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Effects of co-processing variables on properties of metronidazole tablets containing co-processed starch as sole excipient

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Abstract
Formulation development of pharmaceutical products is often subjected to trials and errors, and to find the best formulary could be time consuming and financially wasteful. Factorial experimental design has been proposed to optimized formulation of pharmaceutical products. In this study a 2^3 factorial experimental design has been used to quantitatively study individual and interaction effects of the type of gum (A), concentration of the gum (B) and the compressing pressure (C) on the tablet friability (F_R), tensile strength (T_S) and disintegration time (D_T), on metronidazole tablet formulations. Metronidazole tablets (Metro) containing the co-processed starches as sole excipients were prepared by direct compression method and were evaluated for the tablet friability (F_R), tensile strength (T_S) and disintegration time (D_T). The results were analyzed using drug design expert software and ANOVA. The individual and combined effects of A, B and C on D_T, T_S and F_R were highly significant ($P<0.05$). In general, the ranking of the individual and sum of effects, on F_R was $B \geq A \geq C \geq BC \geq AC \geq ABC$, while that of D_T and Ts were $A \geq B \geq C \geq AC \geq BC = ABC$ and $A \geq B \geq C \geq AB = BC \geq ABC$ respectively. The results generally showed that co-processing variables such as A, B and C individually and together could considerably affect tableting properties such as F_R D_T and T_S.

Keywords: Direct compression; Factorial design; Tensile Strength; Friability; Tablet disintegration

INTRODUCTION

Direct compression (DC) is a process by which tablets are compressed directly from the powder blend consisting of active ingredient/s and suitable excipient/s without granulating the blend. DC eliminates exposure of active pharmaceutical ingredient (API) to heat and moisture during manufacturing. DC offers economic of scale as less equipments and manufacturing stages are involved compared to wet and dry granulation processes, [1,2]. Availability of DC excipients with excellent functionalities which compensate for the poor is tableting properties of most emerging active pharmaceutical ingredients (API), is crucial for most pharmaceutical industries; as more than 80% of the API cannot be compress directly with granulation are not suitable for direct. Starch is a multifunctional excipient widely use in pharmaceutical formulations owing to its biocompatibility,

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biodegradability, diverse intrinsic physico-chemical properties, and relative ease of modification, [3]. Starches from different botanical sources have properties that translate to their functional characteristics and applications which when modified alter their physicochemical and functional properties. Unmodified starch however suffers some limitations as it exhibit poor flow and compressibility, and therefore not suitable for DC [4].

Co-processing starch with some other materials had being suggested strategy of improving its flow and compressibility [5,6]. Co-processing is based on the novel concept of two or more excipients interacting at the sub-particulate level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual material, [7]. However the functionalities of the resulting co-processed excipient depends to a large extend on factors such as the processing techniques, nature of materials used, as well as their proportion, [8]. It is therefore necessary to study the effects of the processing variables on the excipient functionality and the quality attributes of the tablets.

The objective of the present study is to use 2^3 Factorial experimental designs in evaluating the effects of co-processing variables on the tableting properties of metronidazole tablets containing co-processed *Ipomoea batatas* starches (*IPS*) as sole excipient prepared by DC. The formulation factors evaluated in this study are: types of the gum (A); concentration of the gum (B) and the value of the compressing pressure (C). Each factor in a 2^3factorial design is evaluated at two statistical levels [high (+) and low (-)]. For factor A, neem gum is considered the low level (-) while acacia gum is considered the high level (+). The two levels for Factor B are 5% (-) and 10% (+) while for factor C, 8MT compressing pressure is taken as low level (-) and 10 MT considered as high level (+).

EXPERIMENTAL

Materials. The sweet potato (*Ipomoea batatas*) tubers were obtained from UDUS demonstration farm and authenticated by the Department of Pharmacognosy, FOPS, UDU Sokoto, paracetamol powder BP, neem gum and acacia gum were gifts from Lifecare Pharmaceutical Ltd, Kano Nigeria; all other reagents are of analytical grade.

Extraction of starch. *Ipomoea batatas* starch (IPS) was extracted using the modified method described by [9]. Briefly 3.3 kg of *Ipomoea batatas* tubers were peeled, cut into slices and soaked in 6 L of 0.1% sodium bisulfite solution at 40°C for 24 h. Using a UCB-950A industrial blender (Urano, Brazil) operated at full speed, the soaked tubers were ground until a fine slurry is obtained. The obtained slurry was re-suspended in about 5L of water and screened using a sieve (mesh 200). This was thereafter centrifuge (L7-55 Beckman, Germany) at 55,000 rpm to separate the starch from water and other impurities. The obtained starch was thereafter transferred into a stainless steel trays and dried to a constant weight in an oven (Gallenkamp, Model OV-335, Vindon Scientific Ltd, UK) maintained at 40°C and thereafter stored in a desiccator.

Experimental design. Factorial experimental design has been developed for studying typical pharmaceutical development work. This involves the use of mathematical equations to arrive at an optimal solution, [10]. In this present study a 2^3 full factorial design was created to evaluate the effects of three formulations factors, gum type (A), gum concentration (B) and the Compression pressure (C)), tested at two factorial levels designated as -1 and +1 with 0 as the centre point. The continuous responses set for this

study are tablet friability F_R, tablet tensile strength T_S and tablet disintegration time D_T.

RESULTS AND DISCUSSION

The results obtained from the experiments were statistically analyzed using StatGraphics software. The design was evaluated by multiple linear regression analysis, and the mathematical relationships in the form of regression equations for the measured responses are listed in Table 2. The values of F_R, T_S and D_T for metro formulations are given in table 2, while polynomial equations showing quantitative effects of the independent and interaction factors as coefficient values were presented in Table 3.

Tablet friability is a measure of its weakness and lack of cohesiveness within the tablet structure. Friability values of 0 to 1% are considered satisfactory and acceptable, [11,12]. All metro formulations under investigation complied with the official requirements for tablet friability specified for uncoated tablets, [12] except *IPS*$_1$ and *IPS*$_8$ with values above the limit of acceptance. The friability values for the metro formulations evaluated in this study ranged from 0.45 to 1.2 % and ranked $IPS_7 \leq IPS_5 \leq IPS_1 \leq IPS_4 \leq IPS_6 \leq IPS_2 \leq IPS_8 \leq IPS_1$. All the three factors (A, B and C) had negative but beneficial effects on F_R since low value of F_R are most desirable. A positive influence indicates that a particular parameter increased, whereas a negative influence indicates that the value of the parameter decreased.

Table 1: Factor levels for the combinations generated by the 3^2 full factorial designs

Formulation	Gum type (A)	Gum Conc. % (B)	Pressure MT (C)	St. Level	St. Level	Code
IPS$_1$	*Neem (−)*	05	08.0	-1	-1	$A_LB_LC_L$
IPS $_2$	Acacia(+)	10	08.0	+1	-1	$A_HB_HC_L$
IPS $_3$	Acacia(+)	10	10.0	+1	+1	$A_HB_HC_H$
IPS $_4$	Neem *(−)*	10	08.0	+1	-1	$A_LB_HC_L$
IPS $_5$	*Acacia*(+)	05	08.0	-1	-1	$A_HB_LC_L$
IPS $_6$	Acacia(+)	05	10.0	-1	+1	$A_HB_LC_H$
IPS $_7$	Neem *(−)*	10	10.0	+1	+1	$A_LB_HC_H$
IPS $_8$	Neem *(−)*	05	10.0	-1	+1	$A_LB_LC_H$

Table 2: Tableting properties of the formulations

Formulation	F_R (%)	D_T (Min.)	T_S (N/m^2)	Code
IPS$_1$	1.20	0.30	1.11	$A_LB_LC_L$
IPS $_2$	0.89	2.23	2.07	$A_HB_HC_L$
IPS $_3$	0.90	1.71	3.10	$A_HB_HC_H$
IPS $_4$	0.80	0.32	1.91	$A_LB_HC_L$
IPS $_5$	0.50	1.25	1.55	$A_HB_LC_L$
IPS $_6$	0.81	1.00	1.65	$A_HB_LC_H$
IPS $_7$	0.45	0.23	1.24	$A_LB_HC_H$
IPS $_8$	1.10	0.30	1.20	$A_LB_LC_H$

Key: F_R = Friability, D_T = Tablet disintegration time, T_S = Tensile Strength

Table 3: Regression Equations for the Responses

Regression Equations for the Responses	
$Y_{DT} = 0.92 + 0.63A + 0.21B - 0.11C - 0.07AC - 0.02BC - 0.02ABC$	Eq.3
$Y_{FR} = 0.96 - 0.06A - 0.07B - 0.01C - 6.0\times10^{-4}\ AC + 7.0\times10^{-4}\ BC - 4.2\times10^{-5}\ ABC$	Eq.4
$Y_{TS} = 1.73 + 0.36A + 0.35B + 0.07C + 0.03AC + 0.03BC + 0.01ABC$	Eq.5

Where AC= interaction of A and C, BC = interaction of B and C, ABC = sum of interaction of A, B and C

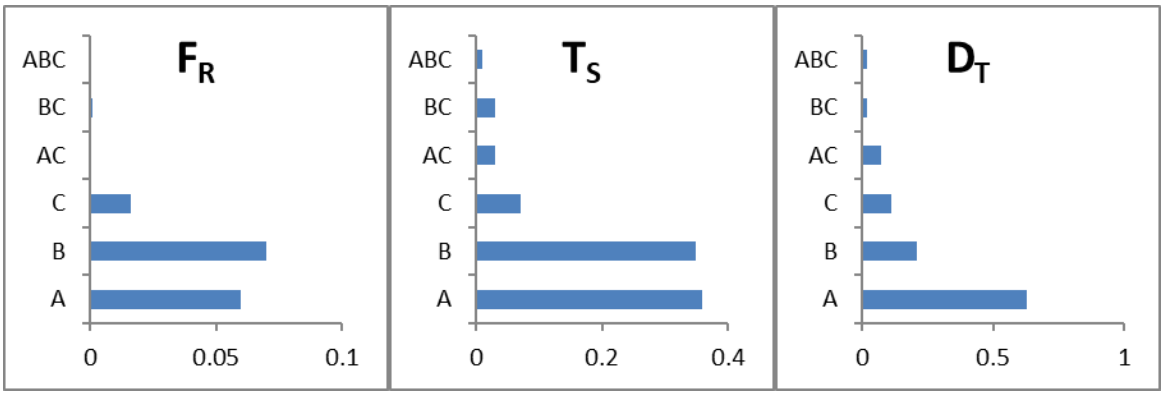

Figure 1: Standardized charts of individual and combine effects on F_R, T_S and D_T

The ranking for the individual and interactive effects of A, B and C on F_R was, B ≥A ≥ C ≥ BC ≥ AC ≥ABC. This implies that B (gum concentration) had most influence on the F_R which may be due to increase particle bonding at higher concentration of gum as a result formation of additional bonds due to the increase in the area of contact between particles when binders are forced into inter-particular spaces at higher gum concentration.

T_S of tablet measures tablet ability to withstand mechanical shocks during normal handling. It is also an indication of the tablet ability to resist cracks, capping lamination and other signs of tablet weakness, and are useful in assessing the usefulness of new DC excipients and formulations, [13]. The values of T_S are seen to generally increase at increased binder concentrations, and this effect was statistically significant ($p \leq 0.05$). It has been established that the presence of high concentration of plasto-elastic materials such as gums leads to an increase in plastic deformation of the formulation and formation of more solid bonds with corresponding increase in T_S [14]. T_S values for the metro formulations ranged from 1.11 to 3.1 %, ranked $IPS_3 \geq IPS_2 \geq IPS_4 \geq IPS_6 \geq IPS_5 \geq IPS_7 \geq IPS_8 \geq IPS_1$

The polynomial expression for individual and interacting variables, (A, B and C) on T_S (eq 2; table 3) shows a positive effect of A, B and C on T_S. The ranking for individual factors was A≥B≥C showing that A had most effects on T_S, this may due to different intrinsic plasticity of gums to impart cohesiveness' and particle bonding. Interaction coefficients AC and BC had equal, positive and higher effects on T_S than ABC.

Rapid disintegration and release of its active ingredient is an essential attribute of conventional tablets. The need for materials for DC tablet manufacturing are expected to be able to impart adequate bonding strength, promote excellent flow, and ensure fast disintegration and release of the active ingredient are among the reasons for the search for DC excipients with multifunctional properties, [15,16]. The effects of A, B and C on D_T is obtained from the co-efficiency of the polynomial equation for D_T (Eq. 3). D_T ranged from 0.23 to 2.23 minutes indicating that all the metro formulations complied with the pharmacopeia requirement for disintegration time of uncoated tablets ($D_T \leq$ 15 minutes). While the effects of A and B on D_T are positive, that of C is negative. The ranking for the individual effect was A≥ B≥ C, These positive values implied that the A would affect the disintegration time of the tablets more than B and C (Figure 1). The values of the interactive effects are obtained from the co-efficiency ABC in Eq (3-5). This indicate that the A, B and C interact with each other to influence the T_S F_R and D_T of metro tablets. These combine effects was ranked, $D_T \geq T_S \geq F_R$ indicating that the combine effects of A, B and C affected the disintegration time

most and a change in A,B and C will seriously affect D_T T_S and F_R of the metro tablets.

Conclusion. The results of the present study suggest that co-processing of gum and starch at different proportions can be use to create new novel excipients which serve as sole excipient in direct tablet compression. It also suggests that the type and concentration of gum used in co-processing determine the release of the drug from tablets as well as the ability to withstand mechanical stress, necessitating careful selection of gum and its concentration to be use in co-processing. This type of study will be useful in development and optimization of materials researches critical to development of drug dosage forms.

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