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Synthesis and characterization of polymeric prodrug conjugate systems based on poly (*p*-hydroxystyrene): *In vitro* hydrolysis behavior and antibacterial activity

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Abstract

The synthesis and *in-vitro* evaluation of a novel polymeric systems based on linear poly(*p*-hydroxystyrene) for targeted controlled release have been described. Linear poly(*p*-hydroxystyrene) (PHS) functionalized with chloroacetyl groups was first prepared by reacting PHS with chloroacetyl chloride, in presence of pyridine as a catalyst, with degree of chloroacetylation ranged from 87 to 96 mol%. The resulting chloroacetylated-PHS (CPHS) was then coupled with each of sodium diclofenac and 1,3-diaminopropane affording the corresponding polymers **P1** and **P3**, respectively, in quantitative loading yields. Their structures were confirmed by means of FTIR, ^{1}H-NMR as well as by elemental analysis. The hydrolysis in the heterogeneous system of CPHS-diclofenac conjugate was performed in buffer solutions (pH 1.2 ,7.4 and 9) at 37 ^{o}C by UV spectroscopy at the absorption wavelength of diclofenac sodium (λ_{max} = 276 nm). The drug could be released by selective hydrolysis of the ester bond at the side of the drug moiety. The hydrolytic behavior was found to be mainly dependant on the pH value of the hydrolysis medium. The obtained results suggested that this polymer could be useful in controlled release systems after *in-vivo* examinations. The antibacterial activities of the modified polymers were also tested against *Staphylococcus aureus*, *Enterococcus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Klebsiella pneumoniae*. They showed good antibacterial activity which differed according to the concentration of the polymer as obtained from minimum inhibitory concentration (MIC) studies

Keywords: Polyhydroxystyrene; Diclofenac; Controlled release; Drug loading, Antibacterial.

1. Introduction

In the last decades, the synthesis of polymeric materials for biomedical applications have been attracted much attention. Since the late of 1960s, advanced controlled drug-delivery systems which are needed to improve drug efficacy have been extensively investigated by means of the chemical attachment of low molecular weight drugs to synthetic or natural polymers. It provides both a constant and prolonged release of drugs with least side effects. This system was called polymer–drug conjugates or polymeric prodrugs (Babazadeh, 2014, Hoste et al., 2004, Ratner et al., 1996). Polymeric prodrugs having several advantages include: (a) Enhancement of drug bioavailability by increasing water solubility of insoluble or low soluble drugs; (b) Protecting drug from deactivation and preserving its activity during

circulation and providing a targeted transport to a specific organ or tissue; (c) Improving the pharmacokinetics of drug; (d) Reduce the antigenic activity of the drug so minimize the immunological body response; (e) The ability of providing passive or active targeting of the drug to the site of its action; as well as (f) The possibility to form a complex drug delivery system, which not only include drug and polymer carrier but also other active components that enhance the specific activity of the main drug. Due to these advantages over the free form of a drug, the polymeric prodrug conjugates are promising polymeric drug delivery systems (Nichifor et al., 1997, Uhrich, 2010).

The polymeric carrier can be a biodegradable polymer or an inert polymer and the drug can be attached directly or by a spacer group onto the backbone of polymer. According to selection of this spacer opens the possibility of controlling the rate and the site of release of the active drug from the conjugate by enzymatic or hydrolytic cleavage (Babazadeh, 2014, Davaran et al., 1999). The drugs may be attached to the polymeric carriers using a number of chemical reactions via participation of functional groups such as carboxyl or hydroxyl which are either originally present in the polymer chain or formed by functionalization. Another possibility is using functionalized monomers to synthesis a reactive polymeric precursor. Mostly, drugs linked directly to the polymer chain exhibit either a reduced or zero biological activity. That's why drugs have to be separated from the polymeric backbone by means of a spacer. Once the polymeric prodrug reaches the target site of its action, the drug can then be split off more easily in its active form. In order to facilitate the release of the drug it must be linked to the macromolecular chain by covalent bonds of slight stability in a biological environment (Jantas et al., 2012). Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID), which therapeutically used for inflammatory and painful diseases of rheumatic and nonrheumatic origins. The therapeutic use of NSAIDs is often bounded by the necessity of delivering the drug to specific sites of the target organ or tissue. Besides, the use of NSAIDs is restricted by their frequently poor water solubility and by their irritant side effects on the gastroenteric mucous. Consequently, to reduce the NSAIDs side effects and to increase their therapeutic efficiency, the controlled release drug delivery of NSAIDs by polymeric carriers has been developed (Davaran and Entezami, 1997, Giammona et al., 1989, Saravanan et al., 2004, Scheytt et al., 2006). In recent years, many studies on the synthesis and hydrolysis properties of polymer–drug conjugates of NSAIDs such as: Naproxen (Bonina et al., 2001), ibuprofen (Babazadeh, 2006, Chang et al., 1998, Davaran and Entezami, 1998, Kim et al., 2005), ketoprofen (Bonina et al., 2001, Kenawy et al., 2008), Indomethacin (Duarte et al., 2006, Bonina et al., 1995, Kim et al., 1998) and fenoprofen (Duarte et al., 2006, Zovko et al., 2001) have been presented. Polymeric antitumor and antimicrobial agents represent an important and new direction that is developing in the field of both pharmacology and biomaterials as well (Kenawy et al., 2014, Mostafa et al., 2013). The antimicrobial property of a polymer plays an important role for many of its applications (Santos et al., 2016).

In this article, the synthesis and hydrolytic behavior of PHS-type polymeric prodrug of diclofenac (CPHS-diclofenac) have been presented. The hydrolytic process has been performed heterogeneously in aqueous buffer solutions (pH 1.2, 7.4 and 9.0) and the amount of the released drug was detected by UV spectroscopy. The polymer obtained from reacting chloroacetylated-PHS (CPHS) with 1,3-diaminopropane has been synthesized and its potent antimicrobial activity was investigated against *Staphylococcus aureus*, *Enterococcus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Klebsiella pneumoniae.*

2. Materials and Methods

2.1. Materials

Poly(*p*-hydroxystyrene) (PHS), chloroacetyl chloride, dimethylsulfoxide (DMSO), 1,3-diamino propane and diethyl ether were purchased from Aldrich, Milwaukee, Wisconsin, USA, and were used without further purification. 1,4-Dioxan (Aldrich, USA) was dried before use. Pyridine was treated and stored under molecular sieves, sodium phosphate dibasic (Na_2HPO_4) and potassium phosphate monobasic (KH_2PO_4) were purchased from Aldrich, Milwaukee, Wisconsin, USA. Diclofenac sodium was purchased from Sigma (USA). The test microorganisms were obtained from the culture collection of the Bacteriology Unit, Faculty of Veterinary Medicine, Kafrelsheikh University, Egypt. Infrared spectra were recorded by Perkin-Elmer 2000 (FTIR) instrument. ^{1}H-NMR spectra were obtained using Bruker DPX 250 MHz spectrometer with DMSO-d6 as solvent and TMS as an internal reference. The UV-VIS spectra were obtained using Perkin Elmer UV/VIS Lambda 2 spectrometer. The degree of esterification of PHS was determined from the elemental analysis of chloride.

Elemental analysis (Cl) was carried out on a Carlo Erba 1106 EA-instrument.

2.2. Synthetic methods

2.2.1. Esterification of PHS with chloroacetyl chloride

To a cooled suspension of poly(*p*-hydroxystyrene) (PHS) (3.0 g, 25 mmol) in 60 mL of 1,4-dioxan, pyridine (4.5 mL, 56.96 mmol) was added. The reaction mixture was cooled to –5 °C in an ice-salt bath followed by adding chloroacetyl chloride (4.6 mL, 57.76 mmol) dropwisely while stirring. The reaction mixture was kept under stirring vigorously for 3 hrs at –5 °C followed by stirring at room temperature for three days. The desired polymer (**P1**) was precipitated by adding dilute hydrochloric acid (1N), filtered off and washed with distilled water several times. The resulting functionalized polymer was then dried in vacuum oven at 40 °C overnight affording the desired polymer in 89 % yield.

2.2.2. Reaction of chloroacetylated PHS with sodium diclofenacate

The chloroacetylated poly(*p*-hydroxystyrene) (CPHS) (**P1**, 2 g , 9.75 mmol $ClCH_2CO$- groups) was dissolved in 30 ml DMSO at room temperature and then 3.4 g (11.5 mmol) sodium diclofenac was dissolved in 10 ml DMSO then added to the reaction mixture portion wise while stirring. The reaction was performed under stirring and at 30 ^{o}C for about 5 hrs. The obtained polymer (**P2**) was isolated by precipitation using cooled distilled water as precipitant and then ethanol washed to remove unreacted sodium diclofenac and then dried under reduce pressure at 60 ^{o}C to constant weight affording finally the desired polymer (**P2**) in 65% yield.

2.2.3. Amination of chloroacetylated linear poly (p-hydroxystyrene)

To a suspension of CPHS (**P1**, 1 g, 5 mmol) in 10 mL dry1,4-dioxane was added 1,3-diamino propane 0.74 g (0.84 mL, 10 mmol). The reaction mixture was continued under stirring in an oil bath for four days at 80 ^{o}C. The crude polymer was filtered off, washed with diethyl ether followed by drying at 40 ^{o}C for 48 hrs affording finally the desired polymer **P2** in 92% yield.

2.3. Determination of total diclofenac content

An amount of 10 mg of the functionalized diclofenac–polymer conjugate (**P2**) was suspended in 10 mL buffer solution of pH = 9.0. The mixture was maintained at 60 $^{\circ}$C for 24 h and the total amount of released diclofenac followed using a UV spectrophotometer by detecting the UV absorption of diclofenac at λ_{max} = 276 nm.

2.4. In vitro drug release

Samples of the CPHS-diclofenac conjugate (about 10 mg containing 96 mol % of diclofenac groups) in a powder form were placed in conical flasks with 50 ml of an aqueous buffer solution (pH 1.2, 7.4 and 9) at 37 ^{o}C. From each sample, 2 mL was collected for analysis at selected intervals and this volume was returned to the release medium to maintain a constant volume. The quantity of the released drug was detected by UV spectroscopy at the absorption wavelength of diclofenac (λ_{max} = 276 nm) using calibration curve which obtained already under the same conditions. The CPHS-diclofenac conjugates were found to be remained insoluble in the reaction medium along the whole hydrolysis experiment.

2.5. Screening of antimicrobial activity

2.5.1. Microorganisms

The antimicrobial activity of the synthesized polymers was tested on different strains of pathogenic bacteria. The gram positive *Staphylococcus aureus*, causes contamination of food and so produces bacterial toxins, *Enterococcus*, the gram negative *Escherichia coli* can cause serious food poisoning in their hosts, *Pseudomonas aeruginosa* known with its antibiotic resistance and its association with serious illnesses – especially nosocomial infections and various sepsis syndromes, *Salmonella typhi* responsible for typhoid fever and *Klebsiella pneumoniae* can cause destructive changes to human and animal lungs if aspirated (inhaled). The test microorganisms were obtained from the culture collection of the Bacteriology Unit, Faculty of Veterinary Medicine, KFS University, Egypt.

2.5.2. Media

Meuller-Hinton agar and nutrient broth were used for bacterial cultures.

2.5.3. Antimicrobial activity test

The antimicrobial activity of the prepared modified polymers bearing an active functional group was detected against different microorganisms as powdered samples by the cut plug method on Mueller-Hinton agar (Kenawy et al., 2009, Pridham et al., 1956). The typical method, "the assay Petri dishes were seeded with the test microorganisms, the plates left to solidify at room temperature. By a sterile cork borer, the wells were made and each was filled with 20 mg of the tested polymers as powder. All plates were then incubated at 30 °C for 24 h, and then the diameters of the inhibition zones were recorded in millimeters (mm). The polymers which found to give the highest inhibition zones were moreover tested in aqueous suspensions at different concentrations in order to quantify its inhibitory effects.

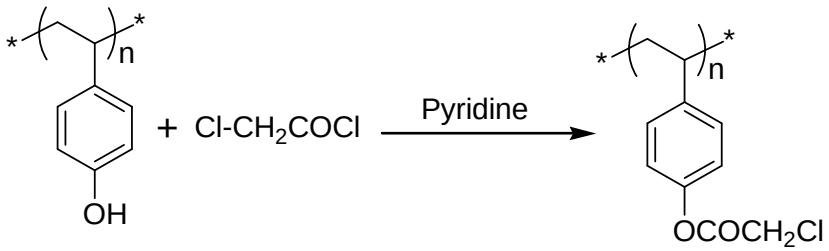
2.5.4. MIC test

Determination of the minimal inhibitory concentrations (MICs) of the most efficient polymer towards the tested microorganisms was detected by the following method: 0.5 ml of each tested bacteria was placed in 9.5 ml of nutrient broth and kept in the incubator for 24 h at 37 °C. The effective polymer was added to the tubes containing the diluted broths and the most sensitive test microorganisms to give the final concentrations from 2.5-40 mg/ml. The cultures containing the test organisms and different concentrations of the selected polymer were incubated for 24 h at 37 °C, then optical density of growth was measured by spectrophotometer at 620 nm for each incubated mixture, results were represented graphically, and MIC was recorded for the tested material (Kenawy et al., 2006, Mahmoud et al., 2001).

3. Results and Discussion

3.1. Synthesis of functionalized polymers

The esterification process was carried out in a homogeneous system to provide a uniform distribution of chloromethyl groups along the polymer chains of poly(*p*-hydroxystyrene) (PHS). Chloroacetylation was performed by reacting PHS with chloroacetyl chloride, in dry1,4-dioxane as a solvent, in presence of pyridine as a base, under anhydrous condition. PHS reacted with different concentrations of chloroacetyl chloride using the procedure described by Kenawy et al (Kenawy et al., 2013) (Scheme 1).



P1

Scheme 1. Synthesis of chloroacetylated linear PHS

The effect of chloroacetyl chloride molar ratios on the degree of substitution is summarized in Table 1. The degree of the chloroacetylation of PHS was calculated from the content of chlorine that determined by elemental analysis. From the data shown in Table 1, the extent of esterification increased with increasing the molar ratio of chloroacetyl chloride to PHS. The degrees substitution increased from 87 to 96% with increasing the molar ratios of chloroacetyl chloride to PHS.

Table 1. Effect of reaction conditions on the degree of substitution for the esterification reaction of linear PHS with chloroacetyl chloride.

Sample	$ClCH_2COCl$ /-OH mole/mole	Cl %		Degree of substitution mol %
		Calc.	Found	
Sample 1	1.9	18	15.66	87.0 %
Sample 2	4.64	18	16.38	91.0 %
Sample 3	6.96	18	16.83	93.5 %
Sample 4	8.9	18	17.28	96.0 %

The elemental analysis of chloroacetylated poly(*p*-hydroxystyrene) (**P1**) with different degrees of substitution was in a good agreement with the calculated values as shown in Table 1. The same conclusion was proved by the infrared studies. Figure 1 shows the FTIR spectra of unmodified PHS, chloroacetylated PHS (containing 96 mol% of chloroacetyl groups). In comparison to the FTIR spectrum of PHS (Figure 1a), the FTIR spectrum of CPHS (Figure 1b) showed new absorption bands at 1731 cm^{-1} attributed for the C=O bond and at 748 cm^{-1} for the C−Cl bond.

Attaching diclofenac to linear CPHS has been readily occurred via an esterification reaction (Scheme 2). The functional chloroacetyl chloride groups of CPHS reacted with the carboxyl group of diclofenac affording a new ester bond between the drug and polymer. The CPHS-diclofenac adduct was dried and collected in good yields 65%. FTIR spectrum of CPHS-diclofenac adduct (Figure 1c) showed a new absorption peak appeared at 3320.8 cm^{-1} due to the N-H stretching vibration of the amino group, and an absorption band at 1577 cm^{-1} corresponding to the carbonyl group of the loaded drug. However, the almost complete disappearance of the −C−Cl absorption band confirming the quantitative attaching of the drug to the chloroacetylated polymer.

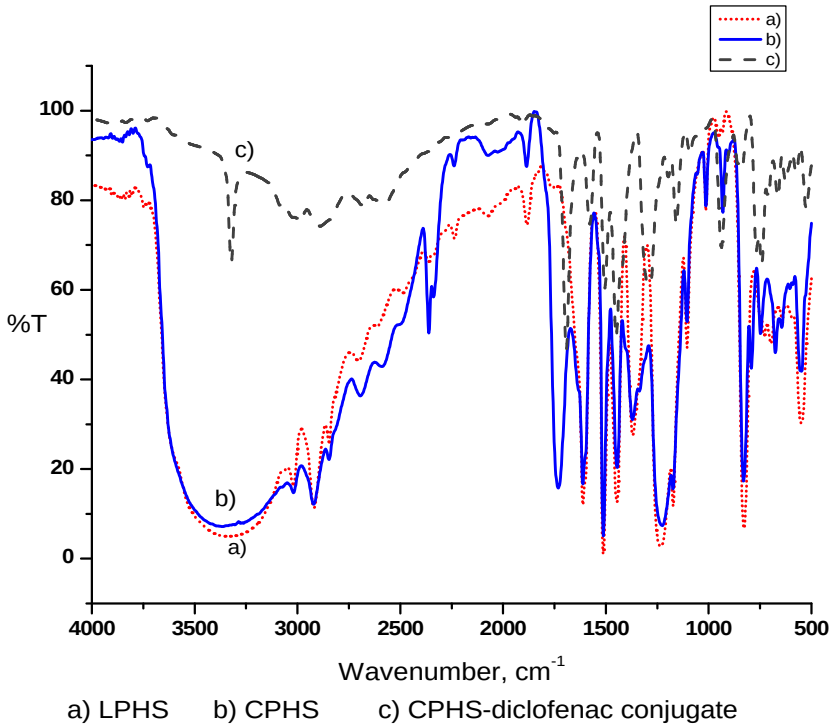
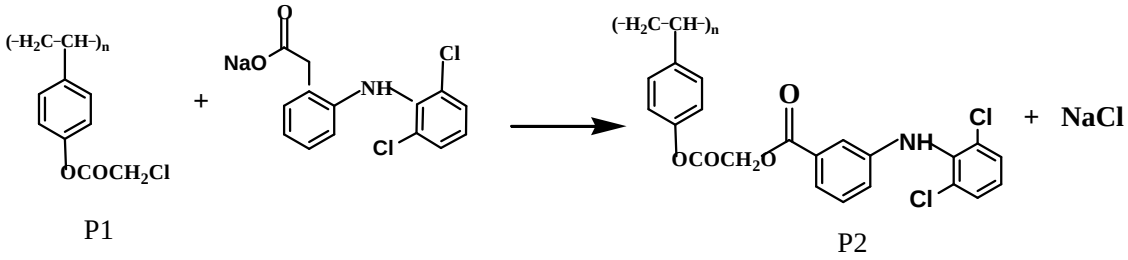


Figure 1. FTIR spectra for each of: a) Linear PHS, b) Linear CPHS (96 mol-% of loaded chloroacetyl groups), c) Conjugate of CPHS-diclofenac (96 mol-% of loaded diclofenac groups).

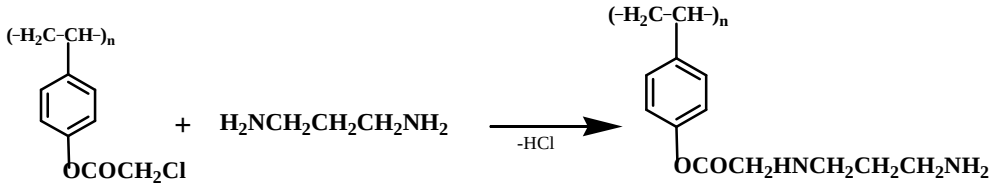
The ^{1}H-NMR spectrum of CPHS showed characteristic signals at 6.5–7.0 ppm (d, aromatic protons), singlet signal at 4.2 ppm (−CH_2Cl), 1.2 ppm (CH_2 doublet) and 2.5 ppm (CH triplet). The spectrum of the CPHS-diclofenac conjugate showed the proton signals of the new peaks of aryl groups in diclofenac which could be seen between 6.5 and 7.7 ppm.



P1 P2

Scheme 2. Synthesis of PHS-diclofenac conjugate

Amination of chloroacetylated poly(*p*-hydroxystyrene) (**P1**; CPHS) to produce polymer **P3** was prepared by reacting **P1** with 1,3-diamino propane in dry 1,4-dioxane by similar previously reported procedure (Hazziza–Laskar et al., 1993) (Scheme 3). This polymer was prepared to examine the effect of the new functional groups on the antibacterial activity and compare it with polymer **P1** (Kenawy et al., 2006). The elemental analysis confirmed that the nitrogen content of polymer **P3** was in good value of content compared to calculated value [N%; Calculated 11.9, Found 9.64] indicating good loading reaction yield.



P1 **P3**

Scheme 3. Reaction of CPHS with 1,3-diamino propane

The amination reaction was also confirmed via FTIR analysis by which the IR spectrum of **P3** (Figure 2) showed a new absorption band at 1452 cm^{-1} due to $N-CH_2$ bond.

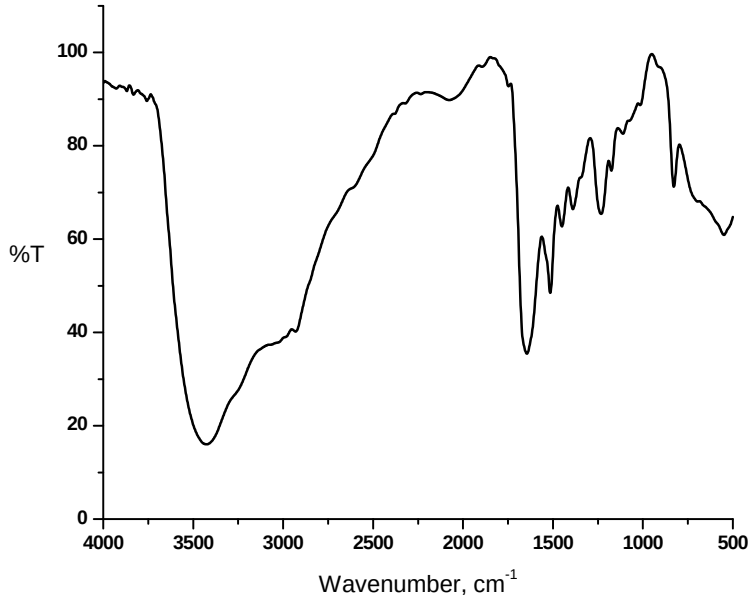


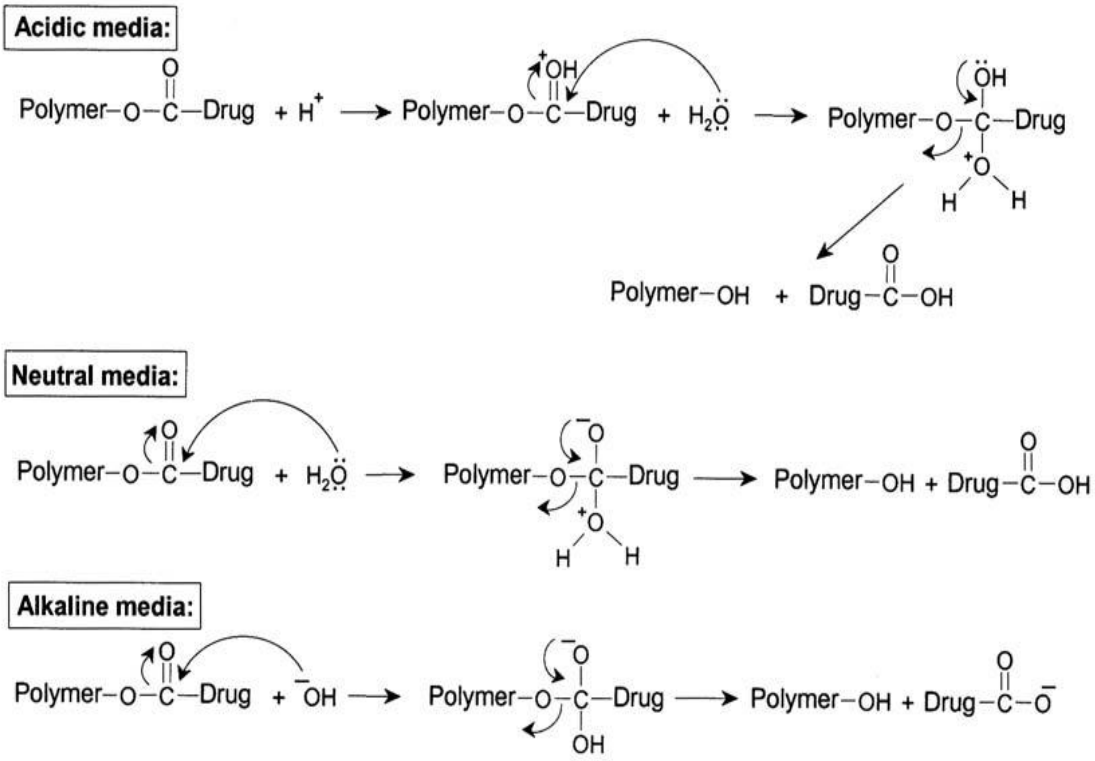
Figure 2. FTIR spectrum of aminated CPHS polymer (**P3**)

3.2. *In vitro* drug release

Aiming to study the potential application of polymer-diclofenac conjugate as pharmaceutically active compound, the in vitro hydrolysis behavior of the polymeric prodrug was studied in aqueous phosphate buffer solutions (pH 1.2, 7.4 and 9) at 37 ^{o}C. The hydrolysis of polymer-drug bond was found to be dependent on its distance from the main polymer chain. However, the length and hydrophilicity of the spacer unit between the polymer backbone and drug can affect the rate of release (Babazadeh, 2007). The polymer–drug conjugate was dispersed in buffer solutions and the released process followed by UV spectrophotometer by detecting the absorbance peak of released drug at 276 nm.

The polymer–drug conjugate released the drug gradually under mild conditions in phosphate buffer by the hydrolysis of the ester bond between the drug and the side chain of the polymer during the hydrolysis experiment time (26 h). Two hydrolysable ester bonds were present in the CPHS-diclofenac conjugate, but hydrolysis occurred on the side ester bond (Scheme 4). Because, the direct ester linked to the main chain of the polymer was less susceptible towards hydrolysis due to the steric hindrance of bulk polymer chains and the decrease in the bond mobility (Babazadeh, 2007). Figure 3 shows the degree of hydrolysis of the conjugate of CPHS-diclofenac (containing 96 mol% of diclofenac groups) as a function of time. At pH of 1.2, the polymer-diclofenac adduct released only 12.3 % of its drug content during the reaction time (26 h) in buffer solution at 37 ^{o}C, while at pH of 7.4 the released drug amount increased to 50.7 % under the same released conditions. Moreover, at pH of 9.0, the polymer-diclofenac adduct released 85.22 % of its drug content. By this way, we have achieved protection of the stomach and targeted controlled release of the drug to colon. Scheme 4 explains the proposed mechanism for hydrolysis of drug from polymer.

The obtained results showed that by passing polymeric prodrug from acidic medium to slightly alkaline pH mediums, the labile bonds are more accessible to hydrolysis. Therefore, in alkaline pH, the polymer-drug bond is easily hydrolyzed to release diclofenac. Thus, the studied polymer could be used in prolongation of transit time and is useful as drug carrier for development as pH-sensitive polymeric prodrugs.



Scheme 4. The hydrolysis mechanisms of polymeric prodrugs in different pH media (Babazadeh et al., 2013).

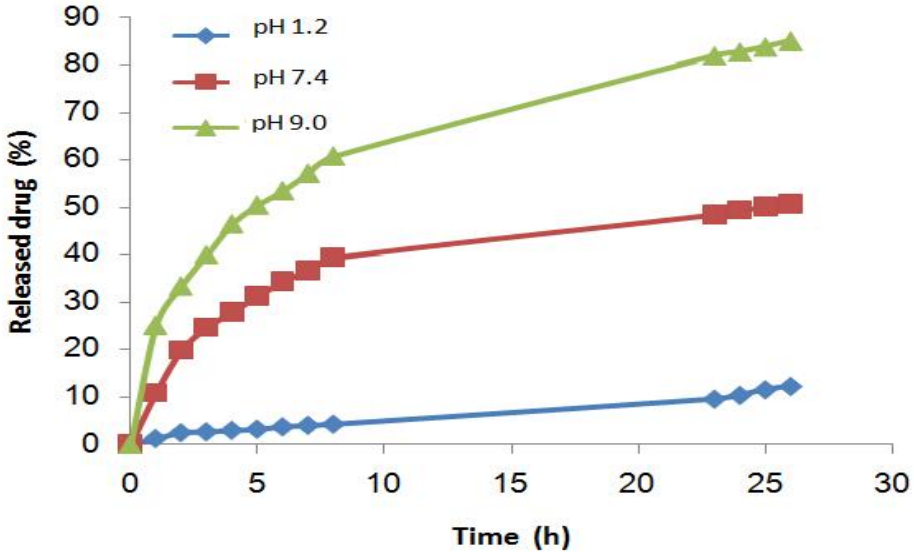


Figure 3. The cumulative drug release % from polymeric carrier as a function of time in phosphate buffer (pH 1.2, 7.4 and 9.0) at 37 ^{o}C.

3.3. Antimicrobial activities of the polymers

To evaluate the antimicrobial activity of the modified polymers **P1** and **P3** as powdered samples, the cut plug method was applied as described by Pridiham et al (Pridham et al., 1956). The wells were made and each was filled with 20 mg of the test polymer. The plates were then incubated at 37 $^{\circ}$C for 24 h. The diameter of the inhibition zone (mm) was measured and the material which produced a highest positive inhibition was selected for further studies. The capability of the modified polymers to inhibit the growth of the examined bacteria on solid media was tested (Table 2). The capability of the synthesized polymers to inhibit the growth of the examined microorganisms on solid media is shown in (Figure 4). Diameter of inhibition zone varied according to the nature of active group of the modified polymers and the selected microorganism. The poly (*p*-hydroxystyrene) in its powder form showed no activity on the tested microorganisms. The modified poly(*p*-hydroxystyrene) **P1** and **P3** showed variable inhibitory effect on the bacteria (diameters of inhibition zones ranged between 10–25 mm) after 24 h of incubation. The modified polymer **P1** was the most effective on both gram positive and gram negative bacteria because it has large clear inhibition zone (diameters of inhibition zones ranged between 21–25 mm) after 24 h of incubation on solid media. Polymer **P3** was mostly effective against *Pseudomonas aeruginosa* (inhibition zone was 17 mm), *Klebsiella pneumoniae*, *Escherichia coli* and *Enterococcus* (the inhibition zones were 15, 12 and 10 mm, respectively). However, it showed no effect against *Staphylococcus aureus* and *Salmonella typhi* (Table 2).

The results of the first screening indicated that polymer **P1** which has chloroacetate groups was the most active as antibacterial agent compared to the original poly(*p*-hydroxysterene) than the other polymer **P3**. Thus, the biocide activity of different concentrations of polymer **P1** against representative Gram-positive bacteria (*Staph. aureus*), Gram-negative bacteria (*E. coli*) and *S. typhi* were assessed in more details. The growth inhibition was quantitatively determined by the ratio M/C of the surviving cell number (Figure 5). The growth inhibitory effect of polymer **P1** differed according to the tested bacteria. The sensitivity of the microorganisms was in the following order *S. typhi* > *Staph. aureus* > *E. coli*. The obtained results showed also that the inhibitory effect increased by increasing the concentration of the polymer (Kenawy et al., 2002).

Table 2. Diameters of inhibition zones (mm) produced by 20 mg powdery polymers of modified poly (*p*-hydroxystyrene) against different bacteria after 24 h by cut plug method on Meuller-Hinton agar at 37 °C.

Tested microorganism	Polymer P1	Polymer P3
Staphylococcus aureus	25 mm	-------
Enterococcus	22 mm	10 mm
Escherichia coli	21 mm	12 mm
Pseudomonas aeruginosa	23 mm	17 mm
Salmonella typhi	22 mm	------
Klebsiella pneumoniae	25 mm	15 mm

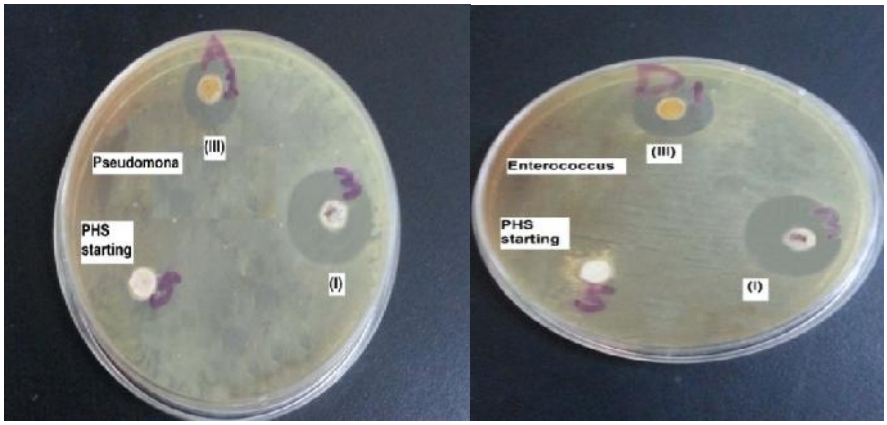


Figure 4. Inhibition zone of polymers PHS starting, (l) and (lll) against different species of microorganisms.

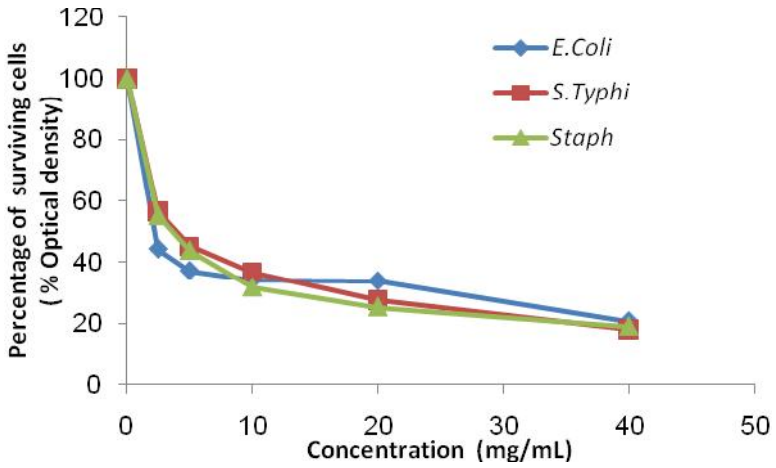


Figure 5. Growth inhibition of CPHS

4. Conclusion

In the present research, we have prepared CPHS as a result of functionalizing PHS with chloroacetyl groups. A novel prodrug was obtained by reacting CPHS with sodium diclofenacate. CPHS was further functionalized with 1,3-diamino propane and the antimicrobial activity of both polymers was tested. The chemical structures of all the synthesized products were confirmed by means of FTIR, ^{1}H-NMR spectra as well as by elemental analysis. The biocide activity varied according to the nature of polymer active groups, its concentration and the test microorganism. The synthesized polymers showed good antibacterial activities. The hydrolysis of the polymer-drug conjugate under physiological conditions was also investigated. The obtained results showed that the percentage of drug released increases with increasing the pH value of buffer solutions. The obtained results suggested that the CPHS-diclofenac conjugate can be considered as a promising carrier for colon targeted controlled release of the drug.

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