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LACTIC ACID AS SPACER BETWEEN POLY ACRYLIC ACID AND 4-AMINOANTIPYRINE

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ABSTRACT

Due to many problems associated with drug release and side effects, we could design a novel drug delivery system through modification of poly acrylic acid (AA) with Lactic acid as a spacer between the polymer and 4-aminoantipyrine. In vitro drug release had been conducted successfully in basic medium in pH 7.4 and acidic medium in pH 1.1 at 37℃. The prepared prodrug polymer was characterized by FTIR and ^1H-NMR spectra. Physical properties and intrinsic viscosity of drug polymer were determined. The good results were obtained in the presence of spacer unit with comparing without spacer unit.

Keywords: Poly acrylic acid, Lactic acid, Prodrug polymer.

Contribution/ Originality

This study contributes in the existing literature Synthesized compound from lactic acid as spacer between poly acrylic acid and 4-aminoantipyrine. This study uses new estimation methodology several physical tools .This study originates new formula.

1. INTRODUCTION

4-aminoantipyrine is a biologically active compound and its analogues and other pyrazole derivatives have shown anti-inflammatory, analgesic, antiviral, and antipyretic properties (Alam *et al.*, 2012; Radi *et al.*, 2012). Dipyrone and some (AA) derivatives have a high potential to attenuate or prevent the anti-platelet effects of aspirin (Yi *et al.*, 2013). Poly lactic acid is at present one of the most promising biodegradable polymers (biopolymers) and has been the subject of abundant literature over the last decade. PAA can be processed with a large number of techniques and is

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commercially available (large-scale production) in a wide range of grades. It is relatively cheap and has some remarkable properties, which make it suitable for different applications. and its biocompatibility in contact with living tissues is exploited for biomedical applications (implants, sutures, drug encapsulation (Avérous, 2011). The basic aim of prodrug design is to mask undesirable drug properties, such as low solubility in water or lipid membranes, low target selectivity, chemical instability, undesirable taste, irritation or pain after local administration, pre systemic metabolism and toxicity (Rautio *et al.*, 2008; Testa, 2009; Stella, 2010). In a polymer-drug conjugate, there are at least three major components: a soluble polymer backbone, a biodegradable linker, and a covalently linked anti-cancer drug which is deactivated as a conjugate, (Figure 1) (Duncan, 2006; Xinxin, 2010).

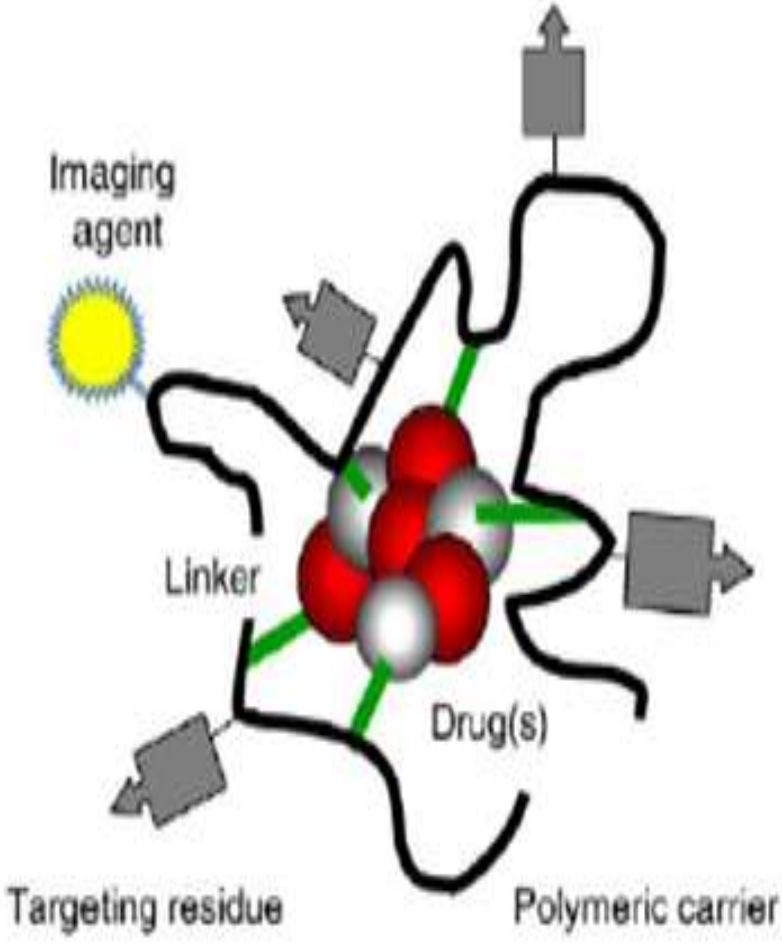


Figure-1. Major components of a polymer-drug conjugate (Xinxin, 2010)

This research concern to minimize delivery problems and reduced gastrointestinal side effects by controlling the rate of hydrolysis, and duration of drug action.

2. EXPERIMENTAL

2.1. Materials and Instruments

The following chemicals were used as received from suppliers;

4-Aminoantipyrine was purchased from Samarra Company; Thionyl chloride was obtained from Fluka. Lactic acid , Acrylic acid and solvents 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. Electronic spectra measurement using CINTRA5-UV.Visble spectrophotometer.

3. POLYMERIZATION OF ACRYLIC ACID (Firyal, 1997)

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.

4. PREPARATION OF POLYACRYLOYL CHLORIDE (Diab, 2003)

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%.

5. MODIFICATION OF POLYACRYLOYL CHLORIDE WITH LACTIC ACID(P_2) (Peter and Renata, 2002)

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.

6. SUBSTITUTION OF POLY [2-((2-METHYLBUTANOYL) OXY) PROPIONIC] WITH 4-AMINOANTIPYRINE(P_3) (Callery and Peter, 2002)

(1g., 0.007mole) of prepared polymer (P_2), was dissolved in 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 (1.41g., 0.007mole) 4-aminoantipyrin, 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 reddish brown polymer (P_3) was obtained with 65%. The yield % of produced polymer was as a viscous material.

7. DETERMINATION OF DEGREE OF LACTIC ACID SUBSTITUTION (Soudabeh and Ali, 1996)

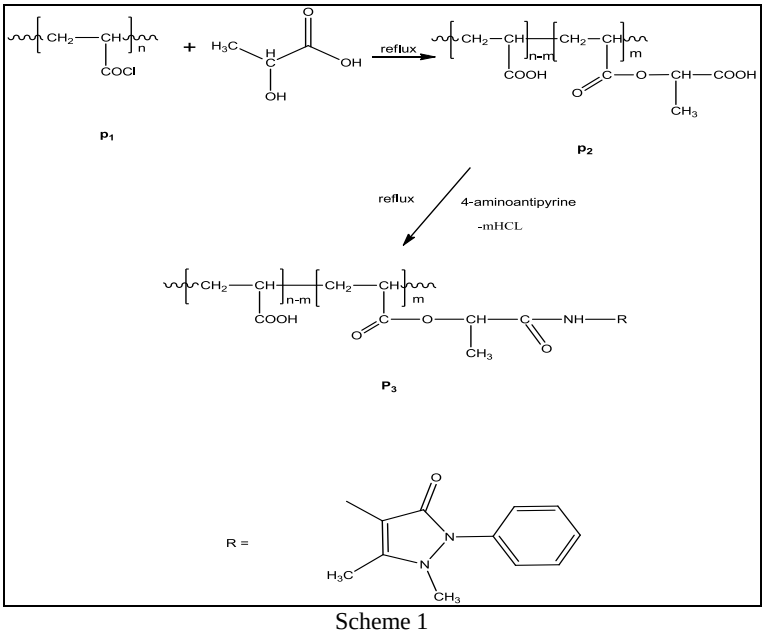
(5mg) of prepared pro-drug polymer (P_3) was dissolved in (2ml) of 0.1 N NaOH, the solution was heated to 70℃, for 15min in a water bath, cooled and the resulting solution was titrated with 0.1N HCL to determine the excess of Na OH solution.

8. CONTROLLED DRUG RELEASE (Drug, 2003; Firyal, 2005; Johnson *et al.*, 2005; Ardeshir *et al.*, 2007; Debjit *et al.*, 2012)

(0.1g.) of dried prepared pro-drug 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 4-Aminoantipyrine release in different pH values at 37℃.

9. RESULTS AND DISCUSSION

In this research, the pro-drug 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 as attachment group, and the other carboxyl groups were reacted with 4-aminoantipyrine produced 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 Scheme 1.:



Scheme 1

The modified polymer P_2 and P_3 were characterized, by FTIR spectrum, Fig (1) shows the broad beak around 3441 cm^{-1} assigned to the remained –OH carboxylic acid of poly acrylic acid, 3392cm^{-1} due to the hydroxyl group of substituted lactic acid group,

2974 cm^{-1} of C-H aliphatic. 2785cm^{-1} of CH_3 methyl, 1718 cm^{-1} represented to (ester carbonyl) and 1730 cm^{-1} due to carbonyl of carboxylic group of unreacted poly acrylic acid and 1126 cm^{-1} of C-O ester. Fig (2), ^{1}H−NMR spectrum of P_2 showed the signals at 2CH_2−CO (2H) d., δ:2.8 ppm of CH−COOH (1H) and δ:2.4 ppm of CH−COOH (1H) S. polymer, and δ: 1.3 ppm due to CH_3 terminal of (3H) d., of Lactic acid., δ: 4.0 ppm of O−CH (1H) Q., and δ 10.8 ppm of COOH (1H)S., The remained carboxylic acid and Lactic acid.

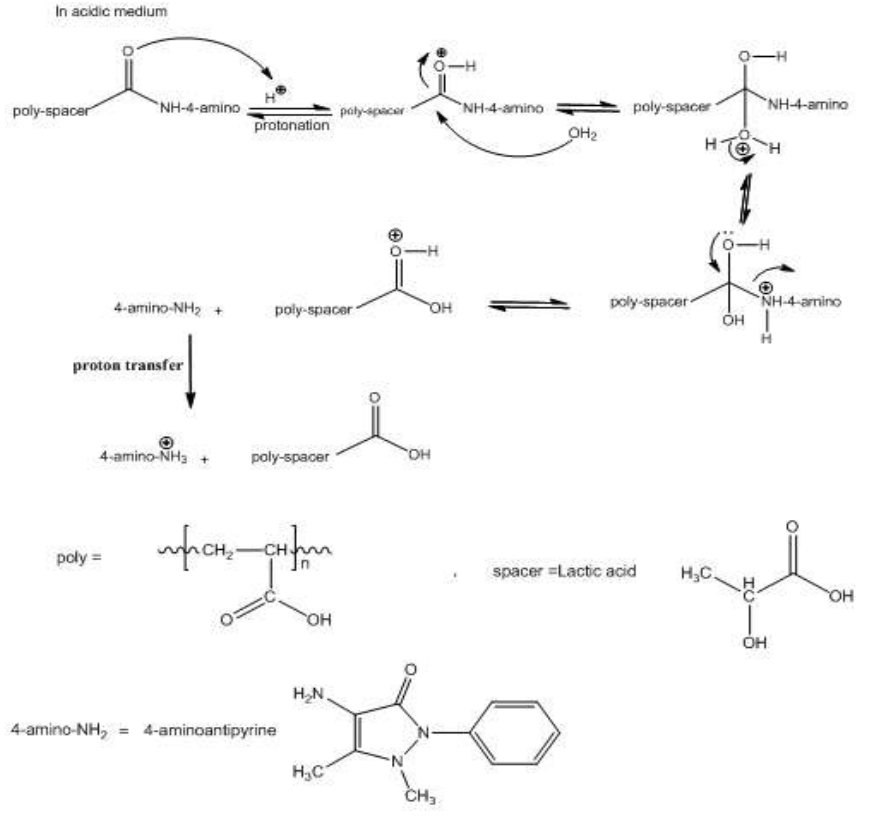
FTIR spectrum, Fig (3) of 4-aminoantipyrin lactic acryl ester polymer P_3 showed the beak at 3417cm^{-1} of remained OH carboxylic and 3277cm^{-1} as shoulder beak due to NH amide, 3063cm^{-1} of C-H aromatic, 1705cm^{-1} is attributed to (carbonyl-ester) and the other absorption appeared at 1722 cm^{-1} is for carbonyl acid and the new absorption were appeared at the beak appeared at 1656 cm^{-1} is due to carbonyl−amide.

(Drug, 2003; Johnson *et al.*, 2005; Debjit *et al.*, 2012) Fig (4) ^{1}H−NMR spectrum of polymer P_3 showed the signals 2.7 ppm of 2CH_2−CO (2H) d., 2.9 ppm of CH−COOH (1H) and 2.8 ppm of CH−COOH (1H) S. polymer, 1.3 ppm of CH_3 terminal (3H)d., δ: 3.6 ppm of CH_3-N (3H) S., and δ: 2.9 ppm of CH_3−C (3H) S., δ: 4.8 O−CH−CO (1H) Q., δ: 7.1 ppm (2H)d. of ortho aromatic ring, δ: 7.6 ppm of(3H) T., of meta and para, and δ: 8.1ppm of NH-CO (1H) S. (Ronald Siegel and Michael Rathbone, 2012; Fiyral Mohammad *et al.*, 2015)

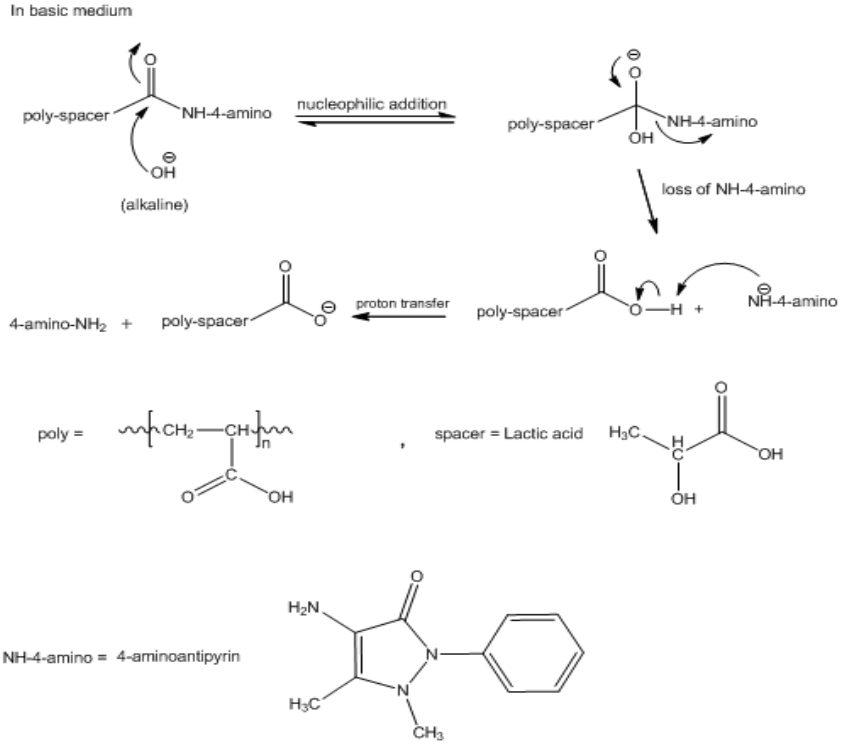
The remained carboxylic acid was 40% was tested by titration of polymeric sample with 0.1N of NaOH in the presence of phenolphthalein as an indicator. The concept of polymeric drug has been subjected with medicine chemists as long consideration synthetic polymers.

The polymer which is substituted by drug groups enhanced the using as prodrug polymers. The UV. Spectrum of P_3 gave absorptions at 200 and 400 nm due to. (n-π*) and (π-π*) due to electron transition for drug conjugation structures.

Fiyral Mohammad *et al.* (2015) 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 mechanisms Scheme 2 & 3:-



Scheme 2



Scheme 3

10. CONCLUSION

It was concluded that the extended side arm of poly acrylic acid with suitable spacer di-functional such as Lactic acid with 4-aminoantipyrine, 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 attack to carbonyl group with respect to water, and the H_2O takes place faster hydrolysis than acidic medium, H^+ which is bonded to oxygen atom of ester as shown in Scheme (2). The spacer effect appeared more enhancements 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

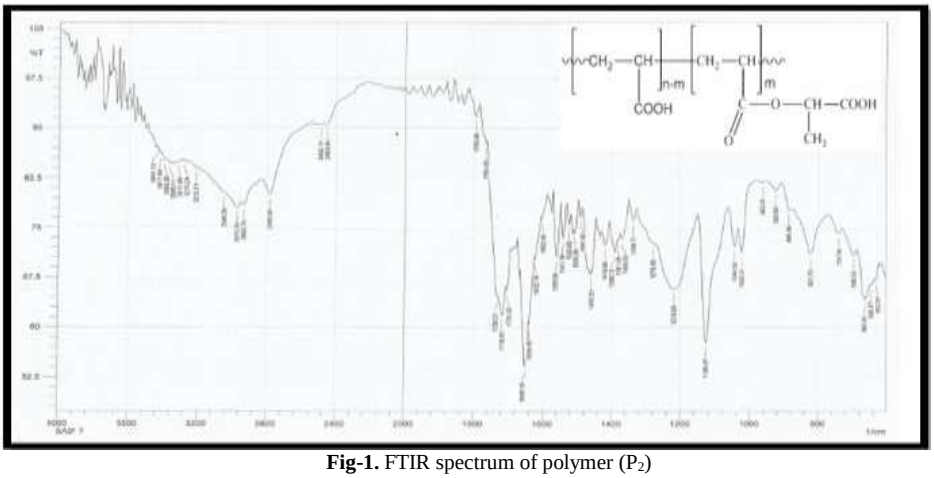
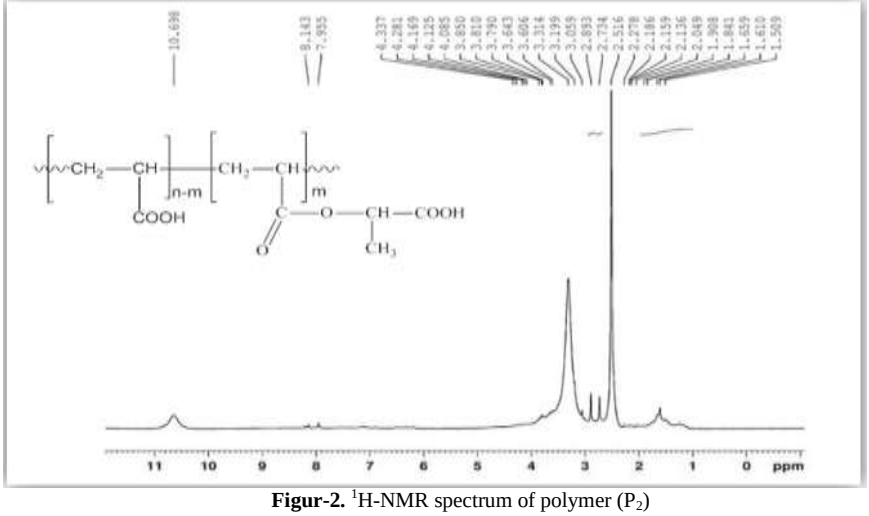


Fig-1. FTIR spectrum of polymer (P_2)



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

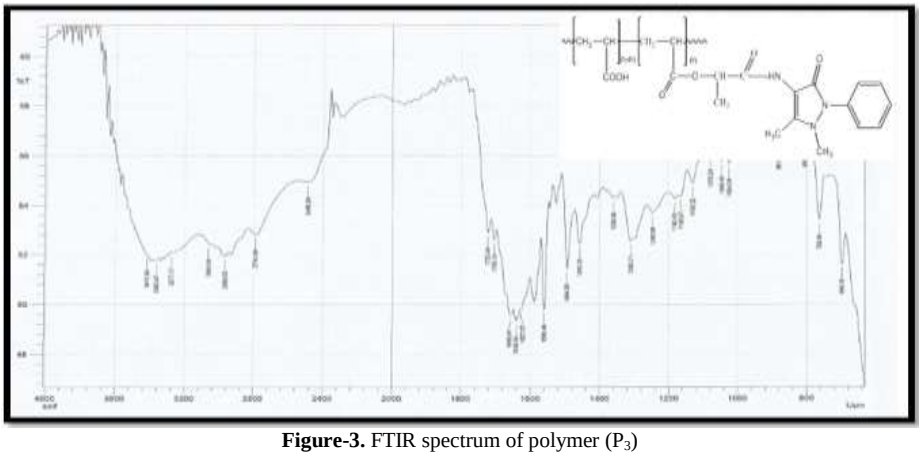


Figure-3. FTIR spectrum of polymer (P_3)

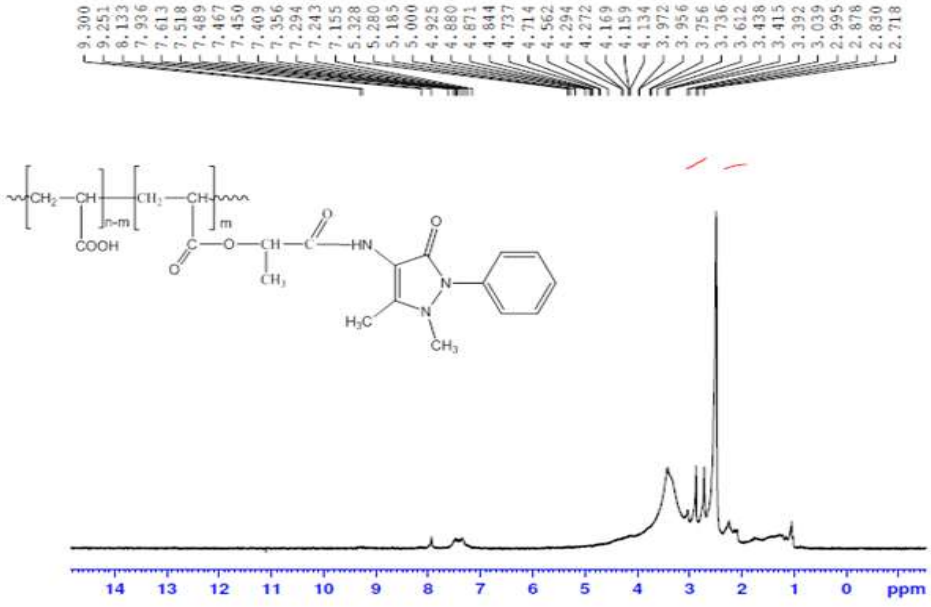


Figure-4. ^{1}H-NMR spectrum of polymer (P_3)

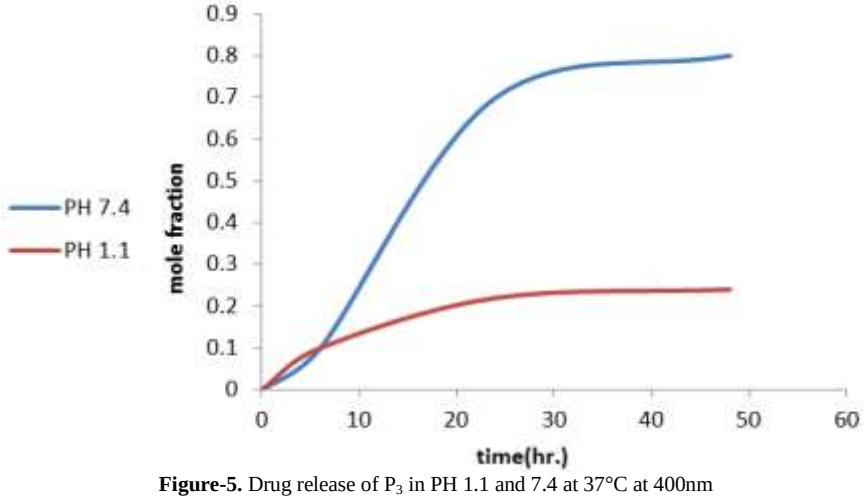


Figure-5. Drug release of P_3 in PH 1.1 and 7.4 at 37°C at 400nm

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