FORMULATION DEVELOPMENT OF *MORINGA OLEIFERA* FILM COATED TABLETS

BY

MUSIBA BALIRUNO DENIS, B.PHARM

U53/81288/2012

Department of Pharmaceutics and Pharmacy Practice,

School of Pharmacy

University of Nairobi

A dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy in Industrial Pharmacy of the University of Nairobi

DECLARATION

This dissertation is my original work and has not been presented for a degree award in any university or published anywhere else.

Principal investigator

Musiba Baliruno Denis, B.PHARM

U53/81288/2012

Department of Pharmaceutics and Pharmacy Practice

University of Nairobi

Signed……Date…….

Supervisors

This dissertation has been submitted for examination with our approval as university supervisors

1. Prof. Kimani A. M Kuria, PhD
   Department of Pharmaceutics and Pharmacy Practice
   University of Nairobi

   Signature……Date……

2. Dr. Lucy J. Tirop, PhD
   Department of Pharmaceutics and Pharmacy Practice
   University of Nairobi
   Signature…….Date……

DECLARATION OF ORIGINALITY

Name of student	Musiba Baliruno Denis
Registration Number	U53/81288/2012
College	Health Sciences
School	Pharmacy
Department	Pharmaceutics and Pharmacy Practice
Course Name	Master of Pharmacy in Industrial Pharmacy
Title of work	Formulation development of *Moringa oleifera* film coated tablets

DECLARATION

1. I understand what plagiarism is and I am aware of the University's policy in this regard.
2. I declare that this dissertation is my original work and has not been submitted anywhere for examination, award of a degree or publication. Where other people's work has been used, it has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.
3. I have not used the services of any professional agencies to produce this work.
4. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her work.
5. I understand that any false claim in respect of this work shall result in disciplinary action, in accordance with University Plagiarism Policy.

Signature ——————————————**Date** ——————————————

Contents

ACKNOWLEDGEMENT

My most sincere thanks go to my project supervisors, Prof. K.A.M Kuria and Dr. L.J Tirop for their input, guidance and encouragement throughout all the phases of this study.

I am also grateful to my course coordinator, Dr. Nasser Nyamweya for his invaluable advice, insights and all help from the formative stages of this study.

My sincere thanks also go to all of the following people for their invaluable contributions and support without which this work would not have become a success;

- Laboratory and Allied Ltd who provided me with corn starch, gelatin, PVP, lactose, SLS, Talc, and Magnesium stearate.
- Laboratory technologist especially Richard, Emmanuel, Joseph, Raphael, Jonathan and Isaiah (MKU) for supporting me while I was in the different laboratories.
- My classmates - Stephen, Silas, and Veronica – it was great pleasure learning together.
- My dear wife, Stella, my son Nathan and my daughter Abigail for their continued sacrifice and endurance of an absentee husband and father.
- My mother, Peruth for her continued prayers that ascend to God daily for all her children.
- My friends especially Jerome, Daniel and Deogracious for the moral support.
- The Almighty God for the privilege of attaining this level of Education that He has given me
- My sponsors, Intrahealth Uganda and Gulu University for all the financial support and facilitation.

DEDICATION

This work is dedicated to my lovely wife, Stella for enduring my absence and for being a good mother to our two little children, Nathan and Abigail.

ABBREVIATIONS AND ACRONYMS

BP	British Pharmacopoeia
CFU	Colony Forming Units
CI	Compressibility Index
Dav	Average particle diameter
Db	Bulk Density
DMSO	Dimethylsulfoxide
DT	Disintegration Time
FDA	Food and Drug Administration
HR	Hausner ratio
MKU	Mount Kenya University
MOP	*Moringa oleifera* powder
N	Newton
Ɵ	Angle of repose
PVP	Polyvinylpyrrolidone
QC	Quality Control
RD	Relative Density
Sg	Specific gravity
V_O	Bulk Volume
ε	Porosity of powder
ρ	Particle Density

DEFINITION OF TERMS

Dosage formulation: Is the process in which different chemical substances, including the active drug are combined to produce a final medicinal product.

Pre-formulation: Is the characterization of a drug's physical, chemical and mechanical properties in order to choose what other ingredients (excipients) should be used in the preparation

Tablets: Are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behavior of the preparation in the digestive tract, colouring matter authorized by the competent authority and flavouring substances

Compressibility: Is the ability of a powder to decrease in volume under pressure

Compactibility: Is the ability of a material to be compressed into a tablet of specified strength (i.e. radial tensile strength or deformation hardness).

Bulk Density: Is the ratio of the mass of untapped powder sample and its volume including the contribution of the interparticulate void volume.

Tapped Density: Is the ratio of the mass of tapped powder sample and its volume obtained after mechanically tapping a container containing the powder sample.

Relative Density: Is the ratio of the density of a substance to the density of a given reference material.

Porosity: Is the ratio of total pore volume to apparent volume of particle or powder.

Uniformity of weight: Is a pharmacopoeial test for different dosage forms including tablets where by 20 tablets are selected at random, weighed and the average weight calculated. Not more than 2 of the individual weights should deviate from the average weight by more than a specified percentage and none should deviate by more than twice of that specified percentage.

Tablet hardness test: Is a measure of resistance to crushing of a tablet that is to say, it is the minimum diametric compression force which fractures a tablet.

Friability: Is a measure of resistance to abrasion that is to say, it is the percentage weight loss resulting from chipping, abrasion and tablets under stress conditions.

Disintegration test: Is a test provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a specified liquid medium under given experimental conditions

LIST OF TABLES

LIST OF PLATES

LIST OF FIGURES

ABSTRACT

Introduction: *Moringa oleifera* is a small fast growing tree many of whose parts are consumed for both their nutritional and medicinal values worldwide. Different parts of the plant used in traditional medicine for the treatment of various diseases have been presented either as bulk powders, granules or manually filled capsules because there are no reports of formulation studies to enable the production of quality conventional solid dosage forms. This study was therefore intended to formulate film coated tablets of *Moringa oleifera* leaves powder.

Materials and Methods: *Moringa oleifera* leaf powder was obtained from Kate's organics, Nairobi, Kenya. Other excipients were obtained as a donation from Laboratory and Allied Ltd, Nairobi, Kenya. Four formulations (F1 – F4) in which the level of disintegrant and the choice and level of binder were varied were made. F1 contained 0.7 % gelatin and 7.3 % corn starch, F2 contained 3.6 % gelatin and 7.3 % corn starch, F3 contained 0.7 % PVP and 9.1 % corn starch and F4 contained 2.2 % PVP and 7.3 % corn starch (% w/w of the total tablet weight).

The equipment used included tablet compression machine (Erweka, electric type, Germany), Disintegration Tester machine (Erweka ZT3, GmbH Heusenstamm, Germany), Friability tester machine (Erweka, Heusenstamm, type TA3R, Germany) and a coating pan (Gryphon class E, No_150445R, England).

Results and Discussion: From preformulation studies, *Moringa oleifera* leaf powder had moisture loss on drying of 7.87 ± 2.915, granules of *Moringa oleifera* had Hausner's Ratio ranging from 1.16 (F3) to 1.18 (F4), Compressibility Index of 14.04 (F3) to 15.25 (F4) and angle of repose ranging from 37.0 ° (F1) to 37.7 ° (F4). Uncoated tablets of all formulations passed uniformity of weight test, hardness test and friability test. Only formulation F3 uncoated tablets passed disintegration test. Antimicrobial assay results of both *M. oleifera* leaf powder and the formulated tablets were comparable. Film coated tablets of only F3 formulation passed both uniformity of weight test and disintegration test. In conclusion, this study indicated that *M. oleifera* film coated tablets can be formulated with 0.7 % polyvinyl pyrolidine as binder and 9.1 % corn starch as disintegrant and further research to establish clinical data for treatment with Moringa leaf powder was recommended before scaling up of *M. oleifera* film coated tablets to commercial production can occur.

CHAPTER ONE: INTRODUCTION

1.1 Background to the study

Moringa oleifera is a rapidly growing perennial softwood tree which for centuries has been advocated for traditional medicinal & industrial uses. It is already a vital crop in India, Ethiopia, the Philippines and the Sudan. It is also being grown in West, East and South Africa, tropical Asia, Latin America, the Caribbean, Florida and the Pacific Islands. All its parts are edible and have been consumed by humans (Fahey, 2005).

M. oleifera leaves are rich in Beta-carotene, Vitamin C, Vitamin B, Calcium, Iron and essential amino acids (Delovee et al., 2009). Thus, the leaves are an outstanding source of nutrients suitable for utilization in many of the developing countries of the world to combat malnutrition (Freiberger et al., 1998; Fahey, 2005). A wide range of pharmacological properties such as anti-inflammatory, antitumor, antimicrobial, hypotensive, hypocholesterolemic and hypoglycemic have been reported for *M. oleifera* leaves in scientific literature (Fahey, 2005). Moringa leaf extracts also present attractive features that could be utilized topically. Ali et al., 2013 looked at *M. oleifera* leaf extracts formulated into a cream for topical application which was reported to prevent and treat oxidative stress mediated diseases and photo aging. However, it is not the intention of the present study to discuss topical dosage formulation of *M. oleifera.*

Also, in another study, a widely claimed use of *M. oleifera* leaves as an ethno medicine for the treatment of diabetes mellitus was scientifically validated (Jaiswal et al., 2009). Moringa seed kernels have been reported to have potential anti-asthmatic activity that may be due to its bronchodilator, mast cell stabilization, anti-inflammatory and anti-microbial properties (Mehta and Agrawal, 2008).

In Kenya and the East African region, *M. oleifera* leaves are used for the treatment of a variety of ailments including Tuberculosis (Otieno et al., 2011).

Recent developments show that herbal products are becoming more popular as compared to synthetic drugs and hence the obvious popularity of *M. oleifera* products (Okoye et al., 2013). Amongst these products, seed oil of *M. concanensis* was extracted and sun screen cream was

formulated using this oil (Kale et al., 2010). The formulation was evaluated and was found to be near the range of good sunscreen activity. Also, a blend of *M. oleifera* seed powder and ferrous sulphate heptahydrate crystals was formulated into a matrix to control coliform bacteria and odor in poultry manure. The formulation was found to suppress manure odors at both short and long term incubation periods in contrast to most commercial products (Manu et al., 2013). The root bark extracts of *M. oleifera* have also been reported to be effective in the treatment of renal calculi since they possess antiurolithiatic properties (Karadi et al., 2008).

The present study is aimed at formulating film coated *M. oleifera* leaf tablets.

1.2 Problem statement

The use of *M. oleifera* products has become more popular now than before for both its nutritional and medicinal purposes. However, the presentation of these products and their quality profiles remain a major concern. This study was therefore aimed at coming up with well characterized film coated tablets of *M. oleifera* leaf powder

1.3 Purpose of the study

To formulate *M. oleifera* leaf powder into an improved, well characterized oral dosage form.

1.4 Objectives

1.4.1 General objective

To formulate and evaluate film coated tablets of *M. oleifera* leaf powder.

1.4.2 Specific objectives

1. To granulate *M. oleifera* leaf powder.
2. To compress the prepared granules into tablets
3. To carry out film coating of the resultant tablets.
4. To evaluate the quality of *M. oleifera* film coated tablets.

1.5 Significance of the study

This study resulted in an improved, easy to administer and reproducible dosage form of *M. oleifera* leaf powder for oral administration. It also improved on the presentation of *M. oleifera* leaf powder as a dosage form for oral administration with enhanced organoleptic properties.

1.6 Anticipated Output

The anticipated output of this study was an improved solid dosage form of *M. oleifera* leaf powder i.e. film coated tablets.

1.7 Delimitations

Preformulation was limited to physical characterization of *M. oleifera* leaf powder and granules. This included determination of average particle diameter, moisture content, porosity, particle density, bulk density, tapped density, angle of repose and compressibility index.

1.8 Limitations

As much as polymorphism would have been very important for the characterization of *M. oleifera* powder, it was not done due to lack of availability of the appropriate equipment. Therefore, preformulation was only limited to determination of physical properties of the Moringa powder.

There are limited or no studies that have been done to determine the dosage of *M. oleifera* and therefore the determination of the dosage form strength was done arbitrarily.

CHAPTER TWO: LITERATURE REVIEW

Moringa oleifera is a small fast-growing tree and its origin has been traced to India. The plant is a deciduous tree and usually grows up to 10 – 12 m tall. Different parts of the plant are consumed as food in many cultures and their nutritional values have been reported in literature (Anwar et al., 2007; Fahey, 2005; Mishra et al., 2012). *M. oleifera* plant is shown in Plate 1 below.

Plate 1: *Moringa oleifera* plant (Wewan Md. Badruddoza, 2013)

The root, bark, pods and leaves of the tree are used in traditional medicine as treatment for various human ailments such as headaches, diarrhoea, worms, stomach ulcers, skin conditions, infections, fevers, urinary conditions, liver and spleen problems, diabetes, hypertension, malignancies, arthritis and rheumatism (Ali et al., 2013; Fahey, 2005; Jaiswal et al., 2009).

Different parts of this plant have hence been presented in different dosage forms (oral and external) for the treatment of both human and veterinary conditions (Das, 2012). For example, seeds have been presented as seed cake for water purification and roots, bark, flowers and pods have been presented as either bulk powders, capsules or tea bags (Saha et al., 2012). All *M. oleifera* leaf products are presented as bulk powders or divided powders in capsules that are manually filled or as granules (Jagtap, 2013).

However, the presentation of most of these products may not enable easy administration, reproducibility of dose and may also have poor patient acceptance because of unpleasant organoleptic properties. Standardization of herbal formulations is essential in order to ensure the quality of drugs based on the concentration of their active principals (Choudhary and Sekhon, 2011).

Formulation of whole powders of herbal medicines in the form of conventional immediate release tablets would ensure maximum benefit from all their nutritive and pharmaceutical constituents, easy administration, better acceptance, prolonged shelf life and quality assurance (Athawale, 2011).

The oral route is most often used in drug administration and has got better patient acceptability. However, in developing a new formulation, attention must be given to factors that improve the drug delivery to the gastrointestinal tract. These factors include but not limited to particle size, disintegration time, dissolution, physicochemical properties and other drug characteristics

A dosage form is developed in a series of stages including preformulation studies and the formulation itself (Klein et al., 2013).

The formulation and preparation of tablets containing a high percentage of active substances which is the case with herbal medicines preparations represents a very complex and effort consuming task. Fulfilling of tablets hardness and disintegration time requirements demands the complete management and knowledge of the formulation factors affecting the quality of the dosage form (Linden et al., 2000).

Quality by design approach to the development of *M. oleifera* leaf tablets links critical material and process parameters to the critical quality attributes of the product. ‘Variability is reduced by

product and process understanding which translates into quality improvement, risk reduction and productivity enhancement (Charoo et al., 2012).

Herbal ingredients are susceptible to degradation in presence of moisture and hence moisture protective coating is necessary to improve the stability and shelf life of the optimized herbal tablets (Athawale, 2011). These requirements informed the current study to carry out formulation development of Moringa film coated tablets.

CHAPTER THREE: MATERIALS AND METHODS

3.1 Research Design

This was an experimental study.

3.2 Location of the study

The study was carried out at the Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, Kenya.

3.3 Equipment/ apparatus

The following equipments were used: tablet compression machine (Erweka, electric type, Germany), Disintegration Tester machine (Erweka ZT3, GmbH Heusenstamm, Germany), Friability tester machine (Erweka, Heusenstamm, type TA3R, Germany) and a coating pan (Gryphon class E, No_150445R, England).

3.4 Materials

The plant material (*Moringa oleifera* leaf powder) was obtained from Tuskys supermarket, Nairobi, Kenya. This was in form of fine powder packed in sachets of 50 g each by Kates Organic, Nairobi, Kenya. The other materials (excipients) were either obtained from the Pharmaceutics laboratory or as donation from Laboratory and Allied Ltd, Nairobi, Kenya.

3.4.1 Determination of average moisture loss on drying

The method described in BP 2009 was adopted with slight modification. Moringa leaf powder (1 g) was weighed in a tared petri dish. The petri dish with its content was placed in an oven and dried at 105 $^{\circ}$C for 3 hr. Thereafter, the petri dish with its content was cooled in a desiccator over anhydrous silica gel and reweighed. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage (Okoye et al., 2013). Triplicate determinations were made and the means of the values reported.

3.4.2 Particle size analysis of *M. oleifera* leaf powder

Particle size analysis was done according to a method described by previous researchers (Okoye et al., 2013). Each sieve was tared to the nearest 0.001 g. Thereafter, 10 g of *M. oleifera* leaf powder was carefully loaded on the coarsest sieve of the assembled stack (1000 µm to 150 µm) and the lid was replaced. The nest was subjected to mechanical vibration using a Shaker for 25 min at 5 min

interval per shaking session. Thereafter, the sieves were carefully separated and each sieve was carefully reweighed with its content. The weights of powder retained on each sieve and the collecting pan was determined by difference. The values were used to calculate the percent of sample retained on each sieve and the average diameter of the particles (Dav) using the formula (Antikainen, 2003).

$$Dav = \frac{\sum(\%\ \text{retained} \times \text{mean aperture size})}{100} \quad \text{..... (Equation 1)}$$

3.4.3 Determination of powder particle density

This was determined using a method proposed by previous researchers (Okoye et al., 2013). Xylene was used as the displacement fluid. The pycnometer, very clean and dry, was weighed and its weight recorded. It was filled with xylene, the counterpoise replaced, and the excess fluid carefully and completely wiped off. The bottle with its content was weighed and the weight recorded. The pycnometer was then emptied, washed thoroughly with soapy water, rinsed with acetone, and dried very well in the hot air oven at 40℃. The dry pycnometer was reweighed to check if there was difference between the new dry weight and the initial one. Thereafter, some quantity of leaf powder being examined was introduced very carefully into the dry pycnometer, the counterpoise was replaced and the bottle with its content weighed. The weight of the powder was therefore determined by difference. A little xylene was introduced into the pycnometer and the bottle shaken carefully to displace the air bubbles entrapped by the powder particles. Finally, the bottle was filled with xylene, its counterpoise replaced, and the excess fluid wiped off thoroughly. The bottle with its contents was again weighed and the reading recorded. This procedure was carried out thrice and the mean value used in calculating the particle density (ρ) using the equation below:

$$\rho = \left[\frac{w}{(a + w) - b}\right] Sg \quad \text{..... (Equation 2)}$$

Where w is powder weight; Sg is the specific gravity of xylene; a is the weight of pycnometer + xylene, and b is the weight of pycnometer + xylene + powder.

3.4.4 Determination of Bulk and Tapped densities, Relative density and porosity

The bulk and tapped densities of *Moringa oleifera* leaf powder were determined by a method proposed by previous researchers (Okoye et al., 2013). The bulk density was determined by pouring 10 g (M) of the powder into a 50 ml glass measuring cylinder and the bulk volume (Vo) determined. The bulk density (Db) was then calculated from the following relationship:

$$Db = \frac{M}{Vo} \quad \text{.....(Equation 3)}$$

Triplicate determinations were made and the mean values reported.

The tapped density of the powder was determined using a Stamp Volumeter. The ten grams (M) of the powder sample after the bulk density determination was subjected to 250 taps mechanically and the volume V_{250} of the powder column determined and applied to evaluate tapped density (Dt) using the following relationship:

$$Dt = \frac{M}{V_{250}} \quad \text{.....(Equation 4)}$$

Triplicate determinations were made and the mean values reported.

Relative density and porosity of powder bed after 250 taps was determined using the equations 5 and 6 respectively:

$$RD = \frac{Dt}{\rho} \quad \text{.....(Equation 5)}$$

$$\varepsilon = 1 - RD \quad \text{.....(Equation 6)}$$

Where RD is the relative density, ρ is particle density, ε is porosity.

3.4.5 Determination of Angle of repose

The Angle of repose was determined by a method proposed by previous researchers (Okoye et al., 2013). The static angle of repose, θ, was measured according to the fixed funnel and free standing cone method. A glass funnel was clamped with its tip of diameter 1 cm at a given height (h = 1.5 cm) above a graph paper placed on a flat surface. The powder/granules sample (10 g) was carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel.

The diameter (d) of the base of the cone was measured. This procedure was repeated three times for each powder/granule sample and the mean was used to calculate the angle of repose for the powder/granules using the formula:

$$\tan \theta = \frac{2h}{d} \quad \text{.....(Equation 7)}$$

3.4.6 Determination of Hausner ratio and compressibility index

Hausner's Ratio (HR)

This was calculated using the formula:

$$HR = \frac{Dt}{Db} \quad \text{..... (Equation 8)}$$

Where Dt is Tapped density; Db is Bulk density

Compressibility Index (CI)

This was calculated using the formula:

$$C\,I = \frac{Dt - D_b}{Dt} \times \frac{100}{1} \quad \text{..... (Equation 9)}$$

3.4.7 Antimicrobial Assay

Assessment of the antimicrobial activity of *M. oleifera* leaf powder was done according to a method described by previous researchers with minor modifications (Marrufo et al., 2013).

3.4.7.1. Extraction

3.4.7.1a Extraction with Chloroform

One hundred grams of the powder was taken into a flat bottom flask and one liter of chloroform was added to it. This mixture was left on the bench for 48 hours with daily swirling of the flat bottom flask. The mixture was filtered and reduced to dryness using a rotary vacuum evaporator. The reduced filtrate was placed in the oven at 37 ℃ and allowed to dry. The wet powder material was spread out on a clean flat surface and allowed to air dry. The percentage yield was calculated.

3.4.7.1b Extraction with Methanol

The dried drug from the previous extraction was mixed with a liter of methanol. The mixture was left for an additional 48 hours with daily swirling of the flat bottom flask. The mixture was filtered and also reduced to dryness in the same manner as the chloroform extract. The percentage yield was calculated.

3.4.7.2 Assay for antimicrobial activity

The inhibition halos test on agar plates was employed to investigate the antimicrobial activity of the chloroform and methanol extracts of *M. oleifera* leaf powder. Tryptone Soya Agar (TSA) and Saboraud's Dextrose Agar (SDA) were prepared according to the manufacturer's specifications. The media were sterilized by autoclaving at 121℃ for 15 minutes. 10 ml of sterile water was added into the subculture of *Staphylococcus aureus* (Gram positive bacteria) and *Escherichia coli* (Gram negative bacteria) in order to prepare their suspensions (SDA). These were found to be more sensitive than other bacteria to the extracts of *M. oleifera* according to findings reported by previous researchers (Marrufo et al., 2013). About 1 ml of each of the bacteria suspension was added to 100ml of TSA.

Approximately 20 ml of the inoculated media was poured into each petri dish and allowed to settle. Four wells were punched into the media once it had fully solidified. Approximately 50 micro liters of the standard drug (Gentamycin 3 µg/ml), 100 mg/ml of methanol leaf extract and 100 mg/ml chloroform leaf extract dissolved in water and Dimethylsulfoxide (DMSO) respectively were transferred into the labeled wells. A blank well was also left with nothing put in it. After 30 minutes under sterile conditions at room temperature, plates were incubated at 37℃ for 48 hr. The diameter of the clear zone on the plate was accurately measured and the antibacterial activity expressed in mm. The blank wells were used as the negative control while wells containing Gentamycin 3 µg/ml were used as the positive controls (Marrufo et al., 2013).

3.5 Preparation of tablets

Four (4) batches of basic formulations of *M. oleifera* leaf powder were prepared. Moringa leaf powder (72.3%) and a disintegrant (corn starch BP 7.3 % or 9.1 % w/w with respect to the total tablet weight) was dry – mixed for 10 minutes in a glass beaker, moistened with the appropriate amount of binder solution (gelatin or PVP) prepared according to the method described by

previous researchers (Okoye et al., 2013) maintaining the volume of the solutions at 0.25 ml in the final tablet. Filler, lactose monohydrate, was used to standardize the weights of the different formulations. Wet massing of the ingredients was carried out in a mortar using a pestle for 10 min. The homogeneous wet mass was then offloaded and screened through a 1700 µm sieve and dried in a hot air oven at 50℃ for 2 hours. Thereafter, the dried granules was screened through a 600 µm sieve in order to generate uniformly sized granules (Armstrong, 2007) and transferred into a glass beaker. Talc (0.1 % w/w) and Sodium Lauryl Sulphate (0.5 % w/w) was added as gildant and anti-adherent. Talc and Sodium Lauryl Sulphate were added at 0.1 % and 0.5 % respectively and mixed for 5 minutes based on specifications of previous researchers (Rowe et al., 2009) . Magnesium stearate (1 % w/w), was then added as a lubricant and mixed for 1 minute. Mixing for 1 min after the addition of Magnesium stearate was done based on specifications by previous researcher (Sarfaraz, 2004). The granulated material was then offloaded into well labeled clean containers ready for compression into tablets using a 10 mm round punch. Samples from the different batches were individually weighed and placed in the compression chamber. For each formulation, the compressive force was adjusted according to the properties of the material (Klein et al., 2013). The compression force of the machine was manually adjusted, *i.e.*, for each material the behavior at a particular applied force was observed. To obtain the tablets, the machine engine was not engaged, so each form of the solid dosage was obtained individually by manual rotation of the punch as proposed by previous researchers (Klein et al., 2013). After compression, the formulations were collected and stored away from light and rehydration (in desiccation chamber) at room temperature until further analysis. The different formulations of Moringa tablets are shown in Table 1.

Table 1: Formulations of Moringa tablets

No –	Material	%age w/w of total tablet weight (450mg)			
		F1	**F2**	**F3**	**F4**
1	Moringa powder	72.3 (325.35 mg)	72.3 (325.35 mg)	72.3 (325.35 mg)	72.3 (325.35mg)
2	Corn starch (disintegrant)	7.3 (32.85 mg)	7.3 (32.85 mg)	9.1 (40.95 mg)	7.3 (32.85 mg)
3	Gelatin	0.7 (3.15 mg)	3.6 (16.20)	-	-
4	PVP (K-30)	-	-	0.7 (3.15 mg)	2.2 (9.90 mg)
5	Lactose(filler)	18.1 (81.45 mg)	15.2 (68.4 mg)	16.3 (73.35 mg)	16.7 (75.15 mg)
6	SLS	0.5 (2.25 mg)	0.5 (2.25 mg)	0.5 (2.25 mg)	0.5 (2.25 mg)
7	Talc	0.1 (0.45 mg)	0.1 (0.45 mg)	0.1 (0.45 mg)	0.1 (0.45 mg)
8	Magnesium stearate	1.0 (4.5 mg)	1.0 (4.5 mg)	1.0 (4.5 mg)	1.0 (4.5 mg)
	Total	**100**	**100**	**100**	**100**

The choice of using corn starch at 7.3 % in formulations F1, F2 and F4 and 9.1 % in F3 in combination with gelatin at 0.7 % and 3.6 % in F1 and F2 respectively and PVP at 0.7 % and 2.2 % in F3 and F4 respectively was based on findings of Okoye et al., 2013 which indicated that these combinations resulted in granules with flow and compressibility properties which are better than for the other combinations. These percentages of the excipients are within the recommended rages for tableting (Rowe et al., 2009).

3.6 Tablet Tests

3.6.1 Appearance

The macroscopic characteristics of tablets of each formulation including the geometric shape, appearance, colour and presence of foreign material or particles was observed.

3.6.2 Uniformity of weight

The uniformity of weight of each batch of tablets was determined using the methodology described in the British Pharmacopoeia (2007), using a range of tolerance of 5 % for tablets with a mean weight above 250.0 mg. Twenty tablets were weighed individually using an electronic weighing balance, Shimadzu model TX3202L made in Philippines and the mean weight was determined.

3.6.3 Hardness

The hardness of the tablets was determined using an electronic tablet hardness tester machine, schleuniger mod 2E/205 made in Switzerland. Ten tablets of each formulation were evaluated (BP, 2007).

3.6.4 Friability

According to the procedure recommended in the British Pharmacopoeia (2007), twenty tablets were weighed and submitted to a friability tester machine (Erweka, Heusenstamm, type TA3R made in Germany). After 25 rpm for 4 minutes, the tablets were de-dusted and weighed again. The difference between the initial and final weights representing the friability (FR), as estimated by the percentage of powder lost was calculated and the results reported.

3.6.5 Disintegration test

According to the method described in the British Pharmacopoeia (2007), 6 tablets of each batch were placed each in a tube (with a mesh at the bottom) immersed in a water bath at 37℃ and the disintegration test machine (Erweka ZT3, GmbH Heusenstamm, Germany) was set to run. The time it took for all the tablets to disintegrate was observed and recorded for each formulation.

3.6.6 Antibacterial Assay of Moringa tablets

Uncoated tablets were selected at random, crushed together in a mortar and pestle and the powder (100 g) was used to obtain chloroform and methanol extracts using the same method previously described for extracting the unformulated *M. oleifera* leaf powder.

The antibacterial activity of the chloroform and methanol extracts was also tested using the same method previously described for the unformulated *M. oleifera* leaf powder.

The results of the unformulated *M. oleifera* leaf powder served as the reference for the tablets in terms of activity against Staphylococcus aureus and E. coli.

3.7 Coating

The tablet formulations were optimized by film coating.

The routine coating pan, Gryphon class E, No_150445R England was used. This was operated at a speed of 24 rpm and temperature of 40℃ to 45℃. Aquarius preferred HSP was used as the coating material. It was chosen for this purpose because it is a fully formulated easily dispersed and ready – to – use coating system. It is composed of Ethyl cellulose modified with Hydroxypropyl cellulose (HPC). The coating solution was prepared at a concentration of 10 % w/v using 75 % v/v ethanol and sprayed manually using a fine hand spray. Spraying the coating solution at 10 % w/v was for faster throughput and reduced labor and energy costs (ashland.com/pharmaceutical, 2012). The use of ethanol as the solvent is because it is less expensive than the organic materials, requires no solvent recovery system and is environmentally friendly. Also, the potential toxicities associated with residual solvents in the products are eliminated as it was reported by previous researchers (Porter and Felton, 2010).

No colorant was added to the coating material such that the tablets retained the green look of a natural herbal product. This is because Fast green FCF (coloring agent) that had been proposed because of being a permissible colorant in food, drug and cosmetics by the FDA (Rowe et al., 2009) was not readily available.

The coating solution was prepared in the following way; generally, in a flat bottomed flask (1 L) properly weighed coating material, Aquarius preferred HSP (40 g), was put. 75 % ethanol (400 ml) solution was added followed by vigorous shaking until all the particles had dissolved. The

solution was filtered through a sieve (muslin cloth) into a glass beaker. The solution was then put into the hand spray for spraying unto the tablets.

One kilogram of placebo tablets was used to increase on the bulk of the tablet bed in the coating pan in which the tablets of interest were put to ensure uniform coating. The tablets were dusted before they were put in the coating pan.

Once in the coating pan, the tablets were warmed up to the temperature of 40℃ to 45℃ until the bed temperature was 35℃ to 45℃. The coating pan was rotated at 24 rotations per minute and spraying was started slowly. The appearance of the tablets was checked regularly and once they were fully covered with the coating solution, spraying was stopped and they were rolled in the coating pan for another 30 min so that they dried. The coating process took 2 hrs.

The quality of the film coated tablets was then evaluated by carrying out uniformity of weight test and disintegration test of the tablets.

CHAPTER FOUR: RESULTS AND DISCUSSION

4.1. Preformulation studies

The MOP was subjected to preformulation studies which included determination of moisture loss on drying, average particle diameter (Dav), particle density (P), bulk (Db) and tapped density (Dt), relative density (RD), porosity (ε), angle of repose (ɵ), Hausner's ratio (HR) and compressibility index (C I). The average moisture loss on drying was 7.87 ± 2.9 %. This value is less than the accepted maximum and this low moisture content can inhibit bacterial, fungal or yeast growth (Government of UK, 2007). *M. oleifera* leaf powder is shown in Plate 2 below. Results of preformulation studies done on *M. oleifera* leaf powder are shown in Table 2 below.

Plate 2: *Moringa oleifera* leaf powder

Table 2: Results of preformulation studies done on *M. oleifera* leaf powder

Dav(µm)	P (g/ml)	Db (g/ml)	Dt (g/ml)	RD	ε	ɵ (^{o})	HR	CI
268.475	1.354 ± 6.8%	0.37	0.50	0.37	0.63	38.3	1.35	38.3

All the results of results of preformulation studies were consistent with findings of previous researchers (Okoye et al., 2013).

4.2 Antimicrobial assay

4.2.1 Extraction

Extraction of 100 g of *M. oleifera* leaf powder (MOP) gave a higher percentage yield compared to extraction of 100 g of Moringa formulated tablets powder with the chloroform extracts being more than the methanol extracts. Results of extraction are shown in Table 3 below and the extracts are shown in Plates 2 and 3 below

Table 3: Results of extraction

Material	**Percentage yield (%)**	
	Chloroform extract	Methanol extract
Moringa oleifera leaf powder (100 g)	6.07	5.49
Moringa oleifera formulated tablet powder (100 g)	4.41	4.17

Plate 3: Moringa powder extracts.

Plate 4: Moringa tablet extracts

4.2.2 Antimicrobial activity

Antimicrobial activity test was included in this study to establish whether *M. oleifera* leaf powder retains activity upon being formulated into tablets and this acted as an assay test since the conventional HPLC, TLC and dissolution tests could not be done *M. oleifera* being a herb with multiple components which have not been quantified.

Both chloroform and methanol extracts of *M. oleifera* leaf powder and Moringa formulated tablets exhibited antimicrobial activity against both test microorganisms (*S. aureus and Escherichia coli)* with zones of inhibition ranging from 8.07 to 13.92 mm in diameter compared to the negative control which ranged from 6.87 and 7.07 mm and the positive control (Gentamycin) which ranged from 26.10 to 28.11 mm. *S. aureus* showed greater susceptibility compared to *E. coli* and this was similar to findings of previous studies (Marrufo et al., 2013). This study revealed that *M. oleifera* leaf extracts have greater activity against gram positive bacteria while gram negative bacteria are more resistant.

Results of antimicrobial activity (zones of inhibition) of *M. oleifera* extracts are shown in Table 4 and 5 below. These are for activities of extracts from the powder and the formulated tablets respectively. It is however important to note that extracts from *M. oleifera* powder exhibited greater activity compared to extracts from the formulated tablets. This is because the quantity of the formulated tablets crushed for this purpose was less as more tablets were to be used for

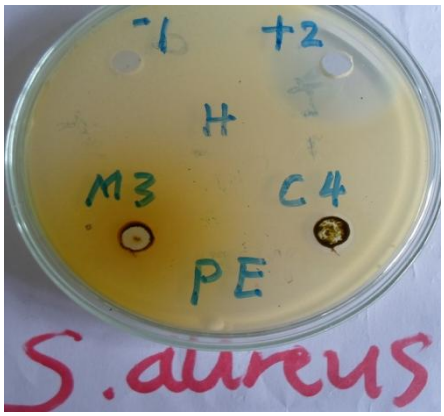
further tests and also for film coating. Also, tablets from the different formulations were mixed and crushed together with the assumption that they had the same antimicrobial activity since they had gone through the same processes. Zones of inhibition are shown in Plates 5 and 6 below.

Table 4: Zones of inhibition of Moringa powder extracts

Microorganism	Zones of inhibition (mm)			
	Chloroform extract	Methanol extract	Gentamycin (positive control)	Negative control
S. aureus	13.92	9.04	28.11	6.87
E. coli	10.71	8.45	26.81	7.07

Table 5: Zones of inhibition of Moringa tablets extracts

Microorganism	Zones of inhibition (mm)			
	Chloroform extract	Methanol extract	Gentamycin (positive control)	Negative control
S. aureus	11.01	8.07	27.57	6.90
E. coli	11.02	8.72	26.10	6.92



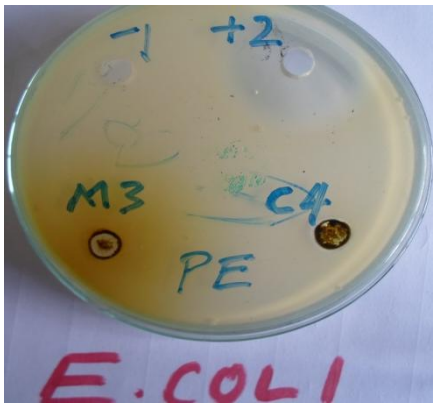


Plate 5: Zones of inhibition of Moringa powder extracts against *S. aureus* and *E. coli.*

Key: M3 - methanol extract in well number 3, C4 – chloroform extract in well number 4, (- 1) – well number 1 is the negative control and (+2) – well number 2 is the positive control (Gentamycin).

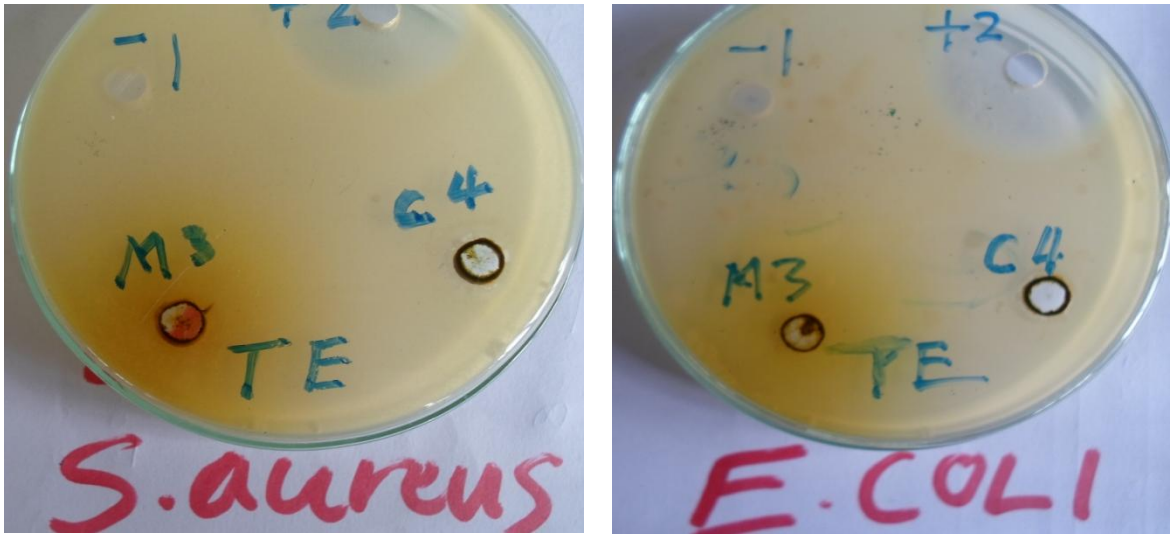


Plate 6: Zones of inhibition of Moringa tablets extracts against *S. aureus and E. coli.*
Key: M3 - methanol extract in well number 3, C4 – chloroform extract in well number 4, (- 1) – well number 1 is the negative control and (+2) – well number 2 is the positive control (Gentamycin).

4.3 Granulation

Granules of the different formulations (F1 – F4) obtained had particle density ranging from 1.16 ± 0.091 (F2) to 1.18 ± 0.092 g/ml (F4), average particle diameter (Dav) ranging from 363.48 µm (F3) to 436.02 µm (F4), bulk density (Db) ranging from 0.48 g/ml (F1 &F3) to 0.50 g/ml (F4) and tapped density (Dt) ranging from 0.56 g/ml (F1 & F3) to 0.59 g/ml. Results of tests done on the formulated granules are shown in Table 6.

Table 6: Micromeritic properties of Moringa oleifera powder and granules of four different formulations

Micromeritic property	MOP	Formulations			
		F1 Granules	F2 Granules	F3 Granules	F4 Granules
Average particle diameter, Dav (µm)	268.475	368.54	366.56	363.48	436.02
Powder particle density, ρ (g/ml)	1.354 ± 6.8%	1.17 ± 6.2%	1.16 ± 7.8%	1.17 ± 7.0%	1.18 ± 7.8%
Bulk density, Db (g/ml)	0.37	0.48	0.49	0.48	0.50
Tapped density, Dt (g/ml)	0.50	0.56	0.57	0.56	0.59
Relative density (RD)	0.37	0.48	0.49	0.48	0.50
Porosity (ε)	0.63	0.52	0.51	0.52	0.50
Angle of repose, ɵ (^{o})	38.3	37.0	37.5	37.5	37.7
Hausner's Ratio (HR)	1.35	1.17	1.16	1.17	1.18
Compressibility Index, C I (%)	26	14.29	14.04	14.29	15.25

CI is a measure of powder bridge strength and stability, and the Hausner ratio (HR) is a measure of the interparticulate friction. Flow character is rated based on compressibility index and Hausner ratio. Lower CI or lower Hausner ratios of a material indicate better flow properties than higher ones. A Carr's CI of < 10 or HR of < 1.11 is considered 'excellent' flow whereas CI > 38 or HR > 1.60 is considered 'very very poor' flow. There are intermediate scales for CI between 11 – 15 or HR between 1.12 – 1.18 is considered 'good' flow, CI between 16 – 20 or HR

between 1.19 – 1.25 is considered 'fair' flow, CI between 21 – 25 or HR between 1.26 – 1.34 is considered passable flow, CI between 26 – 31 or HR between 1.35 – 1.45 is considered 'poor' flow, and CI between 32 – 37 or HR between 1.46 – 1.59 is considered 'very poor' flow (Shah et al., 2008) Based on the results obtained, flow of *M. oleifera* leaf powder was rated as 'poor', that of all formulated granules was rated as good.

The angle of repose, a traditional characterization method for pharmaceutical powder flow, was also used to characterize the granules. Based on the angle of repose, a value of < 30 ° indicates 'excellent' flow whereas > 56° indicates 'very poor' flow. The intermediate scale indicates 'good' (θ between 31 – 35°), 'fair' (θ between 36 – 40 °), 'passable' (θ between 41 – 45 °), and 'poor' (θ between 46 – 55 °) (Shah et al., 2008). Based on this, the flow of both the powder and the granules of all formulations were rated as 'fair'.

Formulated granules had good flowability compared to the powder based on CI and HR with F2 having the best flow (HR = 1.16 & CI = 14.04) and F4 having least flow among the granules (HR = 1.18 & C I = 15.25). The powder flow was rated poor with HR equal to 1.35 and CI equal to 26. However, based on the angle of repose results, both granules (F1 – F4) and the powder flow were rated as fair (37.0 – 38.3). This discrepancy might be due to very qualitative nature of the scale of measurements and ratings for flow properties based on these compendial methods (Shah et al., 2008). The granules are shown in Plate 7 below and graphical representation of the granule properties are shown in Figures 1 and 2 below.

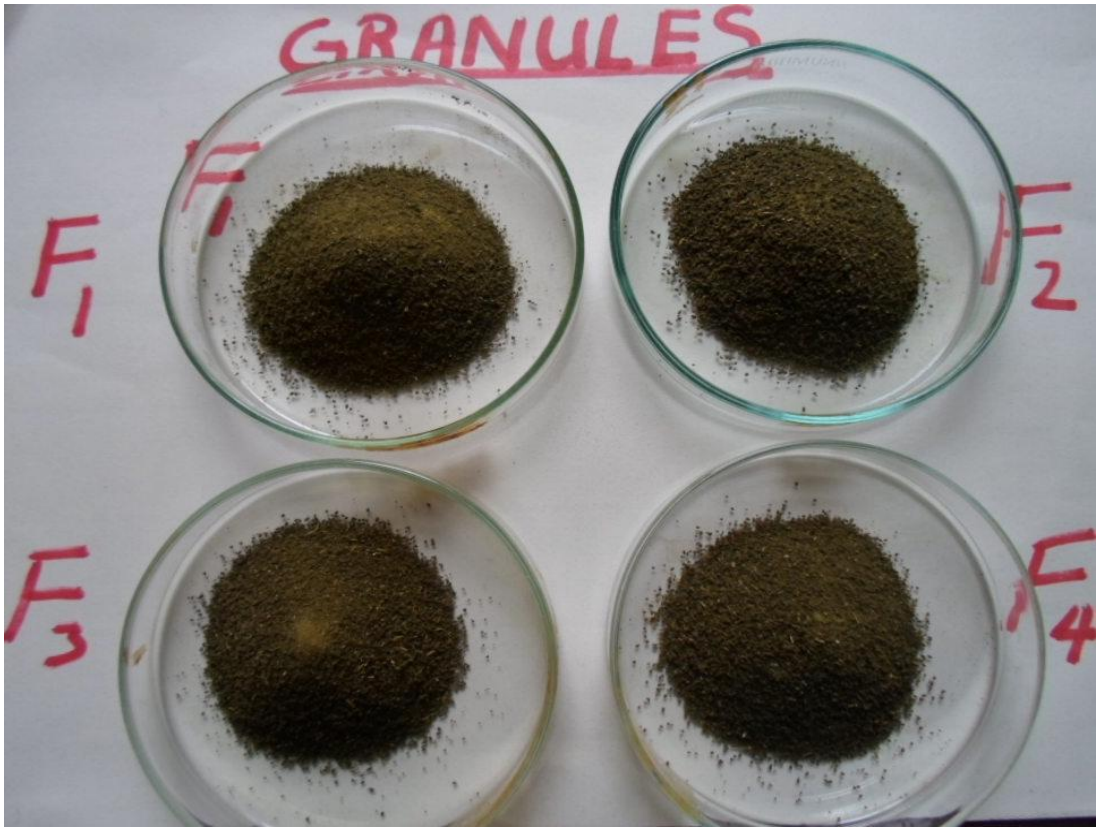


Plate 7: Moringa granules

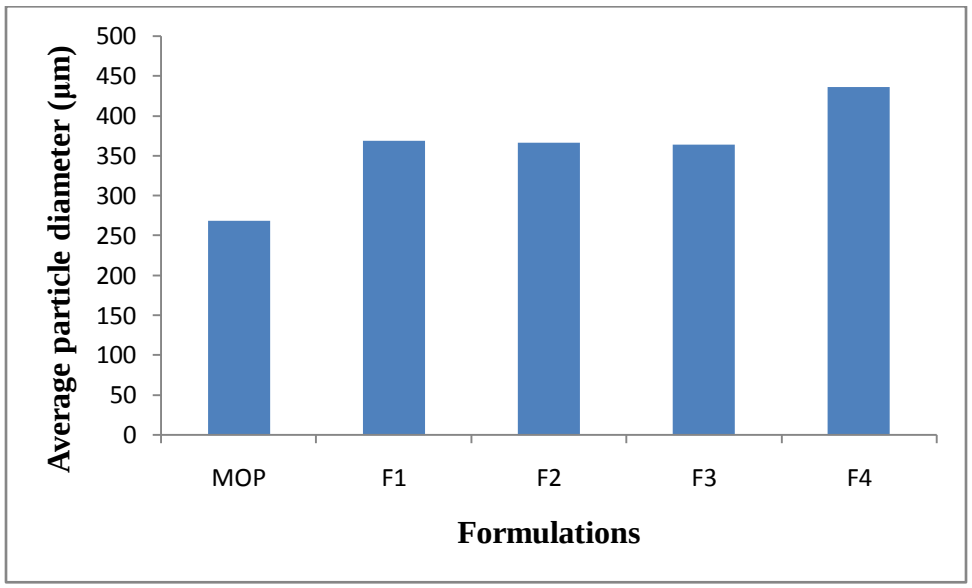


Figure 1: A graph of average particle diameter of MOP and *M. oleifera* granules

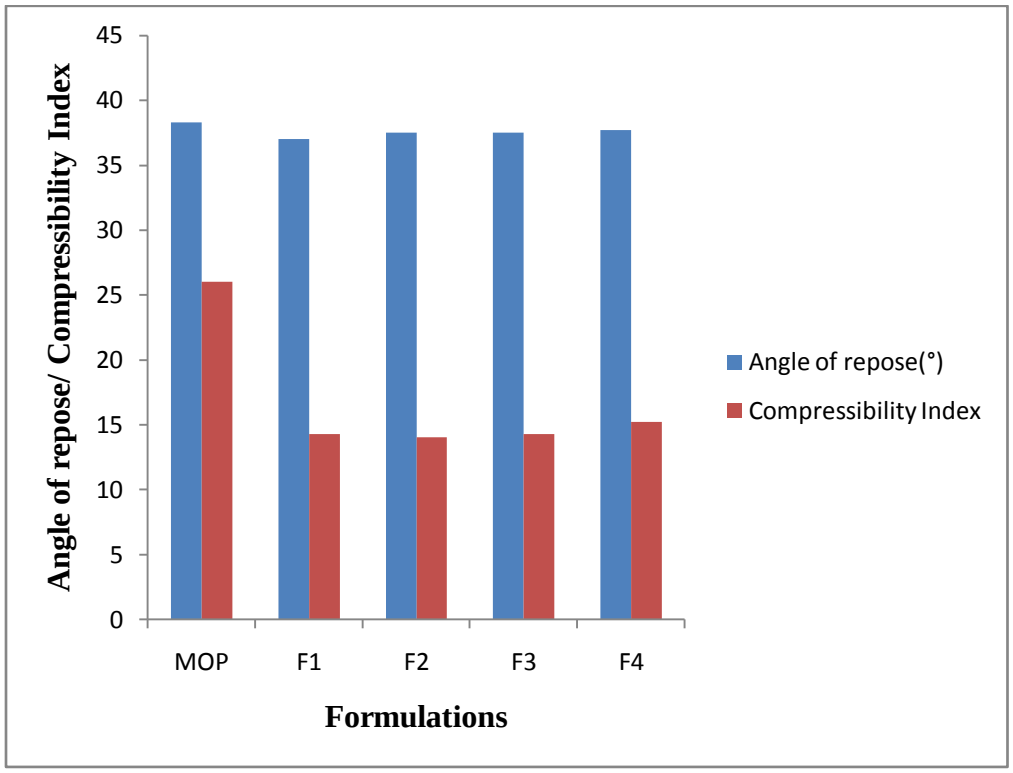


Figure 2: A graph of angle of repose and compressibility Index of *Moringa oleifera* powder and *Moringa oleifera* granules

4.4 Tableting

Four batches (F1 – F4) ranging from 250 to 280 tablets were made at a uniform compression force of about 45N (Schleuniger tablet hardness tester machine) and uniform fill weight of 450mg. Moringa uncoated tablets and the tableting machine used are shown in Plates 8 and 9 below respectively.

Plate 8: Moringa uncoated tablets.

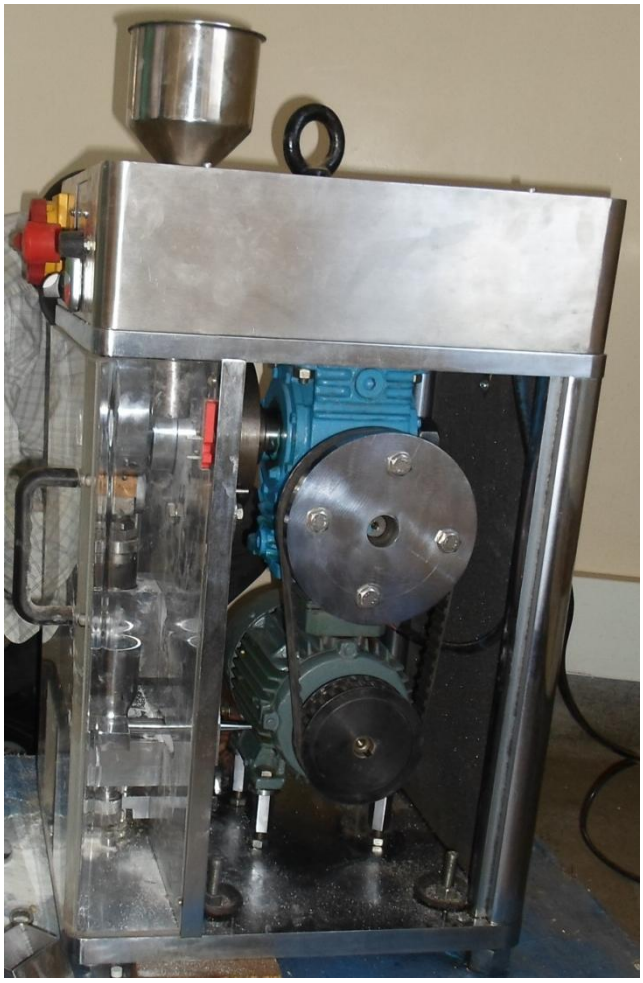


Plate 9: Tableting machine

4.4 Tablet tests

4.4.1 Appearance

Tablets were circular, smooth, shiny and green in colour with some whitish spots visible on the surface. The whitish spots visible on the surface of the tablets were very tiny particulate matter from the leaf midribs that were too tiny to go through a 150 µm sieve and are white in colour. The tablets had thickness ranging from 4.83 to 5.03 mm measured using vernier calipers.

4.4.2 Uniformity of weight

Twenty tablets of each formulation were individually weighed and Table 7 shows results of the uniformity of weight test

Table 7: Results of uniformity of weight of uncoated tablets

Formulations	No_ of tablets weighed	Mean weight (g)	Relative Standard deviation	No_ of tablets within range	No_ of tablets outside range
F1	20	0.447	2.7 %	20	Nil
F2	20	0.471	1.5 %	20	Nil
F3	20	0.4535	2.4 %	20	Nil
F4	20	0.4445	2.8 %	20	Nil

For all the formulations there was no single tablet that deviated from the mean weight of the weighed tablets (20) by more than 5%. Based on compendial standards (Government of UK, 2007), all the formulated uncoated tablets passed the uniformity of mean weight test. Results of quality tests done on the tablets are shown in Table 8.

Table 8: Results of tests of Moringa uncoated tablets (± R.S.D; n = 3)

Quality Tests	Formulations			
	F1	F2	F3	F4
Mean weight (g)	0.447 ± 2.7 %	0.471 ± 1.5 %	0.4535 ± 2.4 %	0.4445 ± 2.9 %
Hardness (N)	46.1 ± 22.3 %	63.1 ± 13.3 %	46.6 ± 6.6 %	43.0 ± 13.0 %
Friability (%)	0.67	0.43	0.67	0.23
Disintegration time (min)	22.05	33.53	13.15	18.61

Tablet hardness ranged from 43.0 ± 13.0% N (F4) to 63.1 ± 13.3% N (F2). Graphs showing test results of the formulated uncoated tablets are given in Figures 3 and 4 below. Based on compendial standards, uncoated tablets of all the formulations passed the uniformity of weight and the Friability tests which are compendia tests. Only formulation F3 tablets passed the disintegration time test. All the six tablets disintegrated within 15 minutes while for the other formulation tablets (F1, F2 and F4), complete disintegration of all the six tablets used in the test

occurred beyond the stipulated 15 minutes (Pharmacopoeia, 2010). The Hardness testing machine and the friability testing machine used are shown in Plates 10 and 11 below respectively.

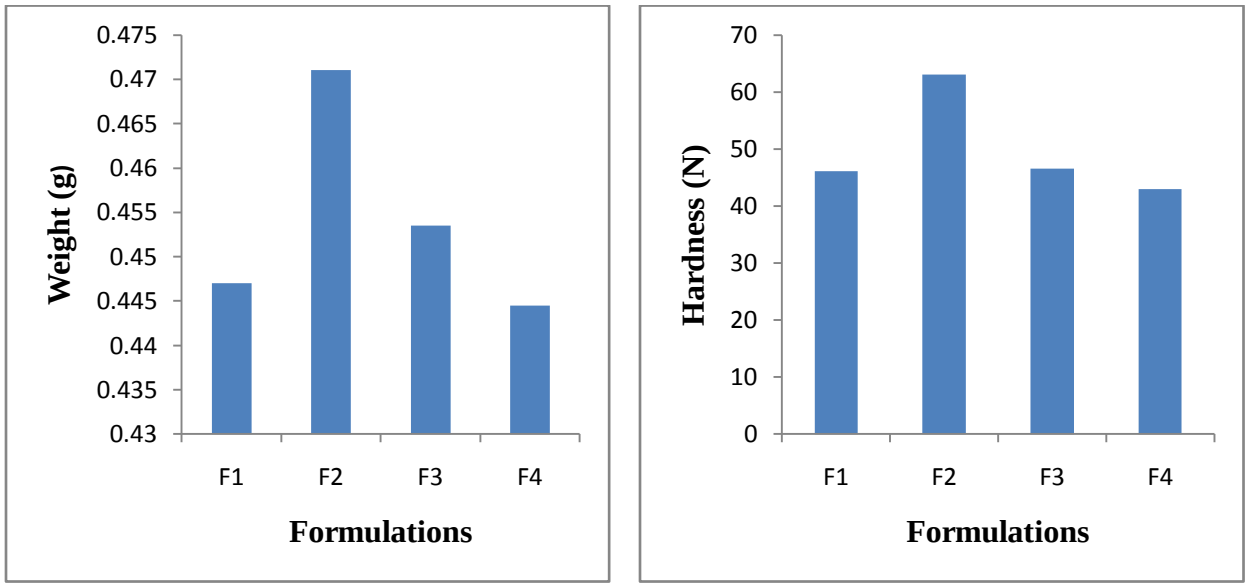


Figure 3: Graphs showing comparison of uniformity of weight and Hardness amongst the different formulations

Plate 10: Tablet Hardness testing machine

Plate 11: Friability testing machine

There was a direct relationship between mean weight and hardness. Formulation F2 tablets had the highest mean weight and they were the hardest. This is because formulation F2 contained 3.6 % gelatin as a binder as compared to F1 (0.7 % gelatin), F3 (0.7 % PVP) and F4 (2.2 % PVP). It should also be noted that F2 granules had the least CI value of 14.04 and the least HR value of 1.16 and therefore had the best flow properties.

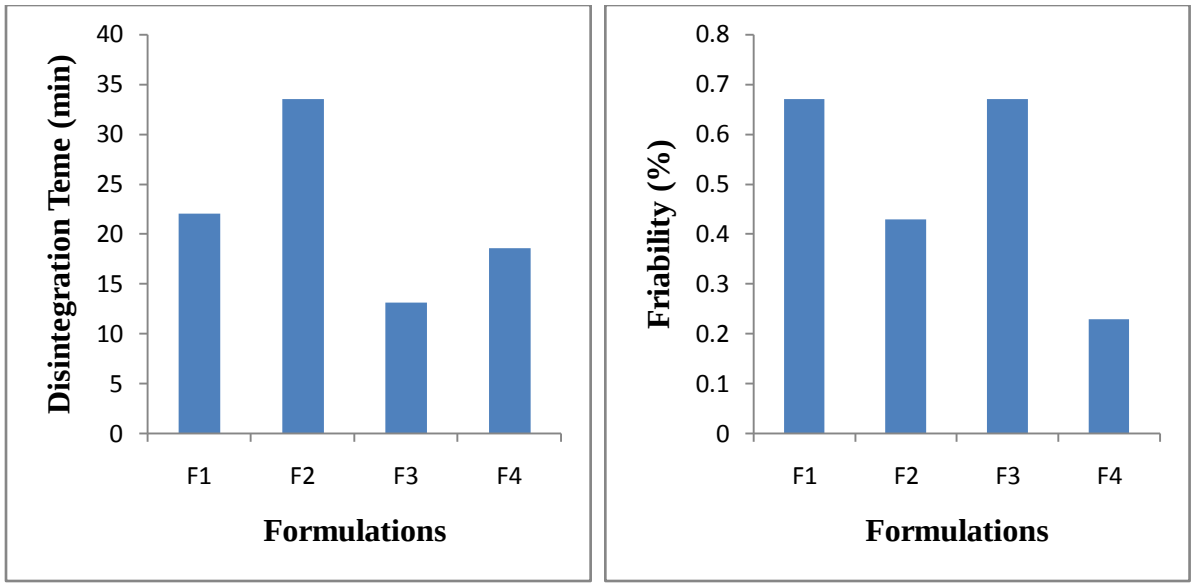


Figure 4: Graphs showing comparison of hardness, disintegration time and friability amongst the different formulations.

There was direct relationship between hardness and disintegration time and these had an inverse relationship with friability. This was especially true with formulations F1, F2 and F4. F3 disintegrated faster than the rest of the formulations and at the same time it was the most friable. However, its friability was within the acceptable range(less than 1 %) (Pharmacopoeia, 2010). This makes polyvinyl pyrolidine (PVP) at 0.7 % w/w of total tablet weight a binder good enough to make strong tablets of *M. oleifera* leaf powder and not too strong to interfere with disintegration.

4.5 Film coating

Film coated tablets were circular, smooth green and shiny in appearance with percentage gains in weight ranging from 0.95 to 1.03. Moringa film coated tablets and the coating pan used are shown in Plates 12 and 13 respectively.

Plate 12: Moringa film coated tablets

Plate 13: Tablet Coating Pan

4.5.1 Tests of Film coated tablets

Film coated tablets were evaluated for uniformity of weight and for disintegration time. Results of mean weight are shown in Table 9.

Table 9: Results of uniformity of weight of Moringa film coated tablets

Formulations	No_ of tablets weighed	Mean weight (g)	Relative Standard deviation	No_ of tablets within range	No_ of tablets outside range
F1	20	0.4485	3.3 %	17	03
F2	20	0.4575	2.6 %	20	Nil
F3	20	0.445	2.9 %	20	Nil
F4	20	0.4400	6.0 %	11	09

Using a range of tolerance of 5 % for tablets with mean weight above 250 mg (Government of UK, 2007), F4 and F1 film coated tablets failed the uniformity of weight test while F3 and F2 passed. This is because more than two individual tablets of these formulations deviated by more 5 %. This could be explained by the fact that the coating process was subject to variations since spraying was manually done and depended on the efforts of the operator. Results of evaluation of the film coated tablets in terms of mean weight and disintegration time are also shown in Table 10. Also, a figure showing graphical representations of the same has been given (Figure 5 below).

Table 10: Mean weight and disintegration time

Test	Formulations			
	F1	F2	F3	F4
Mean weight (g)	0.449 ± 3.3 %	0.457 ± 2.6 %	0.445 ± 2.9 %	0.44 ± 5.9 %
Disintegration time (min)	30.62	50.44	27.00	37.31

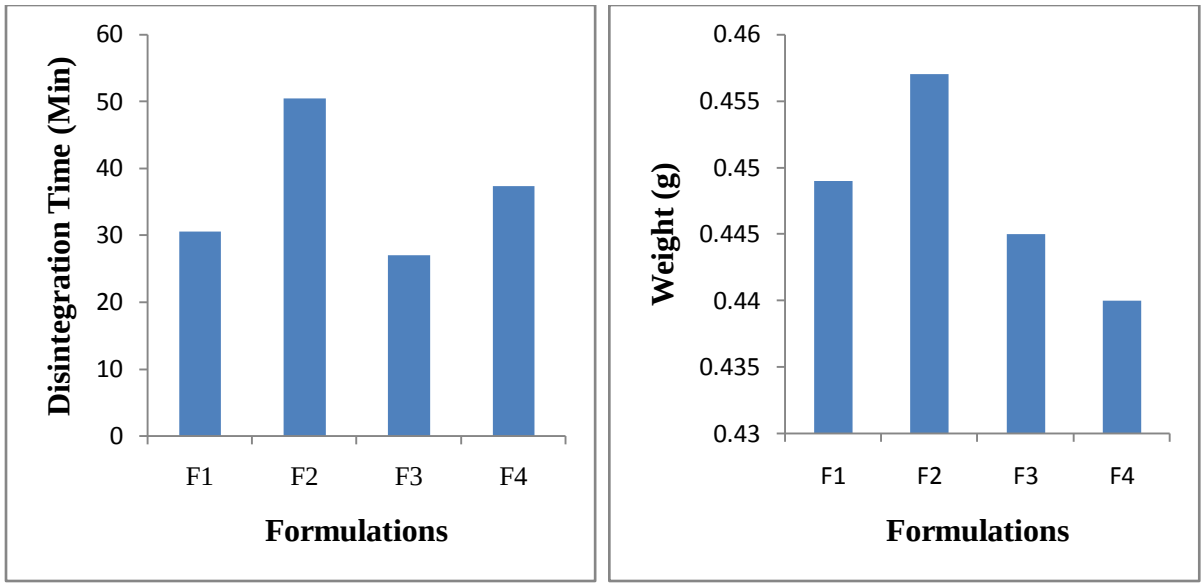


Figure 5: Graphs showing comparison of uniformity of mean weight and disintegration time amongst the film coated tablets formulations

Based on compendial standards (BP, 2007) which indicate that film coated tablets should disintegrate within 30 minutes, only F3 film coated tablets passed the disintegration test. The other formulation tablets (F1, F2, and F4) did not disintegrate within the stipulated 30 minutes. This can be explained by the fact that even the uncoated tablets of these formulations did not pass the disintegration test. I.e. they disintegrated completely beyond the stipulated 15 minutes for uncoated tablets. This could indicate that the binder concentrations (0.7 % & 3.6 % gelatin and 2.2 % PVP respectively) exhibited higher binding properties and therefore produced tablets too hard to disintegrate within the acceptable limits. It could also indicate that the disintegrant (corn starch) at that percentage used (7.3 %) in these formulations was too little to cause sufficient disintegration. The equipment used for disintegration testing is shown in Plate 14.

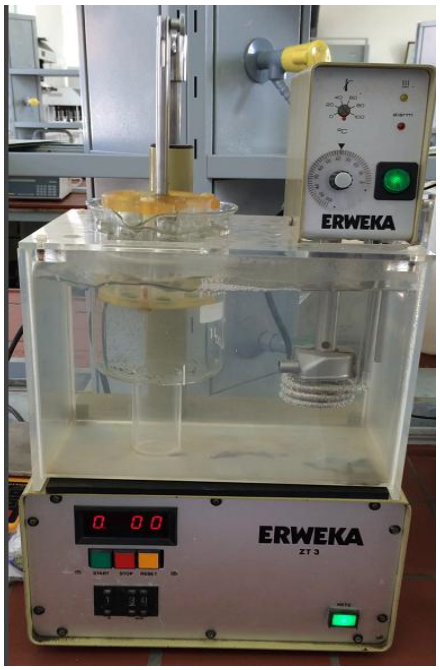


Plate 14: Disintegration testing machine.

4.6 Conclusion

From the above results it can be concluded that *Moringa oleifera* leaf powder has antimicrobial activity which is also retained upon being granulated and compressed into tablets. It can also be concluded that granules of *Moringa oleifera* leaf powder formulated with 0.7 % PVP as binder and 9.1 % corn starch as disintegrant posses values of CI and HR that are rated as having good flow and resultant tablets that are strong enough to pass friability test and at the same time pass disintegration test.

Also, it can be concluded that film coating can improve the appearance of *Moringa oleifera* tablets at the same time reduce dust formation. However, it should be noted that disintegration time was greatly increased with film coating and therefore it should be done cautiously.

All in all, this study indicated that it is possible to make film coated tablets of *Moringa oleifera* leaf powder especially formulated and granulated with 0.7 % PVP as a binder and 9.1 % corn starch as disintegrant. This conclusion is in agreement with findings of previous researchers (Okoye et al., 2013) who demonstrated that granules of *Moringa oleifera* leaf powder possessed good micromeritic properties for tablet or capsule development. It is important to note that it is on the basis of their (Okoye et al., 2013) findings and recommendations that this study was done.

4.7 Recommendations.

Determination of the tablets strength (dose size) was arbitrary due to lack of clinical data giving information such as daily dose, efficacy, potency, effectiveness, and toxicity of *Moringa oleifera* leaf powder. Therefore, further research should be done to establish the above so that the dose size shall be based on clinical data before *Moringa oleifer*a film coated tablets can be scaled up to commercial production.

REFERENCES

Ali, A., Akhtar, N., Mumtaz, A.M., Khan, M.S., Iqbal, F.M., Zaidi, S.S., 2013. In vivo skin irritation potential of a cream containing Moringa oleifera leaf extract. Afr. J. Pharm. Pharmacol. 7, 289–293.

Antikainen, O., 2003. New methods to evaluate applicability of powders and granules for tablet compression. University of Helsinki.

Anwar, F., Latif, S., Ashraf, M., Gilani, A.H., 2007. Moringa oleifera: a food plant with multiple medicinal uses. Phytother. Res. 21, 17–25.

Armstrong, N.A., 2007. Tablet manufacture. Encycl. Pharm. Technol. 3, 2713–31.

ashland.com/pharmaceutical, 2012. Ashland - from matrix to film coating, your full-service pharmaceutical technology resource.

Athawale, R., n.d. International Journal of Ayurvedic and Herbal Medicine 1: 1 (2011) 6–13.

Brittain, H.G., 2001. What Is the" Correct" Method to Use for Particle-Size Determination? Pharm. Technol. 25, 96–98.

Brittain, h.g., 2002. Particle-size distribution, part III: determination by analytical sieving. Pharm. Technol. 26, 56–64.

Charoo, N.A., Shamsher, A.A., Zidan, A.S., Rahman, Z., 2012. Quality by design approach for formulation development: A case study of dispersible tablets. Int. J. Pharm. 423, 167–178.

CH, O., 2001. Representations of particle shape, size, and distribution. Pharm. Technol.

Choudhary, N., Sekhon, B.S., 2011. An overview of advances in the standardization of herbal drugs. J Pharm Educ Res 2, 55–70.

Das, A.J., 2012. Moringa oleifera (Lamm.): A Plant with Immense Importance. J. Biol. Act. Prod. Nat. 2, 307–315.

Dubey, D.K., Dora, J., Kumar, A., Gulsan, R.K., n.d. A Multipurpose Tree-Moringa oleifera.

Fahey, J.W., 2005. Moringa oleifera: A Review of the Medical Evidence for Its Nutritional, Therapeutic, and Prophylactic Properties. Part 1. Phytochemistry 47, 123–157.

Government of UK, 2007. British Pharmacopoeia 2007. Government of UK.

Jagtap, C., 2013. Bird's eye view on herbal market products in india for the treatment of obesity. J. Drug Deliv. Ther. 3.

Jaiswal, D., Kumar Rai, P., Kumar, A., Mehta, S., Watal, G., 2009. Effect of< i> Moringa oleifera Lam. leaves aqueous extract therapy on hyperglycemic rats. J. Ethnopharmacol. 123, 392–396.

Klein, T., Longhini, R., Bruschi, M.L., Mello, J.C.P. de, 2013. Development of tablets containing semipurified extract of guaraná (Paullinia cupana). Rev. Bras. Farmacogn. 23, 186–193.

Linden, R., Ortega, G.G., Petrovick, P., Bassani, V., 2000. Response surface analysis applied to the preparation of tablets containing a high concentration of vegetable spray-dried extract. Drug Dev. Ind. Pharm. 26, 441–446.

Manu, J.M., Barminas, J.T., Aliyu, B.A., Osemeahon, S.A., 2013. Formulation Of Moringa Oleifera Seed Powder And Ferrous Sulfate Heptahydrate Into A Matrix To Control Coliform Bacteria And Odor In Poultry Manure. Int. J. Eng. 2.

Marrufo, T., Encarnação, S., Silva, O.M.D., Duarte, A., Fazenda Neto, F., Barbosa, F.M., Agostinho, A.B., 2013. Chemical characterization and determination of antioxidant and antimicrobial activities of the leaves of Moringa oleifera. Rev. Int. Gest. Conflitos Ambient. 2.

Mehta, A., Agrawal, B., 2008. Investigation into the mechanism of action of Moringa oleifera for its anti-asthmatic activity. Orient. Pharm. Exp. Med. 8, 24–31.

Mishra, S.P., Singh, P., Singh, S., 2012. Processing of Moringa oleifera Leaves for Human Consumption. Bull Env Pharmacol Life Sci Vol. 2, 28–31.

Okoye, E.I., Awotunde, T.O., Morales, T.G., 2013. Formulation and characterization of moringa oleifera leaf granules. i. micromeritic properties. Res. J. Pharm. Technol. 6, 66–74.

Pharmacopoeia, B., 2010. Edition,(2010): London.

Porter, S.C., Felton, L.A., 2010. Techniques to assess film coatings and evaluate film-coated products. Drug Dev. Ind. Pharm. 36, 128–142.

Rowe, R.C., Sheskey, P.J., Quinn, M.E., Press, P., 2009. Handbook of pharmaceutical excipients. Pharmaceutical press London.

Sarfaraz, N.K., 2004. Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Product. Boca Raton FL CRC Press 200, 151–152.

Shah, R.B., Tawakkul, M.A., Khan, M.A., 2008. Comparative evaluation of flow for pharmaceutical powders and granules. Aaps Pharmscitech 9, 250–258.

Wewan Md. Badruddoza, 2013. Moringa oleifera: Its phytochemicals and their uses. Cultiv. Moringa.