Modification of Starch with Allopurinol and Ampicilline as Sulfonamide Derivatives

Firyal M.A., Firas A. Rahi*, Wessal M. KH., Ahmed I. Alshather** and Shurooq S.K.
Department of Chemistry, College of Science, Al-Mustansiriya University, Baghdad-Iraq.
*Department of Pharmaceutical Chemistry, College of Pharmacy, Al-Mustansiriya University, Baghdad-Iraq.
**National Center for Drug monitoring and Research, MOH, Iraq.

Abstract

The available hydroxyl groups on the starch chains potentially exhibit reactivity specific for alcohols which were modified with chlorosulfonic acid at zeroºC to yield starch sulfonic acid P_1, then substitution of P_1 to its corresponding drug derivatives such as with allopurinole or ampicilline P_2 and P_3 respectively. The new prepared starch derivatives were characterized byFT.IR and UV. Spectroscopy. The physical properties were studied. Thermal analyses were recorded and swelling % were studied, Controlled drug release were measured at different pH values at 37ºC. Intrinsic viscosities were measured using Ostwald viscometer at 30ºC. This technique through which stomach drug targeting can be achieved as timed released system.

Introduction

Starch in mainly composed of two homopolymers of D-glucose[1]: amyl -ase, a mostly linear α-D(1,4`)-glucan and branched amylopectin, having the same backbone structure as amylose but with many α-1,6`-linked branch chains two secondary hydroxyl groups at C_2 and C_3 of each glucose residue, as well as one primary hydroxyl group at C-6 when it is not linked[2].Various physical or chemi -cal modifications of starch such as blending, derivation and graft copoly-merization have been investigated to improve the properties of starch [3]. Starch and Chitosan are abundant naturally according polysaccharide.

Both of them are cheap, renewable, nontoxic and biodegradable [4].Starch is a natural polymer which possesses many unique properties and some shortcoming simulanteously [5]. Choice of the initiator is one of the main controlling factors in the graft yield and graft reaction efficiency percent [6, 8]. Many researchers have studied the graft polymerization on starch with vinyl monomers initiated by ceric salts [9,10]. In the work, the modification of starch as natural polymer with some drugs could attach through sulfonamide group which could hydrolyzed for controlled drug release in different pH values, and to minimize the side effect of the substituted drug.

Experimental

Materials and Instruments

Allopurinol and ampicilline were obtained from College of Pharmacy, Starch was purchased from BDH.

All chemical materials were used without further purification.

U.V spectra were recorded by a Shimadzu UV-vis-60.

Shimadzu FT.IR8000 series Fourier transform infra red Spectrophotometer (Japan).

Thermo gravimetric analysis was carried out on a Shimadzu. 60 instrument (Japan), it was heated at10ºC min^{-1}in air (normal).

Sulfonation of Starch P_1

(3g, 0.019mole) of starch was solubilized into 10ml of anhydrous DMF. The mixture was introduced in a round bottomed flask equipped with condenser and droping funnel which contained excess of chlorosulfonic acid (1.5ml, 0.06mole) was added dropwise with vigorously stirred at 0ºC about 1day. The reaction mixture was heated at 40ºC for 1hr. The solvent was evaporated under vacuum; A brown precipitate was formed, washed with ether and dried. It is easy soluble in water or ethanol.

Substitution of sulfonated starch P_2,P_3

1mole ratio of sulfonated starch with 1mole of the suitable drug such as allopurinol or ampicilline were solubil -ized in DMF, the

mixture was stirred and heated at 40ºC for 30mins. The solvent was evaporated and the modi -fied polymer was collected (11), washed with ether and dried. Table 1 lists the physical properties of P_2 and P_3.

Table (1)
Physical properties of P_1-P_3 starch -O- SO_2-X.

Starch No.	*X*	*S.P.º C*	*µin dℓ/g*	*Color*	*Yield %*
P_1	**-OH**	**200-210**	**0.21**	**Brown**	**70**
P_2	***O*-Allopurinol**	**148-155**	**0.23**	**Deep brown**	**45**
P_3	***O*-Ampicilline**	**241-249**	**0.22**	**Gray**	**48**

S.P= Softening point,
µin dℓ/g =Intrinsic viscosity.

Thermal Analysis

Thermal analysis was performed using a TGA instruments Q10 at different scanning calorimeter equip -ped a RCS accessory under nitrogen atmosphere. The standard procedure is applied (11,12): the sample (about5mg) was heated at 300ºC for

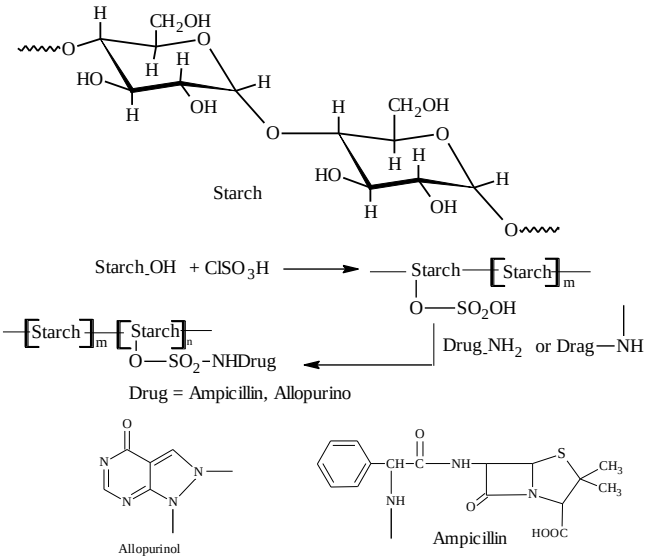
5min in order to eliminate the influence of thermal history and the effect of heat treatment on the crystalline structure of the materials then cooled down to 50ºC and then reheated to 300ºC to record the melting temperature. Quantitative ana -lysiscorrespond -ding to the amount of pendant sulfonic groups incorp -orated into starch was performed by a titration method as follows:0.1g of modified polymer was put in 10ml of ethanol was directly titrated to a phenolphthalene end point using sodium hydroxide (0.05M) in metha -nol. The mole percentage of the sulfo-nated starch, and without modificat -ion was also titrated as a blank value.

Invitro controlled drug release study:

100 mg of P_2 or P_3 drug polymers were placed in 100ml of buffer solution with pH 1.1 or 7.4 at 37ºC.3ml of solution was tested using UV. Spectrophotometry at suitable λ_{max} the measurements of UV. Spectra were recorded continuously for every day. The controlled drug release was included weight% of drug release respect to time as shown in Fig.(1).

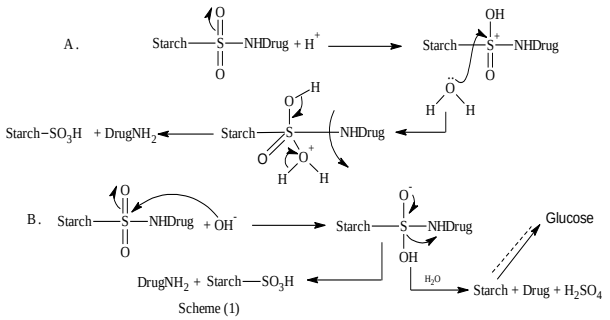
Results and Discussion

To improve the controlled drug release to sustained drug system, the drug was bonded with sulfonated starch as illustrated bellow:



In this work the starch was used as natural polymer because it is totally biodeg -radable in a wide variety of environments. It can hydrolyzed into glucose by microorganism or enzymes and the metabolized into carbon dioxide and water [13].

Starch sulfonamide drug can be utilized as carriers for selective and sustained delivery of drug as pharmaceutical agent. The delivery of drug at a sustained rate, targeted delivery of drugs at specific sites to minimized toxicity and enhanced selectivity for certain antitume agents. The prepared drug starch polymers P_2,P_3 with remaining some of – SO_3H groups through the chains as a pendantgroups (14). These prepared polymers P_2&P_3 could hydrolyses through chemical sulfonamide with gradually release at acidic medium is higher than basic medium as shown in Fig.(1) and as explained in the following mechanism:



Scheme (1)

Fig.(1) shows controlled drug release and according to UV. Spectra in acidic and basic medium are as shown in Fig.(2) at λ_{max}=350nm of starch ampicillin sulfonamide in pH1.1.

This prepared natural drug polymers were appeared asgood thermally stable polymerswith softening point at 148-155ºC of P_2 and at 241-249ºC of P_3. The high swelling % of the two polymers P_2 and P_3 in water due to their solubility, which attributed to remained–SO_3 Hgroups with 25% which was calculated by titration.FT.IR spectrum of P_3, Fig.(4) shows the absorption of OH –Starch at 3450cm^{-1} and 3200cm^{-1} of NH sulfonamide, The C-H aromatic of ampicilline was observed at 3049cm^{-1} and C-H aliphatic was observed at 2965cm^{-1}, the C=O of β-lactame of ampicilline was revealed at 1734cm^{-1} and C=O amide at 1685cm^{-1}, the SO_2 asymmetric and symmetric absorption was appeared at 1370-1170cm^{-1}, the absorption at 1119cm^{-1} is due to C-O stretching of ether-starch. The broad band was observed of 3500-2950cm^{-1} due to OH carboxylic acid of ampicilline.

Fig.(5) FT.IR of P_2 allopurinol starch sulfonamide shows the absorption at 3444cm^{-1} of OH and at 3216cm^{-1} of NH sulfonamide and 3135cm^{-1} of NH of the drug CH-unsaturated at 3076cm^{-1} and CH aliphatic at 2910cm^{-1}, and for C=O group at 1735cm^{-1} and for C=C at 1645cm^{-1}, the asymmetrical and symmetrical SO_2 absorptions were revealed at 1370-1180cm^{-1}.We concluded from these results that the prepared drug starch sulfonamide polymers could release at sustained rate in acidic medium in stomach site with more selectivity action, which could be used as coating with pH sensitive polymer, coating with biodegradable polymers as starch derivatives.

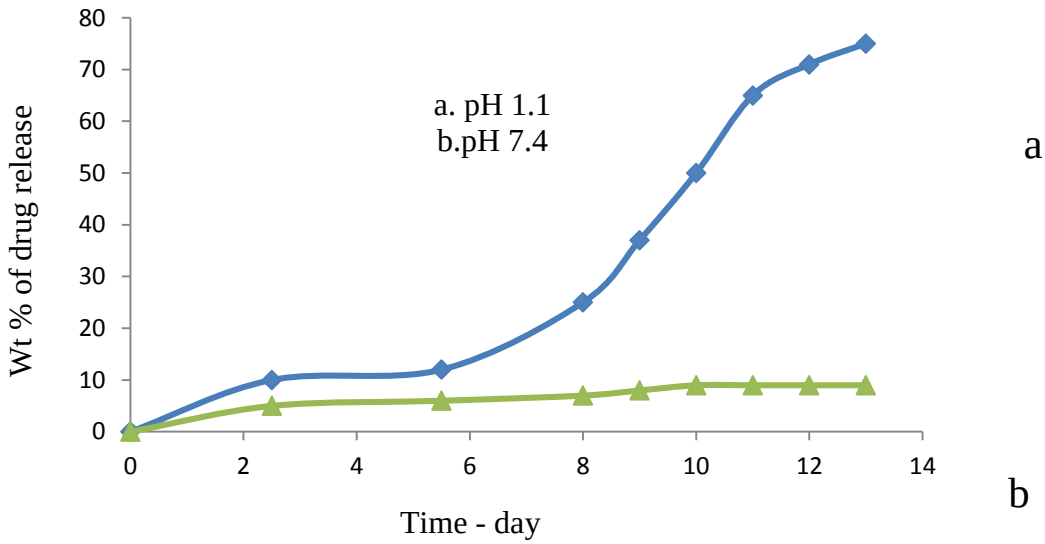


Fig.(1) Controlled drug release at 37ºC of P_2.

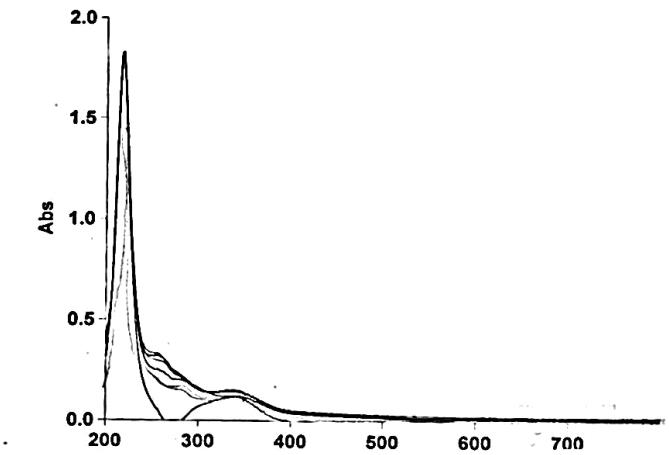


Fig.(2) Uv spectra of Starch Ampicilin sulfonamide at pH 7.4.

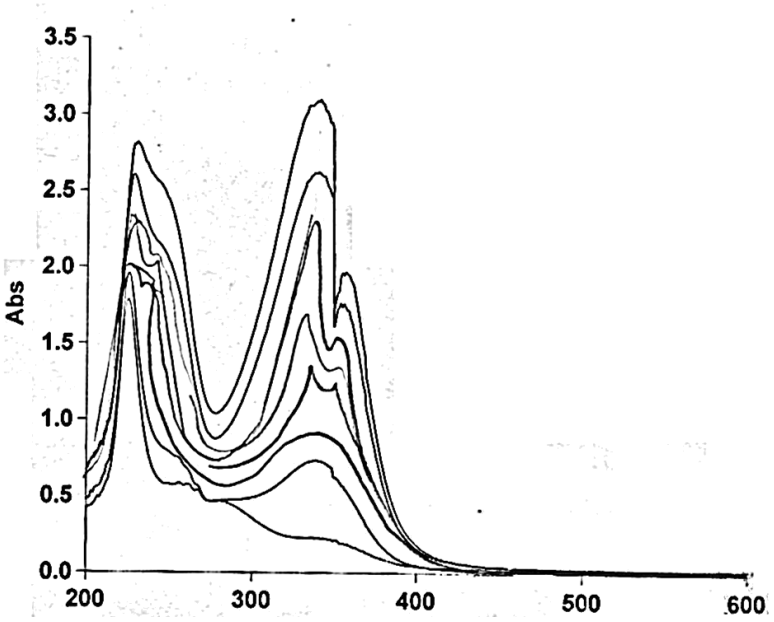


Fig.(3) Uv spectra of controlled drug release at 37°C of P2 at pH1.1.

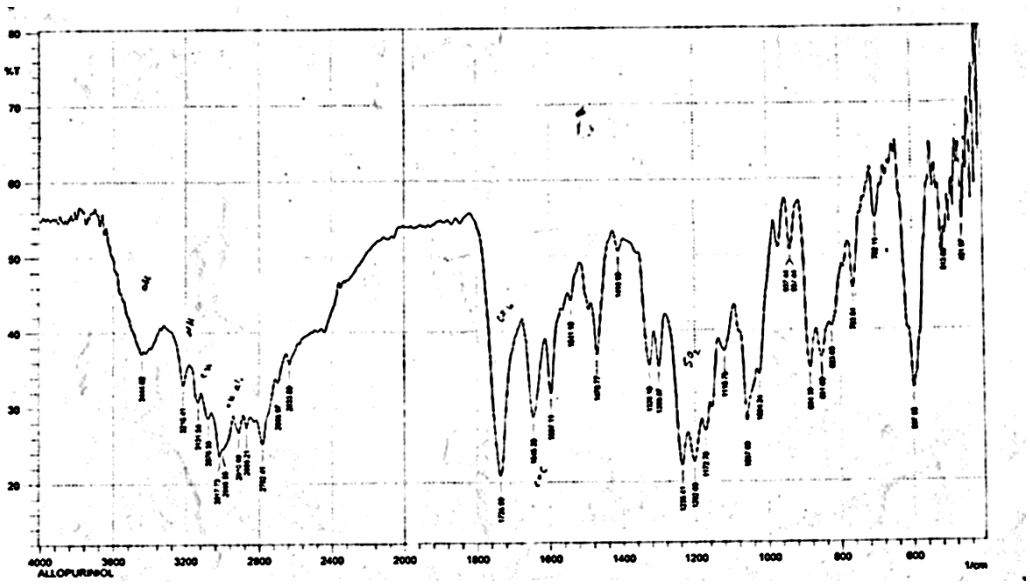


Fig.(4) FTIR of ampicillin with starch sulfonate P2.

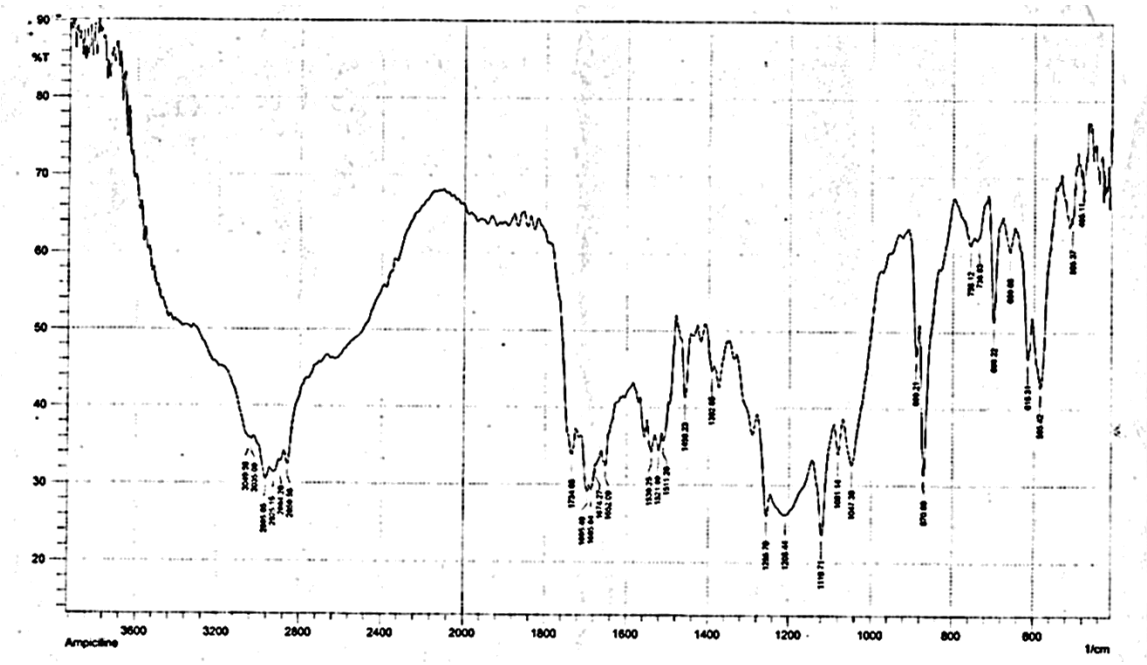


Fig.(5) FTIR of Allopurinol with starch sulfonate P3.

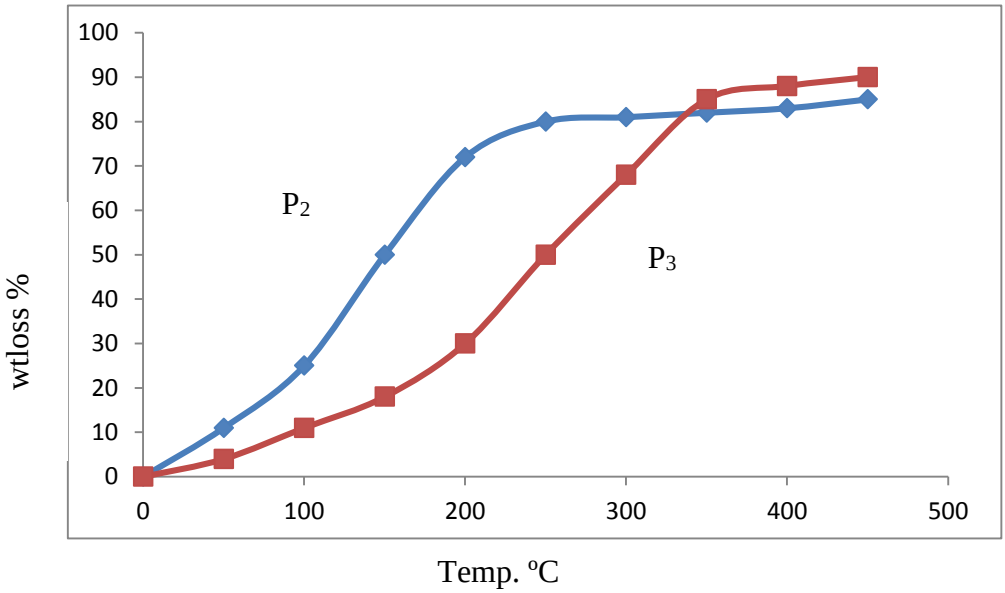


Fig.(6) Thermal analysis of prepared P2& P3.

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الخلاصة

ان وجود مجاميع الهيدروكسيل على سلاسل النشا من المتوقع ان تكون فعالة كمجاميع كحولية حيث حُورت مع حامض الكلوروسلفونك بدرجة صفر درجة مئوية الى النشا المسلفن (P_1). ثم عوض (P_1) الى المشتق الدوائي المقابل مع الالوبيورينول او الامبيسيلين مثل البوليميرين (P_3,P_2). شُخصت البوليميرات المحورة بواسطة مطياف الاشعة تحت الحمراء والاشعة فوق البنفسجية. دُرست الصفات الفيزيائية وأُجريت التحاليل الحرارية، وحسبت النسب المئوية للانتفاخ. وقيست سرع التحرر الدوائي المحكم بدوال حامضية مختلفة بدرجة ٣٧°م. قيست اللزوجة الجوهرية باستعمال جهاز اللزوجة الاوستوالد بدرجة ٣٠°م. هذا التحوير للنشا يهدف الى نظام التحرر الدوائي في المعدة كوسط قاعدي.

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