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Evaluation of modified *Cenchrus americanus* starch as disintegrant in formulation of chlorpheniramine maleate tablets

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Abstract

The aim of this research was to investigate the disintegrant properties of modified *Cenchrus americanus* starch (MCS) in chlorpheniramine maleate tablets formulation. The matured seeds of *C. americanus* were steeped in 4 L of 0.25 % w/v sodium hydroxide at 5 °C for 24h, washed, soaked in distilled water (30 ± 2 °C) for 24 h, and wet milled. The slurry was washed with distilled water through a 200 mesh screen, and the filtrate left undisturbed for 18 h. The top layer sediment was scrapped off, and the starch re-suspended with water. Further washing and sedimentation was done until the top layer of the starch became white. The starch was dried at 40 °C, defatted using Petroleum-Ether, air dried, sized (125µm) and characterized using standard methods. The MCS was used at 5, 10 and 15 % w/w as disintegrant in the formulation of chlorpheniramine maleate granules using the wet granulation method. Primogel at similar concentrations was used as comparing standard. Characterization of the granules for densities and flowability were done. Chlorpheniramine maleate tablets compressed from these granules were evaluated for uniformity of weight, hardness, disintegration time, assay and dissolution. Results showed poor flow properties for the MCS powder while the chlorpheniramine granules exhibited good flow. The tablets showed minimal variation in weight, good hardness (6.06±0.10 - 8.07±1.31 kgF), disintegration time (< 7 min), friability (< 1 %), and dissolution of more than 80 % within 30 min. The MCS compared favourably with primogel as disintegrant in chlorpheniramine tablets formulation and met with British Pharmacopoeia set limits.

Keywords: *Cenchrus americanus*; Disintegrant; Starch; Chlorpheniramine maleate; Tablets

1. Introduction

Orally ingested tablets and capsules have for several decades remained the most popular dosage form for the delivery of drugs or active pharmaceutical ingredient [1, 2]. Also, amongst the aforementioned group of pharmaceutical products, disintegrating tablets constitute the majority [3]. Disintegration is a process through which a solid compact of powders (tablets) break up into smaller fragments which permits the availability of the API within the disintegration media which subsequently aids dissolution [4, 5]. By the careful choice of excipients (chemical properties) and manipulation of processing or formulation steps, tablets can be designed to release their drug content or API as soon as they are orally administered (immediate-release tablets) or take some time after oral ingestion to release their API (modified-release tablets). Whichever method that is employed, the ultimate goal is to achieve a good or enhanced therapeutic efficacy, patient compliance and to reduce the toxicity that could arise from the use of the API [6-8]. Disintegrants may be described as one of the excipients (non-active pharmaceutical agents) which are included in tablet

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[9] formulations to facilitate the break-up of the tablet into smaller fragments in an aqueous environment, which would result to an increased surface area thus promoting a more rapid release of the drug substance or API contained in the tablet for dissolution and absorption [10]. Disintegration takes place after oral ingestion of tablets when the physiological fluid penetrates into the tablet/compact core which will lead to disruption of the particle-particle bonds within the tablet which is responsible for the mechanical strength as well as the structural integrity of the dosage form. The outcome of endeavors by scientists/researchers in excipient development in recent times has resulted in the discovery of many new disintegrants which are capable of enhancing disintegration irrespective of their being used in small quantities in tablet formulations [8,11,12]. Disintegrants are commercially available in either the natural or synthetic forms. The popular and commercially available natural polymers that serve as disintegrants include the starches and gellan gum while the synthetic ones include polyvinylpyrrolidone, modified starches and cellulose, primogel, crosspovidone, etc. [13, 14].

Starch, one of the components of carbohydrates occurs in nature abundantly as a biomass material that is synthesized and stored in different parts of most green plants that contain chlorophyll such as the seeds, stem, tubers, roots and sometimes leaves. It is usually synthesized through the process of photosynthesis. The level of the distribution and storage of starch in a plant is primarily dependent on the type of plant and which part of the plant where it is synthesized. In the green leaves, starch is formed in the chloroplasts while in fruits and tubers, it is formed in the amyloplasts of seeds, fruits and tubers [10]. Irrespective of its site of formation and storage, it serves as a source of food and nourishment to many animals and man who intrinsically cannot synthesize starch because they lack chlorophyll. The plant parts where starch can be found in abundance include roots of cassava and potato, the grains of cereal crops such as wheat, corn or maize, soybean, millet, rice and in tubers of yam, cocoyam, etc.

Starch when extracted or isolated from the plant is used either in the natural or native form in which it was extracted or as a modified derivative. Starch is said to be native when it is in its natural or botanical state while it is designated as modified when some of its physicochemical properties have been changed or altered by deliberate manipulation to cause the acquisition of some new properties aimed to meet some desired specifications. This is because native starch is not suitable for so many of the industrial processes or applications chiefly because it does not easily dissolve in a solvent as well as its inability to retain its properties under rugged industrial conditions [15, 16]. Some desirable properties of the modified starches include improved flowability, disintegration time, direct compressibility, and gelation in both cold and hot water.

Besides the use of starch as food, it is also employed in the textile industry as stiffening agent in fabrics, while the food and cosmetic industry use it as a thickener. In the paint industry it has played the role of filler and thickener and has also been widely applied in the pharmaceutical industry as filler, diluent, binder, disintegrant, glidant, absorbent, suspending agent, gelling agent and thickener [17-20].

Pearl millet (*Cenchrus americanus* Synonym *Pennisetum glaucum*) is the most widely grown type of millet. It has been grown in Africa and the South Asia since prehistoric times. Millet is important because of its uniquely high content of nutrients, including impressive starch levels, vitamin B, calcium, iron, potassium, zinc, magnesium, and fats. It also has significant levels of protein and dietary fiber [17, 21]. Pearl millet is widely grown in the northeastern part of Nigeria (especially in Borno and Yobe States). It is a major source of food to the local villagers of that region. The crop grows easily in that region due to its ability to withstand harsh weather conditions like drought and flood [22].

Chlorpheniramine maleate is a potent anti-histamines that has the capacity to 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 [23, 24]. When histamines are activated in the body, there is vasodilation and increased capillary permeability, flare and itching reactions in the skin and sometimes contraction of smooth muscles in the bronchi and gastro intestinal tract (GIT). Thus antihistamines such as chlorpheniramine maleate plays an important role in the mitigation of urticarial rashes and nasal allergy [24, 25]. Orally administered chlorpheniramine maleate has a high rate of metabolism within the gastro intestinal (GI) mucosa and the liver which results in about 25-60 % of it being available for systemic circulation. In terms of adverse effects, commonly experienced are central nervous system (CNS) depression (lethargy, somnolence) and GI effects (diarrhea, vomiting, and anorexia) [26].

2. Material and methods

2.1. Materials

Hydrochloric acid, Sodium hydroxide pellets, Petroleum ether, n-hexane (JHD), sodium chloride, ethanol, acetone, hydrochloric acid, primogel, millet seeds and distilled water.

2.2. Methods

2.2.1. Procurement of sample

A quantity of 1.5 kg of matured millet seeds were bought from the Elele market, Elele, Rivers State in sufficient quantities.

2.2.2. Identification of sample

The millet seeds were submitted to the Department of Pharmacognosy, Madonna University, Elele where identification and authentication was done.

2.2.3. Processing of sample

A quantity of 1.50 kg of dry matured Pearl millet (*Cenchrus americanus*) seeds were sorted, washed, steeped in 4 L of 0.25 % w/v sodium hydroxide at 5 ^{o}C (that is kept in a refrigerator at 5 °C) for 24 h. It was then washed, steeped and soaked in distilled water at room temperature (30 ± 2 °C) for 1 h, after which the seeds were milled with an equal volume of water in a blender (Kenwood, China) until a fine slurry was obtained. The slurry was filtered through a 200 mesh sized sieve, the residue retained on the screen was properly rinsed with distilled water, and the filtrate allowed to stand for 18 h. The brownish layer that was formed on the top of the sedimented starch was scrapped off with a spatula. Excess water was added to re-suspend the starch sample. Further washing and sedimentation of the filtrate was done until the top layer of the starch became white. The starch extract was dried for 24 h at 40 ^{o}C after which it underwent the process of defatting using Petroleum Ether as the defatting solvent [27]. The starch was air dried and stored away in a desiccator for further usage.

2.3. Characterization

The MCS was evaluated using the following parameters: organoleptic properties, pH, ash content, densities, flow properties and moisture studies.

2.3.1. Organoleptic properties determination

The millet starch was evaluated for some of its organoleptic properties such as texture, color, taste and odor.

2.3.2. pH determination

A 2 g quantity of MCS powder was dispersed in 100 ml of distilled water to form a 2 % w/v dispersion and its pH determined using a pH meter (Hannah, USA). Three replicate determinations were done.

2.3.3. Solubility determination

The solubility of MCS was investigated by dispersing 2 g of the starch in 100 ml of water and some organic solvents such as ethanol, acetone and dilute hydrochloric acid. Its solubility in the different test media was visually observed [10, 28].

2.3.4. Ash value determination

The total ash content of MCS was determined. This was done by the measurement of the residue left after the independent combustion of 10 g of the millet starch in a furnace at 550 °C until no organic matter was remaining [29].

2.3.5. Hydration capacity determination

The hydration capacity of MCS powder was determined using the method developed by Kornblum and Stoopaks [30] with slight modification. A quantity of 1 g of the sample was put in a 15 ml plastic centrifuge tube and 10 ml of distilled water added to it. Each tube was shaken intermittently over a 2 h period and left to stand for 30 min. Centrifugation at 1000 revolutions per minute (rpm) was done for 10 min using a centrifuge model TX 150 (ThermoFisher Scientific, UK). The supernatant layer of the dispersion was carefully decanted and the wet sediment weighed. The hydration capacity was calculated using equation 1:

$$\text{Hydration capacity (H.C.)} = \frac{x}{y} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ 1$$

Where
x = weight of wet sample/ powder sediment and
y = weight of dry sample / powder.

2.3.6. Swelling index determination

The swelling capacity of the modified millet starch powder was determined using the method of Bowen and Vadino [31] with slight modification. A 3 g quantity of the starch sample was placed in a 100 ml graduated glass measuring cylinder and tapped to obtain the tapped volume, V_t. A dispersion of the powdered sample was made in 85 ml of water and this was shaken thoroughly. The volume was made up to 100 ml with water. The mixture was allowed to stand undisturbed for 24 h on a flat surface and the volume of the sediment formed, V_v noted. Triplicate determinations were done and the swelling capacity calculated as a percentage using Equation 2 [31].

$$\text{Swelling capacity (S.C.)} = \frac{Vv - Vt}{Vt} \text{ x } 100 \quad \ldots\ldots\ldots\ldots 2$$

2.3.7. Moisture sorption/hysteresis determination

A quantity of 1 g each of the millet was placed in separate 5 mm diameter porcelain dishes which were placed in desiccators of relative humidity of 94, 84, 75 and 52 % respectively at room temperature of 29 ± 1˚C. The weight gained over a period of five (5) days was calculated for using Equation 3. Triplicate determinations were done [32].

$$\text{Moisture sorbed (MS)} = \frac{W2 - W1}{W1} \text{ x } 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots 3$$

Where
W_1 = weight before exposure and
W_2 = weight after exposure to moisture.

2.3.8. Bulk and tapped density determination

A 15 g quantity of the millet powder was independently poured freely under gravity into a 50 ml clean, dry, graduated measuring cylinder and the volume occupied by the starch noted as the bulk volume (V_b). The bulk density, D_b was obtained from Equation 4 [33].

$$D_b = \frac{M}{Vb} \quad \ldots\ldots\ldots\ldots\ldots\ldots 4$$

Where M = mass of material or powder

The measuring cylinder containing the millet starch was tapped on a flat wooden platform by dropping the cylinder from a height of about 2 – 3 cm until there was no further reduction in the volume of the starch. The tapped density, D_t was calculated using Equation 5

$$D_t = \frac{M}{Vt} \quad \ldots\ldots\ldots\ldots\ldots 5$$

Where
M = mass of the powder or sample,
V_t = tapped volume and
D_t = tapped density

2.3.9. Particle density determination

The liquid displacement method was employed in the determination of the particle density of the starch powder. A 25 ml volume pycnometer was weighed empty (W), and later filled with n-hexane. It was covered with the lid and the excess fluid that spilled was wiped off the pycnometer. This was weighed and its weight denoted as W1. The difference between the weights of the empty pycnometer and when filled with n-hexane was noted as W2. The pycnometer was emptied and 1 g of the powdered sample (W3) was weighed into it, and it was refilled with n-hexane, stoppered, wiped clean of excess fluid and reweighed (W4). Triplicate determinations were done. The particle density (Pd) was calculated from Equation 6 [28, 34]:

$$\text{Pd} = \frac{W2\ x\ W3}{V(W3 - W4 + W2 + W)} \quad \ldots\ldots\ldots\ldots 6$$

2.3.10. Hausner's quotient (ratio) and Carr's index

The Hausner's quotient and Carr's index for the millet powder sample were calculated from Equations 7 and 8 [33].

$$\text{Hausner's quotient (H.Q.)} = \frac{Dt}{Db} \ldots\ldots 7$$

$$\text{Carr's Index (C.I.)} = 1\text{-} \left(\frac{Db}{Dt}\right) \text{x } 100 \ldots\ldots\ldots\ldots 8$$

Where D_b is the bulk density and D_t is the tapped density.

2.3.11. Flow rate and angle of repose determination

The flow rate of the powder was determined by pouring 15 g of the starch powder into a funnel clamped unto a flat surface with the orifice set at 3 cm above the table surface. The orifice was stoppered with a metric rule to prevent a pre-mature discharge of the powders from the funnel. A timer was switched on as the ruler was removed and the time taken for the starch powder to discharge completely without interruption in flow was noted [35-37]. Triplicate determinations were done and the flow rate calculated using Equation 9:

$$\text{F.R.} = \frac{M}{F.T.} \ldots\ldots\ldots\ldots\ldots 9.$$

Where F.T. = flow rate, F.T. = flow time and M = mass of powder used.

The angle of repose was measured using the funnel method. A sufficient quantity of the millet powder was poured into a clamped plastic funnel that has the orifice fixed at 2 cm above a flat surface until the powder heap formed prevented further discharge of the powder from the funnel. The diameter of the powder heap formed was measured and recorded. The flow rate and tangent of the powder heap was calculated as [35-37]:

$$\text{Angle of repose } (\theta) = \tan^{-1} \frac{2h}{D} \ldots\ldots\ldots 10$$

Where h is the height of the powder heap and D is the diameter of the heap.

2.3.12. Porosity determination

The porosity, ϵ of the MCS powder was obtained from the Equation 11

$$\epsilon = 1 - \frac{Db}{Pd} \text{ x } 100 \ldots\ldots\ldots 11$$

Where ϵ = powder porosity, D_b = bulk density and P_d = particle density.

2.3.13. Moisture content determination

The moisture content of the millet starch powder was determined by placing 3 g of the powder in a tarred white porcelain crucible kept in a hot air oven (Mermmet®, England) and drying done at 105 ˚C until a constant weight was obtained. The percentage moisture content was determined using Equation 12 [38].

$$\text{Moisture content (M.C.)} = \frac{Wi - Wf}{Wi} \text{ x } 100 \ldots\ldots\ldots 12$$

Where W_i is the initial weight of powder before drying and W_f is the final weight of powder after drying.

2.4. Preparation of chlorpheniramine maleate granules

Six batches of metronidazole granules were prepared based on the quantities of the ingredients shown in Table 1. Each of the intra granular ingredients required for each batch was weighed into a porcelain mortar and triturated using the doubling up technique and wet granulation method to form a damp mass. Granules obtained by passing the damp mass through a 2 mm stainless steel sieve were dried in an oven at 60 ˚C until sufficiently dried. Further screening was done using a 1 mm sieve and the chlorpheniramine maleate granules were stored for further use.

Table 1 Formula for chlorpheniramine maleate tablets

Formulation/ingredient	MS1	MS2	MS3	PG1	PG2	PG3
Chlorpheniramine maleate (mg)	4.00	4.00	4.00	4.00	4.00	4.00
Millet starch (mg)	15.00	30.00	45.00	0.00	0.00	0.00
Primogel (mg)	0.00	0.00	0.00	15.00	30.00	45.00
Gelatin (mg)	15.00	15.00	15.00	15.00	15.00	15.00
Lactose (mg)	260.00	245.00	230.00	260.00	245.00	230.00
Magnesium stearate (mg)	3.00	3.00	3.00	3.00	3.00	3.00
Talc (mg)	3.00	3.00	3.00	3.00	3.00	3.00
Total tablet weight (mg)	300.00	300.00	300.00	300.00	300.00	300.00

Key: MS1, MS2 and MS3 contains millet starch as disintegrant; PG1, PG2 and PG3 contains primogel as disintegrant

2.5. Evaluation of granules

The chlorpheniramine maleate granules were subjected to these different evaluations:

2.5.1. Bulk density determination of the granules

A 20 g quantity of granules from each batch of the chlorpheniramine maleate formulations were independently poured freely under gravity into a 100 ml clean, dry, graduated measuring cylinder and the volume occupied by the granules noted as the bulk volume (V_b). Triplicate determinations were made and the bulk density, D_b was obtained from Equation 4 [36].

$$D_b = \frac{M}{Vb} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 4$$

Where M = mass of material or powder

2.5.2. Tapped density determination of the granules

The measuring cylinders containing the chlorpheniramine maleate granules were tapped on a flat wooden platform by dropping the cylinder from a height of about 2 – 4 cm until there was no further reduction in the volume of the granules. The tapped density, D_t was calculated using equation 5

$$D_t = \frac{M}{Vt} \quad \ldots\ldots\ldots\ldots\ldots\ldots 5$$

Where M = mass of the powder or sample, V_t = tapped volume and D_t = tapped density

2.5.3. Granule density determination

The granule density determination of the chlorpheniramine maleate granules was done by the liquid displacement method. An empty 25 ml volume pycnometer was weighed and its weight was noted as W. It was filled with n-hexane and covered with its lid. The excess fluid that spilled on the body of the pycnometer was wiped off, and its weight denoted as W1. The difference between the weights of the empty pycnometer and when filled with n-hexane was noted as W2. One (1 g) of the granule (W3) was weighed into it, and it was stoppered, wiped clean of excess fluid and reweighed (W4). The different granule batches were subjected to this procedure. Replicate determinations were done. The granule density (Pd) was calculated using Equation 6 [34]:

$$Pd = \frac{W2\ x\ W3}{V(W3-W4+W2+W)} \quad \ldots\ldots\ldots\ldots\ldots\ldots 6$$

2.5.4. Hausner's quotient (ratio) and Carr's index determination

The Hausner's quotient and Carr's index of the granules were derived from the data obtained for the bulk and tapped density of the individual granules. These data were fitted into Equations 7 and 8 respectively to obtain the Hausner's quotient and Carr's index or percentage compressibility of the individual granules [36, 37].

$$\text{Hausner's quotient (H.Q.)} = \frac{Dt}{Db} \ldots\ldots\ldots\ldots 7$$

$$\text{Carr's Index (C.I.)} = 1\text{-} \left(\frac{Db}{Dt}\right) \text{x } 100 \ldots\ldots\ldots\ldots 8$$

2.5.5. Flow rate determination

The flow rate of the chlorpheniramine maleate granules were determined using 20 g of each batch of granule. The granule was weighed out and poured into a plastic funnel that was clamped unto a flat surface with the orifice set at 4 cm above the table surface. The orifice was stoppered with a metric rule to prevent a pre-mature discharge of the granules from the funnel. A timer was switched on at the time the ruler was removed from the orifice and the time taken for the chlorpheniramine maleate granules to discharge completely without interruption in flow was noted [36-38]. Three replicate determinations were conducted for each granule sample and the flow rate calculated using Equation 9:

$$\text{F.R.} = \frac{M}{F.T.} \ldots\ldots\ldots\ldots\ldots\ldots 9.$$

Where F.T. = flow rate, F.T. = flow time and M = mass of granule used.

2.5.6. Angle of repose determination of granules

The angle of repose was measured using the fixed funnel method. Enough quantities of each of the chlorpheniramine granules were individually poured into a clamped plastic funnel that has its orifice fixed at 2 cm above a flat surface until the granule heap formed prevented further discharge of the granules from the funnel unto the platform. The diameter of the heap of granule formed was measured and recorded. The flow rate and tangent of the granule heap were calculated using Equation 10.

$$\text{Angle of repose } (\theta) = \tan^{-1}\frac{2h}{D} \ldots\ldots\ldots 10$$

Where h is the height of the granule heap and D is the diameter of the heap.

2.5.7. Porosity determination of granules

The porosity, ϵ of each of the chlorpheniramine granules was obtained from equation 11

$$\epsilon = 1 - \frac{Db}{Pd} \text{x } 100 \ldots\ldots\ldots 11$$

Where ϵ = powder porosity, D_b = bulk density and P_d = particle density.

2.5.8. Moisture content of granules

The moisture content of the chlorpheniramine maleate granules were determined by weighing a quantity of 3 g of each granule independently into a tarred white porcelain crucible. This was placed in an oven (Mermmet®, England) and drying done at 105˚C until a constant weight was obtained for each batch of granules. The percentage moisture content was determined using Equation 12 [38]

$$\text{Moisture content (M.C.)} = \frac{Wi - Wf}{Wi} \text{x } 100 \ldots\ldots\ldots 12$$

Where W_i is the initial weight of powder before drying and W_f is the final weight of powder after drying.

2.6. Tableting

Talc and magnesium stearate were added to the chlorpheniramine maleate granules (Table 1) and each batch of the granules mixed in a powder bottle for about 2 min. The respective granules were compressed at a target tablet weight of 300 mg using an 8 cm set of concave shaped punches and dies fitted into a model NP-1 (Erweka, Germany) automated single punch tablet press. Compressions were done for all the batches at a constant pressure of 9.81 kN and dwell time of 20 sec.

2.7. Tablet properties

The chlorpheniramine maleate tablets were allowed a minimum of 24 h to recover from the stresses of compression before their evaluation. The parameters investigated were physical deformities/wholesomeness, uniformity of weight, hardness, disintegration, friability, thickness, content of active ingredient and dissolution profile.

2.7.1. Physical deformities or wholesomeness determination

A general physical inspection of the chlorpheniramine maleate tablets for oil or other stains, chipping of the edges or capping was done.

2.7.2. Weight uniformity determination

Twenty tablets were selected at random from each batch of the chlorpheniramine maleate tablets and each tablet was weighed singly and calculations were done for the mean, standard deviation and coefficient of variance. Acceptance or rejection was based on the British Pharmacopoeia tolerance limits for uncoated tablets weighing ≥ 250 mg [39].

2.7.3. Tablet hardness/crushing strength determination

A total of ten tablets were randomly selected for this test. The radial crushing strength of each of the ten tablets was determined using a Monsanto hardness tester. The mean and standard deviations of values obtained were recorded.

2.7.4. Tablet disintegration time determination

Six tablets randomly selected from each batch of the chlorpheniramine maleate tablets were used for the test. A model ZT-3 double basket disintegration tester (Erweka, Germany) was used for the test. Each of the tablets being investigated was put into the cylindrical hole of each of the six holes of a single basket of the disintegration tester. Each tablet was held in place with a glass disc and each beaker was filled with 500 ml of 0.1 N HCl heated up to 37 ± 1˚C. The bath temperature was also maintained at 37 ± 1˚C and the time taken for each tablet to completely break up and pass through the mesh was noted [39].

2.7.5. Friability determination

A model TAR 200 twin drum electronic friabilator (Erweka®, Germany) programmed to rotate at 25 rotations per minute (rpm) for 4 min was used for the test. Ten tablets randomly selected from each batch of the chlorpheniramine maleate tablets were dedusted, weighed collectively and put in one of the drums of the friabilator. At the end of the test, the tablets were collected and de-dusted again and any broken or chipped tablets were rejected. The tablets were reweighed and the friability or abrasion resistance (F) determined using equation 13.

$$F\ (\%) = \frac{Wo-W}{Wo} x\ \frac{100}{1} \quad \ldots\ldots\ldots\ldots\ldots\ 13$$

Where *Wo* is the initial weight of the tablets before the test and *W* is the final weight of the tablets after the test.

2.7.6. Thickness and diameter determination

Ten tablets were randomly selected from each of the batches of the chlorpheniramine maleate tablets and each of the tablets was measured for its thickness and diameter using a micrometer screw gauge. The mean and standard deviation of results for the thickness and diameter of the tablets were calculated.

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

A quantity of 100 mg of the pure chlorpheniramine maleate powder was weighed and dissolved in sufficient 0.1 N HCl in a 100 ml volumetric flask to obtain the stock solution. The stock solution was serially diluted to obtain chlorpheniramine maleate preparations that were 0.20 mg %, 0.40 mg %, 0.60 mg % and 0.80 mg % strength. Scanning of the 0.20 mg % solution was done in a model 6405 UV/Vis spectrophotometer (Jenway®, England) to obtain the maximum/peak absorbance (λ_{max}) of chlorpheniramine maleate at 265 nm [28,39].

2.7.8. Beer Lamberts plot of chlorpheniramine maleate

The serially diluted solutions of chlorpheniramine maleate containing 0.20 mg %, 0.40 mg %, 0.60 mg %, 0.80 mg % and 1.00 mg % were placed in a quartz cuvette and their absorbance's scanned using a 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.

2.7.9. Assay of chlorpheniramine maleate tablets

Twenty tablets were randomly selected from each batch of the chlorpheniramine maleate tablets and were weighed collectively, then pulverized in a porcelain mortar and an amount of powder equivalent to the weight of one tablet was taken and dispersed in 5 ml of distilled water in a 100 ml volumetric flask. The volume of the dispersion was made up to the 100 ml mark of the flask. It was filtered and the filtrate obtained from the dispersion was diluted and the absorbance was read at 265 nm in the spectrophotometer [39]. The absorbance's obtained for the tablets from the different batches were correlated with the Beers plot earlier established and their concentrations determined using equation (14):

$$y = mx + c \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 14.$$

where y represents absorbance, x represents concentration and m represents the slope and c the intercept.

2.7.10. 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 was heated up to a temperature of 37.0 ± 0.5˚C, and the paddle was set to rotate at a speed of 100 revolutions per min (rpm) [39]. 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 dissolution medium maintained at 37.0 ± 0.5˚C after each withdrawal. The absorbance readings of the filtrates obtained from the withdrawn samples were determined using the spectrophotometer at a wavelength of 265 nm. The absorbance results were converted to concentrations from the standard calibration curve previously determined for diazepam. This was done for all the batches of the chlorpheniramine maleate tablets.

3. Results and discussion

3.1. Bulk and tapped density

The results of the bulk and tapped densities are shown in Table 2. Generally, the bulk densities were lower than the tapped densities. This suggests that the granules of chlorpheniramine maleate formulations (MS1, MS2, MS3, PG1, PG2, and PG3) are compressible, would occupy a lesser volume in a container or packaging material when agitated and would be good for preparation of tablets.

3.2. Angle of repose

The angle of repose of the chlorpheniramine maleate granules are shown in Table 2. There was a gradual increment in the angle of repose as the concentration of the disintegrant used in the formulation increased. The angle of repose ranged from 27.04 ± 0.11 - 28.15± 0.13° for the granules containing modified millet starch and 29.05±0.10 - 30.02±0.01° for the granules containing primogel respectively. These angles of repose show good flow properties for the chlorpheniramine granules [39, 40]. This implies that the granules would enable good die filling and production of tablets with minimal variation in weight of the tablets.

3.3. Flow rate

The flow rate of the chlorpheniramine maleate granules show values that ranged from 9.41±1.47 - 11.01±0.24 g/s (Table 2). The flow rates obtained indicate granules that have good flow and would be suitable for use in high speed tableting machines as there would be good die filling by these granules and subsequently the production of tablets with minimal variation in tablet weight.

3.4. Hausner's quotient

Results of the Hausner's quotient evaluations of the granules are shown in Table 2. Granules having Hausner's quotient value of < 1.25 are regarded as flowable and since all the granules had values less than 1.25, they can be regarded to have passed the criteria of good flow implying that these granules would be good for preparation of tablets with good physical attributes [39, 40].

3.5. Carr's index

Carr's index is an index of powder/granule flowability and the results of this evaluation for chlorpheniramine granules are shown in Table 2. Values obtained ranged from 12.76±0.05 - 19.15±0.04 % and these values fall into the category of good flowing powders/granules [39, 40].

Table 2 Some micromeritic properties of chlorpheniramine maleate granules

Formulation /Parameter	MS1	MS2	MS3	PG1	PG2	PG3
Bulk density (g/ml)	0.41±0.01	0.43±0.03	0.42± 0.20	0.39±0.12	0.40±0.21	0.38±0.03
Tapped density (g/ml)	0.47±0.01	0.51±0.20	0.51±0.15	0.48±0.02	0.48±0.11	0.47±0.10
Angle of repose (°)	27.04±0.11	27.95±0.23	28.15±0.13	29.24±0.01	29.05±0.10	30.02±0.01
Flow rate (g/s)	10.18±0.26	10.53±0.13	11.01±0.24	9.41±1.47	10.62±0.24	9.97±0.22
Hausner's quotient	1.15±0.43	1.19±0.11	1.21±0.10	1.23±0.02	1.20±0.05	1.24±0.01
Carr's index (%)	12.76±0.16	15.68±0.19	12.76±0.05	18.75±0.02	16.67±0.03	19.15±0.04

3.6. Physical properties

3.6.1. Physical deformities

The physical inspection of the tablets showed that they were complete without any cracks, chips, stains or any form of deformities.

3.6.2. Uniformity of weight

Results of the uniformity of weight of the chlorpheniramine maleate tablets are shown in Table 3. There was minimal variation in the weights of the tablets as the coefficient of variance for each of the tablets is less than 5 %. The official compendia stipulates that uncoated tablets weighing greater than 250 mg meet the acceptance criteria as good tablets if they have a variance value of ≤ 5 % [39]. Therefore, the chlorpheniramine maleate tablets passed the test for uniformity of weight.

3.6.3. Hardness

The chlorpheniramine maleate tablets hardness ranged from 6.06 ± 0.10 - 8.07 ± 1.31 kgF (Table 3). Conventionally, uncoated tablets are expected to have hardness of ≥ 4 kgF for them to be considered physically fit for handling, packaging, transportation or shipment [39, 40]. Thus, all the batches of chlorpheniramine tablets passed the hardness test.

3.6.4. Disintegration time

The disintegration time gotten for the disintegration time evaluation of the tablets is shown in Table 3. Generally, the time taken for the tablet to disintegrate reduced as the concentration or quantity of the disintegrant used in the formulation increased. All the chlorpheniramine maleate tablets disintegrated within 7 min and therefore complied with the British Pharmacopoeia upper limit of 15 min for uncoated tablets [39]. However, the disintegration times of the tablets containing primogel were lower than those containing the modified millet starch which implies that primogel is a superior disintegrant to the modified millet starch. This is an important property of a tablet excipient more so when the tablet is formulated to break up in a liquid media when hydrated or stomach when ingested in order to make its API available for dissolution and absorption.

3.6.5. Friability

The friability of the different formulations of chlorpheniramine maleate tablets are shown in Table 3. There was a slight increase in the friability of the tablets as the quantity of disintegrant used in the formulation increased. However, all the tablet formulations complied with the compendial friability requirements of ≤ 1 % [39, 40] implying that they would be resistant to the stresses of abrasion which the tablets may be exposed to in the cause of handling, transportation and storage.

3.6.6. Thickness/Height

The thickness/height of the tablets is shown in Table 3. There were minimal variations in the results obtained. This can be attributed to the good flow properties of the granules a uniform tableting pressure which enabled uniform die filling and subsequent uniform tablet heights.

Table 3 Some physical properties of chlorpheniramine maleate tablets

Batch/Parameter	MS1	MS2	MS3	PG1	PG2	PG3
Uniformity of weight* (mg)	301.21± 0.25	298.16± 0.11	302.26± 0.32	300.10± 0.25	299.51± 0.02	297.24± 0.14
Hardness (kg/F)	6.22± 0.12	6.19± 013	6.06± 0.10	6.42 ± 1.23	6.61 ± 0.25	8.07 ± 1.31
Disintegration time (min)	6.81± 0.23	5.76± 0.27	4.25± 0.11	3.61 ± 0.17	1.47 ± 0.24	0.84 ± 0.04
Friability (%)	0.34± 0.01	0.41± 0.01	0.48± 0.05	0.27 ± 0.03	0.31 ± 0.02	0.35 ± 0.01
Height/Thickness (mm)	3.16± 0.02	3.11± 0.04	3.17± 0.13	3.17 ± 0.45	3.22 ± 0.12	3.18 ± 0.21

3.6.7. Assay of chlorpheniramine maleate tablets

The result of the assay/ content of active ingredient (chlorpheniramine maleate is shown in Fig. 1. All the batches met with their formulation target content or label claim. The British Pharmacopoeia has a limit range of acceptance of 95-105 % for chlorpheniramine maleate tablet formulations [39]. The chlorpheniramine maleate tablets passed the test.

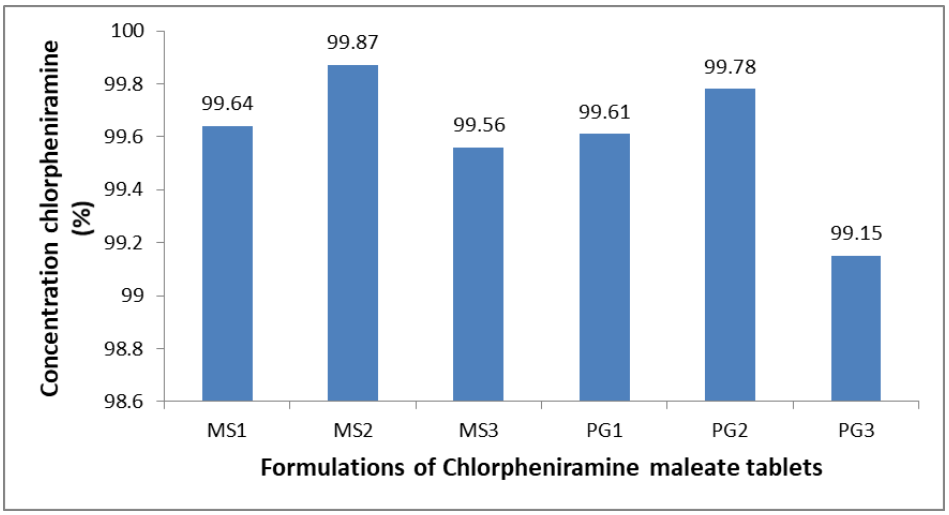

Figure 1 Assay of chlorpheniramine maleate tablets

3.6.8. Dissolution of chlorpheniramine maleate tablets

The profile of chlorpheniramine maleate release from the tablets is shown in Fig. 2. All the formulations exhibited an initial fast release, which was followed by a gradual continuous release of the API up to 30 min. All the formulations irrespective of the disintegrant it contained dissolved/released more than 80 % of its content within 30 min. and therefore met with the set limits of dissolution for chlorpheniramine maleate stated in the BP [39]. The formulations containing a higher quantity of the disintegrant showed a higher release. Comparatively, the formulations containing PG1, PG2, PG3 and PG4 had higher amounts of the drug released than those containing modified millet starch.

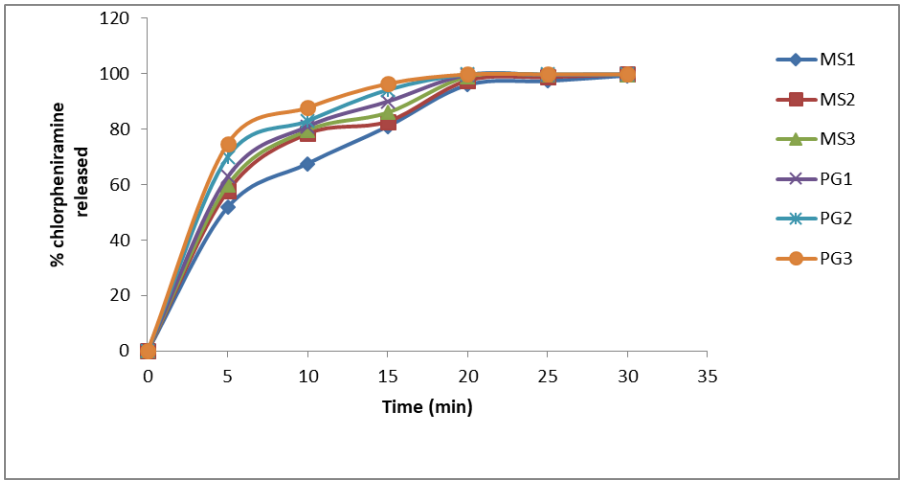

Figure 2 Drug release profile of chlorpheniramine maleate tablets

4. Conclusion

Starch was successfully extracted from the matured seeds of millet. The millet seed starch was modified to enhance its properties and was found to possess all the characteristics associated with starch based on the parameters of assessment. The chlorpheniramine granules formulated with it had good flow properties as assessed by the flow rate, angle of repose, Hausner's quotient and Carr's compressibility index. The chlorpheniramine tablets compressed from these granules had good physical attributes, hardness, friability and disintegration time. The dissolution profile showed that the API was well released from the tablets. The properties of the chlorpheniramine maleate tablets containing the modified millet starch compared well with the chlorpheniramine maleate tablets containing the commercial brand of sodium starch glycollate (primogel). Most of the assessment parameters met with the British Pharmacopoeia set standards. Therefore, modified *Cenchrus americanus* starch served as a good disintegrant in the formulation of chlorpheniramine maleate tablets and its performance compared well with primogel.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest. The research was fully funded by the authors

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