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Research Article

Excipient Properties of Bleached and Acid-Treated Pleurotus tuber-regium Powder in Paracetamol Tablet

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Abstract

Background: Chemical modification of pharmaceutical excipients had led to the discovery of other excipients with improved functionalities. While there is a growing need for chemical modification of excipients, this approach has not been studied in Pleurotus tuber-regium (P. tuber-regium).

Aim: This study was aimed at investigating the excipient properties of bleached and acid treated P. tuber-regium.

Methods: P. tuber-regium powder was processed by bleaching and thereafter treated with 0.1 N HCl and allowed to stand for 10 mins, 30 mins, and 60 min; labeled as A, B, and C, respectively. Volumes of NaOH equivalent to that of HCl were added and allowed to stand at pH 7.0. The disintegrant and binding ability of the powders obtained was investigated in paracetamol tablets prepared using wet granulation method. The resulting granules and tablets were evaluated for flow properties and physicochemical properties, respectively. The Null hypothesis was tested using a 2-Way ANOVA approach.

Results: The bleached powder had higher pH (7.10 ± 0.0), swelling capacity (2.16 ± 0.0 ml), hydration capacity (5.50 ± 0.08 g), true density (4.28 ± 0.0 g/ml) which reduced with increasing exposure to acid. The acid-treated powders were not soluble in distilled water, chloroform, 0.1 N HCl, 0.1 N NaOH, glycerin, methanol, and ethanol at room temperature and 80oC, but the bleached powder swelled in distilled water at 80oC. The bleached and acid-treated sample at 1 h had better flow characteristics. Acid exposure increased disintegration time (20.78 ± 2.00 – 52.07 ± 0.03 secs), hardness, and friability. Acid treatment further imparts a more diffusion-controlled release pattern (r^2> 0.97) and a significant surface area effect on drug release (r2> 0.9).

Conclusion: Acid treatment improved flow properties, prolonged disintegration time, ensures slower release from the dosage form, better diffusion-controlled release pattern, and a significant surface area effect on drug release.

Keywords: Acid-treated; bleached; paracetamol; p. tuber-regium

Introduction

Research in pharmaceutical technology is geared towards innovating and improving excipients, formulations, and facilities [1]. This imposes that excipients with excellent and improved functionalities can be isolated and characterized by agricultural products. In some cases they may be obtained through combination of existing materials [2]. In the pharmaceutical industry, several natural products have been useful as binding, disintegrating, thickening, gelling agents, etc. regarded as pharmaceutical excipients [3]. The earliest of these to be employed in pharmaceutical systems include starches and thereafter celluloses and cellulose derivatives. Modified starch has been used as a new pregelatinized starch product in directly compressible controlled-release matrix system [4]. Cellulose has excellent disintegrant properties, and good physicochemical characteristics, employed as a lubricant, binder, and diluent as a result of its direct compressibility properties [5]. These excipients in addition to the above under

certain circumstances provide certain therapeutic advantages such as improving drug absorption, providing prolonged drug effect, and aesthetic properties.

P. tuber-regium (FR) Singer has been successfully grown in the laboratory [6,7]. It is a basidiomycete that grows wildly in the tropical and subtropical regions of the world [8,9]. The sclerotium is often dark brown on the surface and off-white inside. The sizes and weights of the sclerotium could vary and may be as large as 30 cm and weigh over 5 kg. It enjoys popular use in Nigeria as food and medicine. In the southern part of Nigeria, it is considered a luxury food and important table delicacy, especially among rural dwellers [10]. The sclerotium is often dark brown on the surface and white inside. These are usually harvested from decaying logs, the dark brown exterior is peeled off and the white compact mycelial tissue is used for nutrition or nutraceutical. One of the most common dietary applications of P. tuber-regium in Nigeria is as soup thickener. The white tissue is blended into fine powder and when added to soup, it swells and adds bulk to the soup [11].

Acid treatment of the sample hydrolyses the lignocellulosic biomass. Dilute acid pretreatment hydrolyzes the hemicellulose portion to the biomass and causes structural changes and thereby improving the enzyme accessibility for hydrolyzing cellulose [12]. Sulfuric acid is the most commonly used acid for pretreatment and hydrolysis. In contrast, other acids such as hydrochloric acid, phosphoric acid, and nitric acid are used for pretreatment only. In most cases, acid pretreatment alone is not enough to isolate cellulose as acids cannot completely solubilize hemicellulose. Hence, alkaline treatment coupled with acid treatment is required for complete isolation of cellulose. The advantages of acid treatment are high glucose yield and partial hemicellulose solubilization [13]. The drawbacks are prohibitive costs of acids, which in turn need to be recovered. This study was aimed at investigating the excipient properties of bleached and acid treated P. tuber-regium.

Methods

Materials

All materials were used as received and they include paracetamol powder B.P (Mallinckrodt Inc. USA), Ethanol 95 % (Guangdong Sci-Tech Co. ltd. China), hydrochloric acid (BDH Chemical Limited Poole England), Sodium hydroxide (NaOH) (Burgoyne and Co. Mumbai India), and Sodium hypochlorite 3.5 % (Multipro Enterprise Limited Lagos Nigeria). Talc, magnesium stearate, lactose, was a gift received from Pharmaceutical Technology Laboratory, Delta State University Abraka Delta State.

Preparation of Bleached P. tuber-regium powder

The fresh tubers of P. tuber-regium were collected and the brown layer peeled off to expose the whitish inner sclerotia which were chopped and pulverised using a hand-driven milling machine (03200 Landers and Ciasa Corona). The fine white powder was bleached using 3.5 % hypochlorite [14]. The wet mass was slurred with ethanol 95 % in a stainless-steel vessel and allowed to stand in a water bath at 60 oC or 10 min, 30 min and 60 min. The slurry was squeezed with a muslin cloth. The wet mass gotten was dried in a hot air oven (Leader Engineering St Helens Merseyside England), at 50°C for 24 h. The white powder obtained was labelled P and screened through a 212 µm mesh screen [15].

Acid treatment of P. tuber-regium powder

The bleached P. tuber-regium powder (P) was acidified using 0.1 N HCl and allowed to stand for 10, 30, and 60 min. Thereafter, equal volume of 0.1 N NaOH was added and allowed to stand until the neutralization reaction was complete (i.e. until a stable pH of 7.0 ± 0.3 was obtained). The powder was then washed severally using distilled water. The wet mass was slurred with ethanol 95%v/v and allowed to stand in a water bath at 60°C for 60 min. The slurry was then squeezed with a muslin cloth and allowed to dry in hot air at 50°C for 24h [15]. The dry powder gotten after acid treatment for 10, 30, and 60 min were labeled A, B, and C, respectively. The different batch was characterized using a 1.18 mm sieve size.

Yield

The yield of the bleached and acid treated powders was calculated using the formula below:

$$Yield = \frac{(weight\ before\ processing\ or\ treatment)}{(weight\ after\ processing\ or\ treatment)} \times 100\% \quad (1)$$

Powder Characterization

True Density

The particle density of the respective powders was determined by solvent displacement method using n-hexane as a non-solvent. An empty 25 mL pycnometer was weighed (W). It was filled with n-hexane and weighed (W1). The difference between this (W1) and W was calculated as W2. A 1g quantity of the powder was weighed (W3) and carefully transferred into the pycnometer. The excess fluid was wiped off and the bottle was weighed again (W4). The determination was made in triplicate and the average was taken. Particle density, Pt. (g/mL) was calculated according to the equation:

$$Pt. = \frac{W_2}{v} \times \frac{W_3}{W_3 - W_4 + W_2 + W} \quad (2)$$

Where: v is the volume of the pycnometer (25 ml).

pH Determination

The pH of 2 % w/v aqueous dispersion of powder was determined using a pH meter (Hanna pH meter model H12211) [16].

Solubility

The solubility of 0.1 g of P. tuber-regium was verified in water, ethanol (96%), methanol, chloroform, glycerin, propylene glycol,

dilute, or concentrated mineral acids, respectively at room temperature. Similarly, these were also investigated at elevated temperatures using a thermostated water bath maintained at 60°C.

Hydration Capacity

The hydration (water retention) capacity of the respective powders was determined by the method of Ring, (1985). A 1 g quantity of powder was placed in a 15 mL plastic centrifuge tube and 10 mL of water was added. The tube was shaken intermittently over a 2 h period and left to stand for 30 min. This was then centrifuged for 10 min at 3000 rpm. The supernatant was decanted and the weight of the powder after water uptake and centrifugation, x was determined. The determination was done in triplicate and average taken.

$$Hydration\ capacity = \frac{x}{y} \quad (3)$$

Where x is the weight of moist powder after centrifugation, y is the weight of dry powder.

Swelling Capacity

The tapped volume occupied by 5 g of the powder VX, was noted. The powder was then dispersed in 85.0 mL of water and the volume made up to 100 mL with more water. After 24 h of standing, the volume of the sediment, VV, was estimated. The swelling capacity was computed as follows [17,18]. Determinations were made in triplicates and average taken.

$$Swelling\ capacity = \frac{V_V}{V_X} \quad (4)$$

Preparation of Paracetamol Granules

Paracetamol granules were prepared using the formula in (Table 1). Several batches of granules were prepared with varying concentrations of P. tuber-regium as a binder and disintegrant with lactose as the filler. The granules were prepared by wet granulation method with the disintegrant added intra and extra-granularly.

Table 1: Formulation table for paracetamol tablets.

Ingredients	P1	P2	P3	A1	A2	A3	B1	B2	B3	C1	C2	C3
Paracetamol powder B.P (mg)	500	500	500	500	500	500	500	500	500	500	500	500
Disintegrant (%)	5	5	5	5	5	5	5	5	5	5	5	5
Binder (%)	5	10	15	5	10	15	5	10	15	5	10	15
Lubricant (%)	1	1	1	1	1	1	1	1	1	1	1	1
Glidant (%)	1	1	1	1	1	1	1	1	1	1	1	1
Lactose to (mg)	600	625	635	600	625	635	600	625	635	600	625	635

Note: The different batches were formulated using the four samples P, A, B, and C as such 12 batches were obtained which are P1, P2, P3, A1, A2, A3, B1, B2, B3, C1, C2, and C3. The P, A, B, and C samples were bleached, acid-treated for 10 min, 30 min, and 60 min P. tuber-regium powder, respectively.

Flow Properties of the Granules

Angle of Repose

The angle of repose was determined by the funnel method and 20 g of accurately weighed powder was taken in a funnel. The height of the funnel was adjusted to a constant height of 10 cm from the top to the base. The powder was allowed to flow through the funnel freely into the surface. The diameter of the powder heap formed was measured and angle of repose was calculated using equation 4.

$$Tan\ \theta = \frac{h}{r} \quad (5)$$

Where h and r indicate the height and radius of the powder heap formed respectively.

Bulk Density and Tapped Density

About 20 g of the powder blend was weighed into a 100 ml measuring cylinder. The volume of the powder blend was noted as the bulk volume (Bv). The measuring cylinder was then tapped on a padded surface until there was no change in powder volume (100 taps) and the new volume of the powder blend was noted and recorded as the tapped volume (Tv). The procedure was carried out in triplicate for each batch (F1 – F3).

Both the bulk density and the tapped density were calculated from equations 2 and 3

$$Bulk\ density = \frac{weight\ of\ powder\ blend}{bulk\ volume} \quad (6)$$

$$Tapped\ density = \frac{weight\ of\ powder}{tapped\ volume} \quad (7)$$

Compressibility Index

The compressibility index (Carr's index) was determined using equation 7

$$Carr's\ index\ (\%) = \frac{TD - BD}{TD} x \frac{100}{1} \quad (8)$$

Where TD = Tapped density and BD = Bulk density

Hausner Ratio

The Hausner's ratio was determined using the formula in equation 8

$$Hausner's\ ratio = \frac{TD}{BD} \quad (9)$$

Preparation of Tablets

The different batches of paracetamol granules were mixed with appropriately weighed lubricant (magnesium stearate), glidant (talc) and 50 % of the disintegrant (P. tuber-regium) and compressed to form tablets.

Evaluation of Tablet Properties

Weight Uniformity

From each batch, 20 tablets were randomly selected, and the individual weight of each tablet was determined using an analytical weighing balance. The average weight of the 20 tablets and the standard deviation was calculated.

Tablet Hardness, Thickness and Diameter

The thickness, hardness, and diameter of the tablets were determined using the hardness test machine (Model no: VDIGITAB-1). The determinations were made in triplicate and the average was taken.

Tablet Friability

Ten tablets per batch were weighed and caused to cascade in the drum of the friabilator which rotated at 25 rpm for 4 min. The tablets were dusted and reweighed. The loss in weight expressed as a percentage of the original weight of the ten tablets was calculated as the friability of the tablets.

$$Friability\ (\%) = \frac{W1 - W2}{W1} \times 100 \quad (10)$$

Where W1 = initial weight of 10 tablets

W2 = final weight of 10 tablets after friability test.

Tablet Disintegration Time

Disintegration times of six tablets per batch were individually determined at 37 ± 0.5 oC using the Manesty Machine (Mk IV, Manesty Machines, UK). The determinations were done in triplicate and the average was calculated.

Dissolution of Tablet

The dissolution of the tablets was conducted using the basket method. The equipment was operated at 50 rpm in a dissolution medium comprising 900 mL of 0.1 N HCl (pH 2.4) maintained at 37 ± 1 oC. Samples were withdrawn at 5, 10, 15, 30, 45 and 60 min and each time, replaced with the same volume of the plain dissolution medium. Aliquots were filtered and the absorbance determined with a UV spectrophotometer at 294 nm. The percentage cumulative drug release was plotted against time.

Content Uniformity

Intact five tablets were randomly taken from each batch and crushed. The weight of powders equivalent to 10 mg weight of the drug was analyzed for its total drug content using UV spectrophotometer at 294 nm.

Data Analysis

Data was analyzed using two-way Analysis of Variance (ANOVA). The following Null Hypotheses were tested:

Null hypothesis (Ho1). There is no significant statistical difference in the physicochemical properties of the various samples of P. tuber-regium.

Null hypothesis (Ho2)

There is no significant statistical difference in the flow properties of paracetamol granules formulated with same concentration of P. tuber-regium at different treatment levels.

Null Hypothesis (Ho3)

There is no significant difference in the effect of acid treatment on disintegration time, friability, hardness, and release properties of the conventional paracetamol tablets produced using varying concentrations of different samples of P. tuber-regium.

Results

Yield

The yield of the bleached P. tuber-regium was 40.67 g. The initial starting material (that is, the powdered sclerotia was 400.26g. A 40 g sample was kept in an airtight container while the remainder was further treated with acid to obtain 43.87 g (yield of 35.7 %).

Physical Properties of Bleached and Acid-treated P. tuber-regium

The physical properties of the bleached and acid-treated samples are presented in (Table 2). The pH was between 6.90-7.00 which is within the acceptable pH range of excipients according to the British Pharmacopeia [19]. The acid-treated sample had lower swelling capacity, hydration capacity, and true density. Since the calculated F-value is greater than Fcrit (0.05) (2)3,9, at both 0.05 and 0.01 probability levels, the Null hypothesis is rejected. Thus, there is significant statistical difference in the physicochemical properties of the various samples of P. tuber-regium employed as binders in varying concentrations. The differences noticed are due to the batches (P, A, B, C) and consequently the type of treatment the samples were subjected to. This showed that longer acid residence time significantly lowers the pH, swelling capacity, hydration capacity and true density of the powder.

Table 2: Physical properties of bleached and acid treated P. tuber-regium powders (Values: Mean ± SD).

Parameter	Batches				F-Value	Fcrit
	(P)	(A)	(B)	(C)		
pH	7.10 ± 0.00	6.90 ± 0.00	6.90 ± 0.00	6.70 ± 0.00	11.246	3.863
Swelling capacity (mL)	2.16 ± 0.00	2.11 ± 0.01	2.08 ± 0.06	2.07 ± 0.00		
Hydration capacity (g)	5.49 ± 0.08	5.27 ± 0.08	5.20 ± 0.01	4.86 ± 0.05		
True density (g/mL)	4.28 ± 0.00	4.13 ± 0.00	4.07 ± 0.03	3.87 ± 0.01		

Solubility Evaluation

From the results it was observed that only the bleached P. tuber-regium powder (P) swelled in distilled water at elevated temperature of 80 oC. Other samples were not soluble nor were they swellable in distilled water, chloroform, 0.1 N HCl, 0.1 N NaOH, glycerin, methanol, and ethanol.

Flow Properties

Angle of Repose

The angle of repose of a powder or granules provides an insight into the degree of the cohesiveness of the powder, and hence its flowability. Powders with excellent flow show angle of repose less than 30o, those with good flow show an angle of repose within 31-35o, fair flowing powders show an angle of repose within 36 – 40o, whereas 41-45o, 46-55o, 56-65o and greater than 66o represents the angle of repose for powders with the passable flow, poor flow, very poor flow and very poor flow [20]. As such the granules of batches P1, P2, P3, B1, B2, B3, C1, C2, and C3 exhibited excellent flow properties. But the batches A1, A2, and A3 had good flow properties. Comparing the acid-treated samples, the batches of granules formulated with the 60 min acid treated sample had superior flow as compared to the granules formulated with the 10 min acid treated sample and the 30 min acid-treated sample, thus the granules were less cohesive and had better flow (Table 3).

Table 3: Flow properties of p. tuber-regium samples formulated paracetamol granules.

Batch	Bulk density (g/mL) ± SD	Tapped density (g/mL) ± SD	Hausner's ratio	Carr's index (%) ± SD	Flow rate (g/sec) ± SD	Angle of repose (º) ± SD	F-value	Fcrit
P1	0.45 ± 0.01	0.58 ± 0.02	1.28 ± 0.01	21.80 ± 0.00	1.90 ± 0.00	27.99 ± 0.00	1.854	3.287
A1	0.39 ± 0.00	0.58 ± 0.00	1.46 ± 0.01	31.48 ± 0.00	1.94 ± 0.00	31.17 ± 0.00		
B1	0.43 ± 0.08	0.55 ± 0.64	1.26 ± 0.82	20.29 ± 0.34	1.03 ± 0.91	29.00 ± 1.56		
C1	0.40 ± 0.91	0.53 ± 1.06	1.32 ± 0.73	23.87 ± 0.72	1.04 ± 0.74	27.87 ± 0.05		
P2	0.41 ± 0.00	0.47 ± 0.01	1.14 ± 0.02	12.32 ± 0.00	1.38 ± 0.00	27.95 ± 0.00	1.367	3.287
A2	0.38 ± 0.00	0.56 ± 0.01	1.43 ± 0.00	29.85 ± 0.00	1.56 ± 0.00	30.44 ± 0.00		
B2	0.39 ± 1.04	0.51 ± 0.36	1.31 ± 2.04	23.84 ± 0.61	1.08 ± 0.01	29.57 ± 0.01		
C2	0.39 ± 0.03	0.51 ± 0.30	1.30 ± 0.52	23.52 ± 0.72	1.19 ± 0.04	26.79 ± 0.15		
P3	0.43 ± 0.00	0.55 ± 0.00	1.25 ± 0.00	19.71 ± 0.01	3.01 ± 0.01	26.92 ± 0.02	1.657	3.287
A3	0.38 ± 0.60	0.53 ± 0.12	1.39 ± 0.32	27.82 ± 1.01	1.56 ± 1.03	30.21 ± 0.00		
B3	0.37 ± 0.87	0.50 ± 0.49	1.37 ± 1.63	26.81 ± 1.03	1.13 ± 0.26	28.44 ± 0.02		
C3	0.39 ± 0.07	0.50 ± 0.01	1.27 ± 0.31	21.56 ± 1.82	1.23 ± 0.60	24.73 ± 0.05		

Particle Size Distribution

The particle size distribution of the granules is shown in (Figure 1). The distribution showed that as the concentration of the binder increased the amount of fines produced was reduced. But when comparing the amount of fines across all the samples, the granules formulated with the bleached P. tuber-regium samples produced lesser fines than the acid-treated P. tuber-regium samples. Also as the acid resident time increased the amount of fines produced increased and thus batch C1 (binder concentration of 5%) gave a total amount of fines to be 2.6 %. High amount of fines in a granule result to an increased cohesive force between the particles resulting to poor flow of granules.

Tablet Properties

The result in table 3.4 shows that all the tablets formulated with 5% binder concentration had weight within the range of 599.2 ± 0.23 mg – 601.5 ± 0.17 mg, the tablets formulated with 10% binder concentration had a weight range of 624.4 ± 0.01 mg – 625.3 ± 0.33 mg, and the tablets formulated with 15% binder concentration had a weight range of 634.0 ± 0.02 mg – 635.9 ± 0.00 mg. All the batches

of tablets produced a tablet thickness of 4.14 ± 0.07 mg – 4.57 ± 0.04 mm and diameter of 13.02 ± 0.04 mm – 13.37 ± 0.05 mm. All the batches gave friability values of less than 1% with an exemption of the batch C1 which failed friability test and produced tablets with a friability value of 1.4885 %. This increase in the friability values may also be as a result of the negative effect of acid resident time on the binding properties of P. tuber-regium (Table 4), (Figures 2-4).

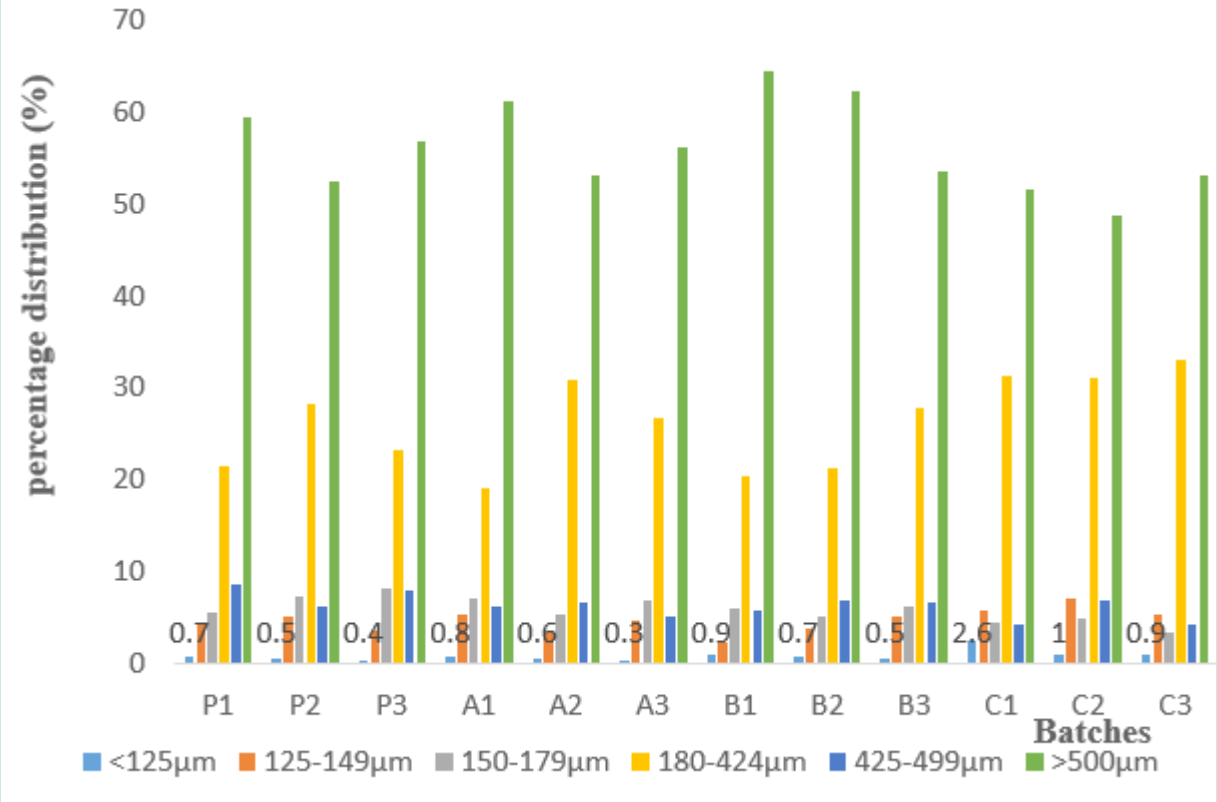

Figure 1: Particle size distribution of paracetamol granules.

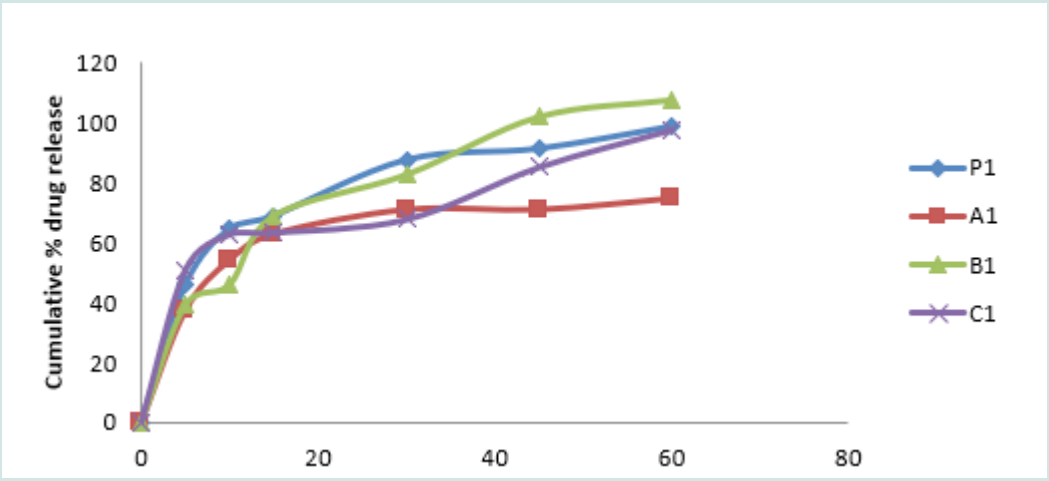

Figure 2: Dissolution profile of 5% P. tuber-regium as binder.

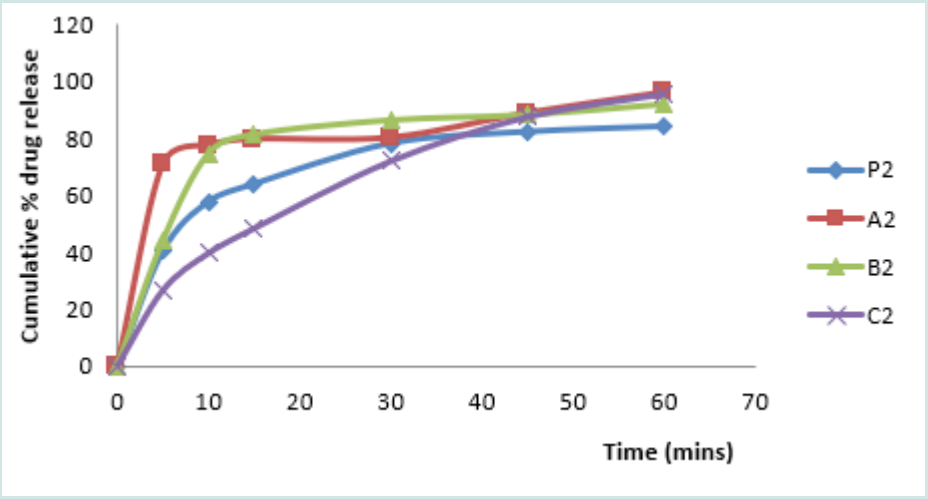

Figure 3: Dissolution profile of 10% P. tuber-regium as binder.

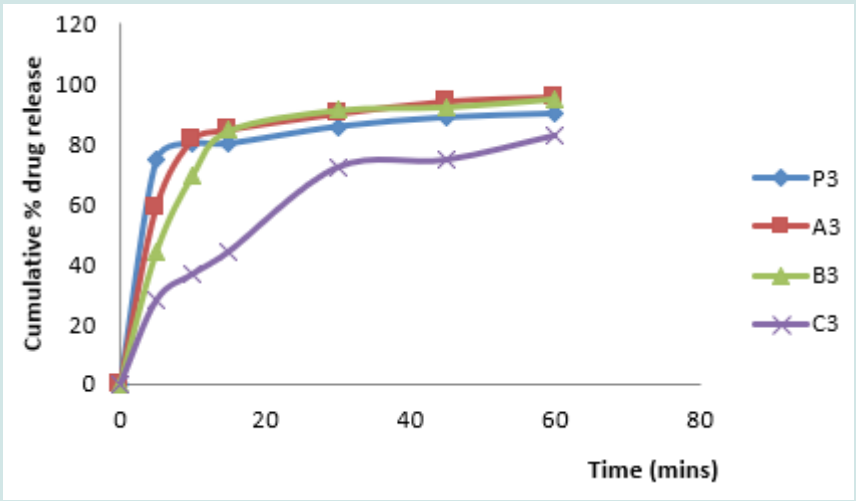

Figure 4: Dissolution profile of 15% P. tuber-regium as binder.

Table 4: Post-compression evaluation of formulated tablets.

Batch	Tablet Weight(mg)	Tablet Thickness (mm)	Tablet Diameter (mm)	Tablet Hardness (Kg)	Friability (%)	Disintegration time (sec)	Content Uniformity (%)
P1	601.5± 0.23	4.57 ± 0.04	13.37 ± 0.05	6.456 ± 1.34	0.971	24.38 ± 1.02	100.00
A1	599.2 ± 0.17	4.14 ± 0.07	13.03 ± 0.01	6.574 ± 1.74	0.6142	28.38 ± 1.02	85.00
B1	600.7 ± 0.03	4.27 ± 0.00	13.10 ± 0.00	5.108 ± 0.58	0.6856	39.23 ± 1.03	110.34
C1	599.4 ± 0.02	4.22 ± 0.01	13.03 ± 0.00	6.338 ± 0.00	1.4885	52.07 ± 0.03	96.55
P2	624.4 ± 0.03	4.45 ± 0.06	13.16 ± 0.07	7.102 ± 2.76	0.789	21.19 ± 1.78	86.21
A2	625.3 ± 0.33	4.36 ± 0.12	13.07 ± 0.00	6.588 ± 0.09	0.4569	22.54 ± 0.88	96.55
B2	624.4 ± 0.01	4.41 ± 0.04	13.08 ± 0.02	6.133 ± 0.01	0.4381	38.41 ± 0.91	93.10
C2	624.7 ± 0.01	4.32 ± 0.00	13.05 ± 0.02	6.798 ± 0.01	0.8650	51.41 ± 1.75	110.34
P3	634.1 ± 0.13	4.20 ± 0.00	13.02 ± 0.04	7.302 ± 0.02	0.510	20.21 ± 1.33	100.34
A3	634.0 ± 0.02	4.32 ± 0.00	13.03 ± 0.00	7.194 ± 0.00	0.5602	20.78 ± 2.00	100.00
B3	635.9 ± 0.00	4.37 ± 0.02	13.05 ± 0.02	6.813 ± 0.00	0.5912	36.12 ± 3.42	96.55
C3	635.1 ± 0.41	4.32 ± 0.17	13.04 ± 0.03	7.965 ± 0.01	0.7532	48.27 ± 2.82	100.00

Effect of Acid treatment on Tablet Parameters

The effect of acid treatment at different concentrations of P. tuber-regium indicated that acid treatment significantly increases disintegration time, hardness, and a non-significant increase in friability. Drug dissolution and release was impeded with acid residence time of 60 min giving a much slower release compared to the other samples (Table 5).

Release Kinetics

The release kinetics is presented in (Table 6). Batch B1, C2 and C3 had high Higuchi's correlation coefficient indicating a more diffusion-controlled release.

Table 5: Effect of acid treatment on tablet parameters.

Parameters	F-value	Fcrit	p-value
Disintegration**	7.015[a], 213.683[b]	6.944[a], 6.944[b]	0.049[a], 8.6E-05[b]
Friability*	2.729[a], 6.050[b]	6.944[a], 6.944[b]	0.179[a], 0.062[b]
Hardness**	11.121[a], 7.049[b]	6.944[a], 6.944[b]	0.023[a], 0.049[b]
Dissolution**	6.748[d]	2.138[d]	6.75E-06[d]

Table 6: Release Kinetics.

Batches	Zero Order		First Order		Higuchi		Korsemeyer-Peppas		Hixson-Crowell	
	K_o	r^2	K	r^2	K	r^2	r^2	n	K	r^2
P1	1.2716	0.6947	-0.0278	0.9518	12.144	0.9161	0.7702	1.0151	-0.0514	0.9339
A1	0.9131	0.5850	-0.0132	0.8091	9.1084	0.8417	0.7576	0.9579	-0.0304	0.7375
*B1	1.5708	0.8426	-0.0253	0.9806	14.081	0.9790	0.8277	1.0527	-0.0534	0.9789
C1	1.1633	0.6969	-0.0267	0.8514	10.938	0.8909	0.7437	0.9801	-0.0475	0.8929
P2	1.0889	0.6559	-0.0262	0.9773	10.568	0.8932	0.7700	0.988	-0.0481	0.8985
A2	0.9590	0.4439	-0.0279	0.8231	10.047	0.7045	0.6809	0.9665	-0.0444	0.7701
B2	1.0944	0.5315	-0.0276	0.9159	11.126	0.7942	0.7462	1.0037	-0.0482	0.7968
*C2	1.4657	0.9056	-0.0143	0.9968	12.788	0.9968	0.8719	1.0418	-0.0378	0.9815
P3	0.8636	0.3636	-0.0118	0.6310	9.502	0.6365	0.6663	0.9586	-0.0273	0.5239
A3	1.057	0.4776	-0.0196	0.8404	11.044	0.7539	0.7108	0.9942	-0.0399	0.7135
B3	1.1871	0.5727	-0.0281	0.9251	11.876	0.8288	0.7595	1.0185	-0.0507	0.8149
*C3	1.2317	0.8488	-0.0122	0.9545	10.988	0.9768	0.8517	1.0038	-0.0324	0.9281

Discussion

Chemical modification of pharmaceutical excipients has led to the discovery of functional excipients. These excipients serve to confer better flowability, compressibility or have impact on drug release profiles. Several samples have been chemically modified such as Xanthosoma sagittifolium [21], and chemically modified starches [22]. The results of these studies have intensified research into employing these excipients in drug formulations. This study was aimed at exploring the excipient functionalities of bleached and acid-treated P. tuber-regium using paracetamol as the model drug. The acid-treated sample had lower swelling capacity, hydration capacity, and true density. There is, however, no study on chemical treatment of P. tuber-regium samples but results available on starches indicated that treatment with acids improves gel consistency and lowers paste viscosity as a result of depolymerization [23]. This mechanism would be implicated in the change in the physical properties of the acid treated samples.

Following granulation, there is no significant statistical difference in the physicochemical properties of the paracetamol granules formulated with same concentrations of P. tuber-regium (bleached, acid treated at 10 min, 30 min and 1 h) as binder. Thus, employing acid treatment improved flow but not to a statistically significant extent. Similar studies had reported improvement in flow properties of powder upon acid exposure from 27.80 ± 1.08 to 19.80 ± 1.25, however on Xanthosoma sagittifolium and for a period of 24 h. The disparity in these two studies could possibly be as a result of acid residence time, the sample under study and the acid treatment time. In another study on the flow properties of fast disintegrating diclofenac granules, P. tuber-regium improved flow in a concentration dependent manner which is in tandem with this index study [24]. Acid-treatment has not been applied to P. tuber-regium but information on Xanthosoma sagittifolium reported improvement in flow properties. The tablet batch consistency in this study indicated that there was uniform die filling during compression. The maximum and minimum weight of tablets was within the British

Pharmacopoeia (BP) specification that states that the variation in the individual weight of the tablets should not be more than ±10 % and not more than two of the 20 tablets should deviate from the average weight by more than ±5 %.

This is an indication of uniform die fill during compression. According to the British Pharmacopoeia, specifications the hardness of an uncoated conventional tablet should be within the range of 4 – 10 kg and all the batches produced tablets that conformed to this specification. The hardness of the tablets increased with increase in binder concentration. There was however a decline in hardness due to acid treatment and acid resident time. The friability values of a tablet that will withstand handling during packaging, transport and storage should be less than or equal to 1 %. All the batches gave friability values of less than 1% with an exemption of batch C1. This increase in the friability values may also be as a result of the negative effect of acid resident time on the binding properties of P. tuber-regium. Studies on P. tuber-regium had shown a concentration dependent effect on tablet hardness and friability, however with untreated samples. In agreement with the British Pharmacopoeia monograph of paracetamol dosage forms, each paracetamol tablet should have paracetamol content of 85 – 115 %. The tablets produced conformed to this specification. For an uncoated conventional tablet to be therapeutically efficacious the formulated tablets should disintegrate into particles before 15 min which is in tandem with this index study.

The disintegration time was also observed to increase as a result of acid treatment and acid resident time. This implies that the batches formulated at 1 h acid treated P. tuber-regium powder disintegrated the slowest whereas those formulated with the bleached P. tuber-regium powder disintegrated the fastest. This may be attested to the reduced swelling and hydration capacity of P. tuber-regium powder as a result of acid treatment and acid resident time. Low disintegration time will facilitate fast break up of tablet and consequent fast release of the drug content [25]. In another similar study, P. tuber-regium resulted in a concentration-dependent increase in disintegration time. However, in their study, the properties of acid treated samples were not evaluated. The BP specifies that uncoated conventional tablets should release more than 75 % of the drug at 45 min [20]. The formulations released > 75 % of the drug in 45 min. This would ensure an improved absorption of the drug in the gastrointestinal tract leading to better bioavailability [26]. The effect of acid treatment on dissolution was significant at 10 % and 15 % binder concentration and hence retarded or slowed drug release. In a similar study drug release was observed to be concentration dependent however, the sample studied was C. olitorious [27].

This has pharmaceutical applicability and at this concentration P. tuber-regium can be employed as a release modifier. Formulation C3 had the slowest release profile conferred on by acid treatment and high binder concentration. This would be somewhat advantageous in the formulation of slow-release dosage forms that serve to reduce dosing frequency and improve compliance. Acid treatment at 10 % binder concentration has the highest r2 value of 0.9056 compared to other batches using the zero-order model. The in vitro release kinetics indicates the pattern and order of drug release from a dosage form [28]. C2 and C3 had higher r2 values using Higuchi's model. In current research, the Higuchi equation has become a very fundamental kinetic equation and the most well-known controlled-release equation [29]. The graphical representation of the cumulative % drug release of paracetamol from batches C2 and C3 matrix is perfectly following Higuchi drug release model as the drug release profile having the highest value of coefficient of correlation (r2 = 0.9968) and (r2 = 0.9768) respectively.

This means that longer acid resident time imparts a better diffusion-controlled release property in the formulation. Thus, the primary mechanism of drug release from C2 and C3 is diffusion-controlled release mechanism. In drug release kinetics, the exponent n ~ 0.45 for cylindrical samples signifies Fickian diffusion, n < 0.45 pseudo-Fickian diffusion, 0.45 < n <0.89 anomalous, non-Fickian diffusion, 0.89 < n < 1 zero order, non-Fickian case II relaxation and n > 1, non-Fickian super case II [30]. The result of this finding indicated n value > 0.89, thus, the drug release from the system follows super case II transport. The Hixson-Crowell cube root law describes drug release from systems where the surface area and the diameter changes as seen in tablets. Batch B1, C2 and C3 had the highest correlation coefficient for the Hixson-Crowell cube root model. This implies that a change in surface area during the process of dissolution has a significant effect on the drug release from the dosage form.

Conclusion

Paracetamol tablets can be formulated using bleached and acid-treated P. tuber-regium powder by wet granulation method. The granules formulated using the acid-treated P. tuber-regium had better flow characteristics which increases as the acid resident time of the samples increased. However, the tablets formed had higher friability values, higher hardness, and prolonged disintegration time with slower release of paracetamol from the dosage form. This study has therefore shown that acid treatment of P. tuber-regium improved flow properties, higher hardness and friability, longer disintegration time and slower release from the dosage form. Acid treatment further imparts a more diffusion-controlled release pattern, and a significant surface area effect on drug release.

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