FORMULATION AND EVALUATION OF A 2-COMPONENT COMPOSITE EXCIPIENT "MICROCRYSTARLAC" AS A FILLER-BINDER FOR DIRECT COMPRESSION

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ABSTRACT: A 2-component composite filler- binder was designed and evaluated for direct compression properties. Tapioca starch (NTS) was modified physically at molecular level by annealing and enzyme hydrolyzed to obtain microcrystalline tapioca starch (MCTS) which was coprocessed with α-lactose monohydrate (LMH) to form Microcrystarlac (MSL). NTS was extracted from cassava tuber (*Mannihot esculenta crantz*) 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 coprocessed with α- lactose monohydrate (α-LMH) at concentrations of 10 to 50 % w/w as a dried mass relative to MCTS. Granule size ranges >75 - 250 µm, and >90 - 250 µm were characterized and compacted at a range of compression load 2.5 to 12.5 KN. Average flow rate, angle of repose and compressibility index were 3 g/s, 32^{o}, 22 % respectively for MSL (granule size range >90 - 250 µm and component ratio, 50:50). The corresponding values for the direct physical mixture of MCTS and lactose are 0.65 g/s, 40^{o}, 53 % respectively. MSL shows improved functionality over direct physical mixture of the primary excipients. MSL was compared with Starlac®, Cellactose® and MCC. The onset of plastic deformation P_y (yield value) are: Cellactose (24.2 MNm^{-2})>MCC (25 MNm^{-2})>MSL (68 MNm^{-2})>Starlac (143 MNm^{-2}). The degree of plastic deformation occurring during compression (P_k) is in the following order: MSL (16.4 MNm^{-2})>Starlac®(17 MNm^{-2})>MCC (18.6 MNm^{-2})>Cellactose® (19.1 MNm^{-2}). MSL is more superior in functionality than Starlac, Cellactose and MCC. The dilution potential obtained for MSL when compacted with paracetamol (PCM) and ascorbic acid (AA) as active drug (API) were: 45 %w/w PCM with MSL, 30 %w/w AA with MSL. The hardness of MSL containing 45 %w/w PCM, was 80 N. MSL can be employed to formulate harder tablet especially poorly soluble and poorly compressible API.

Key words: Microcrystarlac, Coprocessed, Direct compression, Filler-binder, Microcrystalline Tapioca Starch.

INTRODUCTION

The continued popularity of solid dosage forms, the growing performance expectations of excipients to address issues such as disintegration, dissolution and bioavailability also placed a demand for newer excipients with high functional property. Due to these, developing new grades of existing excipients has been the most successful strategy for the development of new excipient in past three decades (Shangraw and Wallace, 1981). New combinations of existing excipients are the options for improving excipient functionality because all formulations contain multiple excipients. Over the years, the development of single - bodied excipient combinations at a subparticle level, call coprocessed excipients, has gained importance (Moreton, 1996).

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The combination of excipients chosen should complement each other to mask the undesirable properties of individual excpients and, at the same time, retain or improve the desired properties of excipient. 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. Maarschalk and Bolhius, (1999), reports coprocessing performed 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) (Maarschalk and Bolhius, 1999). This particular 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 (Casahoursat *et al.,* 1988). 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. In this research, such principle will be employed to design a two component composite filler-binder for direct compression comprising of large amount of enzyme hydrolyzed tapioca starch and α-lactose monohydrate.

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.

Preparation of Two Component Composite Filler-Binder (Microcrystarclac) by Codried method

Table 1: The working formular for preparation of the novel two component composite excipient (microcrystarlac)

Material	Batch				
	%(w/w)				
	1	2	3	4	5
MCTS (g)	90	80	70	60	50
Lactose (g) (α – L-MH)	10	20	30	40	50

A modified method of Tsai *et al* (1998) was adopted for coprocessing the two powder materials to yield 2-component composite granules. The slurry form of annealed enzyme hydrolyzed tapioca starch (MCTS) (sieved fraction, <75 µm) was coprocessed with α- lactose monohydrate (α – L-MH) (sieved fraction, <75 µm. 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, at concentrations of 10 – 50 %w/w as a dried mass relative to MCTS as shown in Table 1. 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 microstructuring 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: MSL and MSL (5 batches) 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), Microcrystarlac (B_4 and B_5), 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 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.

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:

$$MC = (1 - W_t/W_0) \times 100 \quad \text{----------(2)}$$

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 Jones and Pilpel (1966).

$$\theta = \tan^{-1}(h/r) \quad \text{.....(3)}$$

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 Kothari (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.....(4)**

Tapped density (D_t) = Mass/ V_t .....(5)

Carr's Index

The ability of the granules to undergo volume reduction (densification) was derived from the following equation.

CI (%) = $100(V - V_t) / V = 100 (D_b - D_t)/ D_b$.....(6)

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, capcity 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

$$Vc = h\pi r^2 \quad \text{..... (7)}$$

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

$$\text{Compact density } (\rho) = \frac{\text{Weight of tablet}}{\text{Volume of tablet}} \quad \text{..... (8)}$$

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

$$T = 2P/HD\pi \ (N/m^2) \quad \text{.....(9)}$$

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

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

$$C.P. = \frac{\text{Applied force}}{\text{Surface area of tablet}} \quad \text{.....(10)}$$

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 MCTS, microcrystarlac and microcrystarcellac. Formulations were blended by method of dilution and lubricated with 1 % magnessium stearate. Each batch was compressed for 30 seconds on single punch Carver hydrolic 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 vernial caliper. Crushing strength was determined using an electronic/digitalized tablet hardness tester (model EH O1, capcity 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).

RESULTS AND DISCUSSION

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

Material	Flow rate g/sec	Angle of Repose (o)	Bulk density g/cm^3	Tapped density g/cm^3	Compressibilty index %	Hausner Ratio
NTS	2	43.4	0.545	0.817	50	1.5
MCTS(>75-250 µm)	2.5	24.5	0.516	0.712	38	1.4
MSL-B4 (>90-250µm)	6	17.5	0.615	0.696	13.2	1.13
MSL-B4 (>75-250µm)	2.5	27.4	0.625	0.833	33.3	1.33
MSL-B5 (>90-250µm)	3	32	0.605	0.813	34	1.12
MSL-B5 (>75-250µm)	2.1	33	0.683	0.833	22	1.2
MCTS+LMH B_5 (50:50) Physical mixture	0.65	40.2	0.510	0.781	53	1.53
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	59.4	1.6

NB. MSL, MCTS, NTS, and LMH represent: microcrystarlac, microcrystalline tapioca starch, native tapioca starch, and α-lactose monohydrate. B4 and B5 represent batch 4 and batch 5. Batch 4 consist of MCTS, and LMH in ratio 60 : 40 %; while batch 5 consist of MCTS, and LMH in ratio 50 : 35 %

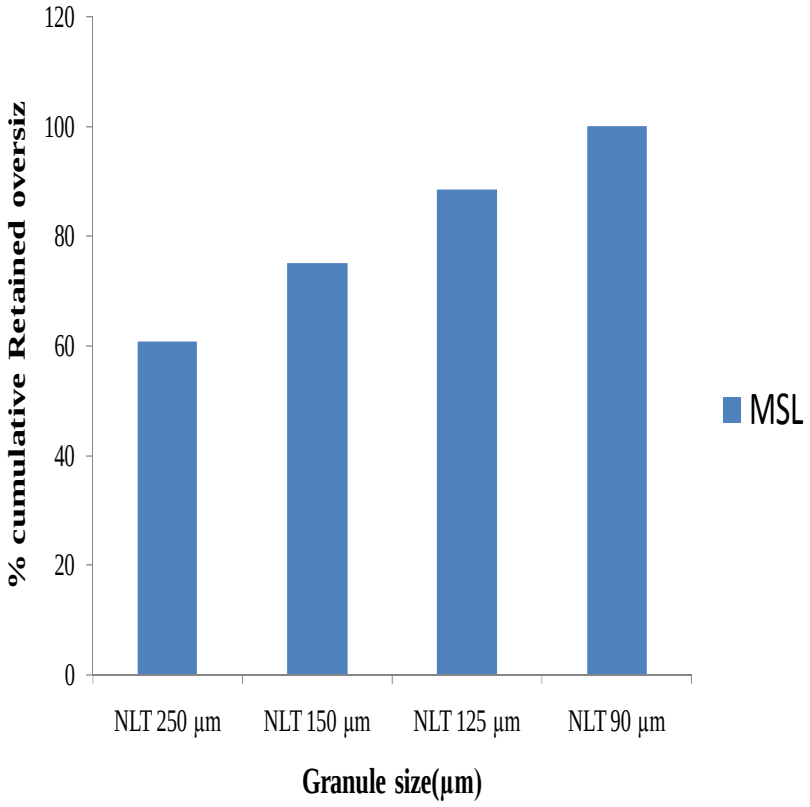

Fig. 1 : Illustrates MSL granule distribution in percent cumulative retained oversize versus granule size(NLT: Not Less Than)

Fig. 2a: Photograph of tablets containing Microcrystarlac,(MSL – B5)

Fig. 2b: Photograph of tablets containing Microcrystarlac 55 % and Paracetamol 45 %, (MSL-PCM 45 %)

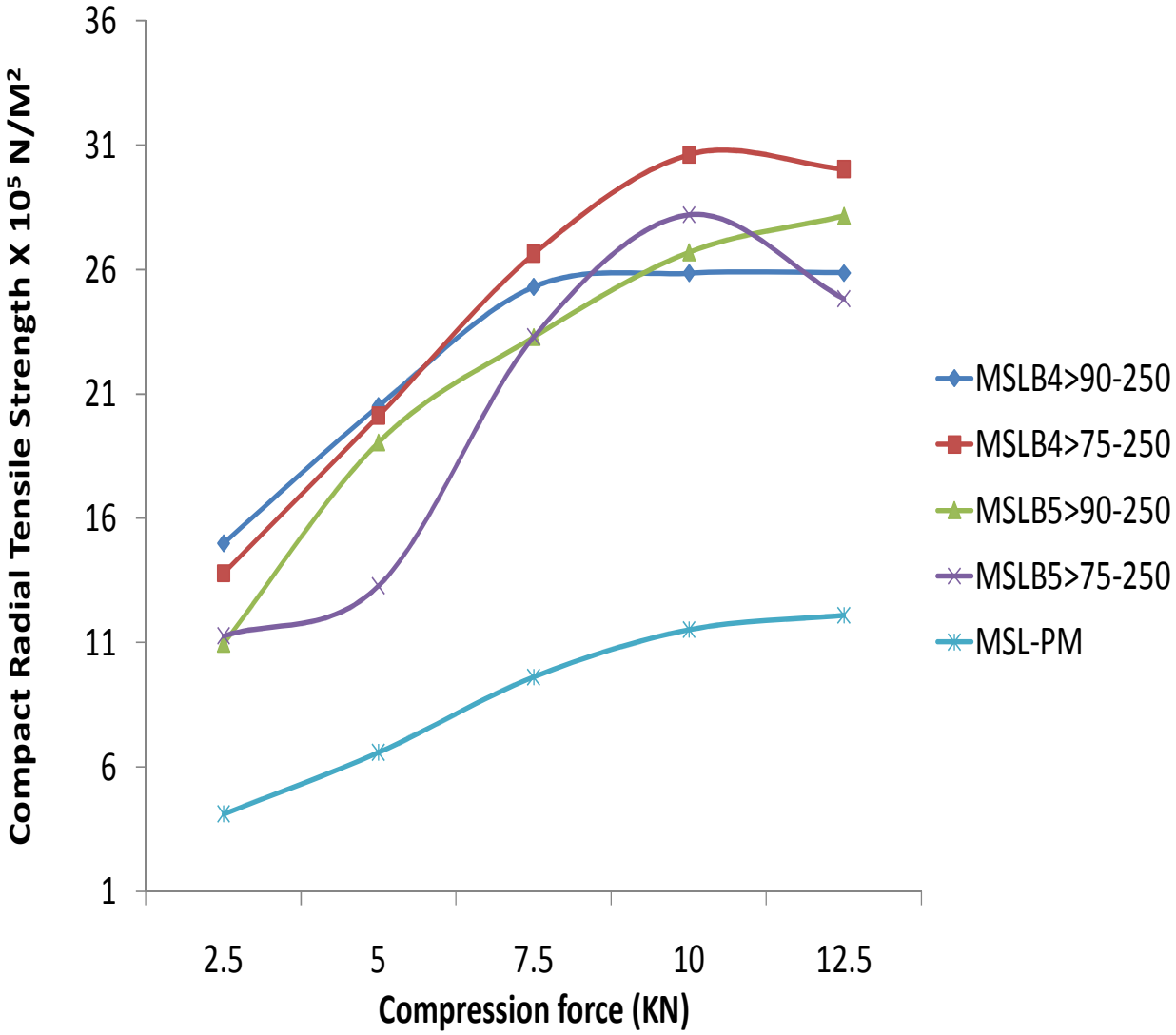

Fig. 3: Effect of compression pressure on tensile strength of microcrystarlac (MSL), and direct physical mixture (MSL-PM -50:50) tablets.

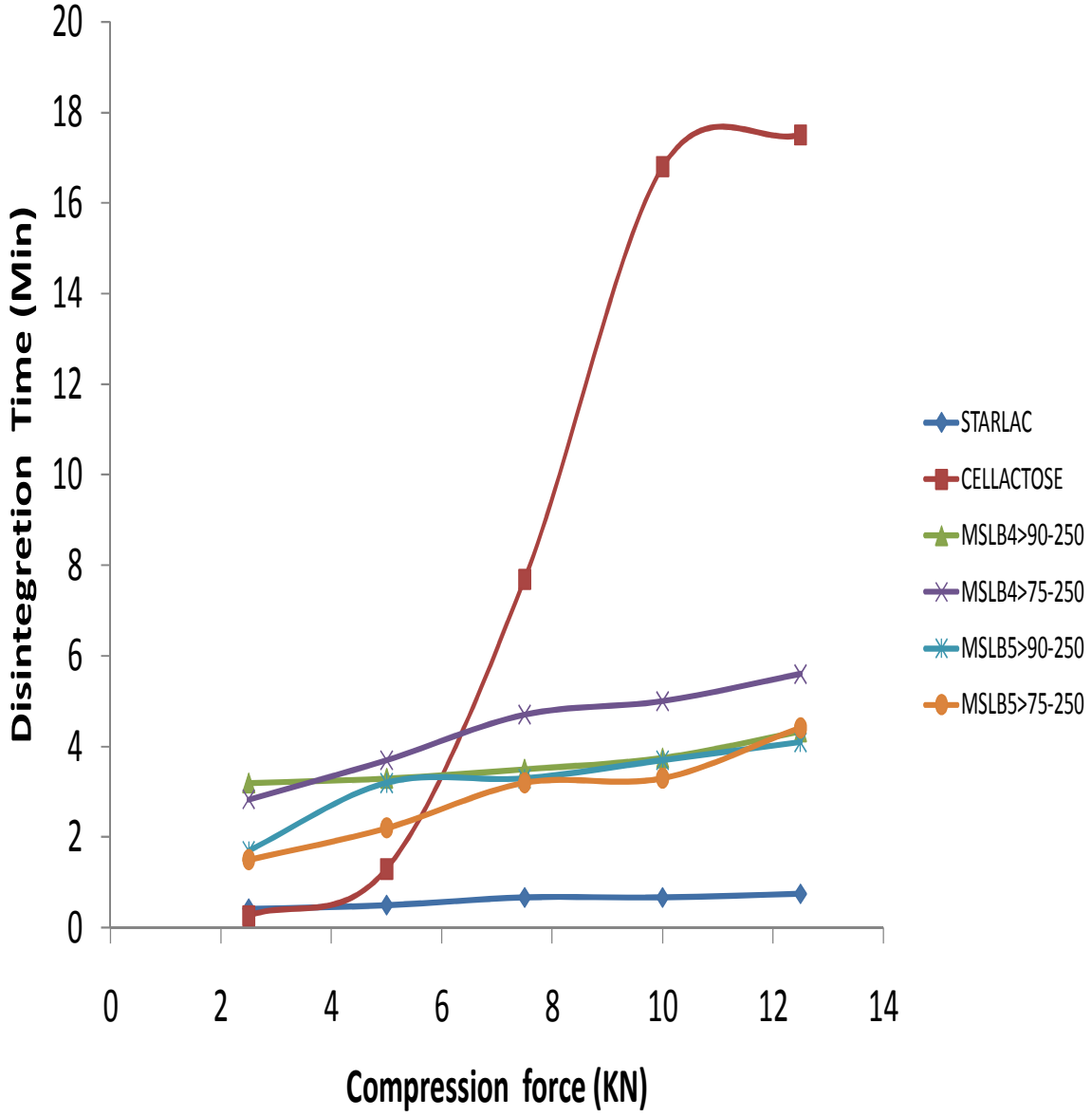

Fig. 4: Relationship between Disintegration Time and compression pressure of compacts containing microcrystarlac (MSL), Starlac, and Cellactose

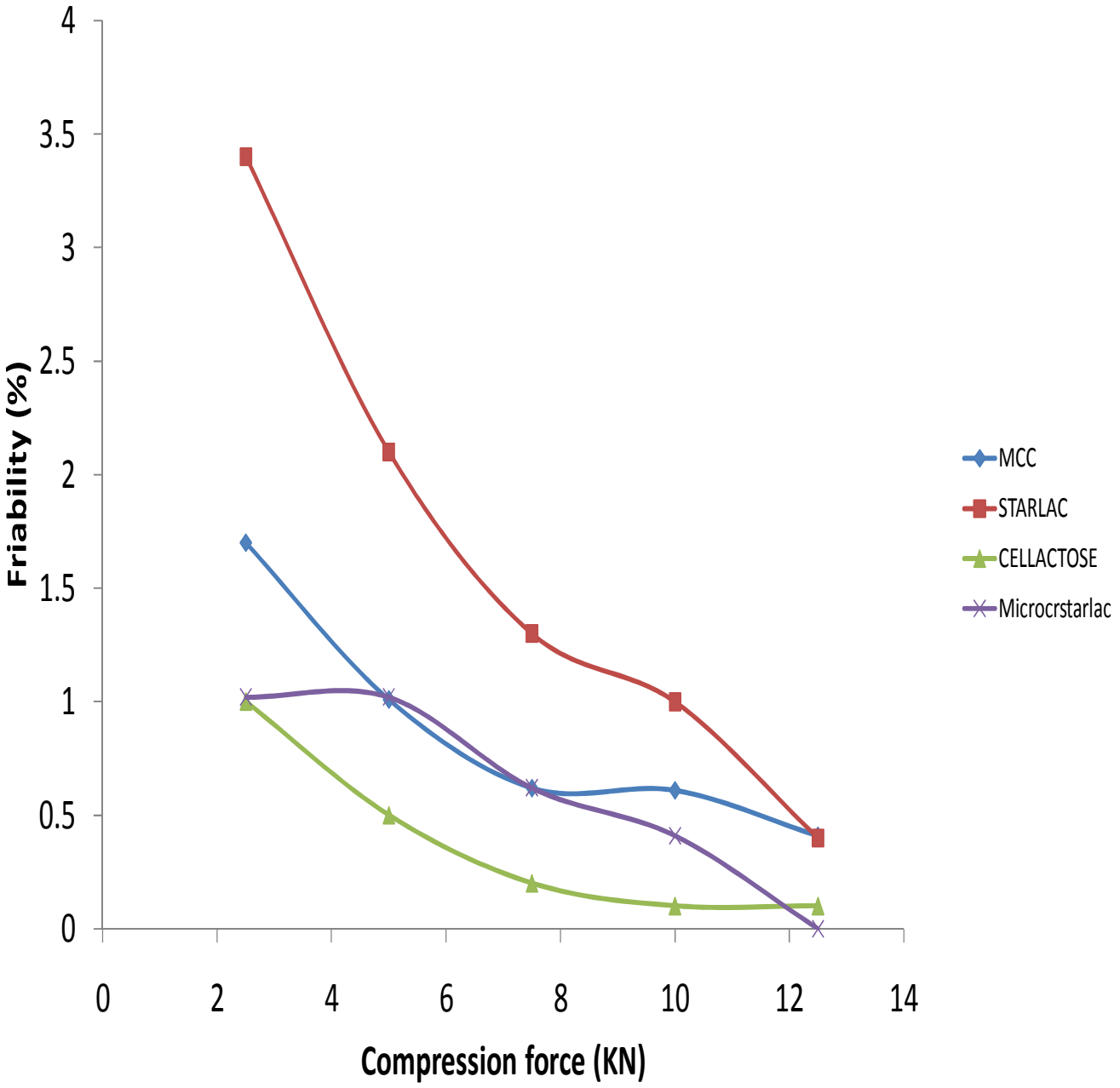

Fig. 5: Influence of increasing compression force on friability of MSL, MSCL, Starlac and Cellactose

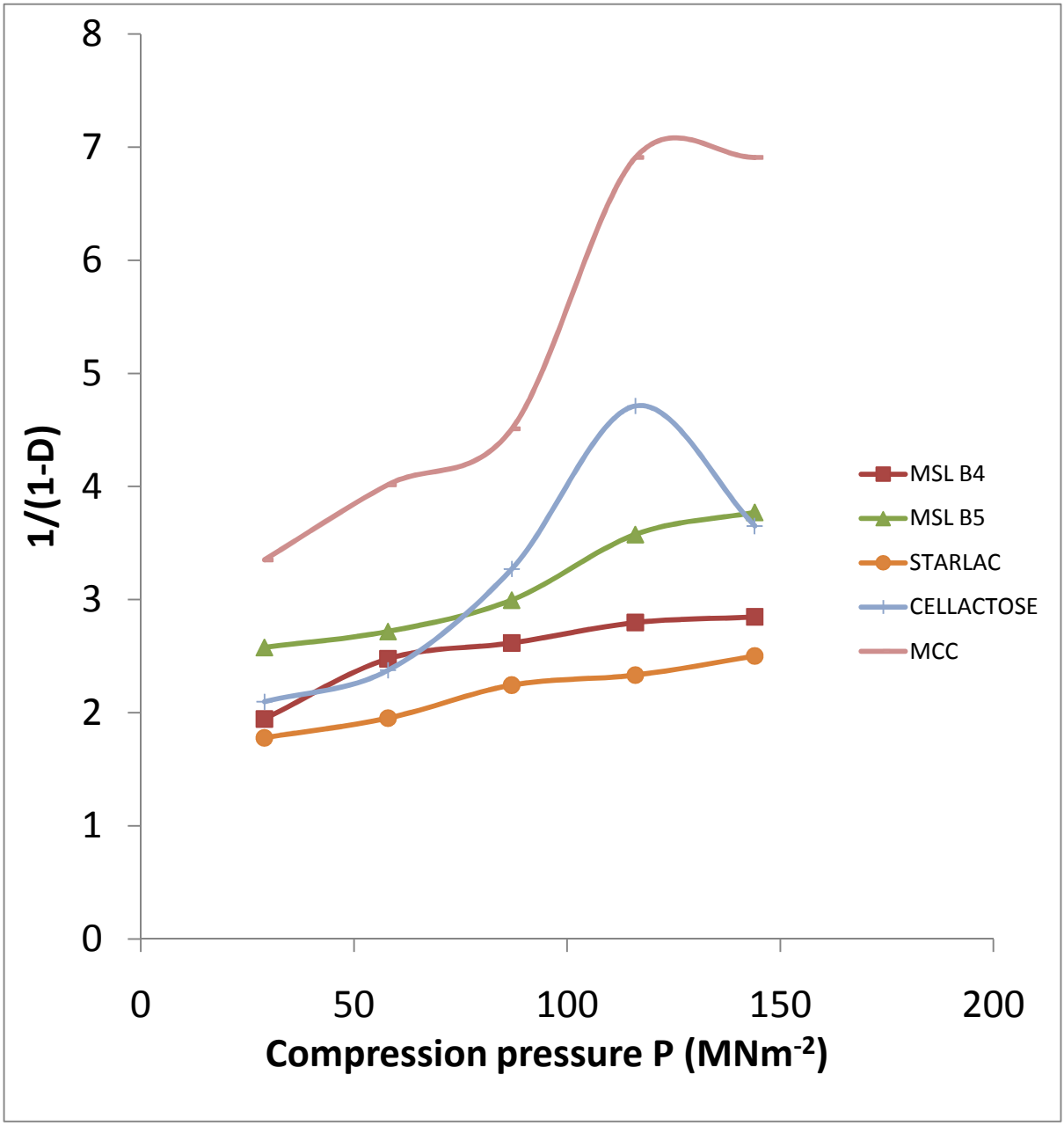

Fig. 6: Heckel's analysis of compact of microcrystalline tapioca starch (MCTS), microcrystarlac (MSL), Starlac, Cellactose, microcrystalline cellulose (MCC).

Table 3: 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
Microcrystarlac (B4)	0.0052	192.3	2.25	0.105	0.453	0.895	0.442
Microcrystarlac (B5)	0.0147	68.0	2.15	0.116	0.425	0.884	0.459
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 represent: initial rearrangement phase of densification, total degree of densification at zero pressure and rearrangement phase of particles in the early stages of compression respectively.

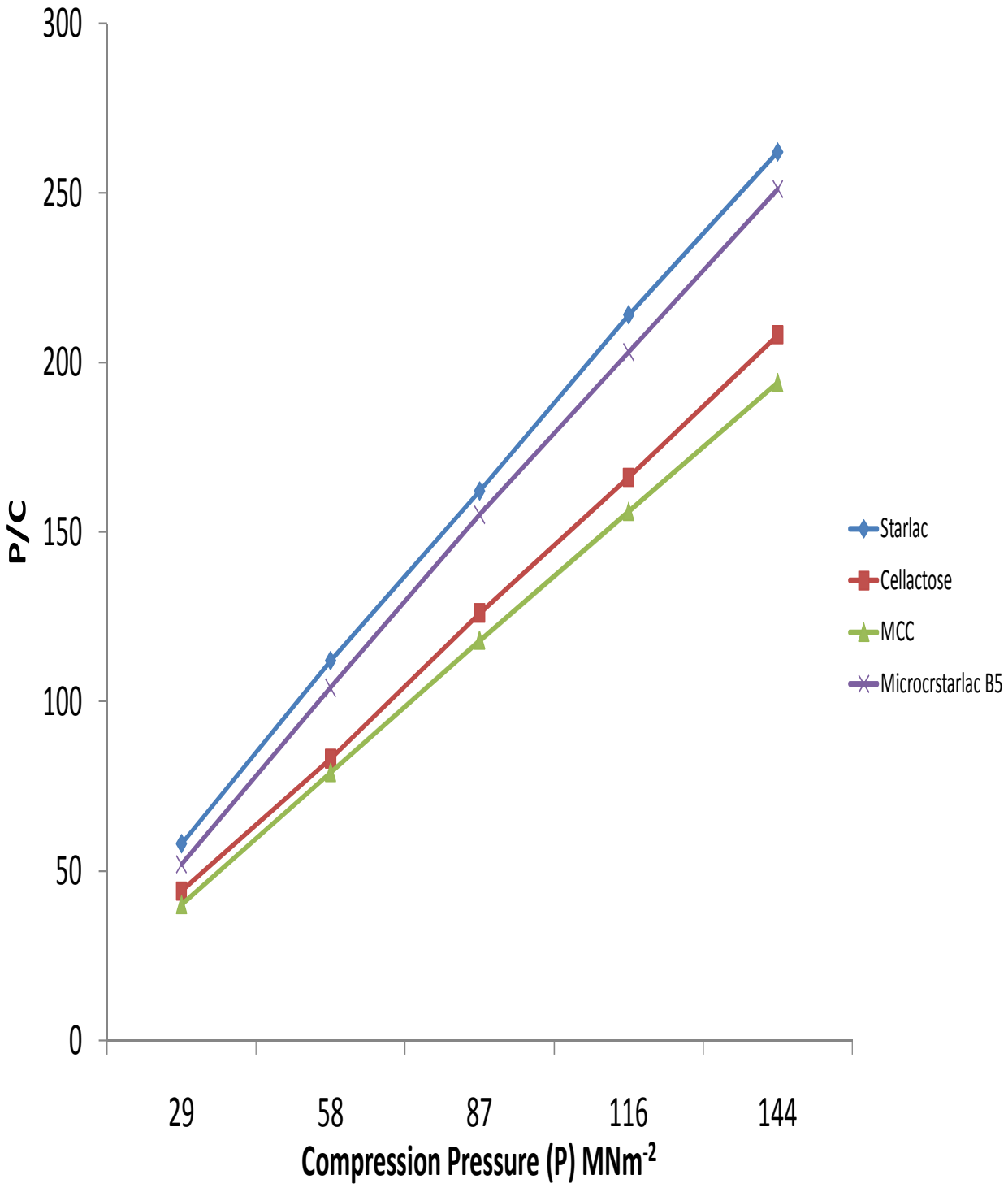

Fig.7 Kawakita analysis of compact of Microcrystarlac(MSL), Starlac, Cellactose and Microcrystalline cellulose

Table 4: 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
Microcrystarlac (50:50)	0.581	1.72	0.419	16.4	16.4

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.

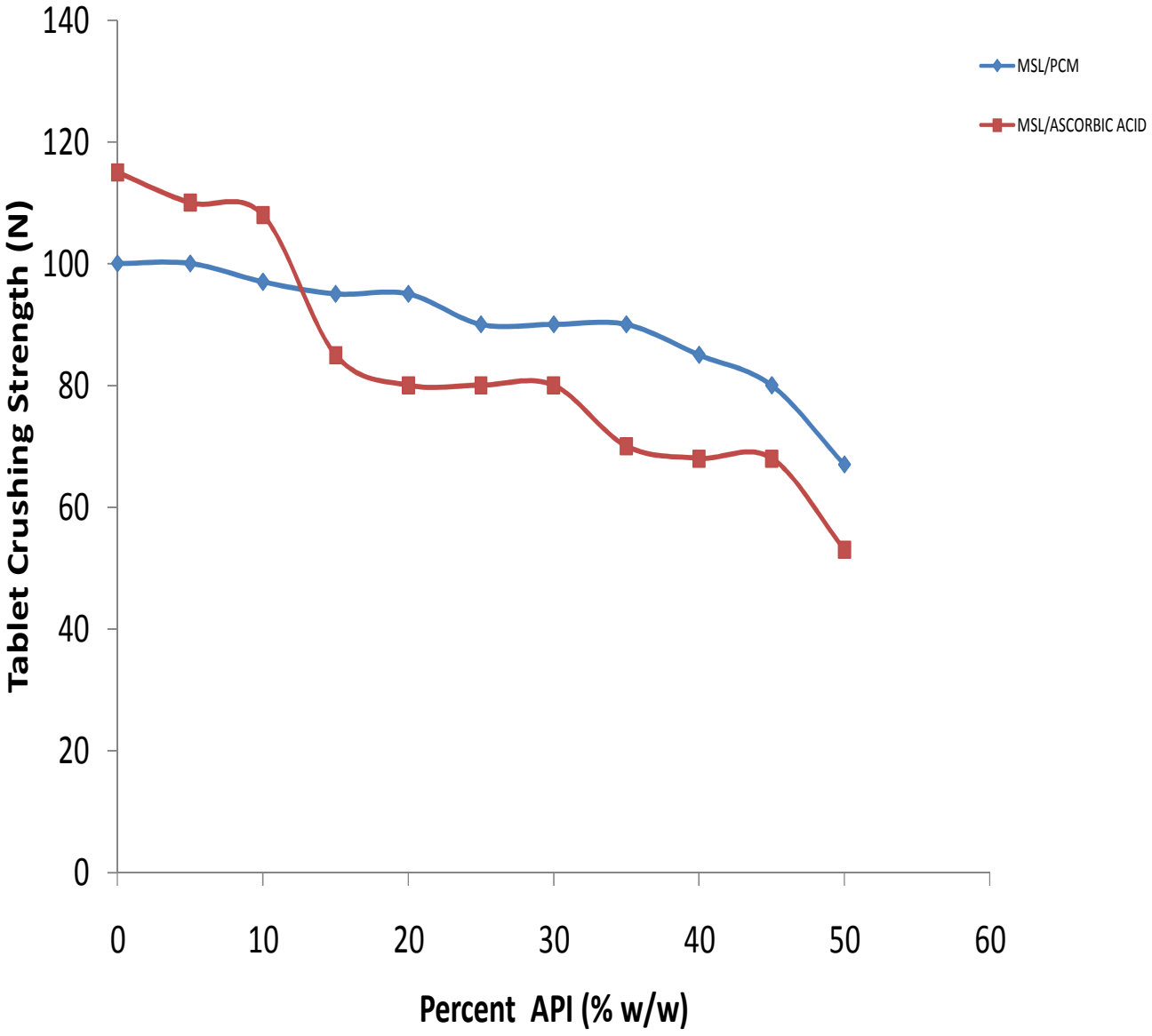

Fig. 8: Relationship between tablet strength and the amount of API that MSL can absorb while still maintaining tablets properties (compacted at 6.0 KN).

Table 5: Tablet properties of compacts at the limiting in-take of the Active Ingrdient

Tablet	Model drug	Dilution capacity (%)	Tablet Hardness (N)	Friabilty (%)	Disintegration Time (Sec)	REMARK
MSL/PCM	PCM	40 45	85 80	0.6 0.7	136 54	Good Good
MSL/AA	AA	30 35	80 80	0.6 1.2	220 214	Good Chipped

NB: MSCL, PCM and AA represent microcrysatarcellac, paracetamol and ascorbic acid respectively.

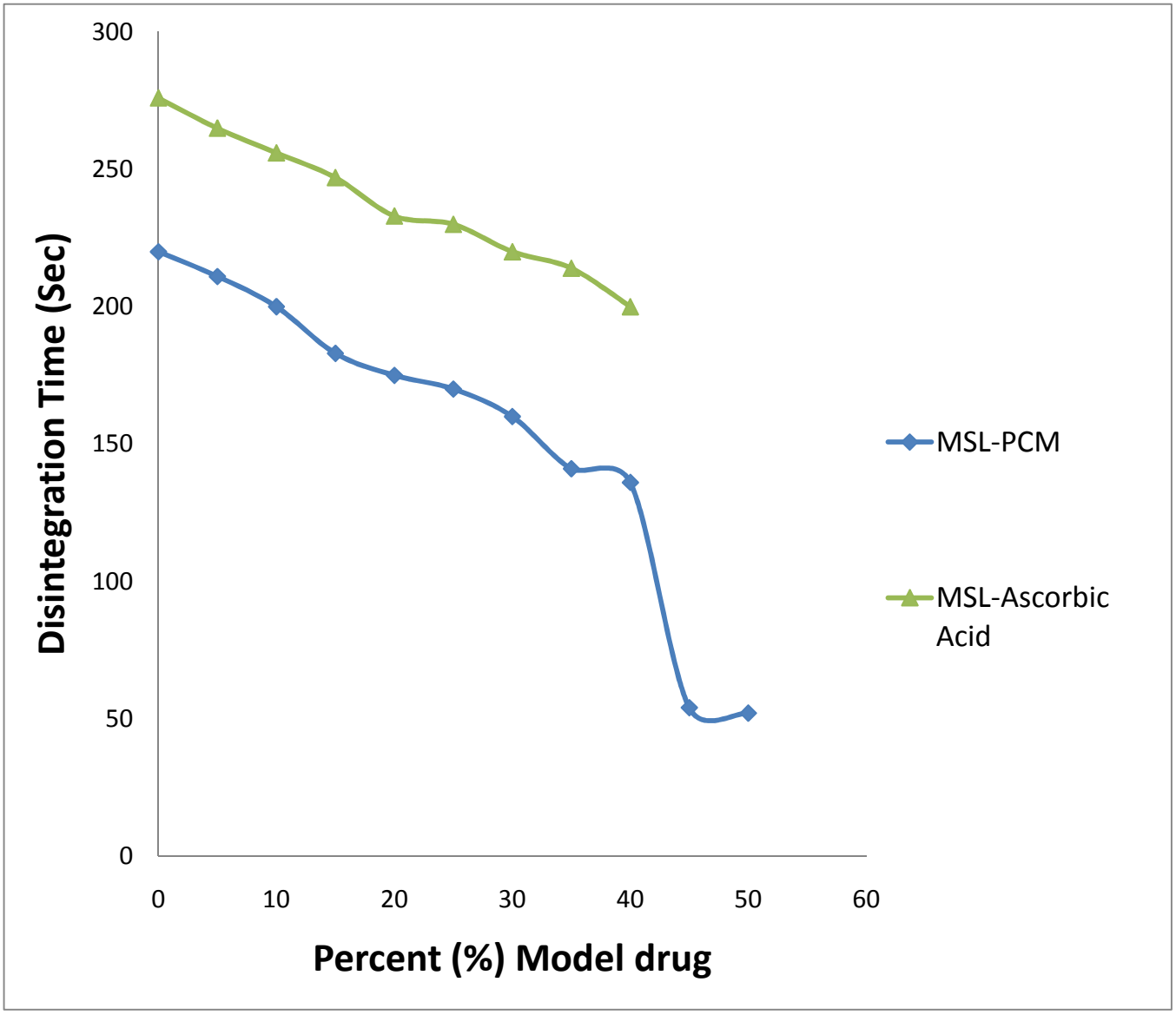

Fig.9: Relationship between tablet disintegration time and the amount of model drug that MSL can absorb while still maintaining tablet properties

Granular Properties

Fig. 1 shows granule distribution of the composite particles of MSL with all the granules (100 %) more than 90 µm out of which over 50 % were greater 250 µm. The percentage ratio of granule distribution used was responsible for the improved flow rate of the composite excipient compare to the physical mixture of the primary excipient. Fig. 2a and 2b show the compacts of coprocessed MSL formed without model drug and with 45 % paracetamol respectively. Table 2 compares the granule properties of coprocessed MSL (MCTS 50 %: LMH 50 %) with the direct physical mixtures of the same ratio, Starlac®, Cellactose® and MCC. The result illustrates an increase in flow properties of coprocessed MSL over that of the direct physical mixture as reflected by flow rate 3 .0 g/s, for the former and 0.65 g/s, for the later respectively. The corresponding angles of repose are 32^o and 42^o respectively. The compressibility indices as reflected in the table are: 34 % and 53 % respectively. All these results point to improve in both flow property and compressibility of MSL after coprocessed over direct physical mixture of the same ratio.

Tablet properties

MSL 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, 1.0, and 12.5 KN. Fig.3 compares the compactibility of various granule fraction of MSL with the direct physical mixture. The various fractions of coprocessed MSL curve show a progressive increase in tensile strength with pressure, and appear more superior to the curve for the direct physical mixture of the primary excipients of the same ratio. This is due to the proper distribution of the granules of MCTS and the particles of LMH within the composite granules thereby preventing segregation and weight variation which is the common problem with the physical mixture as observed here leading to higher standard deviation of tablet weights from the mean. As a result of agglomeration of particles and higher porosity in coprocessed MSL, 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 may be predominant mechanism for all powder material (Heresy and Rees, 1971: York and Pilpel, 1972). The curves are similar to Heckel plot for the same material with the early part showing nonlinearity as a result of fragmentation, rearrangement and elimination of voids, followed by a linear portion illustrating the consolidation behavior as a result of plastic deformation.

Disintegration (DT) MSL The presence of starch granules in MSL is expected to impact disintegration property. The disintegration time is mostly influenced by tablet hardness. Fig.4 shows the effect of increasing compression force on disintegration time for MSL, Starlac, Cellactose and MCC. Disintegration time increases with increase in tablet hardness which is proportional to the applied pressure. The DT for all the compacts of MSL formed between compression force 2.5 N and 12.5 N ranges from < 2min. to 4 min. The B.P.C (1988) specified standard for conventional tablet to be 15 min. MSL with disintegration time of 4 min. can be regarded super disintegrating property as expected of a good coprocessed filler-binder.

Friability MSL Fig.5 shows the effect of increasing compression pressure on the friability of MSL 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 1.0 % to 0.0 % for MSL.

Densification behavior of MSL

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 (Heckel, 1961). 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. 6 shows the plot of ln 1/[1 – D] *vs* p for MSL, Starlac®, Cellactose® and MCC. The plot of MSL 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 (early stage) at low pressure which suggests that MSL 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 MSL. On the second phase from ~87 MNm^{-2} to ~116 MNm^{-2} , however, plastic deformation of MSL particles would be responsible for the densification of MSL 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 show values of the mean yield pressure, P_y; the relative densities D_o, D_A, and D_B for MSL, Starlac®, Cellactose® and MCC. P_y, is inversely related to the ability of the material to deform plastically under pressure. Low value of $\mathbf{P_y}$ indicates a faster onset of plastic deformation (Odeku and Itiola, 1998). The P_y obtained for MSL, Starlac®, Cellactose® and MCC are: 68 MNm^{-2}, 143 MNm^{-2}, 24.2 MNm^{-2} and 25 MNm^{-2} respectively. From the values of P_y stated above, MSL shows faster onset of plastic deformation than Starlac®, but slower than Cellactose® and MCC with lower P_y value. The yield value of MSL reflects better densification at low pressure than Starlac® but less than Cellactose® and MCC. Shangraw *et al.,*(1981) explains 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

vise visa. 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; Mitrevej *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. 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 3 the D_o values for MSL, Starlac, Cellactose and MCC are: 0.425, 0.413, 0.298 and 0.258 respectively. These results show that MSL is more densify during the die filling than Starlac®, Cellactose® and MCC. The D_B values for the same set of materials are: 0.459, 0.404, 0.157 and 0.642. These results reflect the degree of fragmentation at low pressure in the following order: MCC>MSL>Starlac®>Cellactose®. Khan and Rhodes, (1975) has reported some degree of fragmentation in MCC with increase in compression pressure. 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. 7 shows the plot of p/C *vs* p for MSL,"Starlac®, Cellactose® and MCC. 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:

$$p/C = 1.72\ p + 28.13$$

Hence, by relating the two formulae above, the value of "a" is obtained as 0.581 and "b as 0.0609 (1/b = 16.4). The D_i (=1 – a) indicates the packed initial relative density of tablets formed with little pressure or tapping (Lin and "Chain, 1995). Table 4 shows the D_i values for MSL, Starlac®, Cellactose® and MCC as: 0.419, 0.474, 0.286, and 0.231 respectively. It can be seen that at low pressure MSL 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 4 shows the values of 1/b (P_k) obtained for MSL, Starlac®, Cellactose® and MCC as: 16.4, 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. 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, MSL is more plastically deformed during compression than Starlac®, Cellactose® and MCC.

Dilution capacity/potential

Fig.8: shows the relationship between tablet strength and the amount (in percentage) of API that MSL 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 5 shows the summary of the result of the dilution potential. MSL was compacted with paracetamol and ascorbic acid in predetermined percentages as model drug (API).One can see that MSL was able to form acceptable compact with maximum of 45 % of the former (crushing strength is 80 N and friability, 0.7 %, disintegration time, 54 sec.), and with 30 % of the later (crushing strength is 80 N and friability, 0.6 %, disintegration time, 214 sec.). Hence, MSL – PCM- 45 % is more acceptable dilution capacity/potential than MCTS – AA – 30 %.

Disintegration MSL-Model drug Fig. 9 shows the declining disintegration time with increasing percentage API. It can be seen that the disintegration time of MSL – PCM and MSL – AA ranges between ~220 sec. down to ~50 sec., for the former and ~275 sec. down to 200 sec for the later respectively. One can see that the disintegrant properties of MSL 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

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. MSL shows 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})>MSL (68 MNm^{-2})> Starlac (143 MNm^{-2}). The degree of plastic deformation occurring during compression (P_k) is in the following order: MSL (16.4 MNm^{-2})>Starlac®(17 MNm^{-2}) >MCC (18.6 MNm^{-2})>Cellactose® (19.1 MNm^{-2}). From these two parameters (P_y and P_k), MSL has been established to be more superior to the three standard excipients namely: Starlac, Cellactose, and MCC.
The dilution potential obtained for MSL, compacted with paracetamol (PCM) and ascorbic acid (AA) as active drug

(API) are: 45 % PCM with MSL, 30 % AA with MSL. The corresponding hardness is 80 N for the former and 80 N for the later. MSL can be employed preferably to formulate hard tablet especially poorly soluble and poorly compressible API

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