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Research Article

Evaluation of the Effect of Storage on the Physicochemical Properties of Folic acid Tablets Formulated with Sorgum Starch

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ABSTRACT

Assessment of the stability of pharmaceutical formulations is always crutial in pharmaceutical product development. Stability could be viewed from the degradation of the active ingredients or a change in the physicochemical properties of the formulations. The objective of this study was to evaluate the effect of storage on the physicochemical characteristics of sorgum starch-based folic acid tablet formulations *vis-a-vis* tablets prepared with maize starch BP, a standard tablet binder. The folic acid tablets were prepared by wet granulation technique using sorgum and maize starches, and evaluated for physical properties, such as weight variation, thickness, hardness, friability, disintegration time, drug content and *in vitro* drug release study. The formulations were subjected to stability studies as per ICH guidelines at different temperatures and humidity conditions. Results indicated that the folic acid tablets did not show any appreciable changes with respect to hardness, disintegration time, drug content and dissolution profiles. In addition, results revealed that the stability of folic acid tablets formulated with the local sorgum starch as binder compared favourably with those formulated with imported maize starch B.P. when stored under various conditions of temperature and humidity over a period of one year. This study has shown that proper storage conditions are very necessary for folic acid tablets to have long shelf life, as high temperature and high humidity would negatively affect the stability of these tablets.

INTRODUCTION

Starch, a multipurpose excipient in tablet formulations, can be used as a binder, disintegrant, and filler. Natural starches also have been pregelatinized to increase their cold-water swellability and increase their flowability [1]. The compressional characteristics of natural starches in relation to their usefulness in tablet formulations has been established [2, 3]. Sorghum starch obtained from *Sorghum bicolor* L. (Poaceae) has been investigated as binders and disintegrants in tablet formulations [4]. Folic acid (also known as vitamin B9 or folacin) are forms of the water-soluble vitamins. Folic acid is itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver.

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Absorption of folic acid by the body is facilitated by enzymes associated with the mucosal cell membrane. More specifically, absorption primarily occurs in the mucosa of the upper intestine, known as the jejunum and duodenum. Insufficient folic acid in the diet and the inability to absorb folic acid can cause anemia or birth defects, namely, anecephaly and spina bifida, the latter resulting in brain development abnormalities [5].

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. Tablets are simple and convenient to use. They provide an accurately measured dosage of the active ingredient in a convenient portable package, and can be designed to achieve sustained release, protect unstable medications or disguise unpalatable ingredients [6, 7]. They may be classified according to the method of manufacture as either compressed tablets or

molded tablets. The compressed tablets are the most widely used dosage form in the world and the vast majority of all tablets manufactured are made by compression. The compressed tablet is the most popular dosage form in use nowadays. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets [8]. Tablet dosage forms are the most popular and preferred drug delivery systems in terms of precision of unit dose, low cost, patient compliance, and good physical and chemical stability and account for 70 - 80 % of all pharmaceutical dosage forms [9]. Tablets have remained the most common dosage form by which medicaments are usually administered to patients because of their advantages over the other dosage forms [10].

It is always very important to assess the stability (short-term or long-term) of pharmaceutical formulations. Stability could be viewed from the degradation of the active ingredients or a change in the physicochemical properties of the formulations [11, 12]. Expectedly, stability test which involves examining for quality and potency at suitable time intervals, ought to be conducted for a period corresponding to the normal time that the prodcut would remain in stock or in use. Since this test is time-consuming and expensive, accelerated stability tests are employed during the product development stage to enable rapid prediction of long-term stability of the product. It is then possible to identify the most stable formulation without resorting to the lenghty conventional stablity tests.

Till date, it appears that no attempt has been made to study the effects of storage on the physicochemical characteristics of sorgum starch-based tablet formulations. In the present work, a study has been undertaken on the effects of storage on the physicochemical properties of folic acid tablets prepared using sorghum starch as binder *vis-a-vis* maize starch BP, a standard binder.

MATERIALS AND METHODS

Materials

The materials used include folic acid (Hoffman La Roche, Ltd, Switzerland), maize starch (B.P. grade), lactose (DMU Vegal, Holland), magnesium stearate and talc powder (BDH, England). Raw sorgum starch (SAMSORG 16) was procured from the Institute for Agricultural Research, Ahmadu Bello University, Zaria, Nigeria.

Preparation and Physicochemical Properties of Sorgum Starch

Sorghum and official maize starches were prepared according to established procedures [13, 14]. Briefly, a 6 kg quantity of the sorgum (SAMSORG 16) was procured from the Institute for Agricultural Research, Almadu Bello University, Zaria. It was cleaned and sieved to remove any impurities. The grains were washed with distilled water and soaked in dilute hydrochloric acid for 30 h after which they were washed several times with distilled water, milled using Kenwood blender and sieved through a calico cloth. The mixture was allowed to settle overnight and excess water decanted. The starch was then washed with NaOH to neutralize the acid and then purified by centrifigation. The wet starch was then dried in an oven at 60 ºC for 30 min. Preliminary physicochemical tests were then performed on the sorgum and maize starches following standard procedures [4, 14-15].

Preparation of starch mucilage

Starch mucilage was prepared following a method already reported [14] by weighing different amounts of starch powder. Each weighed quantity was then suspended in the required amount of distilled water in a beaker and heated with continuous stirring until the mucilage was formed. The mucilage was used while still hot for a more effective binding.

Preparation of granules

The formulation compositions of different batches of the granules which were prepared by wet granulation method [8, 13] are presented in Tables 1 and 2. Briefly, accurately weighed quantities of the folic acid and the starches were mixed together in an automatic mixer followed by addition of binder mucilage and further mixing.The resulting wet mass was transferred to a granulator fitted with an appropriate sieve. The granules formed were dried and sieved followed by addition of magnesium stearate and talc powder, and mixing in a hand mixer.

Granules size analysis

The sieve method of analysis was employed [4]. Briefly, four sieves (500 µm , 355 µm , 250 µm, and 180 µm pore sizes) were arranged in order of decreasing size in a stack such that the sieve with the largest pore size was at the top. A quantity (100 g) of the granules was poured into the topmost sieve and the Endecott sieve shaker was then switched on for 15 min. The amount of the granules left on each sieve was weighed and

Table 1: Formulation compositions of the tablets

Batch code	Folic acid (mg)	Starch (mg)	Lactose (mg)	Binder (mg)	Talc (mg)	Magnesium stearate (mg)
I	2.50	54.10	-	0.156	3.24	0.36
II	2.50	42.00	12.00	1.093	3.24	0.36
III	2.50	30.00	24.00	1.015	3.24	0.36
IV	2.50	18.00	36.00	0.78	3.24	0.36
V	2.50	-	54.00	0.468	3.24	0.36

Table 2: Composition of starch and lactose in the tablets (total weight = 60 mg)

Batch code	Starch (%)	Lactose (%)	Folic acid (%)
I	90	0	4.1
II	70	20	4.1
III	50	40	4.1
1V	30	60	4.1
V	0	90	4.1

the percentage of the granules on that sieve was calculated.

Tablet compression

The granules were compressed into tablets on a single punch Manesty tableting machine fitted with a circular 5.5 mm set of punches and die, according to an established method [10]. The compression pressure was maintained at 4.5 kg/sq.cm and the speed of compression was 70 tab/min.

Physicochemical Properties of the tablets

Some physicochemical properties of the tablets were evaluated as follows [5-8, 16]:

Uniformity of weight

Twenty tablets from each batch were taken and weighed using an analytical balance (Mettler H35AR, Mettler Instrument A.G. Switzerland). The tablets were weighed individually and the percentage deviation from the mean was calculated for each batch.

Uniformity of thickness and diameter

The thickness and the diameter of six tablets taken from each batch were measured using the Vernier Caliper (Moore and Weight, Sheffield, England) and the mean taken.

Hardness

The Monsanto Tablet Hardness Tester was used to determine the crushing strength of the six tablets taken from each batch and the mean taken.

Friability

Twenty tablets were weighed and subjected to abrasion test in the Roche Friabilitor Erweka Type TA 3R (Erweka Apparatus GmbH, West Germany) operated at 25 rpm for 4 min at 37 ± 0.5 ^{0} C. The tablets were de-dusted and weighed together. The difference in weight was determined and expressed as the percentage friability value.

Packing Fraction

The packing fraction of the tablets was obtained by comparing the bulk density of the tablet with the true density of the ingredients from which the tablets were made. The density of individual ingredients employed in the formulation of the tablets was determined using the specific gravity bottle method. The true density of the tablet material was calculated from the equation:

$$1/em + nA/eA + nA/eA \quad \ldots (1)$$

Where em = True density of tablet material
nA=nB= weight fraction of starch and drug in the tablet.

True and Bulk Densities of the tablet were calculated by dividing the mean weight by volume. The volume of tablet was obtained using the formula for volume of cylinder $\pi d^2 h/4$
Where d=diameter of tablet; h = thickness of tablet.

Disintegration time

The disintegration times of the tablets in distilled water were determined using the Erweka disintegration apparatus (Erweka Apparatus GmbH, Germany) and water thermostatically maintained at 37 ± 0.5 ºC. Six tablets were used and each one placed in the six tubes of the apparatus and the time taken for the tablet to disintegrate and pass through the mess of the apparatus was recorded using a stop clock.

Dissolution rate

The release rate of folic acid from the tablets was determined using United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was

performed using 500 ml of distilled water, at 37± 0.5 ^{0}C and agitation of 50 rpm. A sample (2 ml) of the solution was withdrawn from the dissolution apparatus at predetermined time intervals. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µ membrane filter. Absorbance of these solutions was measured at 283 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard Beer-Lamberts' plot.

Content of folic acid in the tablet

Forty tablets were weighed and powdered. Two equal quantities of the powder were weighed equivalent to 50 mg of folic acid. The weighed sample above was transfered into 250 ml flask and 200 ml of 0.1 N NaOH was added. The mixture was shaken for 25 min, made up to the 250 ml mark with 0.1 N NaOH and filtered. A 5 ml volume of the filtrate was transferred into a 100 ml volumetric flask and sufficient NaOH added to produce 100 ml. The absorbance of the resulting solution was measured at 283 nm. The percentage of folic acid in the tablet was then calculated [5].

Stability studies

The physicochemical properties of the formulations were also asssessed under different storage conditions as per the ICH guidelines [8] with slight modifications.

Statistical analysis

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± SD. ANOVA and student's t-test were performed on the data sets generated using SPSS. Differences were considered significant for p-values < 0.05.

RESULTS AND DISCUSSION

The sorgum starch passed all the preliminary tests (iodine and acidity tests) carried out to indicate the presence of starch [15]. Table 3 shows the moisture absorption and desorption properties of the local sorgum starch and imported maize starch B.P. It is evident from the Table 3 that the two starches absorbed moisture gradually and lost all the moisture almost at the same rate under the experimental conditions. Sorgum starch absorbed larger amount of moisture than maize starch B.P. at all levels of relative humidities employed. At the highest RH investigated i.e. 85 %, sorgum starch absorbed 12.2 % while the maize starch absorbed 11.1 % of moisture. The moisture absorbed is reversible as shown by the amounts of moisture desorbed from the starches (Table 3).

Figure 1a-e shows the particle size distribution of the granules made with the Sorgum and maize starches. Sorgum starch produced smaller granules sizes as well as more fines than maize starch B.P., consistent with previous report [17]. The sorgum starch might contain less amount of amylose relative to the maize starch B.P. The amylose content of starch is the most important for its binding property. It leaches out of the starch particles to form thread – like structures. Earlier researchers reported that it enhances the binding action of the starch [18, 19].

The physical properties of the tablets are shown in Table 4. The large amount of the starch which was used as the disintegrant produced very soft tablets. Batch III tablet formulations containing 50 % starch disintegrant produced tablets with acceptable friability, hardness and disintegration, in accordance with published data [5, 16]. Based on this, batch III tablets were selected for the stability tests. While Table 5 shows the properties of folic acid tablets using the selected starches as disintegrants at 50 % after storage at 0 % R.H. at room temperature of 30 ºC (dry condition) for up to three months at various time intervals; Table 6 shows the properties of folic acid tablets containing the selected starches as disintegrant at 50 % stored at high temperature (40 ºC) under high humidity (humid conditions) for up to 6 months. It could be observed from Table 5 that, under dry condition (i.e. 0 % R.H.) and storage at 30 ºC, there was insignificant difference in the usual parameters of the tablets i.e. hardness, friability and disintegration time, even after three months of production.

Table 3: Moisture absorption and desorption properties of the starches

Parameter	Relative humidity (%)	Starch	
		Maize	Sorgum
Moisture absorption, %	0	0	0
	33	6.2	6.3
	76	9.1	9.4
	85	11.1	12.2
Moisture desorption, %	76	4.2	6.1
	33	6.3	7.1
	0	12.3	13.5

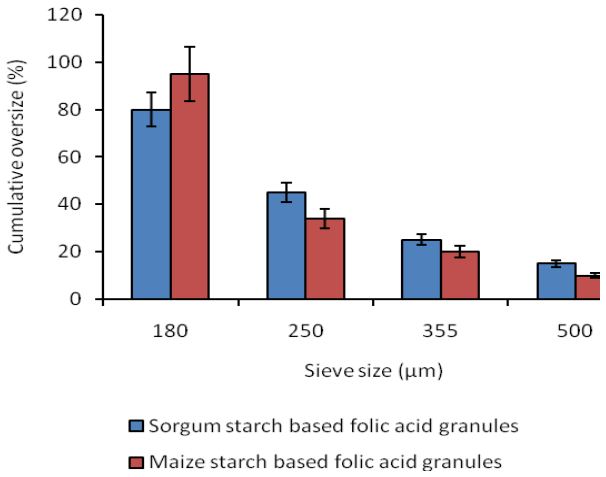

Figure 1a: Cumulative over size against sieve size of granules containing 90 % of the selected starch (batch A).

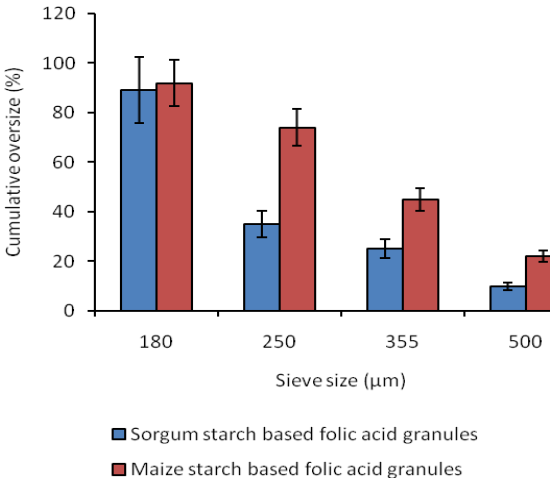

Figure 1b: Cumulative over size against sieve size of granules containing 70% of the selected starch (batch B).

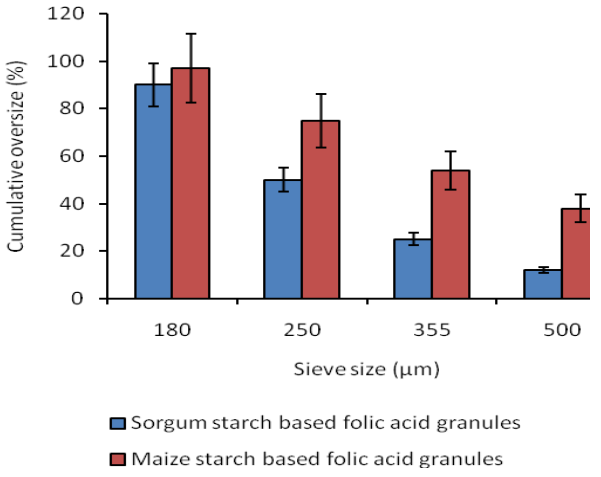

Figure 1c: Cumulative over size against sieve size of granules containing 50 % of the selected starch (batch C).

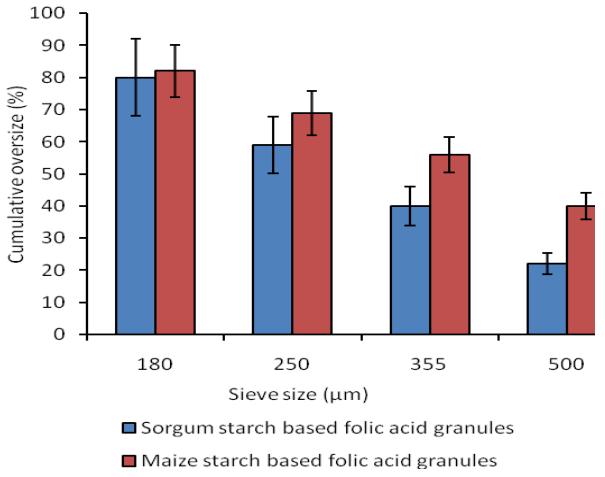

Figure 1d: Cumulative over size against sieve size of granules containing 30% of the selected starch (batch D).

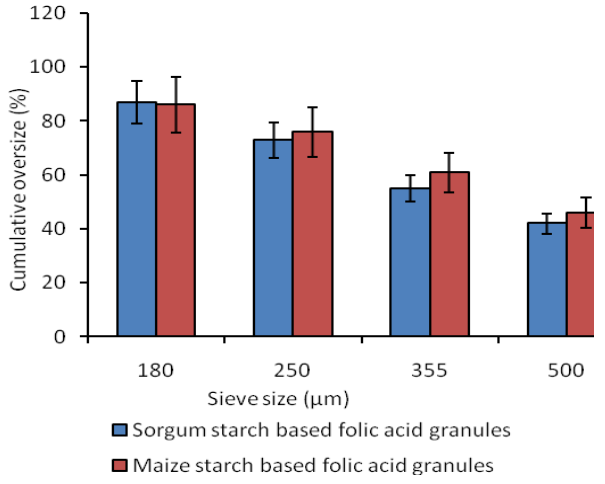

Figure 1e: Cumulative over size against sieve size of granules containing 0% of the selected starch (batch E).

Generally, however, the tablets became softer and brittle, which was more pronounced with sorgum starch-based tablets than maize starch-based tablets. This could be due to loss of moisture from the tablets [5]. However, Table 6 reveals that under saturated vapour pressure, the properties of the tablets changed drastically. Within one month of production, the weights, diameters and thickness of the tablets had increased, and most of the tablets failed the hardness, friability and disintegration time tests. The disintegration time of sorgum starch-based tablets was faster than the maize starch-based tablets using the same binder concentration (5 %), which may be attributed to the differences in the swelling power of these starches, as sorgum starch has greater swelling power than maize starch, consistent with earlier studies [18, 19]. The

increase in tablets weight, diameter and thickness could be attributed to the fact that the tablets absorbed moisture and swelled up. Sorgum starch has greater swelling power than maize starch. Thus, sorgum starch-based tablets were softer than maize starch-based tablets. The differences in the hardness of the two different starches could be attributed to the various starch disintegrant used, the amount of binding property possessed by the various starches and the inability of the starches to adhere to itself and other materials in the tablets in dry state. As expected, the tablets stored under humid conditions absorbed moisture and became very soft, consistent with previous reports [3, 20-22]. From these results, it would be better to store the tablets in dry atmosphere than in humid atmosphere. The place should not be too dry either because moisture would be lost from the tablets, thereby making them more brittle and soft. Tablets would be better stored under temperature- controlled i.e. 26 – 28 ºC and humidity-controlled environment.

The dissolution profile of the folic acid tablets after six months of storage in screw capped containers at 26 ºC under controlled humidity is depicted in Figure 2, while the dissolution profile of the tablets stored in screw capped containers under humid environment at room temperature (i.e. 29 ºC) for six months is shown in Figure 3. It is discernible from Figure 2 that the dissolution profiles of sorgum starch- and maize starch-based tablets followed different release patterns, achieving maximum drug release after 60 and 30 min for sorgum starch- and maize starch-based tablets respectively. Previous report indicated that the dissolution of API was considerably faster from tablets formulated with sorgum starch as disintegrant than those formulated with maize starch [17]. For the sorgum starch based tablets, 45 min into the release studies, about 80 % of the drug was already in solution. Even after 6 months of storage,the tablets passed the dissolution test. Disintegration to a large extent can be the rate determining step in the dissolution process and a direct correlation is expected between the time taken for 50 % of the drug to dissolve (t_{50}), the time taken for 90 % of the drug to dissolve (t_{90}) and the disintegration time. Furthermore, it is deducible from Figure 3 that humidity affected the dissolution rate of the drug from the tablets. For maize starch-based tablets, the drug was already in solution even after 2 min, reaching its peak dissolution (t_{100}) at 60 min. This result was 20 min longer than what was observed when the tablets were stored under controlled R.H. at 26 ºC. Similarly, the dissolution of the drug from sorgum starch-based tablets was much slower than what was observed at 26 ºC and under controlled humidity. The drug was already in solution even after 2 min, reaching its peak dissolution (t_{100}) at 30 min, which was 10 min longer than what was observed when the tablets were stored under controlled R.H. and at 26 ºC. Thus, sorgum starch-based tablets also took a longer time to dissolve. These results show that under moist condition, the release of the drug from the tablets could be very slow. In a moist environment, the starch absorbed moisture and became mucilagenous, and thus acted as a barrier for water penetration, thereby delaying the dissolution of the drug. There was also loss of swelling power of the tablets. Therefore, the tablets could not disintegrate easily and since to a certain extent disintegration is the rate determining step of dissolution process, dissolution was faster, with increased disintegrant concentration, in agreement with previous studies [1, 20, 21, 23].

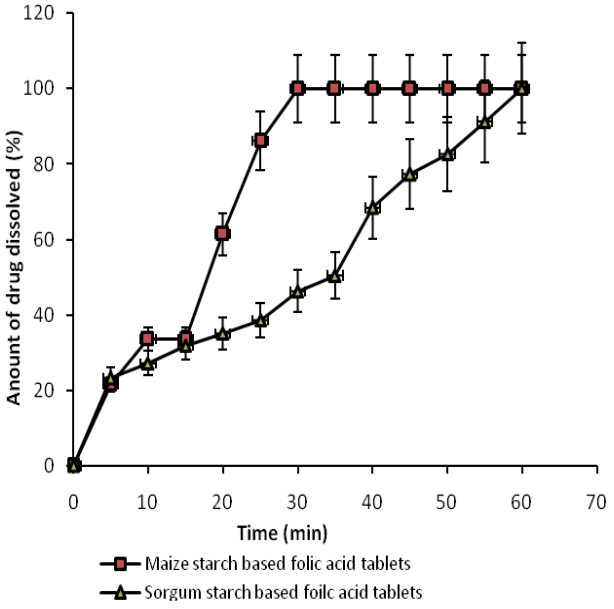

Figure 2: Release profile of the folic acid tablets after six months storage in screw capped containers at 26 ºC under controlled humidity. [Release profile of the folic acid tablets prepared with the selected starches upon storage at 26 ºC].

Table 4: Some physical properties of freshly prepared sorgum starch-based folic acid tablets

Starch	Batch code	Properties				
		Hardness (KgF)	Friability (%)	Packing fraction	Disintegration time (min)	Weight (mg)
Maize	I	1.50±0.009	0.13±0.002	0.85±0.003	1.00±0.023	60.00±1.430
	II	2.50±0.010	0.85±0.009	0.81±0.007	2.00±0.017	58.00±1.670
	III	3.25±0.013	0.80±0.005	0.76±0.002	1.30±0.045	60.00±1.200
	IV	4.25±0.008	0.50±0.001	0.72±0.001	3.00±0.096	59.50±0.998
	V	2.90±0.005	0.80±0.004	0.78±0.009	5.00±0.072	60.00±1.750
Sorgum	I	2.00±0.016	2.60±0.015	0.64±0.008	0.50±0.009	60.00±1.450
	II	1.00±0.007	2.00±0.006	0.74±0.004	1.00±0.018	57.00±1.290
	III	2.00±0.012	0.65±0.008	0.77±0.009	0.30±0.007	58.00±1.640
	IV	1.87±0.009	0.70±0.001	0.69±0.005	1.00±0.025	59.40±1.900
	V	2.00±0.010	0.90±0.003	0.68±0.002	7.00±0.146	58.00±1.780

Table 5: Some physical properties of the folic acid tablets formulations containing 50 % starch disintegrant (batc III) after storage at 0 % R.H. at 30 ^{0}C (dry condition) for specified periods of time.

Starch	Storage period	Properties				
		Hardness (KgF)	Friability (%)	Packing fraction	Disintegration time (min)	Weight (mg)
Maize	24 hrs	2.50±0.018	0.67±0.003	0.82±0.003	1.00±0.012	58.00±1.900
	1 wk	2.50±0.017	0.67±0.001	0.81±0.001	1.00±0.020	58.00±1.210
	1month	1.25±0.006	0.00±0.000	0.86±0.009	3.00±0.019	56.00±1.160
	6 mnths	1.50±0.012	0.00±0.000	0.79±0.005	3.00±0.017	56.00±1.000
	1 yr	1.50±0.003	0.00±0.000	0.76±0.004	2.00±0.027	60.00±2.300
Sorgum	24 hrs	2.00±0.015	1.20±0.008	0.80±0.002	1.00±0.018	58.00±1.820
	1 wk	2.00±0.009	1.20±0.019	0.82±0.003	1.00±0.009	60.00±1.700
	1month	1.00±0.014	0.00±0.000	0.77±0.001	1.00±0.015	60.00±2.000
	6 mnths	0.80±0.011	0.00±0.000	0.85±0.009	1.00±0.012	58.00±1.500
	1 yr	1.00±0.006	0.00±0.000	0.81±0.007	1.00±0.008	58.00±1.320

Table 6: Some physical properties of the folic acid tablets formulations containing 50 % starch disintegrant (batc III) after storage at 0 % R.H. at a high temperature (40 ^{0}C) for specified periods of time.

Starch	Storage period	Properties				
		Hardness (KgF)	Friability (%)	Packing fraction	Disintegration time (min)	Weight (mg)
Maize	24 hrs	2.82±0.014	0.90±0.005	0.67±0.008	1.83±0.017	59.25±2.000
	1 wk	2.16±0.009	0.00±0.000	0.65±0.002	1.17±0.008	60.02±1.930
	1month	2.10±0.007	0.00±0.000	0.64±0.006	3.83±0.012	61.00±2.700
	6 mnths	2.00±0.013	0.00±0.000	0.63±0.009	3.00±0.009	59.75±1.860
	1 yr	1.60±0.008	0.41±0.007	0.60±0.005	3.33±0.006	60.25±1.430
Sorgum	24 hrs	1.00±0.012	0.99±0.016	0.60±0.009	3.28±0.012	59.75±2.100
	1 wk	0.50±0.006	0.91±0.008	0.56±0.007	3.16±0.007	59.25±2.000
	1month	1.00±0.005	1.86±0.005	0.60±0.008	2.00±0.008	60.00±1.670
	6 mnths	1.00±0.018	0.41±0.003	0.58±0.001	2.50±0.011	61.25±1.890
	1 yr	1.00±0.009	0.81±0.009	0.59±0.006	2.75±0.009	60.25±2.650

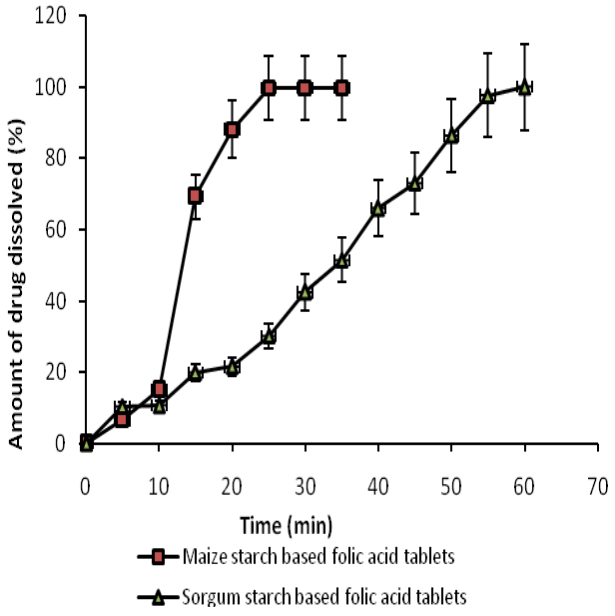

Figure 3: Dissolution rate of the tablets stored in screw-capped containers under humid environment at room temperature (i.e. 29 °C) for six months. [Release profile of the folic acid tablets prepared with the selected starch upon storage at controlled humidity].

The amount of folic acid contained in the tablet of the selected starch 6 months and 1 year after storage at 26 °C under controlled R.H. is presented in Figures 4. One year after storage, the tablets formulated with the two different starches passed the assay test. The values were still within acceptable limits [16]. Even after one year of storage under controlled humidity and at 26 °C, tablets formulated from sorgum starch gave higher content of folic acid than tablets formulated from maize starch B.P. This implies that, although humidity and temperature affected the physical state of various folic acid tablets formulated with the two different starches, the effect on the chemical composition of the tablets within one year at 26 °C under controlled R.H. was rather insignificant ($p>0.05$).

CONCLUSIONS

This study has shown that the stability of folic acid tablets formulated from the local sorgum starch compared favourably with those formulated from imported maize starch B.P. when stored under various conditions of temperature and humidity over a period of one year. Proper storage conditions are very necessary for these tablets to have long shelf life, as high temperature and high humidity would negatively affect the stability of these tablets.

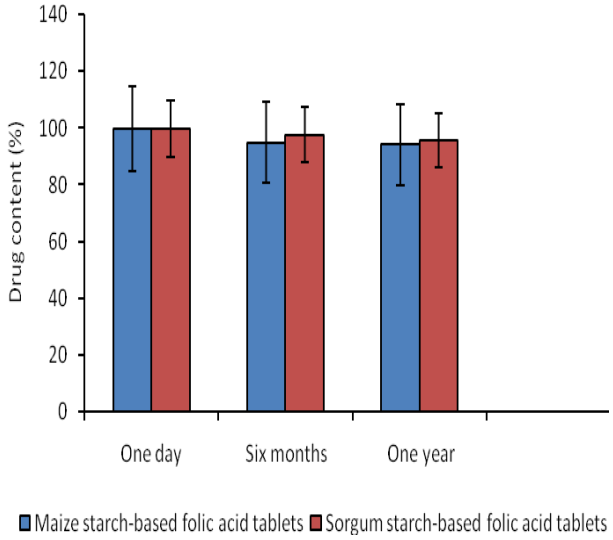

Figure 4. Drug content in the folic acid tablets prepared with the selected starch after specified periods of storage.

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