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Research Article

Cross linked plantain starch-urea as a polymer in matrix tablets of ambroxol hydrochloride

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ABSTRACT

Plantain (*Musa paradisiaca*) starch, prepared as crosslinked starch-urea (CSU), was utilized in the formulation of matrix tablets of ambroxol hydrochloride. CSU was synthesized by gelatinization of plantain starch in urea, crosslinked with calcium chloride. Native starch and CSU were characterized using scanning electron microscopy (SEM), X-ray diffraction (XRD), chemical and material properties. Ambroxol hydrochloride tablets were prepared with CSU, 1:1 blend of CSU and Hydroxyl propyl methyl cellulose (HPMC K15M) and HPMC K15M alone at 20, 30 and 40%w/w. The 3^2 factorial design was used to optimize tablets using polymer type (X1) and polymer concentration (X2) as independent variables, crushing strength-friability ratio (CSFR) and time for 80% drug release (t_{80}) as responses. The SEM revealed changes in the ovoid granules of native starch to larger, irregular granules of CSU. The XRD spectra revealed a more crystalline CSU with higher swelling and better flow. Polymer type had more influence on CSFR and t_{80}. The optimized batch containing CSU at 40 %w/w exhibited highest values of CSFR and drug release. Experimental responses of the optimized batch had close proximity with the predicted value. Cross-linked plantain starch-urea polymer was found suitable as a polymer in matrix tablets of ambroxol hydrochloride.

INTRODUCTION

A matrix drug delivery system is composed of a drug that is either dissolved or dispersed within a polymeric matrix (Jones, 2004; Nokhodchi *et al*, 2012). Matrix tablets offer a wide range of advantages over the conventional dosage form; they are easy to manufacture while frequency of dosing is reduced, since the drug is released over a longer period of time. This is of importance to patients with chronic illnesses who require the plasma drug concentrations to be within therapeutic range. Furthermore, matrix tablets offer reduction in or avoidance of toxic effects from high plasma concentrations or 'dose dumping' (Jones, 2004).

The availability and cost of different classes of polymers is an important consideration in the formulation of matrix tablets. Semi-synthetic polymers such as Hydroxypropyl methylcellulose (HPMC) have been used in matrix tablet formulations. For example, Mohammed *et al* (2013) developed extended release (ER) mini-tablets of theophylline and hydrocortisone using HPMC K15M at different concentrations of 40, 50 and 60 %w/w. The study revealed that increase in HPMC concentration resulted in reduction in rate of drug release. Even though synthetic polymers or semisynthetic polymers such as Hydroxypropyl methylcellulose (HPMC) appear to be popular choices for formulation of hydrophilic matrix system, starch is also another widely used excipient in the pharmaceutical industry owing to its availability, versatility, inert nature, cost effectiveness, biodegradability and adaptability to various modifications. It has been reported that starch reacts with urea to form starch carbamate, a starch – urea polymer (Abdel-Thalouth *et al*, 1981; Hebeish *et al*, 1991). Starch-urea (carbamate) is a starch-based

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polymer that is hydrophilic and water- swellable. Calcium chloride serves as a catalyst in the cross linking reaction between starch and urea resulting in the formulation of cross-linked starch-urea. Cross-linked starch-urea has been reported to be used in the controlled release formulation of insecticide acetamiprid (Yongsong *et al*, 2005). In another study, Chowdary and Chandra (2009) prepared and evaluated cross linked starch – urea for its application in the design of diclofenac controlled release tablets. Release of diclofenac from the matrix tablets was slow and diffusion-controlled.

The performance of starches as pharmaceutical excipients has been reported to be dependent on their sources (Riley *et al*, 2008). Additional efforts have been made in the development of local, underutilized starches which show promising characteristics of high yield and purity as well as being locally available and cheaper for use in local manufacture and/or importation (Odeku, 2013; Okunlola, 2018). Plantain (*Musa paradisiaca*) family Musaceae, is a crop that is extensively cultivated in the tropics as a staple for tens of millions of people of the sub-Saharan Africa. The unripe fruit contains about 48% starch on dry weight basis (Odeku, 2013). In previous studies, native plantain starch has been shown to possess binding and disintegrant properties in tablet formulations (Alebiowu and Itiola, 2001; Akin-Ajani *et al*, 2005). In another study, plantain starch modified by acetylation was investigated and shown to have potential as a sustained release polymer in ibuprofen microspheres (Okunlola and Ghomorai, 2017). No known research on the use of plantain starch -urea has been reported.

In this study, Cross-linked starch-urea polymer was synthesized by gelatinization of plantain starch in the presence of urea followed by crosslinking with calcium chloride. Matrix tablets of ambroxol hydrochloride were formulated using cross-linked plantain starch-urea polymer (CSU), combination blend of CSU with Hydroxyl propyl methyl cellulose, HPMC K15M (1:1) and HPMC alone. HPMC K15M is a hydrophilic polymer of high viscosity grade in view of its greater molecular weight. Thus, the greater degree of entanglement at high molecular weight would reduce the effective molecular diffusion area and hence drug permeation across the matrix gel.

Ambroxol hydrochloride is a secretion-releasing expectorant successfully used for decades in a variety of respiratory disorders (Sweetman, 2002). Ambroxol is contained in several pharmaceutical formulations such as tablets, syrups, lozenges, dry powder and inhalation solution as well as effervescent tablets (Vujovic *et al*, 2017). Ambroxol hydrochloride has a molecular weight of 414.56 and is sparingly soluble in water. Bioavailability of ambroxol administered orally is approximately 70–80% and maximal plasma levels are observed after 2 h. Elimination of ambroxol is biphasic, with an alpha half-life of 1.3 hours and a beta half-life of 8.8 hours. Accumulation of the drug in human lung tissue is at concentrations 15- to 20 times higher than those detected in the circulation (Ren *et al*, 2009).. The main limitation of the drug is the short biological half-life (3-4 h). Thus, conventional tablets need to be administered 2-3 times to maintain plasma drug concentration. Sustained release formulations of ambroxol hydrochloride have been developed in order to reduce the frequency of administration to once daily. This will also offer the advantages of sustained blood levels, attenuation of adverse effects and improved patient compliance. A simple and cost effective approach to control the release of the drug is to disperse it within an inert polymeric matrix and the use of plantain starch-urea as hydrophilic matrices offer an appealing option.

Optimized tablets were prepared using a 3^2 full factorial design to determine the effects of selected independent variables, type of polymer (X_1) and polymer concentration (X_2), on dependent variables crushing strength-friability ratio (CSFR) and t_{80}.

MATERIALS AND METHODS

Materials

Plantains were obtained from local farmers in Ibadan, Oyo State, Nigeria. Hydroxyl propyl methylcellulose (HPMC K15M) was obtained from Oxford Lab Chemicals, Maharashtra, India. Ambroxol hydrochloride was purchased from Xi'an Sgonek Biological Technology Co. Ltd, Xi'an City, China. Magnesium stearate, the technical grade was from Sigma-Aldrich, USA. All other reagents are of analytical grade.

Extraction of Starch

Starch was extracted from peeled unripe plantain that were diced into small pieces. The pieces of plantain (1.75 kg) were soaked in 2 L of distilled water and the mixture was blended to obtain slurry that was strained through muslin cloth followed by sedimentation of the filtrate. The supernatant was decanted at 12 - hour intervals and the starch slurry

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re-suspended in distilled water. The starch cake was collected after 72 hours and dried in a hot air oven (Gallenkamp (Sanyo/Weiss) BS size 1 Oven, model OVH-300-010W, UK) at 50 °C for 48 hours. The dried mass was pulverized using a laboratory blender (Panasonic MX-C400 mixer grinder, MX-AC400, India) for 10 min at speed 2 and then screened through a sieve of size 250µm (Okunlola and Ghomorai, 2017).

Preparation of cross-linked plantain starch-urea

Cross-linked starch-urea polymer was synthesized by gelatinization of plantain starch in the presence of urea and crosslinking by treatment with calcium chloride (Chowdary and Chandra, 2009). Plantain starch (270.0 g) was dispersed in purified water (200mL) to form starch slurry. Urea (26.7 g), calcium chloride (43.0 g) were dissolved in purified water (800 mL) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed continuously for 20 min to form cross-linked starch-urea polymer. The mass formed was spread on to a stainless-steel plate and dried at 60°C for 12 h. The dried mass was pulverized (Panasonic MX-C400 mixer grinder, MX-AC400, India) for 10 min at speed 3 and then screened through a 250-µm mesh sieve

Characterization of native plantain starch and cross-linked plantain starch- urea polymer

Iodine test

Five milliliters of a 5%w/v slurries of plantain starch and cross-linked starch urea in distilled water were treated with two drops of iodine test solution.

Determination of degree of cross-linking using viscosity

The degree of crosslinking was observed by evaluating the viscosity values of the starches using the equation:

$$\frac{A-B}{A} \times 100 \qquad (1)$$

where A = viscosity of native starch and B = viscosity of cross-linked starch

Morphology

The shape and size of the starch granules were characterized using a scanning electron microscope (VEGA3 TESCA, Germany) at an accelerating potential of 20.0 kV, and a light microscope. The powder samples were coated with gold prior to SEM examination.

Viscosity

The viscosity of a 1%w/v aqueous slurry of native and modified starches was determined using The Brookfield viscometer (DV- II + pro model, Brookfield Engineering , USA) using shear rate 50 and 100 rpm with spindle size 4.

X-Ray Diffraction (XRD) analysis

The XRD patterns of the starches were recorded using an X-ray diffractometer (ARL X'TRA ThermoFisher Scientific, Landsmeer, The Netherlands) with copper-cobalt radiation. The scanning region of the diffraction angle (2^{θ}) was from 5^{o} to 70^{o} at a scan rate of 12^{o}/min.

Swelling index

The swelling power of the native and modified starches was determined using the method of (Bowen and Vadino, 1984). Starch and CSU suspension (5%w/v) was prepared at room temperature and the dispersion was allowed to stand for 24 hours before the sedimentation volume (V) was measured. The swelling capacity was calculated as the ratio of sedimentation volume (V) to initial volume (Vo) of the dried starch powder, V/Vo. The determinations were done in triplicate.

Measurement of densities

The particle density of the starch and CSU powders were determined by the pycnometer method using xylene as the displacement fluid. A 50-ml capacity pycnometer was weighed empty (W), filled with the non-solvent (xylene) and the excess wiped off. The weight of the pycnometer with the non-solvent was determined (W_1). The difference in weight was calculated as W_2. A 2g quantity of the sample was weighed (W_3) and quantitatively transferred into the pycnometer bottle. The excess non solvent was wiped off and the pycnometer was weighed again (W_4). The particle density was calculated from the equation:

$$\frac{W2\,.\,W3}{(W3 - W4 + W2 + W)} gcm - 3 \qquad (2)$$

The bulk density of each powder at zero pressure (loose density) was determined by pouring the powder freely, through a funnel, into a measuring cylinder with a diameter of 21mm and a volume of 50ml (Paronen and Justin, 1983; Itiola, 1991). The tapped density was measured by applying 100 taps to 10g of powder in a graduated cylinder at a

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standardized rate of 38 taps per minute (British Standard, 1970). The determinations were done in triplicate.

Angle of repose

The sample powder (10 g each) was made to flow freely through a funnel into an open - ended cylinder placed on a base of similar diameter. From the conical heap formed, the angle of repose was calculated as:

$$Tan\ \emptyset = \frac{height}{radius} \qquad (3)$$

where h is the height of the powder and r is the radius of the base of the cone.

Flow rate

The flow rate of the powder was obtained by determining the time "t" it took 10g of the powder to pass through the orifice of a 10 - mL pipette. The flow rate was calculated as mean of three determinations.

Flow properties

The flowability of the starch and CSU were assessed using the Hausner's ratio and the Carr's index. The Hausner`s ratio was determined as:

$$\frac{Tapped\ density}{Bulk\ density} \qquad (4)$$

The Carr's index (% compressibility) was calculated as shown below:

$$Carr's\ index = \frac{tapped\ density - bulk\ density}{tapped\ density}\ X\ 100 \quad (5)$$

Formulation of ambroxol hydrochloride tablets

Preliminary studies

During the preliminary trials, various formulations of ambroxol hydrochloride tablets were prepared by varying parameters such as ratio of CSU:HPMC, concentration of matrix polymer, compression pressure, compression time etc.

Formulation of tablets

The optimized tablet formulations of ambroxol hydrochloride selected were prepared as follows:

Two hundred grams of tablet formulations were prepared comprising of cross-linked starch-urea (CSU) or combination blend of CSU:HPMC (ratio 1:1) or HPMC alone as matrix polymers at 20, 30 and 40%w/w with ambroxol hydrochloride (30%w/w), talc 2%w/w, magnesium stearate 2%w/w and lactose monohydrate to 100%w/w. The tablets were prepared by wet granulation method. The required quantities of drug, cross-linked starch-urea and lactose (qs) were thoroughly mixed in a mortar using a pestle for 20 min. The binding fluid (a 1 %w/v aqueous dispersion of polyvinyl pyrrolidone) was added and mixed thoroughly for 7 min to form a wetted mass. The mass was passed through 1680 µm to obtain wet granules. The wet granules were dried at 50 ^{o}C for 4 h. The dried granules obtained were then screened through 1190 µm to produce granules for compression. Magnesium stearate was then added and mixed for 5 min. The granules of the ambroxol hydrochloride formulations (200mg) were compressed with a load of 113.12 Mpa for 30 seconds on a Carver hydraulic press (Carver Inc. Menomonee Falls, WI, USA) using a 10.5 mm die and flat-faced punches to produce 100 tablets per batch. The tablets *were stored* over silica gel for 24 h *before tablet* properties *were* determined, to *allow for elastic recovery* and hardening .

Evaluation of ambroxol hydrochloride tablets

FTIR analysis

The pure ambroxol hydrochloride drug, HPMC, CSU, ambroxol hydrochloride tablets containing CSU and ambroxol hydrochloride tablets containing HPMC were analysed by FTIR (FTIR-Thermo Nicolet Nexus 870 Madison, WI, USA) in transmission mode. Transmission spectra were recorded using at least 64 scans with 8 cm^{-1} resolution in the spectral range 4000–400 cm^{-1}.

Tablet weight and thickness

Twenty tablets were selected at random and their average weight was determined within ± 1mg while the thickness of twenty tablets was measured within ± 0.01mm using a micrometer screw gauge.

Mechanical strength of tablets

The crushing strength of ambroxol hydrochloride tablets was determined at room temperature by diametric compression using a tablet hardness tester (DBK Instruments Mumbai, India). The percent friability of the tablets was determined using a friabilator (DBK Instruments, India) rotated at 25 rpm for 4 min. The crushing strength-friability ratio (CSFR) was then calculated from the values of crushing

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strength and friability. All measurements were made in triplicate and the results given are the mean of several determinations.

Tablet release properties

Ten tablets were crushed and dissolved in phosphate buffer pH 6.8 and assayed for drug content using a UV/Visible Spectrophotometer (Jenway UV-7804c print, England) at wavelength 244 nm to determine percentage content of ambroxol hydrochloride in the tablets. Dissolution test was carried out on 12 tablets using the USPXX III (basket method) at 100 rpm in 900 mL of phosphate buffer pH 6.8 maintained at a temperature of 37±0.5 °C. Five milliliter samples were withdrawn and replaced with equal amounts of fresh medium. The samples were then filtered through membrane filters (0.45 µm) and diluted suitably. The amount of ambroxol hydrochloride released was determined at wavelength of 244 nm using a UV/Visible Spectrophotometer (Spectrumlab 752s UV-VIS spectrophotometer, No 752S12090, China). Twelve tablets were used for the study. Determinations were done in triplicate.

Similarity factor

The dissolution profiles were compared using a similarity factor, (f_2) shown in equation 6. The similarity factor is a logarithmic reciprocal square root transformation of one plus the average mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products over all time points.

$$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\} \quad (6)$$

where n is the number of dissolution time points and R_j and T_j are the reference and test dissolution values at time t. The same dissolution conditions were used for the samples and the mean values of 12 tablets were used for all samples.

Two dissolution profiles are considered similar when the f_2 value is 50 to 100. Values less than 50 indicate that the two products do not have similar dissolution behaviour.

Experimental design

A 3^2 full factorial design was used to determine the effects of independent variables X_1 (polymer type) and X_2 (polymer concentration) on dependent variables CSFR and t_{80}. The independent variables selected for the study are given in Table 1 and the batches were prepared according to the experimental design shown in the table.

Based on the Response Surface Method (RSM) approach, polynomial equations were derived from multiple regression analysis of the data using Minitab version 16:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (7)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity (Hermans *et al*, 2012). The relationship between the dependent and independent variables was further elucidated using the response surface plots.

Table 1. 3^2 Full factorial design layout with the coded and actual values of the independent variables.

Batch	X_1	X_2	Polymer type (X_1)	Polymer conc. %w/w (X_2)
1	-1	-1	HPMC	20
2	-1	0	HPMC	30
3	-1	+1	HPMC	40
4	0	-1	CSU:HPMC	20
5	0	0	CSU:HPMC	30
6	0	+1	CSU:HPMC	40
7	+1	-1	CSU	20
8	+1	0	CSU	30
9	+1	+1	CSU	40

RESULTS AND DISCUSSION

Starch yield

The yield of starch was 33.83%w/w. According to Odeku, 2013, the yield of starch in plantain can be as high as 48 % on a dry weight basis, depending on the variety of plantain used (Odeku, 2013). The lower yield obtained could be due to the drying condition, generic variations in the variety of plantain studied , harvesting time, e.t.c. (Olomo and Ajibola, 2003).

Degree of cross-linking of CSU

The extent of crosslinking is usually assessed by evaluating physical changes of cross-linked starches such as viscosity, swelling, solubility and shear

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resistance. The method used was evaluation of viscosity. The degree of cross-linking was 85.0%.

Characterization of starches

The crosslinked starch urea (CSU) was prepared by gelatinization of plantain starch in the presence of urea in a simple and reproducible method involving cross-linking with calcium chloride to yield a harder, crystalline, more free flowing powder than the native starch. The yield of the new starch-based polymer was 90.75±2.11%w/w. The native starch and CSU were characterized and the results are as discussed below:

Iodine test

A blue black colour was obtained for native plantain starch. However, a reddish purple colour was observed with CSU, indicating the presence of α-amylose.

Morphology

The Scanning Electron Micrographs (SEM) images of native plantain starch and CSU are presented in Figures 1a and 1b. The micrograph of plantain starch showed ovoid starch granules with smooth surfaces and mean size of 17.81 ± 3.63 µm. The SEM images of the plantain starch-urea showed that the modification process resulted in disruption in the granular structure of the native starch. The plantain starch-urea were significantly larger (30.45 ± 10.31µm) with irregular shape.

Viscosity

The viscosity of a 2%w/v slurry of native plantain starch and CSU were 60.0 and 4.0 centipoise respectively, at speed of 50 rpm. Crosslinking of plantain starch produced a less viscous polymer with lower value of torque (0.10%) when compared to the native starch (1.50%). This reduction in viscosity could be indicative that higher cross-linking had taken place that is there were sufficient cross-links to retard the swelling of the starch and cause a decrease in viscosity (Kartha et al. 2005). As the shear speed increased from 50 to 100 rpm, the viscosity values and torque increased for CSU (6.0 centipoise and 0.30%, respectively) but there was a sharp reduction in viscosity of native starch (26.0 centipoise), even though the viscosity remained higher than CSU. The torque value of CSU native starch reduced to 1.30% as shear speed increased from 50 to 100 rpm.

(a)

(b)

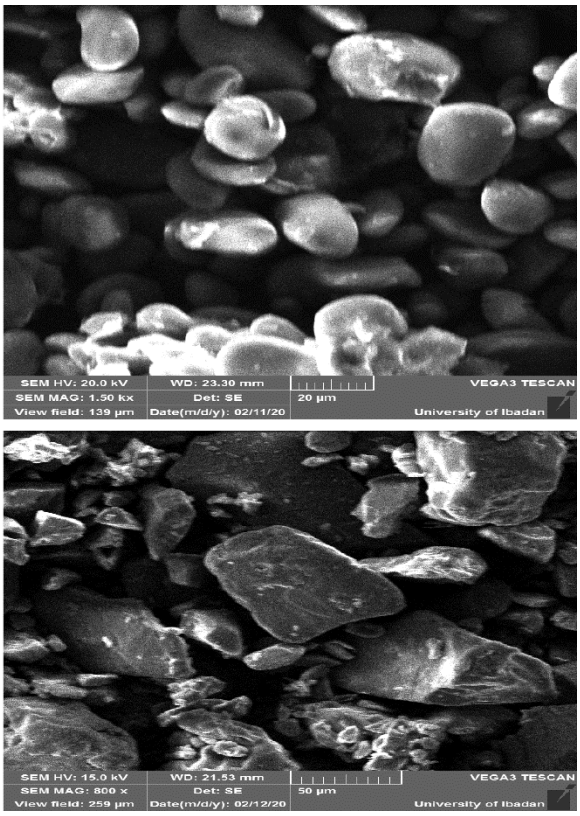

Fig. 1. Scanning electron micrographs (SEM) of (a) native plantain starch, (b) cross-linked plantain starch-urea (Mg x 800).

XRD analysis

The XRD spectra of native starch and CSU are shown in Figure 2. Native plantain starch exhibited a typical B- type crystalline pattern, showing a small peak at 5°, strong peaks at 15 and 17° and a broad peak at 22 - 24° 2θ. In the case of CSU, the pattern showed a peak around 7.61° with major peaks between 2θ = 20 and 23°, suggesting a more crystalline powder.

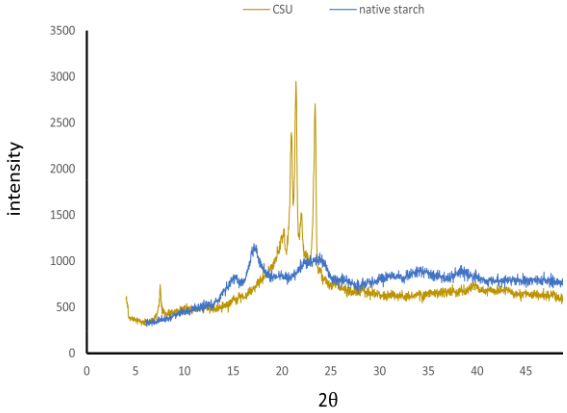

Fig. 2. Xray Diffraction (XRD) spectra of native plantain starch and cross-linked plantain starch-urea.

Material properties of the starches

The results of the material properties including swelling index, densities, flow properties using Carr's

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index, Hausner's ratio and angle of repose, are presented in Table 2.

Table 2. Material and physicochemical properties of native and modified plantain starches (mean ± SD, n =3)

Parameters	Native Starch	CSU
Swelling Index	1.50±0.42	3.90±0.92
Particle density, gcm^{-3}	1.405±0.04	1.412±0.02
Bulk density, gcm^{-3}	0.420±0.01	0.580±0.02
Tapped density, gcm^{-3}	0.655±0.05	0.684±0.05
Hausner's ratio	1.55±0.14	1.18±0.11
Carr's index, %	36.16±2.66	15.10±0.08
Angle of repose, °	63.10±0.60	27.70±0.80
Flow rate, /s	0.06±0.01	**0.11±0.02**

CSU= crosslinked starch urea

Swelling index

The swelling index is used to determine the ability of the starch to absorb moisture which may be attributed to divergent intensity of the molecular association forces inside the particles (Sanni *et al*, 2005). The degree of swelling of a starch has been reported to depend on the species of plant the starch is obtained from (Singh *et al*, 2003). Plantain starch-urea polymer exhibited swelling in water which was significantly higher than that of the native starch owing to disrupted and loose structure of the starch polymer.

Diffusion, swelling and erosion are the three most important rate-controlling mechanisms in controlled delivery of drugs. The drug release from the polymeric system is mostly by diffusion and best described by fickian diffusion. For the formulations containing swelling polymers, other processes include relaxation of polymers chain, inhibition of water causing polymers to swell and changing them from initial glassy to rubbery state. When in contact with biological fluids, HPMC k15M undergoes a glassy–rubbery transition and drug release from it is also strongly influenced by swelling (Pedacchia and Adrover, 2015)

Since the crosslinked starch polymer will swell in water and aqueous fluids and form gelatinous matrices suitable for influencing the release of drugs from dosage forms, it is thought worthwhile to investigate this new starch-based polymer for its application in tablets.

Densities

Particle density has been observed to affect the compaction behaviour of powders since dense and stiff powders require higher compression pressure to produce formulations with improved mechanical strength and cohesive impact (Femi-Oyewo *et al*, 2015). The particle density, bulk and tapped densities of the modified starch were higher than those of the native starch. The bulk density of a starch powder describes its packing behaviour while the tapped density indicates the rate and extent of packing that would be experienced by the material during the various unit operations of tableting. Higher bulk density of CSU is advantageous in tableting because of a reduction in the fill volume of the die.

Flow properties

The value of the Carr's index and Hausner's ratio were obtained from the bulk and tapped densities. The Carr's index and Hausner's ratio measure compressibility and flowability of the powder. The CSU had lower values of Carr's index and Hausner's ratio, indicating that upon modification, the flowability was improved and compressibility reduced. Angle of repose of a powder is also an important qualitative measurement in the tendency of powdered or granulated materials to resist flow. The higher the angle of repose, the more cohesive the powder and the poorer the flow of the powder.

Angle of repose of 40 ° indicates poor flow. The native starch had a higher angle of repose than CSU indicating that the flow property of the starch was improved with modification. The compressibility index of CSU was found to be 15.10% and the angle of repose was found to be 27.70. The flow rate of CSU was also significantly higher than that of native plantain starch. The micromeritic properties indicated good flow and compressibility, important requirements for solid dosage form manufacturing.

Evaluation of ambroxol hydrochloride tablets

FTIR analysis

Figure 3 shows the FTIR spectra of pure ambroxol hydrochloride, tablets of ambroxol hydrochloride containing CSU, tablets of ambroxol hydrochloride containing HPMC, HPMC and CSU polymers. The FTIR spectrum of pure ambroxol hydrochloride drug showed characteristic peaks as intense bands at 627.38 cm^{-1}, 1629.54 cm^{-1} and 1288.07 cm^{-1} corresponding to the presence of functional groups such as aliphatic bromo compound, secondary amine and secondary alcohol. These characteristic peaks were also observed in the spectrum of the tablet formulations of ambroxol hydrochloride containing CSU, blend of CSU: HPMC

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and HPMC alone, suggesting that there was no change in the functional groups nor in the structure of the drug. This confirms that there was no drug-excipient interaction and that the integrity of the ambroxol hydrochloride was maintained.

The tablet properties of the nine batch formulations of ambroxol hydrochloride tablets are presented in Table 3.

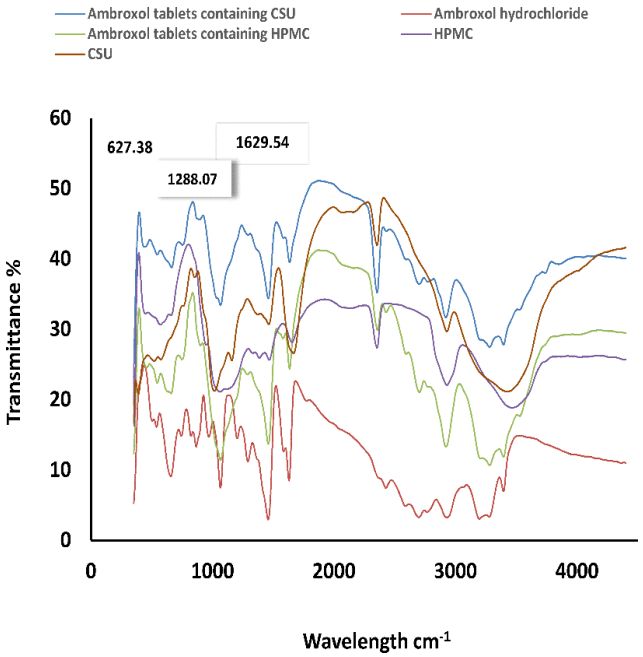

Fig. 3. FTIR of HPMC, CSU, Ambroxol hydrochloride, Ambroxol tablet containing CSU and Ambroxol tablet containing HPMC only.

Tablet weight and thickness

All the formulated tablets passed the weight variation test as the percentage weight variations were within the International Pharmacopeia limits of 7.5% of the weight. The average thickness of all the formulations was found to be within the limit of the British Pharmacopeia specifications (B.P., 1998).

Mechanical properties

Mechanical strength is of importance in tablets because it helps to determine the extent to which the tablets can withstand pressure to the rigors of packaging, transportation and handling. While the friability value provides a measure of tablet weakness, the crushing strength indicates the strength of the tablet (Itiola *et al*, 2006).

The friability test is used to assess the physical strength of compressed and uncoated tablets upon exposure to mechanical shock and attrition (Saleem *et al*, 2014). The lower the friability value, the greater the ability of the tablets to withstand mechanical stress during manufacturing, distribution and handling. Generally, tablets containing HPMC had the highest friability while those containing CSU had the lowest friability at all polymer concentrations used. However, the friability values were greater than 1% in all formulations showing that they did not meet the BPC specifications for friability which specifies ≥ 1% (BP 1998). It was observed that there was an increase in crushing strength with a corresponding decrease in friability value. Plantain – starch urea produced tablets with the highest mechanical strength at all concentrations used. Tablets containing the blend of CSU:HPMC had lower values of crushing strength than those containing HPMC except at polymer concentration of 40%w/w where they produced tablets of higher strength. The crushing strength-friability ratio (CSFR) has been reported to provide a better parameter for measuring tablet strength; the higher the CSFR value, the stronger the tablets (Itiola *et al*, 2006).

Release properties of ambroxol hydrochloride tablets

Assay of drug content revealed 99.16± 1.77% of ambroxol hydrochloride. Tablets with high quality should be designed and manufactured to have a high degree of correlation between the weight and content uniformity with the purpose of ensuring that a consistent dose of the API is maintained between batches so that patients will be able to take an accurate and precise dose of the medication.

The results of values of dissolution time (t_{80}) were obtained from the dissolution profile shown in Figure 4. The results showed there was an immediate release of the drug from all tablets i.e. a burst release. In particular, tablets containing HPMC and the blend gave short dissolution times (t_{80} < 60 min) at all the polymer concentrations used. On the other hand, tablets containing CSU had prolonged dissolution time (t_{80} ranging from 150 – 300 min). Generally, all tablets showed an increase in dissolution time with increase in polymer concentration.

Similarity factor

Similarity factor (f_2) was used in the comparison of dissolution profiles of the formulations. When the two profiles are identical, $f_2 = 100$. An average difference of 10% at all measured time-points results in f_2 value of 50. Any value of f_2 between 50 and 100 indicate

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similarity between two dissolution profiles (Shah *et al*, 1998). An f_2 comparison is considered unnecessary when both the test and reference products exceed 85% dissolved within 15 min. Such products would be considered similar as they meet the "very rapidly dissolving" standards of the European Medicines Agency (CPMP, 2010). All formulations met this criteria. In addition, sufficient sampling times were available with a minimum of 3 excluding t=0; the individual dosage unit for each product was 12 and the sampling times were the similar for the formulations. The f_2 values obtained from this study are presented in Table 4. Generally, similarity was obtained between batches of tablets containing the same polymers i.e., within between those formulations with HPMC only (B_1, B_2 and B_3), within those containing the blend of CSU and HPMC (between B_4 and B_5 and between B_5 and B_6) as well as the within the formulations containing CSU only (between B_7 and B_8 and between B_8 and B_9). Similarity was also observed in the dissolution profiles of formulations containing HPMC only (B_1, B_2 and B_3) and formulation B_4 containing 20%w/w of the blend of HPMC and CSU (f_2 = 52.13. 53.27 and 55.07, respectively). The results however revealed dissimilarity when comparing the release profiles of those formulations containing HPMC or the blend with those containing CSU only at all concentrations ($f_2 < 50$). Generally, two erosion mechanisms exist for a polymer matrix: heterogeneous and homogeneous erosion. The heterogeneous erosion is surface erosion with degradation, which only happens at the surface of a polymer matrix and usually takes place in hydrophobic polymers, as water is excluded. On the other hand, hydrophilic polymers that are known to absorb water undergo homogeneous erosion (bulk erosion) which is the result of degradation occurring through the polymer matrix (Langer and Peppas, 1983). As HPMC is a hydrophilic polymer, the degradation tablet formulations containing HPMC could be defined as homogeneous erosion characterized by an initial burst release (Siepmann and Siepmann, 2008). For the formulations containing CSU, a water-swellable polymer, swelling may also play an important role in the control of drug release from the tablets. Polymer swelling is of significance since it may increase the length of the diffusion pathways, decrease the drug concentration gradients, and potentially decrease the drug release rate (Siepmann and Siepmann, 2008). This may explain why the formulations containing CSU showed more prolonged release of the drug.

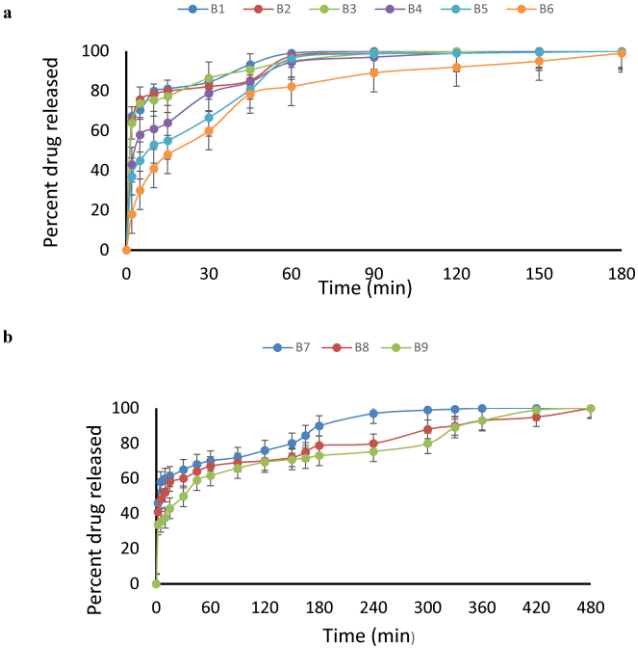

Fig. 4. Dissolution plots of: (a) Batches 1-6, Ambroxol hydrochloride tablets containing HPMC alone and those containing CSU and HPMC (1:1) and (b) Batches 7-9, Ambroxol hydrochloride tablets containing plantain starch-urea

Experimental design

The 3^2 full factorial design involving the response surface methodology (RSM) involves formulation of nine batches (B_1 – B_9). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms (Singh *et al*, 2005). The responses of all the prepared formulations were simultaneously fitted to quadratic models. Polynomial equations generated by Minitab 16 Software were established on the basis of ANOVA. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., whether positive or negative). The high values or correlation coefficient for the dependent variables indicate a good fit.

Positive values of the coefficient indicate that changing the variable (X_1 or X_2) from low to high resulted in increase in response while the negative coefficient implies that changing the variable from low to high resulted in decrease in response. The interaction terms (X_1X_2) show how the response changes when the two factors are simultaneously

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changed. Assessing the mechanical strength and release properties of tablets is essential as a tablet should possess the strength to withstand shock encountered in its production, shipping and dispensing while at the same time should be able to release the medicinal agent(s) into the body in a predictable and reproducible manner.

Factorial equation for CSFR

The following polynomial equation was derived from multiple regression analysis of the data obtained for CSFR:

$$Y_1 = 20.558 + 7.958X_1 + 7.860X_2 + 4.742X_1X_2 + 7.848X_1^2 - 1.197X_2^2$$

The values of CSFR for all the 9 batches ranged from 11.91 to 47.78 and showed good correlation coefficient of 0.9985. The equation of CSFR showed the values of various coefficients of the variables. The effect of both variables X_1 and X_2 were positive indicating that changing from HPMC to the blend of HPMC and CSU resulted in an increase in CSFR which further increased when changed to CSU alone as matrix polymer in the tablet. The p-values of X_1 and X_2 indicated both polymer type and polymer concentration significantly affected CSFR ($p \leq 0.001$). The magnitude of coefficient of X_1 was higher than X_2, suggesting that polymer type had greater influence. The results showed that CSU had the most prominent effect on CSFR when compared to the other polymers. The interaction of both independent variables (X_1X_2) was positive, implying that polymer type and polymer concentrations interacted to improve mechanical strength. The response surface plots of CSFR shown in Figure 5(a) revealed that changing the polymer type (X_1) from HPMC to the blend of CSU:HPMC initially resulted in lower CSFR values at 20 and 30%w/w polymer concentration. However, at 40% polymer concentration, CSFR increased, suggesting that the blend of CSU:HPMC can be suitable for improved mechanical strength of tablets at 40%w/w. On the other hand, at all the polymer concentrations used, CSFR increased significantly when polymer type was changed to CSU.

Factorial equation for time tak en for 80% drug release (t_{80})

Drug dissolution from oral solid dosage forms is the most indicative *in vitro* parameter for the prediction and assessment of in vivo drug bioavailability, performance and therapeutic value (Herman *et al*, 2017). The following polynomial equation was derived from multiple regression analysis of the data obtained for t_{80}:

$$Y_2 = 47.222 + 107.501X_1 + 29.833X_2 + 35.001X_1X_2 - 79.161X_1^2 - 5.835X_2^2$$

The values of t_{80} for all the batches varied from 10.00 to 300 min. Y_2 was influenced by the effects of the independent variables with good correlation coefficient of 0.9858. The value of the coefficients of X_1 and X_2 were positive indicating that changing the polymer type from HPMC to CSU and changing the polymer concentration from 20 to 40% resulted in prolongation of dissolution time Y_2. Both independent variables (X_1, X_2) significantly affected Y_2 but X_1 had a higher magnitude indicating a more significant influence ($p = 0.001$). The value of X_1 and X_2 interaction had a negative value indicating undesirable effects on drug dissolution.

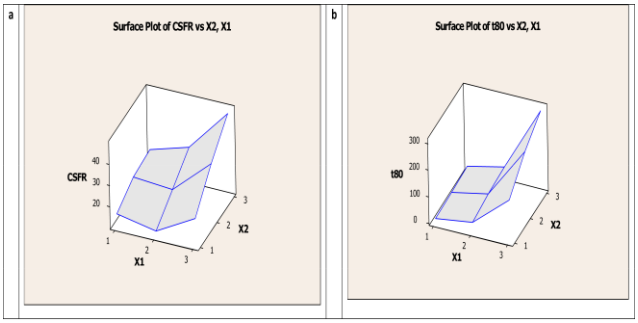

Fig. 5. Response surface plots for the influence of X_1 and X_2 on: (a) CSFR and (b) t_{80}

Response surface plots for t_{80} are shown in Figure 5b. It can be observed that at all levels of polymer concentration, t_{80} increased when polymer type was changed HPMC to CSU:HPMC. Changing the polymer type to CSU resulted in a significant increase in t_{80}. The higher swelling observed with CSU could have resulted in an increased diffusional path length. thereby decreasing the overall rate of drug release from the tablets. The response surface plots reveal that polymer type X_1 had more influence on both CSFR and t_{80} than polymer concentration, X_2.

The hydrophilic matrix tablets release their drug content by one or more of the following processes: the transport of the solvent into the polymer matrix, swelling of the associated polymers, diffusion of the solute through the swollen polymers, and erosion of

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the swollen polymers. Generally, significant burst release was observed in the formulations within the first hour followed by a slower, more prolonged release. The optimum formulation was selected based on the criteria of attaining prolonged dissolution of ambroxol hydrochloride with highest possible mechanical strength. Batch 9 containing CSU at 40%w/w was the optimum formulation. Additional two random batches (C_1, C_2) of ambroxol hydrochloride tablets were prepared for the validation of the experiment design and polynomial equations (Gonzalez-Rodraguez *et al*, 2007). These additional batches are also known as checkpoint batches. The predicted values of these checkpoint batches were compared with the experimental results and the percent prediction error (% PE) was calculated. The results are shown in Table 5. The low range of error confirmed the high prognostic ability of RSM.

Table 3. Tablet properties of ambroxol hydrochloride tablet formulations (mean ± sd, n=3)

Batch	Formulation Composition/ %w/w		Tablet weight g	Tablet thickness mm	Crushing strength Mpa	Friability %	Crushing Strength-Friability ratio (CSFR)	t_{80} min
1	HPMC	20	0.195±0.004	0.159±0.007	30.43±1.40	1.93±0.02	15.77	10.00±2.50
2	HPMC	30	0.195±0.004	0.154±0.003	34.63±1.12	1.00±0.15	21.12	15.00±3.10
3	HPMC	40	0.199±0.003	0.156±0.003	35.07±0.75	1.59±0.10	22.06	20.00±1.33
4	CSU:HPMC	20	0.209±0.008	0.166±0.004	21.90±0.52	1.84±0.16	11.91	33.00±2.70
5	CSU:HPMC	30	0.202±0.006	0.157±0.004	30.97±0.86	1.56±0.11	19.85	45.00±5.00
6	CSU:HPMC	40	0.203±0.006	0.158±0.005	40.97±1.52	1.49±0.07	27.52	52.00±6.50
7	CSU	20	0.198±0.003	0.143±0.002	42.57±1.22	1.89±0.24	22.52	150.00±13.20
8	CSU	30	0.198±0.002	0.148±0.004	51.32±3.89	1.41±0.18	36.40	240.00± 15.50
9	CSU	40	0.196±0.001	0.152±0.002	59.72±0.89	1.25±0.08	47.78	300.00±23.22

Table 4. Similarity factor (f2) for dissolution profiles of ambroxol hydrochloride tablets.

Batch	Similarity factor %							
	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9
B_1	79.16	81.13	52.13	43.40	34.36	44.25	38.40	28.96
B_2	-	82.76	53.27	44.04	34.79	45.72	39.40	29.63
B_3	-	-	55.05	44.79	35.40	45.80	39.67	29.82
B_4	-	-	-	63.67	45.93	47.81	44.42	34.81
B_5	-	-	-	-	54.92	44.21	44.14	37.41
B_6	-	-	-	-	-	39.98	43.16	42.95
B_7	-	-	-	-	-	-	64.25	41.11
B_8	-	-	-	-	-	-	-	50.01

CONCLUSIONS

Modification of the native plantain starch by crosslinking with urea to form plantain starch- urea polymer produced larger granules with improved swelling and flow properties. Tablets containing the plantain starch –urea polymer generally had better mechanical strength (higher Crushing strength-Friability ratio, CSFR) than those containing the standard HPMC or the blend of HPMC and plantain starch-urea at ratio 1:1. Drug dissolution was enhanced by the plantain starch-urea polymer, even though there was initial burst release within the first hour of dissolution. Experimental responses of the optimized batches had close proximity with the predicted value. The studies done was able to show the potential of crosslinked plantain starch - urea (CSU) as a polymer in matrix tablets of ambroxol hydrochloride. Further studies would include the compaction/deformation properties of CSU in comparison to HPMC. It is anticipated that such studies will lead to a better understanding of the tableting behaviour of plantain starch-urea.

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