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MODIFICATION OF *MYRIANTHUS ARBOREUS* GUM: EFFECT ON DISINTEGRATION AND *IN VITRO* RELEASE OF METRONIDAZOLE FROM TABLET FORMULATION

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Modification of natural polymer can lead to improvement of polymer properties. Gums can be modified by physical and chemical methods. The aim of this study was to examine the effect of modification of Myrianthus arboreus gum on disintegration and in vitro release of metronidazole from tablet formulations. The gum was extracted, modified by acid treatment and Carboxymethylation, and used as a binder in metronidazole tablet formulations at concentrations of 2.5% w/w, 5% w/w and 10% w/w. The granule properties were evaluated for bulk and tapped densities, Carr's index, Hausner's ratio and angle of repose. The properties of tablets formulated with the modified gums were compared with tablets formulated with sodium alginate and the unmodified native gum. The results showed that carboxymethylation of Myrianthus arboreus gum led to faster disintegration and drug release. Batch B10 containing 2.5% w/w carboxymethylated Myrianthus arboreus gum (C-MAG) disintegrated in less than 2 minutes and released over 80% of metronidazole in 15 minutes. While acid modification of Myrianthus arboreus gum led to slower disintegration and drug release. Metronidazole tablets formulated with 5% w/w and 10% w/w of acid modified Myrianthus arboreus gum (A-MAG) gave disintegration time of 40.33 minutes and 46.35 minutes, respectively, while drug release in 15 minutes for 5% w/w and 10% w/w were 57% and 16%, respectively. It can be concluded from the study that modification of Myrianthus arboreus gum could lead to multi-functional excipients for drug delivery systems by altering the physicochemical properties of the gum.

Keywords: Carboxymethylation, Metronidazole, *Myrianthus arboreus* gum, Disintegration, *In vitro* release

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INTRODUCTION

Gums are natural polysaccharide made of multiple sugar units linked together to form large molecules. Gums may be classified as natural, semi-synthetic or modified and synthetic. Natural gums have found great use in the pharmaceutical industry owing to their non-toxicity, ready availability and biodegradability. They have been explored as emulsifier, suspending agent, binding agent etc. Most natural gums are safe for oral use in the food and pharmaceutical industries. However, the use of these gums could be associated with certain challenges such as uncontrolled rates of hydration and swelling, pH-dependent solubility, change in viscosity on storage and high susceptibility to microbial contamination.

Modification of natural gums can be a veritable tool to alter their physicochemical properties, improve utility and functionality, as well as overcome various processing and shelf-life challenges, giving rise to tailor-made functionalised excipients for drug delivery systems and thus can compete with commercially available synthetic controlled release excipients (Muller, Le Cert and Frinei 1990; Risica *et al.* 2010).

Physical modification method involves molecular interaction among polymers and can be achieved by exposure to dry heat, saturated steam, microwave technology, UV and gamma radiation (Desai and Park 2006; Khan *et al.* 2006). Temperature is one of the most favourable methods of cross-linking because it avoids both the application of harsh chemical materials for large-scale production and the diversity of equipment and methods used in their application (Micard *et al.* 2000).

Chemical method involves treatment with chemicals and can be achieved through derivatisation of functional groups, grafting with polymers, cross-linking with ions etc. (Rana *et al.* 2011). Derivatisation of functional groups can be carried out by carboxyethylation (Dhande and Chaudhari 2014; Dodi, Hritcu and Popa 2011; Parvathy *et al.* 2005), carbomoylethylation, carboxyethylation (Mourya, Inamdara and Tiwari 2010; Sholapur *et al.* 2012). Other methods are esterification, oxidation and hydroxypropylation.

Carboxymethylation generally increases the hydrophilicity and solution clarity of the polysaccharides and makes it more soluble in aqueous system (Pal 2009; Dey, Sa and Maiti 2011; Prajapati *et al.* 2013). Modification of tamarind kernel powder, cassia tora gum and guar gum has been investigated (Vipul *et al*. 2013). The efficiency of the reaction is affected by factors such as reagent concentration, reaction time, pH, presence of catalyst, gum source and amylose/amylopectin ratio (Henry 2007; Dodi, Hritcu and Popa 2011; Adeyanju *et al.* 2015).

Carboxymethylation is a chemical means of attaching carboxylic acid moiety (COOH), to polymers and has been used to produce carboxyl methylcellulose (CMC) (Aguir and M'Henni 2005), carboxylmethylstarch (Kittipongpatana *et al.* 2006), carboxylmethylinulin and carboxylmethyl xylan (Petzold, Schwikal and Heinze 2006).

Myrianthus is a genus of flowering plants in the nettle family (Urticaceae). They are predominantly found in tropical Africa. The leaves of *Myrianthus arboreus* are a special food condiment in the Delta and Edo States of Nigeria, the fruits are also edible and the plant is known locally as ujuju (Okafor 1997). A number of studies have been carried out on activities of extracts of leaves, stem bark and root bark of *Myrianthus arboreus* plant such as the antioxidant activities (Biapa *et al.* 2007; Odukoya *et al.* 2006; Kasangana, Haddad and Stevanovic 2015), phytochemical and proximate evaluation (Oyeyemi, Arowosegbe and Adebiyi 2014), glucose uptake stimulatory effects (Harley, Dickson and Fleischer 2017) and wound healing properties (Agyare *et al.* 2009; Agyare *et al.* 2014; Agyare *et al.* 2016).

Studies on the extracted gum from the leaves of *Myrianthus arboreus* plant are still scanty, except for the preliminary characterisation of the gum (Alalor, Emoredo and Okafo 2017). The results of the preliminary characterisation which revealed that *Myrianthus arboreus* gum had potential as a pharmaceutical excipient as well as a background knowledge that the quality and usability of crude gums can be improved by modification are the reasons for the present study.

Therefore, the aim of this study was to investigate the effect of modification of *Myrianthus arboreus* gum on disintegration and *in vitro* drug release of metronidazole from immediate release tablet formulation.

METHODS

Extraction of *Myrianthus arboreus* Gum

The fresh young leaves of *Myrianthus arboreus* plant were collected from Evwbosi farm in Delta State, Nigeria. The leaves were washed, sun dried and pulverised. A sample equivalent to 100 g of the dried leaves was weighed and heated at 60°C in 1 litre of distilled water for 4 hours and cooled for 1 hour. The mucilaginous slurry obtained was filtered through a muslin cloth and the viscous filtrate was precipitated with acetone in a volume ratio of 2:1 (Malviya, Srivastava and Kulkarni 2011; Uzma, Pramod and Malviya 2014).

The precipitated gum was washed severally with acetone. The gum was dried in hot air oven at 50°C and pulverised using a mortar and pestle. The dried gum was stored in a labelled container until used (Bamiro *et al*. 2010).

Modification of *Myrianthus arboreus* Gum by Acid Treatment

The extracted gum was acidified using 0.5 M HCl and allowed to stand for 30 minutes and equal volume of 0.5 M NaOH was added. The reaction was neutralised by adding 20 ml of NaOH and 2 ml of HCl to have a pH of 7.0. The viscous solution was precipitated with acetone in a ratio of 1:2 and allowed to dry in hot air oven at 50°C for 24 hours.

Modification of *Myrianthus arboreus* Gum by Carboxymethylation

A 4 g sample of the native gum was swelled in 100 ml of water with stirring, thereafter 20 g of NaOH was added over a period of 20 minutes and the mixture was allowed to stand for further swelling for 60 minutes at 30°C. Then a 10 g quantity of monochloroacetate was added to the mixture over a period of 30 minutes and the mixture was allowed to stand for 1 hour. The temperature of the reaction was raised to 60°C within 1 hour. The reaction was then allowed to proceed for 2 hours, then filtered using a filter paper, washed with ethanol severally and dried in an oven at 45°C (Nemade and Sweeti 2015).

Preparation of Metronidazole Granules

Metronidazole granules were prepared using the wet granulation technique. Twelve batches of granules (B1–B12) were prepared using native *Myrianthus arboreus* gum (N-MAG), acid modified *Myrianthus arboreus* gum (A-MAG), carboxymethylated *Myrianthus arboreus* gum (C-MAG) and sodium alginate separately at concentrations of 2.5%, 5% and 10% ^{W}/w for each of the polymers in mucilage form as binder. Maize starch was used as disintegrant.

Appropriate amounts of the ingredients for each batch as specified in Table 1 excluding magnesium stearate and talc were weighed, mixed and kneaded with the mucilage binder using a mortar and pestle, to form wet mass. The wet mass was forced through a 1 mm sieve. The wet granules so formed were dried in a hot air oven at 60 ± 0.5°C for 24 h. The dried granules were sieved with a 710 µm sieve and stored for further work.

Table 1: Composition of metronidazole tablets

Composition (mg)	Formulation batches											
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**
Metronidazole	400	400	400	400	400	400	400	400	400	400	400	400
A-MAG	15	30	60	–	–	–	–	–	–	–	–	–
N-MAG	–	–	–	15	30	60	–	–	–	–	–	–
Sodium Alginate	–	–	–	–	–	–	15	30	60	–	–	–
C-MAG	–	–	–	–	–	–	–	–	–	15	30	60
Lactose	113	98	68	113	98	68	113	98	68	113	98	68
Maize starch	60	60	60	60	60	60	60	60	60	60	60	60
Mag. stearate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6	6	6	6
Total weight	600	600	600	600	600	600	600	600	600	600	600	600

Notes: A-MAG (acidified *Myrianthus arboreus gum*), N-MAG (native *Myrianthus arboreus gum*), C-MAG (carboxymethyl *Myrianthus arboreus gum*) B1, B2, B3 (A-MAG 2.5%, 5% and 10%), B4, B5, B6 (N-MAG 2.5%, 5% and 10%) B7, B8, B9 (sodium alginate 2.5%, 5% and 10%), B10, B11, B12 (C-MAG 2.5%, 5% and 10%).

Characterisation of Metronidazole Granules

Bulk density

A 20 g quantity of granules was weighed and transferred into a 50 ml measuring cylinder the bulk volume was recorded and bulk density was calculated using Equation 1.1.

$$\text{Bulk density} = \frac{M}{V_0} \tag{1.1}$$

Where, M = mass of the powder, V_0 = bulk or unsettled apparent volume of the powder

Tapped density

Granules equivalent to 20 g was weighed into a measuring cylinder and was tapped until a constant volume was reached. The constant volume was recorded as the final tapped volume of the powder and tapped density was calculated using Equation 1.2.

$$\text{Tapped density} = \frac{M}{V_f} \tag{1.2}$$

Where, M = mass of the powder, V_f = final tapped volume of the powder

Angle of repose

Angle of repose was determined using the common fixed base method with a retaining lip. The height (h) of the heap formed was measured and the diameter (d) of the cone base was also observed and calculated using Equation 1.3 (Malviya, Srivastava and Kulkarni 2011).

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right) \tag{1.3}$$

Where, h = height of the pile, r = radius of the base of the pile, θ = angle of repose

Compressibility index and Hausner's ratio

Using the bulk and tapped densities, compressibility and Hausner's ratio were calculated Equation 1.4 and 1.5, respectively (Rajasekhar and Niranjan 2013).

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \tag{1.4a}$$

$$\text{Carr's index (\%)} = \frac{V_0 - V_f}{V_0} \times 100 \tag{1.4b}$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100 \tag{1.5a}$$

$$\text{Hausner ratio} = \frac{V_0}{V_f} \times 100 \tag{1.5b}$$

Where V_0 = unsettled apparent volume, V_f = final tapped volume

Formulation of Metronidazole Tablets

Metronidazole granules were compressed to tablets after addition of 1% W/w of talc and 1% W/w of magnesium stearate using a single punch tablet machine (Manesty Machine Ltd, B3B Liverpool, England) at 35 arbitrary units on the load scale. The compressed tablets were collected, dedusted and stored in a labelled air tight container.

Evaluation of Tablet Properties

Weight uniformity

From each batch, 20 tablets were selected randomly and their individual weight were determined using Shimadzu analytical weighing balance. The average of the 20 tablets was calculated to get the average weight of the tablets and its deviation.

Friability

Ten tablets were weighed and transferred into the drum of the friabilator (Erweka, Heusenstamm, Germany) and rotated at 100 revolutions for 4 minutes (25 rpm) making, thereafter the tablets were dusted and weighed again. Friability was determined using the equation below:

$$\text{Friability (\% loss)} = \left(\frac{W_1 - W_2}{W_1} \right) \times 100 \quad (1.6)$$

Where, W_1 = weight of 10 randomly selected tablets before friabilation,
W_2 = weight of only the intact tablets after friabilation

Tablet thickness, diameter and hardness

Five tablets were picked from each batch and their individual weights were determined, thereafter the thickness, diameter and hardness of each tablet were determined by placing them into a 3-in-1 digital tester machine (Veego digital hardness tester Mumbai India. Model no: VDIGITAB-1). The tablet was first placed vertically in the thickness jaw of the tester and the apparatus is operated such that the drive jaw moved, touched the tablet and measures the thickness. Then the drive jaw reverses back so that the sample falls into a horizontal position to test the tablet diameter (length) and hardness.

Disintegration test

The test was done using Manesty disintegration apparatus. Water maintained at 37 ± 0.5°C was the disintegration medium. Six tablets were selected at random from each batch and tested according to the procedure described in the British Pharmacopoeia Commission (1998).

Metronidazole calibration curve

A standard calibration curve of metronidazole was prepared as follows: a 1 mg sample of metronidazole was weighed and dissolved in 0.1 N hydrochloric acid (HCl) and made up to 10 ml volume, to give a stock concentration of 0.1 mg/ml (100 µg/ml). Serial dilutions were made to give solution of 50, 25, 12.5, 6.25 and 3.125 µg/ml. The absorbances of these standard solutions were measured at a wavelength of 340 nm using ultraviolet–visible spectrophotometer (PG Instrument, USA). A plot of absorbance against concentrations was done to obtain the calibration curve.

In vitro drug release

Dissolution rate for metronidazole was carried out using dissolution apparatus (Erweka Dt 80, Germany) in 900 ml of 0.1 N HCl maintained at 37 ± 1°C. The paddle method was used at a speed of 50 rpm. A 5 ml sample was withdrawn from the dissolution medium at time intervals between 5 minutes and 60 minutes, and each time, 5 ml 0.1 N HCl solution was replaced to maintain sink condition. The absorbance of the samples was read using UV spectrophotometer (9160-a, Japan) at maximum wavelength of 340 nm.

The cumulative percentage drug release was plotted against time in minutes (Akiffudin *et al.* 2003*)*. The amount of drug release was determined using the equation from the calibration curve.

RESULTS AND DISCUSSION

Micromeritic Properties of Metronidazole Granules

The results of the flow properties of metronidazole granules are presented in Table 2. The bulk and tapped densities for the different batches of metronidazole granule are similar with only slight variations in the values irrespective of the modification technique. The relatively close bulk and tapped density values means that the inter-particulate interactions are less and granules are free flowing.

Table 2: Micromeritic properties of metronidazole granules

Batches	Bulk density (g/ml) ± SD	Tapped density (g/ml) ± SD	Flow rate (g/s) ± SD	Angle of repose (°) ± SD	Hausner's ratio	Carr's index
B1	0.58 ± 0.01	0.64 ± 0.01	3.13 ± 0.18	27.04 ± 1.15	1.11	9.64
B2	0.56 ± 0.01	0.62 ± 0.01	2.72 ± 0.19	31.54 ± 0.98	1.10	9.00
B3	0.52 ± 0.02	0.59 ± 0.02	2.86 ± 0.00	33.09 ± 0.41	1.12	10.58
B4	0.62 ± 0.02	0.68 ± 0.01	3.61 ± 0.24	23.30 ± 0.32	1.09	8.41
B5	0.55 ± 0.01	0.61 ± 0.01	3.08 ± 0.00	31.00 ± 0.77	1.11	9.51
B6	0.55 ± 0.00	0.58 ± 0.00	2.53 ± 0.17	34.04 ± 1.28	1.06	5.48
B7	0.60 ± 0.03	0.68 ± 0.01	3.88 ± 0.21	25.90 ± 1.20	1.14	12.02
B8	0.56 ± 0.00	0.63 ± 0.00	3.55 ± 0.39	23.72 ± 1.09	1.11	10.24
B9	0.60 ± 0.02	0.65 ± 0.02	3.11 ± 0.24	22.34 ± 1.51	1.08	7.12
B10	0.57 ± 0.03	0.70 ± 0.04	3.83 ± 0.30	28.21 ± 0.94	1.23	18.46
B11	0.56 ± 0.51	0.60 ± 0.52	3.54 ± 0.18	28.61 ± 0.5	1.07	6.63
B12	0.64 ± 0.02	0.78 ± 0.04	3.43 ± 0.14	26.68 ± 1.80	1.22	17.95

The relatively close bulk and tapped density values are reflected in the compressibility index and the Hausner ratio as revealed in Table 2 with compressibility index and the Hausner ratio values in the range of 5.48–12.02 and 1.06–1.14, respectively which are also indicative of good flow properties. These observations were further corroborated by the angle of repose values which were in the range of 22.34º–34.04º, indicative of good

flow. Scale of flowability of powders according to Carr (1965) states that angle of repose of 25°–30° indicates excellent flow, 31°–35° indicates good flow; compressibility index of ≤ 10% indicates excellent flow, 11%–15% good flow; Hausner ratio of 1.00–1.11 indicates excellent flow and 1.12–1.18 good flow.

Post-compression Evaluation of Metronidazole Tablet

Friability: Four batches B1, B4, B7 and B10 failed friability test while eight batches B2, B3, B5, B6, B8, B9, B11 and B12 passed the friability test having friability values of less than 1% ^{W}/w (British Pharmacopoeia Commission 2009) (Table 3). The batches that failed could be as a result of insufficient binder used in the metronidazole tablet formulation since the batches all had binder concentration of 2.5%.

Table 3: Physicochemical properties of metronidazole tablets

Batches	Weight uniformity (g) ± SD	Hardness (KgF)	Friability (%)	Content uniformity (%)
B1	0.59 ± 0.00	4.37	2.02	110.90
B2	0.59 ± 0.00	4.64	0.87	112.27
B3	0.59 ± 0.01	5.45	1.0	107.27
B4	0.59 ± 0.00	4.07	5.6	104.09
B5	0.60 ± 0.01	6.17	0.6	111.36
B6	0.60 ± 0.01	7.95	0.2	104.09
B7	0.60 ± 0.00	3.98	6.4	100.90
B8	0.56 ± 0.01	4.16	0.4	102.72
B9	0.59 ± 0.01	5.13	0.58	113.18
B10	0.60 ± 0.00	3.46	4.58	100.00
B11	0.59 ± 0.01	4.59	0.12	97.27
B12	0.59 ± 0.01	4.71	0.12	114.09

Hardness: All the batches except batches B7 and B10 met the specification for hardness of uncoated tablets, values ranged from 4 kg–10 kg. This could be due to low concentration of the binder, however, B1 and B4 having same concentrations as B7 and B10 had good hardness possibly because the acid modification did not change the binder ability appreciably unlike for B7 and B10.

Weight uniformity: All the batches complied with the weight uniformity test because for each batch no individual tablet deviated from their respective mean values by more than ± 5%.

Content uniformity: All the batches complied with the test because the individual contents fell within the official range of 85%–115%. The values obtained were in the range of 97%–114%. According to the European Pharmacopoeia, a batch fails to comply if more than one individual content is outside the range of 85%–115% or if one is outside the limit 75%–125% of the average content (European Pharmacopoeia, 2002).

Disintegration Time

The disintegration times for different batches of metronidazole tablet formulated with gums modified by different techniques are presented in Figures 1 and 2. Metronidazole tablets formulated with C-MAG i.e. batches B10, B11 and B12 all disintegrated within 15 minutes, B10 (2.5 % W/w) disintegrated in less than 2 minutes. On the other hand metronidazole tablets formulated with A-MAG i.e. batches B1, B2 and B3 disintegrated within 45 minutes except for B1 (2.5%) which disintegrated in less than 7 minutes. All three batches of metronidazole tablets (batches B4, B5 and B6) containing N-MAG disintegrated within 43 minutes with B4 (2.5%) disintegrating in 21 minutes, while batches B7, B8 and B9 containing standard gum, disintegrated within 27 minutes (Figure 1).

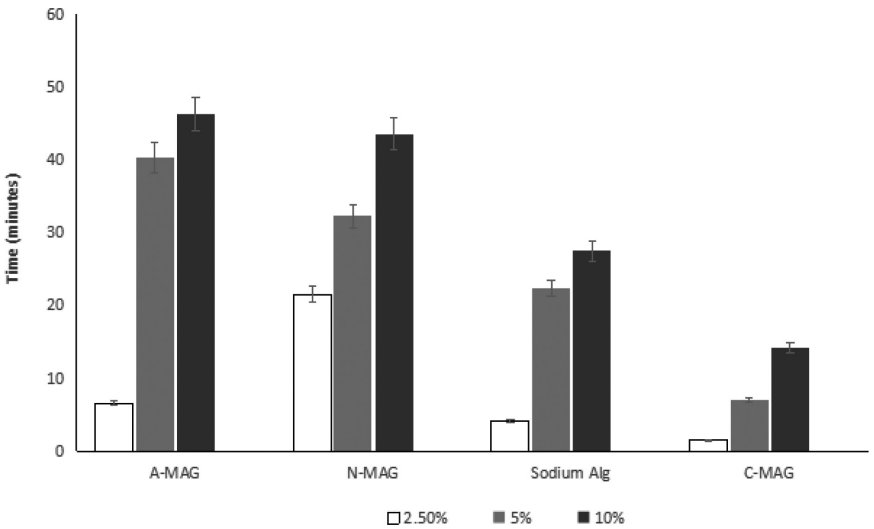

Figure 1: Disintegration times of metronidazole tablet formulation comparing different binder concentrations (2.5% W/w, 5% W/w and 10% W/w) of same gum.

Batches B10, B11 and B12 which were formulated with C-MAG showed better disintegration times for immediate release preparations across all three concentrations of 2.5%, 5% and 10%. This is so because carboxylmethylation of natural gum gives rise to water soluble derivatives which improves the solubility and hydrophilicity of the gum (Olusola, Toluwalope and Olutayo 2014; Dey, Sa and Maiti 2011)

A direct comparison of 2.5%, 5% and 10% of the different gum types as presented in Figure 2 shows that carboxymethylated gum at 2.5% concentration could be suited for fast disintegrating metronidazole tablets having disintegrated in less than 2 minutes. The 5% and 10% concentrations of the acid treated and native gum could be more suited for controlled release formulations (Figure 2).

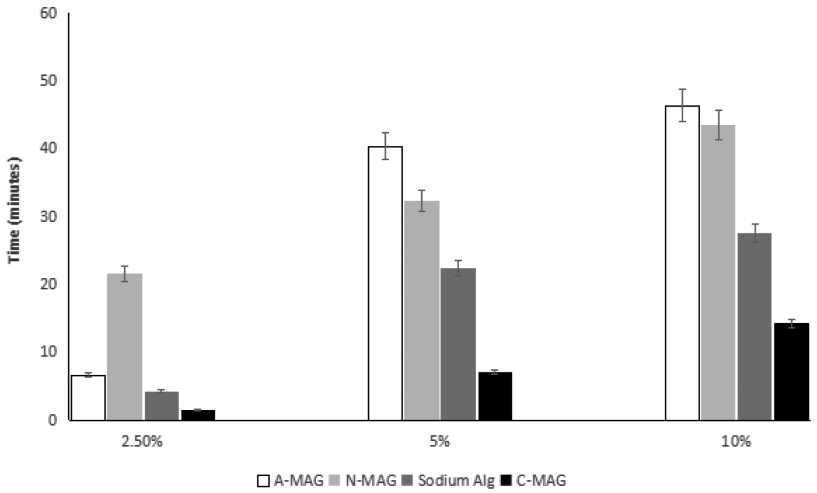

Figure 2: Disintegration times of metronidazole tablet formulation comparing same percentage binder concentrations for different gums.

In vitro drug release

The *in vitro* release profiles of metronidazole are presented in Figures 3, 4 and 5. Figure 3 shows a comparison of the drug release profiles of metronidazole tablet formulated with A-MAG (batch B1), N-MAG (batch B4), sodium alginate (batch B7) and C-MAG (batch B10) at same concentration of 2.5% W/w. The chart reveals that in 15 minutes over 80% of metronidazole is released from all the batches irrespective of the modification technique for *Myrianthus arboreus* gum.

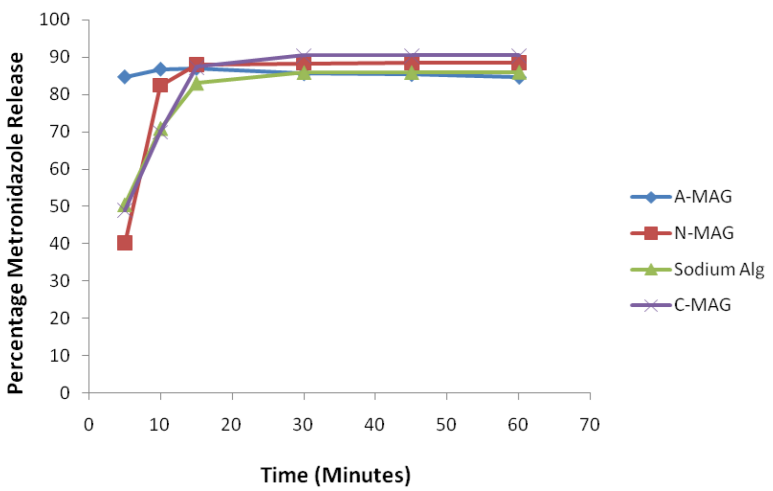

Figure 3: Drug release profile of metronidazole tablets at 2.5% W/w concentration of the various binders.

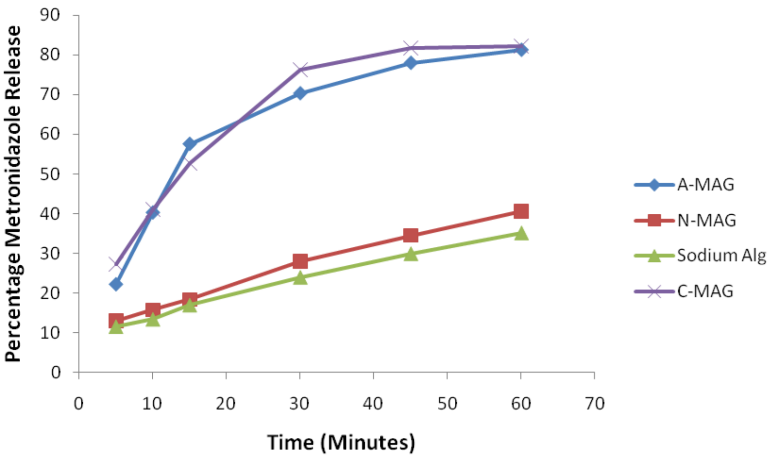

Figure 4: Drug release profile of metronidazole tablets at 5% W/w concentration of the various binders.

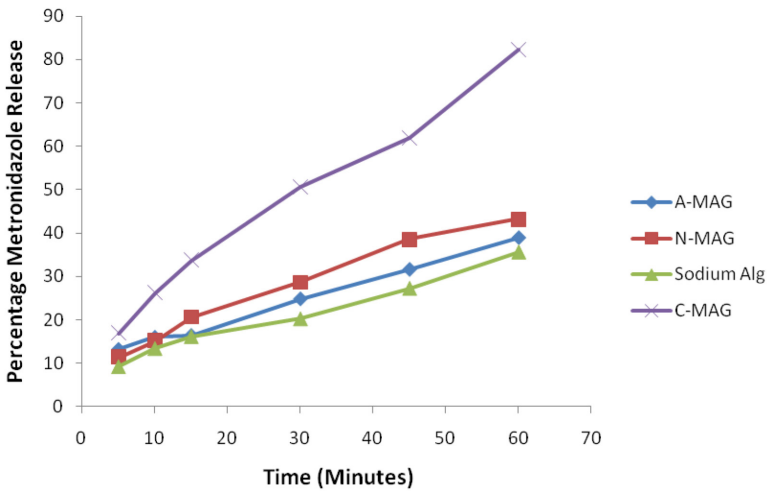

Figure 5: Drug release profile of metronidazole tablets at 10% W/w concentration of the various binders.

The release profile for metronidazole tablets formulated with A-MAG (batch B2), N-MAG (batch B5), sodium alginate (batch B8) and C-MAG (batch B11) at the same concentration of 5% W/w is presented in Figure 4. The formulations with acid modified and C-MAG exhibited similar release profiles, where about 80% release of metronidazole was achieved in 45 minutes. On the contrary, the formulations containing 5% W/w of the N-MAG and the standard polymer, sodium alginate exhibited more of controlled release profiles, releasing 34.57% and 29.97% of metronidazole, respectively, in 45 minutes.

At 10% W/w concentration of the various binders A-MAG (batch B3), N-MAG (batch B6), sodium alginate (batch B9) and C-MAG (batch B12), the release of metronidazole became slower to varying degrees especially for A-MAG, N-MAG and sodium alginate as revealed in Figure 5. But C-MAG still exhibited higher release showing over 60% release in 45 minutes. All the formulation batches with of C-MAG as binder namely: B10 (2.5% W/w), B11 (5% W/w) and B12 (10% W/w) showed faster and higher percentage release of metronidazole due to the fact that carboxylmethylation of natural gum gives rise to water soluble derivatives which improves the solubility and hydrophilicity of the gum (Olusola, Toluwalope and Olutayo 2014; Dey, Sa and Maiti 2011).

CONCLUSION

Modification of the *Myrianthus arboreus* gum led to significant changes in disintegration and *in vitro* release of metronidazole from metronidazole immediate release tablet formulation. Carboxymethylation of *Myrianthus arboreus* gum led to faster disintegration and drug release. Batch B10 containing 2.5% W/w C-MAG disintegrated in less than 2 minutes and released over 80% of metronidazole in 15 minutes. This concentration could be harnessed for immediate release formulations, effervescent, dispersible and even orodispersible tablet formulation. A-MAG at concentration higher than 5% W/w could possibly be employed in the design of controlled release tablets.

Modification of *Myrianthus arboreus* gum could lead to tailor-made multi-functional excipients for drug delivery systems by altering the physicochemical properties of the gum.

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