Research Article

Comparative Functionality Evaluation of Co-Precipitate of *Zea Mays* and *Oryza sativum* Starch in Paracetamol Tablets

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ABSTRACT

This work evaluated paracetamol tablets formulated using binder-disintegrant co-precipitate of *Zea mays* (corn) and *Oryza sativum* (rice) starch. The co-precipitate were prepared using a concentration ratio of 1:1 of the *Zea mays* and *Oryza sativum* starch in a 1:3 volume ratio of starch to acetone. Granules of starch co-precipitate as binder (10 % w/w) and disintegrant at 5, 7.5, 10, 12 and 15 % w/w concentrations formulated by wet granulation were compared with that of Ac-di-sol, a super disintegrant. The basic micromeretic properties of the granules and physicochemical properties of the various tablet batches were evaluated to show the functionality of the starch co-precipitate as a binder and disintegrant in comparison to a super disintegrant Ac-di-sol. The results indicate that all batches of paracetamol granules exhibited good and acceptable flowability. All the paracetamol tablets formulated complied with BP specifications for the disintegration time of normal release tablets. The tablets hardness ranged from 5.97 ± 1.26 to 6.66 ± 1.28 kgf for batches A1 and A3 tablets formulated with 5 and 10 %w/w of starch co-precipitate, while the reference tablets exhibited hardness of 7.46 ± 1.74 kgf, significantly different from the test tablets ($p < 0.05$). Results of tablets friability showed that all the paracetamol tablets passed the friability test. Also, the tablets batches showed good release properties with $T_{100\ \%}$ range between 15-25 minutes in all the batches. The starch co-precipitate exhibited good properties as binder and disintegrant, in paracetamol tablets, and compared favourably with the super disintegrant- Ac-di-sol.

Keywords: Coprecipitation, *Zea mays*, *Oryza sativum*, starch, paracetamol.

INTRODUCTION

Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials and new combinations of existing materials [1]. The combination of existing excipients is an interesting option for improving excipient functionality because all formulations contain multiple excipients. Many possible combinations of existing excipients can be used to achieve the desired set of performance characteristics. Developing new grades of existing excipients (physicochemical) has been the most successful strategy for the development of new excipients in past three decades[2, 3], a process that has been supported by the introduction of better performance grades of excipients such as pregelatinized starch, coprocessing and coprecipitation [3, 4].

The bioavailability of hydrophobic drugs can be increased by strategies designed to enhance the dissolution rate of the drug. This has been achieved in many cases by forming a solid dispersion of the drug in a suitable carrier, often a hydrophilic polymer such as polyethylene glycol (PEG). The drug is dispersed in the carrier by coprecipitation from a suitable solution containing both drug and carrier, by melting both components together, or by some other process involving a phase change [5]. A great number of chemically modified starches have been manufactured in the last decade such as cyclodextrins. Complexes are formed through inclusion in the cavity or through interactions with chemical groups. In order to obtain complexation, the compounds have to bind a complex first in solution. From the usual methods of preparation, kneading, coprecipitation, freeze drying, or spray drying, often the spray-drying technique gives the best results. These new derivatives of starch forms inclusion compounds and are best carriers for the monitoring of the dissolution characteristics of the drug [6].

In various solid dosage forms, starches are widely employed as multipurpose excipients especially as fillers, disintegrants, and binders due to their versatility, ready availability, cheapness and inertness[7]. In recent years pharmaceutical scientists have been paying increasing attention to the extraction, development and use of starches in the formulation of dosage forms[8, 9]. The objectives of the work were to formulate paracetamol tablets using co-precipitated starch from corn and rice as binder and disintegrants, and to compare the disintegrant properties of the starch co-precipitate with a super disintegrant and evaluate the properties of the tablets.

MATERIALS AND METHODS

Materials

Lactose (Merck, Germany), magnesium stearate, paracetamol (May and Baker, England), distilled water (UNN Water Resources, Nsukka, Nigeria). *Zea mays* and *Oryza sativum* starch was obtained from a batch processed in our laboratory. All other reagents and solvents were analytical grade and were used as supplied.

Extraction and purification of starch

Zea mays seed and *Oryza sativum* (rice) grains were purchased from Nsukka market in Enugu State, Nigeria in the month of February, 2010. The grains were cleaned of

dirt and foreign materials and washed with clean water. They were soaked in a 1 % solution of sodium hypochlorite solution for 6 h and washed with this solution 3 times and thereafter, soaked in clean water containing 1 % sodium metabisulphite (anti-oxidant) for 24 h. After washing, the grains were reduced to a fine pulp in a rasping machine of hammer mill type . The pulp was separated from the fibers by means of a muslin cloth and agitation was provided using hands. During screening, the water used contained 1 % sodium metabisulphite in order to avoid discolouration of the starch by oxidative enzymes. The obtained starch suspension was allowed to settle under gravity and the supernatant was decanted. The starch suspension was washed severally using three times its volume of water for 3 days with intermittent shaking and changing of water. Dewatering was done using a bag with pores of about 100 mm and pressure was applied using hand. The starches were dried in an oven at 40 °C and passed through sieve number 100 [10].

Co-precipitation of starch

Co-precipitation of the starches was carried out using acetone as the precipitating agent. A 1:1, ratio of maize starch and rice starch were used to prepare the starch co-precipitate. The starches were first dispersed in warm water in separate beakers; both of the starch dispersions were brought to the same temperature (40°C), mixed together and stirred for five minutes. The mixture of the starches was precipitated using acetone and the mixtures were washed severally with acetone until a strong non-slimy starch was obtained. The co-precipitates were dried in a tray dryer (Manesty Ltd, Liverpool, England), pulverized in an end runner mill (Pascal engineering co Ltd, England) and finally passed through 1.0 mm sieve (Turgens & Co., Germany).

Table 1: Composition of paracetamol tablets

Batch	Paracetamol (mg)	Starch Co-precipitate (paste) (mg)	Starch Co-precipitate (mg)	Magnesium stearate (mg)	Ac-di-sol (mg)	Lactose q.s. (mg)
A1	500.0	60.0	30.0	6.0	-	600.0
A2	500.0	60.0	45.0	6.0	-	600.0
A3	500.0	60.0	60.0	6.0	-	600.0
A4	500.0	60.0	72.0	6.0	-	600.0
A5	500.0	60.0	90.0	6.0	-	600.0
B	500.0	60.0	-	6.0	18.0	600.0

Key: A1-A5 contain 5, 7.5, 10, 12 and 15 %w/w of co-precipitated starch, B contains Ac-di-sol (3 %w/w) as disintegrant.

Preparation of granules

Granules were prepared by wet granulation method using co-precipitated starch as binder (10 %w/w) and disintegrant (5, 7.5, 10, 12 and 15 %w/w), while lactose was used as filler. The powders were dried and mixed for 10 min in a tumbler mixer with the paracetamol powder. The powder mixtures were moistened with the appropriate amount of binder solution. The homogeneous wet mass was then screened through a 1.7 mm sieve and the wet granules dried in a hot air oven at 55 °C for 1 h. Thereafter, the dried granules were screened through a 1.0 mm sieve [11-12]. Details of granulation are given in Table I. A reference tablets batch containing Ac-di-sol as the disintegrant was also formulated.

Characterization of granules

Bulk and Tapped Densities

A 50 g quantity of the granules was placed in a 100 ml measuring cylinder. The volume occupied by the sample was noted as the bulk volume. The bulk density was obtained using Equation 1:

$$\text{Bulk density } (\ell_B) = \frac{\text{Mass of powder (M)}}{\text{Bulk volume of powder } (V_B)} \quad (1)$$

The cylinder was tapped on a wooden platform by dropping the cylinder from a height of one inch at 2 seconds interval until there was no significant volume reduction. The volume occupied by the sample was then recorded as the tapped volume [13-14]. The tapped density was calculated using the formula:

$$\text{Tapped density } (\ell_T) = \frac{\text{Mass of powder (M)}}{\text{Tapped volume of powder } (V_T)} \quad (2)$$

Flow rate and angle of repose

A funnel was properly clamped on to retort stand. The funnel orifice diameter, base diameter and efflux tube length were appropriately measured. A 50 g quantity of the granule was weighed out and gradually placed into the funnel with the funnel orifice closed with a shutter. The time taken for the entire sample in the funnel to flow through the orifice was noted. The flow rate was obtained using the equation 3:

$$\text{Flow rate (w)} = \frac{\text{Mass of powder (g)}}{\text{Time of flow (s)}} \quad (3)$$

The dynamic angle of repose was determined by measuring the height of heap of powder formed using a cathetometer; the radius was gotten by dividing the diameter by two. Angle of repose (Θ) for each granule sample was gotten using the equation[13-14]:

$$\theta = \tan^{-1} \frac{\text{height of powder heap}}{\text{radius of powder}} \quad (4)$$

Compressibility index and Hausner's quotient

Carr's compressibility index (%) of the granules was obtained using the formula:

$$\text{Carr's index (\%)} = \frac{\ell_T - \ell_B}{\ell_T} \times 100 \quad (5)$$

While Hausner's ratio was obtained using Equation 6:

$$\text{Hausner's ratio} = \frac{\ell_T}{\ell_B} \quad (6)$$

Where ℓ_T and ℓ_B are tapped and bulk density respectively.

Preparation of tablets

Initially granules were treated with magnesium stearate. Tablets were prepared by compressing the lubricated granules at 46-48 kgf an automated F3 Manesty Single Punch tabletting machine.

Evaluation of tablets

Disintegration time test

Disintegration time test was conducted using an Erweka ZT 120 basket and rack assembly and 0.1 N HCl maintained at 37.0 ± 1.0 ^{o}C as the disintegration medium. Ten tablets from each batch were used for the test and the procedure being as stipulated in the BP, 2009 for normal release tablets [15].

Uniformity of Weight

Twenty tablets were randomly selected from each batch. The tablets were weighed individually using an electronic balance (Ohaus Adventurer, China) and the individual weights were recorded. The mean weight, standard deviation and percentage deviation were calculated [15].

Tablet friability test

Twenty tablets were randomly selected from each batch of the tablet. The tablets were dedusted and weighed. The tablets were placed into the drum of the friabilator (Erweka GmbH, Germany) and rotated at 25 rpm for 4 min. The tablets were removed from the friabilator, dedusted and reweighed. The friability result was expressed as loss of mass expressed as a percentage of the initial mass[15]. The abrasion resistance B was calculated from the equation below:

$$Friability\ (\%) = \frac{w_i - w_f}{w_i}\ x\ 100 \quad (7)$$

where w_i and w_f are the initial weight and final weight of the tablets respectively.

Hardness/crushing strength test

This test was carried out using a Monsanto-stokes hardness tester. Ten tablets from each batch were randomly selected. Each tablet was placed between the jaws of the hardness tester and force was applied by adjusting the knob of tester until the tablet integrity failed. The results were recorded in kgf.

In vitro release studies

Beer's calibration curve for paracetamol was obtained at a concentration range of 0.1 – 0.8 mg/ml in 0.1 N HCl at a predetermined wavelength of 245 nm. The *in vitro* dissolution profile for each batch of tablets was determined using the paddle method [15], with an Erweka DT 600 Dissolution apparatus. The dissolution medium consisted of 900 ml of freshly prepared 0.1 N HCl. The temperature of the medium was maintained at 37 ± 1 ^{o}C. A tablet from each batch was placed inside a tightly secured basket and the basket was placed in the bottom of the beaker. The paddle was rotated at 100 rpm. At predetermined intervals, 5 ml sample was withdrawn from the dissolution medium, filtered with a non adsorbent filter paper (Whatman No. 1) and the filtrate was assayed using spectrophotometer (Jenway 6305, UK) at 245 nm. An equal volume of the withdrawn sample was replaced with a fresh medium to maintain sink condition. The amount of drug released at each time interval was determined with reference to the Beer's plot for the drug.

Statistical analysis

Statistical analysis was carried out using SPSS version 14.0 (SPSS Inc. Chicago, IL.USA). All values are expressed as mean ± SD. Data were analysed by one-way analysis of variance (ANOVA). Differences between means were assessed by a two-tailed student's T-test. $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Micromeritic properties

The results of the micromeritic properties of paracetamol granules formulated with varying ratios of rice and corn starch co-precipitate are shown in Table 2. The results show that the granules exhibited good flowability and the values obtained are within acceptable limit for the production of good quality tablets. The results of flow rate showed that the granules had good flow. The angle of repose in all the batches ranged from 17.22 to 26.84 ^{o} therefore, the granules exhibited low interparticulate friction and hence good flowability. The results of bulk and tapped densities showed that the granules exhibited low bulk and tapped densities and therefore possess good powder fluidity. The results of Hausner's ratio showed that the values obtained ranged from 1.14 to 1.29. The results of compressibility indices of the paracetamol granules showed that the granules had percent compressibility index that ranged from 13.64 to 22.22 % and hence exhibited good flowability.

Angle of repose measures the degree of interparticulate friction within the particles. And values below 30^{o} denote good flowability. From the results, the granules exhibited angle of repose significantly below 30^{o} ($p < 0.05$). Hausner's ratio less than or equal to 1.25 indicates good

flow, while Hausner's ration greater than 1. 25 indicate poor flow. Therefore, the granules were within the specified limits for good flow. Also, Carr's index of 5 – 16 indicates good flow, while 18 – 23 shows fair flow. Therefore, the granules exhibited good flowability [13-14].

Tablets properties

Uniformity of tablets weight

The results of tablets weight uniformity tests showed that all the paracetamol tablets formulated passed the uniformity of weight test and deviations obtained complied with BP specifications of not more than 5 % for tablets weighing more than 250 mg [15]. Tablets weight uniformity test is important because variation in tablet weight causes variation in drug content. Weight variation could be caused by factors that affect flowability and granules densification behaviours which could be a function of granule shape, particle size of granules and size distribution, particle density and interparticle cohesion among others.

Tablets hardness

The results of tablets hardness showed that all the tablets passed the test for crushing strength, the tablets hardness ranged from 5.97 ± 1.26 to 6.66 ± 1.28 kgf for A1 and A3 tablets, while the reference showed hardness of 7.46±1.74 kgf, significantly different from paracetamol tablets formulated with starch co-precipitate as disintegrant. The results of tablets hardness presented in Table 3 also showed that the tablets exhibited good hardness properties and passed the test for tablets hardness. However, the reference batch containing Ac-di-sol exhibited higher hardness properties more than the test tablets ($p < 0.05$). However, tablet hardness may be a function of the physical properties of granule such as hardness of the granules and deformation under load which may be affected by the type and quantity of binder and lubricant and compression pressure.

Results of tablets friability showed that all the paracetamol tablets passed the friability test with friability of ≤ 1 %, however, batch A2 exhibited friability result of 2.32 %. Friability test measures the resistance of tablets to abrasion [16]. From the results of tablets friability presented in Table 3, all the batches of paracetamol tablets passed the test of friability. Therefore, the tablets can withstand shock or vibrations during handling, packaging and transportation.

Table 2: Micromeritic properties of paracetamol granules

Flow properties	A1	A2	A3	A4	A5	B
Flow rate (g/sec)	13.68	13.74	13.69	12.79	14.07	13.18
Angle of repose (^{o})	18.26	22.98	24.94	17.22	26.84	21.11
Bulk density (g/ml)	0.50	0.49	0.51	0.512	0.50	0.51
Tapped density (g/ml)	0.65	0.62	0.65	0.58	0.63	0.59
Hausner's quotient	1.28	1.25	1.28	1.13	1.25	1.18
Compressibility index (%)	22.21	20.00	22.22	13.64	19.65	15.38

Key: A1-A5 contain 5, 7.5, 10, 12 and 15 %w/w of co-precipitated starch, B contains Ac-di-sol 10 %w/w as disintegrant.

Table 3: Properties of paracetamol tablets

Batch	Weight (mg ± CV)*	Hardness (kgf ± SD)[a]	Friability (%)*
A1	591.00 ± 2.72	5.97 ± 1.26	1.34
A2	599.00 ± 1.67	5.90 ± 0.76	2.32
A3	603.00 ± 1.69	6.66 ± 1.28	0.63
A4	598.00 ± 2.14	6.11 ± 1.57	0.98
A5	594.00 ± 2.20	6.57 ± 1.26	0.67
B	599.00 ± 2.90	7.46 ± 1.74	0.59

*Mean for 20 tablets, [a]Mean for 10 tablets ± SD, CV: coefficient of variation, SD: standard deviation, A1-A5 contain 5, 7.5, 10, 12 and 15 %w/w of co-precipitated starch, B contains Ac-di-sol 3 %w/w as disintegrant.

Disintegration time

Also, results of tablet disintegration time presented in Fig. 1 showed that the disintegration time of paracetamol tablets ranged from 6.66 ± 0.48 to 12.55 ± 1.47 min for A1 and A5 tablets formulated with 5 and 15 %w/w of starch co-precipitate, while the reference tablets containing Ac-di-sol (batch B) had disintegration time of 6.69 ± 1.01 min. Therefore all the paracetamol tablets formulated complied with BP specifications for the disintegration time of normal release tablets of ≤ 15 min. The disintegration time of the tablet formulations was significantly affected by the concentration of the starch co-precipitate used during formulation ($p < 0.05$). Disintegration time of tablets increased as the concentration of the disintegrant increased as shown in Fig. 1. However, tablets disintegration time may be a function of type and concentration of binder, type and concentration of disintegrants and lubricant, physical properties of granule such as hardness of the granules and deformation under load which may be affected by the type and quantity of binder and lubricant and compression pressure [16].

***In vitro* release**

The *in vitro* release profile of paracetamol tablets are shown in Fig 2. From the results, all the tablets batches showed good release properties. The time for maximum release ($T_{100\ \%}$) of drug from A1 tablets was at 15 min.

Batches A2, A3, and A4 had $T_{100\ \%}$ at 20 min, while batch A5 had $T_{100\ \%}$ at 25 min. However, the reference tablets containing Ac-di-sol exhibited $T_{100\ \%}$ at 30 min. The results of the *in vitro* release properties of paracetamol tablets showed that all the tablets exhibited good release properties as normal release tablets and the release properties of paracetamol tablets formulated with starch co-precipitate as the disintegrants were comparable to the release properties of the reference tablets containing Ac-di-sol.

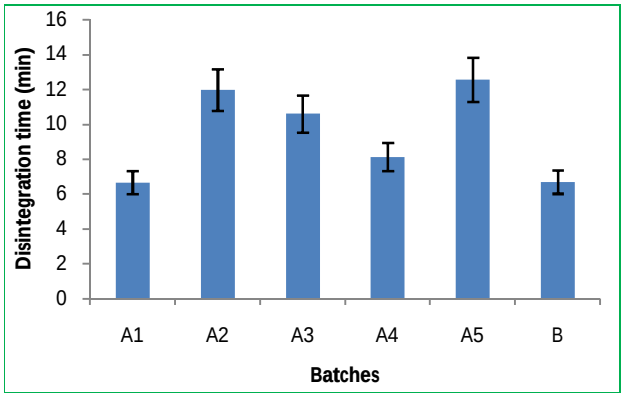

Figure 1: Disintegration time of paracetamol tablets formulated with co-precipitate of *Zea mays* and *Oriza sativum* starch as binder-disintegrant; A1, A2, A3, A4 and A5 contain 5, 7.5, 10, 12 and 15 %w/w of starch co-precipitate (disintegrant), B (reference) contains Ac-di-sol 3 %w/w as disintegrant.

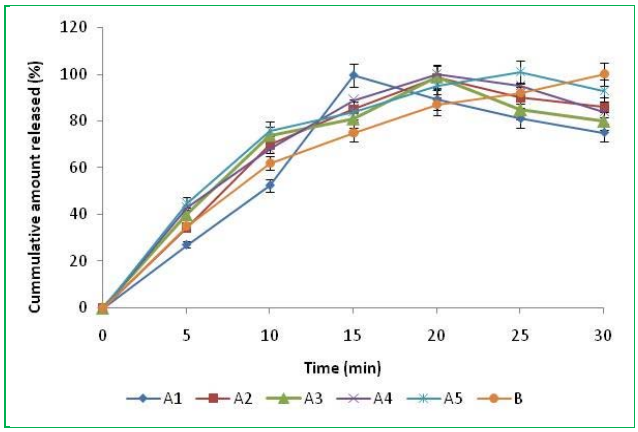

Figure 2: Release profile of paracetamol tablets formulated with co-precipitate of *Zea mays* and *Oriza sativum* starch as binder-disintegrant; A1, A2, A3, A4 and A5 contain 5, 7.5, 10, 12 and 15 %w/w of starch co-precipitate (disintegrant), B (reference) contains Ac-di-sol 3 %w/w as disintegrant.

CONCLUSION

Paracetamol tablets containing *Zea mays* and *Oryza sativum* starch co-precipitate were formulated and the results obtained from the study of tablets properties showed that the tablets had good properties as normal release tablets. Also the properties of the tablets were comparable to the properties exhibited by standard reference tablets formulated with Ac-di-sol as disintegrants. Therefore formulation of co-precipitates of starch is highly recommended as they yield an entirely new polymer with improved properties over the individual polymers.

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