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Synthesis of Poly (Acryl Lactate) with Ampicillin

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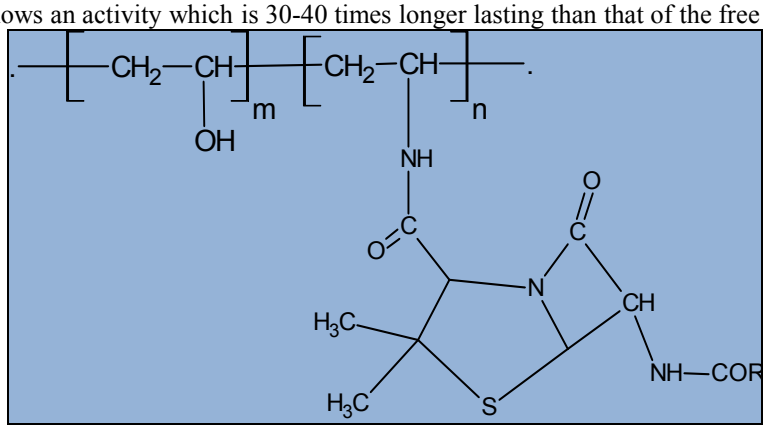
Abstract
Lactic acid was used as di functional spacer could esterified with poly acrylic acid gave its corresponding ester derivative with remain the carboxylic acid of lactate unit which reacted with amino group of Ampicillin forming amide attachment, the prepared prodrug polymer have many improvement, it could enhanced the prodrug with easier hydrolysis through ester- amide groups with extended the arm pendant substituted drug, the modification percentage test was carried out, also it was characterized by FTIR and ^{1}H-NMR spectroscopies. Controlled drug release was studied in different pH values at 37℃. High thermal stability of the drug polymer was observed by TG and DTG indicated the protection of drug with longer date.
Keywords: Lactic acid, poly acrylic acid, Ampicillin.

Introduction

The synthetic polymers with biological materials can also be favorable and desirable. Increasing attention has been paid to development of systems to deliver drugs for long time period at controlled rates [1].Some investigators have focused their attention on the preparation of bioactive polymeric materials, by bounding the drug to a polymer through covalent linking, e.g. chloramphenicol was previously attached to a methacrylic by an acetal function and then copolymerized with 2-hydroxyl methacrylate [2]. More recently, polymers have been used as non-viral vectors for the delivery of genetic materials for gene therapy [3].There have been significant advancements in the area of polymeric drug delivery system (including commercial products). The key point with traditional drug administration is that blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective [4]. Although polymers are used extensively as drug delivery agents, intrinsically bioactive polymers (polymers as active pharmaceutical ingredients) are a relatively development [5]. Partly because of their high molecular weight, polymers would appear to offer several advantages over low molecular weight agents as potential therapeutic agents. The benefits may include lower toxicity, greater specificity of action, and enhanced activity due to multiple interactions (polyvalence) [6]. Demonstrated that derivatives of penicillin bound to a copolymer of vinyl alcohol and vinyl amine (2%) units, shows an activity which is 30-40 times longer lasting than that of the free penicillin.



Synthesized two acrylamides containing proline and hydroxyproline moieties, the acrylamides were polymerized by reversible addition fragmentation chain transfer polymerization to yield well defined amino acid based polymer with thermo responsive properties [7].Biomedical polymers (including additives and degradation products) should not exhibit toxic or irritant qualities, or elicit adverse physiological responses locally or systemically. Toxicity can also be affected by the rate of release of the substance and the biological processing and removal of the substance [8]. Ampicillin is a semisynthetic antibiotic, a member of the penicillin family of antibiotics; it has been synthesized first in 1961, to extent the usefulness of the penicillin to the treatment of infection caused by gram-negative [9]. A variety of ampicillin prodrugs have been prepared to increase the bioavailability, solubility, hydrophobicity of the agent to improve absorption or prevent decomposition in the stomach, where acid catalyzed decomposition may occur. Ampicillin which has both an amino and carboxyl group needs to mask one of them [10].

Experimental

Materials and Instruments

Ampicillin was purchased from Samarra Company; Thionyl chloride was obtained from Fluka. Lactic acid and Acrylic acid were obtained from Aldrich. Dimethylformamide was purchased from Merck. Tri ethyl amine was purchased from Fluka. ^{1}H-NMR spectra were recorded on a Shimatzu spectrophotometer in Dimethylsulphoxide (DMSO). The FTIR spectra were recorded by (4000-400cm$^{-1)}$ on a Shimatzu spectrophotometer. Melting points were determined on callenkamp MF B-600 Melting point apparatus. Thermal analyses were performed using TGA and DTG in Ibn Sina Center, Bagdad, Iraq. Electronic spectra measurement using CINTRA5-UV.Visble spectrophotometer.

Polymerization of Acrylic acid. [11, 12]

In a screw capped polymerization bottle (3g.), of acrylic acid was dissolved in
(10 ml) of DMF, (0.05%) of the monomer weight of di benzoyl peroxide was added as an initiator. The bottle was flashed with nitrogen for few minutes inside a glove and firmly stopped. The solution was maintained at 90℃, using water bath for 1 hr. The solvent was evaporated under vacuum; the product was obtained, washed three times with ether. Dried in a vacuum oven at 50℃, produced 95% of polymer with μ_{in} = 0.46 dL /g.

Preparation of polyacryloyl chloride. [13]

A thionyl chloride (5ml., 0.04mole) was added gradually to a mixture(2.48g., 0.04mole) of poly acrylic acid which was dissolved in 15ml of dioxane placed in a round-bottom flask provided with condenser, the contents were stirred with a magnetic bar at room temperature. The excess of thionyl chloride was distilled off and the poly acryloyl chloride was isolated and dried. Producing white polymer, it was collected on a glass filter, washed repeatedly with ether giving 90%.

Modification of polyacryloyl chloride with Lactic acid(P_2). [14]

In a round bottom flask provided with condenser (3g., 0.041mole) of poly acryloyl chloride was dissolved in 10ml of DMF. Then (3.75g., 0.041mole) of Lactic acid the mixture was refluxed with stirring for 2hrs, the viscous product was obtained, the solvent was evaporated, washed with ether and dried at room temperature. The polymer (P_2) was obtained with 69% as a yellowish brown viscous polymer.

Substitution of Poly[2-((2-methylbutanoyl) oxy) propionic acid]with Ampicillin(P_3) . [15]

(2g., 0.013mole) of prepared polymer (P_2), was dissolved in of dioxane: DMF mixture (10:1vol.), and (1ml) thionyl chloride was added, the mixture was heated at 50℃ the prepared acyl chloride and(1ml) of triethylamine was added to dissolved (4.5g., 0.013mole) Ampicillin, the mixture was refluxed with stirring for 2hrs. The solvent was evaporated under vacuum; the product was washed with water three times, dried under vacuum oven. The yellow polymer (P_3) was obtained with 82%. The softening point of the drug polymer (P_3) was (190-200) ℃.

Determination of degree of Lactic acid substitution. [16]

(5mg) of prepared prodrug polymer (P_3) was dissolved in 2ml of 0.1 N NaOH, the solution was heated to 70℃, for 15min in a water bath, cooled and the resulting solution was titrated with 0.1N HCL to determine the excess of NaOH solution.

Controlled Drug Release. [17, 20]

(0.1g.) of dried prepared prodrug polymer (P_3) was poured in (100ml) of aqueous buffer solution such as (phosphate buffer pH 7.4) or acidic (solution pH 1.1). The buffer solution maintained at 37℃. With continuously stirred and (3ml) of sample was analyzed by UV spectrophotometer and compared with calibration curve which was obtained computerized under similar medium. Fig.(5), showed controlled Ampicillin release in different pH values at 37℃.

The thermal stability study [21]

The thermal stability of some selective prepared polymers was investigated by thermo-gravimetric analysis (TGA) and (DTG). This technique is based on measuring the weight loss as a function of time at constant temperature or as a function of temperature at constant rate of heating. In the present study, the thermal stability of the prepared compounds was tested by thermo-gravimetric technique by measuring the sample weight change at a programmed rate of heating. The change in weight was measured as a function of temperature which gave valuable information about the thermal stability of the prepared compounds.

In this study (P_3), was taken from the prepared polymers under a programmed heating rate of 20 ^{0}C /min. (use Helium as inert gas in rat 20ml/min).Thus the weight-loss vs. temperature thermo-grams were recorded and analyzed. as shown in Table (1), which indicated the high thermal resistance and showed three steps of weight

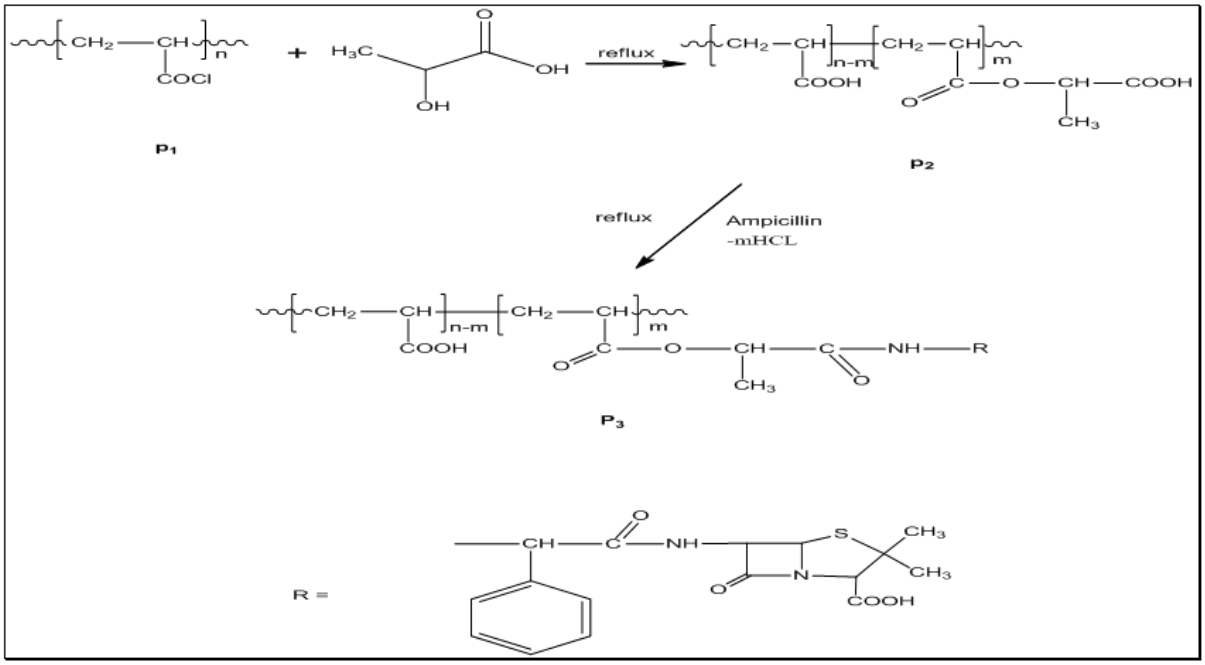
loss-temperature. This high thermal resistance indicated the high molecular weight of the prepared polymers with high interaction between amide hydrogen bonding through the polymer chains.

Table (1): Thermal stability parameter of some of the prepared polymers.

Codes No.	Temp.^{0}C	Weight Loss%	Figure
P_3	254.81 522.66 635.31	4.2791 91.3488 94.6977	6

Results and Discussion

In this research the prodrug was prepared using di-functional spacer groups such as Lactic acid which was inserted between the Lactic acid and poly acryloyl chloride. The carboxylic acid groups was reacted with OH groups of Lactic acid, produced ester attachment group, and the other carboxyl groups were reacted with Ampicillin which could produce amide arm groups. This work aimed to extend the drug pended units to be easy hydrolysis through polymer chains. The high yield was obtained. The reaction was explained as shown below:



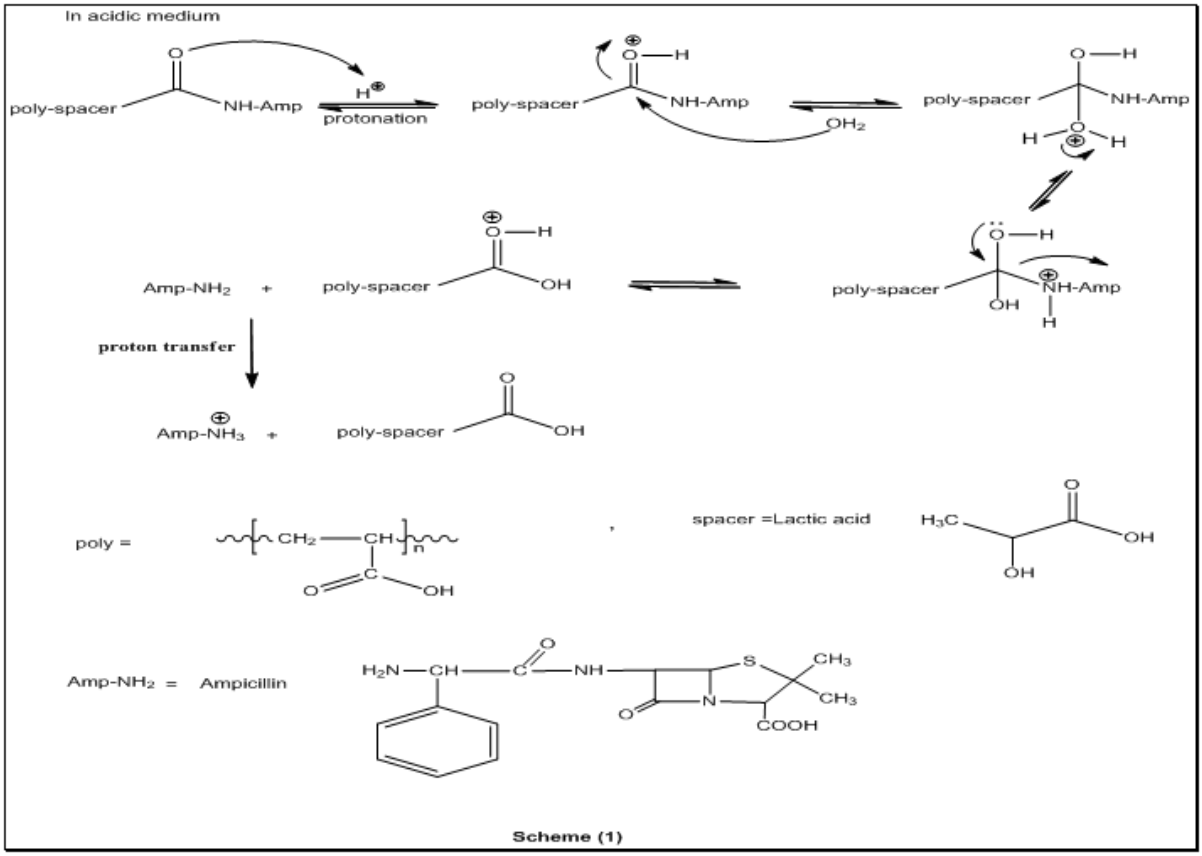
The modified polymer P_2 and P_3 were characterized, by FTIR spectrum, Fig (1) showed the appearance of absorption at around 3441 cm^{-1} assigned to the remained –OH stretching carboxylic group as exhibit a broad at 3200-3500 cm^{-1} of poly acrylic acid, 3392cm^{-1} due to the hydroxyl group of substituted lactic acid group, peaks at 2875-3000 cm^{-1} were asymmetrical and symmetrical stretching of C-H aliphatic, Peak around 1703 cm^{-1} represents stretching vibration of C=O from carboxylic groups, the new absorption was appeared at 1720cm^{-1} represented to (carbonyl-ester).[22] Fig (2) ^{1}H−NMR spectrum of P_2 δ: 2.2 ppm (CH_2−CH, 2H, d.), δ: 1.2 ppm (CH−CO, 1H, T.) poly acrylic acid, δ: 1.1 ppm (CH_2−CH, 2H, d.), δ: 3.7 ppm (CH−CO, 1H, T.),

δ: 1.3 ppm due to (CH_3 terminal, 3H, d.) of Lactic acid, δ: 4.0 ppm (CH−CO, 1H, q.), δ 10.8 ppm (COOH, 1H, S.). FTIR spectrum, Fig (3) of Ampicillin lactic acryl ester polymer P_3 showed the appearance of absorption at 3398cm^{-1} assigned to the remained –OH stretching carboxylic group as exhibit a broad at 3200-3500 cm^{-1} of poly acrylic acid, and 3205cm^{-1} as shoulder beak due to NH amide, peaks at 2850-2958 cm^{-1} were asymmetrical and symmetrical stretching of C-H aliphatic, 3068cm^{-1} of C-H aromatic, Peak around 1700 cm^{-1} represents stretching vibration of C=O from carboxylic groups, 1716 cm^{-1} is attributed to (carbonyl-ester) , the new absorption were appeared at the beak appeared at 1658 cm^{-1} is due to carbonyl-amide. Fig (4) ^{1}H−NMR spectrum of polymer P_3 showed the signals δ: 2.5 ppm (2CH_2−CO, 2H, d.), δ: 2.7 ppm (CH−CO, 1H,T.), δ:1.5 ppm (CH−CO ,1H, T.) of poly acrylic acid, δ: 1.5 ppm (CH_3−CH, 3H, d.), δ:1.3 ppm (2CH_3 terminal, 6H, S.), δ: 4.9 ppm (CH−CH_3 ,1H, q.), δ: 4.8 (CH−N,1H, d.), δ: 4.6 ppm (NH−CH−CO ,1H, S.), δ: 5.2 ppm (CH−CO,1H, d.), δ: 6.6 ppm (CH−Ar, 1H,S.), δ: 7.0 ppm (2H, d.) of ortho aromatic ring, δ: 7.9 ppm (3H, T.) of meta and para, δ: 8.02, 8.2 ppm (NH, 1H, S.), δ: 11.3,11.6 ppm (COOH, 1H, S.).

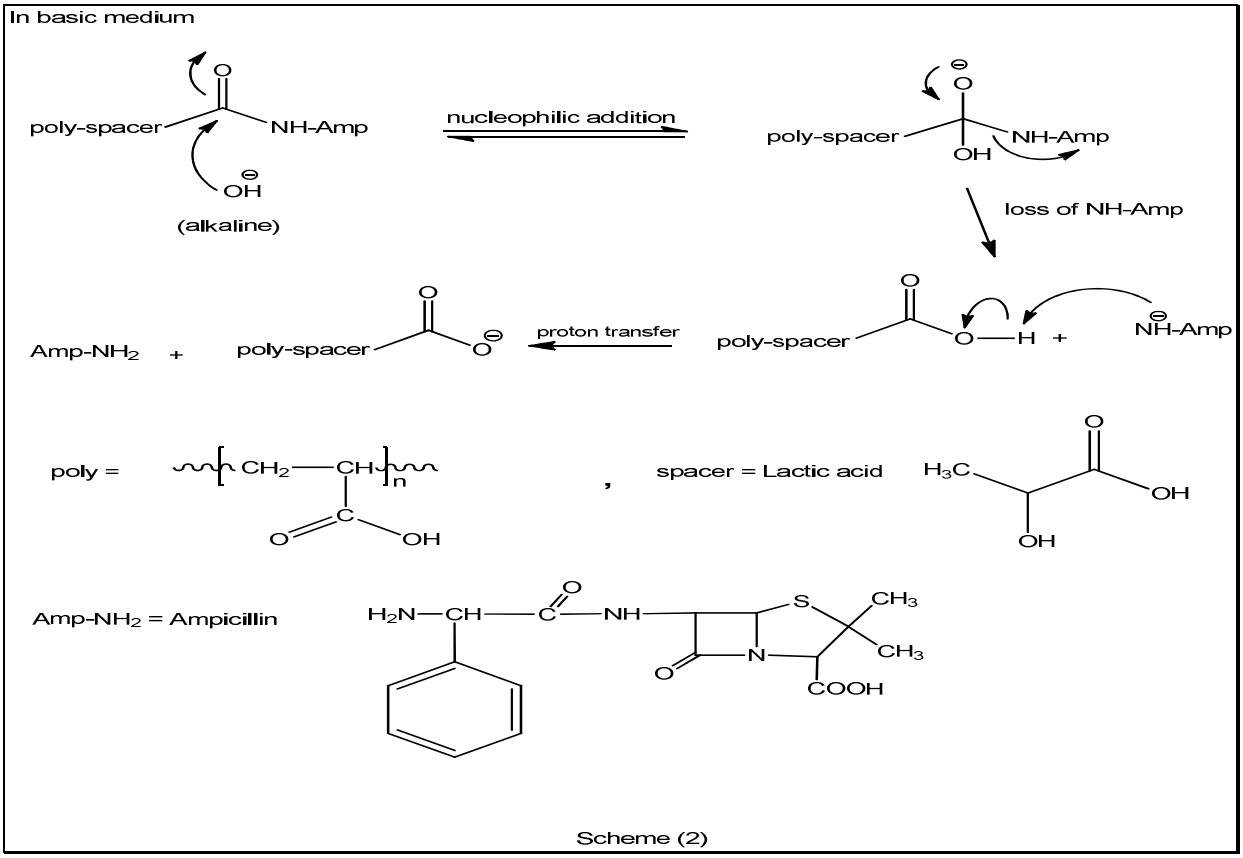
The remained carboxylic acid was 43% was tested by titration of polymeric sample with 0.1N of NaOH

in the presence of phenolphthalein as an indicator. The concept of polymeric drug has been subjected with medicine chemists as long consideration synthetic polymers. The polymer which is substituted by drug groups enhanced the using as prodrug polymers. The UV. Spectra of P_3 gave absorptions at 200 and 350 nm due to (n-π*) and (π-π*) due to electron transition for drug conjugation structures.[23-24]

The controlled release rates were studied as drug polymers which could be hydrolyzed in basic and acidic medium due to ester bonds as shown in the following mechanism:-



Scheme (1)



Scheme (2)

CONCLUSION

It was concluded that, In basic medium, the rate of hydrolysis is higher than acidic medium this is due to the presence of OH^- in alkaline, which acts as a stronger nucleophilic with respect to water, and the H_2O takes place faster hydrolysis than acidic medium, H^+ is bonded to oxygen atom of ester as shown in Scheme (2).the spacer effect appeared more enhancement in hydrolysis of ester or amide groups.

Fig (5) showed the release profile of drug release (mole fraction) versus time

A swelling percentage of the prepared polymer was studied which equals to 10%.

The swelling% was calculated according to the following equation.

$$\Delta m = m_1 - m_\circ / m_\circ \times 100$$

When:-

$m_\circ$ is the weight of dry drug polymer.

m_1 is the swallowed polymer in non-solvent

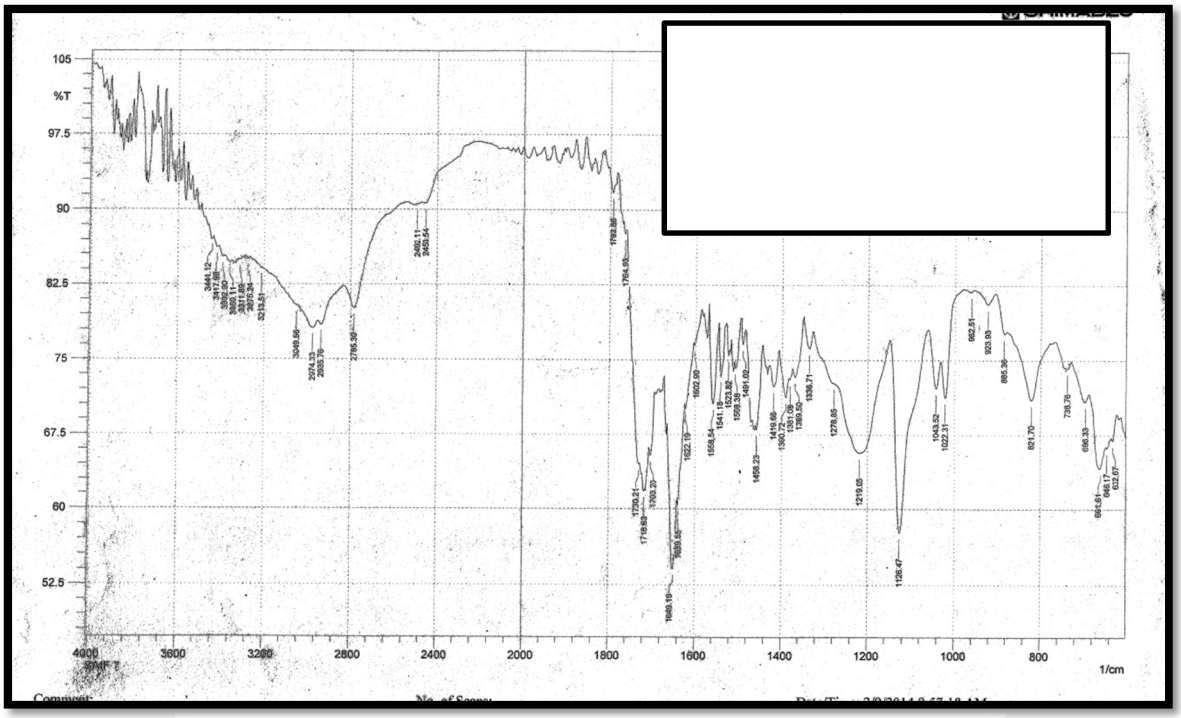


Fig. (1) FT-IR spectrum of drug polymer (P_2)

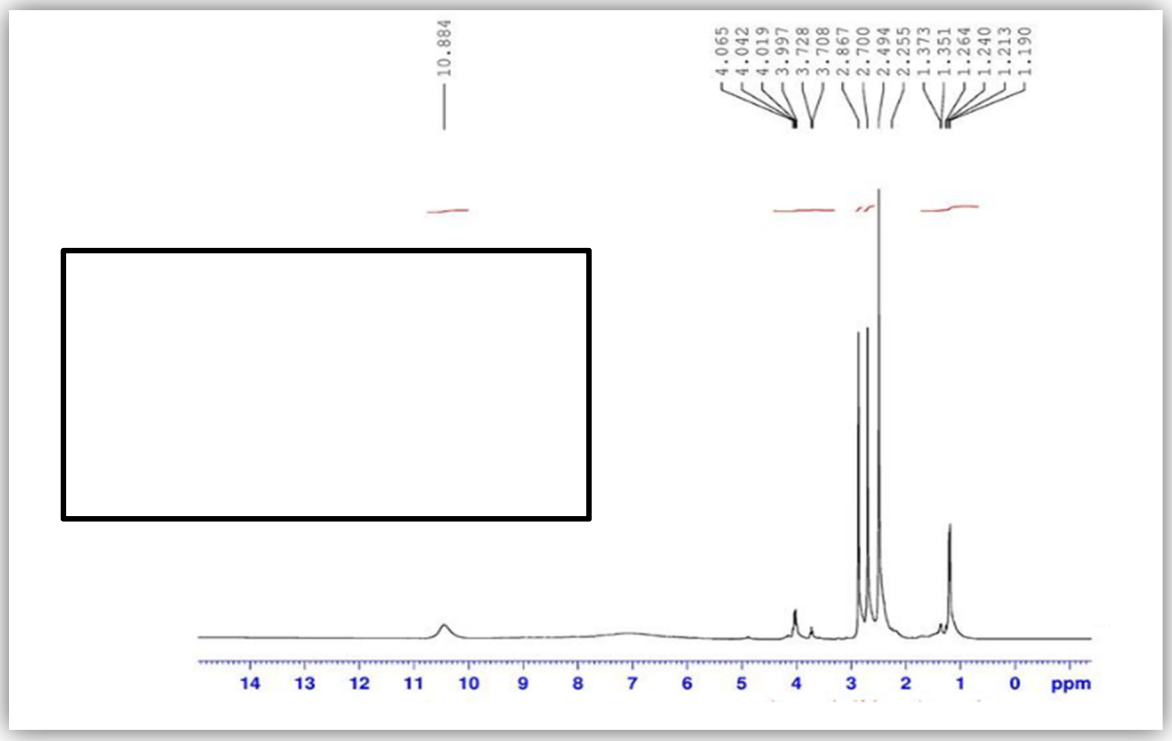


Fig. (2) ^{1}H-NMR spectrum of drug polymer (P_2)

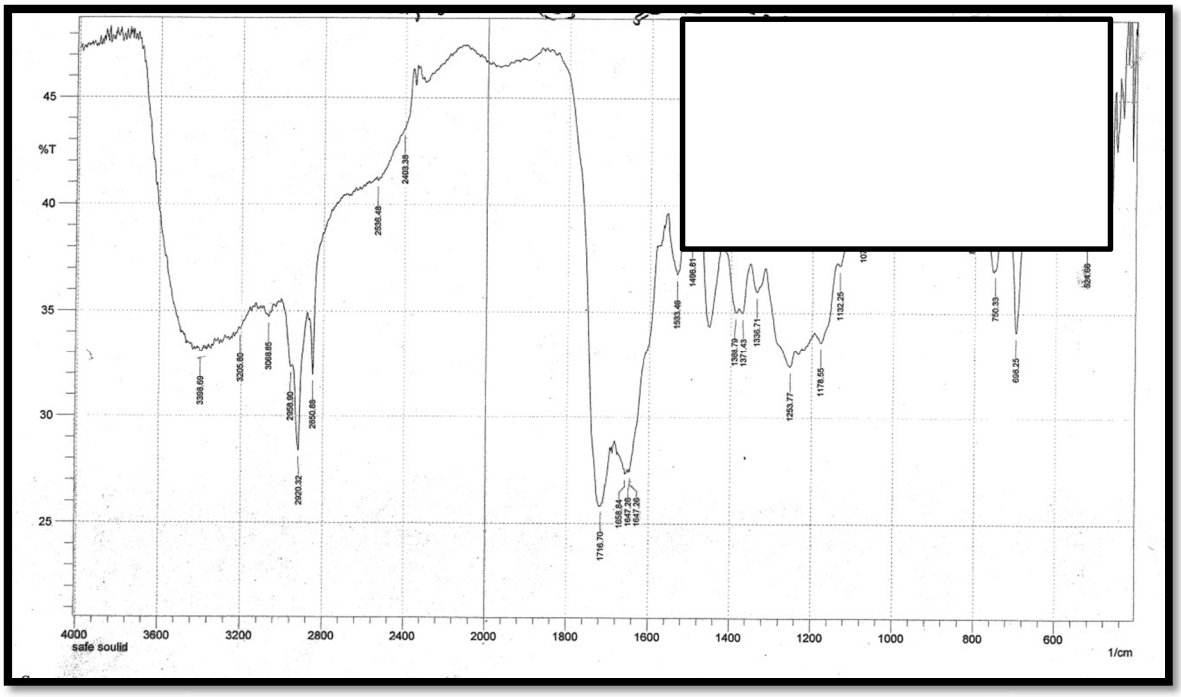


Fig. (3) FT-IR spectrum of drug polymer (P_3)

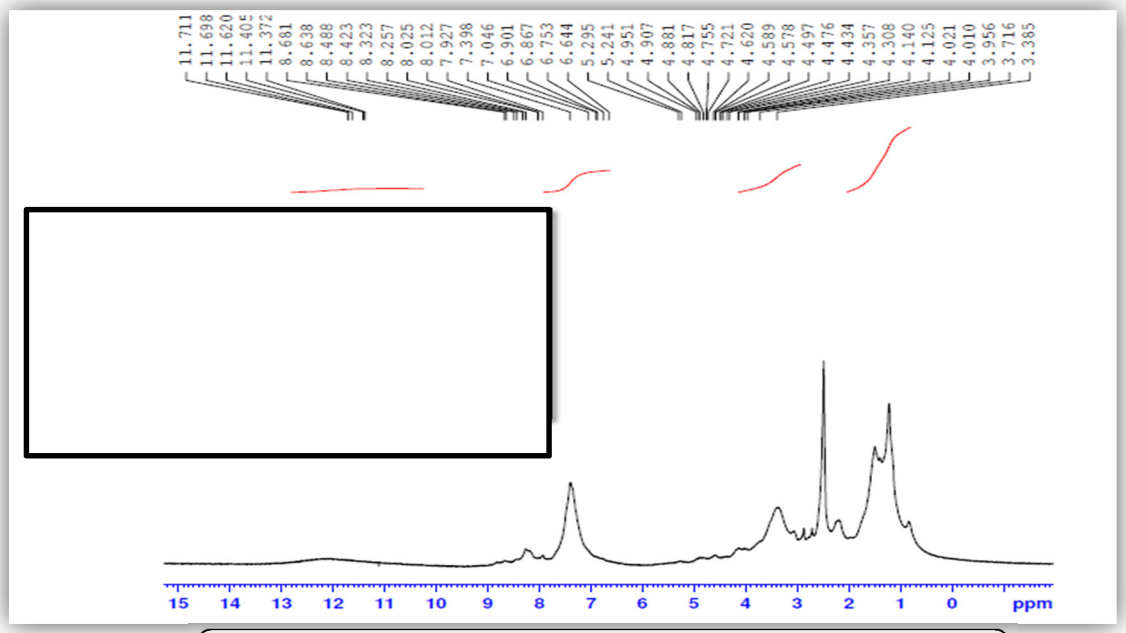


Fig. (4) ^{1}H-NMR spectrum of drug polymer (P_3)

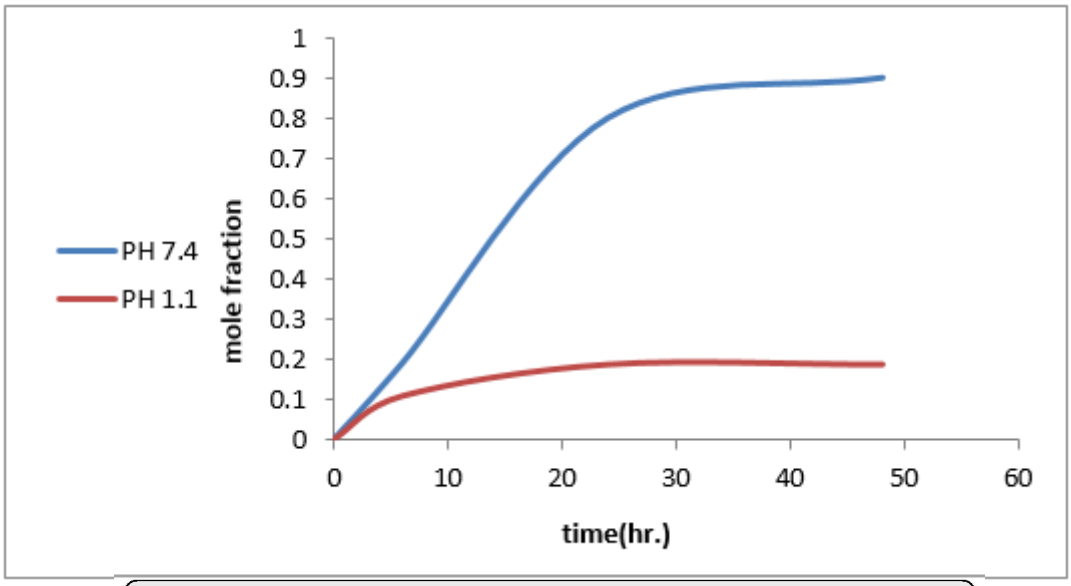


Fig (5) Drug release of P_3 in PH 1.1 and 7.4 at 37°C

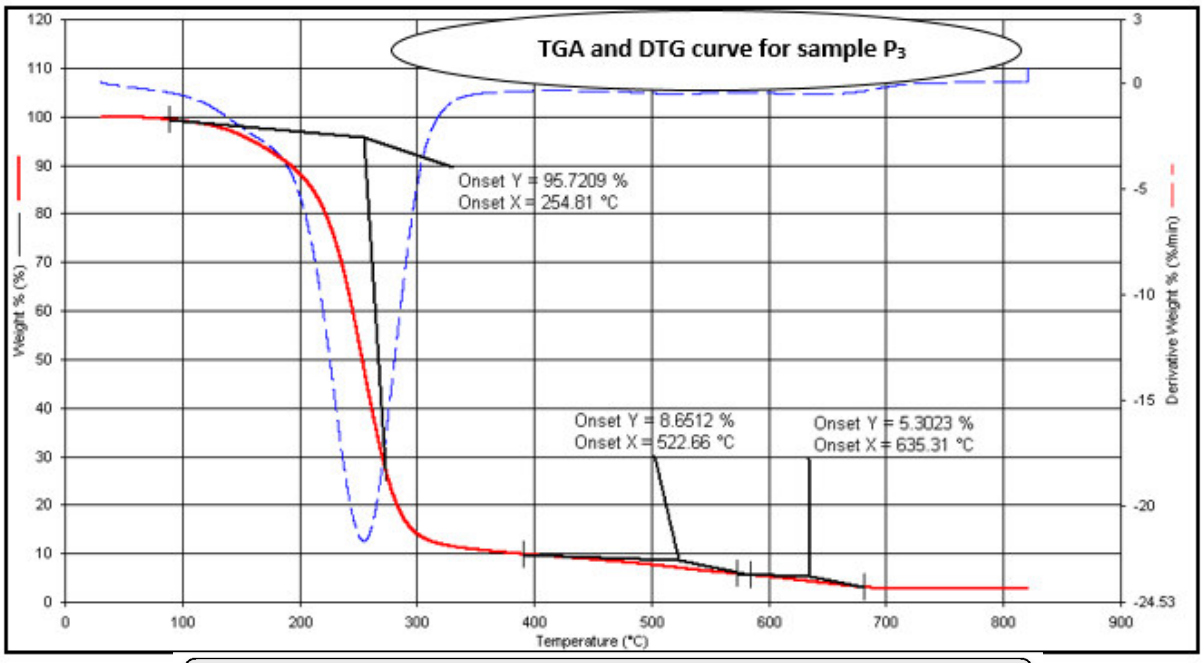


Fig. (6) TG and DTG thermogram for compound (P_3)

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