The Effects of Lubricants on the Disintegration and Dissolution Profile of Metronidazole Tablets Formulated Using *Sida acuta* Gum as a Binder

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Authors' contributions

This work was carried out in collaboration among all authors. Author SEO designed the study and supervised the bench work. Author AJA managed the literature search and wrote the first draft of the manuscript. Author CAA co-supervised the bench-work and managed the analyses of the study. Author DUI carried out most of the bench-work. All authors read and approved the final manuscript.

Article Information

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ABSTRACT

Aims: This research was done to study the effects of types and concentrations of lubricants on the dissolution and disintegration profile of metronidazole tablets formulated using *Sida acuta* gum as a binder.
Methodology: *Sida acuta* gum (SAG) was extracted from powdered dried leaves of *Sida acuta*. Metronidazole granules were produced by wet granulation technique using different concentrations (1 and 2%) of SAG as a binder and mixed with different concentrations (0.5, 1.0, and 1.5%) of magnesium stearate (MS) or sodium lauryl sulphate (SLS) as a lubricant. The granules/lubricant - mix was compressed into tablets and evaluated for hardness, weight uniformity, drug content, disintegration time, friability and *in vitro* drug release.
Results: The hardness for the tablets was from 4.08 to 7.97 Kgf. The friability was from 0.02±0.45 to 3.40±0.43%. Tablets from formulations A1-A3, B2, and B3 failed the friability test. Formulations prepared with 1% SAG were more friable than those formulated with 2% SAG. Disintegration time

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for formulations A1-A3 (1% SAG + MS) ranged from 19.07 to 63.5 min, while that of A4-A6 (2% SAG + MS) was from 39.06 to 81.48 min. Formulations B1-B3 (1% SAG + SLS) had disintegration time that ranged from 4.22 to 6.8 min while that of B4-B6 (2% SAG + SLS) was from 9.35 to 15.90 min. The % drug release at 60 min for formulations that contained SAG and MS was 76.60-104.28% and SAG and SLS was 99.89-101.35%

Conclusion: Metronidazole tablets formulated using SLS as lubricant disintegrated faster than those formulated using magnesium stearate as lubricant. Percentage drug release from tablets containing SLS was slightly higher than those that contained magnesium stearate. Higher concentrations of the lubricants produced softer tablets.

1. INTRODUCTION

Drugs administration through the oral route is the most convenient and frequently used route of drug delivery because it grants the availability of many options in dosage form design [1]. Drugs administered through the oral routes include tablets and capsules. Tablets are the major dosage form among the available oral drug formulations because of their long-term stability, availability, and least production cost [2]. Tablet as a dosage form is the most common drug delivery system and several types of tablets have been formulated. They include; oral tablets for ingestion such as conventional tablets, multiple compressed tablets, layered tablets, modified-release tablets, delayed action tablets, and floating tablets; tablets used in the oral cavity such as lozenges, sublingual tablets, and buccal tablets; and tablets administered by other routes such as vaginal tablets and implants [3]. They are produced using different techniques such as wet granulation, direct compression, or dry granulation. Tablets are made by compressing or moulding granules or powder-mix composed of active pharmaceutical ingredients and excipients. Excipients are inert, non-medicinal substances other than the therapeutic agent(s) contained by drug products that aid the formulation process and improves the quality and effectiveness of the product [4]. Excipients are added intentionally to a drug product to achieve various pharmaceutical purposes, thereby ensuring the acceptability of the product with respect to appearance, manufacturability, and performance. Different quantities of excipients are added to the active pharmaceutical ingredient(s) to produce standard quality tablets [5]. The tablet type and the required process used determine the type of each excipient and quantities to be used. Excipients used for manufacturing of tablets include; binders, disintegrants, fillers, sweeteners, flavours, colourants, sorbents, anti adherent, lubricants, and glidants [5].

Lubricants are excipients used in drug production that are very important in enhancing the efficiency of production and quality of tablets. They enhance the fluidity, filling properties and stop powder from adhering to punch faces and also reduce die-wall friction. They enhance granulation flow from the hopper into the die cavity. The friction that occurs between the die walls and the powder mix during compression and ejection is decreased by the lubricant. They also prevent the mixed powders/granules from adhering to the punches and die of the tableting machine. In some cases, lubricants decrease the friction between particulates and thereby, increase powders or granules flow rates. They give compressed tablets sheen [6]. Lubricants that have low shear strength as well as strong cohesive forces perpendicular to the line of shear are the best.

Lubricants can be classified as hydrophilic or hydrophobic depending on their solubility characteristics. Hydrophilic lubricants include sodium lauryl sulphate, boric acid, sodium acetate, sodium oleate, sodium benzoate, magnesium lauryl sulphate, and carbowax (PEG) 4000/6000. Examples of hydrophobic lubricants are metal (Mg, Ca, Na) stearate, stearic acid, waxes, talc, stear-o-wet, sterotex and glyceryl behenate [7].

Hydrophobic lubricants are usually more effective when compared to hydrophilic lubricants. However, hydrophobic lubricants can change other physicochemical properties of tablets, like its hardness (tensile strength), drug release, and disintegration time [8,9]. The lubrication process involves the lubricant material, the formulation to be lubricated, and the mechanical process, and these result in the final dosage form [10]. Several factors are considered when choosing the desirable lubricant for producing tablets. They include low shear strength, forming a durable layer masking the surface/particles, non-toxicity,

chemical compatibility with active ingredients and other excipients in the formulation, minimal batch-to-batch variability, and having low untoward effects on the final dosage forms performance. Also, it is necessary to consider adequate concentration and mixing time when choosing a lubricant because they significantly impact the pharmaceutical product's performance and its processes. Poor lubrication and improper mixing leads to the production of tablets with pitted surface or causes adhering, capping, and sticking to the die cavity. However, use of too much lubricant and prolonged mixing causes untoward effect to products and also the processes resulting in tablets with decreased rates of dissolution, increased disintegration time, reduced tablet hardness, and compression variability [7]. Poor or excessive lubrication will result in tablets with distorted and may result in rejection of a tablet batch. Lubricants should be added during tablet production after the addition of disintegrants to protect it from being coated or preferably at the end-stage before compression to keep mixing time a minimum. The mixing time for lubricant distribution is usually between 0.5 and 5 min for desirable compactability results and tablets hardness. Choosing lubricant for tablet production demands using systematic approach coupled with careful performance evaluation of the product and process [7]. Lubrication occurs through two mechanisms, fluid lubrication, and boundary lubrication. During fluid lubrication, a film of fluid (e.g. mineral oil) is placed between and demarcates two solid surfaces, preventing them from contacting each other [11]. Desirable lubrication performance which is indicated by the low friction coefficient (~0.001) takes place as the two solid surfaces are totally separated from each other. This depends majorly on the viscosity of the fluid. Boundary lubricant normally forms a very light broken film on the solid surfaces, disrupts the interaction between two solid surfaces, and decreases the friction in between. Since the two solid surfaces are not entirely separated, a relatively high friction coefficient (~0.05-0.15) is expected. Boundary lubricants have very minimal shear strength and this makes them slide very easily when sheared [11].

Magnesium stearate is a light white, very fine, ground or precipitated, low bulk density soft powder, with a faint odor of stearic acid and a unique taste. The powder is greasy when touched and readily sticks to the skin. It is the lubricant most frequently applied in foods, cosmetics, and drug formulations, because of its

good lubrication efficiency [11]. It is used at concentrations 0.25% to 5.0% w/w as capsule and tablet lubricant. The lowest effective concentration (0.25% to 1.0%w/w) is utilized in tablet formulations because of its hydrophobic nature and this may decrease drug dissolution from the tablet, reduce tablet tensile strength and increase tablet friability [12]. Also, magnesium stearate effectiveness as a lubricant depends on its chemical purity, crystal form, and its particle size [11].

Sodium lauryl sulphate is a synthetic alkaline anionic surfactant that is utilized in the production of several non-parenteral pharmaceuticals and cosmetics. It exists as crystals, flakes, or powders that are white or cream to pale yellow in colour. It has smooth feel, bitter taste, soapy, and a weak fatty substances odour. It is effective in acidic and basic conditions as a wetting agent and detergent. It is utilized as a penetration enhancer, emulsifying agent, and as tablet lubricant at a concentration of 1.0–2.0% [13]. It increases the dissolution of drugs that are not readily water-soluble and when compared with the magnesium stearate, it does not reduce the effective tablet-solvent interfacial area during dissolution. Hence, it does not impact the dissolution rate negatively. The increase in dissolution is due to improvement in water penetration into the tablets. This results in exposure of more available active pharmaceutical ingredient surfaces to solvent, thus greater dissolution performance [11].

One major disadvantage of using sodium lauryl sulphate during production of tablet is the incompatibility with the active pharmaceutical ingredient. Ionized sodium lauryl sulphate reacts with active pharmaceutical ingredient at certain conditions to form an insoluble salt, which significantly decreases the drug dissolution and therapeutic effects [11].

Sida acuta gum is obtained by precipitating the filtrate obtained from the aqueous maceration of powdered dried leaves of *Sida acuta* using isopropyl alcohol [14]. *Sida acuta* gum has been employed during tablet manufacturing as a binder [15], as mucoadhesive polymer matrix former [16], and as hydrophilic polymer matrix former [17].

Metronidazole is a synthetic nitroimidazole derivative that has antibacterial and antiprotozoal activities. It is a white to pale-yellow crystalline powder. It has a slight odour, bitter and saline

taste, and a pH (saturated aqueous solution) of about 6.5 [18]. It has solubility at 20 °C of 1 g/100 ml in water, 0.5 g/ 100 ml in ethanol, <0.05 g/100 ml in ether and chloroform. It is soluble in dilute acids but sparingly soluble in dimethylformamide [19]. In water at 25 °C, the solubility increases slightly to 1.1g/100 ml [20].

This research was conducted to study the effects of types and concentrations of lubricants on the dissolution and disintegration profile of metronidazole tablets formulated using *Sida acuta* gum as a binder.

2. MATERIALS AND METHODS

2.1 Materials

Metronidazole (Central Drug House, New Delhi, India), acetone (Guangdong Guangzhou Chemicals, China), isopropyl alcohol (JDH., China) magnesium stearate, sodium lauryl sulphate, talc, lactose (Pharmaceuticals Aliyali Palghar, India), and *Sida acuta* gum (prepared in Pharmaceutics laboratory, Faculty of Pharmacy, Delta State University, Abraka).

2.1.1 Isolation of *Sida acuta* gum

Sida acuta leaves were collected from the Faculty of Pharmacy's botanical garden in Delta State University, Abraka. It was authenticated and assigned a voucher number (PCG/UNN/0093) by Mr. Felix Nwafor, a taxonomist in the Department of Pharmacognosy and Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka. The gum was isolated and purified using the method of Okafo and Chukwu [14].The percentage yield was calculated using equation 1

$$Percentage\ yield = \frac{weight\ of\ gum\ (g)}{weight\ of\ powdered\ dried\ Sida\ acuta\ leaves\ (g)}\ X\ 100 \quad . \ . \ . \ . \ 1$$

2.1.2 Preparation of metronidazole granules

Metronidazole granules were produced by wet granulation technique using the formula in Table 1. Metronidazole powder was mixed properly with lactose and part (1/2) of the required quantity of starch in a mortar. Different concentrations (1 and 2%) of *Sida acuta* gum mucilage were prepared separately and mixed with the respective drug-lactose mixture to form damp mass. The damp mass was passed through a sieve with 1.18 mm mesh size to form granules which were dried in an oven at 50 ±

0.5°C for 6 h. The dried granules were screened through a sieve with 710 μm mesh. This procedure was utilized in the production of granules for the different formulations as in the formula in Table 1.

2.2 Characterization of the Granules

2.2.1 Angle of repose and flow rate

A 10 g quantity of metronidazole granules was weighed and poured into a glass funnel with tip plugged, clamped to retort stand 5 cm above a flat surface. The plug was removed from the funnel's tip and the time it took the granules to flow through the orifice of the funnel was noted. The height and diameter of the cone formed by the granules on the flat surface were recorded [21]. The flow rate was calculated using equation 2.

$$Flow\ rate = \frac{weight\ of\ granules\ (g)}{Time\ of\ flow\ (s)} \quad . \quad . \quad . \quad . \quad 2$$

The angle of repose (θ) was calculated using equation 3.

$$Tan\ \theta = \frac{h}{r} \quad . \ . \ . \ . \qquad\qquad 3$$

Where h = height of heap, r = radius of the heap.

This process was carried out in triplicate and mean plus standard deviation was computed. This procedure was repeated for the granules from the different formulations.

2.2.2 Bulk and tapped densities

A 10 g quantity of granules was weighed and transferred into a 100 ml measuring cylinder attached to the jolting volumeter type STAV II (J. Engelsmann AG, Ludwigshafen, Germany). The volume occupied by the granules was recorded as the bulk volume. The jolting volumeter was set to jolt 100 times and the volume occupied by the tapped granules was recorded as tapped volume [22]. The bulk density was calculated using equation 4.

$$Bulk\ density = \frac{weight\ of\ granules\ (g)}{Bulk\ volume\ (ml)} \quad . \ . \ . \ . \ 4$$

The tapped density was calculated using equation 5.

$$Tapped\ density = \frac{weight\ of\ granules\ (g)}{Tapped\ volume\ (ml)} \quad . \ . \ . \ . \ 5$$

Carr's index: The Carr's index was calculated using equation 6.

$$Carr's\ index = \left(\frac{tapped\ density - bulk\ density}{tapped\ density}\right) X\ 100\ .\ .\ .\ .\ 6$$

Hausner ratio: This was calculated using equation 7.

$$Hausner\ ratio = \frac{tapped\ density}{bulk\ density}\ \ .\ .\ .\ .\ 7$$

2.2.3 Particle size analysis

A 10 g quantity of granules was weighed and transferred into the topmost sieve of a nest of sieves attached to a sieve shaker (Endicott's London minor 2165-09). The sieve shaker was operated for 10 min, after which the granules retained in the different sieves were weighed. This was repeated for all the formulations.

2.2.4 Compression of metronidazole granules

The metronidazole granules were mixed with the remaining portion of maize starch, talc, and different concentrations of the lubricants (magnesium stearate or sodium lauryl sulphate) for a brief period. The granules/excipients-mix were compressed into tablets using a 16 station Rotary tabletting machine (Model CLD3,Clit Jemkay Engs, India) having a 13 mm punch.

2.3 Evaluation of Tablets

2.3.1 Weight uniformity

Twenty (20) tablets were chosen randomly, weighed individually and their mean calculated. The percentage deviation of the respective tablets from the mean was calculated [23]. This procedure was repeated for all the formulations.

2.3.2 Drug content

Five tablets from each formulation were crushed separately in a mortar. Powder equivalent to 100 mg of metronidazole was weighed and dissolved in 100 ml of 0.1 N HCl in a 100 ml volumetric flask. It was filtered and the filtrate diluted adequately. Three aliquots from the dilutions were analyzed in a Cary 60 UV spectrophotometer (Agilent Technologies, Malaysia) and their respective absorbance values were recorded. The contents of the different formulations were calculated by matching the absorbance values to a standard metronidazole calibration curve.

2.3.3 Hardness

The crushing strength (kg/m^2) of five tablets from each formulation was determined using DIGITAB model digital tablet hardness test apparatus (Veego Instruments, Mumbai, India). The values displayed were recorded.

2.3.4 Friability

Ten tablets chosen randomly were weighed and placed in the drum of a friabilator (Veego Instruments, Mumbai, India). The drum was rotated at 25 rpm for 4 min. The tablets were removed, dedusted, and reweighed. The percentage weight loss was determined and used as the measure of friability [24]. The friability was determined using equation 8. This was repeated for all formulations.

$$Friability = \left(\frac{wi - wf}{wi}\right) X\ 100\ .\ .\ .\ .\ .\ 8$$

Where wi = initial weight and wf = final weight

2.3.5 Disintegration time test

The test was conducted using a disintegration test apparatus (Manesty, England). Six tablets from each formulation were put in the respective six tubes of the tablet disintegration apparatus. The tubes were submerged and lifted from the disintegrating medium (0.1 N HCl) maintained at 37±0.5 °C until the tablets break up and pass through the wire mesh at the bottom of the tubes. The time taken for all the particles of each tablet to pass through the wire mesh leaving no palpable mass is recorded as the disintegration time.

2.3.6 *In vitro* dissolution test

One formulated tablet was placed in the basket of an Erweka dissolution unit containing 900 ml of 0.1 N HCl maintained at 37±0.5°C and rotated at a speed of 100 rpm. A 5 ml sample was withdrawn at 5, 10, 15, 30, 45, and 60 min intervals and replaced by a fresh preheated dissolution medium. The samples were filtered and analyzed using a Cary 60 UV spectrophotometer (Agilent Technologies, Malaysia) at a wavelength of 277 nm.

2.3.7 Drug/excipient compatibility

The FTIR spectrum of metronidazole, metronidazole plus magnesium stearate and

metronidazole plus sodium lauryl sulphate respectively were recorded using Shimadzu-IR Affinity 1 Spectrophotometer (Shimadzu, Japan) using potassium bromide pellet technique.

2.4 Data Analysis

All experiments were performed in triplicates for the validity of the statistical analysis and expressed as mean ± SD. Statistical analysis was done using Microsoft Excel.

3. RESULTS AND DISCUSSION

3.1 Percentage Yield of Gum

The gum was light brown in colour and the percentage yield was 17.98%w/w.

3.2 Characterization of Granules

The flow properties of the granules were estimated by determining the angle of repose, flow rate, Carr's index, and Hausner ratio. The result in Table 2 shows that the granules had good flow property and the values obtained were within the specified limits for the production of good quality tablets. The granules had an angle of repose that ranged from 24.76 to 26.50°. These results show that the granules had low interparticulate friction and hence good flow. The compressibility index was in the range of 6.49 to 12.22% and this indicated good flow [25]. Hausner ratio values that ranged between 1.06±0.02 and 1.14±0.00 were obtained. Hausner ratio of less or equal to 1.25 indicates good flow, while values of greater than 1.25 indicate poor flow [26, 27]. The flow rate ranged from 2.46±0.18 to 3.31±0.30 g/s. The results obtained from the different flow parameters showed that the granules exhibited good flowability.

3.3 Particle Size Distribution

The percentage frequency-particle size distribution table (Fig. 1) showed that the size of granules from all the formulations ranged from fines to 500 µm; however, 500 µm sized granules were the most frequent. This showed that majority of the granules were within the range (400-710µm) that is required for good quality tablet production.

3.4 Evaluation of Metronidazole Tablets

The different formulations of metronidazole tablets were evaluated based on uniformity of weight, hardness, friability, % drug released, and

disintegration time test and the results are shown in Table 3.

Hardness shows the ability of the tablets to withstand pressure or stress during further processing, packaging, handling, and transportation. A minimum tablet hardness value of 4 kgf is deemed satisfactory. The hardness of the different formulations of metronidazole tablets ranged from 4.08 to 7.97 Kgf and was all satisfactory.

Friability is a measure of the tablet's ability to withstand abrasion. The friability values for the different formulations ranged from 0.02±0.45 to 3.40±0.43% (Table 3). Friability values of 1% and below are acceptable. Therefore, tablets from formulations A1, A2, A3, B2, and B3 that had friability values of more than 1% failed the test. Formulations A1-A3 and B1-B3 prepared with 1% SAG were more friable than those formulated with 2% SAG (A4-A6 and B4-B6).A higher concentration of the binder produces higher cohesive force and interparticulate binding which results in lower friability [28]. For formulations A1-A3, the friability values (2.58±0.76, 3.20 ±1.21, 3.40 ±0.43) were directly proportional to the concentration of the lubricant (0.5, 1.0, 1.5%) respectively. Also for formulations A4-A6, the friability values (0.31±1.02, 0.42 ±1.22, 0.59 ±0.56) increased as the concentration of the lubricant increased (0.5, 1.0, 1.5%) respectively. Lubricants forms a thin layer over granules thereby reducing the interparticulate cohesion and the more quantity of lubricants used, the more the decrease in interparticulate cohesion which leads to softer tablets [12]. Powdering, chipping, and fragmentation of tablets during handling lead to lack elegance and consumer rejection. These may produce very dirty processes in coating, packaging and other manufacturing areas. They can contribute to weight variation in tablets or even content uniformity problems [29]. Granulations that contain 2 to 4% moisture are used to produce tablets that are less friable than those produced using very dry granulations.

The disintegration time for formulations A1-A3 (1% SAG + magnesium stearate) ranged from 19.07 to 63.5 min, while A4-A6 (2% SAG + magnesium stearate) had a disintegration time of 39.06 to 81.48 min. Formulations B1-B3 (1% SAG + sodium lauryl sulphate) had a disintegration time that ranged from 4.22 to 6.8 min while B4-B6 (2% SAG + sodium lauryl sulphate) had a disintegration time of 9.35 to

Table 1. Composition of metronidazole tablets

Ingredients	A1	A2	A3	A4	A5	A6	B1	B2	B3	B4	B5	B6
Metronidazole (mg)	400	400	400	400	400	400	400	400	400	400	400	400
Sida acuta gum (mg)	6	6	6	12	12	12	6	6	6	12	12	12
Maize starch (mg)	60	60	60	60	60	60	60	60	60	60	60	60
Lactose (mg)	125	122	119	119	116	113	125	122	119	119	116	113
Magnesium stearate (mg)	3	6	9	3	6	9	-	-	-	-	-	-
Sodium lauryl sulphate (mg)	-	-	-	-	-	-	3	6	9	3	6	9
Talc (mg)	6	6	6	6	6	6	6	6	6	6	6	6
Total (mg)	600	600	600	600	600	600	600	600	600	600	600	600

Table 2. Micromeritic values for formulations A1-A6 and B1-B6 granules

| Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr's index (%)	Angle of repose (º)	Flow rate (g/s)
A1	0.58±0.01	0.63±0.00	1.09±0.01	7.94±1.03	26.44±0.02	2.70±0.48
A2	0.65±0.02	0.73±0.03	1.12±0.04	10.96±0.63	25.37±1.07	2.78±0.48
A3	0.60±0.00	0.65±0.04	1.08±0.07	7.69±0.45	26.30±0.81	2.78±0.13
A4	0.63±0.05	0.68±0.07	1.08±0.01	7.35±0.80	25.17±0.69	3.31±0.30
A5	0.59±0.03	0.63±0.06	1.07±0.01	6.35±1.04	25.18±0.89	2.64±0.09
A6	0.59±0.00	0.67±0.03	1.14±0.00	11.94±0.43	26.22±0.12	2.82±0.46
B1	0.62±0.03	0.68±0.09	1.10±0.07	8.82±0.33	26.35±0.17	2.56±0.39
B2	0.68±0.03	0.75±0.73	1.10±0.04	9.33±1.57	26.13±0.41	2.63±0.00
B3	0.64±0.03	0.68±0.03	1.06±0.02	5.88±0.23	26.50±0.83	2.46±0.18
B4	0.59±0.05	0.64±0.08	1.08±0.05	7.81±0.42	25.61±0.72	2.56±0.23
B5	0.58±0.02	0.63±0.02	1.09±0.03	7.94±0.39	24.76±0.70	2.70±0.50
B6	0.58±0.02	0.65±0.02	1.12±0.07	10.77±1.39	25.05±0.10	3.05±0.48
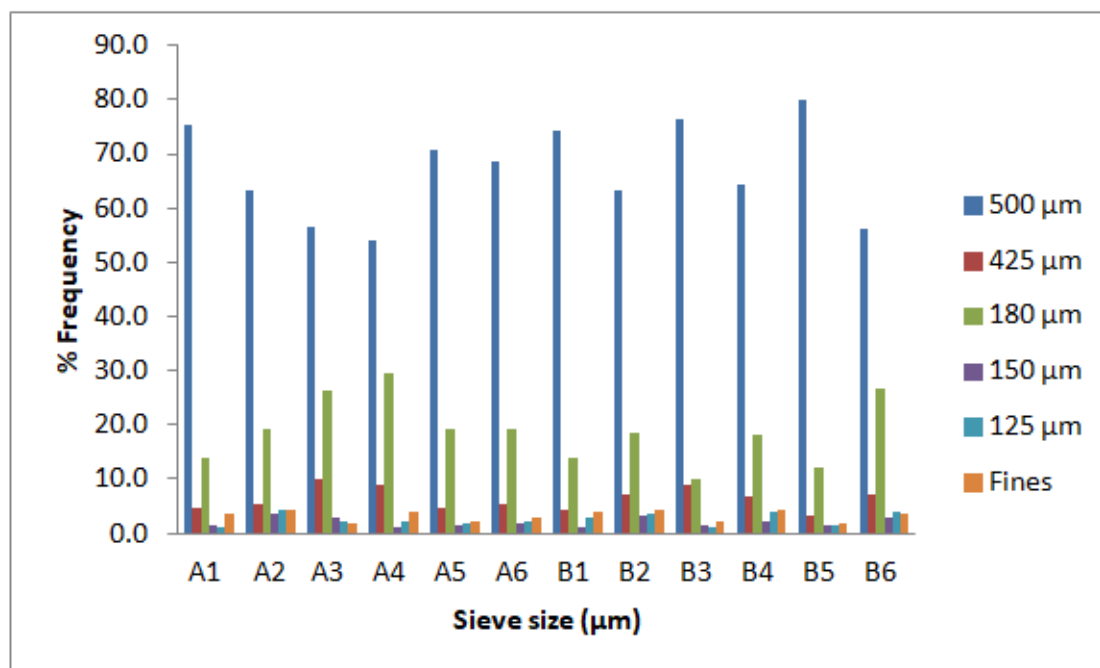
Fig. 1. % Frequency – size distribution of metronidazole granules from formulations A1-A6 and B1-B6

Table 3. Post compression evaluation of metronidazole tablets

Formulations	Tensile strength (MN/m²)	Friability (%)	Content uniformity (%)	Disintegration time (min)
A1	132.97±0.12	2.58±0.76	97.98	19.07±1.43
A2	181.94±0.04	3.20±1.21	99.34	39.76±1.07
A3	142.37±0.03	3.40±0.43	100.54	63.50±0.58
A4	171.51±0.03	0.31±1.02	99.85	39.06±0.98
A5	206.74±0.02	0.42±1.22	97.39	50.09±0.86
A6	209.59±0.01	0.59±0.56	101.09	81.48±1.40
B1	162.46±0.02	0.35±0.65	103.15	4.22±0.13
B2	107.35±0.03	2.02±1.02	99.13	5.40±0.40
B3	137.10±0.02	2.03±0.24	98.50	6.18±0.13
B4	200.83±0.03	0.02±0.45	104.34	9.35±0.68
B5	201.19±0.01	0.10±0.15	102.16	11.52±1.57
B6	228.07±0.02	0.45±0.75	99.01	15.90±0.42

15.90 min. The results show that an increase in binder concentration leads to an increase in the disintegration time of the metronidazole tablets [28]. The tablets formulated using hydrophilic lubricant (sodium lauryl sulphate) showed lower disintegration time than those formulated using hydrophobic lubricant (magnesium sulphate). Sodium lauryl sulphate due to its hydrophilic nature and surface activity enhances wetting and promotes solvent penetration into tablets leading to decrease in disintegration time [30]. Hydrophobic lubricants reduce the effective drug-solvent interfacial area by changing the surface characteristics of the tablets, thereby decreasing their wettability and extending their disintegration time [30]. There was increase in the disintegration time, 19.07±1.43, 39.76±1.07, 63.60±0.58 min and 4.22±0.13, 5.40±0.40, 6.18±0.13 min, as the concentration of the lubricant increases, A1 (0.5%), A2 (1%), A3 (1.5%) and B1 (0.5%), B2 (1%), B3 (1.5%) respectively.

Drug content ranged from 97.39 to 104.34% and uniformity of weight ranged from 0.01 to 2.76%.

3.5 *In vitro* Drug Release

After 30 min of dissolution study, the % drug release for formulations A1, A2, and A3 (containing 1% SAG and MS), was 102.7, 88.51, and 81.76% respectively while% drug release for formulations B1, B2, and B3 (containing 1% SAG and SLS) were 99.45, 99.21 and 98.76% respectively. After 60 min, the percentage drug release for formulations A1-A6 was 104.28, 102.7, 95.38, 102.1, 90.43, and 76.60% respectively whereas the percentage release for formulations B1-B6 was 101.35, 101.33, 99.89, 105.25, 101.24, and 99.99% respectively. This implies that an increase in the concentration of the lubricant will lead to a decrease in the % drug release [8]. This supports the work of Uzunović and Vranić [31] which reported that the presence of magnesium stearate in a formulation allowed the dissolution medium to stay on the surface of the particle resulting in slower wettability and dissolution rate. Ariyasu et al [32] revealed that the decrease in dissolution is due to the increase in the exposed amount of magnesium stearate on the tablet surface and also that tablet dissolution is limited by the diffusion of magnesium stearate.

For formulations A1, A2, and A3 that contained 1% SAG but 0.5, 1.0, and 1.5% magnesium stearate respectively, the % drug release after 30 min was 102.7, 88.51, and 81.76% respectively, and after 60 min was 104.28, 102.70, and 95.385

respectively (Fig. 2). Also for formulations B1, B2, and B3 that contained 1% SAG but 0.5, 1.0, and 1.5% sodium lauryl sulphate respectively, the % drug release after 30 min was 99.45, 99.21, and 98.76% and after 60 min was 101.35, 101.33, and 99.89% respectively (Fig. 2). This signifies that at the same binder concentration, the higher the concentration of lubricant, the lower the quantity of drug released.

3.5.1 Drug-excipients compatibility studies

The FTIR spectra in Figs 3, 4 and 5 showed that there was no incompatibility between metronidazole, SAG, and magnesium stearate (MS) or sodium lauryl sulphate (SLS).The standard IR peaks of metronidazole (Fig 3) were still available when combined with SAG and magnesium stearate (Fig 4) and when in combination with SAG and sodium lauryl sulphate (Fig 5). The IR peak for N=O (1550-1350 cm^{-1}) was seen at 1547, 1515 and 1490 cm^{-1} for metronidazole, metronidazole + SAG +MS, and metronidazole +SAG +SLS respectively. The IR peak for =C-H stretch (3100-3000 cm^{-1}) was seen at 3034, 3029, and 3066 cm-1 respectively. The IR peak for -CH$_3$ bending (1475-1365 cm^{-1}) was seen at 1411, 1382, and 1367 cm^{-1}respectively. The IR peak for –C-O alcohol (1300-1000 cm^{-1}) was seen at 1153, 1116, 1128 cm^{-1} respectively. The C=C stretch (1475-1700 cm^{-1}) was seen at 1689, 1676 and 1577 cm^{-1} respectively.
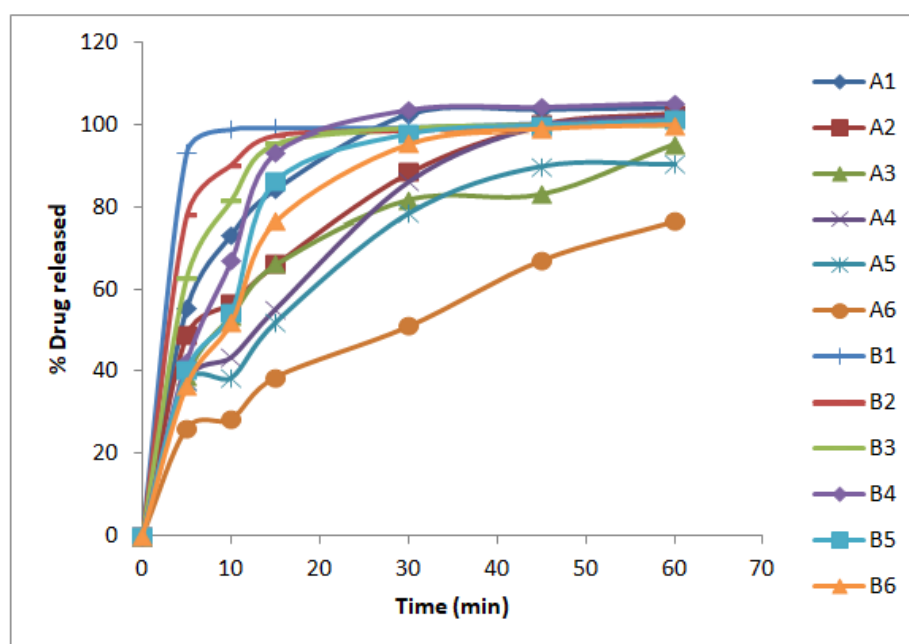

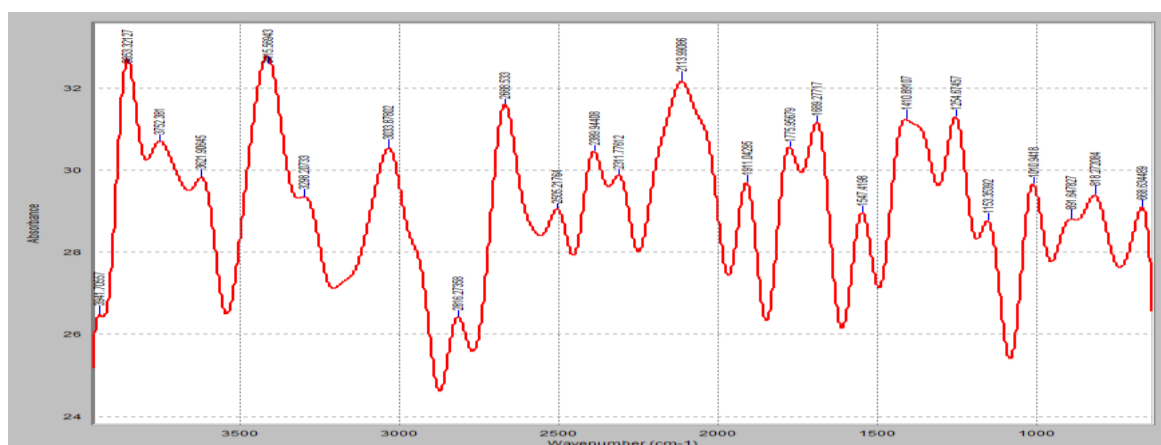**Fig. 2. *In vitro* drug release from formulations A1-A6 and B1-B6**

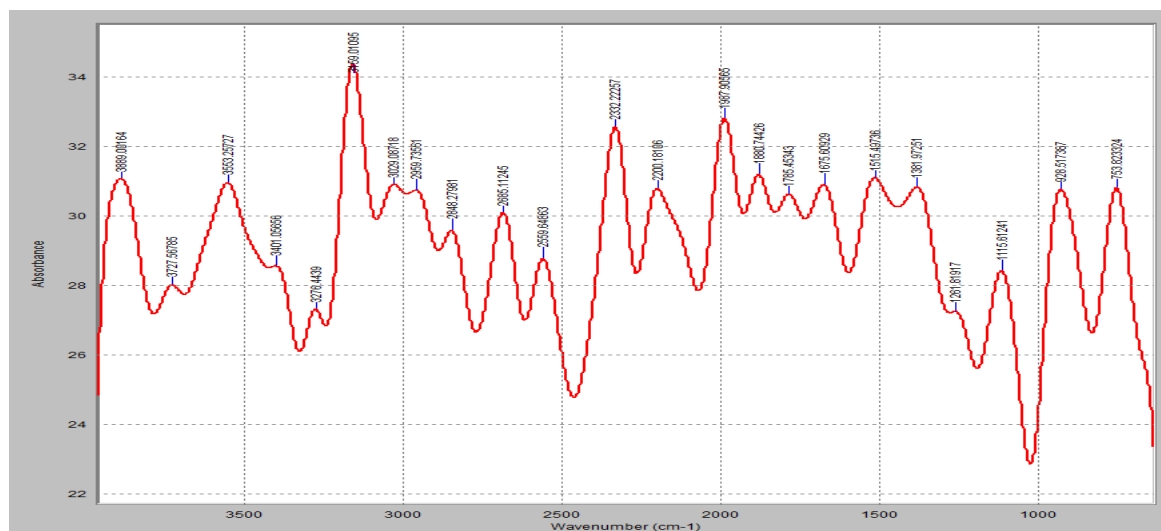**Fig. 3. FTIR spectrum of metronidazole**

Fig. 4. FTIR spectrum of metronidazole + *Sida acuta* **gum + magnesium sulphate**
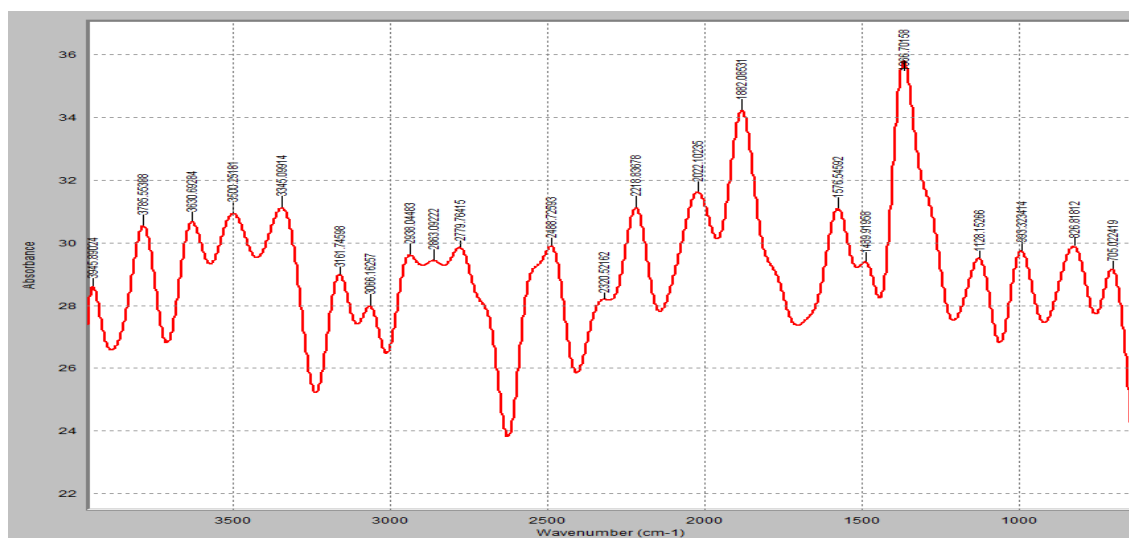

Fig. 5. FTIR spectrum of metronidazole + *Sida acuta* **gum + sodium lauryl sulphate**

4. CONCLUSIONS

Metronidazole tablets were successfully formulated using *Sida acuta* gum as a binder and either magnesium stearate or sodium lauryl sulphate as a lubricant.

The tablets formulated using sodium lauryl sulphate, a hydrophilic lubricant have a lower disintegration time compared to those formulated with a hydrophobic lubricant, magnesium stearate. The percentage drug released by metronidazole tablets formulated using magnesium stearate was close to those formulated using sodium lauryl sulphate. Tablets formulated with a lower concentration of the lubricants disintegrated faster than those formulated with higher concentrations of the same lubricant.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Deore PD, Katti SA, Sonawane SS. Formulation and evaluation of sustain release matrix tablet of fluvoxamine maleate using *Moringa oleifera* gum. Int J Pharm Sci & Res. 2021;12(7):3879-86.
   DOI: 10.13040/IJPSR.0975-8232.12(7).3879-86

2. Zandu SK, Kumari R, Singh I. Formulation and evaluation of fast disintegrating tablets of domperidone using chitosan-glycine conjugates as superdisintegrant. Thai Journal of Pharmaceutical Sciences. 2021;45(1):32-40.

3. Parashar B, Chauhan A, Prashar D, Chandel A, Kumar H, Purohit R. Formulation and evaluation aspects of tablets-an overview. American Journal of PharmTech Research. 2012; 2(1):1-13.

4. Ibezim EC. Pharmacy dictionary. Nsukka: University of Nigeria Press Ltd; 2020.

5. Alderborn G. Tablets and compaction. In: Aulton ME, editor. Aulton's Pharmaceutics. The design and manufacture of medicines. 3rd ed. Edinburgh: Churchill Livingstone Elsevier; 2007.

6. Allen Jr LV, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 9th Ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2005.

7. Li J, Wu Y. Lubricants in Pharmaceutical Solid Dosage Forms. Lubricants.2014 ;2:21-43.
   DOI:10.3390/lubricants2010021

8. Ashford M. Bioavailability – Physicochemical and dosage form factors. In: Aulton ME, editor. Aulton's Pharmaceutics. The design and manufacture of medicines. 3rd ed. Edinburgh: Churchill Livingstone Elsevier; 2007.

9. Selvaraj G, Kaliamurthi S, Thirugnanasambandam R, Palanisamy M. Formulation and evaluation of tablets from antidiabetic alkaloid glycosin. Journal of Medical Sciences. 2015;15:18-24.
   DOI: 10.3923/jms.2015.18.24

10. Naga Raju P, Devala RG, Srinivasa RA, Gnaneshwar RM, Shashidhar RS. Effects of binders, lubricants and fillers on drug release from diltiazem hydrochloide bi-layered matrix tablets obtained by direct compression and wet granulation technique. Int J Pharm 2012;2(1):117-128.

11. Dun J. Lubrication in Pharmaceutical Tablet Manufacturing. A Dissertation submitted to the Faculty of University of Minnesota, in partial fulfillment of the requirements for the degree of Doctor of Philosophy; 2020.

12. Allen Jr LV, Luner PE. Magnesium stearate, In: Handbook of Pharmaceutical Excipients. 6th Edition, Rowe RC, Sheskey PJ, Quinn ME (Eds.). London: Pharmaceutical Press; 2009.

13. Plumb P. Sodium lauryl sulfate, In: Handbook of Pharmaceutical Excipients. 6th Edition, Rowe RC, Sheskey PJ, Quinn

ME (Eds.). London: Pharmaceutical Press;2009.

14. Okafo SE, Chukwu A. Studies on *Sida acuta* Hydrogel I: Processing and physicochemical properties of the derived Hydrogel Obtained from South East Nigeria, International Journal of Pharmacy and Pharmaceutical Sciences. 2017;9(6):5-11.

15. Okafo SE, Chukwu A. Formulation and evaluation of naproxen tablets produced using a natural binder. Nigerian Journal of Pharmaceutical and Applied Science Research. 2020;9(1):10-17.

16. Okafo SE, Okedu O, Alalor C. Formulation and evaluation of mucoadhesive ciprofloxacin tablet using *Sida acuta* gum. African Journal of Pharmaceutical Research & Development, 2017;9(1):40-48.

17. Okafo SE, Chukwu A. Formulation and Evaluation of Diclofenac Matrix Tablets Containing a Hydrophilic Polymer, Sida acuta Gum, World Journal of Pharmaceutical Research. 2017;6(7):36-47.

18. National Toxicology Program, Institute of E nvironmental Health Sciences, National Ins titutes of Health (NTP). National Toxicolog y Program Chemical Repository Database. Research Triangle Park, North Carolina;1 992.

19. O'Neil MJ (ed). The Merck Index – An Encyclopedia of chemicals, drugs, and biological.b13thEdition, Whitehouse Station, NJ: Merck and Co. Inc; 2001.

20. Yalkowsky SH, Yan H. Handbook of aqueous solubility data: an extensive compilation of aqueous solubility data for organic compounds extracted from AQUASOL Database. CRC Press LLC, Boca Raton, FL;2003.

21. Abdullah A, Haque N, Khan DA, Abdullah A, Nazeer M, Aslam F. Formulation and evaluation of orodispersible tablets of piroxicam beta cyclodextrin and tizanidine HCl by using superdisintegrants. International Journal of Biology Pharmacy and Allied Sciences. 2020;9(2):1-10. Available:https://doi.org/10.31032/IJBPAS/2020/9.2.4895

22. Akpabio EI, Effiong DE, Uwah TO, Sunday NI. Formulation and in-vitro evaluation of theophylline hydrochloride effervescent floating tablets: effect of polymer concentration on tablet Buoyancy. Int J Pharm Pharm Sci, 2020;12(1):59-65.

23. Mustarichie R, Gozali D, Herdiana Y. Formulation a ciprofloxacin hydrochloride extended-release tablet with combination of hydroxypropyl methylcellulose (HPMC) K100M and hydroxypropyl methylcellulose (HPMC) K4M by direct compression method. Int J App Pharm, 2020;12(1):25-30.

24. Gunda RK, Vijayalakshmi A, Masilamani K. Development and evaluation of gastroretentive formulations for moxifloxacin hydrochloride. Thai Journal of Pharmaceutical Sciences. 2020;44 (1):30-39

25. Chime SA, Attama AA, Agubata CO, Ogbonna JD, Onunkwo GC. Micrometric and antinociceptive properties of lyophilized indomethacin-based SLMs based on solidified reverse micellar solutions. Journal of Pharmaceutical Sciences. 2012;5(6):3410-3416.

26. Staniforth JN, Aulton ME. Powder flow. In: Aulton ME, editor. Aulton's Pharmaceutics. The design and manufacture of medicines. 3rd ed. Edinburgh: Churchill Livingstone Elsevier;2007.

27. YÜksel N, TÜrkmen B, Kurdoğğlu AH, Barşaran B, Erkin J, Baykara T. Lubricant efficacy of magnesium stearate in direct compressible powder mixtures comprising cellactose® 80 and pyridoxine hydrochloride. FADAB Journal of Pharmaceutical Science, 2007;32:173-183.

28. Ngwuluka NC, Idiakhoa BA, Nep EI, Ogaji I, Okafor IS. Formulation and evaluation of paracetamol tablets manufactured using the dried fruit of *Phoenix dactylifera* Linn as an excipient). Research in Pharmaceutical Biotechnology, 2010;2(3):25-32.

29. Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, editors. The theory and practice of industrial pharmacy. New Delhi: CBS Publishers & Distributors Pvt. Ltd; 2009.

30. Kumar V. Dissolution. In: Remington: The science and practice of Pharmacy. 21st ed. UK: Pharmaceutical Press;2005.

31. Uzunović A, Vranić E. Effect of magnesium stearate concentration on dissolution properties of ranitidine hydrochloride

coated tablets. Bosnian Journal of Basic Medical Sciences 2007;7(3): 279-283.

32. Ariyasu A, Hattori Y, Otsuka M. Delay effect of magnesium stearate on tablet dissolution in acidic medium. International Journal of Pharmaceutics, 2016; 511(2):757-764.
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