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# Synthesis and Characterization of Gelatin-G-Poly (Acryloyl Amide) Proflavine and Controlled Release Study

Fiyral Mohammad Ali [1*] Taghreed Hashim.AL-Noor [2] and Saif Mohsin Ali[3]

1. & 3 AL-Mustansiriyah University, College of Science ,Baghdad -Iraq

2. .Ibn -Al-Haithem College of Education for pure science, Baghdad University

* E-mail of the corresponding author: *Abood121996@yahoo.com or*

drtaghreed2@gmail.com *&Saifaltaei87@gmail.com*

**Abstract**

Gelatin-grafted N- proflavine acryl amide was synthesized through two steps; firstly the Gelatin was grafted with acrylic acid free radically using Ammonium per-sulfate at 60℃, Then it was modified to its corresponding acyl chloride derivation, second step included the substitution with amino group of proflavine, in this research Gelatin was used as a natural nontoxic, water soluble polymer as a drug carrier.

The prepared pro drug polymer was characterized by FTIR and $^{1}$H-NMR spectroscopies, Controlled drug release was studied in different pH values at 37℃. Many advantages were obtained comparing with other known methods.

**Keywords:** *Gelatin, Acrylic acid, Proflavine and Gelatin,.and* pro-drug polymer

## 1. Introduction

Today, the whole world is increasingly interested in natural drugs and excipients. Natural materials have advantages over synthetic materials because they are nontoxic, less expensive and freely available. Furthermore, they can be modified to obtain tailor made materials for drug delivery systems allowing them to compete with the synthetic products that are commercially available [1].Gelatin has multiple functional properties. Gelatin swells in cold water and is completely soluble in hot water. A temperature of about 60 ℃ is necessary in order to release the ordered structure of gelatin in its dry state. Gelatin is a biomaterial with the above mentioned essential properties. Generally, crosslinking in gelatin is used in various purposes such as gelatin swelling, and gelatin hydrogels as biodegradable implants to deliver small and macromolecular drugs. Recently, attention has been focused on employing gelatin substrate to produce hydrogels with a specific response to a biological environment [2-3]. Polymers play a vital role in the drug delivery. So, the selection of polymer plays an important role in drug manufacturing. But, while selecting polymers care has to be taken regarding its toxicity, drug Compatibility and degradation pattern. By this review, we can say that natural polymers can be good substitute for the synthetic polymers and many of the side effects of the synthetic polymers can be overcome by using natural polymers [4]. In some cases the best approach to prepare polymeric carriers of pharmaceutically active compounds is to modify preformed polymers. This method offers the advantage of the availability of a wide range of polymer types and also simplicity of the reactions. The employing of hydrophilic polymers with biodegradable backbones led to the preparation of polymeric systems for oral or topical administration [5]. The basic aim of pro-drug 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 [6-8]. 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 [9-10].

## 2.Experimental

### 2.1. Materials And Instruments

Gelatin was purchased from Merck; Thionyl chloride was obtained from Fluka. acrylic acid was 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 (4000-400$cm^{-1}$) 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.

### 2.2. Copolymerization Of Acrylic Acid With Gelatin.

Preparation Of Graft Co-Polymerization Of Acrylic Acid With Gelatin Backbones **(S1).**

(2g.) of gelatin was dissolved in10ml double distilled water. The mixture was heated in water bath then a definite amount of Ammonium per-sulfate solution (2g.) in 5ml ($H_2O$) was added to gelatin solution and was allowed to stir for (15 min), then (1.5 g.) of acrylic acid was added simultaneously to the mixture with continuously stirred about (10 min). The reaction mixture was allowed to cool to ambient temperature; the product was washed with ethanol, dried in oven at 50℃ for 1 hr. The Pale yellow polymer ($S_1$) was obtained with 69%. The softening point of the drug polymer ($S_1$) was (105-115) ℃.

Substitution Of Graft Poly Acrylic Co-Gelatin With Proflavine (S2).

(1.5g.) of prepared polymer ($S_1$) was dissolved in dioxane: DMF mixture (10:1vol.), and (1ml) of thionyl chloride ($Cl_2OS$) was added, the mixture was heated at 50℃ the prepared acyl chloride and (1ml) of triethylamine was added to dissolved (2g.) proflavine the mixture was refluxed with stirring for 2hrs., the solvent was evaporated under vacuum; the product was washed with ether and dried at room temperature. The red polymer ($S_2$) was obtained with 80%. The softening point of the drug polymer ($S_2$) was (223-227) ℃.

### 2.3. Determination Of Degree Of Proflavine Substitution. [11]

5mg of prepared pro-drug polymer ($P_2$) 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.

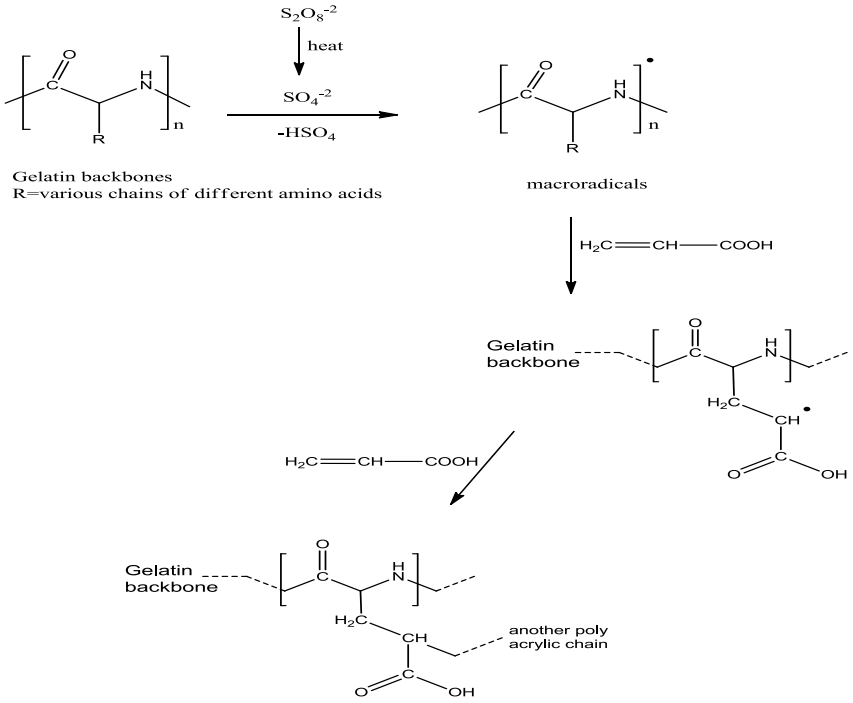
### 2.4. Controlled Drug Release. [12-16]

0.1g. of dried prepared pro-drug polymer ($P_2$) 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. (4). Showed controlled proflavine release in different pH values at 37℃.

**Results And Discussion**

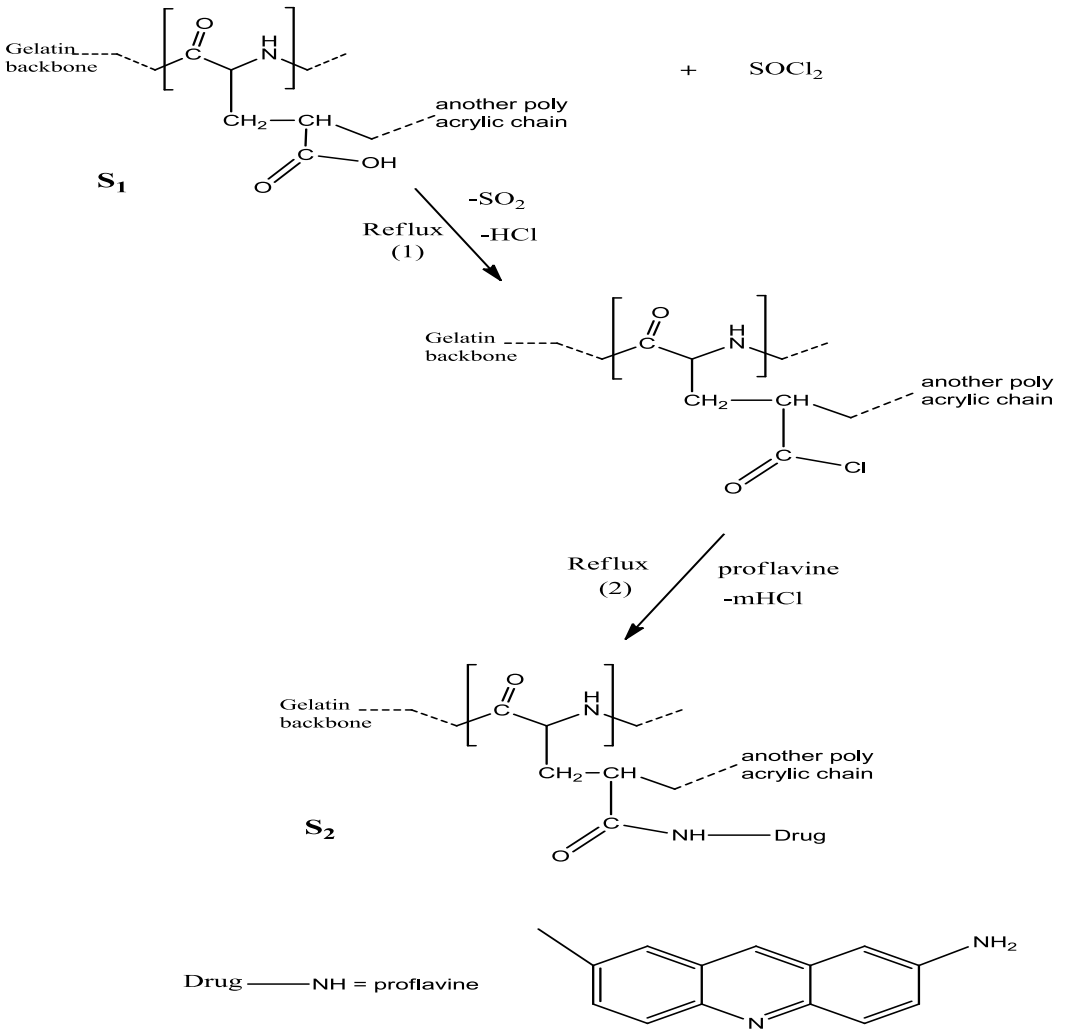
The acrylic acid was simultaneously grafted onto Gelatin backbones in a homogeneous medium using ammonium per-sulfate as a radical initiator.




**SCHEME (1):The synthesis Route of The Gelatin Backbones (S1)**

The first step, the thermally dissociating initiator, i.e. Ammonium-per sulfate, is decomposed under heating to produce sulfate anion-radical. Then, the anion-radical removed hydrogen from one of the functional groups in side chains (R) of the substrate to form corresponding radical. So, this initiated monomer grafting onto Gelatin backbones led to macro-radicals a graft copolymer [17]. The drug polymer was Substitution of Gelatin-g-poly acrylic acid ($S_1$) with proflavine. Gelatin-g-poly acrylic acid converted to Gelatin-g- Poly acryloyl chloride, [18]. Gelatin-g- Poly acryloyl chloride reacts with amine to form an amide, as explained below:-




**SCHEME (2) :** The Synthesis Route Of OF GRAFT POLY ACRYLIC CO-GELATIN WITH PROFLAVINE **(S2)**

The modified polymer ($S_1$) and ($S_2$) were characterized, by FTIR spectrum, Fig(1) showed the appearance of absorption at around 3400 $cm^{-1}$ assigned to the remained –OH stretching carboxylic group of poly acrylic acid, as exhibit a broad bond at 3200-3500 $cm^{-1}$ due to the NH-amine of Gelatin, 2852-2926 $cm^{-1}$ were asymmetrical and symmetrical stretching of C-H aliphatic, 1651$cm^{-1}$ represented stretching vibration of C=O amid to, 1701 $cm^{-1}$ due to carbonyl of carboxylic group of unreacted poly acrylic acid, the bands were observed at 1452 $cm^{-1}$ and 1554 $cm^{-1}$ can be attributed to C=O stretching (symmetrical and asymmetrical modes) in carboxyl amide functional groups of substrate backbone of Gelatin, and abroad bond at 2190 $cm^{-1}$ which correspond to the presence of C-N bond.

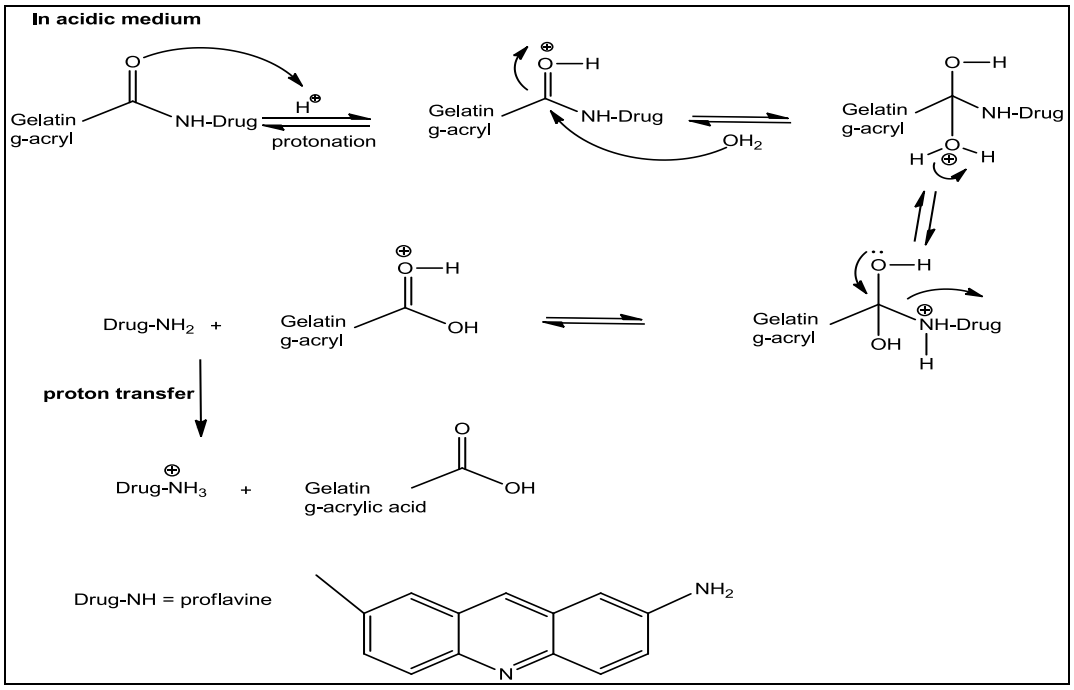
FTIR spectrum, Fig.(2) of proflavine polymer $S_2$ showed the appearance of absorption at 3441$cm^{-1}$ assigned to the remained –OH stretching carboxylic group of poly acrylic acid, as exhibit a broad bond at 3200-3500 $cm^{-1}$ due to the NH-amine of Gelatin, 2773-2929 $cm^{-1}$ were asymmetrical and symmetrical stretching of C-H aliphatic, 3050 $cm^{-1}$ of C-H aromatic, 1630 $cm^{-1}$ represented stretching vibration of C=O amid to, 1714 $cm^{-1}$ due to carbonyl of carboxylic group of unreacted poly acrylic acid, the bands were observed at 1471 $cm^{-1}$ and 1558 $cm^{-1}$ can be attributed to C=O stretching (symmetrical and asymmetrical modes) in carboxyl amide functional

groups of substrate backbone of Gelatin, and abroad bond at 2100 $cm^{-1}$ which correspond to the presence of C-N bond, and the new absorption were appeared at the beak appeared at 1653 $cm^{-1}$ is due to carbonyl−amide. [19]

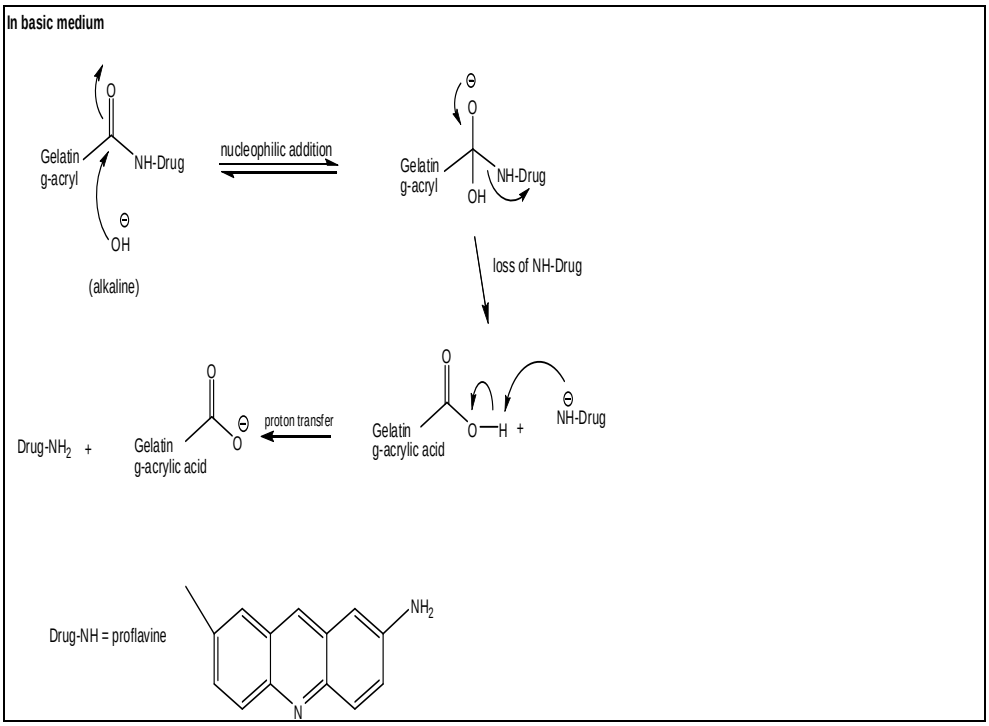
Fig (3) $^{1}H-NMR$ spectrum of polymer $S_2$ showed the signal δ: 1.5 ppm ($2CH_2-CH$, 2H, d.) polymer, δ: 2.2 ppm (CH−COOH, 1H, T.), δ: 2.4 ppm (CH−CO,1H, T.), 2.7 ppm (C−NH,1H, d.) δ: 2.8 ppm (CH−NH, 1H, T.), of Gelatin, δ: 6.9 ppm ($NH_2$, 2H, S.), δ: 7.2 ppm (NH, 1H, d.), δ: 7.6- δ:7.9 ppm (3H)d. of ortho aromatic ring, δ: 8.01-9.01 ppm of (4H) T., of meta and para, δ: 11.3 ppm (COOH, 1H, S.). [20,21]

The remained carboxylic acid was 38% 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 Mefenamic acid groups enhanced the using as prodrug polymers. The UV. Spectra of polymer ($S_2$) gave absorptions at 200 nm and 350 nm due to. (π -π*)(C=C) and (n-π*)*(C=N) due to electron transition for drug conjugation structures. [22]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 mechanism in **Schemes (3) & Scheme (4).**




**Scheme (3) Hydrolysis of ($S_2$) in acidic medium**




**Scheme (4) Hydrolysis of ($S_2$) in basic medium**

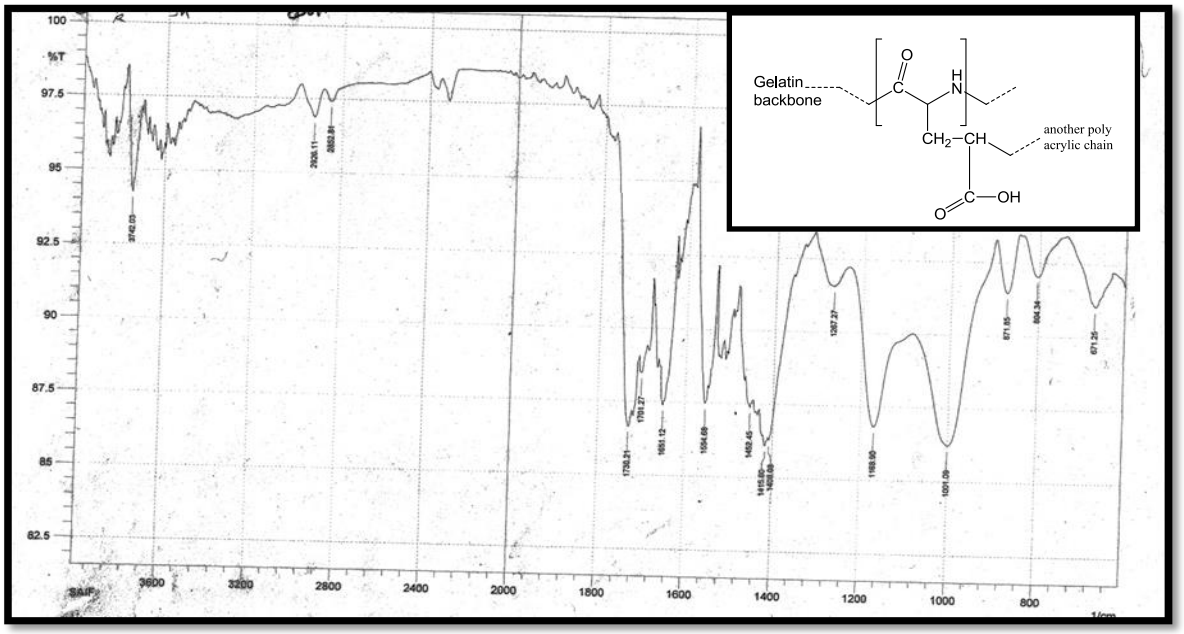



**Fig. (1) FT-IR spectrum of drug polymer ($S_1$)**

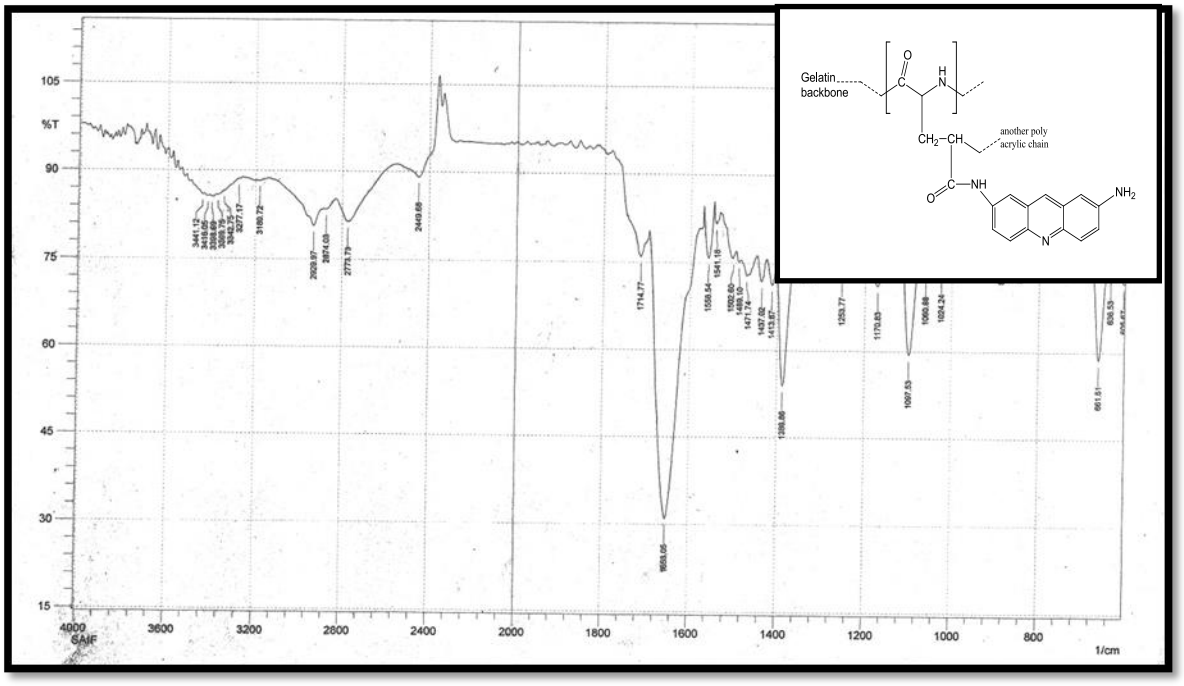



**Fig. (2) FT-IR spectrum of drug polymer ($S_2$)**

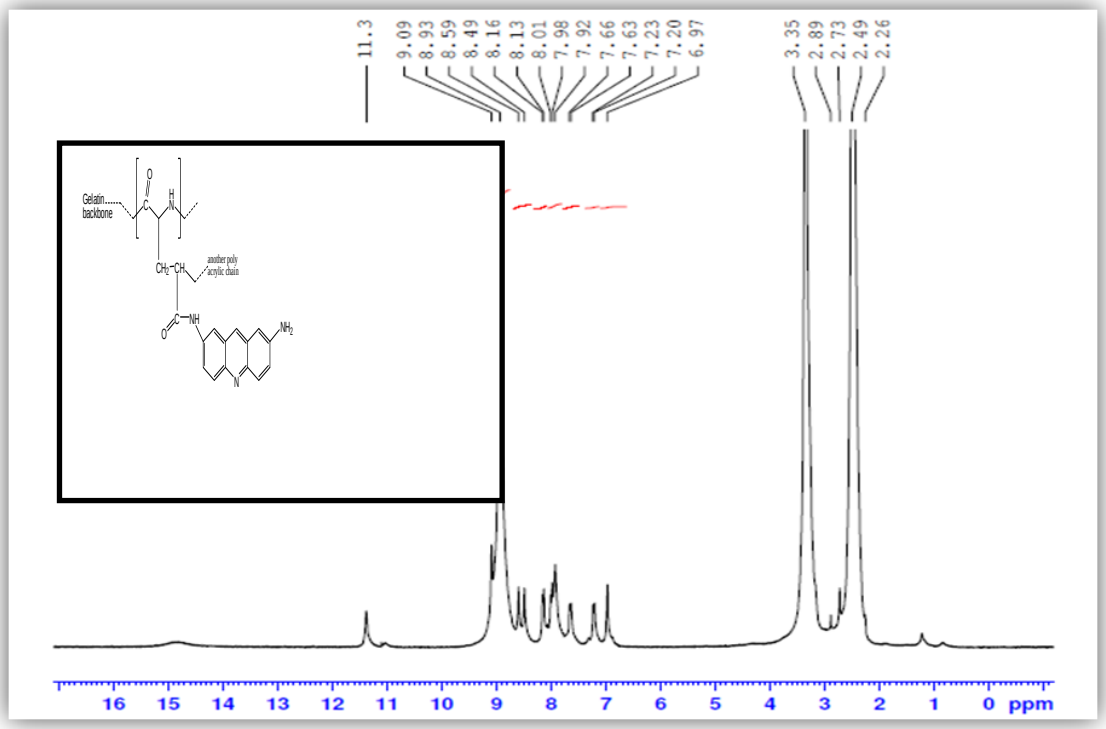



**Fig. (3) $^{1}$H-NMR spectrum of drug polymer ($S_2$)**

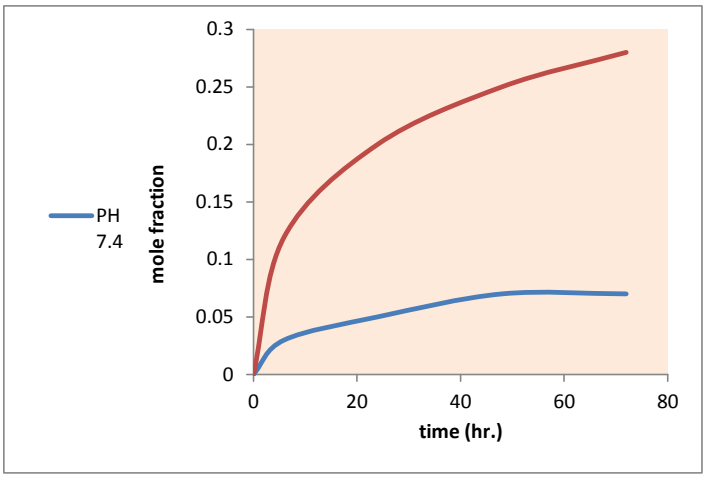



**Fig (4) Drug release of $S_2$ in pH 1.1 and 7.4 at 37 ℃.**

**References**

1. Sandip G., Maru, Sapra B., Prakash, Savaliya B., Dharmesh, Sameer A., Agham, Nikunj J., Aghera, (2012), PhTechMed, Vol. 1, Pp. 2278-1099, ( 2).
2. Einerson N. J., Stevens K. R., and Kao W. J. (2003)., Biomaterials, Vol. 24, P. 509, (2003).
3. Burugapalli K., Bhatia D., Koul V., and Choudhary V., (2001). J. Appl. Polym. Sci. Vol. 82, P. 217.
4. Satturwar P.M.,Fulzele S.V., Dorle A.K., (2003).), Pharm. Sci. Tech., Vol. 4, Pp. 1-6.
5. Llan-is F. W., Linger It. S., and Wise D. T., Eds(1984). CRC Press, Boca Raton, Fla,(Medical Application of Controlled Release), Vol.1, Pp.103-128.
6. Rautio J., Kumpulainen H., Heimbach T., Oliyai R., Oh D., Järvinen T., and Savolainen J., (2008). Nat Rev Drug Discov, Vol. 7, Pp. 255–270 .
7. Stella VJ., (2010). J. Pharm Sci., Vol. 99, P. 4755–4765.
8. Testa B., Curr Opin Chem Biol ,(2009).,Vol. 13, Pp. 338–344.
9. Langer R., (1998). Nature, Vol. 392, P. 5.
10. Brouwers J. R. B., J. Pharm., (1996). World Sci., Vol. 18, P.153.
11. Soudabeh D- and Ali A. (1990) , Iranian polym, J. Vol.,15.(1). pp. 103–145
12. Mahkam M., and Doostie L., Siadat SOR., (2006). Inflammo pharmacology. Vol. 14, Pp. 72-75.
13. Mahkam M., and Allahverdipoor M., (2004)., J Drug Target, Vol. 12, Pp. 151-156.
14. Fang J, Nakamura H and Maeda H, (2011). Adv Drug Deliv Rev, Vol.63(3),
15. Pp 136–151.
16. Ronald A. Siegel and Michael J. Rathbone., ( 2011) (Overview of Controlled Release Mechanisms), Controlled Release Society. Vol. 28 • ( 5) .
17. Debjit Bhowmik, Harish Gopinath, Pragati B., Kumar S., Duraivel K. P. and Sampath Kumar. (2012). The pharma innovation Controlled Release Drug Delivery Systems. J., Vol. 1, P. 10 .
18. Jenkins DW., and Hudson SM., (2001). Chem. Rev., Vol. 101, Pp. 3245-3273.
19. Khudheyer J.K., (2012) "Synthesis and study of some novel polymers containing different drug substituted groups", Ph.D. Thesis, University of Babylon, College of Science, Chem.

20. Silverstein, R. M., and Webster F. X., (1998) " Spectrometric Identification of Organic Compounds", 6th Edn. Wiley, New York.

21.Crew P., Rodringuez J. and Jaspars M., (1998). "Organic structure analysis", Oxford University Press, New York.

22. Taghreed.H.AL-Noor Lekaa K. Abdul Karim, (2015). Chemistry and Materials Research Vol.7 (3), ,pp32-39.

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