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Synthesis, characterization and biohydrolysis drug release studies of polymer carrier with Naproxen

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ABSTRACT

In the present work, the hydroxyl groups of "HPMC, HPC and HEC" polymers bonds with bioactive material "naproxen drug" by esterification process. (direct esterification and indirect esterification). The modified s 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 suger molecule in polymer was determined in all cases.

The hydrolysis of modified polymers is carried out in the heterogeneous phase in a buffer solution of pH (2.0, 7.4 and 9.0) at various temperatures (25, 37, and 45 C^o). The amounts of released naproxen drugs were quantitatively determined by using calibration curve method.

Biodegradation (in vitro degradation) of modification polymers is carried out by enzymatic cleavage (using lipase enzyme) at pH 7.4 (the human blood pH) and 37C^o. The amounts of released naproxen 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 polymer. Drugs release. naproxen

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تحضير وتشخيص ودراسة حياتية لانطلاق الدواء من بوليمر محمل بالنابروكسين

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الملخص

البحث الحالي يتضمن ارتباط بين البوليمرات (HEC, HPC, HPMC) مع المادة الدوائية (نابروكسين) بواسطة مجموعة الهيدروكسيل العائدة للبوليمرات, وتتضمن عملية الاسترة (استرة مباشرة واسترة غير مباشرة) وشخصت البوليمرات 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 البوليمرات المحورة باستخدام محاليل منظمة بقيم الاس الهيروجيني (pH:2.0,7.4 and 9.0) وبدرجات حرارة مختلفةهي C^o (25, 37 and 45) وحسبت كمية نابروكسين المتحرر من عملية التحلل المائي لمشتقات البوليمرات المحورة كميا بواسطة مطيافية الاشعة الفوق البنفسجية باستخدام طريقة المنحي القياسي للمادة الدوائية نابروكسين.وتم كذلك دراسة التحلل الحياتي للبوليمرات المحورة بواسطة التكسر الانزيمي بواسطة انزيم اللايبيز في محلول درجة الحموضة pH=7.4 (حموضة دم الانسان) ودرجة حرارة 37 C^o وقد حسبت كمية النابروكسين المنطلق باستخدام المنحني القياسي وبشكل عام نلاحظ ان انطلاق جزيئات الدواء كان اسرع بوجود الانزيم.

الكلمات الدالة: البوليمر المحور. انطلاق الدواء. نابروكسين.

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1. Introduction

Naproxen considers as akind of propionic acid, known (S)-2-(6-methoxy naphthalene-2-yl) propanoic acid. Non-steroidal anti-inflammatory drug (NSAIDs) are a diverse group of drugs used mainly in treatment of acute and chronic pain.

Generally it (prevents) reduces prostaglandin synthesis. High plasma protein binding is another property of naproxen because it is functional groups. Naproxen is a few soluble compound, thus loading naproxen into chitosan membrane can improvement its decomposition rate and accelerate its analgesic effect [1, 2]. The biological availability across percutaneous absorption of naproxen in humans is only 1-2%, and a few research have been published concerning the use of the prodrug help to increase the dermal permeation of naproxen [3]. There are two methods of loading drugs into the polymers:- physical and chemical loading. Physical methods can be made by matrix or reservoir systems. For the chemical ways, it can be made by using ionic reaction or covalent linkage [4].The drug is lipid soluble, practically insoluble at low pH and highly soluble at high pH. One of the most widely used ways for controlling drug release is to form a matrix system with the approach of hydrophilic, inert and hydrophobic polymers. Ethyl cellulose (EC) is hydrophobic polymer and is essentially tasteless, colorless and pharmacologically inert. It has been widely used as a pharmaceutical solid vehicle in synthesis microcapsules [5]. 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 abetter mechanism to deliver the drug [6].

A controlled release drug delivery system delivers the drug locally or methodically at a predefined rate for a limited period of time. The importance of such systems is to equip desirable delivery appearance that can reach therapeutic plasma levels. Drug release is based on polymer conditions, thus the application of these properties can produce well characterized and reusable dosage forms. Controlled release systems can be indicated by physiological propertise such as motility, ions, pH and enzymes [7]. There are a many number of polymers that are used in sustained release drug delivery for example: Hydrophilic Polymers, Methylcellulose, Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Ethylhydroxyethylcellulose (E-HEC), Sodium-carboxymethylcellulose (Na-CMC) Hydrophobic Polymer,Ethylcellulose, cellulose acetate [8]. HPMC is a non-ionic type of cellulose ether derivative, it is stable over pH range 3.0-11.

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It is used as first choice for the preparation of hydrophilic matrix systems as it equips a occasion mechanism for controlled release of drugs [9]. Treason for its highly desirable acceptance provide:- solubility characteristics of the polymer in gastrointestinal fluid, and in organic and aqueous solvent design, noninterference with tablet decomposition and drug presence, and stability in the presence of heat, light, air or acceptable levels of moisture [10]. HPMC is the most important hydrophilic carrier material used for the formulation of oral controlled drug delivery design. HPMC has been display generally to show a very low order of toxicity in mammalian design [11,12]. For the system of new controlled drug delivery systems which are grounded on HPMC and aimed at providing particular, predefined release profiles, it is widespread to know the exact mass transport mechanisms included in drug release and to be able to predict quantitatively the resulting drug release kinetics [10]. Compared to other swell able polymers used to prolong drug release, HPMC is said to have been the important commonly used due to its fast hydration, robust compression and gelling characteristics. In addition it has very low toxicity and is wide-range available for use. Hence it has been a material of high importance when used as a carrier in drug release design [13].

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, H^1NMR and C^{13}NMR 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.Naproxen, hydroxy propylmethylcellulose HPMC, hydroxyllethylcellulose HEC and hydroxy propylcellulose HPC were obtained from (BDH Chemicals, England). Other reagents and chemicals were obtained from Aldrich (Germany).

A-Synthesis of the modified polymers of HPMC, HPC and HEC with (naproxen) respectively :

i) Direct esterification of Hydroxy propylmethylcellulose HPMC [14]: HPMC (0.1%) and naproxen (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 8h, 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 reparatory funnel, and the upper layer of crude ester

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was removed and washed again with 100ml of distilled water, followed by 25ml of saturated sodium bicarbonate solution and 30 ml of distilled water, The easter modified polymer of HPMC **(A_1)** must of course, be separated between each washing, and then dried under reduced pressure in the presence of phosphorus pentoxide to give a yellow powder (0.36g, yield 55% mp. 231-232C^o), the degree of substation (D.S) is 1.8..

The same method was used for the direct esterification of HPC and HEC with (naproxen) respectively. Modified **(B1)** was obtained as a off whit with (yield 57% mp. 229-230C^o) and **(D.S)**=1.7. Modified **(C1)** was obtained as a whit crystals with (yield 62% mp. 250-251C^o) and **(D.S)**=1.9.

ii)Indirect esterification of HPMC [15]**:** (1.5g, naproxen) was slowly added in to the thionyl chloride. When the addition was completed the solution was refluxed for 6h. The excess of thionyl chloride passes over, followed by naproxen chloride at 176-177C^o (0.77g). HPMC (0.1%) is dissolved in dimethyl sulphoxide in a 100ml bolt-head flask provided with a reflux condenser. The flask was cooled in ice and the (naproxen 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 (30 minute) to the HPMC with frequently shaking. The ice is removed and allowed to stand for over night. 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 white powder of modified polymer HPCM **(A_2)** (0.51g. yield 52% mp. 195-196C^o), and D.S is 2.5.

Similary modiefied polymer **HPC** and **HEC** (with naproxen) indirect esterification.The modified (**B2**) was obtained as a yellow powder with (yield of 76% mp. 198-200C^o (D.S) =2.3. The modified (**C2**) was obtained as a brown dark powder with (yield of 68% mp. 197-198C^o, D.S =2.2).

iii) Indirect esterification by use chloroacetyl chloride: The chloroacetyl **HPMC** [16] (5g) was dissolved in (100ml) dimethyl formamide at room temperature and calculated amounts of potassium salt (3.5g) of (naproxen) were added with stirring. All reactions were performed at 40C^o during 9h and the polymer remained soluble throughout the process. The modified 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. The modified (**A3**) was obtained as a whit powder with (yield of 67%, mp. 181-182C^o, (D.S)=2.5. Similary

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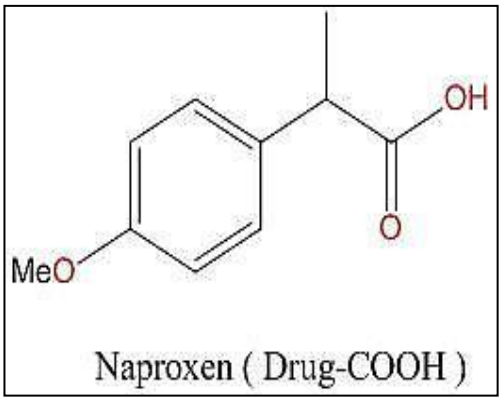
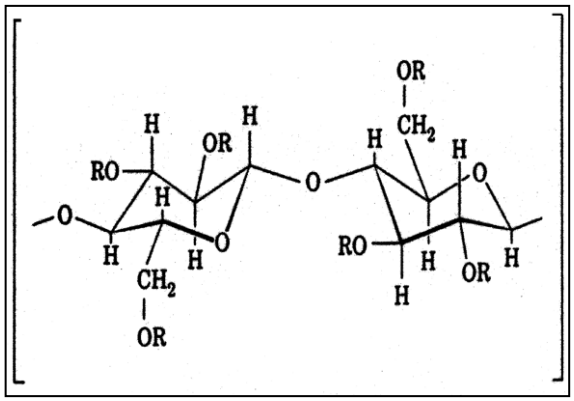
modiefied polymer **HPC** and **HEC** with (naproxen) indirect esterification. The modified (**B3**) was obtained as a yellow powder with yield of 63%, mp. 187-188C^{o}, (D.S)=2.1. The modified (**C3**) was obtained as a milky powder with (yield of 77%, mp. 205-204 C^{o}, D.S=2.4) Determination of degree substitution(D.S) by method of Genung and Mallatt [17].





R= -$CH_2CH(CH_3)OH$ HPMC

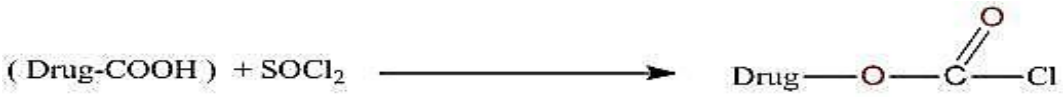
R= -CH_2CH_2OH HEC

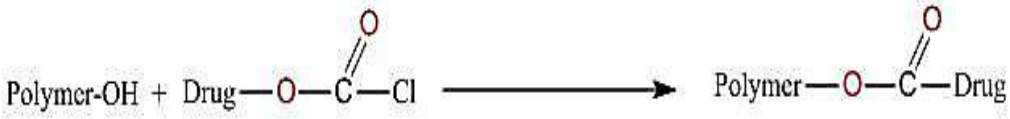
R= -$CH_2CH_2CH_2OH$ HPC

1) Direct esterification :-

Polymer-OH + Drug-COOH ⟶ Polymer—O—CO—Drug

2) Indirect esterification :-





3) Esterification by chloroacetyl chloride :-

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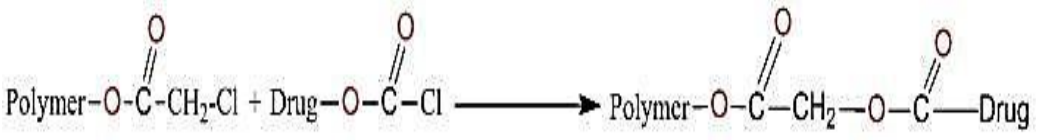

B- Heterogeneous Hydrolysis Reaction:

Hydrolysis test [18] was performed by using modified polymers (**HPMC**, **HPC** and **HEC** with naproxen at different D.S) adducts, which are insoluble in water, but did swell on standing in this medium [12]. The release reactions were carried out in buffer solutions (phosphate buffer) at various pH (2.0, 7.0, and 9.0). Modified 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 toppard 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 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 (naproxen) was quantitatively determined by UV spectroscopy (water as solvent) at λ_{max} 430 nm by using calibration curves.

C- Biodegradation (In vitro degradation):

Modified polymers (**HPMC**, **HPC** and **HEC**) with (naproxen) at different **D.S** 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 (pH7.4 the human blood pH) with 20mg of Rhizopus delemar lipase [19]. 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 naproxen released was determined by UV spectroscopy at λ_{max} 430 nm by using calibration curves.

3-Results and Discussion:

In the present study, the bound of "naproxen"| drug molecule with polymer macromolecule was carried out successfully by three types of esterification processes.

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A) Direct esterification :- Modified polymer **(A1)** was obtained when the HPMC **(polymer-OH)** is treated with naproxen using H_2SO_4 as catalyst in DMSO solvent. This modified **(A1)** was obtained as a yellow powder with (yield of 55%) and **(D.S)**=1.8.The **FTIR** spectrum for pure naproxen powder showed the O – H carboxylic at 3294 cm^{-1} and C-H aliphatic at 2977 cm^{-1}, while the aromatic C – H appeared at 3013 cm^{-1}. A sharp peak appeared at 1729 cm^{-1} it refers to C=O acidic, while the stretching of C-O appeared at 1265 cm^{-1}. The sharp peak which appeared at 1605 cm^{-1} refers to the presence of C=C alkene conjugated bond.For benzene ring in the structure of (naproxen), it shows a very sharp peak at 1609 cm^{-1} according to the C-C aromatic skeletal stretching. In addition to C=C aromatic bond which also appeared as a sharp peak at 1454 cm^{-1}. While **(HPMC)** as pure sample shows **FTIR** peaks as :- O – H stretching peak at 3450 – 3490 cm^{-1}. The band of C-H stretching bands was located at 2923 cm^{-1}. On the other hand, the vibration of the C-O stretching in C6, which is considered as primary alcohol, appeared at 1081 cm^{-1}. Finally, the C-O-C stretching peak was located at 1376cm^{-1}

The **FTIR** spectrum of modified polymer **(A1)** showed a stretching band at 3300 cm^{-1} which is assigned for the OH hydroxyl group stretching vibration and the appearance carbonyl group C=O at 1685 - 1705 cm^{-1} which belong to ester groups and the band located at 3110 cm^{-1} is due to the C-H aromatic band stretching vibration which, when compared with the **FTIR** spectrum of HPMC proved the esterification process between drug and **HPMC** had occurred. The **H^1NMR** spectrum of modified polymer **(A1)** clearly shows a **δ** (3.55 - 3.85 ppm, m) for H-1 and H – 2, **δ** (3.95 ppm, d) for H-3, (5.1 ppm**,** t) for H-4, **δ** (5.4 ppm**,** d) for H-5 and **δ** (5.7 ppm, d) for H-6, these data for glucose moiety in **HPMC** polymer. It also clearly shows a **δ** (7.1 ppm, d) for H- aromatic and **δ** (2.5 ppm, s) for (CH_3) group of (naproxen). The **C^{13}NMR** spectrum of modified polymer **(A1)** shows a **δ** (47.5 ppm) for – CH_3 group of "naproxen", (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) two ester groups and **δ** (130.9-151 ppm) for the (C=C) aromatic band.

The **FTIR** spectrum of modified polymer **(B1)** showed:-for sugar moieties *V* O-H 3300 cm^{-1}, *V* C-C 1490 cm^{-1}, *V* C=O 1650 – 1710 cm^{-1} and the drug *V* C-H cm^{-1} aromatic 3110 cm^{-1}

The **H^1NMR** spectrum of modified polymer **(B1)** shows a **δ** (3.4 - 3.7 ppm, m) for H-1and H – 2, **δ** (4.2 ppm, d) for H-3, (4.8 ppm**,** t) for H-4, **δ** (5.1 ppm**,** d) for H-5 and **δ** (5.3

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ppm, d) for H-6, these data for glucose moiety in **HPC** polymer. It also clearly shows a **δ** (7.4 ppm, d) for H- aromatic and **δ** (2.0 ppm, s) for (CH_3) group of "naproxen".

The **C^{13}NMR** spectrum of modified polymer **(B1)** shows a **δ** (35.6 ppm) for –CH_3 group(of naproxen), (60.5-65.6 ppm) for the C-OH, **δ** (120.1 ppm) for the (C-O- ether group), **δ** (161-163 ppm) for (C=O) two ester groups and **δ** (140-149 ppm) for the (C=C) aromatic band

The **FTIR** spectrum of modified polymer(**C1**) showed:-for sugar moieties *V* O-H 3320 cm^{-1}, *V* C-C 1485 cm^{-1}, *V* C=O 1640 – 1720 cm^{-1} and the drug *V* C-H cm^{-1} aromatic 3095 cm^{-1}

The **H^1NMR** spectrum of modified polymer **(C1)** shows a **δ** (3.1 - 3.3 ppm, m) for H-1and H – 2, **δ** (3.5 ppm, d) for H-3, (4.1 ppm**,** t) for H-4, **δ** (4.5 ppm**,** d) for H-5 and **δ** (4.9 ppm, d) for H-6, these data for glucose moiety in **HEC** polymer. It also clearly shows a **δ** (6.9 ppm, d) for H- aromatic and **δ** (2.7 ppm, s) for (CH_3) group of (naproxen).

The **C^{13}NMR** spectrum of modified polymer **(C1)** shows a **δ** (41.6 ppm) for –CH_3 group (of naproxen), (62.1- 65 ppm) for the C-OH, **δ** (121.5 ppm)for the (C-O- ether group), **δ** (159-164.1 ppm) for (C=O) two ester groups and **δ** (145-152 ppm) for the (C=C) aromatic band.

B) Esterification by acid chloride:- The acid chloride [(naproxen chloride) was prepared from the reaction of naproxen with thionyl chloride] and then treated with **HPMC** in DMSO to give modified polymer (**A2**). this method was chosen because it gives (A2) in good yield, high purity, with short time [20].

The modified (**A2**) was obtained as a white powder with (yield of 52% D.S =2.5). The **FTIR** spectrum for the modified (**A2**), 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 (**A2**) clearly shows a(2.5 – 2.7 ppm, m) for H – 1 and H – 2, (2.9 ppm, d) for H – 3, (3.1 ppm, t) for H – 4, (3.4 ppm, d)for H – 5 and (6.7 ppm, d) for H – aromatic and (2.2 ppm, s) for – CH_3 group of (naproxen).

The results of **H^1NMR** spectral data proved the occurrence of esterification process between starch polymer and naproxen. The **C^{13}NMR** spectra for modified polymer compound (**A2**) show the bands a (37.5 ppm) for – CH_3 group (of naproxen), (67.5 – 73 ppm) for the (C

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– OH) hydroxyl group, (120.2 ppm) for the (C –O -) ether group, (160– 162 ppm) for (C-O-C=O) two ester groups and (135.3 – 142 ppm) for C^{13} (C=C) aromatic band.

The **FTIR** spectrum for the modified (**B2**), show a stretching band located at 3430 cm^{-1} which is due to the O-H hydroxyl group, a stretching band at 1756 cm^{-1} for C=O in the ester group and the band located at 3093 cm^{-1} which is attributed to the C-H stretching in the aromatic ring. The **H^1NMR** spectrum for the modified (**B2**) clearly shows a(2.4– 2.8 ppm, m) for H – 1 and H – 2, (3.0 ppm, d) for H – 3, (3.3 ppm, t)for H – 4, (3.4 ppm, d) for H – 5 and (7.1 ppm, d) for H – aromatic and (2.1 ppm, s) for – CH_3 group of naproxen. The results of **H^1NMR** spectral data proved the occurrence of esterification process between polymer and naproxen. The **C^{13}NMR** spectra for modified polymer compound (**B2**) show the bands a (35.5ppm) for – CH_3 group (of naproxen), (65 – 69.4 ppm) for the (C – OH) hydroxyl group, (122.5 ppm) for the (C –O -) ether group, (159– 161.3 ppm) for (C-O-C=O) two ester groups and (140– 146 ppm) for C^{13} (C=C) aromatic band.

The **FTIR** spectrum for the modified (**C2**), show a stretching band located at 3410 cm^{-1} which is due to the O-H hydroxyl group, a stretching band at 1754 cm^{-1} for C=O in the ester group and the band located at 3090 cm^{-1} which is attributed to the C-H stretching in the aromatic ring. The **H^1NMR** spectrum for the modified (**C2**) clearly shows a (2.9– 3.1, m) ppm for H – 1 and H – 2, (3.3, d) ppm for H – 3, (3.7, t) for H – 4, (3.9, d) for H – 5 and (7.4, d) for H – aromatic and (2.5, s) for – CH_3 group of naproxen. The results of **H^1NMR** spectral data proved the occurrence of esterification process between polymer and naproxen. The **C^{13}NMR** spectra for modified polymer compound (**C2**) show the bands a (31.6 ppm) for – CH_3 group (of naproxen), (64 – 68.2 ppm) for the (C – OH) hydroxyl group, (125 ppm) for the (C –O -) ether group, (161– 164 ppm) for (C-O-C=O) two ester groups and (145– 150.1 ppm) for C^{13} (C=C) aromatic band.

C) Esterification using chloroacetyl chloride:- The polymer chloroacetyl chloride was treated with naproxen salt in DMSO solvent for (8hrs) to obtain modified (**A3**) as a white powder (yield of 67%, mp. 181-182C^o, D.S=2.5).

The **FTIR** spectrum of modified polymer **(A3)** showed a stretching band at 3225 cm^{-1} which is assigned for the O – H. A stretching band located at 1754 cm^{-1} and 1745 cm^{-1} are assigned for the two C=O ester groups and the band appeared at about 3123 cm^{-1} is for the (C-H) aromatic band stretching vibration for naproxen. The results of the **FTIR** spectra, compared with the **FTIR** of **HPMC** and naproxen proved the occurance esterification of

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polymer. The **H^{1}NMR** spectrum of modified polymer **(A3)** clearly shows a **δ** (2.5 - 2.8 ppm, m) for H-1and H – 2, **δ** (3.1 ppm, d) for H-3, (3.4 ppm**,** t) for H-4, **δ** (3.7 ppm**,** d) for H-5 and **δ** (4.1 ppm, d) for H-6, these data for glucose moiety in **HPMC** polymer. It also clearly shows a **δ** (7.4 , d) ppm for H- aromatic and **δ** (2.3 ppm, s) for (CH_3) group of naproxen. The **C^{13}NMR** spectrum of modified polymer **(A3)** shows a **δ** (33.5 ppm) for –CH_3 group(of naproxen), (66 -69.3 ppm) for the C-OH, **δ** (125 ppm) for the (C-O- ether group), **δ** (151.7-157.7 ppm) for (C=O) two ester groups and **δ** (136.9-141 ppm) for the (C=C) aromatic band.

The **FTIR** spectrum of modified polymer **(B3)** showed:- for sugar moieties *V* O-H 3410 cm^{-1}, *V* C-C 1472 cm^{-1}, *V*C=O 1670 – 1720 cm^{-1} and the drug *V* C-H cm^{-1} aromatic 3120 cm^{-1}

The **H^{1}NMR** spectrum of modified polymer **(B3)** shows a **δ** (2.7 - 2.6 ppm, m) for H-1and H – 2, **δ** (2.8 ppm, d) for H-3, (3.1 ppm**,** t) for H-4, **δ** (3.4 ppm**,** d) for H-5 and **δ** (3.8 ppm, d) for H-6, these data for glucose moiety in **HPC** polymer. It also clearly shows a **δ** (7.2 ppm, d) for H- aromatic and **δ** (2.4 ppm, s) for (CH_3) group of (naproxen). The **C^{13}NMR** spectrum of modified polymer **(B3)** shows a **δ** (32.5 ppm) for –CH_3 group (of naproxen), (64-67.3 ppm) for the C-OH, **δ** (123.1 ppm) for the (C-O- ether group), **δ** (158-162 ppm) for (C=O) two ester groups and **δ** (141-146 ppm) for the (C=C) aromatic band.

The **FTIR** spectrum of modified polymer (**C3**) showed :- for sugar moieties *V* O-H 3455 cm^{-1}, *V* C-C 1390 cm^{-1}, *V* C=O 1690 – 1705 cm^{-1} and the drug *V* C-H cm^{-1} aromatic 3087 cm^{-1}

The **H^{1}NMR** spectrum of modified polymer **(C3)** shows a **δ** (2.5- 2.7 ppm, m) pfor H-1and H – 2, **δ** (2.9 ppm, d) for H-3, (3.2 ppm**,** t) for H-4, **δ** (3.5 ppm**,** d) for H-5 and **δ** (3.9 ppm, d) for H-6, these data for glucose moiety in **HEC** polymer. It also clearly shows a **δ** (7.4 ppm, d) for H- aromatic and **δ** (2.3 ppm, s) for (CH_3) group of naproxen. The **C^{13}NMR** spectrum of modified polymer **(C3)** shows a **δ** (37.6 ppm) for –CH_3 group (of naproxen), (65-67.5 ppm) for the C-OH, **δ** (126 ppm) for the (C-O- ether group), **δ** (165-169.3 ppm) for (C=O) two ester groups and **δ** (148-153 ppm) for the (C=C) aromatic band.

D) Chemical and biohydrolysis:- In this work the **(HPMC**, **HEC** and **HPC)** was used as natural polymer because it is totally biodegradable in a wide variety of environments. It can

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hydrolyzed into glucose by microorganism or enzymes and the metabolized into carbon dioxide and water.

Rate of hydrolysis of pendant 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 polymer **(A1)**, 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 polymers **(A1)**, Figs. (1,2 and 3) show the conc. of released (naproxen) time.

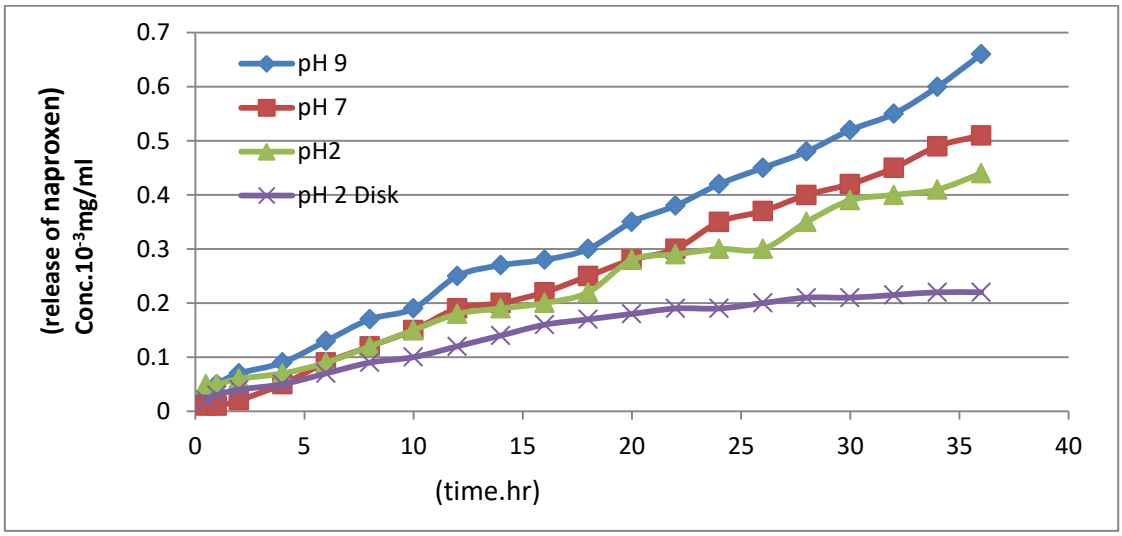

Fig. (1): Release of (naproxen) from the modiefied polymer (A1) at 25 C^{o}

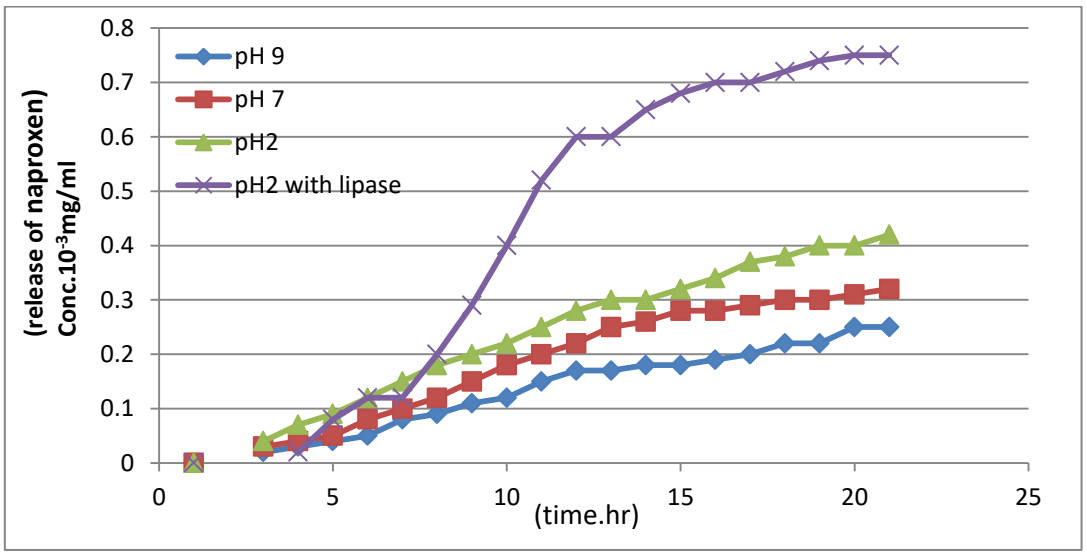

Fig. (2): Release of (naproxen) from the modiefied polymer (A1) at 37 C^{o}

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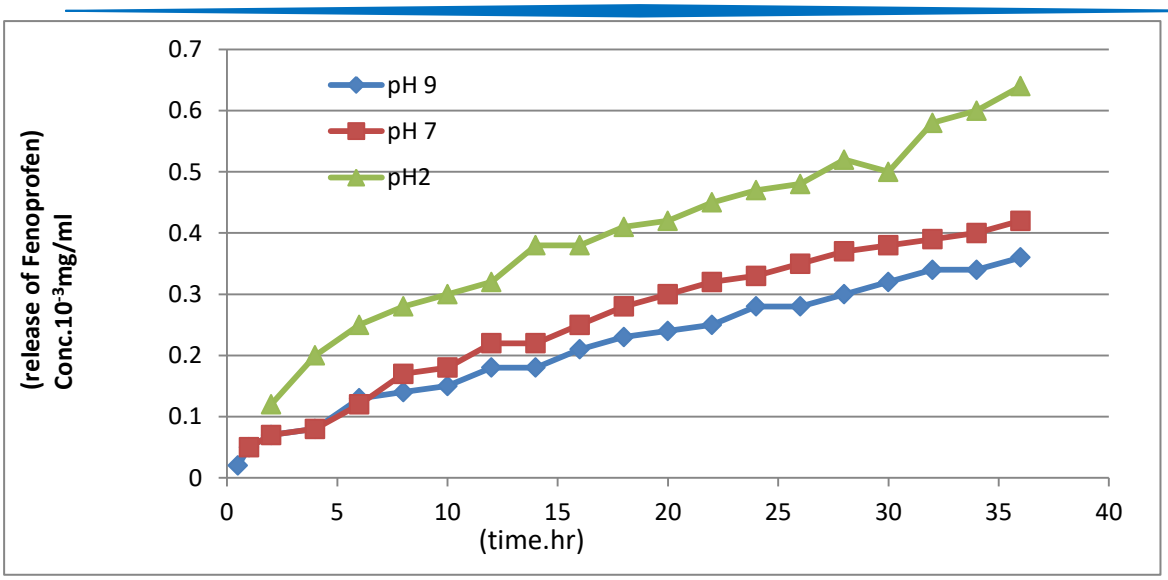

Fig. (3): Release of (naproxen) from the modiefied polymer (A1) at 45 C^{o}

Fig. (4) show a typical profiles of total heterogenous hydrolysis for modified polymers (A1, A2, A3), (B1, B2, B3) and (C1, C2, C3) at different adduct (powder,disk with and without lipase).

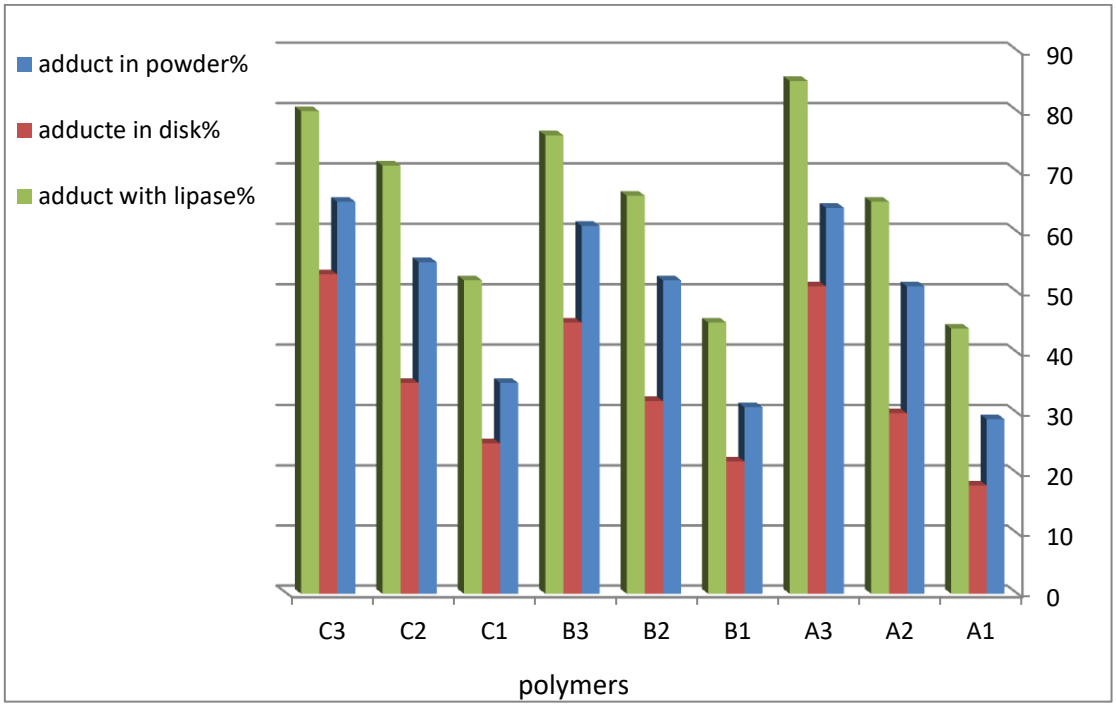

Fig. (4): Release of naproxen from the modiefied polymer at differente adduct

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Fig. (5) show a typical profiles of total heterogenous hydrolysis for modified polymers (A1, A2, A3), (B1, B2, B3) and (C1, C2, C3). As it is seen, the total release of the active compound was reached more quickly in the case of modified polymers (A3, B3 and C3) than (A2, B2 and C2) and (A1, B1 and C1) .

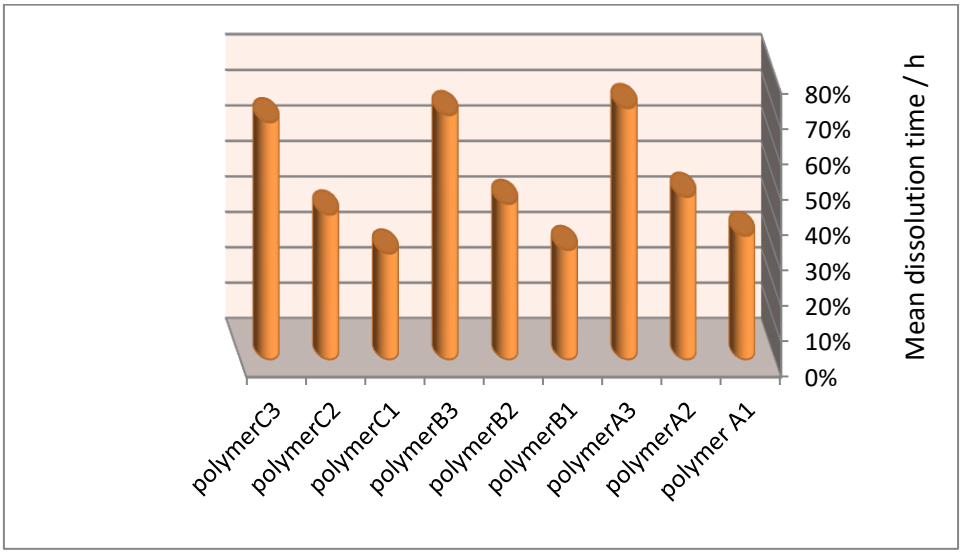

Fig. (5): Meam dissoiution time for modified polymers under study.

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 total release in all case increased with increased the temperatures. As it is seen, the release of bioactive can be accelerated by addition of esterases (lipase enzyme).

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