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Evaluation of Modified Breadfruit (*Artocarpus Altilis*) Starches as Immediate and Sustained Release Polymers in Bilayer Tablets of Ibuprofen

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Ibuprofen, administered as conventional oral tablets every 4 -6 hours, has some gastrointestinal side effects. Its formulation as sustained and immediate release layers in a compact bilayer tablet avoids the challenge of multiple daily dosing, reducing untoward side effects.

Objectives: The objective of the study is to formulate bilayer tablets of ibuprofen using breadfruit (*Artocarpus altilis*) starches modified by carboxymethylation and acid hydrolysis for immediate and sustained release, respectively, in comparison to sodium starch glycolate (SSG) and hydroxypropyl methyl cellulose (HPMC).

Methods: The starches were characterized using Fourier Transform Infrared spectroscopy (FT-IR), X-ray diffraction (XRD) analysis, viscosity, swelling power, densities and flow properties. Bilayer tablets of ibuprofen were prepared using carboxymethylated Breadfruit starch (5.0 and 7.5%w/w) and acid-hydrolyzed starch (17.0%w/w) and evaluated using crushing strength, friability, disintegration and dissolution times (t_{80}).

Results: FTIR and XRD spectra confirmed modification of starches. Carboxymethylation produced starches of higher swelling and flow properties while acid-modification produced higher compressibility. Bilayer tablets containing modified starches had higher crushing strength than the standards. Disintegration time of the fast release layers was 1.00 - 10.37 min. An initial burst release was followed by sustained release (t_{80} = 4.5 - 9.0 h) with tablets containing the acid modified starch having longer dissolution than HPMC. Drug release fitted the First order, Hixson-Crowell and Hopfenberg kinetic models.

Conclusion: Carboxymethylated and acid-modified breadfruit starches were found suitable as cheaper excipients in bilayer tablet formulations for immediate and sustained release of drugs respectively, particularly where high mechanical strength is required.

Keywords: Acid-modification, bilayer tablets, breadfruit starch, carboxymethylation, ibuprofen

INTRODUCTION

The limitations of conventional tablets, such as repetitive dosing and erratic absorption, has led to the concept of controlled drug delivery systems (Niwa *et al*, 2013). Bilayer tablets are tablets consisting of two layers and are suitable for sequential release of two drugs in combination and for separating two incompatible substances (Karwa and Kasture, 2011). They are also suitable for formulating drugs in which one layer is formulated to obtain immediate release, with the aim of reaching a high serum concentration in a short period of time while the second layer is for sustained release, designed to maintain an effective plasma level for a prolonged period of time (Patel 2010). However, one of the major challenges in the formulation of bilayer tablets is lack of sufficient bonding and adhesion at the interface between the

adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses within the tablet. This leads to delamination (layer-separation). In addition, if the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity (Desphande *et al*, 2011). These challenges can be overcome by the use of suitable excipients such as modified starches that can impart mechanical strength to tablets (Pohjas *et al*, 2010; Akin-Ajani *et al*, 2014; Okunlola *et al*, 2015). Chemical modification by carboxymethylation method involves replacing the hydrogen of the starches with carboxymethyl groups and this is achieved by a reaction of starch and sodium monochloroacetate in the presence of sodium hydroxide. The amount of substituted carboxymethyl group is determined by the degree of substitution (DS), which lies between 0 and 3 (Heinze, 2005). The replacement of the hydroxy groups with the bulky functional group reduces the tendency of the starches to crystallize and make them more resistant to damage by heat and bacteria while improving their gel-forming property. The method of acid-hydrolysis involves subjecting native granular starches to treatment with acids, either at room temperature for a period of several days or at elevated temperature for several hours (Tester *et al*, 2000). The amorphous regions of starch are more rapidly hydrolyzed than the crystalline regions during acid hydrolysis at temperatures below the gelatinization temperature with amylopectin being preferentially hydrolyzed than amylose (Tuschoff, 1986). Breadfruit starch is obtained from Breadfruit (*Artocarpus altilis*), a specie of the flowering tree in the Mulberry family Moraceae (Monalisa *et al*, 2015). Despite its nutritional benefits, breadfruit remains underutilized in most tropical areas perhaps due to the perishable nature of the fruits. However, the fruit can be explored in the local pharmaceutical industry as a standard but cheaper alternative source to imported starches. Breadfruit starch was found to be useful as exo-disintegrant in paracetamol tablet formulations, having comparable activity with corn starch BP where it not only produced rapid break-up and dissolution, but also improved the crushing strength of the tablets (Adebayo & Itiola, 2003; Adebayo *et al*, 2008).

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is administered every 4 - 6 hours in 200 or 400 mg doses and has unpleasant gastrointestinal side effects like epigastric pain, gastrointestinal ulcerations, dizziness, etc. (Daniel *et al*, 2012; Rang *et al*, 2016). Formulation of sustained and immediate release layers of ibuprofen in a compact bilayer form avoids the challenge of multiple daily dosing, reducing the unpleasant side effects and aiding patient compliance. The fast release layer of ibuprofen guarantees an immediate relief from pain while the sustained layer ensures the maintenance of an effective plasma level. The aim of the research is to formulate bilayer tablets of ibuprofen using carboxymethylated and acid-hydrolyzed Breadfruit starches as immediate and sustained release polymers respectively. The mechanical and release properties of the bilayer tablets of ibuprofen would be evaluated in comparison to tablets containing the standard sodium starch glycolate as superdisintegrant and hydroxypropylmethyl cellulose as sustained release polymer.

Materials and Methods

Materials

Breadfruits were obtained from local farmers in Ibadan, Nigeria. Ibuprofen was obtained from Nanjing Bangnuo Biotechnology Co. Ltd., China. Sodium hydroxide was from Sigma- Aldrich GmbH, Germany, monochloroacetic acid from Alfa Aesear, Massachusetts, USA, while isopropyl alcohol and hydrochloric acid were purchased from BDH, England. Hydroxypropylmethylcellulose was obtained from Oxford Lab Chemicals, Maharashtra, India.

Extraction of Breadfruit Starch

The fruits were washed with distilled water, peeled, washed again and then cut into small pieces. The small pieces were milled into a fine paste using a laboratory mill and the slurry was strained through a muslin cloth. The filtrate was left to settle. The supernatant was decanted at 12-hour intervals and the starch slurry re-suspended in distilled water for 3 days. The starch cake was collected and dried in a hot-air oven at 50 ºC for 48 h. The dried mass was pulverized using a laboratory blender and then screened through a 125-µm mesh sieve.

Modification of starch by carboxymethylation

Forty grams of native Breadfruit starch was mixed with 2 g of sodium hydroxide and 4 g of monochloroacetic acid in a beaker. One hundred millilitres of isopropylalcohol and 100 mL of water were added with continuous stirring to obtain homogeneity. Subsequent reaction was allowed to proceed at 50 ºC for 2.15 h. Aqueous acetic acid (50%) was added to the resulting mixture until pH 5 was obtained. The modified starch was washed with 80% aqueous ethanol until a neutral pH of 7 was obtained and then dried at 50 ºC for 6 h. The dried starch was powdered, sieved through a 120 mesh sieve (125-µm)

and then stored in an air-tight container (Singh *et al*, 2011).

Degree of Substitution of Carboxymethylated Starch

Modified breadfruit starch (0.5g) was dissolved in 20 mL of 0.2M NaOH. Distilled water (50 mL) was then added and the resulting mixture was transferred into a 100-mL volumetric flask and filled up to volume with water. From this mixture, 25 mL was withdrawn and diluted with 50 mL of distilled water in a flask. The excess of NaOH was back titrated with 0.05M HCl using phenolphthalein as indicator. The titration was done in triplicates and the mean value determined for the volume of HCl used. A blank titration was also done (Javanovic *et al*, 2005).

The degree of substitution (DS) was calculated from equation (1) below:

$$D.S = \frac{162 \times nCOOH}{(mds - 58) \times nCOOH} -- (1)$$

where 162 = molar mass of anhydrous glucose unit (AGU) g/mol; mds = mass of dried sample; 58 = molar mass of CH2COOH; nCOOH = (Vb – V) x cHCl x4

Vb = volume of HCl used for titration of blank in back titration

V = volume used in titration of sample

cHCl was concentration of HCl

4 = ratio of total volume of solution taken for titration

Modification of breadfruit starch by acid-hydrolysis

Three hundred grams (dry basis) of native breadfruit starch were hydrolysed by incubating the starch in 600 mL of a 6% HCl solution for 192 h (8 days) (Atichokudomchai and Varavinit, 2003). The mixture was left unstirred for this period and then neutralized with 10% (w/v) NaOH solution. The starch slurry obtained was washed five times with distilled water and dried in a hot air oven at 40 ºC for 24 hours. The starch was powdered with a laboratory mill and passed through a 125-µm mesh sieve.

Characterization of native and modified Breadfruit starches

Morphology

The mean particle size of 300 starch granules was determined with an optical microscope (Olympus XSZ-107BN, Shinjuku, Japan).

Crystallinity

The native and modified starches were identified and characterized by Fourier Transform infra-red (FTIR) analysis (FT-IR Spectrum BX II by Pekin Elmer Waltham, MA, USA) in transmission mode. About 5 mg of starch was mixed with KBr (400 mg) and then formed into a disc in a press. Transmission spectra were recorded using at least 20 scans with 4cm-1 resolution in the spectral range 4000-400 cm-1

The X-ray diffraction pattern was recorded using an X-ray diffractometer (ARL X'TRA Thermo Scientific Netherlands) with copper-cobalt radiation. The native and modified starch samples were exposed to the X-ray beam at 25ºC. The scanning region of the diffraction angle (2θ) was from 5º to 70º at a scan rate of 12º/ min. The integration time was 0.150s and step was 0.030º.

Swelling Power

The swelling power of the native and modified starches was determined by preparing starch suspension (5%w/v) at room temperature with shaking for 5 min. The dispersion was allowed to stand for 24 hours before the sedimentation volume (V) was measured and the swelling power was calculated as the ratio of sedimentation volume (V) to initial volume (Vo) of the dried starch powder, V/Vo (Bowen and Vadino, 1984).

Densities

The liquid pycnometer method was used to determine the particle density of the starch powders using xylene as the displacement fluid (Okunlola and Odeku, 2011). The bulk density of each starch powder at zero pressure (loose density) was determined by pouring 10 g of the powder at an angle of 45º through a funnel into a glass measuring cylinder with a diameter of 21 mm and a volume of 50 ml. The tapped density was determined by applying 100 taps to 10g of each of the starch samples in a 100-mL graduated cylinder at a standardized rate of 30 taps per minute.

Flowability

The flowability of the starches was assessed using the Hausner's ratio and the Carr's index. The Hausner's ratio was determined as the ratio of the initial bulk volume to the tapped volume while the Carr's index (% compressibility) was calculated as follows:

$$\text{Carr Index} = \frac{\text{tapped index} - \text{bulk density}}{\text{tapped index}} \times 100 \quad (2)$$

To determine the angle of repose**,** an open-ended cylinder of diameter 2.8cm was placed on a base of similar diameter. 10g of starch powder was allowed to flow through a funnel, under the force of gravity, to form a conical heap. The angle of repose was calculated from equation (3):

$$tan\,\theta = h/r \quad (3)$$

where *h* is the height of powder and *r* is the radius of the base of the cone. The angle of repose was calculated from a mean of three determinations.

pH analysis
The pH of 1% w/v aqueous slurry of the native and modified starches was determined using a pH meter (Phillips PHS-25CW Microprocessor pH/mV meter).

Viscosity
The viscosity of 1% w/v aqueous slurry of each of the native and modified breadfruit starches was determined using Brookfield rheometer (DV-II+ Pro model, Brookfield Engineering, USA) using CPE 40 and spindle sizes of 2 and 4 at 27 ± 2ºC.

Preparation of bilayer tablets of ibuprofen
Formulation of Fast Release Layer

The fast release layer was prepared by uniformly mixing ibuprofen (50%w/w) with carboxymethylated breadfruit starch or sodium starch glycolate (5.0 and 7.5%w/w), aspartame (1%w/w), amaranth colorant (1%w/w), magnesium stearate (1%w/w), talc (2%w/w) and microcrystalline cellulose, MCC (to 100%) in a planetary mixer (Model A120, Hobart Manufacturing Co, UK). Magnesium stearate and talc were then added followed by mixing for another 3 min.

Formulation of Sustained Release Layer
The sustained release layer was prepared by wet granulation method. Ibuprofen (74%w/w), acid-modified breadfruit starch or HPMC (17%w/w), sodium carboxymethylcellulose were weighed and passed through a sieve (250μm), dry mixed for 5 min in a planetary mixer (Model A120, Hobart Manufacturing Co, UK) and then moistened with PVP (4%w/w), dissolved in appropriate amount of propylene glycol, to produce granules. Massing was continued for another 5 min and the wet masses were granulated by passing them manually through a mesh 12 sieve (1400 μm). The granules were then dried in a hot air oven for 18 h. The dried granules were screened through a mesh 16 sieve (1000 μm) and stored in an airtight container. The total dose of ibuprofen in the sustained release formulation was calculated as follows (Nabin, 2012):
Loading dose (DL) = 200 mg
To calculate the maintenance dose:
$Dt = DL (1+ 0.693* T/t_{1/2})$
where Dt = the total dose of the drug; T = time in hours during which the sustained release is desired = 8h; $t_{1/2}$ = half-life of ibuprofen = 3 h
Dt = 200 (1+ 0.693 * (8/3) = 200 * 1 + (0.693 * 2.67)
= 200 * (1 + 1.65031)
= 570.062 mg.
Sustained release dose = 570.062 – 200 = 370.062 mg

Compression of bi-layer tablets of ibuprofen
Quantities of the fast release layer formulation, F_1 - F_4 (400 mg) was compressed on a Carver hydraulic press (model) using a 10 mm die and flat-faced punch at an initial compression pressure of 56.5 Mpa for 30 seconds. Over this compressed layer, granules of the sustained release layer S_1 or S_2 (500 mg) was placed and final compression was at 113 Mpa pressure for 30 s to form bi-layer tablets with the formulation combinations: F_1S_1, F_1S_2, F_2S_1, F_2S_2, F_3S_1, F_3S_2, F_4S_1, F_4S_2,

Evaluation of bi-layer tablets

Tablet Weight and Thickness
Ten tablets were selected at random from each batch and their average weight was determined within ± 1mg. Using a micrometer screw gauge, the thickness of ten tablets was measured within ± 0.01mm.

Mechanical Strength
The crushing strength of the tablets were determined at room temperature by diametral compression using a tablet hardness tester. The percent friability of the tablets was determined using a friabilator (DBK Instruments, England) operated at 25 rpm for 4 minutes.

Assay of drug content
Ten tablets were crushed and dissolved in phosphate buffer pH 6.8 and filtered. The filtrate was analyzed using a UV/Visible Spectrophotometer (Spectrumlab 752s, China) at wavelength 270 nm to determine the amount of ibuprofen in the tablets.

Release properties
The disintegration time of the tablets was determined in distilled water at 37±0.5 ºC using a disintegration tester (DBK Instruments, England). Determinations were done in triplicate. The dissolution test was carried out on tablets using the USPXX III basket method (DBK-Dissolution rate test apparatus, England) rotated at 100 rpm in 800 mL of phosphate buffer pH 6.8 for six hours. Samples (10 mL) were withdrawn at intervals and replaced with equal amounts of fresh medium. The sample was diluted and the amount of ibuprofen released was determined at wavelength of 270 nm using a UV/Visible Spectrophotometer (Spectrumlab 752S, China).

Kinetic models of drug release

The results of the drug release for the formulations were fitted to zero order, first order ($\ln Qt = \ln Q_0 + K_1 t$), Higuchi ($Q = K_H\sqrt{t}$), Hixon-Crowell ($Q_0^{1/3} - Q_t^{1/3} = K\,t$), Korsemeyer – Peppas ($Q_t / Q_\infty = K\,t^n$) and Hopfenberg kinetic equations. The model of best fit was identified based on the values of the correlation coefficients.

Statistical analysis

Statistical analysis was done to compare the effects of the starches on the tablet properties using a computer software GraphPad Prism© 4 (Graphpad Software Inc. San Diego, CA, USA). Tukey-Kramer multiple comparison tests were used to compare the differences between the batches es. At 95% confidence interval, probability, p values less than or equal to 0.05 were considered significant.

Results and discussions

Characterization of native and modified Breadfruit starches

The yield of the extracted breadfruit starch was 19.23%w/w. This is in agreement with literature and confirms the efficiency of the extraction method (Rincon and Padilla, 2004). The degree of substitution of the carboxymethylated starch was 2.817. The degree of substitution indicates the number of the hydroxyl groups of the anhydroglucose unit that had been substituted. The high value obtained indicates potential for high swelling due to the introduction of the hydrophilic carboxymethyl groups (Heinze *et al*, 1999). The results of the material and physicochemical properties of the starches are presented in Table 1. Microscopic analysis of the starch granules revealed that the native breadfruit starch had ovoid shapes with size of 10.82 ± 5.72 µm. Modification by carboxymethylation and acid-hydrolysis resulted in larger granules with irregular shape with sizes of 134.30 ± 81.86 and 44.03 ± 28.24 µm, respectively.

The FTIR spectra of the starches are presented in Figure 1.

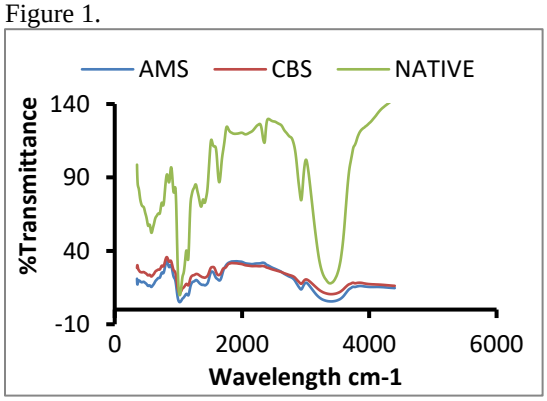

Figure 1. FTIR Analysis of native, carboxymethylated (CBS) and acid modified (AMS) breadfruit starches

The spectra of the acid modified and carboxymethylated breadfruit starches showed significant changes in comparison to the native form. There was reduction in intensity of the absorption band at about 3400cm^{-1} of the carboxymethylated breadfruit starch indicating the substitution of the hydroxyl groups with the carboxymethyl groups. For the acid modified starch, the stretching -OH (3396cm^{-1}) and the stretching -CH at 2920cm^{-1} confirmed the hydrolysis of the glycosidic linkage in the native starch. The XRD spectra of the native and modified starches are presented in Figure 2. These revealed that the relative crystallinity of the native starch was reduced by acid hydrolysis. Also, the reduction in high peaks in the carboxymethylated starch indicated a loss in crystallinity of the native starch and an increase in amorphousness due to carboxymethylation.

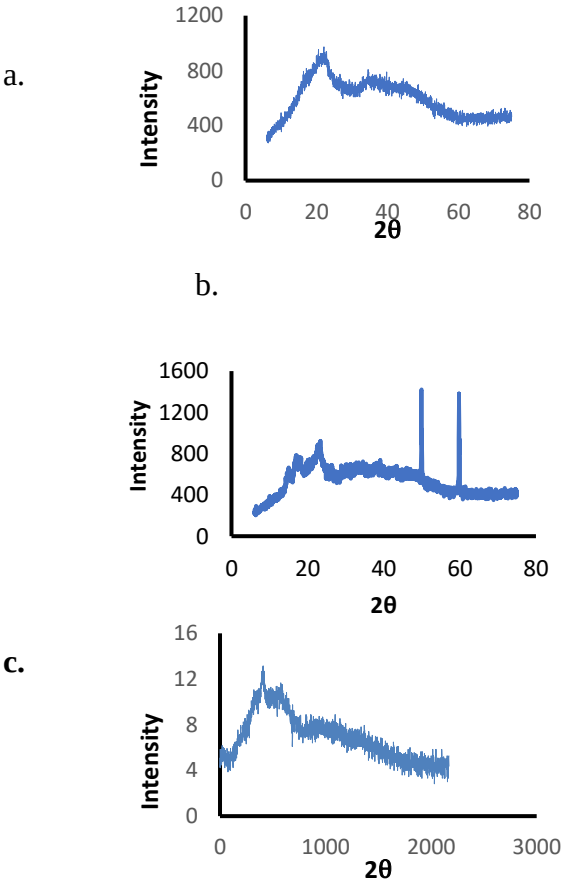

Figure 2: XRD Analysis for (a) native, (b) carboxymethylated and (c) acid modified (AMS) breadfruit starches

This loss in crystallinity could be attributed to the effect of the alkaline environment and water during the modification. These XRD results conform to those obtained from the FTIR spectroscopy. The reduction of crystallinity and increase in amorphousness of the carboxymethylated starches is expected to result in an increase in its swelling properties compared to the native starch.

Bulk density of a material is the ratio of the mass to volume (including all the interparticulate void volume) of an untapped powder. Tapped density however, is the bulk density of the powder after a specified compaction, usually involving the vibration of its container. Tapped density indicates the rate and extent of packing that would be experienced by a material during various unit operations of tableting.
Particle density has been observed to affect the compaction behaviour of powders, as dense, hard materials, may require high compression to produce cohesive, but less friable products (Okunlola and Odeku, 2009). The particle density of the starches were ranked in the order of Carboxymethylated breadfruit starch >Native breadfruit starch > Acid modified breadfruit starch. On the other hand, the bulk and tapped density were in the order Carboxymethylated > Acid modified > Native starch.
Carr's index, Hausner's ratio and angle of repose are parameters used to define the flow properties of a powder. A Carr's index ranking of Native > Carboxymethylated > Acid modified starch was observed while the ranking of the Hausner' ratio was Carboxymethylated > Native > Acid modified starch. This showed that the flow properties of the starch was enhanced by modification. The values of angle of repose, a qualitative measure of the flow properties of a powder, were in the order: Native > Acid modified > Carboxymethylated starch, confirming improvement in the flow properties of the modified starches. The swelling index of the acid modified and carboxymethylated breadfruit starch increased when compared to the native breadfruit starch. Modification of starch by carboxymethylation produced starch with a significant increase in swelling power. This is due to the introduction of hydrophilic carboxymethyl groups into the starch molecules. This increase in water penetration into the starch granules is associated with higher swelling of the starch granules and shows the potential of the carboxymethylated as superdisintegrants.
The viscosity values of the native and modified starches are presented in Table 2. The results revealed only a slight increase in the viscosity of the modified starches when compared to the native form.
Generally, at constant spindle size, increase in speed resulted in decrease in viscosity of all starches.

Table 1: Material and physicochemical properties of native, carboxymethylated and acid-modified breadfruit starch

Starch	Particle size (µm)	Particle shape	Swelling index	pH	Particle density (gcm^{-3})	Bulk density (gcm^{-3})	Tapped density (gcm^{-3})	Carr's index (%)	Hausner's ratio	Angle of repose (°)
Native	10.82±5.72	ovoid	1.28±0.06	4.13	1.44±0.02	0.31±0.00	0.50±0.00	37.50	1.60	54.31±0.98
Acid-modified	134.30± 81.86	irregular	1.74±0.23	5.91	1.38±0.03	0.38±0.00	0.51±0.02	25.00	1.33	39.38±1.73
Carboxymethy-lated	44.03 ± 28.24	irregular	2.32±0.05	6.45	1.49±0.03	0.48±0.00	0.77±0.00	35.20	1.62	29.65±4.36

Table 2: Viscosity of native and modified breadfruit starches

Starch	Spindle size	Speed (rpm)	Viscosity (cPs)
Native	3	50	6.50
		100	5.00
	4	50	5.00
		100	4.00
Acid modified	3	50	7.50
		100	5.50
	4	50	7.00
		100	5.00
Carboxymethylated	3	50	7.50
		100	6.00
	4	50	7.00
		100	4.00

Evaluation of bilayer tablets of ibuprofen

Formulations for the immediate and sustained release layers that made up the bilayer tablets are presented in Table 3. Bi-layer tablets were prepared using the formulation combinations: F_1S_1, F_1S_2, F_2S_1, F_2S_2, F_3S_1, F_3S_2, F_4S_1, F_4S_2. The tablet properties of the bilayer tablets of ibuprofen are presented in Table 4. All the tablets conformed to the United States Pharmacopeia (USP) specifications for weight variation as they were within the limits of ± 5.0%.

Table 3: Formulations for the immediate and sustained-release layers of the bi-layer tablet of ibuprofen

Fast Release Layer				
Ingredient (mg)	F1	F2	F3	F4
Ibuprofen	200	200	200	200
Carboxymethylated breadfruit starch	20.0	30.0	-	-
Sodium starch glycollate	-	-	20.0	30.0
Aspartame	4.0	4.0	4.0	4.0
Talc	8.0	8.0	8.0	8.0
Amaranth	4.0	4.0	4.0	4.0
Magnesium stearate	4.0	4.0	4.0	4.0
Microcrystalline cellulose (MCC) to	400	400	400	400

Sustained Release Layer		
Ingredient (mg)	S1	S2
Ibuprofen	370	370
Acid-modified breadfruit starch	85	-
HPMC	-	85
PVP	20	20
Sodium carboxymethyl cellulose	25	25

The ranking of the crushing strength for the eight batches was in the order of $F_4S_1 > F_3S_1 > F_2S_1 > F_4S_2 > F_1S_2 > F_3S_2 > F_1S_1$. Generally, tablets containing the acid modified breadfruit starches (S_1) had higher crushing strength values compared to those containing HPMC (S_2) except for batch F_1S_1. Acid modification have been shown to impart higher mechanical strength (Okunlola and Odeku, 2009). Also, it was observed that with increase in concentration of the carboxymethylated starch, the crushing strength increased suggesting that higher concentrations of the modified breadfruit starches confered mechanical strength to the tablets.

Friability testing is used to test the durability of tablets during packaging processes and transit. The United States Pharmacopeia states an acceptable friability limit of ≤ 1%. However, all the batches had friability values greater than 1%, including those containing the standards.

Disintegration time assesses the time taken for the drug to break up into granules under carefully specified conditions. The bioavailability of an orally taken drug depends on its disintegration time.

Table 4: Mechanical and release properties of ibuprofen bi-layer tablets (mean ± standard deviation, n =3)

Batch	Formulation	Average weight (g)	Tablet thickness (cm)	Crushing strength (MNm^{-2})	Friability (%)	Disintegration time (min)		t_{80} (h)
						Immediate release layer	Sustained release layer	
1	F_1S_1	0.921±0.027	0.797±0.038	81.00±14.65	1.967±0.071	10.37 ± 0.04	> 480.00	5.70
2	F_2S_1	0.918±0.014	0.806±0.030	116.90±3.61	1.145±1.752	5.08 ± 0.00	> 480.00	9.00
3	F_3S_1	0.922±0.025	0.821±0.025	119.53±4.83	1.486±0.001	2.04 ± 0.00	> 480.00	5.50
4	F_4S_1	0.920±0.028	0.878±0.029	128.53±13.66	1.619±0.129	1.00 ± 0.00	> 480.00	4.50
5	F_1S_2	0.922±0.026	0.844±0.030	113.53±6.91	2.021±0.147	12.40 ± 0.03	191.34 ±1.61	4.40
6	F_2S_2	0.918±0.012	0.862±0.013	115.73±5.65	1.393±0.417	4.26 ± 1.32	185.44 ± 0.06	9.40
7	F_3S_2	0.920±0.022	0.858±0.024	102.33±4.97	1.954±0.298	4.06 ± 0.32	185.64 ± 4.84	4.50
8	F_4S_2	0.917±0.016	0.853±0.019	115.77±4.67	1.617±0.258	3.00 ± 0.03	179.95 ± 2.31	5.20

For the immediate release layer, the disintegration time was in the order $F_1S_2 > F_1S_1 > F_2S_1 > F_2S_2 > F_3S_2 > F_4S_2 > F_3S_1 > F_4S_1$. All the tablets met the British Pharmacopeia specifications for the disintegration of an uncoated tablets (≤15 min). However, tablets containing the carboxymethylated breadfruit starch (F_1 and F_2) had longer disintegration times compared to those containing the standard SSG (F_3 and F_4). It was observed that the higher the concentration of the immediate-release polymer, the shorter was the disintegration times. The ranking of the disintegration time for the sustained release layer was : $F_1S_1 = F_2S_1 = F_3S_1 = F_4S_1 > F_1S_2 > F_2S_2 > F_3S_2 > F_4S_2$. Formulations containing the acid-modified starch showed significantly longer ($p \leq 0.05$) disintegration times of over 480 min.

Dissolution testing provides critical information on the *in-vitro* drug release profile of a drug, either in drug development or in quality control (such as in the assessment of batch to batch consistency of a group of tablets) and in determination of bioequivalence (Dressman *et al*, 1998). There was an initial sharp rise in the dissolution plot due to the fast release of ibuprofen from the immediate release layer (Figure 3). This was then followed by a more steady and sustained release. Tablets containing the acid modified starches generally showed a more sustained release. The time taken for 80% drug release (t_{80}) was obtained from the dissolution plots and were in the rank order: $F_2S_2 > F_2S_1 > F_1S_1 > F_3S_1 > F_4S_2 > F_4S_1 > F_3S_2 > F_1S_2$. This indicates that the bilayer tablets containing the acid modified starches generally had longer dissolution times compared to those containing HPMC as sustained release layer.

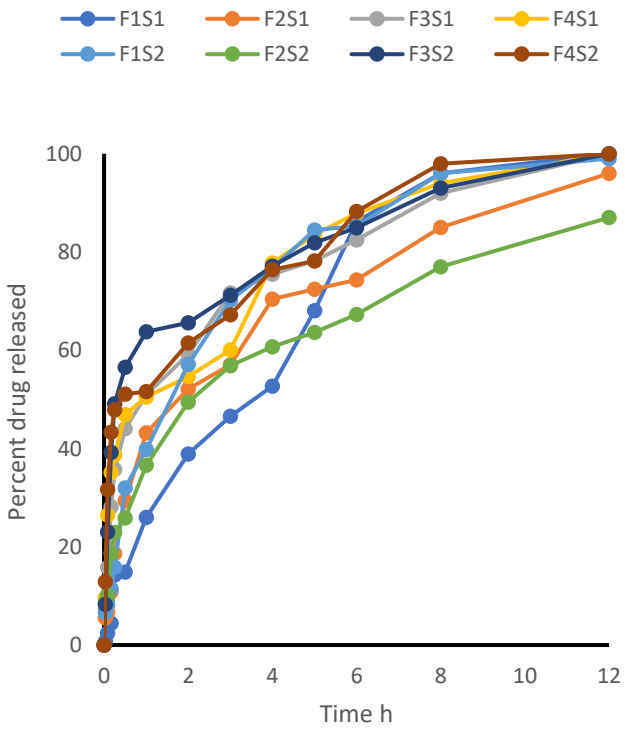

Figure 3: Dissolution plot of batches of ibuprofen bilayer tablets

The physicochemical properties of the drug and the polymer have been shown to govern the release of drug from formulations which could affect their release kinetics. The drug release kinetics of the batches were simulated using zero order, first order, Higuchi, Hixson-Crowell, Hopfenberg, Korsmeyer-Pepppas (Hixson-Crowell, 1931; Higuchi, 1961; Hopfenberg, 1976; Korsmeyer *et al*, 1983) and a. Drug release from batches B_1 - B_3 as well as B_5 and B_6 generally fitted the Hixson-Crowell model implying that the release is from a systems where there is a change in surface area and diameter of particles. Batches B_4 and B_7 fitted the First order kinetic model in which the drug released at each time is proportional to the residual drug inside the dosage form. On the other hand, only Formulations B_8 fitted the Hopfenberg kinetic model, which describes the release of drug from spherical formulations and is used to correlate the drug release from surface-eroding polymer so long as the surface remains constant during degradation process (Hopfenberg, 1976).

From the above study, the prepared bilayer tablets containing the carboxymethylated and acid-modified *Artocarpus altilis* starches achieved the objective of the research work; the sequential release of two layers of ibuprofen for immediate relief from pain, fever and inflammation as well as for sustained release. Conventional tablets of ibuprofen are formulated to be administered 3-4 times a day. This new bilayer formulation reduces the dosage frequency, thus, minimizes side effects and are cost effective. Furthermore, the mechanical strength of the bilayer tablets was enhanced by the starches, with only a few tablets having separation between their two layers.

Table 5: Correlation coefficients obtained using different kinetic models (n = 3)

Batch	Zero order	First order	Higuchi	Hixson-Crowell	Hopfenberg	Korsmeyer	
	R^2	R^2	R^2	R^2	R^2	R^2	n
B_1	0.9016	0.9076	0.9757	*0.9824	0.9714	0.9571	0.7958
B_2	0.8148	0.9644	0.9694	*0.9846	0.9350	0.9690	0.5100
B_3	0.7509	0.9173	0.9338	*0.9774	0.9294	0.9302	0.3877
B_4	0.7636	*0.9665	0.9258	0.9509	0.9623	0.9073	0.3214
B_5	0.8229	0.9816	0.9581	*0.9803	0.9263	0.9761	0.5117
B_6	0.8229	0.9504	0.9744	*0.9909	0.9487	0.9860	0.3972
B_7	0.6549	*0.9175	0.8520	0.9112	0.8673	0.8384	0.3294
B_8	0.7255	0.8894	0.8920	0.7405	*0.9461	0.9073	0.3214

*Highest correlation coefficient for batch

Conclusion

The preparation of bilayer tablets of ibuprofen using carboxymethylated and acid-hydrolysed starches of breadfruit (*Artocarpus altilis*) as novel excipients for immediate and sustained release revealed that bilayer tablets of ibuprofen containing the modified starches generally had higher crushing strengths than those containing SSG and HPMC. Carboxymethylated breadfruit starch produced tablets with fast disintegration though longer than those containing SSG.

Tablets containing the acid modified breadfruit starch as sustained release layer generally had longer dissolution times compared to those containing HPMC. Carboxymethylated and acid modified breadfruit starches can be used as alternative excipients for immediate and sustained release in the formulation of bilayer tablets of ibuprofen.

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