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SHORT COMMUNICATION

ASSESSMENT OF DISINTERGRANT PROPERTIES OF *PLEUROTUS TUBER-REGIUM*, CORN STARCH AND HYDROXYPROPYL METHYLCELLULOSE IN CLOXACILLIN TRIHYDRATE CAPSULE FORMULATIONS

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ABSTRACT

Background and aim: This research is aimed at evaluating *Pleurotus tuber-regium* (PTR) as a local pharmaceutical excipient and compare its disintegrant properties with standard disintegrants, corn starch BP and hydroxylpropyl methylcellulose (HPMC) BP in Cloxacillin trihydrate capsule formulation.
Methods: Micronised powder and powder prepared from the giant mushroom, *P. tuber-regium* (Fr) Sing, corn starch BP and HPMC powders were subjected to physicochemical tests (pH, hydration capacity, swelling capacity) and micromeritic tests. Wet granulation method with 7.5 %w/v microcrystalline cellulose as binder was used to produce Cloxacillin trihydrate granules using concentrations of 5.0, 7.5, 10.0 and 12.5 %w/w of the disintegrants. After drying the wet mass and sieving, granule bulk was lubricated, mixed and hand-filled into gelatin capsules to give Cloxacillin trihydrate 500 mg capsules. Physicochemical properties - weight uniformity, disintegration time and moisture absorption tests were evaluated.
Results: Micromeritic and powder properties of the disintegrants were comparable. At similar disintegrant concentrations, disintegration time of Cloxacillin trihydrate capsules formulated with PTR powder was less than those formulated with corn starch and HPMC. At 7.5 %w/w, disintegration time (minute) were: PTR 6.30 ± 0.23, corn starch 6.40 ± 0.15 and HPMC 8.50 ± 0.02. Disintegration time decreased with increase in disintegrant concentration. Weight variation for all formulations were within Pharmacopoeial standards of not more than ± 5% for solid dosage forms ≥ 324 mg.
Conclusion: *P. tuber-regium* powder as a disintegrant in Cloxacillin trihydrate capsule formulation, showed greater disintegrant ability than formulations with the standard disintegrants. Therefore, the mushroom, *P. tuber-regium* powder could be used as a suitable substitute for corn starch BP and HPMC in Cloxacillin trihydrate capsule formulation.

Key words: Cloxacillin trihydrate capsule, *Pleurotus tuber-regium*, disintegrant properties, corn starch, hydroxylpropyl methyl cellulose .

INTRODUCTION

Bold steps towards attaining sustainable and effective delivery of pharmaceutical care globally has since been undertaken by The World Health Organization (WHO) and International Pharmaceutical Federation (FIP). For pharmaceutical products to be affordable, they must be available to the people who need them at a price they can pay [1, 2]. Careful selection of such products do not only consider effective and cheap pharmaceutical active ingredients, but also readily available, cheap, safe and functional excipients [3, 4].

Most drugs including the generic products are manufactured and imported into Nigeria by multinational pharmaceutical companies and this can increase the unit cost of purchase by the patients. There is therefore the need for our indigenous manufacturers to look inwards for local and natural excipients that abound in the country to help produce drugs that are cost effective. This creates the need to investigate the native *Pleurotus tuber-regium* (Tr) sclerotia as possible excipient in solid dosage formulation. This is a mushroom (basidiomycete) that grows wild in the tropical and subtropical regions of the world. *P. tuber-regium* has also been cultivated for food, medicine, and for scientific research purposes [5,6].

Previous researchers described *Pleurotus* as a common mushroom that forms large sclerotia, which are spherical to oval, dark brown on the outside and whitish on the inside and in some cases subterranean in the host [6]. The fungus infects dry wood, where it produces the sclerotium normally found between the wood and the bark. Milled powder of *Pleurotus* is used locally as a soup thickener in some regions of Nigeria, and is rich in carbohydrate. Swelling is one of the mechanisms of action of starches and some other tablet disintegrants when in contact with water. It was thought therefore, that the powder of *P. tuber-regium* would be a suitable excipient to act as a tablet disintegrant in the formulation of solid dosage form. *Pleurotus* has potential applications for nutritional, medicinal and industrial purposes [7]. Conventional disintegrants in tablet and capsule formulations are starch, among which are maize, potato, and other starches from natural sources and hydroxylpropyl methylcellulose (HPMC) [7].

This research aimed at investigating the comparative disintegrant properties of *P. tuber-regium* starch, Corn starch BP and HPMC- BP in the formulation of Cloxacillin trihydrate capsules.

MATERIALS AND METHODS

Drugs and chemicals: Pharmaceutical grade Cloxacillin trihydrate BP powder (HELM, Portugal) was supplied by Sonitex Nig. Limited, Benin City, Nigeria; Lactose anhydrous powder BP (Merck Darmstadt Germany), Corn starch BP (BDH Chemicals Ltd, England), Hydroxypropyl methylcellulose BP (NFXII, Japan). All excipients were purchased from Sonitex Chemicals Ltd, Benin City, Nigeria.

Preparation of the *Pleurotus tuber-regium* sclerotia and bleaching with sodium hypochlorite solution: *P. tuber-regium* (Tr) sclerotia were purchased at Okada market, Edo State, Nigeria and authenticated by the Department of Pharmacognosy, College of Pharmacy, Igbinedion University, Okada, with an Herbarium number IU-CP-0042.

The outer brown part of *P. tuber-regium* sclerotia (2 kg) was carefully washed in a running tap water to remove the sand, cut into small pieces and dried at room temperature (33±2 °C) for 72 hours. Dried pieces were milled using a blender (Panasonic, Japan) and powder sieved through the aperture of 212 µm and 500 µm sieve sizes, and stored in an air tight glass container. Bleaching was done in line with previous work by Obarisiagbon *et al* [8]. Resulting powder lumps were micronized with a dry mill blender (Moulinex, France) and with a ball mill (Model BS22064, England) to obtain fine powder which was stored in an air tight glass container ready for use.

Determination of micromeritic properties of *Pleurotus tuber-regium*, corn starch BP and hydroxylpropyl methylcellulose BP powders

The micromeritic and some physical properties of the powders were determined using the bulk and tapped densities, angle of repose, Hausner's ratio; and physical properties such as true density (specific gravity), hydration capacity, swelling capacity and pH respectively.

Angle of repose**:** The established method of Jones and Pipel [], was adopted, and modified by Obarisiagbon *et al*. [8,9], was followed, and the angle of repose was calculated using the equation:

$$\text{Tan }\Theta = \frac{h}{r} - - - - - - - - - - - -\text{eq 1}$$

Where h = height of the conical powder heap
r = radius of the circular base.

Mean of 3 determinations was calculated and recorded as the angle of repose for each powder.

Bulk and tapped densities and Hausner's ratio**:** The method of Chaowalit *et al*. [10] was adopted for their determinations, mean of triplicate results calculated and recorded as per equations below:

Bulk density (g/cc^3)

$$= \frac{Weight\ of\ powder\ (g)}{Bulk\ volume\ (vb)} \text{ - -------------------- eq 2}$$

Tapped density (g/cc^3)

$$= \frac{Weight\ of\ powder\ (g)}{Tapped\ volume\ (vt)} \text{ ---------------------eq 3}$$

Results of bulk and tapped densities were computed and used to calculate Hausner's ratio thus:

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density} \text{ ----------eq 4}$$

Compressibility index (%)**:** This was calculated using equation 5

$$\text{Compressibility index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100 \text{ -----eq 5}$$

Determination of pH**:** The aqueous solution of the three disintegrants were each prepared and a pH meter (model benchtop) was used to determine the hydrogen ion concentrations of each.

Determination of moisture content of the disintegrants (%)**:** A thermogravimetric method was used to determine the weight loss on drying of the individual disintegrant sample. The moisture content was calculated using the formula 6 below:

$$\text{Moisture content (\%)} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \text{ -----------eq 6}$$

Hydration capacity (water retention capacity)**:** Powders (1g) each, were placed in a centrifuge tube, covered with 10 ml water. shaken intermittently over a period of 2 hours and left to stand for 30 minutes. This was further centrifuged for 10 minutes at 300 rpm. The supernatant was decanted and weight of the powder after water uptake and centrifugation X was determined.

Hydration capacity = X/y -----------------eq7

Where X is the weight of moist powder after centrifugation and y is the weight of dry powder.

Mean of triplicate determinations were calculated and recorded.

***True density (specific gravity) of the powders*:** The specific gravity bottle method of analysis was employed. The specific gravity bottle of known weight was filled with light liquid paraffin, poured out and a known weight of the powder sample was carefully placed into the specific gravity bottle. This was filled up again with liquid paraffin and weighed. True density of each of the powders was calculated in duplicates and mean values recorded.

$$\text{True Density} = \frac{w \times d}{(a+w)-b} \quad \text{----------------eq 8}$$

Where w = weight of powder, d = specific gravity of light liquid paraffin,
b = weight of bottle + light liquid paraffin + powder

***Swelling capacity*:** The method of Gaila *et al*. [11] was employed to determine the swelling capacities of the powder samples. The swelling capacity was calculated as:

$$\text{Swelling capacity} = \frac{Vv}{Vt} \quad \text{--------------eq 9}$$

Where Vv = volume of sediment after 24 hours, Vt = tapped volume.

The mean of 3 determinations was calculated and recorded for each powder sample.

Preparation of Cloxacillin trihydrate granules by wet granulation method

Wet granulation method of Vadaga *et al.* [12] was employed in the massing of the powder mix using 7.5 %w/v Microcrystalline cellulose (MCC) as a binder in all the batch formulations. The active drug Cloxacillin trihydrate BP, the excipients, and half the amounts of the disintegrants powder *P. tuber-regium,* Corn starch BP, HPMC were separately mixed in a rotating mixer (intragranular disintegrant) for about 5 minutes. The granulating fluid of MCC was applied to granulate the mixed powders. The wet mass was passed through a sieve of pore size 2.0 mm and dried in a hot air oven at a temperature of about 45 ^{o}C for 2 hours, milled and passed through a 710 mm mesh sieve size and kept in an air tight glass container ready for compression. Prior to filling into the empty gelatin capsule the remaining 50% of previously-dried disintegrants were sieved separately onto the granule bed of each batch; appropriate amount of lubricant and talc were added and mixed with a stainless steel spatula for about 5 minutes and hand-filled into the empty gelatin capsule to contain 500 mg of Cloxacillin trihydrate BP. The capsules were dusted and kept in a well-labeled air tight glass container for physicochemical analysis.

Evaluation of physicochemical properties of Cloxacillin trihydrate capsules

***Weight uniformity test*:** Twenty capsules from each batch were randomly selected and weighed together, and then weighed individually using a digital electronic top loading balance (Toledo, Mettler, Switzerland), and the mean weight was calculated and recorded.

***Disintegration test*:** Six tablets were randomly selected from each batch and placed one tablet each in the cylindrical tube of the Disintegration test apparatus (Manesty, Liverpool, England) [13,14]. The cylindrical tube was covered with a wire mesh at the base and immersed in the disintegration medium (800 mL distilled water) maintained thermostatically at 37±0.5 ^{o}C. The time taken for each tablet to break up into particles small enough to pass through the mesh at the base of the cylinder was recorded, and mean of triplicate determination was calculated and recorded as the disintegration time (minute) for each batch.

RESULTS AND DISCUSSION

Results of the micromeritic and powder properties of *P. tuber-regium*, corn starch BP and HPMC are shown in Table 1. The pH of the test disintegrant (*P. tuber-regium*) and the other standard disintegrants were found to be in the slightly acidic range 5.30 - 5.75. Results show that *P. tuber-regium* particles swelled more when in contact with water than the particles of corn starch and HPMC in the order: *P. tuber-regium* (24.20 %) > corn starch BP (21.8 %) > HPMC (20.50 %), respectively. Swelling of the disintegrant in the presence of water increase the internal pressure of the matrix and cause the eventual disintegration of the capsule. Hydration capacity refers to a powder's ability to absorb and hold water as it impacts how quickly the tablet or capsule will break down and dissolve in liquids. The higher their values, the quicker they swell and break down leading to faster disintegration. Result showed the following order: corn starch BP (1.65%) > HPMC (1.60%) > *P. tuber-regium* (1.58%). Moisture content absorbed by the different formulations ranged from HPMC (10.20 %), *P tuber-regium* (10.40 %) to corn starch (11.75 %). These results agree with those of previous research workers [8,15].

The angle of repose is a significant indicator of a powder's flowability, with lower angles generally indicating better flow, hence the order of better flow is: corn starch BP (38.20^{o}) > HPMC (40.30^{o}) > *P. tuber-regium* (45.10^{o}). Hausner's ratio is the ability of a powder to flow easily under pressure or during processing; lower ratios indicating better flowability, hence *P. tuber-regium* (1.24) > HPMC (1.32) > corn starch BP (1.48), respectively. Compressibility index (%), reflects a powder's tendency to consolidate and compact under pressure. Lower values indicate better flowability, while a higher value suggests poorer flow.
Results of compressibility index showed flowability of *P. tuber-regium* (19.51) > HPMC (29.40) > corn starch BP (32.26).

Table 2 shows the results of physicochemical properties of Cloxacillin trihydrate capsule that were evaluated: weight variation (mg), and disintegration time (minute). The mean weight (gm) of the different capsule formulations was not remarkably affected by the type and concentration of the disintegrants. The disintegration time (minute) of the Cloxacillin trihydrate capsules formulated with the different types and concentrations of disintegrants, were less than 15 minutes (the official limit for uncoated tablets and capsules) and the disintegration time was concentration dependent, their values decreasing with increase in concentration of disintegrant. The results show that *P. tuber-regium* starch powder produced Cloxacillin trihydrate capsules properties similar to those of previous studies [14,16].

Table 1. Micromeritic and powder properties of *Pleurotus tuber-regium*,corn starch BP and hydroxypropyl methylcellulose BP

Parameter	***Pleurotus tuber-regium***	**Corn starch BP**	**Hydroxypropyl methylcellulose BP**
pH	5.40	5.30	5.75
Moisture content (%)	10.40	11.75	10.20
Hydration capacity (g/mL)	1.58	1.65	1.60
Bulk properties:			
Bulk density[g/cm^3]	0.33	0.42	0.57
Tapped density[g/cm^3]	0.50	0.62	0.75
True density[g/cm^3]	1.15	1.20	1.35
Flow properties:			
Angle of repose [^{0}]	45.10	38.20	40.30
Hausner's ratio	1.24	1.48	1.32
Compressibility index [%]	19.51	32.26	29.40
Swelling power [%]	24.20	21.80	20.50

Table 2. Physicochemical properties of Cloxacillin trihydrate capsules formulated with different disintegrants

Disintegrant Conc (%w/w)	**Mean disintegration time (min)**			**Weight variation (%)**		
	P. tuber-regium	Corn Starch BP	HPMC	*P. tuber-regium*	Corn Starch BP	HPMC
5.0	8.20±0.20	8.50±0.23	9.80±0.19	0.216±0.05	0.214±0.01	0.215±0.02
7.5	6.30±0.23	6.40±0.15	8.50±0.20	0.210±0.04	0.208±0.12	0.210±0.05
10.0	5.40±0.19	5.80±0.18	7.80±0.22	0.216±0.01	0.216±0.03	0.214±0.05
12.5	4.50±0.15	4.60±0.20	5.50±0.21	0.215±0.02	0.214±0.01	0.215±0.02

HPMC = Hydroxypropyl methylcellulose

CONCLUSION

The differences in the disintegrant properties of the local starch, *P. tuber-regium* in comparison to those of standard disintegrants, Corn starch BP and hydroxypropyl methylcellulose BP in the formulation of Cloxacillin trihydrate capsules were established. Within the limits of the parameters evaluated, disintegration time and weight uniformity, *P. tuber-regium* compared favourably with the standard disintegrants. Therefore, this study has justified the effectiveness of the local starch as a natural disintegrant in the formulation of some solid dosage forms, especially Cloxacillin trihydrate capsules.

Conflict of Interest: The authors hereby declare that there was no conflict of interest in the course of the research.

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