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Comparative Evaluation of the Disintegrant Properties of Rice Husk Cellulose, Corn Starch and Avicel® in Metronidazole Tablet Formulation

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ABSTRACT

Cellulose is a polysaccharide that has been employed in pharmaceutical applications over the years. However, the quest for waste management and an alternative to imported raw materials for locally manufactured drug products necessitated this study. This study was undertaken to explore the application of cellulose extracted from waste, rice husk as a disintegrant in the formulation of metronidazole tablets for immediate release. Cellulose was extracted from rice husk and characterized. Thereafter, a comparative characterization of the attributes of the tablets formulated was undertaken using Corn Starch, microcrystalline cellulose and rice husk as disintegrants. The granules were characterized for flow properties and tablets were evaluated for crushing strength, friability, disintegration and *in vitro* drug release. The tablets formulated with rice husk cellulose were found to be bioequivalent to those of corn starch which is a standard in comparative studies of disintegrants. Hence, rice husk cellulose is an alternative excipient to explore as a pharmaceutical excipient for limited resource economies.

INTRODUCTION

The present trend of sourcing pharmaceutical excipients from natural sources such as plants, animals and agricultural waste is as a result of the steady shift from use of synthetic materials to renewable resources, waste management and green technology. Wastes are material that result after the generation of prime products for which the generators has no further use with regards to his or her own reasons for production and is intended for disposal. Agriculture produces significant amounts of wastes, which contain high quantities of cellulose-a linear polysaccharide constituting the major component of the rigid cell wall of plants. According to statistical Bulletin released by Research Department of the Central Bank of Nigeria on the 30th of December 2002, thirty percent of about four million tons of rice produced in Nigeria is thrown away as waste contributing its own quota to the challenge of environmental pollution. In Africa, the agricultural waste produced in a particular period of the year pose potential pollution problem and therefore an efficient utilization and transformation, to excipient, of such agricultural waste is of great importance not only for minimizing the environmental impact but also for obtaining higher profit. Excipients has been defined, by the International Pharmaceutical Excipients Council, as substances apart from the active drug or pro-drug which has been properly evaluated for safety and is included in a drug delivery system to either aid processing of the system during manufacture, protect, support, or enhance stability, bioavailability or patient acceptability; assist in product identification; enhance any other attribute or overall safety and effectiveness of the product during storage and use (Robertson,1999). Excipients facilitate formulation design and are important in for obtaining the desired properties of the finished drug product.

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Excipients from plant sources are appealing because plant resources are renewable and if maintained and harvested in a sustainable manner, they can be constant sources of raw materials (Beneke et al. 2009). Alpha cellulose has been identified in various studies as a potential pharmaceutical excipient which functions as excellent disintegrant and direct compression diluents in tablet formulations (Okhamafe and Azubuike 1994, Okhamafe et al. 1995). A tablet disintegrant is that excipient which facilitates the breakup of the tablet in a liquid environment into fine particles prior to dissolution of the active drug and its absorption from the gastrointestinal tract.

Disintegration leads to the breakup of the tablet into the component granules thereby presenting a greater surface area of the tablet to the dissolution medium before the active drug substance is finally released from the tablet. An immediate release tablet formulation of a drug is usually not useful until its active component is made available for absorption hence the disintegrant arguably become the most important excipient in a tablet to facilitate immediate drug release. Although modified release dosage forms is the focus of most research due to their benefits such as reduced dosing frequency and attendant improved patient adherence, reduced side effects and increased duration of therapeutic action; immediate release dosage forms still occupy a crucial space in drug delivery especially in disease conditions that require rapid onset of action.

Various workers have studied different aspects of the application of cellulose as a tableting excipient. In this study, cellulose was extracted from rice husk and evaluated as a disintegrant in metronidazole tablets. The attributes of the granules and tablets formulated with rice husk cellulose as disintegrant were compared with those of microcrystalline cellulose and Corn Starch.

MATERIALS AND METHODS

Materials

The materials used were metronidazole BP, lactose BP, Corn Starch BP, Avicel (microcrystalline cellulose), polyvinylpyrrolidone and magnesium stearate, (all obtained from Swiss Pharma Nigeria Limited (Swipha), Lagos, Nigeria).

Extraction of cellulose

Cellulose was extracted from rice husks employing the method of Ohwoavworhua et al (2004). Briefly, 1500g of the rice husk particles was treated with 7.5L of 2%$^{w}/_{v}$ of sodium hydroxide immersed in water bath set at 100^{o}C for 3 hours. The resulting material was further digested with 6L of 17.5% sodium hydroxide solution for 1 hour at 80ºC. This was thoroughly washed with distilled water, filtered and dried in an oven at 60°C for 16 hours. Thereafter, the product (unbleached cellulose) was bleached with 8.5L of 3.2%$^{v}/_{v}$ sodium hypochlorite in the stainless steel vessel at 40°C for 2 hours. The bleached sample was thoroughly washed with distilled water until it was neutral to litmus paper. It was filtered and dried in an oven at 60°C for 16 hours after which it was weighed. The product was sifted through a 375µm aperture sieve, dried further at 60ºC for 1 hour after which it was stored in a closed container.

Characterization of extracted cellulose

Cellulose in comparison with Corn Starch and microcrystalline cellulose was evaluated for swelling index, moisture content and flow properties.

Swelling index

The swelling abilities of rice husk cellulose, Corn Starch and microcrystalline were assessed based on the method by Ohwoavworhua and Adelakun (2005). A weighed quantity (1.0g) of each sample was placed in 15 ml plastic centrifuge tubes and the volume occupied was noted. Thereafter, 10 ml of distilled water was added and stoppered.

The contents were mixed on a vortex mixer (Vortex Gennie Scientific, USA) for 2 min. The mixtures were allowed to stand for 10 min and immediately centrifuged at 1000 rpm for 10 min using a bench centrifuge (GallenKamp, England). The supernatants were carefully decanted and the volumes of sediment measured. The swelling indices were computed using the equation:

$$Swelling\ index = \frac{V_2}{V_1} \qquad \text{Equation 1}$$

Where; V_1 = Volume occupied by the gum prior to hydration. V_2 = Volume occupied by the gum after hydration.

Loss on drying

The moisture contents of rice husk cellulose, Corn starch and microcrystalline cellulose were determined using a modification of a method specified in the B.P (1993) for acacia. A weighed quantity of each sample was transferred into a petri dish and then dried in an oven at 105°C until a constant weight was obtained. The % moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage.

Hausners index

This was calculated as the ratio of tapped density to bulk density of the samples.

Compressibility index

This was calculated using as shown below:

$$Compressibility\ index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density}\ x\ 100 \quad \text{Eq 2}$$

Preparation of granules

Metronidazole granules were prepared by wet granulation with polyvinylpyrrolidone as binder, and lactose as diluent. The composition of the granules batches is shown in Table 1 and the targeted weight of each tablet to be compressed from the granules was 500mg. cornstarch and Avicel was used as disintegrants for comparative studies with rice husk cellulose (RHC).

Table 1: Composition of granules.

Component	Concentration (%$^{w}/_{w}$)
Metronidazole	50
Polyvinylpyrollidone	5
Corn starch/Avicel/RHC	5-10
Lactose	q.s

Determination of granule properties

The angle of repose of granules was determined by the fixed funnel method of Panda et al. (Panda et al. 2008). The bulk and tapped densities were determined by weighing 2 g (W) of the granules and transferred into a 10 mL measuring cylinder. After the initial volume (V_O) was measured and the cylinder was tapped on a hard surface 100 times/until no further change in volume was observed. The tapped volume (V_T) was noted. Bulk density (BD) and tapped density (TD) were calculated using Equations 3 and 4:

$$Bulk\ Density = \frac{W}{V_o} \quad \text{Equation 3}$$

$$Tapped\ Density = \frac{W}{V_t} \quad \text{Equation 4}$$

Preparation of tablets

Metronidazole granules (500mg) was compressed for 30 seconds into tablets with predetermined loads on a Carver hydraulic press (Model C, Carver Inc. Wisconsin, USA), using a 10.5 mm die and flat faced punches lubricated with a 1 % dispersion of magnesium stearate in acetone prior to compression. After ejection, the tablets were stored over silica gel for 24 hour to allow for elastic recovery and hardening.

Evaluation of tablet properties

Twenty (20) tablets were selected randomly from each batch and weighed individually using a top-loading electronic balance. The average weight was noted and standard deviation calculated.

Friability was determined using a friability test apparatus (Veego Scientific devices, Mumbai, Maharashtra, India) at 25rpm for 4 minutes. The friability testing was undertaken in quadruplicate for each batch. Crushing strength was also determined in quadruplicate using a Mosanto hardness tester (Mosanto, Cambridge, UK). Disintegration time was carried out in triplicate in distilled water at 37±0.5^{o}C on a disintegration test apparatus (Manesty Machines, Poole, UK).

In vitro dissolution was undertaken in dissolution medium, hydrochloric acid buffer and the temperature was set at 37±0.5ºC. Six tablets were used and each placed in a rotating basket and inserted into the dissolution medium containing 900mls of the buffer (0.1M HCl).

The rotating basket was set at a speed of 50rpm. Then 5mls was withdrawn from the dissolution medium at time intervals of 10, 20, 30, 40 and 50 minutes respectively. Same volume withdrawn was replaced immediately with fresh buffer. The quantity of metronidazole in the sample solutions was determined by assaying at a wavelength of 277nm using a UV visible spectrophotometer.

RESULTS AND DISCUSSION

Alpha-cellulose extracted was yellowish-white, odourless and possessed a fine texture. The percentage yield of α-cellulose was 33.33%. This compared favorably with yields recorded by some other workers (Ohwoavworhua and Adelakun 2005, Ohwoavworhua et al. 2009, Ohwoavworhua and Adelakun 2010). Ohwoavworhua and co-workers recorded yields of 32%, 23% and 15% respectively for α-cellulose from raw cotton, sorghum stalk and groundnut husk A number of mechanisms have been proposed for the disintegration process. These are porosity and capillary action; heat of wetting and breakage of physicochemical bonds, swelling of disintegrant particles, particle repulsion and swelling of deformed disintegrant particles (Pesonen et al. 1989). Hydration Capacity is one method that has generally been accepted as a means of assessing swelling which is a measure of disintegration ability. Cellulose particle, in water, has been shown to speed up the disintegration process by two mechanisms of capillary or wicking due to interparticulate water and swelling (Ohwoavworhua and Adelakun 2005). Disintegrants generally vary widely in their wicking and swelling properties. Botzolakis and coworkers studied the wicking and swelling properties of pure Ac-Di-Sol, primogel and Corn Starch (Botzolakis and Augsburger 1988). Use of Ac-Di-Sol exhibited the greatest wicking and swelling action followed by primogel and Cornstarch. Their research showed that the swelling property of pure disintegrant correlated best with the swelling of formulation mixtures and the efficiency of these materials in enhancing the dissolution of drug. The hydration capacity is, therefore, a measure of the degree of swelling of cellulose. The increased entrance of water by capillary action through the cellulose molecules results in the disruption of hydrogen bonds holding the molecules together thereby breaking up the tablets formulated with α-cellulose. The hydration capacity of rice husk cellulose was significantly higher than that of Avicel and Corn Starch (Figure 1). This could imply that rice husk cellulose may give a better and rapid disintegant action.

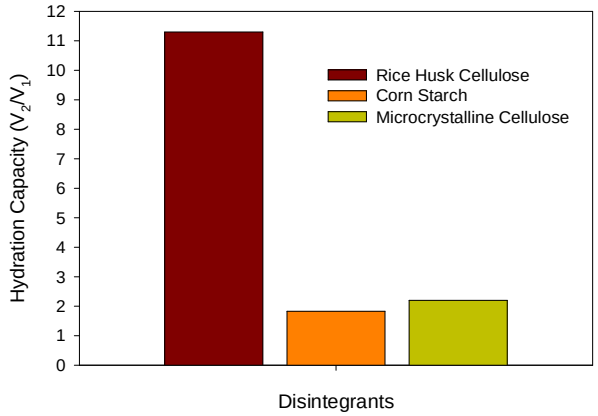

Fig. 1: Comparative hydration capacity of three disintegrants – Rice husk cellulose, Corn Starch and microcrystalline cellulose.

The moisture content of rice husk cellulose was higher than those of Avicel and Corn Starch (Figure 2). The formation of

film of moisture on the rice husk cellulose may function as lubricant in decreasing the friction at the die wall. The film of moisture decreases tablet adhesion to the die wall and allows easy tablet ejection. It also acts as a glidant in increasing the ease with which the individual particles can slip and flow during compression. In addition, residual moisture can enhance compaction of granules/particles. However, it is important to strike a balance between the optimum moisture content required to retain these functions and that required to minimize the incidence of microbial degradations, hydrolysis and enzymatic decomposition during storag.

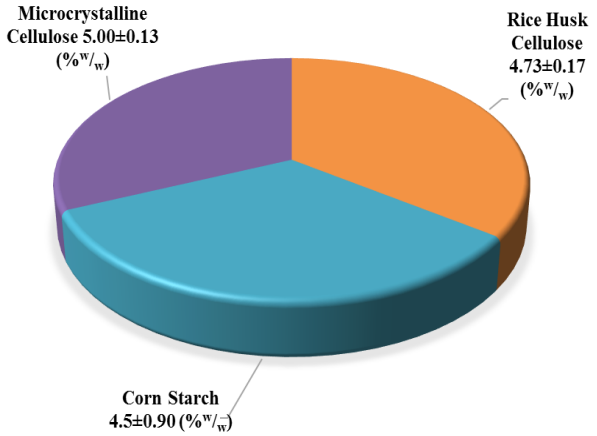

Fig. 2: Comparative moisture contents of three disintegrants - Rice husk cellulose, cornstarch and microcrystalline cellulose.

An insight into the possible compression behavior of granules can be gained by evaluating their flow properties. The results of evaluating the flow properties of the rice husk cellulose, starch and Avicel are shown in Table 2. The angle of repose is one parameter that has been used as a measure of flowability. The angle of repose values in the range of 25– 30° and 31–35° indicate excellent and good flow properties for the material, respectively. If the value is greater than 40°, it suggests poor flow of the material. The angle of repose of the rice husk cellulose which was found to be 37.06° was lower than 38.66° reported for orange mesocarp cellulose (Ejikeme, 2008) and indicated fair flow properties and may not require an aid to flow.

Table 2 Physicochemical characterization of the powders.

Parameter	Rice husk cellulose	Corn starch	Microcrystalline cellulose
Bulk density(g/ml)	0.15± 0.0012	0.30 ± 0.00	0.28± 0.0073
Tapped density (g/ml)	0.23 ± 0.006	0.62 ± 0.00	0.44 ± 0.008
Carr's index (%)	36.09 ± 0.55	51.61 ± 0.012	36.36 ± 0.006
Hausner's ratio	1.53 ± 0.333	2.0 ± 0.002	1.57 ± 0.013
Angle of repose (°)	37.06 ± 0.98	40.00±0.009	36.02 ± 0.003

In summary, granules which exhibit an angle of repose less than 30°, Hausner's ratio below 1.25, and Carr's compressibility below 25% is expected to flow fairly well (Ngwuluka et al. 2012). From Table 2, it may indicate that the three disintegrants have poor flow properties. However, it is worthy to note that Carr's index and Hausner's ratio are not the intrinsic properties of a powder; rather they depend on the technique employed.

In addition, the angle of repose and other derived properties of the powders namely bulk density and tapped density depends on the particle size distribution, particle shape, and tendency of the particles to adhere together. The results of sieve analyses carried out on the granules are shown in Figure 3 and 4. The granules were more coarse than fine. About 50% of the granules for each batch fell within the size range of 355-710µm. Coarse granules imply that after compression, voids are expected which may enhance ingress of water by capillary action thereby facilitating the disintegration of the tablets.

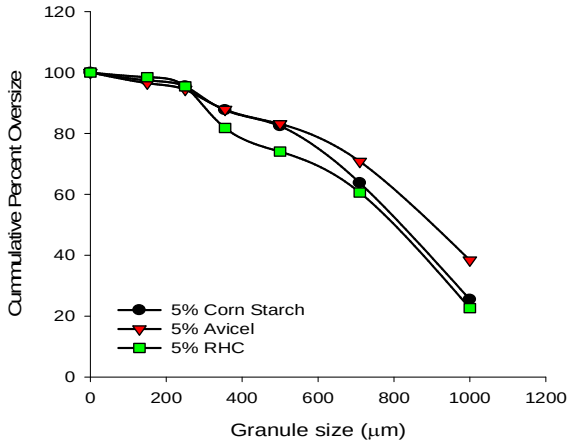

Fig. 3: Particle size distribution of granules prepared with 5% disintegrants.

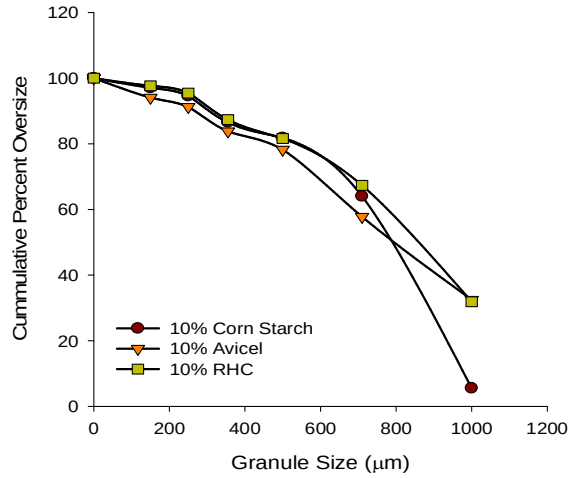

Fig. 4: Particle size distributions of granules prepared with 10% $^{w}/_{w}$ disintegrants.

Table 3 shows the physical properties of metronidazole tablets containing various concentrations of Cornstarch (CS), Rice husk cellulose (RHC), and Avicel (MCC). At low concentrations, the crushing strength of tablets containing various disintegrants was of the rank order CS > RHC > MCC ($p \geq 0.05$), and at higher concentrations, the reverse order obtained. The crushing strength of tablets containing RHC was significantly higher than that of Avicel ($p \geq 0.05$) at all concentrations.

Table 3: Flow properties of granules containing different concentrations of Disintegrants .

eter	A	B	C	D	E	F	G	H	I
Bulk density (g/cm^3)	0.387± 0.003	0.375±0.003	0.375 ±0.003	0.324±0.002	0.333±0.005	0.335±0.002	0.313 ±0.004	0.278 ± 0.00	0.264 ±0.002
Tapped density (g/cm^3)	0.417±0.007	0.389±0.003	0.319±0.000	0.355±0.003	0.419±0.004	0.415± 0.004	0.355±0.003	0.341±0.002	0.314±0.002
Hausner's ratio	1.078	1.037	1.043	1.096	1.258	1.246	1.134	1.227	1.189
Carr's index	7.194	3.599	4.092	8.732	20.523	19.227	11.831	18.475	15.924
Angle of repose (^{o})	32.55 ±0.23	32.84±0.08	33.26±0.42	35.22±0.53	36.88±0.29	37.23±0.80	35.86±0.77	36.54±0.52	37.74±0.31

Table 4: Tablet characteristics for the batches of different concentrations of disintegrants.

Batch	Mean crushing Strength (N)	Friability (%)	Crushing strength/ Friability ratio	Mean disintegration time (minutes)	CSFR/DT
A	126.7 ± 15.6	1.43	88.60	16.00 ± 4.10	5.53
B	79.00 ± 18.2	1.86	42.47	9.60 ± 0.34	4.42
C	134.9 ± 11.6	1.38	97.75	6.08 ± 2.30	16.08
D	44.60 ±7.9	2.68	16.64	9.21 ±2.80	1.81
E	146.3 ± 10.0	0.37	395.41	6.30 ± 0.90	62.76
F	125.70 ± 8.9	0.82	153.29	5.40 ± 0.70	28.39
G	110.00 ± 3.8	0.44	250.00	9.88 ± 6.20	25.30
H	160.70 ± 5.5	0.24	669.58	5.83 ± 1.20	114.85
I	167.83 ± 11.2	0.20	839.15	4.18 ± 0.17	200.75

A, B, C=5% $^w/_w$, 7.5% $^w/_w$ and 10% $^w/_w$ corn starch. D, E, F=5% $^w/_w$, 10% $^w/_w$, and15% $^w/_w$ avicel. G, H, I =5% $^w/_w$, 10% $^w/_w$, and15% $^w/_w$ rice husk cellulose

Table 5: Outcomes of mathematical modeling of the dissolution profiles.

Disintegrant	Zero Order			First Order			DE (%)	MDT (mins)
	R	r^2	K_o	*R*	r^2	K_1		
5% Corn	0.9929	0.9852	2.079	0.9880	0.8464	0.037	52.05	23.98
5% Avicel	0.9992	0.9838	1.949	0.9816	0.8195	0.032	46.87	26.56
5% RHC	0.9689	0.9385	2.186	0.9710	0.7972	0.040	55.34	22.33
10% Corn	0.9990	0.9950	1.973	0.9758	0.8388	0.033	48.50	25.75
10% Avicel	0.9956	0.9878	2.037	0.9917	0.8453	0.035	50.35	24.83
10% RHC	0.9946	0.9728	1.882	0.9637	0.8016	0.030	44.80	27.60
15% RHC	0.9985	0.9911	1.927	0.9725	0.8315	0.032	46.85	26.57

The crushing strength-friability ratio (CSFR) is a better index than hardness test in the assessment of the mechanical strength of a tablet hence mechanical strength of tablets can also be measured by the crushing strength friability ratio. (Odeku and Itiola, 2003). Generally, higher CSFR ratios, indicates stronger tablet. RHC formed the strongest tablets at all concentrations while CS formed the weakest tablets at all concentrations.

Table 4 shows that increase in disintegrant concentration resulted in decrease in disintegration time for all batches. This decrease was highest for rice husk cellulose followed by Avicel and Corn Starch. The crushing strength-friability ratio/disintegration-time ratio evaluates the simultaneous negative effects of the tablet hardness and weakness on its disintegration time (Upadrashta et al. 1992, Alebiowu and Adeagbo, 2009). The rank order effect of the disintegrants on tablet-quality values (HFD/DT) was RHC> MCC>CS ($p > 0.05$).

Figures 5-7 show the dissolution profile of the various batches containing varying concentrations of disintegrants. The BP stipulates that 70% of drug should be released within 30 minutes for uncoated tablets. Only formulation containing 5% RHC as disintegrant met this specification although others released about 80 % of their drug content in 40 minutes. Avicel performed better at 10 % $^w/_w$ over time whereas for RHC, and corn starch best performances was achieved with a lower concentration of 5% $^w/_w$. Bakre and workers while working with metronidazole also found that Avicel had the highest T90 of 25.3% at 10% concentration while corn starch had its highest T90 of 22.5% at 5% $^w/_w$ concentration (Bakre and Jaiyeoba 2009). This is in agreement with the present study.

Mathematical models such as zero and first order, dissolution efficiency and mean dissolution time were used to compare the dissolution profiles of the formulations with the different disintegrants. Between zero order and first order, the best fit model for the formulations was zero order. The dissolution efficiencies and mean dissolution times of the formulations were comparable. A difference of less than 10% between the dissolution efficiencies implies that the drug products are bioequivalent and thus can be used interchangeably (Ngwuluka et al. 2012). Consequently, rice husk cellulose can be used in place of Corn Starch or microcrystalline cellulose as disintegrant in formulation of immediate dosage forms and it will be as effective.

Outcomes of mathematical modeling of the dissolution profileIn addition, similarity factor f_2 was utilized. Corn Starch formulations were used as the reference being the oldest disintegrant and standard used in comparative studies. The results obtained (Table 6) corroborates with the dissolution efficiency comparison. Avicel and rice husk cellulose formulations are bioequivalent and hence can be used interchangeably with Corn Starch formulations. A test product is said to be bioequivalent with the reference product if the similarity factor f_2 values are not less than 50. The accepted similarity factor, f_2, values for two products compared to be said to be bioequivalent is 50-100.

Table 6: Similarity factor f_2.

Reference vs Test	Similarity factor f_2	Outcome
5% Corn vs 5% Avicel	60.71	Accept
5% Corn vs 5% RHC	61.41	Accept
10% Corn vs 10% Avicel	67.97	Accept
10% Corn vs RHC	67.30	Accept

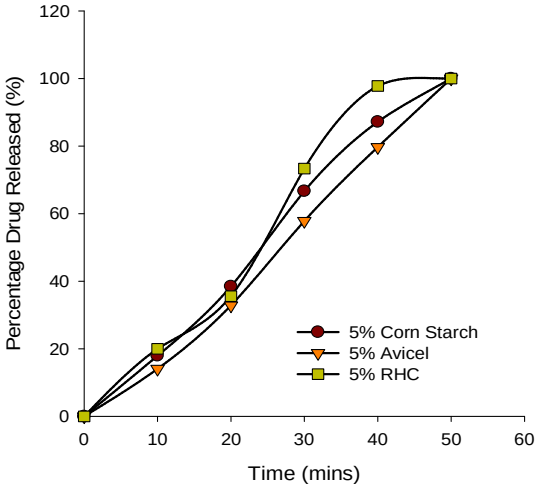

Fig. 5: Comparative dissolution profiles of tablets with 5% of the disintegrants.

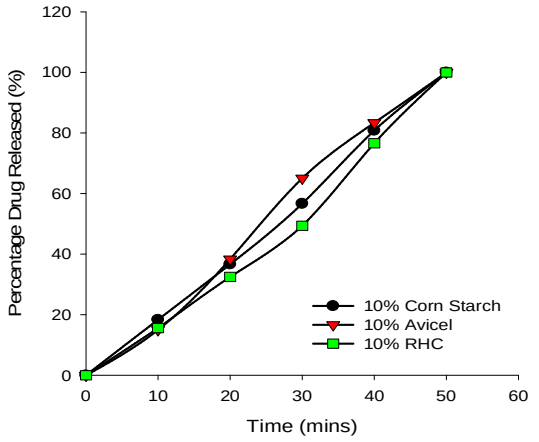

Fig. 6: Comparative dissolution profiles of tablets with 10% of the disintegrants.

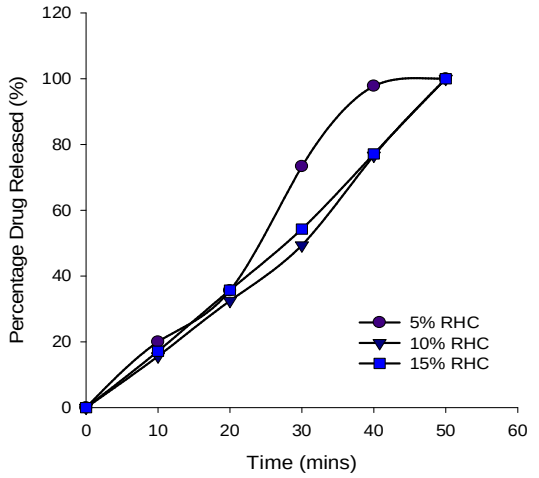

Fig. 7: Dissolution profiles of tablets with rice husk cellulose as a disintegrant at different concentrations.

CONCLUSION

The foregoing has shown that rice husk is a rich source of cellulose. It has disintegrant activity that compares favorably with Corn Starch and microcrystalline cellulose (Avicel®). Therefore, it can be used as a disintegrant and is a viable alternative to Avicel® and Corn Starch especially in resource limited economies

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