**ORIGINAL PAPER**

https://dx.doi.org/10.4314/njpr.v15i2.14

**Nig. J. Pharm. Res. 2019, 15 (2) pp 269 - 282**
**ISSN 0189-8434 e-ISSN 2635-3555** **Available online at http://www.nigjpharmres.com**

# Formulation and Evaluation of Dispersible Isoniazid Tablets for Paediatric Use: An Extemporaneous Model Formulary Application in a Resource Limited Setting

***M. O. OLOGUNAGBA[CDEF], O. C. AKINYODE[BCF] and B. O. SILVA[AEF]**

Department of Pharmaceutics & Pharmaceutical Technology, Faculty of Pharmacy, University of Lagos, Idi-Araba, Lagos.

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

## Abstract

**Background:** Tuberculosis (TB) remains a global burden and public health concern. Isoniazid, a principal anti-tubercular drug (ATD) though effectively used in TB preventive chemotherapy is preferentially available in adult formulations. Its use therefore in paediatric population is challenged with issues of high probability of inaccurate dose administrations, low patient compliance and adherence. This burden may be higher in resource limited settings, thus development of simple child friendly formulations is needful.

**Objectives:** This study aimed to design, develop and evaluate an extemporaneous formulary model of a paediatric oral dispersible isoniazid tablet for use in a resource-limited setting.

**Method:** Paediatric oral dispersible isoniazid granulation batches with varying concentrations (0.5 - 5.5 % w/w) of sodium carboxyl methylcellulose as superdisintegrant were prepared by wet granulation method and compressed. Granulation batches were subjected to pre and post compression evaluations respectively in accordance with established standard methods. Results were statistically analysed using one-way analysis of variance (ANOVA) with significance set at $p < 0.05$.

**Result:** The outcome of the micromeritics variables for the granule batches were indicative of good flow properties. The tablet batches passed all the official tablet evaluation criteria, with no statistical significance between the batches. However, tablet batches that contained lower concentrations of carboxyl methylcellulose failed both the disintegration and dispersion tests. Optimal tablet formulation was obtained with 5.0 % w/w of the superdisintegrant.

**Conclusion:** An optimized formulation of an oral paediatric dispersible isoniazid tablet that could be applied as an extemporaneous compounding model in a resource limited setting has been developed.

**Keywords**: Paediatric Tuberculosis, Isoniazid, Dispersible Tablet, Extemporaneous Compounding.

## INTRODUCTION

There exists an increasing demand for therapeutic effectiveness of dosage formulations through improved patient compliance. Innovative drug delivery technologies as can be found in microencapsulation, nanoencapsulation, sustained / controlled release matrix systems, fast release dispersible systems etc. aim to achieve improved efficacy of the active pharmaceutical ingredients, better patient compliance and the attainment of formulation chemotherapeutic goals (Kuchekar *et al.*, 2005).These novel technologies result in either enhanced bioavailability, dose and dosing frequency reduction or minimization of side effects (Chein, 1992).

Globally, there are increasing efforts to develop the technology of oral fast disintegrating tablet or oral/mouth dissolving drug delivery systems (ODT /ODDDS). This is because comparative to the

conventional tablet systems, the technology presents with the advantages of simplicity of design, ease of handling, good stability with offering of therapeutic benefits such as rapid absorption and onset of action, increased bioavailability, accuracy of dose administration, convenience of dosing (reduction), enhanced efficacy, safety, improved patient acceptance, compliance and adherence (Gohel *et al*, 2004, Kuchekar *et al.*, 2005, Remington, 2005). Thus, patient populations such as the geriatrics, paediatrics, mentally ill and those with dysphagia could benefit from ODDDS formulations.

The rationale behind developing oral disintegrating tablet is the availability of larger surface area in the oral dosage form which allows rapid wetting in the moist buccal environment that leads to rapid disintegration and dissolution in the oral cavity (Habib, 2002). Rapid disintegration of tablet results in fast dissolution and rapid absorption and onset of action, hence improved patient compliance and convenience. The oral or buccal mucosa is highly vascularized, therefore drugs can be absorbed directly and can enter the systemic circulation without undergoing first pass hepatic metabolism.

Dispersible tablets are uncoated or film coated tablets which disintegrate rapidly usually within a matter of seconds when placed in water (Rangasamy, 2009, USP, 2013) to form a stabilized homogenous dispersion/suspension and are thus intended to be dispensed in water of about 5-15 mLs. They comprise of totally water-soluble excipients and components. This formulation technology can also be used for APIs that are unstable in liquid formulations but could be re-constituted as suspensions prior to use (Sureh *et al.*, 2008).

These tablets are expected to have low friability values which infers their good physical strength upon exposure to mechanical shock and attrition that could occur during transportation, storage and dispensing. As opposed, to a suspension, no refrigeration is required. In more recent years , increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in water before being swallowed (Seager *et al*., 1998; Sharma, 2013; Fu *et al*.,2004; Puri *et al*., 2010)

Superdisintegrants are substances (synthetic, semi-synthetic and/ or natural) which are added in small quantities (1-10% w/w) as tablet formulation excipients to effect the fast disintegration of the dosage form in an aqueous environment. The widely used superdisintegrants are crospovidone, croscarmellose sodium and sodium starch glycolate (Gohel *et al.,* 2007). Superdisintegrants exert their actions in powder systems through the mechanisms of improved wettability as a result of increased powder porosity which enhances capillary action. Disintegration process is thus enhanced by superdisintegrants. The superdisintegrant type and the concentration used are critical to the effectiveness as well as an integral to the functionality of the formulated dispersable tablet. Thus, for poorly soluble drugs whose absorption rate is challenged due to its low wettability that results in poor disintegration and dissolution rate (Indurwade *et al.,* 2002; Metker and Kumar, 2011). The faster disintegration of tablets delivers fine suspension of drug particles resulting in a higher surface area and faster dissolution. Poorly soluble drugs can thus be formulated as dispersible tablets to improve their therapeutic effectiveness.

Tuberculosis (TB) is a chronic infectious disease characterised with high mortality and morbidity. It is caused by *Mycobacterium tuberculosis,* a slender, or slightly curved acid-fast bacillus, ranging in length from *1-4 μm*. It has been declared by (WHO, 2010) as a global burden and public health issue as it affects both the adult and paediatric population. However, childhood Tuberculosis is neglected because treatment and clinical care have been mostly extrapolated from studies in the adult population (Swaminathan, *et al*., 2010). Furthermore, even in the early years of anti-TB drug development, children were largely excluded from major clinical trials, thus the evidence base on which treatment of childhood TB is determined is weak and the recommendations in childhood TB is mainly based on extrapolation from the observations in adult patients (Swaminathan, *et al.* , 2010 ; Donald, 2007; Enarson, *et al.*, 2005).

The present standardized chemotherapy of drug-sensitive TB consists of two phases; the first entails a two-month intensive therapy with the principal drugs; isoniazid, rifampicin, pyrazinamide and ethambutol (the latter depending on the healthcare setting and type of disease). This is followed by a continuation phase with isoniazid and rifampicin for at least four months. (WHO, 2017). HIV-infected children with TB require antiretroviral therapy (ART) and co-trimoxazole preventive therapy (CPT) in addition to TB treatment. Preventive therapy which is highly effective in children exposed to TB is treated with a daily intake of rifampicin with isoniazid for three (3) months, alternatively for six-months using isoniazid monotherapy for both adults and children, but with caution to people living with HIV who are on ART because of potential drug-drug interactions.

Isoniazid (INH) is isonicotinyl hydrazine or isonicotinic acid hydrazide (4-Pyridinecorboxylic acid hydrazine) (Shukia and Manvvi *et al.*, 2010). It has an empirical formula of $C_6H_7N_3O$ and a molecular weight of 137.14; pH of 6 -8. INH is a colourless, odourless, white crystalline powder that has an anti-

mycobacterial (bactericidal) property against both extracellular and intracellular organisms. It is a first line agent in the treatment of pulmonary and extra-pulmonary tuberculosis in combination with rifampicin, pyrazinamide and ethambutol. It is a component of all combined anti-tuberculosis chemotherapy recommended by World Health Organization (WHO). INH may be used for tuberculosis prophylaxis, as obtainable in the intermittent prophylactic therapy (IPT) for HIV positive patients. Isoniazid is used in the treatment of pulmonary and extra pulmonary tuberculosis. The usual daily dose is 10-14mg/ kg for adult/children; the maximum daily dose is 300 mg.

The chemotherapy of TB for the paediatric population is however challenged by preferential focus on adult formulations which results in treatment with unsuitable split / broken / divided / crushed adult formulations /tablets as (halves, quarters) or opening of capsules with the addition of the powder to a palatable drink or sprinkling onto food. These protocols are unsuitable because they lead to potential high probability of inaccurate and erroneous dose administration (Pouplin *et al*., 2014), drug exposure and medicine related toxicity as a result of the physiological development (immaturity) of the organs. Furthermore, consideration should be given to the issues such as differences in pharmacotherapy, taste preferences, age, weight, efficacy, ease of use (dose flexibility, drug acceptability, handling convenience, correct use), safety (bioavailability of active substances, safety of excipients, medication stability, patient access , availability and affordability (Tulec and Breitkreutz, 2013; Mulberg *et al*, 2009; WHO, 2014).

The burden of TB in Nigeria is high with the paediatric population contributing significantly to this burden. Curative and preventive paediatric TB chemotherapy is however challenged because of the preferential availability of donated or purchased adult formulations are not acceptable to this population which result in poor compliance and adherence, emergence of resistant strains. WHO in collaboration with other Developmental Partners instituted an advocacy mandate for improved treatment outcome through the provision of appropriate simple, acceptable, cost effective paediatric TB formulations. Extemporaneous compounding and dispensing therefore present as a good start to running with this mandate especially in a high TB burden country like Nigeria, where the greater populace pay out of pocket for their healthcare needs.

Additionally, health budgets are low and often not adequately utilized, which thus positions most health facilities as resource limited. Furthermore, drug logistics management is not effective which may be characterized with "out-of stock-syndrome"/epileptic supplies of TB commodities. It is expedient that TB commodities are tailored for availability, accessibility, affordability, acceptability and cost-effectiveness to this population group

This study therefore sought to design and develop an extemporaneous paediatric compounding formulary model of dispersible isoniazid tablet for use in a resource limited healthcare facility.

## METHODOLOGY

### Materials

Isoniazid obtained as a gift sample from Macleaod Pharmaceuticals Ltd, Mumbai, India, Mannitol, Sodium carboxyl methylcellulose (MW:90,000), Polyvinyl pyrrolidone(MW:40,000), Magnesium stearate (Emerald Consolidated Co. Ltd, Lagos.)

### Equipment

Disintegration apparatus (Copley, United Kingdom) ,Friabilator (Erweka, Germany),Single Punch Hand Tabletting Machine (Escrow, China), Analytical balance (Mettler Toledo, Malaysia),Tray Dryer, Vernier Calliper (Wingmore, China), Hardness Tester (Monsato, America), Glass Mortar and Pestle, Measuring Cylinder, Sieves

### Method

### Granulation

Isoniazid, mannitol (diluent), sodium carboxymethyl cellulose (superdisintegrant) were accurately weighed (as detailed in Table 1 for the specific batches) and geometrically triturated in a glass mortar to obtain fine powder mix. The finely triturated and sieved (size 16) powder mix was wet granulated using 5 % w/w polyvinyl pyrrolidone (MW: 40,000) as the binding agent. The sodium carboxyl methylcellulose (SCMC) was used at varying concentrations of 1.0-10 % w/w for optimization of tablet disintegration time. The damp granulated mass was passed through sieve size 16, to obtain granules, which were subjected to tray drying at 60° *C* for 2 hr. The dried granules were passed through sieve size 22; this procedure was undertaken for all the five formulation batches (F1-F5). The granule batches were individually and appropriately packaged into airtight close-cap wide mouth glass bottles, labelled and stored in a cool dry place until required for further granule evaluations (pre-compression evaluation) and compression to tablets.

**Table 1: Batch Composition of Dispersible Isoniazid Tablet Formulations**

| Ingredients (mg/tablet = w/w) | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Isoniazid | 100 | 100 | 100 | 100 | 100 |
| Mannitol | 88 | 87 | 85.0 | 82.0 | 79.0 |
| Sodium carboxyl methyl cellulose | 1.0 | 2.0 | 4.0 | 7.0 | 10.0 |
| Polyvinyl pyrrolidone | 10 | 10 | 10 | 10 | 10 |
| Magnesium stearate | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Total Tablet Weight | **200** | **200** | **200** | **200** | **200** |

***Batch codes =F1; F2; F3; F4 &F5***

**Pre-Compression Evaluations of Granules**

Pre-compression evaluations (bulk density, tapped density, compressibility index, Hausner's ratio and Angle of repose) of all the five (5) granule batches were undertaken in accordance with standard protocols and methods (Lachman *et al* 1991; Basu *et al*., 2011; Ologunagba *et al*., 2017)

**Bulk and Tapped Densities (BD and TB)**

Both loose bulk density (BD) and tapped density (TD) were determined as described by Ologunagba *et al*., 2017. Accurately weighed amount of sample (20 g) was transferred into a 25 mL measuring cylinder. The volume of packing was recorded. The measuring cylinder was then tapped 100 times on a plane hard wooden surface and the tapped volume was recorded.

LD and TD were calculated by the following formula:

$$LD = \frac{Wt}{VB} \quad (1)$$

Where Wt = Weight of granules

VB = Loose Volume of packing

$$TD = \frac{Wt}{VT} \quad (2)$$

Where Wt = Weight of granules

VT = Tapped Volume of packing

**Compressibility index (CI %)**
**Hausner's ratio (HR)**

Hausner's ratio was calculated as the ratio of tapped density (TD) to the bulk density (BD) as given by the equation below: $HR = \frac{(TD)}{BD}$ (3)

Percent compressibility of granules as determined by Carr's compressibility index was calculated by the following formula**:**

$$\textbf{Carr's Index} = \frac{(TD-LD)}{TD} x100 \quad (4)$$

**Angle of repose (AoR: θ)**

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

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

or (5)

$$\theta = \tan^{-1} \frac{h}{r}$$

Where θ = Angle of repose, h = height, r = radius

Values of angle of repose ≤ 30° indicate free flowing granules and ≥ 40° suggest poorly flowing material.

**Compression of Granulations**

For each granule batch that was to be compressed, the required quantity of magnesium stearate (0.5% w/w) was mixed thoroughly into the batch for 2 min. The blended granule batches were separately compressed using the single punch hand tableting machine. Each formulation batch consisted of fifty isoniazid tablets.

**Post Compression Evaluations**

The compressed tablets from each of the five tablet batches were evaluated for parameters such as weight variation, hardness, thickness, friability, disintegration and dispersion times. The procedure and protocols for each of these parameters are as detailed below:

**Organoleptic Properties:** This included assessment of the appearance (colour, odour, taste, texture) as detailed by Jadhav *et al*, 2011.

**Weight Variation:** The procedure described by Shahi *et al.,* 2008; BP (2009) and Jadhav *et al.*, 2011 with slight modification was employed to determine the weight variation of the tablets. Ten tablets were randomly selected from each batch and weighed on an electronic balance and the mean weight taken. Each tablet was then weighed individually and the standard deviation in weight was calculated for each batch**.**

**Thickness:** Thickness of tablets was determined as described by Shahi *et al*, 2008; BP (2009) and Jadhav *et al*, 2011 using Vernier caliper. Three tablets from each batch were used and an average value was obtained.

**Hardness:** This is the fracture strength, and it is defined as the force required to break a tablet by radial compression. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm$^2$ (Subramanian, 2010). This involved the random selection of five tablets from each batch and the determination of hardness of the tablets. The mean and standard deviation values were calculated for each batch (Subrahmanyam, 2004; BP (2009); Jadhav *et al.*, 2011; Azubuike *et al*., 2017)**.**

**Friability**: Friability of the tablets expressed in percentage (%) was determined using Roche friabilator which subjected the tablets to the combined effects of abrasion and shock. This determination was in accordance with the reported standard protocols and procedures (Subrahmanyam, 2004**;** Kuno *et al.,* 2005; BP (2009); Jadhav *et al*, 2011; Azubuike *et al*., 2017).

Briefly, ten tablets were pre-weighed ($W_i$) and placed into the Friabilator. The Friabilator was operated at 25 rpm for 4 minutes (100 revolutions) at a height of 6 inches in each revolution, and then the tablets were re-weighed ($W_f$) after removal of fines using 60 mesh screens and the percentage of weight loss was calculated .The loss in tablet weight due to abrasion or fracture was the measure of tablet friability.

% Friability was then calculated by: - $Fb = \frac{(Wi-Wf)}{Wi} x100$ (6)

**Disintegration test:** This was undertaken as described by Radke *et al,* 2009 and Jadhav *et al*, 2011 using the 6 station unit of the USP (2010) disintegration apparatus. Tablets were singly introduced into each of the tubes followed by the addition of the disc to each tube. The assembly was suspended in a beaker containing buffered water at 37 ± 2 °C as the disintegration medium. It was operated for several minutes and the time taken for each tablet to disintegrate completely was recorded. Three trials for each batch were performed. The time (in seconds) taken for complete disintegration of the respective batch tablets with no palpable mass remaining in the apparatus was noted as the disintegration time (Parmar *et al.,* 2009; Sharma, 2013).

**Uniformity of Dispersion:** This was undertaken in accordance with the procedure described by British Pharmacopoeia 2010 and Jadhav *et al*, 2011. Briefly, one tablet was placed in a 100 mL water, which was stirred gently to effect complete dispersion. The dispersion was passed through a sieve screen with a nominal mesh aperture of 710 μm (Sieve no. 22). The determination was undertaken thrice per tablet batch and the average value obtained and noted.

**Wetting Volume:** This was undertaken as described by Gosai *et al,* 2008; Jadhav *et al,* 2011. The randomly selected tablet was placed in the center of the Petri dish. This was followed by the drop-wise addition of 5 mL distilled water on the tablet using pipette. The volume required to completely disintegrate the tablet was noted as the wetting volume.

**Wetting Time:** Wetting time of tablet dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. Thus, a randomly selected tablet from each batch formulation was carefully placed on the surface of the tissue paper (12cm x10.75cm) folded twice placed in a Petri dish (10 cm diameter) containing 10 mL of water which was stained with Eosin, a water soluble dye. The time required for water to reach upper surface of the tablet was noted as a wetting time (Subrahmanyam 2004; Mutalik *et al*., 2004; Furtado et *al.*, 2009; Jadhav *et al*, 2011; Rangasamy, 2009). The procedure was undertaken in triplicate for each tablet batch.

**Water Absorption Ratio ($W_{AR}$):** This was in accordance with the method described by Jadhav *et al*, 2011. A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 mL of water. A tablet of known weight (Wa) was put on the tissue paper and allowed to wet completely. The wetted tablet was then reweighed (Wb). This determination was undertaken in triplicate for each

batch. Water absorption ratio, ($W_{AR}$) was then determined using following equation :

$$W_{AR} = \frac{(Wa-Wb)}{Wb} x100 \quad (7)$$

Where, Wa = weight of tablet after water absorption & Wb = weight of tablet before water absorption.

**Dispersion Time**: Tablet was dropped into 6 mL of water contained in a 10 mL measuring cylinder and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and the respective dispersion mean time determined (Nandgude *et al.*, 2006; Furtado *et al.*, 2009 and Jadhav *et al*, 2011).

**Accelerated Stability Study**: The stability determination of the active component of formulations is an important evaluation parameter. This involves the exposure of the formulation to extreme condition of temperature and humidity (accelerated stability test). This test was carried out by exposing the optimized formulation to one month storage condition of 40 ± 2 °C and relative humidity (RH) 75 % ± 5 % in accordance with the ICH guidelines and as described by Subrahmanyam**,** 2004 Jadhav *et al*, 2011). The tablets were withdrawn after a period of 15 and 30 days and analysed for physical characterization (Visual defects), Hardness, Friability, Disintegration, and Dispersion time (Subrahmanyam**,** 2004 and Jadhav *et al*, 2011).

**Statistical analysis:** All the results were expressed as mean value ± standard deviation (SD). One way analysis of variance (ANOVA) with Fisher's Least Significance Difference (LSD) multiple comparisons post hoc were used to test for significance, at a 5% significance level. Statistical difference dealing ($P < 0.05$) was considered significant (Bolton and Bon, 2004).

## RESULTS

The different formulation blends (Table 1) were successfully used to prepare Dispersible paediatric tablets of isoniazid using the wet granulation method. It invoved the minimal utilization of formulation excipients which included different concentrations of sodium carboxyl methyl cellulose, mannitol, polyvinyl pyrrolidone and magnesium stearate. The sodium carboxyl methyl cellulose was used as the superdisintegrant at different concentrations.

The outcome of the micromeritic evaluations of the different tablet granulation batches are as enumerated in Table 2. Bulk density which was found to be in the range of 0.641-0.760 g/cm$^3$ and tapped density between 0.740-0.884 g/cm$^3$. There were no statistical significance within the granule batches of either of these parameters as well as between these two parameters in all the batches. The compressibility index (CI) and Hausner's ratio (HR) values were obtained from these two densities.

The granule batches respectively had compressibility index and Hausner's ratio of between 13.33 and 13.99 % and 1.15 and 1.16 while the angle of repose (A$^o$R) was between 26.56° and 27.32°.

Statistical significance was observed between the bulk, tapped densities and the CI as well as the A$^o$R but not with HR in all the granule formulation batches. The data obtained for post-compression parameters such as thickness, hardness, friability, weight variation is shown in Tables 3.

Tablet thickness of all formulation batches varied from 6.062 to 6.064 mm. The hardness was found to be in the range of 3.40 to 4.3 kg/cm$^2$ for all the formulations, with statistical significance between the formulation batches.

The friability values of all the formulations were observed to be less than 1%, though statistical significance was observed amongst the granule batches.

There was an observed uniformity of weight of the tablets in all the batch formulation with no statistical variation between occurring in the different batch formulations.

The outcome of the disintegration and dispersion time evaluations for all the tablet batches are as presented in Table 4.

All tablets in the different batches disintegrated rapidly in conformity with the specified standards in BP (2010) and USP (2010). The disintegration time of all the tablet batches was within the range of 131.50 ± 3.5 - 334.21 ± 9.5 sec. The disintegration time of all the tablets were found to be within the Pharmacopoeia specified time limit (3 min) for dispersible tablets.

The dispersion times in the batch formulations were within the range of 145.52 ± 2.5 to 390.32 ± ±7.5 sec. Not all the tablet batches passed the uniformity of dispersion evaluation as specified by BP (2010) and USP (2010) as it was observed that relatively larger fragments/particles were generated in batch tablet formulations containing lower concentrations of sodium carboxyl methyl cellulose (SCMC) which were not small enough to pass through the screen of the disintegration vessels. The uniformity of the tablet dispersions increased with increasing concentration of SCMC.

It was also observed that increasing concentration of SCMC resulted in a decrease in both the disintegration and dispersion times of the tablet batches which was also statistically significant (*p value*= 0.00) for these two tablet parameters (dispersion and disintegration times) amongst the different tablet batch formulations. Tablet batch formulation F5 which contained 10 % SCMC showed respectively the shortest disintegration time of 2min: 11.50 sec (131.50 ±2.5 sec) and dispersion time of 2 min : 25.5 sec (145.5 ± 2.5). A linear relationship was observed in this study between disintegration and dispersion times.

The outcome of the post compression evaluations on the wetting time, wetting volume and water absorption ratios for all the tablet batches are as presented in Table 5.

The wetting time of the tablet batches which was found to be statistically significant (*p value*= 0.00) ranged from 51.80 ±1.35 to 100.51 ±1.24 sec, while the wetting volume (*p value*= 0.00) was within the range of 4.03 ± 0.04 to 5. 36 ± 0.04 mL.

The tablets in all the batch formulations were observed to be quickly hydrated (wetted) and possessed high water absorption ratios ranging from 95.50 ± to 175.30 ± % which was statistically significant (*p value*= 0.00) amongst the batch types. Tablet batch formulation F5 which contained 10 % SCMC had the highest water absorption ratio, required the least wetting time and aqueous volume.

**Table 2: Comparative Pre-Compression Evaluation of the Micromeritics Properties of Batch Formulations of Dispersible Isoniazid Granulations**

| Formulation Batch | BD* | TD** | AºR*** | CI (%) **** | HR***** |
|---|---|---|---|---|---|
| F1 | 0.641 ± 0.024 | 0.740 ± 0.036 | 27.32± 1.15 | 13.33± 0.25 | 1.15± 0.01 |
| F2 | 0.611 ± 0.021 | 0.701 ± 0.034 | 28.95 ± 1.36 | 12.88± 0.52 | 1.14± 0.01 |
| F3 | 0.766 ± 0.035 | 0.889 ± 0.038 | 28.61± 1.35 | 13.73± 0.52 | 1.16± 0.02 |
| F4 | 0.671 ± 0.022 | 0.780 ± 0.033 | 27.64± 1.23 | 13.97± 0.63 | 1.16± 0.01 |
| F5 | 0.760 ± 0.032 | 0.884 ± 0.033 | 26.56± 1.05 | 13.99± 0.64 | 1.16± 0.02 |

**Key:** Formulation Batch codes =F1; F2; F3; F4 & F5.
: Vs= versus
Averages of three determinations per parameter ± Standard deviation
BD-Bulk Density; TD-Tapped Density; AºR- Angle of Repose; CI %-Compressibility Index; HR-Hausner's Ratio

Statistical significance (***p-values*** BD*) between granule batch formulations are as indicated:
F1 **Vs** F2; F4 (*p value*=0.209)
F1 **Vs** F3; F5 (*p value*=0.00)
F2 **Vs** F3; F5 (p *value*= 0.00)
F2 **Vs** F4 (p *value*= 0.023)
F3 **Vs** F5 (p *value*=0.794)
F3 **Vs** F6 (*p value*=0.002)

Statistical significance (***p-values*** TD******) between granule batch formulations are as indicated:
F1 **Vs** F2 (*p value* = 0.201)
F1 **Vs** F3; F5 (*p value* = 0.00)
F1 **Vs** F4 (*p value* = 0.190)
F2 **Vs** F3; F5 (p *value* = 0.00)
F2 **Vs** F4 (*p value* = 0.020)
F3 **Vs** F4 (p *value* = 0.003)
F3**Vs** F5 (*p value* = 0.864)
F4 **Vs** F5 (p *value* = 0.004)

Statistical significance (***p-values*** Aº R *******) for comparative granule batch formulations are as indicated below:
F1 Vs F2; F3; F4; F5 (p-value = > 0.05)
F2 Vs F5 (p-value = 0.039)

Statistical significance (***p-values*** CI %********) for comparative granule batch formulations are as indicated below:
F1 Vs F2; F3; F4; F5 (p-value = > 0.05)
F2 Vs F4 (p-value = 0.031)
F2 Vs F5 (p-value = 0.028)

Statistical significance (***p-values*** HR*********) for comparative granule batch formulations are as indicated below:
F1 Vs F2; F3; F4; F5 (p-value = > 0.05)

Comparative statistical significance (***p*-values)** of granule properties BD* TD**, AºR,*** CI**** and HR*****) of all respective granule batch formulations are as indicated:
BD (F1) **Vs** BD (F2; F3; F4; F5): (*p-value* = > 0.05)
BD (F1; F2; F3; F4; F5) **Vs** TD (F1; F2; F3; F4; F5): (*p-value* = > 0.05)
BD (F1; F2; F3; F4; F5) **Vs** AºR (F1; F2; F3; F4; F5): (*p-value* = < 0.00)
BD (F1; F2; F3; F4 F5) **Vs** CI **(**F1; F2; F3; F4; F5): (*p-value* = < 0.00)
BD (F1; F2; F3; F4 F5) **Vs** HR **(**F1; F2; F3; F4; F5): (*p-value* = > 0.05)
TD (F1; F2; F3; F4 F5) **Vs** AºR **(**F1; F2; F3; F4; F5): (*p-value* = 0.00)

TD (F1; F2; F3; F4 F5) **Vs** CI **(**F1; F2; F3; F4; F5): (*p-value* = 0.00)
AºR (F1) **Vs** AºR (F2; F3; F4; F5): (*p-value* = >0.05)
AºR (F1; F2; F3; F4 F5) **Vs** BD, TD, CI, HR (F1; F2; F3; F4; F5): (*p-value* = 0.00)
CI (F1; F2; F3; F4; F5) **Vs** BD, TD, AºR, HR (F1; F2; F3; F4; F5): (*p-value* = 0.00)
CI (F1) **Vs** (F2; F3; F4; F5): (p-*value* = > 0.05)
HR (F1) **Vs** HR (F2; F3; F4; F5): (*p-value* = > 0.05)
HR (F1; F2; F3; F4; F5) **Vs** AºR, CI (F1; F2; F3; F4; F5): (*p-value* = 0.00)
HR (F1; F2; F3; F4; F5) **Vs** BD, TD (F1; F2; F3; F4; F5): (*p-value* = > 0.05)

**Table 3: Post-Compression Properties of Batch Formulations of Dispersible Isoniazid Tablets**

| Formulation Batch | UoW (mg) | *HD (kg/cm$^2$) | **FB (%) | TN (µm) | DM (µm) |
|---|---|---|---|---|---|
| F1 | 0.157± 0.01 | 3.7± 0.02 | 0.738± 0.03 | 6.064± 0.02 | 6.035± 0.02 |
| F2 | 0.149± 0.01 | 3.9± 0.01 | 0.506± 0.04 | 6.044± 0.01 | 6.023± 0.01 |
| F3 | 0.149± 0.01 | 4.0± 0.03 | 0.319 ± 0.01 | 6.042± 0.01 | 6.020±0.01 |
| F4 | 0.149± 0.01 | 4.2± 0.02 | 0.205 ± 0.01 | 6.044± 0.01 | 6.017± 0.01 |
| F5 | 0.150± 0.01 | 4.3 ± 0.02 | 0.140 ± 0.01 | 6.043± 0.01 | 6.021± 0.02 |

*Key: Formulation Batch codes = F1; F2; F3; F4 &F5:*
*UoW = Uniformity of Weight; HD = Hardness; FB =Friability TN=Thickness; DM= Diameter*
*Averages of three determinations per parameter; ± Standard deviation; p-value significance =0.05*

Statistical significance (***p-values*** HD*****) for comparative granule batch formulations are as indicated below
*F1 Vs F3; F4; F5 (*p value*=0.000)
*F2 Vs F3; F4; F5 (p *value*= 0.000)
*F3 Vs F1; F2 (p *value* = 0.000)
*F4Vs F1; F2 (*p value*=0.000)
*F5 Vs F1; F2 (p *value*=0.000)

Statistical significance (***p-values*** FB******) for comparative granule batch formulations are as indicated below
**F1 Vs F2; F3; F4; F5 (*p value* =0.007)
**F3 Vs F1; F2; F4 (p *value* =0.000)
**F4 Vs F3; F5 (*p value* =0.000)

**Table 4: Disintegration Time of Batch Formulations of Dispersible Isoniazid Tablets**

| Evaluation Parameter | Code of Formulation Types | | | | |
|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 |
| DisintegrationTime * (Secs) | 334.21 ± 9.5 | 204.35 ± 8.5 | 179.55 ± 10.5 | 158.45 ±5.5 | 131.50 ± 3.5 |
| Dispersion Time ** (Secs) | 390.32 ±7.5 | 255.40 ± 6.5 | 210.51 ± 5.5 | 185.35 ±4.5 | 145 .52 ±2.5 |

*Key: Formulation Batch Codes =F1; F2; F3; F4 &F5*

Statistical significance (***p-values*** Disintegration Time*****) for comparative granule batch formulations are as indicated below
*F1 Vs F2; F3; F4; F5 (*p value* =0.0000)
*F2 Vs F3 (p *value* =0.003)
*F3 Vs F4 (p *value* =0.009)
*F5 Vs F4 (p *value*=0.002)

Statistical significance (***p-values*** Dispersion Time******) for comparative granule batch formulations are as indicated below
**F1 Vs F2; F3; F4; F5 (*p value* = 0.000)
**F2 Vs F3 (p *value* = 0.003)
**F3 Vs F4 (p *value*=0.009)
**F5 Vs F4 (p *value*=0.002)
**F2 Vs F3 (p *value*=0.003)

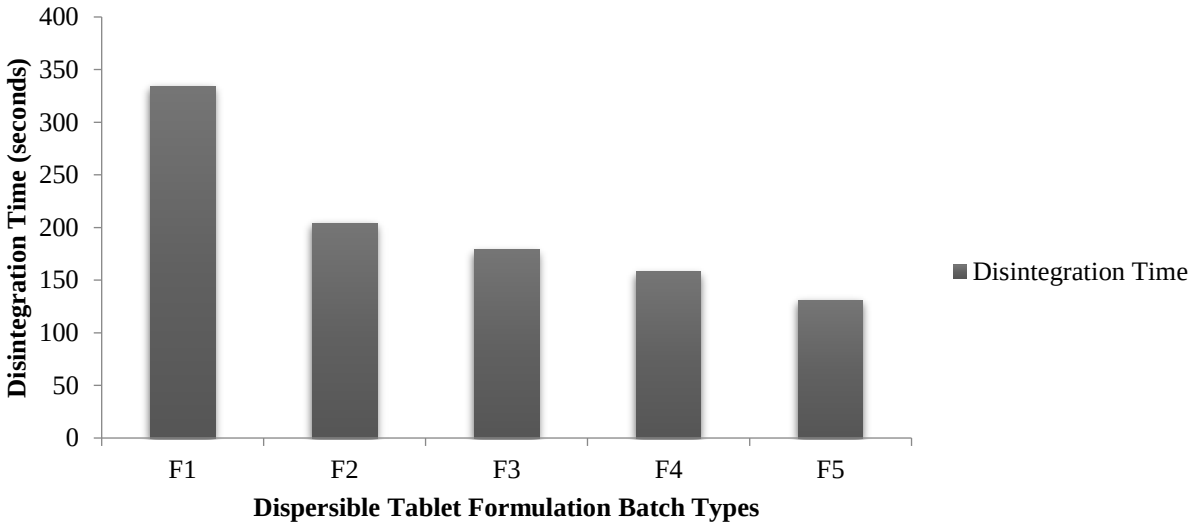


**Figure 1. Comparative Disintegration Time of Paediatric Dispersible Tablets of Isoniazid**

**Table 5: Post-Compression Properties of Batch Formulations of Dispersible Isoniazid Tablets**

| Formulation Batch | Wetting Time (Sec) | Wetting Volume (mL) | Uniformity of Dispersion | Water Absorption Ratio (%) |
|---|---|---|---|---|
| F1 | 100.51 ± 1.24 | 5.36 ± 0.04 | Passed | 95.50 ± 2.30 |
| F2 | 85.24 ± 1.30 | 5.1 9±0.02 | Passed | 112.55 ± 2.03 |
| F3 | 70.50 ± 1.45 | 5.08±0.08 | Passed | 154.52±2.15 |
| F4 | 56.35 ±1.50 | 4.42±0.05 | Passed | 162.45 ±2.10 |
| F5 | 51.80 ± 1.35 | 4.03±0.04 | Passed | 175.35±1.65 |

***Key:*** *Formulation Batch codes =F1; F2; F3; F4 & F5.*
*Averages of three determinations per parameter ± Standard deviation*
*WT*= Wetting Time; WV** = Wetting Volume; WAR*** =Water Absorption Ratio*

Statistical significance (***p-values*** WT*; WV** and WAR ***) for comparative granule batch formulations are as indicated below**:**

F1 Vs F2; F3; F4; F5 (*p value* = 0.000)
F2 Vs F3; F4; F5 (p *value* = 0.000)
F3 Vs F4; F5 (p *value* = 0.000)
F4Vs F5 (*p value* = >0.05)

## DISCUSSION

### Formulation Design and Development

Dispersible paediatric tablets of isoniazid were prepared by wet granulation method with the use of minimal formulation excipients. These include different concentrations of sodium carboxyl methyl cellulose, mannitol, polyvinyl pyrrolidone and magnesium stearate. The sodium carboxyl methyl cellulose was used as the superdisintergrant at different concentrations. It also probably had positive effect on the porosity of the powder blends which resulted in better aqueous wettability and hence fast disintegration. Mannitol was used for its multidimensional benefits as a sweetener as well as a diluent that has good aqueous solubility and good wetting properties which facilitated tablet breakdown /disintegration. Furthermore, its negative heat of solution could contribute to the masking of the unpalatable (bitter) taste of the powder blend as a result of isoniazid (active drug) as well as magnesium stearate which was used as a lubricant. Polyvinyl pyrrolidone (PVP) was used as the binder.

### Pre-compression Evaluation

The bulk density of a material is the ratio of the mass to the volume (including the interparticulate void volume) of an untapped powder or granulation sample while the tapped density is obtained by the mechanical tapping of the sample material in a graduated measuring cylinder until no further volume changes

occur. The bulk density depends on both the density of the sample particles and on the arrangement of the sample particles. These two material attributes are determinants of interparticulate interactions and powder flow characteristics.

For poorly flowing materials, there are greater interparticulate interactions as well as greater difference between the bulk and tapped densities. In this study, there were no statistical significance in the bulk and tapped densities of the different granule batch which indicate good and consistent parking arrangements of the particles of the different granulation batches which probably infers the consistency of the interparticulate interactions within the granulation samples. Furthermore, there were no statistically significant differences between the bulk densities of each of the granule batch with their respective tapped densities. This thus indicates low interparticulate interactions and infers good flow properties for the different granule batches.

Angle of repose (A°R) is characteristic of the internal friction or cohesion of the particles. Its value will be high if the powder is cohesive and low if the powder is non-cohesive. Cohesive powders do exhibit poor flow and vice versa for non-cohesive powders. Poor powder flow could result in irregular die fillings, which would lead to non-uniformity of tablet weights. The flow properties of all the batch formulations as indicated by the values of angle of repose (26.56° to 27.32°) were good and acceptable. Thus, the observed statistical significance between the angles of repose and the respective bulk as well as tapped densities of each granulation batch infers the dependency and the contributory effects of these two parameters on material flow property

Carr's index for the granulation batches showed values (averaged as 13.58 %) that were within the range of good and acceptable flowability. This could be explained by the observed statistically significant relationship (*p-value* = 0.00) between Carr's index with bulk and tapped densities as well as the angle of repose obtained in this study. Furthermore, Hausner's ratios for the granulation batches averaged as 1.154, this value being within the stated limit of good and acceptable material flow (Table 2). There was a statistically significant relationship between this parameter with the angles of repose and compressibility index values but not with either the bulk or tapped densities which probably suggests that good and acceptable material flow attribute using the Hausner's ratio scale is not intrinsically dependent on interparticulate interactions, but that other micromeritics variables could be contributory.

**Post-compression evaluation**

The data obtained of post-compression parameters such as thickness, hardness, friability, weight variation, wetting time, wetting volume, water absorption ratio, uniformity of dispersion, dispersion time and disintegration time are shown in Tables 3, 4 and 5.

The physical characterization of all the formulations showed that the tablets were flat, circular with an off-white colour. All the tablets passed weight variation test as the percentage weight variation was within the Pharmacopoeia limits. The weights of all the tablets in the formulation batch was found to be uniform and had low standard deviation values (uniformity of weight) indicative of efficient mixing the formulation ingredients and most importantly, good micromeritics and flow properties of the granule batch formulations that result in good die filling.

The tablets were found to conform to the specifications of the Pharmacopoeia (BP, 2009) with thickness ranging from 6.042 ± 0.01 to 6.064 ± 0.02 mm. The BP (2009) specifies ± 5% deviation from the mean which all the batches of dispersible isoniazid tablets produced met this requirement. Uniformity of tablet thickness is an important quality and integral attribute that relates to the magnitude of the tablet to withstand breakage/fracture during the stressful processing manufacturing, packaging and handling conditions, furthermore contributes to and assures adequate content of the active ingredient.

Tablet diameters in the batch formulations of this study which ranged from 6.017 ± 0.02 to 6.035±0.02 mm were not significantly different. This tablet attribute is mainly determined by the diameters of the die and punch, as well as the robustness of the material used in fabricating them. If there is negligible expansion of the die during compaction process due to temperature rise as a result of friction, the diameters of tablets resulting from such an operation remain constant. The insignificant difference in the diameters of dispersible isoniazid tablets produced in this study suggests that the expansion of the die during tableting was negligible, thus implying that the dies were fabricated with robust material (Van Evelghem , 2008). While, the hardness was found to be in the range of 3.70 ± 0.02 to 4.3 ± 0.02 kg/cm$^2$. The standard deviation values indicated that all the formulations were within the specifications of the USP (2005). The mechanical strength of tablets is of considerable importance as it determines the ability of tablets to withstand the rigors of handling during subsequent production processes as well as transportation and distribution to end users. In all the batches of tablets produced with the varying SCMC concentration, hardness increased significantly with its increasing concentration. The BP (2009)

specification for conventional tablet hardness is between 5 and 10 kg /cm$^2$ and disintegration time of not more than 15 min. However, for dispersible tablets, whose Pharmacopoeia (BP, 2010 and USP, 2010) specified disintegration time is 3 min, the required and desirable tablet hardness would be > 5 kg /cm$^2$. Thus, the tablet hardness obtained in the batch dispersible formulations were suitable as they possessed the required strength and friability that would maintain the tablet integrity during handling without compromising the required disintegration time of 3 min.

The friability values of all the formulations ranged between 0.319 and 0.326 %, with an average value of 0.323 %. These observed values which are in conformity with the official Pharmacopoeia (BP, 2009) limit specifications of less than the 1% are indicative of their good mechanical resistance.

Granule batches had good and acceptable compressible index and Hausner's ratio values that ensured successful compression into tablets.

The tablets in all the batch formulations dispersed within a short time period, these periods were in conformity to Pharmacopoeia specifications.

This outcome would be attributable to the presence of sodium carboxyl methyl cellulose (SCMC), the superdisintegrant, which absorbs water and swells causing rupture /disintegration of the tablets into smaller particles which becomes readily dispersible in the aqueous environment. Furthermore, the respective decrease in tablet wetting times and wetting volumes from batch formulations (F1 to F5) was due to the corresponding increase in the concentration of sodium carboxyl methyl cellulose, as wetting (hydration) of tablet through capillary action would be faster at higher superdisintegrant concentration and likewise, the required time frame to achieve this action

All the tablet batches passed the uniformity of dispersion evaluation as specified by the Pharmacopoeia (USP, 2010; BP, 2010), this also implies the suitability and efficiency of SCMC which was the superdisintegrant used in this study. Superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formlulations containing high dose drugs, additionally, they effect fast disintegration of tablets into smaller particles to form homogenous suspensions through swelling mechanism, which occurs by wicking effect (capillary action) in an aqueous environment, an effect which is concentration dependent. Thus, in this study, the presence of sodium carboxyl methyl cellulose, a semi-synthetic, hydrophilic polymer with high swelling index facilitated the breaking down of the tablets into smaller particles in the aqueous environment through water absorption and hydration of the tablet by wicking /capillary action which resulted in the swelling and eventual breaking of the tablets into smaller particles.

Dispersion time is a required and quality control attribute of fast disintegrating tablets. The dispersion times of all the tablet batches in this study was within 145.52 ± 2.5 and 390.32 ± 7.5 sec and were found to be within the specified US Pharmacopoeia limit. Capillary effect is dependent principally among other factors, on the intrinsic material attributes of the superdisintegrant and its concentration, thus Formulation that contained the highest concentration of the superdisintergrant (F5) had the least dispersion time and was considered as the optimized formulation. In contrast, the water absorption ratio of all formulations increased from 95.50 ± 2.3 % in F1 to 175.30 ± 1.65 % in F5 with corresponding increase in the concentration of the superdisintegrant, this effect would be due to the higher hydration effect in the tablet system as a result of higher concentration effect of the superdisintegrant.

*In vitro* dispersion and disintergration times is presented in Table 5. All tablets disintegrated rapidly in conformity with the specified standards in USP. The disintegration time of all the tablet batches were within the range of 131.50 ± 3.5- 334.21 ± 9.5 sec.

The observed rapid disintegration into uniform finer particles in batch F5 tablet formulations comparative to the other batches was due to the comparative higher concentration (10.00 % w/w) of the superdisintegrant in the batch, The hydration effect of a superdisintegrant increased with concentration, this also explains why tablet formulations containing lower concentrations of the superdisintegrant appeared to disintegrate much more slowly into less uniform coarser particles but with better and more uniform dispersion with increasing concentration of SCMC and specifically most uniform dispersion in tablet batch F5 formulation.

Dispersion times decreased correspondingly from 390.32 ±7.5 to 145.52 ± 2.5 sec with increasing concentration of the superdisintegrant from 1.0 to 10.0 %. The decrease in wetting and dispersion times in all formulations may be attributed to the presence of superdisintegrant, which absorbs water and swells causing rupture of the tablets.

The results of wetting time and disintegration time in all the tablet batches were found to be within the Pharmacopoeia specified limits for dispersible tablets. The outcome of this study infers that dispersible tablets of isoniazid tablets that will conform to pharmacopoeia specifications can be formulated with the use of SCMS as a superdisintegrant. Tablet formulation batches F4 and F5 that contained higher concentrations of SCMC exhibited superior micromeritic properties and better disintegration and

*in vitro* dispersion times. However, batch F5 dispersible tablet formulation type was found to be the best comparative to the other four formulation types as the tablets showed the highest hardness (4.3 ± 0.02), lowest friability (0.14 ± 0.01) and least wetting time (51.80 ±1.24 sec.), wetting volume (4.03 ± 0.04 mL), highest water absorption ratio (175.35 %), least disintegration times (131.50 ±3.5 secs), least dispersion time (145.52 ± 2.5 secs) and highest uniformity of dispersion which are ideal characteristics of dispersible tablet formulation types.

The observed increase in tablet hardness and reduction in friability of the dispersible tablet formulations with increasing concentrations of SCMC, a critical formulation excipient in this study could be due to the formation of stronger "liquid bridges" in the granulation system as a result of its inherent binder attribute (being a polymer) in the presence of aqueous medium, this effect would increase with concentration.

Furthermore, the observed higher water absorption ratio and corresponding decrease in both the wetting/hydration time with minimal aqueous volume requirement at higher concentration (10 % w/w) of SCMC would be due to increase in capillary mechanism, hence the hydration capacity of this hydrophilic polymer. This study outcome therefore, suggests 10 % w/w SCMC as an optimum superdisintegrant concentration for the formulation of dispersible Isoniazid tablet.

## CONCLUSION

Dispersible isoniazid paediatric tablet formulation that could be applied as a model formulation for use in a high TB burden, resource limited healthcare setting has been developed.

## ACKNOWLEDGEMENTS

The authors are greatly thankful to the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Lagos technical staff for their technical input into this research study.

## REFERENCES

Azubuike, C. P., Rodriguez, H, Okhamafe, A. O., Rogers, R.D. (2012). Physicochemical properties of maize cob cellulose powders reconstituted from ionic liquid solution. *Cellulose.* 19:425-433.

British Pharmacopoeia. The Commission Office London. 2009; 111: 6578-6585.

British Pharmacopoeia Commission. (2013). British Pharmacopoeia, 13th Edition, Stationery Office, Great Britain,

Basu, B., Bagadiya, A, Makwana, S, Vipul, V., Batt, D, Dharamsi, A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. *J Adv Pharm Technol Res*. 2011; 2 (4):266–273. doi:10.4103/2231-4040.90885

Bolton, S., Bon, C., (2004). Pharmaceutical statistics and practical and clinical application. In: Rev and Expanded, 4th ed. Marcel Dekker Inc., New York, pp. 96–146.

Chein, Y.W. 1992. Oral drug delivery and delivery systems. 2nd Ed. New York: Marcel Dekker: 139-196.

Donald, P.R. (2007). The assessment of new anti-tuberculosis drugs for a paediatric indication. *Int J Tuberc lung Dis* 11: 1162–1165.

Enarson, P.M., Enarson, D.A. and Gie, R. (2005) Management of the child with cough or difficult breathing. *Int J Tuberc lung Dis* 9: 727–732

European Medicines Agency. (2013). Revised priority list for studies into off-patent paediatric medicinal products..EMA/98717/2012, Available at: www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf. Accessed August 15, 2013.

Fu, Y., Yang, S., Jeong, S.H., Kimura, S.and Park, K., (2014). Orally fast disintergrating tablets: developments, technologies, taste-masking and clinical studies. *Crit. Rev. Ther. Drug. Carrier Syst.* 21 (6):433-76. DOI: 10.1615/Crit RevTher Drug Carrier Syst. 21.16.10.

Furtado, S., Deveswaran, R., Bharath, S., Basavaraj, B.V., Abraham, S. and Madhavan, V. (2009). Development and characterization of Orodispersible tablets of famotidine containing a subliming agent, *Tropical Journal of Pharmaceutical Research, 8 (2): 153-159.*

Gohel, M., Patel, M., Amin, A., Agrawal, R.., Dave, R. and Bariya, N. (2004). Formulation Design and Optimization of Mouth Dissolve Tablets of Nimesulide Using Vacuum Drying Technique. *AAPS Pharma Science Technology*. 5 (3): 36.

Gohel, M.C., Parikh, R.K., Brahmbhatt, B.K. and Shah, A.R., (2007). Preparation and assessment of novel coprocessed superdisintegrant consisting of crospovidone and sodium starch glycolate, A Technical Note. *AAPS PharmSciTech*, 8 (1): 9.

Gosai, A.R., Patil, S.B. and Sawant, K.K., (2008). Formulation and Evaluation of Orodispersible Tablets of Ondansetron hydrochloride by direct compression using superdisintegrants, *International Journal of Pharmaceutical Sciences and Nanotechnology*. 1 ;( 1).

Habib, W., Khankari, R. and Hontz, J.(2002).Fast-dissolving drug delivery systems:critical review in therapeutics. *Drug Carrier Systems*. 17 (1):61-72.

Huang, Z., Scicolone, J.V., Han, X. and Dave, R.N. (2015).Improved blend and tablet properties of fine pharmaceutical powders via dry particle coating. *Int. J. Pharm.* 478 (2): 447-455.

Indurwade, N.H., Rajyaguru, T.H. and Nakhat, P.D. (2002). Novel approach: fast dissolving tablets. *Indian Drugs*, 39(8): 405-41.

Jadhav, S. B., Kaudewar, D.R., Kaminwar, G.S., Jadhav, A.B., Kshirsagar, R.V. and Sakarkar, D.M. (2011). Formulation and Evaluation of Dispersible Tablets of Diltiazem Hydrochloride. *International Journal of PharmTech Research*. 3 :( 3) 1314-1321. CODEN (USA): IJPRIF ISSN: 0974-4304.

Kuchekar, B.S., Bhise, S.B., and Arungam, V. (2005).Design of fast dissolving tablets. *Indian J. Pharm Edu .and Research*. 35:150.

Kumar, S., Gupta, S.K. and Sharma, P.K. (2012). A Review on Recent Trends in Oral Drug Delivery-Fast Dissolving Formulation Technology. *Advances in Biological Res*. 6 (1): 06-13.

Kuno, Y., Kojima, M., Ando, S. and Nakagami, H. (2005). Evaluation of Rapidly Disintegrating Tablets Manufactured by Phase Transition of Sugar Alcohol. *Journal of Controlled Release*. 105: 16-22.

Lachman, L., Lieberman, A.and Kinig, J. L. 4th ed. Bombay: Varghese Publishing House; 1991. The Theory and Practice of Industrial Pharmacy; pp. 67–8.

Maheshwari, R., Todke, P., Kuche, K., Raval, N. and Tekade, R. K. (2018). Micromeritics in Pharmaceutical Product Development. Chap: 17. Doi.10.1016-B978-0-12-814423-7-00017-4.

Metker, V. and Kumar, A., (2011). Formulation and evaluation of orodispersible tablets of lornoxicam. *Int. J. Drug Dev. & Res*. 3 (1): 281-285.

Mulberg, A., Silber, S. and van den Anker, J., eds. (2009). Paediatric Drug Development. Concepts and Applications. Hoboken, NJ: J. Wiley & Sons;

Mutalik, S., Shetty, R.S. (2004). Formulation and evaluation of directly compressible tablets of *Panchgani lavana*. *Int.J. Pharm*. 278: 423-433.

Nandgude, T.D., Saifee, M., Bhise, K.S. (2006). Formulation and evaluation of fast disintegrating tablets of diphenhydramine tannate. *Asian Journal of Pharmaceutical Science* 1(1):41-45.

Okoye, E.I.,Onyekweli, A.O., and Kunle, O.O. (2013). Micromeritic and Compaction characterization of Lacagregs: A group of novel multifunctional excipients. *Journal of Pharmaceutical and Allied Sciences*. 10 (3): 1934-1954.

Ologunagba, M. O., Azubuike, C.P., Silva, B.O and Sadiku, O.R. (2017) .Characterization of *Chrysophyllum albidum* Linn (family: Sapotaceae) endosperm seed gum for potential application as pharmaceutical excipient. *Trop J Nat Prod Res*. 1(5):217-222.

Parmar, R. B., Baria, A. H., Tank, H. M and Faldu, S. D. (2009). Formulation and evaluation of domperidone fast dissolving tablets, *International Journal of PharmTech Research*. 1; (3): 483–487.

Pouplin, T., Phuong, P.N., Toi, P. V., Pouplin, J. N. and Farrar, J (2014). Isoniazid, Pyrazinamide and Rifampicin Content Variation in Split Fixed-Dose Combination Tablets. *PLOS ONE*; 9: 7. www.plosone.org 1 July; e102047

Puri, D., Mangesh, R., Bhalekar, S. and Sethi, S., (2010). Evaluation of oral fast disintegrating tablet of taste masked famotidine in rat. *Latin American Journal of Pharmacy* .29; (6): 948-954.

Radke, R.S., Jadhav, J.K. and Chajeed, M.R. (2009). Formulation and Evaluation of Orodispersible tablets of Baclofen, *International Journal of Chem Tech Research*. 1 :( 3); 517-521.

Rangasamy, M. (2009). Oral disintegrating tablets: A future compaction. *Drug Invention Today.* 1: 61-65.

Reddy, L.H., Ghosh, B and Rajneesh (2002). Fast dissolving drug delivery system: A review of literature. *Indian J Pharm Sci*, 64 (4):331-336.

Remington. The Science & Practice of Pharmacy (2005). Published by Lippincoat William & Wilkein, vol-1, pp 677, 893.

Seager, H. (1998). Drug-delivery products and the Zydis fast-dissolving dosage form. *Pharma Journal of Pharmacology*, 50:375-82.

Sharma, D. (2013). Formulation development and evaluation of fast disintegrating tablets of salbutamol sulphate for requesting disorders. *ISRN. Pharmaceutics* article 1D674507 https: //dx.doi.org/10.1185/2013/674507.

Shukia, V. and Manvi, F.V. (2010). Effect of two different superdisintegrants on combination dispersible tablets of isoniazid and rifampicin for oral treatment of tuberculosis, *International Journal of Drug Delivery*, 2:322-332. http://wwwarjournas.org/ijdd.html

Subrahmanyam, C.V.S. (2004). "Text Book of Physical Pharmaceutics". 2nd edition. Delhi: Vallabh Prakashan., 210 – 228.

Subramanian, S., Sankar, V., Manakadan, A. A, Ismail, S. and Andhuvan, G. (2010). Formulation and Evaluation of Cetirizine dihydrochloride Orodispersible Tablet. *Pak. J. Pharm. Sci.*; 239 (2): 232-235.

Sureh, B., Rajendra, K., Mittapali, R., Gannu, Y. and Madhusudhan, R. (2008).Orodispersable tablet: An overview, *Asian Journal of Pharmaceutics*. pp 1-11.

Swaminathan, S and Rekha B (2010). Pediatric tuberculosis: global overview and challenges. *Clin Infect Dis* 50 Suppl 3: S184–94.

Tuleu, C.and Breitkreutz, J. (2013). Educational paper formulation-related issues in pediatric clinical pharmacology. *Eur. J. Pediatr*. 172(6):717–720.

United States Pharmacopoeia (2005). USP 28-National Formulary 23. United States Pharmacopoeia Convention Inc; pp.1675, 2000, 2379-2380.

Unites States Pharmacopoeia Convention (2010). USP 38-National Formulary 33, Stationery Office, USA,

Van Evelghem, J. (2008). Improving tablet quality with compression to equal force technology. Pharm Technol: Tableting and Granulation. 32:26-29.

World Health Organization, W.H.O. (2014). Essential Medicines and Health Products Department) in collaboration with other Development Partners: TB Alliance, The Global TB Program, UNITAD and USAID.

World Health Organization, W.H.O. (2017). Guidelines for treatment of drug-susceptible tuberculosis and patient care. https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/

*Address for correspondence: M. O. Ologunagba
Department of Pharmaceutics & Pharmaceutical Technology,
Faculty of Pharmacy,
University of Lagos, Idi-Araba,
Lagos, Nigeria
Telephone: +2348033953141
E-mails: mologunagba@yahoo.com

Conflict of Interest: None declared
Received: July 15, 2019
Accepted: December 24, 2019