

**Substituted Polyitaconic acid with Different Amines as
Biodegradable Polymers.**

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Abstract:

New biodegradable poly itaconic acid which substituted with different primary amines such as 4-aminopyridine, 2-amino pyrimidine, 2-amino naphthol, amoxilline, cephalexine.

All the prepared polymers were characterized by IR., UV. Spectroscopy, thermal analysis, chemical tests, C.H.N analysis and physical properties were studied, and the intrinsic viscosities were determined at 30°C.

The swelling % of the prepared polymers were calculated. We concluded from all the results that the inserted different units as a pendant groups which enhanced the biodegradable and biocompatible behaviors of the prepared polymers.

Introduction

New biodegradable polymers with an aromatic ring in the main chain and with aromatic ring in both the main chain and the pendant group were synthesized by direct polycondensation of L-Lactic acid and aromatic hydroxyacids such as DL- mandelic, p-hydroxybenzoic acid, p-hydroxyphenyl acetic acid using polymer system composed ⁽¹⁾. The use of biodegradable and biocompatible polymers in drug delivery systems has recently been attracting considerable interest, for narcotic agonists ⁽²⁾ local anesthetics ⁽³⁾, steroid hormones ⁽⁴⁾, physiologically active peptides ⁽⁵⁾, and anticancer agents ⁽⁶⁾ for such purposes the carriers supplied are generally composed of relatively high molecular weight polymers which have been synthesized in the presence of catalysts, the use of polymer systems containing an aromatic hydroxy acid in both the

main chain and side chain, such as DL-mandelic acid, p-hydroxy benzoic acid, p-hydroxyphenyl acetic acid, p-hydroxyphenyl propionic acid since studies on the polarizability and biodegradability of aromatic hydroxy acids⁽⁷⁾.

The prodrug polymer was prepared according to ring opening of polyvinyl pyrrolidinone with nucleophilic attack of hydroxyl group or by amoxicillin or ampicillin^(8,9). Ortho and meta aminophenols were allowed to react with itaconic anhydride in dry THF or acetone at room temperature and good yields of the corresponding N-substituted itaconamic acids then condensed with formaldehyde to obtain their resins⁽⁹⁾. Aminophenols were allowed to react with maleic anhydride and phthalic anhydride producing high yield of the corresponding N-(hydroxyphenyl maleamic and phthalamic acids, respectively.

These reacted with formaldehyde (the Novolac like) were produced, then dehydrated to their isoimide⁽¹⁰⁾. The conducted polymer were prepared as poly (ester-amide), by reaction of glycine, alanine, histidine or asparagine with adipoyl chloride in the presence of triethylamine as a catalyst⁽¹¹⁾. N-substituted heterocyclic amine or amino acid polymers were prepared from modification of polyvinylpyrrolidinone with heterocyclic amine or with amino acids⁽¹²⁾.

Experimental

All chemical materials were purchased from Fluka. All available chemical reagents were used without further purification. FTIR spectra were taken on (Fourier Transform Infrared spectrophotometer-shimadzu). C.H.N analysis were determined subsequently by C.H.N analyzer, model LECO, SC132 respectively.

Intrinsic viscosity was measured by capillary viscometer type Ostwald viscometer. Electronic spectra measurements are using a UV-visible spectrophotometer. Polymer swelling % were determined using different non solvents.

Polymerization of itaconic acid free radically (P1)

Literatures procedure was used in the freeradical polymerization⁽¹³⁾ with some modifications(5gm.) of itaconic acid was dissolved in(15 ml)of the freshly distilled THF to this solution was added (0.02%) of weight of monomer of dibenzoyl peroxide and the bottle was purged with dry nitrogen before heating at (95°C)on a water bath for (2hrs.). The resulting clear solution was added to (100ml) of ethanol, viscous polymer was isolated and purified with ethanol, the intrinsic viscosities $[\eta_{in}] = 0.1$ dl/g. with softening point = 80-91°C.

Substituted polyitaconic acid with different amines[P2-P6]

In a round bottom flask equipped with a condenser, a mixture of poly itaconyl chloride (5gm., 0.02mol.) and (15ml.)of dioxan, and (3gm., 0.02mol.)of some primary amine such as 4-pyridine, 2-pyrimidine, 2-naphthyl, amoxilanyl or cephaloxinylamines was refluxed with stirring about (1hr.) by using water bath, cooled, evaporated the solvent, washed the polymeric product with ethanol, dried in a vacuum oven.

Preparation of N-substituted itaconic acid monomers [P7-P11]A

(Five gm.)of itaconic acid was dissolved in(20 ml.) of dioxane was placed in a round bottom flask provided with condenser and separatory funnel, the thionyl chloride(3 ml) was added gradually drop wise to a mixture, the solvent was evaporated, the colored material was isolated, dried under vacuum oven and characterized .Then the suitable primary amine was added to the dissolved itaconyl chloride ,at room temperature about (1hr.) the N-substituted monomer was purified by ethanol and collected.

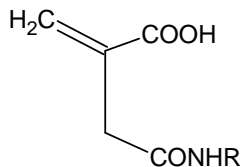
Table 1

Physical properties of N-substituted itaconic acid

monomers [P2-P6] A

NO.6 *JOURNAL OF*
COLLEGE OF
EDUCATION.....2011

369



No.	-R	Color	Yield%	Melting point °C	U.V absorption nm
P ₇ A	2-Pyridinyl	Black	60	85-87	220,300
P ₈ A	2-Pyrimidinyl	Violet	70	120-122	220,336
P ₉ A	2-Naphthyl	Green	65	50-52	300,360
P ₁₀ A	Amoxillinyl	Yellow	63	60-62	230,300
P ₁₁ A	Cephalexiny	Yellow	61	70-72	220,320

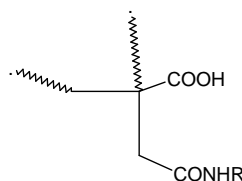
Polymerization of prepared monomers to their corresponding polymers

[P₂-P₆]B

The prepared monomers [P₇-P₁₁]A were polymerized free radically according to the literature procedure were used in the free radical polymerization⁽¹³⁾.

Table 2

Physical properties of prepared polymers[P₂-P₆] B



No.	Conversion %	Softening point° c	η _{in} dl/g
P ₂ B	80	200-210	0.12
P ₃ B	90	250-260	0.22
P ₄ B	85	250-260	0.24
P ₅ B	90	180-190	0.3
P ₆ B	92	200-210	0.30

The swelling % was calculated with different non solvent such as water, hexane, chloroform, the (10-20%) values were observed as shown in Table (3).

Table 3

Polymer swelling percentage of [P₂-P₆]

No.	Swelling %		
	Solvents		
	Water	Hexane	Chloroform

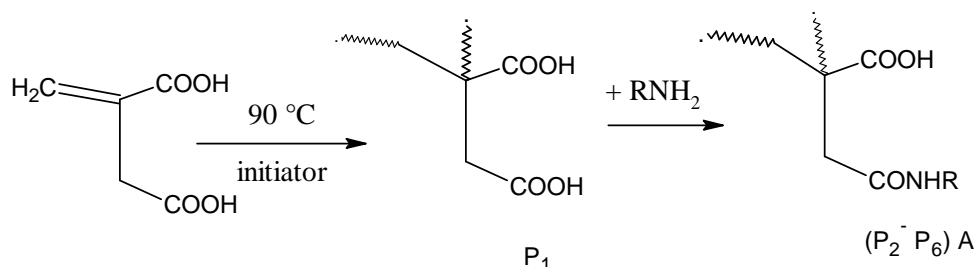
P ₂	10.5	3.2	4.1
P ₃	11.21	4.2	5.6
P ₄	12.5	5.2	3.2
P ₅	13.1	6.7	4.5
P ₆	15.0	4.6	5.5

Controlled release studying

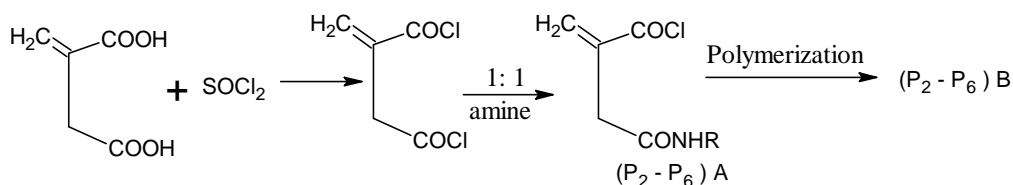
(0.1 gm.) of prepared polymer was kept in a tube containing (100 ml.) of buffer at (37°C) without stirring the sample was analyzed by UV spectra at (315 nm) to determine the amount of the released amine. A calibration curve was drawn these release studies were carried out in different pH values as shown in Fig(8).

Results and Discussion

In this paper, for the first time, itaconic acid was polymerized free radically, then substituted with primary amines such as 4-aminopyridine, 2-aminopyrimidine, 2-aminonaphthal, amoxicillin and cephalexine the following equations illustrated the polymers forming :-



R= 4- pyridinyl, 2- pyrimidinyl, 2- Naphthyl, amoxicillinyl, cephalaxinyl. For the second line the itaconic acid was converted to its acid chloride using thionyl chloride then substituted to its N- substituted monomers (P7-P4) as shown in the following equations:-



N-substituted itaconamic acid monomers [P2-P6]A were characterized by FTIR spectra, it appeared strong bond at (3450-3000 cm^{-1}) explained νOH and (1670, 1636 cm^{-1}) for carbonyl acid and amide groups and disappearing of double bond of itaconic acid at (1600 cm^{-1}) indicated the polymerization of the monomers νNH group at (3200 cm^{-1}) indicated amide group, the

absorption bond at(1300 cm⁻¹) indicated (C-N) Fig (1,2,3,4,5) illustrated FTIR spectra of prepared new monomer and polymers.

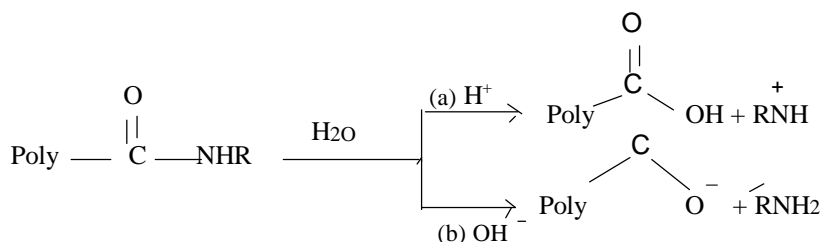
Table (1) shows the physical properties and the UV.absorption which ranged between (300-360nm.) and (250-330 nm.) indicated the (π-π*)and (n-π*) electron transition ,as shown in Fig(6,7).

In another line the N-substituted itaconamide monomers (P7-P11)A were synthesized then polymerized free radically to [P2-P6]B.

Elemental analysis for some prepared monomers were compared experimentally and theoretically which is as exhibited structures .

The obtained monomers with bioactive agent moiety was polymerized with dibenzoyl peroxide as initiator.

The release rates of bio active moiety agents were hydrolysis of amide bond is illustrated as follow:-

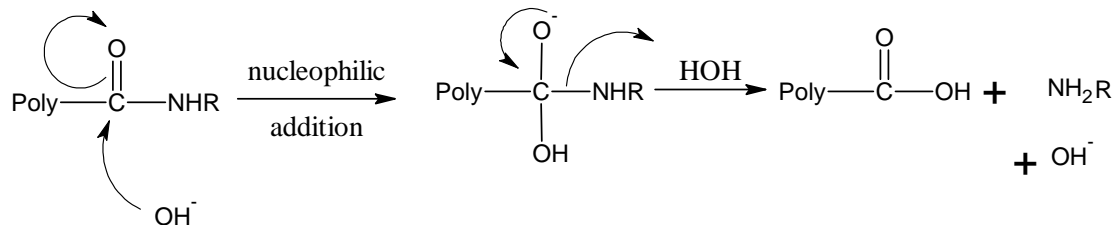


The prepared polymers which substituted with bio active moiety units are desirable because they degrade in the different PH values, Fig (8) shows the rate of hydrolysis in basic is higher than acidic media.

The hydrolysis of amide bond is explained as in the following scheme(1):-

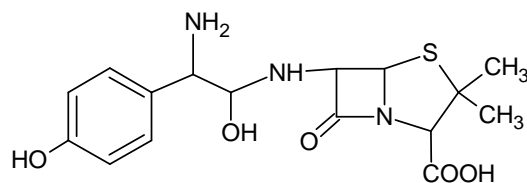
**N0.6 JOURNAL OF
COLLEGE OF
EDUCATION.....2011**

372

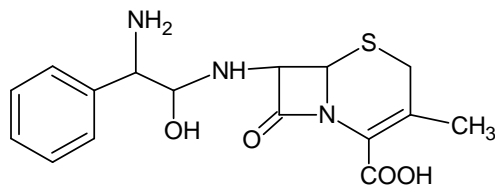


RNH₂= amoxicillin or cephalixin

amoxicillin =



cephalexin =



The two different methods gave same chemical structures of [P₂-P₆] and the other method gave [P₂-P₆]B with higher conversion % and higher intrinsic viscosities with lower swelling % .

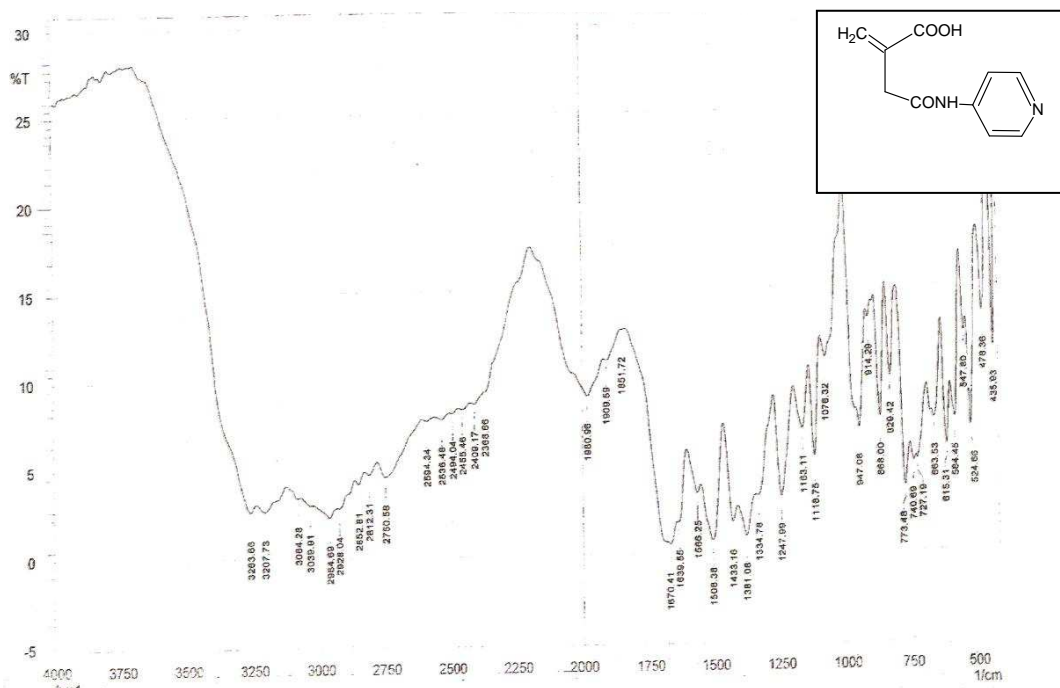


Fig.(1) FTIR spectra of P1A

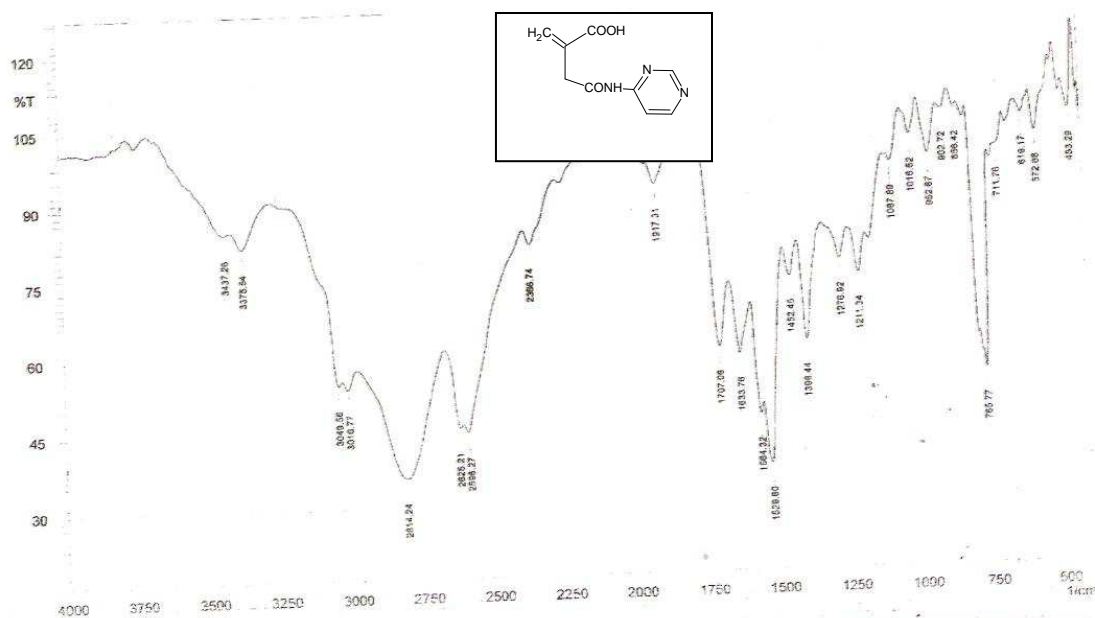


Fig.(2) FTIR spectra of P2A

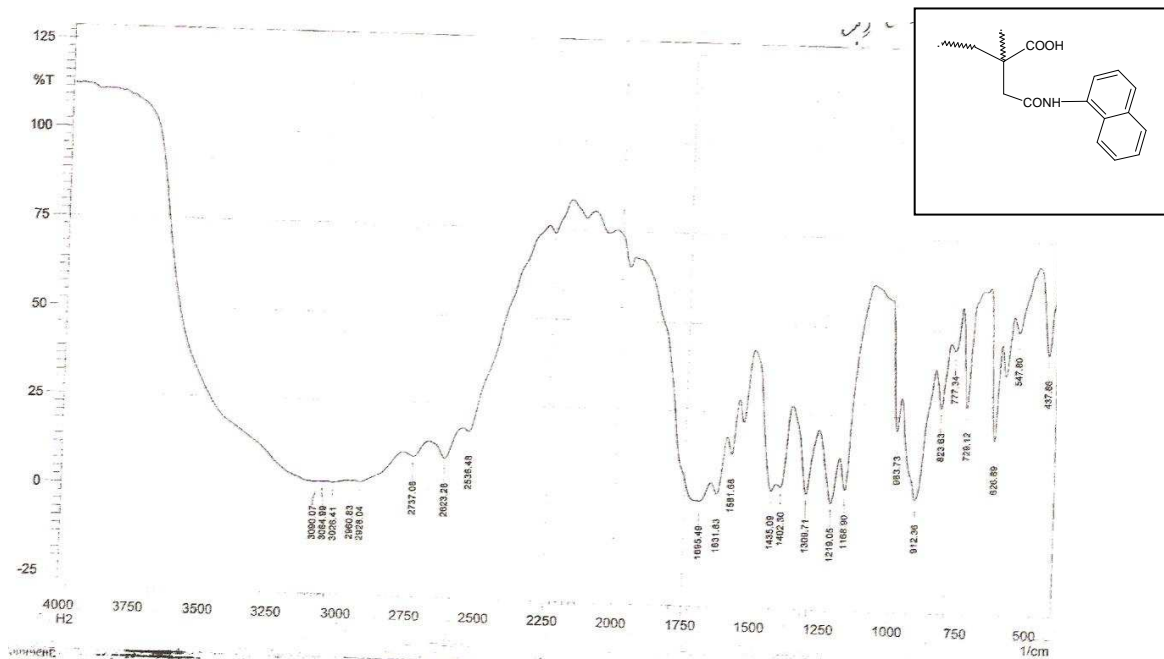
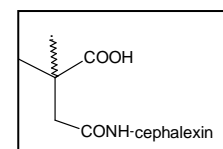


Fig.(3) FTIR spectra of P3B



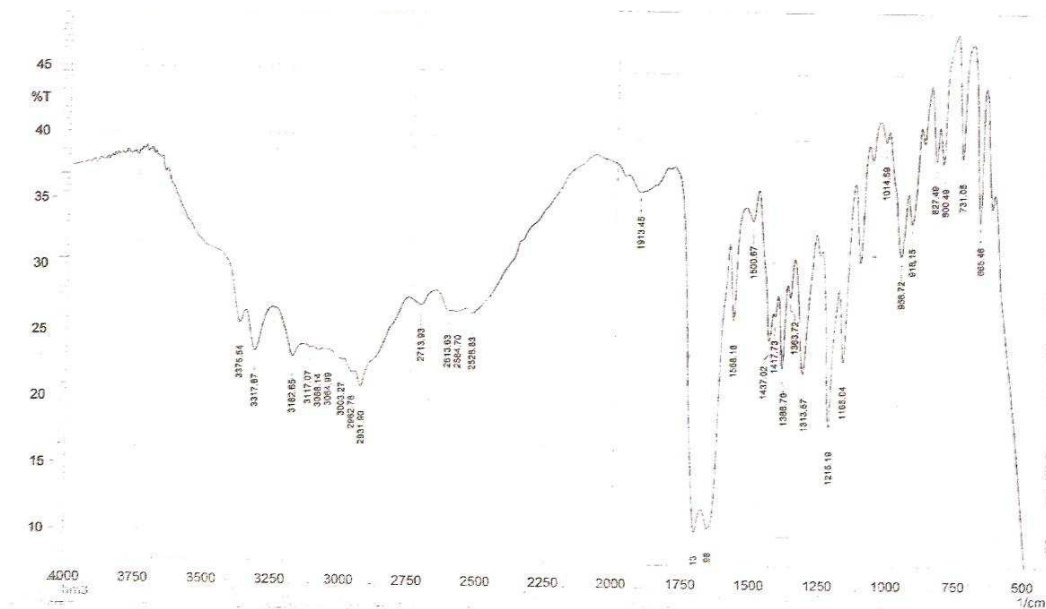


Fig.(4) FTIR spectra of P4B

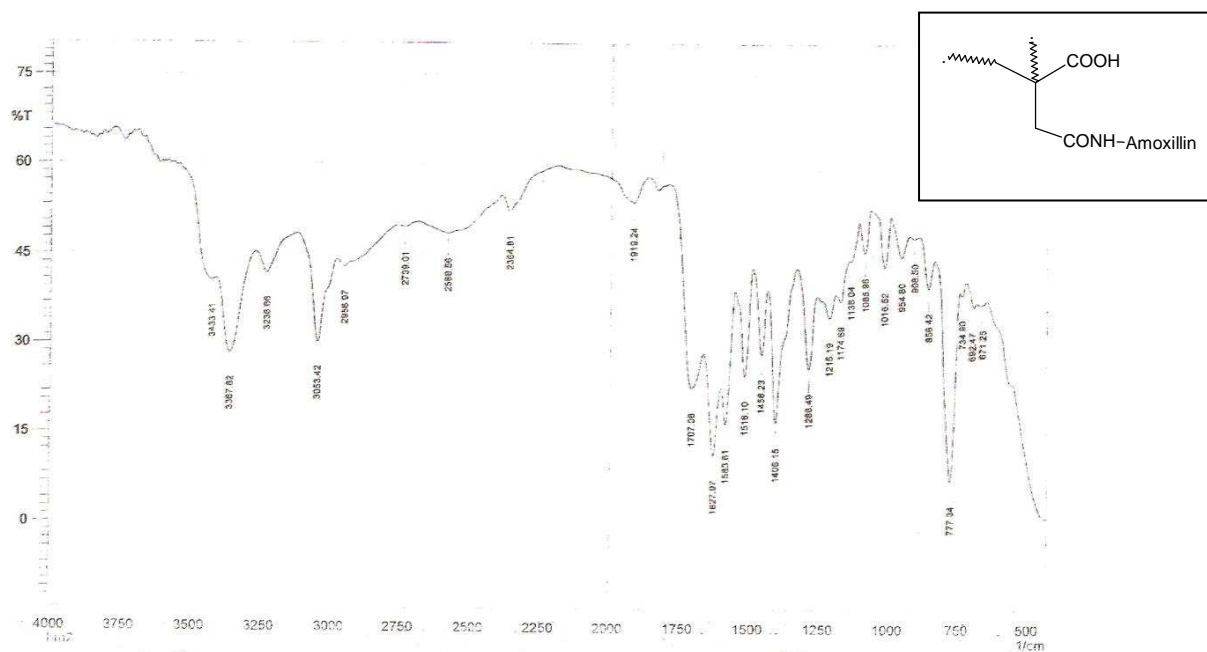


Fig.(5) FTIR spectra of P5B

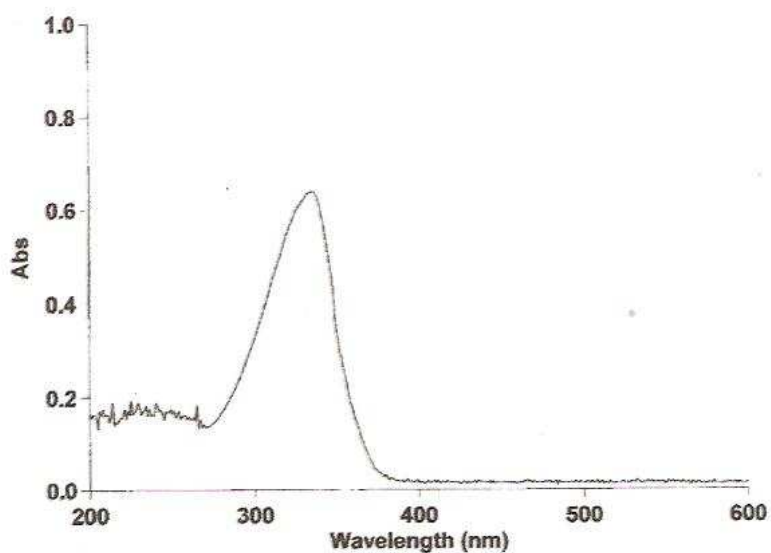


Fig.(6) UV. Spectra of P3B

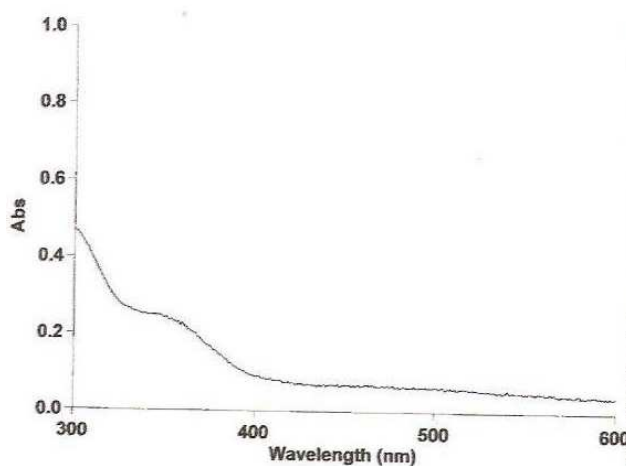


Fig.(7) UV. Spectra of P4B

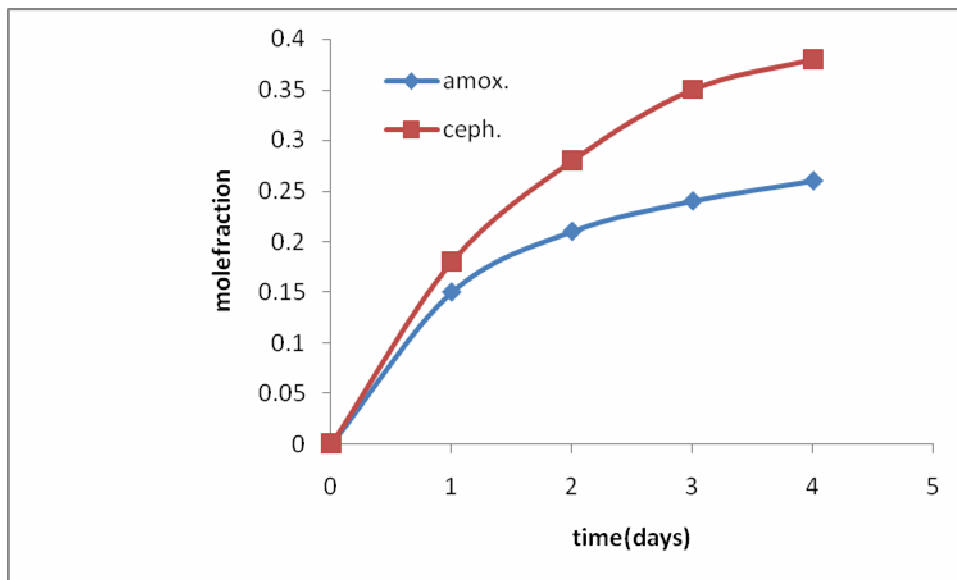


Fig.(8) Controlled release of amoxicillin and cephalixin itaconamide polymers at pH 4 and 37 °C.

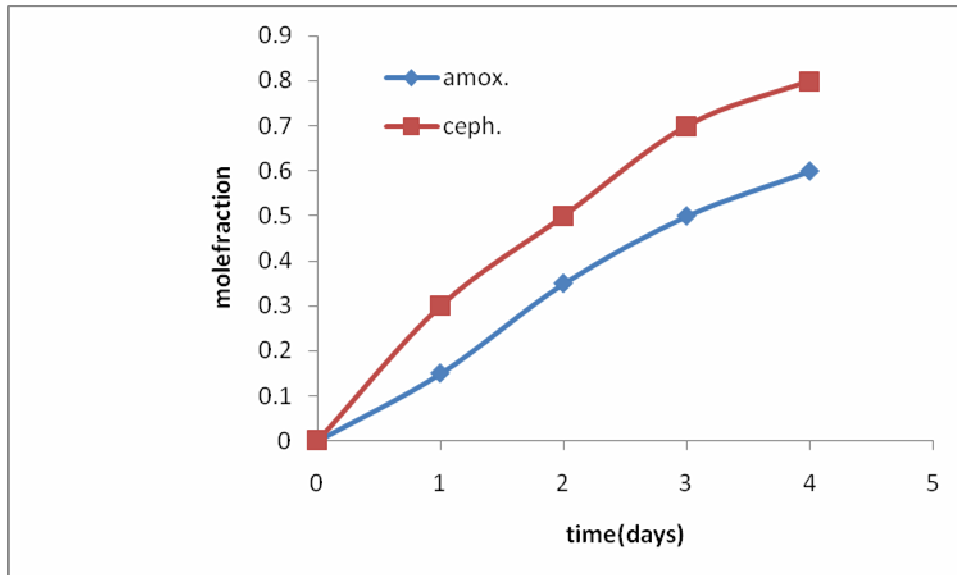


Fig.(8) Controlled release of amoxicillin and cephalixin itaconamide polymers at pH 10 and 37 °C.

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**N0.6 JOURNAL OF
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EDUCATION.....2011**

378

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379

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