

The Influence of Pregelatinized Starch Disintegrants on Interacting Variables that Act on Disintegrant Properties

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The quantitative effect of the nature and concentration of a starch disintegrant and the tablet's relative density on the disintegrant's properties (e.g., disintegration time [DT] and the crushing strength–friability/disintegration time [CSFR/DT] ratio) of a paracetamol tablet formulation has been studied using a 2³ factorial experimental design. The design was also used to study the quantitative effects of pregelatinization on the starch disintegrant's properties. The results suggest that although a decrease in DT was obtained with a change from a natural to a pregelatinized starch disintegrant, this change may not necessarily lead to an increase in the CSFR/DT ratio of tablets. Therefore, interaction of the variables may not be favorable to both DT and the CSFR/DT ratio.

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Disintegration plays an important role in a tablet's dissolution before the active drug substance is finally released from the tablet's structure into the body. The type, concentration, and efficiency of disintegrants to a large extent affects the disintegrant properties (e.g., disintegration time [DT] and the ratio of crushing strength–friability to disintegration time [CSFR/DT]) of formulated tablets (1). The CSFR/DT ratio has been suggested as a better index of measuring tablet quality because, in addition to measuring tablet strength (crushing strength) and weakness (friability), it simultaneously evaluates any negative effect of these parameters on DT (2). In general, high values of the CSFR/DT ratio

indicate a better balance of binding and disintegration properties.

Starch is one of the traditional excipients used in the manufacture of tablets (3). Depending on the application, specific starches are available for use as binders, diluents, and/or disintegrants. Starches are being used as disintegrants because of the swelling properties of starch granules in water. Studies have shown that starches, in their various forms, have a variety of swelling abilities (4–6), which may be responsible for the different disintegration and dissolution times reported by Kottke et al. (3). Because relatively high levels of starch used as a disintegrant often weakens the tablet structure (7), the level of starch disintegrant in a formulated

tablet should be optimized without compromising the release of the active ingredient from the tablet structure.

The pregelatinization of sorghum (*Sorghum bicolor* L. *Poaceae*) and plantain (*Musa paradisiaca* L. *Musaceae*) has been shown to have an effect on the activity of the two materials as starch binders (8,9). But no work has been conducted on the activity of the pregelatinized forms of the starches as disintegrants. Hence, the purpose of this study was

- to study and compare the relative quantitative effects of the nature of a disintegrant (*N*), the concentration of a disintegrant (*C*), and the relative density (*D*) of tablets on the DT and on the CSFR/DT ratio of formulated paracetamol tablets
- to determine the effects that the starches' pregelatinization would have on their quantitative effects.

Materials and methods

Materials. The materials used were paracetamol (British Pharmacopoeia [BP] grade), corn starch (BP grade), and gelatin (all from BDH Chemicals Ltd., Poole, UK). The sorghum and plantain starches and the pregelatinized forms of the three starches were prepared in a laboratory at Obafemi Awolowo University.

Preparation of natural and pregelatinized starches. Sorghum and plantain starches were prepared according to established procedures (10). The fully pregelatinized forms of the two starches and the official corn starch were prepared as described in the *British Pharmaceutical Codex* (11) and by Herman et al. (4). An aqueous slurry of each starch was made with 100 g of starch powder in 100 mL of deionized water and then heated at 55 °C with stirring for 10 min. The resulting paste was crisp-dried (i.e., dry and brittle) in a hot-air oven (Gallenkamp, model OV-335, Vindon Scientific Ltd., Oldham, UK) at 60 °C for 48 h. The dried mass was powdered in a laboratory mill (Christy and Norris Ltd., Chemsford, UK). All the starches were passed through a 120-mesh (120- μ m) sieve before use.

Table I: Values of DT and the CSFR/DT ratio.

	Variables and combination codes	DT (min)	CSFR/DT
Using natural and pregelatinized sorghum starches	$N_L C_L D_L$	6.95	2.12
	$N_L C_H D_L$	4.85	73.58
	$N_L C_L D_H$	26.96	1.55
	$N_L C_H D_H$	10.20	30.73
	$N_H C_H D_L$	0.66	19.83
	$N_H C_H D_H$	2.59	7.21
	$N_H C_L D_H$	12.59	2.89
Using natural and pregelatinized plantain starches	$N_L C_L D_L$	3.11	6.60
	$N_L C_H D_L$	1.28	7.67
	$N_L C_H D_H$	0.89	51.63
	$N_L C_L D_H$	18.67	1.40
	$N_L C_H D_H$	3.21	24.22
	$N_H C_H D_L$	0.36	59.98
	$N_H C_H D_H$	2.28	26.68
Using natural and pregelatinized corn starches	$N_H C_L D_H$	10.31	4.35
	$N_H C_L D_L$	0.79	14.69
	$N_L C_L D_L$	1.57	5.79
	$N_L C_H D_L$	0.91	35.44
	$N_L C_L D_H$	14.89	3.64
	$N_L C_H D_H$	2.98	20.69
	$N_H C_H D_L$	0.27	24.41
Using natural sorghum and plantain starches	$N_H C_H D_H$	2.09	18.24
	$N_H C_L D_H$	8.47	6.27
	$N_H C_L D_L$	0.51	11.57
	$N_L C_L D_L$	6.95	2.12
	$N_L C_H D_L$	4.85	73.58
	$N_L C_L D_H$	26.96	1.55
	$N_L C_H D_H$	10.20	30.73
Using natural sorghum and corn starches	$N_H C_H D_L$	0.89	51.63
	$N_H C_H D_H$	3.21	24.22
	$N_H C_L D_H$	18.67	1.40
	$N_H C_L D_L$	1.28	7.67
	$N_L C_L D_L$	6.95	2.12
	$N_L C_H D_L$	4.85	73.58
	$N_L C_L D_H$	26.96	1.55
Using natural plantain and corn starches	$N_L C_H D_H$	10.20	30.73
	$N_H C_H D_L$	0.91	35.44
	$N_H C_H D_H$	2.98	20.69
	$N_H C_L D_H$	14.89	3.64
	$N_H C_L D_L$	1.57	5.79
	$N_L C_L D_L$	1.28	7.67
	$N_L C_H D_L$	0.89	51.63

Preparation of gelatin solution. A gelatin solution was prepared by weighing the amount of gelatin granules that would produce a 4% w/w concentration of starch disintegrant in the formulation. Until a solution formed, the weighed amount of gelatin was suspended for 10 min in distilled water in a beaker with continuous stirring to allow hydration before heating. The solution was used while still hot for more-effective binding.

Preparation of granules. Three-hundred-gram batches of formulation mixtures of paracetamol and starch containing various concentrations of starch disintegrants (2.5% w/w and 10.0% w/w) were prepared by dry mixing the required quantity of paracetamol and each starch for 5 min in a planetary mixer (Hobart Canada Inc., Don Mill, ON, Canada). They were then moistened with a gelatin binder solution to yield 4% w/w gelatin in the final dried

granulation. The resulting wet masses were granulated by passing them manually through a 12-mesh (1400- μ m) sieve, dried at 60 °C for 6 h, and then received through a 16-mesh (1000- μ m) sieve. Each granulation was determined to be mixed to the degree of >0.95. Particle densities were determined using the pycnometer method with benzene as the displacement fluid.

Preparation of tablets. Five-hundred-and-fifty-milligram quantities of 500–1000- μ m fractions of the granules' formulations, giving a tablet thickness of 3.46 \pm 0.03 mm at zero porosity as calculated from particle density values, were compressed for 1 min into tablets with predetermined loads using a hydraulic hand press (model C, Carver Inc., Menomonee Falls, WI). Before each compression, the die (12.5 mm in diameter) and the flat-faced punches were lubricated with a 2% w/w dispersion of magnesium

Table II: Quantitative effect of the nature of disintegrant (N), the concentration of disintegrant (C), and the relative density (D) of tablets on the DT and CSFR/DT ratio of paracetamol tablets with independent-effect values.

	Variables	Independent coefficient	
		DT (min)	CSFR/DT
Using natural and pregelatinized sorghum starches	N	-7.525	-17.863
	C	-7.805	29.547
	D	9.170	-14.917
Using natural and pregelatinized plantain starches	N	-2.570	5.195
	C	-6.077	33.600
	D	7.787	-19.325
Using natural and pregelatinized corn starches	N	-2.252	-1.267
	C	-4.797	17.877
	D	6.925	-7.092
Using natural sorghum and plantain starches	N	-6.227	-5.765
	C	-8.677	38.705
	D	11.267	-19.275
Using natural sorghum and corn starches	N	-7.152	-10.605
	C	-7.857	36.835
	D	10.187	-14.542
Using natural plantain and corn starches	N	-0.925	-4.840
	C	-7.105	28.370
	D	8.775	-12.645

Table III: Quantitative effect of the nature of disintegrant (N), the concentration of disintegrant (C), and the relative density of tablets (D) on the DT and CSFR/DT ratio of paracetamol tablets with interaction-effect values.

	Variables	Interaction coefficient	
		DT (min)	CSFR/DT
Using natural and pregelatinized sorghum starches	$N-C$	1.625	-20.772
	$N-D$	-3.510	6.772
	$C-D$	-5.530	-12.797
Using natural and pregelatinized plantain starches	$N-C$	1.847	0.210
	$N-D$	-2.067	-2.490
	$C-D$	-5.667	-10.025
Using natural and pregelatinized corn starches	$N-C$	1.487	-5.492
	$N-D$	-1.402	1.357
	$C-D$	-4.347	-3.367
Using natural sorghum and plantain starches	$N-C$	0.752	-8.465
	$N-D$	1.412	2.435
	$C-D$	7.432	18.352
Using natural sorghum and corn starches	$N-C$	1.572	-13.485
	$N-D$	-2.492	6.630
	$C-D$	-6.477	-13.720
Using natural plantain and corn starches	$N-C$	0.820	-5.270
	$N-D$	-1.080	4.195
	$C-D$	-6.580	-8.435

stearate in benzene. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery and hardening and to prevent false low-yield values. Their weights (W) and dimensions were then determined to be within ± 1 mg and 0.01 mm, respectively, and their relative densities were calculated using the equation

$$D = \frac{W}{V_t \rho_s}$$

in which V_t is the volume (cm^3) of the tablet and ρ_s is the particle density (g/cm^3) of the solid material.

Determination of disintegrant properties. **Disintegrant test.** Tablet DT was determined in distilled water at 37 ± 0.5 °C in a BP Manesty disintegration test unit (Manesty Machines Ltd., Liverpool, UK). Six tablets were tested at each relative density. De-

terminations were made in triplicate and the mean values were used.

Determination of tablet crushing strength and friability. A crushing strength tester (Monsanto & Co., USA) was used at room temperature to determine the load (N) required to diametrically break the tablets (crushing strength) into two equal halves. Tablets with signs of lamination or capping were not used.

The percent friability of the tablets was determined using a Roche friabilator (Ereweka T.A., Düsseldorf, Germany) operated at 25 rpm for 4 min. Ten tablets were used at each relative density. Determinations were made in triplicate, and the mean values were used.

Experimental design. To study the effect of N , C , and D on the DT and the CSFR/DT ratio of tablets made from starch disintegrant formulations, experiments were performed in a factorial design involving the application of simple statistics (9,12). The basis of the experimental design was that each of the three variables was used at a high level (H) and a low level (L). The number of experiments in the design was 2^3 (i.e., 8). Various combinations among the variables used in the design were $N_L C_L D_L$, $N_L C_H D_L$, $N_L C_L D_H$, $N_L C_H D_H$, $N_H C_L D_L$, $N_H C_H D_L$, $N_H C_L D_H$, and $N_H C_H D_H$ in which N_L is the nature of the starch disintegrant for natural sorghum starch, natural plantain starch, and natural starch, and N_H is the nature of the starch disintegrant for natural plantain starch, natural corn starch, and pregelatinized starch. Natural plantain starch represents the low level only when combined with natural corn starch, and pregelatinized sorghum starch represents the high level only when combined with natural sorghum starch. C_L is the concentration of the starch disintegrant at 2.5% w/w, and C_H is the concentration of the starch disintegrant at 10.0% w/w. D_L is the relative density of 0.80, and D_H is the relative density of 0.90.

By grouping the results of these combinations into several sets, the authors assessed the effects that each of the three variables had, separately, on the DT and the CSFR/DT ratio of tablets and determined whether the variables were interacting or acting independently of each other. The effects on the DT and CSFR/DT values after increasing N from a low to a high level were found by summing all the DT or CSFR/DT values from the samples that contained high levels of N and then by subtracting the sum of the results of the samples that contained low levels of N , which can also be expressed as

$$(N_H C_L D_L + N_H C_H D_L + N_H C_L D_H + N_H C_H D_H) - (N_L C_L D_L + N_L C_H D_L + N_L C_L D_H + N_L C_H D_H) \quad [2]$$

The effects of C and D were calculated similarly.

To determine whether any interaction existed between any two variables, the results of the combinations in which they

appeared together at either high or low levels were calculated, and the sum of other combinations were subtracted from this to obtain the interaction coefficient. For example, for *N* and *C*, the equation is

$$\begin{aligned} &(N_L C_L D_L + N_L C_L D_H + N_H C_H D_H \\ &+ N_H C_H D_L) - (N_L C_H D_L + \\ &N_L C_H D_H + N_H C_L D_L + N_H C_L D_H) \end{aligned} \quad [3]$$

A result of zero indicates no interaction of variables, but if the interaction coeffi-

cient was significantly different from zero, then interaction of the two variables did exist. The extent of the interaction coefficient being removed from zero is a measure of the magnitude of interaction (9,12). 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% probability level and found to be significantly different from zero.

Results and discussion

Individual effects. Table I shows the value of the DT and the CSFR/DT ratio of paracetamol tablets for the various combinations. These values were used to calculate the independent and interaction coefficient values (using the relevant expressions), which are presented in Tables II and III. There were both positive and negative influences on the DT and the CSFR/DT ratio. A positive influence indicates that a particular parameter has increased, and a neg-

ative influence indicates that the value of the parameter has decreased. Generally, the effect produced by *N* on the DT of paracetamol tablets either for natural–pregelatinized or natural–natural starch disintegrant combinations suggests that an increase from a low level of starch disintegrant to a high level (i.e., from a weaker starch disintegrant to a stronger disintegrant) would lead to a decrease in DT, hence facilitating an increase in the release property of paracetamol tablets.

Considering the effects of the combination of natural–pregelatinized sorghum starch disintegrants, a change from natural to pregelatinized starch disintegrant led to a decrease in DT, which could be a result of the higher swelling ability observed for the pregelatinized starches as reported previously (6). This higher swelling ability could lead to the absorption of large quantities of water into the tablet mass and the subsequent generation of a higher swelling force (13), which would initiate the active mechanism of disintegration at a faster rate than for natural starch disintegrants. The decrease in DT was more noticeable in the case of natural–pregelatinized sorghum than in the case of a natural–pregelatinized combination of plantain and corn starches. This finding suggests that changing from one form of starch disintegrant to another form may not significantly decrease the DT value. The decrease in DT produced by a combination of natural–natural starch disintegrants was much more noticeable in the case of sorghum–plantain and sorghum–corn starches than in the case of plantain–corn starch. This finding implies that sorghum starch is a weaker disintegrant than plantain and corn starches, and that the type of starches used in combination determines the extent of the decrease in DT that can be achieved. This finding also suggests that the disintegrant abilities of plantain and corn starches are very similar; therefore, both starch disintegrants can be substituted for one another.

The effect of *N* on the CSFR/DT ratio, as shown in Table II, suggests that a change in the starch disintegrant may not increase the CSFR/DT ratio. Therefore, no significant improvement existed in the balance of the binding and disintegration properties of paracetamol tablets.

As shown in Table II, the effects of *C* on paracetamol tablets led to a decrease in DT for all combinations. This decrease was caused by an increase in the swelling force, which resulted from increased *C* (13,14). The effect of *C* on the DT suggests that changing the starch disintegrant from a weak disintegrant to a strong disintegrant, with an additional increase in *C*, would lead to a decrease in DT. The large effects produced by *C* on the CSFR/DT ratio implies that an increase in *C* combined with a strong starch disintegrant would lead to a better balance of the binding and disintegrant properties of paracetamol tablets. These effects could also be a result of activating the binding

activity of the starch disintegrants, which would assist not only in breaking down paracetamol tablets but also in bonding the tablet mass.

The positive effect of D on DT (see Table II) implies that D caused an increase in DT, which could also be a result of a decrease in porosity with an increase in D . Consequently, water penetration into paracetamol tablets would slow down, swelling would be reduced, and the development of an active mechanism of disintegration would be retarded. Generally, if a change exists in either the type or form of starch disintegrant, D would lead to an increase in DT. The negative effect observed from the effect of D on the CSFR/DT ratio implies that for any of the combinations, D would not create a better balance of the binding and disintegrant properties because it would always lead to an increase in DT.

Interaction effects. The interaction-effect values (see Table III) present the effects of the variables in their various combinations. The N , C , and D interact with each other to alter the DT and the CSFR/DT ratio of paracetamol tablets. The ranking of the interaction effects on DT was $C-D > N-D > N-C$, with $C-D$ having the largest interaction effect on DT, which suggests that N had the most independent influence on paracetamol tablets. For the CSFR/DT ratio, however, the ranking was $N-C > C-D > N-D$, with $N-C$ having the largest interaction effect, which implies that D was largely independent of the effect of N and C .

Generally, $N-C$ produced a positive effect on DT, implying that $N-C$ interaction had taken place and would lead to an increase in DT. This increase in DT could be a result of high swelling of the pregelatinized starch disintegrants, which could lead to the clogging of tablet pores as the concentration of starch disintegrant increases. If the tablet pores did clog, the uptake of water into the core of the tablets would be retarded (15). This retardation would in effect lead to a slowdown of the expected fast rate of reduction in DT with $N-C$ interaction. Considering the negative effect of $N-C$ on the CSFR/DT ratio, an interaction of $N-C$ (see Table II) is generally thought to impair the balance of the binding and disintegrant properties of paracetamol tablets.

The interaction between N and D produced a negative effect on DT for all the combinations, suggesting that the $N-D$ interaction would lead to a decrease in DT. This decrease could be caused by pregelatinization, which undermines the effect that D has on tablets (i.e., decreasing porosity and water penetration into the tablets, which increases DT because an active mechanism of disintegration cannot fully develop). This finding suggests

that the form of starch disintegrant would have considerable influence on the effect that D has on DT. For the CSFR/DT ratio, $N-D$ had a positive effect (i.e., the interaction of $N-D$ led to an increase of CSFR/DT and therefore would lead to a better balance of the binding and disintegrant properties of paracetamol tablets).

The effects of $C-D$ observed for the DT of all combinations implies that the $C-D$ interaction would reduce DT. This decrease in DT could be caused by the high concentration of starch disintegrant, which could undermine the effect that D has on the tablets (similar to what was discussed in the previous paragraph about the effects of $N-D$ on DT). The negative effect of $C-D$ on the tablets implies that a high concentration of starch disintegrant coupled with a high relative density of the tablets would impair the balance of the binding and disintegrant properties of the tablets.

Conclusions

The results of this study show that

- changing from a weak starch disintegrant to a strong starch disintegrant (i.e., from a natural to a pregelatinized starch disintegrant) decreases the DT value, but this decrease in DT depends on the type of starch disintegrant involved.
- combining various types of starch disintegrants may not cause a noticeable change in DT.
- an increase in C can lead to a decrease in DT, although an increase in D leads to a decrease in DT. Generally, changing from a low to a high level of N and D reduces the CSFR/DT ratio.
- all the interactions led to a decrease in DT, and the interaction of N with D only increased the CSFR/DT ratio.
- before any attempt to manipulate a tablet's disintegrant properties, the concentration and the nature of the starch disintegrant should first be considered.
- a 2^3 factorial analysis design such as the one described in this article could be useful in a pilot case study to determine which process variables should be optimized to achieve the maximum release of the active drug substance in a formulation.

The results of this study also show that the tested starch disintegrants (i.e., sorghum and plantain and their pregelatinized forms) exhibited similar disintegrant activity with the tested disintegrant properties of corn starch, also used in paracetamol tablets.

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