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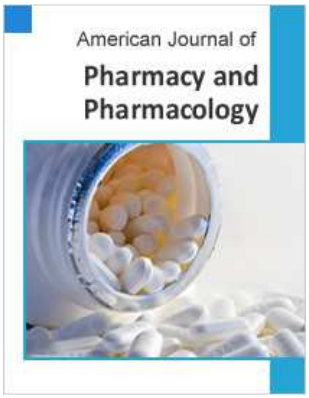

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Assessment of Paediatric Dispersible Paracetamol Tablet Containing *Lentinus tuber regium* Based Co-processed Filler-Binder-Superdisintegrant

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Abstract
Paracetamol (PCM), enlisted in World Health Organization (WHO) Essential Drugs List (EDL) and common for children in liquid formulations is a widely used analgesic/antipyretic for all ages, especially in reducing post-vaccination fever in infants/toddlers. Its paediatric dose is sometimes calculated from the adult formula by health professionals based on its concentration in mg/kg of body weight. This is not always realistic for parents or care-givers to manage at home, especially among the unenlightened class. Children of very wide varying age bracket may receive the same dose for the fact that single paediatric dose of PCM in tablet form is not popular. This study evaluates a co-processed filler-binder-super disintegrant based on edible mushroom, *Lentinus tuber regium* incorporated to trigger rapid dispersion of a paediatric dispersible tablet (PDT) containing 125 mg of PCM prepared by solvent evaporation of alcoholic wet massed excipients. Granules obtained were free from enteric or pathogenic organisms, flowable, compressible and its compression resulted to tablets with crushing strength, 30. 60 ± 1. 01 N; friability, 0. 20 ± 0. 01 % and crushing strength friability ratio (CSFR), 153. 00. Uniform and complete dispersion of the PDT occurred in 28 s in 10 ml of water at 27 ± 2℃. A spectrophotometric assay of the entire dispersion yielded 120. 99±0. 84 mg of PCM *in vitro*. It is hoped that this portable and easily dispersible single paediatric dose of PCM tablet will reduce the pains and sometimes, inaccuracies incurred in calculating paediatric doses of PCM from adult formula, especially among the unenlightened care-givers.

1. Introduction

The paediatric population is a heterogeneous group ranging from newborns to adolescents with wide physical and developmental differences regarding pharmacokinetics and pharmacodynamics. Organ maturation, metabolic capacity, skin maturation and other factors may change with age, especially in early infancy [1, 2]. It is a challenge to find one pharmaceutical dosage formulation appropriate for all age groups. The aim should be to safely cover as wide an age range as possible with a single

formulation. The guiding principle for selecting paediatric dosage forms should be – as for adults – the balance of risks and benefits taking into account the specific needs of this vulnerable population [3]. Current use of medicines for the paediatric population reflects the full range of dosage forms and routes of administration used for adult medicines. Common routes of administration in paediatric patients include oral, parenteral, dermal, pulmonary, nasal, rectal and ocular. There is, however, limited information on the acceptability of different paediatric dosage forms in relation to age and therapeutic needs and on the safety of excipients in relation to the development of the child. A European Medicines Agency (EMA) reflection paper on paediatric formulations [4] provides background information on these issues. Reviews by Ernest et al. [5] and Krause and Breitkreutz [6] discuss the needs and challenges in developing paediatric medicines. The most desirable features of high-quality paediatric medicines that should be common to all dosage forms will include the fact that dosage form must be convenient and reliable in its administration. The administered dose should contain an amount of active pharmaceutical ingredient (API) adjusted to the age and needs of the child. The implication is that more than one dosage form of the API or more than one strength of a dosage form may be needed to cover different age groups. The intended dose volume or size should be appropriate for the target age group. Paediatric medicines should preferably be presented as formulations that are ready to administer. The need for health professionals, parents or caregivers to manipulate the dose prior to administration should be kept to a minimum. However, there might be situations, depending on the formulation properties and the dose range to be covered, where this cannot be avoided. Alternatively, to enable accurate dosing, the dosage form should be designed in a way it could be subdivided easily into smaller, uniform doses of appropriate size and, for liquid forms, the dose volume should be accurately measured. However, break-marks intended to enable accurate subdivision of the tablet to provide doses of less than one tablet should be proven to result in parts that comply with the requirements for uniformity of mass or uniformity of content, as appropriate. The decision whether or not to provide scored tablets will depend on a risk analysis, taking into account the safety and dose of the API. A suitable test is provided in the monograph on tablets in The International Pharmacopoeia [7]. It is preferable that the single part of the broken tablet contains the amount of API suited to the youngest intended age group. Specially designed tablets and tablet punches may be needed.

Dosage forms that, in general, are likely to prove most suitable for global use, including for developing countries, and which should be prioritized, are flexible solid dosage forms such as tablets that are dispersible in liquids suitable also for the younger age groups. The flexible dosage form design may be used for various APIs but may not be suitable for medicines requiring a precise dose titration. The oral route is the preferred and most appropriate route of administration to paediatric patients. This route is generally acceptable in all age groups if the medicine is administered in a suitable dosage form, e. g. in liquid form for children in the youngest age groups who have difficulty in swallowing solid dosage forms. Strictly speaking, the choice of dosage form for oral administration depends on the gut function and, thus, on both age and clinical condition. Oral solid dosage forms include a variety of final forms from powders to coated tablets intended to be swallowed directly or after application to the mouth (chewable tablets, orally dissolving tablets or orodispersible tablets). Some are intended for swallowing after dissolution, dispersion in water or other suitable liquids. Their advantages over oral liquid preparations are improved stability, good dosage uniformity and options for different doses. The ease of administration depends on the child and the particular dosage form. These forms are convenient for packaging and ease of transport [1].

So far, many medicines are still only available in adult strength; therefore the administration of accurate dosage for children is critical. The adjustment of adult formulations to paediatric dosage is often done by cutting or crushing tablets, opening the capsules and using the powder to make a liquid, diluting concentrated preparations, etc. As a direct consequence, children are often given formulations that have not been developed for them. This practice can compromise the efficacy and safety of the treatment. Over the last two years the WHO and the UNICEF have joined their efforts in promoting the development of paediatric pharmaceutical formulations for children of various ages, including dispersible tablets which disintegrate in water or a small amount of breast milk. Paediatric medicines must allow accurate administration of the dose to children of varying age and weight. In addition, the formulation must be acceptable for the child in terms of taste and easy to administer for the care-giving adult. During childhood, there are significant changes in the ability to handle different dosage forms. The WHO has proposed the following age classification: -Pre-term newborn infants (<37 weeks gestation), full-term newborn infants (0 to 28 days), infants and toddlers (1 month to 2 years), children, pre-school (2 to 5 years), children, school (6 to 11 years), adolescents (12 to 16-18 years -dependent on region).

Oral medication is the preferred route of administration to children. Small-volume liquid medicines are appropriate for use in the younger age groups. Children less than 5 years of age usually have problems with swallowing tablets and capsules (i. e. dysphagia). Dysphagia may be overcome by developing solid dosage forms (dispersible tablets) to be dissolved, dispersed or mixed with food, milk or water prior to administration. Dispersible tablets are a convenient formulation for infants, toddlers and pre-school children.

Dispersible tablets are uncoated or film-coated tablets that can be dispersed in liquid before administration giving a homogenous dispersion. Dispersible tablets usually disintegrate within three minutes when put in water or a small amount of breast milk. In general dispersible tablets are more convenient for active pharmaceutical ingredients with

insufficient stability in water, more easily transportable and they generate less handling and transportation costs for the same amount of active ingredient (less volume, less weight), easier to produce and the production costs are less, which makes them more affordable than standard liquid formulations. Other advantages include the fact that they can be used in very young children (0 – 6 months), they are easy to dispense and require minimal manipulation by health professionals and parents prior to use which minimizes the risk of errors. A small amount of water for administration is required and they can be dispersed in breast milk. It is also noteworthy that dispersible tablets have less physical resistance than regular tablets; they are more sensitive to moisture and may degrade at higher humidity conditions. Each tablet must be protected from the ambient humidity. The quality of the packaging is critical to guarantee the conservation of the product. In trying to administer a dispersible tablet, the liquid can be softly stirred to aid dispersion before swallowing. As a proportion of the active substance may remain in the container after swallowing, it is advisable to rinse it with a small amount of water or milk and swallow again. The dispersible tablets should not be divided or chewed [8].

Lentinus tuber regium (LTR) is an edible mushroom which grows naturally in Nigeria during the early and late rainy seasons [9]. They could be cultured on a wide variety of agroforestry products for the production of feed, enzymes and medicinal products [10]. Several medicinal properties have been reported to be found in extracts of *Lentinus* species. Such properties include anti-tumour, attributable to their polysaccharides [11], anti-genotoxic, bioantimutagenic [12], anti-inflammatory, anti-lipidaemic, antihypertensive, anti-hyperglycaemic, antibacterial and antifungal activities [13]. LTR fruit body has been shown to be highly nutritive [14, 15]. Protein evaluation has shown that mushroom proteins have higher quality than green leafy vegetables [16]. It contains carbohydrate yield of 63. 03 ± 1. 12 g %. A considerable fraction of this carbohydrate is contributed by oligosaccharides [11]. Several other health benefits have been attributed to mushroom oligosaccharides and includes immune-modulatory effects which have been shown to be beneficial to individuals living with HIV [17]. LTR has a high crude fibre content (10. 86 ± 0. 58 g %) showing that the incorporation of LTR in diet could aid bowel movement as well as reduce the incidence of colon cancers in its users. Epidemiological studies have found an association between high fibre diets and a lower incidence of cardiovascular diseases and large bowel cancers [18]. Mineral composition analyses indicate that the fruit body is rich in iron (5. 02 mg/100 g) and zinc [11, 14]. This is capable of producing sufficient iron to meet the recommended daily allowance (RDA) for school age children if up to 200 g of LTR is consumed daily. Its high zinc content also suggests that increased consumption of edible mushrooms could help reduce the growing incidence of micronutrient deficiency [11].

A multicomponent novel pharmaceutical grade co-processed excipient, *fizlent* has been characterized [19]. It possess improved flow properties, compressibility and dilution potential of 70-80% (paracetamol) and ≤ 30% for metronidazole, ascorbic acid and ibuprofen respectively. It was developed from *Lentinus tuber regium,* citric acid, tartaric acid and sodium hydrogen carbonate. Evaluation of *fizlent* showed its potential as a useful filler-binder-superdisintegrant especially in direct compression solid dosage forms [19]. Its application as a filler-binder-superdisintegrant in direct compression of ibuprofen tablet has been reported [20].

Paracetamol (PCM) is a core medicine in the World Health Organization's (WHO) Essential Drugs List (EDL) that serves as a list of minimum medical needs for a basic health care system [21]. It is widely used worldwide for its analgesic and antipyretic actions in adults and children aged 2 months and over, and for reducing post-vaccination fever in babies aged 2 – 3 months. It has a spectrum of action similar to that of non-steroidal anti-inflammatory agents (NSAIDs) and resembles particularly the COX-2 selective inhibitors. PCM is, on average, a weaker analgesic than NSAIDs or COX-2 selective inhibitors but is often preferred because of its better tolerance [22]. The antipyretic activity of PCM and possibly the analgesic action, is ascribed to a central inhibition of prostaglandin synthesis in neurons and brain endothelial cells [23, 24]. Some PCM products can be bought over-the-counter (OTC) in a pharmacy or other retail outlets. Around 84% of children in the UK receive PCM by the age of 6 months. Some PCM products have been developed specifically for use in children age less than 16 years. They are mainly available as liquid formulations [25]. In hospitals, calculating the appropriate dose of PCM for a child is based on its concentration in mg per kg of body weight. However, this method of calculating a dose is not always practical for parents or care-givers to manage at home. Therefore, the recommended dosing for liquid PCM given to a child by a parent or care-giver at home is by volume (in mL), which is determined based on the child's age. Often, children of very wide varying age bracket receive the same dose of PCM due to non-availability of exact single dose of its preparations for children. Children need to get the most effective dose of PCM [26].

In this study a paediatric dispersible tablet (PDT) containing 125 mg of PCM was designed and evaluated. The product was designed from a novel *Lentinus tuber regium* (LTR) based co-processed filler-binder-superdisintegrant added to triggers off rapid dispersion of the PDT. This is achievable in less than 30 s in 10 ml of water. The reason for this innovative design is to provide exact paediatric dose of PCM in dispersible solid dosage form. It is hoped that this provision will ease off the pains and sometimes, inaccuracies incurred in calculating doses of PCM for children from adult formula, especially among the unenlightened care-givers in developing nations.

2. Materials and Methods

2.1. Materials

The following materials were used as procured and includes: ethanol (Fischer Scientific, UK), paracetamol,

polyvinyl pyrollidone K30 (PVP) (BoaiNky, China), hydrochloric acid (Sigma-Aldrich, USA), mannitol, polyethylene glycol (PEG-4000) (Kermel, China), Nutrient agar (Oxoid, England), Sabouraud's dextrose agar (Pronadisa, Spain), *Lentinus tuber regium* based co-processed excipient (*fizlent*) was processed in the Pharmaceutical Technology laboratory of the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Port Harcourt, Nigeria.

2.2. Methods

2.2.1. Production of *Fizlent*

The filler-binder-superdisintegrant, *fizlent,* a *Lentinus tuber regium* based co-processed excipient used in this study was processed as described by Ugoeze and Nkoro [19].

2.2.2. Preparation of Granules

Tablets, each containing 125 mg paracetamol and targeted to weigh 200 mg was prepared as shown in Table 1. A homogenous blend of paracetamol, mannitol and *fizlent* powder was dispersed in alcoholic solution of polyvinyl pyrollidone and stirred to allow alcohol to evaporate until a thick paste formed. This was kneaded for 5 min and passed through 1. 7 mm stainless steel sieve (Retsch, Germany). The wet granules were dried in hot air oven (Memmert, England) at 50℃ and screened with 1. 00 mm sieve. The granules were stored in air tight amber coloured glass container.

Table 1. *Formula for the paediatric dispersible paracetamol tablet.*

Ingredient	Amount (%w/w)	Amount per tablet (mg)
Paracetamol	62. 50	125. 00
Mannitol	5. 00	10. 00
PEG-4000	1. 50	3. 00
Polyvinyl pyrollidone K30 (PVP)	3. 00	6. 00
Fizlent	28. 00	56. 00
Theoretical weight	100. 00	200. 00

Fizlent = Lentinus tuber regium based co-processed filler-binder-superdisintegrant

2.2.3. Granule Properties

(i) Densities

A 20 g quantities of the granule was employed in the determination of bulk and tapped densities using Stampfvolumeter (STAV 2003JEF, Germany). Three replicate determinations were carried out for each powder. The bulk and tapped densities were calculated using the following equation:

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume,Vo}} \quad (1)$$

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume,Vf}} \quad (2)$$

(ii) Flow Rate and Angle of Repose

A 50 g each of the respective powders was used to determine flow rate using the funnel method reported by Carstensen and Chan [27, 28]. The angle of repose was determined by clamping a clean glass funnel to a retort stand such that a constant perpendicular height of the funnel efflux tube tip was 1. 70 cm from a horizontal flat base with a clean graph sheet of paper. The granule poured into the funnel until the powder heap formed touched the funnel tip and stopped further outflow of granules from the funnel orifice [29, 30]. The diameter of the circumference of the granule heap was measured. The procedure was carried out in triplicate and flow rate and angle of repose were calculated as follows:

$$\text{Flow rate} = \text{Mass of powder} / \text{Time} \quad (3)$$

$$\text{Angle of repose}, \theta = \tan - 1 \frac{2h}{d} \quad (4)$$

where θ is the angle of repose, *h* is the height of heap of powder, *d* is the diameter of heap of powder.

(iii) Hausner Ratio

This was calculated as the ratio of tapped density to bulk density of the granule [31].

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (5)$$

(iv) Carr's Index (CI)

This was calculated from the bulk and tap densities data when fitted into the equation [32]:

$$\text{Carr's Index} = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 100 \quad (6)$$

(v) Microbiological Evaluation of Granules

Enumeration and isolation of microbial contaminants was carried out using the method of Conn [33] with slight modification. A 10 mg quantity of granule was reconstituted in 100 ml volume of sterile phosphate-buffered normal saline (10 mg %) and shaken vigorously. A 0. 2 ml volume was withdrawn and serially diluted to achieve a 10 fold dilution. A 0. 1ml of the diluted sample was spread - plated on the surface of nutrient agar or Sabouraud's Dextrose agar (SDA) plates. The plates were incubated at 25 - 37℃ for 24 – 72 hrs. respectively. Colonies were counted and the mean number of colony forming units per/g of granule was calculated. All experiments were done in triplicates and controls set up in each round.

Identification of isolated microorganisms was achieved by plating out the diluted samples of granule in selective media viz MacConkey agar (for enteric bacteria), Cetrimide agar (Pseudomonas), Mannitol Salt agar (Staphylococcus) and Sabouraud's Dextrose Agar (mould and yeasts). They were further identified and characterized as in Collee and Miles [34].

2.2.4. Compression of Tablet

The granules were lubricated with PEG-4000 and compressed using a table top single punch tablet press (Erweka, EP-1, Germany) fitted with an 8. 0 mm diameter biconcave punch at compression pressure of 7. 5 tons.

(i). Evaluation of Tablet Properties

The British Pharmacopeia methods were used to evaluate the paediatric dispersible tablets [35]. In determining uniformity of weight, twenty tablet picked at random were weighed individually using analytical electronic balance (Ohaus, China). The diametrical crushing strength of ten tablets were determined with digital hardness tester (Erweka TBH 100, Germany). The friability of ten tablets was evaluated in tablet friabilator (Erweka TAR 220, Germany) set at 25 rpm for 4 min. The disintegration time of 6 tablets were determined by noting the time for complete dispersion of each tablet in 10 ml of water at room temperature (27 ± 2℃) placed in 15 ml dispensing plastic cup.

(ii). Dissolution Test

One tablet was dispersed in 10 ml of 0. 1 N hydrochloric acid at room temperature (27 ± 2℃) and filtered. A 3 ml volume of the filtrate was assayed spectrophotometrically at 245 nm (Jenway, 6405). This was carried out in triplicate.

3. Results and Discussions

Results obtained for the evaluation of the paediatric dispersible PCM granules and tablets are presented in Table 2. The values obtained show that the granules were compressible and flowable [31, 32]. The tablets properties are acceptable and complies with Pharmacopeia specifications. None of the tablet weight deviated from the average weight with value up to 7. 5 % as specified for tablets that weigh up to 80 mg but less than 250 mg [35]. The force required to break the tablet is measured in kilogram or Newton and a crushing strength of 4 kg (about 39 N) is usually considered to be the minimum for satisfactory tablets [36]. The value of crushing strength for the formulation was lower than this reference. However, considering the value of friability less than 1% and high value of crushing strength friability ratio (CSFR), it may be recorded that the tablet have sufficient mechanical strength [35, 37-39]. The paediatric dispersible tablet (PDT) dispersed completely and uniformly in 28 s in 10 ml of water at room temperature (27 ± 2℃). The Pharmacopeia specified 3 min in water at 25±1℃ for dispersible/soluble tablets [35]. Assay of API in the dispersion of paediatric dispersible paracetamol tablet yielded mean value of 120. 99±0. 84 mg in vitro. Microbiological evaluation of granules indicated absence of pathogenic as well as enteric bacteria, Pseudomonas aeruginosa, Staphylococcus aureus, yeast or mould. However, the total viable count of Bacillus subtilis found was below the permissible level of 103cfu/g. According to Joint Report of FIP Working Committee, bacterial load of $10^3 – 10^4$ cfu/g is permissible for oral liquid and solid products [40]. *Bacillus subtilis,* a rod-shaped, Gram-positive soil bacterium is widespread in the air, soil, water and in animal products such as hair, wool and carcasses [41]. The absence of enteric bacteria which causes dysentery and diarrhea; salmonella (typhoid causing agent) and Pseudomonas from the sample is an evidence of application of good personal hygiene, proper treatment of raw materials, water and air all of which will guarantee the quality of the product for paediatric use.

Table 2. *Granule and tablet properties.*

Granule properties		Tablet properties	
Parameter	Value ± SD	Parameter	Value ± SD
Bulk density (g/ml)	0. 42±0. 01	Weight (mg)	198. 86 ± 1. 04
Tapped density (g/ml)	0. 49±0. 01	Crushing strength (N)	30. 60 ± 1. 01
Flow rate (g/s)	3. 10±0. 30	Friability (%)	0. 20 ± 0. 01
Angle of repose	30. 71±0. 42o	Dispersion time (s)	28. 00 ± 0. 12
Hausner ratio	1. 12±0. 01	Total content (mg)	121. 29 ± 1. 02
Carr's index	10. 64±0. 01	CSFR	153. 00

CSFR= Crushing strength friability ratio

4. Conclusion

A multicomponent *Lentinus tuber regium* based co-processed excipient (*fizlent*) have been used as filler-binder-superdisintegrant in the formulation of paediatric dispersible tablet containing 125 mg of paracetamol. The tablets obtained possessed enough mechanical strength and dispersed uniformly and completely in 10 ml of water, releasing up to 97 % of its paracetamol content. The authors conclude that *fizlent* may be applied effectively as superdisintegrant and dispersion agent in the formulation of most oral dispersible solid dosage forms. With the bulk component of f*izlent* consisting of edible mushroom, LTR endowed with severally reported health benefits [9-18]; its current applicability will boost its economic value especially as it is possible to cultivate it [42, 43], its commercial availability could be ensured.

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