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# Compaction characteristics of a micro-structured filler-binder "Microcrystarcellactose B3" for direct compression tableting

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**Abstract**

A research was conducted to develop and evaluate a highly compressible micro-structured filler- binder for direct compression tableting. Tapioca starch (TS) was annealed, hydrolyzed and coprocessed with α-lactose monohydrate (α-LMH) and microcrystalline cellulose (MCC) to yield a novel microcrystarcellactose (MSCL B3). The powder suspensions were prepared at a concentration of 40 %w/w in five separate conical flasks. The TS granules were annealed for 1 h and subsequently hydrolyzed with α-amylase at 58° and pH 7 for 1, 2, 3, 4, and 5 h respectively. The reaction was terminated and neutralized with 0.1 N HCL and 0.1 N NaOH respectively. The enzyme hydrolyzed starch (EHS) at 3 h, sieved fraction >75-250 µm was coprocessed with α-LMH and MCC and compressed with load ranging from 2.5 to 12.5 KN. MSCL B3 (component ratio of EHS, α-LMH, and MCC '35: 35:30') possessed improved functionality over direct physical mixture of the excipients. The $P_y$ (yield values) are: Cellactose (24.2 $MNm^{-2}$) > MCC (25 $MNm^{-2}$) > MSCL B3 (50.0 $MNm^{-2}$) > Starlac (143 $MNm^{-2}$). The degree of plastic deformation occurring "$P_k$" are in the following order: MSCL B3 (17.0 $MNm^{-2}$) = Cellactose ® (17.0 $MNm^{-2}$) > MCC (18.6 $MNm^{-2}$) > Starlac® (19.1 $MNm^{-2}$). MSCL B3 is as good as Cellactose® and more superior in functionality than Starlac® and MCC. The dilution potential for MSCL B3 in PCM and AA tablets were: 45% and 50 % respectively. MSCL B3 can be used to formulate softer tablet of both poorly compressible API and moisture sensitive API

*Keywords*: Microcrystarcellactose; Coprocessed excipient; Directly compressible excipient; Highly functional filler-binder; Tapioca starch

## INTRODUCTION

The need to address issues such as flowability, compactibility, disintegration, dissolution and bioavailability also raises the demand for newer excipients with high functional property. Tailoring of excipients lead to the formation of excipient granulates with superior properties compared to physical mixtures of components or to individual components. Coprocessed excipients have been developed to address the issues of poor flowability compressibility, and disintegration potential. The combination of excipients chosen should complement each other to mask the undesirable properties of individual excipients and, at the same time, retain or improve the desired properties of excipient. Material science plays a significant role in

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altering the physicomechanical characteristics of a material, especially with regard to its compression and flow behavior. Coprocessing excipients offers an interesting tool to alter these physicomechanical properties. Materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle materials.

Pharmaceutical materials exhibit all three types of behavior-, with one type being the predominant response. Coprocessing is generally conducted with one excipient that is plastic and another that is brittle. Maarschalk and Bolhius [1], reported a coprocessed filler-binder made with a large amount of brittle material and a small amount of plastic material as exemplified by cellactose (Meggle corp.) in which 75 % is lactose (brittle material) [1]. This combination prevents the storage of too much elastic energy during compression, which results in a small amount of stress relaxation and reduced tendency of capping and lamination [2]. Moreso, example of the other extreme is SMCC, having a large amount of MCC [plastic material] and a small amount of silicon dioxide [brittle material]). These two situations exemplified the fact that coprocessing is generally performed with a combination of materials that have plastic deformation and brittle fragmentation characteristics.

A combination of plastic and brittle materials is necessary for optimum tabletting performance. Hence, coprocessing these two kinds of materials produces a synergistic effect, in terms of compressibility, by selectively overcoming, the disadvantages. Such combinations can help improve functionalities such as compaction performance, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture or reduced hornification.

## EXPERIMENTAL

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

**Extraction of tapioca starch.** Method of Radley [3] was adopted. Cassava tubers 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. [3], [4].

**Preparation of microcrystalline tapioca starch (MCTS).** A modified method of Tokumane and his team [5] 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.

**Preparation of the composite filler-binder (Microcrystarcellactose) by codried method.** A modified method of Tsai *et al* [6] was adopted for coprocessing the three powder materials to yield 3-component composite granules. The slurry form of annealed enzyme hydrolyzed tapioca starch (MCTS) (sieved fraction, <75 µ) was coprocessed with α- lactose monohydrate (α – L-MH) (sieved fraction, <75 µ), and microcrystalline cellulose (MCC) (sieve fraction, <75 µ). The slurry was made by suspending the MCTS in a solution of Isopropranol and freshly distilled water in ratio 2:1 respectively. MCTS slurry was blended with α – L-MH, and MCC at concentrations indicated in Table 1 as a dried mass relative to MCTS. The composite slurry was stirred vigorously with a stirrer until a semi-solid mass easily ball was formed. The composite mass was then granulated through a 1500 µ and codried at 60$^{o}$C until a constant weight was reached. Codried granules were pulverized and sized by passing through mesh size 500 µm, and the fraction between >75 – 250 µm was reserved. The powder and tabletting properties of the codried products were evaluated and compared to those of corresponding components and physical mixtures.

**Compactibility.** 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 to be coprocessed with lactose and MCC, (2) the best two batches (out of five) of coprocessed filler-binder for micro-structuring before compaction studies. 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 coprocessed filler-binder: MSCL (5 batches each) were subjected to the same procedure to streamline the batches to just two for effective research and particle restructuring. 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 the primary powders [tapioca starch, microcrystalline cellulose (MCC), lactose], annealed tapioca starch (ATS), annealed enzymatically hydrolyzed tapioca starch (MCTS), Microcrystarcellactose ($B_3$), physical mixture of MCTS and lactose; MCTS, lactose and MCC, were 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 12.5

KN to 32.5 KN. Forty 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:

$$D = W/[V_t \times P_s] \quad \ldots\ldots (1)$$

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

Heckel plots of ln (1/ 1 – D) versus applied pressure "P" [7] and Kawakita plots of P/C versus P, [8] 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.

**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:

$$MC = (1 - Wt/W0)\, X\, 100 \quad \ldots\ldots (2)$$

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 [9] Jones and Pilpel (1966).

$$\theta = tan'1\ (h/r) \quad \ldots (3)$$

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

**True (particle) densities.** The true (particle) densities of the primary powders (tapioca starch and mcc-derived), annealed starch, annealed enzymatically hydrolyzed tapioca starch and the composite particles were determined by the liquid displacement method using a specific gravity bottle with Xylene as displacement fluids, and the particle density, $D_p$, computed according to the following equation:

$$Dp = W/[(a + W) - b]\, x\, SG \quad \ldots (4)$$

Where, W, is the weight of powder, SG, is the specific gravity of the solvent, a, is the weight of bottle plus solvent, and, b, is the weight of bottle plus solvent plus powder. The measurement was performed in triplicate.

**Bulk and Tap density.** The bulk and tapped densities were determined by the modified method of Kumer and Kothari [10]. These parameters were determined by weighing 50 g quantity of each granule/powder and pouring into a 100 ml measuring cylinder. The volume ($V_o$) was recorded as the bulk volume. The total weight of the granule/powder was noted. The bottom of the cylinder was raised 10 cm above the slab and made to fall on the platform continuously for 100 taps. The volume of ($V_t$) of the granule was recorded, and this represents the volume of the granules minus the voids and is called the tapped volume. The final weight of the powder too was recorded as the tapped weight. The bulk and tapped densities were calculated as:

$$Bd = W/Vo \quad \ldots\ldots (5)$$

$Bt = W/Vt$ …..(6)

Where, $B_d$ and $B_t$, are bulk and tapped density respectively, and W, is the weight of the powder (50 g). The results presented are the mean of three determinations.

**Carr's Index.**

$Carr's\ Index\ (CI) = (\rho T - \rho o)/\rho o\ x\ 100\ \%$ .... (7)

Where $\rho^o$ is the poured or bulk density and $\rho^k$ is the tapped density.

**Evaluation of tablets**

*Weight variation limit test:* The weights of 10 tablets were determined individually and collectively on a Metler balance (Denver, XP-300, U.S.A). The mean weight, percentage (%) deviation from the mean and standard deviation were calculated.

*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.

*Hardness of tablets.* Crushing strength was determined using an electronic/digitalized tablet hardness tester (model EH O1, capacity 500 N, Indian).

*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 Metier balance (Denver, XP - 300, U.S. A). The tablets were placed in the friability and set to rotate at 25 r.p.m 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.

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

$$Vc = h\pi r2 \quad \text{….. (8)}$$

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

Compact density ($\rho$) =

Weight of tablet / volume of tablet ….. (9)

*Compact radial tensile strength:* This was computed using [11] Fell and Newton equation. The tensile strength of the normal tablets (T) was determined at room temperature by diametral compression [11] using a hardness tester (model EH O1, capacity 500 N, Indian) and by applying the equation:

$$T = 2F / (\pi dt) \quad \text{… (10)}$$

Where T is the tensile strength of the tablet ($MNm^{-2}$), F is the load (MN) needed to cause fracture, d is the tablet diameter (m).

Results were taken from tablets that split cleanly into two halves without any lamination. All measurements were made in triplicate, and the results given are the means of several determinations.

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

C.P. = Applied force / surface area of tablet …(11)

*Disintegration time.* Disintegration apparatus (Erweka, ZT 3, Germany) was employed. Three tablets were placed in each compartment of the disintegration basket which was lowered into a glass beaker (1 L capacity) filled with deionized water to 800 ml mark and in turn was placed in a water bath maintained at 37°C. The time taken for the disassociated tablet particles to pass through the mesh was recorded as the disintegration time. Average of three readings was taken as the disintegration time.

**Kawakita Compact Analysis.** The Kawakita equation has been used to study powder compression using the degree of volume reduction (C) and is written as:

$C = (Vo - Vp) / V = abP / (1 + bP)$ ….. (13)

The above equation can be rearrange to give:

$P/C = P / a + 1/ab$ ….. (14)

Compacts of weight 500 mg were made applying pressure P and values for volume the $V_p$ were determined from parameters obtained from the compacts. Three measurements were

taken, and the constants of the linear equation were calculated separately using compression pressure ranging from 2.5 to 12,5 KN and 5 observation points according to the method of least squares. The behaviour of the primary powders, and the composite particles during the compaction were compared with the commercially available directly compressible excipient using numerical constants obtained from the Kawakita plots.

Where $V_o$ is the initial bulk volume of the powder and $V_p$ is the tablet bulk volume after compression.

$$Vo = W / Bd \quad \text{..... (15)}$$

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

Where $V_p$ is the bulk volume of compact, i.e., compressed powder plus void.

This was derived from the volume of a cylindrical compact given by the following equation:

$$Vp = h\pi r2\ (cm3) \quad \text{..... (16)}$$

The constant **a** is the minimum porosity of the material before compression, while **b** is related to the plasticity of the material. The reciprocal of **b** gives a pressure term $\mathbf{P_k}$ which is the pressure required to reduce the powder bed by 50 % [12,13].

**Determination of dilution capacity.** Ascorbic acid and paracetamol were used as model drugs representing both highly water soluble, moisture sensitive, and elastic/poorly water soluble active ingredient respectively.

Model drugs were blended in deferent ratios, ranging from 0 %, 5 %, 10 %, up to 50 % with MSCL, microcrystarlac and microcrystarcellac. Formulations were blended by method of dilution and lubricated with 1 % magnesium stearate. Each batch was compressed for 30 seconds on single punch Carver hydraulic hand press (model, C, Carver Inc. Menomonee Falls, Wisconsin, U.S.A) at pressure load of 7.5 KN, target weight of 500 mg. Compacts were allowed to relax for 24 h post compression. Compact dimensions (diameter and thickness) were determined using a digitalized Vernier caliper. Crushing strength was determined using an electronic/digitalized tablet hardness tester (model EH O1, capacity 500 N, Indian). A relationship between amount in percent (%) of model drug added to the formulation and the tensile strength will be generated.

In general, the capacity was expressed by the dilution potential as being an indication of the maximum amount of active pharmaceutical ingredient that can be compressed with the excipient, while still obtaining tablets of acceptable quality (that is, acceptable crushing strength average of 60 N, friability, < 1.0 %, good disintegration time < 15 min, and must meet the requirement of U.S.P weight variation limit test).

***In vitro* drug release studies.** Drug availability is an important aspect of drug development and formulation. Drug release from the various tablets was determined using the basket method of U.S.P XXIII dissolution apparatus (model, RC-6, Tian Jin, China). The tests were conducted in 1000 ml 0.1 N HCl medium maintained at 37.0 $\pm$ 0.5°C at a paddle rotation speed of 50 rpm. Five ml (5 ml) of the menstrum (sample) were taken at the end of the specified (predetermined) time period of 5, 10, 15, 20, 30, 45 and 60 min. The samples were filtered and analyzed for paracetamol in one experiment and ascorbic acid in another experiment using U.V-vis Spectrophotometer (Jenway, 6310, U.K) at wavelength of 272 and 265 nm maximum absorption respectively. A five milliliter (5 ml) volume of filtered, fresh dissolution medium was added to maintain a constant volume after each sample withdrawal. The results were mean of three reading.

**Statistical analysis.** Statistical analysis was carried out using the statistical software – GraphPad Prism (version 3).Data obtained from the various experiments were expressed as mean $\pm$ SD. Differences between means were determined using the analysis of variance (ANOVA) and statistically significant difference were set at $P < 0.05$

## RESULTS AND DISCUSSION

Plates 1 to 3 showed the moist, flakes and the granules of freshly air-dried micro-structured MSCL B3**.** Table 2 shows the powder characteristics of primary, coprocessed and standard excipients. Table 3 illustrates the tablet properties of various batches of MSCL. The batch 3 results was considered for further studies. Fig. 1 shows the distribution of the composite particles of MSCL B3 granules obtained by sieving. The granule size ranges from 90 µm to 500 µm out of which over 50 % were greater than 250 µm. The percentage of larger granule present was responsible for the improved flow rate of the composite excipient compare to the physical mixture of the primary excipient. Table 2 compares the granule properties of composite excipient MSCL B3 with the direct physical mixtures of the same ratio, Starlac®, Cellactose® and MCC. MSCL The composite excipient possessed improved flow rate over that of the direct physical mixture as reflected by flow rate 1.6 g/s, for the former and 0.45 g/s, for the later respectively. The corresponding angles of repose are 32$^o$ and 47$^o$ respectively. The compressibility indices as reflected in the table are: 30 % and 52 % respectively. All these results indicate improvement in both flow property and compressibility for MSCL B3 over direct physical mixture of the same ratio.

**Table 1:** The working formula for preparation of the novel three component composite excipient (microcrystarcellactose)

| Material | % (w/w) | | | | |
|---|---|---|---|---|---|
| Batch | 1 | 2 | 3 | 4 | 5 |
| MCTS (g) | 45 | 40 | 35 | 30 | 25 |
| Lactose (g) (α – L-MH) | 45 | 40 | 35 | 30 | 25 |
| MCC (g) | 10 | 20 | 30 | 40 | 50 |

**Table 2:** Powder characteristics of primary of excipients, coprocessed filler-binder and standard coprocessed filler-binder

| Material | Flow rate g/s | Angle of repose (o) | Bulk density (g/cm$^3$) | Tapped density (g/cm$^3$) | Compressibilty index (% ) | Hausner Ratio |
|---|---|---|---|---|---|---|
| NTS | 2.00±0.02 | 43.40±0.00 | 0.545±0.02 | 0.817±0.04 | 50±2 | 1.50±0.02 |
| ATS(>75-250 µm) | 2.60±0.01 | 32.00±0.01 | 0.616±0.02 | 0.895±0.05 | 45 ± 3 | 1.50±0.04 |
| MCTS(>75-250 µm) | 2.50±0.01 | 24.50±0.01 | 0.516±0.04 | 0.712±0.21 | 38 ± 2 | 1.40±0.02 |
| MSCL-B3 (>75-250µm) (35:35:30) | 1.60±0.03 | 32.00±0.20 | 0.526±0.03 | 0.685±0.03 | 30.0± 2 | 1.30±0.20 |
| MCTS+LMH+MCC Physical mixture | 0.45±0.01 | 47.80±0.20 | 0.481±0.02 | 0.735±0.12 | 52 ± 1 | 1.53±0.03 |
| Starlac® | 7.10±0.00 | 19.20±0.10 | 0.641±0.01 | 0.725±0.03 | 13.1 ± 1.1 | 1.13±0.03 |
| cellactose® | 1.84±0.02 | 24.20±0.10 | 0.443±0.03 | 0.532±0.12 | 20.1 ± 2.1 | 1.20±0.01 |

**Plate 1:** Fresh Mixed MSCL B3

**Plate 2:** MCSL B3 moist flakes after 6h of air drying ready for coarse granulation

**Plate 3:** MSCL granules after coarse sieving through 1.5mm mesh

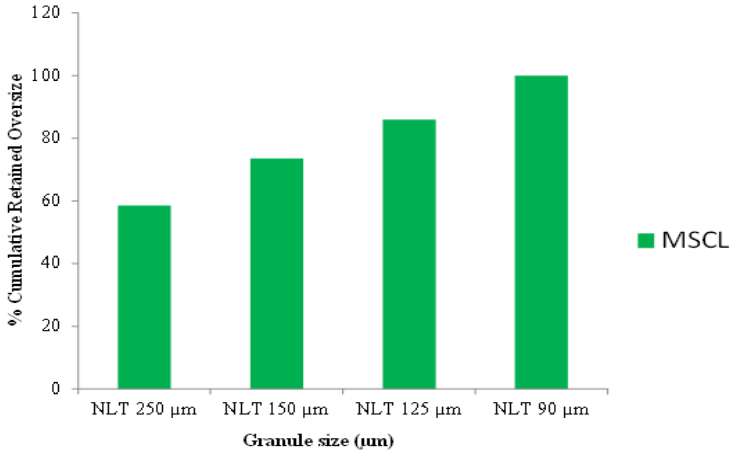


Fig. 1: Illustrates MSCL (35:35:30) granule distribution in percent cumulative retained oversize versus granule size(NLT: Not Less Than)

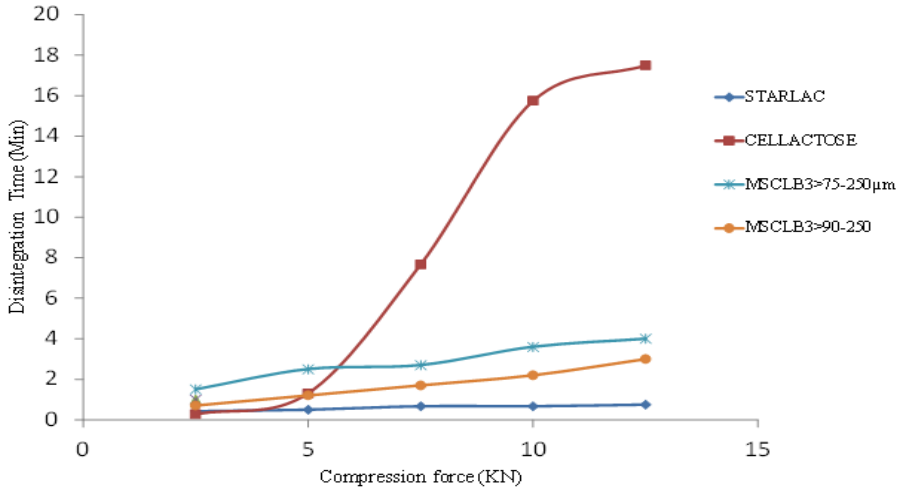


Fig. 2: Disintegration time vs. compression force for MSCL B3, Starlac® and Cellactose® placebo tablets

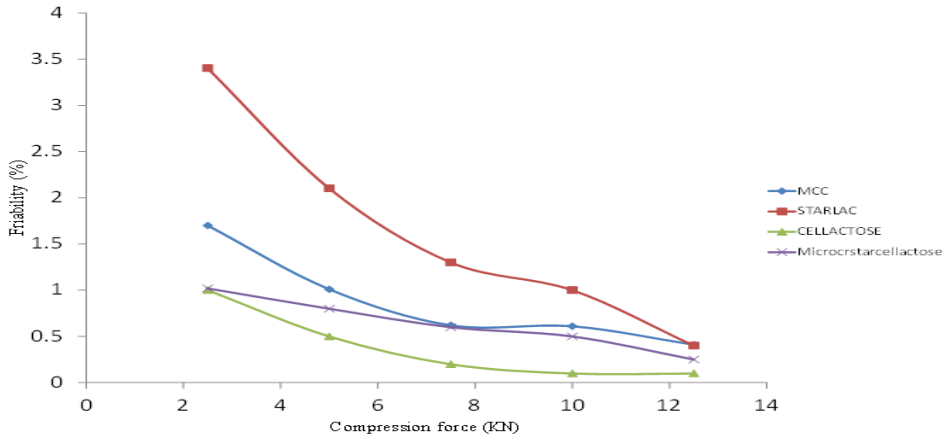


**Fig. 3:** Friability (%) vs. compression force (KN) for MSL, MSCL B3, Starlac ® and Cellactose® placebo tablets

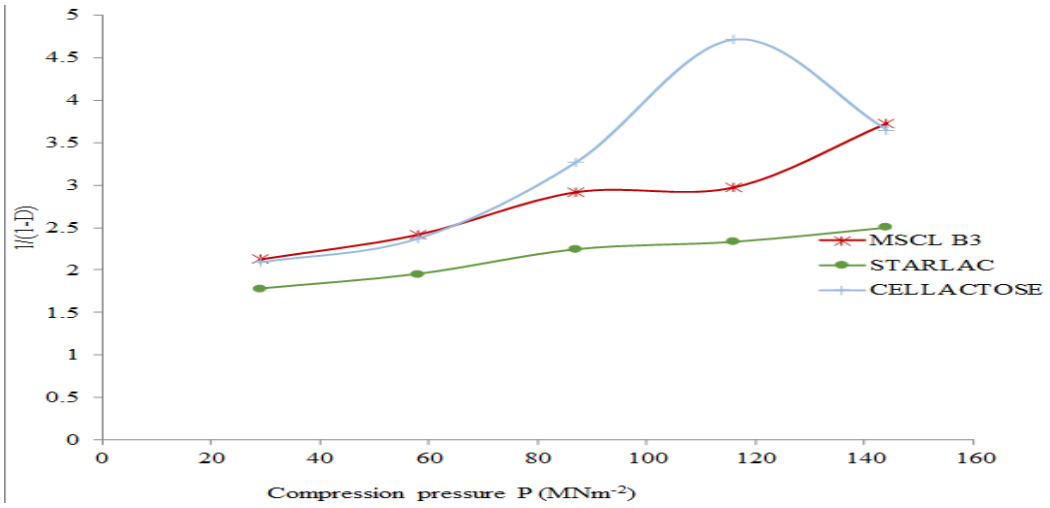


**Fig. 4:** Heckel's analysis of compact of microcrystarcellactose (B3), Starlac, Cellactose,

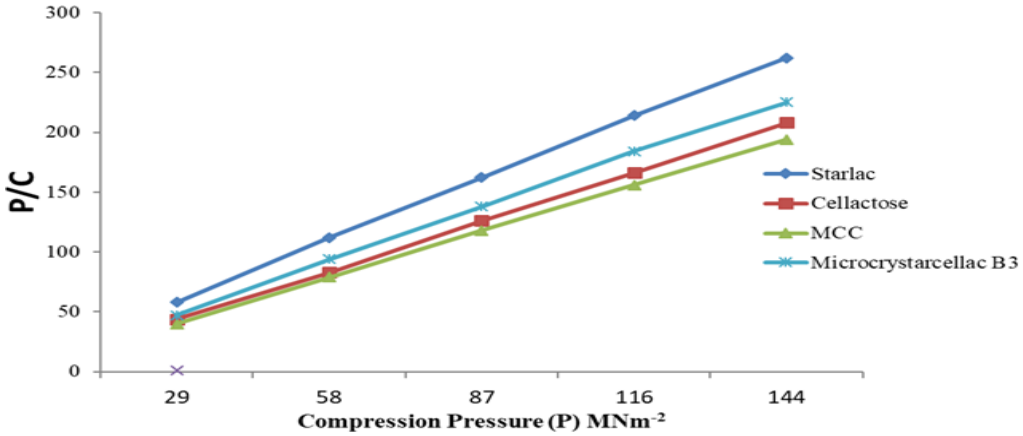


**Fig.5:** Kawakita analysis of compacts P/C vs Compression pressure P ($MNm^{-2}$) of MSCL B3, Starlac®, and Cellactose® placebo tablets

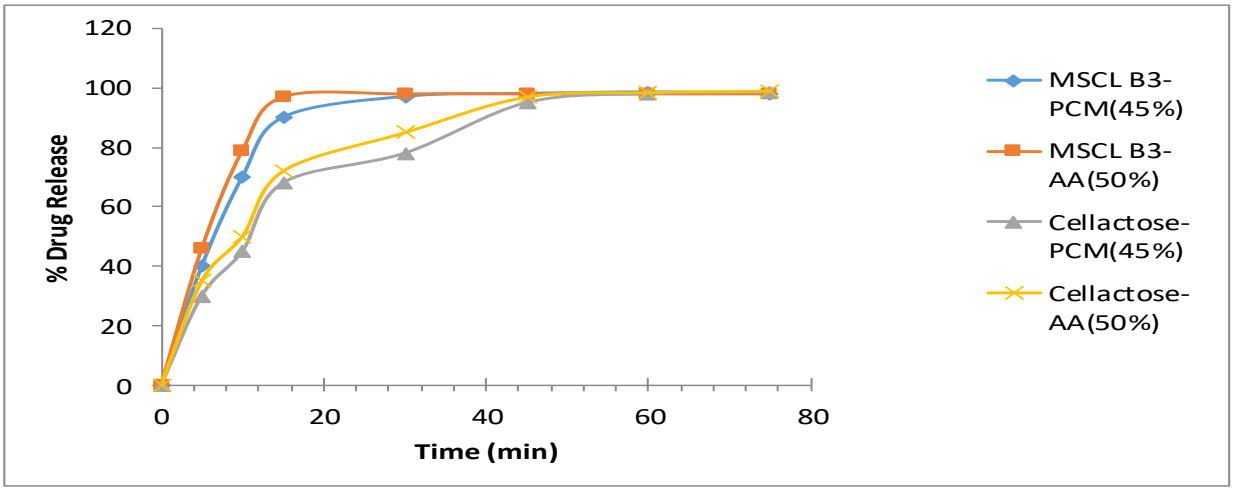


**Fig.6:** Drug Release (%) vs Time (min). Absorbance: PCM-272nm, AA-265nm.

**Table 3:** Tablet properties of various batches of MSCL B3 (MCTS+LMH+MCC).

| Batch % w/w | Compaction force (KN) | Compression pressure. ($N/M^2$) x $10^5$ | Tablet weight (g) n=3 | Tablet thickness (m) x$10^{-3}$ | Crushing strength (N) n=3 | Radial tensile strength ($N/M^2$) X $10^5$ | Friability % n=3 | DT (s) n =3 |
|---|---|---|---|---|---|---|---|---|
| 1 | 4 | 3.3 | 0.500±0.001 | 4.40± 0.01 | 33± 0.9 | 3.8± 0.0 | 7.2± 0.20 | 50± 0.5 |
| 45:45:10 | 5 | 4.1 | 0.500±0.001 | 3.30± 0.00 | 93± 0.7 | 13.5± 0.0 | 5.6± 0.25 | 180± 1.6 |
| | 6 | 4.9 | 0.500±0.000 | 3.45± 0.01 | 120±2.5 | 17.7± 0.0 | 0.73±0.01 | 240± 2.5 |
| 2 | 4 | 3.3 | 0.500 ±0.001 | 4.23 ± 0.01 | 37 ± 0.4 | 4.5 ± 0.0 | 3.80 ± 0.20 | 40 ± 0.2 |
| 40:40:20 | 5 | 4.1 | 0.500 ±0.000 | 3.52 ± 0.02 | 93 ± 0.5 | 13.5 ± 0.0 | 0.44 ± 0.01 | 120± 1.2 |
| | 6 | 4.9 | 0.500 ±0.000 | 3.42 ± 0.01 | 127 ± 1.4 | 18.8 ± 0.0 | 0.28 ± 0.01 | 210 ± 2.2 |
| 3 | 4 | 3.3 | 0.500 ±0.001 | 4.27 ± 0.03 | 40 ± 0.5 | 4.8 ± 0.0 | 2.18 ± 0.10 | 20 ± 0.1 |
| 35:35:30 | 5 | 4.1 | 0.500 ±0.001 | 3.34 ± 0.01 | 98 ± 0.8 | 15.0 ± 0.0 | 0.29 ± 0.01 | 15± 0.0 |
| | 6 | 4.9 | 0.500 ±0.000 | 3.33 ± 0.01 | 130 ± 2.5 | 20.0 ± 0.0 | 0.19 ± 0.01 | 180± 2.0 |
| 4 | 4 | 3.3 | 0.500±0.000 | 4.27± 0.01 | 20± 0.2 | 2.4± 0.0 | 5.80± 0.31 | 20± 0.0 |
| 30:30:40 | 5 | 4.1 | 0.500±0.000 | 3.36± 0.02 | 75± 1.5 | 11.4± 0.0 | 4.73± 0.20 | 60± 0.2 |
| | 6 | 4.9 | 0.500±0.001 | 3.00± 0.00 | 130± 3.0 | 21.9± 0.0 | 0.21± 0.01 | 240± 1.8 |
| 5 | 4 | 3.3 | 0.500±0.001 | 4.30± 0.02 | 17± 0.3 | 2.0± 0.0 | 3.07± 0.23 | 15± 0.00 |
| 25:25:50 | 5 | 4.1 | 0.500±0.000 | 3.30± 0.02 | 70± 1.2 | 10.8± 0.0 | 0.23± 0.01 | 135± 2.5 |
| | 6 | 4.9 | 0.500±0.001 | 3.00± 0.00 | 130± 3.5 | 22.1± 0.0 | 0.15± 0.01 | 360± 2.7 |

*Note: Tablet target and Punch/ die diameter were 500 mg, and 10.5 mm respectively. DT denotes disintegration time while: 1, 2, 3, 4 and 5 represent batches 1 to 5 containing MCTS, α-LMH and MCC*

**Table 4:** Parameter obtained from Heckel Plots for Composite Particles, MCTS, Starlac®, Cellactose® and MCC.

| Material | K | $P_Y$ ($Mnm^{-2}$) | A | $e^{-A}$ | $D_o$ | $D_A$ | $D_B$ |
|---|---|---|---|---|---|---|---|
| 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 |
| Microcrystarcellactose (B3) (35:35:30) | 0.02 | 50.0 | 1.8 | 0.165 | 0.318 | 0.835 | 0.517 |

**Table 5**: Parameters obtained from Kawakita plot

| Material | a | 1/a | 1 – a | 1/b | $P_K$($MNm^{-2}$) |
|---|---|---|---|---|---|
| Starlac® | 0.526 | 1.9 | 0.474 | 19.1 | 19.1 |
| Cellactose® | 0.714 | 1.4 | 0.286 | 17 | 17 |
| Mcc | 0.769 | 1.3 | 0.231 | 18.6 | 18.6 |
| Microcrystar-cellactose B3 (35:35:30) | 0.680 | 1.47 | 0.390 | 17 | 17 |

**Table 6:** Tablet properties of compacts at the limiting in-take of the Active Ingredient

| Tablet | Model drug | Dilution capacity (%) | Tablet hardness (N) | Friabilty (%) | Disintegration time (s) | Remark |
|---|---|---|---|---|---|---|
| MSCL3/ PCM | PCM | 45± 2 | 70± 1 | 0.5±0.0 | 25±2 | Good |
| MSCL3 /AA | AA | 50± 2 | 73±1 | 0.4±0.1 | 119±4 | Good |

**Tablet properties.** MSCL B3 was subjected to compressibility and compactibility 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, 5.0, 7.5, 10.0 and 12.5 KN. Fig.2 compares the compressibility of MSCL B3 with the direct physical mixture of primary excipients. The various granule fractions of MSCL curves show a nonlinear early part followed by progressive increase in compact radial tensile strength with pressure, and all the fractions possessed better compactibility property than the physical mixture of the primary excipients. There is agglomeration of particles and higher porosity in coprocessed MSCL3. Application of pressure yield increase surface area thereby creating more bonds than in direct physical mixture of the component. As the porosity approaches zero, plastic deformation could likely be the

predominant mechanism for all powder material [14,15]. The composite granules Heckel plot curve (Fig.4) has two portions, and the early part representing consolidation as a result of fragmentation, and some degree of plastic deformation, followed by a linear portion illustrating the consolidation behavior as a result of plastic deformation.

**Disintegration Time** The presence of starch granules in MSCL B3 is expected to impact disintegration property. The disintegration time (DT) is mostly influenced by tablet hardness. Fig.3 shows the effect of increasing compression load on disintegration time for MSCL B3, Starlac®, Cellactose® and MCC. Disintegration time increases with increase in tablet hardness, which is proportional to the applied pressure. The DT for MSCL B3 compacts formed between compression force 2.5 N and 12.5 N ranges from < 0.7 min. to 3 min. The corresponding values for Starlac and Cellactose are: all < 1 min., and < 1 min to 17 min., respectively (Fig.2). The B.P.C (1988) specified standard for conventional tablet to be 15 min. MSCL with disintegration time of 3 min. can be regarded as having a good inherent disintegrant property.

**Friability MSCL B3.** Fig.3 shows the effect of increasing compression pressure on the friability of MSCL B3 compacts. There is a direct relationship between tablet hardness and compression pressure. Friability declined with both increase in compression pressure and tablet hardness. It can be seen that as the compression pressure increases from 2.5 N to 12.5 N, friability also decreases from 1.05 % to 0.25 % for MSCL B3.

**Densification behavior of MSCL – $B_2$.**

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

$$\text{In } 1/[1 - D] = kp + A$$

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 [16]. 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. 4 shows the plot of ln 1/[1 – D] *vs* $p$ for the micro-structured MSCL B3, Starlac®, Cellactose® and MCC. The plot of MSCL B3 is divided into three-phases, namely: 29 $MNm^{-2} < p < 58$ $MNm^{-2}$, 58 $MNm^{-2} < p < 116$ $MNm^{-2}$, and 116 $MNm^{-2} < p < 144$ $MNm^{-2}$, each of which basically obeys the Heckel equation. There is nonlinearity in the first phase (early stage) at low pressure, which suggests that MSCL B3 undergo fragmentation and rearrangement before plastic deformation [17]. Under low pressure ($p < 58$ $MNm^{-2}$) the compaction is as a result of elimination of voids among the loose particles through rearrangement, fragmentation and some degree of plastic deformation, leading to rapid densification of the new filler-binder. On the second phase from ~58 $MNm^{-2}$ to ~116 $MNm^{-2}$, however, plastic deformation could be responsible for the densification of the composite 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 3 showed values of the mean yield pressure, $P_y$; the relative densities $D_o$, $D_A$, and $D_B$ for MSCL B3, Starlac®, Cellactose® 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 [18]. The $P_y$ obtained for MSCL B3, Starlac®, Cellactose® and MCC are: 50.0 $MNm^{-2}$, 143 $MNm^{-2}$, 24.2 $MNm^{-2}$ and 25 $MNm^{-2}$ respectively. From the values of $P_y$ stated above, MSCL shows slower onset of plastic deformation than Starlac®, Cellactose® and MCC. The yield value ($P_k$) for MSCL B3 reflects better densification at low pressure than Starlac®, Cellactose® and MCC. Shangraw and his team [19] explained

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 is also applicable to pharmaceutical powders for both single and multi-component systems [20,21]. $D_A$, represents the total degree of densification at zero and low pressures [22-24]. $D_o$, describes the initial rearrangement phase of densification as a result of die filling. $D_o$ is the ratio of bulk density at zero pressure to the true density of the powder. 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 MSCL, Starlac, Cellactose and MCC are: 0.470, 0.413, 0.298 and 0.258 respectively. These results show that MSCL is more densify during the die filling than Starlac®, Cellactose® and MCC. The $D_B$ values for the same set of materials are: 0.162, 0.404, 0.157 and 0.642. These results reflect the degree of fragmentation at low pressure in the following order: MCC>Starlac®>MSCL B3>Cellactose ®. Khan and Rhodes [25] reported some degree of fragmentation in MCC with increase in compression load. Nystrom *et al.* [26] observed that high $D_B$ values are the results of fragmentation while low $D_B$ values are caused by plastic deformation.

**Plot of Kawakita equation.** The Kawakita equation [8] can be written as:

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

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. 5 shows the plot of $p/C$ *vs* $p$ for MSCL B3,"Starlac®, Cellactose® and MCC. It could be seen 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 MSCL B3 is consistent with prediction from the Kawakita equations. By best fitting of the experimental data to the equation above one obtains:

$$p/C = 1.64\ p + 26.73$$

Hence, by relating the two formulae above, the value of "a" is obtained as 0.610 and "b as 0.0613 (1/b = 16.3).

The $D_i$ (=1 – a) indicates the packed initial relative density of tablets formed with little pressure or tapping [13]. Table 5 shows the $D_i$ values for MSCL B3, Starlac®, Cellactose® and MCC as: 0.390, 0.474, 0.286, and 0.231 respectively. It can be seen that at low pressure MSCL B3 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 5 shows the values of 1/b ($P_k$) obtained for MSCL B3, Cellactose®, MCC and Starlac® as: 17.0, 17.0, 18.6, and19.1 respectively. The reciprocal of b yields a pressure term, $P_k$, which is the compression pressure, required to reduce the powder bed by 50 % [12]. 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 [17]. The pressure term $P_k$ has been shown to provide a measure of the total amount of plastic deformation occurring during compression [18]. Hence, from the results of $P_k$ values, MSCL B3 is as good as Cellactose® but more plastically deformed during compression than Starlac®, and MCC.

**Dilution capacity.** Table 6 shows the summary of the result of the dilution potential. MSCL B3 was compacted with

paracetamol and ascorbic acid in predetermined percentages as model drug (API).One can see that MSCL B3 was able to form acceptable compact with maximum of 45 % of the former (crushing strength is 70 N and friability, 0.5 %, disintegration time, 25 s.), and with 50 % of the later (crushing strength is 73 N and friability, 0.4 %, disintegration time, 119 s.). Hence, MSCL B3 – PCM- 45 % and MCTS – AA – 50 % are both acceptable dilution capacity/potential. MSCL B3 can therefore be used for formulating poorly compressible API, highly compressible, moisture sensitive and large dose API.

The *in vitro* drug release study (Fig. 6), showed dissolution efficiency (DE) for MSCL B3 in PCM and in AA tablets as 7.5 and 6.0 min respectively. The corresponding values for cellactose in PCM and AA tablets are: 11.5 and 10 min respectively. The $D_{90\%}$ for the former were determined as: 18 min and 16 min respectively, while for the later were found to be 41 and 36 min respectively (Fig. 6).

**Conclusion.** MSCL B3 have improved functionality over direct physical mixture of the primary excipients. The compression pressure, required to reduce the powder bed by 50 % (onset of plastic deformation) $P_y$ (yield value) are: Cellactose (24.2 $MNm^{-2}$) > MCC (25 $MNm^{-2}$) > MSCL B3 (50 $MNm^{-2}$) > Starlac (143 $MNm^{-2}$). The degree of plastic deformation occurring during compression ($P_k$) is in the following order: MSCL B3 (17 $MNm^{-2}$) = Cellactose® (17 $MNm^{-2}$) > MCC (18.6 $MNm^{-2}$) > Starlac® (19.1 $MNm^{-2}$). From these two parameters ($P_y$ and $P_k$), MSCL B3 has been established to be more superior to Starlac®, and MCC, but equal in functionality to Cellactose®.

Considering the results of the compact studies and the DE and $D_{90\%}$, MSCL B3 can be used to formulate poorly compressible and moisture sensitive API.

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