by a spectrophotometric assay of Paracetamol at 249 nm and was found to be>0.95.

Moisture content

The moisture content of the formulation was determined with an Ohaus moisture balance (Ohaus Scale Corporation, Pine Brook, USA) with 1 g of the Paracetamol in triplicate and the obtained moisture content value was ranged between 0.6 and 2.0 %^{w}/w.

Disintegration time and CSFR/DT

Table 4 shows the values of disintegration time and CSFR/DT of Paracetamol tablets for the different combinations. The values were used to calculate the independent and interaction coefficient values (*i.e.* individual factor effects and interactions) using the relevant expressions and presented in tables 5 and 7 which were further used in determining the rankings in Tables 6 and 8. There were positive individual influences on the disintegration time while the CSFR/DT of the Paracetamol tablets had both positive and negative influences. Positive influence indicates that a parameter in the evaluation will increase while a negative influence indicates that the value of the parameter under evaluation will decrease when there is a change from a low to a high level of a factor respectively.

Individual effects of variables

The individual effects evaluate the influence of binder nature (N), binder concentration (C) and relative density (D) of tablets on disintegration time and CSFR/DT parameters of the Paracetamol tablets.

In all the combinations evaluated (NMG/NL1, NMG/NL2, NMG/NL3), the common ranking obtained for effects on disintegration time is N>>C>>D (Tables 5 and 6). This result suggests that the nature of binding agent N, would have more influence on the disintegration time of the tablets than binder concentration and relative density of tablets. This could be due to the plastic nature of binders which would enhance more particle-particle bonding of the Paracetamol granules. Binder concentration (C) had a higher effect than relative density (D) probably because a higher binder concentration will lead to the formation of additional bonds due to the increase in the contact area between particles when binders are forced into interparticle spaces [19]. The magnitude of ranking obtained also depends on the ratio of NMG present in the coprocessed binder. In the NMG/NL1 combinations where the amount of NMG in the coprocessed binder was 87.5 %w/w, the magnitude of N was 24.002. This result may be attributed to the high amount of NMG present in the combination which would allow for more particle-particle interaction. In comparison to NMG/NL2 and NMG/NL3 combinations, there was a reduction in the magnitude of N to 21.865 and 20.589 respectively. This decrease could be due to the reduction

in the amount of NMG present in the coprocessed excipient. The result could also be partly due to the higher amount of lactose (a water soluble excipient) in NL3, which could make it possible for water to permeate the tablets' structure [20], thereby causing a reduction in the magnitude of N as it influence the disintegration time of the Paracetamol tablets.

Table 4: Values of DT and CSFR/DT ratio

Variables and combination codes	DT (min)	CSFR/DT
(i) NMG and NL1		
NHCHDH	49.312	2.061
NHCLDH	15.985	1.828
NHCLDL	10.962	1.062
NHCHDL	34.673	1.740
NLCHDH	6.404	2.754
NLCHDL	1.180	4.469
NLCLDH	6.171	2.214
NLCLDL	1.170	3.494
(ii) NMG and NL2		
NHCHDH	49.312	2.061
NHCLDH	15.985	1.828
NHCLDL	10.962	1.062
NHCHDL	34.673	1.740
NLCHDH	5.687	2.430
NLCHDL	1.909	2.960
NLCLDH	14.083	1.240
NLCLDL	1.792	2.244
(iii) NMG and NL3		
NHCHDH	49.312	1.061
NHCLDH	15.985	1.828
NHCLDL	10.962	1.062
NHCHDL	34.673	1.740
NLCHDH	6.436	2.454
NLCHDL	2.779	3.039
NLCLDH	14.795	0.892
NLCLDL	4.568	0.784

*NMG: Neem gum, NL1: Neem gum/lactose (3:1), NL2 Neem gum/lactose (1:1), NL3 Neem gum/lactose (1:3), DT: Disintegration time, CSFR/DT: Crushing-strength-friability-ratio

Table 5: Quantitative effect of the nature of binding agent (N), the concentration of binding agent (C), and the relative density (D) of tablets on the DT and CSFR/DT ratio of Paracetamol tablets with independent effect values

Independent coefficient	DT (min)	CSFR/DT
Variables		
(i)NMG and NL1		
N	24.002	-1.560
C	14.320	0.607
D	7.472	-0.477
(ii)NMG and NL2		
N	21.865	-0.546
C	12.190	0.704
D	8.933	-0.112
(iii)NMG and NL3		
N	20.589	-0.370
C	11.723	0.932
D	8.387	-0.097

*NMG: Neem gum, NL1: Neem gum/lactose (3:1), NL2 Neem gum/lactose (1:1), NL3 Neem gum/lactose (1:3), DT: Disintegration time, CSFR/DT: Crushing-strength-friability-ratio, N: Nature of binder, C: Concentration of binder, D: Relative density of Paracetamol tablet

From table 5, it can be observed that all the individual effects on disintegration time were positive. The positive values of the individual effects suggest that changing the variables (N, C or D) from a low level to a high level would lead to an increase in disintegration time. The magnitude of the individual effect of N which is positive also suggests that NMG is a stronger binder than any of the three coprocessed binders. This could be due to the plastic nature of NMG which would enhance better particle-particle interaction between the Paracetamol granules, causing an increase in disintegration time [16]. Increasing binder concentration (C) will also lead to the formation of additional bonds due to the increase in the contact area between particles when binders are forced into interparticle spaces. Also, increasing relative density (D) would cause a decrease in porosity and consequently slow down water penetration into the tablets, ultimately increasing the disintegration time of the tablets produced [20, 21]. However, the magnitude of the individual effect of binder concentration (C) on disintegration time suggests that the amount of lactose (LTC) present in the coprocessed binder influence its effect on disintegration time. For example, although increasing the concentration of NL3 (which contains 87.5 %w/w of LTC) would lead to an increase in disintegration time, the magnitude of the increase is lower than those of NL2 (which contains 50 %w/w of LTC) and NL3 (which contains 12.5 %w/w of LTC) respectively.

Table 6: Rankings obtained for the independent coefficient effects on DT and CSFR/DT of Paracetamol tablets

Formulation	Independent rankings	
	DT (min)	CSFR/DT
NMG and NL1	N>>C>>D	N>C>D
NMG and NL2	N>>C>>D	C>N>D
NMG and NL3	N>>C>>D	C>N>D

*NMG: Neem gum, NL1: Neem gum/lactose (3:1), NL2 Neem gum/lactose (1:1), NL3 Neem gum/lactose (1:3), DT: Disintegration time, CSFR/DT: Crushing-strength-friability-ratio, N: Nature of binder, C: Concentration of binder, D: Relative density of Paracetamol tablet

In the evaluation of CSFR/DT, the common ranking of the individual effects of the variables in the combinations was C>N>D (table 6). There was a negative effect of N on CSFR/DT, suggesting that changing from a low to a high level of N would not lead to a better balance of the binding and disintegration properties of the tablets. This could be due to the plastic nature of NMG which could enhance more particle-particle interaction of Paracetamol granule and consequent stronger bonding, leading to increasing in disintegration time and a subsequent decrease in CSFR/DT. The positive result obtained for the effect of binder concentration (C) on CSFR/DT suggests that changing from a low to a high level of C would lead to a better balance of the binding and disintegration properties of the Paracetamol tablets.

The result may be attributed to the amount of lactose (LTC) present in the coprocessed binders as shown by the magnitude of the individual effects of binder concentration (C) on CSFR/DT. To explain this, NL3 binder containing the highest amount of lactose possess the largest magnitude (0.932) of individual effect of C on CSFR/DT. A negative effect observed for the effect of D on the CSFR/DT ratio implies that in all the combinations, a change in D from a low to a high level would not lead to a better balance of the binding and disintegration properties as it would always lead to an increase in disintegration time. The magnitude of the individual effect of D on CSFR/DT also suggests that the influence of D is dependent on the amount of lactose present in the coprocessed binders. Although, increase in D would cause a decrease in porosity and consequently slow down water penetration into the tablets, an increasing amount of water soluble lactose (a plasto-elastic pharmaceutical diluent) in the coprocessed binders will make it possible for water to permeate the tablet structure [22], thereby undermining the effect D would have had on the CSFR/DT. This implies that in combination or in coprocessing of binders for use in the production of tablets, the nature of the individual excipients in terms of plasticity or elasticity should be given top priority in order to assist in reducing the disintegration time and also enhance a better balance between binding and disintegration properties of the tablets.

Interaction coefficients of variables

The interaction effects (table 7) indicate the influence of the variables in combination while the ranking of interaction effects as shown in table 8 indicates that the N, C and D interact with each other to influence the disintegration time and CSFR/DT of the Paracetamol tablets. In evaluating disintegration time of NMG/NL1 combination, the ranking of interaction effect on disintegration time was N-C>>>C-D>N-D while for the NMG/NL2 and NMG/NL3 combinations, the ranking was N-C>>>N-D>C-D. This shows that N-C has the highest interaction effect on disintegration time in all cases, which further suggests that D was largely independent of the effect of N and C (table 7 and 8).

Table 7: Quantitative effects of the nature of binding agent (N), the concentration of binding agent (C), and the relative density of tablets (D) on DT and CSFR/DT ratio of Paracetamol tablets with interaction effect values

Interaction coefficient	DT (min)	CSFR/DT
Variables		
(i)NMG and NL1		
N-C	14.199	-0.151
N-D	2.359	1.021
C-D	2.460	-0.220
(ii)NMG and NL2		
N-C	16.329	-0.249
N-D	0.898	0.655
C-D	0.276	0.007
(iii)NMG and NL3		
N-C	16.797	-0.977
N-D	1.445	0.141
C-D	0.762	-0.535

*NMG: Neem gum, NL1: Neem gum/lactose (3:1), NL2 Neem gum/lactose (1:1), NL3 Neem gum/lactose (1:3), DT: Disintegration time, CSFR/DT: Crushing-strength-friability-ratio, N: Nature of binder, C: Concentration of binder, D: Relative density of Paracetamol tablet

For the CSFR/DT ratio, the ranking suggests that N-D has the highest effect for NMG/NL1 and NMG/NL2 combinations. This implies that the influence of C on CSFR/DT was largely independent of N and D. This also suggests that a change in the nature of binder will change the effect relative density has on CSFR/DT.

However, for the NMG/NL3 combination, N-C has the highest effect on CSFR/DT suggesting D was largely independent of N and C. It also suggests that a change in the nature of binder changes the binder concentration effects on CSFR/DT.

Generally N-C, C-D and N-D produced a positive effect on disintegration time, suggesting that N-C, C-D or N-D interactions would lead to an increase in disintegration time. This increase in disintegration time could be due to the concurrent effects of the plasto-elastic nature of the coprocessed binders causing extensive deformation of the Paracetamol granules. It could also be due to increasing in the binder concentration which forms additional bonds and an increase in contact area between granules. The result could also be attributed to a decrease in tablet porosity caused by an increase in relative density when binders are forced into interparticle spaces at increasing compressional forces. This may lead to the production of tablets with high crushing strengths, less water penetration capacity and consequently causing an increase in disintegration time.

Table 8: Rankings obtained for the interaction variables on DT and CSFR/DT of Paracetamol tablets

Formulation	Interaction effects	
	DT (min)	CSFR/DT
NMG and NL1	N-C>>>C-D>N-D	N-D>C-D>N-C
NMG and NL2	N-C>>>N-D>C-D	N-D>N-C>C-D
NMG and NL3	N-C>>>N-D>C-D	N-C>C-D>N-D

*NMG: Neem gum, NL1: Neem gum/lactose (3:1), NL2 Neem gum/lactose (1:1), NL3 Neem gum/lactose (1:3), DT: Disintegration time, CSFR/DT: Crushing-strength-friability-ratio, N: Nature of binder, C: Concentration of binder, D: Relative density of Paracetamol tablet

Considering the negative effect of N-C on CSFR/DT, an interaction of N-C is generally seen to impair the balance of the binding and disintegration properties of the Paracetamol tablet. The positive effect of N-D on CSFR/DT implies that the interaction of N-D led to an increase in CSFR/DT suggesting that a better balance exists between the binding and disintegration properties of the Paracetamol tablets. The negative effect of C-D on CSFR/DT shows that the interaction would lead to a decrease in CSFT/DT suggesting an impairment of the balance existing between the binding and disintegration properties of the Paracetamol tablets probably due to higher friability values.

CONCLUSION

It can be concluded from this work that coprocessing Neem gum with lactose at different proportions can result into binders that produce tablets with the same basic formulae but having different disintegration time profile and balance between binding and disintegration properties. The study also concludes that the nature and proportions of individual materials coprocessed together would alter the influence C or D would have on disintegration time and CSFR/DT ratio. Coprocessed binders containing a higher amount of NMG produced Paracetamol tablets with higher disintegration time while those containing higher amounts of LTC had lower disintegration times. Likewise, there was a better balance between binding and disintegration in Paracetamol tablets produced from coprocessed binders containing a higher amount of LTC. A 2^3 factorial analysis design could be useful in pilot studies to determine which process variables (N, C or D) should be optimized to achieve the maximum release of the active drug substance in a formulation.

CONFLICT OF INTERESTS

Declared none

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