AJPS, 2012, Vol. 11, No.1

Preparation of Polyvinylpyrrolidinone With Paracetamol as Drug Polymer

Firyal M.A.AL-Salami, * Abbas N.M. AL-Sharify and* Khudheyer J. K.
Department of Chemistry, College of Science,University of AL-Mustansiriya
**** Babylon University***

الخلاصة:

حضر البوليمر الدوائي من فتح حلقة البولي فاينيل بايرولدينون بواسطة المجموعة الهايدروكسيلية في الباراسيتامول بواسطة الهجوم الباحث عن النواة. البوليمر الدوائي الجديد المحضر بهذا البحث بناتج عالي حوالي 92% وبلزوجة جوهرية (0.61 dl/g)، وشخص البوليمر المحضر بواسطة الاشعة فوق البنفسجية وطيف الرنين النووي المغناطيسي والاشعة تحت الحمراء ودرست الصفات الفيزيائية.

درست سرع التحرر الدوائي في المحيط الحامضي و القاعدي وبدرجة30ْ م و40ْ م. ان سرع التحرر الدوائي لاستر الباراستيمولات في الوسط القاعدي اكثر من الحامضي, وتعتمد سرع التحرر الدوائي على درجة الحامضية وعلى ارتفاع درجة الحرارة, حيث تزداد سرع التحرر الدوائي بارتفاع درجة pH وبارتفاع درجة الحرارة.

Abstract:

The prodrug polymer was prepared according to ring opening of polyvinyl pyrrollidinone with nuecleophilic attack of hydroxyl group of paracetamol.

The new colorless drug polymer was formed with 92% conversion percentage with intrinsic viscosity was equal to (0.61dl/g). The drug polymer was characterized and identified by ^{1}H-NMR, IR and UV. Spectroscopy. Controlled released rates were studied in acidic and basic medium at 30 ^{0}C and 40 ^{0}C.

Rate of hydrolysis of paracetamolate ester acts as base > acid, and the rate of release, depends on temperature and pH values. The results show higher hydrolysis at higher temperature as well as higher pH value.

Keywords: Polyvinylpyrrolidinone; Paracetamol; Drug Polymer

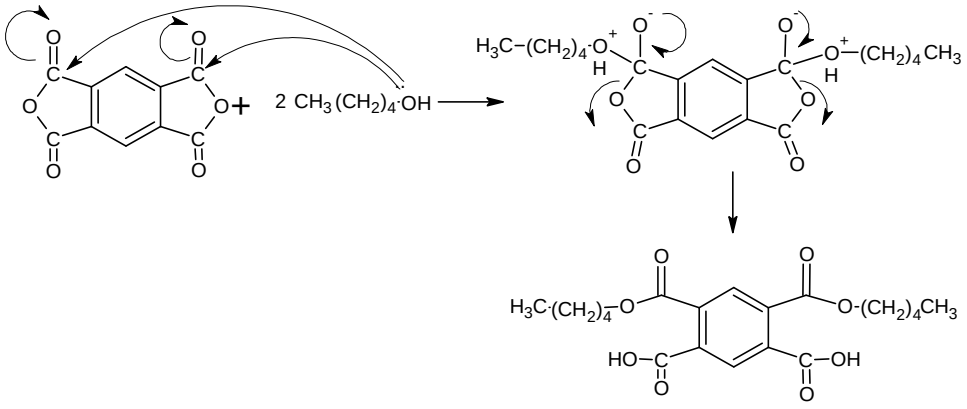
Introduction:

Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced in to medical practice under the name of antifebrin by A. Cahn and P. Heppin1886[1]. But it is unacceptable toxic effects, the most alarming being cyanosis due to

methemoglobinemia, prompted the search for less toxic aniline derivatives[2]. In combination with opioid analgesics, paracetamol can also be used in the management of more severe pain such as post surgical pain and providing palliative care in advanced cancer patients.[3] The onset of analgesia is approximately 11 minutes after oral administration of paracetamol,[4] and its half-life is 1–4 hours. Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the *para* (1,4) pattern[5]. The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen is all conjugated.

The presence of two activating groups also makes the benzene ring highly reactive toward electrophilic aromatic substitution. As the substituents are ortho,para-directing and para with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygens and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the phenoxide anion[6].Industrial preparation of paracetamol usually proceeds from nitrobenzene.[7] In the laboratory, paracetamol is easily prepared by nitrating phenol with sodium nitrate, separating the desired *p*-nitrophenol from the *ortho*- byproduct, and reducing the nitro group with sodium borohydride. The resultant *p*-aminophenol is then acetylated with acetic anhydride.[8] In this reaction, phenol is strongly activating, thus the reaction requires only mild conditions (cf. the nitration of benzene):
p-Aminophenol may be obtained by the amide hydrolysis of paracetamol. *p*-Aminophenol prepared this way, and related to the commercially available Metol, has been used as a developer in photography by hobbyists.[9] This reaction is also used to determine paracetamol in urine samples: After hydrolysis with hydrochloric acid, *p*-aminophenol reacts in ammonia solution with a phenol derivate e.g. salicylic acid to form an indophenol dye under oxidization by air[10] .

Preparation of pyromelletic acid dipentyl esters ,The pyromelletic acid dipentyl esters were prepared by reaction of pyromelleticdianhydride and pentanol. The prepared ester were crystalline solid, with high softening points>300^{0}C and high yields>78%[11].



Materials and Methods:

All chemicals were purchased from fluka and BDH.

Instruction:

1 - Gallen kamp M.F.B-600 melting point apparatus.
2 - Electronic spectra measurements using CINTRA-5-UV-visible spectro-photometer.
3 - Infrared spectra were recorded by using sp3-100 Infrared.
4 - Spectrophotometer pye-unicam (600-4000) cm^{-1}.
5 - Polymer swelling determination used :hexane, acetone as solvents.
6 - ^{1}H-NMR spectra was recorded on a Fourier transform Varian spectrometry, company Bruker, model, Ultra shield 300MHZ, origin: Switzerland,with titramethyl silane as internal standard in DMF measurements were made at the Chemistry Department, AL-Yarmouk University, Jordan.

Preparation of PVP with Paracetamol:

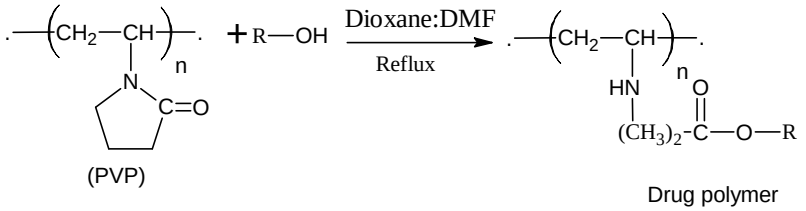
A mixture of (0.045mole) of polyvinylpyrrolidinone was dissolved in 20 ml of 10:1 dioxane:DMF in a round bottom flask, equipped with reflux condenser and a magnetic stirrer, then (0.0165mole)of dissolved paracetamol was added gradually, refluxed for 1hour, then left the mixture about 1hour. The dioxane was evaporated, the viscose colorless pure polymer was obtained with 92% conversion.

Controlled Release Study [13]:

A 100 mg of modified PVP-Paracetamol was kept a cylinder containing 100 ml, in pH 4 or pH 10 and in a water bath at $30C^{0}$ without stirring, A sample from the release medium was periodically withdrawn and analyzed by UV. At 350 nm to determine the amount of the released paracetamol. A calibration curve was constructed with a software built in the computerized UV. spectrophotometer and the amount mg of the released paracetamol was determined directly from the software using the calibration curve. in pH 4 and pH 10 at 30 ^{0}C.

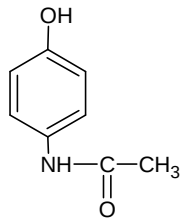
Results and Discussion:

Paracetamol is commonly used for relief of headaches, and other minor aches and is a major ingredient in numerous cold and flu remedies, In combination with opioid analgesic paracetamol could be used also in the management of more servere pain (such as in advanced cancer).In this work the hydroxyl group in the paracetamol could react with polyvinylpyrrolidinone (PVP) with ring opening as shown in the following reaction[14]:-



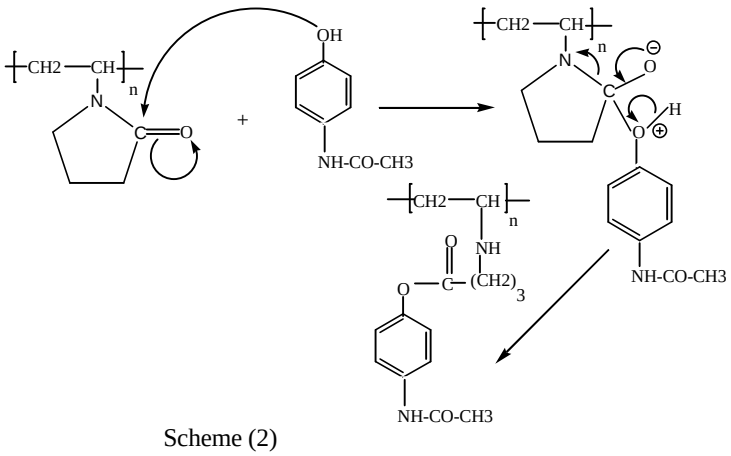
R—OH = Paracetamol

Paracetamol =



Polyvinypyrrolidinon connected with ester of paracetamol moiety affords both protection and specific transport properties with longer acting with lesgastic irritation than parent drug.

The following mechanism shows the modification of PVP with paracetamol[14].



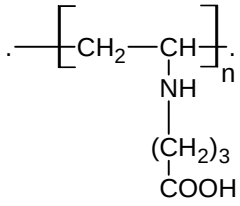
Scheme (2)

The FT-IR spectra of prepared prodrug polymers shows the disappearance of the characteristic bands of the phenol υ(-OH) stretch is a sharp peak at 3600 cm^{-1} , and disappearance of the characteristic bands of the C-O-H bending appears as

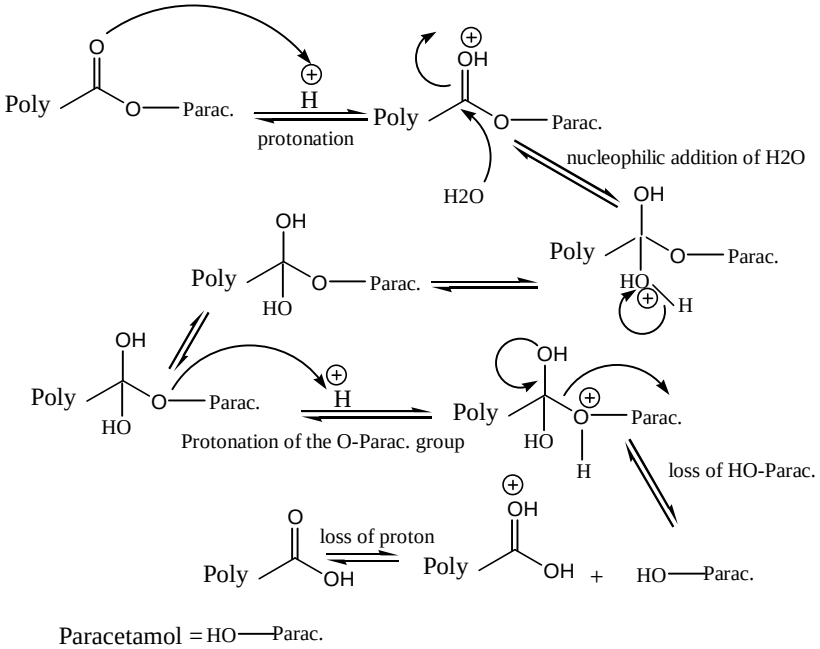
abroad and weak peak at 1440-1300 cm^{-1} and the appearance of υ(C=O) at 1740 cm^{-1} of ester and υ(C-O) at 1760 cm^{-1} conjugation of a single-bonded oxygen atom with C=C of phenyl group and the appearance of υ(-NH) secondary amine at 3400 cm^{-1} Figure-1shows the IR spectra of polyvinylpyrrolidinone with paracetamol as drug polymer .

UV. Spectra of prepared polymer shows the absorption at 250 nm and 350 nm which attributed to (π-π^*) and (n- π^*) electronic transition respectively.

The ^{1}H-NMR spectrum of amide polymer was shown in Figure-2 indicating the signal assignments in the corresponding formula, which shows the following peaks: δ –CO-CH_3 at 2.9 , δCH_2- 1.9 , δCH- at 2.1 , δ CH=CH aromatic ring at 7.5- 8 , δ -NH- at 3.4 , δ –$COOCH_2$ at 4.8. for δ –COOH of 10ppm due to the hydrolysis of some polyvinypyrrolidinon unite as shown bellow :-

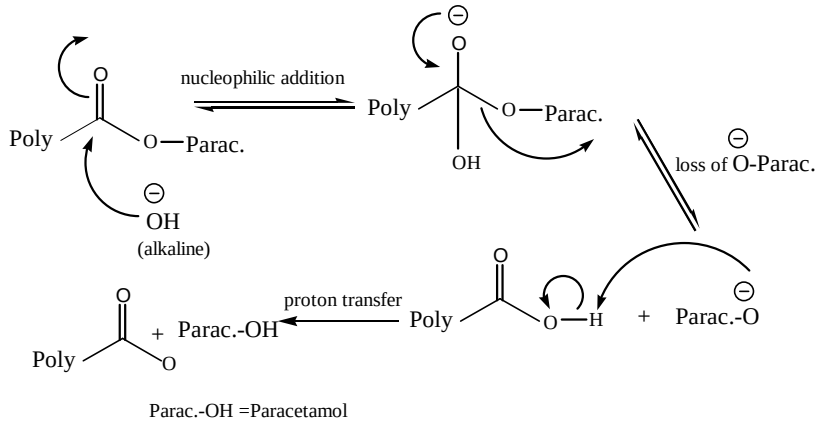


Controlled release rate of the prodrug was studied in acidic and basic medium at $30C^0$,Fig(3) Shows the rate release in different medium. The following mechanism illustrated the release of paracetamol molecules by hydrolysis in acidic medium[13,15]:-



Scheme (3)

The other mechanism of hydrolysis of prodrug polymer in basic medium which illustrated as follow[13,14]:-



Scheme (4)

Figure-3shows the effect of temperature and pH effect on the rate of release and profiles of mole fraction of paracetamol (ratio of the moles of paracetamol to total moles present in the sample) versus time at pH values 4 and 10 in (60:140) (V/V) aqueous buffer/dioxane at 30 ^{0}C and 40 ^{0}C.

Rate of hydrolysis of this ester bond acts as base (pH 10) > acid(pH 4). The result shows higher hydrolysis at higher temperature as well as higher pH value.

In acidic media, H^+ is bonded to oxygen atom of C=O group and increases the positive charge of carbon atom, consequently, it promotes the nucleophilic attack of water.

Due to the presence of OH^- in alkaline media which is a stronger nucleophile in respect to water, the rate of hydrolysis of ester takes place faster than in acidic.

Intrinsic viscosity was determined for the prepared polymer by using Ostwalad viscometer and DMF as a solvent at 30 ^{0}C (η_{in}= 0.61dl/g).

The softening point of the drug polymer was (210-220 ^{0}C)

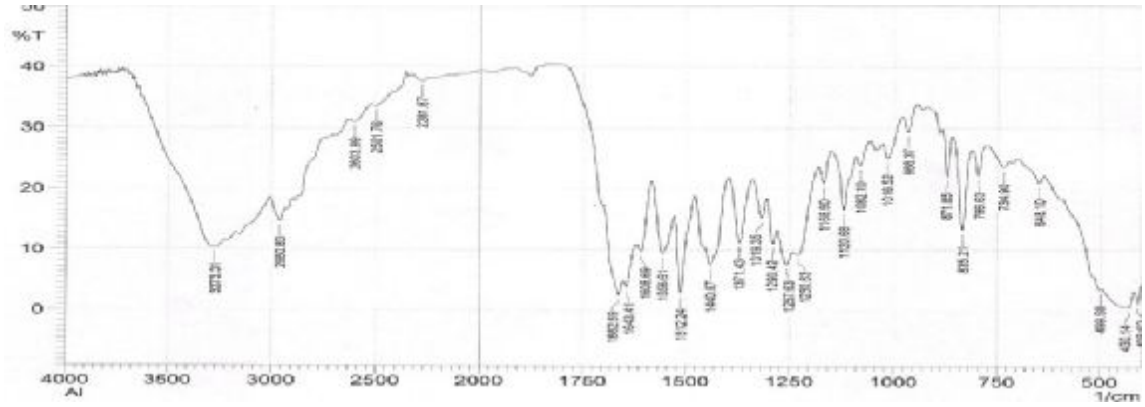


Figure-1: IR spectra of drug polymer

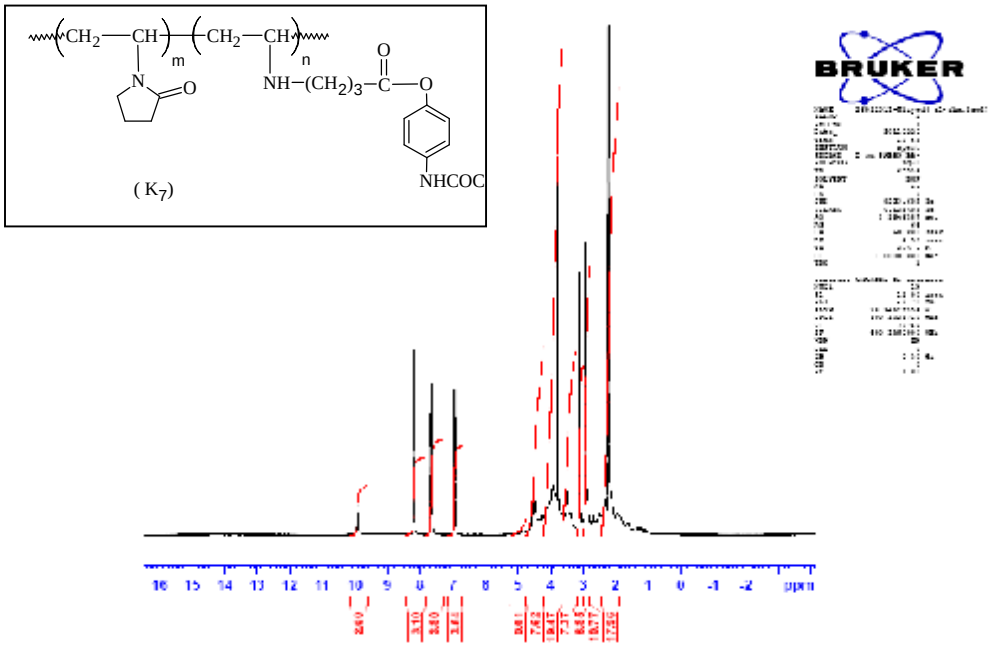


Figure-2: ^{1}H-NMR spectra of PVP with paracetamol drugpolymer

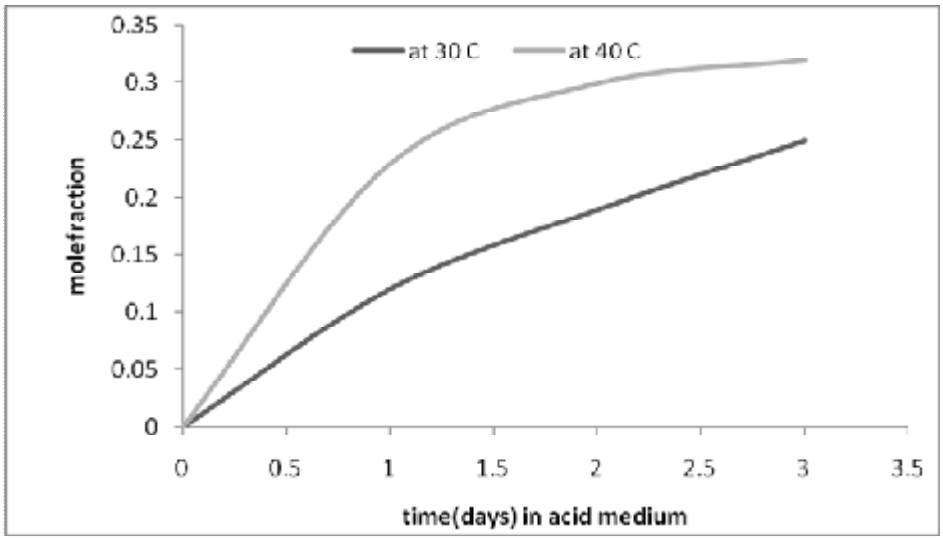


Figure-3a: Controlled release of paracetamol drug PVP in pH 4.

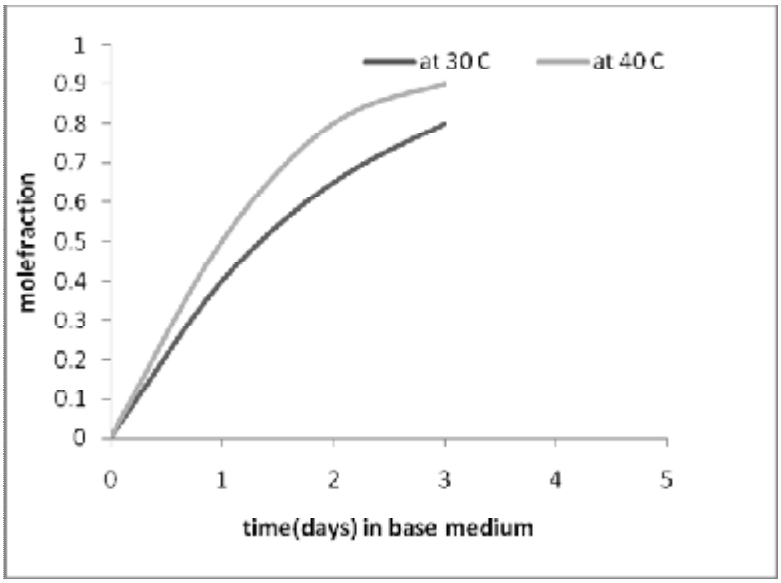


Figure-3b: Controlled release of paracetamol drug PVP in pH 10.

References:

1 - Granberg, R.A and Rasmuson, A.C . (1999). Solubility of paracetamol in pure solvents. Journal of Chemical & Engineering Data 44 (6). Pp. 1391–95.

2 - Moller, P.; Sindet-Pedersen, S.; Petersen, C.; Juhl, G.; Dillenschneider, A. and Skoglund, L. (2005). Onset of acetaminophen analgesia: comparison of oral

and intravenous routes after third molar surgery. British journal of an aesthesia 94 (5). Pp. 642–648.

3 - Khashab, M.; Tector, A.J. and Kwo, P.Y. (2007). Epidemiology of acute liver failure. Curr Gastroenterol Rep 9 (1). Pp. 66–73.

4 - Hawkins, L.C; Edwards, J.N. and Dargan, P.I. (2007). Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature. Drug Saf 30 (6) .Pp. 465–79.

5 - Larson, A.M; Polson, J.A and Fontana R.J. (2005). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Herpetology 42 (6) .Pp. 1364–72.

6 - Bales, J.R.; Nicholson, J.K. and Sadler, P.J. (1985). Two-dimensional proton nuclear magnetic resonance "maps" of acetaminophen metabolites in human urine. Clinical Chemistry 31 (5). Pp. 757–762.

7 - Anthony, S. and Travis, D. (2007). Manufacture and uses of the anilines: A vast array of processes and products. In Zvi Rappoport. The chemistry of Anilines Part 1. Wiley. Pp. 764.

8 - Ellis, F. (2002). Paracetamol: a curriculum resource. Cambridge: Royal Society of Chemistry. ISBN 0-85404-375-6.Novotny PE.,

9 - Elser, R.C. (1984). Indophenol method for acetaminophen in serum examined. Clin. Chem. 30 (6). Pp. 884–6.

10 - Roberts, L. J. and Marrow, J. D. (2001). Analgesic-antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout" in, "Goodman & Gilman's The Pharmacological Basis of Therapeutics 10th Edition by Hardman, J.G. & Limbird, L.E. Published by McGraw Hill. Pp.687–731.

11 - Abdul Salam, A. (2002). Synthesis of novel thermally stable polymers from polycondensation or chain polyimides and their composites with other polymers. Ph.D. thesis. Baghdad University .Pp71.

12 - Firyal, M.A.; Abbas, N.M. and Khudheyer, J.K. (2010). Iraq. Preparation of (N-Procainyl Amic acid) Polymers as drug polymers .fourth Scientific Conference.University of Wasit.Vol.4,Pp. 402-410.

13 - Firyal, M.A.; Abbas, N.M. and Khudheyer, J.K. (2010). Iraq. Modification of PolyVinylpyrrolidinon With Eugenol and Study of Its Controlled Release. fifth Scientific Conference-College of Science-University of Babylon.Vol.5, Pp316-323.

14 - Firyal, M.A. (2005). Modification of acrylic acid and acryloyl chloride polymers. journal of Um-Salama Science Vol.2(4).Pp.645-652.

15- Firyal, M.A.; Abbas, N.M. and Khudheyer, J.K. (2010).Iraq. Synthesis of Poly Paracetamol Acrylate and Study of its Drug Release.fifth Scientific Conference-College of Science-University of Babylon.Vol.5,Pp. 230-236.