Int. J. Chem. Sci.: 13(2), 2015, 725-736
ISSN 0972-768X
www.sadgurupublications.com

CYCLOPOLYMERIZATION OF DIALLYLAMINE AND ITS CONDENSATION WITH CARBOXYLIC DRUGS

KHUDHEYER JAWAD KADEM*

Department of Chemistry, College of Science, Babylon University, BABYLON, IRAQ

ABSTRACT

In this study, the polydiallylamine (P_1) was prepared by free radical cyclopolymerization then the three new drug carriers cyclopolymers (P_2-P_4) were prepared according to substitution polymer P_1 to its amine of prepared diallylamine polymer P_1 to its corresponding N-drug through amide attachments such as N-Ibuprofine, ciprofloxacin and mefenamic acyl chloride, which formed amide bonds. This can be hydrolysed in different pH values at 37°C, as controlled drug release to obtain a sustained drug release. This can lead to improve their activities as a therapeutic material and to prevent any side effect of the drugs. The cyclopolymers (P_1-P_4) were characterized by Fourier Trans Infrared (FTIR), Proton Nuclear magnetic resonance ^{1}H-NMR and UV-Vis spectroscopies. Additionally, intrinsic viscosity was measured and all physical properties were measured.

Key words: Cyclopolymerization, Diallylamine, Condensation.

INTRODUCTION

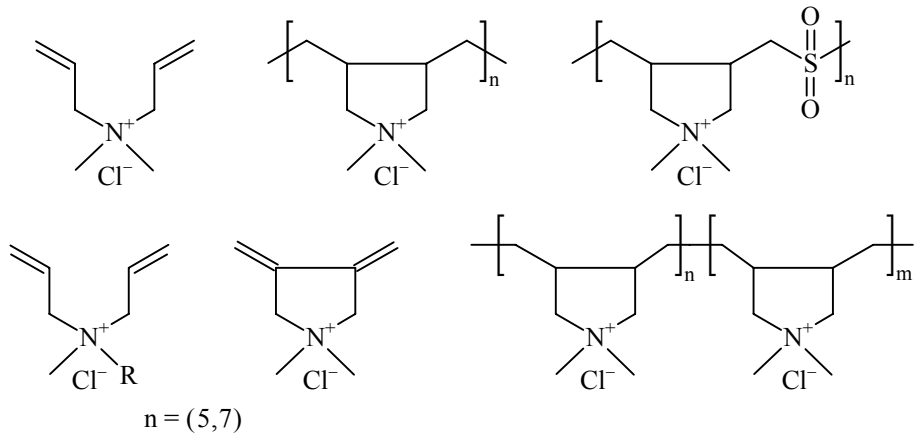
In 1951, Butler was reported that diallyl quaternary ammonium salts can be polymerized in the presence of catalytic quantities of tert-butylhydroperoxide to form water-soluble, non cross linked polymers. A characteristic feature of the free-radical polymerization of allyl monomers is a cyclic intra and intermolecular polymerization mechanism[1]. Polymers derived from radical cyclopolymerizations of 1, 6-dienes have two possible repeating cyclic structures, five- and six-membered rings. A six-membered ring and its radical formed during the propagation step could be more stable than a five-membered ring and its radical formed, respectively. However, a five-membered ring is found quite often as a repeating unit in the polymers derived from 1,6-dienes[2]. Diallyl p-toluene sulfonamide gave cyclopolymers consisting of five-membered repeating units in the mainchain. In these monomers, two allyl groups are attached to the same atoms and the close proximity of the two allyl groups induces cyclization. It is interesting to note that hydrochloride salts of N-alkyl, N,N-diallyl

*Author for correspondence; E-mail: khudheyerbabel@yahoo.com

amines have been reported to form water-soluble polydiallylamine hydrochlorides by gamma irradiation or persulfate initiation. On the other hand, these monomers in their free base tend to form gelduring polymerization under the same conditions[2,3].

N,N-diallyl morpholinium bromide has been synthesized in high yields (96%) by stepwise condensation of morpholine with allyl chloride and allyl bromide. Polymerizability of the quaternary ammonium salt has been studied using various solvents and radical initiators such as $K_2S_2O_8$ and t-butyl hydroperoxide[2,3].

Cyclopolymerization of hydrophilic and hydrophobic diallylmonomers in such high concentrations has been reported to yield random rather than microblocky copolymers even though the hydrophobic monomer possesses surfactant properties[3-6].



The cyclopolymerizations of diallyl quaternary ammonium salts have been thoroughly investigated[7]. The main interest is the potential utility of the resulting polymers in industrial and pharmaceutical applications[8] such as layer-by-layer assembly[9-11], quantum dots, nanoparticle stabilization, paper industry[12], water treatment[13], metal electroplating, corrosion inhibition, cosmetic and hair treatments, antiperspirants, anion-exchange resins, antistatic agents, protein encapsulation, hydrogel formation[10], antibacterial properties and drug delivery applications. The best studied of these compounds are the diallyldimethylammonium salts. In contrast, little work has been performed on the cyclopolymerization of the alkyldiallylammonium derivatives[14]. One route is to prepare modified ODNs is based on the cyclopolymerization of quaternary diallylammonium salts with nucleic bases attached. Poly(diallylquaternary ammonium salts) contain permanent positive groups that render them insoluble in nonpolar organic solvents and hence limit their utility in such applications. Incontrast, polymers prepared from alkyldiallylammonium salts could be deprotonated to yield the corresponding neutral polymers[12].

Novel methods for the preparation of modified oligodeoxy nucleotides (ODNs) have been actively pursued due to their potential use in therapeutic and diagnostic applications. An important prerequisite of synthetic ODNs is their stability against biological nucleases that result in the cleavage of the phosphodiester backbone in RNA and DNA[13]. Extensive work has been conducted to modify or replace the phosphodiester backbone, furanose ring, nucleicbase or a combination of two or more[14,15].

EXPERIMENTAL

Materials

Ibuprofen, mefenamic acid and ciprofloxacin were purchased from Samarra drugs company, diallylamine, dioxane, pyridine, ethanol, dimethyformamide, diethylether were obtained from Sigma and Aldrich chemical Company.

Measurements

Melting points were measured on a Mettler Toledo FP62 apparatus and are uncorrected. ^{1}H-NMR spectra were determined in deuterated DMSO with tetramethylsilane (TMS) as the internal standards on a Bruker AV 300 MH spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to TMS. Infrared spectra were recorded as KBr pellets using a Nicolet 4700 FTIR spectrometer. The FT-IR spectra are reported in wave numbers (cm^{-1}). The UV-VIS absorption spectrum was measured using Shimatzu spectrometer.

Polymerization of Diallylamine[14,15]

In a screw capped polymerization bottle (5 g) of Diallylamine (monomer) was dissolved in 20 mL of Dioxane, 0.05% of the monomer weight of Dibenzoyl peroxide was added as an initiator. The bottle was flashed with nitrogen for few mins. The solution was maintained at 90^0C using water bath for 4 hrs. The solvent was evaporated under vacuum, the brown polymer was obtained, washed three times with ether, Dried in a vacuum oven at 50^0C. The yield was 60% and the intrinsic viscosity was 0.15 dl/g.

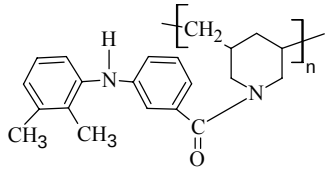
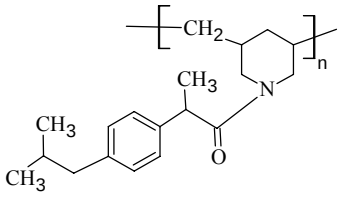
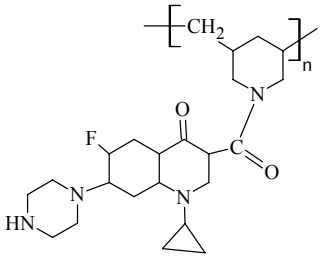
Conversion of carboxylic acid group of drug to its acyl chloride derivative[16]

A thionyl chloride (5 mL, 0.04 mol) was added gradually to (0.04 mol) of dissolved a drug such as Ibuprofin, Ciprofloxacin and Mefenamic in (20 mL) of dimethylformamide the mixture was stirred using ice bath then heated to 60^oC for 1 hr and the yellow product was collected and washed with diethylether.

Substitution of poly diallylamine[16]

A reaction mixture of poly diallylamine (1 mole) and substituted with acyl chloride drugs (1 mole) was dissolved in dioxane (10-15 mL) with 2-3 drops of pyridine and heated in a water bath at 70-80^{o}C for approximately 60-90 min. The process of the reaction completion was followed by thin layer chromatography (TLC). The product was isolated and dried in a vacuum oven before weighting. The physical properties of prepared Poly[N-Drug diallyl amine] were listed in Table 1.

Table 1: Physical properties of prepared prodrug polymer (P_2-P_4)

S. No.	N-Drug polymer	Color	Conversion (%)	n_{in} (dl/g)
P_2		Yellow	65	0.41
P_3		Brown	71	0.54
P_4		Brown	64	0.6

Controlled drug release

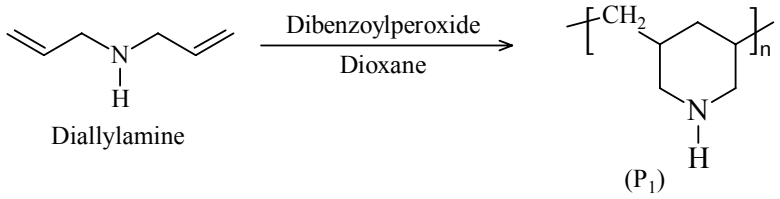
To study the drug delivery for prepared drug polymers, 0.1 g was immersed continuously in 100 mL of solution at 37^{0}C. In order to follow the delivery time, the wavelength of λ_{max} was measured at different times and different pH values using UV spectrometer. The maximum amount of drug available for release was determined by the relations between weight lose % as function of the time.

The study of drug condensed polymers Fig. 7 showed the effect of pH values on the rate of release and profiles of weight % present in the sample versus time at pH 4 and 10 at

37^0C. The amides were hydrolyzed in the presence of base were more cleavage produced the Ibuprofine, Ciprofloxin, Mefenamic acid and Diallyl amine units.

RESULTS AND DISCUSSION

The cyclopolymerization of diallylamine monomer using dibenzoylperoxid as an initiator was carried out as illustrated in the following Equation (1):



Diallylamine

(P_1) …(1)

FTIR spectrum of **P_1** is shown in Fig. 1. It shows a stretching frequency at 3286 cm^{-1} referring to NH secondary amine, at 1648, 1550 cm^{-1} refereed to NH bending, disappearance band at 1610 -11640 cm^{-1} refereed the (C=C) that mean converted alkene to cycloalkane, at 2804, 2922 cm^{-1} refereed CH_2 of alkane.

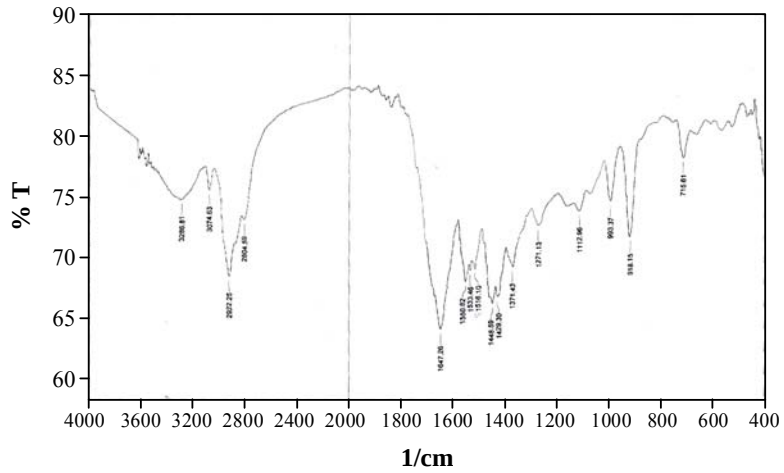
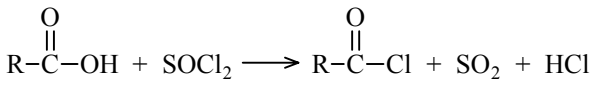


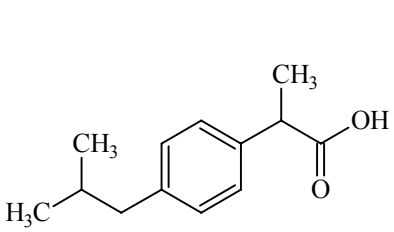
Fig. 1: FTIR spectrum of cyclopolymerization of diallylamine

The second step included conversion of the carboxylic group of the drug (Ibuprofen, Mefenamic acid, Ciprofloxacim) to their acyl chloride group using thionyl chloride, because the OH group of acid is less reactive in comparison with acid chloride, the (Cl^-) group is a better leaving group in comparision with ($^-$OH) group this step is illustrated in the reaction Equation (2).

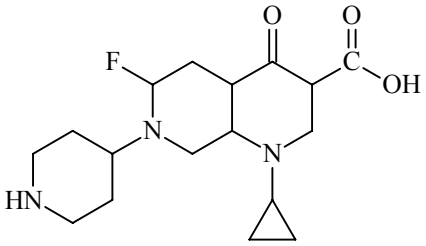


…(2)

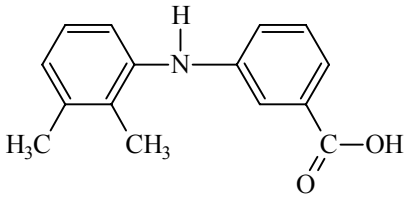
RCOOH = Ibuprofen, mefenamic acid, ciprofloxacin



Ibuprofen

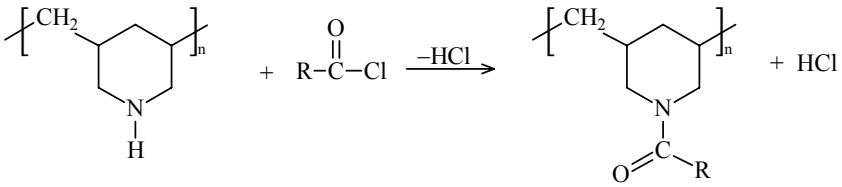


Ciprofloxacin



Mefenamic acid

The prodrug was prepared using functional group of polyallylamine with drugs such as (Ibuprofen, Mefenamic acid, Ciprofloxacim) as their acyl chloride. Amide group was formed that mean modified polymer P_1 as shown in Equation (3).



…(3)

(P_1) (P_2 or P_3 or P_4)

$R-\overset{\overset{O}{\|}}{C}-Cl$ = Mefenamic acylchloride or ibuprofenyl chloride or ciprofloxinylchloride

The prodrug polymer **P_2** (poly-N-diallyl Mefenamate) was characterized by FTIR spectrum. Fig. 2 showed the peak around 3290 cm^{-1}, which assigned to the NH amide (stretching) of mefenamic drug, 1631 cm^{-1}, which assigned to the NH (bending) of mefenamic drug, disappearance peak at 3286 cm^{-1} that mean converted secondary amine

of polymer to tertiary amine substituted, 1685 cm^{-1} assigned to the C=O amide formation, 3050 cm^{-1} assigned to CH aromatic ring of mefenamic drug. ^{1}H-NMR spectrum of polymer P_2 Fig. 3 indicates the conversation of Mefenamic acid to Mefenamic acylchlorid was complete as indicated by the absence of the hydroxyl proton signal in the ^{1}H-NMR spectrum at 11 ppm, δ (8) ppm (CH, aromatic ring in mefenamic drug), δ (3.5) ppm (NH, mefenamic drug), δ (1-2) ppm (CH_3, mefenamic drug, CH_2 of polymer P_2).

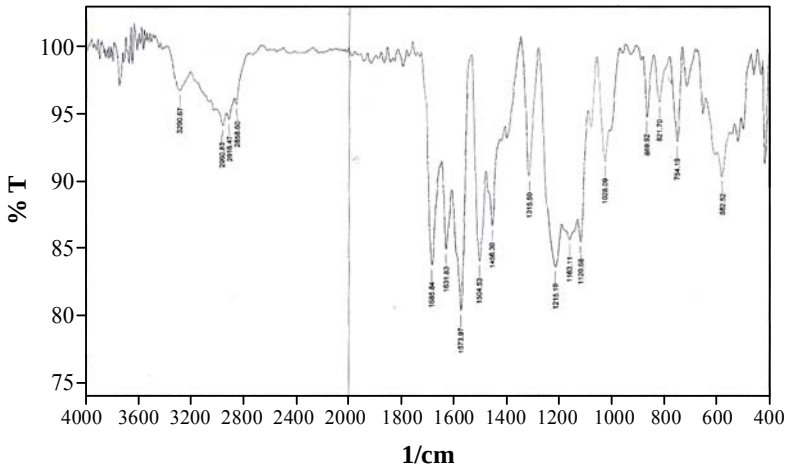


Fig. 2: FTIR spectrum of poly-N-diallyl Mefenamate (P2)

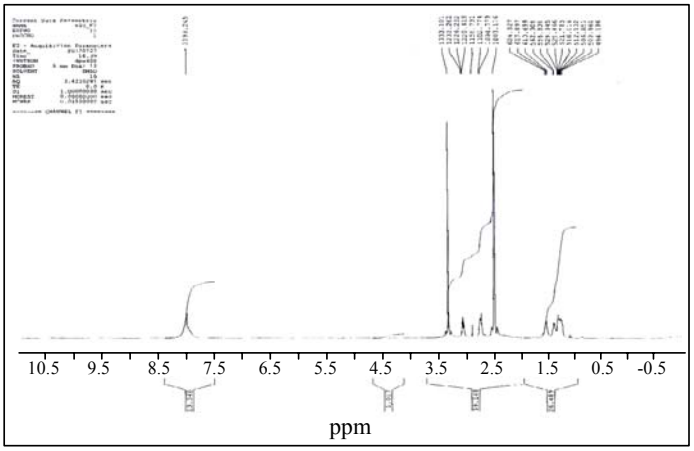


Fig. 3: ^{1}H-NMR spectrum of poly-N-diallyl Mefenamate (P_2)

Fig. 4 shows FTIR spectrum of poly(N-diallyl Ibuprofen) (**P_3**) peak 3093 cm^{-1} of C-H aromatic ring of drug Ibuprofen, New absorption was appeared at 1718 cm^{-1} is attributed to C=O amide, 2955-2872 cm^{-1} due the CH_3 group.

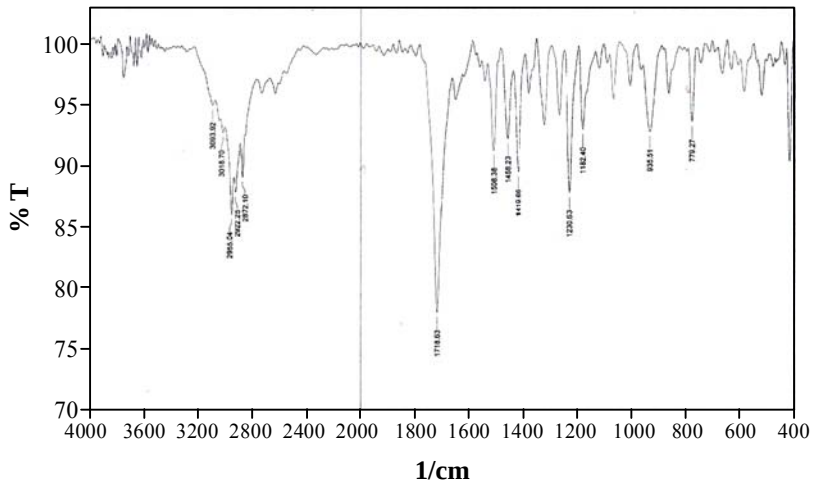


Fig. 4: FTIR spectrum of poly(N-diallyl Ibuprofen) (P_3)

Fig. 5 shows FTIR spectrum of poly(N-diallyl Ciprofloxacin)(**P_4**) peak 3379 cm^{-1} of NH of ciprofloxacin drug, the new absorption was appeared at 1631 cm^{-1} is attributed to C=O amid formation between the polymer and Ciprofloxacin.

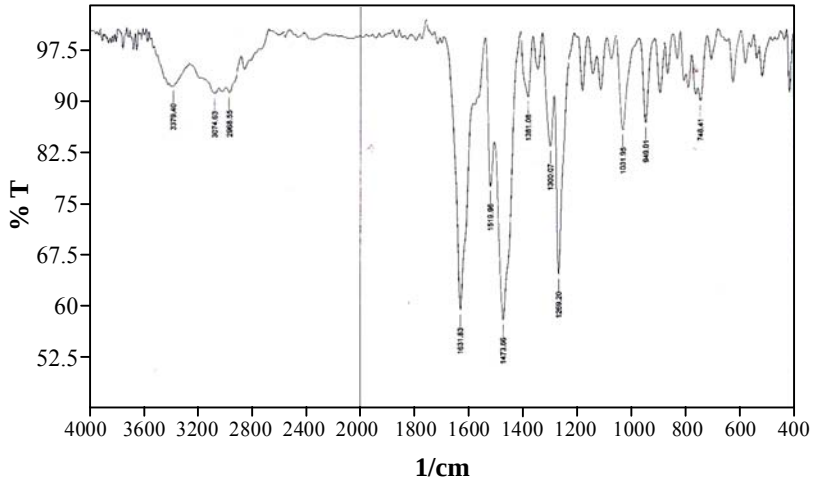
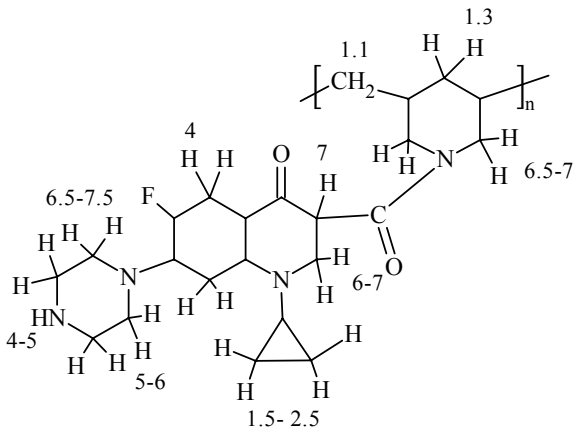
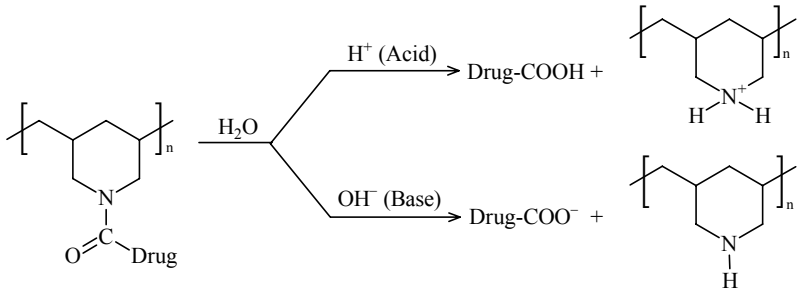


Fig. 5: FTIR spectrum of poly(N-diallyl Ciprofloxacim)(P_4)

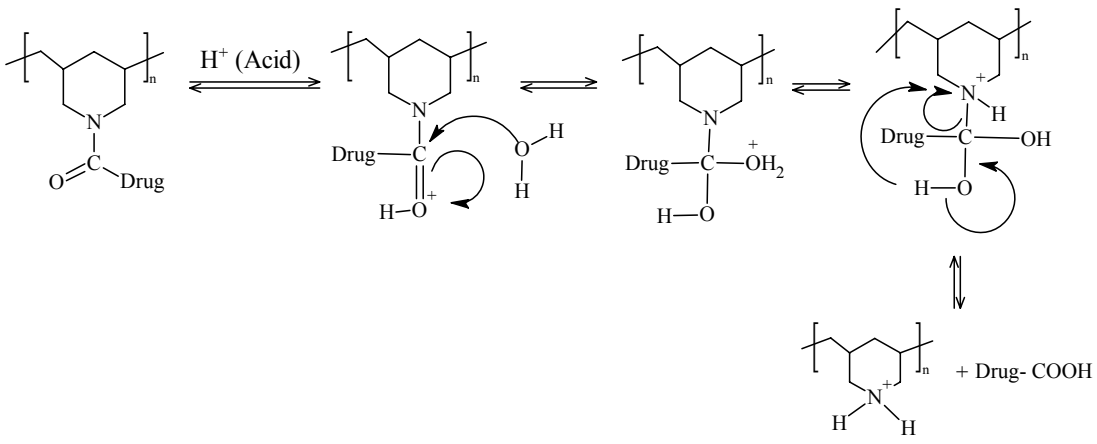
Fig. 6 shows ^{1}H-NMR spectrum, which indicated the absence of the hydroxyl proton at 11-12 ppm of carboxylic acid group in Ciprofloxacin that mean polymercarrier the drug (Ciprofloxacin), found different peak of proton that mean different environments of proton included of poly(N-diallyl Ciprofloxacin) (**P_4**) as shown in the polymer structure below.

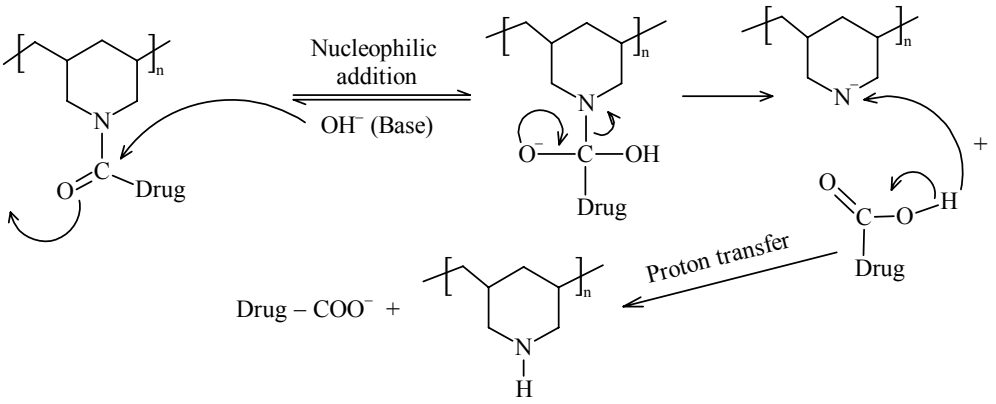


Modification of the prepared cyclopolymer through secondary amine with prepared acylchloride drug derivatives could enhanced the sustained release for long term to minimized the disadvantages of parent drug, through hydrolysis of amide group as illustrated in the following mechanism.



Drug -COOH = Ibuprofen , Mefenamic acid, Ciprofloxacin





(Mechanism of hydrolysis of drug carrier cyclopolymer)

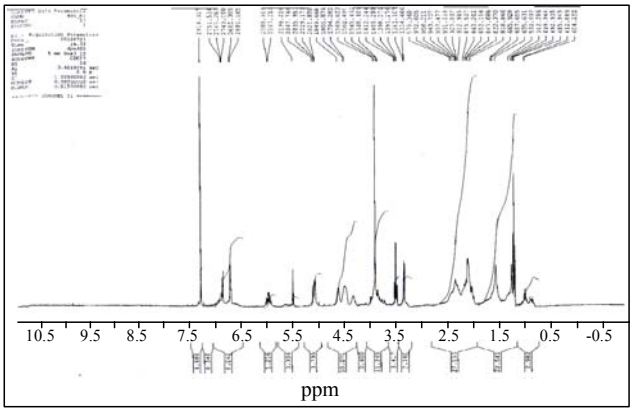


Fig. 6: ^{1}H-NMR spectrum of poly(N-diallyl Ciprofloxacim)(P_4)

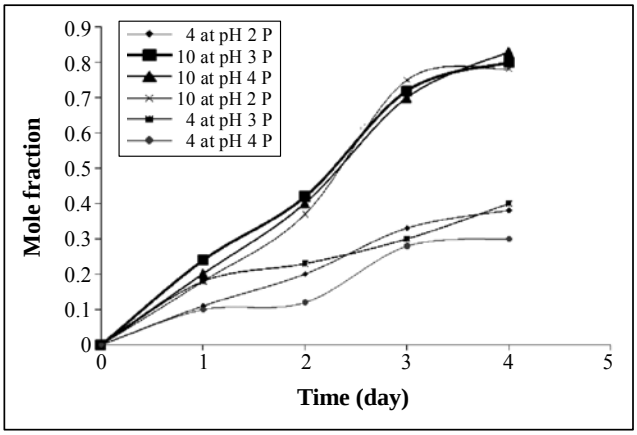


Fig. 7: Controlled drug release of (P_2-P_4) at pH 4, pH 10 at 37^{0}C

CONCLUSION

We concluded that the rate of hydrolysis as in Fig. 7 controlled release of drug in different pH values at 37°C. Hydrolysis of amide bond showed the controlled drug release of polymers (P_2-P_4) in basic medium, which indicated higher hydrolysis rate than acidic medium due to more nucleophilic attack of –OH to carbonyl of amide groups compared with H_2O molecule and proton (H^+).

REFERENCES

1. D. Gao, J. Ma and B. Lv, Characterization and Properties of Polymer Diallyldimethylammonium Chloride/Montmorillonite Nanocomposite Tannage National high-tech Research and Development Plan (863 Plan) (Item No.: 2008AA032311).

2. N. Bicak and B. Filiz Senkal, (Synthesis and Polymerization of N,N-diallyl Morpholinium Bromide) European Polymer J., **36**, 703-710 (2000).

3. Y. Umar, H. A. Al-Muallema, B. F. Abu-Sharkhb and S. K. Asrof Ali, Synthesis and Solution Properties of Hydrophobically Associating Ionic Polymers Made from Diallylammonium Salts/sulfur Dioxide Cyclocopolymerization, Polymer, **45**, 3651-3661 (2004).

4. G. B. Butler and C. H. Do, In, W. Shalaby, C. L. McCormick, G. B. Butler, Editors, Water-soluble Polymers, ACS Symposium Series, 467. Washing, DC: ACS, 151 (1991).

5. K. J. Miller and S. D. Das, Antisense oligonucleotides: Strategies for delivery, Pharm. Sci. Technol, **1**, 377-386 (1998).

6. R. M. Ottenbrite and W. S. Ryan, Jr. (Cyclopolymerization of N, Ndialkyldially Lammonium Halides: A Review and use Analysis, Ind. Eng. Chem. Prod. Res. Develop., **19**, 528-532 (1980).

7. D. H. Solomon and D. G. Hawthorne, (Cyclopolymerization of Diallylamines), J. Macromol. Sci. Rev. Macromol. Chem., **C15**, 143-164 (1976).

8. F. Rullens, P. Y. Vuillaume, A. Moussa, J. L. Habib-Jiwan and A. Laschewsky, Ordered Polyelectrolyte Multilayers, 7. Hybrid Films Self-Assembled from Fluorescent and Smectogenicpoly (Diallylammonium) Salts and Delaminated Clay), Chem. Mater., **18**, 3078-3087 (2006).

9. S. A. Ali and M. T. Saeed, Synthesis and Corrosion Inhibition Study of some 1,6-hexanediamine-based N,N-diallyl Quaternary Ammonium Salts and their Polymers, Polymer, **42**, 2785-2794 (2001).

10. L. M. Timofeeva, N. A. Kleshcheva, Y. A. Vasilieva, G. L. Gromova, G. I. Timofeeva and M. P. Filatova, (Effect of Dielectric Properties and Structure of Aqueous Solutions of Diallylammoniumsalts on their Reactivity in Radical Polymerization, Polym. Sci. Ser. A, **47**, 273-282 (2005).

11. L. M. Timofeeva, Y. A. Vasilieva, N. A. Klescheva, G. L. Gromova, G. I. Timofeeva, A. I. Rebrov and D. A. Topchiev, (Effect of Dielectric and Structural Properties of Solutions on the Polymerizability of Diallylammonium-type Monomers, Phys. Chem., **406**, 53-56 (2006).

12. N. S. Tuzun, V. Aviyente and K. N. Houk, A Theoretical Study on the Mechanism of the Cyclopolymerization of Diallyl Monomers, J. Org. Chem., **68**, 6369-6374 (2003).

13. Y. A. Vasilieva, N. A. Kleshcheva, G. L. Gromova, A. I. Rebrov, M. P. Filatova, E. B. Krut'ko, L. M. Timofeeva and D. A. Topchiev, Synthesis of High-molecular-weight Polyamine by Radical Polymerization of N,N-diallyl-N-methylamine), Russ. Chem. Bull., **49**, 431-437 (2000).

14. G. Odian, Principles of Polymerization, 4th Ed., Wiley-Inter Science: Hoboken, NJ, USA (2004) pp. 144-166.

15. M. Gorbunova, A. Vorob'eva, A. Tolstikov and Y. Monakov, New N-allylated Monomers in the Synthesis of Practical Valuable High-Molecular-weight Compounds, Polym. Adv. Technol., **20**, 209-215 (2009).

16. M. Firyal, N. Abbas and J. Khudheyer, Synthesis and Study of some Novel Polymers Containing Different Drug Substituted Groups, Ph. D. Thesis, Babylon University, College of Science, Iraq (2012) pp. 129-135.

Revised : 08.01.2015 *Accepted : 11.01.2015*