Synthesis of Histidine- Amoxillin Condensed Drug Polymer

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Abstract

A novel drug polymer as a peptid-biopolymer was prepared from histidineacidchloride with amoxillinacidchloride, the condensed polymer was prepared with molar ratio 1:1, this biocompatible, biodegradable, reabsorb able condensed polymers with controlled lifetimes, which can be used as drug carrier polymer. The physical properties were measured and the intrinsic viscosity was measured using Ostwald viscometer, The controlled release rates were studied in different pH values at 37 ^{0}C . The condensed polymer was characterized by UV-vis. FTIR and ^{1}H-NMR spectroscopy, This biomaterial polymer can be used as non-toxic substance. When it undergo hydrolytic degradation.

الخلاصة

حضر البوليمر الدوائي من تكاثف الهستدين كلوريد الحامض مع الاموكسيلين كلوريد الحامض بنسبة مولية 1:1، ويكون ملائم للتحلل والامتصاص ومسيطر علية لمدة اطول باستخدام بوليمر حامل للدواء . قيست الخواص الفيزيائية وقيست اللزوجة الجوهرية باستخدام اوستولد فسكوميتر ، ودرس سرعة التحررالدوائي بدوال حامضية مختلفة وبدرجة 37م . البوليمر المتكاثف شخص بمطياف الاشعة فوق البنفسجية والاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي . البوليمر الدوائي المحضر اقل سمية عند تحللة .

Introduction

In recent years efforts have directed towards the preparation of biocompatible, biodegradable, reabsorbable condensed polymers with controlled lifetimes, which can be used to manufacture temporary implants or in controlled drug release . Poly(lactic acid), poly(glycolic acid) and their copolymer have been intensively used in clinical applications[1]. Segmented poly (ether-ester –amide)s were obtained from sebacoyl chloride, α,ώ-hydroxyl terminated poly(L-lactide) monomers and hydrophilic diamine. 4,7,10-trioxa-1,13-tridecanediamine [2].

The polyvinylpyrrolidinone was modified with amoxillin to drug polymer with high release in basic medium at pH10 [3].

Cephalexin [4] is a member of the cephalosporin group of antibiotics, and is prescribed for a variety of mild infections. It is not as wide ranging in its action as some other antibiotics, but it is useful for treating infections of the respiratory tract as well as skin conditions (including acne) and soft tissue infections. The antibiotic can be prescribed on its own or as a follow up after an injection of a stronger cephalosporin has been administered. It is also used as a low dose antibiotic that can be administered over an extended period of time. It is a fairly short acting antibiotic and therefore is not as convenient as some others because it must be taken fairly frequently (every four hours).The side effects of the pure drug are usually fairly mild, and the danger of overdose is low. However, it can be administered as one of several preparations including cephalexin hydrochloride monohydrate, which can have more severe side effects including nephrotoxicity and cholstatic jaundice. Added to this, the safety of some of these preparations has not been fully determined for use in children. Recent tests have also been carried out to ascertain the suitability of the drug for use in veterinary practices. A polymer is a large molecule composed of many smaller units called monomers that are bonded together

If an application requires rapid development and commercialization, than the polymer selection will most likely be made frorr among those polyesters that have already received regulatory approval. Another factor to be taken into account is choice is choice, whether to use homopolymers consisting of single monomeric repeating unit or copolymers containing multiple monomer species. A review that describes in detail the relationship between polymer properties and performance in drug delivery applications have been published(2). Ultimately all these properties will influence the performance of the drug delivery system via changes to the relative rates of mass transport(e.g., water in and solute or drug out of the system) and the degradation rate of both, the polymer and the device[4,5].

In some cases, the term biodegradation is limited to the description of chemical processes (chemical changes that alter either the molecular weight or solubility of the

polymer) while ' bioerosion' may be restricted to refer to physical processes that result in weight loss of a polymer device. The possibility for a polymer to degrade and to have its degradation by-products assimilated or excreted by living system is designated as bioresorbable[5] .

Ethylenediaminetetraacetic acid (EDTA) as a stable and common complexing compound was inserted into the polymer backbone with polyaddition reactions separately between hexamethylenediamine (HMDA) or polyethylene glycol. The prepared polymers were soluble in water and carboxy functional groups have been connected to the polymer chains [6]. Many condensed polymers we prepared by reaction of amine acids such as glycine, alanine, hestidine and aspargene with adipoyl chloride in presence of triethylamine as a catalyst [7]. The polycondensed polyamino acid with heterocyclic compounds were synthesized [8,9].

Degradation by erosion normally takes place in devices that are prepared from soluble polymers. In such instances, the device erodes as water is absorbed into the systems causing the polymer chains to hydrate, swell, disentangle, and ultimately dissolved away from the dosage form. Alternatively, degradation can also result from chemical changes to the polymer including cleavage of covalent bonds, ionization and protonation either along the polymer backbone or on pendent side chains [4].

Experimental

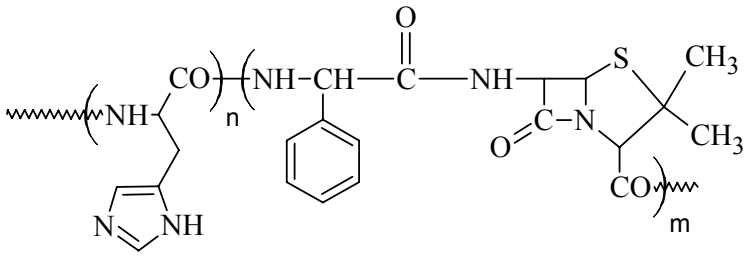
Materials: Amoxillin was provided from Sammura Company, and all other chemicals were purchased from Merck, and hestidine was obtained from Fluka.

All available chemical reagents were used without further purification. FTIR spectra were taken on a Shimadizu spectrophotometer recorder over the range500-4000cm^{-1}. Ultraviolet spectra was recorded using Shimadzu UV-VIS recorder. 1H-NMR spectra were carried out on a Brucker AC, 500 spectrophotometer

Polycondensation of histidine with amoxillin

The histidine was converted to its acidchloride and amoxillin was converted to its acidchloride by treating with thionylchloride at 0 ^{0}C., the equivalent molar ratio were introduced in a single- neak round-bottom flask containing freshly dried solvent of dioxane, and equippied with a condenser, stirred at 1hr. then the solvent was evaporated and the residue was washed with ether for several times, finally it was dried under vacuum until the constant weight was obtained. The physical properties were presented in Table (1).

Table (1).Physical properties of prepared condensed polymer



Polymer No	Color	Conversion%	Intrinsic viscosity $[\eta]_{in}$=dl/g	UV. absorption nm
P_1	Brown	73	0.5	230-300

Controlled drug Release [10]

A 100 mg of condensed amoxillinhistidine drug polymer was kept in a cylinder containing 50:50ml of buffer:dioxane and in a water bath at 30^0C without stirring. A sample from the release medium was periodically withdrawn and analyzed by UV. At 300nm to determine the amount of the released amoxillin. A calibration curve was constructed with a software built in the computerized UV. Spectrophotometer, the amount 0.1 mg of the released amoxillin was determined directly from the software for many days, using the calibration curve in different pH values at 37 ^{0}C as shown in Fig.(4).

Swelling Percentage of prepared polymer was studied which equals to 8% in acetone and 10% in hexane as shown in Fig.(5).swelling% was calculated according to

$\Delta m = m_1 - m_0 / m_0 \times 100$

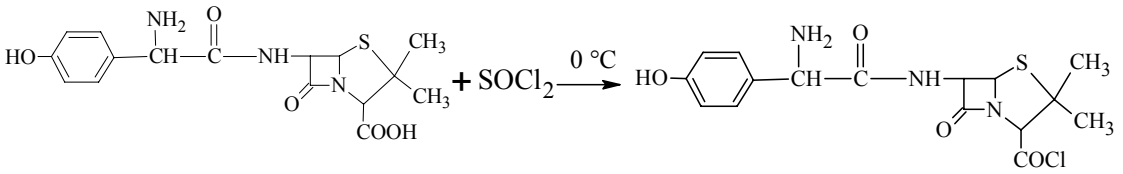
When m_0 is the weight of a dry drug polymer

m_1 is the swallowed polymer in non solvent

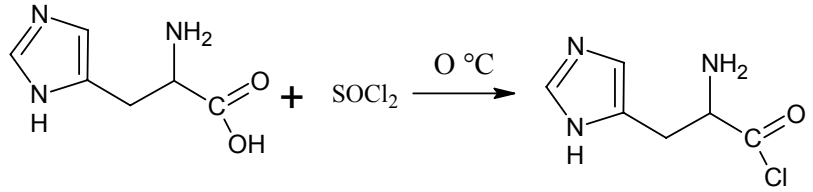
Swelling curves of drug polymer in water with pH 4 and pH 10 at 37 ^{0}C shown in figure (3).

Results and Discussion:

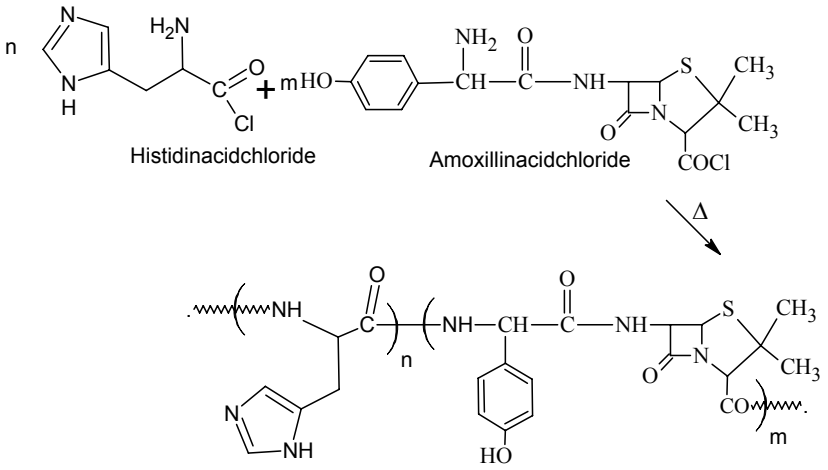
The modification of amoxillin to its acid chloride was carried out by thionylchloride as shown in the following reaction :-



The histidine was converted to its acid chloride also using thionylchloride at 0 ^{0}C as shown in following reaction:-



The two modified amoxillin and histidine acidchlorides were condensed with 1:1 molar ratio as explained in the following reaction: -



Spectroscopic Characterization

The FTIR spectra of condensed amide polymer exhibited the prominent amide bond at 1730 cm^{-1} and υ-NH group at 3147cm^{-1} with comparison with amoxillin or histidine compounds and υ(-OH) at 3405cm^{-1} and υ C-N at 1324 cm^{-1} and υ (C-O) at 1114 cm^{-1} and υ(CH_3, CH_2, CH) at 2931-2623 cm^{-1} as shown in Fig.(1).

The UV. Spectra of condensed polymer at 320 nm and 290nm due to (n-π *) and (π-π*) electron transitions respectively.

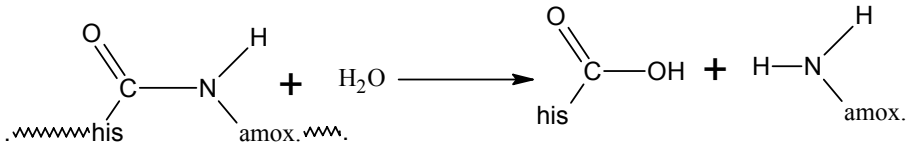
The ^{1}H-NMR spectrum of amide polymer was shown in Fig. (2) indicating the signal assignments in the corresponding formula, which shows the following peaks:-

δ(1.4ppm) 2H for (NH amide) , δ(2.6ppm) 6H of CH_3, δ(2.9ppm) of (N-CH-C=0) , δ(4ppm) of OH , δ(5ppm) of NH amoxillin ,δ(3.8ppm) of (NH histidin) δ(7ppm) of CH=)

, δ(7.8ppm) of CH=N , δ(8ppm) of aromatic

The physical properties of prepared polymer were studied such as intrinsic viscosity which was measured at 30 ^{0}C with Ostwald viscometer by using dioxane as a solvent.($[\eta]_{in}$= 0.5dl/g).

Fig.(4) shows the effects of pH values on the rate of controlled release and profiles of mole fraction of amoxillin ratio to total moles present in the sample versus time at pH values 4 and 10 at 37 ^{0}C. The only nucleophilic acyl substitution reaction that amides is hydrolysis, Amides are fairly stable in water, but the amide bond is cleaved on the heating in the prescience of strong acid or bases, Norminally this cleavage produces an amine and carboxylic acid.



histidine amoxillin

The release of the drug at suitable condition gradually with outside effect, this hydrolysis of amide group which shown in the following mechanism [7,8]

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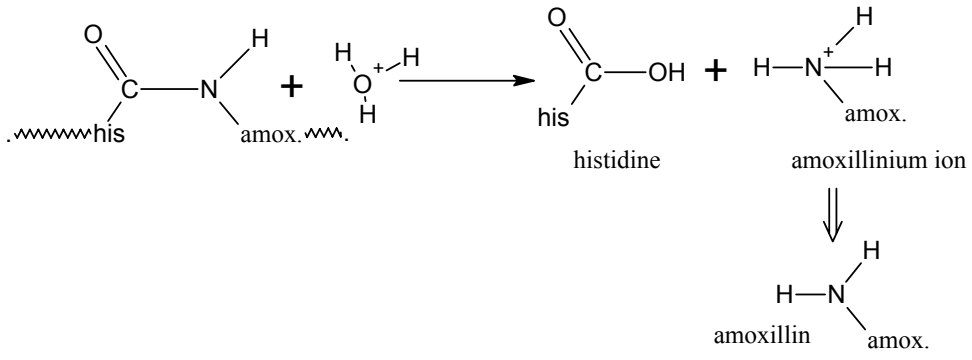
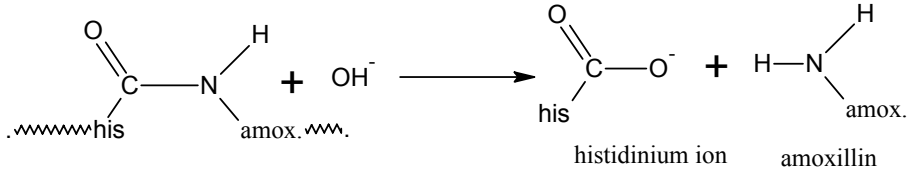
In acid, however, the amine is protonated giving an ammonium ion :-



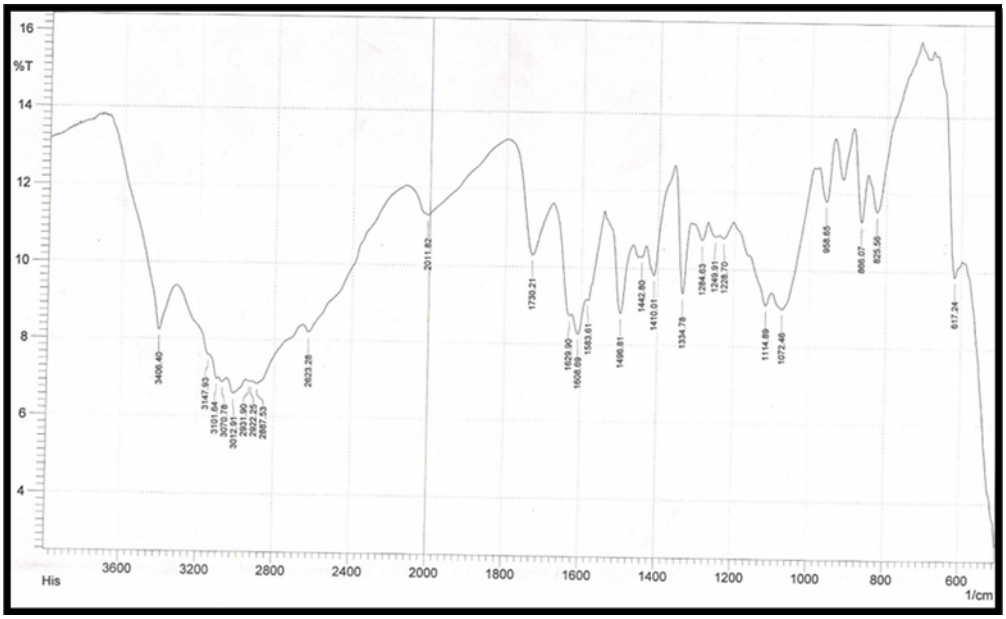
In base the carboxylic acid is deprotonated, giving a carboxylate ion :-



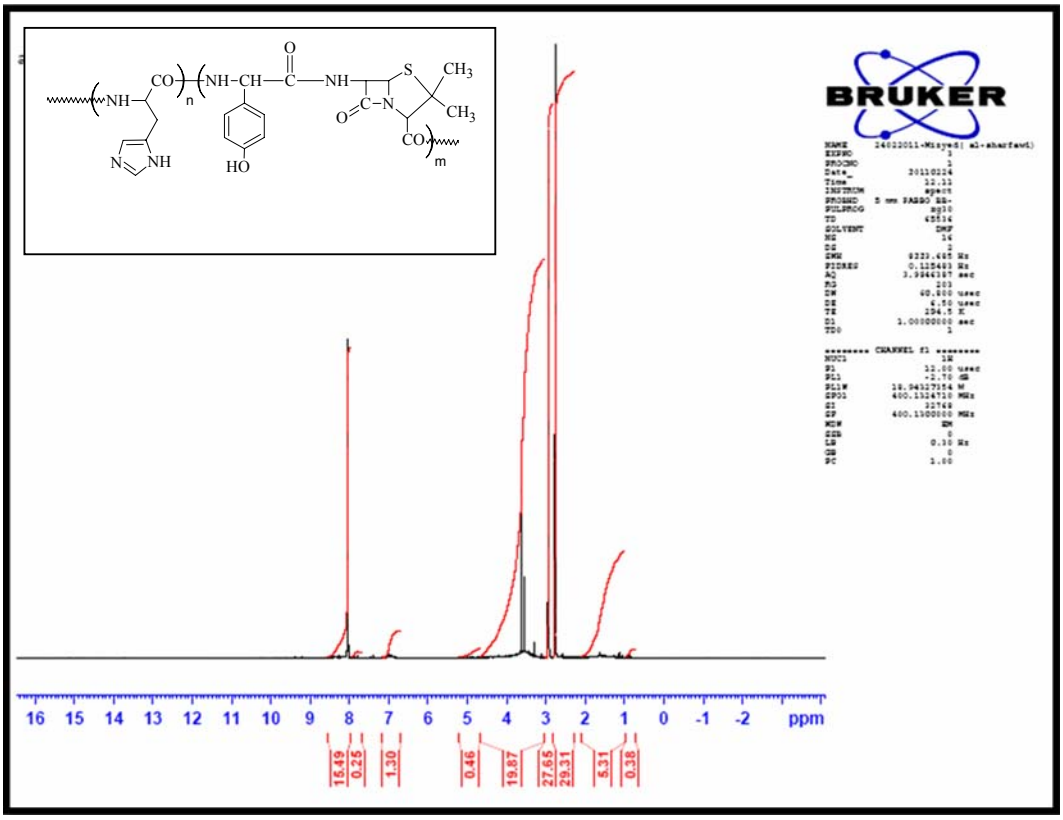
The purpose of this research was to synthesize polymer based smart bioactive amoxillin prodrug polymer and one of the main goal in this work is investigation of efficient drug carrier and the effect of pH values on drug release at 37 ^{0}C as illustrated in Fig(4) .The hydrolysis rate of this amide bond acts as base > acid. The result indicated higher hydrolysis in basic medium [9,10] .

Conclusion

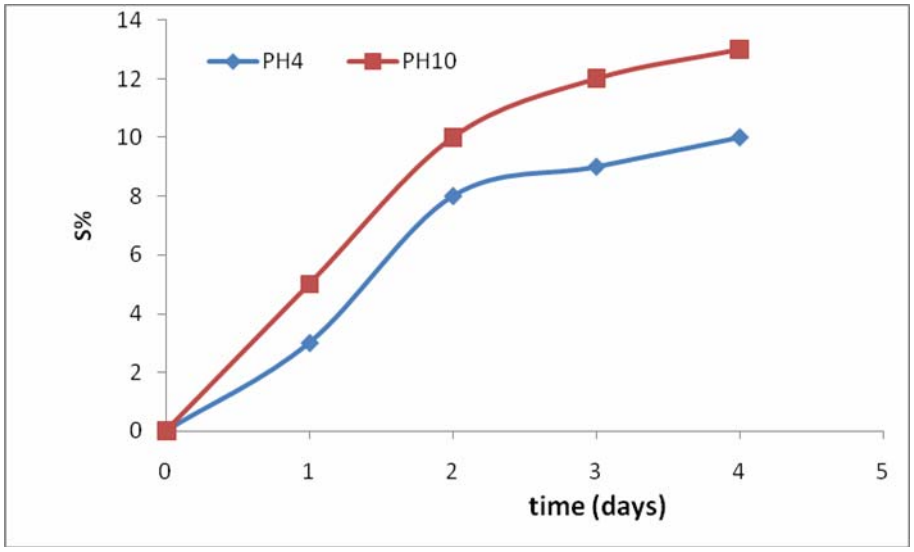
The results show that the water soluble polyamide which can be conveniently and quickly prepared in a one –step reaction in solution, the histidine connected with amoxillin with amide group with moiety affords both protection and specific transport properties with longer acting release with higher reactivity in suitable site and this type of drug polymer which hydrolysis in fabrications conditions to delivery of agents for therapeutic against diseases.



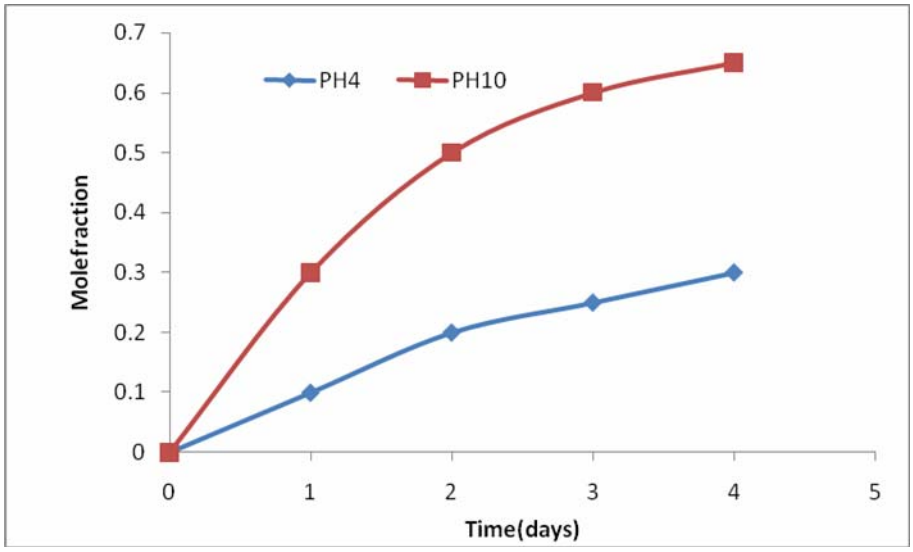
Fig(1) FTIR spectra of Polycondensation of histidine with amoxillin



Fig(2) 1H-NMR spectra of Polycondensation of histidine with amoxillin



Fig(3) Swelling curve of Polycondensation of histidine with amoxillin



Fig(4) Controlled release of Polycondensation of histidine with amoxillin

References

1. Domb A., Amselem S., Maniar M., In :Dumitrrin S. editor ***Polymeric biomaterials***, New York.Dekker, 1994, 399.
2. Angelo S., Galletti P., Maglio G., Malinconico M., Morelli P., and Palumbo R. ***J. Polym***., 2001, **42**, 3383-3392.
3. Firyl M.A. , Abbas N.M. and Khudheyer G.K., ***fifth Scientific Conference-College of Science-University of Babylon***., 2010, **5,** (224-229).
4. Leong KW. Biodegradable polymers as drug delivery system. In :Tarcha, PJ, editors. ***J.Polymers for Controlled Drug Delivery***. CRC Press: Boca Raton; 1991, 128.
5. Heller J. Fundamentals of Polymer Science. In: Robinson JR,Lee VHL, editors. Controlled Drug Delivery: ***Fundamentals and Applications***. 2nd ed. Marcel Dekker: New York; (1987).p.164.
6. Nasser A. and Zyedeh Z., ***Iranian poly.J.***, 2003, **2(4)**, 291-296
7. Firyl M.A., Abeer A., ***J. College of Education***, 2010, **143**, 330-345.
8. Verreck G., ***Leuve, Belgium*** (2005).
9. Firyl M.A., and Shatha M.A., ***J. College of Education***, 2008, **3**, 58-78.
10. Firyal M. , Abbas N. and Khudheyer G., ***Fourth Scientific Conference University of Waist.*** Iraq, 2010, 402-410.