

FULL PAPER

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

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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 H₁ and chitosan-diclofenac H₂ prodrug and release of drug. The structure of H₁ and H₂ was analyzed by FT-IR, ¹H-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.

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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 $400-4000\text{ cm}^{-1}$ by Bruker 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

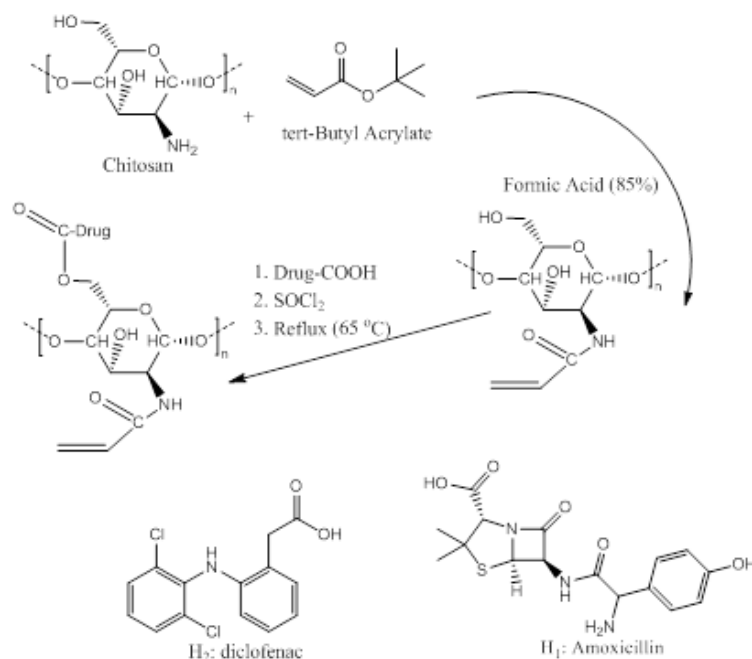
all other chemicals were used without farther purification. Differential scanning calorimetric analysis was performed in (BAHR, Germany). $^1\text{H-NMR}$ was measured by Bruker 400 MHz, switzer land. In addition, swelling percentage, viscosity, and solubility were measured. Both controlled drug released 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 $55\text{ }^\circ\text{C}$ 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 $55\text{ }^\circ\text{C}$. 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 (H₁, H₂)

Results and discussion

The structure of polymer prodrugs (H₁ and H₂) was analyzed with FT-IR spectrum and ¹H-NMR spectrum after synthesis of polymer prodrugs.

FT-IR spectrum of H₁ 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 H₂ was appeared in 3323.54 cm⁻¹ (NH) as a sharp peak and carbonyl peak appeared in the 1695.07 cm⁻¹ (Figure 2).

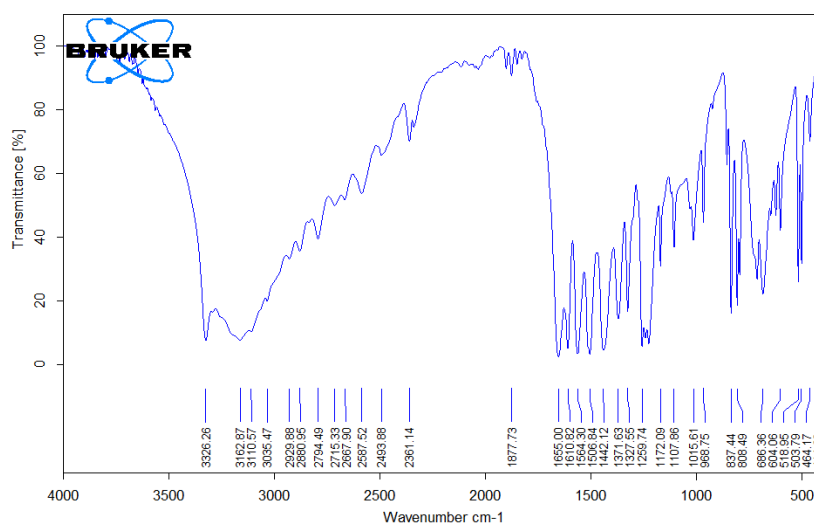


FIGURE 1 FTIR spectrum of H₁ polymer

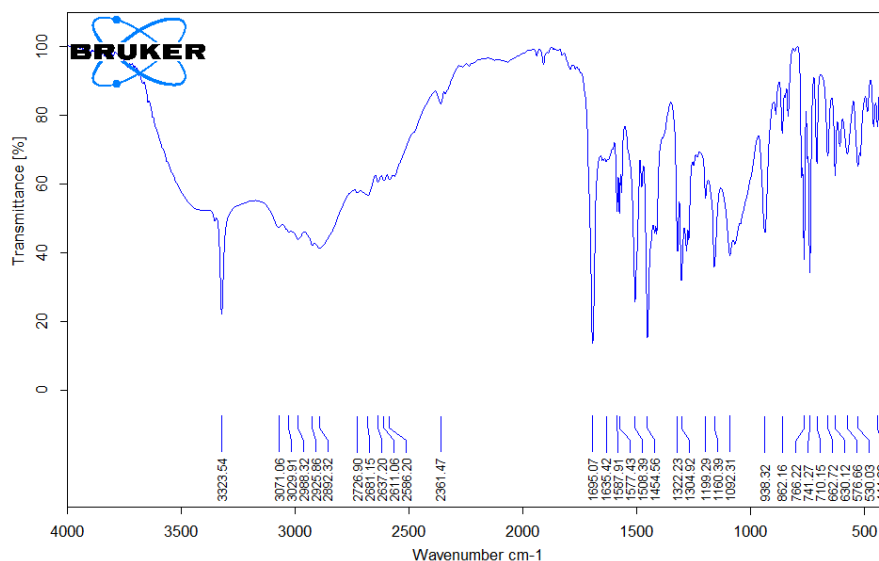


FIGURE 2 FT-IR spectrum of H₂ polymer

The ¹H-NMR spectrum for H₁ and H₂ polymers was illustrated in the Figures 3 and 4. The signal about 1-1.5 ppm is for CH₃ protons and the signal about 2 ppm is related to CH₂ 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 6.93 ppm is marked to aromatic ring, and for an amide group the signal is appear about 7-7.99

ppm. While ¹H-NMR spectrum of polymer H₂ in the Figure 3 consists of many signs the first signal in the range 1.5-2.0 ppm to indicate the protons of CH₃ 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.

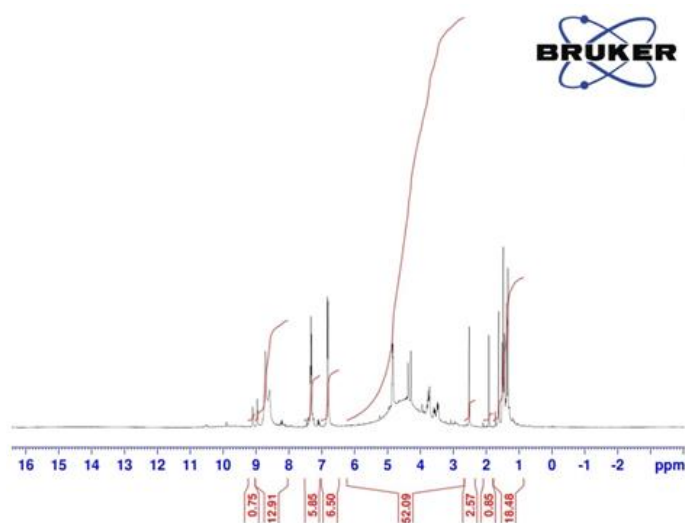


FIGURE 3 ¹H-NMR spectrum of H₁ polymer

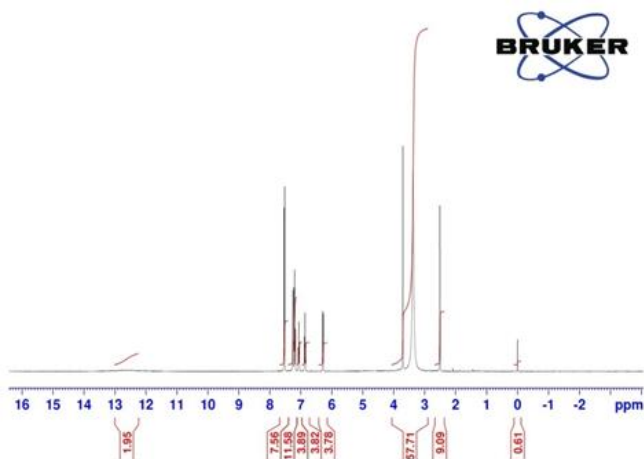


FIGURE 4 $^1\text{H-NMR}$ spectrum of H_2 polymer

Thermal analysis

DSC and TGA analyzed for synthesized $\text{H}_1\text{-H}_2$ were indicated that the polymers have good thermal stability (Figures 5 and 6).

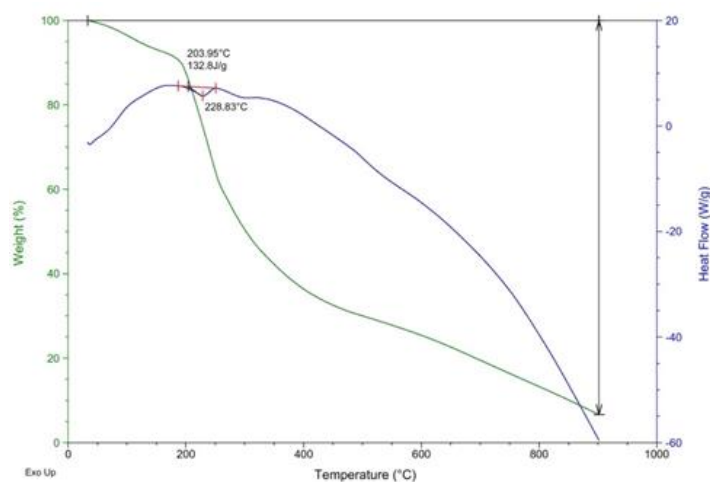


FIGURE 5 DSC-TGA for H_1 polymer

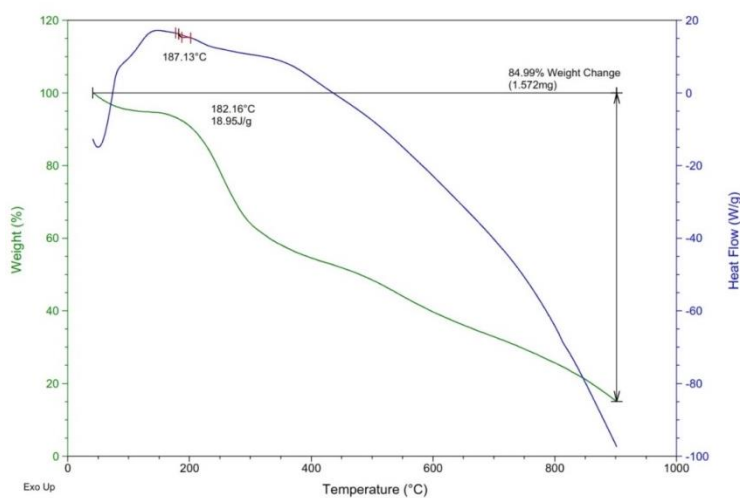


FIGURE 6 DSC-TGA for H_2 polymer

Viscosity of polymers

The physical properties of synthesized polymers were illustrated as presented in the

TABLE 1 Physical properties of H₁ and H₂ polymers

Polymer	Color	melting point (°C)	$\eta = \text{dl/g}$
H ₁	Orange powder	133-137	0.86
H ₂	White powder	150-154	0.69

Table 1. Viscosity of polymers measured 0.86 and 0.69 dl/g for H₁ and H₂, respectively.

Solubility of polymers in different organic solvents

Solubility of H₁ and H₂ 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 H₁, H₂ 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 ₂ O	EtoH	CH ₃ Cl 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 °C, 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 (%):

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

$$\text{Swelling percentage} = \frac{\text{wt of welling sample} - \text{wt of dried sample}}{\text{wt of dried sample}} \times 100\%$$

The results of the swelling percentage of prepared polymer (H₁- H₂) were obtained 10 % and 12%, respectively (Table 3).

TABLE 3 Swelling percentage for H₁, H₂ polymers

Polymers	Swelling %
H ₁	10
H ₂	12

Release of drug

Drug release of prodrug polymers was 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 H₁ and H₂ 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

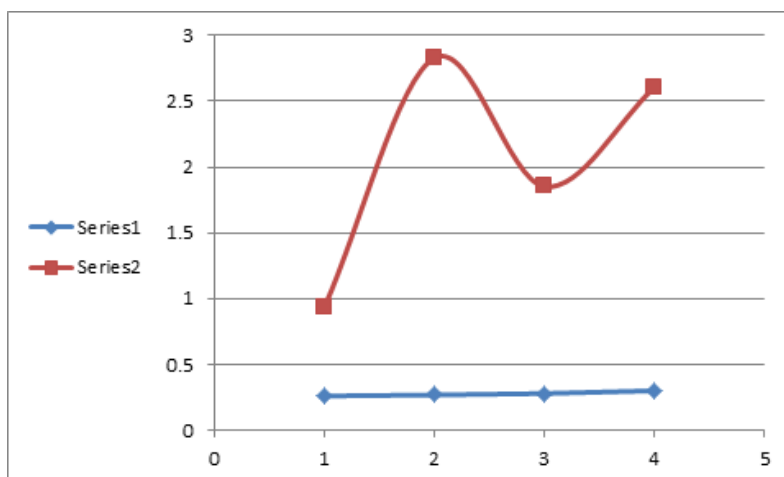


FIGURE 7 Control drug release in pH 2

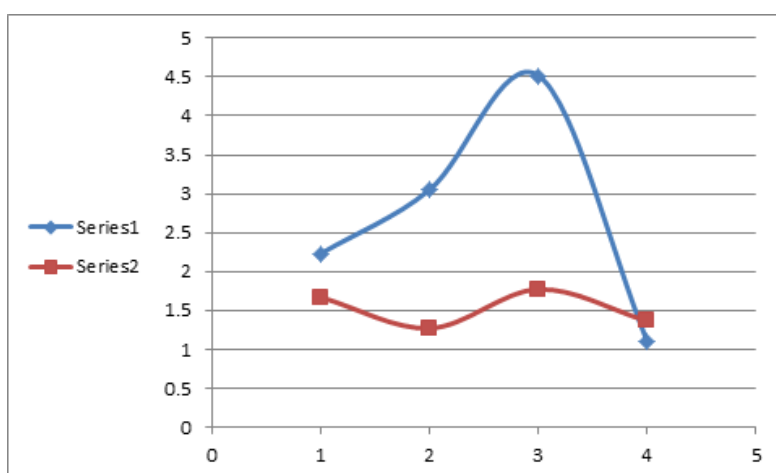


FIGURE 8 Control drug release in pH 7

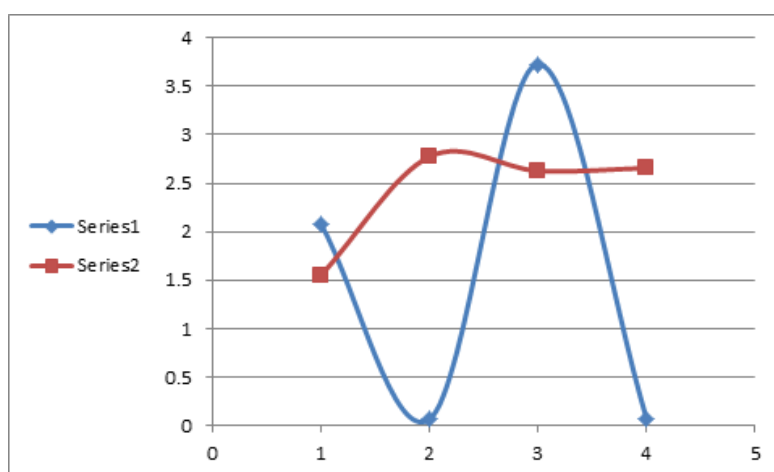


FIGURE 9 Control drug release in pH 8

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, $^1\text{H-NMR}$ 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 H₁, respectively.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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