Tableting Performance of Silicified Cassava Starch as a Directly Compressible Excipient

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ABSTRACT
The aim of this study was to evaluate the direct compression behaviour of co-processed cassava starch and colloidal silica in the formulation of metronidazole tablets. Cassava starch was extracted from freshly harvested roots of Manihot glaziovii obtained from IITA farms, Shika, Zaria. Subsequently, it was co-processed with colloidal silica at varying ratios (95:5, 96:4, 97:3, 98:2 and 99:1). Preliminary screening was conducted on the five combinations by determining the crushing strength and disintegration time to select the optimal ratio. Characterization studies were carried out on all combinations by determining its powder properties. Tablets were then formulated by direct compression using metronidazole as a model for poorly compressible drugs in comparison with Prosolv® and StarLac®. The results obtained from the study revealed that tablets produced with the co-processed excipient compared well with Prosolv® and StarLac®. This confirms that there was an improvement in the direct compression functionality of starch when co-processed with colloidal silica.

KEYWORDS: Direct compression, co-processing, cassava starch, colloidal silica, Prosolv® and StarLac®

INTRODUCTION
Excipients play a prominent role in the success of any tableting operation. They have attained a functional status in any formulation because they contribute critically to the processing, safety, stability, and performance of the dosage form [1, 2]. In recent times, much attention has been given to the production of tablets by the direct compression method. This interest has been attributed to the fact that this method is a simple and cost-effective process. It involves fewer stages of operation (i.e. blending and compression) and can be used to manufacture heat-sensitive and/or moisture-sensitive drugs.

Several Pharmaceutical manufacturers have embraced this method thereby placing a heavy burden on excipient manufacturers to develop suitable excipients that meet the requirements for direct compression. With the advent of direct compression method, the search for highly functional directly compressible excipients has been on the rise. An ideal directly compressible excipient should possess good flow properties, low segregation tendency, and suitable compression behaviour [3].

One viable method that has been employed to develop robust excipients for direct compression is co-processing. Co-processed excipients are the combinations of two or more existing excipients formed by an appropriate process such as spray-drying, blending, milling, or wet and melt granulation, providing them with advanced physico-technical properties, without any associated chemical change. These products are single-bodied excipients acting as filler, binder and disintegrant providing optimal particle size, shape, distribution, density and morphology, thus enabling direct compression [4-6]. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. An excipient of reasonable price has to be combined with the optimal amount of a functional material in order to obtain integrated
product, with superior functionality than the simple mixture of ingredients. Co-processing is interesting because the products are physically modified in a special way without altering the chemical structure. Excipient mixtures in co-processing are produced to make use of the advantages of each component and to overcome specific disadvantages, if any.

In a study carried out by Rojas and Kumar [7], novel Cellulose II was co-processed with amorphous silicon dioxide in the following ratios; 98:2, 95:5, 90:10 and 80:20 w/w. The composites were produced by spray-drying, wet granulation and spheroidization techniques and the resulting powder and tableting properties were assessed. Silification of Cellulose II at 5 % and 10 % produced the strongest compacts for the spray-dried and wet granulated materials, respectively. Silification did not affect the fast disintegration properties of Cellulose II.

The performance of chitin metal silicate (CMS) co-precipitates as a single multifunctional excipient in tablet formulation using direct compression and wet granulation was evaluated [8]. Tablets of acceptable crushing strength with friability values well below the maximum 1 % and disintegration time (< 1 min) were obtained.

In our study, the functionality of cassava starch for direct compression will be enhanced by co-processing with optimal proportions of colloidal silicon dioxide (SiO$_2$). Starches have been used extensively as a diluent, binder and disintegrant in tablet formulation. However, because of its poor compression and flow properties, it has not been useful in direct compression.

The compressibility of a material can be improved by adding a compressibility-enhancing agent like silicon dioxide (0.1 – 20 %) [9]. This study will look at the potential of combining the excellent disintegration property of cassava starch and the inherent compressibility of silicon dioxide in a single excipient for improved tableting performance.

EXPERIMENTAL
Materials
A list of materials used includes Colloidal Silica (CAB-O-SIL®, CABOT GmbH, Germany), PROSOLV® SMCC HD 90 (JRS Pharma GmbH & Co. KG, Rosenberg, Germany), StarLac® (Roquette Pharma, France), Metronidazole (BDH Chemicals Ltd Poole, England). Cassava starch was extracted in the process lab of the department. All other materials and solvents used were of analytical grade.

METHODS
Extraction of Cassava Starch
Cassava roots were freshly harvested from the International Institute for Tropical Agriculture (IITA) Farms, Shika, Zaria, and taken to the Department of Biological Sciences, Ahmadu Bello University, Zaria, for identification. It was given the voucher no: 900187. Starch was then extracted using an established procedure. The starch obtained was dried in a hot-air oven at 40 °C for about 5 hr and then stored in an air-tight container in preparation for further use.

Preparation of Co-processed Excipient
The method of Olowosulu et al [10] was adopted with slight modifications for co-processing.

150 g of a suspension containing 40 % w/w of cassava starch was prepared in a 500 ml beaker using 90 ml distilled water. Colloidal silica 3.2 g was weighed and dispersed in the starch slurry with constant stirring for 5 mins. The mixture was transferred to a thermostatic water bath at 54 °C with constant stirring for another 15 mins. Subsequently, it was brought down and allowed to cool to room temperature before ethanol 100 ml was added to the mixture to precipitate the co-processed excipient. The co-precipitate was separated from the mixture and spread in a tray to dry in open air. It was then passed through a sieve (0.8 mm) and the drying completed in the oven at 40 °C. This process was carried out for five different combinations namely; 95:5, 96:4, 97:3, 98:2 & 99:1. The quantities of cassava starch and colloidal silica for each combination are given in the table below:

<table>
<thead>
<tr>
<th>Batch</th>
<th>CS (g)</th>
<th>SiO$_2$ (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95:5</td>
<td>60</td>
<td>3.2</td>
</tr>
<tr>
<td>96:4</td>
<td>60</td>
<td>2.5</td>
</tr>
<tr>
<td>97:3</td>
<td>60</td>
<td>1.9</td>
</tr>
<tr>
<td>98:2</td>
<td>60</td>
<td>1.2</td>
</tr>
<tr>
<td>99:1</td>
<td>60</td>
<td>0.6</td>
</tr>
</tbody>
</table>

NB: CS is cassava starch; SiO$_2$ is colloidal silica
Determination of Powder Properties

Particle size analysis was carried out using the sieve method. Test sieves ranging from 75 - 500 μ were arranged in descending order beginning with the largest sieve on top. 20 g of the sample was placed on the 500 μ sieve and allowed to vibrate for 10 mins in the Endecott sieve shaker. The powder retained on each sieve was weighed and the mean particle size determined using the formula given below:

Mean particle size

\[ \text{Mean particle size} = \frac{100}{\sum [\% \text{ retained on each sieve} \times \text{ sieve size}]} \] ...................................(1)

Twenty grams (20g) of sample was placed in the Erweka flow rate apparatus and allowed to flow through the funnel's orifice. The time taken for the powder to flow through the orifice was recorded. The flow rate was calculated using the equation given below and the mean of three determinations was recorded.

Flow rate

\[ \text{Flow rate} = \frac{\text{weight of the powder in grams}}{\text{time in seconds}} \] ...................................(2)

The angle of repose was determined using the fixed funnel method. A clean glass funnel was clamped on a retort stand such that the height from the tip of the funnel to the base was 7 cm. 20 g of the sample was poured into the funnel and it was allowed to flow freely under the influence of gravity. A conical heap of powder was formed. The parameters of height and radius were measured off and used to determine the angle of repose.

\[ \theta = \tan^{-1} \frac{h}{r} \] ...................................(3)

The particle density was determined using a liquid displacement pycnometric method with xylene as the displacement fluid [11].

Twenty (20) grams of the powders were gently poured into a 50 ml graduated cylinder through a funnel. The volume of the powder was then determined and the bulk density (BD) was calculated. The graduated cylinder was tapped from a height of 25 mm and the resulting reduction in volume was measured after attaining a constant volume, and then the tapped density (TD) was calculated. Hausner's ratio and Carr's index were estimated by incorporating the values of bulk and tapped densities in the equations given below:

\[ \text{HR} = \frac{TD}{BD} \] ...................................(4)

\[ \text{Cl} = \frac{TD - BD}{TD} \times 100\% \] ...................................(5)

Where TD is tapped density; BD is bulk density.

5g of the sample was weighed and subsequently poured into a 50ml measuring cylinder. The volume occupied was noted as \( V_1 \). Little quantity of water was added to make a suspension and the volume was made up to 50 ml with water. It was allowed to stand for 24 hours and then the final volume was noted as \( V_2 \). The swelling capacity was calculated using the formula \( \left( \frac{V_2}{V_1} \right) \) [12].

Photomicrographs of representative samples of the co-processed excipient and the corresponding physical mixture were taken using a camera attached to an optical microscope. The pictures were taken at 100x and 250x.

Fourier transform infrared spectroscopy (FT-IR) scan was carried out with a FT-IR instrument (FT-IR-8400S SPECTROPHOTOMETER) using thin pellets containing 1 mg of the sample dispersed in 100 mg of KBr. The spectrum was recorded at room temperature as an average of 30 scans in the 400 to 4000 cm\(^{-1}\) range with a spectral resolution of 1 cm\(^{-1}\).

Preparation of Tablets

A 12 mm single punch eccentric tablet press machine (Korsch, Erweka, Berlin, Germany) was used to compress flat-faced tablets containing 200 mg metronidazole from the powder mixtures. After compression, the tablets were kept for 24 hr to allow for elastic recovery before evaluation of tablet properties. The tablet formula is given below:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Batches of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>I (95:5) II (96:4) III (97:3) IV (98:2) V (99:1) VI VII VIII</td>
</tr>
<tr>
<td>Co-processed excipient</td>
<td>200</td>
</tr>
<tr>
<td>PROSOLV® (98:2)</td>
<td>-</td>
</tr>
<tr>
<td>StarLac® (85:15)</td>
<td>-</td>
</tr>
<tr>
<td>Cassava Starch</td>
<td>-</td>
</tr>
</tbody>
</table>

Total (mg) | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400

N.B: Batches VI, VII & VIII represents tablets prepared with PROSOLV®, StarLac® and Cassava Starch respectively.

Evaluation of tablet properties

Weight variation test

The mass of 20 tablets from each batch was weighed using Mettler P163 balance (Mettler Instruments, Switzerland), and the average mass was determined. The percentage deviation from the average mass was calculated [13].

Crushing strength determination
Twenty tablets taken randomly from each batch were tested for hardness using Monsanto hardness tester (Monsanto Chemical Co., USA). The average hardness (kgf) and standard error were calculated for each batch.

**Friability test**

Twenty tablets were taken randomly and weighed accurately and placed in a friabilator (Erweka, Germany). After 100 rotations (25 rotations per minute, for 4 min), the tablets were removed and re-weighed accurately. The loss in mass was determined.

**Disintegration test**

One tablet was placed in each tube of the basket rack assembly and a disc was added on each tube. The rack was immersed in distilled water at 37 ± 2°C and the apparatus (Erweka, Germany) was operated at a frequency rate between 29-32 cycles per minute. The time taken for the tablet to disintegrate and pass through the screen was recorded [13].

**Dissolution studies**

The drug-release profile of StarSil (99:1), Prosolv® and StarLac® was determined using the Erweka dissolution apparatus. 600 ml of 0.1 N HCl was used as dissolution medium for metronidazole. 2 ml sample was withdrawn after 5, 10, 20, 30, 45 and 60 minutes and the absorbance determined at a wavelength of 277 nM. The amount of drug released with time was determined using the equation, \( y = 0.0673x + 0.0077 \), and a graph showing the relationship between percentage drug released against time was plotted.

**Data and Statistical Analysis**

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± SD. ANOVA was performed on the data sets generated using SPSS®16. Differences were considered significant for p-values < 0.05.

**RESULTS AND DISCUSSION**

The results of the powder properties are presented on Table 3. The values obtained for particle size ranged from 239 – 347 µm with batch V (99:1) having the largest particle size. There was a corresponding decrease in particle size as the content of colloidal silica was decreasing across the batches. However, this trend was not seen in the last two batches (IV & V). Particle size is one of the principal determinants of powder behaviour such as packing and consolidation, flow ability, compaction etc, and it is therefore one of the most common and important areas of powder characterization. Due to the influence of particle size on powder performance, it is one of the prime considerations in selecting excipients to develop or improve formulation. This is particularly important with direct compression formulations where excipient flowability and compaction performance are critical. Excipients for such application should exhibit narrow size distributions with moderate-to-coarse particle size, having a mean size from 100 to 200 µm.

The flow of powder during manufacture dictates the quality of the product in terms of weight, hardness, and content uniformity of the tablets. Therefore, the measurement of the flow properties of powder mixtures is essential before tableting and capsule filling.

The angle of repose and flow rate are parameters used to measure the flow properties of powder mixtures and granules. The maximum value recorded for angle of repose was 30.5 ° (99:1) implying that all the batches possessed good flow properties suitable for direct compression since values for angle of repose ≤ 30 ° generally indicate a free-flowing material. This was expected since colloidal silica has been used originally as a glidant in tablet formulation to enhance the flow during processing. The results of the flow rate corresponded well with the angle of repose. The success of the tableting operation is determined by the capacity of the tableting mix to flow well during compression.

Batch V (99:1) had the highest bulk and tapped densities which may be attributed to its having an optimal quantity of colloidal silica with minimal porosity due to its compressibility enhancing behaviour.

Hausner’s ratio and Carr’s index were estimated from the values of bulk and tapped densities for all the batches. Again, a trend was observed that as the content of colloidal silica decreased, the Compressibility index increased for the batches I – III. This however, was not the case for batches IV & V. Carr’s index is an index for compressibility and values less than 20 % is an indication of good compressibility profile. The maximum value obtained for CI was 12.28 suggesting that all the batches passed the compressibility test. This observation was further confirmed by the values obtained for Hausner’s ratio (HR).

Swelling capacity gives a clue to the disintegrating ability of a material. The values recorded ranged from 1.1 – 1.4 for all the batches. This moderate
swelling capacity may be attributed to the hydrophobic nature of colloidal silica which does not allow maximum uptake of water. The concentration of silicon dioxide in the co-processed excipient did not affect the swelling capacity significantly.

Table 3: Powder Properties of Co-processed excipient

<table>
<thead>
<tr>
<th>Powder properties</th>
<th>I (95:5)</th>
<th>II (96:4)</th>
<th>III (97:3)</th>
<th>IV (98:2)</th>
<th>V (99:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size (µm)</td>
<td>292.59</td>
<td>260.57</td>
<td>239.16</td>
<td>311.27</td>
<td>347.14</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>27.5(0.7)</td>
<td>28.5(0.7)</td>
<td>28(2.8)</td>
<td>28.5(0.7)</td>
<td>30.5(0.7)</td>
</tr>
<tr>
<td>Flow rate (g/sec)</td>
<td>5.09(0.2)</td>
<td>6.13(0.1)</td>
<td>5.8(0.1)</td>
<td>5.9(0.1)</td>
<td>5.91(0.1)</td>
</tr>
<tr>
<td>Bulk density (g/ml)</td>
<td>0.51</td>
<td>0.53</td>
<td>0.5</td>
<td>0.54</td>
<td>0.65</td>
</tr>
<tr>
<td>Tapped density (g/ml)</td>
<td>0.53</td>
<td>0.59</td>
<td>0.57</td>
<td>0.59</td>
<td>0.71</td>
</tr>
<tr>
<td>Carr’s Index (%)</td>
<td>3.77</td>
<td>10.17</td>
<td>12.28</td>
<td>8.47</td>
<td>8.45</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.04</td>
<td>1.11</td>
<td>1.14</td>
<td>1.09</td>
<td>1.09</td>
</tr>
<tr>
<td>Swelling capacity</td>
<td>1.2</td>
<td>1.3</td>
<td>1.1</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Particle density</td>
<td>1.2</td>
<td>1.3</td>
<td>1.1</td>
<td>1.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>
The photo micrographs captured for the co-processed excipient and its physical mixture are displayed as Plates I – IV above. These pictures do not show any discernible differences in the shape and morphological appearance of the particles. The particles appear spherical in shape with a large density of starch particles. The colloidal silica particles are not so obvious in the co-processed excipient because it has been embedded in the particle structure of the starch during co-processing.

The IR Spectra of the physical mixture and the co-processed excipient are presented as Figures 1 & 2. The FT-IR Spectra of the physical mixture and co-processed excipient showed almost similar characteristic peaks which implies that the integrity of the individual components were maintained even after co-processing confirming the absence of any chemical change.
Figure 2: FT-IR Spectra of the co-processed excipient (99:1)
The properties of tablets invariably determine the performance of the tablets. Tablets are expected to be sufficiently hard so that they can withstand post-compaction operations like coating, handling, transportation and storage. It is also expedient that the tablet disintegrates when swallowed to release...
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the drug and improve oral bioavailability in order to enhance efficacy of the drug.

<table>
<thead>
<tr>
<th></th>
<th>I (95:5)</th>
<th>II (96:4)</th>
<th>III (97:3)</th>
<th>IV (98:2)</th>
<th>V (99:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crushing strength (kgf)</td>
<td>11(0.9)</td>
<td>9.5(0.5)</td>
<td>8.7(1.3)</td>
<td>8.5(0.5)</td>
<td>6.7(0.6)</td>
</tr>
<tr>
<td>Disintegration time (min)</td>
<td>42.5(24)</td>
<td>19.2(0)</td>
<td>13(0)</td>
<td>6.5(0)</td>
<td>0.45(0)</td>
</tr>
</tbody>
</table>

Several standard test procedures were used to evaluate the properties of tablets produced with co-processed excipient (StarSil) in comparison to standards (PROSOLV® and StarLac®). The results obtained are presented in Tables 4 & 5.

Table 4: Properties of StarSil tablets without drug

Initially, tablets were produced alone with StarSil (100 %) and the properties of crushing strength and disintegration time was determined. It was observed that crushing strength and disintegration decreased as the content of colloidal silica was lowered. Batch V (99:1) containing 1 % of colloidal silica gave a crushing strength of 6.7 kgf and disintegrated in less than a minute (Table 4).

When metronidazole was introduced as the active drug in the formulation, the following properties were observed as presented in Table 5 below:

Table 5: Tablet Properties of Cassava Starch, StarSil, Prosolv® and StarLac® compressed with Metronidazole

<table>
<thead>
<tr>
<th></th>
<th>I (95:5)</th>
<th>II (96:4)</th>
<th>III (97:3)</th>
<th>IV (98:2)</th>
<th>V (99:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight variation (mg)</td>
<td>395 (15)</td>
<td>387 (13)</td>
<td>390 (10)</td>
<td>387 (15)</td>
<td>382 (14)</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.6</td>
<td>0.7</td>
<td>0.5</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Disintegration time (mins)</td>
<td>32 (2)</td>
<td>24 (4)</td>
<td>11 (3)</td>
<td>27 (4)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

Note: The value in the bracket indicates the Standard Deviation.

* Capped: The tablets formulated with cassava starch capped at very low Pressure and could not compress at high pressure. Therefore, tablet evaluation could not be done. This confirms the inferiority of cassava starch as a directly compressible excipient.

All the batches of tablets produced passed the weight variation test including the two standards (PROSOLV® and StarLac®) as the mean weight fell within the permissible limit of ± 5 % (380 – 420 mg) (EP, 2007). The crushing strength values for batches I – IV exceeded the limit for of 4 – 7 kgf. The friability values did not exceed the maximum limit of 1 % for all batches except for the batch containing StarLac®. This could be attributed to the high content of starch (85 %) in StarLac®. For the disintegration time, batch V (99:1), PROSOLV® and StarLac® all disintegrated within a minute. The percentage of metronidazole released after 30 minutes for StarSil (99:1), Prosolv® and StarLac was 79, 83 and 80 % respectively.

The results of the statistical analysis shows that the differences seen in the weight variation, crushing strength and disintegration time between the various groups were statistically significant at p < 0.05 (p = 0.00, 0.002 and 0.008 respectively). However, differences seen in the dissolution parameters were not statistically significant at p < 0.05 (p = 0.329).

In the pharmaceutical industry, chemical stability and bioavailability as well as the mechanical strength of the tablets are the main concerns. The tablet should have optimum mechanical properties in order to withstand post-compaction operations.
CONCLUSION
In this study, we have been able to establish that the co-processing of cassava starch and colloidal silica improved the compressibility of starch. At silicified levels of 1%, a superdisintegrating ability was conferred on cassava starch. The properties of the tablets produced compared reasonably well with PROSOLV® and StarLac®. Therefore, this composite multipurpose excipient can be used in the formulation of poorly compressible drugs by direct compression.

REFERENCES