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MICROWAVE GENERATED MULTIFUNCTIONAL PHARMACEUTICAL EXCIPIENT DERIVED FROM MICROCRYSTALLINE CELLULOSE–STARCH MICROPARTICULATE COMPOSITES: STATISTICAL DEVELOPMENT AND PHYSICOCHEMICAL EVALUATION.

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ABSTRACT

The choice of excipients remains a critical factor in pharmaceutical formulations. Manufacturing and characterization of a novel multifunctional pharmaceutical excipient using Microwave Induced Diffusion Technique (MIND) and its effect on flow, packing and compression properties were evaluated. Microcrystalline cellulose–corn starch composites (MCCS) have been specially prepared by mixing colloidal dispersions of microcrystalline cellulose (MCC) with corn starch (CS) employing the microwave for exercise as multifunctional excipients with direct compression and enhanced disintegration abilities. The I-optimal design was used with parts of starch and microcrystalline as independent variables. The evaluation of agglomerates was done in terms of fines and Carr's index. The tablets manufactured were assessed for their friability, tensile strength and disintegration time. Full and refined models were developed and studied using Regression analysis. The exercise of a composite index was established for the choice of the foremost acceptable batch. These optimized composites were evaluated in terms of the particle size distribution, granular friability, dilution potential study, Kawakita's equation and Heckel analysis and a Paracetamol was used as model drug for the preparation of tablets. Results demonstrates that microwave generated MCCS composites possesses better properties than native MCC and CS. Based on Carr's index, friability, tensile strength, disintegration time and composite index, the batch (O1) containing Corn Starch (30%), Microcrystalline cellulose (70 %) was selected as the optimum. The present study emphasizes the point that the microwave drying technique may be embraced for the economic progression of a multifunctional directly compressible excipient in inclination to the spray-drying technique.

KEYWORDS: Microwave, Microcrystalline cellulose, Corn starch, Microcrystalline cellulose–Corn starch composites, direct compression, Co-processing, Multifunctional excipient.

INTRODUCTION

In the new era, tablets as dosage form will cover 80% of all dosage forms administered to humans. Ease of manufacturing, the convenience of oral administration, precise dosing, and significantly enhanced stability contrasted with oral liquids and semisolids make the tablet a prevailing and versatile dosage form. However, a correlation of wet granulation and direct compression methods highlights the relevant complexity of the former. The major impediments of the wet-granulation method include a enormous processing steps, the inclusion and removal of solvent (usually water), and potential stability problems with thermolabile drugs as well as drugs that degrade by hydrolysis.[1] These factors result in supplemental spending on material handling, equipment, and vitality. Hence, the current inclination in the pharmaceutical industry is passionate to embrace direct compression technology.[2]

Various forms of additives for directly compressed tablet manufacture are developed recently to circumvent economic disadvantages of the inclusion of granulation procedures and to qualify the process. Direct compression is additionally a lot of appropriate for active ingredients that are sensitive to moisture or unstable at high temperatures, and there aren't any variations on the quality into the product.[3] However, the employment of the additives for direct compression of tablets isn't common as a result of the heterogeneous distribution of the active components in every tablet that may be a drawback for very potent medicine administered in little doses. There are limitations on the amounts of additives

to enhance the flowability and compressibility & preventing segregation of the components.[4,5]

The dynamic landscape of the pharmaceutical business is increasing the industrial pressure on R&D teams to shorten time thus on the market new product. Hence, formulators are in a requirement of a set of functionalities and performance from their pharmaceutical excipients. Selecting the simplest excipients, however, may be a juggling act, requiring a balance between time and price efficiencies additionally as anticipated product performance.[6,7]

There are moderately 1,200 pharmaceutical excipients accessible within the confines of the market with diverse functionalities like fillers and diluents, binders, coating agents, disintegrants, flavours, colorants, lubricants and glidants, solvents, preservatives, sweeteners, and antiadherent.[8] Growing variety of ingredients will significantly increase the steps concerned in producing, the complexities in the formulation and ultimately the price incurred. Formulators are currently looking at to be used of excipients with totally different functionalities that are understood as multifunctional pharmaceutical Excipient (MFE). Multifunctional excipients are a category of excipients that has pre-processed and co-processed excipients that give value-added functionalities to the formulation.[9,10] These functionalities embody flowability, compressibility, particle size distribution, shape, porosity, etc. presently there are varied industrial Multifunctional Pharmaceutical excipients are offered like Ludipress (Co-processed milk sugar, PVP), (Co-processed MCC, HPMC, and CPVD), Provosolv ODT (Co-processed Microcrystalline polysaccharide, mixture silica, Mannitol, Fructose, Crospovidone) etc. Shows enhanced functionality.[11-13]

In Current Research work, efforts have been taken to formulation multifunctional pharmaceutical excipients based on Starch and MCC using Microwave induced diffusion as technique. In existing research authors have engendered such system by use of Microwave (MW) irradiation which is green and effective instrument for generating molecular dispersions.[14]

Starches from particular sources have long been employed in tablet formulations as a diluent, binder, and disintegrant depending on the strategy of incorporation and therefore, the amount used. The starch, united states formulary (USP) grade, could also be readily obtained from either the grain of rice, wheat, tubers of potato or tapioca. However, the compressibility and flowability of starch are remarkably poor due to the tiny size vary of starch grains (2-8 μm). It's a self-lubricating agent. However, if the drug content is between 5 - 100 percent, then the addition of alternative lubricating agents is required. It gets muffled once it's combined with massive amounts of magnesium stearate, i.e. larger than 0.5 %.[15]

Between directly compressible fillers, microcrystalline cellulose is that the most compressible and has the best dilution potential. Nevertheless due to the high value and poor fluidity in comparison therewith of most alternative direct compression vehicles, it's typically not used as the sole diluent in tablet formulations, conversely, is conventionally combined with optional direct compression vehicles to enhance the flowability and cut back the price of the product. Due to its high binding and smart disintegrating properties, microcrystalline cellulose is of interest to be combined with alternative less compressible excipients as another element in coprocessed direct tableting excipients as mentioned above.[15]

Although starch shows smart compressibility, it may be even significantly enhanced by addition of MCC. Therefore, it was of interest to make co-processed excipient of starch and MCC. In a current analysis varied techniques had been utilized to express absolute best way to develop Starch- MCC composites.

1. MATERIAL AND METHODS

2.1. Materials

Corn starch (CS) was obtained as a generous gift (UNIVERSALSTARCH-CHEMALLIED, Maharashtra, India.) Microcrystalline cellulose (MCC) was obtained from a commercial source (RanQ Pharmaceuticals & Excipients Pvt. Ltd, Maharashtra, India) Paracetamol and Aspirin was obtained as a gift sample from Glenmark Pharmaceuticals, India.

2.2. Preparation of Composite Particles using Microwave Induced Diffusion

A physical mixture of CS and MCC was prepared by in blending starch and MCC in the desired ratio as per Table 1 (50:50, 40:60 and 30:70). CS and MCC were weighed and co –sifted from the 250-micron sieve. The blend was taken from the stainless steel vessel and desired quantity of distilled water was added to make a slurry under stirring (Table 1). This mix was kept under stirring to get a homogeneous dispersion at 1200 RPM for 12 hours to assure homogenization and association of CS and MCC particles. Obtained mixture was transferred into a glass beaker and microwaved (Catalyst 2R, Catalytic Systems, India.) for 5 minutes at 600 W, obtained slurry was mixed with the help of glass rod. This resulting mixture was exposed to microwave for 8 minutes at 450 W, resulting aggregates were then passed through mesh 20 and then 30 sieves. This mixture was then placed again in a microwave oven at 200 W to obtain a moisture content below 5 % w/w. Obtained aggregates were then passed through mesh 40, 60 and finally 80. The mixture was stored in a screw-capped bottle until needed.

2.3. Experimental Design

In a mixture design wherever the composition is the factor of attention, the levels can't be chosen randomly. All fractions of the components should aggregate to

unity.[16] In a design so constrained a simplex lattice design is strongly suggested.[17] It's every so often physically difficult to use a component over the full factor space. The range over which the components are varied could also be restricted, leading to a tiny low space of interest. Such space is usually an irregular polyhedron encircled by extreme vertices. The solitary design available for this case may be a D-optimal design.[18] D-optimality is illustrated to the covariance matrix of the parameter estimates, thus it will govern that factors are not significant. I-optimality minimizes the average prediction variance with the model so it's more naturally applied when the form as the model is thought, and "good" prediction over design space is desired. For this reason, I-optimality finds a lot of use during an optimization context.[19] Preliminary experiments were performed to select the levels of excipients of the composite variables, which were judged on the mixture's ability to form the best composite. The mixture study was a two-component system, Parts of CS (X1) and Parts of MCC (X2). Based on preliminary investigations the range of each component was selected as per Table 1.

A design expert software package (Version 8.0.4; Stat-Ease, Inc., MN, USA) was employed to generate the pattern. The software selected a set of candidate points as a principal design. These included factorial points (high and low level from the constraints on each factor), centers of edges, constraint planes centroid, axial checkpoint, and an overall Center Point. The base design consisted of 13 runs. This design allowed for the fitting of a full quadratic model on the three responses. The I - optimal experimental domain and the observed responses are shown in Table 2 and in Figure 1. Fitting of the quadratic model for the data was performed with (Version 8.0.4; Stat-Ease, Inc., MN, USA).

2.4. I - optimal Optimization

The aim of the optimization was to get the defined targets for all six responses concurrently with respect to the predefined constraints. At this stage, the outlined anticipated areas of three responses were superimposed, and the region of particular significance was originated.

Table 1: Experimental ranges for independent variables.

Batch Code	Run	Type	Corn Starch: X1 (Parts)	Microcrystalline cellulose: X2 (Parts)	Distilled Water (Parts[1])
MS1	1	Vertex	10.00	90.00	300
MS2	2	Center	20.00	80.00	300
MS3	3	Axial CB	15.00	85.00	300
MS4	4	Vertex	10.00	90.00	300
MS5	5	Axial CB	25.00	75.00	300
MS6	6	Center	20.00	80.00	300
MS7	7	Vertex	30.00	70.00	300
MS8	8	Vertex	10.00	90.00	300
MS9	9	Third Edge	16.67	83.33	300
MS10	10	Third Edge	23.33	76.67	300
MS11	11	Vertex	30.00	70.00	300
MS12	12	Vertex	30.00	70.00	300
MS13	13	Center	20.00	80.00	300
Variable			**Level**		
			Low	**High**	
Parts of starch (X1)			10	30	
Parts of MCC(X2)			70	90	

[1]Parts for manufacturing composites are considered on the g/g basis.

2.5. Evaluation of Microwave generated composites

2.5.1. Moisture Content

The moisture content of composite powder samples was accurately measured by a fast infrared moisture analyzer (METTLER TOLEDO, Germany). Approximately 1 g of each testing sample was dispersed over a disc, and the result was recorded until a constant reading was achieved.[20]

2.5.2. Percentage of fines in composites

The percentage of fines are determined as the percentage of the composites passing through 200# (74 µm). The composites were agitated on an Electromagnetic Sieve Shaker (EMS-8, Electrolab, India) on 200# for 5 min to reveal the percentage of fines. The 30/200 (590/ µm) sieve fraction was used for additional assessment.[21]

2.5.3. Bulk Density and Tapped density determination

The loose bulk density and tapped bulk densities can be determined by using a density measuring apparatus (EDT-1020, Electrolab, India.). An amount of the sample (20 g) is placed on a graduated cylinder, and the volume (bulk volume) is determined after applying three taps. Tapped density is measured by transferring (20 g) of the material to a 100 ml graduated cylinder. The unsettled apparent volume is noted. The cylinder is tapped at a rate of 300 drops/min over a fixed drop distance of 14 ± 2 mm. After the first 500 drops, the volume of the material

within the cylinder is measured. Further tapping (750 and then 1 250 drops successively) is applied for the difference between two volumes following successive tapping is less than 2.0%. This final volume is taken as the tapped volume. Bulk/tapped densities were calculated according to following equations.[22]

$$\text{Bulk density}(\rho b) = \frac{Weight}{Bulk\ volume} \quad (1)$$

$$\text{Tapped density}(\rho t) = \frac{Weight}{Tapped\ volume} \quad (2)$$

2.5.4. Carr's Compressibility Index and Hausner's ratio

This is the percentage difference between the tapped density and the bulk density, conjointly brought up as the compressibility index. Hausner's ratio records the ratio of the tapped to bulk density. The Carr's Compressibility Index and Hausner's ratio were calculated conferring to equations 3 and 4 respectively. Hausner's ratio differs from about 1.2 for a free-flowing powder to 1.6 for cohesive powders. Values of Carr's index of around 5 to 12% indicate free flowing powder; 23 to 35% designate poor flow, and >40% an extremely poor flow.[22,23]

$$\text{Carr's Index} = \left(\frac{\rho t - \rho b}{\rho t}\right) X\ 100 \quad (3)$$

$$\text{Housner ratio} = \frac{\rho t}{\rho b} \quad (4)$$

2.5.5. Angle of Repose

The angle of repose is frequently used to determine the flow of powders and is the maximum angle Θ between the plane of powder and horizontal surface. The value of Θ less than 30° usually manifests free flowing material, up to 40° designates reasonable flow potential, and above 50° indicates the power flows with pronounced difficulty. A clean glass funnel was clamped in a retort stand defined the perpendicular height to the tip of the funnel was 10 cm from the flat table surface with a sheet of paper. 10 g of sample was poured through the funnel, with a gap of funnel stopped up with a cotton wool. This was took off and a powdered heap was shaped. The peak was measured as H (cm). The diameter to the circumference of the heap was divided to give the radius, R. The angle of repose can be calculated using equation 5.[22,24]

$$\tan\theta = \frac{H}{R} \quad (5)$$

Where θ is the angle of repose, H is the height of the powder heap and R is radius of heap base.

2.5.6. Water absorption ratio (%)

A piece of tissue bifold double was placed in a tiny Petri plate with internal diameter 60 mm containing 10 ml water. A tablet was placed in the paper, and the time essential for complete wetting was then calculated. The water absorption ratio (R) was determined using the subsequent equation.

$$\text{Water absorption ratio (R)} = \frac{Wa - Wb}{Wb} X\ 100 \quad (6)$$

Where Wb is the weight of the tablet before water absorption and Wa is the weight of the tablet after water absorption.[25]

2.5.7. Tablet manufacture

The composites (97%) of batches MS1–MS13 was blended with 2% talc for 5 min and with 1% magnesium stearate for 2 min. Tablets were compressed employing a Rimek ten stations rotary tablet machine using 11-mm diameter flat-faced punches and dies (Cadmach Machinery Private Ltd., India). The average tablet weight was 400 mg. The minimum distance between the upper and lower punch was between 0.30 and 0.40 cm throughout the preparation of the tablets.

2.5.8. Tablet evaluation

2.5.8.1. Tensile strength

The assessment of tablet dimensions was done employing a micrometer. The crushing strength was determined after 24 h (time for stress relaxation) of compression, utilizing an Erweka hardness tester (TBH 125 Series, ERWEKA GmbH, Germany.) The tensile strength (MPa) of the tablets was computed using Equation 7 using the diameter (D, cm), thickness (L, cm), and crushing strength (P, kg).[26]

$$T = \frac{0.0624\ X\ P}{D\ X\ L} \quad (7)$$

2.5.8.2. Friability

The friability was computed as the percentage weight loss of 20 tablets tumbled in a friabilator (Model EF2, Electrolab, India) for 4 min at 25 r/min. The dust was took off from the tablets, and the loss in weight often caused by fractures or abrasion was recorded as percentage friability.[27]

2.5.8.3. Disintegration time

Disintegration testing (Model ED2, Electrolab, India) was performed according to USP24 on six tablets at 37ºC in 900 ml distilled water.[28]

2.5.8.4. Calculation of composite index

On accomplishment of the individual tests a weighted composite index was accustomed to obtain a single score using two responses, i.e., Carr's index (%), and Friability (%). As it's difficult to predict the relative influence of distinct constraint to the "true" composite score, a choice was made to allocate an arbitrary value of one-half to each of the two response variables a score 100 for an optimum result for each of the two responses, and each formulation result was remodelled to a value between 0 and 50. For Carr's index, the lowest value (12.00) was

allocated a score equal to 50, and the highest value (40.00) was allocated a score of zero. For friability (%), the lowest value (0.35) was assigned a score of 50 and the highest value (1.45) was assigned a score of zero. The batch having the highest composite index would be viewed as the batch fulfilling the desired standards.

The raw data transformations were as Equation:

$$Value\ of\ Carr's\ index\ or\ friability = \frac{Yi-Ymin}{Ymax-Ymin} X\ 50 \quad (8)$$

Where Yi is the experimental value of the individual response variable and Ymax and Ymin are the maximum and minimum values of the individual response variable, respectively[21,29,30]

$$\text{Composite index} = \text{transformed value of Carr's index} + \text{transformed value of friability (\%)} \quad (9)$$

2.6. Evaluation of optimized composites

2.6.1. Fourier transform infrared (FTIR) spectral study

FT-IR spectra of pure excipients MCC, CS and optimized MCCS composites were taken to access interaction if any between MCC and CS in the microwave treated mixtures. Material to be analysed was blended with potassium bromide (KBr) of IR grade in the ratio of 1:100 and compacted using motorized pellet press (Kimaya engineers, India) at 15 tons pressures. The pellets were then examined using FT-IR spectrophotometer (Shimadzu 8400S, Japan). The FT-IR spectra of mixtures was contrasted with that of the FT-IR Spectra of pure polymers and composites for change if any, in the principal peaks of spectra of pure drug and polymers.

2.6.2. Differential scanning calorimetry

DSC of Pure excipients MCC, CS and optimized MCCS composites were executed to evaluate what changes had actually made when MCCS composites were formed. The samples were kept at DSC reference pan and DSC curves were obtained by Differential Scanning Calorimeter (DSC 60, Shimadzu, Japan) at a heating rate of 10 °C/min from 0 to 300 °C in nitrogen atmosphere.

2.6.3. Determination of particle shape

Motic (optical) microscope together with a digital camera (Olympus) was utilized to evaluate the particle shape in the present study. To start with, all magnification lenses have been calibrated using slide provided by the producer. Composites were transferred to slide, and the slide was fixed in the position along the stagecoach. 10X magnification lens was assigned for determination of particle shape. Then the inbuilt camera was turned on. Later on, the coarse and fine adjustment image were captured by using Motic Images plus 2.0 software.[31,32]

2.6.4. Particle size distribution

Sieving is one in every of the basic ways for classification of powders, and it is the prime method for setting the size distribution of coarse powders. This may be done by sieve size analysis employing a sieve shaker. The particle size distribution was determined using random samples of optimized composites with a nest of standard sieves (100, 120, 140, 170 and 200#). The 100, 120, 140, 170 and 200# have openings of 149, 125, 106, 90 and 74-µm. A 20 g quantity of the powder was placed on the top sieve and the setup was shaken up at an amplitude of 1.50 mm/g for 5 min. The weight of material held on each sieve was found. From the percentage weight of agglomerates retained on each sieve, the mean composite diameter was estimated.[21,22] The average diameter is computed using the equation:

$$\text{Avereage diameter} = \frac{\Sigma(\%\ \text{retained}) X (\text{mean apperture})}{100} \quad (9)$$

2.6.5. True density

The specific gravity bottle methodology was adopted for determination of true density, and acetone was used as displacement fluid. The bottle was cleaned and full of acetone, all spilled over liquid (acetone) was wiped away with an absorbent material. The weight of the bottle filled with acetone was noted as (a), the bottle was emptied, cleaned and dried. 2g of excipient was weighed into the specific gravity bottle, the weight of the composite powder was noted as (w). The specific gravity bottle containing the composite was almost filled with acetone, stirred with glass rods and allowed to stand for 10 minutes for air bubbles to be freed. The bottle was then carefully filled with acetone, and the final weight of the bottle was noted as (b). True density was afterwards calculated as:

$$\ell = \frac{w}{[(a+w)-b]} . S \quad (10)$$

Where ℓ is the particle density of Composite and S is the specific gravity of Acetone = 0.786.[33]

2.6.6. Determination of tablets packing fraction

The packing fraction of the tablets from each size fraction is computed from the particle densities of the tablet compositions. The packing fraction, Pf, is calculated utilizing the following equation:

$$Pf = \frac{W}{\pi r^2 . t . l} \quad (11)$$

Where W is the mean weight of the tablets, r is the radius, t is the tablet thickness, and l is the particle density using fluid displacement method.[34]

2.6.7. Porosity

Porosity is the space between the particles. The volume occupied by powder is known as bulk volume. This can

be inferred from the values of true and bulk densities when fitted into the Equation.[22]

$$\text{Porosity(e)} = \left(\frac{\rho b}{D}\right) X\ 100 \quad (12)$$

Where, ρb is the bulk density, D is the true density, and e is the porosity.

2.6.8. Moisture uptake study

Two grams sample from the optimized composites was dispersed uniformly on a 5 cm diameter Petri dish, and the dish was stored at 75% relative humidity at 40˚C in stability chamber (Newtronic, India). The percent gain in weight was observed after 24 h.[22]

2.6.9. Composite friability index

Composites of the optimized batch were rotated for 5, 10, 20, 30, 40, 50, and 60 min at 25 RPM in a Roche friabilator (model EF2, Electrolab, India). The samples were critically assessed in terms of their particle size distribution, and the mean particle size was calculated. The friability index (FI) was computed as the ratio of the average particle size of the friabilator-treated composites to the mean particle size of the untreated composites (initial). The negative natural logarithm of the friability index of the composites was plotted against the time of rotation in the friabilator. The gradient of the line gave the friability rate constant.[2]

2.6.10. Loading capacity

Compacts incorporating different ratios of binary mixtures of paracetamol and each of the powders of the novel excipients (MCCS composites). The mixtures were such that each of the 400 mg tablets comprised paracetamol and the excipients in ratios (400:0, 300:100, 200:200, 100:300, 0:400). The tablets were prepared by compressing the powder mixtures at a compression pressure of 25 kN using a single press compression machine (Cadmach engineering, Ahmadabad, India.) fitted with an 11.0 mm flat faced punch and die. The compacts were stored in an airtight container for 24 h before evaluation. The tablets were tested for hardness Erweka hardness tester (TBH 125 Series, ERWEKA GmbH, Germany.) and friability (Model EF2, Electrolab, India). The punch and die were lubricated with a 10% (w/v) dispersion of magnesium stearate in ethanol.[35]

2.6.11. Disintegration efficiency

Compacts containing 300 mg of aspirin crystals and 10% (w/w) of either MCC, CS or the different samples of the novel excipients (MCCS) were prepared by mixing the aspirin crystals and the excipient in a bin blender and compressed with a compression load of 2 MPa using a compression machine (Cadmach engineering, Ahmadabad, India.) fitted with an 11.5 mm flat faced punch and die. The aspirin tablets were reserved in a desiccator for 24 h before estimation of the hardness with a hardness tester (TBH 125 Series, ERWEKA GmbH, Germany) and friability with a friabilator (Model EF2, Electrolab, India). The disintegration time for the various aspirin compacts in 0.1N HCl was determined using a disintegration apparatus (Electolab ED-2L, India).[35]

2.6.12. Lubricant sensitivity

Lubricant sensitivity analysis was accomplished by the method described by Rojas et al.[36] with slight alteration. MCCS composites and magnesium stearate (1% w/w) were mixed using a double cone blender for 10 to 60 min. After blending, the powder mass was screened through ASTM 22 mesh screens. Tablets of 400 mg were compressed at 70 MPa compression pressure. In the similar way, additional set of tablets was prepared without lubricants. Lubricant sensitivity (LS) was calculated by the Equation

$$LS = \frac{H_0 - H_{lub}}{H_0} \quad (13)$$

Where H_{lub} and H_o are the hardness of the tablets prepared with and without lubricants.

2.6.13. Heckel compressibility analysis

Heckel analysis was performed using the equation below,

$$\ln\left(\frac{1}{1-D}\right) = KP + A \quad (14)$$

$$\varepsilon = 1 - D \quad (15)$$

Where D is the relative density of the compact at pressure P, ε is the porosity of powders, and K and A are constants. It symbolises the powder compaction by die filling and particle rearrangement just before deformation and bonding of distinct particles take place. The slope of the Straight line, K is reciprocal of the mean yield force, PY of the material and ε is the porosity of a powder bed.[37]

2.6.14. Tablet elastic recovery test

400 mg sample was placed in a die with the diameter of 11.5 mm on a compression machine. Compression pressure was set to 200 MPa at the constant speed of 10 mm/min. The Elastic Recovery can be conveyed using the thickness of each tablet under maximum pressure (Hc) and at about 24 hours after tablet ejection (He) is given by,[38]

$$ER = \frac{H_e - H_c}{H_c} X\ 100 \quad (16)$$

Approximately 24 hours after the tablet was ejected, its weight, diameter, and thickness were estimated, and its apparent density was computed. The internal tablet porosity (Є) from the true density (ρt) was measured with a pycnometer.

$$\in = \frac{1-\rho_a}{\rho_t} \quad (17)$$

2.6.15. The Kawakita analysis

The packability of optimized composites was assessed by tapping the agglomerates in a measuring cylinder. The information was examined using Kawakita's[39] and Kuno's[40] equation, Equation and, respectively.

$$\frac{n}{C} = \frac{1}{ab} + \frac{n}{a} \quad \textbf{(18)}$$

$$a = \frac{V_0 - V_{inf}}{V_0}, C = \frac{V_0 - V_n}{V_0} \quad \textbf{(19)}$$

Where "a" and "b" are constants, n is the tap number, and Vo, Vn, and Vinf are the powder bed volumes initially, after the nth tapping and at equilibrium, respectively.

$$\rho_f - \rho_n = (\rho_f - \rho_0)e^{(-kn)} \quad \textbf{(20)}$$

Where ρo, ρn, and ρf, are the apparent densities initially, after the nth tapping (5, 10,15, 20, 25, 50, 75, 100, 200, 300, and 400) and at equilibrium (500th tap) respectively, and k is a constant.

2.7. Formulation and evaluation of tablets containing model drug

To establish the compressibility and the tableting enactment of the developed multipurpose excipient, paracetamol (50 % w/w) was selected as a model drug. Composites of optimized batch O1 were mixed with paracetamol and talc (2 % w/w) for 5 min in a bin blender. The mix was then mixed with magnesium stearate (1 % w/w) for 2 min and the final mixture was directly tableted (400 mg) on a Rimek 10 stations rotary tablet machine (Cadmach Machinery Private Ltd., Ahmedabad) using 11.5 mm diameter flat-faced punches. The tablets were assessed with respect to weight variation, friability, tensile strength, disintegration time, and in-vitro drug release.

2.7.1. Hardness, Thickness, and Diameter

Hardness, thickness, and diameter of tablets prepared were determined using Tablet Hardness Tester (TBH 125 Series, ERWEKA GmbH, Germany.) The results are the average of 10 determinations.[15]

2.7.2. In-vitro drug release

The in-vitro drug release of paracetamol tablets was investigated using a USP apparatus (model TDT-60T, Electrolab, India.) equipped with baskets (50 r/min) at 37 ± 0.5ºC with phosphate buffer (pH–5.8) as the dissolution medium. At predetermined time intervals, 10 ml samples were withdrawn, passed through a 0.45 µm membrane filter, and assayed at 243 nm in a UV/vis spectrophotometer (Shimadzu 1601, Tokyo, Japan) to determine the percentage drug released. The same volume (10 ml) of the fresh dissolution medium was added immediately after samples were withdrawn.

2.7.3. Short-term stability study

The formulations containing paracetamol were exposed to a short-term stability study. The tablets were reserved in a closed glass container for 3 months at 40˚C at 75% relative humidity in stability chamber (Newtronic, India). The tablets then were assessed with respect to the pattern of drug release.

2.9. Statistical analysis

The student t-test was used to find the statistical significance. A value of $p < 0.05$ was considered statistically significant. All tests were performed in the replicate of six independent samples.

2. RESULTS AND DISCUSSION

3.1. I – Optimal Design

The levels of experimental design could not be preferred randomly, where the composition is a factor of significance because the sum of all the fractions of constituents equals to unity. Specific experimental constraints are not considered in classical experimental designs, and thus they will not reveal better prediction power.[41] The I-optimal design was used for optimizing the proportion of all two excipients viz. microcrystalline cellulose and starch. Thirteen different batches were prepared and measured. (Table 2) In the present investigation, a blend of MCC and CS was strained to control the deleterious effect on the compatibility of MCC. Based on statistical analysis (analysis of variance; ANOVA) (Table 3), a special cubic model (3rd order polynomial model) was chosen for inferring data results from the I-optimal design for angle of repose and percent fines, but for Carrs index, friability, tensile strength and disintegration time linear model was fitted to the data. ($P<0.05$).

Table 2: Composition of batches prepared and observed responses.

Batch Code	Moisture Content (%)	Fines (%)	Bulk Density (gm/ml)	Tapped density (g/ml)	Carr's index (%)	Friability (%)	Tensile strength (MPa)	D.T.* (sec)	Water absorption ratio (%)	Composite index
MS1	3.96	7.47	0.33	0.43	23.33	1.20	1.66	42	113.30	41.26
MS2	2.36	2.4	0.34	0.43	21.14	0.65	2.46	55	105.47	70.21
MS3	2.62	5.36	0.31	0.40	23.69	0.61	2.23	50	108.67	67.42
MS4	3.79	6.03	0.34	0.44	24.50	0.82	1.84	52	101.33	56.25
MS5	2.31	3.71	0.31	0.39	21.23	0.50	2.63	85	101.87	76.71
MS6	3.78	3.37	0.34	0.44	22.95	0.96	2.49	63	105.55	52.69
MS7	3.11	1.69	0.35	0.42	15.60	0.58	3.07	86	118.28	83.25
MS8	3.77	7.53	0.34	0.45	24.07	0.80	1.80	57	107.96	57.90
MS9	4.64	4.83	0.32	0.42	24.05	0.65	2.39	72	105.93	64.88
MS10	4.98	2.99	0.34	0.44	24.56	0.87	2.36	92	108.55	54.15
MS11	3.39	2.37	0.36	0.43	17.14	0.40	2.93	80	110.95	88.72
MS12	3.61	1.8	0.35	0.42	17.48	0.49	2.89	76	107.41	83.71
MS13	3.73	3.25	0.36	0.45	21.43	0.53	1.66	90	118.28	74.79

3.1.1. Percentage fines

The mathematical model generated for the responses Y_1 (Percent Fines) is as follows

$$Y_1 = +1.96X_1+7.00X_2-8.23X_1X_2+4.91X_1^2X_2+25.35X_1X_2(-X_1X_2+1^2+X_2^2)$$

Figure 1(A) shows two-component mix plot predicted from the special cubic model. In these graphs, the response is expressed as the function of CS and MCC. As it was gathered from ANOVA Table 3 X_1X_2 interaction factors are significant model terms in case of % fines. The amount of fines in the formulation can impact flow, consolidation, and compaction hence major importance is convoluted. Table 2 shows the percentage of fines for batches MS1–MS13. The batches containing a low level of CS (1 part) showed a slightly higher percentage of fines than other batches (3 Parts) due to lack of binding activity of starch. It is worthwhile to note that an inverse relationship was observed between the amount of starch and the percentage of fines. No batch exhibited fine more than 8 %. The limit for fines was set at 10 %.

3.1.2. Angle of Repose, Carr's Compressibility Index and Hausner's ratio

The mathematical model generated for the responses Y_2 (Angle of Repose) and Y_3 (Carr's Compressibility Index) are as follows,

$$Y_2=+24.37X_1+31.50X_2+37.93X_1X_2-30.29X_1^2X_2$$
$$Y_3=+17.05X_1+23.81X_2+9.93\ X_1\ X_2$$

Figure 1 (B) shows two-component mix plot predicted from the special cubic model for the angle of repose and a linear model for carr's index. In these graphs, the response is expressed as the function of CS and MCC. As it was collected from ANOVA Table 3 X_1X_2 factors are significant model terms in case of an angle of repose, while a linear mixture of X_1 and X_2 as significant model terms in case of carr's index Figure 1(C). The density and flow properties of the primary and novel excipients are elaborated in Table 2. Angle of Repose, Carr's Compressibility Index and Hausner's ratio were used to measuring the flow properties and compressibility of the excipients. The angle of repose (θ) gives an indication of the inter-particulate frictional forces functioning within the powder system by enumerating the resistance of the powder mass to flow. It was detected (Table 2) that the novel excipients generally have better flow properties than the native excipients. All composites with a greater amount of starch showed upright compressibility index while as the quantity of starch significantly decreases, composites express poor flow. The better flowability of the agglomerates may be due to fuse agglomeration of MCC and CS particles in proximity of water in the microwave.[21] These descriptors of powder flowability use different principles to assess this property in a powder system and do not necessarily have to correlate. While some tests would simply yield a ranking order for powders, others are able to describe the behavior of the powder under certain conditions thus enabling the ability to predict the behavior of such powder during manufacturing. A form of correlation is provided by the fact that the novel excipient MCCS with a high value of HR, also had the highest angle of repose among the co-processed excipients. This suggests that microwave generated co-processed excipients are effective in the production of novel excipients with enhanced flowability.[31]

3.1.3. Friability

The mathematical model generated for the responses Y_4 (Friability) is as follows,

$$Y_4=0.50\ X_1+0.89\ X_2$$

Figure 1(D) shows two-component mix plot projected from the special linear model for friability. In these graphs, the response is shown as the function of CS and MCC. As it was gathered from ANOVA Table 3. X1 and X2 linear mixtures show significant model terms in case of friability. Excessive friability is unsuitable because dusting, and crumbling of the tablets result in at least some loss of the active ingredients, influences the tablet

appearance and consumer appeal, and diminishes the effectiveness of any tablet marking. The friability of tablets lowered with the rise in starch concentration. Tablets of batches with 10 parts of the starch show more friabilities this may be the result of indigent binding at a low concentration of starch and poor compressibility. However, the batches having a medium to high level of CS (X1) exhibited lower values of friability (< 1%), probably as a result of good binding of MCC particles.

3.1.4. Tensile strength

The mathematical model generated for the responses Y5 (Tensile strength) is as follows,

$Y5=+2.96\ X_1+1.78\ X_2$

The Figure 1(E) shows two-component mix plot predicted from the special linear model for Tensile strength. In these graphs, the response is shown as the function of CS and MCC. As it was gathered from ANOVA Table 3. X1 and X2 linear mixtures show significant model terms in case of Tensile strength. Tablet strength is a significant property for safe transportation and handling by patients as well as for accomplishing the coating in a coating machine. Mechanical strength also assesses quality assurance during pharmaceutical production. Insufficiently hard tablets, in addition to exhibiting the effects of immoderate friability, are prone to breakage and chipping particularly during transportation. The tensile strength of the tablets augmented with an increase in the percentage of CS. All experimental trials have shown tensile strength ranging from 1.69 to 3.12 MPa. These results indicated that the amount of binders played a significant role in the production of satisfactory composites by the microwave-induced diffusion. Hence, a medium to high level of both the variables should be selected for further study.

3.1.5. Disintegration time & water absorption ratio

The mathematical model generated for the responses Y6 (Disintegration time) is as follows,

Y5=+2.96 X1+1.78 X2

Figure 1 (F) shows two component mix plot predicted from the special linear model for Disintegration time. In these graphs, the response is shown as the function of CS and MCC. As it was gathered from ANOVA Table 3. X1 and X2 linear mixtures show significant model terms in case of Disintegration time. As anticipated, the disintegration time of the tablets augmented with a rise in the CS percentage. Disintegration time for tablets prepared using composites was projected to be less than 5 minutes. All experimental trials from MS1 to MS13 have shown disintegration time under 92 seconds. Tablets of batches MS1, MS4 and MS8 shown disintegration time less than 60 seconds. The effect of an increase in the percentage of CS on the disintegration time of the tablets was found significant, which might be due to the high tensile strength of the tablets and high binding of CS. The reason found in support is water absorption ratio, Table 2 shows higher water absorption ratio for composites with more amounts of MCC. As in the case of the direct relationship between the wetting time and disintegration time, it can be concluded that composites with more starch require large time for disintegration due to wetting and gelling phenomenon, and inversely with less starch. It can be established that a high level of MCC and low level of starch should be selected for further study. The disintegration data clearly specifies multifunctionality of composites.

Table 3: Regression output for I optimal Design for batches (MS1 to MS13).

Coefficient	Angle of Repose	Carr's Index	% Fines	% Friability	Tensile strength	Disintegration Time
R^2	0.811	0.836	0.948	0.443	0.803	0.572
Adjusted R^2	0.773	0.803	0.922	0.393	0.785	0.533
P	0.0002	0.0001	0.0001	0.013	0.0001	0.0028

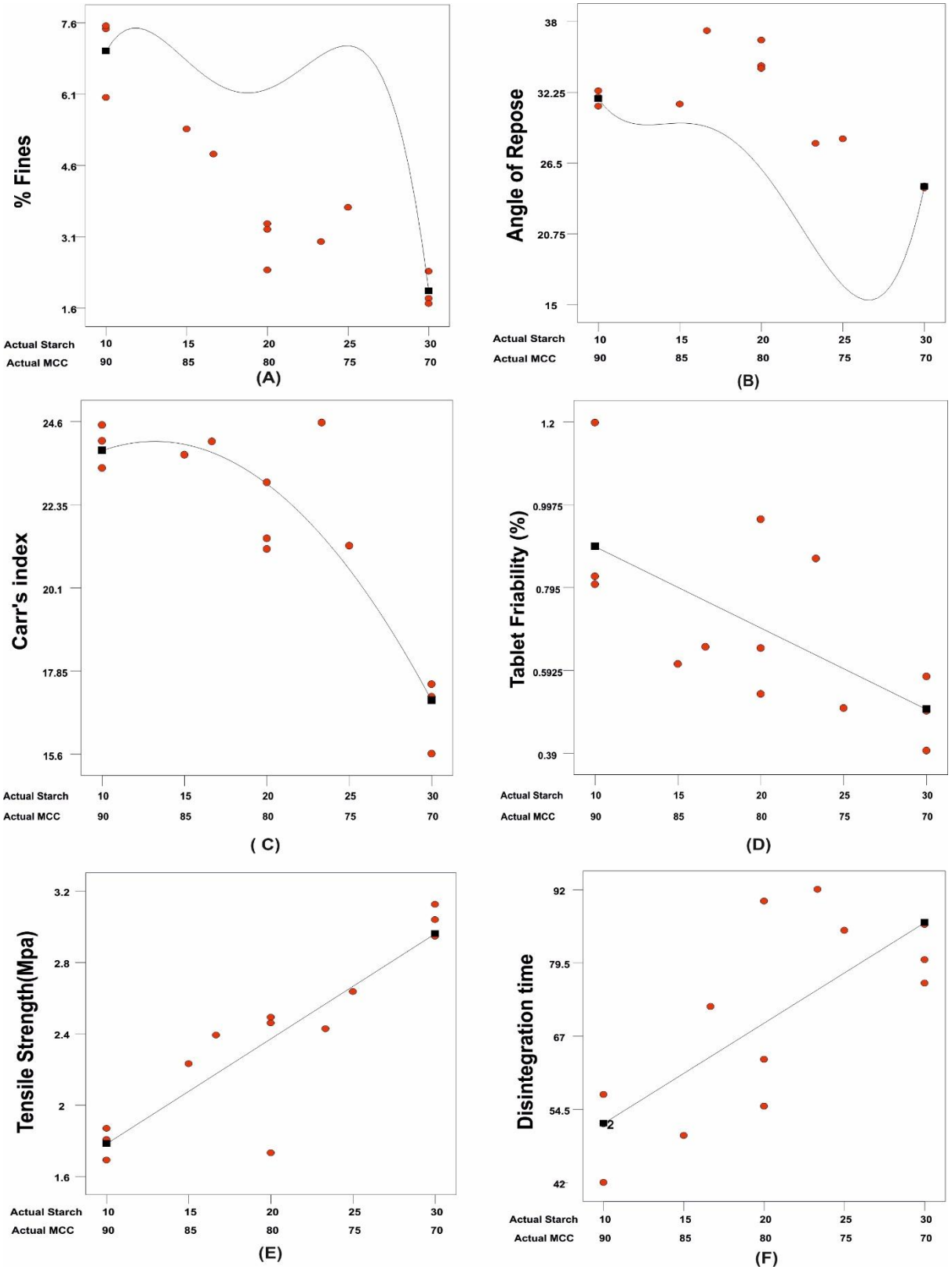

Figure 1: Two-component mix plots for (A) Percent Fines (B) Angle of Repose (C) Carr's Index (D) Tablet Friability (E) Tensile strength (F) Disintegration Time.

3.2. I optimal optimization results

The two responses were plotted collectively by the design expert software to estimate an overall optimum region. The factors X1, and X2 at 70 and 30 provided the optimum response of Y1: 1.96 % and Y2: 24.57 Y3: 25.12 Y4: 0.5 % Y5: 2.96 mPa Y6: 86.36 Sec. In order to assess the reliability of the developed mathematical model, the optimized composite formulation was formed corresponding to above-mentioned factor levels. The magnitude of percentage prediction error was

significantly lower for Y1 to Y5 (Table 4) which demonstrates the robustness of the mathematical model and high prognostic ability of the experimental design.

Table 4: Experimental and Predicted Values for the Optimized MCCS Composites.

Response	Experimental value[a]	Predicted value	Percent prediction error[b]
Y1	1.88±0.50	1.96	4.25
Y2	25.57±0.38	24.57	3.91
Y3	17.14±0.35	17.05	0.53
Y4	0.43±0.01	0.50	16.27
Y5	2.94±0.20	2.96	0.68
Y6	88.67±5.03	86.36	2.61

[a]**Mean of 3±SD**

[b]**Percentage error was calculated using the formula [(Experimental value−Predicted value)/Experimental value] ×100**

3.3. Moisture Content

The composites of batch MS1 – MS 13 exhibited a moisture content between 2.31 – 4.98 %. All composites exhibit less moisture content as ample drying occurs in the microwave. It's detected that moisture doesn't drop below 2 %.

3.4. Calculation of composite index

Batches MS1 to MS13 met the selection criteria for Carr's index and angle of repose. To select the most appropriate composition and its optimum concentration, a composite index was calculated, as reported by Taylor et al.[29] A composite index was calculated to apply equal weight to Carr's index and angle of repose. On the basis of the results shown in Table 2, MS7, MS11 and MS12 with the composition of MCC, CS (70:30) shown maximum index value of 83.25, 88.72 & 83.71 respectively. Composite index close to 100 indicates the suitability of composition in terms of flow and compaction.

3.5. Characterization of optimized batch

3.5.1. Fourier transform infrared (FTIR) spectral study

FT-IR spectroscopy is a quick and simple technique for distinguishing compounds. The IR spectrum of a given compound is unique and distinctive. This is because the IR spectrum distinguishes between the different kinds of bonds in a molecule. The infrared spectrum analysis of CS, MCC, Physical mixture of CS and MCC and MCCS Composites was executed for studying structural alterations and interaction between the reacting moieties and are presented in Figure 2. The IR spectra of CS exhibited a peak at 3434 cm^{-1} and 2931 cm^{-1} representing O–H and C–H stretches, respectively. The absorption band at 1652 cm^{-1} is due to absorbed water in the amorphous region of starch. The peak at 1241 cm^{-1} signifies CH_2OH group whereas peak at 1159 cm−1 embodies coupling mode of C–C and C–O stretching vibrations.[42] The characteristic peaks of cellulose at 3446 cm^{-1} (O-H stretching vibration band), 1431 cm^{-1} (intramolecular hydrogen bonds at the C6 group and O-H in-plane bending vibration), and 889 cm^{-1} (antisymmetric out-of-phase stretching vibration).[21] Most of these peaks are present both in the physical mixture and optimized MCCS composites. The presence of similar absorption frequencies within the fingerprint region of absorption reflects the similarities of the polymers, which are primary monomers of glucose. The presence of another prominent peak in the fingerprint region in the composite at 753.13cm^{-1} could arise due to the exposure of a new functional group due to dislocation and reorientation of the monomers of the polymer chain. Apart from these prominent peaks acknowledged, other peaks were existing in the spectrum. The non-recognition of these heights could be due to either intra- or inter-molecular shielding of functional groups represented by these peaks that prevented the detection of their oscillations. The characteristic differences between the spectrum of MCCS composites and those of CS and MCC show consumption of some functional groups and suggest that a new polymer type was made.

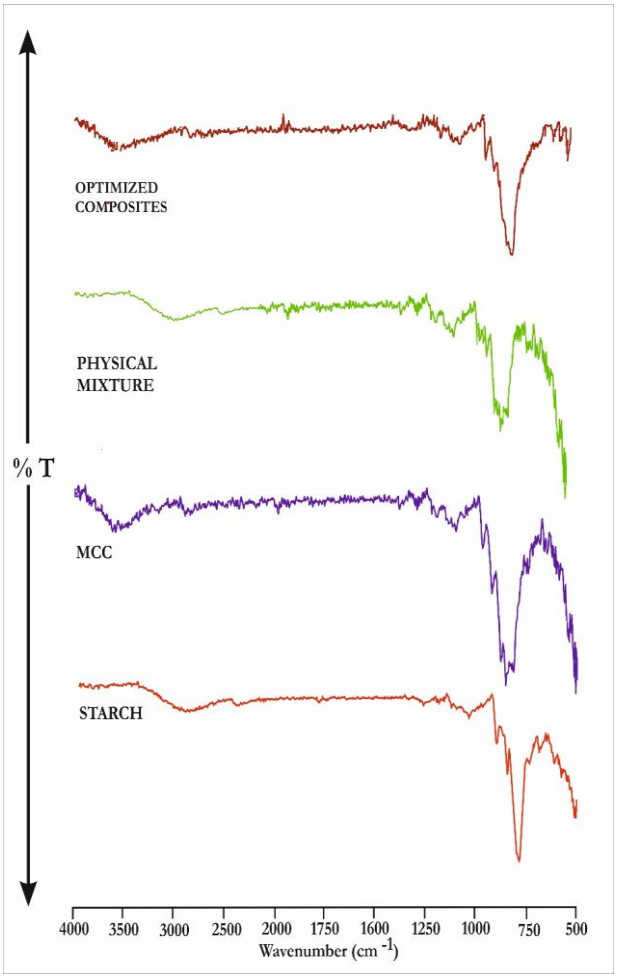

Figure 2: FT- IR Spectrum of (A) starch (B) Microcrystalline Cellulose (C) Physical Mixture of starch and MCC (7:3) (D) Optimized starch MCC Composites (O1).

3.5.2. Differential scanning calorimetry

Polymer DSC is a utilitarian method of describing polymers based on their exothermic and endothermic thermal transitions. The DSC thermograms of CS, MCC, Physical mixture of CS and MCC and MCCS Composites are embodied in Figure 3. From the DSC curves, the glass transition temperature (Tg) & melting temperature (Tm) were obtained. The first endothermic peak denotes glass transition temperature (Tg) and second endothermic peak denotes the melting temperature.[43] The CS, MCC, Physical Mixture and optimized composites show Tg 104.6°C, 91.0°C, 121.3°C & 102.3°C respectively; Tm ascertained were 270.6°C, 307.1°C, 280°C & 278.6°C respectively. The rise in Tg typically infers that a rigid network is augmented. The thermal characteristics of a hybrid polymer are based along the differential separation and recognition of various passages in relevance to the element materials. The thermograms of the MCCS samples indicate that all the samples are distinguished by glass transition (Tg) temperatures and cold crystallization peaks as compared to those of CS and MCC, which are differentiated by Tg and melting peaks. Two prominent transitions indicate the thermograms of MCC and CS, first endothermic transition peak, which corresponds to the Tg and an endothermic peak that conforms to their running. The thermogram of the MCCS composite also has two transitions: an initial endothermic peak which corresponds to the Tg and an exothermic transition, which corresponds to the polymer cold crystallization.[35] Evaluation of the thermograms of the CS, MCC, and therefore the composite indicates that a novel polymer type resulted from the microwave treatment of CS MCC mixtures.

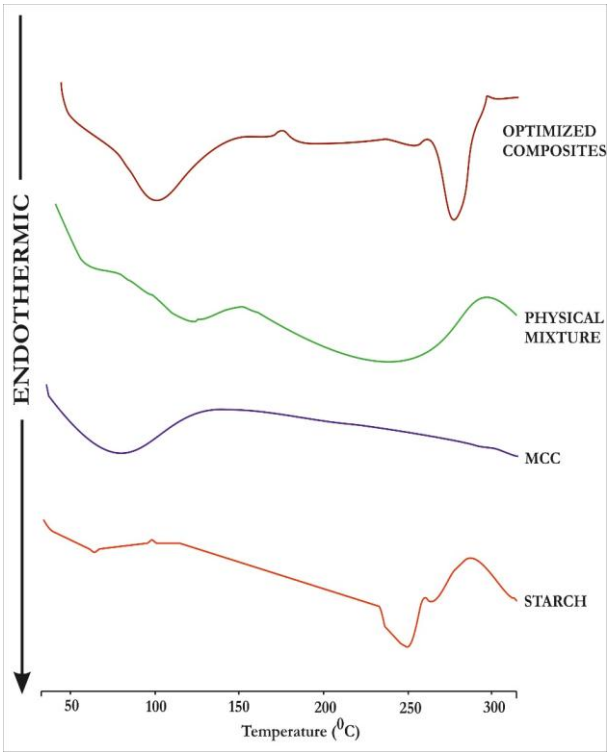

Figure 3: DSC of (A) starch (B) Microcrystalline Cellulose (C) Physical Mixture of starch and MCC (7:3) (D) Optimized starch MCC Composites (O1).

3.5.3. Determination of particle shape

Motic images of the optimized batch are given in Figure 4. Particle shape was found to be irregular spherical. Particle size calculated using image pro software was found in a range of 80 to 156 µm.

3.5.4. Particle size distribution

The composites of batch MS1 – MS13 demonstrated a particle size distribution specified that all the agglomerates passed through a 80 mesh (180 µm), and no more than 30% passed through a 120 mesh (125 µm) and 50 % passed through a 140 mesh (106 µm) each, whereas most agglomerates were retained on a 200 mesh (74 µm). The composites of batch O1 exhibited particle size 100.90±0.74 µm.

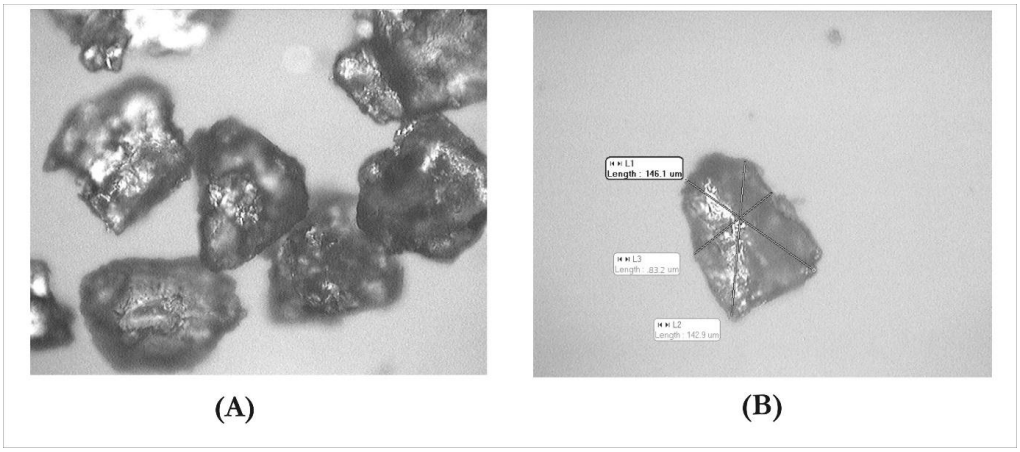

Figure 4: Photomicrographs of Optimized starch MCC composites at 10X.

3.5.5. True density and Porosity

Enhanced porosity accelerates the degree of deformation of excipients manifested during the compression that matches to an increased tensile strength of the produced tablets.[44] The optimized batches have shown true density between 1.35 to 1.41and porosity ranging through 45.68 % to 48.02 %. The porosity of optimized composites was found to be more than the physical mixture and individual excipient indicative of tensile strength increase, which is mentioned in successive discussions.

3.5.6. Moisture uptake study

After 24 h storage at 75 % relative humidity and 40˚C, composites of optimized batch adsorbed 5.33±0.33% w/w moisture. This may be due to the adsorptive nature of the cellulose. The results showed that the optimized composites are not much sensitive to moisture. Little moisture uptake by composites may be due to moisture uptake properties of cellulose.

3.5.7. Composite friability index

For checking the mechanical strength of composites, strength and composite's friability are critical factors as they reveal the quality of the tablets. The directly compressible excipient is exposed to stress during processing (i.e. mixing, transportation), and friable hybrids may not produce acceptable tablets. The composite friability index can be used as a quality control instrument. The granular friability index and friability rate constant for optimized batch found to be 0.98 and 0.004 min-1, respectively after 60 minutes. The composite friability index close to one besides the friability rate constant close to zero indicates that agglomerates are mechanically strong and deliver a low friability as far as external abrasion is concerned.

3.5.8. Disintegration efficiency

The choices of dosage form tablets are those meant to be consumed completely and to disintegrate and release their actives quickly in the gastrointestinal tract. The proper selection and efficiency of the disintegrants are of prime significance to the formulation of such tablets, since disintegration is the first step and may limit one in the release of the active from the tablet, especially when the API has limited solubility.[35] The comparative disintegration time of aspirin tablets prepared with MCC, CS and MCCS composites as the disintegrants are presented in Figure 5. Aspirin was preferred as the drug for this study owing to its good compatibility and low solubility in water. The compacted aspirin deprived of excipient and that prepared with MCC presented similar characteristic as each didn't disintegrate even after 2 h whereas physical mixture showed disintegration time of (37.73±1.85 Min). Conversely, aspirin compacts prepared with CS and MCCS composites disintegrated within 10 min. Aspirin MCCS compacts (7.14±0.73 Min) had shorter disintegration time than starch compacts (10.26±0.78 Min) (Figure 5). Diverse mechanisms have been proffered for the mechanism of disintegrants. These comprises deformation recovery, water wicking, swelling amongst others. Starch is a traditional disintegrant and its disintegrating capability has been moderately supported by a combination of different mechanisms of disintegration, but most strongly by swelling, water wicking and deformation recovery theories. However MCC has been used as a disintegrant in some formulations, not as efficient as a starch on a gram per gram basis. Its disintegrant ability has been ascribed mostly to water wicking and swelling. The combination of the disintegration and hardness properties of the aspirin tablets show that tablets formulated with MCCS composites have superior quality for peroral tablets relative to those formulated with MCC and starch. While aspirin tablets prepared with MCC showed poor disintegration property those prepared with starch exhibited poor hardness.

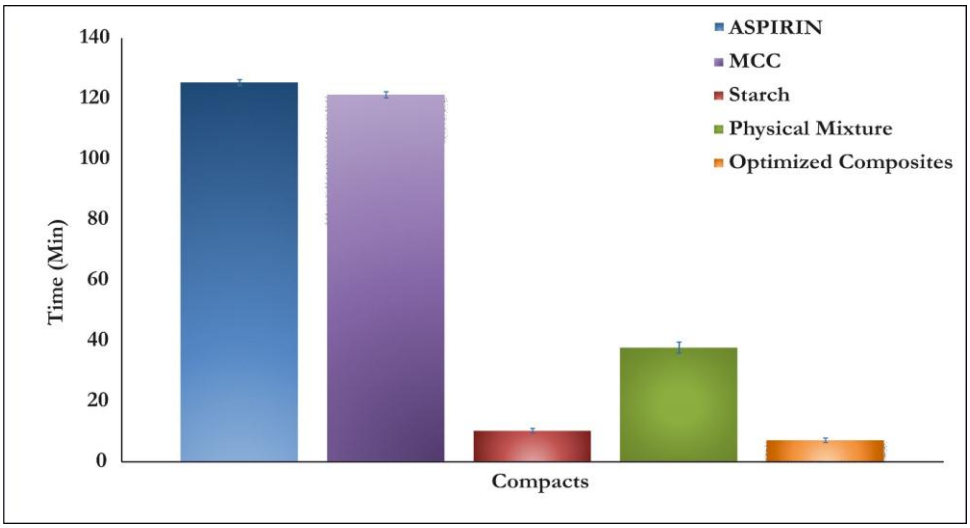

Figure 5: Disintegrant Efficiency of (A) starch (B) Microcrystalline Cellulose (C) Physical Mixture of starch and MCC (7:3) (D) Optimized starch MCC Composites (O1).

3.5.9. Lubricant sensitivity

Magnesium stearate is often used in tablet formulations to affluence friction between the material and tooling used. The addition of magnesium stearate drops the hardness of tablets. It is well recognized that extended mixing of magnesium stearate yields a film around the agglomerates and inhibits the agglomerates from binding. This effect is more distinct in the case of plastic deforming material than for material undergoing brittle fracture. In light of these arguments and from the data shown in Table 4, one can clinch that protracted mixing of magnesium stearate reduces the hardness of the tablets. The lubricant sensitivity ratio is a quantitative measure of expressing the ability of the material to mix with lubricant; the greater the lubricant sensitivity ratio, the greater the ability to mix with a lubricant. The mixing time has a greater effect on the tensile strength compared to the effect at the compression time. Hence, one may conclude that the agglomerates of batch MCCS is only slightly sensitive to the lubricant.[21] These results suggest that materials with low Py value are is sensitive to magnesium stearate, and hence ductility of the material decreases. As seen in Figure 6, the trend for lubricant sensitivity ranged as CS>Physical Mixture>MCC>Optimized MCCS composites. Figure 6 shows the relationship between blending time and lubricant sensitivity. In the case of MCCS, a plateau in sensitivity is attained within 30 min of blending. This suggests covering effect of magnesium stearate reaches a limit between 30 min and newly available sites for particle binding are made later on. Long mixing time with lubricant had a major effect on the lubricant sensitivity of CS.

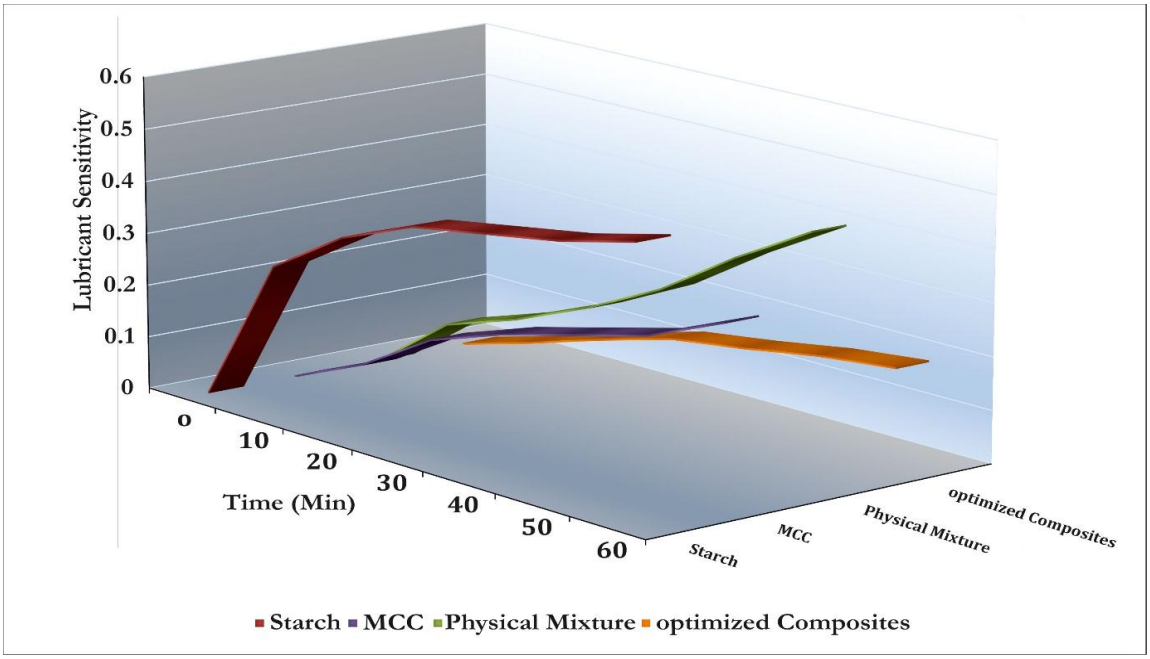

Figure 6: Lubricant Sensitivity of (A) starch (B) Microcrystalline Cellulose (C) Physical Mixture of starch and MCC (7:3) (D) Optimized starch MCC Composites (O1).

3.5.10. Loading capacity

High carrying or loading capacity is a significant property of direct compression materials.[45,46] The loading capacities of the MCCS in comparison with those of MCC and CS were determined by measuring the hardness of compacts prepared with the diverse ratios of the excipient and Paracetamol mix. Paracetamol (PAR) was used for evaluating the loading capacity because of its poor compaction property resultant from its ability to undergo substantial elastic recovery after drawing of the compaction pressure.[47] Carrying capacity measures the amount of drug substance in the tablet, usually a poorly compressible API that can be appended to the excipient, while still maintaining satisfactory physical strength with regard to hardness and/or friability. Broadly speaking, the more API that can be appended to the excipients the higher its carrying capacity. The hardness of the compacts prepared with MCC, CS, and MCCS enhanced as their ratio relative to that of PAR in the compacts increased. Compacts prepared with MCC and MCCS showed similar hardness attributes as it increased considerably after the PAR and excipient (E) ratio of P300: E100 (Figure 7). Compacts prepared with MCC had the highest hardness at the varying ratio mixtures after P300: E100. The functional properties of directly compressible composites could be due to the reprocessing of MCC. Reprocessing of MCC by techniques implying wetting is acknowledged to lower the hardness of its compacts.[48] The general reorientation of polymer molecular structure due to the solubilization and regeneration may contributed to the changes in the hardness of the compacts as compared to those of the unprocessed MCC. The fall off hardness of the paracetamol compacts prepared with CS is essentially due to the indigent intrinsic compatibility of both paracetamol and starch.[49] Restrained not only by their

intrinsic properties but also by their physical properties, which are dependent on the material's processing approach. Excipient's bulk and tapped densities, which are controlled principally by processing techniques pertain inversely with the powder's loading capacity. The bulk and tapped densities of the MCC, CS, and MCCS is presented in Table 2 correlates well with their loading capacities as characterized by the hardness of their compacts (Figure 7). The loading capacity of the diverse materials as evaluated by their compact hardness efficiency at equal excipient and paracetamol mixture can be embodied as follows (MCC > MCCS > Physical Mixture > CS).

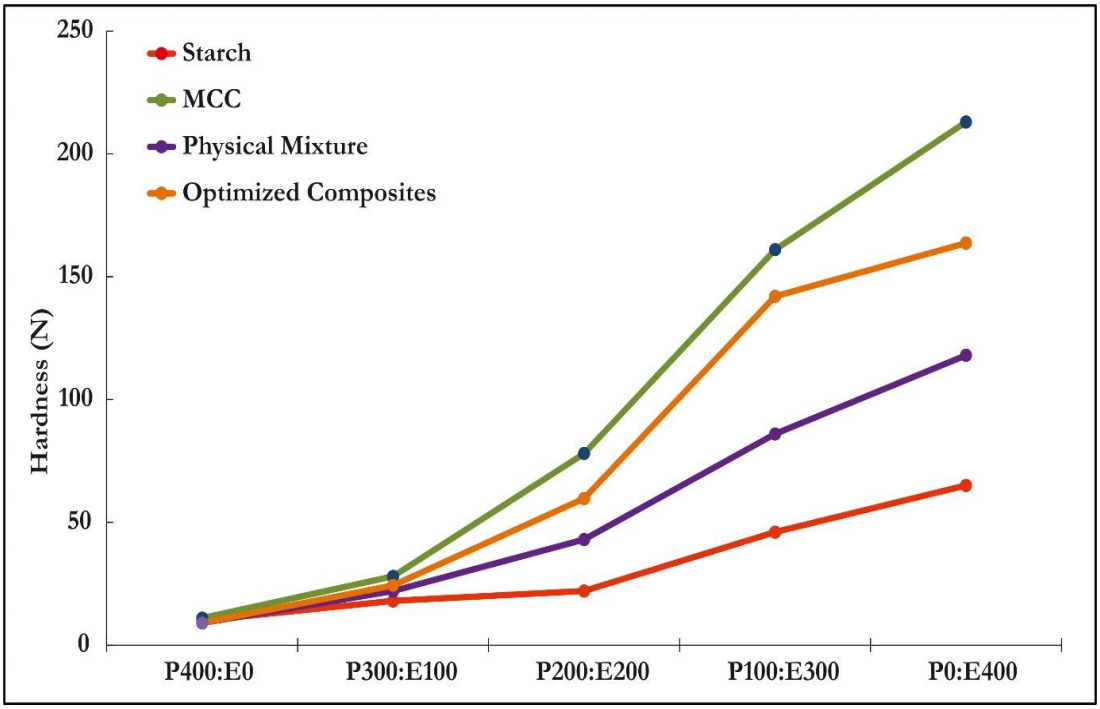

Figure 7: Loading Capacity of (A) starch (B) Microcrystalline Cellulose (C) Physical Mixture of starch and MCC (7:3) (D) Optimized starch MCC Composites (O1).

3.5.11. Heckel compressibility analysis.

Heckel analysis is a traditional approach for transforming a parametric observation of the force and displacement signals to a linear relationship for materials withstanding compaction. The equation is constructed upon the expropriation that the dependence of densification on compaction pressure is first order.[31] The yield pressure (Py) was calculated from the reciprocal of the slope k of the regression line(Table 6)[21] A rank order of CS>MCC>Physical Mixture> Optimized MCCS Composites was observed for the Py (Figure 8). This signifies that the onset of plastic deformation is quicker in the native than the Multifunctional excipients. High Py clearly signify higher yield strength, compelling stronger forces of compaction to initiate deformation. This may not be suitable for high-speed tableting machines where minimum dwell time is attainable for compression of powders to form compacts.[31] According to Heckel, the linear part of the curve illustrates the plastic deformation of the material and elastic deformation is considered insignificant. It can be concluded that, at the low pressure, the curved region of the plot is corresponding with distinctive particle movement in the unavailability of inter particle bonding, and that the transformation from curved to linear coincides to the minimum pressure necessary to obtain a consistent pressure. The agglomerates, which had lower values, undergo plastic deformation because of the rebounding of fundamental crystals shorter than those of the original powder. CS mainly deforms by fragmentation, and cellulose is considered slightly elastic in nature. The Py value demonstrates the compression attribute of the material. The lower the Py value, the greater the plastic deformation. From the data shown in Table 6, it can be inferred that MCCS optimized composites revealed plastic deformation due to inter particulate bonding in cellulose and starch composites, compared with plain Starch and cellulose.[21]

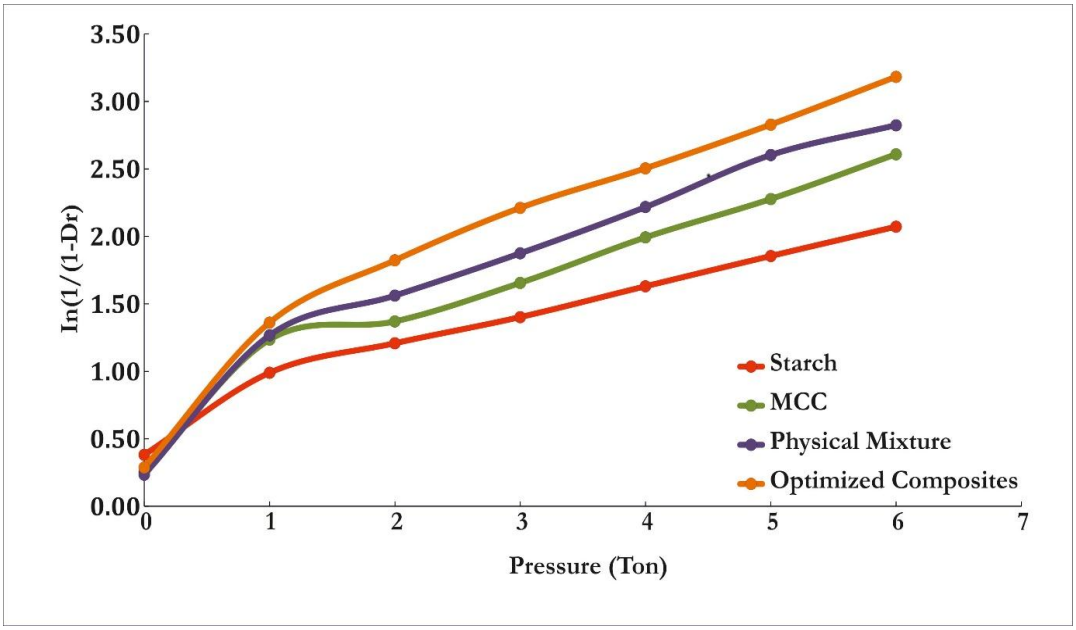

Figure 8: Heckle Plots for (A) starch (B) Microcrystalline Cellulose (C) Physical Mixture of starch and MCC (7:3) (D) Optimized starch MCC Composites (O1).

3.5.12. Tablet elastic recovery test

The elastic recovery is the typical behavior of the plastic material, including CS and MCC. The results of tablet elastic recovery tests are elaborated in Table 5. Elastic recovery (ER) was higher in the case of tablets compacted with MCC and physical mixture while less for CS and optimized composites. The (ER) estimates the elasticity of the compact particles, and a high value is interrelated with a decrease in tablet strength due to the reduction in bonding surface area. The ER has also been coupled with a tendency of tablets to undergo capping and lamination. ER usually expresses the release of potential energy amassed in the material by tableting. Moreover, the interaction between particles dominates the relaxation behavior of tablets. For instance, compacts manufactured from materials with weak inter particle attraction possessed more relaxation than tablets made of materials with strong particle attraction. Thus, the ability of the tablet to tolerate ER due to the release of stored elastic energy is a significant factor in determining the success of a compaction process.[50] In the case of Plastic and viscoelastic materials, stronger forces result in greater deformation and more elastic behavior of tablets after the compacting force is removed. The higher elastic recovery of MCC might be due to an elongated shape and hydrophobic surfaces of MCC, which is resisting particle densification.[51] ER of Physical Mixture is also an reliable manifestation of properties of MCC. The lowest ER of MCCS tablets reflected higher inter-particulate bonding between MCCS composite particles. MCCS composites showed lowest ER. This might be due to masking of hydrophobic surfaces of MCC and intermolecular bonding between CS and MCC.[52,53]

3.5.13. Determination of tablets packing fraction

The results of Packing fraction are well illustrated in Table 5. The packing fraction values propose that there must be the existence of spherical particles, which is relevant with photomicrographs.[54] The packing fraction, which is an effective measure of the degree of consolidation of tablet upon compaction, showed an increase in value as compression forces in the formulations. The packing fraction was found to be best for optimized MCCS composites particularly revealing particles are denser in bulk. The significantly augmented plasticity leads to increased contact area but to lower strength of bonding per unit area of inter particle contact, for a fixed consolidation state or level of packing fraction or total tablet porosity.[55] The results of packing fraction accompanied by that of tensile strength, it could be well inferred that the inter particle voids at the highest pressure are greatly reduced.[56] The packing fraction results clearly indicate the use of optimized MCCS composites for greater consolidation.

Table 5: Diameter, Height and Elastic Recovery of Starch, MCC, Physical Mixture and Optimized MCCS Composites.

Tablet parameters	Diameter (mm)	Height (mm)	Elastic Recovery (%)	Packing Fraction
Starch	11.5	3.07	14.66	0.85
MCC	11.5	2.46	25.61	1.02
Physical Mixture	11.5	2.73	23.44	0.93
Optimized Composites	11.5	2.88	8.31	1.03

3.5.14. The Kawakita analysis

Plots of N/C against the number of taps as shown in Figure 9 gave a linear relationship with correlation r >0.964. Values of a, i.e. the maximum volume reduction after tapping, obtained from the slope of the straight lines are presented as percentages in Table 6. The rank order of ‘‘a’’ is CS>Physical Mixture>MCC>MCCS optimized Composites. A base value of “a” signifies that the powder system has packed more closely on initial pouring into the cylinder, which clearly implies that the powders were well packed ahead of tapping since tapping did not give a discreet improvement in their packing. For powders with low ‘‘a’’, tapping minimizes the voids by displacing air from the powder bed, without changing the size and shape of the particles.[31] The “b” value of the optimized MCCS (0.02) demonstrated that the packing velocity of the composites was quicker than that of starch and cellulose powder. The smaller value of “K” in Kuno’s equation supports the above findings (Table 6). The slow packing velocity resembles to the proportion of the consolidation of the powder bed per tap. As a result of enhanced packability, optimized composites showed improved compression compared with starch and cellulose powder.[21]

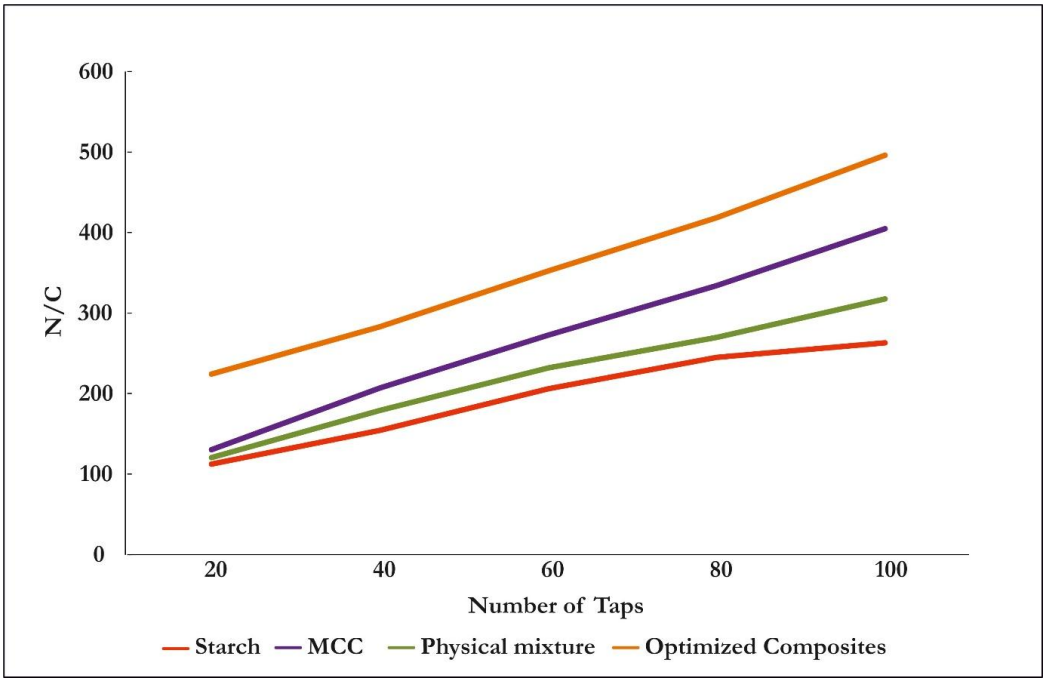

Figure 9: Modified Kawakita Plots of (A) starch (B) Microcrystalline Cellulose (C) Physical Mixture of starch and MCC (7:3) (D) Optimized starch MCC Composites (O1).

Table 6: Heckle, Kawatika and Kuno’s parameters for Starch, MCC, Physical Mixture and Optimized MCCS Composites.

Material	Kawatika		Kuno		Heckle		
	a	b	K	Consolidation index	A	K	Py
Starch	0.51	0.02	0.36	-1.15	0.26	0.77	3.88
MCC	0.30	0.05	0.57	-2.20	0.35	0.86	2.86
Physical mixture	0.41	0.03	0.45	-1.62	0.40	0.93	2.52
Optimized Composites	0.29	0.02	0.60	-2.22	0.44	1.08	2.28

3.6. Formulation and evaluation of tablets containing model drug

From the results shown in Table 7, one can conclude that the composites of optimized MCCS composites showcased adequate tableting characteristics with paracetamol. The model drug formulation exhibited weight variations < 5%, friability < 1%, and a disintegration time < 7 min. An in-vitro drug release profile of paracetamol tablets was compared with the market formulation (Glaxo SmithKline Pharmaceuticals Ltd). The in-vitro drug release profiles of marketed and test formulation are shown in Figure 10. An in-vitro dissolution study showed that more than 80 % of the drug was released within 10 minutes from tablets prepared with optimized MCCS composites exhibiting similarity factor more than 80.

Table 7: Percentage composition of the tablets using model drugs.

Ingredients/parameters	
Paracetamol (%)	50
Optimized MCCS composites (%)	47
Talc (%)	2
Magnesium stearate (%)	1
Average weight (mg)	400
Tablet hardness (N)	65.2
Friability (%)	0.59
Disintegration time (min)	4.46

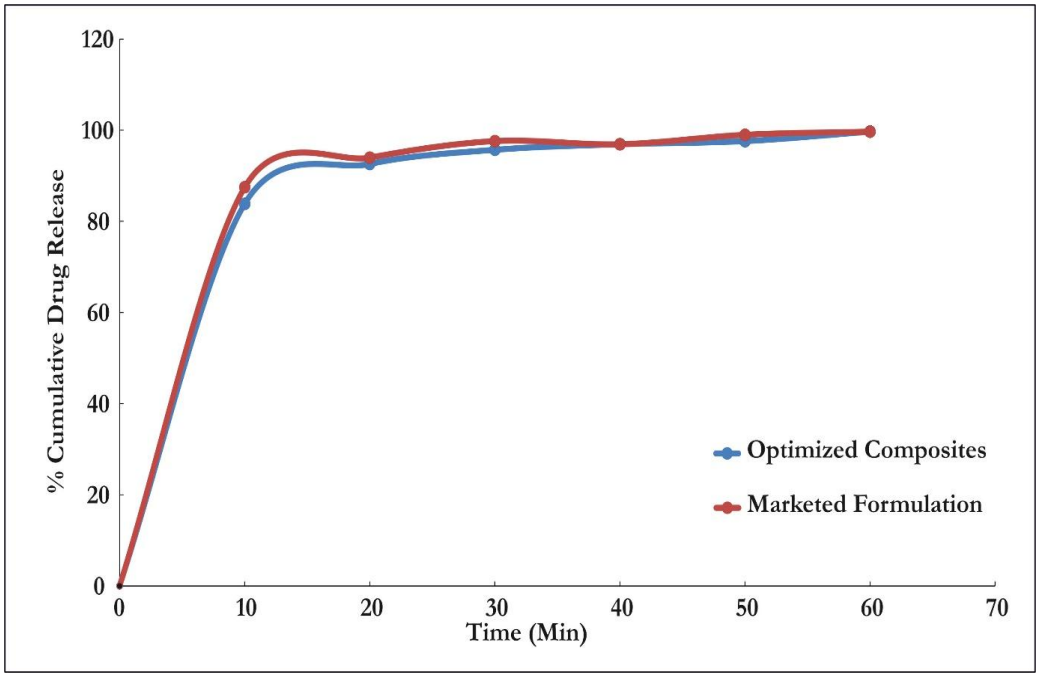

Figure 10: In Vitro Drug release of tablets with Optimized starch MCC Composites and Marketed formulation.

3.7. Short-term stability study

Tablets containing paracetamol were subjected to a short-term stability study (3 months, 45˚C/75% RH). The f1 value was less than 10 and the f2 value[24] was greater than 80 for the drug release profile of both tablet formulations before and after the stability study.

3. CONCLUSION

The Microwave induced diffusion technique has been found to be potential alternative method for the production of directly compressible excipients. Starch as binder produces agglomerates with a low percentage of fines and good flowability. The tablets had a lesser disintegration time due to presence of CS. Based on Carr's index, friability, tensile strength, disintegration time and composite index, the batch (O1) containing Corn Starch (30%), Microcrystalline cellulose (70 %) was selected as the optimum. The agglomerates of the optimum batch performed better than corn starch, cellulose powder and the physical mixture having the same composition in terms of the Kawakita and Kuno parameters. Heckel analysis showed that the agglomerates undergo plastic deformation compared with corn starch, cellulose and the physical mixture. The agglomerates exhibited a reasonable dilution potential.

From the results of this study, it can be concluded that co-processed excipients containing corn starch, cellulose can be used as potential multifunctional directly compressible excipients. Clearly, from the results of the present study, Microwave modification of MCC and cellulose leads to considerable improvement in functionality and compactability. The Microwave Induced Diffusion technique also requires only a short processing time which is, an advantage over spray-drying.

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