Evaluation of fast disintegrating tablets of paracetamol prepared from a blend of croscarmellose sodium and *Pleurotus tuber-regium* powder

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Abstract: The study investigated the combination effects of the mixture of croscarmellose sodium and *Pleurotus tuber-regium* powder on the granules and tableting parameters of paracetamol tablets. Five batches (A-E) of paracetamol tablets were formulated using wet granulation method with various combination ratios of croscarmellose sodium and *Pleurotus tuber-regium* powder as disintegrant incorporated both intra- and extra granularly. Their granule properties such as bulk and tapped densities, angle of repose, Carr's index, Hausner's ratio and post compression parameters such as friability, hardness, disintegration time and drug release profiles were evaluated. The results showed a decrease in disintegration time with increasing concentration of *Pleurotus tuber-regium* powder with disintegration times ≤ 3.58 min. There was an increase in hardness (values ≥ 4.34 kp) and a decrease in friability (values ≤ 0.6 %) of the tablets with increasing concentrations of *Pleurotus tuber-regium.* All the tablets exhibited comparable drug release profiles with over 80 % of their drugs released in 1 h. Harder and less friable fast disintegrating tablets of paracetamol can be obtained with *Pleurotus tuber-regium* powder in combination with croscarmellose sodium. The combination of croscarmellose sodium and *Pleurotus tuber-regium* possesses potentiative effect on their disintegrant activity.

Keywords: *Pleurotus tuber-regium*, croscarmellose sodium, combination, granules, tablets.

INTRODUCTION

Fast disintegrating or fast dissolving tablets (FDTs) are tablets that disintegrate and/or dissolve rapidly in the saliva without the need for water. These forms of tablet are gaining prominence as solid dosage forms and emerging as one of the popular and widely accepted drug delivery forms, especially for paediatric and geriatric patients. In order to solve the problem of difficulty in swallowing and to improve patient compliance, fast disintegrating tablets are now considered as ready alternatives to conventional tablet and capsule formulations (Sehgal *et al.*, 2012).

Pleurotus tuber-regium is a tropical mushroom that produces an underground tuber also known as a sclerotium as well as an umbrella or areal part (mushroom). Both the mushroom and sclerotium are edible. The sclerotium is spherical to ovoid and can be as large as 30cm or more in diameter while the mushroom has a cap which curves upward to form a cup-like shape (Oso, 1977). It is dark brown on the outside and white on the inside and is usually harvested from decaying logs. It is most commonly used in Nigeria as a dietary condiment in thickening of soup. The white tissue is grinded into fine powder and added as a soup ingredient. When added to soup, it swells and adds bulk to the soup. Iwuagwu and Onyekweli, 2002 investigated its possible use as a tablet disintegrant as a result of its swelling property.

In recent times, focus is shifting to the use of natural superdisintegrants in the formulation of fast disintegrating tablets due to the added advantage of chemical inertness, non-toxicity, biodegradability and for their cost effectiveness and wider availability. They are also eco-friendly and provide nutritional supplement (Malafaya *et al*., 2007, Malyiya *et al*., 2011).

The purpose of this study is to investigate the effect of combining *Pleurotus tuber-regium* powder with croscarmellose sodium on the physicochemical properties of paracetamol granules and tablets.

MATERIALS AND METHODS

Materials

Paracetamol powder (Edo Pharmaceuticals, Benin City, Nigeria), croscarmellose sodium (Ac-Di-Sol®) (FMC BioPolymer, USA), maize starch BP and talc (BDH Chemicals, UK), lactose (Merck Dermstard, Germany), magnesium stearate (Hopkin and William, UK) were used as supplied. *Pleurotus tuber-regium* tubers were purchased from a local market in Benin City, Edo State, Nigeria and processed into powder in our laboratory. All sieves were British Standard Sieves (Endecotts Ltd. London, England).

Methods

Preparation of Pleurotus tuber-regium powder

Dry tubers of *P. tuber-regium* were processed into powder using an earlier reported method (Iwuagwu and

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Onyekweli, 2002). The outer dark brown layer of the sclerotia was scraped off with a knife and the inner white tissue was chopped into pieces. The pieces were minced into powder in a dry mill and their sizes further reduced using a ball mill. The resulting powder was passed through a 210 µm laboratory sieve to obtain fine powder.

Preparation of maize starch BP mucilage

Maize starch BP (10g) was weighed (B154, Toledo, Switzerland) into a beaker containing 5ml of distilled water and stirred to make a slurry. Boiling water was added to make up to 100ml volume with continuous stirring to give a 10% w/v maize starch mucilage, used as the binder (Odeku and Itiola, 2002, Karr *et al*, 1990).

Preparation of paracetamol granules

The formula used in preparing the paracetamol granules using the wet granulation method are shown in table 1. Each batch was prepared by weighing and mixing for 5 min half of the amounts of croscarmellose sodium and/or *P. tuber-regium* powders with the required amounts of lactose and paracetamol. The powder mix was granulated with sufficient quantity of the maize starch mucilage (binder) and the wet mass was passed through a 1.40 mm sieve and then dried at 60ºC for 30 min in a hot air oven (Gallenkamp, UK). The dry mass was passed through an 850 µm sieve and further dried for 30 min. The granules were subjected at this stage to various flow properties analyses.

Thereafter, the glidant (magnesium stearate), lubricant (talc) and the other half of the disintegrant (s) were intimately mixed with the dry granules in geometric proportion in readiness for compression. Granules sufficient to produce 100 tablets per batch was prepared.

Granule analysis

Pre-compression analyses were carried out on the granules using standard procedures; bulk density, tapped density, Carr's (Compressibility) index, Hausner's quotient or ratio, flow rate and angle of repose (Eraga *et al*., 2015).

Bulk density

Paracetamol granules (30g) was weighed and poured gently into a 100ml measuring cylinder. The volume occupied by the granules was recorded as the bulk volume. Triplicate determinations were carried out and the average values generated were used to calculate the bulk density employing Equation 1.

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Volume of granules}} \quad (1)$$

Tapped density

The measuring cylinder containing the 30g granules was tapped mechanically on a flat surface for about a 100 times to a constant volume which was recorded as the tapped volume. Triplicate determinations were carried out and the average values generated were used to calculate the tapped density using Equation 2.

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume of granules}} \quad (2)$$

Carr's (Compressibility) index

Using Equation 3, the difference between the tapped and bulk densities of the granules divided by the tapped density was calculated and the ratio expressed as a percentage to give the Carr's index.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (3)$$

Hausner's ratio

The ratio of the tapped density to the bulk density of the granules was calculated as the Hausner's ratio or quotient with Equation 4.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (4)$$

Flow rate

The time taken for 50g of the paracetamol granules to pass through the orifice of an Erweka flow tester (Model: GT, GmbH, Germany) was recorded. This was carried out in triplicates and the mean value recorded.

Angle of repose

The hollow tube method was used. A short hollow tube of 3 cm in internal diameter sitting on a circular horizontal surface of same diameter was filled with granules. The tube was withdrawn vertically and excess granules allowed to fall off the edge of the circular horizontal surface. The height of the heap was measured. The angle of repose, θ, was calculated using Equation 5.

$$\theta = \tan^{-1}\frac{h}{r} \quad (5)$$

Where h is the height of the heap of granules and r is the radius of the circular base

Compression of granules

Batches of the granules were compressed into tablets using a single punch tableting machine (F-3 Manesty Machines, UK) at a compression pressure of 25.5N. The die volume was adjusted to compress tablets of uniform weight by using granules weighing between 660mg. The tablets made were then kept in air tight containers and stored in a desiccator until evaluation.

Characterization of tablets

The following post compression tests were carried out on the compressed tablets using standard procedures: uniformity of tablet weight, crushing strength (hardness), friability, disintegration time and dissolution test (BP, 2003).

Uniformity of weight
Twenty tablets from each batch were used for the test. The weight of each tablet was determined and the mean or average weight and standard deviation was computed.

Hardness test
Using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India), the crushing strength of each of ten tablets per batch was determined. The mean hardness value and standard deviation was calculated.

Friability test
Pre-weighed tablets (10) were placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm. After 4 min, the tablets were brought out, de-dusted and reweighed. Their percentage loss in weight value was calculated. Triplicate determination was carried out and the mean and standard deviation were reported.

Disintegration time
The time taken for six tablets per batch to disintegrate in distilled water at 37±0.5°C were determined using the BP disintegration tester (MK IV, Manesty Machines, UK). The mean or average time and standard deviation was calculated.

Wetting time and water sorption ratio
A weighed tablet was placed on a soaked mass of cotton wool in a petri dish and small amount of amaranth powder was placed on the upper surface of the tablet. The time taken for the development of a red colour on the upper surface of the tablet was taken as the wetting time (Patel *et al.,* 2007). The wetted tablet was then reweighed and the water sorption ratio of the tablet was calculated as the difference between the final and initial weights with respect to the initial weight and expressed as a percentage. Triplicate determinations were carried out and the average wetting time and water sorption ratio with their standard deviations were calculated.

Dissolution test
The *in vitro* dissolution analyses of the various batches of the paracetamol tablets were carried out using the BP paddle method. A dissolution apparatus (Caleva ST7, UK) containing 900ml of 0.1M HCl solution maintained at 37±0.5°C with a revolution speed of 50 rpm was used. Samples (5ml) were withdrawn from the dissolution fluid at specific time intervals over a period of 60min and replaced with an equivalent volume maintained at same temperature (37±0.5°C). The withdrawn samples were filtered and diluted appropriately with 0.1M HCl solution. The resulting solutions were subjected to spectrophotometric analysis at λmax of 245nm (T70, PG Instruments Ltd). The amount and the percentage of drug released at each time interval was calculated using the equation from the standard calibration plot obtained from pure paracetamol powder.

STATISTICAL ANALYSIS

Statistical difference in the tablet parameters (disintegration time, wetting time and moisture sorption ratio) of the various batches were subjected to student's t-test at 5% level of significance using GraphPad InStat 3.10.

RESULTS

Granule properties
The results from the flow properties analysis of the formulated paracetamol granules are shown in table 2. The bulk and tapped densities of the granules were between 0.43-0.49 and 0.50-0.58mg/ml, respectively, while the flow rate of the granules was within the range of 3.82-4.58g/sec. The angle of repose of the granules in batches B, D and E were 26.8, 27.4, 29. 9º, respectively, indicating good flow of the granules. Batches A and C granules had angles of repose of 30.0 and 30.7º respectively, which indicates fair/passable flow of the granules. The Hausner ratios and Carr's indices of the granules ranged from 1.17-1.26 and 14.80-20.32%, respectively, indicating relatively 'good' to 'fair' flow properties (Carr, 1965).

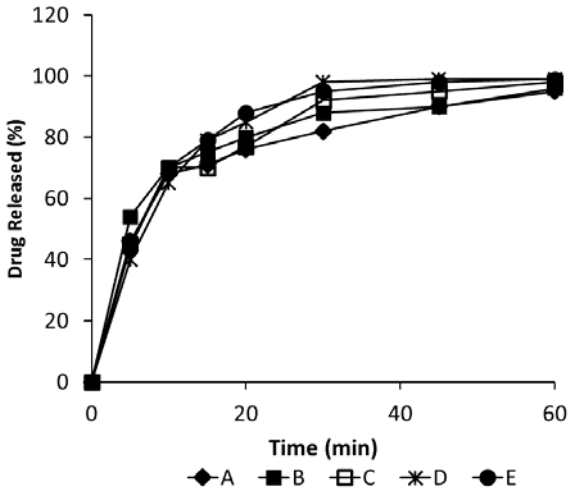

Fig. 1: *In vitro* drug release profile of the different batches of paracetamol tablets

Tablet properties
Physical characteristics
The tablets were off-white, with slightly bitter taste and no odour. The tablet surfaces were elegant and smooth to touch. The intensity of the off-white colour increases across the batches from A-E. The off-white colour is due to the presence of *P. tuber-regium* powder in the formulation.

Weight and dimensions
The results from the evaluations of the formulated paracetamol tablets are presented in table 3. The mean

Table 3: Some physicochemical properties of the paracetamol tablets

Parameter	Batch A	Batch B	Batch C	Batch D	Batch E
Weight (g)	0.661 ± 0.009	0.660 ± 0.008	0.662 ± 0.025	0.663 ± 0.024	0.660 ± 0.021
Diameter (mm)	12.59 ± 0.017	12.59 ± 0.019	12.60 ± 0.015	12.59 ± 0.024	12.59 ± 0.009
Thickness (mm)	3.85 ± 0.016	3.83 ± 0.032	3.85 ± 0.197	3.87 ± 0.056	3.84 ± 0.057
Hardness (kp)	4.34 ± 0.422	4.66 ± 1.130	5.01 ± 1.432	6.37 ± 1.672	7.70 ± 1.204
Friability (%)	0.6 ± 0.015	0.6 ± 0.011	0.5 ± 0.015	0.4 ± 0.017	0.3 ± 0.014
Disintegration time (min)	3.58 ± 0.665	3.42 ± 0.411	1.37 ± 0.138	1.08 ± 0.043	1.31 ± 0.216
Wetting time (min)	5.45 ± 0.664	3.47 ± 0.763	3.35 ± 0.171	2.65 ± 0.516	3.05 ±0.561
Moisture sorption (%)	50.58 ± 0.650	52.49 ± 0.865	66.43 ± 1.015	91.6 ± 1.665	85.32 ± 0.544
$T_{70\%}$ (min)	15 ± 1.15	10 ± 2.10	10 ± 1.25	10 ± 0.95	10 ± 1.05

Mean ± standard deviation, $T_{70\%}$ = time to achieve 70% drug release.

weight of the tablets was between 0.660-0.663g, while the mean thickness and diameter ranged between 3.83-3.87 mm and 12.59-12.60mm, respectively.

Hardness and friability

The mean hardness of the tablets was between 4.54-7.7 kp with the highest values observed in Batch E tablets. The hardness of the tablets was found to be satisfactory, as a crushing strength above 4 kp is considered satisfactory for tablets (Rudnic and Schwartz, 2000). The 10% maize starch mucilage used as binder in the formulation also contributed to the hardness of the tablets. The percentage friability of the tablets was between 0.3-0.6% with the highest values observed in Batch A tablets. The friability of the tablets was observed to decrease with increased concentrations of *P. tuber-regium* powder. The increase in the hardness of tablets and a decrease in friability from batch A-E suggests that increasing the concentration of *P. tuber-regium* increases the tensile and mechanical strength of the tablets.

Wetting time, moisture sorption and disintegration time

The highest wetting time was obtained from the tablets in batch A at 5.45 min which showed that the tablets in this batch possessed fairly good moisture sorption capacity of 50.6 % compared with batches B-E, with wetting times of 3.47, 3.36, 2.65, 3.05 min, respectively and moisture sorption of 52.5, 66.4, 91.6, and 85.3%, respectively. The disintegration times of the various batches was from 1.08 -3.58min with decrease in disintegration time with increase in *P. tuber-regium* powder concentration.

Dissolution rate

The dissolution of the tablet indicated more than 70% of the drug was released within 45 min (fig. 1) which complied with Pharmacopoeia specifications (BP, 2011), which states that 70% of the loaded drug should be released within 45 min of the dissolution test. Even though this specification is for conventional immediate release tablets, it is also applied to fast disintegrating tablets. In all the batches, it was observed that as the concentration of *Pleurotus tuber-regium* increases, the drug release rate also increased. The percentage of drug released was greatest in Batch E and least in Batch A, this show that *Pleurotus-tuber-regium* increases the dissolution rate of the drug.

DISCUSSIONS

The disintegrant property of *P. tuber-regium* has been previously established. Its disintegration activity occurs at 2-10% w/w concentrations (Iwuagwu and Onyekweli, 2002). Since the goal of this study was to achieve super disintegration property, *P. tuber*-regium has been used in combination with croscarmellose sodium. Croscarmellose sodium is effective as a disintegrant at 2 %w/w concentration while *P. tuber-regium* was added up to 10 %w/w. A higher amount of croscarmellose sodium could produce faster disintegrating tablets but that would result in increased material utilization and consequently increase cost of production.

According to the European Pharmacopoeia, 2008, a disintegration time of less than 3 min is expected for FDTs. Tablets in Batch A and B had an average disintegration time of 3.58 and 3.42 min respectively, hence did not meet Pharmacopoeia standards. But for tablets in batches D-E, the disintegration time was within pharmacopoeia limits. Also batches D-E showed superior wetting times indicating an increase in water uptake with the addition of *P. tuber-regium* thus suggesting that wicking and swelling may be the mechanisms of its disintegration action. Wetting time gives an idea of how fast the tablet will absorb moisture when placed on the tongue without agitation, it also give an idea of how fast the tablets will disintegrate. The lower the wetting time, the faster the disintegration of the tablets (Bandari *et al.*, 2008; Bhowmik *et al*, 2009).

A combination of one part croscarmellose sodium to ten parts of *P. tuber-regium* as seen in batch D resulted in optimal disintegration property of the tablets. This batch of tablets also exhibited excellent hardness and wetting time. There may be need to continually vary the relative concentrations of both disintegrants for any tablet to be produced until optimal performance is achieved. Also,

Table 1: Formula of prepared paracetamol granules and tablets

Batch (Mix ratio)	Drug	Croscarmellose sodium	*P. tuber-regium*	Lactose	Glidant & Lubricant (1 %w/w)	Total
A (1:0)	500	10	-	140	10	660
B (1:2)	500	10	20	120	10	660
C (1:5)	500	10	50	90	10	660
D (1:10)	500	10	100	40	10	660
E (0:10)	500	-	100	50	10	660

NB: All weights are in mg units

Table 2: Flow properties of the prepared paracetamol granules

Properties	Batch A	Batch B	Batch C	Batch D	Batch E
Tapped density (g/ml)	0.571±0.065	0.580±0.051	0.571±0.062	0.500±0.044	0.526±0.061
Bulk density (g/ml)	0.476±0.011	0.488±0.045	0.455±0.045	0.426±0.022	0.438±0.024
Flow rate (g/sec)	4.26 ± 0.24	4.58±0.12	3.82±0.14	4.08±0.35	4.34±0.16
Angle of repose (°) Limit: < 30°	30.01±0.538	26.83±1.324	30.70±0.911	27.43±1.024	29.90±1.455
Hausner's ratio Limit: < 1.18	1.20±0.12	1.19±0.21	1.26±0.10	1.17±0.09	1.20±0.26
Carr's index (%) Limit: < 15	16.64±0.02	15.86±0.08	20.32±0.14	14.80±0.04	16.73±0.04
Flow characteristics	Fair	Good	Fair	Good	Fair

Mean ± standard deviation

even though the proportion of *P. tuber-regium* in this batch of tablet is high, it has been used in its crude form. Its natural source is a major advantage because of the resulting diversification from known synthetic or semi-synthetic products and subsequent reduction in cost to achieve the production of a much desired super disintegrating tablets of paracetamol.

CONCLUSION

Paracetamol tablets from a combination of *Pleurotus tuber-regium* powder and croscarmellose sodium showed greater disintegrating ability and better dissolution than those from *Pleurotus tuber-regium* or croscarmellose sodium alone at the concentrations investigated. Also, *Pleurotus tuber-regium* improved the mechanical and tensile strength of the tablets resulting in less friable tablets with fast disintegrating properties even at low compression pressures.

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