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New Method for synthesis hydroxyurea and Some its polymers supported derivatives as new controlled release drugs

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Abstract

The study involves developing new method for the common anticancer drug known "hydroxyurea". The new method is based on localy available cheap raw materials ((biuret)) via transferring it to ethyl allophone, then to ethyl carbamate and Finally to hydroxyurea by its recation with hydroxylamine hydrochloride. The products and intermediates were characterized by various available techniques, i.e. CHN, IR, mp. and functional group analysis. The prepared hydroxyurea was combined with two classes of polymers i.e. Natural polymers: carboxy methyl cellulose, pectin and pectic acid, and synthetic polymers: poly(vinyl alcohol) and tetramethyl urea. In the first category of polymers, the carboxy group of the poly(saccharide) repeating unit was transferred to the reactive acid chloride group which was reacted with the amino group of the hydroxyurea. Amide linkage was formed between the drug and the polymer backbone. In the second category of polymers, the drug was linked to the polymer backbone by their reaction with sebacoyl chloride as spacer thus forming ester linkage between the spacer and hydroxyurea. The third class of polymer supported drugs were prepared by condensation of hydroxyurea with tetramethylol urea currently prepared in our laboratories forming polymer network Matrix consisting of hydroxyurea. The obtained products, as polymer supported anticancer drugs, were characterized by IR, NMR, UV, CHN and functianol group analysis.

Finally, samples from the prepared polymer supported drugs were evaluated as controlled release drugs dopted in vitro procedure. The obtained data showed that the evaluated polymer supported drugs have sustained release characteristics.

Keywords: Hyderoxyurea, Drug Delivery System and controlled release drugs

1. Introduction

A recent WHO report estimated that 7.6 millions people died of cancer in 2005, representing 13% of all deaths worldwide. The report suggests that 84 millions people will die of cancer between 2005 and 2015. Cancer is the second leading cause of death in developed countries and among the three leading causes of death in developing countries [1]. Cancer is a heterogeneous group of diseases characterized by uncontrolled growth of the cells. Cancers are generally classified by the type of cells or organs from which they originate[2]. Currently anticancer (drugs) are available that significantly reduce the mortality rates for some cancers (e.g. leukemia and testicular and ovarian cancer), and give longer overall patient survival times. One of the most important of these anticancer (Drugs) is called the hydroxyurea. Hydroxyurea and its derivatives exhibit versatile biological activities. Hydroxyurea is currently used in the treatment of various neoplastic and non-neoplastic diseases such as cancer, sickle cell anemia and HIV. Hydroxyurea (HU) is a common antimetabolic cytostatic compound used to treat some types of cancer and a number of its derivatives exerting stronger antitumor potency and lower general cytotoxicity have been synthesized[3].

On the other hand, delivery of a drug to a specific site within the body is a necessity for improving disease treatment and is an ongoing aim of the pharmaceutical scientist. Through selective accumulation in the pathological site and lower accumulation elsewhere, the drug's therapeutic value is increased[4].This technology is called controlled drug delivery technology which represents one of the most rapidly advancing areas of science in which chemists and chemical engineers are contributing to human health care. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, and improved patient compliance and convenience. Such systems often use synthetic polymers as carriers for the drugs. By so doing, treatments that would not otherwise be possible are now in conventional use[5-10].

In this paper, new method for synthesis hydroxyurea and its polymer supported derivatives as new controlled release drugs.

2.Experimental

2.1.Reagents

Acetonitril, hexane, pectin, pectic, and poly(vinyl alcohol) from (Fluka Co.), sodium cyanate, absolute ethanol, carbon tetrachloride, triphenylphosphine, hyrochloric acid, urea and carboxy methyl cellulose from (BDH Co), hyroxylamine hydrochloride, formaline and ferric chloride from (Merck Co.), triethylamine, sebacoyl chloride, biuret and diethyl ether from (Riedel-de Haen). Physical measurements, and FTIR spectra were recorded on a (Fourier-transform infrared-Spectrophotometer) FT.IR.8400, Shimadzu Co by using a KBr disc in the range (500 – 4000) cm^{-1}. Nuclear Magnetic Resonanace Spectrophotometer, 400 MHz BRUKER, University of baith, Syria. Elemental Analysis,hospital Hawalli, Kuwait. The Electrothermal melting point apparatus (mp) of the compounds was determined with a 535394 – B190K, BUCHI. IR, UV-Visible spectrophotometer and melting point was performed by Chemistry Department – College of Education for Pure Sciences – Basrah University.

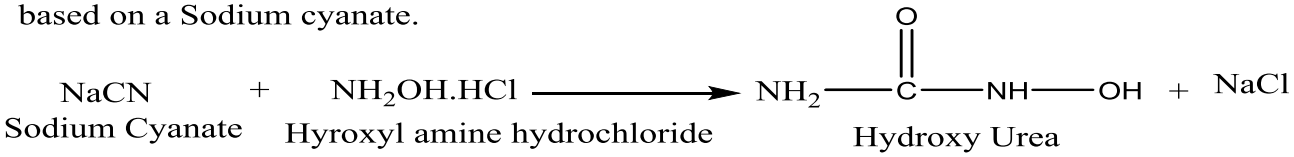
3. Methods

3.1 New Methods for Synthesis of Hydroxyurea

3.1.1 The method based on a Sodium Cyanate

In a round – bottom flask fitted with mechanical stir, put (7.9 g, 1 mole) hydroxylamine hydrochloride dissolved in10 ml water and (8.9 g, 6 mole) Sodium cyanate dissolved in 10ml water with stirring for 72 hours at room tempurture. The mixture product was a mixture of hydroxylurea and sodium chloird salt. The solvent was removed by rotary evaporater at 55 ^{0}C and the hydroxyurea was extracted from warm ethanol. After evaporation of the ethanol, the hydroxyurea was recrystalised with ethanol several times. The compound has been characterized by elemental analysis and IR spectra [11-13].

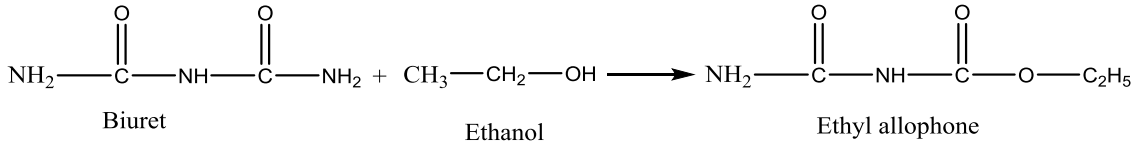
based on a Sodium cyanate.



3.1.2 The method based on a Biuret

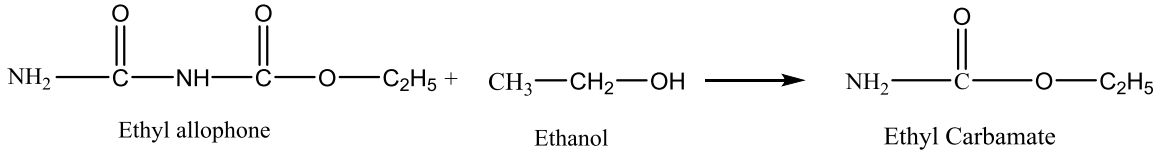
a- Synthesis ethyl allophone

In a round – bottom flask fitted with mechanical strrire, put (10 g, 0.1 mole) biuret and (250 ml, mole) absolute ethanol (Normalty 0.84 HCl). The mixture was heated (140-145^{0}C) under pressure for two hours . At the end of the reaction, the solvent was romved by rotary evaporator. Then the product was filtered and recrystalised several times from ethanol. The compound has been characterized by elemental analysis and IR spectra, (yield 97% and mp 190^{0}C)[14].



b-Synthesis of ethyl carbamate

In a round – bottom flask fitted with mechanical strrire, put (25g, 0.25 mole) biuret and (500 ml) absolute ethanol (Normally 0.55 HCl). The mixture was heated at (156-157)^{0}C and under pressure about four hours. Then, the product was cooled and filtered, and the viscous products were purified by distillation. The compound has been characterized by elemental analysis and IR spectra, (yield 98% and mp 51-52^{0}C) [14].



c-Synthesis of Hydroxyurea

In a round – bottom flask fitted with mechanical strrire, put (10g, 0.1 mole) biuret and (250 ml, 2.575mole) sodium hydroxide which was dissolved in 500 ml water. Then, the mixture was added to 1.25 mol from ethyl carhamat . The mixture was stirring for 72 hours at room temperature. At the end of the reaction, the product was

cooled and neutralized with HCl. The product was filtered then extracted by ether.The ether layer which was saturated by alcohol was ignored.Then the aqueous layer was evaported by rotary evaporator at 55 ^{0}C.The solid product was extracted by 500 ml boiling ethanol. After that, it was filtered, washed with ethanol, and recrystalised several times from ethanol. The compound has been characterized by elemental analysis and IR spectra, (yield 73% and mp 134^{0}C)[15].

3.2 New methods for polymer supported of Hydroxyurea

3.2.1 The supported technology based on a poly(vinyl alcohol)

In a round – bottom flask fitted with mechanical strrire, put (44g, 1 mole) poly(vinyl alcohol), (0.5 mol) sebacoyl chloride, and (76 g ,1 mole) hydroxyurea in (5 mole) carbon tetra chloride which was stirred at room temperature. During the stir, the add (3-4 drops) triethylamine from seperation funnal. After the completion of reaction, The prodect was formed, washed by hexane and ethanol several times.Then, it was dried under vacuum (0.1 mmHg) at 25 ^{0}C.The compound has been characterized by elemental analysis and IR spectra.(yield 91%).

3.2.2 The supported technology based on: carboxy methyl cellulose, pectin, and pectic acid

In a round – bottom flask fitted with mechanical strrire, put (87g, 0.24 mole) pectin, (0.4 mol) carbon tetrachloride and (0.24 mole) triethylamine, (62g, 0.24 mole) triphenylphosphine, (30 ml) acetonitrile, and (15.2g, 0.2 mole) hydroxylurea which was stirred at room temperature for four hours. After the completion of reaction, the solvent acetonitrile was romved by rotary evaporator. 40 ml hexane was added to the product and filtered off to remove the triphenyl phosphenoxide and triethylamine hydrochloride. After that, it was washed several times by ethanol, then dried under vacuum (0.1 mmHg) at 25 ^{0}C for 4 hours. The compound has been characterized by elemental analysis, NMR, and IR spectra. The yield is (91%). This method is followed for polymers (CMC and poly(pectic))[16].

3.2.3 The supported technology based on tetramethyl urea.

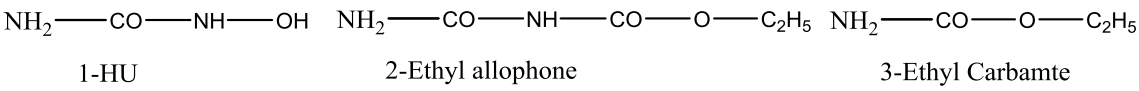
a-preparation of the resin tetra methyl urea.

The resin tetramethyl urea was prepared according to adopting literature [11] and was identified by CHN and mp. The product has melting point (220 –222) ^{o}C, with(Orange yellow crystal, 93% yield).

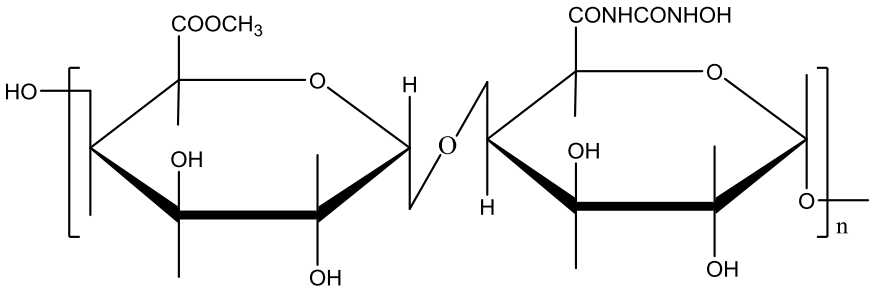
The structure is shown in Figure (4).

b-supported technology based on tetramethyl urea.

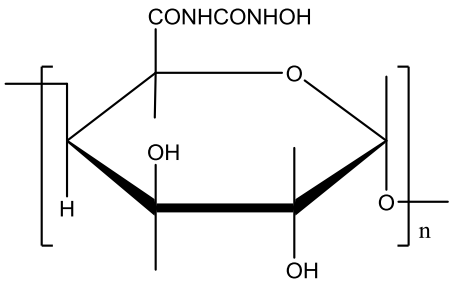
In a round – bottom flask, dissolved (0.1 mol) tetramethyl urea in (200ml) ethanol and stirred by adding (0.8 mol) hydroxylurea. After that, the mixture was stirred by mechanical stir for 1 hour. The ethanol was romved by rotary evaporator at 55 ^{0}C. The compound has been characterized by elemental analysis, and IR spectra. The yield is (95%) [17].



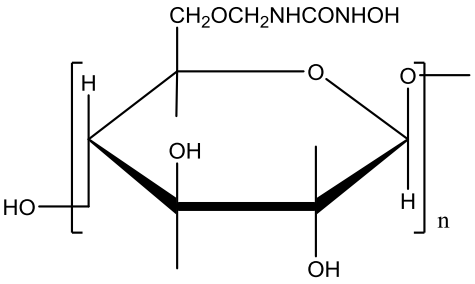
1-HU 2-Ethyl allophone 3-Ethyl Carbamte



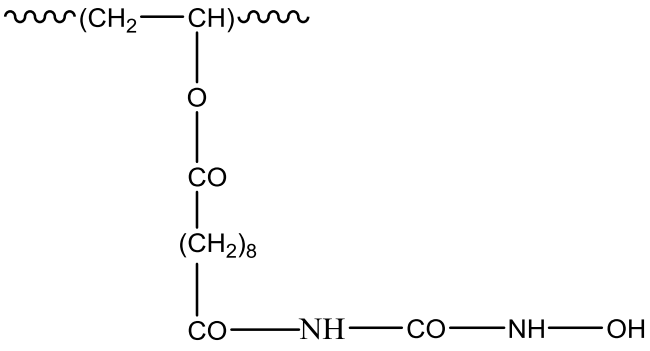
4- Pectine Supported HU



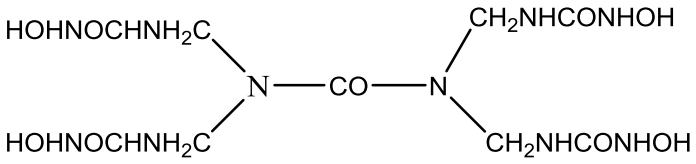
5- Pectic Supported HU



6- CMC Supported HU



7- PVA Supported HU



8-TMU Supported HU.

Fig.1 The general chemical structures of the prepared compounds

4. Results and Discussion

4.1Production of the Drug

Anticancer drug is considered as a drug imported and very important which has agreat shortage because of the cost of manufacturing and production compared to the consumption of the large. Also, it is because most of the pharmaceutical cancer is taken in large doses for a long time.

In this paper, we develop new method for the common anticancer drug known as "hydroxyurea",by using new method which is based on locally available cheap raw materials instead of the following method which depends on ionexchange (Ammberlite IR-410)[18].

While the new method is based on a locally available cheap raw materials (biuret) via transferring it to ethyl allophone then to ethyl carbamate and finally to hydroxyurea by its recation with hydroxylamine hydrochloride. This method is more economic and the starting matreials are available and very cheap as well asit avoid toxic cyanide ions.The products and intermediate were characterized by various available techniques, i.e. CHN, IR, and mp.

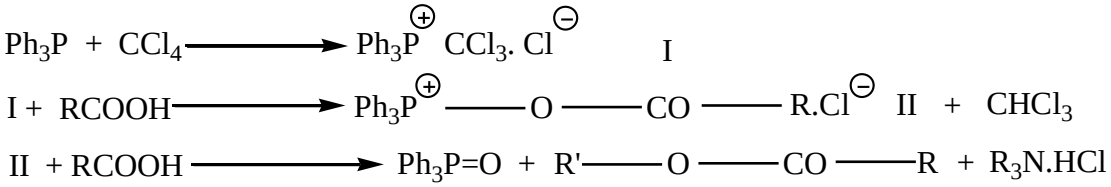
4.2 Supporting the drug based on polymer;

The prepared hydroxyurea was combined with two classes of polymers i.e. Natural polymers: carboxy methyl cellulose, pectin and pectic acid. and synthetic polymers: poly(vinyl alcohol) and tetramethyl urea. In the first category of polymers the carboxy group of the poly(saccharide) repeating unit was transferred to the reactive acid chloride group which was reacted with the amino group of the hydroxyurea, amide linkage was formed between the drug and the polymer backbone.

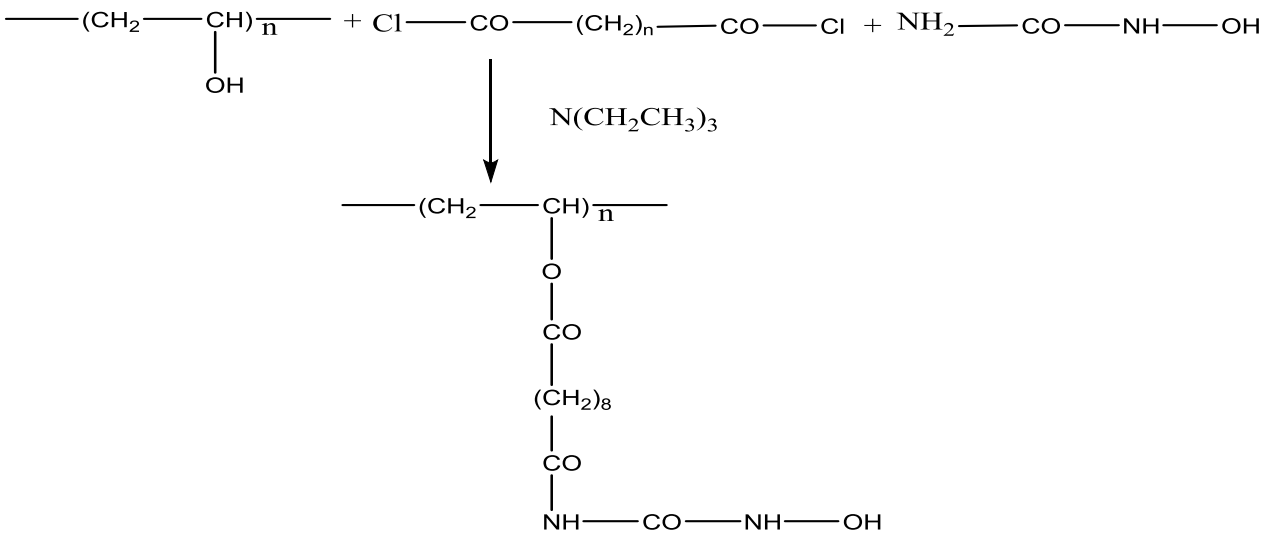
This reaction take place through proper mechanism involving reactive intermediate formed via the reaction of triphenylphosphine with CCl_4. This intermediate is reacted with carboxylic group of the (poly(saccharide) repeating unit) forming another intermediate II and chloroform. The second intermediate II react with alcohol (methylol group) in presence of triethylamine as HCl acceptor. This mechanism can be represented by the following reactions[19].

R-COOH = Polysccharide (Pectin, Pectic, CMC) carboxylic acid.

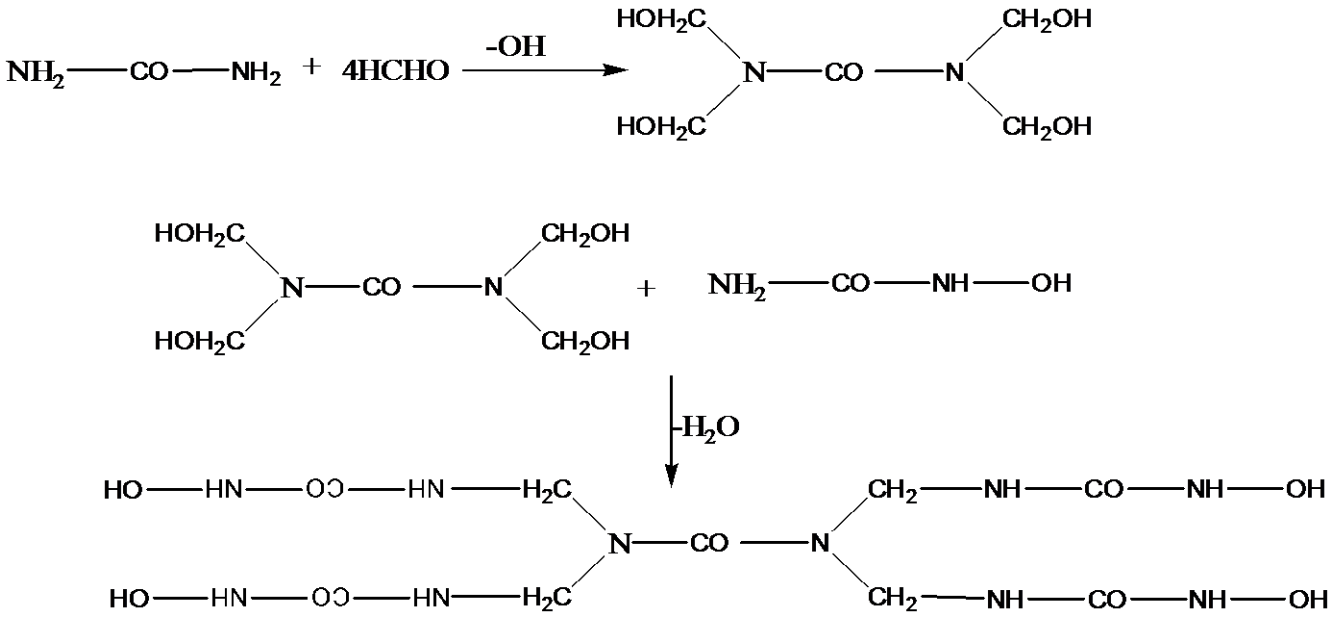
R' – NH_2 = Hydroxyurea.



In the second category of polymers, the drug was linked to the polymer backbone by their reaction with sebacoyl chloride as spacer and conjugation agent among the drug and polymer, thus forming ester linkage between the spacer and hydroxyurea. The reaction takes place between the hydroxyl groups of poly(vinyl alcohol) unit forming ester linkage with sebacoyl chloride, while at the other side of sebacoyl chloride, the reaction take place between the sebacoyl chloride and amine group of the hydroxyurea forming amide linkage. In both of the linkage between drug and polymer forming by lost of HCl molecule then reaction with the triethylamine(as HCl acceptor).



The third class of polymer supported drugs was prepared by condensation of hydroxyurea with tetramethylol urea currently prepared in our laboratories and forming polymer network matrix consisting of hydroxyurea.The cross-linking increases with the heat forming ether linkage by losing of H_2O molecule. So, the process takes place to form IPNs loading by drug. Both of the drug hydroxyurea and the resin dissolve in the ethanol and then the mixture is heated at 55 ^{0}C. The linkage formed between the amine group in the drug and hydroxyl group in the resin is like the following [20]:



4.3 Identification of Prepared compounds

The chemical structure of the prepared compounds were confirmed by the FTIR, CHN,and H^1NMR.

4.3.1 FTIR Spectra

FTIR Spectra of the synthesized compounds were carried out. Characterized bands were given in table 1 [21,22].

Table 1: Characterized Bands in FTIR Spectra for Prepared Compounds

Co	Wave numbers (cm-1)							
	OH, NH_2	NH_I	NH_{II}	$CH_{3alfatic}$	C=O	C-O	C-N1	C-N2
HU	3200-3420	1610	1470		1670		1410	1120
EA			1490	2850	1695	1050	1400	
EC	3290-3410	1625		2890	1695	1130	1470	
PVA+HU	3180-3495		1460	2900	1550	1100		1200
Pn+HU	3250-3490		1470	2870	1630	1100	1400	
Pc+HU	3210-3420		1400	2850	1500	1000		1210
CMC+HU	3240-3491		1405	2880	1550	1000		1200
TMU+HU	3180-3495		1395	2860	1550	1050		1200

4.3.2 Elemental analysis (CHN)

The structures of the products were confirmed by their elemental analysis, table 2, shows that the difference between the found values and calculated values of carbon, hydrogen, and nitrogen elements are situated within the range which confirm the correctness of the suggested structures of the prepared compounds.

Table 2: Elemental analysis of the products

Compounds		Chemical Formula	M.Wt	Practical Value %			Theoretical Value %		
				C	H	N	C	H	N
1	HU	$CH_4N_2O_2$	76	15.80	5.59	36.81	15.79	5.30	36.84
2	EA	$C_4O_3N_2H_8$	132.11	36.45	6.32	21.33	36.36	6.10	21.20
3	EC	$C_3H_7NO_2$	89.05	40.53	7.83	15.86	40.44	7.92	15.72
4	PVA+HU, for one unite	$C_{13}H_{22}N_2O_5$	286.32	54.14	7.77	9.43	54.53	7.79	9.42
5	Pn+HU, for one unite	$C_{14}H_{20}N_2O_{13}$	424.31	38.00	4.31	8.07	38.05	4.56	8.87
6	Pc+HU, for one unite	$C_7H_{10}N_2O_7$	234.164	36.31	4.92	11.11	35.90	4.30	35.90
7	CMC+HU, for one unite	$C_8H_{14}N_2O_7$	250.21	39.24	5.11	8.12	39.64	5.14	8.40
8	TMU+HU, for one unite	$C_9H_{20}N_{10}O_9$	412.32	28.30	5.55	28.99	28.38	5.44	28.36

4.3.3 H^1NMRSpectra

H^1NMR Spectra of the synthesized compounds were carried out by usingchemical shifts of H^1NMR for the prepared compounds in d $CDCl_3$which are given in table 3 and the spectra were shown in Figs (2 and 3) [22,23].

The NMR spectrum of the drug (HU)shows three signals at δ=(6.2)ppm related to (OH) and δ=(8.4-8.8)ppm related to the (-NH- , -NH_2-).So that, the bands of the drug (HU) which appear of bands at δ=(7.20 – 7.67)ppm consequently of the connect of the drug (HU) with polymer and thus leads to draw the electronic density due to carbonyl groups and this causes down field for drug bands which are shown in all NMR spectra.

The NMR spectrum of polymer drug(Pectin+HU) shows bands at δ=(7.20-7.67)ppm which can be related to the drug (HU) which supported the polymer. In the NMR spectrum of polymer, drug (pectine+HU) showed triplet at δ=(1.32 – 1.36)ppm which is related to glycoside bond protons in the pectin. Other band at δ=(1.75)ppm is related to the methyl group in the pectine. Single band at δ=(2.10)ppm is related to the outhydoxel group protons which contact with thering of the polymer pectine. While the inside hydroxyl group protons contact with the ring appearance at δ=(3.4)ppm. Eight bands at δ=(3.006 - 3.073)ppm are related to the protons (-CH_2-OH). Distinguished signals at δ=(7.20)ppm are related to the hydroxel group protons of the drug with double from quartet signals at δ=(7.407)ppm. Also the protons of (-NH-) group of the drug at δ=(7.610)ppm.

While the NMR spectrum of polymer drug (PVA+HU) shows multi bands at δ=(1.14-1.23)ppm which can be related to the (-CH_2-) in the spacer. Triplet bands at δ=(1.29-1.23)ppm are related to the protons of (-CH_2-) which are near of the oxygen molecule. Also, triplet bands at δ=(1.33-1.37) ppm are related to the protons of (-CH_2-) for the polymer unit which is the hydroxyl group after and befor connection. Five bands at δ=(1.51-1.56)ppm are related to the protons of carbon which consist of hydroxyl group recated with the drug. Single bands at δ=(2.03)ppm are related to (OH) which did not react to the polymer (PVA). Also, are triplet bands at δ=(2.20-2.30)ppm quartet bands at δ=(4.03-4.33)ppm are related to the residual the catalast which is used in the reaction.

Six bands at δ=(3.01-3.08)ppm are realeted to the protons of (-CH-) which are connected with free hydroxyl group. Single bands at δ=(7.20)ppm are related to the proton of the (-OH) group of the drug. And double from the quartet bands at δ=(7.42)ppm and δ=(7.61)ppm which are related to the protons (-NH-) group of the drug.The spectrum is shown in Fig.7.

4.4 In Vitro Release Study of the New Drug Supported Polymers.

Controlled release systems aim to improve the effectiveness of drug therapy [2]. These systems modify several parameters of the drug: the release profile and capacity to cross biological carriers (depending on the size of the particle), biodistribution, clearance, and stability (metabolism) among others. In other words, the pharmacokinetics and the pharmacodynamics of the drug are modified by these formulations. Controlled release offers numerous advantages over conventional dosage forms. This approach increases therapeutic activity and decreases side effects, thus reducing the number of drug dosages required during treatment. Controlled release methods offer an appropriate tool for site-specific and time-controlled drug delivery.These new types of polymers were synthsised and investigated in vitro in the presence of phosphate buffer solution under standard reported procedure[24-28].

4.5 Experimental and Results

In this study, the hydroxylurea dryg supported polymer was investigated in the hope of developing a new controlled release system.Several samples from (pectin & CMC) (weighting 242 mg) having same drug content (180 mg), were pressed to discs (10 mm diameter), The samples were suspended in 50 ml of phosphate buffer solution with pH(7.3) at constant temperature (37 ^{0}C) by using ($FeCl_3$). The drug concentration was determined at different intervals of time (6 days) from the calibration curve which was obtained by plotting the U.V. absorbance with concentration(Fig.4). The concentration of the released drug was measured by using U.V. spectrophotometer technique depending on standared calibration curve betwwen absorbance and concentration at 530 nm, and the concentration of the reasled drug was determined from the calibration curve. The measurement were carried out at 6 days intervals.

For the system containing 88% drug polymer (CMC), the rate of drug release was very high. Then the whole loaded drug was released at constant rate within the first four days thus linear relationship was obtained between (%) drug release vs. time (Fig. 5), but at 71% (pectin), the rate of release decreased remarkably and the complete release of the loaded drug took place within 6 days at constant rate. This behaviour indicates that the drug release is diffusion controlled for both water molecules (into the matrix) and released drug molecular (out of the matrix). The drug release depends on two factors, biodegradation of the chemical bond formed between the drug and polymer, which takes place at the physiological pH (7.3), which is completely dependent on pH. The second factor is diffusion controlled step.

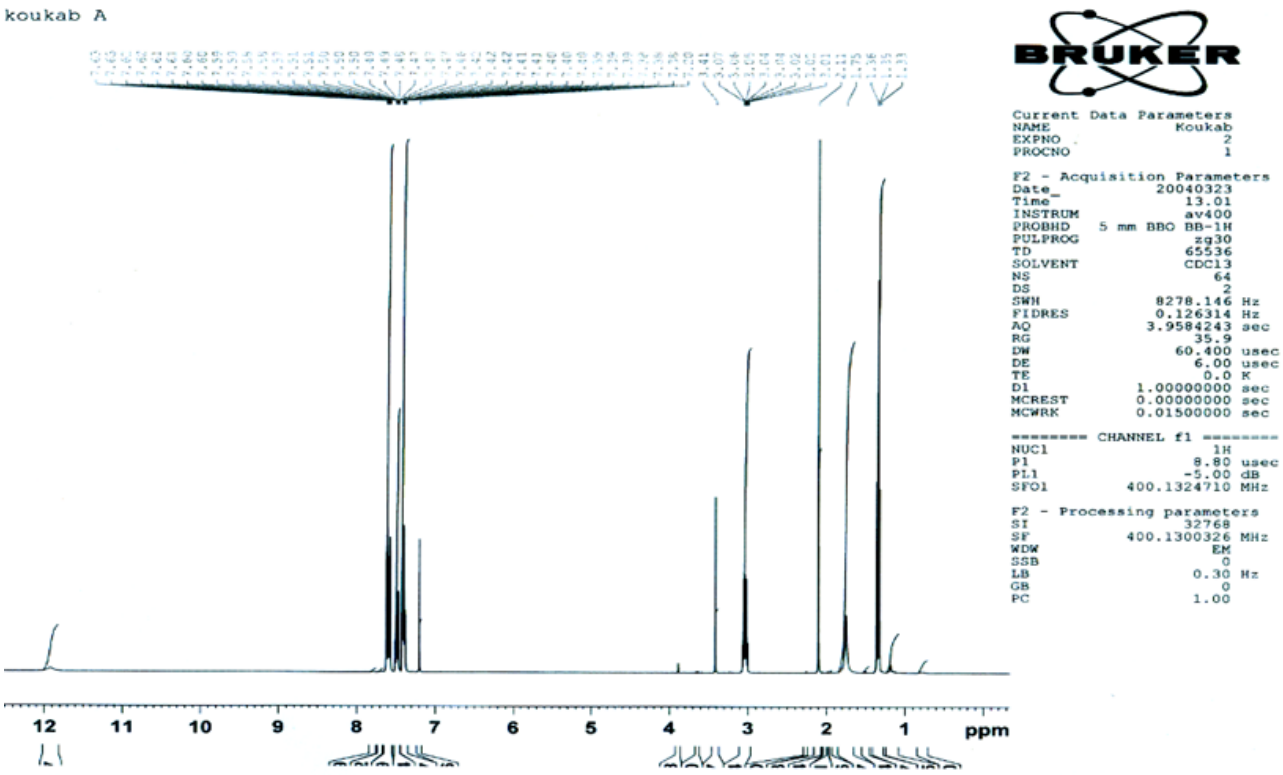


Fig.2 HNMR Spectrum of HU supported polymer pectine

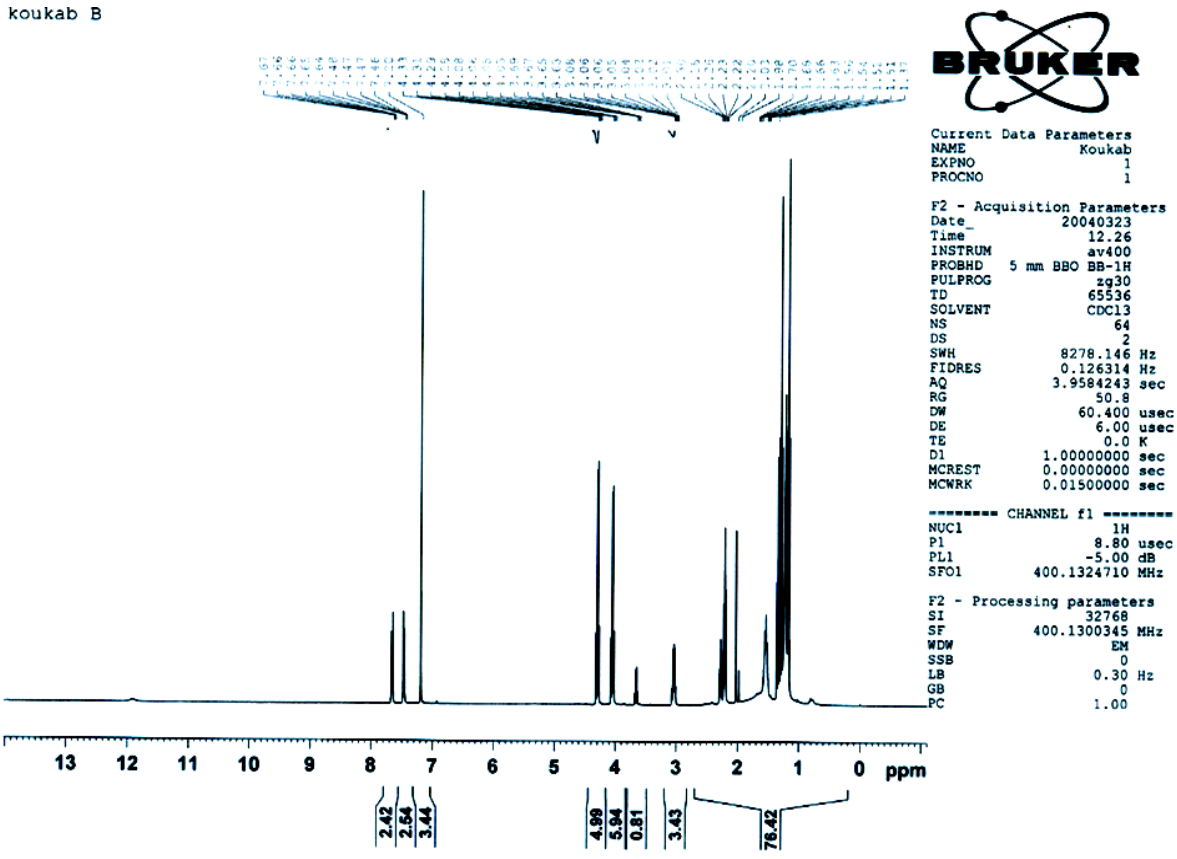


Fig.3 HNMR Spectrum of HU supported polymer poly(vinyl alcohol)

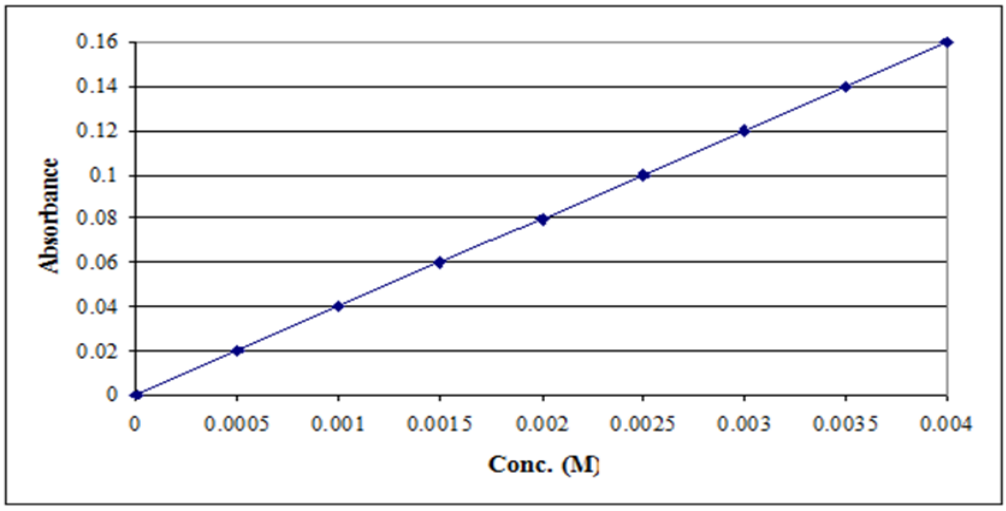


Fig. 4 The calibration curve of drug (hydroxylurea) at 530 nm, at the pH 7.3, at 530 nm

Table: 3 Evalution of the Drug (HU) released (mg) as a function of Time (day)

PH = 7.3 T = 37˚C	Day / mg					
	1	2	3	4	5	6
Pectin	34.2	36	20.79	20.91	5	4
CMC	39.4	41.7	43.5	36.7	8.5	6

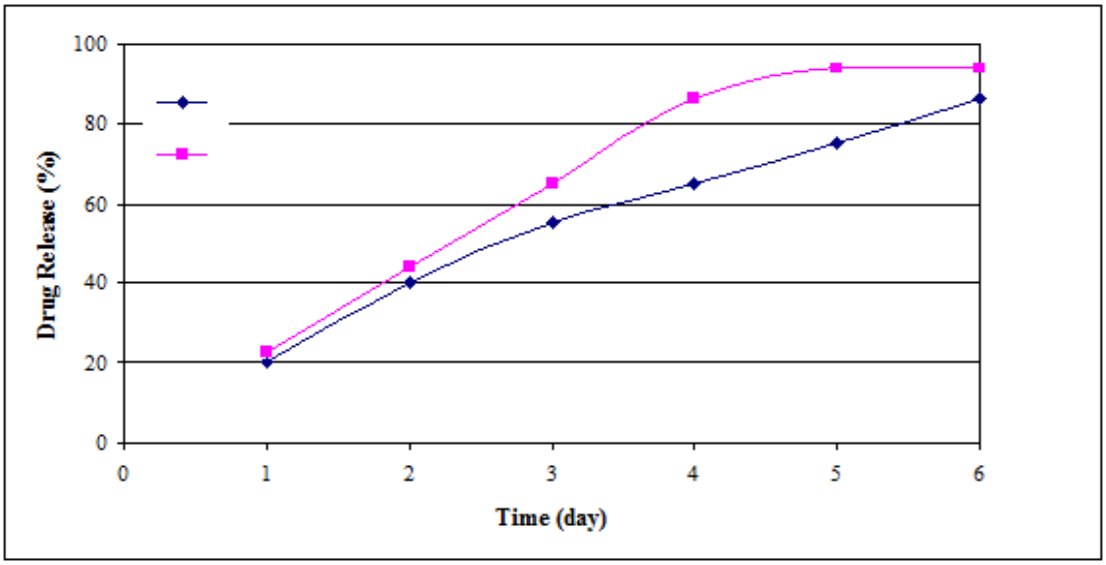


Fig.5 The effect of the drug concentration on drug release at pH=7.3

5.Conclusion.

The study showed that new method for synthesis hydroxyurea is based on localy available cheap raw materials, also the drug supported polymeric systems are efficient tecqniques for slow drug release systems. Also, the systems showed promising behaviour regarding their sustained release properties as studied externely in vitro.

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طريقة جديدة لتحضيرالهيدروكسي يوريا وبعض مشتقاته من البوليمرات المسندة كأنظمة الانحلال المقنن الجديدة

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المستخلص

تم في البحث تحضير المادة الدوائية هيدروكسي يوريا Hydroxyurea المضادة للاورام السرطانية anticancer المختلفة ، وتعتبر هذه المادة الدوائية من المواد المهمة في معالجة الامراض السرطانية بصورة مفردة او عن طريق اخذها مع ادوية اخرى .

لقد تم اعتماد تقنيات جديدة في تحضيرها ، وتمتاز هذه التقنيات الجديدة بكلفتها الواطئة من خلال اعتمادها على مواد اولية محلية اضافة الى ذلك انها اقل سمية مقارنة بالتقنيات القديمة المعتمدة على سيانات الصوديوم ذات السمية العالية .التقنية الجديدة المطورة على مستوى انتاجي في مختبرات جامعة البصرة تعتمد على مادة البايوريت التي تتكون كناتج عرضي في الشركة العامة للاسمدة الجنوبية ويمكن انتاجها صناعياً ، حيث تم تحويل البايوريت الى الوفانات الاثيل وثم تحويلها الى كاربامات الاثيل والتي يتم مفاعلتها مع هيدروكسيل أمين هيدروكلورايد .

تم تشخيص المادة الفعالة المحضرة بتقنيات مختلفة والممثلة بتقنية الاشعة تحت الحمراء IR وتحليل العناصر CHN وقياس درجة الانصهار ، بالاضافة الى كشف المجاميع الفعالة .يشمل الجزء الثاني من البحث ربط المادة الفعالة هيدروكسي يوريا على نوعين من البوليمرات والمتمثلة بالبوليمرات الطبيعية والصناعية بهدف انتاج تركيبات دوائية جديدة من النوع ذات الانحلال المقنن Controlled release drugs المناسبة للاستخدام الموضعي بعد استئصال الاورام السرطانية لتقضي على بقايا الخلايا المسرطنة ان وجدت لكي لاتستعيد نشاطها ثانية . حيث تم اسناد المادة الدوائية على السكريات المتعددة المتمثلة بالبكتين والبكتك و كاربوكسي مثيل سيليلوز من خلال تحويل المجموعة الكاربوكسيلية للسكر المتعدد الى هاليد الحامض والذي بدوره يهاجم مجموعة الامين الدوائية مكوناً روابط امايدية .اما بالنسبة للبوليمرات الصناعية (بولي(كحول الفاينيل) و راتنج رباعي مثيلول يوريا) فقد تم اسناد المادة الدوائية على بولي كحول الفاينيل باستخدام الفاصل spacer كلوريد سباسويل والذي يحتوي على مجاميع كلورايد من الطرفين ، حيث يهاجم كلوريد الحامض الطرف الاميني من الدواء مكوناً روابط امايدية ، اما الطرف الثاني من كلورايد سباسويل يهاجم مجموعة الهيدروكسيل العائدة للبوليمر مكوناً روابط استرية .وتم اسناد المادة الدوائية على الراتنج رباعي مثيلول يوريا والذي تم تحضيرة في مختبراتنا ، حيث اعتمدت فكرة الربط على حدوث تداخلات وتشابكات بين سلاسل الراتنج والمادة الدوائية لتكوين سبيكة بوليمرية .تم تشخيص النواتج بالتقنيات الكيميائية المعروفة مثل الاشعة تحت الحمراء IR ، والرنين النووي المغناطيسي NMR ، وتحليل العناصر CHN ، وكشف المجاميع الفعالة . واخيراً اثبتت التركيبات الدوائية الجديدة المحضرة بانها تمتاز بتقنية التحلل المقنن وتحرر المادة الفعالة .

الكلمات المفتاحية: الهيدروكسي يوريا، نظام الدواء المقنن، ادوية الانحلال المسيطر عليه .