Effects of Plantain and Corn Starches on the Mechanical and Disintegration Properties of Paracetamol Tablets

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ABSTRACT

The effects of plantain starch obtained from the unripe fruit of the plant *Musa paradisiaca L.* (Musaceae) on the mechanical and disintegration properties of paracetamol tablets have been investigated in comparison with the effects of corn starch BP using a 2^3 factorial experimental design. The individual and combined effects of nature of starch binder (N), concentration of starch binder (C), and the relative density of tablet (RD) on the tensile strength (TS), brittle fracture index (BFI), and disintegration time (DT) of the tablets were investigated. The ranking of the individual effects on TS was RD > C >> N, on BFI was C >> RD > N and on DT was N > C > RD. The ranking for the interaction effects on TS and DT was N-C >> N-RD > C-RD, while that on BFI was N-C >> C-RD > N-RD. Changing nature of starch from a "low" (plantain starch) to a "high" (corn starch) level, increasing the concentration of starch binding agent from 2.5% to 10.0% wt/wt, and increasing relative density of the tablet from 0.80 to 0.90, led to increase in the values of TS and DT, but a decrease in BFI. Thus, tablets containing plantain starch had lower tensile strength and disintegration time values than those containing corn starch, but showed better ability to reduce the lamination and capping tendency in paracetamol tablet formulation. The interaction between N and C was significantly ($P < .001$) higher than those between N and RD and between C and RD. There is therefore the need to carefully choose the nature (N) and concentration (C) of starch used as binding agent in tablet formulations to obtain tablets of desired bond strength and disintegration properties. Furthermore, plantain starch could be useful as an alternative binding agent to cornstarch, especially where faster disintegration is required and the problems of lamination and capping are of particular concern.

KEYWORDS: plantain starch, corn starch, binding agent, paracetamol, tensile strength, Brittle fracture index, disintegration time.

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INTRODUCTION

Starches have been used extensively as fillers, binders, and disintegrants in tablet formulations, and recently a lot of effort has been expended on the development of new starches from local sources as pharmaceutical excipients. One of these starches, plantain starch, obtained from the unripe fruit of the plant, *Musa paradisiaca L.* (*Musaceae*), has been investigated as binder and disintegrant in tablet formulations.[1,2] Further work has suggested that the pregelatinized forms of plantain starch facilitated faster onset of plastic deformation of material but reduced the amount of plastic deformation that occurred during the compression process, and increased the bond strength but decreased the brittleness of the tablets when compared with sorghum and corn starches.[2-4] However, the quantitative effects of important formulation and processing variables on the mechanical strength and disintegration properties of tablets using native plantain starch in comparison with official starches such as corn starch, have remained largely uninvestigated. Thus, in the present work, a study has been made of the relative quantitative effects of the nature (N) of starch binder, concentration (C) of starch binder, and the relative density (RD) of the tablets on the mechanical and disintegration properties of paracetamol tablets, using factorial experimental design,[5] which has already proved useful in the analysis of the quantitative individual and interaction effects of various formulation factors on tablet properties.[6-8]

Two important parameters that have been used to assess the mechanical properties of pharmaceutical tablets are tensile strength (TS), which is a measure of the bond strength of tablets, and brittle fracture index (BFI), which is a measure of the lamination and capping tendency of tablets.[8-10] The brittle fracture index (BFI) was devised by Hiestand et al,[11] and is obtained by comparing the TS of a tablet with a hole in its center, which acts as a built-in stress concentrator defect, with the TS of a tablet without a hole — both at the same relative density.[9-11] The BFI is a measure of localized stress relief within the tablet (at the edge of the hole) by plastic deformation. A low value of BFI is desirable for the minimization of lamination and capping during tablet production.

Paracetamol, an important analgesic and antipyretic agent, was chosen for the present work due to its poor compression properties, and therefore requires a binding agent among other excipients to form good quality tablets.

MATERIALS AND METHODS

Materials

The materials used were paracetamol British Pharmacopoeia (BP), lactose BP, corn starch BP, and magnesium stearate (all obtained from Neimeth Pharmaceuticals International Plc, Lagos, Nigeria). Plantain starch obtained from the unripe fruit of *Musa paradisiaca* was prepared in our laboratory and the description of the preparation has been given elsewhere.[1,12] Starch mucilage was prepared by suspending the starch powder in distilled water, the aqueous slurry of the starch was then heated over a water bath with continous stirring until a mucilage was formed.[1]

Preparation of granules

In a Kenwood planetary mixer (Kenwood Electronics UK Ltd, Herts, UK), 250-g batches of a basic formulation of paracetamol (82% wt/wt), corn starch (10% wt/wt), and lactose (8% wt/tw) were dry-mixed for 5 minutes and then moistened with 40 mL of distilled water or appropriate amounts of starch mucilage to produce granules containing different concentrations of the starch as binders. Massing was continued for 5 minutes and the wet masses were granulated by passing them manually through a number 12 mesh sieve (1400 µm), dried in a hot air oven for 18 hours at 50°C, and then resieved through a number 16 mesh sieve (1000 µm). The granules were then stored in airtight containers.

Preparation of tablets

Tablets (500 mg) were prepared from the 500- to 1000-µm granules by compressing them for 30 seconds with predetermined loads on a Carver hydraulic hand press (Model C, Carver Inc, Menomonee Falls, WI). Before each compression, the 10.5-mm die and flat-faced punches were lubricated with a 2% wt/vol dispersion of magnesium stearate in ether:ethanol (1:1). Tablets with a hole (1.59 mm diameter) at their center were made using an upper punch with a hole through the center and a lower punch fitted with a pin.[9,13] After ejection, the tablets were stored over silica gel for 24 hours to allow for elastic recovery and hardening, and to prevent falsely low yield values. Their weights (w) and dimensions were then determined to within ± 1 mg and 0.01 mm respectively.

The bulk density, ρ_B, of each tablet was calculated from the equation:

$$Bulk\ Density\ (\rho_B) = \frac{Weight\ (g)}{Volume\ (cm^3)} = \frac{w}{\pi\ r^2 h}$$

where r is the radius of the tablet and h is the thickness of the tablet (including the hole when present). The relative density (RD) of the tablet was then calculated from the equation:

$$Relative\ Density\ (RD) = \frac{Bulk\ Density\ (\rho_B)}{Particle\ Density\ (\rho_s)}$$

The particle density (gcm^{-3}) of each solid material was determined by the pycnometer method with xylene as the displacement fluid.

Testing

The TSs of the normal tablets and apparent TSs of those containing a hole (TS_o), were determined at room temperature ($25 \pm 2°C$) by diametral compression[14] using a Kanara hardness tester (Kanara Industrial Corporations, Bombay, India) and by applying the equation:

$$TS\ (or\ TS_0) = \frac{2F}{\pi\ dt}$$

where TS (or TS_o) 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 tablet thickness (m). Results were taken only from tablets, which split cleanly into 2 halves without any sign of lamination. All measurements were made in quadruplicate, and the results given are the means of 4 determinations.

The BFI of the tablets was calculated using equation:

$$BFI = \frac{TS}{TS_0} - 1$$

where TS is the tensile strength of the tablets without a hole, and TS_o is the apparent tensile strength of the tablets when a hole is present.

Disintegration tests

The disintegration times, DT, of the tablets was determined in distilled water at $37 \pm 0.5°C$ using a Veego disintegration tester (Veego Scientific Devices, Mumbai, Maharashtra, India). All measurements were made in quadruplicate, and the results given are the means of 4 determinations.

FACTORIAL EXPERIMENTAL DESIGN

To study the effect of nature of starch binder (denoted by N), concentration of starch binder (denoted by C), and relative

density (denoted by RD) on the mechanical and disintegration properties of paracetamol tablets, the experiments were performed in a factorial design, which involved the application of simple statistics.[5] The basis of the experimental design was that each of the 3 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 $2^3 = 8$.

Using the above nomenclature the various combinations between the variables used in the design were as follows:

$N_L C_L RD_L$, $N_L C_H RD_L$, $N_L C_H RD_H$, $N_L C_L RD_H$

$N_H C_L RD_L$, $N_H C_H RD_L$, $N_H C_H RD_H$, $N_H C_L RD_H$

N_L = Nature of starch binder (plantain starch)

N_H = Nature of starch binder (corn starch)

C_L = Concentration of starch binder (2.5% wt/wt)

C_H = Concentration of starch binder (10.0% wt/wt)

RD_L = Relative density (0.80)

RD_H = Relative density (0.90)

By grouping the results into several sets, it was possible to assess the effects that each of the 3 variables had separately on the mechanical and disintegration properties of the tablets and also to determine whether the variables were interacting or acting independently of each other.

The effects of increasing N, from its "low" level to its "high" level on the various parameters were found by summing all the results (TS or BFI or DT) of samples containing a "high" level of N and subtracting the sum of the results of samples containing "low" levels of N. That is:

$$1/4 \left[(N_H\,C_L\,RD_L + N_H\,C_H\,RD_L + N_H\,C_H\,RD_H + N_H\,C_L\,RD_H) \right.$$
$$\left. - (N\,L\,C_L\,RD_L + N_L\,C_H\,RD_L + N_L\,C_H\,RD_H + N_L\,C_L\,RD_H) \right]$$

The amount by which the result of this treatment departed from 0 was a quantitative measure of the effect of N on the values of the relevant parameter. Similar expressions were used for finding the effects of C and RD.

To determine whether there was any interaction between 2 variables, the TS (or BFI or DT) results of the combinations in which they appear together at either "high" or "low" levels were summed and the sum of other combina-

tions subtracted from this to obtain the interaction coefficient. For example, for N and C:

$$1/4 \left[(N_L\,C_L\,RD_L + N_L\,C_L\,RD_H + N_H\,C_H\,RD_H + N_H\,C_H\,RD_L) \right.$$
$$\left. - (N_L\,C_H\,RD_L + N_L\,C_H\,RD_H + N_H\,C_L\,RD_L + N_H\,C_L\,RD_H) \right]$$

A result of 0 indicates no interaction, but if the interaction coefficient was significantly removed from 0, it is concluded that the 2 variables concerned were interacting with each other. The extent of removal from 0 is a measure of the magnitude of interaction.[5] Similar expressions were used for estimating the interactions between N and RD, and between C and RD.

Statistical Analysis

Statistical analysis to compare the individual and interaction effects of the formulation variables on the mechanical and disintegration properties of the tablets was done with the Kruskal-Wallis test, a nonparametric multiple comparison test, using the computer software Graphpad Prism 4 (GraphPad Software Inc, San Diego, CA). Individual differences between the formulations were performed using the Dunn's multiple comparison tests. At 95% confidence interval, *P* values less than or equal to .05 were considered significant.

RESULTS AND DISCUSSION

Representative plots of log TS, BFI, and DT versus RD for paracetamol tablets containing 2.5% wt/wt of the starches as binding agents are presented in Figures 1, 2, and 3, respectively. The values of TS, BFI, and DT at 2 selected relative density values of 0.8 and 0.9, which are representative of the range of relative density values normally achieved for commercial paracetamol tablets, used for the factorial experiment, are presented in Table 1. These values were used to calculate the individual and interaction coefficients for the variables using the relevant equations. The individual and interaction coefficient values are presented in Table 2. These values provide a clear indication of the quantitative effects of the 3 variables studied on the TS, BFI, and DT of the paracetamol tablets.

In comparing the formulations, the ranking of the individual (independent) coefficient values for the formulations on TS was RD > C >> N, on BFI was C >> RD > N, and on DT was N > C > RD. All the individual effects on BFI were negative indicating that the values of the parameter decreased in all cases.
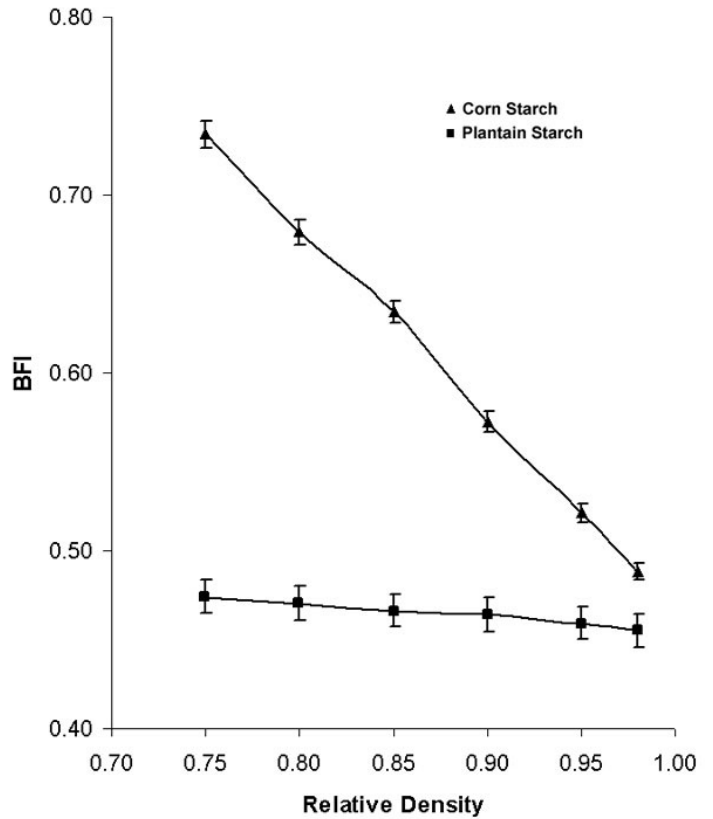
The effect of C indicates that increasing the concentration of the starch binder from 2.5% to 10% wt/wt led to an increase in the plastic deformation of the formulation
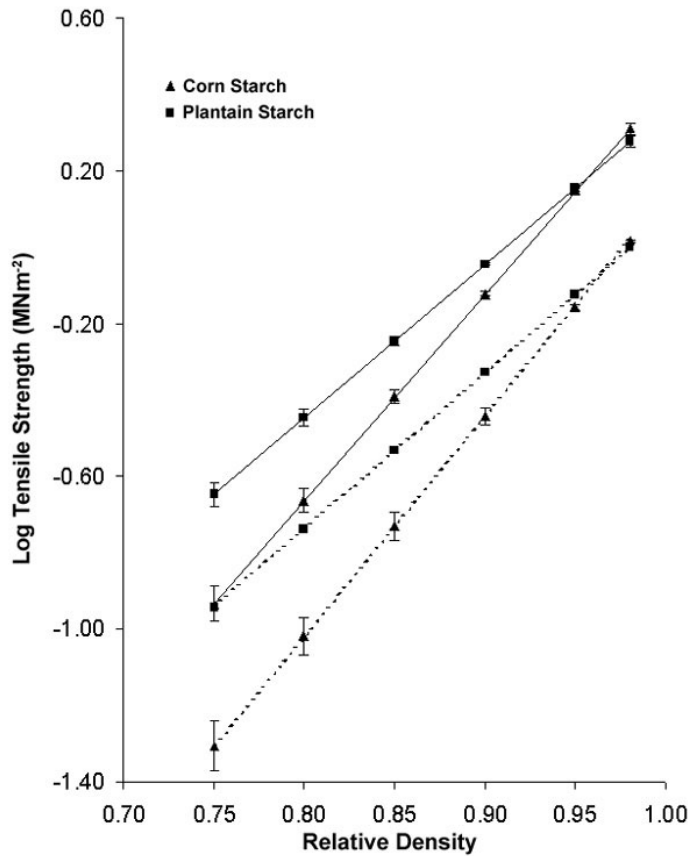
Figure 1. Log tensile strength (MNm-2) versus relative density for paracetamol tablets containing 2.5% wt/wt starch binder with (- - - - -) and without (———) a hole at their centre.

Figure 2. Brittle fracture Index (BFI) versus relative density for paracetamol tablets containing 2.5% wt/wt starch binder.

during compression and subsequently to the formation of more solid bonds in the tablet[9] leading to an increase in the TS and in the DT of the tablet. However, the effect of C on the BFI was negative, indicating that the values of BFI for the formulation decreased with increase in binder concentration. This indicates that the presence of binder at interparticulate junctions facilitates plastic deformation for the relief of localized stresses.[8,9] It is notable that the effect of C on BFI was significantly ($P < .001$) higher than the effects of the other variables, N and RD, showing its importance in determining the brittle properties of tablets.

RD had the highest effect on TS but the least effect on DT. Increasing the RD from 0.8 to 0.9 led to an increase in the TS of the tablet and DT. This may be because as the RD of the tablet increases, more solid bonds will be formed between the particles leading to an increase in TS. Furthermore, the starches are forced into interparticulate spaces thereby increasing the area of contact between the particles leading to formation of additional solid bonds that will result in a reduction in the size of the capillary spaces between the particles, which reduced the rate of the penetration of water into the tablet to effect bond separation,[9]

and thus an increase in the DT of the tablets. This result is in agreement with those obtained by Odeku and Itiola[8] when comparing the effects of khaya gum and polyvinyl-pyrrolidone on the TS and disintegration and dissolution properties of paracetamol tablets.
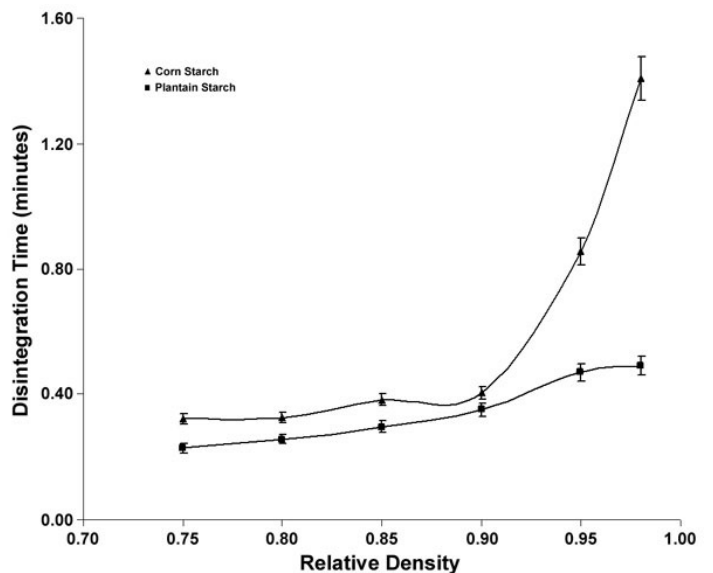
Figure 3. Disintegration time (minutes) versus relative density for paracetamol tablets containing 2.5% wt/wt starch binder.

The influence of N on the TS and DT of the tablets was positive, indicating that tablets containing corn starch as binder, which represented the "high" level of N, had higher TS and DT than tablets containing plantain starch, which represented the "low" level. Thus, corn starch is a stronger binding agent than plantain starch in this particular context. However, all the tablets complied with the BP (1998) requirement on disintegration (ie, disintegration within 15 minutes). Plantain starch could therefore be useful as an alternative binding agent to produce tablets with particular TS and faster disintegration profile. On the other hand, the influence of N on BFI was negative indicating that plantain starch produced tablets with lower BFI values than corn starch. Thus, tablets containing plantain starch, despite their lower bond strength, had better ability to relieve localized stresses than tablets containing corn starch as binding agent.[15]

The interaction coefficient values (Table 2) indicate the effect of the variables in combination. It can be seen that all the variables, N, C, and RD, interacted with each other to alter the TS, BFI, and DT of the tablets. For the formulations, the ranking of the interaction effects on TS and DT was N – C >> N – RD > C – RD, while that on BFI was N – C >> C – RD > N – RD. In all cases, the interaction between N and C had the largest interaction effect on the tablet properties, which suggests that RD had the most independent influence on the mechanical and disintegration properties of paracetamol tablets. Furthermore, statistical analysis showed that the interaction between N and C was significantly ($P < .001$) higher than those between N and RD and those between C and RD. This is probably because the nature of binder determines the softness and plastoelastic properties of the binder and in effect the amount of deformation the binder undergoes under high compressional forces.[16] The number of bonds formed will depend considerably on the concentration of binder employed.[8,10] Thus the nature and concentration of the starch binder employed in a formulation need to be carefully chosen to enable the production of tablets with adequate bond strength to withstand the rigors of handling.

Table 1. Tensile Strength (TS), Brittle Fracture Index (BFI), and Disintegration Times (DT) of Paracetamol Tablets for Factorial Experimental Design

Variables and Combination Codes	TS (MNm^{-2})	BFI	DT (min)
$N_L C_L R_L$	0.358	0.470	0.256
$N_L C_L R_H$	0.904	0.464	0.350
$N_L C_H R_L$	0.488	0.435	0.287
$N_L C_H R_H$	1.279	0.315	0.350
$N_H C_L R_L$	0.217	0.679	0.326
$N_H C_L R_H$	0.755	0.572	0.403
$N_H C_H R_L$	1.025	0.205	0.526
$N_H C_H R_H$	1.524	0.118	0.577

Table 2. Individual and Interaction Effects of Nature of Starch Binder (N), Concentration of Starch Binder (C), and Relative Density (RD) on the Tensile Strength (TS), Brittle Fracture Index (BFI), and Disintegration Times (DT) of Paracetamol Tablets

Variables	TS	BFI	DT
Independent coefficient			
N	0.123	–0.028	0.147
C	0.521	–0.278	0.101
RD	0.594	–0.080	0.071
P	< .001	< .001	< .001
Interaction coefficient			
N-C	0.268	–0.186	0.086
N-RD	–0.075	–0.017	–0.020
C-RD	0.052	–0.024	–0.014
P	< .001	< .001	< .01

CONCLUSION

The results obtained suggest that a change in the starch binder from corn to plantain starch would lead to a decrease in the TS, disintegration, and the lamination tendency of paracetamol tablets. Furthermore, an increase in RD of the tablet and C of binder resulted in tablets with higher TS and DT, but lower BFI. The interaction between N of binder and C of starch binder had the highest effects on the mechanical and disintegration properties of paracetamol tablets. Thus, the N and C of starch used as binding agent in tablet formulation need to be carefully chosen during tablet formulation to obtain tablets of desired mechanical and disintegration properties. Furthermore, plantain starch could be useful as an alternative binding agent to corn starch, especially where faster disintegration is required and the problems of lamination and capping are of particular concern.

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