Flow, compaction and tabletting properties of co-processed excipients using pregelatinized Ofada rice starch and HPMC.

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Original Article

ABSTRACT

The growing popularity of direct-compression process necessitates an ideal filler–binder that can substitute two or more excipients. Pregelatinization of starches significantly improves swelling and flow properties but produces tablets with low mechanical strength. When used as a binder in many tablet formulations, hydroxyl propyl methyl cellulose (HPMC) imparts mechanical strength but because of its poor flow during high speed tablet manufacturing, granulation of HPMC-based formulations is required prior to compaction. Directly-compressible co-processed excipients were developed utilizing pregelatinized starch of the indigenous Ofada rice starch (*Oryza glaberrima* Steud Family Poaceae) and HPMC. Co-processed excipients of various combinations of pregelatinized Ofada rice starch and HPMC K15M (15 cps) were prepared using a co-fusion method (97.5:2.5; 95:5; 92.5:7.5; 90:10; 85:15; 80:20). The flow and compaction properties of the co-processed excipients, as well as, individual excipients were evaluated using density, Hausner ratio, Carr's index, angle of repose, angle of internal friction, the Kawakita model, consolidation index and rate. Aceclofenac tablets were formulated using direct compression with starch, HPMC and specific co-processed excipients as filler-binders. Pregelatinization produced starch with larger granules and improved flow characteristics. FTIR spectra of the co-processed excipients confirmed absence of any chemical interaction. The angle of repose, Hausner ratio, Carr's index, angle of internal friction indicated that flow properties improved with increasing starch content of the co-processed excipients. Kawakita plots, consolidation index and consolidation rate demonstrated cohesiveness while compressibility and rate of packing were enhanced. Aceclofenac tablets containing co-processed excipients exhibited a crushing strength ≥ 66.03 ± 1.58 MNm^{-2}; friability ≤ 1%; disintegration time ≤ 10.75 ±3.10 minutes and dissolution time (t80) ≤ 30.00 ± 3.07 minutes. The co-processed excipients of pregelatinized Ofada rice starch and HPMC could be cheaper alternatives to other synthetic excipients used in direct compression of tablets assuming the starch would meet all compendial specifications.

Keywords: Aceclofenac tablets, co-processing, compaction properties, flow properties, Ofada rice starch, pregelatinization

INTRODUCTION

The direct compression process is highly influenced by powder characteristics such as flowability, compressibility, and dilution potential (1). However, no single excipient is likely to exhibit all these ideal characteristics. Co-processed excipients have been developed by combining two or more excipients (2). The resulting excipients possess the advantages of better performance than can be achieved using a simple physical admixture of the same combination of excipients (3,4). The co-processed excipients offer

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substantial benefits such as greater compatibility, improved blending properties, better intrinsic flow, greater lubricating and binding efficiencies, content uniformity, dilution potential and improved disintegration and dissolution profile. (5-7). Major limitations of co-processed excipient mixtures are the fixed ratios of excipients in a mixture and the relatively high cost of commercially available directly compressible co-processed excipients compared to their respective raw materials from which they are made (8).

Rice is one of the most important crops in Nigeria (9). Ofada rice is a generic name used to describe the indigenous rice species *Oryza glaberrima* Steud Family Poaceae, cultivated mainly in South West Nigeria (10). The high starch content of the rice makes it an inexpensive source of starch that could be utilized in the pharmaceutical industries. While the modification of starches by pregelatinization can significantly enhance their swelling and flow properties, they yield tablets of low crushing strength-friability ratio, indicating poor mechanical strength (11). On the other hand, direct compression of tablet formulations using hydroxyl propyl methyl cellulose (HPMC), an excipient that is known for its cohesive property and ability to impart mechanical strength, is challenging because it may impart poor flow properties to the formulations, causing problems during high speed tablet manufacturing (12). Thus, granulation is required for such HPMC-based formulations.

In this study, directly-compressible co-processed excipients were developed utilizing pregelatinized starch of Ofada rice (Oryza glaberrima Steud; family Poaceae) and Hydroxyl propyl methyl cellulose (HPMC) at different ratios. The flow and compaction properties of the co-processed excipients were evaluated in order to determine whether this method yielded directly-compressible products with improved properties as compared with the individual starting materials. Selected combinations of the co-processed excipients were then used in the formulation of tablets of aceclofenac sodium and the formulated tablets were evaluated for mechanical strength and release properties.

MATERIALS AND METHODS

Materials

Grains of Ofada rice were obtained from Shagbon village in Ogun State, Nigeria. Hydroxylpropylmethylcellulose, HPMC K15M (viscosity grade 15 cps) was obtained from Oxford Lab Chemicals, Maharashtra, India. Aceclofenac BP was obtained from Indo Gulf Co., Mumbai, India. Sodium starch glycolate (SSG) was obtained from Patel Chem Ltd, Ahmedabad, India. Talc was obtained from Sigmet Chemical Corporation Pvt Ltd., Mumbai, Maharashtra, India. All other reagents were of analytical grade.

Methods

Starch extraction and modification by pregelatinization

Starch was extracted from the Ofada rice grains as described previously (13). Briefly, an aqueous slurry of 500 g of native Ofada rice starch in 2 liters of distilled water was heated at 100°C stirring continuously for 45 minutes. The resulting paste was dried in a hot air oven at 60°C for 48 hours. The dried mass (moisture content 8%) was powdered and passed through a 250- μm sieve.

Morphology

The shape and size of the starch granules were characterized using a scanning electron microscope (Hitachi SU8030 FE-SEM Tokyo, Japan) at an accelerating potential of 5.0 kV. All samples were sputter-coated with Au/Pd prior to examination.

FT-IR analysis

The starches were analyzed using FTIR (FTIR-Thermo Nicolet Nexus 870 Madison, WI, USA) in transmission mode. Transmission spectra were recorded using at least 64 scans with 8 cm^{-1} resolution in the spectral range 4000-400 cm^{-1}.

X-ray Diffraction analysis

The X-ray diffraction pattern was recorded with a copper anode x-ray tube (Cu-Kα1 radiation) using an X-ray diffractometer (Rigaku D-max Tokyo, Japan). The sample was exposed to the X-ray beam at 40 kV

and 20mA. The scanning region of the diffraction angle (2) was from 5° to 60° at step size count of 2 s.

Swelling index

The swelling index was calculated as described previously by determining the ratio of the volume of the wet slurry of the powder after 12 hours to the initial volume of the dry starch (13).

Powder density measurements

The particle densities of the starches (Multivolume pycnometer 1305, USA), as well as, the bulk density and tapped density (100 taps) were determined in triplicate.

Flowability

The flowability of the starches was evaluated using the Hausner ratio shown in Equation 1 and Carr's index shown in Equation 2:

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density} \quad \text{Eq. 1}$$

$$Carr's\ index = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} x\,100 \quad \text{Eq. 2}$$

Angle of repose

Starch powder (10 g) was made to flow freely through a funnel into an open-ended cylinder placed on a base of similar diameter. The distance from the tip of the funnel to the base was 6.5 cm. From the conical heap formed, the angle of repose was calculated as shown in Equation 3:

$$\mathrm{Tan}\,\phi = \frac{h}{r} \quad \text{Eq. 3}$$

where, h is the height of the powder and r is the radius of the base of the cone.

Determination of flow rate

The flow rate of the powder ($g.s^{-1}$) was obtained by determining the time "t" it took 30 g of the powder to pass through the orifice of a 10 mL pipette. The flow rate was calculated as the mean of three determinations using Equation 4:

$$Flow\ rate = \frac{30}{t} \quad \text{Eq. 4}$$

Co-processing of Ofada rice starch and HPMC

Batches of 100 g of pregelatinized Ofada rice starch and HPMC at specific ratios were prepared. The HPMC (2.5, 5, 7.5, 10, 15 and 20 g in 100 mL) was dissolved in a beaker in a sufficient amount of distilled water to form a viscous, homogenous solution. In another beaker, distilled water was added to the Ofada rice starch powder to form a slurry (97.5, 95, 92.5, 90, 85 and 80 g in 200 mL). Both excipient slurries were heated over a water bath at 80°C for ≤ 30 minutes. The HPMC solution was added to the starch slurry whilst stirring at 300 RPM for 20 minutes at low heat (40°C) until a thick mass had formed. The resulting homogenous mass was dried in a hot air oven at 40°C for 72 hours. The dried mass was milled into powder using a blender (Phillips HR 1702), sieved through a mesh (250 μm) and stored in amber colored screw capped bottles. The size distribution was not determined.

Characterization of co-processed excipients

Morphology

The shape of the co-processed excipients was examined using a scanning electron microscope and the size of 300 particles were determined using an optical microscope at magnification x 10.

Moisture content

One hundred grams of co-processed excipient was spread in a Petri dish and placed in a hot air oven at 110 ± 5°C (Laboratory Oven TT-9083 Techmel & Techmel, Texas, USA). The percentage decrease in weight was noted at time intervals of 30 minutes until there was no significant change in weight. The percentage moisture was determined using Equation 5:

$$\%\ moisture = \frac{initial\ weight\ of\ starch - final\ weight\ of\ stacrch}{initial\ weight\ of\ starch} x\,100 \quad \text{Eq. 5}$$

Determination of powder densities and porosity

The particle and bulk densities were determined and the relative density (RD) was obtained from the ratio of bulk to particle density while the porosity (ε) was obtained from the expression 1-RD.

Determination of flowability

The flowability of the co-processed excipients was determined using the Hausner ratio, Carr's Index, angle of repose and flow rate (FR).

Determination of angle of internal friction

The porosity of the powder bed was determined using the Equation 6:

$$\varepsilon = 1 - \frac{Pb}{Pt} \qquad \text{Eq. 6}$$

where, P_b and P_t are the bulk and particle densities respectively. From the plots of ε^2 N/(1-ε) (porosity factor) versus N (number of taps), the angle of internal friction was determined (2).

Determination of compaction properties

The volume occupied by starch powder (30 g) as it flowed through a funnel into a 100-mL cylinder was noted. The starch powder was tapped 100 times and the volume occupied after each set of 10 taps was determined.

The reduction in the volume of the powder due to tapping was evaluated using Equation 7 (14):

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \qquad \text{Eq. 7}$$

where, N is the number of taps while *a* and *b* are constants that describe the compressibility and cohesiveness of powders (1/*b*) respectively. Term C describes the volume reduction during the tapping and was determined using equation 8:

$$C = \frac{(V_0 - V)}{V_0} \qquad \text{Eq. 8}$$

where, V_o is the loose volume of the powder before tapping and V is the volume of the powder after a fixed number of taps (14).

By determining the relative decrease in powder volume and density as a function of applied load, the consolidation behavior of the co-excipients and their constituent excipients was evaluated using the equation 9: (15)

$$\frac{(Log(\rho_T - \rho_B)}{\rho_T} = K\,Log\,N + C \qquad \text{Eq. 9}$$

where, ϱ_T and ϱ_B are the tapped and bulk densities respectively, N is the number of taps, C is the consolidation index and K is the rate of consolidation.

Formulation of Aceclofenac tablets using co-processed Ofada rice starch and HPMC

Aceclofenac tablets (200 g) batches of basic formulation of aceclofenac sodium (50%w/w), sodium starch glycolate (4% w/w), talc (2%w/w) and the selected co-processed excipients B_1 (Ofada starch only), B_3 (95:5), B_4 (92.5:7.5), B_5 (90:10) and B_8 (HPMC only) (43%w/w) were dry mixed in a planetary mixer (Model A120, Hobart Manufacturing Co, UK) for 6 minutes at a speed 107 RPM. Magnesium stearate (1% w/w) was added just before blending and then mixed for 1 minute. Each formulation (200 mg) was compressed with a predetermined load (113 Mpa) on a Carver hydraulic press (Carver Inc. Menomonee Falls, WI, USA) using a 10.5 mm die and flat-faced punches for 30 seconds. Approximately 200 tablets of each batch were produced.

Evaluation of aceclofenac tablets

Tablet weight and thickness

Twenty tablets were selected at random and their average weight was determined within ± 1 mg (Ohaus analytical balance E10640) while the thickness of twenty tablets was measured within ± 0.01mm using a micrometer screw gauge.

Mechanical strength of tablets

The crushing strength of aceclofenac tablets was determined at room temperature by diametric compression using a tablet hardness tester

(DBK Instruments Mumbai, India) while the percent friability of the tablets was determined using a friabilator (DBK Instruments, India).

Release properties of tablets

The disintegration time of the tablets was determined in distilled water at 37±0.5°C using a disintegration tester (DBK Instrument, England). Ten tablets were crushed and dissolved in phosphate buffer pH 6.8 and assayed for drug content using a UV/Visible Spectrophotometer (Jenway UV-7804c print, England) at wavelength 275 nm to determine percentage content of aceclofenac in the tablets. Absorbances were measured and the concentration of drug in the tablet was determined using the calibration curve of drug in phosphate buffer as shown in Equation 10:

$$\%\,Assay = \frac{Absorbance\ of\ sample}{Absorbance\ of\ pure\ drug} x\,100 \qquad \text{Eq. 10}$$

The percent drug content was 96.5 ± 3.10%. A dissolution test was carried out on the tablets using the USPXX III paddle method at 100 RPM in 900 mL of phosphate buffer pH 6.8 maintained at a temperature of at 37 ± 0.5°C for 8 hours. Samples (5 mL) were drawn and replaced with equal amounts of fresh medium. The samples were filtered using a Whatman paper filter (0.45 μ) and appropriately diluted. The amount of aceclofenac released was determined at wavelength of 275 nm using a UV/Visible Spectrophotometer).

RESULTS

The Scanning Electron Microscope (SEM) images, FTIR and X-ray diffraction spectra of native and pregelatinized Ofada rice starches are shown in Figure 1. The values of swelling index and densities of the native and pregelatinized Ofada starches are presented in Table 1. The flow properties of the starches were determined using Hausner ratio (HR), Carr's index (CI), angle of repose (AR) and flow rates and their results are also presented in Table 1.

The scanning electron micrographs shown in Figure 2 a, b and c show the morphology of the modified starch, HPMC and the co-processed excipients developed from pregelatinized Ofada rice starch and HPMC. The FTIR spectra of the pregelatinized Ofada starch, HPMC and the developed co-processed excipients are shown in Figure 2 d. The values of particle, bulk and tapped densities, Hausner ratio, Carr's index, angle of repose and angle of internal friction for the co-processed excipients as well as those of the individual excipients are presented in Table 2.

Figure 3a shows the plot of $\varepsilon^2 n/(1-\varepsilon)$ (porosity factor) versus number of taps (N). This gives a straight line with intercept on the y- axis. The angle of internal friction was determined from the angle made between the ordinate line and the abscissa. The compaction properties of the starch, HPMC and co-processed excipients were assessed using the values of *a* and *b* obtained from the Kawakita plots, the consolidation index and consolidation rate and these are presented in Table 3. Figures 3 b and c show the plots of Kawakita and of Log $(\varrho_T - \varrho_B) / \varrho_T$ *versus* Log N respectively.

The tablet properties of aceclofenac containing selected co-processed excipients and pregelatinized Ofada starch and HPMC alone were evaluated. The values of tablet weight, thickness, friability, crushing strength and disintegration time are presented in Table 4. The dissolution profiles of the tablets are shown in Figure 4. From the dissolution plots, the time taken for 80% drug release (t_{80}) were determined and their values are presented in Table 4.

DISCUSSION

Starch morphology

The SEM images of the granules of native Ofada rice starch showed polygonal and angular-shapes with mean particle sizes of 2.20 ± 0.05 μm. The particle size was observed to increase significantly on modification by pregelatinization ($p < 0.05$), forming irregularly-shaped aggregates of mean size 14.80 ±1.55 μm. The presence of large void spaces, which is characteristics of larger particles, gives a limited surface area available for interparticulate bonding with consequent enhancement of flow of the modified starch (16). Particle shape can affect compaction characteristics just as it affects the packing behavior of starches. Starches

Table 1 Material and flow properties of native and pregelatinized Ofada rice starch -mean ± sd, n = 3)

OFADA STARCH	SWELLING INDEX	PARTICLE DENSITY gcm^{-3}	BULK DENSITY gcm^{-3w}	TAPPED DENSITY gcm^{-3}	HAUSNER RATIO	CARR'S INDEX %	ANGLE OF REPOSE	FLOW RATE g/s
Native	1.70±0.04	1.48±0.19	0.42±0.01	0.56±0.01	1.33±0.02	25.00±2.00	45.85±3.00	0.01±0.00
Pregel	4.46±0.10	1.43±0.05	0.51±0.00	0.63±0.04	1.23±0.01	19.05±1.56	39.54±2.33	0.02±0.00

Table 2 Densities and flow properties of co-processed excipients of Ofada rice starch and HPMC

EXCIPIENT	OFADA: HPMC	PARTICLE DENSITY gcm^{-3}	BULK DENSITY gcm^{-3}	TAPPED DENSITY gcm^{-3}	HAUSNER RATIO	CARR'S INDEX %	ANGLE OF REPOSE °	ANGLE OF INTERNAL FRICTION °	FLOW RATE g/s
B_1	100:0	1.43 ± 0.05	0.51±0.06	0.63 ± 0.04	1.24 ± 0.01	19.05 ± 1.56	35.54 ± 2.33	49.02 ± 0.48	1.03 ± 0.03
B_2	97.5:2.5	1.40 ± 0.04	0.49± 0.05	0.60 ± 0.02	1.22 ± 0.01	18.33 ± 1.56	30.54 ± 2.50	50.61 ± 1.18	1.15 ± 0.03
B_3	95:5	1.59 ± 0.12	0.54 ± 0.02	0.59 ± 0.02	1.09±0.03	8.47±2.38	28.66±0.73	52.61 ± 1.01	1.36 ±0.00
B_4	92.5:7.5	1.58 ± 0.08	0.52 ± 0.01	0.57 ± 0.02	1.10 ± 0.01	8.77 ± 1.56	29.26±2.25	54.03 ± 0.48	1.23 ± 0.05
B_5	90:10	1.51 ± 0.05	0.46 ± 0.01	0.54 ± 0.00	1.17±0.02	14.81±1.83	30.86±1.14	58.21 ± 1.25	1.07 ± 0.01
B_6	85:15	1.49 ± 0.04	0.44 ± 0.02	0.52 ± 0.00	1.18±0.05	15.38 ±3.63	31.02±5.20	59.76 ± 1.03	0.88 ± 0.00
B_7	80:20	1.41 ± 0.15	0.42 ± 0.01	0.50 ± 0.01	1.19 ±0.00	16.00 ±0.19	33.26±2.25	61.00 ± 1.01	0.86 ± 0.00
B_8	0:100	1.34 ± 0.05	0.36± 0.03	0.49 ± 0.05	1.36 ±0.01	26.53 ±0.43	48.22±8.40	63.88 ± 0.80	0.46 ± 0.00

Table 3 Compaction properties of the batches of co-processed excipients of pregelatinized Ofada starch and HPMC

EXCIPIENTS	OFADA: HPMC	KAWAKITA COMPRESSIBILITY a	KAWAKITA COHESIVENESS b	CONSOLIDATION RATE K	CONSOLIDATION INDEX C	CORRELATION COEFFICIENT
B_1	100:0	0.137	1.820	0.193	- 0.820	0.8734
B_2	97.5:2.5	0.162	0.899	0.128	- 0.634	0.8829
B_3	95:5	0.173	0.903	0.136	- 0.573	0.9953
B_4	92.5:7.5	0.216	0.370	0.127	- 0.570	0.9877
B_5	90:10	0.221	0.371	0.071	- 0.390	0.9782
B_6	85:15	0.236	0.254	0.066	- 0.437	0.9876
B_7	80:20	0.246	0.284	0.061	- 0.376	0.9632
B_8	0:100	0.290	0.270	0.210	- 0.966	0.9864

Table 4 Mechanical and release properties of aceclofenac tablets containing selected co-processed excipients of Ofada starch and HPMC

BATCH OF EXCIPIENT IN TABLETS	TABLET WEIGHT (g)	TABLET THICKNESS (mm)	CRUSHING STRENGTH (MNm^{-2})	FRIABILITY (%)	DISINTEGRATION TIME (min)	t_{80} (min)
B_1	0.202 ± 0.058	260 ± 2.53	36.13 ± 3.27	3.78 ± 0.05	3.10 ± 1.20	15.00 ± 2.27
B_3	0.199 ± 0.040	255 ± 0.75	66.03 ±1.58	0.58 ± 0.01	5.25 ± 1.12	19.50 ± 1.50
B_4	0.203 ± 0.025	250 ± 5.75	70.13 ±1.80	0.40 ± 0.01	7.00 ± 0.27	27.00 ± 2.52
B_5	0.201 ± 0.010	245 ± 5.75	83.87 ± 6.14	0.37 ± 0.00	10.75 ± 3.10	30.00 ± 3.07
B_8	0.205 ± 0.005	243 ± 5.75	90.50 ± 5.54	0.25 ± 0.01	33.50 ± 2.27	51.00 ± 4.51

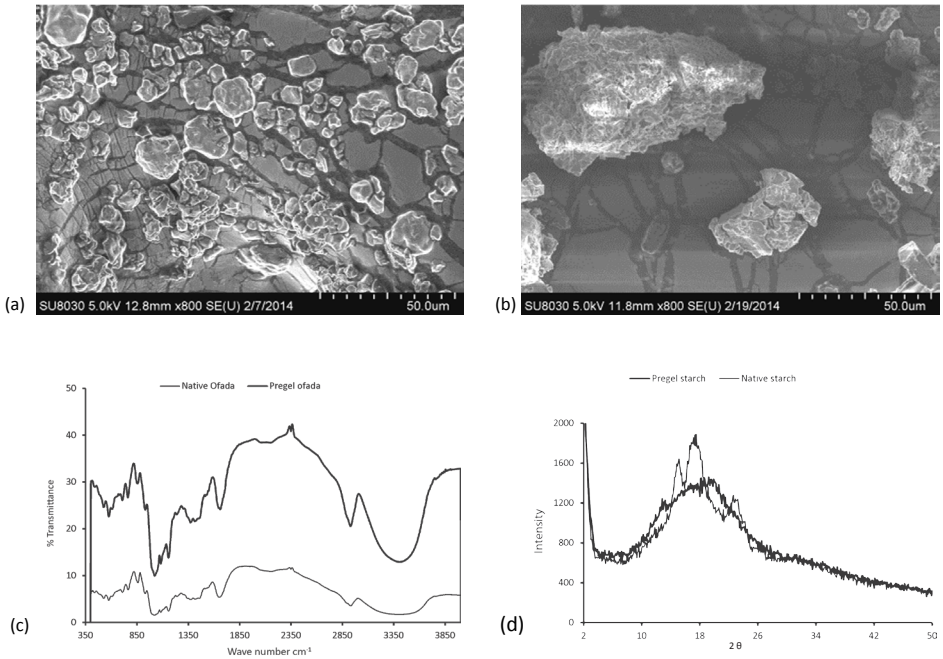

Figure 1 SEM of: (a) native and (b) pregelatinized Ofada rice starch Mg x 800 (c) FTIR spectra and (d) X-ray diffraction spectra of native and pregelatinized Ofada rice starches.

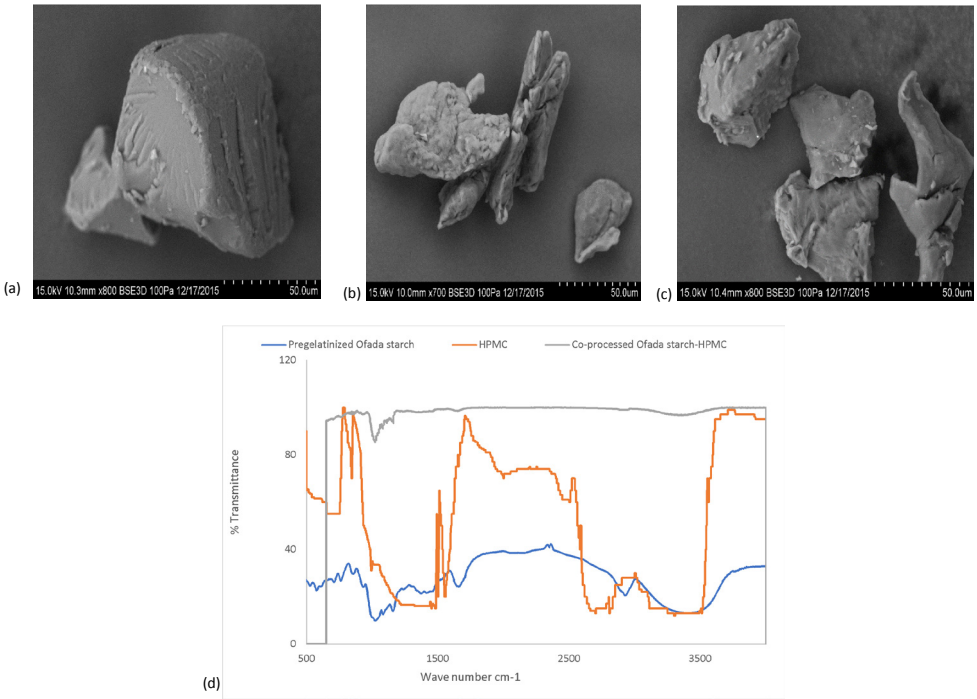

Figure 2 SEM of (a) Pregelatinized Ofada starch, (b) HPMC, (c) Co-processed Ofada-HPMC excipients and (d) FTIR spectra of (a), (b) and (c).

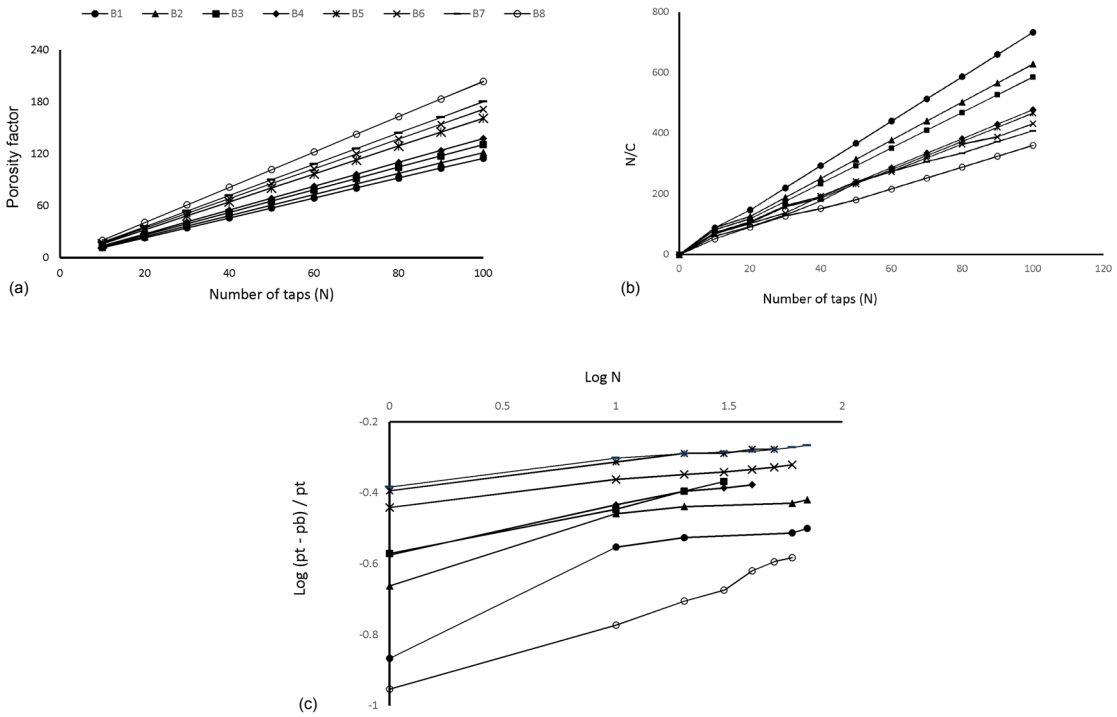

Figure 3 (a) Plots of porosity factors as a function of the number of taps (N), (b) Kawakita plots and (c) Plot of Log $(\varrho_T - \varrho_B)/\varrho_T$ versus Log N for pregelatinized Ofada starch, HPMC and the co-processed excipients

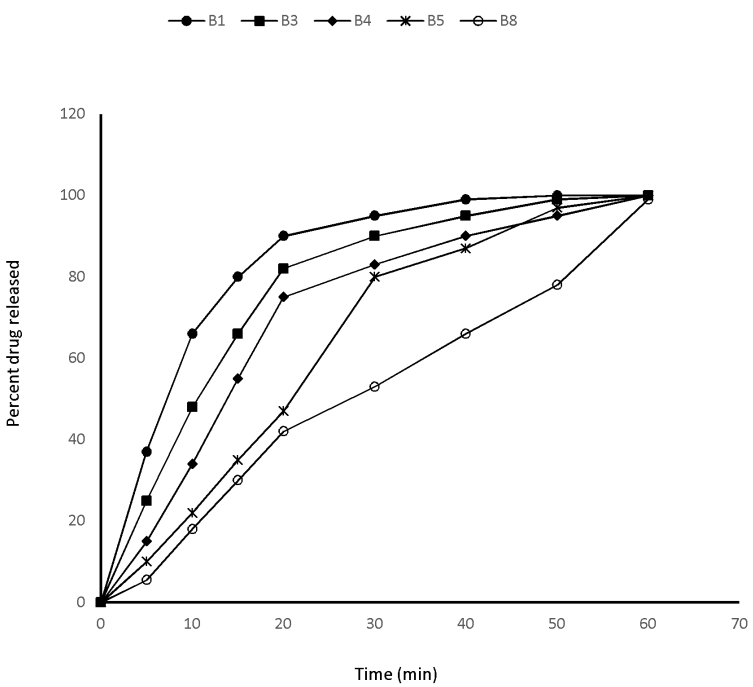

Figure 4 Dissolution profile of aceclofenac tablets containing pregelatinized Ofada starch, PHMC and some co-processed excipients

with finer particles tend to have a higher number of particles per unit weight which can be indicative of achieving homogeneity when mixing the substance with an active pharmaceutical ingredient (API) (17).

In the FTIR spectra of both starches, the band at 2925 - 2933 cm^{-1} is attributed to -CH2 symmetrical stretching vibrations while the band stretch around 3420 - 3538 cm^{-1} in the spectrum for pregelatinized starch is attributed to hydroxyls on the molecules. Characteristic absorption bands were observed at 3300 and 1610 cm^{-1} due to bound water and at 1350 cm^{-1} due to the bending vibrational modes of O -C -H, C- C -H, and C -O H. In the region between 1200 and 900 cm^{-1}, several strong absorption peaks assigned to C-C and C= O stretching modes were observed. The formation of amorphous structure occurs upon pregelatinization, with decrease in the ordered structure of the native starches, characterized by reduction in the band intensity at 1042 cm^{-1}. In the X-ray diffraction pattern of the starches, the typical A-pattern that is normally observed for native cereal starches can be seen for the native Ofada rice starch, revealing strong reflections at 2θ of between 13° and 23°. For the pregelatinized starch, no clear crystalline structure can be observed; the A-pattern was disorganized by the process.

Swelling index

The swelling index of powder can be defined as the increase in the volume or weight of starch when allowed to swell freely in water (18). Pregelatinised Ofada rice starch showed significantly higher swelling ($p < 0.05$) than the native form. The swelling index of starches is of great significance in tablet formulation because the disintegrating properties of starches appear to be influenced by their swelling and wicking action (19).

Densities of the starches

Particle density affects the packing behavior of materials during tableting, especially at the initial phase of compression particularly the phase of elasto-plastic flow (20, 21). The results showed the bulk density and tapped density of the pregelatinized starch were greater than those of native starch. The higher value of bulk density may be considered advantageous in tableting because of the reduction in the fill volume of die (20). Increase in consolidated bulk density is advantageous in tableting because the volume of die fill would be reduced as well as improved flow rates and these combined effects enhance uniformity of tablets.

The flow properties of starches

The Hausner ratio is defined as the ratio of tapped to aerated bulk densities. Native Ofada rice starch had a high Hausner ratio of 1.33. On the other hand, pregelatinized Ofada starch had a Hausner ratio of less than 1.25, indicating better flow relative to the native form (22). Carr's index measures compressibility of a powder and provides an indirect measure of a material fluidity; the higher the value, the more cohesive is the powder indicating poor flow (23). Generally, Carr's index up to 16% would show good flow behavior, while those above 25% indicate cohesiveness or poor flow behavior (24). The modified starch had lower Carr's index suggesting improved flow. The angle of repose can be used to assess interparticulate frictional forces operating within the powder system, measuring the resistance of the powder mass to flow. An angle of 30° or below indicates free flow while angle of 40° or above indicates poor flow (25). The angle of repose is also affected by particle size distribution and usually increases with decrease in particle size. Results revealed that modification of native starch by pregelatinization which produced larger particles significantly reduced angle of repose ($p < 0.05$) indicating better flow in agreement with the values of Carr's index and flow rate.

Evaluation of the co-processed excipients

Moisture content

The moisture content of the co-processed excipients was 9.45 ± 1.18%.

Morphology

Particle shape and size can be used to identify and distinguish between different polymers. The particles of the

co-processed excipients formed larger aggregates with irregular shapes that suggested increased mechanical interlocking of particles and enhanced compressibility.

FT-IR analysis

The FTIR spectra of HPMC showed characteristic peaks at 1652.89 cm^{-1} assigned to the C=C stretching in the aromatic ring and a peak at 1455.4 cm^{-1} respectively assigned to the C-H deformation. The FTIR spectra of co-processed excipients showed retention of all the major peaks of their starting materials confirming the absence of chemical interaction between the two excipients during co-processing.

Densities and flow properties

Particle, bulk and tapped densities of the co-processed excipients were observed to reduce with increase in HPMC content. Materials with low particle density at a given pressure would yield more cohesive compacts than those with higher values. This implies that the developed co-processed excipients would form tablets at lower compression pressure when compared to starch alone. The flow properties of co-processed excipients were assessed using, Hausner ratio (HR), Carr's index (CI), flow rate, angle of repose and angle of internal friction (22, 24). HPMC (B_6) had the highest values with CI > 26.53 and HR > 1.36 indicating good compressibility but poor flow. Flow properties improved as the content of Ofada starch in the co-processed excipients increased. Of note are the co-processed excipients B_3 and B_4 (Starch: HPMC = 95:5; 92.5:7.5 respectively) which gave excellent flow properties with CI of <10 and HR of <1.11 (24). The values of angle of repose also suggested that the co-processed excipients had significantly ($p < 0.05$) better flow when compared to their individual starting materials with flowability increasing with starch content.

It has been reported that the angle of internal friction is a more useful indicator of flow pattern than the angle of repose because of the poor reproducibility of the latter (25). The angle of internal friction was obtained using the relationship between porosity of powder and number of taps applied to the powder bed with higher angles indicating greater cohesiveness. Powder flow involves frictional contact of individual particles and such interparticulate friction has been demonstrated to have significant effects on powder packing (26). The values of the angle of internal friction confirmed that the co-processed excipients had significantly better flow properties when compared to HPMC. The results indicate that co-processing the modified Ofada rice starch with HPMC in specific amounts could aid in removing pockets of unwanted air in tablets particularly when using direct compression of tablets as air pockets may result in capping and/or lamination of the tablets (27). Flow rate increased significantly with the starch content ($p< 0.05$) with co-processed excipients B_3 (Starch: HPMC = 95:5) showing the highest value.

Compaction properties of co-processed excipients

The capacity of a material to form compact tablets with adequate tensile strength under the impact of densification is referred to as compactibility. Tensile strength of a compact will increase as porosity of the compact reduces (28). The Kawakita's equation relates the degree of volume reduction of a powder bed to the applied pressure under tapping. The linear relationship obtained suggest that the equation can be used to interprete the densification of the powders. The Kawakita coefficient 'a' refers to the minimum porosity of the powder bed before compression which is related to its compressibility and is obtained from the slope (28). A low value of 'a' indicates that the powder system packed more densely on initial pouring (29). The value of 'b' is an inverse measure of cohesiveness and is obtained from the intercept of the plot. The higher the 'a' value of the powder, the better the compressibility; an essential requirement in direct compression of tablets. HPMC had the highest values, hence its cohesiveness and ability to impart high mechanical strength in tablet formulations.

Tablet properties of aceclofenac

Aceclofenac tablets containing selected co-processed excipients B_3, B_4 and B_5 (Ofada: HPMC 95:5, 92.5:7.5 and 90: 10, respectively) and those containing only pregelatinized Ofada starch (B_1) and HPMC (B_8) were

formulated and evaluated for their tablet properties. The co-processed excipients were selected based on flowability and cohesiveness. The percentage weight variation and average thickness values of aceclofenac tablets were within the United States Pharmacopeia limits. The ranking of crushing strength was B_8 > B_5 > B_4 > B_3 > B_1 while the reverse was the ranking of friability. Tablets containing pregelatinized Ofada rice starch alone had the lowest crushing strength and highest friability which failed to meet Pharmacopoeia specifications of ≤ 1% for uncoated tablets (30). Crushing strength increased while friability decreased with increase in HPMC content. Mechanical strength determines the extent to which tablets can withstand the rigors of packaging, transportation and handling.

Aceclofenac belongs to BCS Class II as it possesses poor aqueous solubility and high permeability (31). The formulations in this study aimed to provide improvement in solubility while at the same time reduce the GI adverse effects of aceclofenac. The disintegration and dissolution times (t_{80}) of the co-processed excipients had similar ranking as crushing strength. All the tablets except those containing HPMC alone (B_8) passed the disintegration and dissolution times (≤ 15 minutes and ≤ 30 minutes, respectively) (30). The amount of sodium starch glycolate incorporated into the formulation was 4% w/w. It appears the formation of a viscous gel layer of sodium starch glycolate around aceclofenac particles during the dissolution process formed a barrier that could make it difficult for the dissolution medium to penetrate into the tablet or granules (32). This could have retarded the diffusion of the drug solution from the tablet to the dissolution medium hence the relatively high dissolution times observed. Incorporation of pregelatinized Ofada starch in the co-processed excipients aided disintegration and dissolution of aceclofenac tablets within an acceptable period whilst incorporation of HPMC imparted sufficient mechanical strength. Aceclofenac tablets containing Excipient B_3 (Starch: HPMC 95:5) appeared to be the optimimum formulation in terms of adequate mechanical strength and release of drug content. However, since the physical mixture was not made and examined, it cannot be ascertained if a physical mixture of 95:5 pregelatinized starch:HPMC would perform comparably to its counterpart coprocessed mixture.

CONCLUSION

Ofada rice starch was modified by pregelatinization and used to prepare co-processed excipients with HPMC at various ratios using a simple and reproducible co-fusion method. Co-processing resulted in improved flow, cohesiveness and compressibility. Aceclofenac tablets that included the co-processed excipients provided good mechanical strength and release properties. If the indigenous rice starch could meet all USP specifications (such as limits of inorganic impurities and specific tests), then the co-processed excipients of pregelatinized Ofada rice starch and HPMC could be suitable for use as less expensive alternatives to imported directly-compressible excipients. It remains to be determined if a physical admixture of pregelatinized Ofada rice starch and HPMC would perform comparably to the co-processed mixture presented here.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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