Glycine Poly Acrylate with 4-Aminoantipyrine

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Abstract: In this research a new modified polyacrylic acid with amino acid Glycine as di functional spacer was attached with poly acrylic acid to its corresponding acrylamide polymer, then they remained Carboxylic acid of Glycine could be converted its acryl chloride by using thionyl chloride then substituted with 4-aminoantipyrine,the design a novel drug delivery system through modification Poly acrylic acid could conducted successfully as in vitro study in different pH values 7.4 and pH 1.1 at 37℃. The prepared prodrug was characterized by FTIR, 1H-NMR spectroscopic. The good results were obtained comparing with the studied of controlled drug release without spacer as know conclusion, the more sustained release of drug over long times and this include situation requiring the slow release of water –soluble drug polymer.

Keywords: Poly Acrylic Acid, Glycine and pro drug polymer and 4-Aminoantipyrine

I. INTRODUCTION

Glycine is the simplest amino acid; its side chain consists of just a single hydrogen atom. Because of its simplicity, it has only one form, not two (L- or d-) like other amino acids. It is an abundant amino acid and is not considered essential. Supplementation with glycine, however, has been shown to support healthy kidney and liver function as well as nervous system health [1]. Amino acids undergo reactions characteristic of both their amine and carboxylic acid functional groups. Acylation is a typical reaction of the amino group [2]. Protease- catalyzed coupling of N-protected amino acids and peptides with 4-aminoantipyrine [3]. There is a great interest in peptide-based biopolymers, since they can be applied for a variety of purposes such as drug delivery devices, scaffolds for tissue engineering and repair, and as novel biomaterials. Peptide-based polymers are common in nature and often exhibit special characteristics [4]. In the biomedical area, polymers are generally used as implants and are expected to perform long term service. This requires that the polymers have unique properties that are not offered by polymers intended for general applications. In general, the desirable polymer properties in pharmaceutical applications are film forming (coating), thickening (rheology modifier), gelling (controlled release), adhesion (binding), pH-dependent solubility (controlled release), solubility in organic solvents (taste masking), and barrier properties (protection and packaging) [5,6]. All controlled release systems aim to improve the effectiveness of drug therapy. This improvement can take the form of increasing therapeutic activity compared to the intensity of side effects, reducing the number of drug administrations required during treatment, or eliminating the need for specialized drug administration (e.g., repeated injections). Two types of control over drug release can be achieved, temporal and distribution control [7, 8]. 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, presystemic metabolism and toxicity [9, 10]. The major attributes of polymeric drug carriers are their depot effects, unique pharmacokinetics, body distribution, and pharmacological efficacy. Most medications are micro molecular in size and are relatively free to diffuse throughout the biological system. Consequently, drugs have been inherently difficult to administer in a localized, concentrated mode within the primary target tissues and organs. Polymers, however, diffuse slowly and are often absorbed at interfaces; the attachment of pharmaceutical moieties can produce a biopolymer with distinct pharmacological behavior. These polymeric drug carriers have desirable, Properties such as sustained therapy, slow release, and prolonged activity [11].

II. EXPERIMENTAL

A. Chemicals: All chemical reagents and solvents used were of analytical grade and were used without further purification and were used as received , 4-Aminoantipyrine was purchased from Samarra Company; Thionyl chloride was obtained from Fluka. Glycine and Acrylic acid were obtained from Aldrich. Dimethylformamide was purchased from Merck. Tri ethyl amine was purchased from Fluka.

B. Instrumentals: ^{1}H-NMR spectra were recorded on a Shimatzu spectrophotometer in Dimethylsulphoxide (DMSO). IR- spectra were taken on a (Shimadzu, FTI R- 8400S) Fourier Transform Infrared Spectrophotometer (4000- 400) cm-1 with samples prepared as KBr discs. Melting points were determined on callenkamp MF B-600 Melting point apparatus. UV-Vis spectra were recorded on a CINTRA5- Ultra Violet-Visible Spectrophotometer .The proposed molecular structure of the compounds were drawing by using chem. office prog, 3DX (2006).

C. Polymerization of Acrylic Acid [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 900 C, 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 500 C, produced 95% of polymer with μin = 0.46 dL /g.

D. 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%.

E. Modification of polyacrylic acid with Glycine(P2) [14]: In a round bottom flask provided with condenser (1.5g., 0.02mole) of poly acryloyl chloride was placed in 10ml of DMF, Then (1.5g., 0.02mole) of Glycine 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 (P2) was obtained with 58% as a white solid polymer.

F. Substitution of poly [2-(acetic acid) acrylamide] with4-amino antipyrine (P3) [3]: (1.5g. 0.01mole) of prepared polymer (P2), was dissolved in of dioxane : DMF mixture (10:1vol.), and (1ml) was added, the mixture was heated at 50 0C the prepared acyl chloride and (1ml) of triethylamine was added to dissolved Then (2.36g.,0.01mole) 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 (P3) was obtained with 67%. The softening point of the drug polymer (P3) was (170) ^{0}C.

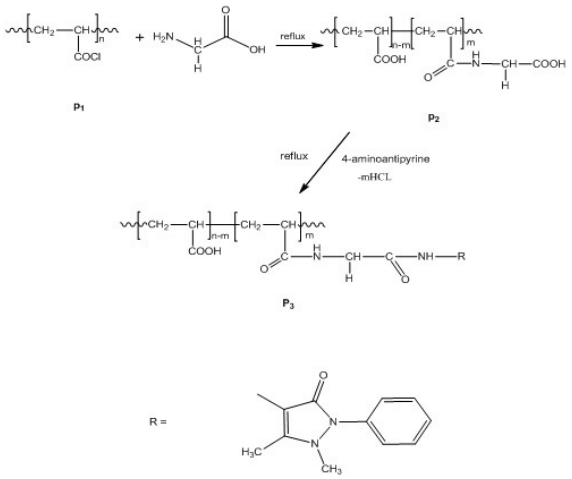
G. Determination of degree of Glycine substitution.[15]: (5mg) of prepared prodrug polymer (P3) was dissolved in 2ml of 0.1 N Na OH, the solution was heated to 700, for 15min in a water bath, cooled and the resulting solution was titrated with 0.1N HCl to determine the excess of NaOH solution.

H. Controlled Drug Release. [16-20]: (0.1g.) of dried prepared prodrug polymer (P3) 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 ^{0} .

III. RESULTS AND DISCUSSION

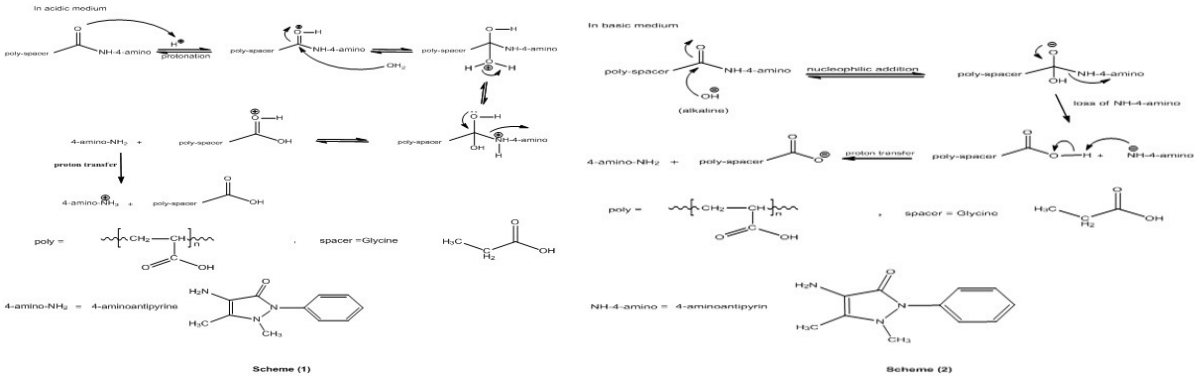
In this research the pro drug was prepared using di-functional spacer groups such as Glycine which

was inserted between the Glycine and polyacryloyl chloride. The carboxylic acid groups was reacted with NH groups of Glycine, produced amide attachment group, and the other carboxyl groups were reacted with 4-aminoantipyrine 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 by reaction of poly acrylic acid and Glycine as spacer side arm units as shown below:



The modified polymer P2 and P3 were characterized, by FTIR spectrum, Fig (1) showed the appearance of absorption at around 3400 cm-1 assigned of remained OH stretching carboxylic group 3200-3500 cm-1, and N-H stretching from an amide group, peaks at 2821-3028 cm-1 were asymmetrical and symmetrical stretching of C-H aliphatic, peak around 1700 cm-1 represents stretching vibration of C=O from carboxylic groups, the new absorption was appeared at 1627 cm-1 is attributed to (carbonyl amide).Fig (2) 1H–NMR spectrum of P2 showed the signals at δ: 2.9 ppm (CH–CO, 1H, T.), δ: 1.17 ppm (CH_2–CH, 2H, d.) polymer, δ: 3.05 ppm (CH–CO, 1H, T.), δ: 2.7 ppm (CH_2–CH, 2H, d.), δ: 3.5 ppm due to (CH_2–CO, 1H, S.), δ: 7.9 ppm (NH–CO, 1H, S.), δ 8.5 ppm (COOH, 1H, S.). [16-17]FTIR spectrum, Fig (3) of 4-aminoantipyrin Glycine acryl amide polymer P3 showed the appearance of absorption at 3398cm-1 assigned of remained OH stretching carboxylic group 3200-3500 cm-1, and 3238 cm-1 as shoulder beak due to NH amide, peaks at 2779-3003 cm-1 were asymmetrical and symmetrical stretching of C-H aliphatic, 3061cm-1 of C-H aromatic, peak around 1705 cm-1 represents stretching vibration of C=O from carboxylic groups, the absorption was appeared at 1637 cm-1 is attributed to (carbonyl amide), and the new absorption were appeared at the beak appeared at 1651 cm-1 is due to carbonyl–amide. Fig (4) 1H–NMR spectrum of polymer P3 showed the signals δ: 1.4 ppm (CH2–CH, 2H, d.) polymer, δ: 1.5 ppm (CH2–CH, 2H, d.), δ: 2.5 ppm (CH–COOH, 1H, T.) polymer, δ: 3.1 ppm (CH–CO, 1H, T.), δ: 2.7 ppm (CH2–CO, 2H, S.) of Glycine, δ: 2.9 ppm (CH3-C, 3H, S.), δ: 3.3 ppm (CH3–N, 3H, S.), δ: 7.3 ppm (2H)d. of ortho aromatic ring, δ: 7.6 ppm of (3H) T., of meta and para, of 4-aminoantipyrine, δ: 8.1 ppm (NH, 1H, S.), δ: 11.1 ppm (COOH, 1H, S.).

The remained carboxylic acid was 37% 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 P3 gave absorptions at 200 and 400 nm due to. (n-π*) and (π-π*) due to electron transition for dreg conjugation structures.[18-21] 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 :-



IV. CONCLUSION

It was concluded that the extended side arm of poly acrylic acid with suitable spacer di-functional such as Glycine 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 H2O 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.

$\Delta m = m1 - m^\circ / m^\circ \times 100$

When:-

m° is the weight of dry drug polymer.

m1 is the swallowed polymer in non-solvent

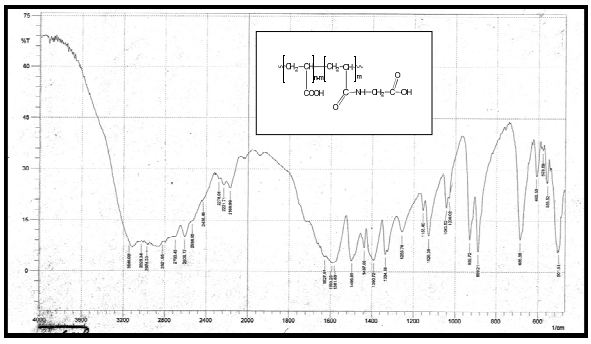


Figure 1: FT-IR spectrum of drug polymer (P2)

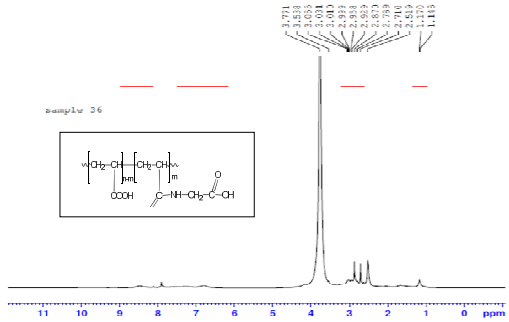


Figure 2: 1H-NMR spectrum of drug polymer (P2)

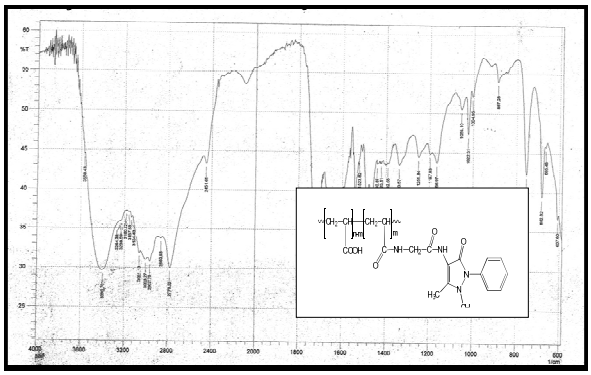


Figure 3: FT-IR spectrum of drug polymer (P3)

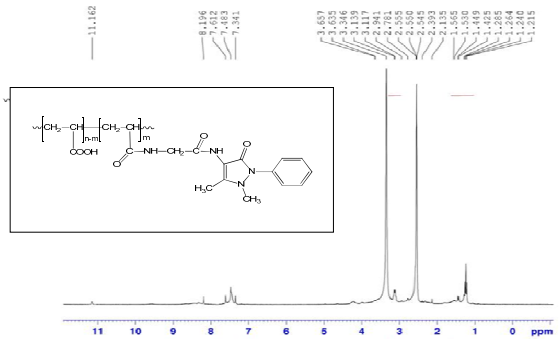


Figure 4: 1H-NMR spectrum of drug polymer (P3)

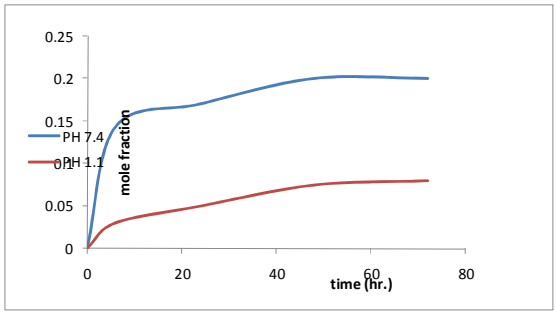


Figure 5: Drug release of P3 in pH 1.1 and 7.4 at 37°C

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