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Formulation of Gastroretentive Microballoons of Metoprolol Succinate Using Acetylated Cocoyam (*Xanthosoma sagittifolium*) Starch as a Sustained Release Polymer

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Gastroretentive microballoons of metoprolol succinate (an adrenergic beta receptor blocker) were formulated using acetylated starch from cocoyam (*Xanthosoma sagittifolium*) in order to release the drug at a controlled rate and increase bioavailability. Acetylated cocoyam starch (DS 1.106 ± 0.054) was characterized and used in various combinations with Eudragit S100 to produce microballoons of metoprolol succinate at varying polymer:drug ratios. The microballoons were characterized for morphology, entrapment efficiency, *in vitro* buoyancy and dissolution time (t_{50}). Metoprolol microballoons containing acetylated starch had higher entrapment efficiency and *in vitro* buoyancy (>12 h) than those containing Eudragit S100 alone. The dissolution time (t_{50}) increased with polymer: drug ratio with formulation of starch: Eudragit S100 1:3 showing sustained drug release (t_{50} = 185.50 min) at polymer:drug ratio 6:1 which was comparable to dissolution time of Eudragit S alone at a similar polymer: drug ratio. Acetylated cocoyam starch showed potential as a cheaper, alternative polymer in gastroretentive drug delivery systems for high entrapment, prolonged buoyancy and sustained drug release.

Keywords: Acetylation**,** Cocoyam starch**,** Gastroretentive drug delivery systems, Metoprolol succinate, Microballoons.

INTRODUCTION

Microballoons (also called hollow microspheres) can be described as spherically shaped particles with a void at the core (1). They are gastroretentive drug delivery systems operating on the basis of non-effervescent systems. Microballoons loaded with drug in their outer polymer shell are prepared by methods such as solvent evaporation or solvent diffusion/evaporation to create a hollow inner core. The active pharmaceutical ingredient is mixed with the selected polymer and dissolved in ethanol or dichloromethane solution. A stable emulsion is formed and the organic solvent is evaporated from the emulsion by increasing the temperature under pressure or by continuous stirring (2). The void at the core is created by the evaporation of the solvent which forms the hollow internal cavity in the microballoon formulation.

As the microballoon system floats on the gastric fluid, the active pharmaceutical ingredient is released slowly at a desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. The polymer type selected determines the flow properties as well as the release properties of the microballoons formed. Polymers used in the preparation of the microballoons include polylactic acid, Eudragit® S100, hydroxy propylmethyl cellulose, chitosan, acrylic, methyl cellulose, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene and cellulose acetate (2).

Cocoyam (*Xanthosoma sagittifolium*, family Araceae) is one of the most important staple foods in Africa, with Nigeria, Ghana and Cameroon contributing over 60% of the total African production (3). Cocoyam is a highly starchy food with its corm (the swollen underground storage stem of the plant) containing one of the highest amounts of starch. Cocoyam starch is biodegradable, low in cost and biocompatible (4). The potential of cocoyam starch as a pharmaceutical binder was investigated in paracetamol tablet formulations

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and reported to be comparable with those prepared with cornstarch BP (5). In another study, the bio-adhesive properties of native, pregelatinized and acetylated cocoyam starches were evaluated and found useful in targeted mucoadhesive drug delivery (6). Acetylation of native starch involves the esterification of the alpha- d- glucose units of the starch by nucleophilic reactions resulting in the substitution of the free proton of the hydrophilic hydroxyl groups on C_2, C_3 and C_6 with the hydrophobic acetyl group. The acetylated starch often shows an increase in hydrophobicity resulting in an increase in the shear strength as well as in heat and acid stability of the starch (7,8). Thus, in this study, the potential of acetylated cocoyam (*Xanthosoma sagittifolium*) starch would be evaluated as a sustained release polymer in microballoons of metoprolol succinate in comparison to the established polymer, Eudragit® S100.

Metoprolol is an adrenergic beta receptor blocker indicated in the management of heart failure, myocardial infarction, angina pectoris and hypertension It has an average half-life of 3 to 4 hours. It has a bioavailablity of 40-50% (immediate-release). The duration of action of metoprolol is 3 to 6 hours when taken orally. Hence, the development of metoprolol succinate microballoons as a gastro retentive formulation would be useful in order to release metoprolol succinate at a controlled rate, allowing more of the drug to be absorbed through the walls of the stomach and into system circulation (9).

EXPERIMENTAL

Materials

Cocoyam tubers (*Xanthosoma sagittifolium*) were obtained from Bodija Market, Ibadan, Oyo state, Nigeria. Metoprolol succinate was obtained from Xi'an Sgonek Biological Technology Co.Ltd, Xi'an City, China. Other materials used were anhydrous ethanol, acetone, acetic acid (Tedia Company Inc, Ohio, USA), pyridine, absolute ethanol (Sigma-Aldrich GmbH, Germany), potassium hydroxide, hydrochloric acid, phenolphthalein (Zayo-Sigma, Lagos, Nigeria), liquid paraffin, xylene, Eudragit® S100, dichloromethane, Tween 80 (BDH Limited, Poole, England).

Methods

Extraction of starch

The starch was extracted from cocoyam by peeling and cutting the tubers into smaller pieces followed by wet milling to obtain a slurry. The starch slurry was strained through a muslin cloth and the filtrate was left to settle. The supernatant was decanted at 12 h intervals and the starch slurry re-suspended in distilled water. Sodium meta-bisulphite was added to prevent colour change due to oxidation. The starch cake was collected after 72 h and dried in a hot air oven at 60 °C for 48 hours. The dried mass was pulverized and then screened through a sieve of 250 μm (8).

Acetylation of starch

Fifty grams of native starch was suspended in 550 mL of de-ionized water in a 2000 mL beaker. The suspension was pregelatinized by stirring at 80 °C for 30 min over a water bath. The pregelatinized starch was precipitated with one litre of anhydrous ethanol, stirring under a high shear homogenizer. The precipitated material was filtered and the residue washed with acetone, filtered again and dried. The dried powder was screened (sieve size 250 μm). Twenty five grams of the pregelatinized starch was dispersed in 200 g of pyridine in a 1 litre round- bottom flask. One hundred grams of acetic acid was added to the dispersion. The round bottom flask was dipped into an oil bath and rotated at low speed inside a fume cupboard. The temperature was maintained at 100 °C. The reaction was carried out for 4 h with continuous stirring. The reaction mixture was transferred to a beaker and cooled to room temperature to stop the reaction. The product was precipitated from 1300 mL of absolute ethanol under high shear homogenization. The precipitate was filtered, washed well with ethanol to remove the pyridine odour in the precipitate and then filtered again. It was dried in an oven and then screened using sieve size 250 μm (8, 10).

Determination of degree of substitution

One gram of acetylated starch mixed with 50 mL of 5% ethanol in a flask with a loose stopper. The mixture was stirred while heating in a water bath at 50 ^{0}C for 30 min. After cooling to room temperature, 40 mL of 0.5 N potassium hydroxide (KOH) solution was added to the mixture. The flask was fitted with a tight stopper and kept at room temperature with occasional shaking for 72 hours for complete saponification. An excess of alkali in solution was titrated with 0.5 N hydrochloric acid (HCl) solution using phenolphthalein as the indicator. A blank test was performed. The percent of acetyl group and degree of substitution (DS) were calculated as shown (10, 11) below:

$$Ac.grp\ (\%) = \frac{(Vb-VS) \times M_{HCl} \times 0.043 \times 100}{Sample\ weight\ (g)} \quad (1)$$

$$Degsub. = \frac{162 \times \%Acetyl\ group}{4300-(42 \times \%Acetyl\ group)} \quad (2)$$

Where Ac.grp (%) is % of acetyl groups, Degsub is the degree of substitution, Vb is the volume of blank (ml), Vs is the volume of sample (ml), 162 is the molecular weight of the anhydroglucose unit, 42 is the molecular weight of replaceable acetyl group and 4300 is the molecular weight of the acetyl group attached with 100 anhydroglucose units.

Characterization of native and acetylated cocoyam starches

Morphology

The shape and size of the native and acetylated starch granules were observed using a light microscope and a scanning electron microscope (Hitachi SU8030 FE-SEM Tokyo, Japan) at an accelerating potential of 5.0kV. All samples were supercoated with Au/Pd prior to examination.

Fourier Transform Infrared (FTIR) Analysis

The starches were analysed by FTIR (FTIR-Thermo Nicolet Nexus 870 Madison, WI, USA) using KBr in transmission mode and the transmission spectra were recorded using at least 32 scans with 8 cm^{-1} resolution in the range of 4000- 400 cm^{-1}.

Densities

The bulk density of the native cocoyam starch and acetylated cocoyam starch at zero pressure were determined by pouring 10 g of the powder at an angle of 45^o through a funnel into a 100 mL glass measuring cylinder. The bulk density was measured as the ratio of mass to volume occupied by the starch. The tapped density was measured by applying 100 taps to 10 g of the starch sample in a graduated cylinder at a standardized rate of 30 taps per minute from a height of 2.50 cm. The particle densities of the starches were determined by the pycnometer method using xylene as non- solvent. A 50 mL capacity pycnometer was weighed empty (W) and then filled with non- solvent and the excess wiped off. The weight of the pycnometer with non- solvent was determined (W1). The difference in weight was calculated (W2). A 2 g quantity of the sample was weighed (W3) and quantitatively transferred into the pycnometer. The excess non- solvent was wiped off and the pycnometer was weighed again (W4). The particle density was calculated from Equation 3.

$$\frac{W2W3}{50(W3-W4+W)}\ gcm^{-1} \quad (3)$$

Flowability

The flowability of the starches were assessed using the Hausner's ratio (HR) and Carr's index (CI).

$$HR = \frac{Tapped\ density}{Bulk\ Density} \quad (4)$$

$$CI = \frac{(Tapped\ density-Bulk\ Density)\ X\ 100}{Tapped\ density} \quad (5)$$

An open ended cylinder was placed on a base of similar diameter. Starch powder (5g) was allowed to flow freely through a funnel under gravity, to form a conical heap. The angle of repose was calculated from

Tan = h/r (6)

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

pH

The pH of 1%w/v starch slurry in deionized water was measured at 27.5±0.5^{0}C using a pH meter (Phillips S-25CW Microprocessor pH meter, China).

Viscosity

The viscosity of a 1 w/v% slurry of native and acetylated cocoyam starches was determined on Brookfield rheometer (DV-III+ pro model, Brookfield Engineering, USA) using spindle size 3 at speeds of 50 and 100 rpm.

Swelling index

Starch powder (5g) was placed in a 100-mL measuring cylinder and the volume occupied was noted (V_1). Deionised water (90 mL) was added; the dispersion was shaken for 2 min and then made up to volume with deionised water. The slurry was allowed to stand for 24 h before sedimentation volume was read (V_2). The swelling index was calculated as V_2/V_1.

Preparation of microballoons of metoprolol succinate using the solvent evaporation method

Microballoons were prepared by the solvent evaporation technique. A weighed amount of drug (100 mg per formulation) and Eudragit S100 or combination of acetylated starch:Eudragit S100 were dissolved in a mixture of ethanol (10 ml) and dichloromethane (10 m at room temperature, 27.5±0.5^{0}C). The drug-polymer dispersion was added drop-wise into 250 mL of water containing 0.01% Tween 80 maintained at a temperature of 40–50 °C and subsequently stirred at an agitation speed of 500 rpm to allow the volatile solvent to evaporate. The formulated microballoons were filtered, washed with distilled water, and dried at 40 °C. Nine batches of microballoons were formulated and are shown in Table 1.

Table 1: Composition of metoprolol-loaded microballoons containing acetylated cocoyam starch and Eudragit S100

Formulation	Polymer type (Starch: Eud*)	Polymer: drug ratio
F1	0:1	2:1
F2	0:1	4:1
F3	0:1	6:1
F4	1:2	2:1
F5	1:2	4:1
F6	1:2	6:1
F7	1:3	2:1
F8	1:3	4:1
F9	1:3	6:1

Key: *Eud = Eudragit® S100

Evaluation of microballoons

Percentage Yield

The percentage yield of the hollow microspheres was calculated using the following equation.

$$Yield = M/Mo\ x\ 100 \qquad (7)$$

Where M = weight of beads, Mo = total expected weight of drug and polymer.

Particle size and shape

The morphology of the sample was evaluated using a scanning electron microscope (Hitachi SU8030 FE-SEM Tokyo, Japan) at an accelerating potential of 5.0kV.All samples were coated with Au/Pd prior to examination. The mean particle size of microballoons was determined using an optical microscope (BH-2 BHS, Olympus, Tokyo, Japan).

Fourier Transform Infrared (FTIR) analysis

The pure drug, acetylated starch, Eudragit S100 and microballoons were analysed by FT-IR in transmission model (Buckscientific, M530 model, USA). The transmission spectra were recorded using at least 32 scans with 8 cm^{-1} resolution in the spectral range of 4000-400 cm^{-1}.

Porosity

The porosity of the microballoons was determined using the density values in Equation 8.

$$Porosity\ \varepsilon\ =\ (1-\ Pb\ /Pt\ )\ x\ 100 \qquad (8)$$

Where Pb is bulk density and Pt is the true density.

Flowability

The flowability of the microballoons was assessed using the Hausner's ratio, the Carr's index and the angle of repose. 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 using Equations 4 and 5 while angle of repose was calculated using Equation 6.

Entrapment efficiency

The amount of drug entrapped was estimated by crushing the quantity of microballoons containing 50 mg of the drug in 100 mL of 0.1N HCl (pH 1.2) inside a 100 ml volumetric flask. The solution was filtered and the absorbance was measured after suitable dilution, spectrophotometrically (UV-1700 Pharmaspec Shimadzu, Japan) at 270 nm. The amount of the drug entrapped in the microballoons was calculated using the following:

$$E.E.=\frac{Drug\ amount}{Theoretical\ drug\ load}\times 100 \quad (9)$$

Where E.E. is the entrapment efficiency and drug amount is the actual amount of drug present.

In vitro buoyancy

Microballoons (100 mg) were spread over the surface of a USP dissolution apparatus (type I) filled with 900 ml simulated gastric fluid of pH 1.2 containing 0.02% Tween 20. The medium was agitated by rotating the paddle at 100 rpm for 12 h. The floating and the settled portions of microballoons were recovered separately. The microballoons were air-dried and weighed. Percentage buoyancy was calculated as the ratio of the mass of the microballoons that remained floating (W_f) to the total mass of microballoons (W) as shown in Equation 10:

$$\frac{Wf}{W}X\ 100 \qquad (10)$$

In vitro drug release studies

The release rate of microballoons was determined using the United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of microballoons equivalent to 25 mg dose of drug was placed in the basket of dissolution apparatus containing dissolution medium (0.1N HCl pH 1.2). The dissolution fluid was maintained at 37 ± 1 °C and rotation speed at 50 rpm. Samples (10 mL) were withdrawn at different intervals and replaced with equal amount of the dissolution medium. The amount of metoprolol succinate released was determined at wavelength 270 nm, using Spectrumlab75s UV-VIS spectrophotometer using the Beer-Lambert equation obtained from the standard calibration curve.

Statistical analysis was carried out using analysis of variance (ANOVA) on a computer software GraphPad Prism© 4 (Graphpad Software Inc. San Diego, CA, USA). At 95% confidence interval, probability, p values less than or equal to 0.05 were considered significant.

RESULTS AND DISCUSSIONS

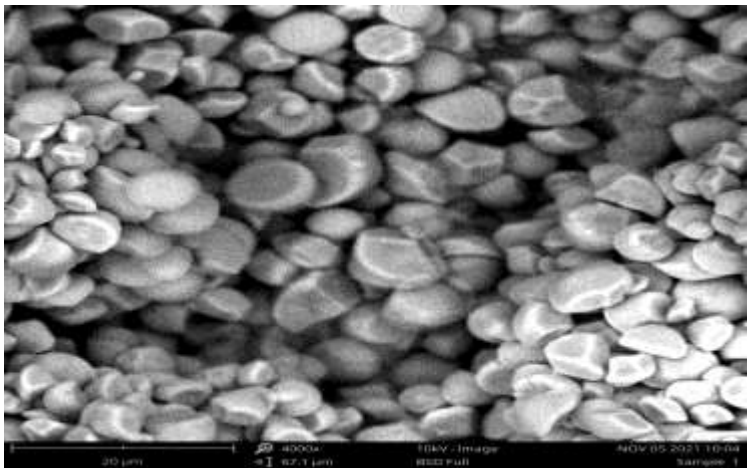
Characterization of native and acetylated cocoyam starches

The yield of cocoyam starch was 34.48%w/w on a dry weight basis. The yield is considered to be satisfactory in comparison to that reported in literature (12). On modification by acetylation, the yield of acetylated starch was 85%w/w. The acetyl content of the modified cocoyam starch was 9.747 ± 1.184% with degree of substitution

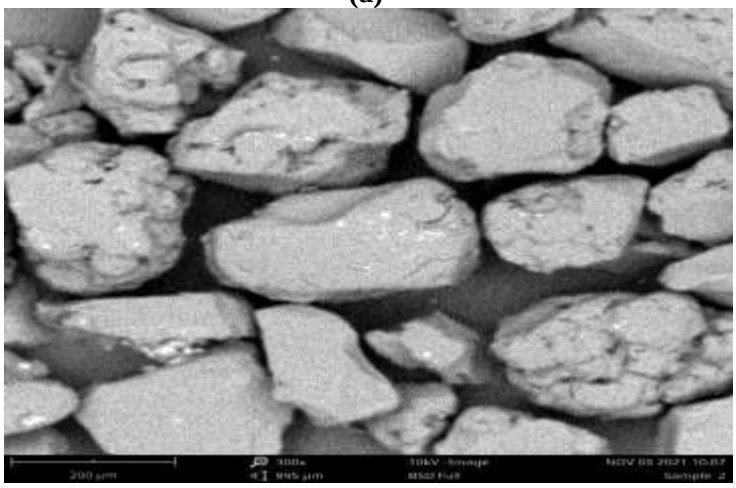
of 1.106 ± 0.054. It has been reported that acetylation increases the lipophilicity of any starch compound (10). The reduction in aqueous solubility could be attributed to decrease in hydrogen bonding due to loss of hydroxyl groups and their replacement with the less polar acetyl groups. As the degree of substitution of hydroxyl groups for acetyl groups on starch molecules increases, starch moves from being hydrophilic to having increased lipophilic nature (13). The number of acetyl groups incorporated into the starch molecule is dependent on the reactant concentration, pH, reaction time, presence of catalysts as well as the nature of the starch and its origin (10). The values of degree of substitution greater than 2 have been of research interest for controlled drug delivery (14). However, acetylated starch of modest degree of substitution less than 2 has been employed in formulation of films and microparticles in other studies (15).

Morphology

The scanning electron micrographs (SEM) images of the native and acetylated cocoyam starches are presented in Figure 1. The SEM image of native starch showed ovoid granules with smooth surfaces. The mean granule size was 26.22±1.08µm. The SEM images of the acetylated starches showed that the modification process of acetylation resulted in disruption in the granular structure of the native starch, producing significantly larger granules (176.85± 6.25µm) with rough and porous surfaces and irregular shapes.



(a)



(b)

Figure 1: SEM of (a), native and (b), acetylated Cocoyam starches mg (×300 magnification)

FTIR Analysis

The FTIR spectra of both the native and modified starches are presented in Figure 2 and these showed characteristic broad absorption bands of C-O-H stretching at 3550- 3412 cm^{-1}. Similarly, the bands at 1650-1850 cm^{-1} attributed to characteristic C=O stretching on the anhydro-glucose ring were present in both native and modified starch but were of different peak heights signifying modification of the starch.

Densities and flow properties

The values of densities, Carr's index, Hausner's ratio, angle of repose, swelling index and pH are presented in Table 2. Substitution of hydroxyl group (molecular weight= 17.007g/mol) with acetyl group (molecular weight= 43.045g/mol) is expected to cause an increase in densities of the starch polymer following acetylation as there is a direct relationship between molecular weight of polymers and density of polymers (16).

The Hausner's ratio (tapped to bulk density) provides an indication of the degree of densification. On the other hand, Carr's index is a measure of compressibility of a powder; the higher the Carr's index, the better the compressibility but the poorer the flowability (17). The results of Carr's index, Hausner's ratio revealed that modification of native cocoyam starch by acetylation produced starches with slightly improved flow. This was further confirmed by the values of the angle of repose.

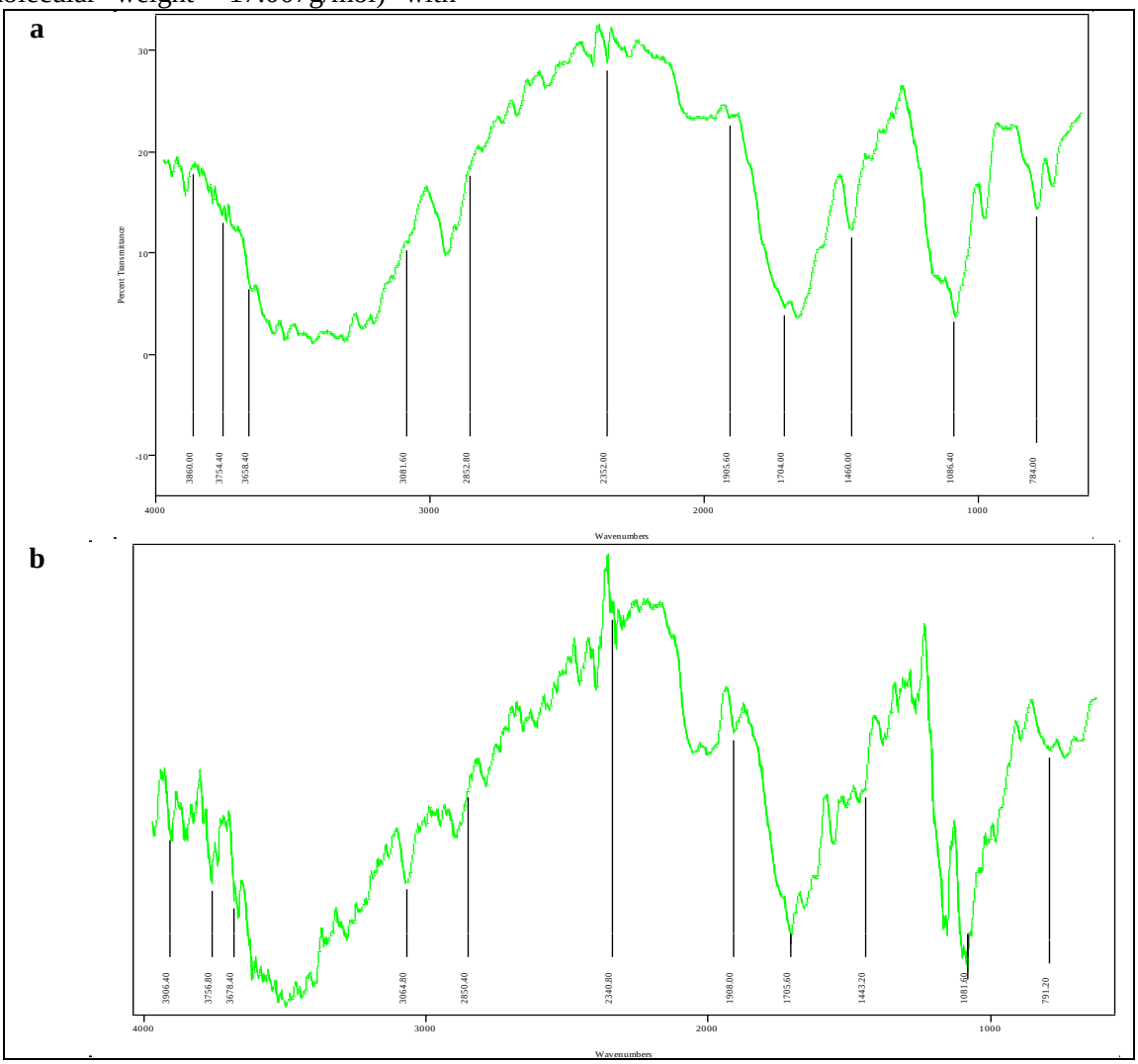


Figure 2: FTIR spectra of (a), native and (b), acetylated cocoyam starches

Swelling

There was an increase in the swelling capacity of cocoyam starch after acetylation, compared to the native starch. This is in line with previous research which has shown that acetylation of starch increases water absorption capacity and swelling power, making starch more useful industrially (Adewumi *et al*, 2020). The increased swelling index of starch is also important for it to exhibit the required polymer properties in a formulation intended to be retained on the gastric fluid for a while. The increased swelling capacity may be related to the degree of substitution (DS < 2) in the acetylation process.

pH

The acetylation of starch increased the acidity of cocoyam starch as expected (18). This is reflected in the reduced pH of acetylated starch in comparison with native cocoyam starch, which makes it suitable as an excipient for gastroretentive drug delivery.

Table 2: Morphology and material properties of native and acetylated cocoyam starches (mean ± standard deviation, n=3)

Cocoyam starch	**Native**	**Acetylated**
Particle shape	Ovoid	Irregular
Particle size (µm)	26.22 ±1.08	176.85±6.25
Particle density*	0.861±0.001	1.511 ±0.043
Bulk density*	0.429 ±0.010	0.698 ± 0.014
Tapped density*	0.690 ±0.024	1.225 ± 0.043
Hausner's ratio	1.61 ±0.03	1.76 ±0.10
Carr's Index (%)	37.86±1.13	42.97±3.21
Angle of repose	68.19±0.51	39.60 ±0.56
Swelling index	0.75 ±0.00	4.88 ±0.37
pH	5.80± 0.00	4.17 ±0.20

*gcm^{-3}

Viscosity

The values of viscosity of the starches are presented in Table 3. Modification of cocoyam starch by acetylation resulted in only a slight increase in viscosity even with increase in speed

Table 3: Viscosity properties of native and acetylated cocoyam starch at spindle size 3 with varying speeds (mean±standard deviation, n=3)

Starch	Speed (rpm)	Viscosity (cP)
Native	50	5.0±0.3
	100	7.5±0.5
Acetylated	50	6.0±0.4
	100	9.0±0.5

Characterization of metoprolol microballoons

Microballoons were prepared by the solvent evaporation method, using Eudragit S100, an established hydrophobic polymer, either alone or in combination with the novel acetylated cocoyam starch in order to manipulate the formulation yield, buoyancy, encapsulation efficiency and release kinetics of metoprolol from the formulations. The central hollow core of microballoons is most likely due to the difference in diffusion rate and miscibility of ethanol and dichloromethane in aqueous phase. In the primary stage of microballoons formation, ethanol diffuses readily from the aqueous phase due to its high miscibility followed by the slow diffusion of dichloromethane leading to the development of the central hollow space filled with water. This water evaporated from the cavity through the porous surface while drying at controlled temperature, eventually forming hollow microballoons (19). The properties of the microballoons including yield, bulk and tapped densities, Carr's index, Hausner's ratio, porosity, entrapment efficiency, *in vitro* buoyancy and dissolution times (t_{50}) were determined and the results are presented in Table 4.

Table 4: Properties of metoprolol-loaded microballoon formulations (mean±sd, n= 3)

Formulation	Yield (%)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's Ratio	Carr's index (%)	Porosity (%)	Entrapment efficiency (%)	*In vitro* buoyancy (%)	t_{50} (min)
F1	76.33± 0.47	0.25 ± 0.00	0.38 ± 0.00	1.52 ± 0.04	34.21 ± 0.00	34.21 ± 0.00	70.95 ± 0.18	35.01 ± 1.15	>240.00
F2	90.20± 1.50	0.40 ± 0.00	0.71 ± 0.00	1.77 ± 0.00	43.66 ± 0.00	33.66 ± 0.00	63.47 ± 0.18	43.30 ± 1.66	180.20 ±9.15
F3	96.00± 1.00	0.91 ± 0.00	1.100 ± 0.00	1.21 ± 0.00	17.27 ± 0.00	29.00 ± 0.00	61.85 ± 0.00	51.75± 1.43	185.00 ±8.10
F4	73.33± 0.80	0.42 ± 0.00	0.48 ± 0.00	1.14 ± 0.02	12.50 ± 0.00	10.50 ± 0.00	58.10 ± 0.35	73.44 ± 0.00	125.50 ±11.65
F5	74.00± 0.95	0.50 ± 0.00	0.56 ± 0.00	1.12 ± 0.00	10.71 ± 0.00	12.71 ± 0.00	69.05 ± 0.00	75.57 ± 2.86	130.50 ±9.70
F6	97.00± 3.22	0.80 ± 0.00	0.83 ± 0.00	1.04 ± 0.05	3.61 ± 0.00	13.61 ± 0.00	71.57 ± 0.00	89.16 ±1.95	166.60 ±9.00
F7	72.70± 0.50	0.25 ± 0.00	0.33 ± 0.00	1.32 ± 0.00	24.24 ± 0.00	23.24 ± 0.00	72.07 ± 0.35	67.475 ± 1.94	108.00 ±10.20
F8	87.20± 4.00	0.33 ± 0.00	0.43 ± 0.00	1.30 ± 0.00	23.26 ± 0.00	24.26 ± 0.00	72.32 ± 0.35	77.86 ± 1.61	160.00 ±15.77
F9	92.43 ± 3.77	0.34 ± 0.00	0.50 ± 0.00	1.47 ± 0.00	32.00 ± 0.00	32.00 ± 0.00	80.55 ± 0.00	79.37 ± 1.58	185.50 ±7.55

Morphology

The SEM image of microballoons containing the acetylated starch and Eudragit S100 are presented in Figure 3 and this revealed hollow structures with near spherical shape. The microballoons had rough surfaces and some degree of porosity with visible large holes on the surface. The mean size of microballoons was 190.00 ± 11.80 µm.

FTIR

The FTIR spectra of the pristine drug, the cocoyam starch, Eudragit S100 and microballoons showed there was no interaction between drug and the acetylated starch and Eudragit S100, suggesting that the drug was well entrapped into the polymer.

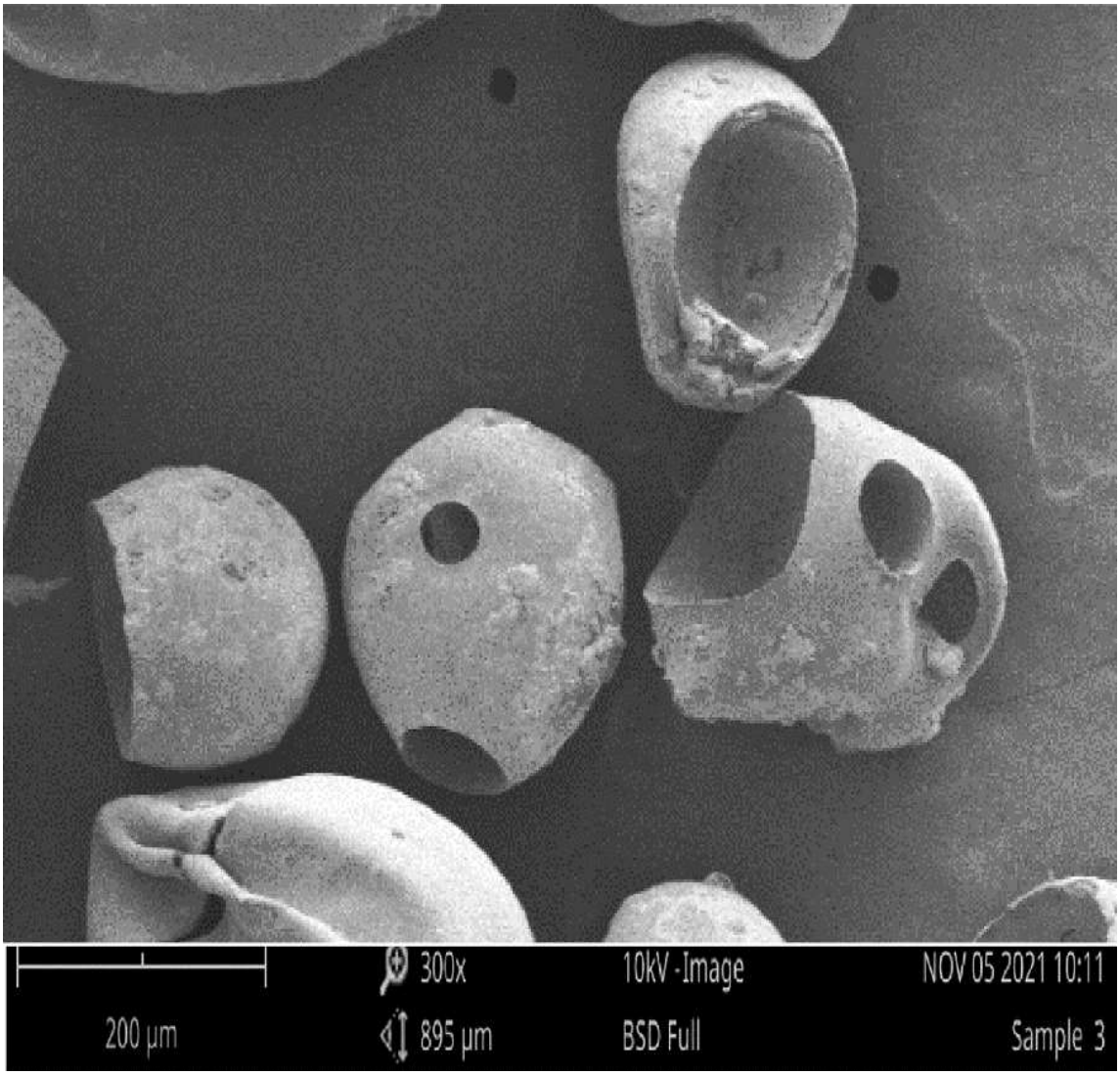


Figure 3. SEM images of microballoons (×300 magnification)

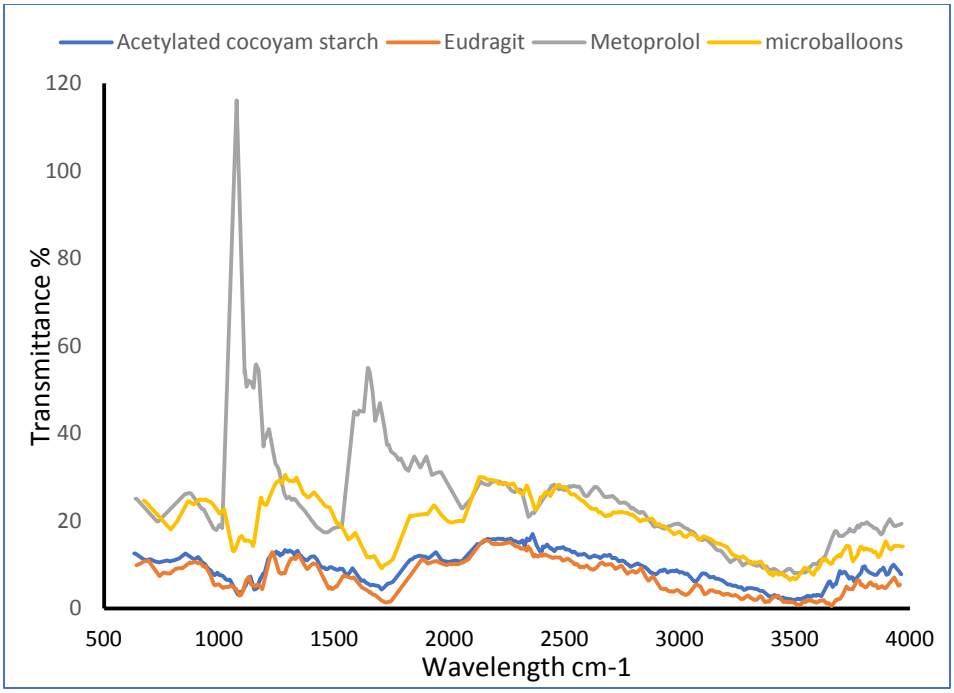


Figure 4. FTIR spectra of (a), metoprolol succinate; (b), acetylated cocoyam starch; (c) Eudragit S100; (d), microballoon

Yield

Microballoons were weighed after drying, and the percentage yield of microballoons containing acetylated cocoyam starch was high and comparable with those containing Eudragit S100 alone. Microballoons with higher acetylated cocoyam starch content showed percentage yield ranging from 73.33±0.80 to 97.00±3.77%. Generally, the percentage yield of the microballoons increased with polymer:drug ratio.

Densities and flow properties of microballoons

From the values of the bulk and tapped densities the Carr's index and Hausner's were determined. Carr's index values of <10 or Hausner's ratio of <1.11 is considered 'excellent' flow whereas CI > 38 or HR > 1.60 is considered 'very poor' flow. The results revealed good flow properties for those formulations containing the combination of starch and Eudragit S100 (F4 - F9). In particular, the flow properties of the formulations F4 - F6 containing starch: Eudragit S100 at ratio 1:2 improved with the content of acetylated cocoyam starch.

Porosity

Characteristic hollow cavities were observed in the structure of the microballoons. The porosity is known to contribute to the floating behaviour of the microballoons (19, 20). The porosity was ranked in the order F4 < F5 < F6 < F7 < F8 < F9 < F1 < F2 < F3. Porosity appears to increase with polymer:drug ratio but reduced with the amount of acetylated cocoyam starch. Generally, the formulations containing Eudragit S100 had the highest porosity.

Entrapment efficiency

The drug entrapment efficiency of all formulation batches were found to be in the range of 58.10 ± 0.35% to 80.55 ± 0.00 %. Microballoons containing acetylated cocoyam starch showed significantly higher ($p<0.05$) entrapment than those containing eudragit only. For formulations containing starch and Eudragit, S100 the entrapment efficiency increased with

polymer:drug ratio. Drug encapsulation efficiency was found to increase with amount of polymer due to an increase in cross linking structure and viscosity of internal phase resulting in reduced migration of drug in the aqueous phase (19). On the other hand, entrapment efficiency reduced with polymer:drug ratio in microballoons containing Eudragit S100 only.

In vitro buoyancy

The microballoons showed a floating ability or buoyancy varying between 35.01 ±1.15 % and 87.86± 1.61 % for up to 12 h. The buoyancy is attributed to the air core hollow structure of microballoons formed after the evaporation of solvent (20). The buoyancy increased with content of acetylated starch due to swelling property imparted to the formulations as well as the hollow core formation which made their densities less than that of gastric fluid. Formulation F8 containing acetylated starch:Eudragit S100 1:3 gave the highest percentage buoyancy. Thus, it may be deduced that these microballoons can float in gastric fluid, retarding the passage of the microballoons into the intestinal region and increasing their residence time in the stomach.

Dissolution time

The dissolution study was carried out to determine the release time of metoprolol from all the formulations in simulated gastric fluid. The plots of percent drug released versus time were obtained and these revealed an initial burst release followed by sustained release for some of the formulations (21) (Figure 5). The polymer content of the formulations containing the combination of starch and Eudragit S100 (F4 - F9) was a major factor governing drug release from the microballoons. As the polymer content increased, the overall drug release rate from the polymer matrix decreased owing to increase in the diffusion path length of the drug (20).

It was observed that the formulation F1 containing Eudragit S100 alone showed the most sustained release (t_{50} .> 240 min).. Drug release from microballoons containing acetylated cocoyam reduced with polymer: drug ratio. Formulation F9 (starch: Eudragit S100, 1:3) gave comparable dissolution time, t_{50} of 185.50±7.55 min, as that containing Eudragit S100 alone at a similar polymer:drug ratio of 6:1 (t_{50} = 185.00 ±8.10 min).

CONCLUSION

Microballoon formulations of metoprolol succinate containing acetylated starch with Eudragit S100 at varying ratios were prepared by the solvent evaporation method. Generally, microballoons containing acetylated starch had higher entrapment efficiency, higher *in vitro* buoyancy with prolonged but shorter dissolution times when compared to the microballoons containing Eudragit S100 alone polymer: Acetylated cocoyam starch has showed potential as a cheaper, alternative polymer in gastroretentive drug delivery systems.

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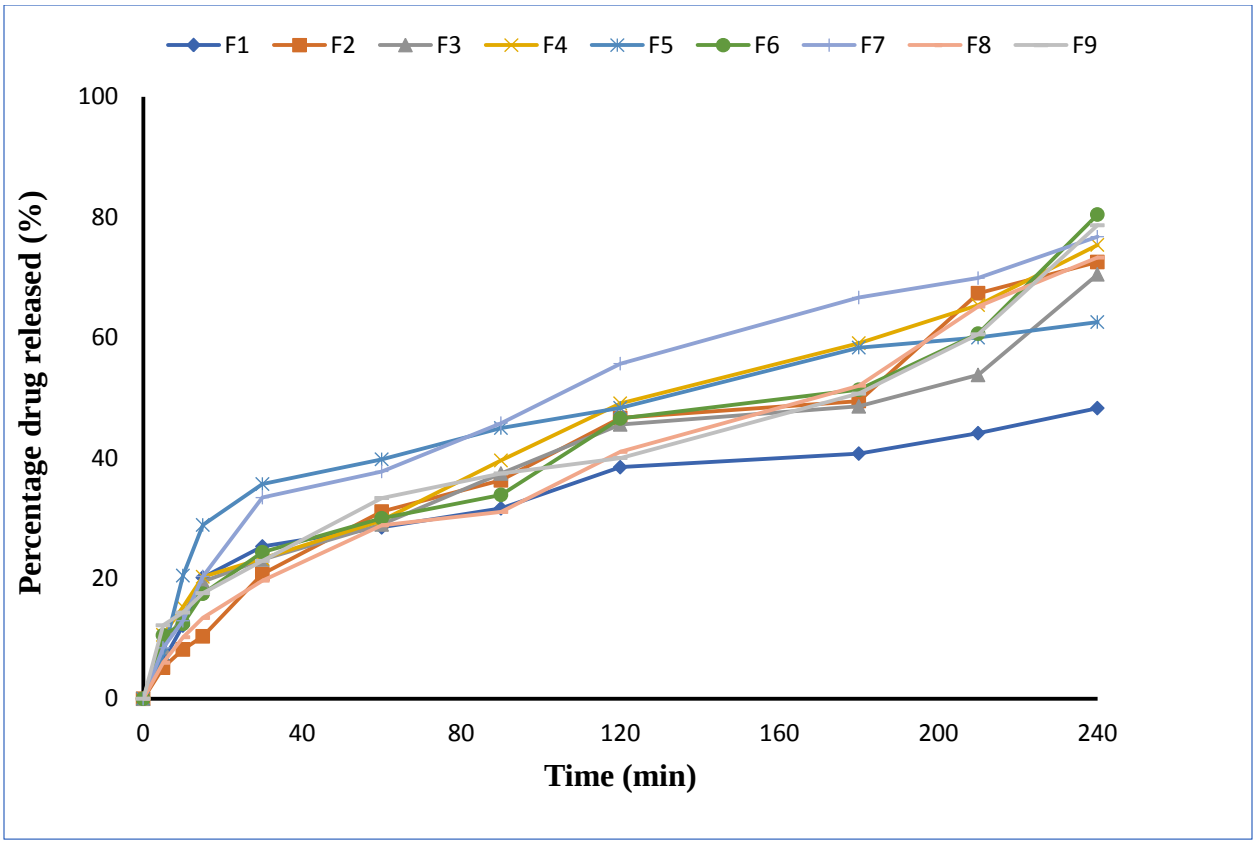

Figure 5: Dissolution profile of metoprolol-loaded microballoon formulation

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