Synthesis and Characterization of Novel ProDrug Polymers and Their Controlled Release

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Abstract

Many crosslinked polymers have been prepared through many steps, including the esterification of triethanolamine with maleic anhydride toproduce compound (A_1) then the carboxylic acid groups of (1) were converted to amide attachments when they reacted with some drug-NH_2, The unsaturated maleamides (A_2-A_5) were polymerized free radically by using dibenzoyl peroxide as an initiator at 90℃. such as Amoxicillin, 4-Amino antipyrine, Cephalexin, and Procaine drug polymers (A_6-A_9).All prepared monomers and polymers have been characterized by FTIR and ^{1}H-NMR and UV. Spectroscopies. The swelling percentage is higher than 90%. The rate of hydrolysis of a controlled drug release was studied in different pH values at 37℃, at λ_{max}, 270nm and 220nm in basic and acidic medium. TGA and DSC are recorded; It isappeared that the prepared drug polymers have high thermal properties.

Key words: Poly ester-amide, Prodrug, Drug polymer, Controlled release.

الخلاصة

بسبب العديد من المشاكل المرتبطة بتحرر الدواء، وتذليل مراحل متابعة الدواء، فضلا عن تقليل مخاطر الإفراط في الجرعة والحصول على العديد من الفوائد، فقد تم تحضير العديد من البوليمرات المتشابكة بعدة خطوات والتي تتضمن استرة ثلاثي إيثانول أمين مع أنهيدريد المالئيك لانتاج المركب (A_1) ثم تحويل المجاميع الكربوكسيلية في المركب (A_1) إلى المالي أميدات المقابلة عند مفاعلتها مع الادوية الامينية $-NH_2$ ، تم بلمرة المونمرات غير المشبعة المعوضة (A_2-A_5) بالجذور الحرة باستخدام داي بنزويل بيروكسيد بادئاً في 90℃ مثل بروكائين، سيفالكسين، أموكسيسيلين،4- امينوانتي بايرين. شخصت البوليمرات الدوائية المحضرة (A_6-A_9). شخصت بواسطة FTIR و^{1}H-NMR والتحليل الطيفي(UV.). ودرست نسبة انتفاخ المئوية، وقست سرعة التحلل الدوائي المحكم في دوال قاعدية وحامضية وبدرجة 37℃. عند اقصى طول موجي 270nm و200nm ودرست التحاليل الحرارية مثل المسح التفاضلي المسعري، والتحليل الحراري الوزني، وتبين ان البوليمرات الدوائية المحضرة الجديدة تمتلك استقرارية حرارية عالية.

الكلمات المفتاحية: بولي استرامايد، بوليمرات دوائية، التحرر الدوائي، ناقل دواء.

Introduction

Prodrugs have been designed and developed to overcome pharmaceutical and pharmacokinetic barriers in clinical drug application and many characteristic such as low oral absorption,and lack of site specificity, chemical instability, toxicity, and poor patient acceptance with bad taste (Han, 2000; Andrzej, 2006; Rondd, 2012). Many biopolymers were synthesized and have been the subject of abundant literature over the last decade (Averous, 2011), and for many applications implants, sutures drug encapsulation (Rautio, 2008; Van de velde, 2002). Aliphatic polyester is one well-known biodegradable synthetic prodrug polymers(Nishide, 2000, Pranamude, 2001, Jarerat 2001, Tokiwa, 2003, Andrzej, 2006).and several available drug polymer

such as poly (L-Lactide) and some prodrugs which were known as an excellent bio compatible and biodegradable polymer (Tokiwa, 1977). Several poly (ester-amide) containing α-amino acids have been synthesized and the effects of the α-amino acids building block on biodegradable was reported (Fan, 2001). Modification of the properties of polyesters by incorporation of hydrogen-bonded amid groups has been extensively investigated. The materials are either random copolyesteramides in which the proportion of ester-amide groups can be varied through the whole range of composition or alternating or patterned polyesteramides with regularly recurring successions of the characteristic groups in the main chain. Those of the first type are synthesized by the copolymerization of polyester-forming condensate with, eg. Nylon salts, aminocarboxylic acid, or amino alcohols, or by copolymerizing lactones with lactams and poly aspartic acid copolymer(Yokoyama, 1990; Berdy, 1987). The second type are obtained by the polyesterification of amide-containing or the polyamidation of ester-containing precursors, and of by reaction of dicarboxylic acid cyclic anhydrides with oxazolidin-2-ones and of dicarboxylic acids with bis(oxazoline)s and other ester-amide prodrug was synthesized as ciprofloxacin procaine mole and polymer as a prodrug polymer (Firyal, 2014).

The aim of this work is to synthesis poly (ester-amide) prodrug polymers which successful for long term drug delivery and highly desirable situation with highly swelling %; with many advantages have been obtained from this new preparation of scientific and therapeutic uses.

Experimental

Instrumentation

Melting points were measured using Gallen Kamp M.F.B-600 melting point apparatus. Infrared spectrophotometer -260 at room temperature. (DSC) and (TGA) were recorded using (PL-STA 1500, Rheometric Sentific UK). The inherent viscosities were measured at 25 ℃. Swelling % of polymers was determined by using 0.1g of polymer with water for 1 day. 1H-NMR spectra were recorded on a Shimadzu spectrophotometer in Dimethylsulphoxide (DMSO6). The FTIR spectra were recorded by (4000-400cm-1) on a Shimadzu spectrophotometer. Electronic spectra measurement using CINTRA5-UV.Visble spectrophotometer.

All chemicals were purchased from Fluka and BDH. All available chemical reagents were used without further purification.

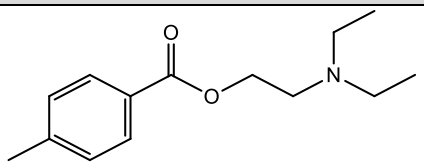
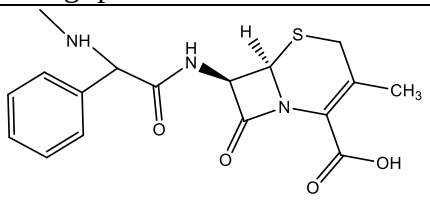
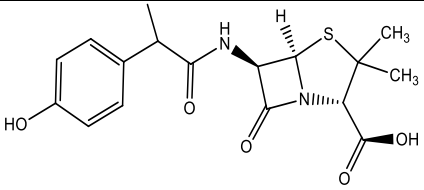
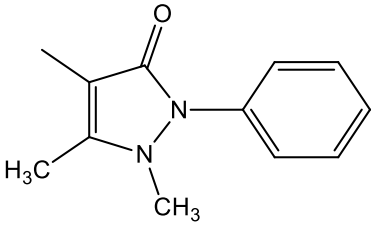
Synthesis of (Tri ethyl maleic acid) amine (A1)

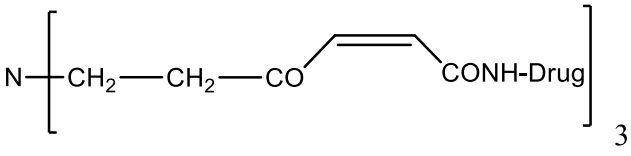
(2.94g, 0.03mole) maleic anhydride was dissolved in 10ml acetone, and (1.41 g, 0.01mole) of Triethanolamine, the mixture was stirred for 1hr. The white precipitate was filtered and recrystallized from ethanol with 76%product, M.P. = 58-60℃.

Substitution of prepared (A1) with Amino drugs (A2-A5)

(4.18g, 0.01mole) of A1 was dissolved in 10ml of Dioxane, (0.03 mole) of thionyl chloride was added gradually through dropping funnel, at 0℃ with stirring. The yellow product was obtained the excess of thionyl chloride was filtered off. For the remained product as acyl chloride derivative was added 0.01 mole of Drug-NH2 such as Amoxicillin, 4-amino antipyrine, Procaine and Cephalexain. The mixture was refluxed with stirring for 1hr. The product was filtered and recystalized from ethanol.The pr0duct was dried under vacuum, Table (1) List the physical properties

Table (1) physical properties of prepared dr ug (A_2-A_5)

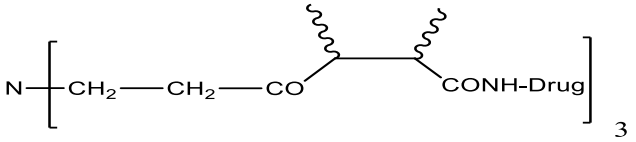
Pol. No.	Structure of -Drug	m.p.℃	Color	Yield %
A_2	 -Drug=procaine	70-73	White	70%
A_3	 -Drug= Cephalexin	55-58	Yellowish white	65%
A_4	 -Drug= Amoxicillin	50-52	Yellow	60%
A_5	 Drug=4-Aminoantipyrin	45-48	White	72%



Polymerization of prepared monomers Free radically (A_6-A_9)

In a screw capped polymerization bottle 1g. of one of the monomers (A_2-A_5) was dissolved in 5ml of DMF, 0.05% of the monomer weight of dibenzoyl peroxide was added, the bottle was flushed with N_2 gas for few minutes inside a glove and firmly stopped. The mixture was heated at 90℃ about 1hr. The colored polymers (A_6-A_9) were obtained washed and dried at 50℃. The physical properties are listed in Table (2).

Table (2) physical properties of drug polymers (A_6-A_9)



Pol. No.	$[\eta]_{in}$ =dl/g	Color	Softening point ^{0}C	Conversion %
A_6	0.84	Brown	>300	70%
A_7	0.88	Dark brown	>300	75%
A_8	0.89	Brown	>300	85%
A_9	0.82	Yellow	>300	80%

Controlled Release study(Ronald, 2012; Fang, 2011; Debjit, 2012)

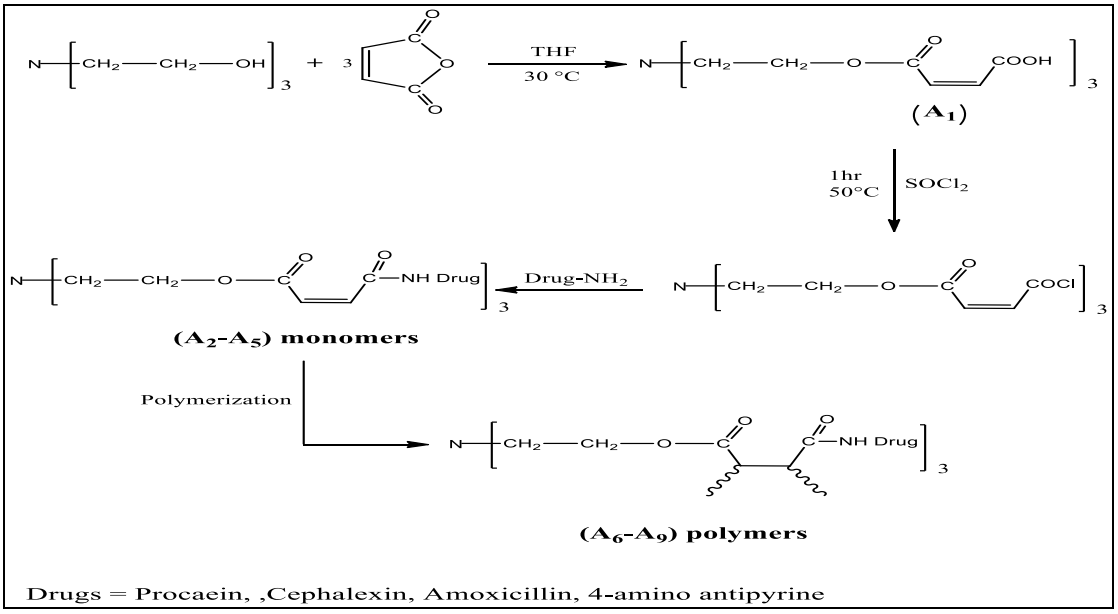
A 50 mg of prepared polymer was kept in a cylinder containing 50ml of buffer solution and in a water bath at 37℃ without stirring. A sample from the release medium was periodically withdrawn and analyzed by UVat 320nm to determine the amount of the release. Mole fractions were constructed from UV. spectrophotometer, at λ max . 270nm were determined directly for days, in pH 7.4 and pH1.1 as shown in Fig. (13A and 13B) respectively.

Measurement of swelling % (stella, 2001)

0.1 gm of drug polymers were weighted accurately, and placed into flasks with 10ml solution of a given pH and kept in a thermostated bath at 37℃. Solutions with pH 1.2 (simulated gastric fluid), and pH 7.4 of (phosphate buffered saline) were measured at different times.

Swelling percentage of prepared polymers were studied in water according to S% = M_1-$M_\circ$ / $M_\circ$. 100. When $M_\circ$ is the weight of dry polymer at time $_\circ$. M_1 is the swollen polymer in water at time t.

Focuses this review on new drug polymers to development of drugs, to enhance their quality and to achieve the best drug delivery system; they are also desirable to retain the drug molecular in specific parts of the body for a longer duration, Triethanolamine amine was reacted with maleic anhydride produced compound A_1 then reacted with thionyl chloride converted to corresponding acyl chloride. The substituted with drug amine is shown as below:-



Scheme (1) Synthesis of Drug polymers

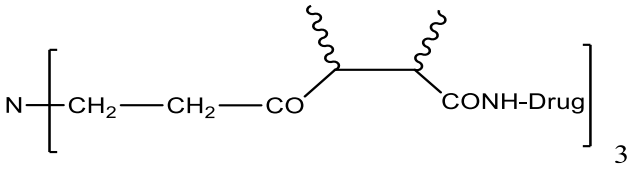
Fig (1) Shows the FTIR spectrum of polymer (A_1) exhibits the characteristic absorption bond at 1720 cm^{-1} due to the C=O stretching vibration of the carboxylic groups. The absorption at 1667 cm^{-1} was attributed to the formation ester groups. The other absorptions revealed at 3046 cm^{-1} assigned to =CH unsaturated of maleic, and 2966 cm^{-1} of C-H aliphatic.

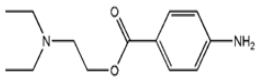
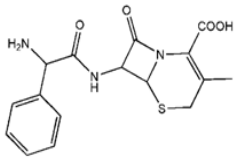
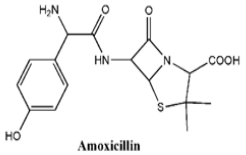
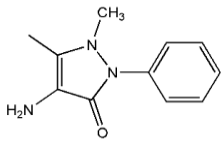
Polymer (A_6) showed the absorption at 3200 cm^{-1} assigned to –NH stretching of amide group, and as exhibit a bond at 1633 cm^{-1} due to the C=O amide, and at 1714 cm^{-1} due to C=O ester, 2033 cm^{-1} and 2972-2847 cm^{-1} were a symmetrical and symmetrical stretching of C-H cm^{-1} aromatic and aliphatic respectively indicated procaine amide prodrug polymer A_6.as show fig(2), Fig (3) shows that FTIRspectrum of polymer (A_7) showed the absorptions of NH amide at 3250 cm^{-1} and 1639cm^{-1} of C=O amide, 1714 cm^{-1} of C=O ester, 1600-1550 cm^{-1} of C=C aromatic, at 3400 cm^{-1} assigned to the OH carboxylic acid of drug.

Also polymer (A_8) showed the appearance of absorption at 3400 cm^{-1} assigned to the OH phenolic of amoxicillin, and abroad bond at 3500-3000 cm^{-1} of OH stretching carboxylic group, and as exhibit a band at 3200 cm^{-1} due to NH amide and at 1635 cm^{-1} of C=O amide and 1714 of C=O ester and at 1720 cm^{-1} of C=O carboxylic(fig4).

On the other head polymer A_9 showed the a symmetrical and symmetrical stretching of C-H aliphatic, 3050 cm^{-1} of C-H aromatic, 1630 cm^{-1} represented to stretching vibration of C=O amide, 1716 cm^{-1} due to carbonyl of ester, 2100 cm^{-1} which correspond to presence of C-N bond. Table (2) lists the main absorptions of prepared polymer (A_6-A_9).

Table (3) Spectral data for compounds (A_6-A_9)



Comp. No.	drug	υOH cm^{-1}	υNH amid cm^{-1}	υCH aro. cm^{-1}	υCH al. cm^{-1}	υC=O amid cm^{-1}	υC=O ester cm^{-1}	υC=C cm^{-1}	υC-O cm^{-1}
A_6	 2-(diethylamino)ethyl 4-aminobenzoate **(Procaine)**	-	3338	3059	2974 - 2874	1683	1714	1658	1271
A_7	 **Cephalexin**	3550	3212	-3062 3020	2962 - 2956	1664	1710	ar1647 1413al	1116
A_8	 **Amoxicillin**	3273	3254	-3051 3014	2974 - 2870	1700	1710ester 1778 acid	1631ar 1450al	1168
A_9	 **4-Aminoantipyrine**	-	3485	3082	2979 - 2880	1650 1635 Cyclic amid	1716	1537 ar 1452al	1151

In addition these compound were charactrised by ^{1}H-NMR spectrum of polymer (A_1) showed the signals at δ 3.2-3.7 ppm ($3CH_2$-O) T., δ 6.1 ppm CH=CH-CO 3(2H) S., and δ2.4-2.9 ppm ($3CH_2$)-N.as show in (Fig 6).

Fig (7) ^{1}H-NMR spectrum of polymer (A_6) showed the signal δ 1.5 ppm 3($2CH_3$) T., δ 3.1 ppm ($3CH_2$) m., δ 7.3ppm of 3(2H) d. ortho aromatic and 8.0-8.3 ppm of m., 3(2H) aromatic of procaine amide, δ 3.2- 3.7 ppm ($3CH_2CO$) T. and 6.1-6.5 ppm of (H-C=C-H) S. unpolymerize and 3(H-C-CH) of polymerized maleate at δ 4.1-5.3 ppm S.

Swelling percentage of polymers (A_6-A_9) have a high values because of the presence of hydrophilic amino groups, ranged 82-91%

Fig (8) ^{1}H-NMR spectrum of polymer (A_7) showed the signal δ: 12-13ppm of OH carboxylic S., δ 7-8ppm of 5H aromatic d. δ 6.7 of 3(OCCH-CHCO) S., δ: 2-4ppm (3CH-S) S. δ:1ppm S.

Fig (9) ^{1}H-NMR spectrum of polymer (A_8) showed the signals at δ: 1.5 (3x $2CH_3$) S. δ: 2.3(3xCH lactam) S., δ: 6.2-7ppm 3(4H aromatic) d.,

δ: 3-4ppm of 3(O-CH_2-) and 3(N-CH_2) T., δ: 13-14 ppm of (OH) S. and δ: 6.9 ppm of (NH) S.

Fig (10) ^{1}H-NMR spectrum of polymer (A_9) showed the signals at δ: 1.9ppm of 3($2CH_3$-C=) S., δ: 3.4-3.9 ppm of 3(OCCH-CHCO) S., δ: 2.3ppm (3xCH_2-N) T. and δ: 3.9ppm (3xCH_2O) T.

Thermal analysis of prepared novel polymers were recorded, Fig (11A) showed TGA for (A_7) indicated the thermal stability between 321^{0}C for 50% weight loss and 340.1^{0}C for 95% weight loss.

Fig (12A), TGA showed thermal stability of prepared drug polymer (A_8) showed the stability at 210^{0}C with 80% weight loss and 95% thermal degradation at 340^{0}C.

Fig (11B), DSC thermogram of polymer (A_7) and Fig (12B) DSC thermogram of polymer (A_8) had a high Tg in all the curves with more shifted to a high temperature with increasing the substitution of drug unit.

The hydrolysis solution was detected by UV spectrophotometer at λ_{max} 270nm(fig 13B) pH 7 and 37℃ indicated prodrug release gradually under mild conditions. The order of hydrolytic rate of the polymer was as in basic medium more than acidic due to cleavage of drug-NH_2. The electropositive charge of the polymer chains cause both intermolecular and intermolecular repulsion and the H^+ ions attacks the ester groups and the reversibility of acid catalyzed hydrolysis in acidic media. Also the cleavages of amide bonds were compared in a phosphate buffer solution. The in vitro hydrolysis studies showed the potential utility of the prodrug polymer a macromolecular have therapeutic efficiency of the physiochemical rate of the drug regeneration with a suitable specific site.

This strategy focused on new prodrugs for assuring the slow release to introduce a long-chain aliphatic ester to slow the hydrolysis it is useful for the treatment of psychoses through requirement of medication for extended periods.

We could designed some prodrugs which could be efficient and selective on their site and metabolized to non-toxic derivative, also they a achieved the best drug delivery system. Through crosslinked drug polymers through the slow rate of swelling properties.

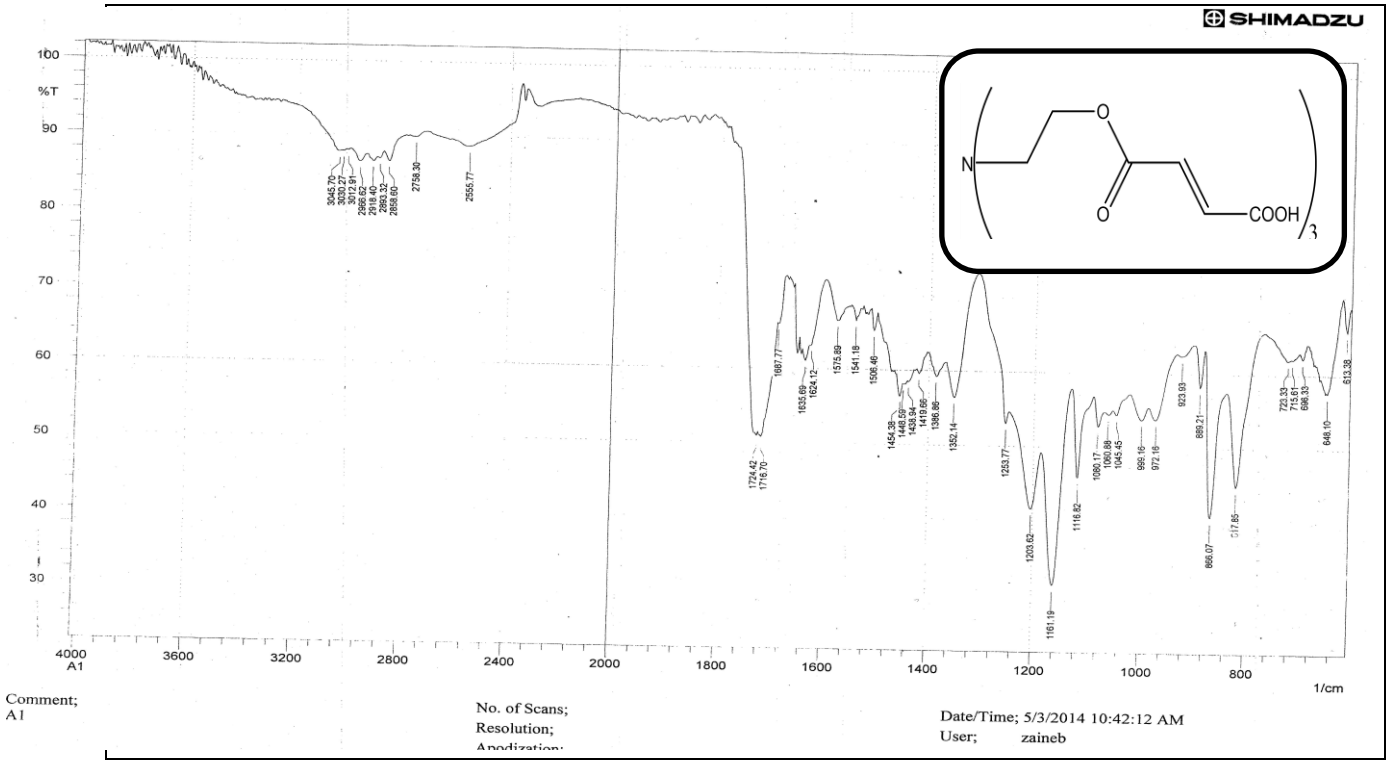


Fig (1) FTIR spectrum of polymer (A_1)

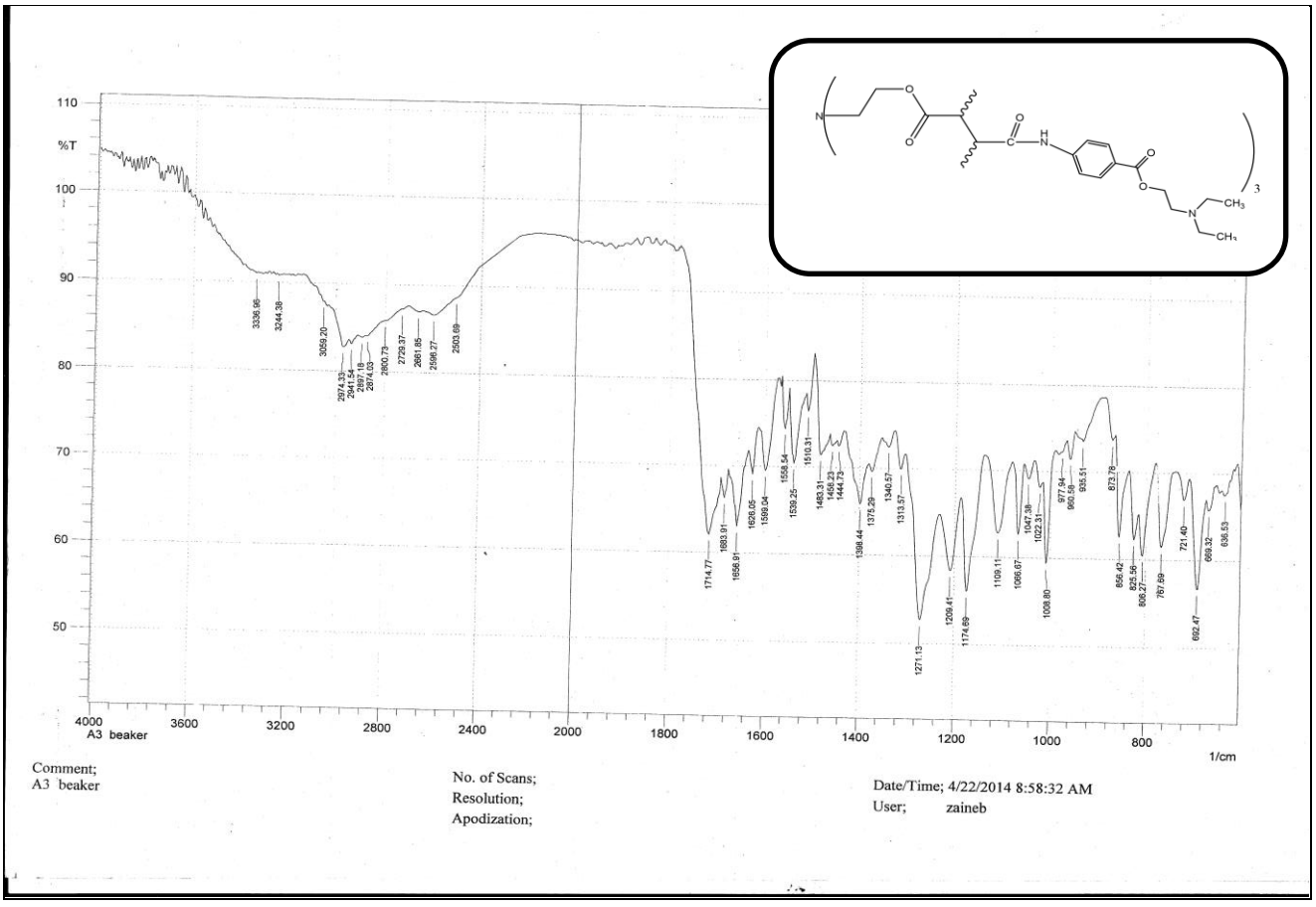


Fig (2) FTIR spectrum of polymer (A_6)

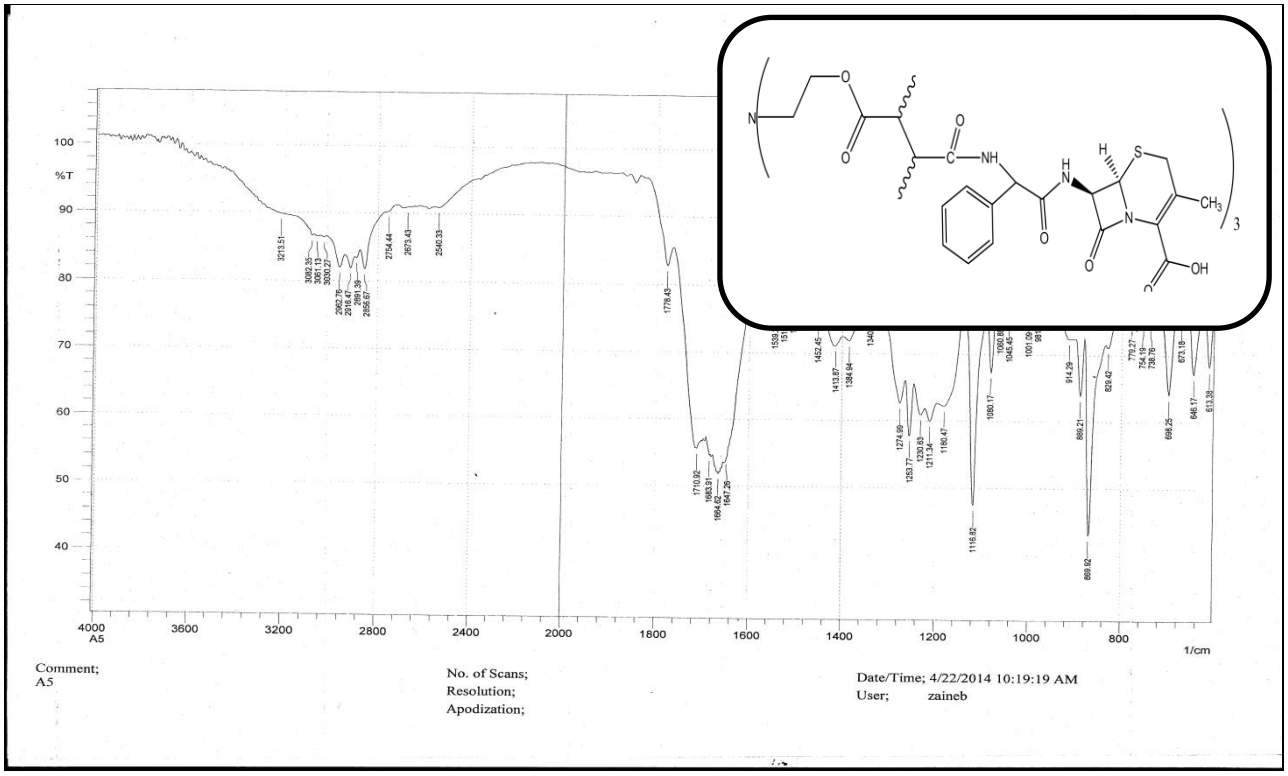


Fig (3) FTIR spectrum of polymer (A_7)

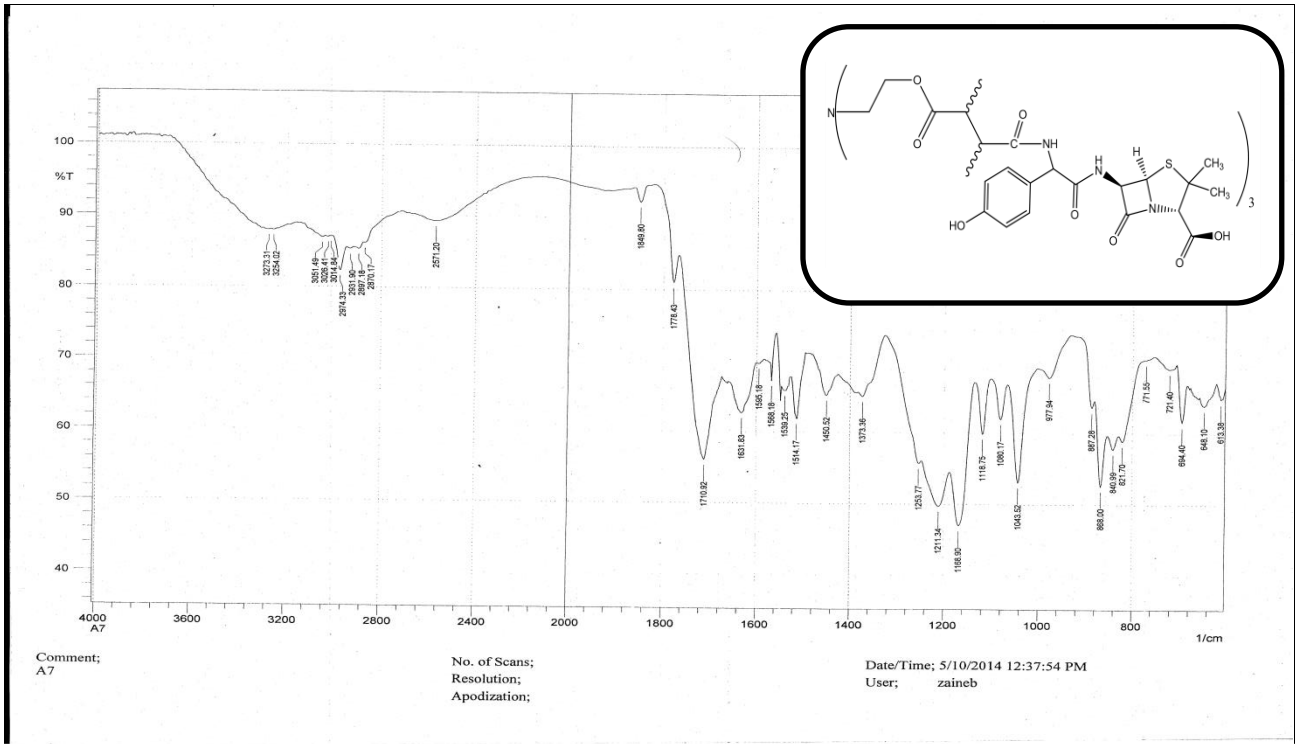


Fig (4) FTIR spectrum of polymer (A_8)

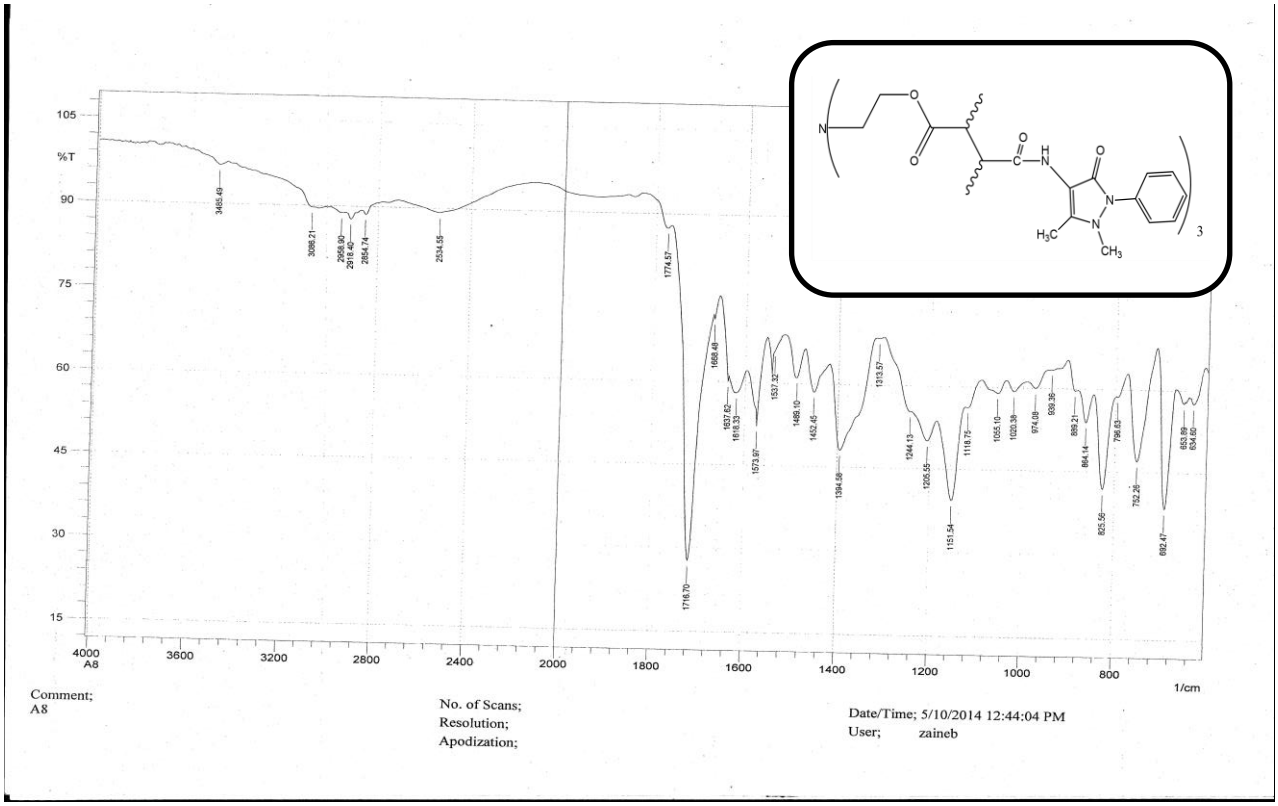


Fig (5) FTIR spectrum of polymer (A_9)

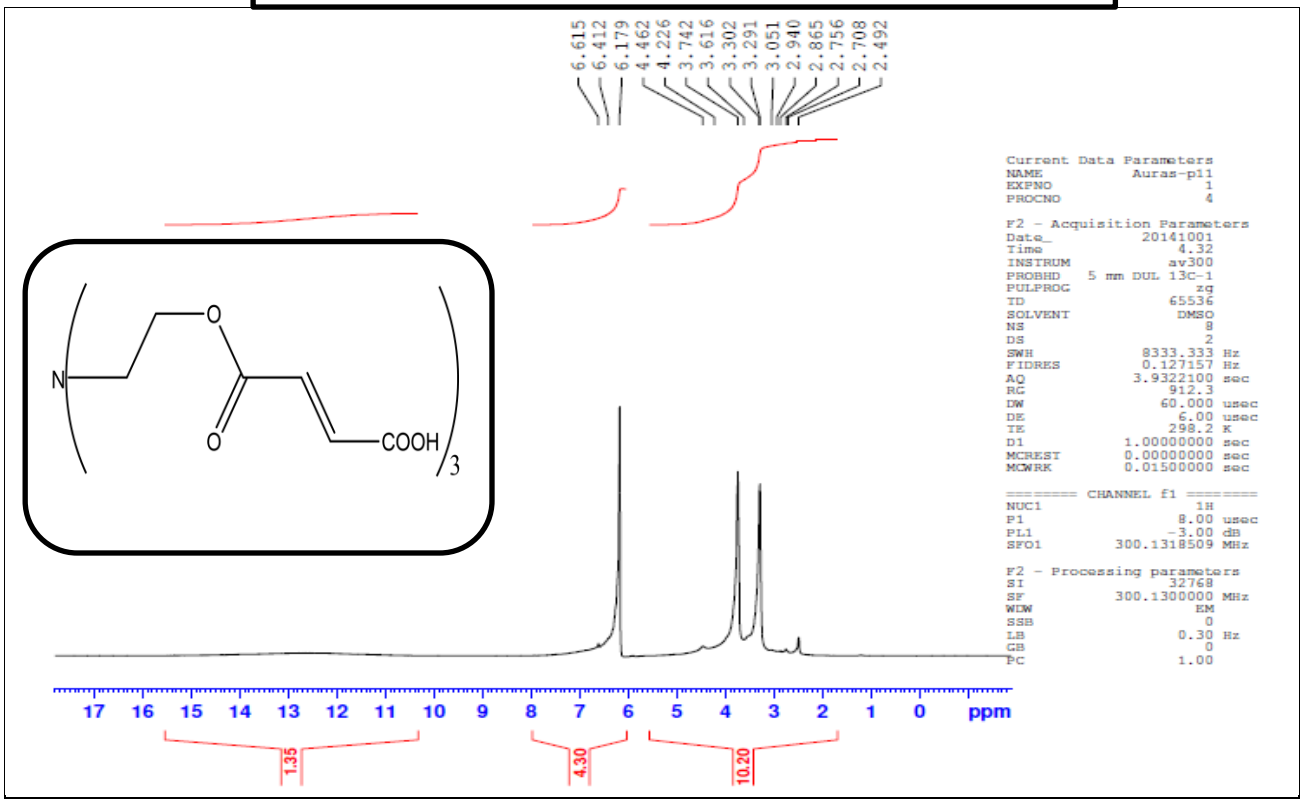


Fig (6) ^{1}H-NMR spectrum of polymer (A_1)

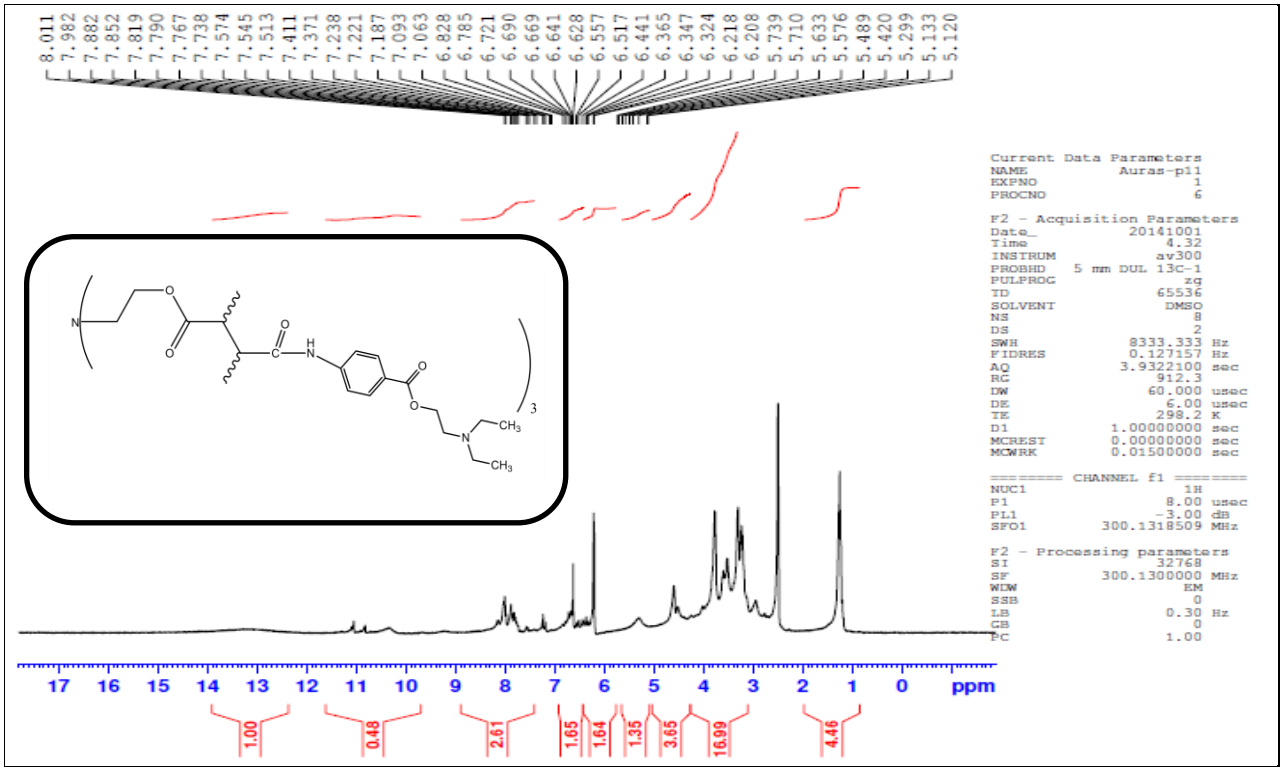


Fig (7) ^{1}H-NMR spectrum of polymer (A_6)

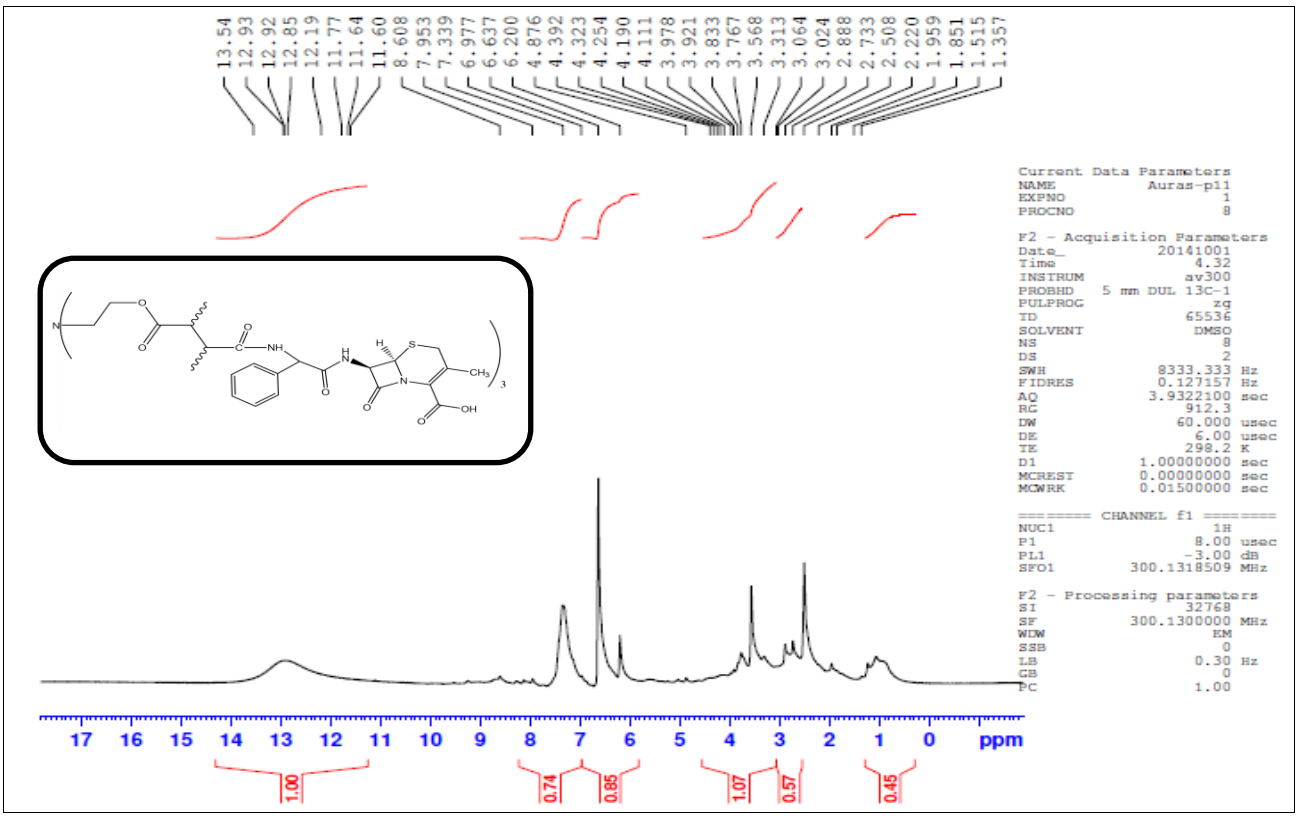


Fig (8) ^{1}H-NMR spectrum of polymer (A_7)

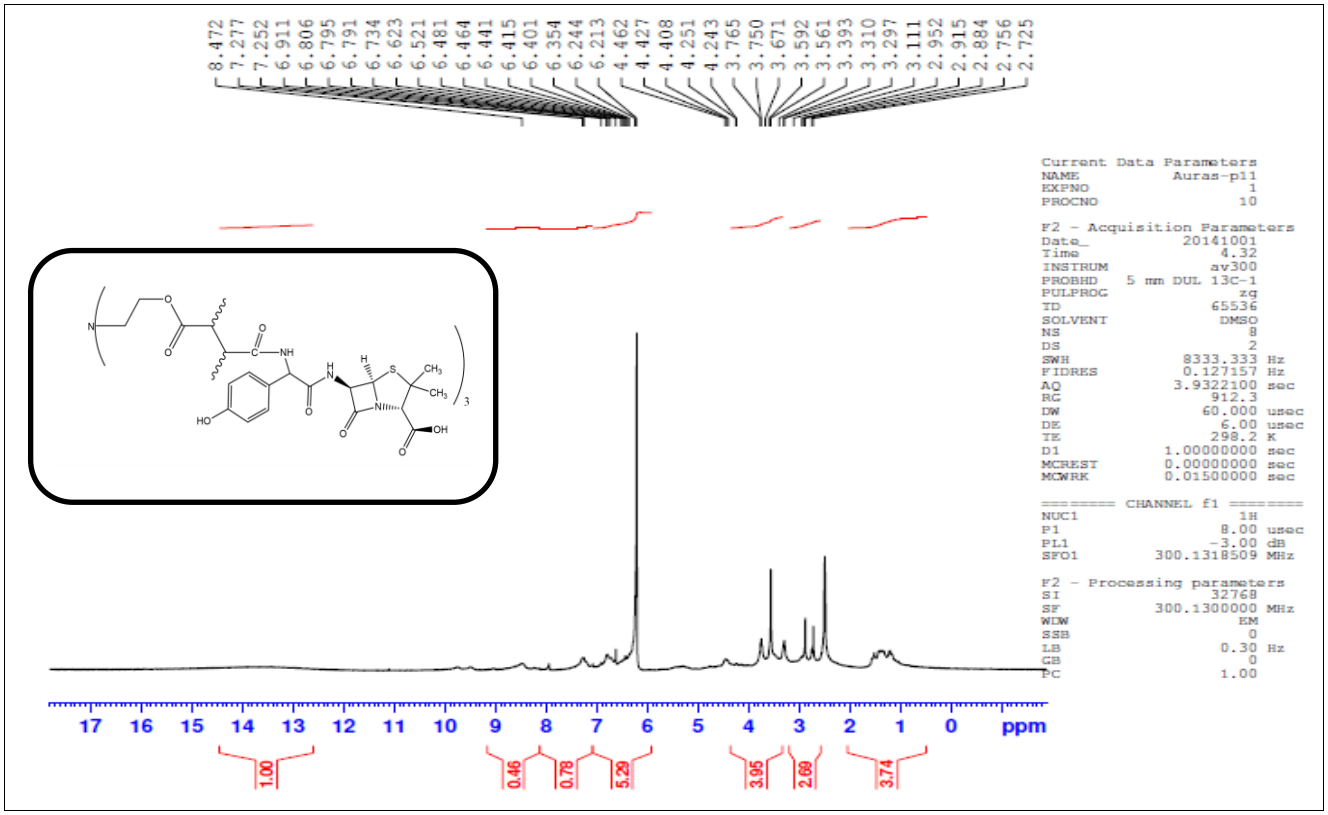


Fig (9) ^{1}H-NMR spectrum of polymer (A_8)

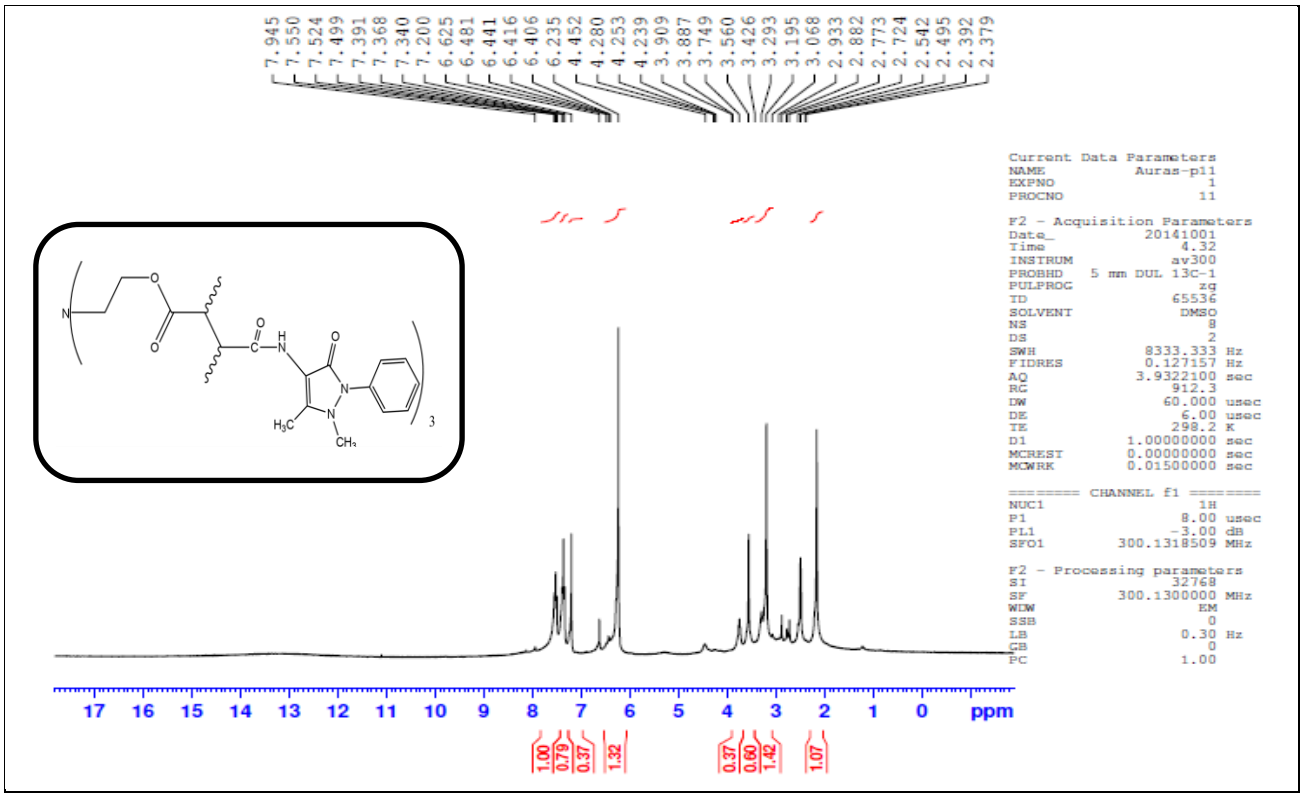


Fig (10) ^{1}H-NMR spectrum of polymer (A_9)

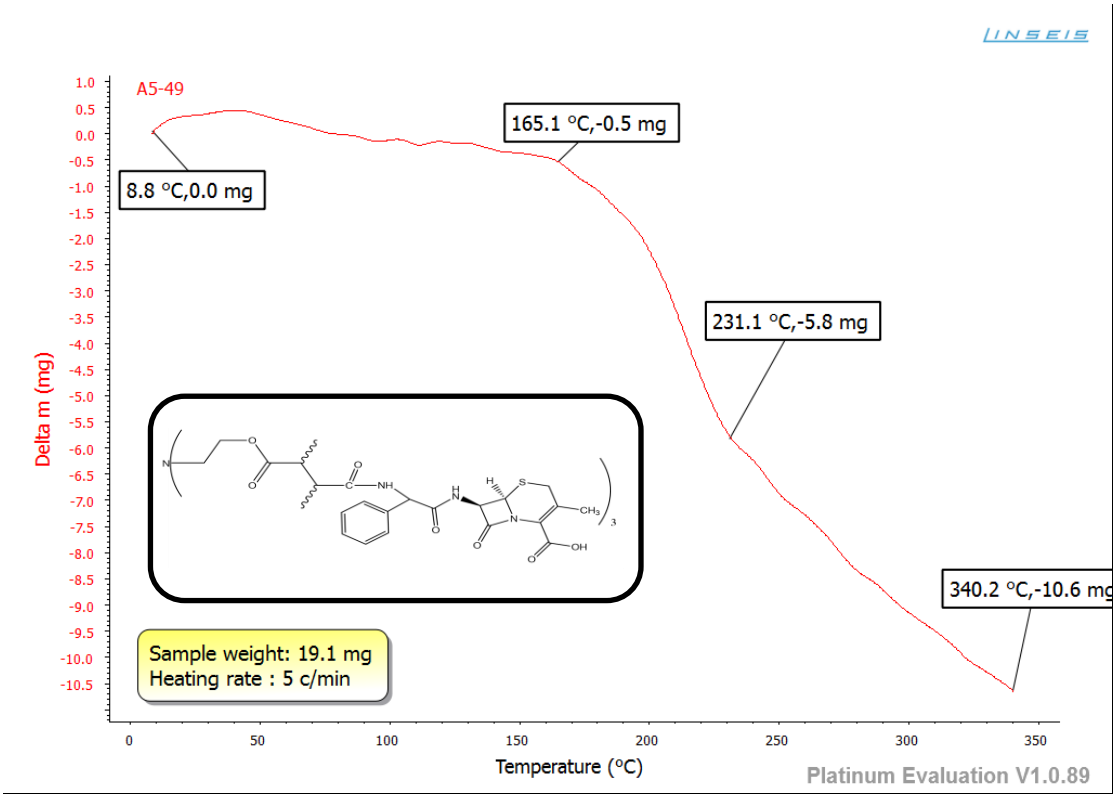


Fig (11A) TGA thermogram of compound (A_7)

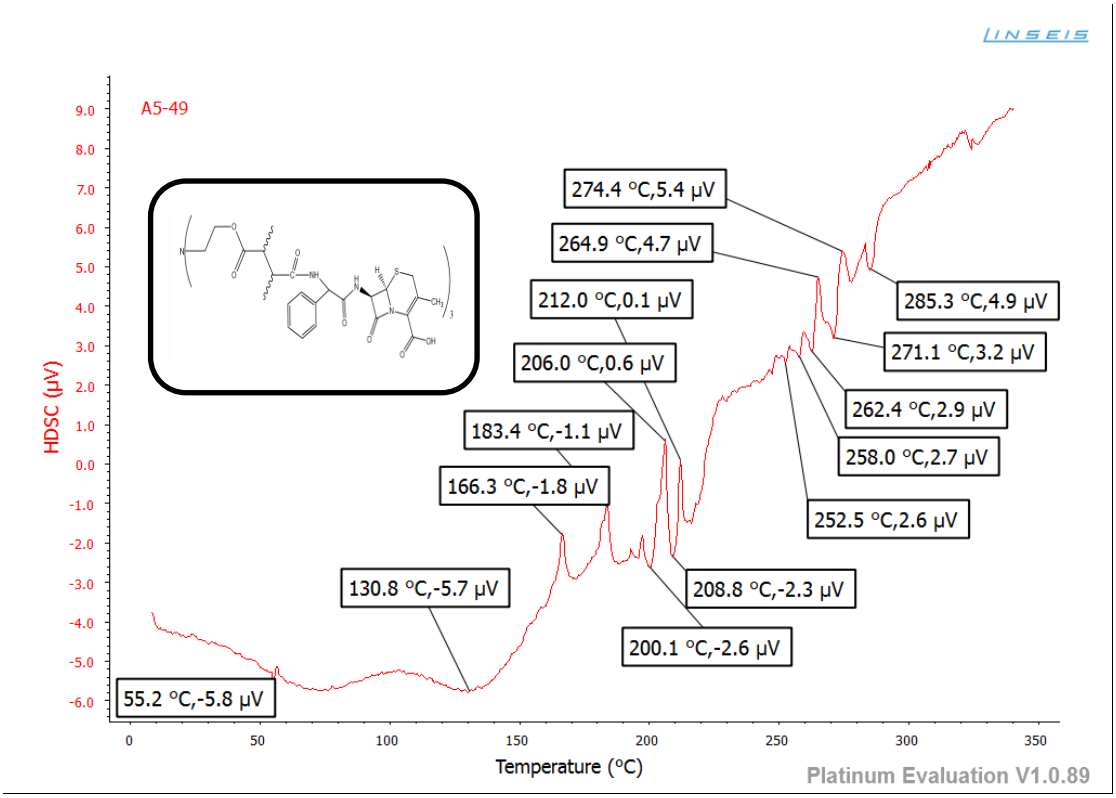


Fig (11B) DSC thermogram of compound (A_7)

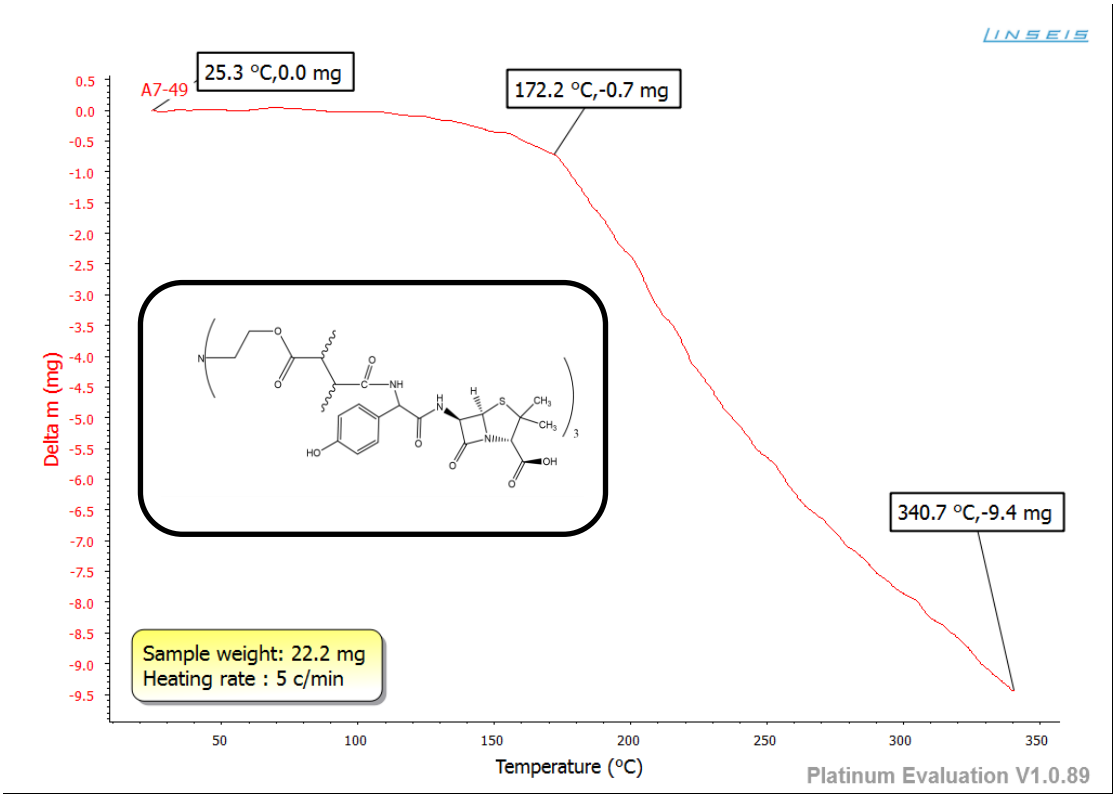


Fig (12A) TGA thermogram of compound (A_8)

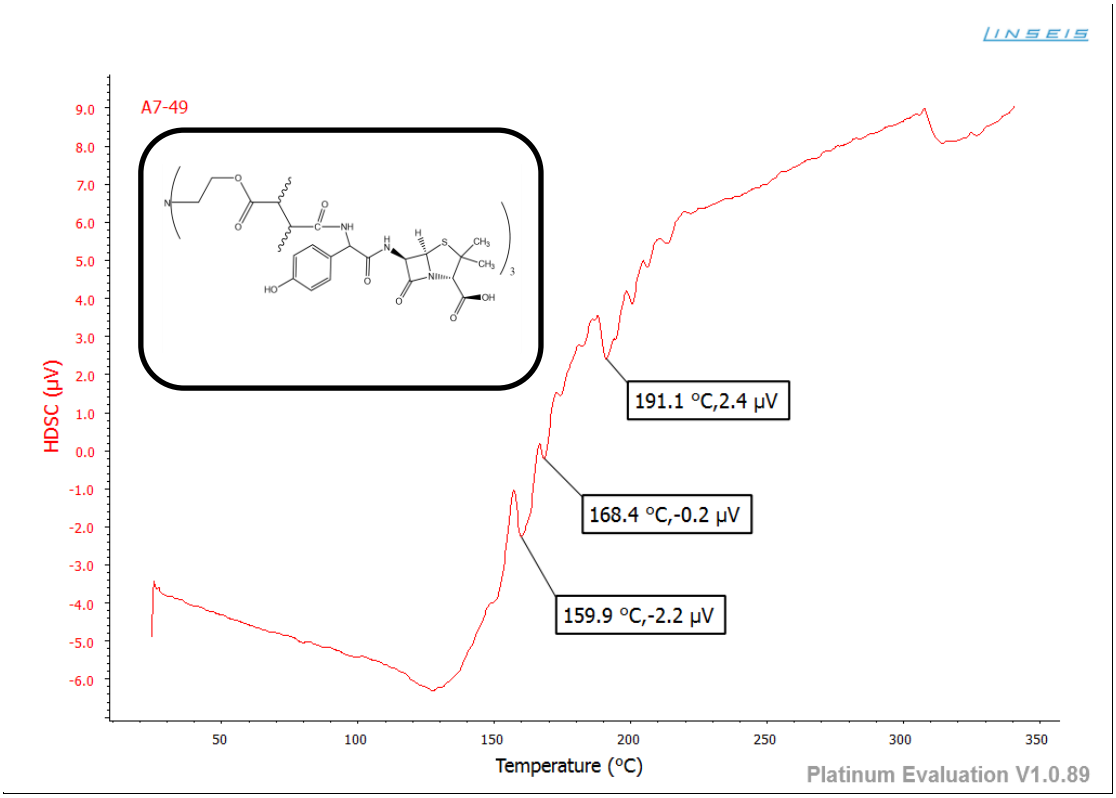


Fig (12B) DSC thermogram of compound (A_8)

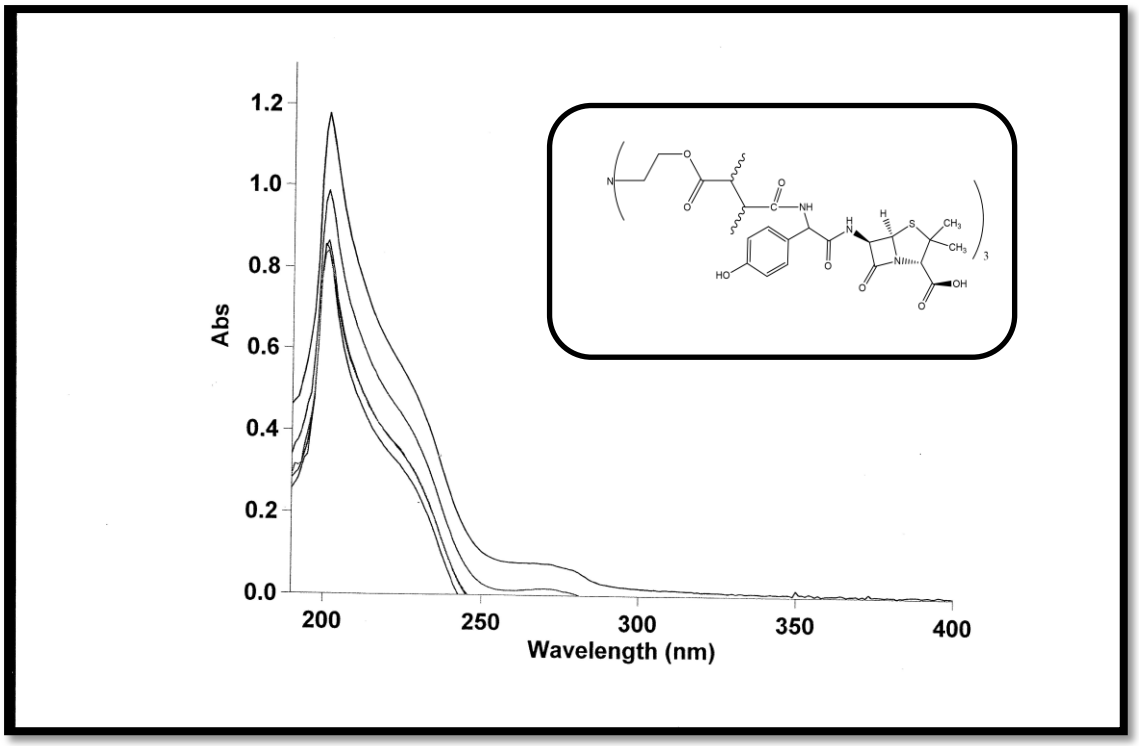


Fig (13A) UV. Spectra of prodrug (A_8) in pH 1.1

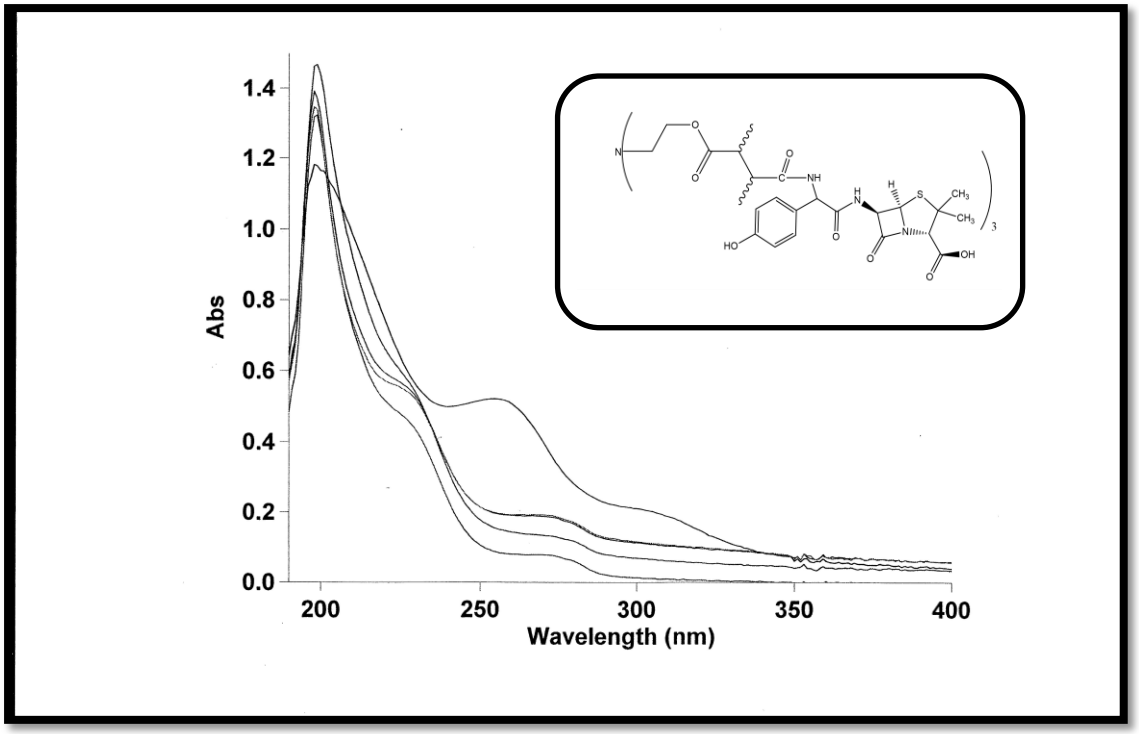


Fig (13B) UV. Spectra of prodrug (A_8) in pH 1.1

Reference

Andrzej S., Anna F., "prodrugs and soft drugs "pharmacologic Reports", 58, 599-613,(2006).

Andrzej S., Anna F., Prodrugs and soft drugs, Pharmacological Reports 58, 1599-613 (2006).

Averous L., Polylactic acid synthesis, properties and application ch.21 indd 435 (2011).

Berdy J., Aszalos A. and Mcnitt K.L. "CRC handbook of antibiotic compounds", Vol. 14, CRC Press, Inc., Boca Raton, Fla., (1987).

Debjit B. Harish G., Dragati K., Duraivel K., Sampak K., "controlled release drug delivery system" Pharma Innovation J., Vol. 1, No. 10 (2012).

Fan Y., Kobayashi M. and Kis H., "Synthesis and specific biodegradation of novel polyester-Amides containing Amino Acid Residues", J. polymer Sci. A: Polymer Chem., 39, 1318-1328, (2001).

Fang J., Nakamura H. and Maeda H. "The EPR effect, unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect", Adv. Drug Deliv Rev 63(3):136-151, (2011).

Firyal M., Firas A. and Ahmed y.,(Synthesis of prodrug ciproflaxacine mole amide polymer, Iraq National j. of Chemistry (NJC) Vol. 56, P. 416-425(2014).

HanH-K, Amidon GL, Targeted prodrug design to optimize drug delivery, AAPS pharm SC., 2, 1-11,(2000).

Jarerat A. and Tokiwa Y., "Degradation of poly (L-Leastidy) by fungus", Macromol Biosci J., l, 136-140, (2001).

Nishide H., Suzuki S., Konno M. and Tokiwa Y., "Microbial Abilization of poly CB-propiolation by sewage sludge and isolated strains polym. Degrade." stab. j. G7, 291-297, (2000).

Pranamude H., Tsuchi A. and Tokiwa Y., "Poly clactide degrading enzyme produced by any colatopsis SP." Macromol, Biosci. J., I, 25-29, (2001).

Rautio J., oh D., Jarvinen T., Savolainen J., "Prodrugs design and clinical applications" Nat. Rev. Drug Discov, 7, 7, 255-270, (2008).

Ronald A. and Michael J. "Overview of Controlled Release", Mechanisms Controlled Release Society, J. Rathbone 33 (1): 19-42, (2012).

Rondd A. and Micheal J., Rathbone overview of controlled release mechanism, Controlled Release Society (2012).

Stella V., Prodrugs, prodrugs some thoughts and current issues, J. Pham. Sci. Vol. 99, 4755-47

Tokiwa Y. and Suzuki T, "Hydrolysis of polyester by lipases", Natural J., 270, 76-77, (1977).

Tokiwa Y.and Jereat A., "Microbial Degradation of aliphatic polyesters", Macromol Symp. J., 201, 2283-290, (2003).

Van de velde k. and Kiekens P., "Biopolymers overview of several properties and consequences on their applications polymer Test", 21, 433-442, (2002).

Yokoyama M, Miyauchi M, Yamada N, Okano T, Kataoka K, Inoue S., "Polymer micelles as novel drug carriers: Adriamycin conjugated poly(ethylene glycol)-poly(aspartic acid) block copolymer. J control release. 11, 269-278, (1990).