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Effects of Modification and Incorporation Techniques on Disintegrant Properties of Wheat (*Triticum Aestivum*) Starch in Metronidazole 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. Natural polymers serve as cheap, non-toxic, biocompatible excipients in drug delivery.
Objectives. Starch from wheat (*Triticum aestivum*) was investigated as a disintegrant in metronidazole tablet formulations in comparison with sodium starch glycolate (SSG), a standard, synthetic but relatively more expensive disintegrant.
Material and Methods. Native wheat starch (NAS) was modified by pregelatinization (PGS) and microwave irradiation (MCW). The starches were characterized using swelling capacity, angle of repose, density measurements, Carr's index and Hausner's ratio. Metronidazole tablet formulations were made with the starches incorporated by intragranular (IG), extragranular (EG) or intra/extragranular (IG/EG) methods. Tablet properties of crushing strength, disintegration time and dissolution tests were determined.
Results. Native wheat starch had better hydration capacity than the modified starches, with PGS having a higher swelling capacity than the MCW. Modified starches formed better compacts than both NAS and SSG as indicated by the higher crushing strength of tablets containing modified starches. Intragranular incorporation gave a higher crushing strength than both EG and IG/EG methods. The ranking for disintegration time of tablets was IG/EG > IG > EG among the incorporation methods and SSG > PGS > MCW > NAS among the starches (EG > IG/EG). The difference between IG/EG and EG was significant ($p < 0.05$) but not significant between IG and other incorporation methods (MCW > SSG > PGS). Native and modified wheat starches exhibited better disintegrant properties than sodium starch glycolate in metronidazole tablet formulations.
Conclusions. The mode of disintegrant incorporation and modification of wheat starch had different effects on tablet properties of metronidazole formulations. The modification technique and method of disintegrant incorporation should be determined based on desired tablet properties (**Polim. Med. 2014, 44, 3, 147–155**).

Key words: disintegrant properties, wheat starch, starch modification, metronidazole.

The oral route provides the most convenient means of drug delivery. Tablets are widely used due to their ease of administration, compactness, dosage precision and economy of production. Drug release from a dosage form can be enhanced by the addition of suitable disintegrants. Hence, the choice of disintegrants and its consistence of performance are critical to the formulation of tablets [1].

Starches are widely available and have proven to be effective excipients in tablet production due to their relative inertness, and cheapness, and have been used as binders, disintegrants, glidants and fillers [2, 3]. Starches have a great affinity for water and swell when moistened, thus facilitating the rupture of the tablet structure and the subsequent release of the contained medicine. However, native starches are weak structurally and functionally too restricted in tablet manufacturing, hence the need to increase their function through modification [4].

The basic starch material that is presented in the dry powder form for food and/or pharmaceutical raw materials is termed native starch. These starches are of limited usefulness due to the absence of certain functional properties. Hence the need for modification in order to render them useful for various purposes. Native starch can be modified, causing a change in its physical

and/or chemical characteristics. These changes may be achieved by altering starch properties such as pasting temperature, retrogradation tendency, viscosity, surface charge and hydrophilic/hydrophobic nature [4].

Disintegrants are important excipients which facilitate the breakdown of the tablets into particles when in contact with the aqueous environment of the gastrointestinal tract. They thereby increase tablet surface area promoting rapid release of the drug substance [5]. Disintegrants could be incorporated in tablet formulations as exo, endo or exo-endo disintegrants. Disintegrants could be incorporated in different ways by wet granulation in tablet formulations. The intragranular incorporation method is when the disintegrant is added together with the granulating fluid into the formulation. Disintegrants could also be added to the already made granules; in this case the incorporation method is termed extragranular. A portion of the disintegrant could be added intragranularly while the remaining portion is added extragranularly; this is the intra/extragranular method of incorporation. It is essential to determine the effect of the incorporation method on the disintegrating properties of the tablets.

While there have been previous studies on starches as disintegrants, there seems to be no investigation on the disintegrant properties of native and modified wheat starch and the effect of the mode of its incorporation on performance. Hence, this work was aimed at determining the effect of modification (pregelatinization and microwave irradiation) and mode of incorporation (exo, endo or exo-endo) of wheat (*Triticum aestivum*) starch as a disintegrant in metronidazole tablet formulations.

Material and Methods

Materials

The materials used include metronidazole (Vision Pharmaceutical Co. Ltd., China), wheat (*Triticum aestivum*) obtained from Bodija market in Ibadan, Nigeria and authenticated at the University of Ibadan Herbarium and sodium starch glycolate (JRS Pharma, Germany). All other materials used were of analytical grade.

Methods

Extraction of Wheat Starch

Wheat starch was extracted from wheat grains following the previously described procedure [6, 7]. The wheat starch powder obtained was sieved with mesh size 0.25 mm and stored in an airtight container.

Modification of Wheat Starch

Pregelatinization

An amount (50 g) of wheat starch was weighed and 10 mLs of water added and placed over a boiling water-bath. The mixture was continuously stirred over the water-bath and 30 mLs of water was added again with continuous stirring. This process was continued until the starch was well prepared using 73 mLs of water in all. The paste was spread on a wide porcelain tile and dried in a hot air oven at 60ºC for 24 h. The resulting pregelatinized starch was milled in a laboratory blender (Model 857, Willamette Industries, USA) and sieved with mesh size 0.25 mm.

Microwave Irradiation

A 45 g quantity of starch was weighed and made into a slurry with distilled water. The prepared slurry was evenly spread on tiles and each dried in a microwave oven for 20 s. Thereafter, the tiles were put in an oven and dried for 24 h at 60°C. They were then scraped off the tiles and milled using a pestle, mortar and a laboratory blender. The powder obtained was sieved using a sieve with mesh size of 0.25 mm.

Characterization of Wheat Starch

Swelling Capacity

The swelling capacity was determined using established procedures [8]. The tapped volume (V_x) occupied by the powders was determined and recorded. 5% starch suspension was prepared at room temperature with shaking for 5 min. The dispersion was allowed to stand for 24 h before the sedimentation volume (V_v) was measured and the swelling capacity was calculated using the equation:

$$\text{Swelling capacity} = V_x/V_v \quad (1)$$

Angle of Repose

The flow properties of the granules were determined using the fixed funnel method of determining angle of repose [9]. The angle of repose was calculated using the equation:

$$\text{Tan } \theta = \frac{h}{r} \quad (2)$$

where h is the height of powder and r is the radius of the base of the cone. The angle of repose was calculated from a mean of three determinations.

Particle Size

The mean particle size of the native, pregelatinized and microwave irradiated starches was determined by optical microscopy using a calibrated eye piece. This was done on 300 particles and used to determine the mean projected diameter (d).

$$d = \Sigma nd/\Sigma n \quad (3)$$

where d is granule diameter retained on sieve range, while n is the frequency number in the corresponding size range.

Density Measurements

The bulk, tapped and particle densities of the starch samples were determined from the following equations:

$$\text{Loose bulk density (LBD)} = \text{Weight of starch/Volume of the packing} \quad (4)$$

$$\text{Tapped density (TD)} = \text{Weight of starch/Tapped volume of packing} \quad (5)$$

The particle density was determined using liquid pycnometer method, with xylene as the displacement liquid [4]. The relative density of each starch powder was computed, which is the ratio of the bulk density to the particle density:

$$\text{Relative density (Dr)} = \text{bulk density/particle density} \quad (6)$$

Compressibility index

The compressibility index of each starch was determined using Carr's compressibility index:

$$\text{Carr's index (\%)} = \text{tap density} - \text{bulk density/tap density} \times 100 \quad (7)$$

Photomicrograph

The photomicrographs of the starches were taken using a microscope (Olympus Optical Co., Japan) fitted with a camera.

Granule Preparation

Metronidazole tablet formulations were made from this formula:

Metronidazole (API)	200 mg
Gelatin (binder)	16 mg
Wheat starch/sodium starch glycolate (disintegrant)	16 mg (4%)
Lactose (bulking agent)	to 400 mg

Granules were prepared using the wet granulation method. Three sets of granules were prepared from each starch sample: intragranular (IG), extragranular (EG) and intragranular/extragranular (IG/EG) methods of disintegrant incorporation. For IG disintegrant incorporation, wheat starch was mixed with other materials before being made into granules, wheat starch was added to the already formed granules to make the EG incorporation while 50% of the required wheat starch was incorporated as intragranular and the remaining 50% as extragranular for IG/EG disintegrant incorporation. Gelatin was used as the aqueous slurry made with hot distilled water. The wet masses, after being thoroughly mixed in a mortar, were forced through mesh 12 (1400 um), spread on appropriately labeled square ceramic tiles and dried for 24 h in an oven set at 60°C. The dried granules were thereafter stored in appropriately labeled air-tight plastic containers.

Granule Size Distribution

Standard sieves of the following sizes were used: 12 mesh (1400 um), 16 mesh (1000 um), 30 mesh (500 um), 44 mesh (335 um) and the receiver. These were stacked in decreasing order of aperture size (as above). The approximately 20 g of each set of granules was weighed and placed on the topmost sieve (mesh 12), covered and manually shaken for 2 min. Thereafter, the granules retained on each sieve were carefully removed and weighed; including the weight of the fines retained by the receiver.

Preparation of Dablets

Quantities (400 mg) of each batch of granules of size 500–1000 μm were compressed into tablets using a hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, U.S.A.), fitted with a pressure gauge reading up to 2.5 metric tons. Tablets were compressed from each set of the granules (IG, EG, IG/EG) at different compression pressures.

Evaluation of Tablets

Crushing Strength

The crushing strength of the tablets were determined by diametral compression at room temperature (Fell and Newton, 1970) using a hardness tester (DBK instrument, 400065 model EH 01; Mumbai). Only results that were taken from tablets which split cleanly into two halves without any sign of lamination were considered valid. Measurements were made in triplicates and the results are means of the determinations.

Disintegration Time Test

The disintegration time of the tablets was determined in distilled water at 37 ± 0.5°C using a disintegration tester (DBK tablet disintegration test apparatus, England). Determinations were done in triplicates.

Dissolution Test

The test for drug release was done on tablets using the USPXX III basket method (DBK Dissolution rate test apparatus, England) rotated at 50 rpm in 900 mL of 0.1M HCL, maintained at 37 ± 0.5°C. Samples (5 mL) were withdrawn and replaced with equal amounts of fresh medium. The sample was diluted and the amount of metronidazole released was determined at wavelength of 265 nm, using a UV/Visible spectrophotometer.

Statistical Analysis

The samples were analyzed in replicates and results evaluated using one-way ANOVA. Duncan's multiple range test was used to rank the starch types and to determine the parameters that show a statistically significant difference.

Results

The physicochemical properties of the starches are presented in Table 1. Results of the angle of repose showed that all the polymers had poor flow properties with values above 58°. The Carr's index, a measure of compressibility, varied with modification, with the round micro-waved wheat starch being the most compressible at 16.42% (Table 1). Hausner's ratio values are also given in Table 1 and correlated directly with the compressibility index. The swelling capacity was observed to be highest with sodium starch glycolate, 6.71, and least with the microwaved wheat starch, 1.80.

The tablet and drug release properties of the formulations are given in Tables 2, 3 and 4. The values for crushing strength, disintegration time and dissolution time are presented depending on the mode of incorporation of the disintegrants respectively.

Photomicrographs of the native and modified starches with sodium starch glycolate are presented in Fig. 1–4. Modification affected both particle shape and size. The release profiles are presented in Fig. 5–7 depending on the mode of disintegrants incorporation. The time taken for 80% of the drug in the formulations (t_{80}) to be released was determined and compared.

Table 1. Physicochemical and micromeritic properties of polymers

Samples	Particle size (μm)	Particle shape	Particle density (g/cm^3)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)	Swelling capacity
Native wheat starch	1.1	oval	1.536	0.45	0.69	34.78	1.53	66.16	2.25
Microwave-modified wheat starch	1.64	round	1.180	0.56	0.67	16.42	1.20	64.88	1.80
Pre-gelatinized wheat starch	1.33	polygonal	1.235	0.50	0.67	25.37	1.34	58.77	4.63
Sodium starch Glycolate	1.35	ovoid aggregate	1.490	0.30	0.60	38.33	1.62	58.24	6.71

Table 2. Tablet properties of formulations incorporating Extragranular disintegrant (mean ± sd, n = 3)

Starch sample	Compression pressures	Mean weight (g)	Thickness (mm)	Crushing strength (N)	Disintegration time (min)	Dissolution time, t_{80} (min)
Native starch	0.50	0.389 ± 0.02	4.17 ± 0.01	42.35 ± 3.20	1.20 ± 0.10	
	0.75	0.386 ± 0.01	4.12 ± 0.00	56.20 ± 1.26	2.26 ± 0.14	
	1.00	0.389 ± 0.02	4.14 ± 0.01	41.50 ± 3.21	2.57 ± 0.11	
	1.25	0.390 ± 0.06	4.37 ± 0.02	64.45 ± 2.11	1.20 ± 0.08	12.6 ± 3.25
Microwave-Modified	0.50	0.378 ± 0.03	4.16 ± 0.03	47.35 ± 1.14	2.29 ± 1.04	
	0.75	0.381 ± 0.02	4.25 ± 0.01	54.30 ± 3.25	2.31 ± 0.89	
	1.00	0.384 ± 0.06	4.46 ± 0.03	58.40 ± 4.22	2.52 ± 0.14	
	1.25	0.385 ± 0.09	4.25 ± 0.01	69.30 ±1.25	3.64 ± 0.11	30.4 ± 5.47
Pregelatinized	0.50	0.437 ± 0.03	4.25 ± 0.04	54.20 ± 3.40	4.56 ± 1.04	
	0.75	0.397 ± 0.07	4.15 ± 0.01	67.30 ± 4.14	5.83 ± 0.88	
	1.00	0.400 ± 0.12	4.20 ± 0.13	65.25 ± 2.22	6.69 ± 1.26	
	1.25	0.402 ± 0.06	4.10 ± 0.01	93.25 ± 3.14	8.50 ± 1.14	15.0 ± 2.20
Sodium starch glycolate	0.50	0.392 ± 0.04	4.08 ± 0.12	56.00 ± 2.11	5.50 ± 2.17	
	0.75	0.385 ± 0.02	4.20 ± 0.06	83.00 ± 6.25	9.05 ± 1.26	
	1.00	0.389 ± 0.01	4.25 ± 0.01	75.15 ± 2.48	10.99 ± 0.89	
	1.25	0.386 ± 0.03	4.37 ± 0.03	68.45 ± 3.27	11.16 ± 1.08	19.0 ± 3.76

Table 3. Tablet properties of formulations incorporating intragranular disintegrant (mean ± sd, n = 3)

Starch sample	Compression pressures	Mean weight (g)	Thickness (mm)	Crushing strength (N)	Disintegration time (min)	Dissolution time, t_{80} (min)
Native starch	0.50	0.387 ± 0.11	4.10 ± 0.02	56.80 ± 4.12	2.42 ± 1.02	
	0.75	0.388 ± 0.09	4.14 ± 0.01	77.75 ± 6.17	3.75 ± 0.98	
	1.00	0.389 ± 0.02	4.19 ± 0.02	57.45 ± 2.84	3.12 ± 1.24	
	1.25	0.383 ± 0.12	4.37 ± 0.03	78.35 ± 3.25	3.29 ± 2.14	42.1 ± 3.55
Microwave-Modified	0.50	0.395 ± 0.08	4.19 ± 0.05	52.40 ± 2.58	1.35 ± 1.06	
	0.75	0.393 ± 0.13	4.21 ± 0.02	59.40 ± 1.28	2.62 ± 0.85	
	1.00	0.394 ± 0.07	4.19 ± 0.10	62.45 ± 2.65	3.62 ± 1.22	
	1.25	0.398 ± 0.01	4.06 ± 0.06	77.15 ± 4.41	4.19 ± 1.08	38.3 ± 1.12
Pregelatinized	0.50	0.395 ± 0.09	4.17 ± 0.03	58.65 ± 3.25	2.39 ± 0.55	
	0.75	0.398 ± 0.11	4.29 ± 0.12	75.35 ± 3.19	3.57 ± 1.21	
	1.00	0.399 ± 0.16	4.12 ± 0.08	87.00 ± 5.22	4.85 ± 0.42	
	1.25	0.398 ± 0.05	4.22 ± 0.07	97.10 ± 4.14	4.93 ± 1.47	10.4 ± 1.80
Sodium starch glycolate	0.50	0.397 ± 0.01	4.22 ± 0.03	97.72 ± 7.19	2.81 ± 1.02	
	0.75	0.399 ± 0.14	4.08 ± 0.03	112.8 ± 3.02	2.95 ± 1.08	
	1.00	0.399 ± 0.07	4.33 ± 0.13	108.2 ± 3.54	4.61 ± 0.45	
	1.25	0.395 ± 0.16	4.16 ± 0.02	128.5 ± 2.47	5.94 ± 2.01	16.1 ± 2.45

Table 4. Tablet properties of formulations incorporating intra/extragranular disintegrant (mean ± sd, n = 3)

Starch sample	Compression pressures	Mean weight (g)	Thickness (mm)	Crushing strength (N)	Disintegration time (min)	Dissolution time, t_{80} (min)
Native starch	0.50	0.387 ± 0.12	4.10 ± 0.03	53.00 ± 2.62	1.59 ± 0.44	
	0.75	0.388 ± 0.09	4.22 ± 0.12	73.15 ± 2.45	2.63 ± 0.36	
	1.00	0.390 ± 0.02	4.38 ± 0.03	62.65 ± 4.20	3.53 ± 0.14	
	1.25	0.391 ± 0.01	4.24 ± 0.08	99.10 ± 5.22	5.51 ± 1.17	10.0 ± 1.58
Microwave-Modified	0.50	0.393 ± 0.06	4.12 ± 0.02	64.65 ± 3.34	2.47 ± 0.44	
	0.75	0.393 ± 0.02	4.15 ± 0.09	55.40 ± 2.10	3.41 ± 1.07	
	1.00	0.391 ± 0.01	4.40 ± 0.13	83.80 ± 6.27	4.45 ± 1.78	
	1.25	0.390 ± 0.05	4.34 ± 0.18	87.85 ± 4.17	4.41 ±1.96	15.5 ± 3.25
Pregelatinized	0.50	0.385 ± 0.02	4.10 ± 0.06	46.75 ± 3.29	4.10 ± 0.92	
	0.75	0.383 ± 0.01	4.10 ± 0.05	52.00 ± 6.47	4.01 ± 1.24	
	1.00	0.384 ± 0.03	4.20 ± 0.15	87.60 ± 8.57	6.62 ± 1.58	
	1.25	0.385 ± 0.03	4.37 ± 0.85	78.55 ± 4.14	6.17 ± 1.87	7.4 ± 1.40
Sodium starch glycolate	0.50	0.389 ± 0.06	4.33 ± 0.56	64.05 ± 2.28	4.65 ± 0.95	
	0.75	0.401 ± 0.04	4.18 ± 0.12	81.30 ± 6.64	7.52 ± 2.05	
	1.00	0.388 ± 0.01	4.31 ± 0.08	92.25 ± 4.11	7.94 ± 1.85	
	1.25	0.396 ± 0.03	4.36 ± 0.27	91.05 ± 4.23	10.55 ± 2.62	12.2 ± 2.58

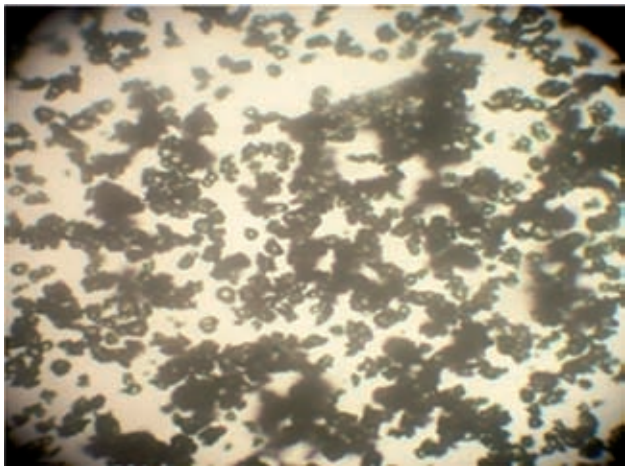

Fig. 1. Photomicrograph of native wheat starch (×100)

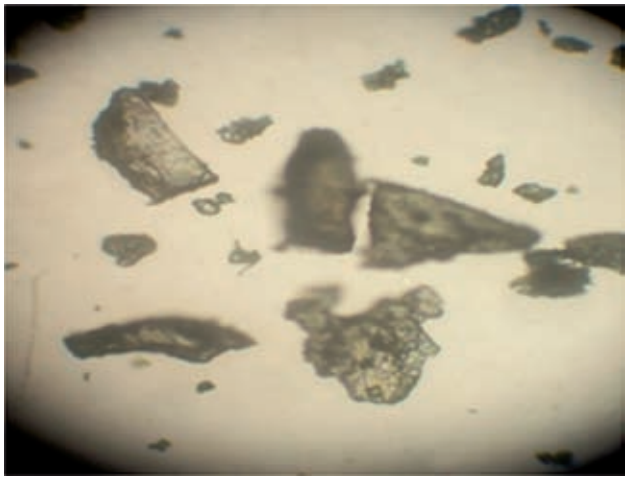

Fig. 2. Photomicrograph of pregelatinized wheat starch (×100)

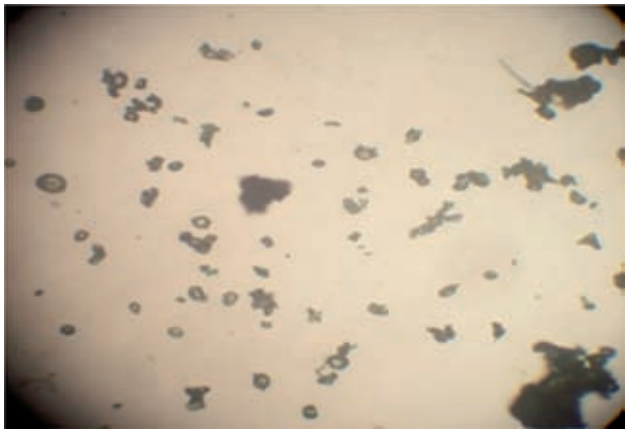

Fig. 3. Photomicrograph of microwave irradiated wheat starch (×100)

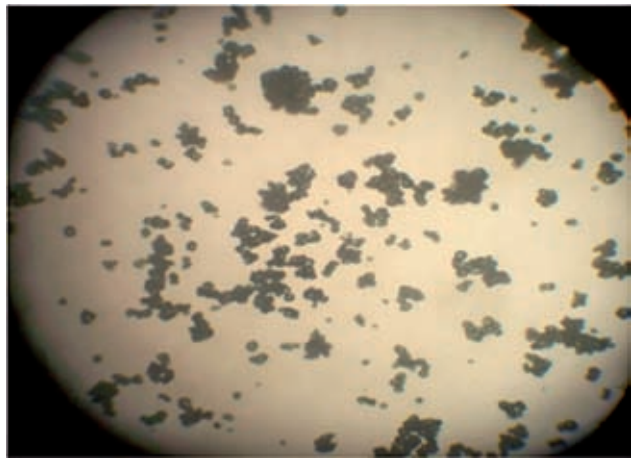

Fig. 4. Photomicrograph of sodium starch glycolate (×100)

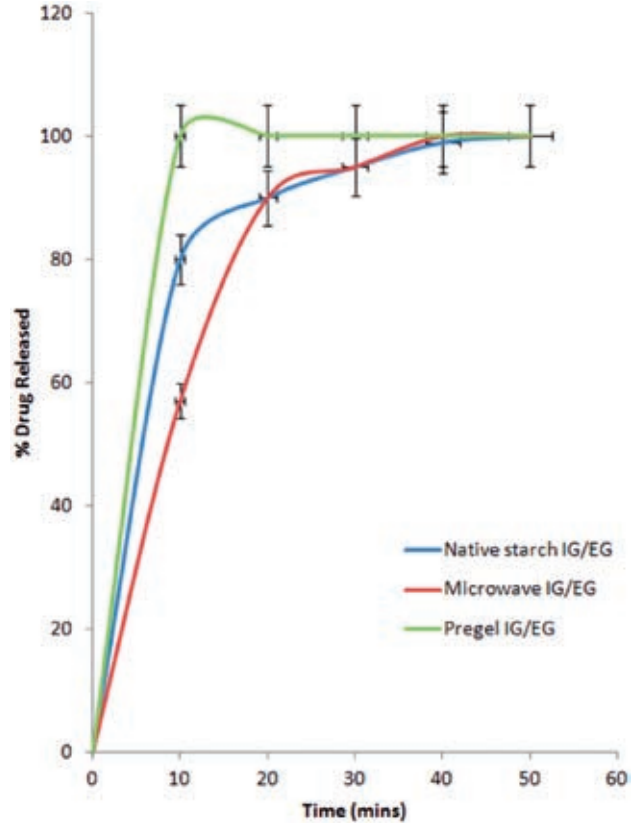

Fig. 5. Dissolution profile of metronidazole tablet formulations incorporating Intragranular/Extragranular (I.G/E.G) disintegrants

Discussion

The physicochemical properties of the starches are presented in Table 1. The modified starches were larger in size than the native, although the difference in sizes was not significant ($p > 0.05$), and the starches were of different shapes (Fig. 1–4). The bulk densities of the

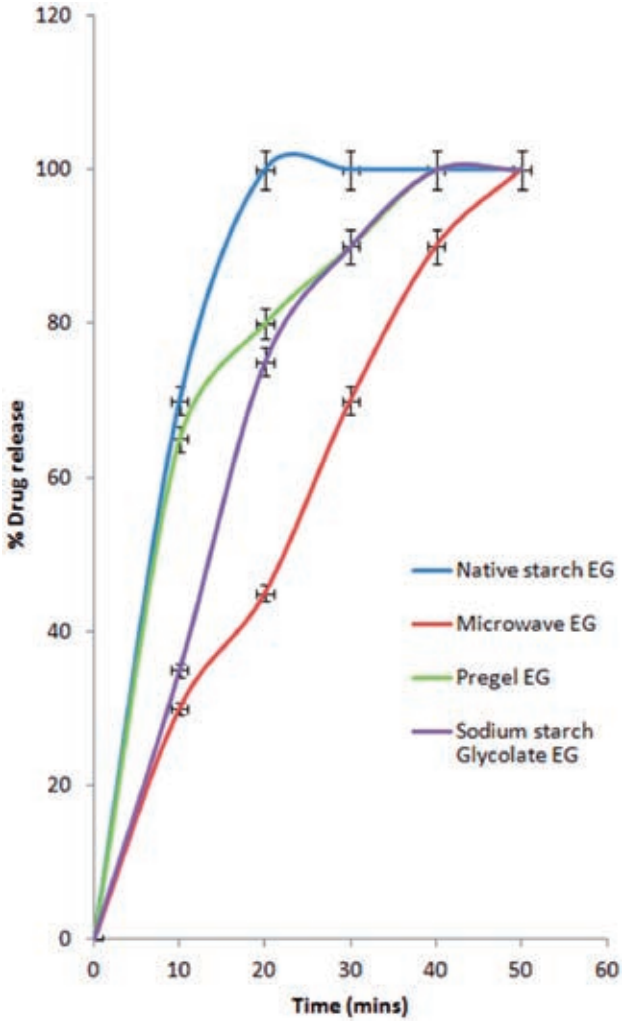

Fig. 6. Dissolution profiles of metronidazole tablet formulations incorporating Extragranular (E.G) Disintegrants

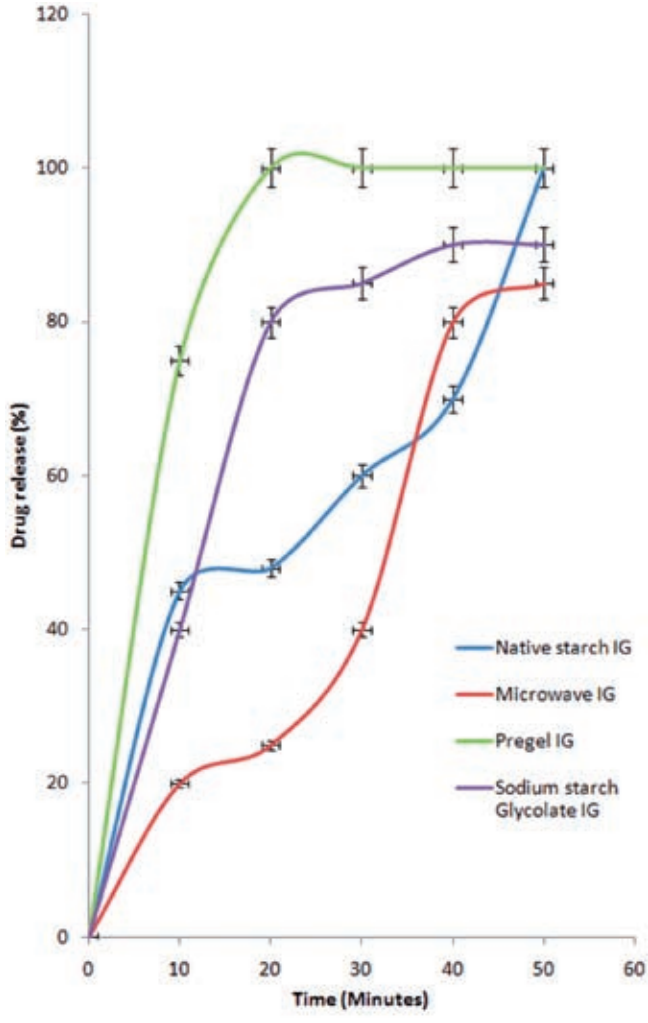

Fig. 7. Dissolution profile of metronidazole formulations incorporating Intragranular (I.G) disintegrants

pregelatinized and microwave irradiated starches were similar and significantly different from that of the native wheat starch and sodium starch glycolate. Factors that affect powder bulk density include particle shape, particle size and size distribution, and the tendency of the particles to adhere to one another. Powder packing may allow many voids, resulting in a powder of low bulk density. However, high bulk density powders may occur due to the sifting of smaller particles between the larger ones [10, 11]. Modified starches tend to be more densely packed than the native starch.

The ranking of the particle density was NAS > SSG > > PGL > MCW. The particle or true density is the density of the powder excluding all voids. Several critical pharmaceutical operations, such as mixing, granulation and die filling, are affected by the particle density of the powders used. Particle density has been demonstrated to affect the initial phase of compression in the preparation of tablets [12]. Microwave irradiation more significantly reduced the bulk density of the native starches than pregelatinization.

One of the parameters used in assessing the integrity of tablets is the crushing strength. Crushing strength is a measure of the bond strength and ability of the tablets to withstand the stress of packaging, transportation and handling. However, it is not always essential to seek to have high crushing strength for tablets because excessively high crushing strength is an indicator of poor tablet disintegration. The tablets containing modified starches had higher values of crushing strength than those with native starch. The rank order was SSG > PGL > MCW > NAS. The mode of disintegrant incorporation had different effects on the formulations, depending on the nature of the disintegrant. For instance, in formulations containing pregelatinized wheat starch as a disintegrant, the rank order of crushing strength of tablets for methods of disintegrant incorporation was IG > EG > IG/EG while the IG/EG method had the highest crushing strength for both native and microwave irradiated starches, with the rank order of IG/EG > IG > EG. This suggests the need for critical consideration of starch modification and the appropri-

ate selection of a disintegrant incorporation method for optimum tablet crushing strength. Moreover, the choice to modify the gum for disintegrant purposes should be determined by the intended mode of incorporation.

Tablets are not expected to be brittle, but rather they are expected to be hard and strong throughout the shelf life [13].

The disintegration time values for all the formulations fall within British Pharmacopoeia limits [14]. Generally, formulations containing SSG had the highest disintegration time values, the rank order was SSG > PGL > MCW > NAS. This suggests that modification is a feasible way of increasing the disintegration time of wheat starch. The results further suggest that the modification method employed should determine the incorporation method, in order to get a desired disintegration time, as it was discovered that the trend of disintegration time among the incorporation methods was determined by the type of modification on the starch. The least dissolution values were obtained from the pregelatinized starch, which can be correlated with the swelling capacity of the starch. This strongly suggests that the major mechanism for disintegration and consequent drug release is by swelling action of the modified starch. The highest disintegration time observed for SSG is attributable to its tendency to gel due to high viscosity. This reduces water penetration into tablets, thereby increasing disintegration time [14, 15]. Disintegration is a necessary condition for dissolution and subsequently a rate-limiting step in the absorption process [16] and previous studies have shown that the type of excipients and process parameters affect drug disintegration [17]. Hence, the incorporation mode is a process parameter that needs to be critically considered.

The effectiveness of tablets depends on the drug dissolving in gastrointestinal tract fluids prior to absorption into the systemic circulation. The rate of dissolution of tablets is critical to this process and is influenced by factors such as tablet hardness and porosity [18]. The IG/EG incorporation method produced formulations with the shortest dissolution time for all the starch forms. Formulations containing pregelatinized starch had the lowest t_{80} value. The rank order was MCW > NAS > SSG > PGL ($p < 0.05$). The results suggest pregelatinization to be a suitable modification of wheat starch to achieve a formulation with fast rate of dissolution.

The mode of incorporation of wheat starch and type of modification had significant effects on the mechanical and release properties of metronidazole tablet formulations. The modification technique and method of disintegrant incorporation should be determined based on desired tablet properties. Tablet formulations incorporating pregelatinized wheat starch as intragranular/ /extragranular disintegrants had a faster rate of disintegration than sodium starch glycolate.

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