ORIGINAL PAPER

https://dx.doi.org/10.4314/njpr.v21i2.6

Nig. J. Pharm. Res. 2025, 21 (2) pp 105-114
ISSN 0189-8434 e-ISSN 2635-3555 **Available online at http://www.nigjpharmres.com**

The Effect of Particle Size on the Disintegrant Property of Manihot esculenta Starch in Directly Compressed Paracetamol Tablet Formulations

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article.

Abstract

Background: Starch is one of the most widely used excipients in tablet formulations. The source and processing of starch can influence its properties.
Objective: The study investigated the effect of particle size on the disintegrant ability of oven and spray-dried cassava (Manihot esculenta) starch in paracetamol tablet formulations.
Methods: Cassava starch was isolated from its tubers and oven-dried following standard methods. Particle size ranges of 107-125 and 126-300 µm of the oven-dried isolated starch, commercial spray-dried cassava starch, and maize BP were used to produce five (5) batches of paracetamol powder blends that were evaluated for flow properties such as Hausner's ratio, Carr's index, and angle of repose. Powder blends were compressed via direct compression into tablets and evaluated for weight uniformity, friability, disintegration time, and dissolution profiles.
Results: The powder blends exhibited fair to poor flow with angles of repose between 37.93 and 47.84° and Carr's indices greater than 20 %. All the tablets had uniform weights and were moderately hard (4.43-6.90 kgF) and highly friable (2.71-4.50 %). Tablets formulated with 126-300 µm of the isolated oven-dried starch had the fastest disintegration time while the corresponding tablets from spray-dried starch had the longest disintegration time. Drug release was higher from tablets formulated with oven-dried starch and similar to those with maize starch BP than those with spray-dried starch.
Conclusion: The study revealed that particle size was critical to the disintegrant ability of Manihot esculenta starch in the formulated paracetamol tablets. Oven-dried starch of particle size range 126-300 µm produced rapidly disintegrating tablets.

Keywords: *Manihot esculenta* starch, direct compression, disintegration, tablets

INTRODUCTION

In recent times, there has been a shift of attention towards maximizing the use of already existing excipients to achieve dosage forms with improved performance as the development of newer drug excipients can be time-consuming and expensive (Yang et al., 2016; Yu et al., 2021). This has resulted in the emergence of drug delivery systems using co-processed or modified excipients and non-traditional polymers of natural origin among researchers (Benabbas et al., 2021; Ingle et al., 2021; Olayemi and Nock-Anyebe, 2021; Obidiro et al., 2022)

Several studies have shown that excipients' particle size and distribution as well as its morphology influences the manufacturing process and performance of the resulting dosage form (Eraga et al., 2015; Alyami et al., 2017; Azad et al., 2021). Hence particle characterization of excipients in the pharmaceutical industry has become a critical process since it significantly impacts the final drug product.

Pharmaceutical particle engineering, a process designed to modify drug particles into specific shape, size distribution, and composition for improved performance, has found applicability in other industries such as in the production of excipients (Cun et al., 2021). Drying technology strategies are one of the major processes that influence particle characteristics of pharmaceutical materials (Vehring et al., 2008; Vass et al., 2019; Ekdahl et al., 2019; Pardeshi et al., 2021).

Native starch from Manihot esculenta (Crantz) tubers is used as a disintegrant in its powder form while its mucilage is used as a binder in tablet formulations (Gopi et al., 2012; Adjei et al., 2017; Charoenthai et al., 2018). Although the native form of the starch has not shown any promising binder/filler (direct compression) properties, some studies have shown that the various modified forms of the starch exhibit this quality to a significant level (Apeji et al., 2013; Eraga et al., 2017). On the other hand, cassava starch in its native and modified forms has shown good tablet disintegrant properties. Some studies have demonstrated its superior disintegrant property and optimum tablet mechanical properties. Hence, its suggestion as a potential substitute for the commonly used maize starch BP in tablet production (Adjei et al., 2017; Nwachukwu and Ubieko, 2020).

As drying methods have been reported to significantly impact the morphology, functional, and pasting properties of starches with spray-drying causing alterations such as folds, wrinkles on particle surfaces, hence reduced crystallinity while oven drying at low temperatures (40-60 °C) retains the A-type crystalline pattern of the native starch (Marta et al., 2022; Zhao et al., 2024; Marinopoulou et al., 2025). This study aimed to investigate the effect of particle size on the disintegrant ability of oven-dried cassava (Manihot esculenta) starch in comparison with spray-dried cassava starch and maize starch BP.

MATERIALS AND METHODS

Materials

Paracetamol powder and maize starch BP were gift samples from Jopan Pharmaceutical Nigeria Limited. Spray-dried cold-water cassava starch (RENEW®) (Cormart Nigeria Ltd). Hydrochloric acid, di-calcium phosphate, lactose monohydrate, magnesium stearate and talc (BDH Chemical, UK). All sieves were Endecott, UK and water was double distilled. Freshly harvested cassava (*Manihot esculenta*) tubers were processed into starch powder in the research laboratory of the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Methods

Extraction of *Manihot esculenta* starch

Starch from the freshly harvested cassava (*Manihot esculenta*) tubers was extracted following an already reported method (Eraga *et al*., 2017). About 4.5 kg of tubers were washed thoroughly and peeled. The peeled tubers were sliced into pieces and washed again before being wet milled with an electric blender (Moulinex, France). The wet slurry passed through a 1.0 mm sieve to separate the chaff from the starch. A litre of distilled water containing 30 mL of 3.5 %w/v sodium hypochlorite was used to disperse the starch filtrate and allowed to stand overnight. A muslin cloth was used to filter the mixture, and the filtrate was left to stand for 6 h before carefully decanting the supernatant. The starch sediment was re-suspended in extra distilled water and left to stand for 4 h before decanting the supernatant. This process was repeated several times, with the supernatant tested with a litmus paper until it gave a neutral pH. The wet starch sediment was air-dried for 24 h and further dried in a hot air oven (Gallenkamp, United Kingdom) at 60°C for 3 h. The dried starch was pulverized into powder and stored in an airtight container.

Preliminary evaluation of extracted starch

Organoleptic properties

The taste, odour, and colour of the starch were assessed by three (3) subjects, with the matching responses of two subjects recorded.

Chemical test
A 5.0 mL aliquot from a 10.0 %w/v starch suspension was introduced into a test tube, and a few drops of 0.01 M iodine solution were added. The resulting colour change was recorded.

Solubility
A 100 mg quantity of the extracted native starch was placed in 10.0 mL of water in a test tube at room temperature and shaken. The dispersion was left standing for 30 min and then filtered. The filter paper with the residue was air-dried to a constant weight. The difference in weight between the filter paper alone and with the residue was used as a measure of the extent of starch powder solubility.

Moisture content
A crucible containing about 1.0 g of the starch was placed in a hot air oven operated at 105 °C for 4 h. The crucible content was weighed at the end of the experiment and the difference between the starting and final weights of the starch was calculated as the moisture content (Eraga *et al*., 2015).

Separation of starch powder into different sizes
Twenty (20) grams of extracted starch was poured into the sieve stack arranged in descending order from 300, 125, 107 µm to pan on a sieve shaker (Endecott, UK) and operated for 15 min. Portions of the starch powder accumulated under the 300 and 125 µm size sieves were separately collected for tablet formulation. The purchased spray-dried cold starch (RENEW®) was subjected to the same procedures, and two portions of similar sizes were also separately collected.

Formulation of paracetamol powder blends
Using the formula in Table 1, five (5) batches of paracetamol powder blends were prepared by weighing the quantities of ingredients required for each batch and mixing in a geometric progression in a mixer. Ingredients sufficient to produce 100 tablets per batch were thoroughly mixed and the powder blends were subjected to pre-compression evaluations.

Table 1: Formula used in the preparation of paracetamol powder blends and tablets

Ingredients (mg)	Particle size (µm)	Batches				
		A	B	C	D	E
Paracetamol	-	350	350	350	350	350
Di-calcium phosphate	-	69	69	69	69	69
Oven-dried cassava starch	107 - 125	50	-	-	-	-
	126 - 300	-	50	-	-	-
Spray-dried cassava starch (RENEW)®	107 - 125	-	-	50	-	-
	126 - 300	-	-	-	50	-
Maize starch BP	30	-	-	-	-	50
Lactose	-	150	150	150	150	150
Magnesium stearate	-	3	3	3	3	3
Talc	-	3	3	3	3	3

Pre-compression evaluations
Bulk and tapped densities
Powder blend weighing about 6.0 g was poured into a 100 mL measuring cylinder and the volume occupied was recorded. The bulk density was calculated by dividing the weight of the powder with the volume. The same measuring cylinder with the powder was tapped gently 100 times on a flat wooden surface and the new volume occupied was recorded. The tapped density was then calculated by dividing the mass of the powder with the volume obtained after tapping.

Carr's index and Hausner ratio
The tapped density value of the powder was used to divide the difference between the tapped and bulk densities and the ratio obtained was expressed as a percentage to determine the powder's Carr's index, while simply dividing the tapped density with the bulk density yielded the Hausner's ratio.

Angle of repose
About 10.0 g of the powder blend was allowed to flow under gravity through a funnel with an orifice diameter of 0.85 cm and clamped about 5.0 cm from a flat horizontal platform. The height and base diameter of heap formed on the flat horizontal platform was recorded. The ratio of the powder heap height to base diameter was used in calculating the angle of repose with Equation 1.

$$\theta = tan^{-1} (h/r) \quad \ldots . \quad (1)$$

Where h is the height of the heap of powder and r is the radius of the circular base

Compression of powder blends

Powder blends weighing 625 mg per tablet were compressed into tablets using a manually operated single punch machine (Type F3 Manesty Machines, UK) at a load of 30 KN. The pressure was maintained for all batches of paracetamol tablets. The tablets were collected, dedusted and stored in an airtight container for further evaluation.

Post-compression evaluations

Physical examination

The compressed paracetamol tablets from each batch were examined for any surface defects such as cracks, caps, or pits.

Tablet weight

Twenty tablets of each batch were individually weighed using the electronic weighing balance (College B154, Mettler Toledo, Switzerland). The mean weight and standard deviation were calculated.

Tablet friability

Ten tablets each batch were weighed together and placed in a friabilator (Erweka GmbH, Germany) rotated at 25 rpm for 4 min. The tablets were dusted and re-weighed at the end of the experiment. The percentage loss in weight was calculated to be the friability of the tablets.

Crushing strength (Hardness)

The mean crushing strength of 10 tablets per batch was determined by diametrial compression of each tablet with a motorized hardness tester (Campbell Electronics, Model HT-30/50, India).

Crushing strength-Friability

This parameter was computed as the product of tablet crushing strength (hardness) and friability.

Disintegration time test

Using a BP disintegration tester (MK IV, Manesty Machines, UK), the time taken for each of six tablets to break up was determined with a disintegration fluid of 500 mL distilled water maintained at 37 ± 1 °C. Time taken for all tablet particles to pass through the 2 mm diameter wire mesh was recorded as the disintegration time for each tablet.

Disintegration efficiency ratio

The disintegration efficiency ratio (DER) was determined using the ratio of crushing strength, (Cs), friability (Fr) and disintegration time (Dt) as in Equation 2.

$$DER = {}^{(Cs/Fr)}/_{Dt} \ldots\ldots (2)$$

The dimensionless disintegrant quantity (DER_c) was calculated using the ratio of the DER of tablets formulated with either oven-dried cassava starch or spray-dried cassava starch to those formulated with maize starch BP as given in Equation 3.

$$DERc = {}^{DER_{sample}}/_{DER_{standard}} \ldots\ldots (3)$$

Dissolution test

The dissolution profiles of the paracetamol tablets were determined using the BP paddle method for the various batches of the tablets (Caleva ST7, UK). Using 900 mL of 0.1 N HCl solution maintained at 37 ± 1 °C as a fluid medium and a paddle rotation of 50 rpm, dissolution was carried out for 60 min. Aliquot (5.0 mL) of the dissolution fluid was withdrawn at predetermined times and replaced with an equivalent volume kept at the same temperature (37 ± 1 °C) each time. Withdrawn samples were filtered and their absorbances were read at λmax of 243 nm. Percentage drug released at the predetermined times was calculated with values gotten from the regression analysis plot earlier drawn for pure paracetamol powder.

Statistical analysis

All data obtained were in triplicate and expressed as mean ± standard deviation. using GraphPad InStat software version 3.10, differences between means were subjected to student t-test at $p \leq 0.05$ level of significance.

RESULTS

Starch powder properties

Organoleptic analyses of the extracted native cassava (Manihot esculenta) starch showed a white, tasteless, odorless and smooth powder. Starch presence was confirmed by the blue-black colouration produced by the reaction between iodine solution and the starch aqueous dispersion. The starch powder was only slightly soluble in water at room temperature and exhibited a moisture content of 20.7 ± 2.40 %.

Pre-compression properties of powder blends

The results from the pre-compression evaluations of the prepared paracetamol powder blends are presented in Table 2. The bulk and tapped densities result of the various powder blends showed a greater particle consolidation with the spray-dried cassava starch batches C (107 - 125 µm) and D (126 - 300 µm). Carr's indices and Hausner's ratios ranged between 24.50 - 45.05 % and 1.32 - 1.82, respectively, with batches C and D powder blends having higher values.

Angles of repose for all the batches were ranged from 37.93 to 47.84° with batches C and D powder blends having the least values compared to the other batches. The flow characteristic of batches A (107 - 125 µm) and B (126 - 300 µm) powder blends prepared with oven-dried cassava starch was similar to maize starch BP batch (E) with particle size of 30 µm.

Table 2: Pre-compression properties of the paracetamol powder blend

Parameters	Batches				
	A	B	C	D	E
Bulk density (g/mL)	0.487 ± 0.012	0.425 ± 0.011	0.333 ± 0.041	0.500 ± 0.023	0.444 ± 0.030
Tapped density (g/mL)	0.645 ± 0.042	0.625 ± 0.021	0.606 ± 0.028	0.714 ± 0.064	0.645 ± 0.060
Carr's index (%)	24.50 ± 0.130	29.97 ± 0.132	45.05 ± 0.091	30.88 ± 0.082	31.16 ± 0.102
Hausner's ratio	1.320 ± 0.014	1.437 ± 0.112	1.820 ± 0.062	1.428 ± 0.098	1.453 ± 0.122
Angle of repose (°)	47.84 ± 0.112	43.72 ± 0.181	37.93 ± 0.211	38.76 ± 0.120	45.83 ± 0.112

Post-compression properties of tablets

Physical examination of the formulated tablets showed batches A, B and E with smooth tablet surfaces but batch C tablets exhibited some pits while batch D tablets had cracks resulting from capping of the tablet. The capped tablets crumbled to touch in the handling processes of evaluation; hence they could not be assessed.

The results from the evaluations carried out on the batches of tablets formulated via direct compression are outlined in Table 3. Weight uniformity of the four (4) intact batches of paracetamol tablet formulations showed a mean weight ranging from 615 to 622 mg. Increasing the particle size of the powder blends as seen in batches B and D did not affect the average weight of the tablets.

Mechanical properties of the tablet formulations varied across the batches. Friability of all the batches ranged from 2.71 to 4.5 % with batch B having the highest value (4.5 %). Tablet hardness was between 4.43 and 6.69 kgF with batch B having the highest value (6.69 kgF). The crushing strength-friability ratio (CSFR) was highest for tablets formulated with oven-dried starch of particle size range 126 - 300 µm (30.10) and the rank order was Batch B > Batch E > Batch A > Batch C. Disintegration time was between 29.7 sec (0.14 min) and 25 min; batch C exhibited the longest disintegration time (25.0 min) while tablets of batches A and D disintegrated within the same time (1.0 min). DER as shown Table 3 reveals values between 0.04 and 2.18 with tablets formulated with oven-dried starch of particle size range 126-300 µm having the highest value and the least being tablets formulated with spray-dried starch of particle size range 107-125 µm.

Table 3: Post-compression properties of the paracetamol tablets

Parameters	Batches			
	A	B	C	E
Weight (mg)	618.0 ± 0.02	615.0 ± 0.01	622.0 ± 0.01	618.1 ± 0.04
Friability (%)	2.71 ± 0.10	4.5 ± 0.12	3.01 ± 0.01	4.32 ± 0.01
Hardness (kgF)	5.35 ± 0.25	6.69 ± 0.10	4.43 ± 0.34	5.89 ± 0.260
CSFR	14.50	30.11	13.33	25.44
Disintegration time (min)	1.00 ± 0.84	0.50 ± 0.14	25.00 ± 0.20	1.00 ± 0.44
DERc	1.45	2.18	0.04	-

Drug release profiles from the dissolution studies carried out on the batches of paracetamol tablets are presented in Figure 1. The tablets exhibited varied drug release pattern ranging from 24 to 99.3 % by the end of the dissolution period. Drug release from batches A (98.7 %) and E (99.3 %) were the highest followed by 85.7 % release from batch B and the least release (24.0 %) was from batch C.

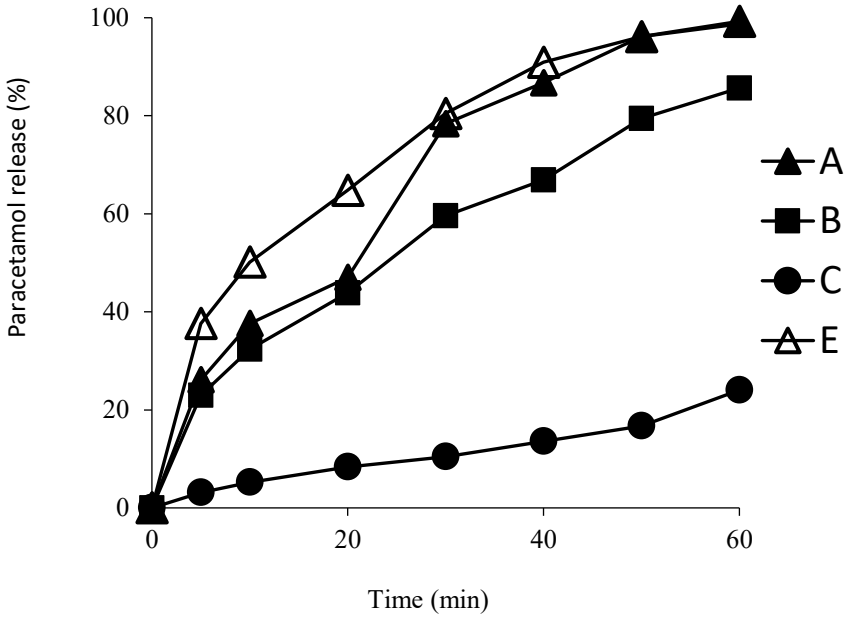

Figure 1: Dissolution profiles of paracetamol tablet formulations

DISCUSSION

Excipients for pharmaceutical formulations are required to be of high standards and perform suitably during the manufacturing processes in the final drug formulation. Flowability of the prepared paracetamol powder blends, as determined by their angles of repose (Table 2) revealed powder blends with fair to poor flow. Also, the powder blends had high Carr's indices (> 25 %), which showed that the blends had low propensity to deformation under pressure, while their Hausner's ratio values showed cohesive powder blends with poor flow. This evident lack of flow shown by the powder blends may be attributable to particle consolidation also seen in their bulk powder evaluations, which may be the result of their particle sizes and distribution and most probably, their particle shapes (Eraga et al., 2015; Alyami et al., 2017; Azad et al., 2021).

Batches C and D had the poorest flow and this could be the result of the process of spray-drying, which conferred on the particles, the size distribution and shapes that facilitated greater powder consolidation. Increasing the particle sizes between batches A and B of the oven-dried starch showed no improvement in flow, possibly due to the high moisture content of the starch. British Pharmacopoeia recommends a 5.0-7.0 % moisture content for powders as increased moisture can lead to liquid bridge formation, hindering powder movement (BP, 2009; Crouter and Briens, 2014; Suhag et al., 2024). However, flow was observed to improve with an increase in particle size of the spray-dried blend (Batch D). Improvement of flow properties with increasing particle size as seen in batch D is consistent with increase in the number of larger spaces in-between the particles leading to decrease in surface free energy of the particles, decrease in frictional forces between the particles resulting in faster flow (Eraga et al., 2014; Shah et al., 2023).

Although this study was carried out using specified particle sizes, there was no significant improvement in flowability with increase in particle size. This may be attributed to differences in particle distribution and shapes which facilitated the filling of the spaces or voids created by the larger particles with the smaller particles making the powders cohesive. These

deficiencies observed in the flowability of the powder blends of the different batches could be remedied with the inclusion of powder flow aids or enhancers to prevent high tablet weight variation in high-speed industrial presses (Tadauchi et al., 2022; Kumar et al., 2026).

Only four of the five batches of powder blends produced intact tablets able to withstand evaluation procedures as batch D tablets crumbled when handled. This could be attributed to the poor compressibility and compactibility of the powder blends. The inclusion of a dry binder to the formulation and an increase in the compression pressure of the tablets may be practical solutions to the problem (Audu-Peter and Ibrahim, 2014; Adeleye, 2019).

The average weights of all the tablets were within official specifications requiring that not more than two tablets should deviate by ± 5.0 % and none should have up to a ± 10 % deviation from the mean tablet weight (BP, 2009). This showed that the powder blends are capable of producing tablets of consistent weights.

Tablet hardness showed that batch C had the least hardness while tablets of batch B were stronger than those of batches A and E. This showed that increasing the particle size of the oven-dried cassava starch showed produced stronger tablets (Batch B) than batch A and the corresponding spray-dried cassava starch (Batch C). This corresponds with the results of Carr's index (Table 2) which showed batches A and B had better propensity to be compressed than batches C or E. However, all the tablets had hardness values (4 - 8 kgF) within the acceptable range for conventional, uncoated tablets (Odeku and Itiola, 2003).

Friability is a parameter that assesses the tendency of tablets to undergo stress, abrasion and fragmentation, which affects the appearance of the tablets (Gupta et al., 2020). Irrespective of the particle sizes, all the tablet formulations were friable with friability values above the acceptable limit of < 1.0 % according to USP (2018). Hence, for a viable commercial tablet, the formulation of the directly compressed tablets can be further optimized to achieve friability specification. Such optimization may involve the selection of a dry binder and possibly the use of a higher compression pressure in the tableting process.

There was no correlation between tablet hardness and friability as the strong tablets were observed to be highly friable. This could be attributed to low binder deficiency in the tablet formulations as has also been reported by other authors (Eichie and Kudehinbu, 2009). The inclusion of a dry binder to the formulations coupled with a higher compression force may have resulted in more robust tablets and could be considered in further studies.

The crushing strength-friability ratio (CSFR) has been demonstrated to be better at assessing tablet mechanical strength than tablet hardness alone or friability alone (Odeku and Itiola, 2003). Tablets formulated with batch B powder blends had the highest CSFR which revealed that they are strong. It also showed the propensity of oven-dried starch of particle size range of 126-300 µm to produce tablets of good mechanical strength.

Disintegration portrays ability of tablet formulations to breakdown in a fluid. This is an important parameter because it is often assumed as a percussor to drug release and ultimately to its bioavailability (Parma et al., 2009). Tablet disintegrants are required to bring about tablet break-up irrespective of the intended route of administration. When oral tablets encounter moisture in the stomach or in the mouth, for rapid dissolving tablets, they should begin to dissolve. Since swelling type disintegrants absorb moisture, causing them to swell, the size or size distribution of the disintegrant particles may determine the rate of moisture absorption, which is critical to the efficacy of such a disintegrant (Markl and Zeitler, 2017; Bauhuber et al., 2021). Tablets from batch B had the fastest disintegration time followed by those of batches A and E and were within the acceptable limit set for disintegration time of uncoated tablets (15 min) according to the USP (2018). Even though the tablets from batch C had the least hardness, they were observed to have the longest disintegration time and did not meet the acceptable limit. Increasing the particle size as in batch B brought about the fastest disintegration which could also be attributed to high powder porosity which could have been the reason for high friability, high tablet porosity resulting in rapid disintegration (Kottke and Rudnic, 2002).

Observation from Table 3 showed that oven-dried cassava starch effected faster disintegration than the spray-dried cassava starch and maybe due to a high percentage of moisture absorbed by powder particles of these sizes. This high moisture absorption may be attributed to the exposure of a larger surface area for sorption of moisture which is in line with some studies where it was supported that a large surface would facilitate internal absorption of moisture (Nokhodchi et al., 1997; Johnson and Brennan, 2000; Koumbogle et al., 2023). This study showed that the mode of drying and particle sizes of the disintegrant is critical to its ability to cause disintegration.

Another assessment tool to measure the balance between tablet strength and disintegration property of tablets is the DERc (dimensionless disintegration quantity) derived from the disintegrant efficiency ratio; DER (Pachuau et al., 2017). DERc values greater than one (1) indicates that the investigated disintegrant has better disintegrant ability than the reference disintegrant. Although batches A and B had values higher than 1, batch B had the highest value indicating that it possesses better disintegrant property than the batches A and E.

Dissolution profiles of the formulated tablets revealed that batch E had the highest drug release at the end of the dissolution period, followed by batch A and batch B. In this study, dissolution profile directly correlated with the disintegration time as is often suggested. A tablet must disintegrate before the incorporated drug is released into solution. Some authors maintains that disintegration and dissolution times are correlated as the particle size and surface area exposed as the tablet disintegrates determines the rate and extent of drug dissolution (Markl and Zeitler, 2017; Nickerson et al., 2018). Drug release from batch B (larger particle size) was observed to be lower than that of batch A. However, tablets formulated with the oven-dried cassava starch showed higher drug release above those formulated with spray-dried starch.

CONCLUSION

This study revealed that particle size and method of drying have significant effect on the disintegrant efficiency of formulated tablets. Results showed that oven-dried cassava starch has better disintegrant ability than the spray-dried cassava starch. Increasing the particle size of the oven-dried cassava starch effected faster disintegration of formulated tablets over those formulated with lower particle size. Properties of oven-dried cassava starch tablets were comparable to those of maize starch BP and could be a viable substitute as a disintegrant in tablet formulations.

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Conflict of Interest: None declared
Received: September 9, 2025
Accepted: March 23, 2026