**IJPSR (2012), Vol. 3, Issue 07** **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 March, 2012; received in revised form 27 June, 2012; accepted 30 June, 2012

# FORMULATION AND EVALUATION OF MICROCRYSTALLINE TAPIOCA STARCH AS A FILLER-BINDER FOR DIRECT COMPRESSION

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**Keywords**:
Microcrystalline Tapioca Starch, Annealed Enzyme Hydrolyzed Tapioca Starch, Highly Functional Tapioca Starch, Directly Compressible filler-binder, Microcrystalline Tapioca starch

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## ABSTRACT

Tapioca starch (NTS) was modified physically at molecular level by annealing and subsequently subjected to enzyme hydrolysis to obtain a more functional filler-binder "microcrystalline tapioca starch (MCTS)". NTS was extracted from cassava tuber (*Mannihot esculenta cranzt*) using a standard method. The powder suspensions were prepared in concentration of 40 %w/w in five separate conical flasks. The starch granules were annealed for 1 h and subsequently hydrolyzed with α-amylase at 58$^{o}$ and pH 7 for 1, 2, 3, 4, and 5 h in a water bath. The reaction was terminated and neutralized with 0.1 N HCL and 0.1 N NaOH respectively. The MCTS was washed, recovered by sedimentation and air dried at room temperature for 72 h. Following characterization, the granules that were modified for 3 h, sieved fraction >75-250 µm was selected and compacted at a range of compression load 2.5 to 12.5 KN. The average granule size of NTS, annealed tapioca starch (ATS), and MCTS were 10 µm, 11.5 µm, and 13 µm respectively. Average flow rate, angle of repose and compressibility index were 2 g/s, 43$^{o}$, 50% for NTS respectively, and 2.5 g/s, 35$^{o}$, 37.5 % for MCTS. The crushing strength for NTS, ATS and MCTS are: 30 N, 90 N and 100 N after 3 h of annealing and hydrolysis respectively, compressed at 6 metric units. MCTS was compared with Starlac®, Cellactose® and MCC. The onset of plastic deformation $P_y$ (yield value) were: Cellactose (24.2 $MNm^{-2}$)>MCC (25 $MNm^{-2}$)> MCTS (143 $MNm^{-2}$) =Starlac (143 $MNm^{-2}$). The degree of plastic deformation occurring during compression ($P_k$) is in the following order: Starlac® (17 $MNm^{-2}$)>MCTS (17.7 $MNm^{-2}$)>MCC (18.6 $MNm^{-2}$)>Cellactose® (19.1 $MNm^{-2}$). MCTS is more superior in functionality than Cellactose and MCC. The dilution potential obtained for MCTS, compacted with paracetamol (PCM) and ascorbic acid (AA) as active drug (API) were: 20 %w/w PCM and 40 %w/w AA with MCTS. The hardness of MCTS containing 40 % AA was found to be 58 N; MCTS can be used to formulate tablets of both poorly compressible and moisture sensitive API.

**INTRODUCTION:** There is growing popularity of the direct compression process and a demand for an ideal filler-binder that can substitutes two or more excipients.

The continued popularity of solid dosage forms, a narrow pipeline of new chemical excipients, and an increasing preference for the direct compression process creates a significant opportunity for the development of high functionality excipients.

Solid substances are characterized by three levels of solid state: the molecular, particle, and bulk level. These levels are closely linked to one another, with the changes in one level reflecting in another level. The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo - polymorphism and the amorphous state.

Particle level comprises individual particle properties such as shape, size, surface area, and porosity. The bulk level is composed of an ensemble of particles and properties such as flowability, compressibility, and dilution potential which are critical factors in the performance of excipients. The interdependency among the levels provides the scientific framework for the development of new grades of existing excipients and new combinations of existing excipients (Bansal and Nachaegari, 2002).

Hence, the creation of a new excipient must begin with a particle design that is suited to deliver the desired functionalities (Reimerdies and Aufmuth, 1992). Varying the crystal lattice arrangement by playing with parameters such as the conditions of crystallization and drying can create particles with different parameters It is also possible to engineer particles without affecting the preceding molecular level. Avicel 101 and 102 (Microcrystalline cellulose) and spray dried lactose are examples in which such an approach has been successfully applied.

Tukomane *et al.*, (2007) used scanning electron micrographs to study the morphological changes and the mode of enzyme attack during enzyme hydrolysis, they found that, the α – amylase preferentially attacked the interior of the starch granule, leaving a deep round hole on the starch granule surface. It was found by X-Ray diffraction that both annealing and amylolysis did not alter the A – type diffraction pattern. The % relative crystallinity of enzyme – hydrolyzed starch was raised with increasing hydrolysis time and with decreasing amylose content. In this research, microcrystalline tapioca starch will be produced by annealing and enzyme hydrolysis, this will then be evaluated for powder and tablet characteristics.

Tablet evaluation will be carried out using both Heckel and Kawakita equation and data analysis.

**MATERIALS AND METHODS:**

**Materials:** Cassava tuber *(Mannihot esculenta crantz)* obtained from University of Agriculture Abeokuta, Ogun State, Nigeria. Phloroglucinol, iodine, xylene, Starlac (Roquette, France), Cellactose (Meggle, Germany), microcrystalline cellulose (Avicel 101).

**Methods:**

**Extraction of Tapioca Starch:** Method of Radley, 1976 was adopted Cassava tuber were washed and peeled to remove the outer skin and rind with the aid of a handy stainless knife. The peeled tubers were washed with freshly distilled water and rasped.

The rasp consists of a sheet of metal plate perforated with nails, clamped around a stainless bucket with the protrusions facing outwards. The tubers were then manually rasped to a pulp on the stationary grater (which is the metal plate perforated by nails). Water was applied in small quantities continuously to the rasper. The process was continued until the whole tubers were turned into a fine pulp in which most but not all of the starch granules were released.

After rasping, pulp from the sump was then pumped on to a nylon fastened /clamped around a stainless bucket. A small spray of water was applied to assist the separation of starch granules from their fibrous matrix and to keep the screen mesh clean while water was added, the mass were turned manually to aid the release of the granules. Starch granules carried with the water fall to the bottom of the bucket in which the sieve was placed. The starch milk was then allowed to sediment, by standing for a period of 8 h. The starch settled at the bottom of the bucket and the supernatant liquor decanted.

The sediment/fine granules were centrifuged. After the removal of free water from the starch, cake was obtained. The starch cake was then crumbled into small lumps (1-3 cm) and spread out in thin layers on stainless trays and air dried for 120 h. (Radley, 1976; Grace, 1977).

**Preparation of microcrystalline Tapioca Starch (MCTS):** A modified method of Tokumane *et al.*, 2007 was adopted.

Five hundred gram (240 g) of tapioca starch granules were weighed into five places and each placed in a 1000 ml capacity conical flask. Six hundred millimeters (600 ml) of freshly distilled water was added to each content of the flask to make a suspension (= 40 %w/w). The pH of the medium was adjusted to between 6.5 and 7.0. All the flasks were placed on a digitalized water bath and the starches were annealed at 60 $^{o}$C for 30 min. Each flask was dosed with 0.5 ml of α-amylase (0.1 % v/w d.s) at 60$^{o}$C on water bath and was allowed to stand for hydrolysis to take place at various length of specified time: 60, 120, 180, 240, and 300 min).

At the end of the first 60 min., the enzyme reaction in one of the flasks was terminated by adjusting the pH to 2.0 with 0.4 N HCl after which the pH was raised to 6.5 with 0.4 N NaOH. The medium was filtered through a Buckner funnel; the residue was washed 3 times, with distilled water and finally dehydrated by adding enough isopropanol (99 %) (a water – miscible solvent) and the resulting dehydrated highly crystalline starches were air dried . These procedures were repeated for the remaining hydrolyzed starches at other times.

The hydrolyzed starches were evaluated for % level of crystallinity, powder properties, and compressibility.

**Moisture content:** The moisture content (MC) of the powder was determined by weighing 100 g of the powder after which it was heated in an oven at a temperature of 105 °C until a constant weight was obtained.

The moisture content was then calculated with the following formula:

$$MC = (1 - W_t/W_0) \times 100 \quad \ldots\ldots (1)$$

Where, $W_t$ and $W_0$ represent weight of powder after time't' and the initial weight before heating respectively.

**Determination of Flow Rate and Angle of Repose:** Angle of repose was determined by the method of Jones and Pilpel (1966).

$$\theta = \tan^{-1} (h/r) \quad \ldots\ldots (2)$$

The flow rates were determined with the aid of Erweka flowability tester (model GDT, Germany).

**Bulk Density and Tapped Density:** Bulk and tapped densities were determined by the method of Kumer and Kothan (1999). Sixty gram (60 g) of the granules was weighed and transfered into a 100 ml measuring cyclinder. The volume (V) was recorded as the bulk volume. The total weight of the powder and cylinder was noted. The bottom of the cylinder was raised about 10cm above the slab and made to full on the platform continuously for 100 taps. The volume ($V_t$) of the granules was recorded.

Bulk volume is represented by 'V, while tapped volume is $V_t$.

Bulk density ($D_b$) - Mass/V …… (3)

Tapped density ($D_t$) = Mass/ ……(4)

**Carr's Index:** The ability of the granules to undergo volume reduction (densification) was derived from the following equation.

$$CI (\%) = 100(V - V_t) / V = 100 (D_b - D_t)/ D_b \quad \ldots\ldots (5)$$

**Compactability:** The preliminary study was carried out to select few promising batches: (1) the best batch out of the five batches of hydrolysed starch (MCTS) having the best tablet properties was determined. The native tapioca starch, annealed tapioca starch, and the microcrystalline tapioca starch at various time of hydrolysis were compressed on a single punch Erweka tabletting machine (Erweka, AR 400. Germany), fitted with 10.5 mm diameter flat faced punch and die. Tablet target was 500 mg, and pressure load used range from 4 to 7 KN.

The batches chosen here were subjected to particle sieving and further employed for compaction studies.

**Compaction Studies:**

**Preparation of Compacts:** Compacts of weights, 500 mg, of each of tapioca starch, annealed tapioca starch, microcrystalline tapioca starch (MCTS), made using a single punch carver hydraulic hand press (model, C, Carver Inc. Menomonee Falls, Wisconsin, U.S.A ) at machine compression force ranging from 2.5 KN to 12.5 KN. Fourty compacts were made at each compression level for individual material.

Before compression, the die (10.5 mm diameter) and the flat faced punches were lubricated with a 1 % w/v dispersion of magnesium stearate in ethanol-ether (1:1). The compacts were stored over silica gel for 24 hours (to allow for elastic recovery and hardening and to prevent falsely low yield values) before evaluations. The dimensions (thickness and diameter) and weight uniformity of ten compacts were determined. The relative density, D, were calculated as the ratio of density of the compact, $D_t$ to the particle density, $D_p$ of individual powder or composite. The data obtained using 'ejected tablet method (out-of-die)' were used to obtain the Heckel plots.

The weights, W, and dimensions were then determined respectively, and their relative densities, D, were calculated using the equation:

$$D = W/ [V_t \times P_s] \quad \text{.....(1)}$$

Where $V_t$ is the volume of the tablet in $cm^3$, and $P_s$ is the particle density of the solid material in $gcm^{-3}$.

Heckle plots of ln (1/ 1 – D) versus applied pressure "P" (Heckel, 1961) and Kawakita plots of P/C versus P, (Kawakita and Ludde, 1970/71) were constructed for the composite excipients.

Linear regression analysis was carried out over a compression range 2.5, 5, 7.5, 10, and 12.5 KN. The parameters from Heckel plots were calculated. The Kawakita equation was employed to determine the extent of plastic deformation the material undergoes.

**Evaluation of Tablets:**

1. **Weight variation Limit Test:** The weights of 10 tablets were determined individually and collectively on a Metler balance (Denver, XP-300, USA). The mean weight, percentage (%) deviation from the mean and standard deviation were calculated.

2. **Thickness of Tablets:** The thickness of the tablets was measured with the aid of micrometer screw gauge. Five tablets were selected randomly and the thickness for each was measured and the mean value determined.

3. **Hardness of tablets:** The hardness of the tablets formulated was determined as the crushing strength digitalized tablet hardness tester (Model EH O1, Capacity 500 N, Indian).

4. **Friability:** The friability test was performed for the tablets formulated in a friabilator (Erweka, TA 3R). The weight of 10 tablets was determined on a Metler balance (Denver, XP - 300, USA). The tablets were placed in the friability and set to rotate at 25 rpm for 5 min after which the tablets were de-dusted gently and their weight determined. The difference was calculated and the percentage loss in weight and hence the value of the friability was calculated.

5. **Compact Volume:** The volume of a cylindrical tablet having radius 'r' and height 'h' is given by the following equation;

$$Vc = h\pi r^2 \text{----------} \quad (6)$$

6. **Compact density:** The compact density of a tablet was calculated from the following equation

$$\text{Compact density } (\rho) = \frac{\text{Weight of tablet}}{\text{Volume of tablet}} \text{ ..... } (7)$$

7. **Compact Radial tensile strength:** This was computed using Fell and Newton (1970) equation.

$$T\text{-}2P/HD\pi \ (N/m^2) \quad \text{.....(8)}$$

Where, T is the tensile strength ($N/m^2$); H, thickness of a tablet (m), D, diameter of a tablet (m); P, applied force (crushing force) (N).

8. **Compression pressure:** This was derived from the relationship between the applied pressure and surface area.

$$\text{C.P.} = \frac{\text{Applied force}}{\text{Surface area of tablet}} \quad \text{.....(9)}$$

**Heckel Equation and Data Analysis:**

**Heckel Analysis:** The Heckel analysis is used determine the volume reduction mechanism under the compression pressure (Celik, 1992; Heckel, 1961a)

$$\ln [1/(1- D_R)] = KP + A \quad \text{.....(10)}$$

Plotting the value of $\ln [1/(1- D_R)]$ against applied pressure, P, yields a linear graph having slope, k and intercept, A.

Where, $D_R$ is the relative density

**Kawakita Equation and Data Analysis**

**Kawakita Analysis:** The kawakita equation is given as:

$$P/C = P/ a + 1/ab \quad \text{.....(11)}$$

Plotting the value of P/C against applied pressure, P,

Where, $C = (V_o - V_p) / V_o$, C is the degree of volume reduction; $V_o$ is the initial volume of the powder bed, $V_p$ is the final volume after compression

$$V_o = W/B_d$$

Where, W is the weight of loose powder, $B_d$ is the bulk density of the powder.

$V_p$ = Volume of a cylindrical tablet ($V_p = h\pi r^2$) $cm^3$.

**RESULTS:**

**TABLE 1: COMPARISON BETWEEN THE MICROSCOPIC STRUCTURE OF NATIVE TAPIOCA STARCH (NTS), MICROCRYSTALLINE TAPIOCA STARCH (MCTS) AT X 40 MAGNIFICATION**

| Parameter | NTS | (MCTS) |
|---|---|---|
| Shape | Mostly round, subspherical, Polyhedral, half moon, oval | Mostly round and half moon, subspherical |
| Striation | Faint in appearance | More visible, concentric |
| Helium | Mostly dot at centre, few linear and cleft. | Dots, cleft, linear at mostly centre. Mostly cleft type |
| Aggregate | Mostly 2 – 3 | 2 – 3 |
| Average granule size | 10 µm | 13 µm |

NB. NTS and MCTS represent native tapioca starch and microcrystalline tapioca starch.

**TABLE 2: CHARACTERISTICS OF MICROCRYSTALLINE TAPIOCA STARCH (MCTS) TABLETS MADE FROM THE HYDROLYZED STARCHES AT VARIOUS LENGTH OF TIME, TARGET WEIGHT IS 500 mg, AND PUNCH/DIE DIAMETER IS 10.5 mm.**

| Material (h) | Compaction Force (KN) | Compression Pressure $n/m^2 \times 10^5$ | Weight of Tablet (g) n=3 | Thickness of Tablet (m) $\times 10^{-3}$ | Crushing Strength (N) n=3 | Radial Tensile Strength ($n/m^2$) X $10^5$ | Compact Density ($g/cm^3$) | Friability | DT (Sec) n =3 |
|---|---|---|---|---|---|---|---|---|---|
| | 5 | 6.4 | 0500 | 3.65 | 20 | 2.8 | 1.13 | 3.37 | 35 |
| **MCTS-1 h** | 6 | 7.6 | 0.500 | 3.61 | 55 | 7.8 | 1.13 | 2.22 | 55 |
| | 6.5 | 8.3 | 0.500 | 3.35 | 60 | 9.1 | 1.22 | 1.12 | 60 |
| | 5 | 6.4 | 0.500 | 3.61 | 45 | 6.4 | 1.13 | 2.11 | 77 |
| **MCTS-2 h** | 6 | 7.6 | 0.500 | 3.42 | 75 | 11.2 | 1.19 | 2.15 | 82 |
| | 6.5 | 8.3 | 0.500 | 3.28 | 95 | 14.8 | 1.24 | 3.19 | 106 |
| | 5 | 6.4 | 0.500 | 3.66 | **40** | **5.6** | 1.12 | **1.04** | 72 |
| **MCTS-3 h** | 6 | 7.6 | 0.500 | 3.45 | **85** | **12.6** | 1.18 | **1.04** | 75 |
| | 6.5 | 8.3 | 0.500 | 3.43 | **90** | **13.4** | 1.19 | **1.05** | 80 |
| | 5 | 6.4 | 0.500 | 3.73 | 20 | 2.7 | 1.09 | 2.18 | 20 |
| **MCTS-4 h** | 6 | 7.6 | 0.500 | 3.43 | 60 | 8.9 | 1.19 | 2.11 | 30 |
| | 6.5 | 8.3 | 0.500 | 3.23 | 65 | 10.3 | 1.26 | 2.11 | 36 |

NB. 1, 2, 3, and 4 h, represent hour of hydrolysis.

**TABLE 3: POWDER CHARACTERISTICS OF NATIVE TAPIOCA STARCH, ANNEALED TAPIOCA STARCH (ATS-3 h), AND MICROCRYSTALLINE TAPIOCA STARCH (MCTS-3 h)**

| Material | Flow rate (g/sec) | Angle of Repose (θ) | Bulk Density ($g/cm^3$) | Tapped Density ($g/cm^3$) | Compressibility Index % | Hausner's Ratio |
|---|---|---|---|---|---|---|
| **NTS** | 2 | 43.4 | 0.545 | 0.817 | 32.2 | 1.5 |
| **ATS (>75-250 µm)** | 2.6 | 32 | 0.616 | 0.895 | 31.2 | 1.5 |
| **MCTS (>75-250 µm)** | **2.5** | **24.5** | 0.516 | 0.712 | **27.5** | 1.38 |
| **Starlac®** | **7.1** | **19.2** | 0.641 | 0.725 | **13.1** | **1.13** |
| **Cellactose®** | **1.84** | **24.2** | 0.443 | 0.532 | **20.1** | **1.2** |
| **MCC** | 0.75 | 48 | 0.389 | 0.620 | 37.3 | 1.6 |

NB. NTS, ATS, MCTS, and MCC represent: native tapioca starch, annealed tapioca starch, microcrystalline tapioca starch, and microcrystalline cellulose respectively.

**TABLE 4: COMPACT CHARACTERISTICS OF NATIVE, ANNEALED TAPIOCA STARCH (ATS) AND MICROCRYSTALLINE TAPIOCA STARCH (MCTS). TARGET WEIGHT IS 500 mg, AND PUNCH/DIE DIAMETER IS 10.5 mm.**

| Material | Compaction Force (KN) | Compression Pressure $N/M^2 x10^5$ | Weight of Tablet (g) | Thickness of Tablet (m) $x10^{-3}$ | Crushing Strength (N) | Radial Tensile Strength $n/m^2 x10^5$ | Compact Density ($g/cm^3$) | Friability | DT (Sec) n=3 |
|---|---|---|---|---|---|---|---|---|---|
| **NTS** | 6 | 4.9 | 0.500 | 3.30 | 3 | 5.79 | 1.235 | Failed | 14 |
| **ATS-3 h** | 6 | 4.9 | 0.500 | 3.67 | **90** | 10.4 | 1.111 | **2.50** | 25 |
| **MCTS-3h** | **6** | 4.9 | 0.500 | 3.45 | **85** | **12.6** | 1.18 | **1.04** | 80 |

NB. NTS, ATS-3 h, and MCTS-3 h denote: native tapioca starch, annealed tapioca starch at 3 hour, and annealed enzyme hydrolyzed tapioca starch (MCTS) at 3 hour respectively.

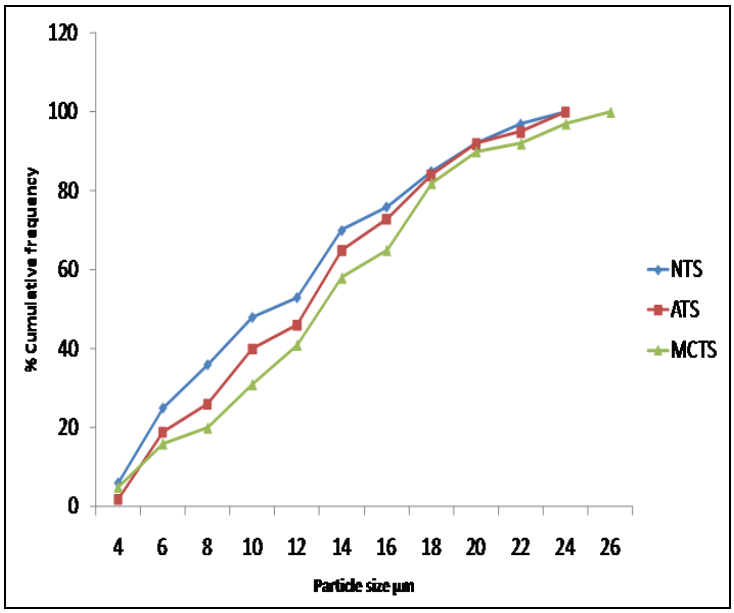


**FIG. 1: PARTICLE SIZE DISTRIBUTION OF NATIVE TAPIOCA STARCH (NTS), ANNEALED TAPIOCA STARCH, AND MICROCRYSTALLINE TAPIOCA STARCH**

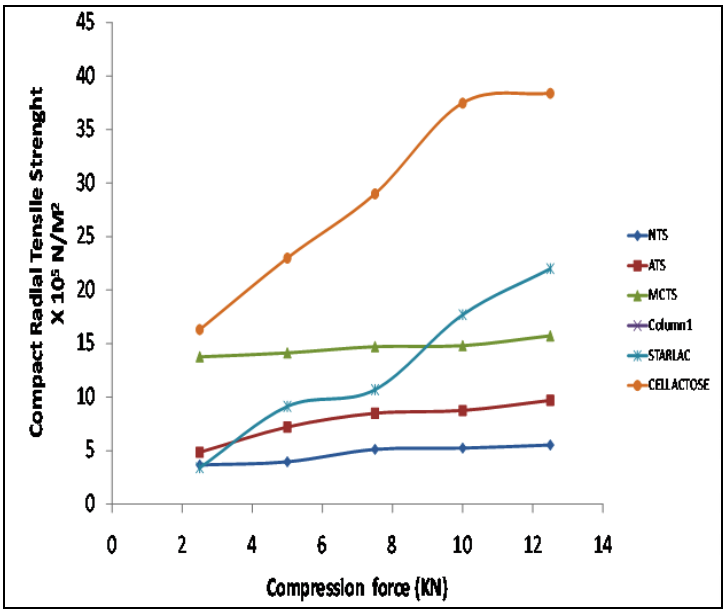


**FIG. 3: RELATIONSHIP BETWEEN COMPRESSION PRESSURE OF COMPACTS CONTAINING NATIVE TAPIOCA STARCH (NTS), ANNEALED TAPIOCA STARCH, AND MICROCRYSTALLINE TAPIOCA STARCH**

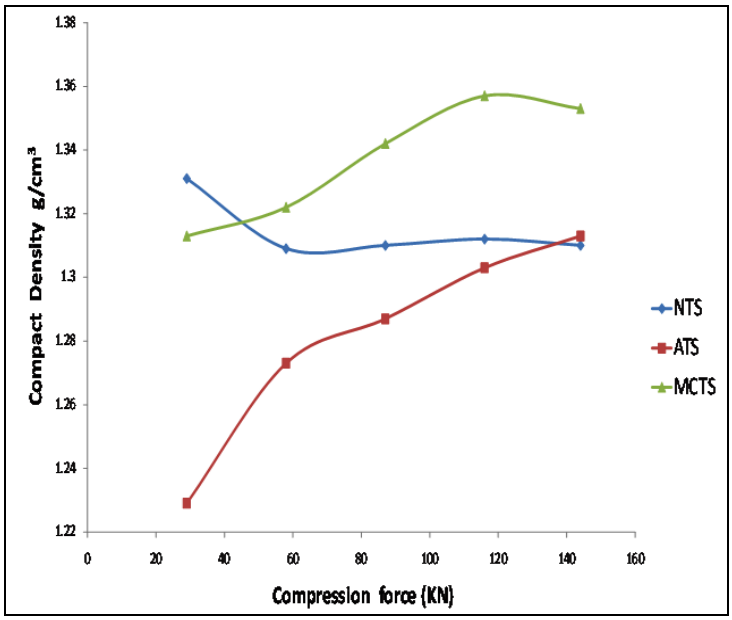


**FIG. 2: INFLUENCE OF COMPRESSION ON NATIVE TAPIOCA STARCH (NTS), ANNEALED TAPIOCA STARCH, AND MICROCRYSTALLINE TAPIOCA STARCH**

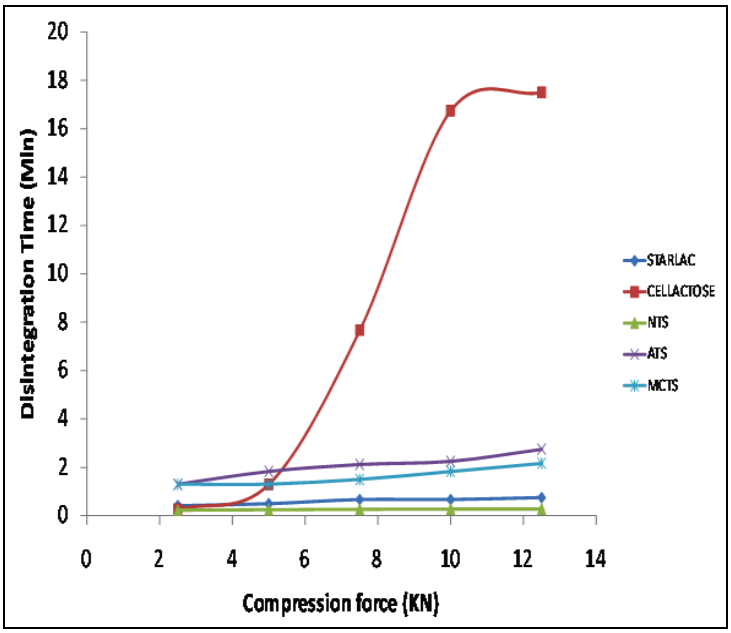


**FIG. 4: RELATIONSHIP BETWEEN DISINTEGRATION TIME AND COMPRESSION PRESSURE OF COMPACTS CONTAINING NATIVE TAPIOCA STARCH (NTS), ANNEALED TAPIOCA STARCH, AND MICROCRYSTALLINE TAPIOCA STARCH**

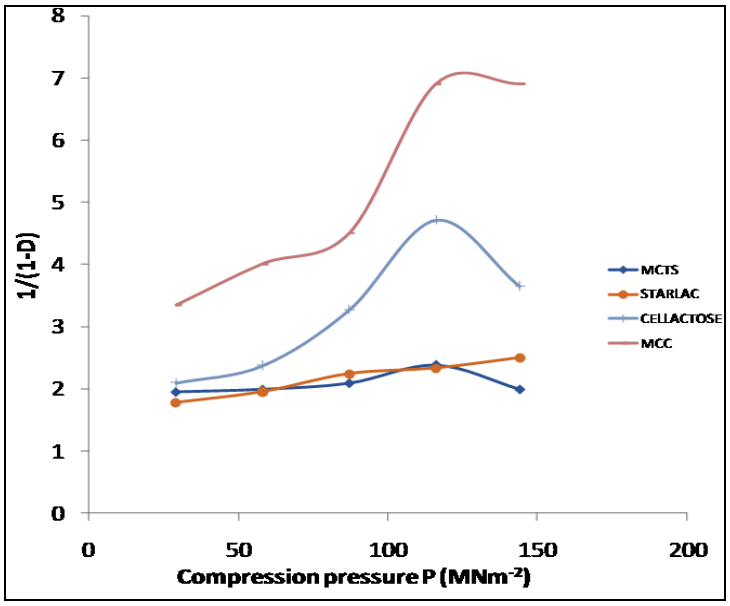


**FIG. 5: HECKEL'S ANALYSIS OF COMPACT OF MICROCRYSTALLINE TAPIOCA STARCH (MCTS), STARLAC, CELLACTOSE, MICROCRYSTALLINE CELLULOSE (MCC)**

**TABLE 5: PARAMETER OBTAINED FROM HECKEL PLOTS FOR COMPOSITE PARTICLES, MCTS, STARLAC®, CELLACTOSE® AND MCC**

| Material | K | $P_Y$ ($MNm^{-2}$) | A | $e^{-A}$ | $D_o$ | $D_A$ | $D_B$ |
|---|---|---|---|---|---|---|---|
| **MCTS** | **0.007** | **143** | **1.7** | 0.183 | **0.337** | 0.817 | 0.480 |
| **Starlac** | **0.007** | 143 | **1.7** | 0.183 | **0.413** | 0.817 | 0.404 |
| **Cellactose** | **0.041** | **24.2** | **0.6** | 0.545 | **0.298** | **0.455** | **0.157** |
| **MCC** | **0.04** | **25.0** | **2.3** | 0.100 | **0.258** | **0.900** | **0.642** |

NB: A and $K_{represent}$: constants of Heckel equation. $P_Y$ represent: mean yield value. $D_o$, $D_A$, and $D_B$ represents: initial rearrangement phase of densification, total degree of densification at zero pressure and rearrangement phase of particles in the early stages of compression respectively.

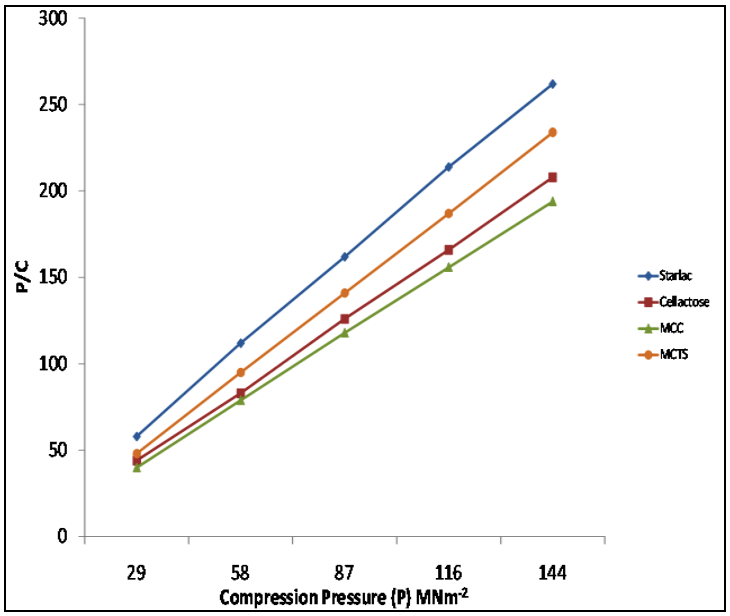


**FIG. 6: KAWAKITA ANALYSIS of COMPACT OF MICROCRYSTALLINE TAPIOCA STARCH (MCTS), STARLAC, CELLACTOSE, MICROCRYSTALLINE CELLULOSE (MCC)**

**TABLE 6: PARAMETERS OBTAINED FROM KAWAKITA PLOT ANALYSIS**

| Material | a | 1/a | $D_i$ =(1 – a) | 1/b | $P_K$($MNm^{-2}$) |
|---|---|---|---|---|---|
| **Starlac** | 0.526 | 1.9 | 0.474 | 17 | **17** |
| **Cellactose** | 0.714 | 1.4 | 0.286 | 19.1 | 19.1 |
| **MCC** | 0.769 | 1.3 | 0.231 | 18.6 | 18.6 |
| **Microcrystalline Tapioca Starch (MCTS-3h)** | 0.680 | 1.47 | 0.320 | 17.7 | **17.7** |

NB: 'a' and 'b' are constants of Kawakita equation ('a' gives minimum porosity of the bed prior to compression, while 'b' gives the coefficient of compression is related to the plasticity of the material). Di indicates the packed initial relative density of tablets formed with low pressure. $P_k$ gives and inverse measurement of plastic deformation occurring during compression

**FIG. 7: PHOTOGRAPH OF TABLETS CONTAINING MICROCRYSTALLINE TAPIOCA STARCH 60 % AND ASCORBIC ACID 40 %, (MCTS-AA-40 %)**

**FIG. 8: PHOTOGRAPH OF TABLETS CONTAINING MICROCRYSTALLINE TAPIOCA STARCH 75 % AND PARACETAMOL 25 %, (MCTS-PCM-25 %)**

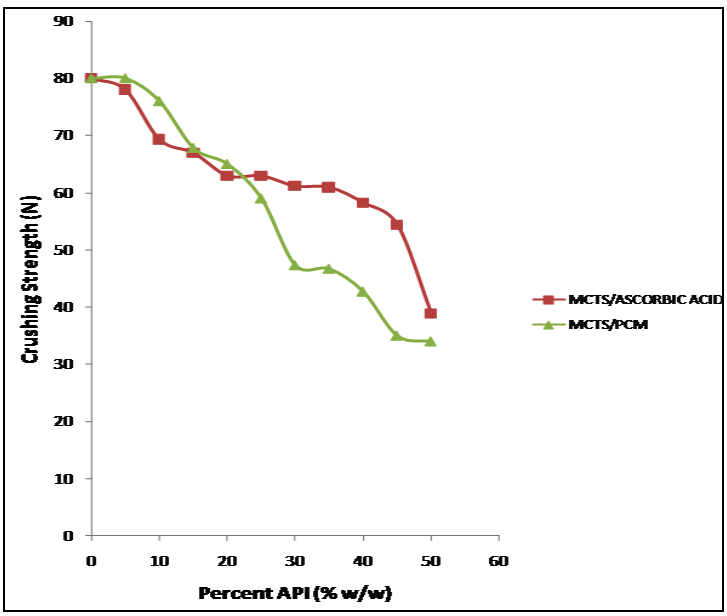


**FIG. 9: RELATIONSHIP BETWEEN TABLET STRENGTH AND THE AMOUNT OF API THAT MCTS CAN ABSORB WHILE STILL MAINTAINING TABLETS PROPERTIES (COMPACTED AT 7.5 KN)**

**TABLE 7: TABLET PROPERTIES OF COMPACTS AT THE LIMITING IN-TAKE OF THE ACTIVE INGREDIENT**

| Tablet | Model drug | Dilution capacity (%) | Tablet Hardness (N) | Friability (%) | Disintegration Time (Sec) | REMARK |
|---|---|---|---|---|---|---|
| MCTS/PCM | PCM | 20 | 59 | 0.8 | 81 | Good |
| | | 25 | 46.7 | 1.6 | 60 | Chipped |
| MCTS/AA | AA | 35 | 61.5 | 0.8 | 144 | Good |
| | | 40 | 58.3 | 1.0 | 123 | Good |

NB: MCTS, PCM and AA represent microcrystalline tapioca starch, paracetamol and ascorbic acid respectively.

**TABLE 8: SUMMARY OF DILUTION CAPACITY**

| COPROCESSED FILLER -BINDER | MODEL DRUG | CAPACITY / POTENTIAL (%) |
|---|---|---|
| MCTS | PCM | 20 |
| MCTS | AA | 40 |

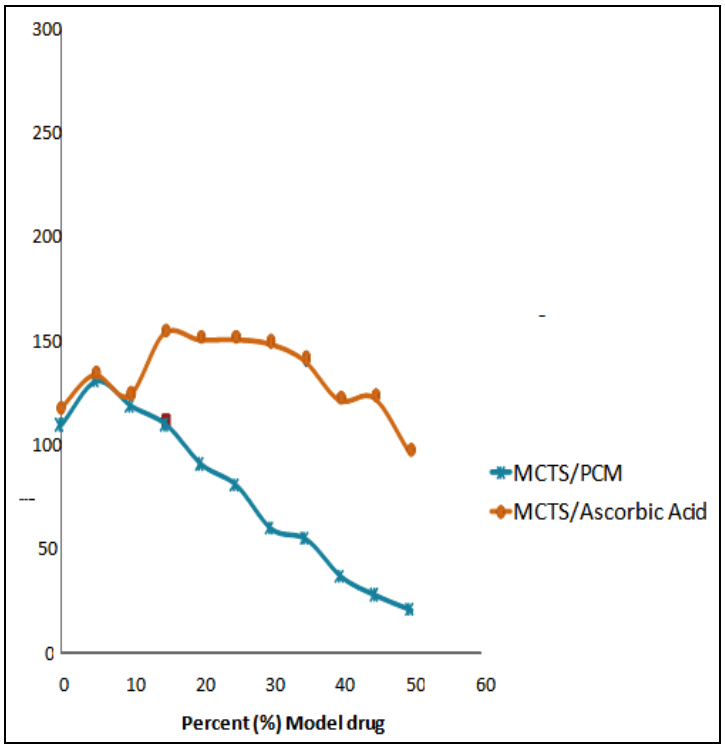


**FIG. 10: RELATIONSHIP BETWEEN TABLET DISINTEGRATION TIME AND THE AMOUNT OF MODEL DRUG THAT MCTS, MSL AND MSCL CAN ABSORB WHILE STILL MAINTAINING TABLET PROPERTIES**

**Granular properties:** One of the objectives was to modify the starch granules physically by annealing and at molecular level by enzyme hydrolysis.

After annealing and enzyme hydrolysis, the average granule size was found to be 13 µm (**Table 1 and Figure 1**), this shows that there is an increase in granule size after annealing and enzyme hydrolysis of starch granules. This has helped in improving the flow property of MCTS over the NTS as starch utilization as filler-binder is hindered by its poor flow due to its smaller granule size. Wang *et al*., (1997) explain that, annealing break some hydrogen bonds unwinding the interwoven chain of polysaccharides and weakens the granular membrane and aid penetration of the enzyme, while the enzyme drill holes through the membrane to act on the disorganized polysaccharide chains. Tukomane *et al.,* (2007) used scanning electron micrographs to study the morphological changes and the mode of enzyme attack during enzyme hydrolysis; they found that, α – amylase preferentially attacked the interior of the starch granule, leaving a deep round hole on the starch granule surface.

**Table 3** compares the granule properties of ATS with that of NTS, and MCTS-3 h. The result illustrates an increase in flow properties as reflected by flow rate 2.0 g/s, 2.6 g/s and 2.5 g/s for NTS, ATS and MCTS-3 h respectively. Improving granule size at particle level has been translated to improving flow at bulk level. The corresponding angles of repose are $43^{o}$, $32^{o}$ and $35^{o}$ respectively. The compressibility as reflected in the table for NTS, ATS-3 h and MCTS-3 h are: 32.2 %, 31.2 % and 27.3 % respectively. All these results point to increase in both flow and compressibility of tapioca starch after annealing and enzyme hydrolysis.

**Tablet properties: Table 2** shows tablet properties of MCTS at various time of hydrolysis. It can be seen that the tablets of MCTS-3 h gave the best compacts in terms of tensile strength, friability and disintegration time.

MCTS was subjected to compressibility and Compactability studies. The material was compacted using a single punch Carver hydraulic hand press (model, C, Carver Inc. Menomonee Falls, Wisconsin, U.S.A ) over a pressure range of 2.5 to 12.5 KN. **Fig. 2** compares the compressibility of MCTS with ATS and NTS. The MCTS curve shows a progressive increase in compact density with pressure, spanning from 1.31 to 1.35 $g/cm^3$. This shows clear improvement over compressibility of NTS. Moreover, **Fig. 3** shows the result of the compactability studies, it illustrates the relationship between compression pressure and radial tensile strength.

The compactness of MCTS is seen to span over <14 to >15 x $10^5$ N/$M^2$, while that of ATS stretched across <5 to >9 x $10^5$ N/$M^2$, and NTS, <4 to >5 x $10^5$ N/$M^2$. This result revealed higher bonding effect following annealing and enzyme hydrolysis of NTS.

Based on this result, MCTS-3 h was selected to be tailored with lactose and MCC in the next stages,

**Disintegration (DT)** Starch granules possessed inherent disintegration property. The disintegration time is mostly influenced by tablet hardness. **Table 4** shows the value of the disintegration time for MCTS-3 h as 80 sec. this DT is about six (6) times the value for NTS (which is 14 sec.), and three (3) times the value for ATS (which is 25 sec.). The B.P.C (1988) standard specified standard for conventional tablet to be 15 min. ATS with disintegration time of 82 sec. (1 min. 22 sec.) can be regarded as a super disintegrant.

**Densification behavior of MCTS-3 h:**

**Plot of Heckel equation.** The widely used and relatively simple equation is given by:

$$\ln 1/[1 - D] = kp + A$$

Where, D is the relative density of the compact, 1 – D is the pore fraction, and *p* is the pressure. 'A' and '*k*' are constants of Heckel equation. The parameter A is said to relate to low pressure densification by interparticle motion, while the parameter *k* indicates the ability of the compact to densify by plastic deformation after interparticle bonding. **Fig. 5** shows the plot of ln 1/[1 – D] *vs p* for MCTS, co processed filler-binders and marketed standard co processed excipients and MCC. The plot of MCTS can be divided into three-phases, namely: 29 $MNm^{-2} < p < 87$ $MNm^{-2}$, 87 $MNm^{-2} < p < 116$ $MNm^{-2}$, and 116 $MNm^{-2} < p < 144$ $MNm^{-2}$, each of which basically obeys the Heckel equation.

There is linearity in the first phase at low pressure which suggests that MCTS deform mainly by plastic deformation (Odeku and Itiola, 2007). Under low pressure ($p < 87$ $MNm^{-2}$) the compaction would mainly result in the elimination of voids among the loose particles through rearrangement, fragmentation and some degree of plastic deformation, leading to rapid densification of MCTS.

On the second phase from ~87 $MNm^{-2}$ to ~116 $MNm^{-2}$, however, the sliding, rearrangement and plastic deformation of MCTS particles would be responsible for the densification of MCTS compact. The third phase from ~116 $MNm^{-2}$ to ~144 $MNm^{-2}$, here, following decompression, an expansion in tablet height is represented by increased tablet porosity.

**Table 5** show values of the mean yield pressure, $P_y$; the relative densities $D_o$, $D_A$, and $D_B$ for MCTS, microstructured filler-binders, standard co processed excipients and MCC. $P_y$, is inversely related to the ability of the material to deform plastically under pressure. Low value of $P_y$ indicates a faster onset of plastic deformation (Odeku and Itiola, 1998). The $P_y$ obtained for MCTS-3 h, Starlac®, Cellactose® and MCC are: 143 $MNm^{-2}$, 143 $MNm^{-2}$, 24.2 $MNm^{-2}$ and 25 $MNm^{-2}$ respectively. From the values of $P_y$ stated above both tailored filler-binder "Microcrystarlac" and the standard excipient, "Starlac®" has the same $P_y$ value illustrating same onset of plasticity, while Cellactose® and MCC with lower $P_y$ have faster onset of plastic deformation compare with the two former filler-binders.

The high yield value of MCTS-3 h reflects more resistance to pressure, less densification and low compressibility than Cellactose® and MCC, but equal with Starlac®. Shangraw *et al.,* (1981) explain that, a large value of slop (i.e., low $P_y$ value) is an indication that the onset of plastic deformation occurs at relatively low pressure and vice versa.

This analysis has been extensively applied to pharmaceutical powders for both single and multi-component systems (Duberg and Nystrom, 1986; Itiola, 1991).

$D_A$, represents the total degree of densification at zero and low pressures (Paronen and Juslin, 1983; Mitreve *et al*., 1996), (Roberts and Rowe, 1985). $D_o$, is used to describe the initial rearrangement phase of densification as a result of die filling. $D_o$ is equal to the ratio of bulk density at zero pressure to the true density of the powder (Chowhan and Chow, 1981). The relative density, $D_B$, describes the phase of rearrangement of particles in the early stages of compression and tends to indicate the extent of particle or granule fragmentation.

From Table 5, the $D_o$ values for MCTS-3 h, Starlac, Cellactose and MCC are: 0.337, 0.417, 0.298 and 0.258 respectively. These results show that MCTS-3 h is more densify during the die filling than Cellactose and MCC but less than Starlac. The $D_B$ values for the same set of materials are: 0.480, 0.404, 0.157 and 0.642. These results reflect the degree of fragmentation at low pressure in the following order: MCC>MCTS-3 h>Starlac®>Cellactose®. Khan and Rhodes, (1975) has reported some degree of fragmentation in MCC with increase in compression pressure. Doelker, 1988; Nystrom *et al.,* 1993 observed that high $D_B$ values are caused by fragmentation while low $D_B$ values are associated with plastic deformation.

**Plot of Kawakita equation** Kawakita equation can be written as [Kawakita and Ludde, (1970/71)]:

$$P/C = 1/a\ P + 1/ab$$

Where, a and b are constants ('a' gives the value of the minimum porosity of the bed prior to compression while 'b', which is termed the coefficient of compression, is related to the plasticity of the material) and C is the volume reduction, i.e., $C = (V_o - V)/V_o$ (here $V_o$ and $V$ are initial volume and the volume after compression, respectively). The Kawakita equation indicates that $p/C$ is proportional to the applied pressure $p$. **Fig. 6** shows the plot of $p/C$ *vs* $p$ for MCTS, microstructured filler-binders, and standard marketed excipients "Starlac®" and "Cellactose®". One can see that a linear relationship exists between $p/C$ and $p$ in the whole pressure range investigated at correlation coefficient ($R^2$ = 0.999), which indicates that the densification behavior of MCTS is consistent with prediction from the Kawakita equations. By best fitting of the experimental data to the equation above one obtains:

$$p/C = 1.47p + 26$$

Hence, by relating the two formulae above, the value of "a" is obtained as 0.680 and "b as 0.057 (1/b = 17.7).

The $D_i$ (=1 – a) indicates the packed initial relative density of tablets formed with little pressure or tapping (Lin and "Chain, 1995). **Table 6** shows the $D_i$ values for MCTS-3 h, Starlac, Cellactose and MCC as: 0.320, 0.474, 0.286, and 0.231 respectively. It can be seen that at low pressure MCTS-3 h tablet is better packed than Cellactose and MCC tablets, but less in packing relative to Starlac tablet. This result is not far from the fact that packing of a material with applied pressure is determined by deformation propensity.

Table 6 shows the values of 1/b ($P_k$) obtained for MCTS-3 h, Starlac, Cellactose and MCC as: 17.7, 17.0, 19.1, and 18.6 respectively. The reciprocal of b yields a pressure term, $P_k$, which is the compression pressure, required to reduce the powder bed by 50 % (Shivanand and Sprockel, 1992). The value of $P_k$ gives an inverse measurement of plastic deformation during compaction process.

The lower the value of $P_k$, the higher the degree of plastic deformation occurring during compression (Adam and Mckeown). The pressure term $P_k$ has been shown to provide a measure of the total amount of plastic deformation occurring during compression (Odeku and Itiola, 1998). Hence, from the results of $P_k$ values, MCTS-3 h is more plastically deformed during compression than Cellactose and MCC but less than Starlac.

**Dilution Capacity/Potential: Fig. 7 and 8** shows pictures of tablets of MCTS containing 40 % of ascorbic and 25 % of paracetamol respectively. **Fig. 9** shows the relationship between tablet strength and the amount (in percentage) of API that MCTS can absorbed while still maintaining tablet properties. It can be seen that tablet strength declined with increasing amount of API until it reaches a point where the tablet strength, friability and the physical structure failed to meet the official standard.

**Table 7** shows the summary of the result of the dilution potential. MCTS was compacted with paracetamol and ascorbic acid in predetermined percentages as model drug (API). One can see that MCTS was able to form acceptable compact with maximum of 20 % of the former (crushing strength is 59 N and friability, 0.8 %, disintegration time, 81 sec.), and with 40 % of the later (crushing strength is 58 N and friability, 1.0 %, disintegration time, 123 sec.). Hence, MCTS – Ascorbic scid-40 % is more acceptable dilution capacity/potential than MCTS – Paracetamol – 20 %.

**Disintegration MCTS-Model drug: Fig. 10** shows the declining disintegration time with increasing percentage API. It can be seen that the disintegration time of MCTS – PCM and MCTS – AA ranges between 125 sec. down to 25 sec., for the former and 150 sec. down to 100 sec for the later respectively. One can see that the disintegrant properties of MCTS is more pronounced in the formulation containing poorly compressible and water insoluble API than in formulation containing highly water soluble and moisture sensitive API.

**CONCLUSION:** MCTS is more superior in functionality than Cellactose and MCC. The dilution potential obtained for MCTS, compacted with paracetamol (PCM) and ascorbic acid (AA) as active drug (API) are: 40 % AA with MCTS; 20 % PCM with MCTS. The hardness of MCTS containing 40 % AA was found to be 58 N and that of 20 % with PCM is 59 N. MCTS can conveniently be used to formulate softer tablet of moisture sensitive API in ratio of 60 % (MCTS) to 40 % (API).

**REFERENCES:**


1. Bansal, A,k., and Nachaegari, S.K "High functiorality Excipients for Solid Oral Dosage Forms," in Business Briefings Pharmagenerics (World Markets Research Centre, London, U.K 2002), pp. 38-44.
2. Reimerdes, D. and Aufmuth, K.P. " Tableting with Coprocessed Lactose- Cellulose Excipient, '[1]'*Manufacturing Chemist,* 63 (12), 23 -24 (1992).
3. Tukomane T; Leerapongnun P, Shobsngob S., and Varavinit S. (2007) “Preparation and Characterization of Annealed Enzymatically hydrolyzed Tapioca starch” *Coden STRKA6*. (1) pp.33-45.
4. Grace, M. R., (1977). Cassava Processing. Plant Production and Protection series No. 3 FAO, Rome.
5. Radley, J. A., (1976). Starch Production Technology. Applied Science Publishers, London, p. 587.
6. Knutson C. A., (1990). Annealing Starches at Elevated Temperatures. *Cereal Chemistry* 67 : 376 – 384.
7. Wang, W. J., Powell, A.D., and Oates, C.G. (1997). Effect of annealing on the hydrolysis of sago starch granules. Carbohydrate Polymers, 35, 195 – 202.
8. Lin, C., and Cham. T. Compression behaviour and Tensile Strength of Heat-treated Polyethylene glycols. Int. J. Pharm. (1995) 118: 169 – 179.
9. Kawakita, K., and Ludde, K. H. (1970/71) Some Considerations on Power Compression Equations. Powder Technology, 4: 61 – 68.
10. Heckel, R. W. (1961). Density-Pressure Relationships in Powder Compaction. Trans. Met. Soc. AIME. 221 (1961): 671.
11. Fell, J.T., Newton, J. M. (1970) Determination of Tablet Strength by Diametral-Compresion Test. J. Pharm. Sci. 59:688 – 691.
12. Fell J.T., and Newton, J.M., (1968). The tensile strength of Lactose Tablets. *J. Pharm. Pharmacol. 20* (8): 657-758
13. Paronen P and Juslin, M. (1983). Compression characteristic of four starches. *J. Pharm. Pharmacol.* 35 627-635.
14. Mitrevej, A., Sinchaipanid, N, and Faroongsang, D., Spray-Dried Rice Starch: Comparative Evaluation of Direct Compression Fillers, *Drug Dev.Ind.Pharm., 22:587*-594, 1996.
15. Khan, K.A. and Rhodes, C.T, The Production of Tablets by Direct Compression, *Can. J. Pharm. Set,* 8: I -5, 1973.
16. Shangaw, R.F. Wallace, J.W. "Morphology and Functionality in Tablet Excipients for Direct Compression: Part 1, *"Pharm. Technol.* 5 (9), 69-78 (1981).
17. Duberg, M. and Nystrom, C. (1986). Studies on direct compression of tablets. XVII Porosity-pressure curves for characterization of volume reduction mechanisms in powder compression. *Powder Technol.* 46, 67-75.
18. Fell, J, T and Newton, J.M. (1970a) Determination of tablet strength by diametral compression test. *J.Pharm. Sci.* 59, 688 - 691.
19. Heckel, R W. (1961 a) .Density-pressure relationships in powder compaction. *Trans. Metal. Soc.* AIME. 221, 671 - 675.
20. Nystrom, C, Alderborn, G. Duberg, M. and Karehill, P.G. (1993). Bonding surface area and bonding mechanism; two important factors for the understanding of powder compactability. *Drug Dev. Ind. Pharm.* 19, 2143 -2196.
21. Tukomane T; Leerapongnun P, Shobsngob S., and Varavinit S. (2007) “Preparation and Characterization of Annealed Enzymatically hydrolyzed Tapioca starch” *Coden STRKA6*. (1) pp.33-45.
22. Itiola, O.A.,(1991). “Compressional Characteristics of three Starches and the Mechanical Properties of their Tablets”. *Pharm. World J*. 8 (3), 91 – 94.
23. Shivanand, P., and Sprockel, O.I., (1992). “Compaction Behaviour of Cellulose Polymers”. *Powder Technol*. 69 (2), 177 – 184.
24. Ring, S. G., Some studies on gelatin. Starke, 1985; 37: 80 – 87.
25. Odeku, O.A., and Itiola, O.A., (1998). Evaluation of Khaya Gum as a Binder in a Paracetamol Formulation. *Pharm. Pharmacol. Commum*. 4:183 – 188.
26. Kumer, V, Kothari, S. H. (1999). Effect of compressional force on the crystallinity of directly compressible cellulose. Int. J. Pharm., 177, 173 – 182
27. Paronen, P and Illka, J. (1996). Porosity-pressure functions. In Alderbon, G. and Nystrom, C. (Eds), Pharmaceutical Powder Compaction Technology, Mercel Dekker Inc. New York, Pp 55-75.
28. Roberts, R.J and Rowe, R.C., (1985). The effect of Punch velocity on the compaction of a very variety of materials. J. Pharm. Pharmacol., 37, 377-384.


**How to cite this article**:
Shittu A.O., Oyi A.R., Isah A.B., Kareem S.O. and Ibrahim M.A.: Formulation and Evaluation of Microcrystalline Tapioca Starch as a Filler-Binder for Direct Compression. *Int J Pharm Sci Res*, 2012; Vol. 3(7): 2180-2190.