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Comparative Evaluation of the Disintegrant Properties of *Pleurotus tuber-regium* in the Formulation of Ciprofloxacin Hydrochloride Tablets

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ABSTRACT

Micronised Pleurotus tuber-regium powder obtained from *Pleurotus tuber-regium* (Fr) sing, an edible basidiomycete was physicochemically characterized. The physicochemical properties of ciprofloxacin tablets made using various concentrations of the powder as disintegrant (employed both intra and extra granularly) were determined. The values were compared with those of the tablets prepared from similar concentrations of maize starch BP and potato starch BP respectively. At the same concentrations, the disintegration times of ciprofloxacin tablets containing *Pleurotus tuber-regium* powder was found to be shorter than those of ciprofloxacin tablets containing maize and potato starch BP. For example, at a disintegrant concentration of 7.5% w/w, the disintegration time of ciprofloxacin tablets containing *Pleurotus tuber-regium* powder, maize and potato starch BP powders were 2.45 $\pm$ 0.19, 2.80 $\pm$ 0.15 and 2.60 $\pm$ 0.21 minutes respectively. Generally, the disintegration time decreased as the concentration of the disintegrant increased. The friability of the tablets containing 7.5% w/w disintegrant concentration was 1.11 $\pm$ 0.12%, 1.50 $\pm$ 0.03% and 1.40 $\pm$ 0.02% for *Pleurotus tuber-regium*, maize and potato starch respectively. The hardness of the ciprofloxacin tablets produced decreased gradually with an increase in the disintegrant concentration. This may be attributed to an increase in powder fines as the disintegrant powder is increased, as long as the compression pressure is held constant.

INTRODUCTION:

The production of affordable pharmaceutical dosage forms is a necessary step the WHO has taken towards attaining sustainable and effective delivery of pharmaceutical care globally. Affordability in this sense is the extent to which pharmaceutical products are available to the people who need them at a price they can pay[1]. These dosage forms are mostly generics and usually involve careful selection of not only effective and cheap pharmaceutical active ingredients but also readily available, cheap, and functional excipients. To realize more cost-effective products, these excipients should be multifunctional. It is disturbing that in Sub-Saharan Africa where safe natural products for pharmaceutical industry resources exist in abundance, there is still a continuous decline in the affordability of pharmaceutical generic products. These generic products are manufactured basically by multinationals, hence the clarion call for our indigenous manufacturers to look inward and source for excipients that abound around them. This informs the need to investigate the native *Pleurotus tuber-regium* (Tr) sclerotia as an excipient in solid dosage formulation. It is a mushroom (basidiomycete) that grows wild in the tropical and subtropical regions of the world. It has also been cultivated for food, medicine, and scientific research purposes.[2,3]

According to Okhoya and Okogbo (1990), it is 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.[4] The fungus infects dry wood, where it produces the sclerotium usually found between the wood and the bark. Milled powder Pleurotus is used locally as a soup thickener in some regions of Nigeria, as a result of its ability to swell in water and add to the bulk of the soup. The powder is obtained from the mycelia of the edible giant mushroom which contains a high amount of carbohydrate. Since swelling is one of the mechanisms of action of starches and some tablet disintegrants, it was thought that the powder of *Pleurotus tuber-regium* would be able to act as a tablet disintegrant when added to the formulation of the dosage form.[5] Pleurotus has potential applications for nutritional, medicinal, and industrial purposes. The species do not produce toxins generally associated with some mushrooms.[5]

The annual harvest of *Pleurotus tuber-regium* in Nigeria is not well documented, but a careful observation of many local markets shows that its product is very well underutilized and poorly stored resulting in large wastages.[6] Disintegrant is a term used to describe the agent(s) added to compressed tablets and capsules to cause them to break apart (disintegrate)

when placed in an aqueous environment. The disintegrant's major function is to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the mechanical body of the tablet.[7] Disintegrants are required to break up capsules, tablets, and granules into primary powder particles to increase the surface area of the drug particles exposed to the gastrointestinal fluids. A tablet that fails to disintegrate or disintegrate slowly may result in incomplete absorption or a delay in the onset of action of the drug. It is also reported that the compaction force used in tablet manufacture can affect disintegration – the higher the force the slower the disintegration time.[7] The most traditionally used disintegrants in conventional tablets formulation are starch; among which potato, maize, and corn starches are the common types used. The typical concentration range of starch disintegrant in a tablet formulation is up to 10% w/w. However, it has been shown that starch does not swell when exposed to water at the temperature found in the gastric fluids. Hence the suggestion that the disintegrating force of starch is not due to swelling alone, but is also due to capillary action.[8,9] In the formulation and manufacture of tablets as dosage form, starches have been used for its multifunctional roles as fillers, binders, and disintegrants. In Nigeria and other developing nations, starches as well as the active ingredients are imported for use in the pharmaceutical industries.

This study was aimed at investigating the comparative disintegrant properties of *Pleurotus tuber-regium* starch, potato starch, and maize starch BP respectively, in the formulation of Ciprofloxacin hydrochloride tablets. Other physicochemical properties such as crushing strength, weight variation, and friability were investigated.

MATERIALS AND METHODS:

Commercial Ciprofloxacin hydrochloride (HELM, Portugal) supplied by Rovet Chemicals Ltd, No 1, Wire Road, Benin City, Nigeria. Pleurotus tuber-regium (PT) sclerotia were purchased from Uselu Market in Benin City, Egor Local Government, Edo State, Nigeria: authenticated by Prof. Gbolade of the Department of Pharmacognosy, Igbinedion University Okada, Edo State, Nigeria. Lactose monohydrate (Merk Darmstadt, Germany), Maize starch BP (BHD Chemicals Ltd, England), Hydroxypropyl methylcellulose (HPMC), NFX11, Japan, and Potato starch BP (International Starch Institute, Denmark). These excipients were purchased from Sonitex Chemicals Ltd, Benin City, Nigeria.

Preparation of the *Pleurotus tuber-regium sclerotia* powder and subsequent bleaching with Sodium hypochlorite solution:

The dry sclerotia (3.0 kg) were carefully peeled and washed several times with distilled water. They were cut into small pieces and shed-dried at room temperature (33 $\pm$ 2^{o}C) for 2 weeks and milled using a blender (Panasonic, Japan), sieved through the aperture of 212 um, 355 um, and 500 um sieve sizes respectively, and stored in a sealed dry glass container. Three (3) liters of sodium hypochlorite was used to mix the *Pleurotus tuber-regium* fine powder in a stainless steel container, stirred, and placed in a hot water bath at a temperature of 60^{o}C for 3 hours with occasional stirring. The resulting slurry was squeezed using a fine muslin cloth and washed severally with distilled water to remove the smell of the bleach. The final slurry was then squeezed using a fine muslin cloth and dried in the hot air oven (Kotterman, Germany) at a temperature of 50^{o}C for 24 hours. The resulting powder lumps were micronized first with a dry mill blender (Moulinex, France) and then with a ball mill (Model BS22064, England) to obtain fine powder which was stored in an airtight container until ready for use.

Flow characteristics of *Pleurotus tuber-regium*, maize starch BP and Potato starch BP powders

The flow characteristics of the three (3) powders *Pleurotus tuber-regium* (test material), maize starch BP and Potato starch BP were determined using the angle of repose and the Hausner ratio.

The angle of repose: Twenty (20 g) of the different starch powders were each weighed and poured separately into a plugged glass funnel with the tip, 10 cm above the flat surface to a workbench. The powders were allowed to flow freely through the orifice of the funnel to form a cone whose height and diameter was determined. This is the modification of the Jones and Pipel method (1966)[10]. The angle of repose was calculated using the equation.

$$\text{Tan } \theta = h/r$$

$$\Theta = \text{Tan}^{-1} (h/r) \text{ ---------- 1}$$

Where h = height of the conical powder heap

r = radius of the circular base

The mean of two determinations of θ was computed and recorded. This procedure was repeated for all the starch powders.

Bulk density, tapped density, and Hausner ratio: Bulk and tapped densities were determined by a modification of the method of Kumer and Kothari (1999)[11]. Twenty (20 g) of the starch powder was carefully weighed and transferred into a 100 ml measuring cylinder and the bulk volume V_1 was recorded. The measuring cylinder was subjected to 100 taps using the tapped density apparatus, and the new volume V_2 was recorded as the tapped volume. The bulk and tapped densities were calculated as:

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk Volume } (V_1)} \quad \text{---------- 2}$$

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped Volume } (V_2)} \quad \text{---------- 3}$$

The Hausner ratio was then calculated as:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{---------- 4}$$

True density (specific gravity) of the starch powders: The specific gravity was determined using the specific gravity bottle method. The specific gravity bottle of known weight was filled with light liquid paraffin. This was poured out and a known weight of the starch powder was carefully placed into the specific gravity bottle. This was filled up again with liquid paraffin and weighed. The true density of the starch powder was then calculated as:

$$TD = \frac{w \times d}{(a + w) - b} \quad \text{---------- 5}$$

Where TD = true density

w = weight of powder

d = specific gravity of light liquid paraffin

b = weight of bottle + light liquid paraffin + starch powder

a = weight of bottle + weight of liquid paraffin

The mean of two determinations was recorded and the procedure followed to determine the specific gravity of the remaining starch powders.

Swelling capacity: The swelling capacity of the starch powders was determined by a modification of the methods of Bowen and Vadino[12] and Iwuaguen an Okoli[13]. The tapped volume occupied by 5 g of the powder V_t, was noted. The powder was then dispersed in 85 ml of water and the volume was made up to 100 ml with more water. After 24h of standing, the volume of the sediment, V_v estimated. The swelling capacity was calculated as:

$$\text{Swelling capacity} = V_v/V_t \quad \ldots\ldots\ldots\ldots\ldots\ldots 6$$

The mean of two determinations was calculated and recorded, and the process repeated for the other two starch powders.

Hydration capacity (water retention capacity): This was determined by the method of Ring[14] one (1 gm) of powder Y was placed in a centrifuge tube and covered with 10 ml of water. The tube was shaken intermittently over a 2 hr period and left to stand for 30 min. This was then centrifuged for 10 min at 300 rpm. The supernatant was decanted and the weight of the powder after water uptake and centrifugation, X was determined.

$$\text{Hydration capacity} = X/y \quad \text{---------- 7}$$

Where X is the weight of moist powder after centrifugation and y is the weight of dry powder. The means of two determinations were recorded for each starch powder.

Preparation of ciprofloxacin hydrochloride granules: The wet granulation method was employed using 5% w/v, Hydroxypropyl methylcellulose (HPMC) as a binder in all the batch formulations. The granules were prepared using the test drug ciprofloxacin hydrochloride. Half the total amount of the disintegrant (maize starch BP, Potato starch BP and the test material *Pleurotus tuber-regium*) for each batch and other appropriate excipients were intimately mixed in a rotating mixer (intragranular disintegrant) for 5 minutes. The mix was granulated with the binder solution of HPMC to wet mass the powders until adequate granules were formed. The wet mass obtained was passed through a sieve of pore size 2.0 mm and dried in a hot air oven at a temperature of $40^o \pm 2^oC$ for 2 hours. The dried granules were then milled and passed through a 710 mm mesh size and kept in airtight containers until ready for use.

The dry granules (30 g) of each batch were carefully weighed, mixed with appropriate amounts of sieved magnesium stearate and talc powders, and 50% of the disintegrant (extragranular) and mixed in the rotating mixer for 2 minutes. The blend was compressed in a single punch tableting machine (Manesty) fitted with 12.5 mm flat-faced punches at a constant pressure of 4 units and a tablet weight of 600 mg, containing 500 mg of ciprofloxacin hydrochloride. The resulting tablets were dusted and stored in well-labeled glass jars in a humidity chamber containing dry silica gel before being subjected to physicochemical parameter tests after 72 hours of storage at room temperature.

Evaluation of the physicochemical properties of Ciprofloxacin tablets:

Weight uniformity: The weight of twenty (20) tablets from each batch was weighed individually using a digital electronic balance (Toledo, Mettler, Switzerland), and the mean weight calculated and recorded.

Friability: The friability of the tablets of the different batches was determined using the Roche friabilator (Erweka, GmbH, Germany). Ten (10) tablets of each batch were randomly selected, weighed (W1), and made to cascade in the drum of the friabilator which rotated at 25 rpm for 4 min. The tablets were then removed and dusted and reweighed (W_2). The loss in weight was expressed as a percentage of the original weight of the 10 tablets and calculated as the friability of the tablets:

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} \times \frac{100}{} \quad \text{---------- 8}$$

Where W_1 = initial weight of the 10 tablets

W_2 = final weight of the 10 tablets

Hardness (crushing strength): The hardness of 5 tablets randomly selected from each batch was determined using the Monsanto hardness tester (Monsanto Chemical Co, Ireland, England). Each tablet was placed between the spindle and anvil of the tester and was adjusted to zero. The knob was then screwed to apply a diametric compression force on the tablet. The hardness (kg) was recorded as the point the tablet yielded. The procedure was repeated for the 5 randomly selected tablets and the mean hardness was computed and recorded. The procedure was repeated for all the batches of ciprofloxacin tablet formulations.

Tablet Disintegration Test: Six tablets were randomly selected from each batch and placed one each in the cylindrical tube of a tablet disintegration test machine (Manesty, Liverpool, England). The cylindrical tube was covered with a mesh screen at the base and immersed in the disintegration medium (700 ml distilled water) maintained thermostatically at 37^{o}C ± 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 each cylinder was recorded and the mean disintegration time was calculated and recorded for each batch.

RESULTS AND DISCUSSION:

RESULTS:

The results of the physicochemical and powder properties of *Pleurotus tuber-regium*, maize starch BP and Potato starch are shown in Table 1.

Table No. 1: Physicochemical and powder properties of *Pleurotus tuber-regium*, Maize starch BP and Potato starch BP

Parameter	Pleurotus tuber-regium	Maize starch BP	Potato starch BP
pH	5.20	5.40	5.75
Hydration capacity	1.68	1.70	1.62
Moisture content	10.75	12.20	10.40
Bulk properties:			
True density (g/cm^3)	1.12	1.10	1.15
Bulk density (g/cm^3)	0.33	0.42	0.53
Tapped density (g/cm^3)	0.41	0.61	0.72
Flow properties:			
Angle of repose (^{o})	50.10	37.40	38.30
Hausner's ratio	1.36	1.51	1.42
Compressibility index (%)	31.20	34.20	29.40
Swelling powder (%)	20.10	21.80	20.40

Table 1 shows the physicochemical and powder properties of the three types of starch powders used as disintegrants in the formulation of the ciprofloxacin hydrochloride tablets. The pH value of the test disintegrant (*Pleurotus tuber-regium* powder) and the other two standard disintegrants (maize and potato starches) were found to be in the slightly acidic range of 5.20 – 5.75. The hydration capacities also compared favorably in the range of 1.62 – 1.70. Generally, their flow properties needed to be enhanced, hence the need to granulate the primary powder materials and the drug into granules. The result shows that Pleurotus tuber-regium starch, maize starch, and potato particles can swell when in contact with water to 20.10%, 21.80%, and 20.40% of their original sizes. These values are compared to favorably without significant differences. From the values of the parameters evaluated, the powder properties of *Pleurotus tuber-regium* compared favorably with those of maize and potato starches.

Table No. 2: Results of the evaluation of the physicochemical properties of ciprofloxacin tablets

Disintegrant type	Disintegrant concentration (% w/w)	Mean weight (g)	Friability (%)	Hardness (kg/f)	Mean Disintegration time (min)
Pleurotus tuber-regium starch	2.5	601 ± 0.21	1.10 ± 0.01	8.4 ± 0.12	4.30 ± 0.20
	5.0	600 ± 0.19	1.15 ± 0.02	8.1 ± 0.11	3.54 ± 0.21
	7.5	602 ± 0.22	1.11 ± 0.12	7.5 ± 0.10	2.45 ± 0.19
	10.0	600 ± 0.21	2.10 ± 0.10	6.5 ± 0.09	1.50 ± 0.20
Maize starch BP	2.5	600 ± 0.19	1.20 ± 0.04	9.2 ± 0.15	5.10 ± 0.15
	5.0	599 ± 0.18	1.26 ± 0.04	8.6 ± 0.13	4.20 ± 0.13
	7.5	601 ± 0.18	1.50 ± 0.03	7.8 ± 0.10	2.80 ± 0.15
	10.0	601 ± 0.19	2.50 ± 0.02	7.0 ± 0.10	1.65 ± 0.08
Potato starch BP	2.5	602 ± 0.20	1.45 ± 0.01	8.7 ± 0.12	5.40 ± 0.20
	5.0	600 ± 0.18	1.21 ± 0.01	8.1 ± 0.10	3.80 ± 0.19
	7.5	601 ± 0.20	1.40 ± 0.02	7.2 ± 0.13	2.60 ± 0.21
	10.0	600 ± 0.21	2.30 ± 0.03	6.8 ± 0.11	1.56 ± 0.09

Table 2 shows the results of the physicochemical properties of the tablets. The mean weight of the various tablet formulations was not appreciably affected by the type and concentrations of the disintegrants. The disintegrant type and concentration in the formulation affected the hardness values of the ciprofloxacin tablets; the higher the concentration the weaker the tablet hardness. This was in the order of decreasing concentration of maize starch BP > Potato starch BP > *Pleurotus tuber-regium* starch with increasing values of disintegrant concentration (9.2 $\pm$ 0.15 to 7.0 $\pm$ 0.10 kgf) for Maize starch, (8.7 $\pm$ 0.12 to 6.8 $\pm$ 0.11) for Potato starch and (8.4 $\pm$ 0.12 to 6.5 $\pm$ 0.09) for *Pleurotus tuber-regium*), as shown in Figure 1. The lowering of the tablet hardness with an increase in disintegrant concentration could be due in part to the increased amount of fines which is capable of weakening the tablet hardness[15]. However, the friability of the tablets produced using *Pleurotus tuber-regium* starch as a disintegrant was less friable than those produced with Potato starch BP and Maize starch BP at all concentrations and the same compression pressure (see Figure 2). The different formulations of ciprofloxacin tablets produced with the 3 disintegrant types had their disintegration time less than 15 minutes (the official standard for uncoated tablets), the values were concentration-dependent. However, the mean disintegration time of those produced using *Pleurotus tuber-regium* as disintegrant were lower (4.30 $\pm$ 0.20 – 1.50 $\pm$ 0.15 min) for 2.5% w/w to 10.0% w/w (see Figure 3). The results show that *Pleurotus tuber-regium* starch powder produced favorable ciprofloxacin hydrochloride tablet properties similar to those of British Pharmacopoeial standard disintegrants – Maize starch BP and Potato starch BP respectively.

It is well known that the disintegration of tablets plays a significant role in the dissolution process since it determines the extent of the surface area of the drug particles with the surrounding fluid. The most widely reported mechanism of action of the disintegration of starch is believed to depend on swelling and wicking[16]. However, when starch is wetted and converted to paste, it loses most of its swelling properties, but may still affect tablet disintegration within acceptable limit; this is probably due to the capillary action (wicking) of starch which is believed to depend on the porosity of the tablet matrix[17].

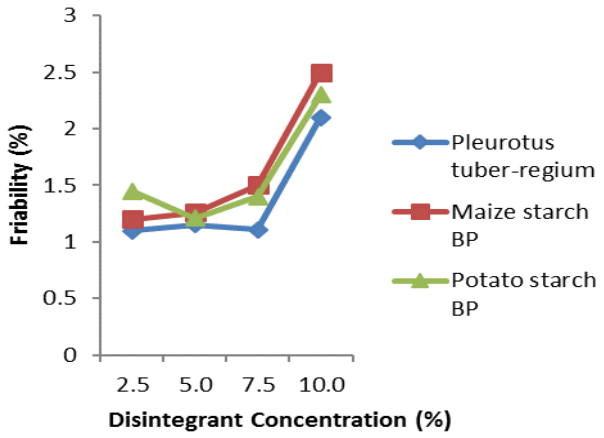

Figure No. 1: Effect of disintegrant conc. (% w/w) on tablet hardness

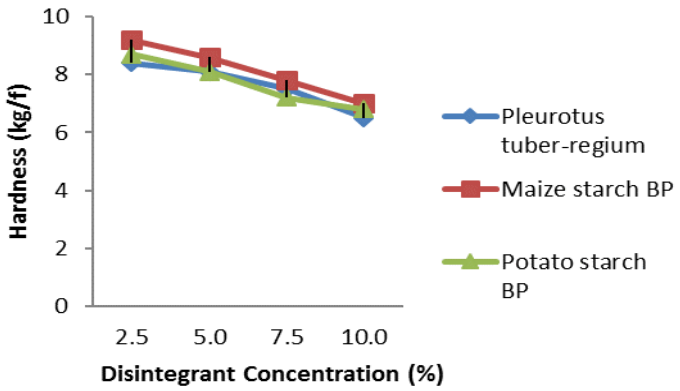

Figure No. 2: Effect of disintegrant conc. (% w/w) on tablet friability

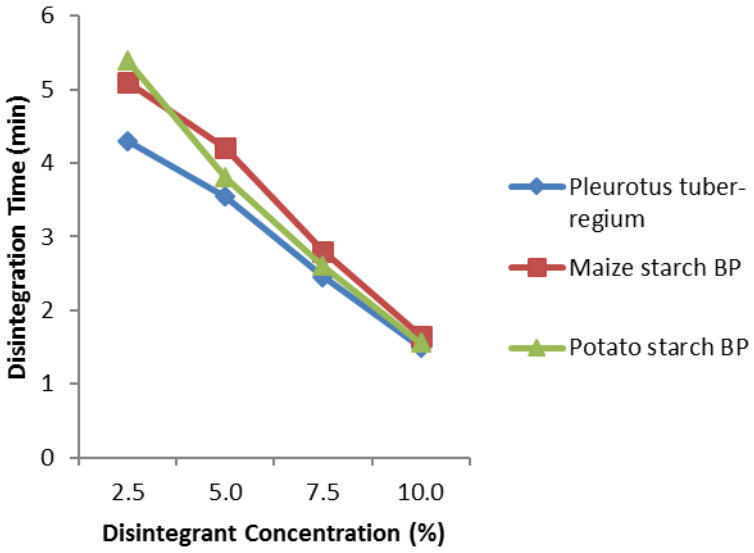

Figure No. 3: Effect of disintegrant conc (% w/w) on disintegration time of tablets

CONCLUSION:

The study has established some physicochemical properties of *Pleurotus tuber-regium* powder. The evaluation of its disintegrant properties relative to those of maize starch BP and potato starch BP in the formulation of ciprofloxacin hydrochloride tablets has also been established. Within the limits of the parameters evaluated, *Pleurotus tuber-regium* compared favorably with the standard disintegrants, maize starch BP and potato starch BP; with the test disintegrant, *Pleurotus tuber-regium* showing slightly better disintegrant properties in ciprofloxacin tablets. The study is also in agreement with the reports of some previous authors on the effectiveness of *Pleurotus tuber-regium* as a disintegrant in the formulation of other solid dosage forms. *Pleurotus tuber-regium* starch powder is an example of a multifunctional pharmaceutical excipient since the starch can be used as a binder, and even as a filler in the design of pharmaceutical dosage forms. It is economical, can easily be cultivated, safe, biodegradable, and biocompatible. It is therefore recommended as a suitable pharmaceutical excipient which can be further researched for effective utilization.

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