PHYSICOCHEMICAL CHARACTERIZATION OF ACID MODIFIED DIOSCOREA STARCH AND ITS EVALUATION AS DIRECTLY COMPRESSIBLE EXCIPIENT IN TABLET FORMULATION

Bilal Tessema, Anteneh Belete, Tsige Gebre-Mariam*

Department of Pharmaceutics and Social pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, P.O. Box. 1176, Addis Ababa, Ethiopia

*For Correspondence: tsigegmwm@gmail.com

INTRODUCTION

Starch is a semi-crystalline biopolymer that serves as a carbohydrate reserve in many plants, including cereals, roots, tubers, seeds, and fruits (Elessandra & Alvaro, 2011). Starch is a polymer composed of glucose molecules that are linked together in two different forms: amylose (20-30%), amylopectin (70–80%). Starch is the main carbohydrate reserve in yam tubers, accounting for 70 - 80% of the dry weight (Odeku & Akinwande, 2011). The proximate composition of D. abyssinica on dry weight basis was found to be 0.1% ash, 0.5% protein, 1.0% fat and 98.4% starch; the amylose content was estimated to be 29.7% (Gebre-Mariam and Schmidt, 1998).

Studies have shown that the properties of some starches have been improved by physical and chemical modifications (Omojola et al., 2011). Acid modified starches are produced commercially by hydrolyzing the starches with hydrochloric or sulfuric acid at temperatures below the gelatinization temperatures. The extent of hydrolysis depends on the starch consistency, acidity of the medium, hydrolysis temperature and duration of hydrolysis (Omojola et al., 2011). Acid hydrolysis of starch involves the cleavage of the glucosidic bonds between the monomeric units which involves both protonation of the glycosidic oxygen and addition of water to yield the reducing sugar end group (D-glucose) of the starch (Odeku & Akinwande, 2011). This process diminishes the molar mass and increases the solubility and relative crystallinity of the starches (Omojola et al., 2011).

The properties of excipients that ensure a robust and successful directly compressible adjuvant are good flowability, good compressibility, low lubricant sensitivity, and high dilution potential (Parrott, 1989). The choice of excipients becomes critical in terms of its functionality as regards direct compression and rapid disintegration abilities. Only few polymers possess multiple functionalities especially in terms of good flow, direct compression and enhanced disintegration abilities. Thus, novel polymer biomaterials with effective multifunctional properties are continually being sought for drug delivery purposes. This study was designed to evaluate the efficacy of acid modified D. abyssinica starch as a potential pharmaceutical directly compressible excipient in paracetamol tablets.
MATERIALS AND METHODS

Materials

Paracetamol powder (China Associate Co Ltd, China), Ac-Di-Sol® (FMC Corporation, USA), hydrochloric acid (37% w/w, Jiangxi Bolai Pharmacy Co., Ltd, China), magnesium stearate (Bulyinos Chemicals Ltd, England) and Starch 1500 (Shandong Xinda Biotechnology Co. Ltd, China) were used as received. Tubers of D. abyssinica were obtained from local farmers in Sawula, Gamo Gofa Zone, SNNPR, Ethiopia.

Starch isolation

Starch isolation was carried out by the method described by Gebre-Mariam and Schmidt (1998). Yam tubers were washed, peeled and trimmed to remove defective parts. The tubers were then sliced, diced and blended. The flesh was suspended in large quantities of distilled water containing 0.075% (w/v) of sodium metabisulfite. The material was allowed to settle, and the sedimented starch was repeatedly treated with sodium metabisulfite solution until the supernatant was free from coloring materials and the suspension was translucent. The material was then passed through fine muslin to remove cell debris and the translucent suspension was collected, filtered through a fine sieve (224 µm) and allowed to settle. The sedimented starch was washed several times with distilled water, followed by sieving after each washing until the wash water was clear and free of suspended impurities. The resulting starch was sieved and dried in air at room temperature.

Preparation of acid modified starch

Two grams of native dioscorea starch was hydrolyzed in 10 ml of 6% (w/w) HCl solution at room temperature for 2, 4, 8, 16 and 32 days. After hydrolysis, the suspension was neutralized with 10% (w/v) sodium hydroxide solution to terminate the hydrolysis. The starch slurry was washed several times with distilled water until the pH of the filtrate was 7.0. The resulting acid hydrolyzed starch was dried in a hot air set at 25 mbar pressure 350 mbar (BÜCHI, B-290, Switzerland). Starch solution was pumped into the drying chamber of the apparatus at pumping rate of 7.5 ml/min. A flow of heated air set at 25 m³/h at 115°C and atomizing pressure 350 mbar aspirated by a pump induces the quick evaporation of the solvent from the drops, leading to the formation of solid particles.

Characterization of starches and Starch 1500®

Determination of density and related properties

Thirty grams of starch were transferred into 250 ml measuring cylinder. The volume occupied by the starch powder was read and the bulk density was calculated as g/ml. The bulk in the cylinder was then tapped for 1 min using tapped densitometer (ERWEKA, Type svm, Germany). This provided a fixed drop of one-half inch at rate of 250 taps/min. The volume occupied by the starch was recorded and tapped density was calculated as g/ml. The Carr’s index and Hausner ratio were calculated from the density results using equations 1 and 2:

\[
\text{Hausner's Ratio} = \frac{D_b}{D_t}
\]

Eq. 1

\[
\text{Carr's index} = \left( \frac{D_t - D_b}{D_t} \right) \times 100
\]

Eq. 2

where \(D_b\) is bulk density and \(D_t\) tapped density.

Flow rate and angle of repose

Flow rate and angle of repose of the starch powders were determined using the funnel method. Starch powder (30 g) was allowed to flow through funnel having a 15 mm aperture from a 10 cm height. The duration of flow was recorded and flow rate was determined by dividing the mass in gram by time in seconds. Angle of repose was calculated according to the equation 3 below.

\[
\text{Angle of repose (θ)} = \tan^{-1}\left( \frac{h}{r} \right)
\]

Eq. 3

where, \(h\) is the height and \(r\) is the radius of the starch powder pile.

Swelling power and solubility

Swelling power and solubility were determined in accordance with methods described by Daramola et al (2006). Starch (0.5 g) was weighed directly into a pre-weighed centrifuge tubes, and 10 ml distilled water was added in each tube. The tubes were then kept in a thermostatically controlled water bath (GFL®, D3006, Germany) at a temperature of 25, 35, 45, 55, 65, 75, and 85°C for 30 min with frequent mixing at 5 min intervals. The tubes were then cooled to room temperature and centrifuged at 3000 rpm for 15 min, and the supernatant was carefully decanted and the weight of the residues (Ws) obtained were weighed. The supernatants were dried to constant weight (Ww) in an oven (Kottermann® 2711, Germany) at 105°C for 12 h. The water solubility index (WSI) and swelling power (SP) were calculated as follows:

\[
\text{WSI} = \frac{W_w}{W_0} \times 100\%
\]

Eq. 4

\[
\text{SP} = \frac{W_w}{0.5X(100-WSI)}
\]

Eq. 5

Moisture content

The moisture content was determined as per the methods described by Olayemi et al (2008) in triplicate. Accordingly, 2 g of starch was weighed into weighed, dried Petri dish and heated in an oven (Kottermann® 2711, Germany) at a temperature of 130
\[^{13}C\] for about 2 h. The sample was then taken out of the oven, weighed and the moisture content was reported as percentage.

\[
\text{Moisture content (\%) } = \frac{W - W_f}{W_f} \times 100 \quad \text{Eq. 6}
\]

Where \(W\) and \(W_f\) are the weight of starch before and after drying, respectively.

**Tablet compression**

Lubricant sensitivity of spray dried NDS and spray dried AMDS was evaluated according to the method described by Parrott (1989). Tablets containing spray dried NDS, spray dried AMDS or Starch 1500\(^{®}\) were compressed with magnesium stearate at concentrations of 0, 0.5%, 1%, 1.5%, 2% (w/w). Fifty grams batch of each mixture was blended for 5 min in a Turbula\(^{®}\) mixer then, 10 mm flat surfaced compacts of the starches were produced with 400 mg size by compressing the powder blends at a fixed compression force on eccentric tablet machine (EK0 Korsch, 7891, Berlin, Germany).

Disruption potential of spray dried NDS and spray dried AMDS was evaluated as per the method described by Mitrevej et al (1996). All the components (Table 1) except magnesium stearate were blended in a Turbula\(^{®}\) mixer for 10 min followed by addition of lubricant (magnesium stearate) and further blended for 5 min. The blend was then compressed into tablets of 400 mg size at a fixed compression force on eccentric tablet machine (EK0 Korsch, 7891, Berlin, Germany).

**Evaluation of tablets**

**Crushing strength**

After 24 h of production, ten tablets were taken from each batch and the crushing strengths of the tablets were determined using hardness tester (Schelinguer, 2E/205, Switzerland).

**Tensile strength**

The radial tensile strength was calculated using the data obtained from crushing strength, diameter, and thickness of tablets using equation 7.

\[
\sigma_r = \frac{2F}{\pi DT} \quad \text{Eq. 7}
\]

Where, \(\sigma_r\) is the tensile strength, \(F\) is the force required to break the tablet (Crushing strength), \(D\) is the diameter of the tablet, and \(T\) is the tablet thickness.

**Friability**

Ten tablets of known weights from each batch were placed in a friability tester (ERWEKA, TAR 20, Germany) and were subjected to combined effects of abrasion and shock by placing them in the plastic chamber that revolves at 25 rpm for 4 min. The tablets were then dusted and weighed, and the percent loss in weight was calculated as friability.

**Disintegration test**

Disintegration test was carried out according to USP 30/NF-25 specification (2007). Six tablets of known weight from each batch were placed in a disintegration tester (CALEVA, G.B. Caliva Ltd., UK) filled with distilled water at 37 ± 2 °C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh.

**Dissolution test**

The dissolution test was carried out according to the USP/NF specification using dissolution apparatus Type II (ERWEKA, DT600, Germany), rotated at 50 rpm in 900 ml of phosphate buffer (pH 5.8), maintained at 37 ± 0.5 °C. Samples of 10 ml were withdrawn at different time intervals and replaced with equal volumes of fresh medium. The samples were appropriately diluted and the amounts of paracetamol released were determined.
using UV/Visible spectrophotometer (JENWAY, 6505, England) at 243 nm. Standard calibration curve of paracetamol was used for determining the quantities released.

Statistical analysis
Statistical analysis was carried out using Analysis of variance (ANOVA) with statistical software Origin 8 (OriginLab™ Corporation, USA). Tukey multiple comparison test was used to compare the individual difference in the physicochemical and tablet properties of the starches. At 95% confidence interval, p values less than or equal to 0.05 were considered statistically significant. The results are reported as mean and standard deviation (SD).

RESULTS AND DISCUSSION
Acid recovery yield
The recovery yield of the acid-hydrolyzed starch is presented in Figure 1. The recovery yield of acid-hydrolyzed starch decreased gradually with increasing acid hydrolysis time. Hydrolysis was rapid for about the first 8 days and much slower from 8 to 32 days. The initial rapid hydrolysis phase was mainly attributed to the hydrolysis of the amorphous phase, and the later slower phase to the hydrolysis of the crystalline phase.

Figure 1: Recovery yield of Dioscorea starch after acid hydrolysis.

The amorphous areas of the starch granules have a looser structure than the crystalline regions which is easier for attack by the hydrogen ions (Wang & Wang, 2001; Franco et al., 2002; Jiang et al., 2011). Based on the result, hydrolysis of day eight was selected for further studies since hydrolysis of starch for the first eight days were rapid and beyond day eight, the reaction was very slow and could be considered as constant.

Powder properties of starches
The powder properties of NDS, Spray dried NDS, Oven dried AMDS and Spray dried AMDS and Starch 1500® are presented in Table 2. The rank order of the moisture content is NDS > spray dried AMDS > Starch 1500® > oven dried AMDS > spray dried NDS. The NDS appears to have the maximum moisture content this might be because it was air dried in comparison to oven dried AMDS (at 40 °C) and spray dried NDS and AMDS. In this study, all of the starches have moisture content within the limits recommended for commercial starches of 10-20 % (Soni et al., 1993). Reduction in moisture content reduces chances of microbial spoilage and hydrolysis thereby increasing the stability and shelf-life of the derivatives (Lateef & Kolawole, 2009; Kemas et al., 2012).

Bulk and tapped densities give an insight on the packing arrangement of the particles and the compaction profile of a material (Russel and Lantz, 2005). In this study, the rank order of bulk and tapped density was Starch 1500® > spray dried AMDS > oven dried AMDS > NDS > spray dried NDS. The particle size and shape of the starches may be responsible for the differences in the density values which affect the packing arrangement of the powder particles. AMDS showed comparable bulk and tapped densities with that of Starch 1500® (p > 0.05) (see Table 2).

Haussner ratio and Carr’s index are considered as indirect measurements of powder flowability (Lateef & Kolawole, 2009). Hausner ratio less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow and Carr’s index values 5 to 10, 12 to 16, 18 to 21, and 23 to 35 represent excellent, good, fair and poor flow properties, respectively (Wells, 2002). NDS showed significantly higher Carr’s index and Hausner ratio than AMDS and Starch 1500® (P < 0.05) indicating poor compressibility and flow property of NDS. The spray dried AMDS showed comparable Carr’s index and Hausner ratios to that of Starch 1500® (P < 0.05).

Table 2: Powder properties of Dioscorea starches and starch 1500®.

<table>
<thead>
<tr>
<th>Powder property</th>
<th>NDS</th>
<th>S.d NDS</th>
<th>O.d AMDS</th>
<th>S.d AMDS</th>
<th>Starch 1500®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moisture content (%)</td>
<td>15.33 ± 0.09</td>
<td>9.86 ± 0.11</td>
<td>11.53 ± 0.14</td>
<td>9.37 ± 0.10</td>
<td>11.07 ± 0.05</td>
</tr>
<tr>
<td>Bulk density (g/ml)</td>
<td>0.61 ± 0.02</td>
<td>0.60 ± 0.02</td>
<td>0.65 ± 0.01</td>
<td>0.67 ± 0.01</td>
<td>0.67 ± 0.02</td>
</tr>
<tr>
<td>Tapped density (g/ml)</td>
<td>0.72 ± 0.14</td>
<td>0.71 ± 0.05</td>
<td>0.75 ± 0.00</td>
<td>0.76 ± 0.01</td>
<td>0.77 ± 0.18</td>
</tr>
<tr>
<td>Hausner ratio</td>
<td>1.19 ± 0.03</td>
<td>1.18 ± 0.02</td>
<td>1.16 ± 0.23</td>
<td>1.13 ± 0.15</td>
<td>1.14 ± 0.24</td>
</tr>
<tr>
<td>Carr’s index (%)</td>
<td>15.37 ± 0.15</td>
<td>15.5 ± 0.08</td>
<td>13.23 ± 0.39</td>
<td>11.95 ± 0.06</td>
<td>11.99 ± 0.13</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>* 25.93 ± 0.89</td>
<td>* 21.37 ± 1.39</td>
<td>* 20.13 ± 1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow rate (g/sec)</td>
<td>* 7.13 ± 0.94</td>
<td>* 13.24 ± 0.76</td>
<td>* 12.23 ± 0.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD (n = 3), * angle of repose & flow rate could not be determined, S.d spray dried, O.d oven dried

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The angle of repose \( \theta \) could be used as a qualitative measure of the cohesiveness or the tendency of powdered or granulated materials to flow. Flow is graded as excellent, good, fair and passable for angle of repose 25-30\(^\circ\), 31-35\(^\circ\), 36-40\(^\circ\) and 41-45\(^\circ\), respectively (Mukesh et al., 2011). Comparable angle of repose was recorded for spray dried AMDS (21.37 ± 1.39\(^\circ\)) and Starch 1500 (20.13 ± 1.02\(^\circ\)) (P < 0.05); characteristics of material with excellent flow property (Mukesh et al., 2011). Moreover, direct measure of the flow property showed that spray dried AMDS and Starch 1500\(^\circ\) have comparable flow rates of 13.24 ± 0.76 and 12.23 ± 0.93, respectively (P < 0.05). Better flow properties of the spray dried AMDS might be attributed to spray drying process since the method is known to produce free flowing spherical particles (Limwong et al., 2004).

**Solubility and swelling power**

The solubility and swelling power measurements were carried out at different temperatures between 25 and 85 °C (Figure 2 and 3). As clearly indicated in Figure 2, there was rapid increase in the swelling power of all the starches studied as the temperature increased up to 75 °C, and at slower rates above 75 °C. This might be due to the loss of granule structures of the starches at higher temperatures resulting in slower swelling capacity (Chang et al., 1995). This type of behaviour was also observed by Iromidayo et al. (2010). It can be seen that the swelling profile of AMDS (both oven & spray dried) is significantly lower than that of the native starch (p > 0.05). These could be due to acid hydrolysis which reduces polymer chain length and hydrolyse the amorphous part of the starch granules (Wang & Wang, 2001; Odeku and Picker-Freyer, 2009; Himjyoti et al., 2011). Significant change was not observed between the swelling power of NDS and AMDS after spray drying (p < 0.05).

As depicted in Figure 3, the AMDS (both oven & spray dried) are more soluble than the native starches. The increase in solubility values may be due to shortening of the chain lengths of the starch, corresponding to the weakening of the hydrogen bonds (Osunsam et al., 1989). It has also been reported that the high solubility of acid modified starch with increasing temperature may be due to the loss of granular structure and release of amylose fraction of the starch, as the amylose molecules are preferentially solubilized and leached from swollen granules (Stone et al., 1984). Similar results were also reported by Odeku & Picker-Freyer (2009) and Mutungi et al. (2010). The solubilities of NDS & AMDS were not affected by drying method since comparable solubilities were found between air and spray dried NDS as well as between oven and spray dried AMDS (P > 0.05).

**Effect of lubricant concentration on crushing strength and friability**

The crushing strength and friability of tablets produced from spray dried NDS, spray dried AMDS and Starch 1500\(^\circ\) at different lubricant concentrations are depicted in Figures 4 and 5, respectively. As shown in Figure 4, the crushing strength values decreased as the concentration of lubricant increased. This might be due to the altered physical properties caused by the lubricant that create a waxy covering and interfere with the interactive bonding forces between the particles to be compressed thus interfering with the eventual strength of the resulting tablets (Jarosz & Parrott, 1984; Mollan & Celik, 1996). The crushing strength of spray dried AMDS tablets were significantly higher than those of spray dried NDS and Starch 1500\(^\circ\) tablets at all level of magnesium stearate concentrations. Spray dried AMDS provided hard tablets with an average crushing strength of 50.9 N up to 1% (w/w) magnesium stearate.
Friability is the ability of a tablet to withstand the movement of shipping and handling without breaking or chipping (Sheskey et al., 1995). Friability value less than 1% weight loss is considered acceptable (BP, 2009). Figure 5 shows the friability profiles of spray dried NDS, spray dried AMDS and Starch 1500® at different magnesium stearate concentrations. As clearly indicated in the figure, tablets formulated from Starch 1500® at 0 and 0.5% magnesium stearate concentrations and tablets containing spray dried AMDS at magnesium stearate concentration of 0 to 1% had acceptable friability values (< 1%) but spray dried NDS showed friability values of > 1% at all magnesium stearate concentrations; moreover, tablets formulated with 1.5% magnesium stearate concentration broke during friability evaluation. Furthermore, less friable tablets were obtained from spray dried AMDS than Starch 1500® at all levels of magnesium stearate concentration.

Effect of lubricant concentration on disintegration time

Figure 6 shows the relationship between the lubricant concentration and disintegration time of tablets prepared with spray dried NDS, spray dried AMDS and Starch 1500®. One of the undesirable side effects of lubricant addition to pharmaceutical formulation is the prolongation of tablet disintegration time (Timucin & Murat, 2008). Generally, disintegration time increased with increased concentration of magnesium stearate. These results are in agreement with the result of Aoshima et al. (2005). This delayed disintegration might be due to the hydrophobic membrane that magnesium stearate forms on the surface of the powder particles which limits the hydration of tablets (Sameer et al., 2009). Tablets formulated from spray dried AMDS possess a markedly shorter disintegration period than Starch 1500®, though their strength is much higher. Relatively increased disintegration period of tablets formulated from Starch 1500® might be attributed to the formation of gel-like layer which is formed in combination with water (Jitka & Irena, 2011).

Effect of paracetamol concentration on crushing strength

Figure 7 shows the relationship between tablet strength and the amount (in percentage) of paracetamol that the starches can accommodate. It can be seen that tablet strength declined with increasing amount of paracetamol. The crushing strength of spray dried AMDS tablets were hard enough up to 40% of paracetamol. The crushing strength of the spray dried AMDS tablets was significantly higher as compared to spray dried NDS and Starch 1500® tablets (p < 0.05) at all levels of paracetamol concentration. This might be due to the reduction of amyllose content through acid hydrolysis possibly enhancing the close packing of amyllopectin (Atichokudomchai et al., 2001).
Disintegration time of directly compressed paracetamol tablets

Disintegration exposes a greater surface area of tablets to the dissolution medium; hence it plays an important role in a tablet’s dissolution before the active drug substance is finally released from the tablet’s structure into the body (Lateef & Kolawole, 2009). Figure 8 shows the declining disintegration time of tablets formulated from spray dried NDS, spray dried AMDS and Starch 1500 with increasing paracetamol concentration. Reduction of disintegration time might be explained on the basis of tablet weakness with paracetamol content increment. Generally the disintegration time is related to hardness. When the hardness increases, the disintegration time increases and the dissolution rate also decrease (Adenuga et al., 2008). The disintegration time of the spray dried AMDS was intermediate between spray dried NDS and Starch 1500. Moreover, the disintegration times of all paracetamol tablets were much lower than the Pharmacopeal limit of ≤15 min (USP, 2007).

Dissolution of directly compressed paracetamol tablet

Figure 9 shows the dissolution profiles of F11, F14, F21, F24, F31 and F34. The amount of paracetamol released from the tablets was increased as the concentration of paracetamol increased; however, the variation was not significant (p > 0.05). This might be attributed to the reduction of tablet hardness upon increasing paracetamol concentration which results in faster dissolution rate. The amounts dissolved from formulations at lower amounts of paracetamol concentration (20% w/w) in 30 min were in the order: spray dried NDS (95.1 %) > spray dried AMDS (94.3 %) > Starch 1500 (91.5 %); however, the variation was not significant (p > 0.05). All formulations fulfilled the specification of the USP 30/NF 25 (2007), i.e., > 80% of the tablet content should be released within 30 min.

CONCLUSION

The physicochemical properties of AMDS compared well, in many respects, with those of Starch 1500. No significant difference was found in tapped & bulk densities of AMDS and Starch 1500. Spray dried AMDS showed excellent flow property and compactibility, which indicates its potential use as a directly compressible excipient.

The lubricant sensitivity test revealed that spray dried AMDS showed less lubricant sensitivity than that of spray dried NDS and Starch 1500 by yielding tablets with higher crushing strength and acceptable friability values up to 1% magnesium stearate concentrations. Moreover, spray dried AMDS revealed higher dilution potential than those of spray dried NDS and Starch 1500 accommodating up to 40% of paracetamol concentration with acceptable pharmacopeial range of friability, disintegration time and drug release rate. The higher compressibility, lower lubricant sensitivity and
good dilution potential make AMDS a good candidate for directly compressible excipient.

REFERENCES