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The effect of particle size on the disintegrant activity of *Pleurotus tuber-regium* powder

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ABSTRACT

The investigation studied the effect of particle size on the disintegrant activity of *Pleurotus tuber-regium* powder in comparison with maize starch BP and microcrystalline cellulose. *P. tuber-regium* sclerotia were processed into powders of different particle sizes (< 300, 300-600 and > 600 µm). The different size fractions were subjected to moisture sorption test. Magnesium trisilicate granules were formed with the different size fractions of *P. tuber-regium* powders, maize starch BP and microcrystalline cellulose and compressed into tablets. The granules and tablets were evaluated for their physicochemical properties. The moisture sorption capacity of the powdered fraction was of the order (< 300 µm) < (300-600 µm) < (> 600 µm). The granules and tablets formulated were comparable in granule flow properties, tablet weight variation, hardness and friability. However, tablets formulated with *P. tuber-regium* powder particle size > 600 µm performed better with a shorter disintegration time of 4.62 min against those of maize starch BP, 12.65 min and microcrystalline cellulose 11.20 min. *Pluerotus tuber-regium* powder compared favourably with maize starch BP and microcrystalline cellulose (Avicel® PH 102) when used as a disintegrant. It may therefore be inferred that *P. tuber-regium* may serve as a suitable disintegrant in compressed tablets especially at particle size equal to or greater than 600 µm, and where shorter disintegration times are desired.

INTRODUCTION

Tablets are solid pharmaceutical dosage forms intended for oral administration containing drug substances with or without suitable diluents and they have been traditionally prepared by either compression or moulding methods. The European Pharmacopoeia (1997) defines a tablet as a solid preparation containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles [1]. Tablets are intended for oral administration, they come in various sizes and shapes. Substances added to tablet formulations are known as excipients, additives or adjuncts. They help to ensure the enhancement of the physical appearance, improve stability and aid disintegration and dissolution after administration. A tablet may be characterized by a number of specifications i.e. diameter, shape, thickness, friability, hardness, disintegration time and dissolution characteristics [2]. Amongst these specifications, disintegration is arguably the most important since a drug in a tablet is not available for absorption unless the tablet disintegrates, and the faster the disintegration, the quicker the dissolution and onset of action. This process of disintegration is normally achieved with the aid of a disintegrant. The important role of a disintegrant in tablet formulations has initiated a search for new and improved compounds as disintegrants from both synthetic and natural sources [3-5].

Pleurotus tuber-regium is a tropical sclerotial mushroom [6]. The mushroom produces a sclerotium of underground tuber. The mushroom and tubers are both edible. The sclerotium is spherical to ovoid and can be quite large, up to 30 cm or larger, in diameter. It is dark brown on the outside and white on the inside. In Nigeria *P. tuber-regium* is used both as food and medicine [7,8]. It is used locally as soup thickener because of its ability to swell in water and add bulk to the soup [9]. A preliminary investigation into the swelling ability of the mushroom powder (since swelling is one of the mechanisms of action of some tablet disintegrants), found it comparable with maize starch BP as a tablet disintegrant [10].

The objectives of this study are to determine the effect of particle size on the disintegrant activity of *P. tuber-regium* powder and to compare its disintegrant activity with maize starch BP and

microcrystalline cellulose (Avicel® PH l02).

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Avicel® PH 102) FMC Corporation, USA; magnesium stearate and silica gel, Hopkin and William, UK; maize starch BP, talc and sodium chloride, BDH Chemicals, UK; and lactose, Merck Dermstard, Germany, were used as supplied. *Pleurotus tuber-regium* tubers were purchased locally and processed into powder in our laboratory. All sieves were BSS (Endecotts Ltd. London, England).

Methods

Preparation of P. tuber-regium powder

Dry tubers of *P. tuber-regium* were processed into powder using an earlier reported method [10]. The powder was classified into different fractions by passing it through three sieves of different mesh sizes to obtain powder particles sizes of < 300 µm, 300-600 µm and > 600 µm. The resultant powder size fractions were packed and stored in an airtight container until evaluation.

Determination of moisture sorption

Three desiccators containing in each 5 g of dry silica gel, a supersaturated solution of sodium chloride and l00 ml of water to simulate 0 %, 75 % and 100 % relative humidity (RH) respectively, were prepared. The desiccators were allowed to stand for 30 min to equilibrate.

Pre-weighed watch glasses containing 5 g powder of the different size fractions of *P. tuber-regium* powders were placed in the desiccators; i.e. three watch glasses containing *P. tuber-regium* particles of sizes < 300, 300-600 and > 600 µm in each of them per desiccator. The weight increase or decrease of the watch glasses as a function of time was monitored over a 4 day period.

Preparation of granules

The wet granulation method of massing and screening was used in preparing all the batches of magnesium trisilicate granules using the calculations shown in Table 1. The magnesium trisilicate powder was weighed into a mixer. Half of the weighed amount of disintegrant was incorporated intragranularly to the powder mix in geometric proportions during the mixing.

Sufficient quantities of the binder solution (10 %w/v) required to form a wet mass was gradually added to the dry powder mix. The wet mass was passed through a 2.0 mm sieve mesh and the resulting granules dried at 60 ºC for 30 min in a hot air oven (Gallenkamp, UK). The granules were rescreened through an 850 µm sieve and further dried for 30 min. The dry granules were subjected to various analyses after the other half of the disintegrant and glidant previously weighed and mixed in a mortar were added in geometric proportion and intimately mixed in readiness for compression. The batch containing Avicel® was prepared with 25 mg of the disintegrant per tablet.

Granule analysis

Bulk and tapped density

A 30 g quantity of the magnesium trisilicate granules was poured gently into a 100 ml graduated measure. The volume of the powder was read and the bulk density calculated. The graduated measure was tapped 100 times on a wooden platform to a constant volume. The volume was noted and used in calculating the tapped density.

Carr's index, Hausner's ratio, flow rate and angle of repose

The Carr's index expressed as percentage was calculated as the difference between the tapped and bulk density of the granules divided by the tapped density while the ratio of the tapped density to the bulk density of the granules was calculated as the Hausner's quotient. The time taken for 30 g of the granules to pass through the orifice of an Erweka flow tester was recorded. The mean value of triplicate determinations was recorded as the flow rate of the granules. The hollow tube method was used in the measurement of angle of repose. 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 1.

$$\theta = \tan^{-1}(h/r) \qquad \text{-----(1)}$$

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 compression pressure of 30 arbitrary units. The die volume was adjusted to compress tablets of uniform weight by using granules

Table 1: Formula of prepared magnesium trisilicate tablets

Ingredients	Quantity/Tablet	Quantity/Batch
Magnesium trisilicate	500 mg	100 g
Disintegrant*	50 mg	10 g
Binder solution (10 %w/v maize starch)	q.s	q.s
Magnesium stearate	1 %w/w	1 %w/w

*The disintegrant; *P. tuber-regium* powder of particle size < 300 µm or 300-600 µm or > 600 µm or maize starch BP or Avicel®

weighing 600 mg. The tablets made were then kept in air tight containers and stored in a desiccator until evaluation.

Characterization of tablets

The following tests were carried out on the compressed tablets using standard procedures: tablet weight uniformity, hardness, friability and disintegration time [11].

Uniformity of weight, hardness, friability and disintegration time

The weight of each of 20 tablets was determined from each batch using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed. The hardness of each of ten tablets per batch was determined (Campbell Electronics, Model HT-30/50, India). The mean hardness was calculated. For friability, the weight of ten tablets was determined on the electronic balance. The tablets were then placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm which exposed the tablets to rolling and repeated shock resulting from free fall within the apparatus. After four min, the tablets were brought out, dedusted and reweighed. The weight was then recorded and friability calculated as percentage loss in weight. The disintegration times of six tablets per batch of the tablets were determined in distilled water at 37 ± 0.5 °C using the BP disintegration tester (MK IV, Manesty Machines, UK).

Statistical analysis

All data obtained were subjected to student t-test ($p < 0.05$) to test for significance of difference using GraphPad InStat software version 3.10.

RESULTS

Powder moisture sorption

The moisture sorption profile of *P. tuber-regium* powder is shown in Figure. 1. Generally, the powder sorbed moisture at relative humidities of 75 % and 100 % while there was desorption at 0 %. Powder particles of size less than 300 µm in 100 % RH

Table 2. : Some physicochemical properties of the magnesium trisilicate granules

Granules		Bulk Density (g/L)	Tapped Density (g/L)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)	Flow Rate (g/sec)
P. tuber-regium	300 µm	0.37	0.51	27.45	1.37	34.8	4.52
	300-600 µm	0.38	0.52	26.92	1.36	34.5	4.55
	> 600 µm	0.41	0.54	24.07	1.31	33.4	4.56
Maize Starch BP		0.41	0.53	22.64	1.29	34.8	5.27
Avicel®		0.38	0.47	19.14	1.27	34.5	5.05

Table 3. : Some physicochemical characteristics of the magnesium trisilicate tablets

Starch		Tablet Weight* (g)	Tablet Dimensions (mm)		Tablet Hardness (kp)	Friability (%)	Disintegration Time* (min)
			Diameter*	Thickness*			
P. tuber-regium	300 µm	0.58 (0.01)	12.50 (0.03)	3.23 (0.01)	12.50	0.35	9.15 (1.26)
	300-600 µm	0.58 (0.01)	12.50 (0.01)	3.22 (0.02)	12.50	0.34	5.20 (1.32)
	> 600 µm	0.59 (0.02)	12.50 (0.03)	3.21 (0.03)	12.50	0.34	4.62 (0.83)
Maize Starch BP		0.58 (0.02)	12.55 (0.01)	3.21 (0.04)	12.55	0.66	12.65 (0.45)
Avicel®		0.59 (0.02)	12.55 (0.03)	3.20 (0.02)	12.55	0.68	11.20 (0.35)

*Standard deviation in parenthesis

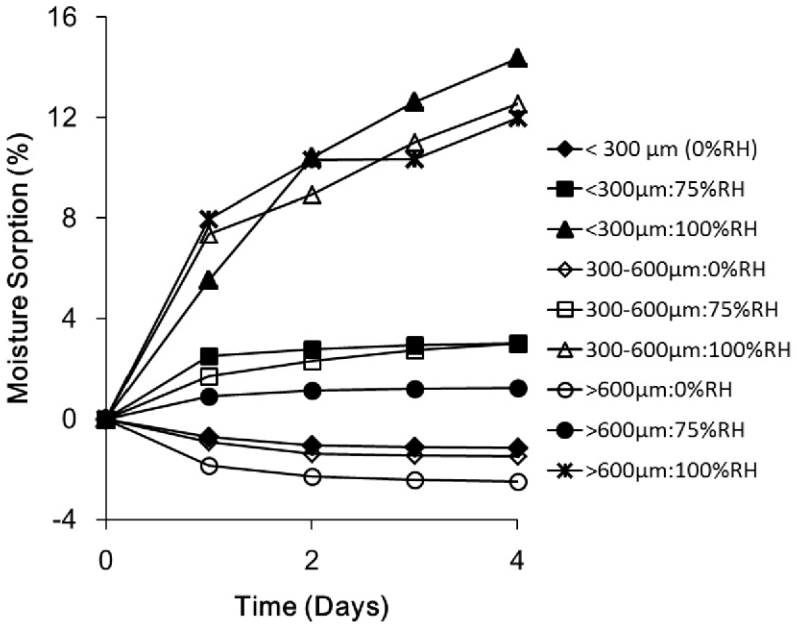

Figure 1: The moisture sorption profile of *P. tuber-regium* powder

absorbed the highest percentage of moisture after 4 h while those of particle size greater than 600 µm in 0 % RH lost the highest percentage of moisture. All the particle sizes lost some amount of moisture at 0 % RH, but at 75 % RH, there were no significant difference in percentage moisture sorbed compared to sorption at 100 % RH values.

At 100 % RH, powders of particle size greater than 600 µm absorbed the highest amount of moisture within the first 24 h, closely followed by the 300-600 µm size particles. After 48 h, particles size less than 300 µm had sorbed as much moisture as those greater than 600 µm. After 96 h, a gradual increase in the moisture absorption above the other particle sizes was still observed for powders of particle size 300 µm while powders with particle size greater than 600 µm absorbed moisture to an extent that was more or less constant and even falling lower than that absorbed by particle size 300-600 µm.

Conclusively, after four days, desorption followed the order (> 600 µm) > (300-600 µm) > (< 300 µm) while sorption followed the order (> 600 µm) > (300-600 µm) > (< 300 µm) while sorption followed the order (< 300 µm) > (300-600 µm) > (> 600 µm). From the foregoing observations it can be inferred that particle size has a significant ($p < 0.05$) effect on moisture sorption/ desorption as a function of the prevailing relative humidity.

Granule properties

As shown in Table 2, the physicochemical properties of the granules showed a direct proportionality between granule flow and particle size. There was a general improvement ($p < 0.05$) in the flow properties of the granules with increasing particle size. There were increase in the flow rate, bulk and tapped densities and a decrease in the angle of repose, Carr's index and the Hausner's ratio with increase in the particle size.

Tablet properties

Table 3 shows some physicochemical parameters of the magnesium trisilicate tablets formulated. The weight uniformity test on the tablets indicated no significant difference ($p>0.05$) in the weights of tablets from the various batches and hence conformed to the British Pharmacopoeia (2009) specification [11], i.e., that not more than two of the individual weights should deviate from the average weight by more than ±5 % and none should deviate by more than ±10 %.

Also, there were no significant differences amongst the tablet dimensions, and no difference at all amongst the tablet hardness. This could be attributed to the fixed amount of binder used since tablet hardness is chiefly attributed to the binder used in its formulation. All the tablets from all the batches of granules gave good hardness values above 4 kp since hardness values greater than or equal to 4 kp are considered optimal and acceptable [2]. The friability values of the tablets increased with decreasing particle size of *P. tuber-regium* and were less than those of tablets made with maize starch BP and Avicel® (Table 3). However, all the tablets met the BP specification of a maximum loss of 1 % of the mass of the tablets tested or a 0.8 - 1.0 % loss in weight of the tested tablets without capping, lamination or breaking up in the course of the test [11].

All the formulated tablets disintegrated within 15 min (Table 3) as specified by BP 2009 for uncoated tablets [11], but the results showed a reduction in the disintegration time with increase in the particle size of *P. tuber-regium*. Comparing the disintegration times of the tablets prepared from the different particle sizes of *P. tuber-regium* with those of maize starch BP and Avicel®, the superior disintegration times of tablets made with *P. tuger-regium* was evident especially when *P. tuber-regium* particle size greater than 600 µm was used.

DISCUSSION

Pharmaceutical excipients must meet optimum specification standards to function adequately in any dosage formulation. Excipients such as disintegrants should be able to effect disintegration in its incorporated dosage system spontaneously, taking into consideration the route of administration of the formulation. Oral tablets are expected to start disintegrating upon contact with moisture in the stomach (or in the mouth for fast disintegrating tablets). Swelling type disintegrants absorbs moisture to swell and the size or size distribution of the

disintegrant particles is key to the rate of moisture absorption which in turn is crucial to the efficiency of such a disintegrant.

The study reveals that particle size is critical to the moisture sorption/desorption of the test disintegrant; *P. tuber-regium* powder, and its disintegrant efficiency in formulated tablets. The high percentage of moisture absorbed by powder particles of size less than 300 µm in 75 and 100 % relative humidities makes this particle size not ideal for tablets meant to be stored in high relative humidity especially the tropics. The high moisture absorption may be attributed to the exposure of a larger surface area for sorption of moisture which is in line with Nikhodchi *et al* [12], who are of the opinion that the large surface facilitates internal absorption of moisture and not surface adsorption.

The improvement in the flow properties of the granules with increasing particle size is consistent with the formation of larger granules as the particle size increased leading to larger voids in between the larger granules. This increase in particle sizes would also lead to decrease in surface free energy of the granules and decrease in frictional forces between the granules leading to faster flow [13].

A tablet must disintegrate before the drug is released into solution. Some authors maintain that disintegration and dissolution times are correlated as particle size and consequently the surface area into which a tablet disintegrates correlate with dissolution time of the active drug [14,15]. The disintegration times of tablets formulated with *P. tuber-regium* powder particle size greater than 600 µm were less than 5 min, and this agreed with the moisture sorption results since the disintegrating medium must penetrate the tablet for disintegration to occur [16-18]. This finding also agrees with the results obtained by Iwuagwu and Onyekweli who showed that the swelling capacity and water retention capacity of Pleurotus powder were over two times those of maize starch BP [10].

CONCLUSION

Pluerotus tuber-regium powder has been demonstrated to be moisture sensitive. The amount of moisture sorbed by the powder is significantly affected by the relative humidity of the storage environment as well as particle size of the powder. *P. tuber-regium* powder compared favourably with maize starch BP and microcrystalline cellulose (Avicel® PH 102) when used as a disintegrant. It may therefore be inferred that *P. tuber-regium* may serve as a suitable disintegrant in compressed tablets especially at particle size equal to or greater than 600 µm, and where shorter disintegration times are desired.

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