Received: 19 March 2023 | Revised: 20 May 2023 | Accepted: 23 May 2023
DOI: 10.22034/ecc.2023.398052.1648
Eurasian Chemical Communications
SAMI

FULL PAPER

Synthesis and characterization of some new prodrug polymer based on chitosan with tertiary-butyl acrylate and study some application

Wisam Abdul Jaleel Jawad* |**Faris H. Mohammed**

Department of Chemistry, College of Science, University of Babylon, Babylon, Iraq

Chitosan is a product of the deacetylation of chitin and widely found in the nature. Therefore, the modification of chitosan has been an important aspect of chitosan research. Chitosan have a good solubility, pH-sensitive target also increasing number of delivery systems. The study synthesized rization of some chitosan- amoxicillin H_1 and chitosan-diclofenac H_2 prodrug and release of drug. The structure of H_1 and H_2 was analyzed by FT-IR, ^{1}H-NMR, and character TGA. Drug release of prodrug polymers was measured in three different pH (pH=2, 7, and 8) at 37 °C. From the obtained results, these polymers appear good drug release in a basic medium for an ester bond of polymers as compared with amide bond of the other polymer.

***Corresponding Author:**
Wisam Abdul Jaleel Jawad
E-mail: wisamabduljaleel227@gmail.com
Tel.: +9647732867186

KEYWORDS

Amoxicillin; diclofenac sodium; chitosan; tertiary-butyl acrylate.

Introduction

Chitosan is a linear aminopolysaccharide of glucoseamine and N-acetyl glucosamine units, and it is can be obtained by alkaline acetylation of chitin extracted from cell walls of some fungi and another sources [1,4].

The consecutive characteristics of chitosan make it is polymer with many advantages for various application. Chitosan physically and biologically functional, it is biodegradable and biocompatible with many organs, cells, and tissues.

Likewise, chitosan was biodegradable, non-toxic, and antimicrobial properties, so chitosan is popular as antimicrobial agent either alone or blended with other natural polymers [5-7].

Chitosan hydrogels were classified into (chemical and physical) hydrogels for chemical hydrogels formed by irreversible covalent bonds, while physical hydrogels were constituted by various irreversible bonds [8,9].

To determine chemical structure, it can be chemically and enzymatically modified. The modification of chitosan can be materialized into physical and chemical processes to develop the mechanical and chemical

properties. Chitosan is a multinucleophilic polymer because of the presence of amino group at C-2 and hydroxyl groups at C-3 and C-6 in the GICN residue. Chitosan membrane is swollen in water and amino groups were protonated and left hydroxide ions free in water, which can add to the ionic conduction in the membrane [11].

Tertiary-Butyl acrylate is a simple organic compound that contains (C, H, and O) inside its structure [12]. It is a mono functional monomer with a characteristic high reactivity of acrylates and a bulky hydrophobic residue, also a very useful feed stock for chemical syntheses and because it is readily undergo to a different reactions with a wide variety of organic and inorganic compounds [13-18].

Tertiary-Butyl acrylate (TBA) is one of the fuel oxygenates used to replace tetra ethyl lead as anti-knock agent in gasoline alone or with methanol as co-solvent [19].

In this work, new prodrug polymer was synthesized based on chitosan and investigate some applications. First, amoxicillin prodrug polymer H_1 and diclofenac sodium prodrug polymer H_2 were synthesized by reaction of chitosan and tertiary-butyl acrylate. Drug release of these polymers was investigated.

Experimental

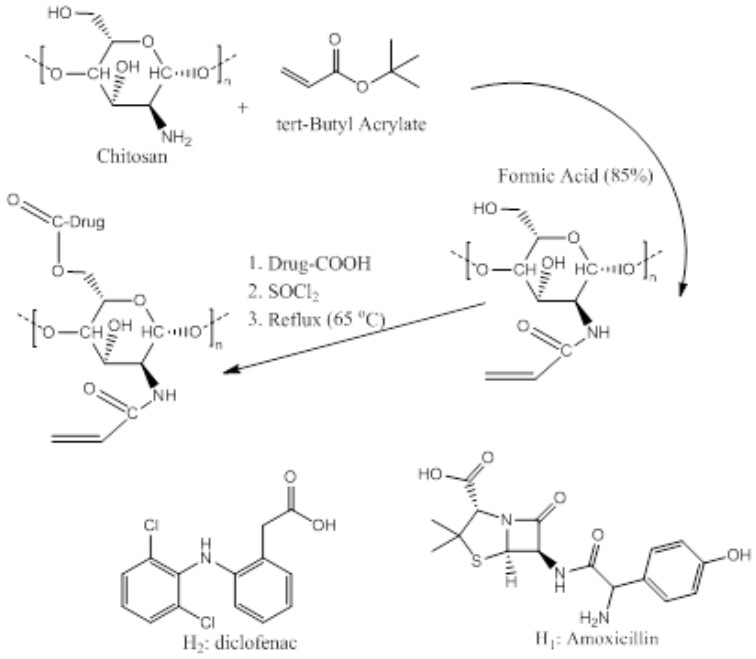
Melting points were measured using thermal microscope (Kofler-method). Infrared spectro photometer measurements were performed by Bruker FT-IR. FT-IR was obtained in absorption range 400-4000 cm^{-1} by Brucker FT-IR. UV-Visible measurements were double beam scanning spectro photometer varian at room temperature. All chemicals were purchased from CDH, Merck, Alfa, BDH, and all other chemicals were used without farther purification. Differential scanning calorimetric analysis was performed in (BAHR, Germany). ^{1}H-NMR was measured by Brucker 400 MHz, switzer land. In addition, swelling percentage, viscosity, and solubility were measured. Both controlled drug released and biological activity of prodrug polymers were studied.

Synthesis of amoxicillin prodrug polymer H_1

1 g of chitosan (0.00065 mol) was dissolved in 25 mL of glycial acetic acid and 1 g of tertiary-butyl acrylate (0.0078 mol) dissolved in 25 mL of distilled water, the mixture of both of them were mixed in around bottom flask (50 mL) and heated at 55 °C for 45 min, and then 1 g of amoxicillin was added to the mixture in round flask and 10 drops of $SOCl_2$ and refluxed with stirring about 1 hat 55 °C. The colored solution was collected and washed with diethyl ether three times and dried at room temperature (Scheme 1).

Synthesis of diclofenac sodium prodrug polymer H_2

A mixture of 1 g of chitosan (0.00065 mol) after it is dissolving in glycial acetic acid was putted in a beaker and mixed with 1 g of tertiary butyl acrylate (0.0078 mol). After that, the mixture above was placed in around bottom flask equipped with condenser and magnetic stirrer, and then 1 g of diclofenac sodium was added to the mixture also 10 drops of thionyl chloride was added gradually to round flask and refluxed for 1 h. The product was left one day and washed three times with suitable solvent diethyl ether to collect pure polymer (Scheme 1).



Scheme 1 polymer synthesis of (H_1, H_2)

Results and discussion

The structure of polymer prodrugs (H_1 and H_2) was analyzed with FT-IR spectrum and ^{1}H-NMR spectrum after synthesis of polymer prodrugs.

FT-IR spectrum of H_1 was displayed in the Figure 1. Absorption peak of NH groups was appeared in the 3326.26 cm^{-1}. Absorption peak of C=O amide was appeared in about 1655.00 cm^{-1}. The main peak of H_2 was appeared in 3323.54 cm^{-1} (NH) as a sharp peak and carbonyl peak appeared in the 1695.07 cm^{-1} (Figure 2).

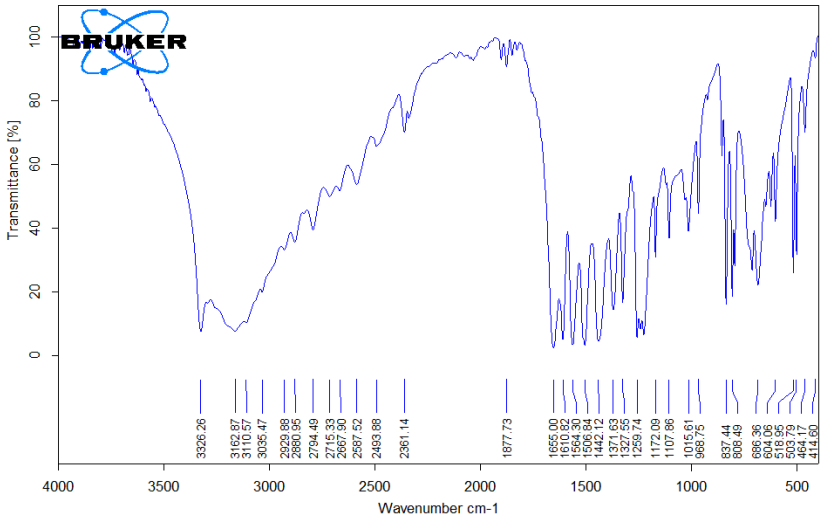


FIGURE 1 FTIR spectrum of H_1 polymer

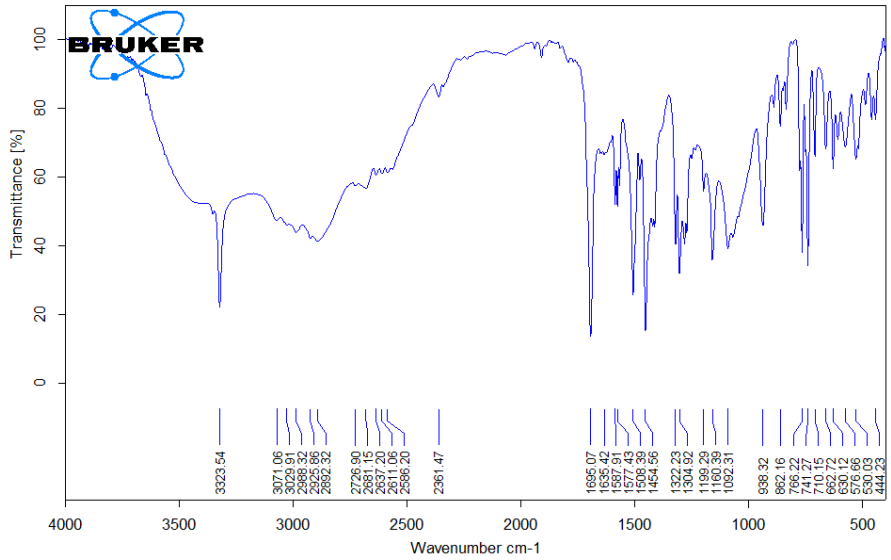


FIGURE 2 FT-IR spectrum of H_2 polymer

The ^{1}H-NMR spectrum for H_1 and H_2 polymers was illustrated in the Figures 3 and 4. The signal about 1-1.5 ppm is for CH_3 protons and the signal about 2 ppm is related to CH_2 protons. Also, the signal about 2.5 ppm to DMSO is considered as a suitable solvent for achieving the spectroscopic measurements, so the signal appears of 3-4 ppm is indicated for carboxylate group, and 6.99 is marked to aromatic ring, and for an amide group the signal is appear about 7-7.99 ppm. While ^{1}H-NMR spectrum of polymer H_2 in the Figure 3 consists of many signs the first signal in the range 1.5-2.0 ppm to indicate the protons of CH_3 and the signal about 2.5 for DMSO as a solvent for the spectrum measurements. In addition, the signal 3-4 ppm is for an ester group, and the signal in 6.93 ppm, on the other hand 7.20-7.53 ppm signal in for an aromatic ring and the range signal about 12.63 ppm is related to carboxylic group.

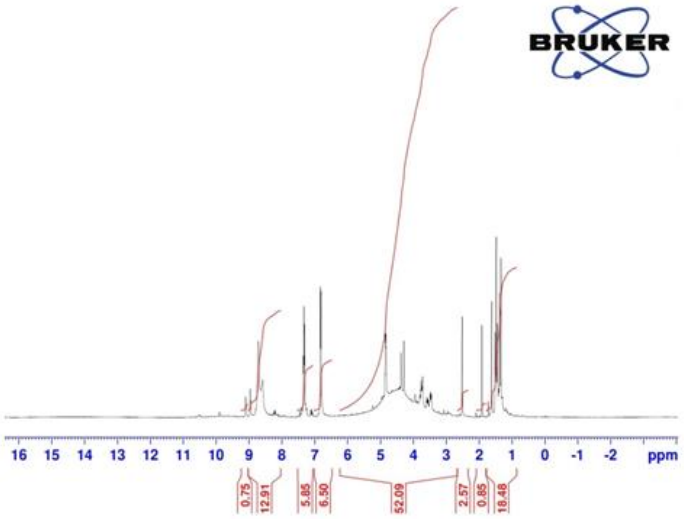


FIGURE 3 ^{1}H-NMR spectrum of H_1 polymer

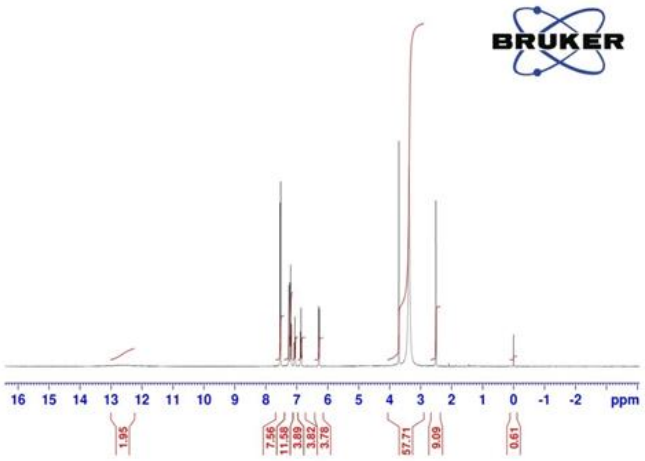


FIGURE 4 ^{1}H-NMR spectrum of H_2 polymer

Thermal analysis

DSC and TGA analyzed for synthesized H_1-H_2 were indicated that the polymers have good thermal stability (Figures 5 and 6).

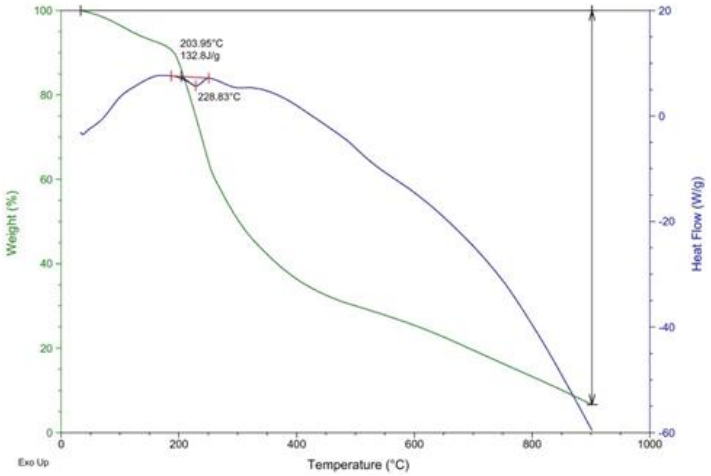


FIGURE 5 DSC-TGA for H_1 polymer

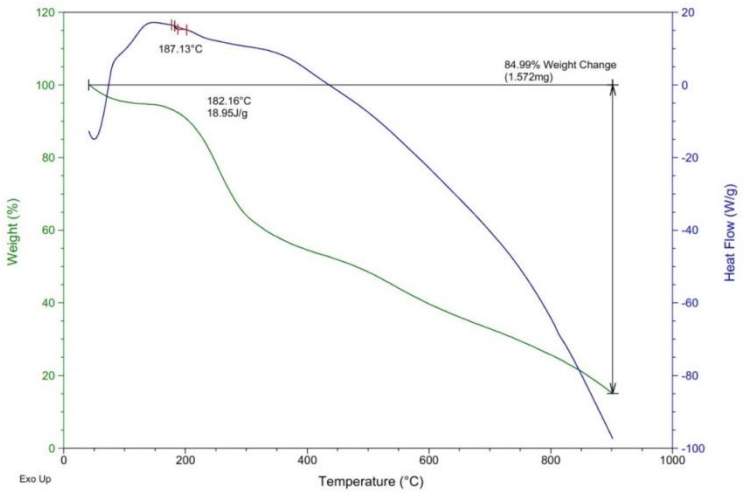


FIGURE 6 DSC-TGA for H_2 polymer

Viscosity of polymers

The physical properties of synthesized polymers were illustrated as presented in the Table 1. *Viscosity of polymers measured* 0.86 and 0.69 dl/g for H_1 and H_2, respectively.

TABLE 1 Physical properties of H_1 and H_2 polymers

Polymer	Color	melting point (°C)	η = dl/g
H_1	Orange powder	133-137	0.86
H_2	White powder	150-154	0.69

Solubility of polymers in different organic solvents

Solubility of H_1 and H_2 polymers was measured in different solvents (polar and non-polar) and there results were indicated in the Table 2. According to Table 2, both of the polymers H_1, H_2 were completely soluble in all solvents according to polar groups in these prodrugs and to achieve the chemical rule "like dissolve like".

TABLE 2 Solubility of polymers

Prodrug polymer	H_2O	EtoH	CH_3Cl_3	Tri ethyl ether	DMSO	DMF	1,4 Dioxane	Chloroform	Methanol	Acetonitrile
H_1	+	+	+	+	+	+	+	+	+	+
H_2	+	+	+	+	+	+	+	+	+	+

Swelling Ratio

Through dissolving 0.1 g of each polymer in 50 mL distilled water, the swelling percentage was determined.
Each polymer was left to soak for 1 h at 25 ℃, the hydrogel was separated from the bath, blotted with filter paper to extract surface water, and also swelling percentage was calculated by following equations.

Swelling percentage (%):

$$\frac{wt\ of\ hydrogel}{wt\ of\ hyfrogel} \times 100\%$$

Swelling percentage =

$$\frac{wt\ of\ welling\ sample - wt\ of\ dried\ sample}{wt\ of\ dried\ sample} \times 100\%$$

The results of the swelling **percentage** of prepared polymer (H_1- H_2) were obtained 10 % and 12%, respectively (Table 3).

TABLE 3 Swelling percentage for H_1, H_2 polymers

Polymers	Swelling %
H_1	10
H_2	12

Release of drug

Drug release of prodrug polymers was be measured in three different pH acidic functions for solutions (pH=2, 7, and 8) at 37 °C using a UV-Visible spectro photometer, as demonstrated in Table 4 and Figures 7-9. From the obtained results, these polymers H_1 and H_2 appear good drug release in a basic medium for an ester bond of polymers as compared with amide bond of the other polymer.

TABLE 4 Control drug release in pH (2, 7, 8)

pH= 2.0		
time/day	**H_2**	**H_1**
1	0.261	0.938
2	0.269	2.83
3	0.280	1.8511
4	0.301	2.609
pH= 7.0		
time/day	**H_2**	**H_1**
1	2.232	1.67
2	3.0530	1.272
3	4.5159	1.7716
4	1.0960	1.365
pH= 8.0		
time/day	**H_2**	**H_1**
1	2.078	1.55
2	0.0669	2.7761
3	3.730	2.627
4	0.0667	2.6574

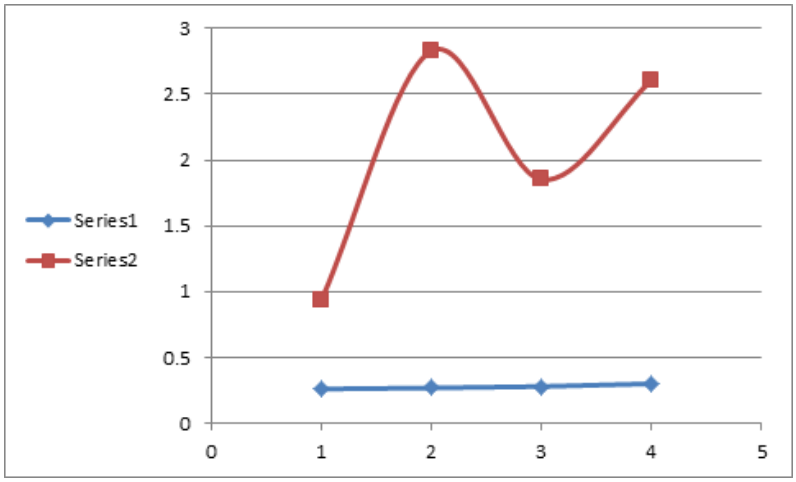


FIGURE 7 Control drug release in pH 2

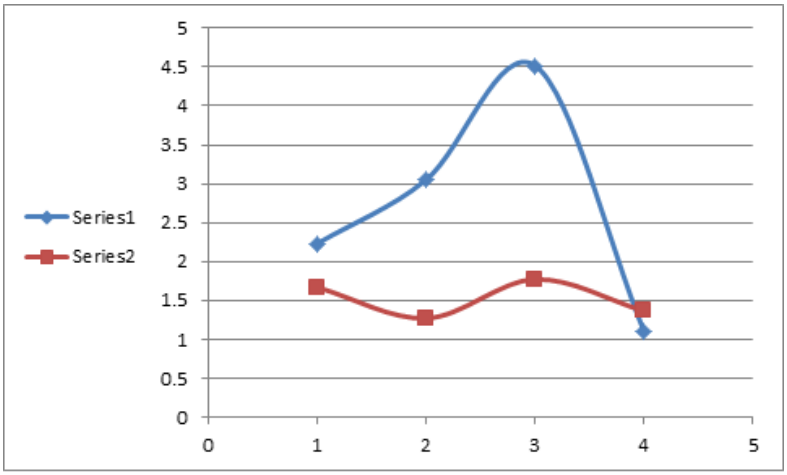


FIGURE 8 Control drug release in pH 7

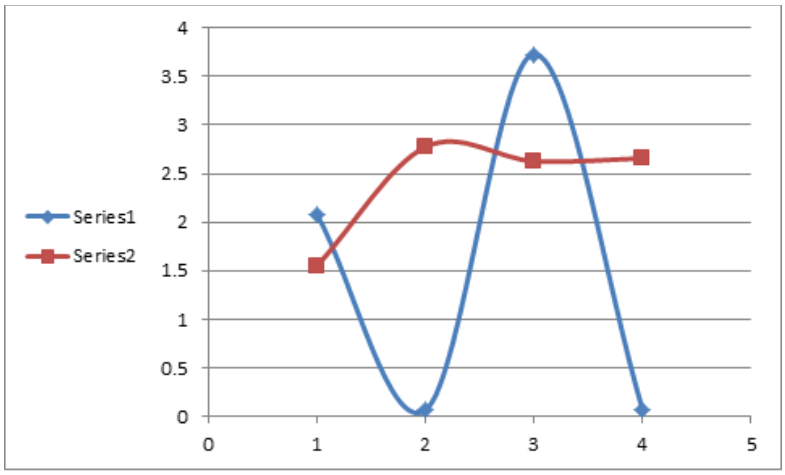


FIGURE 9 Control drug release in pH 8

Conclusion

New prodrug polymers were based on chitosan- drug was prepared through an esterification reaction. Their structures of polymer have been confirmed using FT-IR, ^{1}H-NMR spectroscopy, and TGA analyze. These polymers show good drug release in

basic medium for ester bond as compared with amide bond of the second polymer H_1, respectively.

Acknowledgements

The financial support for this research was provided by Ministry of Higher Education Malaysia under FRGS Grant no. 2019-0147-103-02.

Conflict of Interest

The authors declare that there is no conflict of interest.

Orcid:

Wisam Abdul Jaleel Jawad:
https://orcid.org/0009-0002-1267-4857
Faris H. Mohammed:
https://orcid.org/0000-0002-4725-2569

References

[1] R.A.A. Muzzarelli, *Filmogenic properties of chitin/chitosan, in Chitin in Nature and Technology*, R. C. Muzzarelli, G. W. Jeuniaux, Eds., Plenum Press, New York, NY, USA, **1986**, 389–396. [crossref], [Google Scholar], [Publisher]

[2] A.A. Chis, A.M. Arseniu, C. Morgovan, C.M. Dobrea, A. Frum, A.M. Juncan, A. Butuca, S. Ghibu, F.G. Gligor, L.L. Rus, Biopolymeric prodrug systems as potential antineoplastic Therapy, *Pharmaceutics*, **2022**, *14*, 1773. [crossref], [Google Scholar], [Publisher]

[3] A. Marwah, R. Wasan, Fabrication of environmental monitoring amperometric biosensor based on alkaloids compound derived from catharanthus roseus extract nanoparticles for detection of cadmium pollution of water, *Chem. Methodol.*, **2023**, *7*, 358-371. [crossref], [Google Scholar], [Publisher]

[4] V. Tallapaneni, L. Mude, D. Pamu, V.V.S.R. Karri, Formulation, Characterization and in vitro evaluation of dual-drug loaded biomimetic chitosan-collagen Hhybrid nnocomposite scaffolds, *J. Med. Chem. Sci.*, **2022**, *5*, 1059-1074. [crossref], [Google Scholar], [Publisher]

[5] W.K.H. Al-Behadili, Y.M. Jawad, W.S. Abdul Whaab, Effect of solvent on intensity of absorption and fluorescence of eosin Y dye and spectral properties of Eosin Y dye, *J. Med. Chem. Sci.*, **2023**, *6*, 322-334. [crossref], [Google Scholar], [Publisher]

[6] S. Jabar, M. Al- Shammaree, S.A.W. Cytotoxicity and anticancer efect of chitosan-Ag NPs-doxorubicin-folic acid conjugate on lngs cell line, *Chem. Methodol.*, **2023**, *7*, 1-14. [crossref], [Google Scholar], [Publisher]

[7] Y.K. Sadiq, K.A. Saleh, Synthesis and characterization of chrome (VI) ion/iron oxide/chitosan composite for oxidation of methylene blue by photo-fenton reaction, *Chem. Methodol.*, **2023**, *7*, 112-122. [crossref], [Google Scholar], [Publisher]

[8] B. Ghassemi, F. Dehghan Nayeri, R. Hosseini, The effects of chitosan nanoparticles on genes expression of artemisinin synthase in suspension culture of Artemisia annua L: A comparative study, *Int. J. Adv. Biol. Biomed. Res.*, **2021**, *9*, 214-227. [crossref], [Google Scholar], [Publisher]

[9] F. Mohajer, G. Mohammadi Ziarani, A. Badiei, New advances on modulating nanomagnetic cores as the MRI-monitored dug release in cancer, *Appl. Organomet. Chem.*, **2021**, *1*, 143-147. [crossref], [Google Scholar], [Publisher]

[10] N.A. Nugrahani, A.R. Pudji Rahayu, Solution for root canal treatment failure: comparison of antibiofilm between aloe vera extracts and chitosan shrimp shells of the formation biofilm enterococcus faecalis, *J. Med. Chem. Sci.*, **2022**, *5*, 393-399. [crossref], [Google Scholar], [Publisher]

[11] E.R. Hayes, D.H. Davies, Characterization of chitosan. I, Thermoreversible chitosan gels, in Proceedings of the 1st International Conference on Chitin and Chitosan, **1978**, 193. [Google Scholar], [Publisher]

[12] S. Hirano, S. Kondo, Y. Ohe, Chitosan gel: a novel polysaccharide gel, *Polymer*, **1975**, *16*, 622. [Google Scholar], [Publisher]
[13] S. Hirano, R. Yamaguchi, N. Fukui, M. Iwata, A chitosan oxalate gel: its conversion to an N-acetylchitosan gel via a chitosan gel, *Carbohydr. Res.*, **1990**, *201*, 145– 149. [crossref], [Google Scholar], [Publisher]
[14] H. Yasar, D.K. Ho, C. De Rossi, J. Herrmann, S. Gordon, B. Loretz, C.M. Lehr, Starch-chitosan polyplexes: A versatile carrier system for anti-infectives and gene delivery, *Polymers*, **2018**, *10*, 252. [crossref], [Google Scholar], [Publisher]
[15] H. Horo, S. Das, B. Mandal, L.M. Kundu, Development of a photoresponsive chitosan conjugated prodrug nano-carrier for controlled delivery of antitumor drug 5-fluorouracil, *Int. J. Biol. Macromol.*, **2019**, *121*, 1070-1076. [crossref], [Google Scholar], [Publisher]
[16] H. Sashiwa, Y. Shigemasa, Chemical modification of chitin and chitosan. 2: preparation and water soluble property of N-acylated or N-alkylated partially deacetylated chitins, *Carbohydr. Polym.*, **1999**, *39*, 127–138. [crossref], [Google Scholar], [Publisher]
[17] Technical Information, O-BASF, tert-Butyl Acrylate (TBA): https://www.basf.com/global/documents/en/products-and-industries/specialty-monomers/ti/iso_Decyl_Acrylate_F.pdf, Supersedes edition dated March **2018**.
[18] Tertiary Butyl Alcohol (TBA) Biodegradation, March 5, **2012**: https://www.api.org/-/media/Files/EHS/Clean_Water/Bulletins/26_Bull.pdf. [crossref], [Google Scholar], [Publisher]
[19] J.J. Clark tert-Butyl alcohol: chemical properties, production and use, fate and transport, toxicology, and detection in groundwater and regulatory standards, **2001**, *7*, 92-106. [crossref], [Google Scholar], [Publisher]

How to cite this article: Wisam Abdul Jaleel Jawad *, Faris H. Mohammed. Synthesis and Characterization of some new prodrug polymer based on chitosan with tertiary-butyl acrylate and study some application. *Eurasian Chemical Communications*, 2023, 5(9), 842-851. **Link:** https://www.echemcom.com/article_172139.html