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Synthesis and Preliminary Pharmaceutical Evaluation of New Polymeric Prodrug of Levofloxacin as a Drug Delivery System

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Abstract

In this work, a new polymeric prodrug was successfully synthesized by Fischer-esterification between chitosan as biodegradable polymer and levofloxacin as drug material. Levofloxacin was linked directly to the chitosan through a degradable ester bond at (chitosan: levofloxacin) ratios of (1:1), (1:2), and (2:1). The resulting product was characterized by Fourier transform infrared spectroscopy, ultraviolet spectroscopy, thermogravimetric analysis, and differential scanning calorimetry to confirm its structure. Furthermore, the physical properties of the product were determined. The polymer–drug conjugate was evaluated for its drug content and in vitro drug release at pH 1.2 at a condition similar to physiological conditions. Profile of the in vitro drug release showed that levofloxacin was released in a sustained manner from pro(1:2). A high swelling index for pro(1:2) confirmed this finding. Therefore, the ester bond hydrolyzed in acidic media to release the drug. Antibacterial assay was conducted for synthesized prodrug against *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* species. The polymeric prodrug could be used successfully as a controlled drug delivery system.

***Keywords*:** Antibacterial activity,Chitosan, Ester hydrolysis, Levofloxacin, Polymeric prodrug, Sustained released.

INTRODUCTION

Natural polymeric materials, such as polysaccharides and peptides, are currently attracting attention as biodegradable drug carriers [1]. They may reduce undesirable drug effects, improve drug efficiency, and optimize the therapeutic application of drugs. These materials have been used to improve solubility and membrane permeability and prolong the release of drugs as depot forms and drugs targeted at site-specific[2].

Polymeric prodrugs are considered a novel approach to drug delivery systems. These systems contain macromolecular chains as drug carriers bounded physically or by chemical linkage to the drug molecule as side groups. These systems deliver drugs by cleavage of the covalent bonds, induce chemically or biologically, increase stability, water solubility, and drug therapeutic efficiency, and reduce dose frequency and adverse and toxic effects of therapeutic agents by controlling the release regarding the site, duration, and rate [3,4].

Chitosan is alinear natural polysaccharide that consists of b-(1,4)-linked glucosamine units (2-amino-2-deoxy-b-D-glucopyranose) with some proportions of N-acetyl glucosamine units (2-acetamido-2-deoxy-b-D-glucopyranose) [5], as shown in Figure 1. Chitosan is considered one of the most known nontoxic polymers in advanced mobile hydrogel formulation because it is biocompatible and biodegradable and has bacteriostatic activity [6].

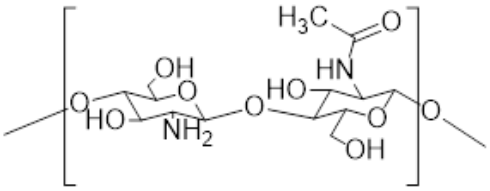

Figure 1: The chemical structure of chitosan[7].

Chitosan is an exceptional candidate for achievement in cosmetics[8], pharmacy[9], medicine[10], and agriculture[11]. It is also used in agricultural commodity preservation [12] and food[13]and wastewater treatment[14]. Chitosan has been used widely in other industries and exhibits remarkable biological properties, such as antibacterial,

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antimicrobial, coagulating activities, wound healing capacity, bioadhesiveness[8]andwool fibers asnanochitosan[15].

Bergera*et al*. [16] demonstrated that chitosan hydrogels are either covalently or ionically crosslinked similar to different advanced mobile hydrogels. Covalently crosslinked chitosan hydrogels do not show pH-sensitive swelling or drug release due to the powerful covalent bonds between chitosan chains, whereas ionically crosslinked chitosan networks usually show pH-sensitive swelling and drug release through their porous structure.

The polymeric prodrug has been successfully synthesized as an amide linkage between chitosan and ciprofloxacin as a drug delivery system. The drug shows sustained release in alkaline media more than that in acidic media. The biological assay reveals that antibacterial activity has been potentiated. Thus, each substance acts as promoiety for the other[17].

An electrostatic interaction has been used to synthesize polymer–drug conjugate of chitosan–ciprofloxacin (CH–CFX) as a complex between the amino group of chitosan and carboxyl group of ciprofloxacin drug by using a mixture of glacial acetic, water, and isopropyl alcohol, and solution casting method has been used to make the film. CH–CFX complex has several times greater antibacterial activity than the parent drug ciprofloxacin[18]. Furthermore, the prodrug of chitosan–prednisolone succinate has been prepared by the same method[19]. A colon-specific prodrug has been synthesized by the reaction of 1-acetic acid-5-fluorouracil (FUAC) with chitosan as an amide linkage of chitosan–1-acetic acid-5-fluorouracil (CS–FUAC) conjugates. The synthesized compound has a significantly longer half-life and greater stability than FUAC. The toxicity level indicated for CS–FUAC by hemolytic activity is lower than that for 5-FU, and CS–FUAC is more cytotoxic than the free drug. Therefore, this conjugate is considered a potential colon-site specific agent to deliver drugs for colon cancer therapy with low side effects[20].

The polymeric prodrug may be a suitable method for developing a controlled release formulation. In this study, we aimed to synthesize the chitosan–levofloxacin polymeric prodrug ester as a promising carrier with sustained-release characteristics. Thus, a new drug delivery system of chitosan–levofloxacin prodrug was synthesized. Furthermore, the antibacterial activity and drug release profile were evaluated.

MATERIALS AND METHODS

Chemicals

All used chemicals with analytical grade were purchased from commercial sources. Chitosan was purchased from China. Levofloxacin was obtained as a gift from the Pioneer Company. The other chemicals were acetone (99% purity, Chem-Lab NV., Belgium), sulfuric acid (99% purity, Aldrich 49/1586-LTD, Germany), sodium hydrogen carbonate (Scharlau, Barcelona, Spain), hydrochloric acid (35%–36.6% purity, Atom Scientific, UK), and acetic acid glacial (HIMEDIA, India). All chemical ingredients were used without further purification.

Instrumental measurements

The Fourier transform infrared spectroscopy (FTIR) spectrum was recorded by an 84005 SHIMADZU spectrophotometerat the University of Basrah, College of Education for Pure Sciences. Thermal stability of differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) was assessed using an SDT Q600 V20.9 Build 20 thermogravimeterat the University of Tehran, Central lab. An ultraviolet (UV) detector (CECILL CE 2700 UV–visible double beam spectrophotometer) was used to estimate the drug content utilizing 1 cm cells, and the amount of levofloxacin released from the tablet was determined using a GB CALEVA dissolution apparatusat the University of Basrah, College of pharmacy.

Synthesis of chitosan–levofloxacin prodrugs

The prodrug esters were synthesized according to Hefni, *et al*. [21] at three different chitosan–levofloxacin ratios (1:1, 1:2, and 2:1). The three ratios are denoted as pro(1:1), pro(1:2), and pro(2:1), respectively. Certain amounts of chitosan (calculated as monomers 1.6, 0.8, and 1.6 g) were dissolved in specific volumes of 1% glacial acetic acid (80, 60, and 100 ml) in 250 ml round flasks with continuous stirring at room temperature of 25 °C on a hotplate stirrer overnight until clear solutions were obtained. Certain amounts of levofloxacin (3.61, 3.61, and 1.8 g) were added to chitosan solution until they became homogenous. The desired volumes of 2M H_2SO_4 (1.25, 3, and 5 ml) were added drop-wise as a catalyst for the reaction. The mixture was refluxed for 8 h at 100 °C by using a condenser and a hotplate stirrer.After cooling, the mixture was neutralized to pH 7 by using 5% $NaHCO_3$ (to remove unreacted acid) and then precipitated with acetone for a few hours. Thereafter, it was filtered using Whatman filter paper and washed several times with acetone. Finally, it was left to dry at room temperature of 25 °C, milled by a mortar, and collected for characterization**.**

Swelling index study

The swelling behavior of the tablets was measured by studying the weight gained by tablets. This study was performed utilizing a basket of CALIVA dissolution

apparatus. The preweighted tablets were placed in a dissolution basket. The basket was immersed in a 100 ml beaker containing 25 ml of 0.1 N HCl (pH 1.2). At time intervals of 2, 15, 30, 60, 120, 180, 240, and 300 min, the basket was removed, and excess of solution was removed with a tissue paper and reweighted using a sensitive balance[22]. The percentage of swelling index SI (i.e., the swelling degree of the tablet due to absorbed medium) was calculated using the following equation:

$$SI=(weightoftabletsattime\ (t)-Initialweightoftablet)/Initialweightoftablet\times 100$$[23].

Estimation of drug content for prodrugs

The synthesized polymeric prodrugs (100 mg) were dissolved in a volumetric flask containing 100 ml of 0.1N HCl solution until a clear solution was obtained from the complete release of drug content by hydrolysis from the drug–polymer backbone. The drug contents were filtered using a filter paper, and 1 ml of that solution was diluted to 10 ml with 0.1N HCl. Drug contents were estimated spectrophotometrically by measuring the absorbance of the filtered solution at 293 nm using a UV double beam spectrophotometer.

In vitro drug release study

The drug release analysis for polymeric prodrug tablets was performed in vitro by using the dissolution apparatus. A total of 500 mg of polymeric prodrugs containing an equivalent amount of levofloxacin was compressed into tablets (with 150 mg calcium carbonate and 130 mg microcrystalline cellulose (Avicel) as a compressing agent and binder, respectively) with a single punch tablet machine. In vitro behavior of each tablet was studied in 900 ml of 0.1N HCl pH 1.2 for 5 h at 37 °C and 50 rpm. At different time intervals, samples of 5 ml were withdrawn and replaced with the same volume of 0.1N HCl to maintain the sink condition. Then, these samples were filtered by a 0.45 µg syringe filter and assessed spectrophotometrically using a UV spectrophotometric analyzer at λ_{max} 293 nm. The drug release was calculated in triplicate.

Antibacterial activity

The antibacterial activity of polymeric prodrugs was conducted *in vitro* against three types of bacteria (Escherichia coli, Pseudomonas aeruginosa as gram-negative bacteria, and Staphylococcus aureus as gram-positive bacteria) using the paper disc agar diffusion technique on Muller Hinton agar as a culture media for antibacterial activity[24]. Standard solutions were prepared by dissolving 1 mg of each compound (levofloxacin, chitosan, pro(1:1), pro(1:2), and pro(2:1)) in 10 ml (0.1N) HCl as a solvent. The recommended concentrations of 20 and 100 µg/ml were used in this study. The plates were incubated for 24 h at 37 °C. The HCl 0.1N was used as control and levofloxacin as drug and standard. The diameters of inhibition zone were measured in millimetersby a physical ruler [25].Tests were carried out at the University of Basrah, College of pharmacy.

RESULTS AND DISCUSSION

The polymeric prodrugs were synthesized by direct esterification of chitosan and levofloxacin. All polymeric prodrug esters in this study were synthesized by Fischer-esterification using sulfuric acid as a catalyst. The mechanism of esterification of chitosan involved the transfer of the proton to carbonyl oxygen from the acid catalyst, which increased the electrophilicity of carbonyl carbon. The carbonyl carbon was attacked by an alcoholic–nucleophilic oxygen atom. Then, activated complex was formed by the transfer of a proton from the oxonium ion to the second molecule of alcohol. The new oxonium ion was formed by the protonation of one hydroxyl group of the activated complex. Ultimately, the oxonium ion was dehydrated by losing water molecule and subsequently produced chitosan–ester by deprotonation[26]. The mechanism of chitosan esterification is illustrated in Figure 2.

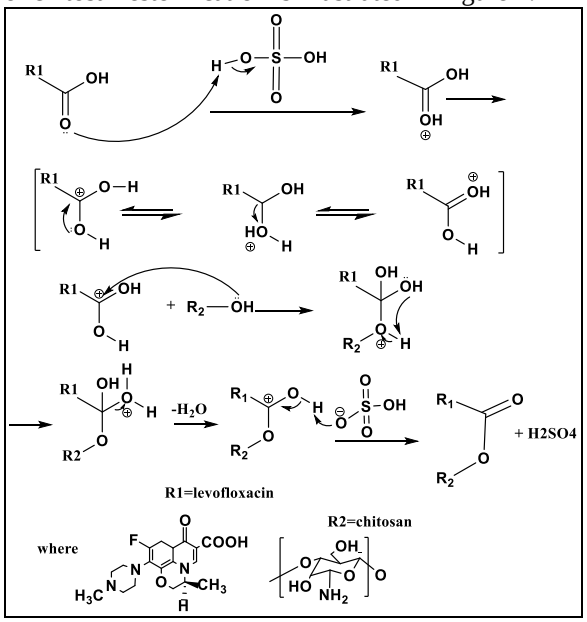


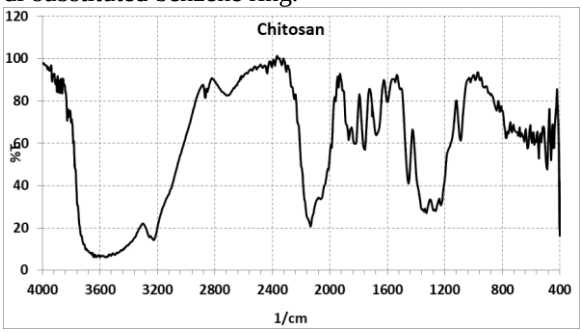
Figure 2: Schematic esterification of chitosan with levofloxacin [26]

The polymer–drug conjugates were synthesized at different ratios to estimate a successful reaction and increase the product yield by adding an excess amount of each reactant[27]. The physical properties of the prodrugs are listed in Table 1.

Table 1: Physical properties of chitosan-levofloxacin prodrugs.

Products	Color	solubility	Percentage of yield
pro(1:1)	White powder	0.1N HCl	52.6%
pro(1:2)	White powder	0.1N HCl	70.79%
pro(2:1)	Paige	0.1N HCl	28.6%

The FTIR spectra of chitosan, levofloxacin, and chitosan–levofloxacin ester derivatives are shown in Figure 2. The spectrum of chitosan (Figure 3a) showed peaks at 3483–34120 cm^{-1} (attributed to the N–H, O–H, and hydrogen-bonded O–H stretching), 2924 and 2881 cm^{-1} (symmetric and asymmetric CH_2 stretching, respectively), 2376 cm^{-1} (C–N asymmetric stretching), 1651 cm^{-1} (C=O amide II stretching of an acetyl group), 1600 cm^{-1} (amide II band and N–H stretching), and 1458–1022 cm^{-1} (C–O stretching of 2° OH and C–O stretching of the bridge). The prodrug spectrum in Figure 3b revealed broad and strong bands at 3402 cm^{-1} (attributed to N–H stretching and hydrogen bonding), 2924 and 2856 cm^{-1} (CH_3 and CH_2 stretching for chitosan and levofloxacin, respectively), and 2382 cm^{-1} (asymmetric C–N stretching). The appearance of a peak at 1700 cm^{-1} as a shoulder confirmed the ester formation (C=O ester). The characteristic band of NH_2 of chitosan shifted from 1600 cm^{-1} to 1597 cm^{-1} in the prodrug due to protonation of NH_2 to NH_3^+ with the remaining acetic acid. The disappearance of the characteristic band at 1022 cm^{-1} of 1° OH of chitosan indicated the ester formation. The disappearance of OH stretching at 3259 cm^{-1} of levofloxacin confirmed the esterification process between chitosan and levofloxacin. The peak at 1456 cm^{-1} was related to C=C of levofloxacin, that at 1377 cm^{-1} was assigned to the C–F stretching band, that at 1149–1035 cm^{-1} was attributed to the superimposed C–O–C stretching band of chitosan and levofloxacin, and that at 973–684 cm^{-1} was related to the mono and di-substituted benzene ring.



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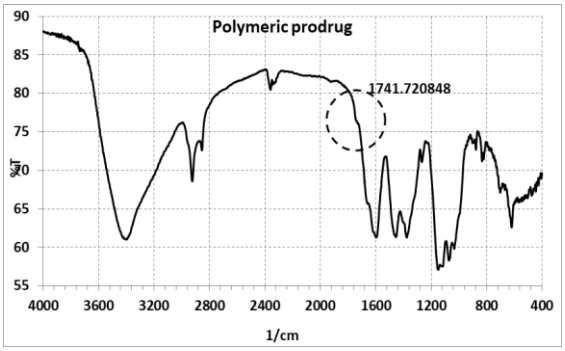


(b)

Figure 3: FTIR spectrum of (a) Chitosan, (b) Polymeric prodrug.

The TGA curves of chitosan and its derivatives are shown in Figure 4. The thermogram revealed that chitosan had two degradation stages. The first one started at 79.94 °C and up to 110 °C, which was due to water loss and was related to the hydrophilicity of chitosan. The second stage started at 275 °C, which was attributed to the decomposition and depolymerization of the polysaccharides' basic unit[28]. The TGA curve showed that all polymeric prodrugs had two degradation stages as a result of water evaporation. Pro(1:2) had the shortest phase, which started at 70-120 °C, compared with the two others. The second stage started at 250 °C for the three products. This latest phase referred to the decomposition of the products. The interaction of chitosan with levofloxacin required lower temperature for melting and degradation of polymeric prodrug than that for chitosan and levofloxacin. This phenomenon happened due to the reduction in water holding capacity during the interaction. The data confirmed that the synthesized ester was formed[29].

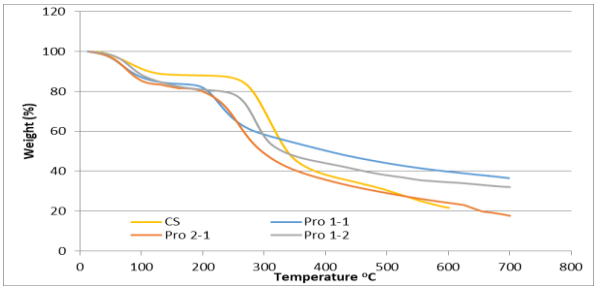


Figure 4: TGA thermogramm of chitosan and polymeric prodrugs

The DSC results are shown in Figure 5 for chitosan and the synthesized polymeric prodrug. The DSC curves of chitosan revealed that the original chitosan had one endothermic phase at 101.86 °C and one exothermic phase at 329.55 °C. The endothermic phase resulted from the evaporation of water, which

caused a reduction in temperature. The exothermic phase was due to decomposition and heat generation. Chitosan is a polysaccharide that has a high affinity for water. Thus, the endotherm is generally attributed to water evaporation. The strength of the interaction between water and polymer was affected by their capacity to hold water, which varied in these molecules[30]. The DSC thermogram showed that all three polymeric prodrugs had a different result from that of chitosan and levofloxacin. Pro(1:1) and pro(1:2) only had exothermic phases at 249.09 °C and 271.90 °C, respectively. These findings confirmed that these products had undergone thermo-decomposition faster than the original chitosan and levofloxacin. Pro(2:1) only had an endothermic phase at 125.92 °C. The disappearance of an endothermic fusion peak indicated that the chitosan reacted with levofloxacin[29].Since the endothermic peak resulted from water evaporation and after ester formed between (OH) hydroxyl group of chitosan and (COOH) carboxyl group of levofloxacin this might reduce free water for evaporation.

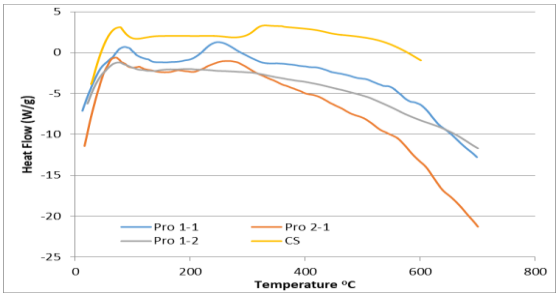


Figure 5: DSC thermograms of chitosan and polymeric prodrugs

Polymeric prodrugs were scanned by the UV spectrophotometer and revealed the same spectra as that of the free drug but at lower absorbance due to that the drug amount incorporated in prodrugs was small. Thus, polymer–drug conjugate could release levofloxacin by hydrolysis of the ester bond in acidic media. Furthermore, levofloxacin contents were measured and found to be 0.394, 0.494, and 0.130 g/g in pro(1:1), pro(1:2), and pro(2:1), respectively. The increase in the amount of drug reacted with polymer increased the drug content within the product. This condition might contribute to the excess amount of drug, which ensured that each hydroxyl group of chitosan reacted with a carboxyl group of levofloxacin to produce an ester linkage. Thus, pro(1:2) had more drug content than pro(1:1), whereas pro(2:1) had the lowest amount due to more O–H groups than COOH groups of chitosan (Figure 2).

The swelling study of the prepared tablets with time is illustrated in Figure 6. The weight of the prepared tablet increased directly with the hydration rate. Thereafter, the weight reduced gradually because the tablet external gelling layer exhibited dissolution in the solvent used[31]. The data revealed that pro(1:2) showed the highest swelling ratio compared with pro(1:1) and pro(2:1). This finding might be due to that it exhibited higher hydration than the other. These findings explained the swelling of pro(1:2) within the dissolution time.

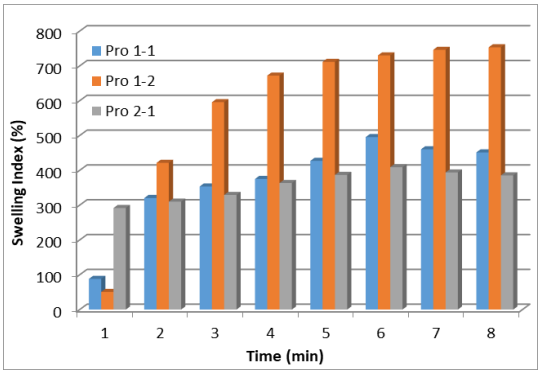


Figure 6: Swelling study of polymeric prodrug tablets.

The results of the in vitro drug release study showed that the drug release amounts were 19.5, 3.1, and 0.6 mg from the synthesized pro(1:1), pro(1:2), and pro(2:1), respectively, after 1 h at pH 1.2 (Figure 7). Pro(1:1) released approximately 50% and 72% of its drug content in the first and second hours. Then, the drug release slowed down at a constant percentage (around 1%/h) for the next 3 h. After 5 h, the total release reached 74%. Meanwhile, pro(1:2) released approximately 6% of its drug content at the first hour of the dissolution process. For the next four hours, the drug release increased slightly in linear behavior at a constant rate (nearly 3 mg/h). After 5 h, the total drug release reached 16%. For pro(2:1), the drug release revealed a steady-state manner at 5% from the first half-hour until the end of the process. This behavior might be attributed to the covalent or inter and intra-hydrogen bonds, which prevented the drug release. This type of bond was produced due to the high amount of polymer within the polymeric prodrug. Accordingly, pro(2:1) could not be considered a successful controlled release drug delivery system. The drug release results concluded that pro(1:2) can be used as a successful controlled released drug delivery system.

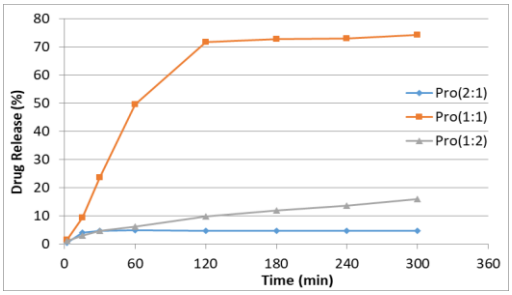


Figure 7: Percent of levofloxacin released from polymeric prodrug as a function of time at 0.1N HCl and 37°C.

Drug released from polymeric prodrug can be explained by the hydrolysis of ester linkage in acidic media, as shown in Figure 8. The hydrolysis rate of drugs linked to polymers is affected by many factors, such as chemical nature, the strength of the linker between the drug and polymer, the surrounding condition, and the presence of spacer, which affects the drug release (depending on its length and hydrophilicity). The drug is released from the polymeric prodrug in an acidic media by a mechanism called acid-catalyzed hydrolysis. Thus, the oxygen atom of the ester linkage will be protonated followed by a concomitant attack on the carbonyl carbon. Here, the catalyst of the process was regenerated. However, the reactions of hydrolysis catalyzed by acid were reversible and directed toward equilibrium with equilibrium constant[32].

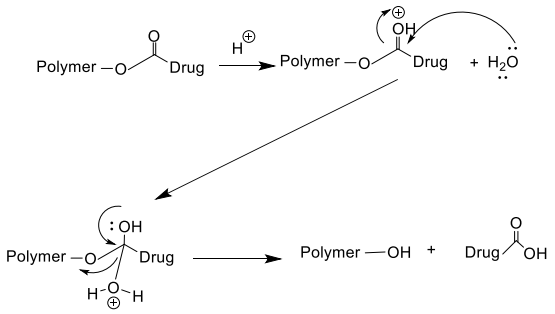


Figure 8: Mechanism of ester hydrolysis in aqueous acidic media[33].

Antibacterial activity results for levofloxacin and its polymeric prodrugs are illustrated in Table 2 and Figure 9. The antibacterial activity of levofloxacin, pro(1:1), and pro(1:2) was recorded with different degrees against S. aureus at maximum and minimum concentrations. Meanwhile, pro(2:1) had the lowest antibacterial at the maximum concentration only. This finding could be due to that the drug amount incorporated within pro(2:1) was insufficient to inhibit bacterial growth even at maximum concentration.

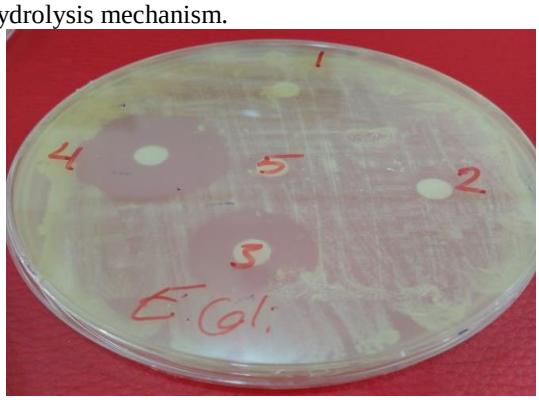
Table 2: Antibacterial activity of levofloxacin and its polymeric prodrugs.

Compounds	Concentration µg/ml	Inhibition zone diameter (mm)[a]		
		Staph. aureus	*E. coli*	*Ps. aeruginosa*
Levofloxacin	20	20	20	0
	100	30	27	0
Chitosan	20	0	0	0
	100	0	0	0
pro(1:1)	20	10	0	0
	100	11	0	0
pro(1:2)	20	10	0	0
	100	11	14	0
pro(2:1)	20	0	0	0
	100	6	0	0
0.1N HCl	0	0	0	0

[a]Hole diameter (= 5mm) was not subtracted.

E. coli species showed bacterial growth inhibition only with levofloxacin and pro(1:2) at maximum concentration. Neither levofloxacin nor its prodrugs demonstrated any antibacterial activity against P. aeruginosa species at studied concentrations. The bacterial resistance depended on the isolated species in general.

In contrast to a polymeric prodrug of chitosan–ciprofloxacin prepared by ionic interaction[18], the antibacterial activity of chitosan–levofloxacin reduced by half due to that the amount of drug incorporated was lower as estimated spectrophotometrically by UV in the drug content. The results proved that the synthesized ester by chemical interaction could release drugs by an acid hydrolysis mechanism.



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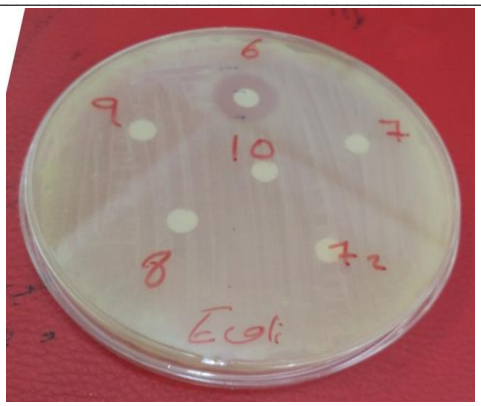

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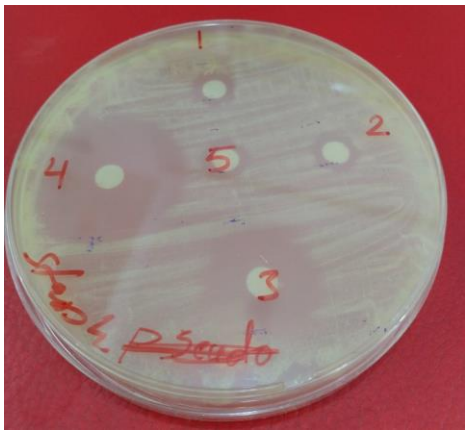

(c)

Figure 9: Compounds activity against (a, b) *E. coli* and (c) *Staph. aureus*.

CONCLUSION

In this work, a new polymeric prodrug of chitosan–levofloxacin esters was synthesized and characterized by FTIR, UV, TGA, and DSC and was scanned for its antibacterial activity. Polymeric prodrugs were evaluated for drug content estimation, swelling index, and in vitro drug release. The results demonstrated that pro(1:2) had the highest drug content andswelling index compared with the others and showed sustained release in acidic media. Our work findings revealed that pro(1:2) is a suitable system for the delivery of drugs. This developed polymeric prodrug delivery system can also be used as a promising carrier to prolong the residence time of drugs and improve their therapeutic effect and bioavailability in the future.

ACKNOWLEDGEMENT

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التصنيع والتقييم الصيدلاني الأولي لمنتج بوليمرجديد من levofloxacinكنظام لتوصيل الدواء

الخلاصة

في هذا العمل ، تم تصنيع دواء أولي بوليميري جديد بنجاح عن طريق الأسترة فيشر بين (chitosan) كبوليمر قابل للتحلل و (levofloxacin) كمادة دوائية. حيث تم ربط(levofloxacin) مباشرة من خلال رابطة استر قابلة للتحلل بنسب مختلفة من (chitosan: levofloxacin) وكانت النسب (1: 1) و (1: 2) و (2: 1). تم فحص المركب الناتج بواسطة تحليل فورييه للتحليل الطيفي بالأشعة تحت الحمراء ، التحليل الطيفي للأشعة فوق البنفسجية ، التحليل الوزني الحراري ، والمسعرات الحرارية التفاضلية للتأكيد على هيكلها. علاوة على ذلك ، تم تحديد الخصائص الفيزيائية للمنتج. وتم تقييم المحتوى الدوائي في المركب الجديد ومعدل اطلاق الدواء في المختبر عند الرقم الهيدروجيني 1.2 في حالة مشابهة للظروف الفسيولوجية للمعدة. أظهرت النتائج لإطلاق الدواء في المختبر أن (levofloxacin)تم إطلاقه بطريقة مستمرة من المركب(2 :1) pro. وتم تاكيد هذه النتائج بواسطة قيمة مؤشر الانتفاخ المرتفع المركب (2 :1) pro. لذلك ، تتحلل رابطة الإستر في الوسط الحمضي يؤدي الى اطلاقالدواء. تم إجراء الفحص المضاد للبكتيريا بأستخدام المركبات الجديدة ضد Pseudomonas aeruginosa وEscherichia coliو Staphylococcus aureus . يمكن الاستنتاج ان العقاقير الأولية البوليمرية الجديدة يمكن استخدامها بنجاح كنظام إيصال دوائي خاضع للرقابة