Effects of Breadfruit and Cocoyam Starch Mucilage Binders

On Disintegration and Dissolution Behaviors of Paracetamol Tablet Formulations

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The breadfruit tree (Artocarpus communis, Frost, Moraceae family) is native to Malaysia, the South Pacific, and the Caribbean. The trees can grow as tall as 130–180 ft (40–55 m). Their two major fruiting seasons are in April and August, but it also fruits year round. The fruit, which can weigh as much as 5 kg, contains ~26% w/w starch on wet basis.

Binder properties of mucilage of starches extracted from breadfruit and cocoyam were investigated in paracetamol tablet formulations using tablet physical properties, disintegration times, and dissolution rates as assessment parameters. Tablets of satisfactory properties comparable with those prepared with cornstarch BP mucilage binder were obtained. The effect of these binders on tablet properties was related to their surface tension and viscosity. Results suggest the suitability of breadfruit and cocoyam mucilage as binders in paracetamol tablet production.

The role of excipients in determining the quality of a formulation and in many cases the bioavailability of drug from tablets has received considerable attention. As part of the efforts to reach international harmonization of pharmaceutical excipients, the Joint Conference on Excipients identified starch as one of the top 10 excipients (1). Starch is a multipurpose excipient in tablet formulation, and it is used as a binder, disintegrant, and filler (2). The relevance of starch mucilage as a binder in the granulation of hydrophobic drug substrates has been established (3). Although cornstarch is the most frequently used excipient in tableting, previous studies of breadfruit and cocoyam have shown some promise (4,5). Preliminary evaluation of these starches following official and unofficial protocols showed that they possess some of the desirable features of good excipients (5–7). Breadfruit and cocoyam starches, respectively, were found to possess superior hydration and moisture sorption capacities when compared with cornstarch BP (4), which suggests their suitability as mucilaginous binding agents.

Binders provide the necessary binding force that holds powders together to form granules, which under compression form a tablet. Usually the stronger (i.e., more efficient) the binder,

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Cocoyam corms. Dasheen (Colocasia esculenta) is native to India and Southeast Asia. It is now found widely in the tropics. The plant is herbaceous and grows as tall as 2 m and matures in 240–300 days after planting. It produces a high yield of 4–15 tons hec^{-1} of corms that have a starch content of ~19% w/w starch on wet basis.

the higher the compactibility of the tablet, and conversely, the longer the disintegration time of the resulting tablet (8). The pasting and film-forming characteristics of polymeric binders are known to influence their distribution over substrates during granulation and in turn determine to a large extent the properties of the resulting granules and tablets (3,9). Kottke and Rhodes observed that the mucilage of various brands of cornstarch binder produced tablets with no significant difference in dissolution profiles (10). However, the differences that may arise from the variation in the amylose–amylopectin ratio in starch products from various botanical sources may produce mucilages with different pasting characteristics and therefore different binder–substrate interaction (11).

Disintegration usually exposes a greater surface area of tablets to the dissolution medium. However, the literature shows that the physiological availability of drugs from solid oral dosage forms cannot be ascertained by simple in vitro disintegration tests (12). The dissolution rate of drugs from solid dosage forms is more critical to the bioavailability of drugs because dissolution is usually the rate-limiting process in the absorption of poorly soluble drugs (12,13). Thus, the rate of dissolution may be directly related to the effectiveness of a tablet product as well as to the bioavailability differences between formulations.

Various types of equations have been developed for the analysis of dissolution-rate data. Popular ones among them are those of Carstensen, El-Yazigi, Kitazawa, Noyes-Whitney, and Wagner (14). The Kitazawa equation uses the ultimate amount of drug released (W_∞) in the analysis of the dissolution profile. In its simplified form, the equation is written as

$$\ln\left[\frac{W_\infty}{\left(W_\infty - W\right)}\right] = Kt \qquad [1]$$

in which W_∞ is the amount of drug released at infinite time (i.e., the total amount that could be released); W is the amount released at various time t; K is the release-rate constant, a first-order rate that decreases with the amount of drug left to be released; and ln is the natural logarithm. Usually, plots of $\ln[W_\infty/(W_\infty - W)]$ versus time generate multiple regression lines intersecting at various times. The times correspond to the phases in which the dosage form changes its physical form from solid through granules to fine particles. The Kitazawa equation has had wide application in the analysis of dissolution profiles of various drug substances (15,16).

This study investigated the effect of the nature of two starch mucilage binders on physical properties, disintegration, and dissolution behavior of formulated paracetamol tablets. Cornstarch BP was used as a reference starch binder and paracetamol, a drug with known capping and lamination problems that normally requires a binder and disintegrant to form satisfactory tablets, was used as the model substrate.

Materials

The collection, identification, and processing of breadfruit and cocoyam starches have been reported previously (4,5). Cornstarch BP was obtained from BDH Chemicals (Poole, UK), paracetamol BP was obtained from the Liaoyuan Pharmaceutical Plant (Linhai, China), and polyvinylpyrrolidone with a molecular weight of 25,000–30,000 was obtained from Merck (Darmstadt, Germany).

Methods

Gelatinization and pasting characteristics of the starches. Samples of each starch powder were moistened with water and loaded into a capillary tube by means of intrusion. The temperature of gelling and the time from swelling to full gelatinization were measured with a melting-point apparatus (Electrothermal Engineering Ltd., Southend-on-Sea, England). The pasting characteristic of each starch powder was observed after suspending 1 g of powder in 10 mL of distilled water and heating, with stirring, on a steam bath. The time until paste formation was 3.5 ± 0.2 min, 5.2 ± 0.3 min, and 1.5 ± 0.2 min, respectively, for breadfruit, cocoyam, and cornstartch.

Viscosity of starch mucilage. An Ostwald U-tube manometer (BS/U size E, Technico, England) was used to determine the viscosity of 0.5, 1.0, 2.0, and 3.0% w/w mucilage in the Newtonian range. The viscosity of the material was calculated using the equation

$$\eta_2 = \frac{\eta_1 \rho_2 t_2}{\rho_1 t_1} \qquad [2]$$

in which ρ_1 is the density of reference fluid (water), ρ_2 is the density of starch mucilage of known concentration (g/cm^3), t_1 and t_2 are the efflux times of water and starch mucilage, respectively, and η_1 and η_2 are the viscosities of water (η_{water} = 1.002 cP at 20 °C) and test solution, respectively (17). The data were plotted as viscosity versus concentration, and the intrinsic viscosity at zero concentration was obtained by extrapolation of the linear portion of the graph to the y-axis.

Surface tension of mucilage. The authors chose the drop-weight method to determine the surface tension of mucilage (18). A glass burette with a smooth dropping section having 1.225-mm internal diameter cut out of its teat was used. During the test, the pressure head of fluid was kept constant, and drops falling throughout a specified range were weighed on a Mettler AB 54AR (Mettler Inst. AG, Herisau, Switzerland). The surface tension was calculated using the equation

$$\Upsilon = \frac{\phi m g}{2\pi r} \qquad [3]$$

in which m is the mass of the drop, r is the radius of the dropping teat, g is the acceleration resulting from gravity, Υ is the surface tension, and ϕ is a correction factor.

Table I: Physical qualities and in vitro availability parameters of paracetamol tablets containing starch mucilage binders.*

Binder	Concentration (%w/w)	Tensile Strength (MNm^{-2})	Disintegration Time (min)	**HFR/D$_T$	†T_{80} (min)
Breadfruit	2.5	173.9 ±4.0	0.57 ±0.07	630.2	8.8
	5.0	184.7 ±5.5	0.79 ±0.09	529.0	15.0
	7.5	192.3 ±2.0	4.48 ±0.11	109.1	30.1
	10.0	228.9 ±9.4	7.41 ±0.61	78.1	35.3
Cocoyam	2.5	157.3 ±4.9	0.56 ±0.08	757.4	5.3
	5.0	179.7 ±5.3	0.60 ±0.21	889.7	9.5
	7.5	183.9 ±3.2	1.30 ±0.90	468.9	19.9
	10.0	185.5 ±2.6	2.90 ±0.78	307.1	22.2
Corn	2.5	164.6 ±3.9	0.67 ±0.09	454.7	11.2
	5.0	174.1 ±4.9	0.76 ±0.10	441.3	16.2
	7.5	187.9 ±3.6	2.22 ±0.06	176.7	31.8
	10.0	192.5 ±4.8	7.78 ±1.05	57.2	37.0

* Tablets were compressed to a predetermined thickness to give relative density. D = 0.90, which is representative of commercial paracetamol tablets.

** HFR/D$_T$ is the ratio of tablet hardness divided by the product of its friability and disintegration time.

† T_{80} is the time required for 80% of drug to go into solution during the dissolution rate test.

The derived parameters are HFR/D$_T$ and T_{80}.

Table II: Surface parameters and gelatinization behavior of breadfruit, cocoyam, and cornstarch mucilages.

Parameters/Binders	Breadfruit	Cocoyam	Cornstarch
*Intrinsic viscosity (cP)	2.784	2.348	3.018
Surface tension (mNm^{-1})	58.6 (±0.11)	57.5 (±0.06)	62.0 (±0.10)
Temperature of gelatinization (°C)	87.9 (±0.9)	90.0 (±0.3)	85.7 (±0.5)
Time range between swelling and gelatinization (min)	3.5 (±0.2)	5.2 (±0.3)	1.5 (±0.2)

Values in parentheses are the standard deviation.
The derived function/parameter is intrinsic viscosity.

Preparation of granules. Breadfruit, cocoyam, or cornstarch powder equivalent to 2.5, 5.0, 7.5, and 10% w/w, respectively, in the final dried granules was suspended in distilled water. Mucilage of each starch was prepared by heating the slurry, with stirring, on a thermostated hot plate. Water was added to correct weight lost from evaporation.

With prepared hot mucilage, a Sigma blade mixer (Erweka GmbH, Offenbach, Germany) produced 240-g batches of paracetamol granules using the wet-massing technique. Wet massing was performed for 5 min, and then the wet mass was passed through a 1700-μm sieve. The granules were tray dried at 60 °C for 12 h in a BTL cabinet oven (Baird and Tatlock, London, England). The dried granules were screened through a 1000-μm sieve. The size fraction in a range of 500–1000 μm was separated and used for the rest of the studies. The degree of mixing of drug in the granules was assessed by BP 1998 spectrophotometric assay for paracetamol at 257 nm. The paracetamol content was determined, and the degree of mixing was calculated using the equation

$$M = \frac{1-\delta}{\delta_0} \qquad [4]$$

in which δ is the standard deviation of analyzed sample and δ_0 is the standard deviation of the completely unmixed system (19). δ_0 is obtained from the equation

$$\delta_0 = \sqrt{y-(1-y)} \qquad [5]$$

in which y is the proportion of paracetamol in the mixture. M was found to be consistently higher than 95% ($n = 4$, p is <0.05).

Preparation and evaluation of tablets. A hydraulic press (model C, Carver Inc., Menomonee Falls, WI) compressed 600-mg tablets using a 12.5-mm-diameter flat-face punches-and-die assembly. The dwell time was 1 min. Lubrication of punches and die was done with 1% w/v dispersion of magnesium stearate in chloroform. After ejection, tablets were stored over silica gel for 24 h to allow for hardening and elastic recovery. Tablet weight and dimensions were taken, and the relative density was computed using the equation

$$D = \frac{w}{v_t} \cdot \rho_s \qquad [6]$$

in which w is the weight of the tablet (g), v_t is the volume of the tablet (cm^3), and ρ_s is the density of granules (g/cm^3). The crushing strength of tablets was determined using a hardness tester (Monsanto, Cambridge, UK). Ten tablets were tested at each compression pressure. Tablet disintegration time was determined in distilled water at 37 ±0.5 °C in a BP disintegration test unit (Manesty Machines, Poole, UK). Tablets were considered to have disintegrated when all particles had passed through the wire mesh.

The rate of dissolution of paracetamol from the tablets was studied in a rotating basket BP Apparatus II operated at 50 rpm using a digital tablet dissolution test apparatus (Veego, Mubai, India) (7). The dissolution medium was 900-mL phosphate

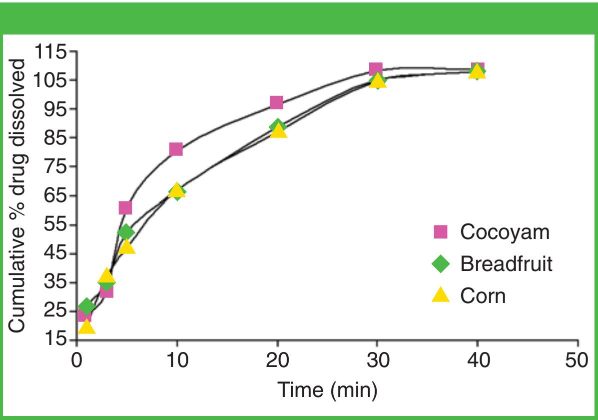

Figure 1: Dissolution profiles of paracetamol tablets ($D = 0.90$) containing 5% w/w of various starch mucilage binders.

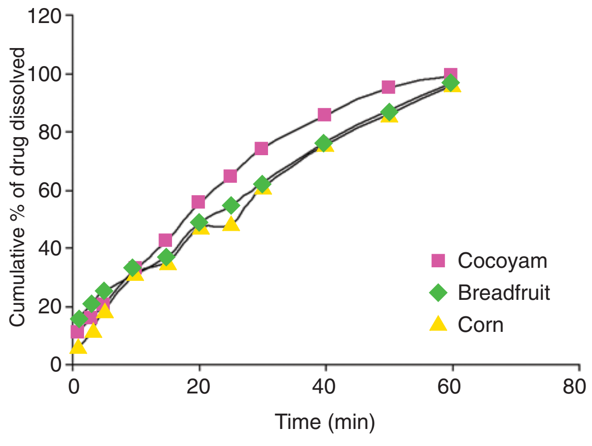

Figure 2: Dissolution profiles of paracetamol tablets ($D = 0.95$) containing 5% w/w of various starch mucilage binders.

buffer with pH 5.8 at 37 ± 0.5 °C. At specified time intervals, 5-mL samples were withdrawn and immediately replaced with 5-mL samples of fresh buffer solution maintained at the same temperature. The amount of paracetamol in each sample was analyzed spectrophotometrically at 257 nm with an SP6-450 UV-vis spectrophotometer (Pye Unicam, Middlesex, England).

Table III: Parameters obtained from the Kitazawa plots of paracetamol dissolution from tablets containing starch mucilage binders.

Mucilage	Kitazawa Plot Parameters*					
Binders	**t_1 (min)**	**t_2 (min)**	**k_1(min^{-1})**	**k_2 (min^{-1})**	**k_3(min^{-1})**	**$\geqslant r$****
Breadfruit	15.0	32.5	0.022	0.028	0.139	0.970
Cocoyam	12.0	30.5	0.024	0.050	0.212	0.994
Corn	14.5	31.0	0.038	0.047	0.125	0.966

*Parameters were obtained from regression of $\ln[W_\infty/(W_\infty - W)]$ on t.

**r is the correlation coefficient of the various slopes, which was found to be equal to or greater than the quoted values.

Results and discussion

Table I shows the physical properties and in vitro availability parameters of paracetamol tablets containing various starch mucilage binders. The tensile strength of tablets containing various binders was of the rank order breadfruit > cocoyam > corn ($p < 0.01$), and the friability was of the reverse order ($p < 0.05$). Tablets containing the various binders disintegrated rapidly, generally within 8 min. Disintegration time was less with cocoyam mucilage binder than with breadfruit and cornstarch, respectively. Similarly, the time for 80% drug dissolution (T_{80}) was less with cocoyam than with breadfruit and cornstarch mucilage binders, respectively ($p < 0.05$).

Studies of various physicochemical properties of the mucilage binders showed some observable correlations with the tablet properties and the in vitro availability parameters. Table II shows that the intrinsic viscosity of cocoyam mucilage was significantly less than that of breadfruit and cornstarch mucilage, respectively. Similarly, the surface tension was lower with cocoyam than with breadfruit and cornstarch mucilage, respectively. The observed effect of these binders can be attributed to their physicochemical properties. Literature reports have shown the importance of binder distribution, which depends significantly on a binder's physicochemical properties; on the physical and compressional characteristics of the resulting granules; and on the physicochemical properties of the tablets (9). In addition, the effect of surface properties such as wetting, spreading of binder over substrates, binder–substrate adhesion, and binder cohesion in determining optimum granulation with polymer binders has been reported (3,20). The lower viscosity and surface tension of cocoyam starch mucilage probably enabled better penetration and spreading over paracetamol powder during wet massing, thereby producing more-porous granules. In addition, the interstices lined by the mucilage film may create hydrophilic channels around the hydrophobic drug particles, thereby enhancing the disintegration and dissolution processes of tablets containing the mucilage binder.

Surface tension and viscosity of mucilage binders are important determinants of other physical phenomena of granulation such as adhesion, cohesion, wetting, and spreading (18,20). An understanding of the physical properties of starch mucilage binders, especially viscosity and surface tension, may therefore contribute significantly to the understanding of the granule and tablet properties of various substrates.

The hardness–friabrasion/disintegration-time ratio has been identified as a better index of tablet quality than has the traditional hardness–friability ratio (5,21). This index not only assesses the tablet strength (i.e., hardness) and weakness (i.e., friability), but it simultaneously evaluates any negative effects of these parameters on disintegration. The rank order effect of binders on tablet-quality values (HFD/D_T) was cocoyam > breadfruit > corn ($p < 0.001$).

Figures 1 and 2 show the dissolution profiles of tablets containing various starch mucilage binders. Tablets with

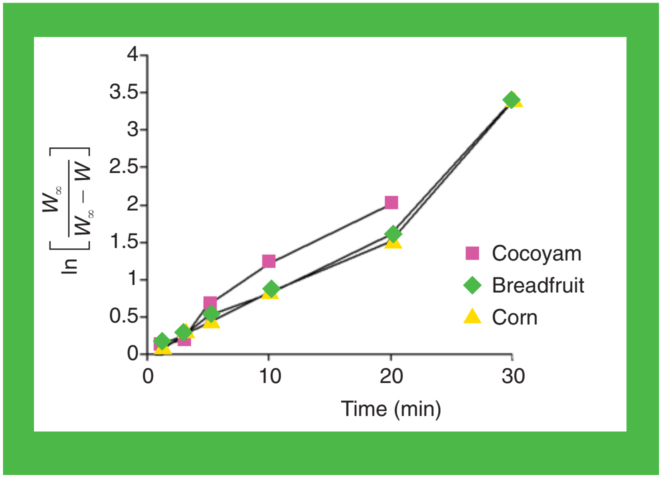

Figure 3: Kitazawa plots for the kinetics of paracetamol dissolution from tablets ($D = 0.90$) containing starch mucilage binders.

cocoyam starch binder produced faster dissolution profiles than did those with breadfruit and cornstarch binders, which otherwise have comparable profiles. As shown in Figures 3 and 4, analysis of dissolution data with the Kitazawa plot produced linear graphs with three segments corresponding to the phases of drug dissolution from the tablet surface, the aggregate granules, and from de-aggregated (i.e., fine) particles. As shown in

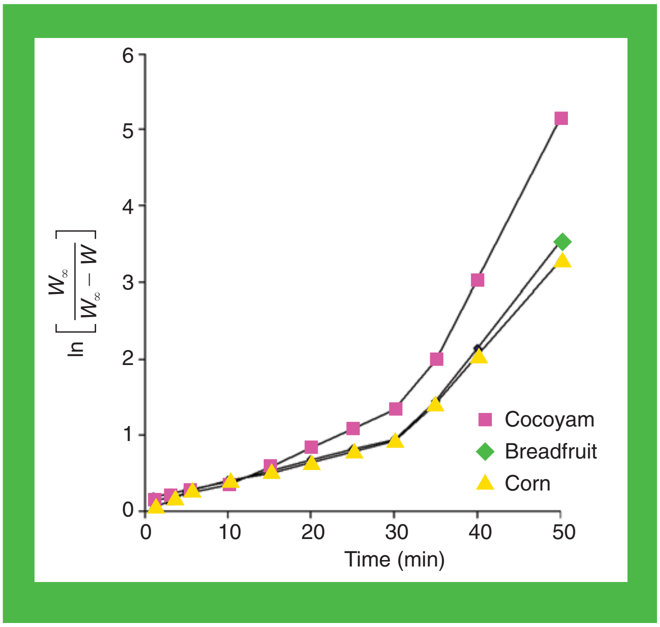

Figure 4: Kitazawa plots for the kinetics of paracetamol dissolution from tablets ($D = 0.95$) containing starch mucilage binders.

Table III, the segments intercepted at t_1 and t_2 between segments one and two and segments two and three, respectively. The indices t_1 and t_2 correspond to the point in time when the tablet disintegrated and the time when the granules fully de-aggregated, respectively, during the dissolution process. The increase in slope indicates the explosive increase in dissolution rate on disintegration as well as on final de-aggregation. In some instances, as shown in Figure 3, the demarcation between the first two phases might not be sharply defined.

The observation of three segments in this study (see Figure 4) compared with the two reported by Kitazawa et al. (15) for caffeine can probably be attributed to the difference in chemical nature of the drugs and the tablet breakup process. Paracetamol is a hydrophobic drug; therefore, an increase in particle surface area by disintegration and de-aggregation will significantly increase its dissolution rate. The apparent lack of correlation between disintegration time t_1 estimated from the dissolution profile and D_T obtained from the disintegration test is attributable to the difference in agitation intensity that was operative in the two determinations. The rigorous stirring in the Manesty disintegration-test apparatus is not comparable with the streamlined flow that was operative in the dissolution-test apparatus. Hence, the Manesty disintegration-test unit produced dramatically decreased disintegration time. However, D_T showed poorer correlation ($r \geqslant 0.894$) with T_{80} than did t_1 ($r \geqslant 0.963$), as had been reported in the literature (22,23). Apparently the poor correlation for some agents reported in the literature may be mainly a result of the difference in hydrodynamic effect of the test apparatus.

Conclusion

Incorporation of breadfruit and cocoyam starch mucilage binders in paracetamol tablet formulations produced tablets with short disintegration times and fast dissolution rates comparable with those of official cornstarch mucilage binders. A credible association exists between binder physical properties such as surface tension and viscosity and the physicomechanical and in vitro dissolution rate of the resulting tablets.

HFR/D_T analysis indicated that tablets with cocoyam mucilage binder had greater overall quality than those with breadfruit or cornstarch mucilage binders. The study results suggest that breadfruit or cocoyam starch mucilage may be used as binders in tablet formulation of particular drug substances.

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