Original Research Article

Direct Compression and *In Vitro* Release of Chlorpheniramine Maleate from Tablets Containing Fluid Bed Dried and Lyophilized Microcrystalline Cellulose Derived from *Cocos nucifera*.

ABSTRACT

Aims: To investigate the mechanical and *in vitro* release properties of chlorpheniramine maleate (CM) tablets formulated with fluid bed dried and lyophilized microcrystalline cellulose (MCC) derived from the fruit husk of *Cocos nucifera* (CN).

Study design: Experimental design

Place and Duration of Study: Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka from January 2015 to December 2016.

Methods: Chips of matured (CN) fruit husk were de-lignified by soda treatment methods to obtain alpha cellulose which was hydrolyzed with mineral acid (Hydrochloric acid) to obtain CN-MCC. A portion of the damp CN-MCC was fluid bed dried at 60 °C for 2 h (coded MCCF-Cocos) and the remaining CN-MCC was lyophilized at -45 °C for 3 h (coded MCCL-Cocos). The MCC powders were blended with 20, 30 and 40 % w/w CM and directly compressed at 9.81 megaPascal (mPa). The CM tablets containing MCCF-Cocos (coded CM-CF) and MCCL-Cocos (coded CM-CL) were evaluated using standard methods.

Results: Both batches had tablets with minimal weight variation; CM-CL tablets were mechanically stronger (P = .037) and less friable than CM-CF tablets. CM-CL tablets took a long time to disintegrate than CM-CF tablets. Comparatively, CM tablets containing AVC-102 (coded CM-AV) were mechanically stronger, less friable and had a longer disintegration time than CM-CL and CM-CF tablets. The dilution potential of CM-AV was greater than CM-CL and CM-CF tablets. CM release was faster in CM-CF. There was more than 80 % release of CM from CM-CF, CM-CL and CM-AV tablets within 30 min. Although CM-CL tablets were mechanically stronger than CM-CF, the data for all batches of the tablets obtained fell within the

British Pharmacopoeia set limits for uncoated tablets.

Conclusion: Chlorpheniramine maleate tablets containing fluid bed dried and lyophilized microcrystalline cellulose obtained from *C. nucifera* had good mechanical and *in vitro* release properties.

Keywords: Direct compression, chlorpheniramine maleate, microcrystalline cellulose, Cocos nucifera, fluid bed dried, lyophilization.

1. INTRODUCTION

Compressed tablets are the most widely used solid dosage form [1]. They are expected to satisfy a number of physical requirements in terms of uniformity of weight, hardness, disintegration ability upon hydration and friability. In order to ensure that these tablet characteristics are in place in accordance with the chosen ingredients, tablet manufacture can be achieved by using any of these three different processing technologies: direct compression, dry granulation and wet granulation [1,2]. Of these methods, wet granulation is traditional and most popular although the trend within the last three decades is tilting towards direct compression [3]. This is because direct compression provides both pharmaceutical researchers and industries the shortest, most effective and least complex way to produce tablets [4]. The Active Pharmaceutical Ingredient (API) can be blended with the excipient and the lubricant and compressed, which makes the product easy to process without any additional processing steps. Thermolabile or moisture sensitive ingredients which could lose their integrity if processed through the wet granulation technique are good candidates for direct compression as they can be produced without exposure to both heat and moisture [5]. One of the major challenges of tablet production is that many excipients and APIs have intrinsic poor flowability and compressibility characteristics [6]. This challenge can be overcome by the careful selection of excipients and API that would exhibit good flowability and compressibility when mixed as a powder for tablet manufacture. Such powder blends enable the optimization of the APIs as well as the production of tablets with good mechanical properties. Thus the search for new excipients or the modification of existing ones to help in the achievement of this goal is on the increase. Naturally sourced pharmaceutical excipients such as cellulose have been given much attention because of the qualities possessed by them which include: natural abundance, eco-friendliness, bio-degradation, ease of handling and processing, ability to be manipulated into desired end products, low cost of starting materials and non-toxicity of its derivatives [7,8,9]. Microcrystalline cellulose, a derivative of cellulose is a multi-functional excipient in tablet manufacture as it serves as a dry binder, filler and disintegrant [10]. There are claims that MCC is the best dry binder for pharmaceutical use especially in the direct compression technology [10,11].

Cocos nucifera (Arecaceae) is one of the prominent members of the large palm family. It grows well in the tropical and sub-tropical regions of the world [12]. In these regions, it can be seen growing in large numbers along the coastline or as a cultivated plant inland. Matured coconut trees bear fruits in clusters. Each fruit consists of the exocarp, mesocarp and endocarp [13]. The mesocarp is mostly made up of a fibrous material [13,14]. The husk which consists of the exocarp and mesocarp is littered as an agricultural waste in many coconut growing areas of the world after its seed has been removed from the fruit. This makes it a cheap source of raw material for the production of microcrystalline cellulose. The processing steps such as the method of drying – spray drying, lyophilization and fluid bed drying has been reported to greatly influence some of the physical properties of MCC. Such

physical properties include the particle morphology, size, porosity, discreteness or aggregation [15,16].

Chlorpheniramine maleate is one of the most potent anti-histamines and is known to be less sedative than promethazine [17]. Anti-histamines reduce or eradicate the effect of histamines in the body by selectively competing for and occupying the receptor sites in the effector cells in preference to histamine [18,19]. The activation of histamine results in vasodilation increased capillary permeability, flare and itch reactions in the skin and to some extent contraction of smooth muscles in the bronchi and gastrointestinal tract (GIT). This characteristic makes them very useful in the alleviation of urticarial rashes and nasal allergy [19, 20]. Chlorpheniramine maleate is well absorbed after oral administration, but because of a relatively high degree of metabolism in the gastrointestinal (GI) mucosa and the liver, only about 25-60 % of the drug is available to the systemic circulation. The most commonly seen adverse effects are central nervous system (CNS) depression (lethargy, somnolence) and GI effects (diarrhoea, vomiting, and anorexia) [21].

The aim of this work was to evaluate the effect of the fluidized bed and lyophilization of MCC derived from *Cocos nucifera* on the tabletting, physical properties and *in vitro* release of chlorpheniramine maleate tablets prepared by direct compression. Commercial MCC (AVC-102) was used as the basis for comparison.

2. MATERIALS AND METHODS

2.1 Materials

Chlorpheniramine maleate (Evans Nig. Plc.), sodium hydroxide (Merck, Germany), hydrochloric acid (BDH, Poole England), talc, magnesium stearate (Sigma, USA), sodium hypochlorite (JIK, Reckitt & Colman Nig. Plc), Avicel® PH 102 (FMC Biopolymer, USA). Dried chips of matured coconut fruit husk.

2.2 Methods

The method of Nwachukwu and Ofoefule [16] for the preparation of MCC from CN was adopted. Dried chips of about 2-4 cm in length obtained from the matured fruit husks of *Cocos nucifera* trees growing within Mgbuoba town, Port Harcourt, Nigeria were digested in 3.5 % w/v and 17.5 % w/v solutions of sodium hydroxide at boiling temperatures for 4 and 1 h respectively to obtain alpha (α) cellulose. Intermittent bleaching was done during the digestion using 0.4 % w/v sodium hypochlorite. The hydrolysis of the CN α cellulose using 2.5 N hydrochloric acid solution yielded Cocos nucifera microcrystalline cellulose (CN-MCC). The CN-MCC was washed to neutrality using large amounts of distilled water and was squeezed through a muslin cloth to obtain a damp product which was divided into two portions. The fluid bed drying at 60 ± 1°C for 2 h or lyophilization at -45 ± 1°C for 3 h of either portion of the damp MCC was carried out. The resultant fluid bed dried MCC (coded *MCCF-Cocos*) and lyophilized MCC (coded *MCCL-Cocos*) were evaluated for their physicochemical and micromeritic properties using standard evaluation methods. Investigation on this has been earlier reported by Nwachukwu and Ofoefule [16]. The formulation of CM tablets was done using the quantities of the ingredients shown in Table 1. For each batch, the correct amount of each of the ingredients was weighed and mixed carefully in a mortar using the doubling up technique. The different powder blends were directly compressed into tablets targeted to weigh 300 mg per tablet. A total number of one hundred (100) tablets were prepared per batch using a single punch tablet press (Model C, Carver Inc., Winscosin, USA) fitted with 10 mm flat faced set of punches and die at a dwell time of 30 sec. A total of four batches were formulated for each MCC. One batch (Batch I)

which contained none of the derived MCC served as the control. A commercial brand of MCC (AVC-102) was used as the standard microcrystalline cellulose powder. All the tablets for all the batches were compressed at a uniform compression pressure of 9.81 megaPascal (mPa).

Table 1: Formula for chlorpheniramine maleate tablets.

Type of MCC	Ingredient/ Batch	CM (mg)	Polymer (mg)	Corn starch (mg)	Magnesium stearate (mg)	Talc (mg)	Total weight (mg)
MCCF-Cocos	CMCF-1	0.00	280.50	15.00	3.00	1.50	300.00
	CMCF-2	60.00	220.50	15.00	3.00	1.50	300.00
	CMCF-3	90.00	190.50	15.00	3.00	1.50	300.00
	CMCF-4	120.00	160.50	15.00	3.00	1.50	300.00
MCCL-Cocos	CMCL-1	0.00	280.50	15.00	3.00	1.50	300.00
	CMCL-2	60.00	220.50	15.00	3.00	1.50	300.00
	CMCL-3	90.00	190.50	15.00	3.00	1.50	300.00
	CMCL-4	120.00	160.50	15.00	3.00	1.50	300.00
AVC-102	CMAV-1	0.00	280.50	15.00	3.00	1.50	300.00
	CMAV-2	60.00	220.50	15.00	3.00	1.50	300.00
	CMAV-3	90.00	190.50	15.00	3.00	1.50	300.00
	CMAV-4	120.00	160.50	15.00	3.00	1.50	300.00

2.3 Characterization of chlorpheniramine maleate formulations

2.3.1 Some micromeritic properties

The micromeritic evaluation of some of the powdered formulations of chlorpheniramine maleate contained in Table 1 was done to establish their densities and flow behaviour.

2.3.1.1 Bulk and tapped densities

A quantity of 15 g of the chlorpheniramine maleate powder blends of each of the batches in Table 1 was poured into a clean dry transparent graduated 50 mL glass measuring cylinder kept on a flat platform and the volume occupied by the powder bed noted (bulk volume). The bulk density was derived using Equation 1 [11]:

Bulk density = (mass of powder)/(bulk volume of powder)…… 1

The tapped density was obtained by tapping the chlorpheniramine maleate powder in the measuring cylinder several times on a padded flat surface until a constant volume of the powder was obtained (the tapped volume). The tapped density was derived using Equation 2 [11]. The determinations were done in triplicates.

Tapped density = (mass of powder)/(tapped volume of powder)…… 2

2.3.1.2 Angle of repose

A quantity of 50 g of the chlorpheniramine maleate powder blend was used for the determination of the angle of repose. Using the Pilpel method [12] the powder was poured into an open-ended pipe of 3 cm diameter and 60 cm length kept on a white sheet of paper spread upon a flat platform. By gradually pulling up of the cylindrical pipe a cone of the powder was formed on the flat surface. The height and diameter of the powder heap formed were measured. Replicate determinations were made and the angle of repose determined using Equation 3 [11].

AOR = tan-1 2h/d …….. 3

2.3.1.3 Hausner's quotient and Carr's Index

The determination of the Hausner's quotient and Carr's index for the different chlorpheniramine maleate powder blends were done using Equations 4 and 5 respectively [12,13].

Hausner's quotient (H.Q.) = Dt/Db …… 4

Carr's Index (C.I.) = (1 – Db/Dt) x 100 ……..….. 5

Where Db is the bulk density, and Dt is the tapped density.

2.4 Compaction of chlorpheniramine maleate tablets

The different chlorpheniramine maleate powder blends (Table 1) were compressed into tablets using a single punch hydraulic tablet press (Model C, Carver Inc., Winscosin, USA) fitted with a set of flat faced 10 mm stainless steel punches. One hundred (100) tablets were compressed from each chlorpheniramine maleate powder blend at a target tablet weight of 300 mg per tablet and at a uniform compression pressure of 9.81 megaPascal (mPa) and dwell time of 30 sec. A batch that did not contain chlorpheniramine maleate (the batch I) was also compressed into tablets and used as control.

2.4.1 Evaluation of chlorpheniramine maleate tablets

After compression, the tablets were properly stored in a desiccator containing silica gel for a period of 24 h to allow the tablets to recover from compression effects. Using standard methods, the tablets were evaluated for uniformity of weight, crushing strength, friability, disintegration, the content of active ingredient and dissolution.

2.4.1.1 Tablet physical appearance

Physical evaluation for some organoleptic properties of the compressed tablets from each batch of chlorpheniramine maleate tablets was done.

2.4.1.2 Uniformity of weight

The determination of weight variation of the tablets involved the collective weighing of twenty tablets that were randomly picked from each batch of the chlorpheniramine maleate tablets. [14,15]. Their mean weight and coefficient of variation were determined. The acceptance or rejection criterion was based on the stipulation of the British Pharmacopoeia 2012 [15].

2.4.1.3 Crushing strength test

In order to determine the crushing strength, ten tablets that were randomly picked from each batch of the different chlorpheniramine maleate tablet formulations were determined using a Monsanto hardness tester (Singhla Scientific Industries, India) and the value at which each tablet broke was recorded. The mean value and standard deviation were determined per batch [15].

2.4.1.4 Friability or abrasion test

The determination of the friability required that ten tablets randomly selected from each batch of the chlorpheniramine maleate tablets were dusted of any powder particles, collectively weighed and put in one of the drums of the friabilator, a model TAR 200 (Erweka®, Germany) twin drum electronic friabilator programmed to revolve at 25 rotations per minute (rpm) for 4 min. After which, the tablets were removed from the friabilator, were de-dusted and any broken tablets amongst them rejected. The tablets were reweighed collectively and the friability (F) calculated from Equation 6 [16].

$$F = [(Wo-W)/Wo] \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 6$$

Where Wo is the initial weight and W is the final weight.

2.4.1.5 Disintegration test

Six tablets were randomly selected from each batch of the chlorpheniramine maleate tablets. A model ZT-3 disintegration tester (Erweka®, Germany) was used. One tablet was put in each of the six tubes of the basket of the disintegration test apparatus and held in place with a glass disc. The basket was dipped inside a 1 L beaker containing 500 mL of 0.1N HCl solution warmed up to 37 ± 1˚C and an oscillation speed of the disintegration equipment set at 29 ± 1 cycle per minute (cpm). The time taken for the last tablet to break up completely and pass through the mesh was noted [15].

2.4.1.6 Determination of wavelength of maximum absorption (λ_{max}) of chlorpheniramine maleate

One hundred milligrams (100 mg) of the pure chlorpheniramine maleate powder was dissolved in a sufficient quantity of 0.1 N HCl in a 100 mL volumetric flask and the volume was made up to the 100 mL mark with the 0.1 N HCl [15] to obtain the stock solution of 1 mg/mL which is equivalent to 1.00 mg %. The serial dilution of the stock solution enabled chlorpheniramine maleate preparations that were 0.20 mg %, 0.40 mg %, 0.60 mg % and 0.80 mg % strength to be obtained. In order to determine the maximum/peak absorbance (λ_{max}) of chlorpheniramine maleate, the 0.20 mg % solution was scanned in a Jenway model

6405 UV/vis spectrophotometer (Jenway®, England) at wavelengths ranging from 220 to 400 nm.

2.4.1.7 Standard calibration curve of chlorpheniramine maleate

The serially diluted solutions of chlorpheniramine maleate containing 0.20 mg %, 0.40 mg %, 0.60 mg %, 0.80 mg % and the stock solution of 1.00 mg % were placed in a quartz cuvette and their absorbance's scanned using a Jenway model 6405 UV/Vis spectrophotometer (Jenway®, England) set at a wavelength of 265 nm. A plot of the concentrations against absorbance readings was made and the slope determined.

2.4.1.8 Assay of chlorpheniramine maleate tablet

Twenty tablets were selected at random from each batch of the chlorpheniramine maleate tablets and were weighed collectively, pulverized in a porcelain mortar and an amount of powder equivalent to the weight of one tablet was taken and dispersed in 15 mL of distilled water in a 100 mL volumetric flask. The volume of the preparation was made up to the 100 mL mark and the filtrate obtained from the dispersion was diluted and the absorbance read at 265 nm of the Jenway model 6405 UV/Vis spectrophotometer (Jenway®, England) [15]. The absorbance obtained for the tablets from the different batches were correlated with the standard calibration curve earlier established and their concentrations determined using the Beer Lambert's Equation which is stated as Equation 7 [17]:

$$A = KC \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \; 7$$

Where A is absorbance, C is concentration and K is proportionality constant known as molar absorption.

2.4.1.9 Dissolution studies of chlorpheniramine maleate

The dissolution or drug release studies of the chlorpheniramine maleate tablets were conducted using a six station model DT 600 (Erweka, Germany) dissolution equipment. The paddle method was used for the evaluation. Each beaker containing 900 mL of 0.1 N HCl solution was heated up to a temperature of 37.0 ± 0.5˚C, and the paddle was set at a speed of 100 rotations per min (rpm) [15]. One tablet was placed in each beaker for the test. Five (5 mL) samples were withdrawn at 10 min intervals up to 30 min with an equal replacement with 0.1 N HCl maintained at 37.0 ± 0.5˚C after each withdrawal. The absorbance readings of the filtrates obtained from the withdrawn samples were determined using a Jenway model 6405 spectrophotometer at a wavelength of 265 nm. The absorbance results were converted to concentrations from the Beer Lamberts calibration curve previously determined for chlorpheniramine maleate. This was done for all the batches of the chlorpheniramine maleate tablets.

2.5.11 Statistical evaluation

The analysis of data obtained was statistically done using ANOVA and students t-test (SPSS version 21). Values were considered significant at P = 0.00 or less than 0.05.

3. RESULTS AND DISCUSSION

3.1 Some micromeritic properties of chlorpheniramine maleate formulations

The results of some micromeritic properties of powders of the chlorpheniramine maleate and excipients blends are shown in Table 2. The bulk densities of CMCF powder formulations > CMCL formulations > CMAV formulations. This implies that the order of bulkiness of the powders were CMCF > CMCL > CMAV formulations. The tapped densities of the different formulations were greater than their bulk densities showing a good volume reduction of the powders as a result of tapping or agitation of the powders. This suggests that the powders are compressible. The flow rates of the powders show that CMAV formulations flowed better than the CMCF and CMCL formulations respectively (Table 2). Only batch CMCL-1 had an interrupted flow and was classified as non-flowing. The angle of repose data of CMCF-1 to CMCF-4 and CMAV-1 to CMAV-4 (Table 2) categorizes them as powders with the excellent flow while the Hausner's quotient and Carr's index categorizes them as powders with a good flow [22, 24]. The CMCL-1 to CMCL-4 formulations which contains the lyophilized MCC (*MCCL-Cocos*) had an angle of repose ranging from 30.83 ± 0.02 to 35.24 ± 0.32° which classifies them as good flowing powders. Similarly, the Hausner's quotient data (1.14 ± 0.32 to 1.18 ± 0.55) and Carr's index values (12.50 ± 0.25 to 15.22 ± 0.20 %) also classifies them as powders with good flow [22, 24]. The correlation between the angle of repose, flow rate, Hausner's quotient and Carr's index shows the overall good flow of the powdered formulations. The flow parameters obtained shows that the powder blends would enable the production of tablets with good mechanical properties and minimal weight variation.

3.2 Evaluation of chlorpheniramine maleate tablets

The chlorpheniramine maleate tablets were allowed a minimum of 24 h post-compression-relaxation time before tablet characterization tests were conducted. Some of the characterization tests done were uniformity of tablet weight, hardness, friability, disintegration, tensile strength and dissolution.

3.2.1 Uniformity of weight

Results of weight evaluation tests of chlorpheniramine tablets are shown in Table 3. The weight of the tablets ranged from 292.90 ± 2.39 to 308.30 mg ± 2.30 %. All the batches conformed to British Pharmacopoeia specifications for the coefficient of variance of uncoated tablets that weigh above 250 mg which is given as ± 5 % [15]. The tablets can, therefore, be considered as adequate.

Table 2: Some micromeritic properties of chlorpheniramine maleate powder blends

MCC	Batch	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Flow rate (g/sec)	Hausner's Quotient	Carr's Index (%)
MCCF-Cocos	CMCF-1	0.46±0.10	0.52±0.20	26.96±0.04	5.33±0.16	1.13±0.15	11.54±0.42
	CMCF-2	0.59±0.05	0.66±0.15	28.15±1.05	5.54±0.50	1.12±0.21	10.61±0.50

	CMCF-3	0.61±0.14	0.69±0.10	29.30±1.20	6.23±0.33	1.13±0.45	11.59±0.35
	CMCF-4	0.64±0.10	0.71±0.05	29.81±0.63	6.25±0.25	1.11±0.10	9.86±0.20
MCCL-Cocos	CMCL-1	0.37±0.01	0.43±0.02	35.24±0.32	N.F	1.16±0.02	13.35±0.10
	CMCL-2	0.39±0.01	0.46±0.10	33.51±0.15	2.20±0.34	1.17±0.22	15.22±0.20
	CMCL-3	0.40±0.02	0.47±0.50	31.05±0.10	2.58±0.22	1.18±0.55	14.89±0.15
	CMCL-4	0.42±0.05	0.48±0.20	30.83±0.02	3.02±0.10	1.14±0.32	12.50±0.25
AVC-102	CMAV-1	0.33±0.15	0.38±0.21	27.95±0.01	5.27±0.15	1.15±0.13	13.16±0.20
	CMAV-2	0.35±0.10	0.39±0.02	28.43±0.50	6.10±0.13	1.11±0.20	10.26±0.10
	CMAV-3	0.37±0.20	0.43±0.01	29.00±0.45	6.45±0.55	1.14±0.15	13.35±0.30
	CMAV-4	0.40±0.05	0.46±0.10	30.05±0.24	6.57±0.40	1.15±0.02	13.04±0.25

*N.F represents 'no flow'.

3.2.2 Crushing strength

The crushing strength test values for all the batches of chlorpheniramine maleate tablets are as shown in Fig.1 and they ranged from 3.22 ± 0.21 to 25.13 ± 2.36 kgF. The formulations containing the lyophilized MCC powders formed tablets with crushing strength that were significantly higher (P = .037) than those of fluidized dried MCC. According to the British Pharmacopoeia (2012), uncoated tablets are said to have passed this test when the values obtained are between 4.00 to 7.50 kgF [23]. All the chlorpheniramine batches of tablets passed the test except batch CMCF-4 (3.22 ± 0.21 kgF) which contained 40 % w/w chlorpheniramine maleate (CMCF-4). The chlorpheniramine maleate (CMCL) tablets containing lyophilized CN-MCC at all concentrations compared favourably with chlorpheniramine maleate tablets containing AVC-102 (CMAV) tablets at all concentrations. The similarity in their data for crushing strength could be as a result of the high porosity and low bulk volume characteristics of the MCCs used in the formulations [22]. Most commercial grades of MCC such as AVC-102 are spray dried during preparation to facilitate the particles to acquire a loose aggregated nature with a lot of inter particulate voids [10]. The loose nature of these MCC can be seen by their low bulk density values which are similar to what was obtained from the lyophilized MCC batches. This feature enables a high carrying capacity of the API as it contains a high number of points for the API particles to be attached. The control batches of tablets had higher crushing strengths and crushing strength friability ratio (CS-FR) than the batches that contained CM powder (Table 2) implying that they are mechanically stronger.

3.3 Disintegration

The disintegration time of the chlorpheniramine maleate tablets is shown in Table 3. The ability of a normal release tablet is a relevant step that would ensure dissolution and bioavailability of the Active Pharmaceutical Ingredient contained by the tablet. All the batches of tablets that contained CM in the range of 20-40 % w/w disintegrated within 4.00 min (Table 3). The disintegration times of the CM tablets decreased as the dilution factor or concentration of its CM content increased. The disintegration time of CMAV tablets were

greater than obtainable in CMCL while CMCF had the least values. Generally, there was a significant difference (P = .003). Both the control and other batches disintegrated within 4 min. Thus, all the batches passed the disintegration test for both the BP and USP specifications which stipulate that tablets should fully disintegrate between 15 and 30 min time periods respectively.

3.4 Friability

The results obtained from friability evaluations are shown in Table 3. Data obtained ranged from 0.50 ± 0.01 to 4.12 ± 1.24 %. The tablets containing the fluidized dried MCC at 40 % API concentration consistently had higher friability values than those that contained 20 and 30 % of the CM. The order of friability was CMCF-4 > CMCF-3 > CMCF-2. Generally, the friability of the tablets that were formulated with the fluidized dried MCC was significantly higher (P = .042) than tablets formulated with lyophilized MCC. Most batches except CMCF-3, CMCF-4, CMCL-4 and CMAV-4 had values below the BP 2012 acceptable upper limit values of not more than 1 % and they are considered adequate in terms of friability [15]. The tablets that did not meet the BP specification are expected to crumble under the stress of handling, packaging and transportation.

3.5 Dilution potential

A tablet can be regarded as having the ability to carry a high percentage of the API as long as a firm hard compact or tablet is formed. Thus based on the crushing strength value, all the batches of tablets had crushing strength values that were greater than 4.00 kgF except batch CMCF-4. All others were able to carry up to 40 % of the chlorpheniramine maleate. Although the BP 2012 states that uncoated tablets with values of 4.00 kgF and above should be accepted as adequate in terms of hardness, however, hardness alone does not give the overall picture of the mechanical properties of a compressed tablet. Compressed tablets with hardness/crushing strength greater ≥ 4.00 kgF and friability ≤ 1 % are considered adequate for handling and transportation [15]. Fluid bed dried CN-MCC containing 20 % chlorpheniramine maleate (CMCF-2) and lyophilized CN-MCC containing 20 and 30 % chlorpheniramine maleate (CMCL-2 and CMCL-3) confirmed to these requirements. The AVC-102 containing 20, 30 and 40 % chlorpheniramine (CMAV-2, CMAV-3 and CMAV-4) passed the test. The AVC-102 had a dilution potential/capacity of up to 40 % while the dilution potential of CMCF and CMCV tablets was 30 %.

Table 3: Some physical parameters of chlorpheniramine maleate tablets

MCC	Batch	Weight uniformity [mg ± % CV]*	Friability (%)	Crushing strength-Friability ratio (CS-FR)	Disintegration (min)
MCCF-Cocos	CMCF-1	297.30 ± 1.80	0.50 ± 0.01	29.04 ± 0.18	0.62 ± 2.25
	CMCF-2	297.50 ± 2.30	0.92 ± 0.04	6.17 ± 0.25	1.09 ± 0.06
	CMCF-3	292.90 ± 4.39	1.43 ± 0.72	2.80 ± 0.19	0.23 ± 0.03
	CMCF-4	295.35 ± 1.62	4.12 ± 1.24	0.85 ± 0.14	0.14 ± 0.04
MCCL-Cocos	CMCL-1	292.80 ± 6.55	0.18 ± 0.03	96.17 ± 0.37	1.41 ± 1.86
	CMCL-2	292.00 ± 2.22	0.67 ± 0.09	9.30 ± 0.11	1.49 ± 0.55
	CMCL-3	295.40 ± 1.40	0.98 ± 0.12	5.23 ± 0.20	0.45 ± 0.06
	CMCL-4	296.65 ± 2.02	1.12 ± 0.16	4.62 ± 0.50	0.37 ± 0.03
AVC-102	CMAV-1	301.60 ± 2.48	0.56 ± 0.05	44.93±0.58	1.22 ± 0.86
	CMAV-2	292.00 ± 2.22	0.85 ± 0.09	8.32 ± 0.33	3.56 ± 0.92
	CMAV-3	295.40 ± 1.40	0.87 ± 0.09	7.41 ± 0.10	1.26 ± 0.05
	CMAV-4	296.65 ± 2.02	1.02 ± 0.22	5.51 ± 0.16	0.26 ± 0.05

3.6 Assay of chlorpheniramine tablets

Assay results of chlorpheniramine maleate tablets 48 h post-compression are shown in Table 4. The content of CM ranged from 99.36 ± 0.82 to 100.24 ± 1.08 %. All the batches of the chlorpheniramine maleate tablets can be adjudged to have passed as they complied with specifications as contained in the United States Pharmacopoeia (USP 2009) which states that chlorpheniramine maleate tablets should contain not less than 90 % or more than 110 % of the labelled amount [23]. This indicates that proper blending of the CM with the excipients was done and tablets produced were of fairly uniform weights that were acceptable.

3.7 Dissolution profiles of chlorpheniramine maleate.

Results of the release behaviour of chlorpheniramine from tablets containing CN fluidized and lyophilized dried MCC are shown in Figs. 2 – 4. The tablets containing the fluidized MCC released faster than those containing lyophilized MCC. More than 80 % of the CM content of CMCF-4 was released within 5 min while it took up to 15 min to obtain a similar release from CMCF-2 and CMCF-3. There was a maximum release of CM from all the batches of tablets investigated and maximal release was attained within 30 min. The difference in the release behaviour observed can be attributed to differences in the hardness of the tablets as CMCF-2 and CMCF-3 batches were harder than the CMCF-4 batch. Amongst the different MCCs at an equivalent concentration of CM content of their tablets, the CM release pattern showed a similarity without a significant difference (P =.076)

between CMCF-2 and CMCL-2 (Fig.2). There was, however, a significant difference (*P* =.023) in CM release between CMCF-2, CMCL-2 and CMAV-2. The CM release was lower in the CMAV-2 tablets. The tablet batches showed an initial fast release within 2 min after which a slower and consistent release occurred up to 30 min. The burst effect may be as a result of the CM powder at the periphery of the surfaces of the tablets which may have dissolved quickly upon hydration by the dissolution medium while the later gradual effect could be attributed to the CM that was dissolved as the tablets disintegrated [24].

The CM release pattern for the tablets containing 30 % w/w of CM is shown in Fig. 3. A similar burst effect was also observed for the three batches of tablets containing the different MCCs. The CM release was higher in CMCF-3 within 8 min than in CMCL-3 and CMAV-3. Thereafter, the release of CMCL-3 was slightly higher than that of CMCF-4 though with no significant difference (*P* = .062) in the percentage of CM released. The CMAV-3 tablets were least in terms of CM release and there was a significant difference (*P* = .024) in the percentage CM release when compared with release from CMCF-3 and CMCL-3 batches. The difference in mechanical strength of the tablets and the different disintegration behaviour of the tablets could have resulted in the differences in the CM release observed amongst the CMCF-3, CMCL-3 and CMAV-3 tablets. Generally, all the tablets from the different batches had their API content released within 30 min. They released their CM content maximally within a 30 min period. The tablets met the USP specification of drug dissolution for uncoated CM tablets which is given as not less than 80 % of the labelled amount within 30 min [23].

Figure 4 shows the pattern of CM release from the batches of tablets containing 40 % of CM. An initial burst release was observed for all the tablets from all the batches within 2 min. There was a consistently and statistically significant (*P* = .025) higher percentage of CM release from CMCF-4 than from CMCL-4 and CMAV-4. Drug release from CMCL-4 tablets was slightly higher than those of CMAV-4 tablets but statistically, the CM release was not significantly different (*P* = .091). More than 80 % of CM was released within 30 min showing compliance with the dissolution test [23].

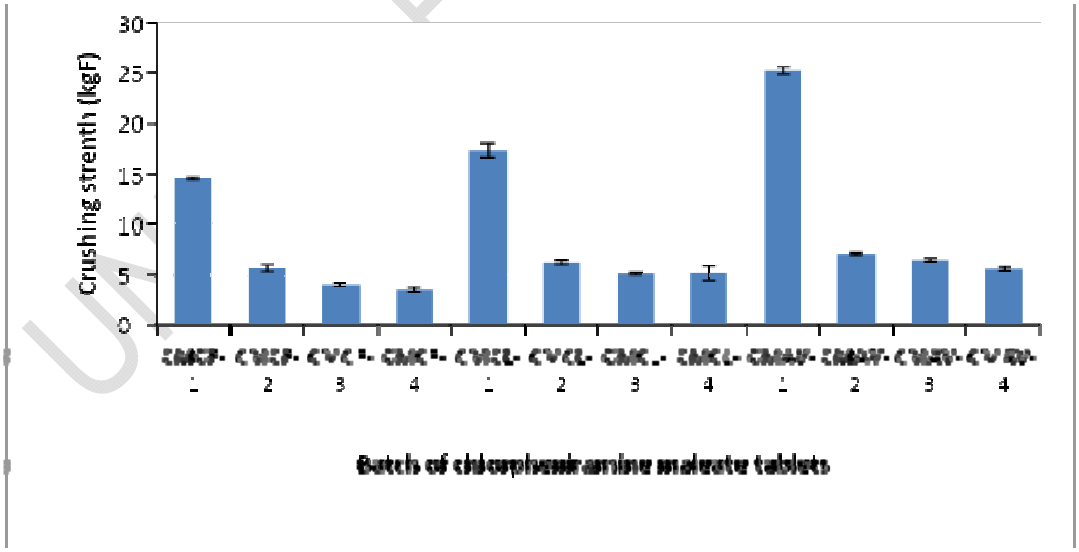

Fig. 1: Crushing strength of chlorpheniramine maleate tablets

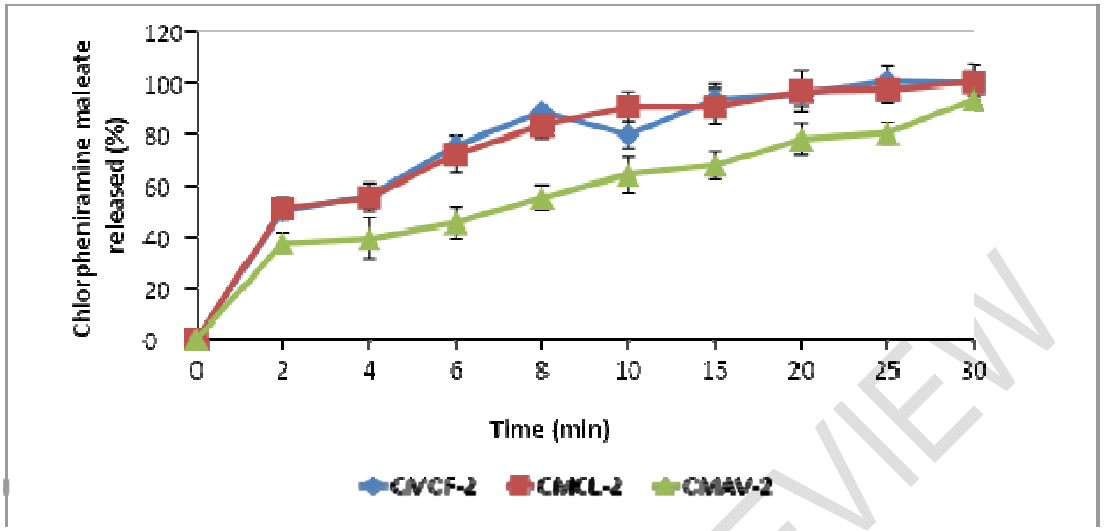

Fig. 2: Chlorpheniramine maleate release from CMCF-2, CMCL-2 and CMAV-2 tablets

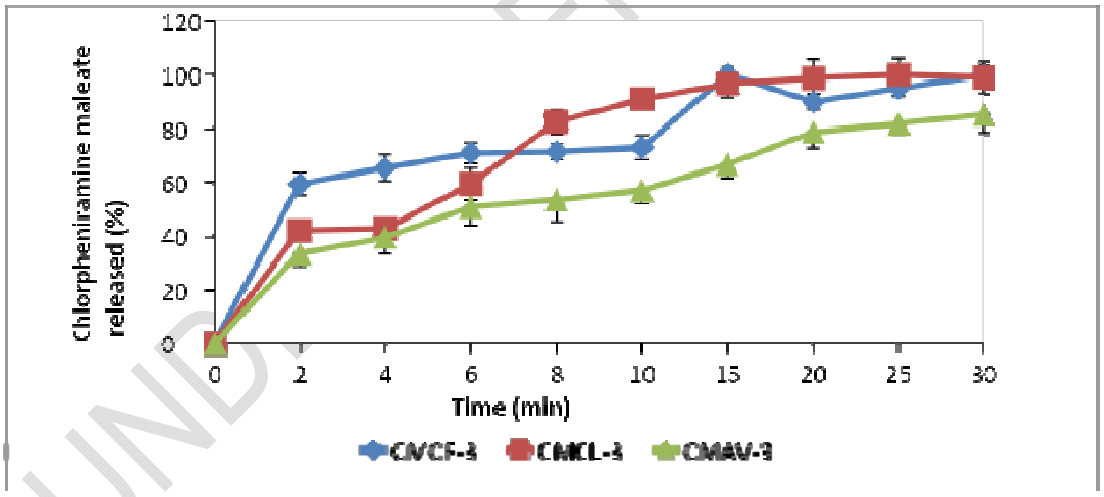

Fig. 3: Chlorpheniramine maleate released from CMCF-3, CMCL-3, and CMAV-3 tablets

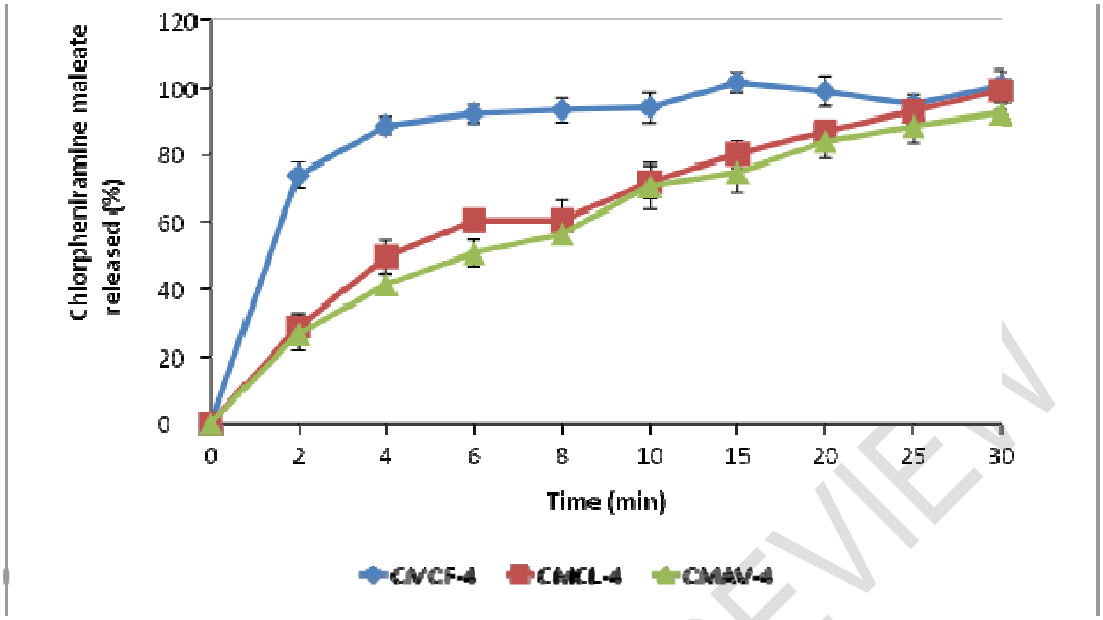

Fig. 4: Chlorpheniramine maleate release from CMCF-4, CMCL-4 and CMAV-4 tablets

Figure 5 shows the release of CM from tablets of CMCF-2, CMCF-3 and CMCF-4 and *MCCF-Cocos.* The order of release was CMCF-4 > CMCF-3 > CMCF-2. A similar pattern of release was observed for tablets containing *MCCL-Cocos* and AVC-102. The order of release was CMCL-4 > CMCL-3 > CMCL-2 and CMAV-4 > CMAV-3 > CMAV-2 respectively (Figs. 6 and 7).

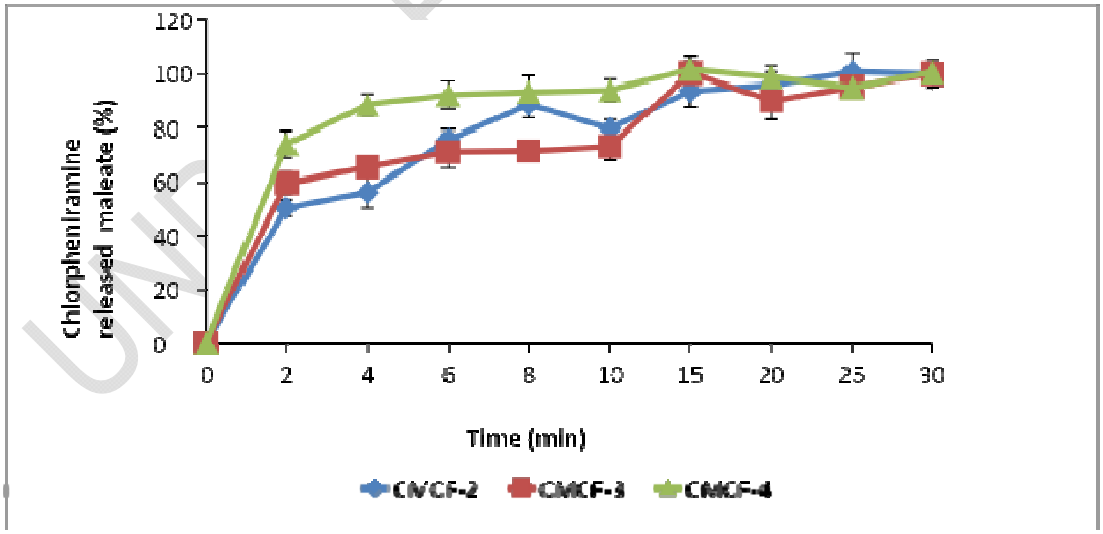

Fig. 5: Percentage of chlorpheniramine release from CMCF-2, CMCF-3 and CMCF-4 tablets

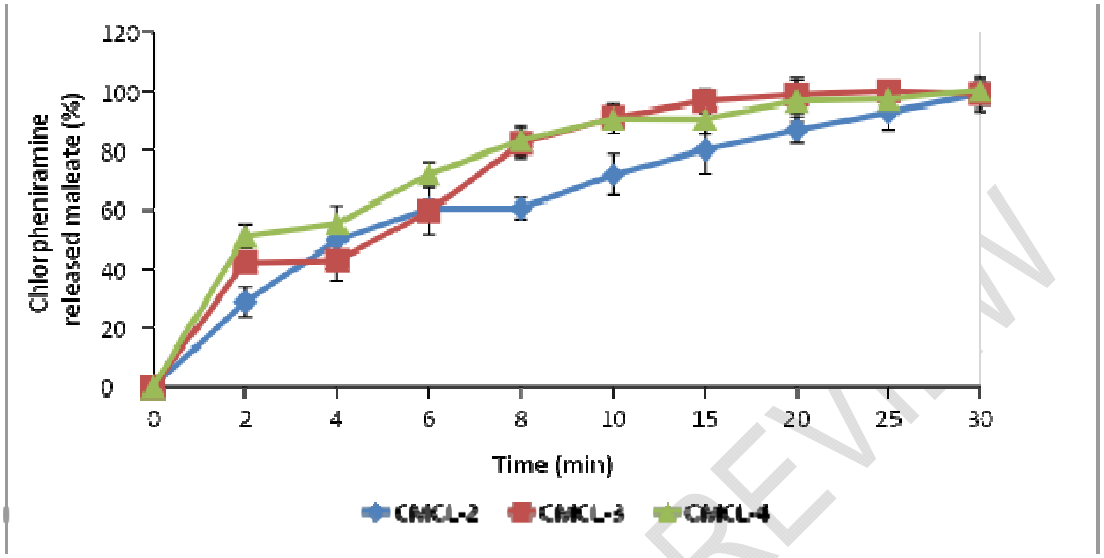

Fig. 6: Percentage of Chlorpheniramine release from CMCL-2, CMCL-3 and CMCL-4 tablets

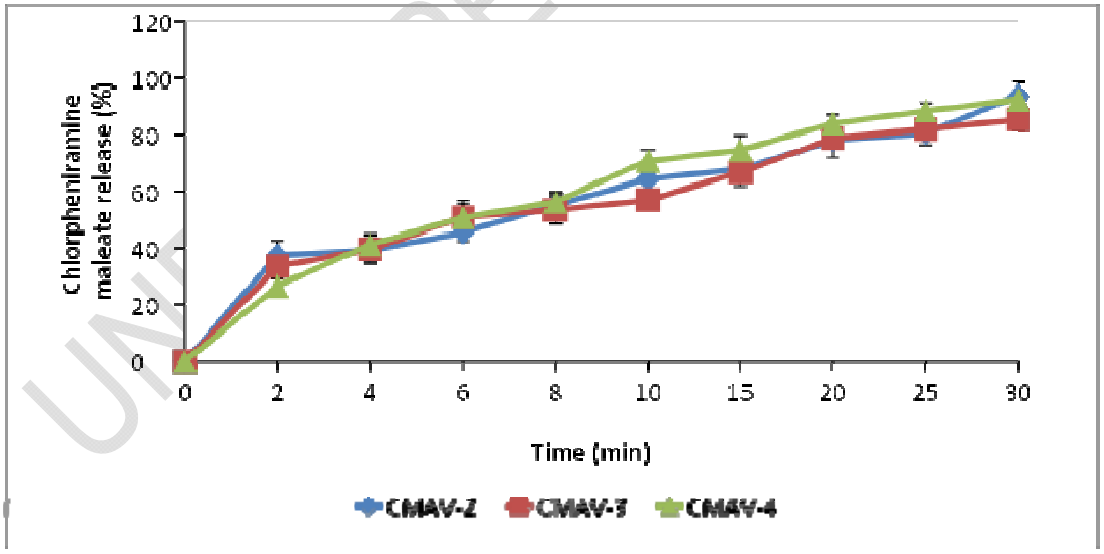

Fig. 7: Percentage of chlorpheniramine release from CMAV-2, CMAV-3 and CMAV-4 tablets

3.7 Stability studies result from chlorpheniramine maleate tablets.

Table 4 shows the results obtained from the assay of chlorpheniramine maleate tablets after a six month storage period under ambient conditions. The assay results indicate slight drug content reductions that were not significant (P = .068) in the content of active ingredient with reference to the assay results obtained at the time of compression. Values obtained ranged from 97.50 – 99.46 %. These values fell within the acceptable BP or USP compendial requirements [15,23]. The MCCs used in the formulations can be assessed as compatible with the CM since there was no appreciable degradation in the content of the API as a result of factors such as thermal degradation due to variations in temperature, oxidation due to air, hydrolysis due to moisture effects and photolysis due to degradation by light.

Table 4: Assay of chlorpheniramine maleate tablets

S/N	Batch	Initial per cent (%) concentration at the time of formulation.	Percent (%) concentration after 6 months
1	CMCF -2	99.92 ± 0.80	98.21 ± 0.35
2	CMCF -3	99.47 ± 0.8	99.14 ± 0.62
3	CMCF -4	99.99 ± 0.02	99.34 ± 0.03
4	CMCL -2	99.80 ± 0.28	98.61 ± 0.05
5	CMCL -3	100.06 ± 0.12	99.13 ± 0.74
6	CMCL -4	100.01 ± 0.19	99.17 ± 0.15
7	CMAV -2	100.24 ± 1.08	98.18 ± 0.29
8	CMAV -3	99.75 ± 0.65	99.08 ± 0.05
9	CMAV -4	100.11 ± 0.13	99.17 ± 0.21

4.0 Conclusion

The MCCs obtained from CN (*MCCF-Cocos* and *MCCL-Cocos*) showed good flow and compressibility behaviour and the CM tablets obtained from the blend of powders of either *MCCF-Cocos* and CM or *MCCL-Cocos* and CM showed minimal variation in tablet weights. The mechanical properties of the CMCF tablets were less than the CMCL tablets. This was evidenced in the lower crushing strength data and higher friability values of the tablets at similar concentrations. The crushing strength decreased as the quantity or amount of CM contained by the tablets increased while the friability increased as the amount of the CM contained by the individual batches of the tablets increased. The control batches that did not contain CM were significantly (P = .002) harder than the batches that contained CM. The tablets containing CM disintegrated faster than the control batches. All the tablets disintegrated within 15 min which is the BP upper limit of disintegration time for compressed uncoated tablets. Comparatively, CMAV tablets were mechanically stronger and possessed a lower friability than the CMCF and CMCL tablets. The dissolution behaviour of the CMCF,

CMCL and CMAV tablets also met with the USP specification for dissolution of CM from uncoated tablets as more than 80 % CM was released within 30 min. In terms of dilution potential, the best mechanical characteristics were observed at ≤ 30 % w/w of CM in all the MCCs that were investigated. The assay results show that neither the type of MCC or amount of it used caused any appreciable degradation of CM on storage at ambient conditions after six months. Thus, *MCCF-Cocos* and *MCCL-Cocos* served as good directly compressible excipients in the formulation of CM tablets. The CM tablets had good mechanical and *in vitro* release properties.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

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