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Full Length Research Article

Synthesis and Characterization of Starch-Graft-Acrylamide Hydrogel for Oral Drug Delivery

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ABSTRACT
In this research, starch was extracted from fresh sweet potato and was used to prepare starch-g-acrylamide hydrogel using free radical polymerization method with potassium per sulphate and N'N-Methylene bisacrylamide as initiator and cross-linker, respectively. The swelling capacity and pH sensitivity of the synthesized hydrogel were investigated in solutions of various pH (1-12). The drug loading and release experiment was also carried out using promethazine (PMZ) as the model drug at 25^{o}C and 37^{o}C, respectively while the release study was carried out in an enzyme-free simulated gastric intestinal fluid (SGF) and simulated intestinal fluid (SIF). The result showed a 905% swelling at pH 11, suggesting increased swelling capacity at higher pH values. Drug loading result indicated 99% of the drug was entrapped by the hydrogel as confirmed by UV-visible spectrophotometry. SIF and SGF Simulation indicated a 24% and 9% drug release for the first ten hours. At the end of 48 hours the release was 96% and 89%, respectively indicating the hydrogel released more promethazine in SIF than in SGF. The results obtained in this work suggest that starch-graft-acrylamide hydrogel is a potential vehicle for oral drug delivery.
Keywords: Starch, Acrylamide, Hydrogel, Drug delivery.

INTRODUCTION
An area of research that received great attention and progressed greatly in the past few decades is the utilization of hydrogels in the biomedical applications as drug carriers (Peppas, 2000). The most interesting class of polymers in the application of drug delivery system using solid matrices is the hydrogel (Sadeghi, 2011). Initially, drugs could only be administered in a limited manner due to limitations of transportation route through body harmful environment. Thus, limited mobility and other problems associated with old method have made the drug delivery tedious and reduced the efficacy of the administered drugs (Azman *et al*., 2015). Great development has been achieved with the invention of biomaterial carriers, which could be encapsulated with drug, allowing the drug to safely reach the targeted body site without any harm. These carriers allow the drug to simply access the body sites which were previously inaccessible (Peppas, 2000).

Hydrogels are three-dimensional cross-linked polymer matrices that are capable of absorbing large amount of water or biological fluids without being dissolve (Esra *et al*., 2007). The hydrogels ability to absorb water is due to the presence of hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution is due the crosslinks between the network chains (Ahmed, 2015). Since the pioneering work of Wichterle and Lim in 1960 on crosslinked hydrogels (Kopecek, 2007) and because of their hydrophilic character, biocompatibility and biodegradability hydrogels has been an area of great interest to biomaterial scientists for many years (Kono and Teshirogi, 2015). Hydrogels have been actively studied, particularly those experiencing reversible volume changes in response to external stimulus, such as pH, temperature and ionic concentration. These "smart" hydrogels have found applications in biomedicine and biotechnology including soft contact lenses (Soleimani and Sadeghi, 2012), immobilization of enzymes and proteins (Niamlang *et al.,* 2013), antibodies and antigens and matrices for drug delivery systems (Park *et al*., 2013). The ability of these hydrogels to respond to their environment increase drug loading and provide protection from environmental conditions such as those found in the gastrointestinal tract (Michel *et al*., 2011).

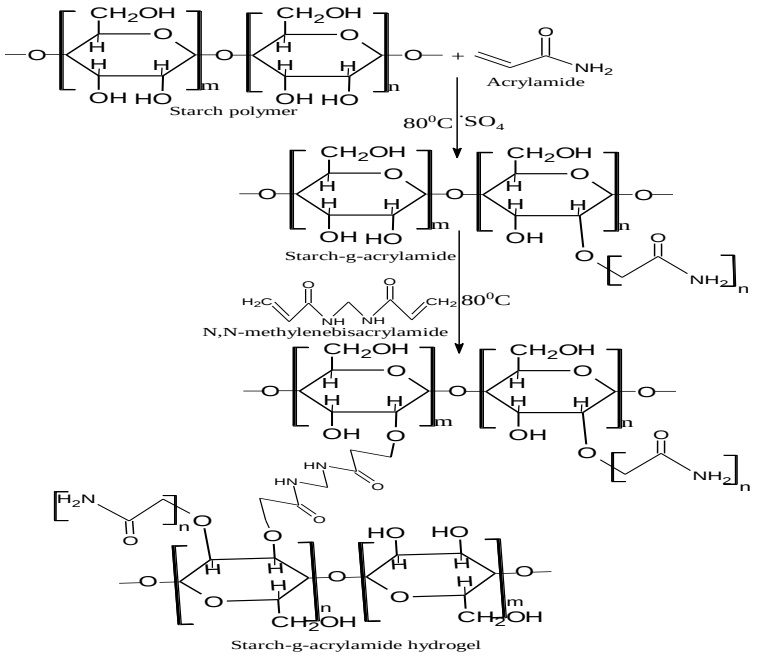
In this regard, stimuli responsive hydrogels can be useful for the design of a specific site drug delivery system; for instance, colon-targeted drug delivery systems (Usman *et al*., 2015). Another important advantage of these hydrogels is that the active ingredient remains on the organ or tissue for longer times than when taken using conventional method (Shanta and Harding, 2002). Drug delivery systems through hydrogel enhances therapeutic efficacy, minimize side effects, and improve patient compliance (Muhammad *et al*., 2016). The hydrogels simply work in response to an environmental stimulus such as temperature, ion concentration, pH and electric field and release its contents in a fashionable manner over a specified period of time. One of the properties of hydrogel is its unique ability to swell thousand times its dried weight (Jamingan *et al*., 2015). This research is aimed at synthesizing biodegradable and biocompatible hydrogels for oral drug delivery that could overcome some of the persistent problems and limitations associated with the conventional drug administration.

MATERIALS AND METHOD

Native sweet potato tuber was purchased from Dawanau market, Kano state. Acrylamide (98%) and ethanol (96%) were purchased from LobaChemie, N'N-Methylene bisacrylamide (97%) from Sigma Aldrich, USA. Potassium persulphate (98%) from Qualichem,.All other reagents are of analytical grade and were used as received. All glasswares were cleaned thoroughly, rinsed with deionised water and dried in an oven at 100 ºC overnight.

Synthesis of Starch-g-Acrylamide Hydrogel Film

Starch acrylamide hydrogel was synthesized using a modified procedure as described by Soleimani and Sadeghi (2012). Potato starch (4 g) was dissolved in 100 ml of distilled water in a three-necked round bottom flask and placed in a pre-heated water bath with constant stirring in nitrogen gas atmosphere. After 15 minutes, acrylamide (8 g) was dissolved in 50 ml of distilled water and added into the three-necked round bottom flask containing the starch solution under vigorous stirring (200 rpm) at 55ºC. After 15 minutes, the mixture became homogeneous and potassium persulphate (0.1 M) and N'N-methylene bisacrylamide (0.2 M) as an initiator and crosslinker, respectively were added. The Synthesis was allowed to proceed for 2 hours at 65 - 75 ºC, after which the synthesized hydrogel was washed with ethanol followed by water and dried to a constant weight in an oven at 60 ºC.



Scheme 1: Synthesis of starch-g-acrylamide Hydrogel

CHARACTERIZATION

Fourier Transform Infrared Spectroscopy (FTIR)

Aliquot (0.2 g) of the prepared hydrogel was ground to powder and its FTIR spectrum was obtained using CARRY 4000 FTIR AGILENT spectrometer within the range of 4000 – 600 cm^{-1}.

Scanning Electron Microscopy (SEM)

Powdered form of the synthesized hydrogel was taken to observe its surface morphology before and after drug loading by scanning at different magnifications using Scanning Electron Microscope Phenom Pro X Model.

Swelling Studies

The swelling capacity of hydrogel was evaluated according to the method of Ahmed (2015). The swelling behaviour of the hydrogel film was carried out in solutions of various pH (1-12) and was determined gravimetrically. A solution of pH 1-12 was prepared and a known weight of the dried hydrogel films was immersed in each solution and left until an equilibrium was reached after which the swollen hydrogel films were removed and weighed, while weighing the swollen hydrogel films the water on the films surface were wiped with filter paper so as to ensure only the entrapped liquid by the hydrogel films was weighed. The swelling percentage of the hydrogels was calculated according to the following equation:

$$S(\%) = \frac{Ws - Wd}{Ws} x100$$

Where W_s and W_d are the weights of the swollen and dried hydrogel films respectively.

Preparation of Promethazine Solution

A promethazine solution of 1 mg/ml was prepared by taking 1 g of the drug, dissolved in distilled water, and made up to the mark of 1 L capacity volumetric flask.

Drug Loading

The loading of promethazine drug was done by weighing a known weight (2 g) of the hydrogel and immersed into the solution containers for adsorption to take place for 24 hours (equilibrium swelling) after which the hydrogel was removed from the solution and dried at room temperature for 48 hours. The residual concentration of the solution was measured to determine the percentage of drug entrapment in the hydrogel using Perkin Elmer UV- Visible Spectrometer at a wavelength of 254 nm. The percentage drug entrapment was calculated using the following equation.

$$\%A = \frac{Ci - Cf}{Ci} \times 100$$

Where C_i and C_f are the initial and final concentration of the drug respectively (Muhammad *et al*., 2016)

In Vitro Release of Promethazine Drug

The *in vitro* release of the entrapped promethazine drug was carried out by placing the hydrogel pellet loaded with the promethazine drug in an enzyme-free simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) at 37ºC. The release study was carried out in INNOVA 4000 INCUBATOR SHAKER with reciprocating motion of (100 rpm). After each periodic interval, the release medium was replaced with a fresh simulated gastric fluid and simulated intestinal fluid.

RESULTS AND DISCUSSION

Figure 1 shows the FTIR spectrum of the synthesized hydrogel with the key functional groups highlighted.

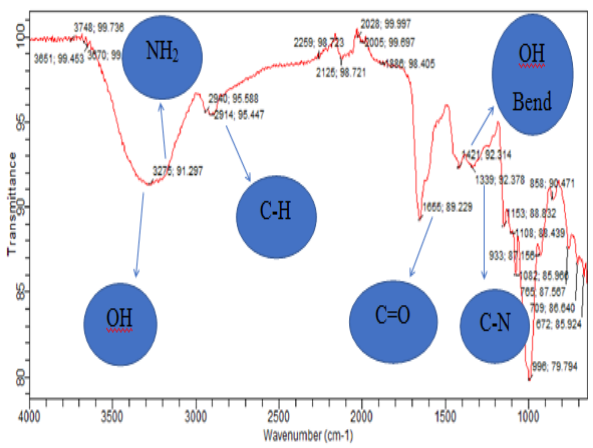
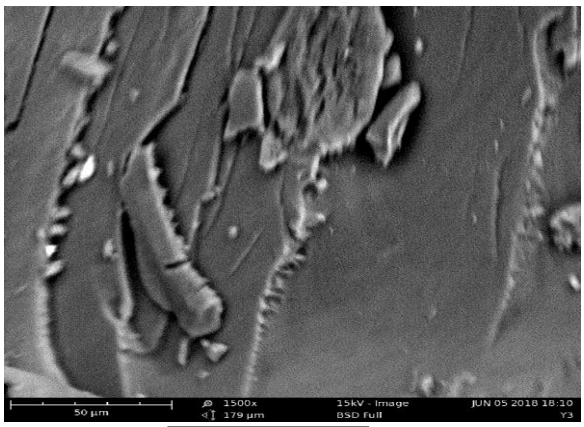


Figure 1: FTIR Spectrum of Starch-g-acrylamide Hydrogel

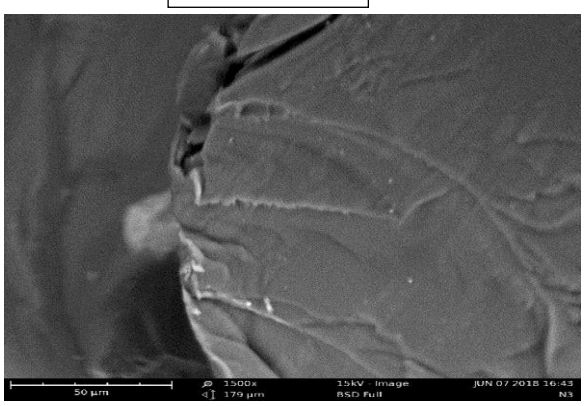
The IR spectrum showed the absorption bands at 3275 cm^{-1} for (N-H stretching), 1655 cm^{-1} for (C=O of amide stretching), 2936 cm^{-1} for (C-H)

and broad band at 3650 cm^{-1} for (OH stretching). There is also a band at 1339 cm^{-1} for (-C-N-) group of the crosslinking agent (N'N-methylene bisacrylamide) and a presence of another band at 1421 cm^{-1} for (OH) bending. Since the polymeric hydrogel has been extracted to remove the soluble content, the presence of these key functional groups in the spectrum has indicated the successful formation of starch-g-acrylamide hydrogel.

Figure 2 shows the images obtained from scanning electron microscopy of the prepared hydrogel before and after drug loading. The first image (Figure 2a) shows the surface of the hydrogel before promethazine loading while Figure 2b is the surface of the hydrogel after loading.



A **Before loading**



B **After loading**

Figure 2: SEM images of S-g-Acrylamide Hydrogel Before and After Promethazine Loading

It can be seen clearly from the images that the hydrogel surface is rough and there are micropores for the accommodation of water/biological fluids and drug particles.

Figure 3 shows the percentage swelling of the prepared hydrogel in solutions of various pH (1-12).

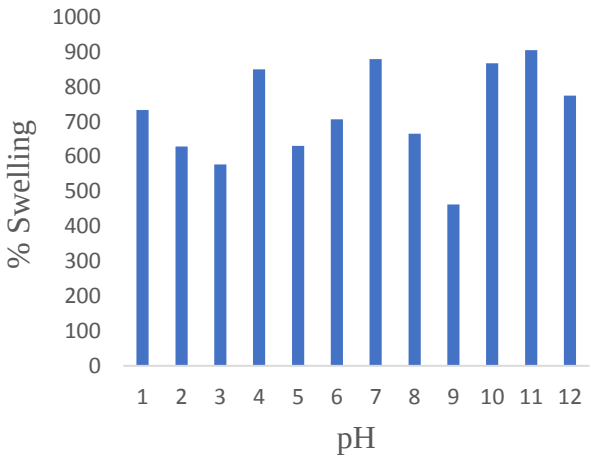


Figure 3: Percentage Swelling of Starch-g–acrylamide Hydrogel.

The swelling percentage of starch-g-acrylamide hydrogel suggests the hydrogel has lower absorption ability at lower pH when compared to the higher pH. This is because at higher pH (greater than 7), there was an increase in the amount of the ionized groups which generate an electrostatic repulsion between the adjacent ions in the polymer structure of the hydrogel. Hence, this has resulted in the enhancement of water intake capacity of the hydrogel and subsequently increases the swelling capacity of the hydrogel (Mateen *et al*., 2016). Meanwhile at lower pHs the swelling percentage is also appreciable, this is because of the conversion of free hydroxyl groups to oxonium salt, which reduces the voids and this resulted in the low water intake by the hydrogel. Kunal et al. (2015) have previously reported similar results. Furthermore, the existence of hydrogen bond between the starch and the carbonyl groups of the acrylamide may also play a role in reducing the swelling capability of the hydrogel, because the hydrogen bond will always bring about additional cross-links to the hydrogel and this will directly reduce the swelling capability of the hydrogel. However, the decrease in swelling capacity of the hydrogel observed at higher pH (12) may be attributed to the fact that, at higher pH there is existence of sufficient sodium ions (Na^+) and charge screening effect of these

excess Na^+ in the swelling media. Furthermore, this may shield the carbonyl ions and prevents effective anion-anion repulsion, which would have resulted in higher swelling. This finding agrees with the work of Sadeghi, 2011.

The percentage drug release of the prepared hydrogel at various times in an enzyme-free SIF and SGF is presented in Figure 4.

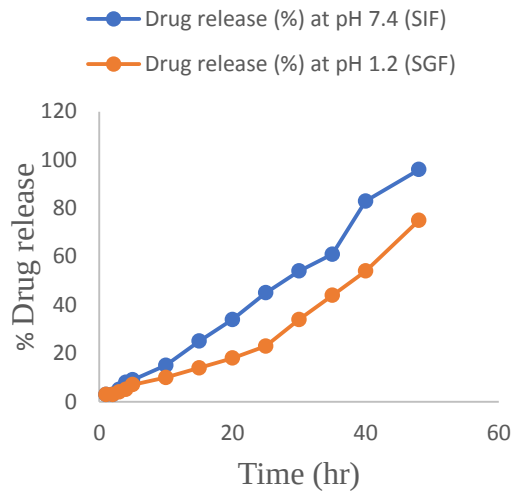


Figure 4: *In vitro* Release Studies of PMZ Loaded Starch-g-acrylamide in enzyme-free SGF and SIF.

After 24 hours of hydrogel swelling in the promethazine drug solution, about 99% of the drug was entrapped in the hydrogel. The results showed that during the first five hours the release was found to be 7 % in SGF while it was 10% in SIF, after 10 hours the release was 24 % in SIF as compared to 9 % in SGF. At the end of 15 hours, the release was found to be 15 % and 27 % in both SGF and SIF, respectively. The low release in SGF as compared to that of SIF can be attributed to the pH sensitivity of the hydrogel since the hydrogel has to swell before it releases its contents. At the end of 48 hours 89% and 96% of the drug was released in both SGF and SIF, respectively. Similar results have been reported by other researchers (Kono and Teshirogi, 2015).

CONCLUSION

In conclusion, the synthesized hydrogel was demonstrated to have excellent fluid absorption and retention capacity in solutions of various pH. The drug loading and release of the synthesized hydrogel have indicated that the hydrogel has excellent drug entrapment and release capacity.

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