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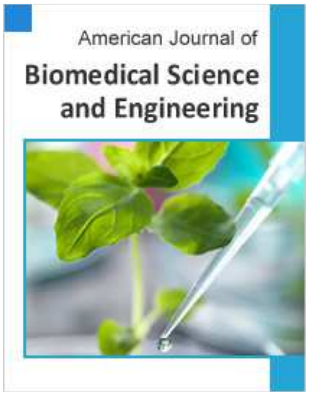


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# Application of Periwinkle Shell Bio-ash (*Ugoeze-bio-ash*) as $CO_2$ Donor in the Formulation of an Effervescent Low Dose Aspirin Tablet

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## Abstract
Aspirin, a non-steroidal anti- inflammatory drug is one of the most widely used and prescribed analgesic, antipyretic and anti-inflammatory agent utilized prophylactically to avert thrombo-embolic diseases. An oral effervescent tablet containing 75 mg aspirin was formulated with periwinkle shell bio-ash (*Ugoeze-bio-ash)* expected to generate carbon dioxide in the presence of water and other excipients such as citric acid triggering a rapid effervescence of the tablet to release its drug content. Tablet properties were considered using the British Pharmacopeia methods. From the results, intact, off-white, round and convex shaped effervescing tablets with low crushing strength, friability less than 1 % and disintegration time less than 5 min were obtained. Stability studies showed that the tablets prepared with *Ugoeze-bio-ash* did not show much changes in properties after 12 months when further analysis were carried out on them. *Ugoeze-bio-ash* could be a useful pharmaceutical excipient in the formulation of several effervescent pharmaceutical solid dosage forms. Its continual utilization as locally sourced raw material will add economic value to periwinkle shell which so far has limited application and still constitute environmental menace in the Niger Delta region of Nigeria.

## 1. Introduction

The process or method of administering a pharmaceutical compound for the purpose of creating a therapeutic effect for animals and humans is known as drug delivery [1]. Tablets are the most widely utilized oral dosage form. The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolonged. This can be overcome by administrating the drug in liquid form even though many active pharmaceutical ingredients (APIs) have limited level of stability in the liquid form. For achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract is to control the gastric residence time using a gastro retentive dosage forms that will provide as with new and important therapeutic options; so effervescent tablets act as an alternative dosage form [2]. Effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates that react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration [3]. Effervescence is defined as the evolution of bubbles of gas from a

liquid as a result of the chemical reaction. Effervescent mixture have been known and used medicinally for many years. Such powder was used as saline. Cathartics were available in the eighteenth century and were subsequently listed in the official compendia as compound effervescent powder. The most common reaction for pharmaceutical purpose is the acid base reaction between sodium bicarbonate and citric acid. Acid-base reactions between alkali metal bicarbonates and citric or tartaric acid have been used for many years to produce pharmaceutical preparations that effervesce as soon as water is added [4]. The tablet is added into a glass of water just before administration and the drug solution or dispersion is taken immediately. The tablet is quickly broken apart by internal liberation of carbon dioxide in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in the presence of water. Due to liberation of carbon dioxide gas, the dissolution of API in water as well as taste masking effect is enhanced. Other advantages of effervescent tablets compared with other oral dosage forms includes an opportunity for the formulator to improve taste. The effervescent tablet have major advantage that the drug product is already in solution at the time it is consumed. Thus the absorption is faster and more complete than with conventional tablet. Faster absorption means faster onset of action. Effervescent drugs are delivered to the stomach at a pH that is just right for absorption. Such medications are administered in liquid form, so they are easy to be taken as compared to tablets or capsule. The number of people who cannot swallow tablet or who dislike swallowing tablet and capsule is growing. With an effervescent dosage form, one dose can usually be taken in just 80-120 ml (about half a tumblerful) of water. Effervescent tablet dissolve fully in a buffered solution. Reduced localized contact in the upper gastrointestinal tract leads to less irritation and greater tolerability. Buffering also prevent gastric acids from interacting with drug themselves, which can be a major cause of stomach irritation. Drugs delivered with effervescent base, taste better than most liquids, mixture and suspensions. Superior taste masking is achieved by limiting objectionable characteristics and complementing formulations with flavours. Moreover they produce fizzy tablets, which may have better consumption appeal than the traditional dosage form. Drugs delivered with effervescent technology have predictable and reproducible pharmacokinetics profiles that are much more consistent than the tablets or capsule. Researchers have shown that effervescent tablets enhance the absorption of number of active ingredients compared to conventional formulations. This is because the carbon dioxide created by the effervescent reaction can enhance active ingredient permeability due to an alteration of paracellular pathway. The paracellular pathway is the primary route of absorption of hydrophilic active ingredients in which the solutes diffuse into the intercellular space between epithelial cells. It is postulated that the carbon dioxide widens the intercellular space between cell which leads to greater absorption of active ingredients (both hydrophilic and hydrophobic). The increased absorption of hydrophobic active ingredients could be due to the non-polar carbon dioxide gas molecules thus creating an increased hydrophobic environment, which would allow the hydrophobic active ingredients to be absorbed [5-8].

In the present study, an oral effervescent low dose aspirin tablet was designed using periwinkle shell bio-ash (*Ugoeze-bio-ash)* as carbon dioxide donor. Aspirin (2-acetoxybenzoic acid) is acetyl salicylic acid (ASA), a non-steroidal anti-inflammatory drug that is a derivative of salicylic acid. It is one of the most widely used and prescribed analgesic, antipyretic and anti-inflammatory agent. Because of its ability to bind irreversibly to blood platelets and inhibit platelet aggregation, aspirin is used prophylactically to prevent thrombo-embolic diseases [9]. Its ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase enzyme. It acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase enzyme. This makes aspirin different from other non-steroidal anti-inflammatory agents (NSAIDs) such as diclofenac and ibuprofen which are reversible inhibitors [10]. Prostaglandins are local hormones produced in the body and have diverse effects in the body including the transmission of pain information to the brain, modulation of the hypothalamic thermostat and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are primarily caused by blood clots and low doses of aspirin are seen as an effective medical intervention for acute myocardial infarction. Incidence of stroke and related cases are prevalent [11]. There are two distinct uses of aspirin for prophylaxis of cardiovascular events: primary and secondary prevention. Primary prevention is about decreasing strokes and heart attacks in the general population of those who have no diagnosed heart or vascular problems. Secondary prevention concerns patients with known cardiovascular disease [12]. Availability of low dose aspirin will be very useful for both needs. People with angina, or who have already suffered a heart attack or stroke, are at risk of having another episode because of the atherosclerosis in their arteries and in this case, low dose aspirin is used to lower the risk of this. Effervescence low aspirin provides much relief for patients having difficulty in swallowing tablets as well as those in prolonged illness who are prone to nauseatic sensations if they have to swallow a tablet.

By the design of this study, *Ugoeze-bio-ash* generates carbon dioxide when in contact with water in the presence of such excipients as citric acid causing a rapid effervescence of the tablet to release its drug content. Utilizing *Ugoeze-bio-ash* in this study harnesses locally sourced raw material, thus adding economic value to periwinkle shell which have limited application and still constitute environmental menace in the Niger Delta region of Nigeria. The periwinkle shell is very rich in calcium and can be manipulated to yield various

calcium compounds which can serve as pharmaceutical excipients**.** The shell is the hard, rigid outer calcium carbonate covering of certain animals. Several animals, particularly those that live in the sea possess exoskeleton, but usually, only those of molluscs are considered to be shells. The shell is made of chitin and nacre, an organic mixture of outer layer of horny conchiolin which is a scleroprotein, followed by an intermediate layer of calcite or aragonite and also a layer of calcium carbonate. Nacre is secreted by the ectodermic cells of the mantle tissue of certain species of mollusc. The blood of mollusc is rich in liquid form of calcium which concentrates out and can crystallize as calcium carbonate. The layers of calcium carbonate may incorporate conchiolin which binds the calcium carbonate crystals together. Large amounts of shells may form sediment and become compressed into limestone [13]. Periwinkle, noted as *Tympanotonus fuscata* var radula (L) is covered with shell and belongs to the phylum, mollusca. They are commonly found in lagoons, estuaries, mangroves, shallow waters and occasionally in inter-tidal zones where they burrow into the mud in beds of the river. They are endemic to West Africa [13-21]. It is common as sea food and cheap source of animal protein in the Niger Delta region of Nigeria where its collection and marketing constitute an important industry [22]. The empty shells are discarded as waste and its accumulation adds to the environmental menace. In this same region of Nigeria, some people use these shells as cheap substitute for chippings in building constructions. Some local livestock farmers pulverize the shells and add it to livestock feed as source of calcium supplement. Other uses of periwinkle shell have been reported. Periwinkle shell ash (PSA) has been investigated as a pozzolanic material, a step taken to improve on the strength and durability performance of concrete. PSA has also been investigated for its suitability as partial replacement for ordinary Portland cement in concrete [18, 23-26]. The properties of biomaterial of *Tympanotonus fuscata* (periwinkle) shell as pharmaceutical excipient has been reported [27, 28].

# 2. Materials and Methods

## 2.1. Materials

The following materials were used as they were procured. Calcium carbonate, absolute alcohol (Surechem, England), citric acid (anhydrous), mannitol (DK chemicals, China), magnesium stearate (BDH, England), aspirin, hydrochloric acid, methanol (Sigma). Periwinkle shell bio-ash (*Ugoeze-bio-ash*) was processed in the Pharmaceutical Technology laboratory of the Faculty of Pharmaceutical Sciences, University of Port Harcourt as described in the methods.

## 2.2. Methods

### 2.2.1. Collection of *Tympanotonus fuscata* Shell

*Tympanotonus fuscata* (periwinkle) shell was collected from Borokiri area of Port Harcourt, Nigeria.

### 2.2.2. Preparation of Sample

Periwinkle shells weighing 500 g was washed, dried completely at 60$^{o}$C. It was heated in a muffle furnace (Haraeus, D-2800 Bremen Germany) at 900$^{o}$C for 3 hr. The whitish mass left was pulverized and washed severally with n-hexane and dried at 60 $^{o}$C. It was passed through sieve 150 µm size and stored in airtight bottle. This bio-ash is referred to as *Ugoeze-bio-ash* in this study.

### 2.2.3. Characterization of *Ugoeze-bio-ash*

#### (i). Acute Toxicity

Acute toxicity was determined as described by Ugoeze and Chukwu [27].

#### (ii). Elemental Analysis

Elemental analysis was carried out by digesting 1 g of *Ugoeze-bio-ash* with concentrated nitric acid. The solution was diluted and analysed for some metals using Buck Scientific Atomic Absorption Spectrophotometer (AAS – VG 210, USA).

#### (iii). Solubility Profile

The solubility of the powder was investigated in dilute mineral acids, water, alcohol and other organic solvents at both room and elevated temperatures.

#### (iv). Moisture Content

The moisture content was determined by placing 1 g of powder in a moisture balance (Citizen, MB 50 China) adjusted to 120 ℃. The percent moisture content was displayed by the equipment.

#### (v). Particle Size Analysis

The particle size of *Ugoeze-bio-ash* was investigated using 100 g quantity of powder shaken through a cascade of test sieves of sizes 1.00, 0.850, 0.710, 0.600, 0.500, 0.250 and 0.150 mm with a cover at the top and a receiver at the lowest end arranged in a descending order of size placed on a sieve shaker (Retsch, Germany) and ran for 10 min.. The amount of powder retained in respective sieves was calculated in percentages while the mean particle size of the powder was determined from the relationship:

$$Mp = \Sigma (\%\ \text{retained}) \times (\text{mean aperture size}) / 100 \quad (1)$$

where Mp = mean particle size

#### (vi). Densities

The bulk and tapped densities of the powder was determined using 50 g of sample in Digital Automated Tap Density Test Apparatus (VTAP/Matic –II, Veego, India) maintaining tap height of 14 ± 2 mm, tap rate of 251 taps/min. Adopting the methods used by Odeku, *et al* [29], the true density of the powder was determined using n-hexane as the displacement fluid. An empty 25ml pycnometer was weighed (W). It was filled with n-hexane, and excess fluid wiped off. The filled bottle was weighed ($W_1$). The difference between this and W was calculated as $W_2$. A 0.5g quantity of the sample was weighed ($W_3$) and carefully transferred into the

pycnometer. The excess fluid was wiped off and the bottle was weighed again ($W_4$). Three replicate determinations were carried out and the mean value was used to calculate the true density, $P_t$ (g/ml) according to the following equation:

$$P_t = W_2 \times W_3/V(W_3 - W_4 + W_2 + W) \quad (2)$$

where V = 25ml (volume of pycnometer).

The bulk and tapped densities were calculated from the relationships:

$$\text{Bulk density} = \text{Mass of powder/bulk volume of powder} \quad (3)$$

$$\text{Tapped density} = \text{Mass of powder/tapped volume of powder} \quad (4)$$

### (vii). Flow Properties

The flow rate was determined using the funnel method reported by Carstensen and Chan [30]. The time for a 50 g quantity of sample placed in the funnel to freely flow out was noted. The flow rate was calculated from the relationship:

$$\text{Flow rate} = \text{Mass of powder/time} \quad (5)$$

The angle of repose was investigated using 50 g of powder poured into a cylindrical plastic pipe fixed on to a flat base whose diameter measures 4.00 cm and the same as the internal diameter of the cylindrical pipe. The cylinder was slowly pulled out vertically so as to form a cone of powder on the base. The height of the cone was measured. This is a modification of the method of Jones and Pilpel [31]. The angle of repose, θ, is given by the following equation:

$$\theta = \tan^{-1}(h/r) \quad (6)$$

where h is height powder heap and r is radius of circular base.

Determinations were made in triplicate and the mean angle of repose was calculated.

The Hausner's ratio and Carr's index (CI) were calculated from the values obtained for bulk and tapped densities above as follows [32, 33].

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (7)$$

$$\text{Carr's Index} = \left\{1 - \left[\frac{V}{V_o}\right]\right\} \times 100 \quad (8)$$

where: v = Tapped volume and $v_O$ = Bulk volume.

### 2.2.4. Preparation of Effervescent Low Dose Aspirin Tablet

Effervescence low dose aspirin was formulated as shown in the Table 1. Batches A and B were prepared with *Ugoeze-bio-ash* and calcium carbonate respectively. Calcium carbonate in batch B was used to compare *Ugoeze-bio-ash.* Aspirin and citric acid were blended into fine powder and then other ingredients were added in turn. 5 ml of absolute alcohol was used to wet the powder blend and it was kneaded for 5 min. The damp mass was screened through 1.7 mm stainless steel sieve and dried in the oven (Memmert, England) at 50 $^{o}$C for 30 min. It was rescreened with 1.00 mm stainless steel sieve. Each batch of granules was lubricated with magnesium stearate and compressed into tablets at 7 tons using a single punch tablet press (Erweka, EP-1, Germany) fitted with an 8.0 mm diameter biconcave punches.

### 2.2.5. Standardization of Aspirin

A 100 mg of aspirin was dissolved in 100 ml volumetric flask using 0.05M acetate buffer (pH 4.5). Volumes of 0.1-1.0 ml respectively of the stock solution were made up to 100 ml to obtain concentrations of 0.1-1.0 mg %. Each sample was spectrophotometrically determined (Jenway, 6405) at 242 nm [35]. The calibration curve was plotted to obtain the equation: $y = 0.0441x$; $R^2 = 0.9985$.

### 2.2.6. Determination of Tablet Properties

The British Pharmacopeia methods were used to evaluate the tablets [34]. Tablet uniformity of weight was evaluated by weighing twenty randomly selected tablets on analytical electronic balance (Ohaus, China). The diametrical crushing strength of ten tablets was determined with digital hardness tester (Erweka TBH 100, Germany). The friability of ten tablets was determined in tablet friabilator (Erweka TAR 220, Germany) set at 25 rpm for 4 min. The disintegration time was determined by placing one tablet each time in a 250 ml beaker containing 200 ml of water at room temperature. Bubbles of gas was evolved. When the evolution of gas around the tablet or its fragments ceases, the tablet was considered completely disintegrated. Other tablet parameters considered were tablet appearance, thickness and total content. Ten intact tablets were randomly taken from each batch and crushed. The weight of powders equivalent to the mean weight of the respective batches were analysed spectrophotometrically for its total drug content.

***Table 1.*** *Formulation effervescent low dose aspirin tablet.*

| Ingredient | Amount (%) | Amount per tablet (mg) |
|---|---|---|
| Aspirin | 30.00 | 75.00 |
| Ugoeze-bio-ash | 20.00 | 50.00 |
| Citric acid | 25.00 | 62.50 |
| Sodium starch glycolate | 10.00 | 25.00 |
| Mannitol | 14.50 | 36.25 |
| Magnesium stearate | 0.50 | 1.25 |
| Total | 100.00 | 250 |

### (i). Dissolution Test

The dissolution of the tablets were carried out using the basket method. The equipment was operated at 50 rpm in a dissolution medium comprising 500 ml of acetate buffer (pH 4.5) maintained at 37 ± 0.5 $^{o}$ C [30]. Samples were withdrawn at predetermined intervals of 10 min and each time, replaced with the same volume of the plain dissolution medium. Withdrawn samples were filtered and their respective absorbance were determined with a UV spectrophotometer at 242 nm.

### (ii). Tablet Stability Studies

The tablets prepared with *Ugoeze-bio-ash* and calcium carbonate were left in amber coloured air-tight glass bottle in a laboratory environment, 28-32 $^{o}$ C for 12 months. The

samples were investigated for physical parameters such as colour changes, crushing strength, drug content and percentage drug released.

## 3. Results and Discussion

The physico-technical properties of Ugoeze-bio-ash are shown in Table 2. It was odourless, non-pungent, non-irritating and off-white powder. Its production yield was of 81.40 ±1.47 %. This high yield may show the possibility of producing this raw material at industrial scale. The solubility of *Ugoeze-bio-ash* was similar to calcium carbonate, being neither soluble in water nor organic solvents, but effervesces in the presence of dilute mineral acids. Elemental analysis shows that Ugoeze-bio-ash contains 18.65% calcium, 0.05 % magnesium, 0.009 % iron and carbonate as 30.96 % calcium carbonate. Lead, mercury, barium and arsenic were not detected. The value of $LD_{50}$ obtained is an indication of safety for its use in human being [27]. Its lower moisture content in comparison with calcium carbonate shows that *Ugoeze-bio-ash* may be suitable for use as excipient in the formulation of hydro-degradable drugs. The values of bulk and tapped densities for both powders were significantly far apart ($p<0.05$) and indicates poor flowability. Other flow parameters confirm that the flowability of both powders were poor [32]. Table 3 shows the properties of granules prepared with *Ugoeze-bio-ash* and calcium carbonate respectively. Considering the values of Hausner's ratio and Carr's index, the granules obtained with *Ugoeze-bio-ash* and calcium carbonate in wet granulation (Table 1) showed there was improvement in flowability especially with *Ugoeze-bio-ash* when considering the insignificant difference in the values of its bulk and tapped densities ($p>0.05$).

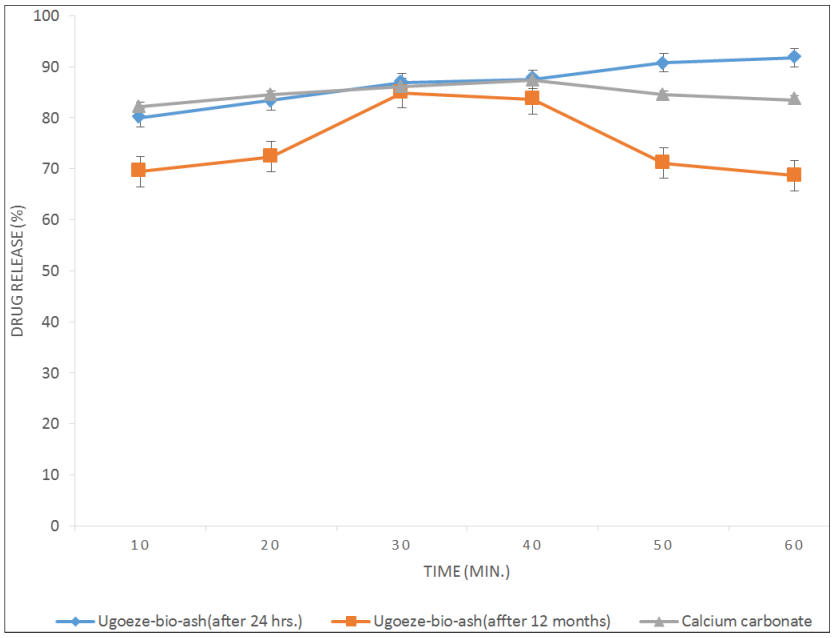


***Figure 1.*** *Dissolution profile for low dose aspirin tablet.*

The results obtained from the evaluation of tablet properties are presented in Table 4. Intact, off - white, round and convex shaped tablets were obtained. Deviation of the mean tablet weight was less than 5%. The British Pharmacopeia specifies that tablets weighing 250 mg or more should not deviate by more than 5% [34]. The crushing strength obtained for the effervescent tablets were low. A tablet breaking force of 4 kg is usually considered to be the minimum for satisfactory uncoated tablets [36]. Oral tablets normally have a crushing strength of 4-10 kg. However, hypodermic and chewable tablets are usually softer (about 3 kg) and some sustained release tablets are harder (about 10-20 kg). Tablet crushing strength has been associated with other tablet properties such as density and porosity. Crushing strength generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression [37, 38]. The value of tablet friability obtained for both batches of tablets were less than 1 %. Another measure of the mechanical strength of pharmaceutical tablets is the crushing strength-friability ratio (CSFR). The crushing strength provides a measure of tablet strength while friability is a measure of tablet weakness. Studies have shown that the higher the CSFR, the stronger the tablet [38, 39]. The values of CSFR obtained for both batches were low. This was further shown in the values of tensile strength for all the batches of tablets. Though the entire batches of tablets produced with *Ugoeze-bio-ash* or calcium carbonate appear mechanically weak, their friability were less than 1 %. Their crushing strength, though, less than 3 kg may be adjudged satisfactory since they were designed as effervescent tablets. Considering disintegration time, dispersible tablets are expected to disperse in 3 min while effervescent tablets are expected to disintegrate within 5 min [3]. For most uncoated tablets, the British Pharmacopeia [34] specifies 15 min (although it varies for some uncoated tablets) while for coated tablets, up to 2 hrs. may be required. Thus,

the tablet disintegration test is limited to manufacturing control of batch-to-batch variations in individual products and is not most of the time a measure of bioavailability [40]. Nevertheless, it is used to provide a simple and useful means for monitoring and controlling the quality of tablets. Complete disintegration of tablets prepared with either *Ugoeze-bio-ash* or calcium carbonate occurred in less than 5 min. The results of the stability studies showed that the tablets prepared with calcium carbonate turned dark brown and mottled with colours after the first 3 months of storage. It was discarded having shown evidence of degradation and instability. The tablets prepared with *Ugoeze-bio-ash* was not discoloured after 12 months. Further analysis carried out on its tablet parameters yielded results which were not very different from the early results (Fig. 1).

## 4. Conclusion

The application of periwinkle shell bio-ash as carbon dioxide donor in the formulation of effervescent tablets containing 75 mg aspirin yielded good and stable tablets with qualities comparable to those of the British Pharmacopeia standards. This material could be a useful pharmaceutical excipient in the formulation of several effervescent pharmaceutical solid dosage forms. Its continual utilization as locally sourced raw material will add economic value to periwinkle shell which have limited usage and still constitute environmental menace in the Niger Delta region of Nigeria.

***Table 2.*** *Properties of Ugoeze-bio-ash compared to calcium carbonate powder.*

| Parameter | Value | |
|---|---|---|
| | **Ugoeze-bio-ash** | **Calcium carbonate** |
| Colour | Off white | white |
| Odour | Odourless, | Odourless |
| Texture | Coarse | Smooth |
| Processing yield | 81.40±1.47 | ND |
| Particle size (mm) | 0.078 | 0.275 |
| pH (1% w/v) | 12.52±0.03 | 10.91±0.03 |
| $LD_{50}$ | > 15,000 mg / kg | ND |
| Moisture content (%) | 1.09±0.01 | 4.67±0.08 |
| Bulk density (g/ml) | 0.79±0.04 | 0.31±0.01 |
| Tapped density (g/ml) | 1.21±0.20 | 0.61±0.07 |
| True density | 2.04±0.02 | 0.27±0.01 |
| Flow rate (g/s) | 7.16±0.48 | Non flowable |
| Angle of repose | 36.57± 1.47 | 42.28± 1.38 |
| Hausner's ratio | 1.53± 0.21 | 1.97±0.03 |
| Carr's index | 39.34±0.26 | 52.80±0.31 |

ND = Not determined.

***Table 3.*** *Granule properties for the low dose aspirin tablet.*

| Parameter | Mean Value | | |
|---|---|---|---|
| | Wet granulated powder blend | | |
| | **Ugoeze-bio-ash** | **Calcium carbonate** | **P-value** |
| Bulk density (g/ml) | 0.61±0.01 | 0.62±0.01 | 0.288 |
| Tapped density(g/ml) | 0.67±0.02 | 0.73±0.01 | 0.010 |
| True density(g/ml) | 1.41±0.003 | 1.49±0.004 | 0.000 |
| Flow rate(g/s) | 4.99±0.04 | 4.86±0.05 | 0.025 |
| Angle of repose | 36.74±0.41 | 35.16±0.38 | 0.008 |
| Hausner's ratio | 1.09±0.02 | 1.18±0.02 | 0.005 |
| Carr's index | 8.043±1.94 | 14.03±0.97 | 0.009 |

***Table 4.*** *Properties of low dose aspirin tablet.*

| Tablet parameter | Value ± SD | | |
|---|---|---|---|
| | **Ugoeze-bio-ash (After 24 hrs.)** | **Calcium carbonate (After 24 hrs.)** | **Ugoeze-bio-ash (After 12 months)** |
| Weight (mg) | 247.42 (0.96) | 249.34 (0.85) | 245.34(0.79) |
| Thickness(mm) | 3.22(0.15) | 3.24(0.12) | 3.12(0.18) |
| Hardness(kg) | 2.60(0.41) | 2.33(0.27) | 2.49(0.67) |
| Friability (%) | 0.89 (0.03) | 0.93(0.04) | 0.97(0.13) |
| Disintegration(min) | 4.00 (0.21) | 3.56 (0.24) | 4.97(0.31) |
| Drug content(mg) | 72.22(0.24) | 73.80(0.32) | 69.54(0.89) |
| Tensile strength | 0.064(0.26) | 0.057 (0.31) | - |
| CSFR | 2.92(0.23) | 2.51(0.25) | - |

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