

# Humidity Effect on the Disintegrant Property of $\alpha$ -Cellulose and the Implication for Dissolution Rates in Paracetamol Tablets

Michael U. Uhumwangho\* and Roland S. Okor

Department of Pharmaceutics and Pharmaceutical Technology, University of Benin,  
Benin City, Nigeria

(received December 16, 2003; revised September 22, 2004; accepted September 28, 2004)

**Abstract.** A study has been carried out to determine the effect of humidity on the disintegrant property of  $\alpha$ -cellulose in tablet formulations. Paracetamol tablets containing  $\alpha$ -cellulose (5% w/w) as disintegrant were employed in the study. The tablets were tested for hardness, disintegration time and dissolution rates before and after their exposure to different relative humidities (RH) of 1%, 78% and 100% at 30 °C (room temperature) for various time intervals upto a maximum of 2 weeks. Humidity effect on the particle structure of  $\alpha$ -cellulose was determined by photomicroscopy. Tablets exposed to RH of 1% and 78% disintegrated very fast, within a minute, similar to the fresh samples. In contrast, tablets exposed to RH 100% for  $\geq 24$  h failed to disintegrate within 60 min even though the tablets became softer. Tablet dissolution rate was also markedly impaired in this set of tablets. Exposure of the  $\alpha$ -cellulose powder to RH 100% for 24 h caused the particles to gel, which accounted for the impairment of its disintegrant property.

**Keywords:**  $\alpha$ -cellulose, disintegrant property, gel formation, humidity effect

## Introduction

The polymer  $\alpha$ -cellulose is that part of cellulosic materials which is insoluble in 17.5% w/w solution of sodium hydroxide at 20 °C (Seymour, 1971). This property distinguishes it from  $\beta$ - and  $\gamma$ -celluloses. It is obtained from wood pulp (Nitz, 1994) or more recently from agricultural wastes such as maize cob, rice husk or groundnut shell (Okhamafe *et al.*, 1991). It has potential in tablet formulations as a disintegrant and a direct compression base (Okhamafe *et al.*, 1992). The polymer is readily hydrated being capable of absorbing approximately 4 and a 1/2 times its own weight of water (Okhamafe *et al.*, 1991). This swelling ability is its greatest asset as a disintegrant in tablet formulations. Swelling of the  $\alpha$ -cellulose inside the tablet causes localized stress, which leads to tablet rupture. The hydrophilic swelling property of  $\alpha$ -cellulose has also been exploited in controlled drug release from matrices which are non-disintegrating tablets (Okor *et al.*, 1992).

The previous studies (Nitz, 1994; Okor *et al.*, 1992; Okhamafe *et al.*, 1992; 1991) on the applicability of  $\alpha$ -cellulose in tableting relate to freshly made tablets only, with no consideration for ageing effects. Therefore, information on its long-term performance under different conditions of storage is rare in the literature. In the tropics, high humidities prevail throughout the year. Hence, in the present study, humidity effect on the particle structure and disintegrant property of  $\alpha$ -cellulose was investigated.

## Materials and Methods

**$\alpha$ -Cellulose powder.** The polymer  $\alpha$ -cellulose was used as the test disintegrant. It was obtained locally as a fine white powder of irregular shaped particles from an agricultural waste, maize cob, by sodium hydroxide and sodium sulphite digestion process already described in detail elsewhere (Okhamafe *et al.*, 1991). It is readily hydrated and swells in water and other aqueous fluids. Maize starch (BP grade) was also used as disintegrant in a comparative study. Magnesium stearate (BDH) was used as lubricant. Paracetamol powder (pharmaceutical grade) was used as the test drug. It was selected for the study because it forms poorly disintegrating tablets on its own (i.e., without a disintegrant).

**Granulation and tableting.** Paracetamol granules were formed by wet granulation technique using starch mucilage (20% w/w) as the binder fluid and dried on a tray in a hot air oven (Kottermann, Germany) to moisture content,  $1.3 \pm 0.2\%$  w/w. The lubricant (1% w/w) and the disintegrant (5% w/w) were added to the granules and compressed with a single punch machine (Manesty, Type F<sub>3</sub>) to form flat faced tablets of diameter 12.5 mm, thickness 3.38 mm, and weight 550 mg. The compression load was 27.5 (arbitrary unit on the load scale) and held on the tablet for 30 sec for consolidation before releasing the load.

**Evaluation of the tablets. Storage tests.** Twenty tablets, freshly made, were stored in each of the three chambers of different relative humidities (RH) of 1%, 78% and 100% for various time

\*Author for correspondence

intervals up to a maximum of two weeks to avoid possible microbial degradation. To obtain RH 1%, a desiccator was charged with dried silica gel and to obtain RH 78% or 100% a beaker containing a supersaturated solution of sodium chloride or distilled water was placed, respectively, in a glass chamber. Ambient temperature in the chambers was  $30 \pm 2$  °C.

**Moisture uptake experiments.** The weight of 10 freshly made tablets was individually determined and the mean weight ( $M_0$ ) obtained. The tablets (10 each) were stored under the different RH values described above at room temperature for two weeks. At selected time intervals, the samples were removed from the chambers to determine their mean weight,  $M_t$ . The percent of moisture uptake (degree of hydration of the tablet) was calculated from the expression as follows:

$$\frac{M_t - M_0}{M_0} \times 100\%$$

The experiment was carried out in triplicate by using different batches of the tablets.

**Disintegration test.** The method described in the British Pharmacopoeia (BP, 1988) was employed. Six tablets were used in each determination, which was carried out in triplicate.

**Dissolution test.** The stirred beaker method was employed, details of which have been described previously (Okor *et al.*, 1991). The leaching fluid was 0.1 N hydrochloric acid maintained at  $37 \pm 2$  °C. Samples (5 ml) were withdrawn from the leaching fluid at selected time intervals and analysed for content of paracetamol, spectrophotometrically at  $\lambda_{\max}$ , 245 nm. The dissolution rates were obtained by dividing the maximum amount of drug released by the time (M/T). The determination was carried out in triplicate and the mean results reported.

**Hardness test.** This was carried out using the Monsanto hardness tester (Brook and Marshall, 1968). Ten tablets were used in each determination, which was applied to three batches of tablets to obtain mean results.

**Test for reversibility of humidity effect on the tablets.** Tablets of an initial moisture content  $1.3 \pm 0.2\%$  (w/w) were placed in a humidity chamber (RH 100%) for 24 h, after which they were dried at 60 °C for 3 h in a hot air oven to a moisture content of about 1.2% (w/w). The dried tablets were re-evaluated for hardness, disintegration times and dissolution rates. The test was carried out in triplicate to obtain mean results. Control tablets were stored in a desiccator (RH 1%) for 24 h and similarly tested.

**Test for humidity effect on the particle structure of the disintegrant powders.** The disintegrant powder ( $\alpha$ -cellulose

or maize starch) was dried at 60 °C for 3 h in a hot air oven. A sample of the dried powder was spread thinly on a microscope slide, which was stored in a desiccator (RH 1%) or in a humidity chamber (RH 100%) for 24 h at  $30 \pm 2$  °C. The slides were examined under a microscope at the magnification of  $\times 40$ . Photomicrographs of representative fields of view were taken.

## Results and Discussion

**Moisture uptake profiles of the tablets.** No measurable moisture uptake was recorded for tablets stored in the desiccator (RH 1%) while those stored under RH (78%) showed no appreciable moisture uptake over the 2-week period. The results for tablets exposed to RH 78% and 100% are given in Table 1 where it can be seen that moisture uptake was about twice greater in tablets containing  $\alpha$ -cellulose compared with maize starch. The maximum uptakes were about 4% (tablets with  $\alpha$ -cellulose) and 2% (tablets with maize starch).

**Humidity effect on tablet disintegration time.** The results on the effect of humidity on tablet disintegration time are presented in Table 2. Tablets stored in the desiccator or in the humidity chamber (RH 78%) disintegrated rapidly within

**Table 1.** Effect of humidity on the moisture uptake (degree of hydration) of tablets containing  $\alpha$ -cellulose or maize starch as disintegrant (5% w/w)

Storage time (h)	Moisture uptake (% w/w) in the tablets containing the disintegrant	
	$\alpha$ -Cellulose	Maize starch
RH 78%		
3	0.2	
6	0.2	
9	0.2	0.1
12	0.3	0.1
24	0.7	0.3
48	0.9	0.4
72	1.0	0.4
96	1.2	0.7
RH 100%		
3	0.8	0.3
6	0.9	0.5
9	1.0	0.6
12	1.2	0.8
24	2.1	1.7
48	2.3	1.8
72	3.1	2.0
96	4.3	2.0

Note: there was no measurable moisture uptake at RH 1% (i.e., when tablets were stored in a desiccator)

a minute, similar to the freshly made tablets. Also, tablets with maize starch as the disintegrant, which were exposed to the higher humidity (RH 100%), disintegrated rapidly. This means that humidity had no effect on the disintegration profile of these tablets. However, in the case of tablets with  $\alpha$ -cellulose the higher humidity increased the disintegration time remarkably with an increase in the duration of exposure. These tablets failed to disintegrate within 60 min after their exposure to the high humidity for  $\geq 24$  h. This humidity seriously affected the disintegration time of these tablets.

**Table 2.** Effect of humidity on the disintegration time of tablets containing  $\alpha$ -cellulose or maize starch (5% w/w) as disintegrant

Storage time (h)	Disintegration time (min) of tablets with disintegrant	
	$\alpha$ -Cellulose	Maize starch
RH 1%		
0	0.7	0.5
3	0.7	0.5
6	0.7	0.5
9	0.7	0.5
12	0.7	0.5
24	0.7	0.5
48	0.7	0.5
72	0.8	0.5
96	0.7	0.5
RH 78%		
0	0.7	0.5
3	0.7	0.6
6	0.6	0.6
9	0.7	0.7
12	1.2	0.7
24	1.4	0.7
48	2.3	0.7
72	2.3	0.7
96	2.2	0.8
RH 100%		
0	0.70	0.51
3	0.68	0.50
6	0.65	0.88
9	2.05	0.85
12	21.00	1.01
24	> 60.00	1.62
48	> 60.00	2.10
72	> 60.00	2.82
96	> 60.00	3.02

**Humidity effect on tablet hardness.** There was no marked change in the hardness of tablets stored at RH 1% and RH 78%, but at the higher relative humidity (100%) tablet hardness decreased appreciably with an increase in the duration of exposure (Table 3). For instance, after 24 h exposure, tablet hardness decreased from an initial value of about 11.5 kg ( $\alpha$ -cellulose) and from about 10.5 kg to 7.4 kg (maize starch). The decrease was, therefore, more pronounced in tablets containing  $\alpha$ -cellulose as the disintegrant.

**Humidity effect on tablet dissolution rates.** The amounts of drug dissolved were plotted against time (Fig. 1). The disso-

**Table 3.** Hardness profile of tablets stored under different relative humidities for various time intervals containing  $\alpha$ -cellulose or maize starch as the disintegrants

Storage time (h)	Hardness (kg) of tablets with disintegrant	
	$\alpha$ -Cellulose	Maize starch
RH 1%		
0	11.5	10.5
3	11.2	10.5
6	11.0	10.2
9	11.1	10.1
12	11.4	10.1
24	11.5	10.5
48	11.2	10.8
72	11.5	10.2
96	11.1	10.4
RH 78%		
0	11.5	10.5
3	11.0	10.3
6	10.8	10.0
9	10.1	9.3
12	10.0	9.0
24	9.0	8.6
48	8.2	8.0
72	7.6	7.9
96	7.0	7.2
RH 100%		
0	11.5	10.5
3	10.0	10.0
6	9.0	9.6
9	8.8	9.1
12	8.2	8.8
24	5.1	7.4
48	4.0	6.1
72	2.0	4.2
96	2.0	3.5

lution rates were obtained as described above and are presented in Table 4. The results showed that storage of the tablets at RH 78% had no appreciable effect on their dissolution rates. At the higher RH of 100%, tablets with  $\alpha$ -cellulose exhibited a retarded dissolution rate. In contrast, the dissolution rates of the tablets with maize starch were not affected by exposure to the higher humidity to any appreciable extent.

**Reversibility of humidity effect on the tablets.** Three sets of tablets were involved in this study: (i) tablets stored in a desiccator (RH 1%) for 24 h, (ii) tablets exposed to RH 100%, and (iii) dried tablets previously exposed to RH 100%. Results of their hardness, disintegration time and dissolution rate are presented in Table 5. The results showed that exposure of the tablets to the higher humidity decreased tablet hardness, prolonged the disintegration time (> 60 min), and retarded the dissolution rates of tablets with  $\alpha$ -cellulose. Of these three parameters, drying reversed only tablet hardness.

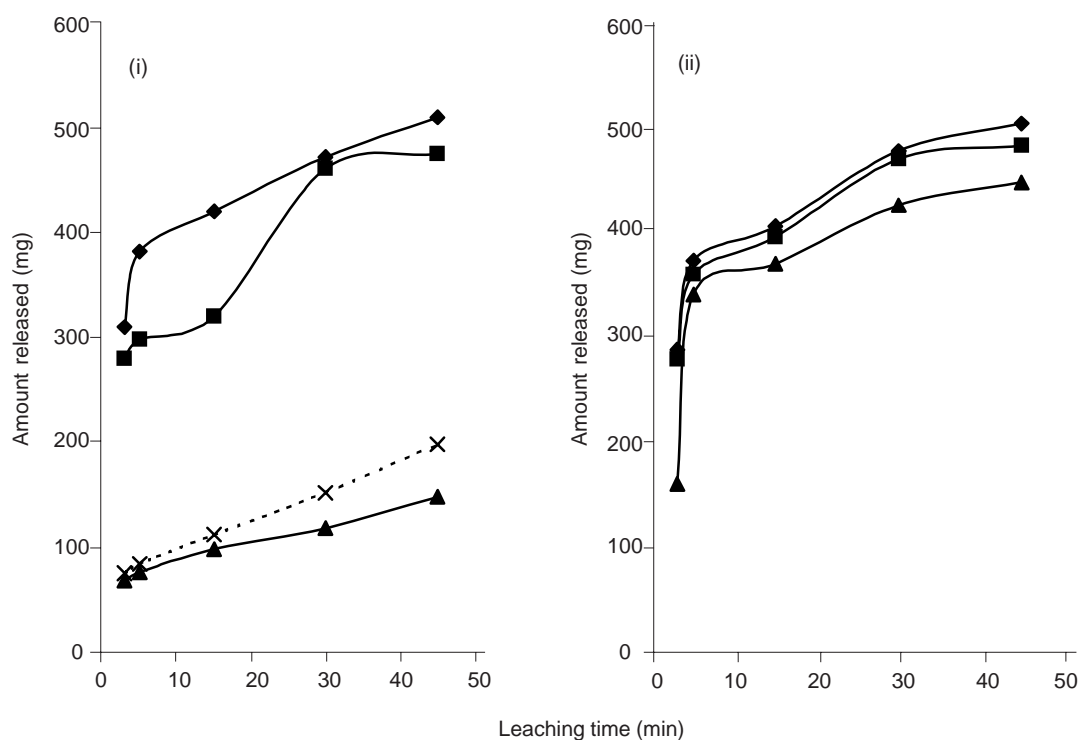
**Humidity effect on the particle structure of the disintegrant powders.** Photomicrographs of the powder samples stored in a desiccator (RH 1%) and under high humidity (RH 100%) are presented in Fig. 2. In the control samples,

**Table 4.** Amount dissolved in 45 min from tablets stored for 24 h in a desiccator (RH 1%) and in humidity chambers, RH 78% and 100%

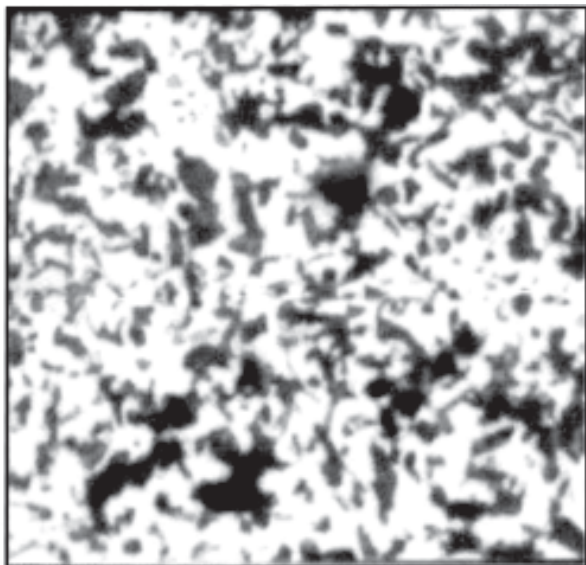
RH %	Dissolution rate (mg/min) of the tablets with the disintegrant	
	$\alpha$ -Cellulose	Maize starch
1 (control)	11.33	11.24
78	10.56	10.78
100	3.29	10.00

**Table 5.** Comparison of hardness (kg), disintegration time (min) and dissolution rate (mg/min) of tablets containing  $\alpha$ -cellulose (i) stored for 24 h in a desiccator, (ii) exposed to RH 100% for 24 h, and (iii) dried after previous exposure to RH 100% for 24 h

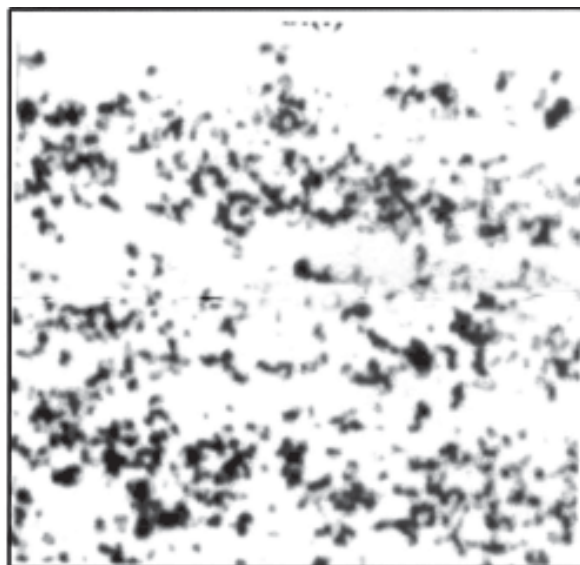
Parameters evaluated	Set of tablets		
	(i)	(ii)	(iii)
Hardness (kg)	11.5	2.0	9.2
Disintegration time (min)	0.7	60.0	60.0
Dissolution rate (mg/min)	10.6	3.3	4.4



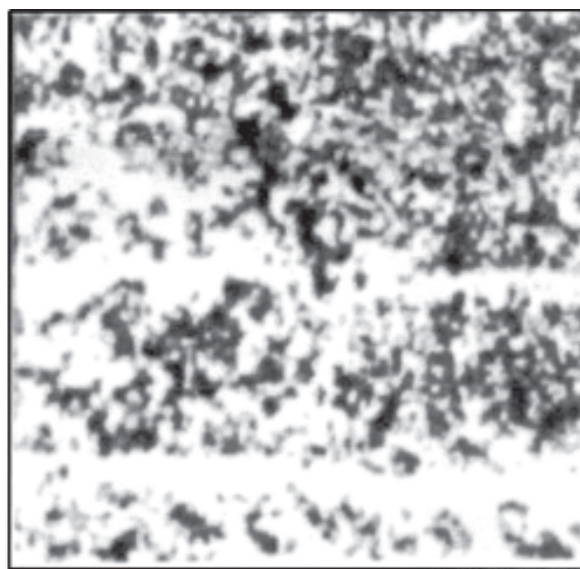
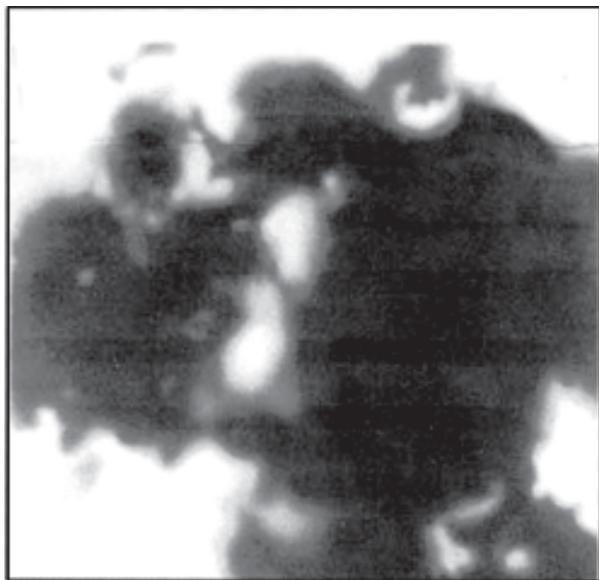
**Fig. 1.** Dissolution profile of tablets stored under different relative humidities RH 1% ( $\blacklozenge$ ), 78% ( $\blacksquare$ ) and 100% ( $\blacktriangle$ ) for 24 h: disintegrant (i)  $\alpha$ -cellulose or (ii) maize starch, (5% w/w); ( $\times$ )  $\alpha$ -cellulose released from redried tablets after previous exposure to RH 100% for 24 h.

$\alpha$  - Cellulose

Maize starch



Samples exposed to RH 100% for 24 h



**Fig. 2.** Photomicrographs showing the gelling effect of humidity on the particle structure of  $\alpha$ -cellulose and maize starch powder.

the particles were discrete and appeared in the micrographs as elongated fibres. Exposure of the maize starch powder to high humidity appeared not to have any effect on the structure of the particles, as they remained discrete. In the case of  $\alpha$ -cellulose, however, high humidity caused the particles to swell and fuse to a coherent mass, indicating that the particles had gelled.

Exposure of the tablets to the higher RH of 100% impaired the disintegrant property of  $\alpha$ -cellulose, whereas maize starch was not susceptible to this humidity effect. This

finding relates to the observation that  $\alpha$ -cellulose powder gelled at room temperature upon moisture sorption, while maize starch did not display a similar gelling. The results of the moisture uptake experiments under these conditions showed that the tablets containing  $\alpha$ -cellulose as the disintegrant were more easily hydrated than similar tablets containing maize starch as the disintegrant. Besides, maize starch would only gel at high temperatures ( $> 60^\circ\text{C}$ ), which explains why the disintegration time of tablets containing this disintegrant was not suscep-

tible to the humidity effect at room temperature. The disintegrant property of  $\alpha$ -cellulose depends on its ability to swell in the tablet to cause its rupture whenever the tablet is placed in an aqueous fluid (Okhamafe *et al.*, 1992, 1991). Having swelled and gelled due to moisture sorption, the capacity of  $\alpha$ -cellulose to further swell when the tablet was placed in the disintegration fluid will be compromised. The lower RH (1% and 78%) did not impair its disintegrant property because of the negligible moisture uptake under these conditions.

Drying of the tablets after their initial exposure to higher humidity did not reverse the observed humidity effect on the tablets with  $\alpha$ -cellulose. Instead, the tablets became harder. This finding suggests that the  $\alpha$ -cellulose gel in the tablets may have formed a xerogel (dried gel) during drying of the tablets. Xerogels are known to function as binders rather than as disintegrants because of their tensile strength and rigidity (Richards, 1972).

The tablets became softer due to hydration when stored under higher humidity. The decrease in hardness was more pronounced in the tablets with  $\alpha$ -cellulose compared with maize starch because of the higher potential of the former for moisture uptake (Table 1). This decrease in hardness was expected to lead to a faster disintegration rate since it reflects a weaker interparticulate bonding within the tablets. On the contrary, the disintegration time (in case of the tablets with  $\alpha$ -cellulose) actually became prolonged. This apparent abnormality is attributable to the impairment of the disintegrant property of  $\alpha$ -cellulose, as already discussed above. Although the tablets became softer, some degree of internal swelling was required before the tablets can disintegrate.

The dissolution rates of the tablets with  $\alpha$ -cellulose, that were exposed to higher humidity, were markedly retarded (Table 4) as the tablets failed to disintegrate throughout the time course of the leaching experiment. Tablets with maize starch, which were similarly exposed to the higher humidity, gave fast dissolution rates because they disintegrated

readily. The explanation is that disintegration increases the particle surface area for dissolution.

## Conclusion

The study has shown that humid conditions can cause gelling of  $\alpha$ -cellulose powder at room temperature and by this mechanism impairs its disintegrant property in tablet formulations, with serious implications for dissolution rates. This finding underlines the need to protect such tablets from moisture.

## References

- BP. 1988. *British Pharmacopoeia*, vol. II; p. A<sub>101</sub>, Her Majesty's Stationery Office, London, UK.
- Brook, D. B., Marshall, K. 1968. Crushing strength of compressed tablets. 1. Comparison of testers. *J. Pharm. Sci.* **57**: 481-484.
- Nitz, O. T. 1994. Cellulose. In: *The Encyclopaedia Americana*, vol. 6; p. 139, International Edition, Grolier Incorporated, New York, USA.
- Okhamafe, A. O., Igboechi, A. C., Obasaeki, T. O. 1991. Cellulose extracted from groundnut shell and rice husk. 1. Preliminary physicochemical characterisation. *Pharm. World J.* **8**: 120-123.
- Okhamafe, A. O., Igboechi, A. C., Ubrufih, C. E., Akinyemi, B. O., Ighalo, M. O. 1992. Celluloses extracted from groundnut shell and rice husk. 2. Disintegrant properties. *Pharm. World J.* **9**: 11-16.
- Okor, R. S., Iwu-Anyanwu, U., Okhamafe, A. O. 1992. Swellability of acrylate methacrylate-cellulose matrix systems and the effect on solute diffusion rates. *J. Appl. Polym. Sci.* **44**: 749-750.
- Okor, R. S., Otimenyin, S., Ijeh, I. 1991. Coating of certain matrix core with aqueous-based systems of acrylates methacrylates, a watersoluble copolymer and drug release profile. *J. Controll. Release* **16**: 349-354.
- Richards, J. H. 1972. *Disperse Systems in Tutorial Pharmacy*, S. T. Carter (ed.), p. 70, 6<sup>th</sup> edition, Pitman, London, UK.
- Seymour, R. B. 1971. Carbohydrates. In: *General Organic Chemistry*, pp. 432-433, Barnes and Noble Inc., New York, USA.