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Full Length Research Article

BINDER PROPERTIES OF TRECULIA AFRICANA GUM IN IMMEDIATE RELEASE METRONIDAZOLE TABLETS

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ABSTRACT

The study is aimed at investigating the binder properties of*Treculia africana* seed gum in metronidazole tablets in order to find a suitable locally sourced alternative for use as pharmaceutical binder in tablet dosage forms. The treculia gum was extracted from the seeds of *Treculia africana* by defatting using chloroform and methanol in the ratio of 2:1 and cold precipitation in acetone using acetone/gum powder mucilage in the ratio of 3:1. Tablets of metronidazole containing 0 1, 2, 3 and 4% w/w concentrations of *Treculia africana* gum were prepared using wet granulation method. The tablets were evaluated for weight variation, hardness, friability, disintegration time and dissolution time according to the British Pharmacopoeia standards. Results showed that tablet crushing strength values of 2 – 8 kgf, disintegration time of 0.49 -1.31 minutes and friability values of 0.582-5.801%.The dissolution test result showed that all the batches had more than 80%release of their metronidazole content within 45 minutes and more than 95% release within one hour. The tablets produced using treculia gum especially at 3% and 4% w/w gum concentrations conformed with the official quality control standards as stipulated in the British Pharmacopoiea. Therefore, *Treculia Africana* gum could serve as a local alternative for use as binder in tablet production.

INTRODUCTION

The sourcing of pharmaceutical raw materials for drug formulations is an issue of great concern in the pharmaceutical industries (Onwualu *et al.*, 2013). The aforestated problem affects pharmaceutical industries in developing economies since they have to import most of these raw materials at high costs, due to cost of shipping and high money exchange rates. Binders are usually one of the most important ingredients in tablet formulation because they help to produce free flowing granules for easy mechanization of tablet production (Chaudhary *et al.*, 2012). Natural binders of plant origin are usually easy to source and isolate with less equipment requirement.Gum from the seeds of *Treculia Africana* was used in the preparation of metronidazole tablets. *Treculia africana* is a tree species known as African breadfruit. It is abundant in west and central Africa (Aderibigbe *et al.*, 2010).

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Unfortunately, some natives of these regions do not attach any economic importance to this plant and so, they allow the fruits to waste. The seed gum of *Treculia africana* has found importance in pharmaceutical production of metronidazole tablets. Metronidazole is a nitro imidazole antibiotic medication used particularly for anaerobic bacteria and protozoal infections. (Freeman *et al*., 1997). Metronidazole may rank the second to fourth most empirically used drug in Nigeria, (Kamaldeen *et al*., 2013) Therefore, there is need to develop local raw materials such as treculia gum for the production of metronidazole tablets.

MATERIALS AND METHODS

Materials

- Metronidazole (BDH Chemical Limited Poole, England).
- Lactose (BDH Chemical Limited Poole, England).
- Magnesium stearate (BDH Chemical Limited Poole England).

- Maize starch (BDH Chemical Limited Poole England).
- Binder (Treculia , locally prepared; Acacia (BDH, Chemical Limited, Poole, Syria).
- Acetone (Analar, BDH Chemical Limited Poole England).
- Methanol (Analar, BDH Chemical Limited Poole England).
- Chloroform (Analar, BDH Chemical Limited Poole England).

Extraction of Treculia Gum

Fresh seeds of *Treculia Africana* were dehusked by boiling in water at 80°C for 4 hours to soften the husk before removal. The husks were removed and the seeds air dried. The seeds were reduced to powder by milling using a mechanical grinding machine (03200 Landers and Ciasa, Corona). The powder was defatted by soaking in a closed container containing chloroform and methanol mixture in the ratio of 2:1 for 24 hours after which it was sieved using a muslin bag. The residue was air dried for 12 hours and then, it was oven dried for another 6 hours at 60°C.

A mucilage of the gum was formed by boiling the powder in water for 3 hours and the mucilage was sieved using a muslin bag. The treculia gum was precipitated by cold maceration in acetone at an acetone/gum mucilage ratio of 3:1. The gum was air dried for 3hours and then, it was oven dried at 60°C for 3hours. The dried gum was milled into a powder and stored in suitable container (Uzondu *et al.*, 2014).

Formulation of Metronidazole Tablets

Five batches of metronidazole tablets were prepared (using the wet granulation method) containing 0%, 1%, 2%, 3% and 4% of treculia gum as binder.The granules were evaluated for flow properties (using Carr's index, Hausner's ratio and angle of repose) before being compressed into tablets.[7]

Evaluation of Granules Properties

Determination of Bulk and Tapped Densities

A 30g quantity of granules was gently poured into a clean, dry 100ml measuring cylinder and the volume recorded. The cylinder was then tapped for 50 times from a constant height and the tapped volume recorded. The bulk and tapped densities were calculated with the formulae stated below (Hancock *et al.*, 2003).

Bulk Density = Mass of Granules/Bulk Volume…… (1)

Tapped Density=Mass of Granules/Tapped Volume…….. (2)

Determination of Angle of Repose (Ø)

A 30g quantity of the granules from each batch was allowed to flow through a funnel of orifice diameter 0.3 cm from a height of 7cm on a plain sheet of paper. The height of the conical heap (h) formed was measured by means of a graduated rule and a pin while the diameter (d) / radius (r) of the granule heap was determined from circular outlines of the base of the granule heaps. The angle of repose (Ø) of each granule batch was calculated from the equation below (Rahim *et al.*, 2014).

Tan Ø = Height of heap (h)/Radius of the heap (r) …… (3)

$Ø = Tan^{-1} (h/r)$ …… (4)

Where r= d/2 ……... (5)

Derived Powder Properties of Metronidazole Granules

The Hausner's ratio and Carr's compressibility index were derived from the bulk and tapped densities values as shown below (Rakhi *et al.*, 2008).

Determination of Hausner's Ratio

The Hausner's Ratio was calculated using the formula below:

Hausner's Ratio = (TD)/ (BD) ……..…..……...… (6)

Where, TD = Tapped Density and BD = Bulk Density (Rakhi *et al.*, 2008).

Determination of Carr's Compressibility Index

The Carr's Compressibility Index was calculated using the formula below:

Carr's Index = (TD - BD) / (TD) x 100……..... (7)

Where, TD = Tapped Density and BD = Bulk Density (Rakhi *et al.*, 2008).

Evaluation of Tablet Properties

The properties of the five batches of tablets produced were determined to ensure compliance with pharmacopoeia standards. The following tests described below were performed.

Weight Uniformity

Twenty tablets from each batch were randomly selected, weighed individually using an electronic weighing balance (Model SPG 450). The mean and the standard deviation were calculated (Chalapathi *et al.*, 2010).

Diameter and Thickness of Tablets

Ten tablets from each batch were selected and the tablets' diameter and thickness were measured using metre rule and venier calliper and their mean were calculated (Chalapathi *et al*., 2010).

Hardness Test

Ten tablets from each batch were used for the hardness test and the Monsanto hardness tester was employed. The tablet to be tested was placed between the spindle and the anvil, then pressure was applied by turning the knob just sufficient to hold the tablet in position. The reading on the pointer on the scale was adjusted to zero and pressure was then increased as uniformly as possible until the tablets cracked and the pointer value was read, which indicated the pressure required by the

tablets to break. Different values were obtained for different batches and they were recorded (Khan *et al*, 2013).

Friability Test

The friability test was done by randomly selecting ten tablets from each batch which were weighed together using an electronic weighing balance (Model SPG 450).The weighed tablets were subjected to abrasive shock at 25 rpm for 4 minutes using a friabilator (Model B and T DC-01).The tablets were dedusted and re-weighed and the percentage weight loss was calculated (BP, 2011).

Disintegration Time Test

A Manesty tablet disintegration unit (Manesty M/C4, England) was used for the disintegration time test. The disintegration time was determined by placing six tablets obtained from each batch in the six perspex tubes in the basket immersed in a freshly prepared 0.1N HCl solution maintained at 37 ±1°C. The time taken for the tablet to break up into small aggregates was noted as the disintegration time (BP, 2011).

Dissolution Profile Studies

The Erweka dissolution unit (DT model) was used and the dissolution medium (0.1 NHCl) was maintained at 37 ±1°C. A 900ml volume of freshly prepared 0.1 N HCl was used for each run (60 minutes) of the dissolution experiment. A 5ml sample was withdrawn from the dissolution medium at 5, 10,15,20,25,30,35,40, 45,50,55 and 60 minutes intervals. For every 5ml sample withdrawn, another 5ml of the 0.1 N HCl solution maintained at the same temperature was added to maintain the volume of the dissolution medium at 900 ml. The absorbances of the samples withdrawn (from dissolution medium) were determined at a wavelength of λmax = 253nm using a UV spectrophotometer (Model SPG 450) and the absorbance values were converted to concentration terms using Beer's plot of metronidazole (BP, 2011; Kapoor *et al*., 2011).

RESULTS AND DISCUSSION

Micromeritic Properties of Granules

The results of the flow properties of the granules (for tablet production) generated are presented in table1above:

The bulk and tapped densities were calculated from the bulk and tapped volumes. The bulk and tapped densities were then employed in the determination of derived granule properties such as Carr's compressibility index and Hausner's ratio. The later parameters are indirect measures of granule flow.

Table 1. Micromeritric Properties of Granules

Binder Conc .(%)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's ratio	Angle of Repose (º)
0	0.43±0.11	0.56±0.16	23	1.30	23.8±2
1	0.48±0.13	0.57±0.13	15	1.18	24.9±3
2	0.44±0.15	0.57±0.12	16	1.29	23.4±2
3	0.45±0.10	0.58±0.11	22	1.28	26.8±1
4	0.49±0.13	0.56±0.12	12.5	1.14	25.7±2

The granule flow properties as determined (Table 1) showed that all the granules had good to excellent flow properties except the batches that had zero percent and three percent binder concentrations. Good flowability shows that the granules have less interparticulate attractions and so, they will not easily consolidate to block the hopper orifice during tableting (Hancock *et al.*, 2003; Rahim *et al*., 2014; Rakhi *et al.*, 2008).

Evaluation of Tablet Properties

Table 2 above shows some of the tablet properties of metronidazole tablets prepared with treculia gum

Weight Uniformity

According to USP, for tablets weighing greater than 325mg, not more than two tablets should deviate from the average by more than ±5%. All the tablets prepared had percentage weight deviation of not more than ±0.001% (Table 2) which conforms to the USP specification. The aforestated result implies that the content of each of the batches are likely going to be uniform within the USP specifications. Tablets out of this range may be as a result of uneven handling of granules into the die or irregular movement of the lower punch producing a die space of varying capacity. Based on the specification, it can be said the tablets prepared passed the weight uniformity test (Chalapathi *et al.*, 2010).

Tablet Hardness

In accordance with the standards contained in the British Pharmacopoeia, which states that tablet hardness results should fall within a range of 4- 8kgf. From the results above (Table 2), it can be noted that all the tablets passed the test (Khan *et al*., 2013). Therefore, these tablets may be able withstand vibrations (from transportation and handling) without breaking.

Tablet Friability

According to BP and USP, the total weight loss should not be more than 1% and no tablet should show any type of breakage or crack. From the results in Table 2 above, only tablets prepared with 3% and 4% concentrations of treculia gum passed the test. This test is remarkably important because it helps to determine the ability of the tablets to withstand vibrational force exerted on it during transportation. Changes of more than 1% in tablet weight may lead to substantial variation/reduction in content of active ingredient and so, therapeutic efficacy of the tablet may be compromised (BP, 2011).

Disintegration Time of Tablets

This disintegration time test is used to estimate the time it would take the tablets to disintegrate in the gastro environment. The British Pharmacopoeia specifies that an uncoated tablet is expected to disintegrate within 15 minutes. The result in table 2 shows that all the metronidazole tablets produced, disintegrated within 90 seconds and this conforms to the BP specification.

Tablet Diameter and Thickness

The Table 3 below shows the mean thickness and diameter of tablets prepared with treculia gum. The tablets showed no variation in thickness and diameter. This result further confirmed the uniformity in weight exhibited by the tablets (Chalapathi *et al.*, 2010).

Table 2. Mechanical Properties of Tablets Produced using Treculia Gum

Tablet Property	Binder Concentration (%)				
	0	1	2	3	4
Hardness (kgf)	1.30±2.10	4.80±0.22	5.86±1.23	6.50±2.12	7.05±2.21
Disintegration Time (min)	0.90±0.12	0.49±0.06	1.08±0.14	1.13±0.18	1.31±0.12
Friability (%)	8.521	5.801	3.092	0.836	0.582
Average Tablet Weight (mg)	500±0.00499	500±0.00287	500±0.0030	500±0.00325	500±0.00308

Table 3. Mean Tablet Diameter and Thickness

Tablet Parameters	Binder Concentration (%w/w)				
	0	**1**	**2**	**3**	**4**
Mean Tablet Thickness (cm)	0.3±0.00	0.3±0.00	0.3±0.00	0.3±0.00	0.3±0.00
Mean Tablet Diameter (cm)	1.2±0.00	1.2±0.00	1.2±0.00	1.2±0.00	1.2±0.00

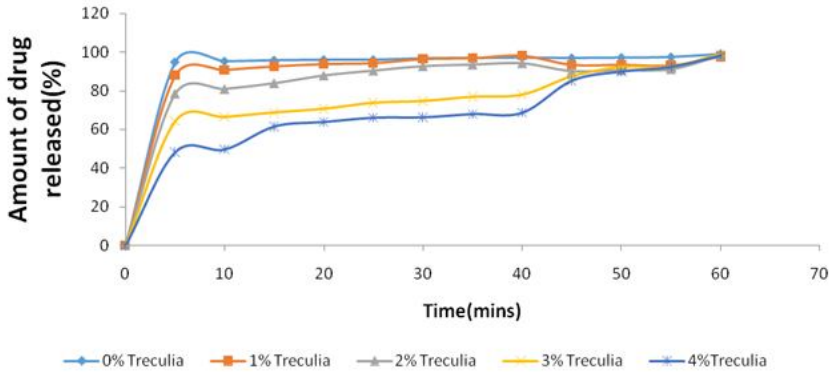

Figure 1. Dissolution profiles of metronidazole from tablets prepared with *treculia* gum as binder

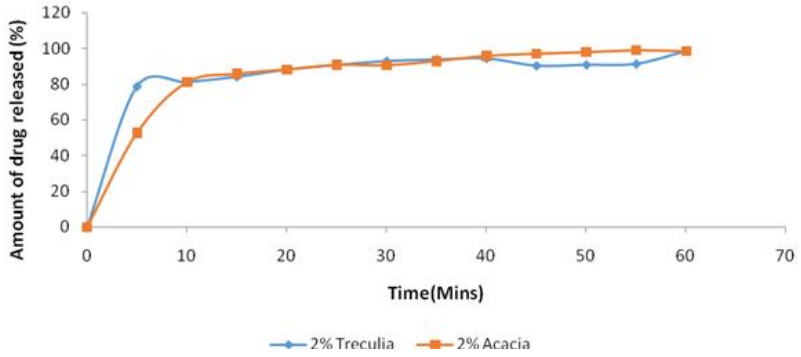

Figure 2. Dissolution profiles of metronidazole tablets prepared with 2% *Treculia* and 2% Acacia gums as binder

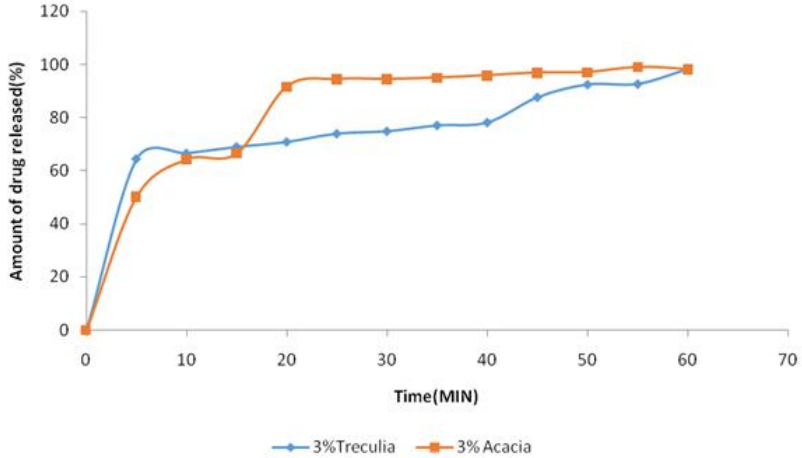

Figure 3. Dissolution profile of metronidazole tablets prepared with 3% *Treculia* and 3% Acacia gums as binder

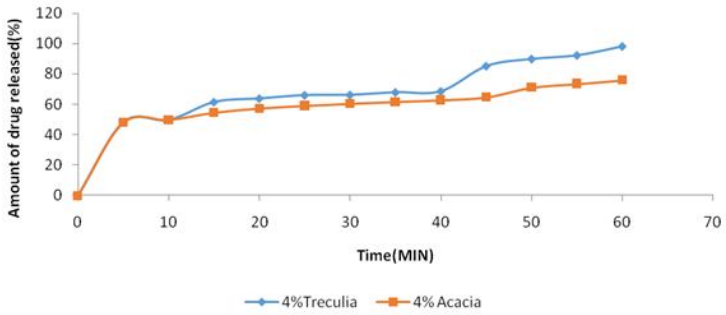

Figure 4. Dissolution profiles of metronidazole tablets prepared with 4% *Treculia* and 4% Acacia gums as binder

Dissolution Profile of Tablets

The dissolution of a drug in the gastro intestinal tract is the rate determining step in the bioavailability of drug. The release of the drug from the granules may be expressed as the rate of dissolution, or as the time required for a certain quantity of drug to be dissolved. Dissolution profile provides information on the evaluation of the physiological availability of the drug substance. The drug release profile results show that all the tablets prepared released more than 80% of stated drug content within 50 minutes and more than 95% of drug was also released within 60 minutes (Fig. 1). The aforestated result conformed with British Pharmacopoeia specification on dissolution of immediate release tablets such as metronidazole tablet. A critical look at the dissolution profile revealed that there was a graded variation in initial drug release across the tablet batches. The tablet batch containing 0% treculia gum had the largest burst release of 95% within 5 minutes (Fig. 1), while the tablets containing 4% treculia gum exhibited the least burst release of 48.3% within 5 minutes (Fig. 1). This is obviously attributed to the percentage composition of binder (treculia gum) present in each batch; increase in binder concentration resulted to corresponding decrease in initial drug release (BP, 2011; Kapoor *et al.*, 2011). Also, from Figures 2 to 4, it is clear that treculia gum compared favourably with acacia gum (reference standard) as binder.

Conclusion

The metronidazole tablets containing treculia gum at concentrations of 3% and 4% satisfied all the quality control standard parameters as stipulated in the British Pharmacopoeia. Therefore, *Treculia Africana* gum could serve as a local alternative for use as binder in tablet production.

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