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Production and Evaluation of Disintegrant Properties of Microcrystalline Cellulose Derived from *Saccharum officinarum* L (Poaceae) in Metronidazole Based Formulation

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ABSTRACT: ***The aim of the study was to produce microcrystalline cellulose from Saccharumofficinarum and to evaluate its use as a disintegrant in metronidazole tablet formulation. Cellulose was produced and characterized. This was followed by a comparative characterization of the tablets formulated by using Saccharumofficinarummicrocrystalline cellulose (SO-MCC), maize starch and crosscarmellose sodium (Ac-di-sol®) as disintegrants. The granules were evaluated for flow properties and the tablet evaluated for hardness, friability, disintegration and dissolution properties. For disintegration studies, the disintegrants disintegrated within 10 minutes in this order: Ac-di-sol® >SO-MCC>Maize starch. All the tablets exhibited high release profile which conformed to British Pharmacopoeia standards. Hence, SO-MCC can be used as an alternative disintegrant in terms of cost and availability.***

Keywords: Saccharumofficinarum, microcrystalline cellulose, disintegrant properties, metronidazole tablets.

1. INTRODUCTION

Tablets are common dosage form which comprises a drug and other excipients (adjuvants) mainly disintegrating agents, binders, diluents, lubricants, colorants, surfactants and plasticizers[1]. Excipients are widely applied in drug formulation and they modify the physical, physico-technical and physicochemical properties of drug and these may lead to changes in the biopharmaceutical performance of the system[2]. Disintegrantsas example of excipients ensure tablets breakup when introduced into an aqueous medium by increasing the surface area, leading to more rapid release of the API (active pharmaceutical ingredient) from the tablet matrix and thus influence the bioavailability of the drug. When included in tablet formulation via the granulation process they are reported to be more effective when used intra-and extra-granularly [3]. Microcrystalline cellulose (MCC) is one of the commonly used excipient in tablet dosage productions. MCC, a purifiedalpha cellulose in which the amorphous fraction is removed by acid hydrolysis. It has excellent disintegrant and dry binding properties [4]. *Saccharumofficinarum*L (Poaceae) of tall perennial grasses that have jointed, stout, fibrous stalks that are rich in sugar and measure 2-6 metres (6-19) feet tall. *Saccharumofficinarum* products include ethanol, table sugar, molasses, rum etc. The remaining baggase after the crushing of sugar cane may be used to generate electricity and heat. It may also serve as raw material for pharmaceuticals and food processing industries because of its high cellulose content.[5]. Metronidazole is a poorly compressible anti-helminthic, anti-protozoal agent that is effective against trichomoniasis, giardiasis among other parasitic diseases [6]. It is poorly water soluble at 0.1g (100ml of water)[7].

The objective of the present study is to examine the potentials of microcrystalline cellulose produced from *Saccharumofficinarum* as a disintegrant in comparison to maize starch and cross carmellose sodium (super disintegrant) in metronidazole tablet formulation.

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2. MATERIAL AND METHOD

Metronidazole (Beijing Star Technology Development Co.Ltd, China), Sodium hydroxide, hydrochloric acid (BDH Chemical Ltd, England), sodium hypochlorite (Jik, Reckit and Colman Nigeria, Ltd). Distilled water (Lion water, Nsukka, Nigeria),Maize Starch (SPAC Starch India), Ac-di-sol®(FMC Biopolymer, Philadelphia), all other chemicals used were of analytical grade. *Saccharumofficinarum* stem was purchased from Nsukka metropolis, Enugu state Nigeria.

2.1 Production Of Microcrystalline Cellulose (MCC)

The protocol for the extraction of MCC was that the Ohwoavworhuaet.al[2] with slight modifications. The sugarcane stem were first cut into small sizes, oven dried at 60°C for 48 hours, milled and weighed. A 300g quantity were treated with 4L of NaoH (2%), boiled at 80°C for 3h with a heater. This was washed with distilled water severally and filtered using sieve number 40 mesh size. It was bleached with 10% aqueous dilution of sodium hypochlorite for 30 minutes at 100°C, washed and filtered. The materials were further treated with 2L of 17.5% NaoH at 80°C for 1h. The resulting alpha cellulose was washed thoroughly with distilled water and subjected to whitening process with 10% sodium hypochlorite for 15 minutes at 80°C, this was washed with water until neutral. The cellulose materials was filtered, processed and manually reduced to small pieces and dried at 60°C with a hot mermmet oven for 1 hour. For the production of MCC, 50% of the α-Cellulose was acid hydrolyzed using 1L of 2.5N hydrochloric acid (HCL) at 100°C for 15 minutes. The produced MCC was washed thoroughly with water for complete removal of HCL, sieved, pressed and dried at 60°C. The dried sample obtained was milled and passed though sieve number 40 to get the fine powder of SO-MCC.

2.2 Characterization Of MCC

2.2.1 Fourier Transform – InfraRed (FT-IR) Spectroscopy of SO-MCC

The surface of SO-MCC sample was characterized using Perkin-Elmer spectrum 1000 Fourier transform infrared (FT-IR) spectrophotometer. SO-MCC sample was scanned 46 times at a resolution of 8cm^{-1} between 4000 and 650cm^{-1}. This was conducted to determine the functional groups present in the MCC.

2.2.2 Photomicrograph of MCC

Particle calibration and measurement was done by examining a small amount of sample at 400X magnification using a compound microscope (Motic B3, Motic Carlsbad, CA, USA) and the motican 2.0 image system and software.
Further characterization was done on the SO-MCC in comparison with maize starch and Ac-di-sol® for hydration and swelling capacity.

2.2.3 Hydration Capacity

The hydration capacity of SO-MCC, maize starch and Ac-di-sol® were assessed using the principle of Kornblum and stoopak[8]. A weighed quantity (2.0g) of each sample was placed in 15ml plastic centrifuge tubes and 100ml of distilled water was added and stoppered. The content was agitated for 3 minutes, allowed to stand for 10minutes and centrifuged at 1000rpm for 10 minutes using bench top centrifuge (Gallen Kamp, England). The supernatant was carefully decanted and the sediment was weighed. The hydration capacity was therefore calculated using the formula:

$$\text{Hydration capacity (HC)} = \frac{\text{weight of sediment – weight of tube}}{\text{Weight of dry sample}} \quad (1)$$

The swelling capacity (%) was measured at the same time as the hydration capacity determination using the method of Okhamafe etal[9] and calculated using the equation:

$$S = \frac{V_2 - V_1}{V_1} \times 100 \quad (2)$$

Where S = % Swelling capacity
V_2 = Volume of hydrated or Swollen material
V_1 = Tapped volume of the material prior to hydration

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2.3 Preparation of Granules

Metronidazole granules were prepared by wet granulation with maize starch as binder and lactose as bulking agent. The composition of the granules is shown in table 2 and the targeted weight of each tablet to be compressed from the granules was 400mg. Maize starch and Ac-di-sol® was used as disintegrant in comparison to SO-MCC.

2.3.1 Determination of Granule Properties

The flow properties of the granules were evaluated using bulk and tapped densities, Carr's index (CI), Hausner's ratio (HR), flow rate and angle of repose.

2.3.1.1 Bulk and Tapped Density

A 20g quantity of the granule was poured into a 100ml measuring cylinder. The measuring cylinder containing the granules was gently tapped three times on a flat surface to get the bulk volume. It was then tapped continuously on the flat surface until maximum packed volume was achieved. The bulk and tapped densities[10], CI and HR were calculated from the equation below:

$$\text{Bulk density} = \frac{\text{mass of material (M)}}{\text{bulk volume of the material } (V_B)} \quad (3)$$

$$\text{Tapped density} = \frac{\text{mass of material (M)}}{\text{tapped volume of the material } (V_T)} \quad (4)$$

$$\text{Carr's index} = \frac{\text{tapped density- bulk density}}{\text{Tapped density}} \times 100 \quad (5)$$

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad (6)$$

2.3.1.2 Flow Rate

The flow rate of the granules was determined simultaneously with angle of repose using the fixed height funnel method[11]. A plastic funnel with an orifice diameter of 1cm fitted firmly by the means of a clamp and retort stand support with its tip 7cm above a piece of white paper placed on a flat horizontal surface was used. A 25g quantity of each batch sample was transfered into the funnel and the time taken to exit completely was taken and calculated as:

$$\text{Flow rate (FR)} = \frac{\text{mass of granule}}{\text{flow time}} \quad (7)$$

2.3.1.3 Angle of Repose

The mean height of heap and the diameter of the powder heap were determined three times. Using a meter rule, the angle of repose was calculated from the formula:

$$\Theta = \tan^{-1} \frac{\text{height}}{\text{Radius}} \quad (8)$$

2.4 Production of Tablets

The metronidazole granules were compressed into tablets using a single punch tableting machine (F3 No 181 174, Manesty, England) fitted with 9.5mm punches to a target weight of400mg.

2.4.1 Tablet Evaluation

2.4.1.1 Weight uniformity test

Twenty (20) randomly selected tablets, were weighed and the average weight was calculated.

2.4.1.2 Tablet Friability

Ten (10) tablets were collectively weighed and transferred into the Roche friabilator to rotate at 25rpm for 4 minutes after which the tablet were re-weighed. The percentage friability was therefore determined using the formula:

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$$F\ (\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \qquad (9)$$

2.4.1.3 Hardness Test

Ten (10) tablets were randomly selected and the hardness (kg/f) was determined by the Monsanto hardness tester and the mean was calculated.

2.4.1.4 Disintegration Time Test

The disintegration time of six randomly selected tablets from each batch were evaluated in 900ml of 0.1N hydrochloric acid (HCL) at 37± 1^{o}C using Erweka multiple unit disintegration apparatus (Germany).

2.4.1.5 Dissolution Test

The magnetic stirrer method was used at temperature and revolution of 37± 1^{o}C and 100rpm respectively. The dissolution medium was 500ml of 0.1N HCL in 1L beaker. 10ml volume of the sample of the dissolution medium was withdrawn at 2,5,10,15,20,30,40,50 and 60 minutes. For each withdrawal, 10ml 0f fresh 0.1N HCL was added into the medium. Absorbance was taken at 277nm using UV/VIS spectrophotometer. The concentrations were then calculated with reference to metronidazole calibration curve.

2.5 Statistical analysis

The data obtained were analyzed for mean, standard deviation, coefficient of variation percentages using Microsoft excel 2007 software.

3. Results and Discussion

MCC was produced from *Saccharumofficinarum*(L) Poaceae by initial treatment of the dried stem with sodium hydroxide for the removal of lignin and hemi-cellulose. Further treatment with the bleaching agents helped in removal of any traces of lignin and hemi-cellulose[12]. The α-cellulose obtained was white in color. The MCC produced finally through α-cellulose treatment with acid was a white and coarse powder.

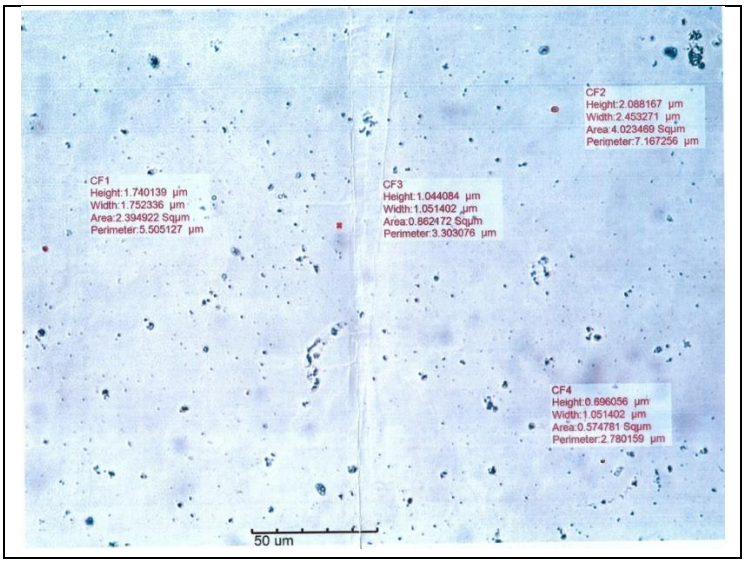

Figure 1: Photomicrograph image of SO-MCC

The photomicrograph image of SO-MCC presented in figure 1 showed non-aggregated rod shaped fibres with variable height in the range of 0.6 – 2.0µm. Such rod like shapes of the MCCs from different lignocellulose materials have earlier been reported[13].

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The FT-IR spectroscopy of SO-MCC as shown in figure 2 showed peaks at 3382.2cm^{-1} and 2892.4cm^{-1} which indicates –OH and C-H stretching respectively. It also showed a peak around 1025cm^{-1} wave number which showed presence of C-O bond. Microcrystalline cellulose and indeed pure cellulose materials, basically comprises –OH, C-H and C-O groups as earlier reported[14].

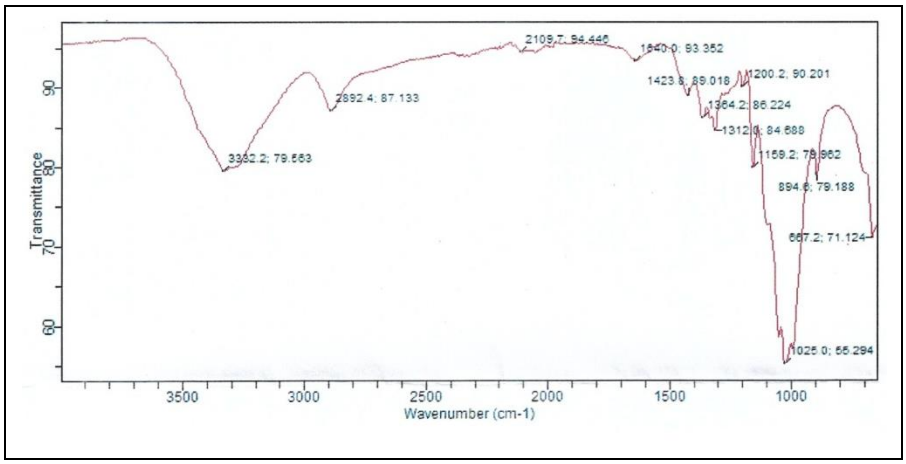

Figure 2: FT-IR image of SO-MCC

Hydration capacity is an accepted method for the measurement of swellability which is a measure of disintegration ability[15] . Cellulose particle in water has been shown to fasten the disintegration process by two mechanisms of capillary or wicking due to interparticulate water and swelling[16]. Disintegrants have been shown to vary greatly in their wicking and swelling properties[17].

Table 1: Physicochemical properties of the disintegrants

Parameter	Sugar cane cellulose	Maize starch	Ac-di-sol
Hydration capacity	4.00	2.05	6.00
Swelling capacity	47.16%	23.58%	65%

Results of hydration capacity as shown in table 1 showed that Ac-di-sol® had the highest value of 6, followed by SO-MCC and maize starch. This may imply that Ac-di-sol® may give a faster disintegrant action when compared to others.

Table 2: Formula for the Preparation of Metronidazole Tablets Using SO-MCC (MA1 – MAIV), Ac-di-sol® (MBI – MBIV) and Maize Starch (MCI – MCIV) as Disintegrants at varying concentrations

Batches	Metronidazole (mg)	SO-MCC (mg)	Ac-di-sol (mg)	Maize starch (mg)	Maize starch (20 % w/w)	Magnessium stearate (1 %)	Lactose (q.s) (mg)
MA I	200	0%	-	-	80	4	116
MA II	200	5%	-	-	80	4	96

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MA III	200	10%	-	-	80	4	76
MA IV	200	15%	-	-	80	4	56
MB I	200	-	(0%)	-	80	4	116
MB II	200	-	(1%)	-	80	4	112
MB III	200	-	(2%)	-	80	4	108
MB IV	200	-	(3%)	-	80	4	104
MC I	200	-	-	(0%)	80	4	116
MC II	200	-	-	(5%)	80	4	96
MC III	200	-	-	(10%)	80	4	76
MC IV	200	-	-	(15%)	80	4	56

Table 3: Granule Properties of Metronidazole Based Formulation Using SO-MCC, Ac-di-sol® and Maize Starch As Disintegrants. Values are replicate of three determinations and are presented as mean± standard deviation (STD).

Disintegrant	Batches	% disinteg -rant	Mass of granule (g)	BD (g/ml)	TD (g/ml)	FR (g/s)	AR (^{0}C)	CI (%)	HQ
SO-MCC	MA I	0	25	0.50±0.00	0.69±0.01	4.20±0.05	29.98±0.00	27.54	1.38
	MA II	5	25	0.45±0.00	0.60±0.01	4.46±0.00	29.14±0.00	25	1.33
	MA III	10	25	0.35±0.00	0.50±0.00	2.27±0.00	29.98±0.02	30	1.43
	MA IV	15	25	0.35±0.00	0.48±0.01	2.43±0.00	29.98±0.01	27.08	1.37
Ac-di-sol	MB I	0	25	0.52±0.01	0.70±0.01	5.43±0.00	29.98±0.00	25.71	1.35
	MB II	1	25	0.52±0.00	0.61±0.02	5.32±0.00	27.43±0.00	14.75	1.17
	MB III	2	25	0.50±0.00	0.63±0.00	4.72±0.00	29.14±0.00	20.63	1.26
	MB IV	3	25	0.50±0.01	0.63±0.00	5.20±0.00	26.56±0.01	20.63	1.26
Maize starch	MC I	0	25	0.56±0.00	0.69±0.01	5.95±0.00	28.30±0.01	18.84	1.23
	MC II	5	25	0.51±0.00	0.63±0.02	4.72±0.00	28.30±0.01	19.05	1.24
	MC III	10	25	0.51±0.00	0.64±0.00	5.21±0.14	29.14±0.01	20.31	1.25
	MC IV	15	25	0.51±0.00	0.64±0.00	4.90±0.15	29.98±0.00	20.31	1.25

The results of the granule properties of SO-MCC, Ac-di-sol® and maize starch are shown in table 3. The bulk and tapped densities of the granules gives an understanding on their packing and densification behavior[18]. The Hausner's ratio, Carr's index and angle of repose are considered as indirect measurements of powder flowability[19]. Hausner's ratio determines the degree of interpaticulate

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friction and values ≤ 1.25 indicates good flow while Hausner's ratio ≥ 1.25 indicate poor flow. Carr's index in the range of 5-16% indicates good flow, 18-21% shows fair flow while values above 38% signify very poor flow. Angles of repose ≤ 30° indicate a free flowing material and ≥ 40° suggest poor flow[20].

When all this indices of flow: flow rate, angle of repose, Carr's index and Hausner's ratio are taken together, it was observed that all the batches had an angle of repose < 30°, Carr's index < 38% while three out of the twelve batches had Hausner's quotient ≤ 1.25. The flow rate results showed that SO-MCC had the fastest flow rate when compared to other disintegrants.

The results of tablet properties of metronidazole are shown in table 4. All the test results were compared to the British Pharmacopoeia standards[21].

Table 4: Tablet Properties Of Metronidazole Based Formulation Using SO-MCC, Ac-di-sol® and Maize Starch as Disintegrants. Values and replicate of three determinations and are presented as mean± SD and coefficient of variation (CV)

Disintegrant	Batches	% disintegrant	Friability (%)	Hardness Test (kg/f)	Disintegration time(minutes)	Weight CV (%)
SO-MCC	MA I	0	0.95±0.07	6.90±0.88	8.20±0.06	3.00
	MA II	5	0.90±0.14	5.55±1.62	7.46±0.03	1.98
	MA III	10	0.85±0.07	5.45±1.43	6.42±0.05	1.68
	MA IV	15	0.9±0.14	5.40±1.50	6.19±0.02	2.11
Ac-di-sol	MB I	0	0.95±0.07	4.90±0.74	6.44±0.03	2.26
	MB II	1	0.90±0.00	4.6±0.66	6.27±0.02	2.17
	MB III	2	0.8±0.00	4.4±0.84	5.41±0.01	2.96
	MB IV	3	1.00±0.00	4.1±1.03	4.18±0.00	3.43
Maize starch	MC I	0	1.00±0.00	7.10±0.77	9.55±0.07	3.33
	MC II	5	0.85±0.07	6.15±1.06	8.22±0.01	4.78
	MC III	10	0.95±0.07	5.10±0.91	7.25±0.00	4.77
	MC IV	15	1.00±0.00	4.5±0.89	7.16±0.07	3.13

- Weight uniformity test

The results of tablets weight uniformity showed the coefficient of variation obtained was below 5% stipulated for tablet weights greater than 250mg[22]. The stated results indicate that the tablets passed the weight uniformity test. Weight uniformity affects drug content and overall bioavailability of drug[23].

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- Tablet Friability

The result of tablet friability showed that all the batches of metronidazole prepared with the three disintegrants met the BP specifications with percentage friability in the range between 0.8 to 1%.

- Hardness Test

The result of tablet hardness as seen in table 4 shows that all the batches had good hardness profile and met with BP specifications[23] for tablet hardness (P≥4≤8).

- Disintegration test

The results of disintegration test shown in table 4 shows that increase in disintegrant concentration resulted in decrease in disintegration time for all the batches. Ac-di-sol® a super disintegrant gave the fastest disintegration time followed by SO-MCC and maize starch. It is also worth mentioning that all the batches disintegrated within 15 minutes as stipulated in BP for uncoated tablets.

- Dissolution test

Figure 3-5 showed the dissolution profile of the various batches containing varying concentrations of the disintegrants. The BP stipulates that 70% of drug should be release within 30 minutes for uncoated tablets. All batches passed this test but worthy of note is that there appears to be no correlation between disintegration time and dissolution rate[24].

Figure 3: Graph of percentage drug release against time for metronidazole tablets formulated with SO-MCC as disintegrant

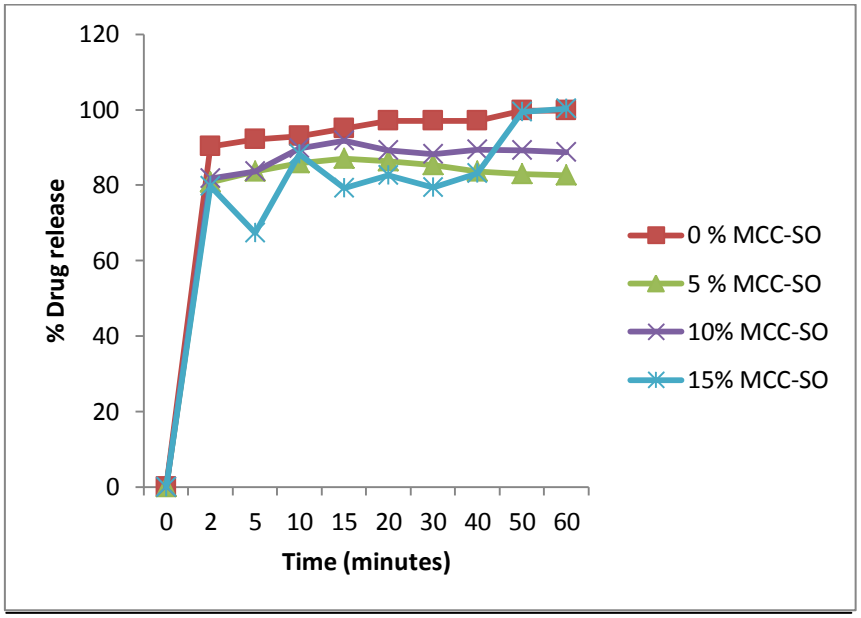

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Figure 4: Graph of percentage drug release against time for metronidazole tablets formulated with Ac-di-sol® as disintegrant

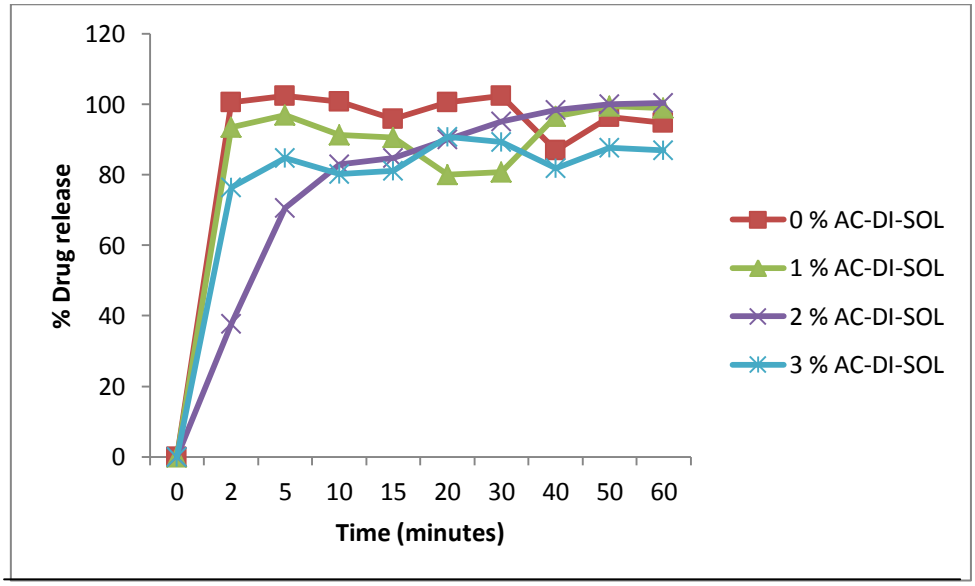
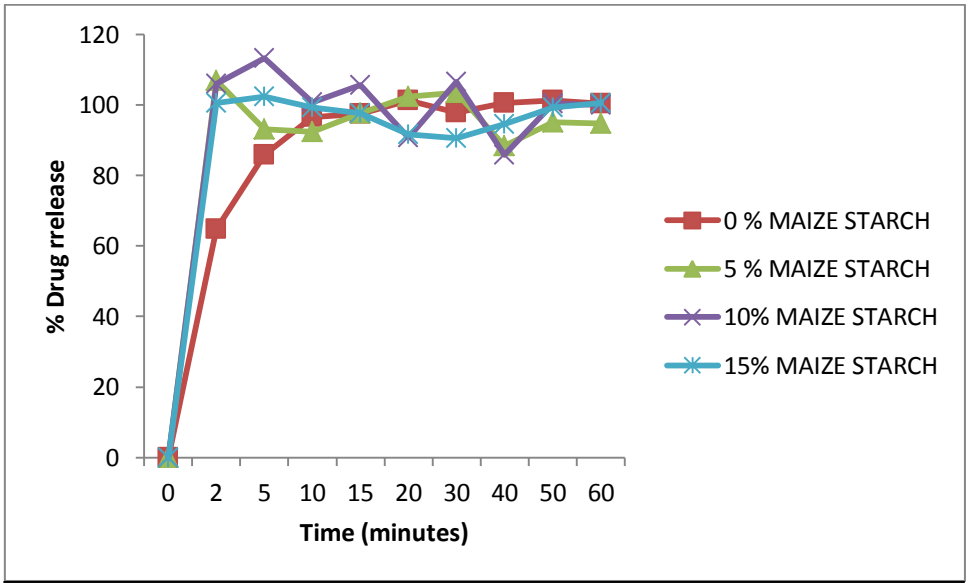


Figure 5: Graph of percentage drug release against time for metronidazole tablets formulated with maize starch as disintegrant



4. CONCLUSION

The study has shown that *Saccharumofficinarum* L Poaceae microcrystalline cellulose has disintegrant activity that compares favourably with Ac-di-sol® a super disintegrant and maize starch. As a result, it can be used as a disintegrant and as alternative to Ac-di-sol® and maize starch in terms of cost and availability.

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