ORIGINAL ARTICLE

Tableting Performance of Maize and Potato Starches Used in Combination as Binder/Disintegrant in Metronidazole Tablet Formulation

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ABSTRACT

Objectives: This study aimed to characterize the tableting performance of maize and potato starches, when used in combination either as a disintegrant or binder in solid dosage form development.

Materials and Methods: Wet granulation was used to process metronidazole granules incorporating either maize starch, potato starch, or a combination of the two starches as binders or disintegrant at 10% $^w/_w$. Granule analysis was carried out on the various formulations and subsequently compressed into tablets weighing approximately 500 mg following the addition of extragranular excipients. Tablet properties were assessed after 24 h of storage.

Results: Analysis of granule properties did not reveal a wide variation across the formulations irrespective of the type and combination of starches used in the formulation either as binder or disintegrant. It was observed, however, that there were slight differences in particle size, bulk and tapped densities of granule formulations containing the combined starch as excipients compared to granule formulations containing individual starch as the excipient. Tablets prepared using the combined starches as binder had lower tensile strength and disintegration time compared to other formulations incorporating the individual starches as binders. However, when evaluated as disintegrant, the tablet formulation containing the combined starches produced tablets with relatively lower disintegration time compared to formulations containing the individual starches as disintegrant.

Conclusion: The study concludes that the combination of maize and potato starches as excipients in tablet formulation influenced the outcome of granule and tablet properties.

Key words: Maize starch, potato starch, binder, disintegrant, tablet, excipient

INTRODUCTION

With regard to oral drug delivery, tablets remain the most commonly prescribed dosage form among health practitioners and this is simply because tablets are easy to administer, relatively stable and less cumbersome to handle compared to other dosage forms like liquid formulations and parenteral.[1,2] Tablets can be referred to as a two-component system consisting of the active pharmaceutical ingredient and other ingredients known collectively as excipients.[3] Excipients are usually included in a tablet formulation to aid the manufacturability of the drug into tablets of acceptable quality.[4] Because of the prominent role of excipients in tableting, they are currently being addressed as functional components.[5]

Though inert, most excipients possess some degree of functionality that makes it possible for drugs not only to be processed into solid compacts but also to ensure that the tablet releases the drug timely to exert its action in the body.[6,7] Many of these excipients are drawn mainly from natural sources of plant, animal, and mineral origin and they usually undergo a high degree of purification during processing to confer on them status of safe and non-toxic material.[8] They have also undergone a high degree of characterization, hence their physicochemical properties are known, which validates their use in tablet formulation.[9,10]

Currently, starch is listed as one of the most commonly used excipients in tablet formulation. Starch is obtained from a wide

variety of sources, which including cereals and tuber crops.[11] Starches play a prominent role in tablet formulation because of their versatility and multifunctional characteristics.[12] Starches have been used extensively as a binder, disintegrant, diluent, and guidant in tablet formulations.[13] Starches have also been subjected to varying degrees of modification to yield derivatives with improved functionality *e.g.* pregelatinized starch.[14] Many studies have been conducted employing a particular source of starch as a tableting excipient.[14-17]

Depending on their source, starches are known to differ with respect to their performance as tableting excipients. Many studies have compared the tableting properties of starches from different sources and discovered differences that were statistically significant ($p < 0.05$). A study conducted by Olayemi et al.[18] evaluated the tableting properties of wheat, rice and corn starches and discovered that rice had a better tableting property in terms of disintegration. Hence, most studies in the past have employed the use of starch from a single source in tablet formulation. Very few studies have been conducted to explore the combination of starches from various sources in tablet formulation. Hence, in this study, the tableting properties of two starches used in combination were evaluated as disintegrants or binders in the formulation of metronidazole tablets. Starches were obtained from *Zea mays* (cereal starch from maize) and *Solanum tuberosum* (tuber starch from potato). These starches were combined in equal proportion and used as either a binder or disintegrant in metronidazole tablets prepared by wet granulation.

MATERIALS AND METHODS

Materials

Metronidazole (Hopkin and Williams, New Delhi, India), maize starch (Burgoyne Burbidge & Co. India, Mumbai), potato starch (Roquette Pharma, France), acacia (Kerry EMEA region, Draycott mills, Glos. GL115NA, UK), lactose, croscarmellose sodium (DFE pharma, Klever strasse 187, D-47574 Koch, Germany), colloidal silicon dioxide (Evonik Industries, Germany), sodium stearyl fumarate (JRS Pharma GmbH CO.KG, 73494, Rosenberg, Germany) were purchased from their respective companies. All other chemicals used were of pharmaceutical grade.

Methods

Preparation of metronidazole tablets

Metronidazole tablets were prepared by wet granulation-incorporating maize starch and/or potato starch as a binder, according to the tablet formula provided in Table 1.

Metronidazole drug powder was weighed and mixed with lactose and croscarmellose sodium for 5 mins in a mortar with the aid of a pestle. Maize starch paste was prepared as a binder and incorporated into the powder mix to facilitate binding and formation of granules. The wet mass of the powder mix was force-screened through a sieve of 1.6 mm to generate granules and then placed in the oven to dry at 40°C for 20 min to allow for partial drying. The partially dried granules were passed through another sieve of 1 mm and then returned to the oven for complete drying at 40°C for 1 h. The dried granules were then kept away in a safe place for further studies. Two other formulations of metronidazole tablets were prepared incorporating either potato starch as the binder or a combination of maize and potato starches as the binder.

The entire process was repeated to prepare three formulations of metronidazole tablets incorporating maize starch and/or potato starch as disintegrants according to the tablet formula given in Table 1.

The granules obtained above were characterized for their physicochemical properties, lubricated with extragranular excipients, and compressed into tablets weighing ~500 mg on an Erweka tablet press using 12 mm punch and die set. The tablets were allowed to relax upon storage and their properties were evaluated after 24 h.

Particle size analysis

The mean granule size (MGS) for each granule formulation was obtained by sieve analysis. A representative quantity of

	Formulations containing starches as binders			Formulations containing starches as disintegrants		
Ingredients	I	II	III	IV	V	VI
Metronidazole (40%)	30	30	30	30	30	30
Lactose (40%)	30	30	30	30	30	30
Maize starch (5, 10%)	7.5	-	3.75	7.5	-	3.75
Potato starch (5, 10%)	-	7.5	3.75	-	7.5	3.75
Cros sod (5%)	3.75	3.75	3.75	-	-	-
Acacia (5%)	-	-	-	3.75	3.75	3.75
CSD (4%)	3	3	3	3	3	3
SSF (1%)	0.75	0.75	0.75	0.75	0.75	0.75

Table 1. Tablet formula for formulations I-VI

I-III: Formulations containing starches as binders
IV-VI: Formulations containing starches as disintegrants
Cros sod: Croscarmellose sodium, CSD: Colloidal silicon dioxide, SSF: Sodium stearyl fumarate

the granules was poured into a nest of sieves arranged in descending order (1000 μm, 710 μm, 300 μm, 180 μm, 125 μm, and pan) and agitated for 10 mins in the Endecott test sieve shaker. The fraction of granules recovered from each sieve was weighed out and the MGS was computed using equation 1 below:

$$MGS = \frac{[\Sigma(\% \, retained) \times (sieve \, size)]}{100}$$ equation (1)

Microscopy
Each sample of granule formulation was viewed under a light microscope and the images of the granules were captured using a digital camera. Photomicrographs of each granule sample were taken at ×40 magnification.

Angle of repose (AoR)
The fixed funnel method was used to measure the AoR of granules.[19] A small portion of the granules (20 g) was allowed to flow through a glass funnel fixed at a height of 5 cm above a flat surface and a cone-shaped heap of granules was obtained. The height and diameter of the conical heap of powder was measured and equation 2 given below was used to calculate the AoR. The AoR was reported as the mean of three replicates for each formulation.

$$Tan \, \theta = \frac{h}{r}$$ equation (2)

Where *h* is the height of the powder, *r* is the radius of the circular base and θ is the AoR.

Bulk and tapped densities
Measurement of bulk and tapped densities of each granule formulation was carried out according to the method described by Singh et al.[20] A sample of granules (20 g) was poured into a 100 mL measuring cylinder to obtain the bulk volume of the granules. The cylinder was then tapped to a constant volume and the volume was recorded as the tapped volume. This was repeated two more times for each granule formulation. Equations 3 and 4 given below were used to calculate bulk and tapped densities, respectively.

$$Bulk \, density \, (BD) = \frac{Mass \, of \, granules}{Bulk \, volume \, (BV)}$$ equation (3)

$$Tapped \, density \, (TD) = \frac{Mass \, of \, granules}{Tapped \, volume \, (TV)}$$ equation (4)

Carr's index (CI) and Hausner's ratio (HR) were obtained using the equations 5 and 6 below:

$$CI = \frac{TD - BD}{TD} \times 100$$ equation (5)

$$HR = \frac{TD}{BD}$$ equation (6)

Moisture content (MC) determination
The residual MC of granules was determined using gravimetric analysis. A portion of the granules (1 g) was sampled for each formulation and dried to a constant weight in the hot-air oven at 105°C. MC was then calculated using equation 7 below:

$$\% \, MC = \frac{Initial \, weight - Final \, weight}{Initial \, weight} \times 100 \, \%$$ equation (7)

Weight variation tests
The weights of 20 tablets selected at random for each formulation were obtained using an electronic scale. The mean tablet weight was calculated and recorded with the standard deviation.

Content uniformity test
The content uniformity test was carried out to estimate the amount of drug contained in the tablet. The weight of 5 tablets was obtained and powdered using a mortar and pestle. An equivalent weight of one tablet was weighed out from the powdered mass and dissolved in 100 mL of 0.1 N HCl. The mixture was filtered and a dilution of the solution (1 in 100) was prepared with 0.1 N HCl before the absorbance reading was taken at 277 nm using the ultraviolet (UV) spectrophotometer. The percentage drug content was calculated using the straight-line equation, *y*= 0.0395x + 0.1314, generated for the calibration curve of metronidazole, where *y* is the absorbance and *x* is drug concentration (μg/mL).

Tensile strength
The force required to fracture a tablet along its diameter was measured using a Monsanto hardness tester. A mean of 5 determinations was obtained and recorded with its standard deviation. The tensile strength of each tablet formulation was resolved using equation 8 below.

$$TS = \frac{2F}{\pi dt}$$ equation (8)

Where *F* is the breaking force, *d* is the diameter and *t* is the thickness.

Tablet friability
Tablet friability was obtained for each tablet formulation using the Friabilator machine. Ten tablets were sampled at random, and their collective weight was obtained by weighing on an electronic scale. The tablets were transferred into the friabilator, which was allowed to revolve for 4 min at 25 rpm. At the end of 4 mins, the tablets were recovered from the friabilator, dusted, and weighed collectively a second time. Friability was computed as the percent loss in weight using equation 9 below.

$$Friability = \frac{Initial \, weight - Final \, weight}{Initial \, weight} \times 100 \, \%$$ equation (9)

Disintegration test

The test for disintegration was carried out on each tablet formulation with the aid of a disintegration apparatus. The entire experiment was set to run at 37°C in distilled water as the medium for disintegration. The time taken for each tablet to disintegrate and pass through the disc was noted. The mean of six replicates was recorded for each formulation.

In vitro dissolution studies

Drug release profile of each tablet formulation was assessed using 0.1 N HCl as sample medium for dissolution. A single tablet was placed in a basket and immersed in a beaker containing 900 mL of 0.1 N HCl regulated at 37°C and allowed to rotate at 100 rpm. Portions (5 mL) were withdrawn intermittently at 5, 10, 20, 30, 45, and 60 mins, respectively, and replaced with an equal volume of 0.1 N HCl after each withdrawal. The collected samples were filtered and sufficiently diluted with 0.1 N HCl before taking the absorbance readings at 277 nm using the UV spectrophotometer (UV-1800 Spectrophotometer, Shimadzu Corporation, USA). The amount of drug released (%) was calculated based on the equation, $y= 0.0395x + 0.1314$, derived from the calibration curve of metronidazole and a plot against time was generated for the six formulations.

Statistical analysis

No statistical analysis was carried out of the results obtained.

RESULTS AND DISCUSSION

Granule properties

Granule properties of formulations containing starches as binders (I-III) are presented in Table 2. Particle size of granules represented as MGS ranged from 309.74 349.69 µm with formulations II and III having the least and largest MGS, respectively. Although, the MGS did not appear to differ significantly across the granule formulations, it was observed that formulation III granules that combined the two starches in equal proportion as a binder had the highest MGS. This can be attributed to the combined cohesive effect of both starches as binders put together. Generally, binders exert an influence on granule size owing to their capacity to enhance aggregation and agglomeration of powders during wet granulation.[21] This is

consistent with the findings of Abdallah et al.[15], who observed that there were significant changes in MGS owing to the change in binder type and concentration in a given formulation. The flowability of granules as assessed by measuring the AoR shows that the results of this parameter ranged from 30.32-34.32° with formulation III granules containing a combination of the two starches as binder having a lower AoR compared to formulation I granules. This is a requirement for the successful formulation of robust tablets. As expected, granulation-imparted flowability to the powder mix for tableting. Generally, lower AoR corresponds to an improvement in the flow of granules and powders and this can be attributed to the increase in particle size which was observed in formulation III granules. With respect to flowability of granules and powders, there is interplay of forces including particle size and shape of granules that combine to define the flowability of the granules.[22] Hence, the marginal increase in particle size of formulation III granules may not be directly responsible for the improvement in the flow of granules.

There was a marginal increase in the bulk and tapped densities of formulation III granules containing both starches as binders, suggesting an improvement in the compressibility of granules. This can be attributed to the combined effect of both starches as binders in the formulation resulting in a greater degree of cohesion and subsequently densification during compression.[23] High bulk density corresponds to a greater degree of volume reduction because of decrease in porosity and closer packing of granules.[24] Other parameters like CI and HR did not follow the same relationship as seen with the AoR. However, the values obtained for both parameters confirmed that granules have acceptable flowability. This is based on the requirement that CI and HR should not exceed 20% and 1.2 respectively for good powder and granule flowability.[25] This agrees with the findings of Oyi et al.[26], where the flowability of granules was confirmed to be excellent owing to the low values of CI and HR, respectively.

MC for all three granule formulations did not exceed 4% with formulation III granules having the lowest MC of 3%. Studies have shown that MC is implicated in the flowability of powders and granules and so it is imperative to optimize MC to ensure acceptable flow of granules. This agrees with the findings of Emery[27], whose studies confirmed the role of

Table 2. Granule properties of formulations I-VI

Granule parameters	Formulations containing starch as binder			Formulations containing starch as a disintegrant		
	I	II	III	IV	V	VI
Mean granule size (µm)	337.18	309.74	349.69	386.41	369.73	371.02
Angle of repose (º)	32.32 ± 0.15	30.32 ± 0.58	30.50 ± 0.82	28.66 ± 0.38	29.31 ± 0.37	29.40 ± 0.42
Bulk density (g/cm³)	0.41 ± 0.01	0.43 ± 0.01	0.44 ± 0.01	0.49 ± 0.01	0.60 ± 0.01	0.64 ± 0.01
Tapped density (g/cm³)	0.46 ± 0.01	0.51 ± 0.02	0.52 ± 0.01	0.58 ± 0.01	0.70 ± 0.02	0.70 ± 0.02
Carr's index (%)	10.29 ± 2.77	15.22 ± 0.47	15.39 ± 0.24	14.82 ± 0.26	14.93 ± 0.32	9.53 ± 0.21
Hausner's ratio	1.12 ± 0.03	1.18 ± 0.01	1.18 ± 0.00	1.17 ± 0.00	1.18 ± 0.00	1.11 ± 0.00
Moisture content (%)	4	4	3	3	3	2

MC in defining the flowability of a formulation designed for tableting. MC did not differ significantly across the granule formulations, implying that granulation and drying conditions were kept constant.

Photomicrographs of granule formulations (I-III) are displayed in Figure 1. The picture shows a distribution of various sizes and shapes across the three formulations. The photomicrograph did not show a clear distinction as to distinguish each granule formulation, implying that the type of binder used may not have a significant effect on the morphology of granules considering that the binders used had some degree of similarity except for the source of starch. Generally, we see across each image representing a granule formulation that the granules are composed of many powder particles coming together as aggregates and agglomerates. This is essentially the reason for granulation to improve the flowability and compressibility of powders induced by the cohesive effect of binders.[24,28,29] This is consistent with the normal distribution of particle sizes in granules produced by wet granulation.[30] The differences observed in the granule properties were minimal across the three formulations. These slight differences could be attributed to the composition of each formulation as they differed in their binder content. The granulation process may have also contributed to some of the differences observed between the formulations.

Granule properties of formulations containing starch as disintegrant (IV-V) are also presented in Table 2. MGS for the formulations ranges from 371.02-386.41 µm with formulations IV and V having the highest and least MGS. The particle size of the formulations did not appear to differ significantly, however, it was observed that formulation VI containing the combined starches as disintegrant had a relatively similar MGS with formulation V granules, but was lower than that of formulation IV. This implies therefore that the combined effect of both starches as disintegrants did not promote an increase in MGS of granules, as was seen in formulation III, when both starches were incorporated as binders. This may be because incorporating starches as disintegrants promotes disaggregation and fragmentation rather than aggregation and agglomeration, which increases MGS.[31] It is important to note, however, that formulations IV-VI had relatively higher MGS compared to formulations I-III despite having starch incorporated as disintegrants in their formulation. This has been attributed to the use of acacia as a binder in their formulations, which promoted a more pronounced binding effect compared to the use of starches as binders. Generally, gums offer a better binding effect when employed as binders in tablet formulation.[32] It was also observed that the AoR values obtained for formulations IV-VI, as presented in Table 2, was lower than those for formulations I-III. This can be attributed to the larger MGS of formulation IV-VI granules, which directly influences the flow of granules.

The bulk and tapped density values of formulation VI containing both starches as disintegrants were relatively higher compared to formulations IV and V, implying a greater degree of densification occurring in the granules during tapping, which simulates the application of force during compression. This has also been attributed to the MGS of formulation VI granules, which was lower compared to formulation IV. As revealed by other studies, small-sized granules generally facilitate a greater degree of densification because of the ability of the small particles to fill in pore spaces, thereby reducing the porosity and volume occupied by the densely packed granules.[33]
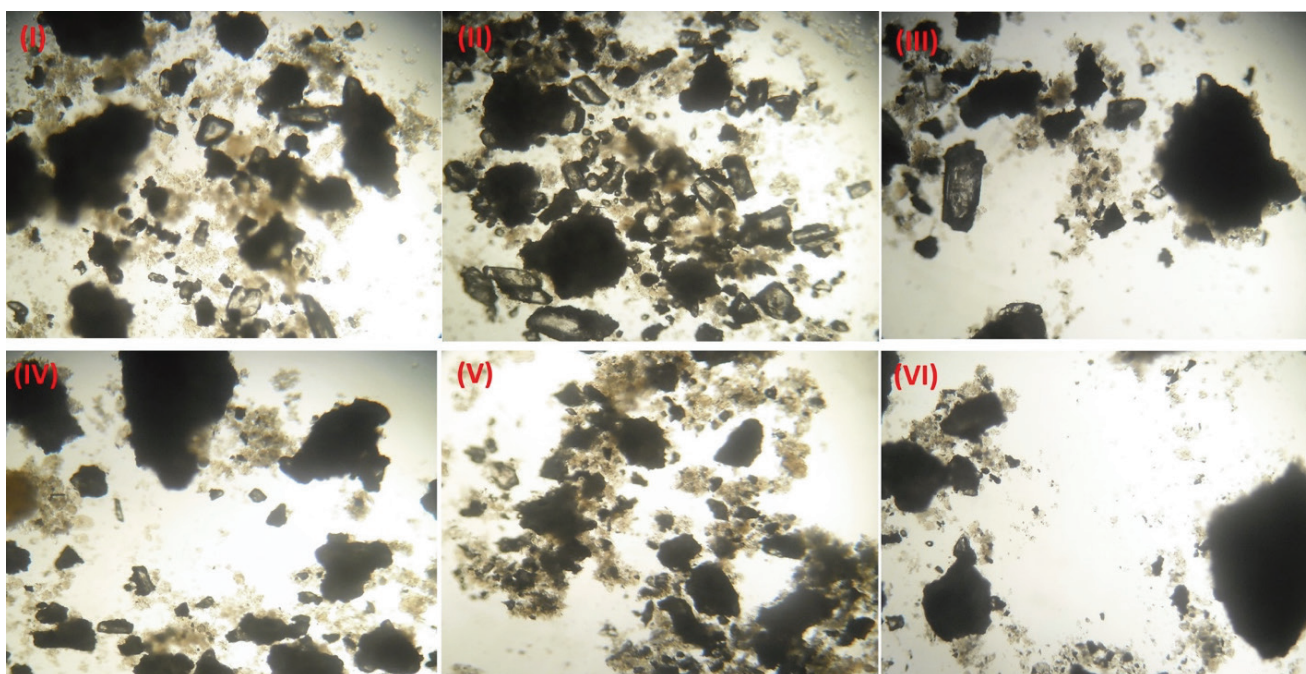

Figure 1. Photomicrographs of granule formulation (I-VI)

The values of CI and HR (Table 2) for formulations IV-VI were consistent with free flowing granules as they ranged from 9.53-14.82% and 1.11-1.18, respectively. MC did not reveal any much difference across formulations IV-VI as it ranged from 2-3%. However, formulation VI containing both starches as disintegrants had a lower MC of 2%. Photomicrographs of formulation IV-VI granules displayed in Figure 1 show similar morphology across the formulations. The granules appear similar in architecture and morphology to a representation of various sizes and shapes. The appearance of the granules does not appear to have been affected significantly by the difference in formulation of granules with respect to the starch type and composition. This implies therefore that the inclusion of excipients in a formulation will exert its effect primarily within the internal structure of the granulation and not necessarily on the external aspects of the granulation. Modification of the external appearance of granules may occur when extragranular excipients are incorporated before tableting.

Physical properties of metronidazole tablets

Tablet properties of formulations I-VI are presented in Table 3. The mean tablet weight of formulations I-III ranged from 490-521 mg, with formulation III having the highest mean tablet weight. This may be related to the larger MGS of formulation III granules, which may have caused preferential filling of the die cavity with large sized granules producing oversized tablets. This is consistent with the findings of Tan et al.[34], who evaluated the effect of granule size on tablet weight variation. Content uniformity of the three tablet formulations reflected the mean tablet weight as formulation III tablets had the highest percentage drug content compared to the other two formulations. This also agrees with the findings of Zaid et al.[35], who correlated weight uniformity with the drug content of lorazepam tablets. The tensile strength of tablets ranged from 0.49-1.14 MPa with formulation II tablets containing potato starch as the binder having the highest mean tensile strength of 1.14 MPa. This is consistent with the report of Szepes[13] in a review published in 2009, where potato starch is described as having multifunctional properties including diluent, binder and disintegrant properties. Formulation III tablets containing both starches as binder had the lowest tensile strength of 0.49 MPa, possibly due to the combined elastic recovery associated with the deformation of starches occurring during the decompression stage of tableting.[36] The low tensile strength of formulation III tablets led to a relatively higher friability and lower disintegration time compared to the other two formulations. This was expected as the low tensile strength of tablets implies that the tablets are brittle and porous in microstructure, thereby facilitating rapid ingress of water leading to fast disintegration.[37] Drug-release profiles shown in Figure 2a. The time taken to release 80% of the drug was under 10 mins for all three formulations. All the formulations therefore passed the test for dissolution as more than 70% of the drug was released in 45 mins.

Tablet properties of formulations IV-VI as presented in Table 3 shows a greater degree of uniformity in tablet weight, possibly due to the excellent flowability of granules, confirmed by the flow indices of AoR, CI and HR. The percentage drug content of all three formulations, however, appeared high, exceeding the recommended range of 95-105% as *per* BP requirements.[38] The tensile strength of tablets ranged from 1.02-1.84 MPa, with formulation VI having the least tensile strength. This could be attributed to the combined effect of both starches exerting their effect as a disintegrant, thereby hindering the formation of interparticulate bonds during compression.[39] Friability and disintegration results were consistent with the tensile strength values recorded across the three formulations (IV-VI) as higher tensile strength of tablets (formulation IV) produced less friable tablets, which took a longer time to disintegrate. Comparing the disintegrant properties of both starches, formulation V tablets containing potato starch as the disintegrant disintegrated faster compared to formulation IV tablets containing maize starch as disintegrant. However, when both starches were combined as disintegrant in formulation VI tablets, the disintegration time was lowered compared to either of the formulations containing the different starches as disintegrant. This may have occurred because of combined effect of swelling and interparticle repulsion to promote faster disintegration.[31]

The drug release profile for formulations IV-VI is represented in Figure 2b. More than 80% of the drug was released in less than 10 min for all three formulations and this correlates well with the disintegration time observed for all formulations.

Table 3. Tablet properties of formulations I-VI

Tablet parameters	Formulations containing starch as binder			Formulations containing starch as a disintegrant		
	I	II	III	IV	V	VI
Mean weight (mg)	490.7 ± 5.46	495.05 ± 3.17	521.9 ± 4.85	499.75 ± 6.82	498.35 ± 7.97	498.60 ± 4.25
Content uniformity (%)	103.5	101.2	114.6	114	112	110
Tensile strength (MN/m²)	0.99 ± 0.17	1.14 ± 0.05	0.49 ± 0.06	1.84 ± 0.01	1.25 ± 0.05	1.02 ± 0.06
Friability (%)	0.8	0.8	0.9	0.81	0.81	0.60
Disintegration time (min)	0.7 ± 0.19	0.83 ± 0.12	0.30 ± 0.03	14.92 ± 0.20	11.33 ± 1.51	10.83 ± 1.72

MN: Meganewton
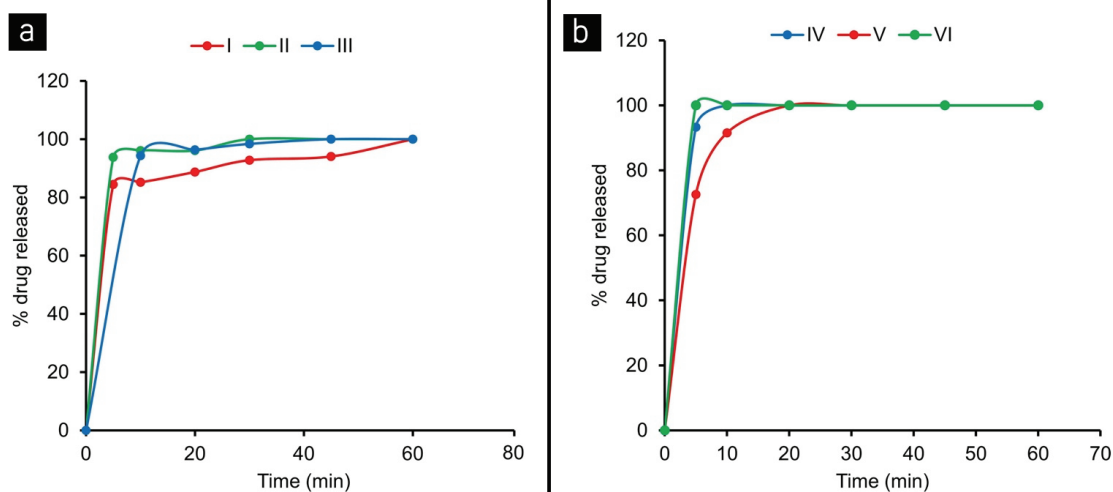
Figure 2. Dissolution profiles for (a) formulations I-III (b) formulations IV-VI

CONCLUSION

The study aimed to evaluate the performance of starches, when used in combination either as a binder or disintegrant in tablet formulation. The outcome of the study shows that combining maize starch and potato starch in equal proportion as a binder did not yield a superior performance compared to the performance of the individual starches in formulation as a binder. However, when both starches where combined in the same proportion as a disintegrant in tablet formulation, they gave a better performance in terms of faster disintegration compared to the performance of the individual starches as disintegrant in a tablet formulation. This implies, therefore, that combining starches of different sources as a tableting excipient may most likely influence its functionality in tablet formulation.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.E.A., R.T.K., S.H.I., Design: Y.E.A., R.T.K., S.H.I., Data Collection or Processing: R.T.K., S.H.I., Analysis or Interpretation: Y.E.A., R.T.K., S.H.I., S.N.A., A.O.A., A.R.O., Literature Search: R.T.K., S.H.I., Writing: Y.E.A., R.T.K., S.H.I., S.N.A., A.O.A., A.R.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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