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Synthesis, Characterization and Biohydrolysis Drug Release Studies of Polymercarrier with Ketoprofen.

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Abstract

In the present work, the hydroxyl groups of starch polymers bonds with bioactive material (Ketoprofen drug) by esterification process. (direct esterification and indirect esterification). The modified starch polymers are characterized by some spectroscopic methods such as FTIR ,UV, H^1. NMR and C^{13}.NMR. The degree of substitution (D.S) of the hydroxyl groups in starch molecule was determined in all cases. The hydrolysis of modified starch polymers is carried out in the heterogeneous phase in a buffer solution of pH (2.0 , 7.0 and 9.0) at various temperatures (25, 37, and 45 C^o). The amounts of released Ketoprofen drugs were quantitatively determined by using calibration curve method. Biodegradation (in vitro degradation) of modification starch polymers is carried out by enzymatic cleavage (using lipase enzyme) at pH 2.0 and 37C^o. The amounts of released ketoprofen were quantitatively determined by U.V visible spectrophotometry by using the usual calibration curve method. In general, it was found that the release in presence of enzyme was faster than in hydrolysis process.

Keywords: modification starch, Drugs release, ketoprofen.

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تحضير وتشخيص ودراسة حياتية لانطلاق الدواء من بوليمر محمل بالكيتوبروفين.

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الملخص

البحث الحالي يتضمن ارتباط بين النشا مع المادة الدوائية (كيتوبروفين) بواسطة مجموعة الهيدروكسيل العائدة للنشا، وتتضمن عملية الاسترة (استرة مباشرة واسترة غير مباشرة) وشخصت بوليمرات النشا المحورة بواسطة بعض الطرق الطيفية وهي تقنيات الاشعة تحت الحمراء (IR)، واطياف الاشعة الفوق البنفسجية والمرئية (UV) وتقنية الرنين النووي المغناطيسي للبروتون والكاربون (H^1NMR،C^{13}NMR). كذلك تم حساب درجة التعويض (D.S) في جميع الحالات وقد تبين ان اعلى درجة التعويض تنتج عندما تكون الاسترة بواسطة كلورو اسيتايل كلورايد.

وتم دراسة التحلل المائي في الطور غير المتجانس لمشتقات النشا المحورة باستخدام محاليل منظمة بقيم الاس الهيروجيني pH(2.0,7.0 and9.0)، وبدرجات حرارة مختلفة هي($45C^o$ and 37 ,25) وحسبت كمية كيتوبروفين المتحرر من عملية التحلل المائي لمشتقات النشاء كميا بواسطة مطيافية الاشعة الفوق البنفسجية باستخدام طريقة المنحي القياسي للمادة الدوائية كيتوبروفين.

وتم كذلك دراسة التحلل الحياتي لمشتقات النشا بواسطة التكسر الانزيمي بواسطة انزيم اللايبيز في محلول درجة الحموضةpH=2.0 ودرجة حرارة $37C^o$ وقد حسبت كمية الكيتوبروفين المنطلق باستخدام المنحني القياسي وبشكل عام نلاحظ ان انطلاق جزيئات الدواء كان اسرع بوجود الانزيم.

الكلمات الدالة: النشاء المحور، انطلاق الدواء، كيتوبروفين.

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1. Introduction

The past few decades have been a tremendous advancement in the area of drug delivery using polymeric particulate carrier systems for small and larg molecules. Enhanced medical treatment do not always require a stronger medicine/drug but a better mechanism to deliver the drug [1].Starch and Chitosan are abundant naturally according polysaccharide. Both of them are cheap, renewable, nontoxic and biodegradable [2]. Starch in mainly composed of two homopolymers of D-glucose [3].

Starch is a natural polymer which possesses many unique properties and some shortcoming simultaneously [4]. A majority of drug delivery systems using natural polymers have been based on proteins (e.g., collagen, gelatin, and albumin) and polysaccharides (e.g., starch, dextren, hyaluronic acid, and chitosan) [5]. very large chains, contain a variety of functional groups, can be blended with other low- and high–molecular-weight materials, and can be tailored for any applications. Polymers are becoming increasingly important in the field of drug delivery. Advances in polymer science have led to the development of several novel drug-delivery systems. A proper consideration of surface and bulk properties can aid in the designing of polymers for various drug-delivery applications [6]. Sodium starch glycolate Super disintegrant for tablets and capsules in oral delivery [7].

2. Experimental

Melting points were determined using an open – ended capillary method and are uncorrected. The purity of synthesized compounds was checked by TLC. Infra red spectra (FTIR) were recorded on Shimadzu FT-IR-8300 spectrophotometer and H^1NMR spectra were recorded on a BRUKER-400 MHz operating at 300 MHz with tetra methyl silane as internal standard in $CDCI_3$ and DMSO-d_6 as solvent.

A-Synthesis of the modified starch polymers:

i)direct esterification of starch [8]. Starch (3g,2M) and ketoprofen (1g,0.5M) were dissolved in dimethyl sulphoxide (25ml). Sulphoric acid (2ml,0.2M,98%) was then added drop wise while stirring at (50-60C^o) for 4h,and the temperature was lowered to drop to 25C^o,and the reaction continued for overnight. The mixture was poured into 100ml of distilled water in a sepratory funnel, and the upper layer of crude ester was removed and washed again with 100ml of distilled water, followed by 25ml of saturated sodium bicarbonate solution and 50ml of distilled water, The Easter must, of course, be separated between each washing, and

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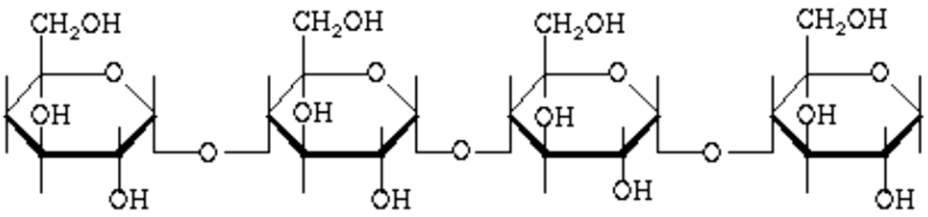
then dried under reduced pressure in the presence of phosphorus pentoxide to give a white powder (0.24g, yield 52%), the FTIR spectrum (KBr disc) shows a band located at 1650 cm^{-1} which is assigned for C=O, the degree of substation (D.S) is 1.6 .

ii)Indirect esterification of starch [9]**.** (1.5g) ketoprofen was slowly added in to the thionyl chloride. When the addition was completed the solution was refluxed for 3h.The excess of thionyl chloride passes over, followed by ketoprofen chloride at 165-166C^{o} (0.77g) . Starch (1g) is dissolved in dimethyl sulphoxide 5ml in a 100ml bolt-head flask provided with a reflux condenser. The flask was cooled in ice and the ketoprofen chloride was introduce slowly and insert acotten wool (or calcium chloride) guard tube into the mouth of the condenser. The acid chloride was added slowly (45 minute) to the starch with frequently shaking. The ice is removed and allowed to stand for overnight. The reaction mixture was poured into water. It was wased with little sodium bicarbonate solution, then with distilled water, and dried with anhydrous calcium sulphate to give a yellow powder (0.56g.yield 76%), the FTIR spectrum (KBr.disc) show aband located at 1755cm^{-1} which is assigned for C=O, and the degree of substitution D.S is 2.5.

iii)Indirect esterification by use chloroacetyl chloride

The chloroacetyl starch [10] (5g) was dissolved in (100ml) dimethyl form amide at room temperature and calculated amounts of potassium salt (2.5g) of ketoprofen were added with stirring. All reactions were performed at 40C^{o} during 8h and the polymer remained soluble throughout the process. The modified starch polymers were isolated by precipitation with distilled water. All sample were purified by reprecipitation by using dimethyl sulphoxide as solvent and ethanol as precipitant, and then dried under reduced pressure in the presence of phosphorus pentoxide . Determination of degree substitution (D.S) by method of Genung and Mallatt [11].



Cell = starch

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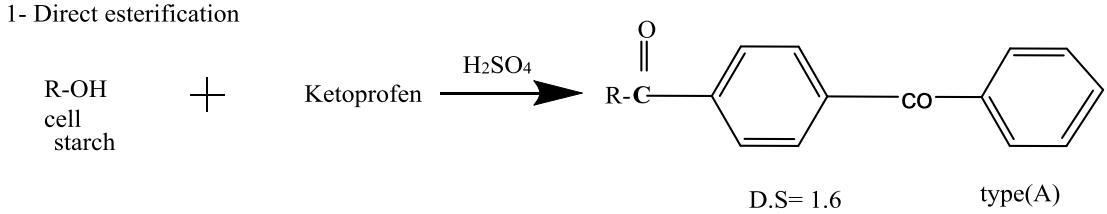
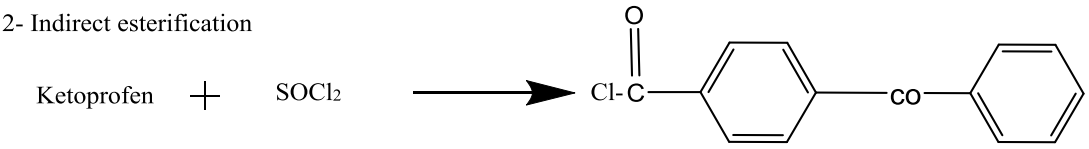
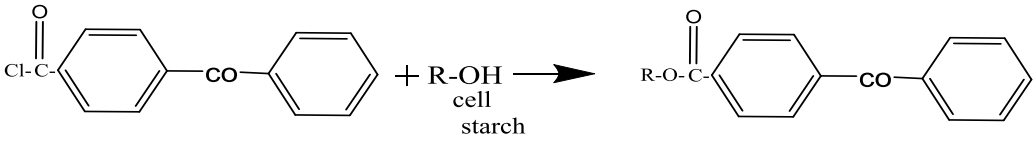
1- Direct esterification



D.S= 1.6 type(A)

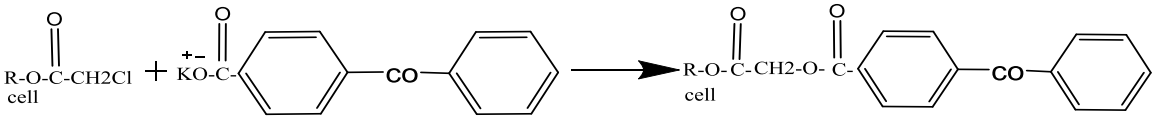
2- Indirect esterification





D.S =2.5 type(B)

3- Esterification by $ClCH_2COCl$



D.S =2.5 type(C)

B- Heterogeneous hydrolysis reaction:

Hydrolysis test [12] was performed by using modified starch polymers adducts, which are insoluble in water, but did swell on standing in this medium. The release reactions were carried out in buffer solutions (phosphate buffer) at various pH (2.0,7.0,and 9.0). Modified starch polymers samples were ground and sieved to a particle size lower than (120μm). About (100mg) of each adduct sample in fine powder form was placed in a glass support. The device was placed in pyrex Stoppard test tubes, each containing (25ml) of an aqueous buffer solution. In other cases, sample preparation for release experiments was as follows: about 100mg of each adduct in powder form (<120μm) was compressed at high pressure to form discs. The resulting discs were placed in pyrex Stoppard test tube, each one contains 25ml of

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an aqueous buffer solution. In all cases, the pyrex Stoppard test tube were immersed in a thermostatically controlled bath at (25, 37, and 45 C^o). A periodic assay of samples was obtained by pipetting a (1.0ml) sample. The amount of released ketoprofen was quantitatively determined by UV spectroscopy (water as solvent) at λ_{max} 286 nm by using calibration curves.

C- Biodegradation (In vitro degradation):

Modified starch polymers was ground and sieved to a particle size less than 120μm. A bouth100mg of each adduct sample in fine powder form was placed in glass support containing 2.5ml of an aqueous buffer solution (pH 2.0) with 20mg of Rhizopus delemar lipase [13]. The pyrex Stoppard test tubes were immersed in a thermostatically controlled bath at 37 C^o. A periodic assay of samples was obtained by pipetting 1.0ml sample. The concentration of ketoprofen released was determined by UV spectroscopy at λ_{max} 286 nm by using calibration curves.

3. Results And Discussion:

In the present study, the bound of ketoprofen drug molecule with starch macromolecule was carried out successfully by three types of esterification processes.

A) Direct esterification:-

Modified starch polymer (A) was obtained when the starch (R_{cell}-OH) is treated with ketoprofen using H_2SO_4 as catalyst in DMSO solvent. This modified (A) was obtained as a whit crystals with (yield of 52%) and the degree of substitution (D.S)=1.6. The FTIR spectrum showed a stretching band at 3300 cm^{-1} which is assigned for the OH hydroxyl group stretching vibration and the appearance of two carbonyl groups C=O at 1650 cm^{-1} and 1700 cm^{-1} which belong to ester groups and the band located at 3210 cm^{-1} is due to the C-H aromatic band stretching vibration which ,when compared with the FTIR spectrum of starch proved the esterification process between drug and starch had occurred. The H^1NMR spectrum clearly shows a δ (3.55 - 3.85, m) ppm for H-1and H – 2 , δ (3.95, d) ppm for H-3, (5.1, t) ppm for H-4, δ (5.4, d) ppm for H-5 and δ (5.7, d) ppm for H-6 ,these data for glucose moiety in starch polymer. It also clearly shows a δ (7.1, d) ppm for H- aromatic and δ (2.5, s) ppm for – CH_3 group of ketoprofen. The C^{13}NMR spectra show the band a δ (47.5) ppm for – CH_3 group(of ketoprofen) ,(63.6-73.8) ppm for the C-OH , δ (117.8) ppm for the (C-O- ether

group), δ (155.7-160.2) ppm for (C-O-C=O) two ester groups and δ (130.9-151) ppm for the (C=C) aromatic band.

B) Esterification by acid chloride:-

The acid chloride [(ketoprofen chloride) was prepared from the reaction of ketoprofen with thionyl chloride] and then treated with starch in DMSO to give modified polymer (B). this method was chosen because it gives (B) in good yield, high purity, with short time[14].

The modified (B) was obtained as a yellow powder with (yield of 76% D.S =2.5). The FTIR spectrum, show a stretching band located at 3460 cm^{-1} which is due to the O-H hydroxyl group, a stretching band at 1745 cm^{-1} for C=O in the ester group and the band located at 3080 cm^{-1} which is attributed to the C-H stretching in the aromatic ring. The H^1NMR spectrum for the modified starch (B) clearly shows a (3.55 – 3.85 ,m) ppm for H – 1 and H – 2, (3.95,d) ppm for H – 3, (5.1, t) for H – 4 , (5.4, d) for H – 5 and (5.7,d) for H – aromatic and (2.5,s) for – CH_3 group of ketoprofen. The results of H^1NMR spectral data proved the occurrence of esterification process between starch polymer and ketoprofen. The C^{13}NMR spectra for modified starch polymer compound(B) show the bands a (47.5)ppm for – CH_3 group (of ketoprofen), (63.6 – 73.8) ppm for the (C – O-H) hydroxyl group, (117.8) ppm for the (C–O -) ether group, (155.7 – 160.2) ppm for (C-O-C=O) two ester groups and (130.9 – 151) ppm for C (C=C) aromatic band.

C) Esterification using chloroacetyl chloride:-

The starch chloroacetyl chloride was treated with ketoprofen salt in DMSO solvent for (8hrs) to obtain modified starch (C) as a white powder (yield of 63%, mp. 197C^o ,D.S=2.5). The FTIR spectrum showed a stretching band at 3225 cm^{-1} which is assigned for the hydroxyl group. A stretching band located at 1754 cm^{-1} and 1745 cm^{-1} are assigned for the two C=O i ester groups and the band appeared at about 3123 cm^{-1} is for the (C-H) aromatic band stretching vibration. The results of the FTIR spectra, compared with the FTIR of starch and ketoprofen proved the occurance esterification of starch.

D) Chemical and biohydrolysis:-

In this work the starch was used as natural polymer because it is totally biodegradable in a wide variety of environments. It can hydrolyzed into glucose by microorganism or enzymes and the metabolized into carbon dioxide and water [14]. Rate of hyrolysis of pendant

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bioactive agents from polymer – bioactive compound adducts depend upon a number of factors, including the sample form and the hydrophilic character of the adduct as well as the pH value of the medium. Fig. 1 show a typical profiles of heterogenous hydrolysis at 25C^{o} ,pH 2.0 of the modified starch polymer (A) , adduct in powder or disc form. As it is seen, the total release of the active compound was reached more quickly in the case of the adduct in powder form, as it would be expected. In the case of modified starch polymers (A), (B) and (C), Figs. 1,2 and 3 show the conc. of released aspirin time. The Fig. 4 show the modified starch by chloroacetyl chloride the total release was reached quickly.

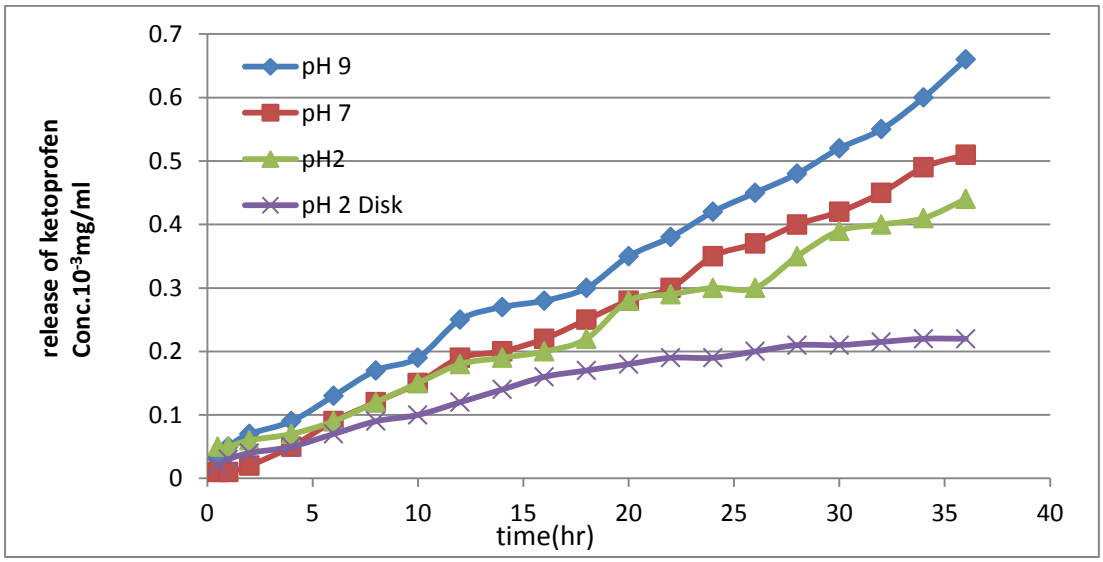

Fig. 1: Release of Ketoprofen from the modified polymer (A)at 25 C^{o}.

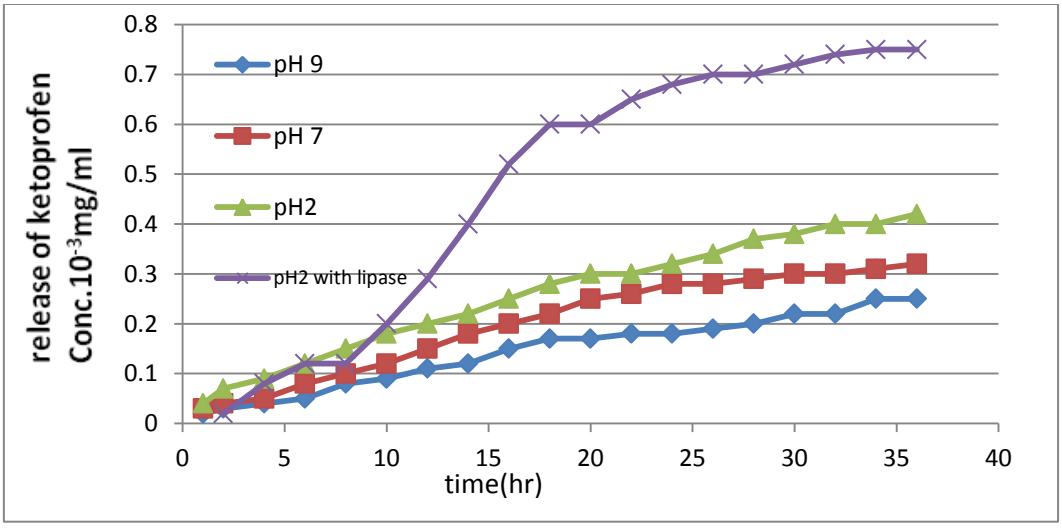

Fig. 2: Release of Ketoprofen from the modiefied polymer (A) at 37 C^{O}.

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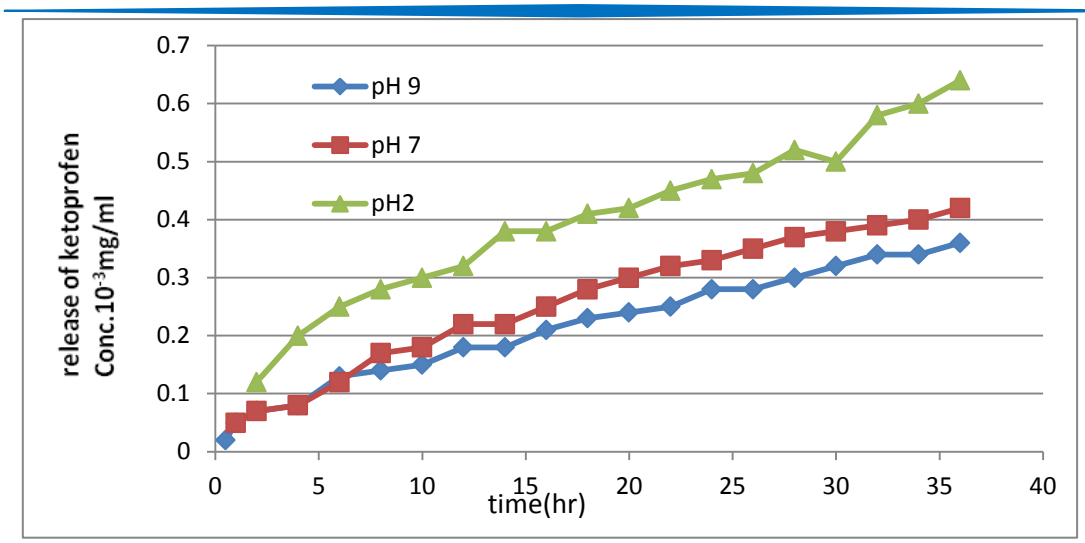

Fig. 3: Release of Ketoprofen from the modiefied polymer (A) at 45 C°.

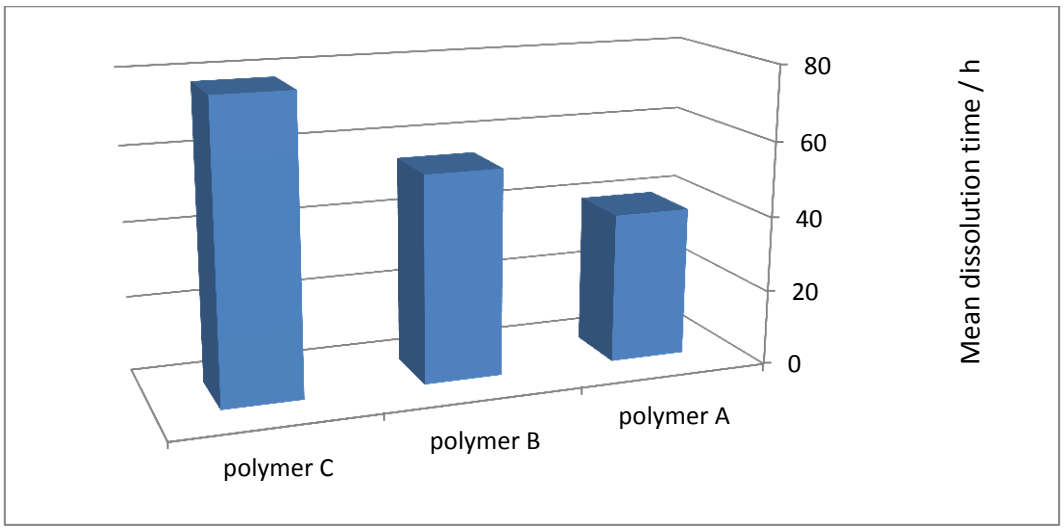

Fig. 4: Meam dissoiution time for modified polymers under study.

4. Conclution:

In the work described, the coupling of starch with bioactive (chloroacetyl chloride method) gave higher D.S=2.5. It is found that the total release of the active compound was reached quickly in the case of the adduct in powder form and the release of bioactive can be accelerated by addition of esterase's (lipase enzyme) and increases the temperature.

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