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Evaluation of Processing Methods for Formulated Tablets of *Loranthus micranthus*

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

Abstract

Background: *Loranthus micranthus* is one of the many plants that has documented evidence of safety and efficacy in the management of many ailments and widespread use in almost every part of Nigeria. It is desirable to formulate it into a suitable dosage form for use by the populace.

Objectives: The research was aimed at formulating the aqueous leaf extract of *L. micranthus* into a tablet dosage form by wet granulation and direct compression methods.

Methods: For wet granulation method, maize starch, gelatin, polyvinyl pyrrolidone and acacia were used as binders for the formulations each was used at 2, 3, 4 and 5 % w/w concentration in the tablet. The direct compression method involved the preparation of an extract containing material (ECM). Microcrystalline cellulose, pregelatnised starch, starlac and spray dried lactose were used as filler binders for the direct compression. All the formulated tablets were assessed by comparing the crushing strength-friability ratio (CSFR) and the disintegration time (DT) to select an optimum formulation that meets both mechanical and release properties.

Results: Using wet granulation method, maize starch and gelatin (at 3 %w/w) binder concentration as well as gelatin at 2 %w/w binder concentration produced the optimal formulations. The tablets formulated by direct compression all disintegrated within 10 min and below with microcrystalline cellulose (MCC) tablets disintegrating at 7 min. In dissolution studies, all the optimized formulations released more than 70 % of the extract within 40 min with MCC releasing up to 98 % in 30 min.

Conclusion- Direct compression of the extract containing material produced improved tablet formulations than the wet granulation method.

Keywords: Extract containing material, Wet granulation, Direct compression, Physicochemical properties

INTRODUCTION

Plants have always been an important source of drugs. The plant kingdom is a treasure house of potential drugs and in recent years there has been an increasing awareness about the importance of medicinal plants (Abdu *et al*., 2016; Soundharya and Manoharan, 2020; Manwar *et al*., 2021). *Loranthus micranthus* Linn (mistletoe) is a hemiparasitic plant that grows on different host trees and shrubs. It depends on the host plant for water and mineral nutrition, even though it produces its own carbohydrates through photosynthesis (Ali *et al*., 2005). It grows on many host trees like *Kola acuminata*, *Baphia nitida*, *Persia americana*, *Irvingia gabonensis*, *Citrus simensis*, *Pentacletra macrophylla*, *Treculiar africana*, and *Ficus exaperata* (Ali *et al*., 2005; Osadebe *et al*., 2012). *Loranthus micranthus* Linn belongs to the family Loranthaceae, popularly called Kauchi in Hausa, Afomo onisana in Yoruba, Owube or Awurisi in Igbo (Ani *et al*., 2020).

Loranthus micranthus has been widely used in ethnomedicine for various purposes, including antihypertensive, anticancer, antispasmodic, antidiabetic, and for treatment of epilepsy, headache, infertility, menopausal syndrome and rheumatism. In Nigeria and other parts of Africa, the plant (*Loranthus micranthus*) has been used in ethnomedication against diabetes, hypertension, schizophrenia and as an immune booster (Osadebe and Ukuweze, 2004; Osadebe and Omeje, 2009; Isikhuemen *et al*., 2020; Olakanmi *et al*., 2020). Obatomi *et al*., 1996; Osadebe and Omeje, 2009; Ameer *et al*., 2010 all reported the antihypertensive activity of the plant extracts and Udekwu *et al*. (2020) reported that the aqueous extract of the plant is not toxic. The plant is usually prepared as a decoction, infusion and maceration these are bulky to handle, prone to microbial spoilage and generally unstable. Formulation into a tablet dosage form will provide an easy to handle, convenient and relatively more stable dosage form to administer the extract. The objective of the study is to formulate *Loranthus micranthus* extract into a tablet dosage form and evaluate the tablet properties with a view to developing an optimized tablet formulation to be used in the treatment of diabetes.

METHODOLOGY

Materials

Loranthus micranthus leaves, distilled water, starch, polyvinyl pyrollidone, magnesium stearate, talc, petroleum ether, microcrystalline cellulose, spray dried Lactose, hydrochloric acid (BDH, England), acacia (Tic Gums, U.S.A), gelatin (Sigma, Germany), starLac (Roquette Pharma, France). HCl, copper (ii) sulphate, petroleum ether, ferric chloride, ammonia solution, sulpuric acid, chloroform, (Merk, Germany).

Equipment

Sieve shaker (EFL 74I6, England), Flow rate meter (GDT Nr 42232, Germany), Tableting machine (Erweka AR 400, Germany), UV spectrophotometer (UV/Vis-1700 Shimadzu, Japan), blender (Kenwood, England), Oven (Gallenkamp, England), Furnace, crucibles, Moisture analyser (Sartorius, Germany), disintegration tester (Erweka Z T3, Germany), dissolution apparatus (Nr 43041, Germany), Hardness tester (TBH 100, Germany), friabrilator (TA3R, Germany), beakers , measuring cylinders, volumetric flasks cuvettes, soxhlet extractor, Dessicator.

Methods

Collection

The plant was collected from the host trees (*Azadirachta indica*) in Maiduguri metropolis in the month of July. It was then transported to the Department of Biological Sciences in Ahmadu Bello University Zaria for identification and a specimen number (2839) was assigned to it for future reference.

Preparation

The leaves were dried indoors at room temperature for one month until they were crispy dried. The dried leaves were then powdered using a domestic blender (Kenwood SB266, England), which was washed and cleaned prior to the grinding.

Characterization of the powdered leaves and Extract containing material (ECM)

1. Flow rate

The flow rate of the powdered leaves and extract containing material was assessed using 10 g of the respective powders with a Flow rate meter (GDT Nr 42232, Germany).

2. Angle of repose

The angle of repose of *L.micranthus* powdered leaves and ECM was determined by using a glass funnel clamped on a retort stand 10 cm away from the flat surface of the bench. 10 g of the powder sample was placed inside the funnel and allowed to flow freely to form a conical heap (Halgoudar *et al*., 2022). The angle of repose was then calculated from the heap using the equation as follows;

$$\tan\theta = h/r \quad \text{---------- (1)}$$

Where h = height and r = radius of the circular heap.

3. Bulk and tapped density

The volume occupied by a 10 g weight of powder sample in a dry measuring cylinder was measured. The bulk density was calculated using the formula;

$$Bulk\ density = (weight\ of\ powder)/(\text{volume of powder}) \quad \text{..... (2)}$$

The measuring cylinder was then tapped 50 times on a wooden table from a height of about 2cm and the tapped volume recorded (Chavan *et al*., 2020). The tapped density was calculated as;

$Tapped\ density = (\text{weight of powder})/(\text{tapped volume of powder})$..... (3)

4. Carr's index

Carr's index was calculated using results obtained from bulk and tapped densities above using the equation below (Sreedharan *et al*., 2020).

$$Carr's\ index\ (\%) = \frac{\text{Tapped density} - \text{bulk density}}{tapped\ density} \times 100$$

5. Hausner's ratio

Hausner's ratio was determined using the results obtained from both bulk and tapped density. It is calculated using the formula below (Shriwas *et al*., 2019).

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad \text{..... (5)}$$

6. Hydration capacity

One gram of the powder was weighed and poured into centrifuge tubes. 10 ml of distilled water was added and mixed for 2 min. The mixture was centrifuged for 10 min at 1000 revolutions per minute (rpm). The supernatant obtained was decanted and the sediment weighed. The hydration capacity determined using the equation below respectively (Mua'zu *et al*., 2013).

$Hydration\ capapcity = WS/WD$..... (6)

Where, WS and WD are the weights of the sediment formed and weight of the dry sample

Extraction

The dried leaves were extracted with distilled water as solvent. The powdered leaves (500 g) of *Loranthus micranthus* parasitic on *Azadirachta indica* was first defatted with 1.0 L of petroleum ether and then macerated with 3.0 L of distilled water and extracted at room temperature for 48 h with agitation. The resulting aqueous extract was concentrated in an evaporating dish over a water bath maintained at 100 °C for 3 h to obtain the aqueous extract.

Phytochemical screening of the aqueous extract

This was carried out to detect the presence of secondary metabolites such as alkaloids, flavonoids, tannins, phlobatannins, glycosides, phenols and sterols in the aqueous extract of the leaves using standards methods.

Test for Alkaloids

One gram (1 g) of the extract was stirred with 20 ml of 1 % aqueous hydrochloric acid on a water bath and filtered. The filtrate was basified with concentrated ammomuim hydroxide and extracted with chloroform. The chloroform layer was then extracted with 2 ml of 1 % HCl. The aqueous layer was divided into three portions for the following tests: To the first portion, 1 ml of freshly prepared Dragendorff's reagent was added drop-wise and observed. To the second portion 1 ml of Mayer's reagent was added drop-wise and observed. The third portion was used as control. Appearance of rose red to brownish and white to yellowish or cream color respectively indicates the presence of alkaloids (Evans, 2002).

Test for Saponins

(a) Frothing test: Five hundred milligram quantity of the extract was dissolved in 10 ml of water and shaken vigorously for 30 seconds and allowed to stand for one hour, the occurrence of a frothing column (or honey comb-like froth) of at least 1 cm in height and persisting for at least 30 minutes indicates the presence of saponins (Sofowora, 2008).

(b) Haemolysis test: Two millilitres (2 ml) of sodium chloride (1.8 % solution in distilled water) was added to two test tubes A and B. Two millilitres of distilled water was added to test tube A, and 2 ml of the extract was added to test tube B. Five drops of adult human blood obtained from a volunteer were added to each tube and the tubes were inverted gently to mix the contents. Haemolysis in tube B containing the extract but not in tube A (i.e. control), indicated the presence of saponins in the extract (Evans, 2002).

Test for steroids/terpenes

(a) Lieberman-Burchard test: One milliliter (1 ml) of acetic anhydride was added to 0.5 g of the extract dissolved in 1 ml of chloroform. Concentrated sulphuric acid was then added gently by the side of the test tube to form lower layer and at the junction of the two liquids. Formation of reddish brown or violet brown ring, the upper layer bluish green or violet indicates the presence of sterols and or triterpenes (Evans, 2002).

(b) Salkowski test: Two millilitres (2 ml) of chloroform was added to 0.5 g of the extract and 1 ml of concentrated sulphuric acid was carefully added to the side of the test tube to form a lower layer. A reddish brown coloration at the interface indicated the presence of steroidal nucleus (Sofowora, 2008).

Test for cardiac glycosides

Keller-Killiani test: A 0.5 g weight of the extract was dissolved in glacial acetic acid containing ferric chloride and one drop of sulphuric acid was added to the solution. The appearance of reddish-brown colouration at the interphase indicates the presence of deoxysugar (Sofowora, 2008).

Test for Tannins

(a) Ferric chloride test: A 0.5 g weight of the extract was dissolved in 5 ml of water each and filtered. Two drops of ferric chloride solution were added to the filtrate. Appearance of blue-black or green or blue-green (condensed/cathehic tannins) precipitate indicates the presence of tannins (Evans, 2002).

(b) Lead sub-acetate test: To 0.5 g of the extract, 2 ml of ethanol was added followed by two drops of lead sub-acetate solution; appearance of whitish-yellow precipitate indicates the presence of tannins (Evans, 2002).

Test for flavonoids

Sodium hydroxide test: A 0.5 g weight of the extract was dissolved in water and filtered, 2 ml of 10 % aqueous sodium hydroxide solution was then added. The solution was observed for the presence of yellow colour. A change in colour from yellow to colourless on addition of dilute hydrochloric acid was used as an indication for the presence of flavonoids (Evans, 2002).

Test for anthraquinones

Borntrager's test: A 0.5 g weight of the extract was boiled with 10 ml of aqueous sulphuric acid and filtered hot. The filtrate after cooling to room temperature was shaken with 5 ml chloroform, the chloroform layer was separated and half of its volume, 10 % ammonium hydroxide was added. A pink, red or violet colouration in the ammonia phase (lower phase) is an indication for the presence of anthraquinone derivatives (Evans, 2002).

Preparation of Granules by Wet Granulation

A weight of 100 mg of the aqueous extract was prepared per tablet (batch size of 50 tablets), maize starch, acacia, gelatin and polyvinyl pyrrolidone were used as binders for the tablet formulation. Four (4) batches of the weighed extract and the disintegrant (maize starch) were dry mixed in a porcelain pestle and mortar for five minutes. Subsequently, sufficient lactose (as diluent) was added separately to each batch after five minutes of mixing. Maize starch at 2, 3, 4 and 5 % w/w binder concentrations were also added to each batch after formation of a binder solution and mixed until a damp solid mass was formed. The mass formed was then passed through 1.7 mm stainless steel sieve to form granules. The wet granules were dried at 40 ^{0}C for one hour and then passed through a 1.0 mm stainless steel sieves in order to produce uniformly sized granules. The procedure was repeated with polyvinyl pyrrolidone, gelatin and acacia at the same binder concentrations (Chavan *et al.,* 2020).

Compression of Granules into Tablets

The granules were thoroughly mixed with extra granular excipients (magnesium stearate and talc). The granules were then compressed in a single punch tableting machine (Erweka AR 400, Germany) with punch sizes 8 mm with compression pressures of 73.5 kN (Kilo newton). The tablets were kept in an air tight container for 24 h prior to quality control tests to allow for recovery.

Table 1: Formula table for the wet granulation tablets

INGREDIENT	F 1	F 2	F 3	F 4
LME (mg)	100.0	100.0	100.0	100.0
Diluent (mg)	71.6	69.6	67.6	65.6
Disintegrant (mg)	20	20	20	20
Binder concentration (%w/w)	2	3	4	5
Binder Quantity (mg)	4.00	6.00	8.00	10.0
Glidant (mg)	4.00	4.00	4.00	4.00
Lubricant (mg)	0.40	0.40	0.40	0.40
Tablet weight (mg)	200.0	200.0	200.0	200.0

Key: LME=*Loranthus micranthus* extract; maize starch, PVP, gelatin and acacia were used as binders at 2, 3, 4 and 5 %w/w concentrations.

Formulation of the Tablets by Direct Compression

An extract containing material (ECM) was prepared for direct compression because the extract was softening on compression with the direct compression excipients (it is a soft extract). The extract containing material was prepared by mixing the *L.micranthus* extract with starch at a ratio of 1:4. Twenty grams of the extract was weighed and added to 80 g of starch, this was dispersed with 200 ml of distilled water and then heated over a water bath. This was allowed to pregelatinize at a temperature of 57 ^{0}C before drying in an oven at 40 ^{0}C. It was then size reduced and passed through a 500 µm sieve. The extract containing material was then directly compressed into 500 mg tablets by combining with pregelatinized starch (PGS), micro crystalline cellulose (MCC), spray dried lactose (SDL) and starlac® (STL) at a 1:1 ratio. Punch size of 12 mm was used and tablets were compressed manually at a pressure of 78.5 kN.

A larger die cavity size was used for the ECM tablets in order to accommodate as much of the extract as possible because bulk of the ECM was composed of starch. Each 250 mg of the ECM contains 50 mg of the extract.

Table 2: Formula table for the direct compression tablets

INGREDIENTS	F1 PGS	F2 SDL	F3 MCC	F4 STL
ECM (mg)	250.0	250.0	250.0	250.0
Filler Binder (mg)	249.0	249.0	249.0	249.0
Talc (mg)	0.50	0.50	0.50	0.50
MGT (mg)	0.50	0.50	0.50	0.50
Tablet weight (mg)	500.0	500.0	500.0	500.0

ECM=Extract containing material, PGS= pregelatinized starch, SDL= spray dried lactose, STL= starlac, MGT= magnesium stearate.

Quality Control Tests on the Tablets Produced

Tablet weight variation

Twenty (20) tablets were randomly selected from each batch and each tablet weighed and the weight recorded. The mean weight of the twenty tablets for each batch were calculated (Bavage *et al*., 2020).

Crushing strength

The Erweka hardness tester (TBH 100, Germany) was used in measuring the crushing strength of the tablets. Three (3) tablets were randomly selected from each batch. Each of these tablets were placed between the anvil and the spindle of the Erweka hardness tester and subjected to increasing pressure by turning the knob in a clockwise direction at constant rate until the tablet was crushed. The value of the pressure applied at this point gives a measure of the tablet hardness in KgF. The mean of the three determinations were taken for each batch (Vaishali *et al*., 2019).

Friability test

Twenty tablets (20) tablets were randomly picked from each batch and weighed accurately. They were then placed inside the drum of a friabrilator (TA3R, Germany) and operated for four (4) minutes at a speed of 25 rpm. Thereafter, the intact tablets were removed from the drum, dusted and weighed. The percentage loss of weight was calculated and recorded as friability value for that batch (Vaishali *et al*., 2019).

Disintegration test

Six tablets were randomly selected from each batch and placed individually in the six tubes of the rack of a disintegration tester (Erweka Z T3, Germany).The rack was then raised and lowered at constant rate in distilled water contained in a glass jar suspended in a water bath whose temperature was thermostatically maintained at 37±1°C the time taken for the last tablet or its fragment to pass through the 2mm mesh into the disintegrating medium (distilled water) was recorded for each batch (Onunkwo *et al*., 2004; Vaishali *et al*., 2019).

***In-Vitro* Dissolution Studies**

This was performed on the optimized formulations for both wet granulation and direct compression tablets for the extract and powdered leaves.

I. Scanning and determination of wavelength of maximum absorbance (λmax)

In order to ascertain the wavelength of maximum absorption of the extract, the solubility of the extract in 0.1N HCl was determined. Different concentrations of the extract (10, 20 and 30 µg per per ml) in 0.1 N HCl was scanned using a UV/VIS spectrophotometer (UV/Vis-1700 Shimadzu, Japan). A spectral scan (200-600nm) was performed against 0.1 N HCl as blank and the wavelength corresponding to maximum absorbance was then recorded (Owusu *et al*., 2021).

II. Preparation of standard stock solution

Accurately weighed 100 mg of extract was dissolved in 5 ml of distilled water in 100 ml volumetric flask and volume is then made up to the mark with 0.1 N HCl to give a clear solution of 1000 µg per ml concentration (Owusu *et al*., 2021).

III. Preparation of standard solutions and construction of Calibration Curve

A series of different concentrations of extract were prepared from the stock solution. 0.1, 0.2, 0.3, 0.4, 0.5, 0.6……0.9 and 1.0 ml solutions were pipetted out from the working stock solution and transferred into 10 ml volumetric flasks. 10, 20, 30, 40 up to 100 µg per per ml solutions were obtained respectively on making up the solution to 10 ml with 0.1 N HCl. The absorbances of all these solutions were measured against a blank (0.1 N HCl) at a wavelength (λ max) of 206 nm using a UV spectrophotometer (UV/Vis-1700 Shimadzu, Japan). A standard plot of absorbance v/s concentration of extract was constructed and this gave the standard calibration curve of the extract. This curve was used to determine *in vitro* drug release and drug content of herbal tablets (Owusu *et al*., 2021).

IV. Dissolution test

Drug release was assessed by dissolution test using USP type II dissolution apparatus dissolution apparatus (Nr 43041, Germany) at 50 rpm in 900 ml of 0.1N HCl maintained at 37 ± 0.5˚C. The tablet was allowed to sink to the bottom of the flask before stirring. 5 ml of the sample was withdrawn using a

syringe filter at regular intervals of ten minutes and replaced with the same volume of pre-warmed (37 ± 0.5°C) fresh dissolution medium. The drug content in each sample was analysed using UV spectrophotometer method at a wave length of 206 nm which is the wavelength of maximum absorbance determined (Owusu *et al*., 2021).

V. Drug content uniformity test

From each batch, 20 tablets were taken, weighed and crushed. An adequate amount of this powder theoretically equivalent to 100 mg and 50 mg of the drug (for the aqueous extract and ECM tablets respectively) was accurately weighed and shaken with 150 ml of 0.1N HCl for 10 min. The mixture was diluted with 0.1N HCl to produce 200ml and filtered. 10 ml of the filtrate was then diluted to 100 ml with distilled water and the absorbance measured at 206 nm. The drug content in the formulation was calculated using the standard curve (Owusu *et al*., 2021).

Stability studies

The optimized formulations were evaluated for drug content uniformity, mean tablet weight crushing strength, friability and disintegration time after six months to ascertain if there were any significant changes in these tablet properties. Paired sample t-test was carried out to determine if the changes to these parameters were statistically significant.

RESULTS AND DISCUSSION

Formulating herbal materials into conventional dosage forms will require expertise in dosage form design and preparation (Adigwe *et al*., 2022). The complex nature of plant derived materials as drugs presents a wide variety of formulation problems that require extensive investigation before an optimum formulation can be made (Lockwood, 2013). Phytochemical screening of the extract (Table 3) revealed the presence of alkaloids, glycosides, tannins, steroids and triterpenoids, flavonoids, anthraquinones, resins and phlobatanins. The saponins were not detected in this study, similar results were obtained by Egbuonu and Nwankwo (2011) in which saponins, alkaloids and glycosides were absent in the extract. Orji *et al.* (2012) however detected saponins in the extract. Moglad *et al*. (2022) also detected all the secondary metabolites including the saponins in another specie of the plant (*Loranthus acaciae*). The physicochemical properties of the powdered leaves and the extract containing material (Table 4) show that the extract containing material had a flow rate of 1.55 g/sec while the powdered leaves had a flow rate of 2.48 g/sec, the moisture content of the ECM was observed to be 5.18 % while that of the powdered leaves was 4.7 %. Hydration capacity is a measure of how much the powder is able to take up water, the powdered leaves had a higher hydration capacity than the ECM. Both the powdered leaves and ECM had high values of angle of repose, this indicates poor flow property which may be due to their cohesive nature and small particle size. The two powders showed a passable flow from the values of the angle of repose observed (Aulton, 2013) and the results also indicate a fair flow property for the powdered leaves and a passable flow for the ECM based on Carr's index and Hausner ratio criteria (Aulton, 2013). Weight variation is a very important test because it is usually associated with variation of the content of the active ingredient especially for tablets in which the active ingredient constitutes a larger bulk of the formulation (Alderborn, 2013). Tablet friability is a measure of the resistance of the tablets to abrasion and a loss in weight less than 0.5 to 1 % of the initial weight of the tablet is considered as acceptable limits. Hardness or crushing strength indicates the mechanical strength of the tablets and it should fall within acceptable limits of 3-6 kgF (Muazu and Suleiman, 2014). Disintegration is defined as the process of breakdown of tablet into small particles, uncoated tablets are supposed to disintegrate within 15 min. The properties of the wet granulated tablets (Table 5) showed that all the batches passed weight variation test. Crushing strength and disintegration times increased steadily with increase in binder concentration. This is as expected because the binder or adhesive holds the particles together and a higher binder concentration will increase the bond

Table 3: Phytochemical screening of the aqueous extract

Phytoconstituent	*Method Used*	*Results*
Alkaloid	Meyer's test	+
	Dragendorff's test	+
Saponins	Frothing test	-
	Hemolysis test	-
Steroids & triterpenoids	Lieberman's test	+
Cardiac glycosides	Salkowski test	+
Tannins	Soluble	+
	Condensed	+
Flavonoids	Lead sub- acetate test	+
Anthraquinones	Borntrager's test	+
Phlobatanins	HCL test	+
Resins	Copper (II) Sulphate test	+

Table 4: Physicochemical properties of the powdered leaves and Extract containing material

Parameter	**Powdered Leaves**	**ECM**
Flow rate (g/sec)	2.48	1.55
Hydration capacity	1.50	0.72
Moisture content (%)	4.7	5.18
Angle of repose (º)	42.6	43.8
Bulk density (g/ml)	0.37	0.40
Tapped density (g/ml)	0.46	0.51
Carr's index (%)	19.7	21.6
Hausner ratio	1.24	1.28

Table 5: Properties of the wet granulation tablets

Batch	**Weight variation (mg±SD)**	**Friability (%)**	**Crushing strength (KgF±SD)**	**Tensile strength (MNm^{-2})**	**Disintegration time (min)**
A2	208±6.0	1.20	2.7±0.60	0.47	10.0
A3	202±7.0	0.95	4.3±0.80	0.11	10.0
A4	206±7.0	0.90	6.9±0.80	1.30	17.0
A5	197±10	0.80	6.9±0.70	1.27	18.0
B2	195±5.0	1.30	3.4±0.80	0.64	20.0
B3	197±8.0	1.10	4.2±0.80	0.75	22.0
B4	196±5.0	0.90	5.2±0.80	1.03	25.0
B5	197±5.0	0.80	5.7±0.70	1.05	25.0
C2	206±9.0	1.00	3.2±0.60	0.57	14.0
C3	201±6.0	1.00	4.3±0.40	0.75	15.0
C4	201±7.0	0.90	4.3±0.70	0.75	18.0
C5	200±9.0	0.80	4.8±0.80	0.92	20.0
D2	199±8.0	2.30	1.3±0.40	0.21	10.0
D3	198±7.0	1.20	2.1±0.22	0.39	13.0
D4	198±8.0	0.50	5.7±1.20	1.13	18.0
D5	206±7.0	0.60	5.7±1.1	1.19	25.0

Key: ± Standard deviation
A=maize starch, B=PVP, C=gelatin and D=acacia.
The numbers 2, 3, 4 and 5 represent the respective binder concentrations

strength of the tablets which will in turn increase the crushing strength and prolong the disintegration time. Batches A2 (maize starch 2 %), B2 (PVP 2 %), B3 (PVP 3 %), D2 (acacia 2 %) and D3 (acacia 3 %) all failed friability test, this is likely due to their relatively low binder concentrations, their crushing and tensile strengths were also relatively lower than the other formulations. Batches A4, A5, B2, B3, B4, B5, C4, C5, D4 and D5 all failed the disintegration test (they all had longer disintegration times). The longer disintegration times could be attributed to the relatively high binder concentration in these formulations. All the formulations of batch B (PVP) failed the disintegration test even at low binder concentration possibly due to higher bond strength with the extract. PVP was shown by Gunatilake *et al*. (2016) to have the highest bond strength and longest disintegration time in paracetamol tablets than maize starch. Batches C2 and C3 (gelatin 2 and 3 % respectively) produced tablets with good properties, similar findings were reported by Muazu and Suleiman, (2014) with *Moringa oleifera* extract where the same binder (gelatin) produced relatively better tablet formulations than MCC as a binder. The extract (Plate I) was converted into a free flowing powder (ECM) to enable direct compression. The directly compressed tablet formulations (Table 6) all passed weight variation requirements. All the batches also passed the limits for friability crushing strength and disintegration time. Batch E2 (with MCC as filler binder) had the shortest disintegration time. This is likely due to the ability of MCC to swell on contact with water. E1 (with pregelatinised starch PGS as filler) also swells in contact with water and this may explain the shorter disintegration time observed. The fast disintegration times observed with the directly compressed tablets is likely because of the relatively higher total starch content in the formulations (Chaerunisaa *et al*., 2016). Wet granulation usually produces tablets that have stronger bond strength than direct compression and this might explain also the relatively faster disintegration observed with the directly compressed tablets compared with the wet granulated tablets. On studying the effect of binder concentration on the crushing strength of the wet granulated tablets (Table 5) it shows an increase in crushing strength with increase in binder concentration, similar results were obtained by Ayorinde *et al*., (2011) with gelatin and Albizia gum as binders. A decrease in tablet friability is also seen with increase in binder concentration. PVP failed disintegration test at all concentrations for the tablets of the wet granulated tablets, this suggest that the extract and PVP form very strong bonds which are difficult to break, making it difficult for the particles to separate. It is observed that maize starch, acacia and gelatin all passed disintegration test at the lower binder concentrations but failed at 4 and 5 %. This also suggests the formation of very strong bonds between the extract and these binders at 4 and 5 % binder concentrations. All the tablets failed disintegration test at 4 and 5 % binder concentrations, this suggest that the lower binder concentrations are more suitable for their formulation with the *Loranthus micranthus* extract. The aim of dissolution testing is to measure the rate and extent of solution formation from a dosage form (Asare *et al*., 2021). The dissolution profile of the 3 % batches of the wet granulated tablets as well as the direct compression batches were studied. All the batches showed an initial slow release rate followed by a sharp increase. For the 3 % batches of the wet granulated tablets (Figure 1), A3 (maize starch) which was the optimized formulation had the fastest dissolution profile, this is probably due to its short disintegration time (10 min) D3 (acacia) closely followed. Only F3 (PVP) failed the dissolution test because of its relatively longer disintegration time of 22 min (Table 5). With the directly compressed tablets (Figure 2), E2 with MCC as direct compression excipient showed a rapid dissolution, all the directly compressed tablets had superior dissolution profiles than the wet granulated tablets. Tablets prepared by direct compression disintegrate directly into drug particles instead of granules and exhibit comparatively faster dissolution (Iquba *et al*., 2014). The release profile of the optimized formulations showed that up to 98 % of the drug (extract) was released in 30 min for MCC compared to 85 % and 58 % for maize starch and acacia respectively. For immediate release products, a single-point specification is used to ensure prompt dissolution; normally, no less than 75 % of the must be dissolved within 45 min (Freire and Basit, 2013). The optimized formulations (A3 and E2) met this requirement as at least 75 % of drug was released within 45 min (Table 8). The optimized formulations (A3 and E2) were tested for percent drug content, average tablet weight, crushing strength, friability and disintegration time after six months (Table 7) and they all showed a slight reduction in the % drug content after 6 months, the decrease was higher for A3 than E2. All the parameters tested remained within pharmacopoeial limits after six months, statistical analysis (paired sample t-test) further confirmed that there was no significant difference between the various formulations ($p>0.05$) parameters at zero and six months.

Table 6: Properties of the directly compressed tablets

Batch	Weight variation (mg±SD)	Friability (%)	Crushing strength (KgF±SD)	Tensile strength (MNm^{-2})	Disintegration time (min)
E1	502±0.8	1.0	4.0±0.13	0.48	8.0
E2	501±0.5	0.7	5.0±0.23	0.63	7.0
E3	501±0.4	1.0	5.0±0.31	0.60	10.0
E4	502±0.5	1.0	5.0±0.20	0.63	10.0

Key: ± Standard deviation
E1=pregelatinised starch, E2= microcrystalline cellulose, E3= spray dried lactose and E4= starlac

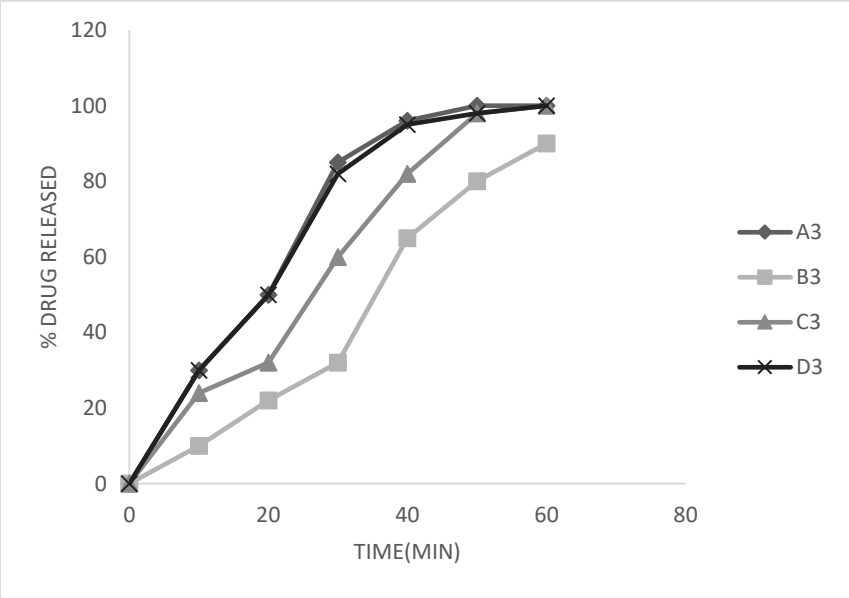

Figure 1: Dissolution profile of the 3 % batches of the wet granulated tablets

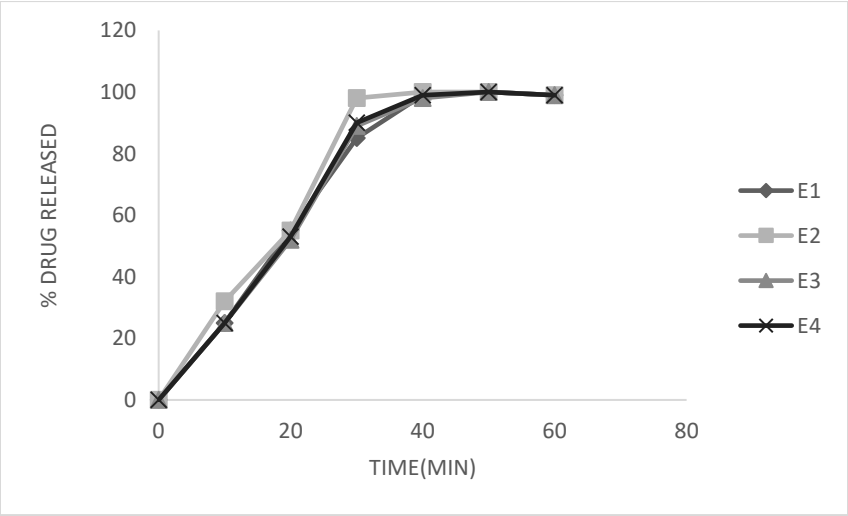

Figure 2: Dissolution profile of the directly compressed tablets.

Table 7: Stability studies of the optimized formulations after six months

Batch	**A3**		**E2**	
Time of testing (Months)	0	6	0	6
Drug content (%)	97.50	96.5	97.05	97.00
Mean tablet weight (mg)	202	201	501	501
Crushing strength (KgF)	4.3	4.3	5.0	5.0
Friability (%)	1.0	1.0	0.7	0.7
Disintegration time (min)	10	10	7.0	8.0

Plate I: Picture of the Soft Extract and Extract containing material

CONCLUSION

The directly compressed tablets showed optimal properties in terms of mechanical strength and drug release compared to wet granulation method. The results obtained show that using wet granulation method, maize starch at a binder concentration of 3 % w/w is best for the extract and with direct compression method, MCC is the best filler binder. All the optimized formulations maintained acceptable mechanical and release properties after six months.

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