International Journal of Technical Research and Applications e-ISSN: 2320-8163,
www.ijtra.com Volume 3, Issue 3 (May-June 2015), PP. 300-306

SYNTHESIS OF DRUG CARRIER POLYACRYLIC ACID WITH SPACER GROUP

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Abstract- In this work a new prodrug polymer was prepared with two attachment groups (amid-ester), using di functional spacer such as ethanol amine, which could react with polyacrylic acid producing amide group, with remain ethanol terminal group which could react with captopril acyl chloride, producing ester group with extended the arm substituted drug to improve the hydrolysis and to prevent the steric effect of polymer chains. Many advantages enhanced the prodrug of polymer. The prepared polymers were characterized by FTIR, 1H –NMR spectroscopies. Controlled drug release was studied in different pH values at 37℃, using UV. Spectra with comparing with calibration curve. The modification percentage test was studied, and swelling percentage was calculated and all physical properties were observed.

Keywords: Drug Carrier Polyacrylic Acid, Captopril and prodrug polymer.

I. INTRODUCTION

Hydrophobically modified poly (acrylic acid) (HMPAA) shows some interesting rheological properties in semidilute aqueous solutions, such as interchain aggregation followed by an increase in the apparent molecular weight and enhanced viscosity as well as shear sensitivity [1]. HMPAA is prepared by modification of PAA in its acidic form by alkyl amines in an aprotic solvent in the presence of N, N′-dicyclohexylcarbodiimide (DCCD) [2]. Polyacrylic acid based polymers are mainly used for oral and mucosal contact applications such as controlled release tablets, oral suspensions and bio-adhesives. It is also used as a thickening, suspending and emulsion stabilizing agent in low viscosity systems for topical applications. For bio-adhesive applications, high molecular weight acrylic acid polymer cross-linked with divinyl glycol is extensively formulated in a variety of drug delivery systems for mucosal applications. Buccal, intestinal, nasal, vaginal and rectal bio-adhesive products can all be formulated with such polymers [3]. One of the limitations of the reactions on polymers is the fact that the reactivity of the drug on the polymer chains may be low when it is directly attached to the main chain of the polymer [4].This may be caused by steric hindrance of the neighboring side groups. In fact the limited efficiency of polymeric prodrugs is a reflection of the limited loading and a too slow hydrolysis of the drug from polymer backbone. This problem has been overcome by spacing the reactive groups from the main chain via spacer arms. 'The bridging groups or spacer arms must be inserted to aid hydrolysis or enzymatic breakdown of the labile bonds. The activity can also be controlled by varying the degree and type of substitution along the backbone of a polymer selected. Advantage of such polymer reactions are that the molecular weight and the molecular weight distribution of the polymer have already been established [4].

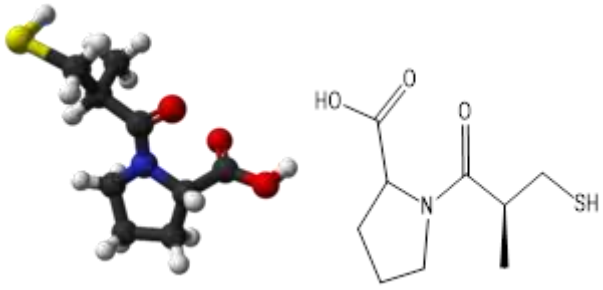


Figure (1): Structure of Captopril

Captopril is used therapeutically as an anti-hypertensive agent. Captopril is widely used for the arterial hypertension. It acts as a potent and specific inhibitor of angiotensin converting enzyme. It is used in the management of hypertension, in heart failure, following myocardial infarction and in diabetic nephropathy. It seems to be one of the most widely used drug for hypertension and heart problems [5]. Captopril is used as first line therapy in people with type II diabetes and hypertension. They are effective in lowering blood pressure, usually well tolerated, and have an excellent metabolic profile [6].

II. EXPERIMENTAL

A. Materials and Instruments

Captopril (IUPAC) name: (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid was purchased from Samarra Company; Thionyl chloride was obtained from Fluka. Hydroxyl amine and Acrylic acid were obtained from Aldrich. Dimethylformamide was purchased from Merck. 1H-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 call enkamp MF B-600 Melting point apparatus. Electronic spectra measurement using CINTRA5-UV.Visble spectrophotometer.

B. Polymerization of Acrylic acid. [7, 8]

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 μin = 0.46 dL /g.

C. Modification of polyacrylic acid with ethanol amine(P_2). [9, 10]

(3g., 0.041 mole) acrylic acid was dissolved in 10ml of DMF, and (2.5g., 0.041mole) of ethanol amine, the mixture was stirred vigorously at room temperature for 1 hr., the viscous product was obtained, the solvent was evaporated, washed with ether and dried at room temperature. The hydroxyl ethyl acrylamide polymer (P_2) was obtained with (73%) as a yellow viscous polymer.

D. Substitution of Poly [N-(2-hydroxyethyl)-2-methylbutanamide] with Captopril acyl chloride (P_3). [11]

(2g., 0.017mole) of prepared polymer (P_2) was dissolved in 5ml of DMF, and (3.7g., 0.017mole) of prepared captopril acyl chloride was added, 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 yellowish polymer (P_3) was obtained with 65%. The softening point of the drug polymer (P_3) was (200-210) ℃.

E. Determination of degree of captopril substitution. [12]

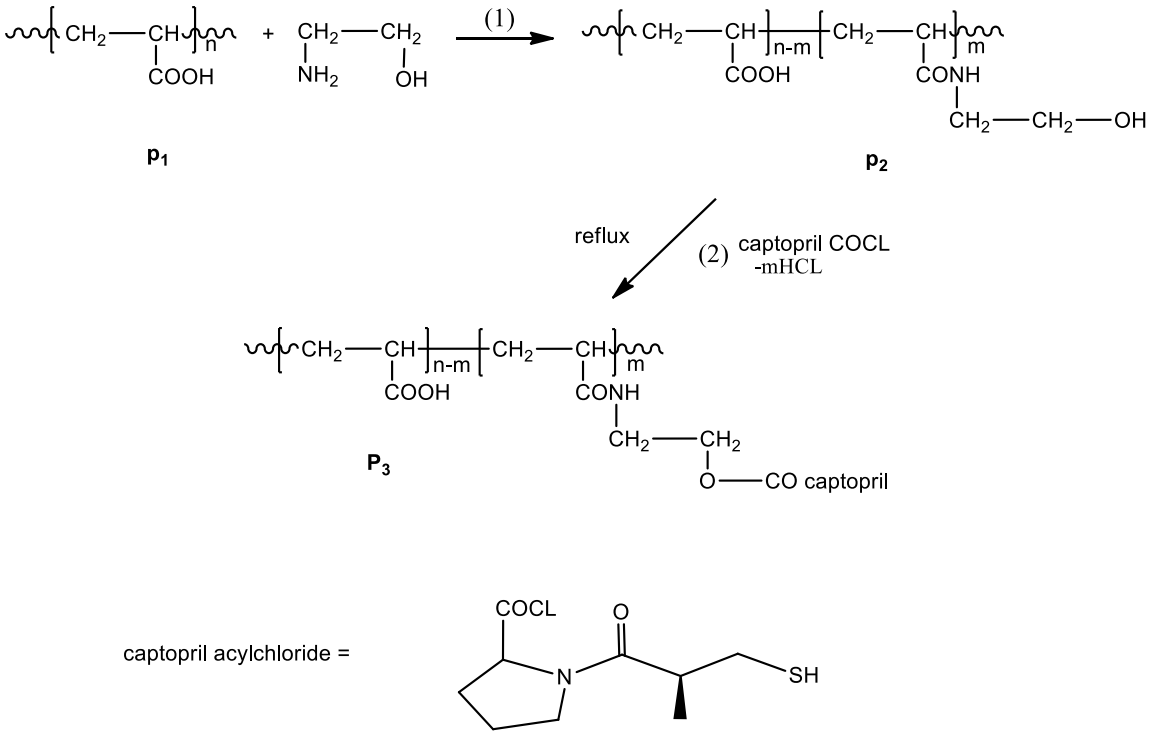
5mg of prepared prodrug polymer (P_3) was dissolved in (2ml) of (0.1N) NaOH, the solution was heated to 70℃, for 15min in a water bath, cooled and the resulting solution was titrated with (0.1N) HCL to determine the excess of NaOH solution.

F. Controlled Drug Release. [13-18]

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. (6) Showed controlled captopril release in different pH values at 37℃.

G. Results and discussion

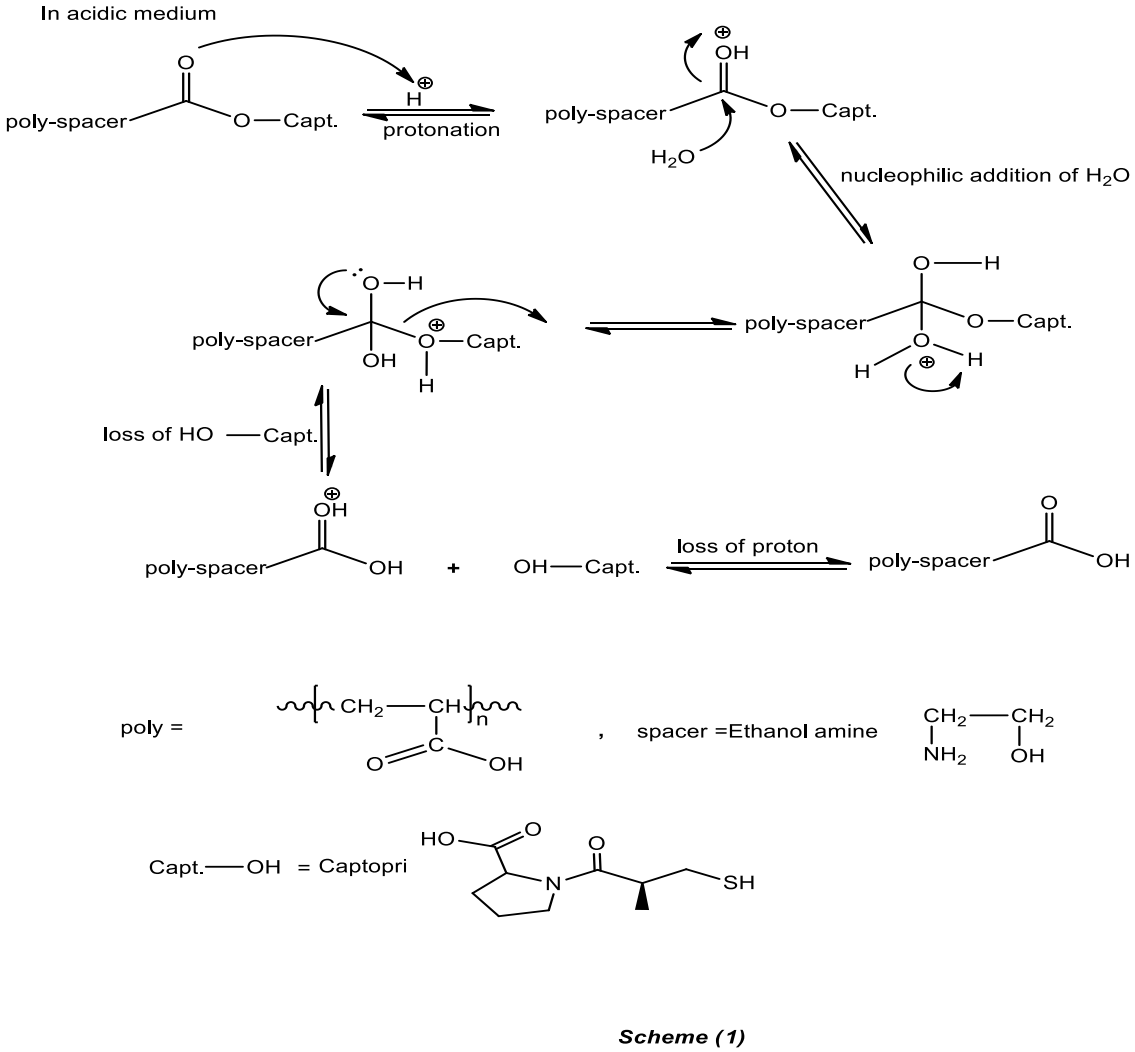
In this research the prodrug was prepared using di functional spacer groups such as ethanol amine which was inserted between the captopril and polyacrylic acid. The carboxylic acid groups was reacted with amino groups of ethanol amine, produced amide attachment group, and the other hydroxyl groups were reacted with prepared captopril acyl chloride which could produce ester arm groups.[14-15] This work aimed to extend the drug pended units to be easy hydrolysis through polymer chains. The high yield was obtained by reaction of polyacrylic acid and ethanol amine as spacer arm units as show below:



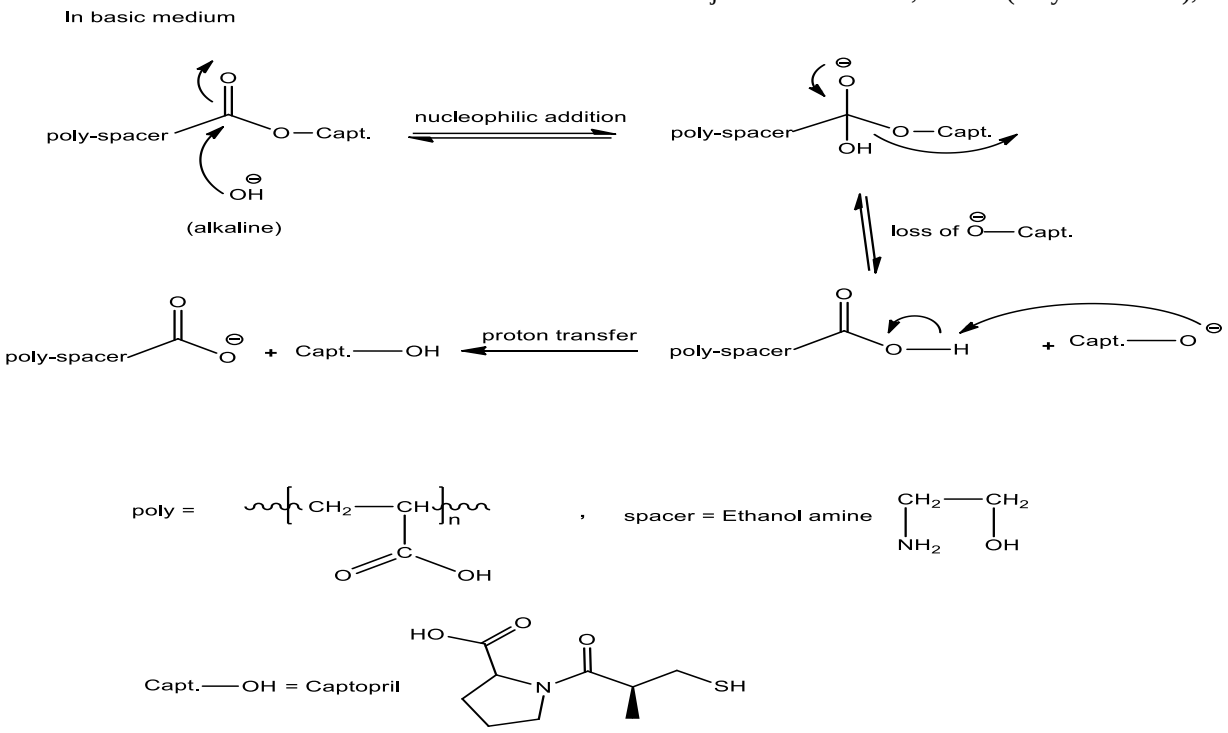
The modified polymer (P_2) and (P_3) were characterized, by FTIR spectrum, Fig(2) shows the beak around 3416 cm^{-1} assigned to the remained –OH carboxylic acid of poly acrylic acid, 3350cm^{-1} due to the hydroxyl group of substituted ethanol group, 2949 cm^{-1} of C-H aliphatic. 1651cm^{-1} represented to (amide carbonyl) and 1700 cm^{-1} due to carbonyl of carboxylic group of unreacted poly acrylic acid. Fig(3) ^1H-NMR spectrum of P_2 showed the signals at δ: 2.5 ppm and 2.1 ppm assigned to the (CH−CO) chain, (CH_2−CH) chain of poly acrylic acid as d. and T. also 3.4 ppm T. of (2H−OH) and δ: 3.8 ppm due to CH_2−N of (2H) T. of ethanol amide. δ: 4.3 ppm of OH (1H) S., and δ 8.0 ppm of NH (1H) S. of amide. FTIR spectrum, Fig (4) of captopril ethyl acryl amide polymer P_3 showed the beak at 3431cm^{-1} of remained OH

carboxylic and 3120 cm^{-1} as shoulder beak due to NH amide, the new absorption was appeared at 1707 cm^{-1} is attributed to (carbonyl-ester) and the other absorption appeared at 1687cm^{-1} is for cyclic carbonyl amide and the beak appeared at 1649 cm^{-1} is due to carbonyl−amide. Fig (5) 1H−NMR spectrum of polymer P_3 showed the signals 1.3 ppm and 1.8 ppm of CH_2−CH polymer and δ: 2.9 ppm of $2CH_2$−O (4H) T., δ: 3.5 ppm CH−N (1H) δ: 2.7−2.8 due to $3CH_2$ cyclic, and δ: 1.5 ppm S−H (1H) S., δ: 8.0 ppm of NH (1H) S., δ 8.5 ppm of COOH (1H) S. δ: 9.7 ppm (5−H) (1H) S.[15-17]

The remained carboxylic acid was 34% 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 Captopril groups enhanced the using as prodrug polymers. The UV.Spectra of (P_3) gave absorptions at 200 and 400 nm due to (n-π*) and (π-π*) due to electron transition for Captopril conjugation structures. [18].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)

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 (6) 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 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 water

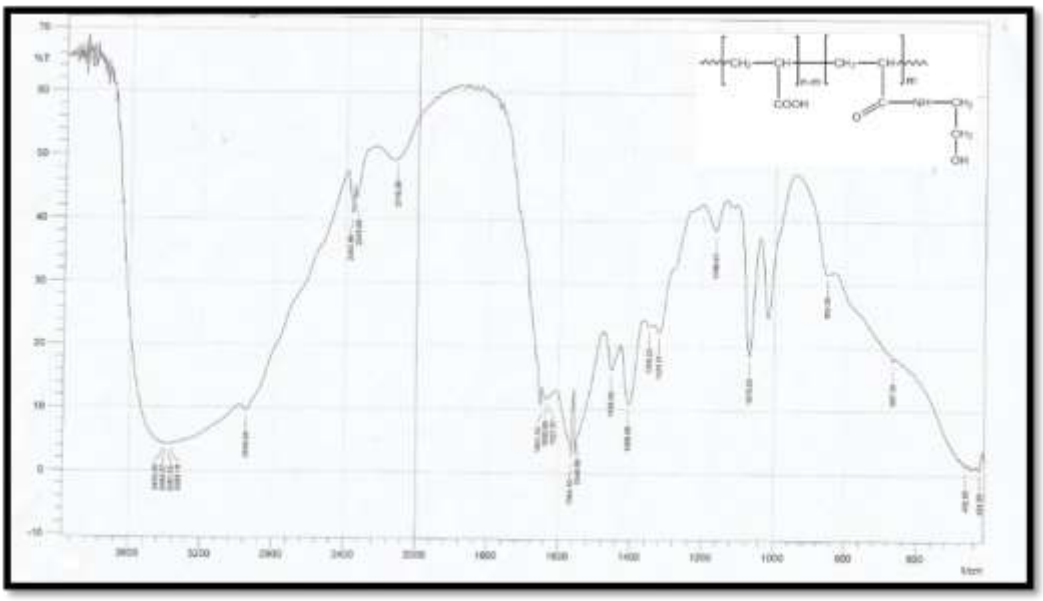


Fig (2) FTIR spectrum of ethanol acryl amide polymer (P_2)

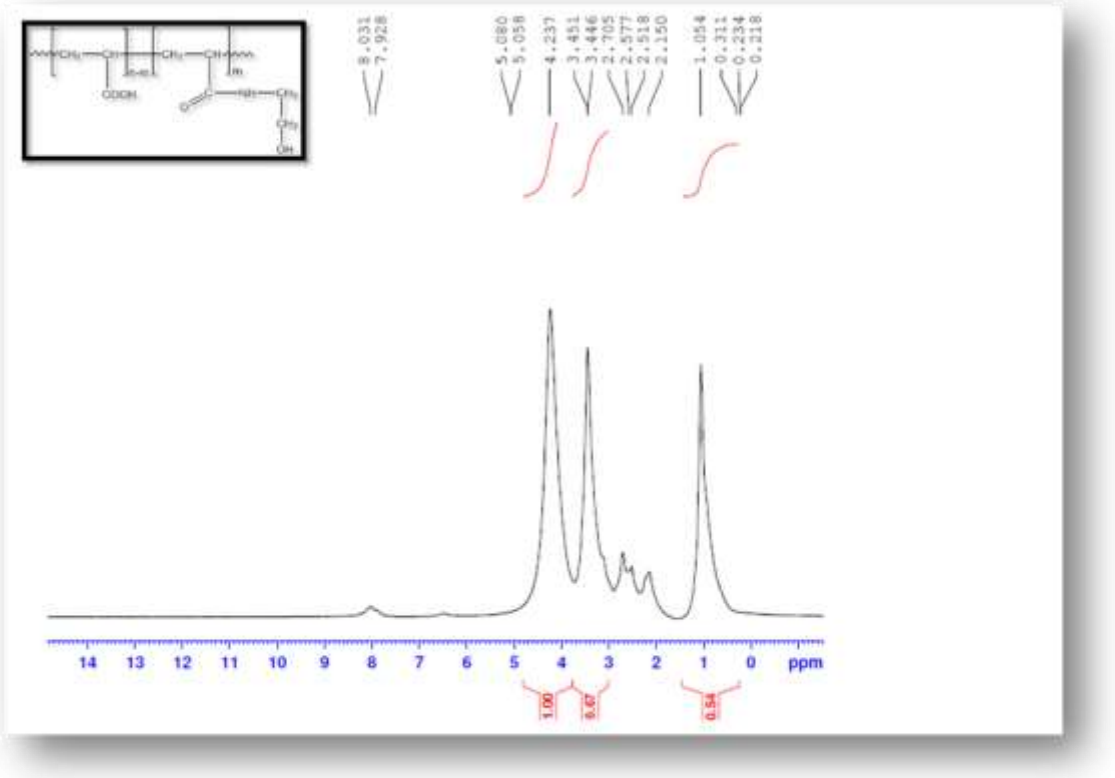


Fig (3) ^{1}H-NMR spectrum of ethanol acryl amide polymer (P_2)

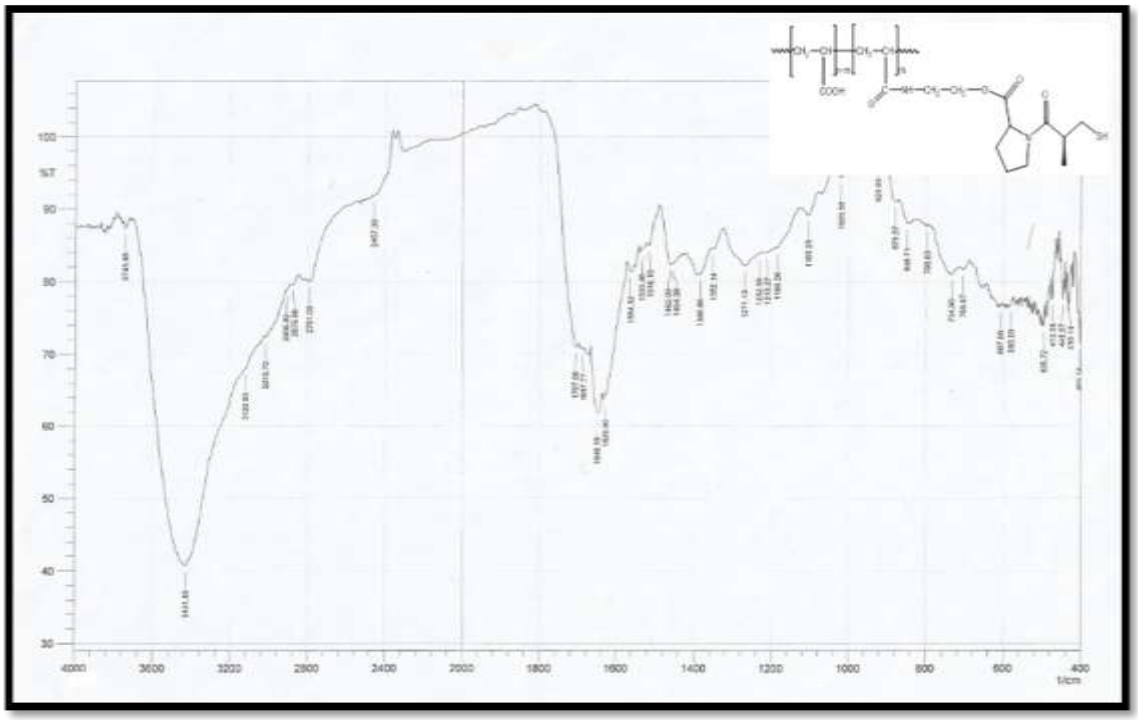


Fig (4) FTIR spectrum of Captopril ethyl acryl amide polymer (P_3)

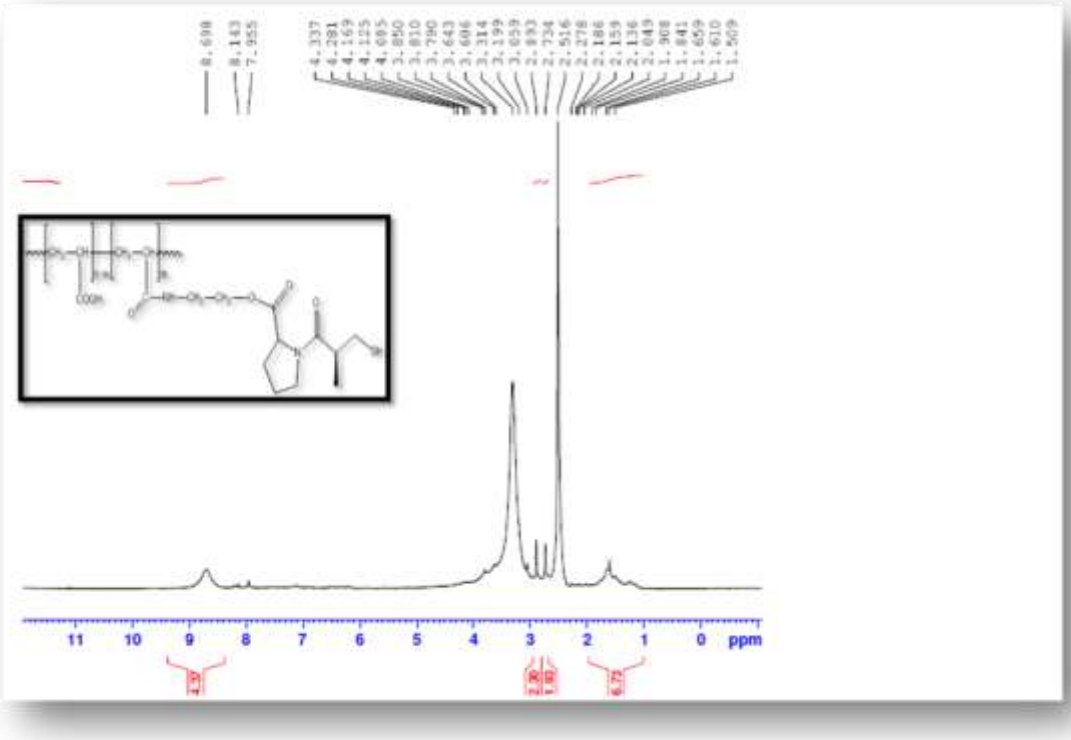


Fig (5) 1H-NMR spectrum of Captopril ethyl acryl amide polymer (P_3)

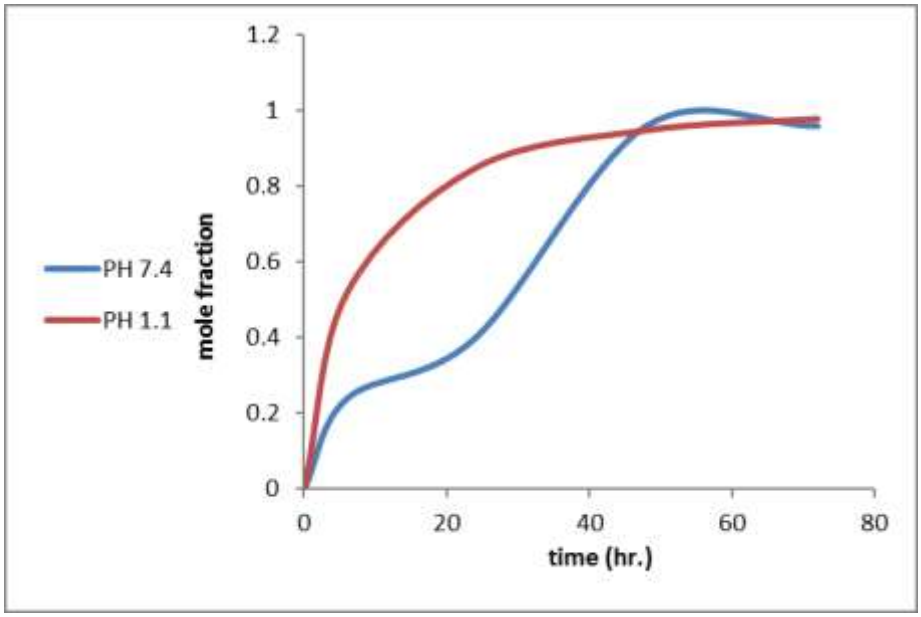


Fig (6) Drug release of P_3 in pH 1.1 and 7.4 at 37°C at 400nm

III. CONCLUSION

In this work it was concluded that the presence of difunctional spacer group was inserted between the drug and polymer backbone through ester group which could easy hydrolysis as arm pendant group, with decreasing of steric effect of polymer chain.

We can recommended that the other carboxylic drugs could be used, to improve the prodrug and to increase lipid or water solubility, and to improve that taste of a drug to make it more patient compatible, reduce toxicity, increase chemical stability, increase biological stability, change the length of time of duration of action and deliver the drug to specific site in the body.

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