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Evaluation of the binding properties of gum obtained from dried leaves of *Cochoros olitorious* on metronidazole tablets formulation

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Abstract
The binding properties of the gum obtained from fresh leaves of *Cochorus olitorious* (family (Malvceae) were evaluated, characterized and compared with that of standard gums (sodium CMC and tragacanth). Using the technique of wet granulation method, metronidazole tablets (400 mg unit strength) were prepared with binder concentration of 0%, 2% and 5%w/v respectively. The compressibility properties of the tablet formed were analyzed using density measurement while mechanical properties were analyzed using angle of repose, crushing strength and percentage friability. The tablet release properties were assessed using disintegration and dissolution technique. Tablets produced with *C. olitorious* gum showed acceptable crushing strength (4.41kgf), disintegration time (2.12minutes) and dissolution rates at low binder concentration of 2%w/v but probable impact of sustained release could be effected if higher concentration of up to 5% w/v was used for the formulation. This result is in comparison to standard binders used for the study.

Keywords: *Cochorus olitorious*, Tragacanth, sodium CMC, gum, binder and metronidazole

Introduction
The development of new excipient from plants for its potential use as a binding agent in Pharmaceutical tablet formulation has continued to be of great interest. This is because different binding agent could impart various mechanical strength and drug release properties for pharmaceutical purposes [1]. Gums are often chosen as binders for tablet formulation because of their physico chemical profile such as: relative inertness, ready availability and cheapness hence the increasing interest in the use of natural gums and binders for tablet formulation.

These natural gums are usually polysaccharides made from sugar and uronic units that dissolve or swell in water but are sparingly soluble in organic solvents [2]. Natural gums serve as binders and are non-polluting but renewable source for sustainable supply of cheaper pharmaceutical excipients [3]. In recent times, plants gums and mucilage's has evoked tremendous interest due to their diverse applications in pharmaceutical formulation of both solids and liquid dosage forms serving as thickener, suspending agents, emulsion stabilizers, binders and film formers. With these relevance (s), there has become a renewable demand for natural gums and mucilages; hence the necessity to explore newer sources to meet these needs [4].

Natural gums are mainly long, straight or branched chain polysaccharides that contain hydroxyl groups which can be bonded to water molecules. They can be neutral or anionic and it is their structure, the type and number of monosaccharaides and configuration that denotes their characteristic property [5]. These natural gum are better tolerated by patients as well as the public because they have fewer side effects compared with their synthetic counterparts as they are usually obtained from edible sources and also the cost of the gums are low as a result of their lower production cost when compared to synthetic materials [6].

Due to the differences in the collection of natural gums at different seasons, as well as differences in sources, climatic conditions and regions, the presence of chemical constituent present in a given plant source may vary. The equilibrium moisture content present in a gum may be about 10% or more, therefore during production, they are exposed to the external environment and are easily prone to microbial contamination [6], although this can be prevented by use of preservatives.

Natural gums used as binders are employed as agents to impart cohesiveness to granules ensure intactness of tablets after compression and helps to improve flow quality by the formation of granules of desired hardness and size [1]. These natural polymers could also possess such properties as: disintegrants, fillers, sustained release and stability enhancing properties [7].

Binders can be classified based in their sources or the basis of their application such as natural polymers, semi synthetic polymers, sugars and hydrated silicates. The choice of a suitable binder for tablet formulation requires extensive knowledge of the relative importance of the binder properties for enhancing the strength of the tablet and also of the interaction between the various materials constituting a tablet [1].

Cochorus olitorious is a plant of the kingdom Plantae and family melvaceae. It is a tall plant of tropical Africa and Asia although it has since spread to Australia, South America and some part of Europe. The growth of *C. olitorious* seedlings is fast; flowering starts about a month after emergence and continues for 1-2 months. Seeds are sown between February to June and in moist soil, germination occurs in 2-3 days [8]. *C. olitorious* leaves are used to flavor soups and vegetable dishes and are used to make mucilaginous soups where they serve as soup thickeners. They are consumed for their flavor and nutritional value as a source of beta- carotene and the leaves are consumed for food while the stalks are used for industrial products such as ropes, pulp paper, fiber and composite [9]. The *C. olitorious* plant in Nigeria is known as *Ayoyo, Ewedu* and *ahihiare* by the Hausa, Yoruba and Ibo tribes respectively.

Metronidazole: This is a nitro inidazole compound clinically effective in protozoal infection known as *trichomoniasis amoebiasis* and *giardiasis* as well as a variety of infections caused by obligate amoebic bacteria including bacteroides, clostridium and helicobacterial species [10]. It can be formulated in a solid dosage from such as capsules and tablets, occurring in strengths of 200, 250, 400 and 500mg. It can also be formulated into such forms as creams, gels and syrups and known to be used as cream or gels for treatments of propioni bacterium acnes [11]. Metronidazole is a pro drug requiring reductive activation of the nitro group by susceptible organisms. It is completely and promptly absorbed after oral administration reaching concentrations in plasma of 8 to 13mg within 0.25 to 4hrs after a single 500mg dose [11]. The metronidazole appears in cerebrospinal fluids, saliva and human milk in concentration similar to those in the plasma.

Tablets

Reference to the British pharmacopeia, tablets are solid single dosage form comprising of medicaments usually with excipients compressed or molded into circular shapes with flat, convex faces or suitable shapes. They are formulated to release the active ingredients in a way that will achieve desired effect. In addition to the active ingredient, tablets contains a number of inert materials known as excipient that are mixed with medicaments or added to granules and these includes binders, disintegrants, glidants and lubricants. The tablet can be formulated by various methods involving: wet granulation, dry granulation or direct compression.

The objective of this study is to evaluate the binding properties of the gum extracted from *C. olitorious* dried leaves in comparison with other standard polymers (sodium carboxymethyl cellulose (NaCMC) and tragacanth) in the formulation of conventional metronidazole tablets of 400mg unit strength.

Materials used

Materials used were all of Pharmaceutical grades and includes:

Sodium carboxymethyl cellulose (Griffin and Geogy, England), tragacanth, magnesium stearate, lactose, maize starch, talc, metronidazole powder (Yinha arrti pharm. Company, China), pH meter (PHS-25, England), electronic balance (Adventurer T^M AR2139, China), dissolution apparatus (Erweka TDH 600, Germany), disintegration apparatus (Erweka, Germany), UV spectrophotometer (6405 UV, Jenway). Extracted crude gum from *C. olitorious* dried leaves

Method

Extraction and Phytochemical investigation

The extraction, phytochemical and some physico chemical examination of the extracted crude *C.olitorious* gum were carried out as earlier reported [12].

Physico technical properties of Gum

All the physico technical and physico chemical properties of the gum and subsequent granules formed were determined in triplicate and the mean and standard deviation calculated and such properties includes:

Flow rate: Using the flow through the hopper method, 30g of powder in a batch were allowed to pass through the orifice of a funnel and the time taken to pass through was recorded. The flow rate vas determined by the relation-

Quantity of powder (g) per unit time (seconds) ... (1)

Bulk density (D_B): A 10g quantity of the powdered gum was introduced into a clean dry 100ml measuring cylinder and the volume occupied noted. This is expressed as g/ml and given by the relation

$$D_B = M//V_B \quad \ldots (2)$$

Where M is the mass of powder

V_B is the bulk volume of the powder

Tapped density (D_T): A 10g of the gum powder was introduced in to a clean dry 100ml measuring cylinder. The measuring cylinder was then tapped 50 times on a paddled table top to obtain a fixed height of the powder and the volume was read. This is expressed in g/ml and given by the relation

$$D_T = M/V_T \quad \ldots (3)$$

Angle of repose (°): A 20 gram of the gum powder was placed in a blocked glass funnel which was clamped on a retort stand at a distance of 2 cm from a flat surface. The powder was then allowed to flow through the funnel orifice of about 1.5 cm diameters by removing the block. The height (h) as well as the radius of the heap formed was noted. The angle of repose (°) was calculated according to the formula

$$\text{Tan } \theta = h/r \quad \ldots (4)$$

Hausner's quotient (H): This involves the determination of the percent of void space (porosity) present in a powder and it is calculated in terms of true identity and bulk density as

$$\frac{I\text{-}D_B}{D_T} \text{ X } 100 \quad \ldots (5)$$

Where DB= bulk density, DT = true identity

Compressibility index: (Carr's index): This is also known as percentage compressibility, a method of measuring powder flow from bulk density measurement as is given as

$$\% \text{ Compressibility} = \frac{D_T\text{-}D_B \text{ x } 100}{D_T} \quad \ldots (6)$$

Preparation of metronidazole granules

Table 1: Working formulae for the preparation of metronidazole granules

Ingredent	Weight per tablet	Equivalent weight in 200 tablets
Metronidazole	400mg	80g
Maize starch	48mg	9.6g
Binders		
Polymers: *C. olilorious*, NaCMC and Tragacanth	0% w/v, 2% w/v, 5% w/v	
Exo disinfectant/lubricant/glidant		Qs
Dried maize starch	8.0% w/v	8.0% w/v
Magnesium stearate	0.2% w/v	0.2% w/v
Talc	2.0% w/v	2.0% w/v

Using the technique of wet granulation method of tablet formulation, metronidazole (MTZ) granules were made based on the formulae in Table I. The *C. olitorious* gum was used as test samples while tragacanth and NaCMC were employed as reference binders while all were made in concentrations of 0% w/v, 2% w/v and 5% w/v.

Metronidazole powder was geometrically diluted with maize starch (the disintegrant) in a porcelain mortar. The binder mucilage prepared from the various concentrations of the gum was incorporated into the content of the mortar until a wet coherent mass was obtained. The damp mass was then passed through a 2mm sieve aperture to break down the mass and then dried at 50 °C in an oven for 30minutes. The granular mass obtained was again passed through a 1mm sieve to ensure uniform size granules and then dried again in an oven at 50 °C for 1 hour. The dried granules were then mixed with the exo disintegrant, lubricant and glidant properly and then stored for use in further analysis.

Physico technical characterization of the granules

Characterization of granules based on physico technical properties such as angle of repose, bulk and tapped density, Hausner's quotient and compressibility index were carried out adopting standard procedures and according to the methods adopted for gum powder characterization.

Compression of tablets

After the addition of exo excipients, the mixed granules were compressed into tablets using the single punch tableting machine adjusted at varying pressures until best tablets were formed. The formed tablets were left for 2hours before evaluation to allow for elastic recovery.

Quality control of tablets

Weight variation (uniformity of weight)

The weights of 24 randomly selected tablets were taken as a whole and individually from a batch using an electronic balance and the mean weight was calculated. The difference in weight of the individual tablets from the mean was determined.

Friability test

Ten tablets from a batch were randomly selected and placed in a sieve; loose dust was removed with the aid of a soft brush. The dedusted tablets were weighed and caused to cascade in the drum of a fribilator which rotates at 25rpm for 4minutes. The tablets were dedusted and reweighed. The percentage friability was determined using the formula

$$\% \text{ Friability} = \frac{\text{Initial weight-final weight X } 100}{\text{Initial weight}} \quad \ldots (7)$$

Crushing strength: The crushing strength of 10 tablets per batch was determined using the Erweka TDH 100 hardness tester and the mean crushing strength determined.

Disintegration test: The disintegration rate of six tablets randomly selected from each batch was individually determined in a BP specified apparatus (Erweka) containing purified water at 37±0.5 °C. The mean disintegration time was calculated.

Drug content determination: Twenty tablets were randomly selected from each batch weighed and crushed to fine powder. The powder equivalent to the average weight of the tablet was weighed and transferred into a 100ml volumetric flask and dissolved with 0.1N HCl. shaken and made up to volume (100ml) with same solvent, 5ml of the solution was withdrawn using a pipette made up to 100ml with the solvent (0.1N) HCl) and filtered using a filter paper (Whatman No 41). The drug content was determined by measuring the absorbance of the filtrate at 345nm using the UV spectrophotometer.

Preparation of standard calibration curve

Pure metronidazole powder (100mg) was placed in a 100ml volumetric flask dissolved with 0.1N HCl and made up to the mark with same solvent. 1 in 10 ml dilutions were made with the solvent and the absorbance determined by UV spectrophotometer at 345nm. A standard calibration curve was plotted adopting the Beer lambert's relation.

Dissolution

The dissolution rates of the active drug (mtz) from the tablets were determined using USP apparatus II paddle. A 900ml volume of freshly prepared dissolution medium (0.1N HCl) was transferred into the dissolution jars and maintained at

37±0.5 °C. The paddle was caused to rotate at 50rpm. Samples were withdrawn at 10, 20, 30, 40, 50 and 60 minutes and spectrophotometric ally analyzed for metronidazole at 345nm. Samples of the dissolution medium and the percentage drug release was calculated as

Concentration= slope X absorbance ± intercept … (8)

Amount of drug released (mg) = Concentration X dissolution batch volume X dilution factor … (9)

$$\text{Percentage drug released} = \frac{\text{Amount released at time (t) X 100}}{\text{Total amount released}} \quad \ldots (10)$$

All the data obtained were analyzed statistically by determining the mean, standard deviation and regression and coefficient of variation.

Result

Table 2: Physicotechnical characterization of gum

Test	*C. olitorious*	NaCMC	Tragacanth
Bulk density (g/ml)	0.480±0.01	0.428±0.01	0.256±0.00
Tapped density (g/ml)	0.588±0.00	0.451±0.01	0.293±0.00
Hausner's Quotient (H)	1.14±0.03	1.05±0.02	1.15±0.01
Compressibility index (%)	13.98±1.13	4.98±1.21	12.53±0.09
Angle of repose (°)	30.1±0.06	29.1±0.06	29.7±0.06

Table 3: Physico technical properties of MTZ granules

Granule property	Batch identification/Binder concentration								
	C_1 (0%w/w	C_2 (2%w/w)	C_3 (5%w/w)	N_1 (0%w/w))	N_2 (2%w/w)	N_3 (5%w/w)	T_1 (0%w/w)	T_2 (2%w/w)	T3 (5%w/w)
Flow rate (g/sec)	10.68±0.05	8.63±0.00	8.15±0.02	10.68±0.05	6.87±0.01	6.80±0.02	10.68±0.05	8.64±0.02	8.82±0.04
Angle of repose (o)	26.7±0.21	21.8±0.71	24.3±0.63	26.7±0.21	24.1±0.14	20.1±0.17	22.4±0.78	24.0±0.35	26.7±0.5
Bulk density (g/ml)	0.59±5.77	0.54±5.77	0.49±5.77	0.59±5.77	0.47±5.77	0.47±5.77	0.59±5.77	0.54±5.77	0.54±0.72
Tapped density (g/ml)	0.74±0.01	0.62±0.01	0.58±0.00	0.74±0.01	0.53±0.00	0.56±0.07	0.74±0.01	0.65±0.01	0.67±0.01
Hausner's quotient (H)	1.25±0.01	1.15±0.01	1.16±0.01	1.25±0.01	1.14±0.01	1.22±0.01	1.25±0.01	1.20±0.01	1.24±0.00
Compressi bilty index (%)	19.97±0.75	13.08±0.85	13.80±0.85	19.97±0.75	12.10±0.29	17.60±1.90	19.97±0.75	17.04±0.80	19.76±0.68

Table 4: Evaluation of tablet properties

Batch number	Binder concentration	Hardness (kgf)	Weight variation (%)	Friability (%w/v)	Disintegration Tme (minutes)
C_1	0%w/w	2.90±0.32	3.9	3.8	0.40
C_2	2%w/w	4.41±0.86	4.5	0.9	3.12
C_3	5%w/w	7.25±0.59	4.9	1.1	10.12
N_1	0%w/w	2.90±0.32	3.9	3.8	0.40
N_2	2%w/w	4.33±0.81	4.9	1.2	4.20
N_3	5%w/w	6.81±0.61	3.7	1.2	20.0
T_1	0%w/w	2.90±0.32	3.9	3.8	0.40
T_2	2%w/w	4.95±1.02	4.7	1.3	1.70
T_3	5%w/w	7.12±0.66	4.6	1.1	12.75

Batch content and identification

Note: C: *Cochorus olitorious*, N: NaCMC T: Tragacanth

Table 5: Kinetics of Drug release for batch C_2, N_2 and T_2

Time (minutes)	Absorbance			Concentration (mg/ml)			% Drug release		
	C2	N2	T2	C2	N2	T2	C2	N2	T2
10	0.132	0.108	0.106	0.073	0.059	0.059	82.3	67.2	66.0
20	0.137	0.129	0.121	0.076	0.071	0.067	85.9	80.5	75.6
30	0.136	0.131	0.134	0.075	0.072	0.074	84.7	81.6	83.5
40	0.139	0.136	0.130	0.077	0.075	0.072	86.6	84.7	81.0
50	0.140	0.123	0.133	0.078	0.068	0.073	87.3	76.65	82.8
60	0.140	0.130	0.131	0.078	0.072	0.072	88.2	81.02	81.6

Table 6: Kinetics of drug release for batch C3, N3 and T3

Time (minutes)	Absorbance			Concentration (mg/ml)			% Drug release		
	C3	N3	T3	C3	N3	T3	C3	N3	T3
10	0.094	0.095	0.065	0.169	0.171	0.117	38.0	38.5	26.3
20	0.120	0.105	0.031	0.217	0.189	0.056	48.7	42.6	12.0
30	0.134	0.118	0.020	0.242	0.213	0.036	54.4	47.9	8.1
40	0.134	0.128	0.023	0.242	0.231	0.041	54.4	51.9	9.2
50	0.140	0.126	0.019	0.253	0.227	0.034	56.8	51.2	7.6
60	0.139	0.128	0.021	0.250	0.231	0.038	56.4	51.9	8.5

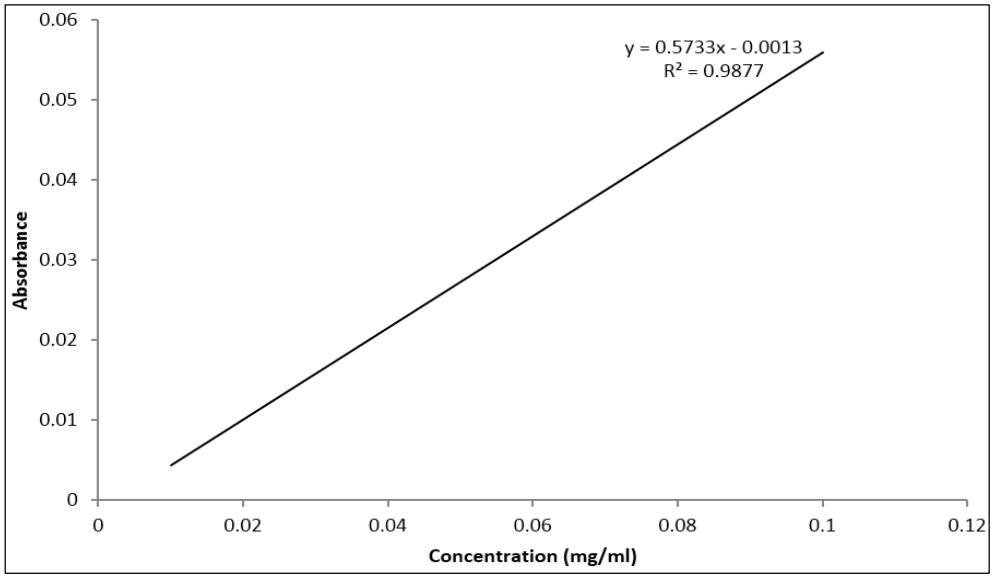

Fig 1: Standard calibration curve for Mtz powder at 345nm

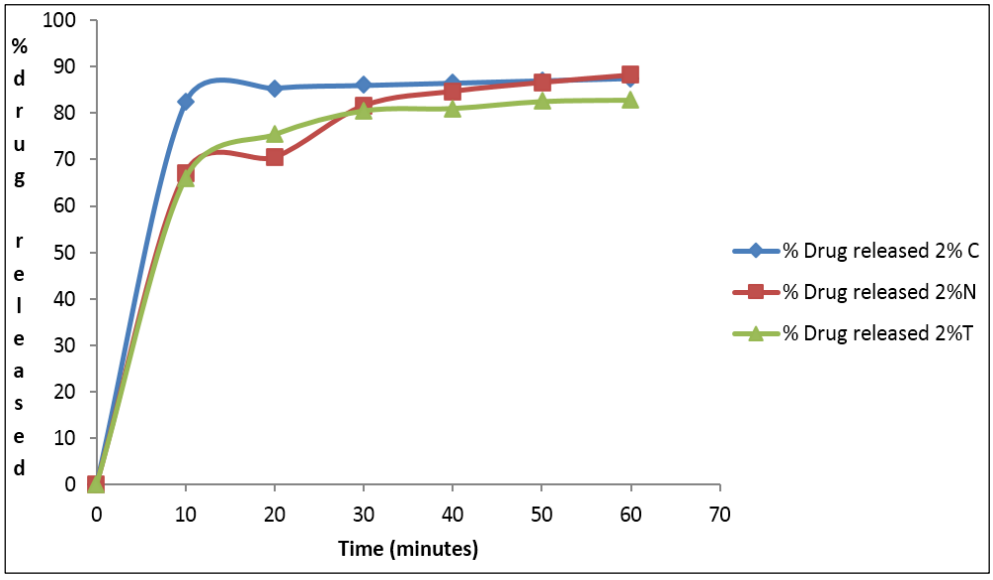

Fig 2: Dissolution profile of metronidazole tablet formulated with 2% w/w binder (polymer) concentrations

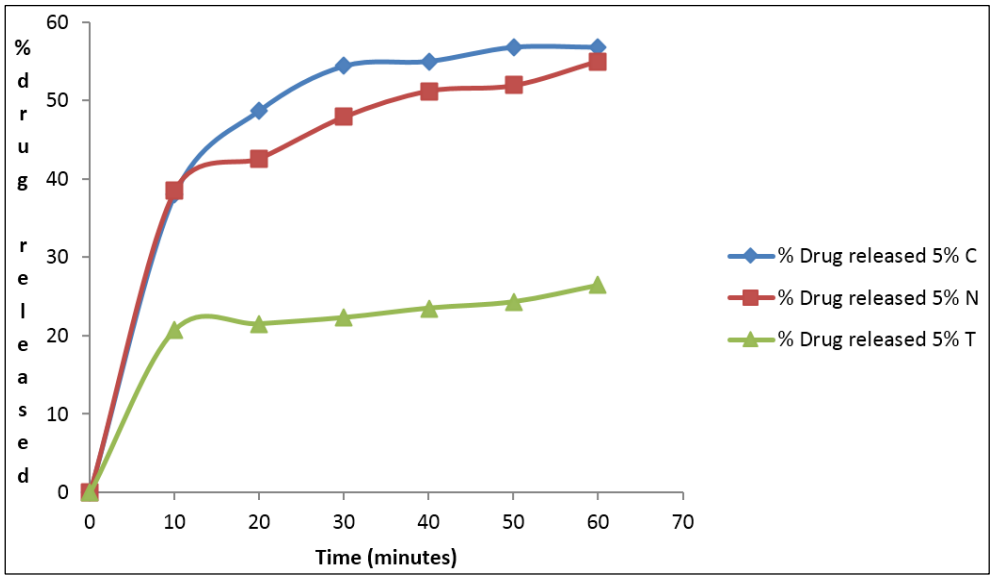

Fig 3: Dissolution profile of metronidazole tablet formulated with 5% w/w binder (polymer) concentrations

*Where C = Cochorous olitorious N = sodium carboxymethyl cellulose T = tragacanth

Discussion

The bulk density of a powder is the ratio of the mass of the untapped powder samples and its volume including the contribution of inter particulate void spaces while the tapped density explains the density of the powder after packing. It gives insight of how well the powders will compact to form tablet [13]. *C. olitorious* gum powder had a tapped density of 0.56g/ml, sodium CMC 0.45glml and tragacanth 0.29g/ml.

Angle of repose is a characteristic of the internal friction or cohesion of the particles. It gives insight to the flow ability of the powder or granule assessed. Its values will be high if the powdered polymer is cohesive and low if non-cohesive [2, 14], hence *C. olitorious*, tragacanth and sodium CMC powder were observed to have a good flow property as shown in their possession of lower angle of repose in table 2 with values of 30.1°, 29.7° and 29.1° respectively.

The compressibility index has been proposed as an indirect measure of bulk density size, surface area and cohesiveness of materials. It shows the ability of the granules to form a compact and a decrease in volume under pressure [7]. From the result in table 3, a direct relationship was found to exist as increasing binder concentration lead to an increase in compressibility index and consequently the Hausner's ratio. The granules batches C2, and C3 had fair flow property having compressibility index ranging from 12-14% and 1.14-1.23 respectively while the batches N1, C1 and T3 had fair flow property with compressibility index ranging from 17-20% and Hausner's ratio ranging from 1.14-1.25. The granules formed from the various batches were observed to have good flow property as shown by their low angle of repose (20.1 to 27.3°), however there was no direct correlation observed between the concentration of the gums and their flow rate but the result reveals that the formulated granules possess good flow property.

Crushing strength is a measure of the force required to break or crush a tablet an important in- process test to assess the chipping or crushing ability of tablets yet determine how hardness could influence or cause a delay in tablet dis integration [15]. The primary role of binders is to provide the cohesiveness essential for the bonding of solid particles under compaction to form a tablet [16]. These binders may improve tablet hardness by enhancing inter granular and intra granular compaction forces. A range 0f 4-7 kgf have been given as values obtainable for crushing strength of tablets [17] as excess amount of binders, solvent and compression pressure may make the compressed tablet too hard such that its disintegration may not occur within desired time. Therefore binders concentration must be controlled to produce tablets that are not too hard as to impair its absorption or too soft as not to withstand handling stress. From the result in table 3 the tablets formed had a mean crushing strength of 2.90-7.25 kgf and correlation was observed between increase in binder concentration and crushing strength especially in C3 and T3 and this may also be linked to method of incorporation of the excipients and binders solution.

Friability is another mechanical property of tablet and it depict the surface deformation of the tablet which could occur as a result of the morphology of the tablet as the rougher the surface of the tablet, the more friable it would be [18]. It is expected not to exceed a value of 1% [19], however it is worthy to note that the tablet batches failed the friability test except for batch C2 (2%w/v *C.olitorious* gum). This outcome could be due to the method of incorporation of the binders into granules, as well as the quantity of water and wetting agent employed in mixing the binders before incorporation as observed by [2]. Other factors could be attributed to the compression pressure, such as air entrapment within the granules or powder before mixing [10].

Dis integration test measures the time it takes a tablet to break into granules and smaller particles in physiological medium. It is an important step in the release of drugs from Pharmaceutical dosage form and the requirement for uncoated tablets is 15minutes [17]. The result of the disintegration compliments that of the crushing strength and friability. The higher disintegration time observed for batches N3 could be attributed to greater increase in binding bridges and bonds of the granules during compaction of the tablet mass. Dissolution study also gives an insight into the release of a drug from a dosage form. [7], it is an indirect measure of drug availability especially in the assessment of formulation factors and manufacturing methods that affects dissolution and this includes the type and concentration of the binder, hardness of the tablet, particle size, distance of diffusion, solubility of the drugs and manufacturing process [20]. From the result in fig. 2 and 3, it can be observed that as the binder concentration is increased, the rate of drugs release is decreased. This can be attributed to the formulation of higher binding bridge or bonds in the tablet leading to a slower drug release. The formulation produced with *C. olitorious*, passed the official dissolution test of not less than 85% of the labelled amount of metronidazole that must dissolve in 60 minutes [17], as opposed to those formulated with sodium CMC and tragacanth especially with higher binder concentration (5% w/v). The ease of dissolution of formulation containing *C.olitorious* could be linked to the fact that dissolution is a function of disintegration which could be related to the acceptable swelling and hydration properties of *C. olitorious* [21], as tablet would most often dis integrate before it releases its content.

Considering the drug content analysis, all the batches analyzed were within BP specification of 85 to 115% [16], indicating that appropriate quantities of metronidazole were approximately weighed and used in the formulation.

Conclusion

Varieties of natural polymers have been of use in pharmaceutical preparations and examples of such include natural gums and mucilage's which possesses bindingl disintegrating and sustained release properties.

The extraction of gum from *C. olitorious* dried leaves is an easy and cost effective process and the binding efficacy is similar and comparable to that of some synthetic polymers such as sodium caboxy methyl cellulose. The extracted *C. olitorious* gum exhibited an appreciable physicochemical properties that is best suited for the development of metronidazole tablet as indicated in the drug release studies

Metronidazole tablet produced from *C. olitorious* gum as obtained from the preliminary study, was observed to have faster onsset of drug release at lower concentration (2% w/w) while at higher concentration (5% w/w) there was a slow but steady and increasing rate of drug release.

With the associated properties therefore, gum from *C. olitorious* leaves could be useful as an excipient in tablet formulation especially as it possesses high binding and reasonable dissolution profile especially at moderate concentration of (4% w/w).

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