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Preparation, characterization and antimicrobial activity of chitosan-fatty acid derivatives as a drug delivery system: intercelation and in vitro release of ciprofloxacin

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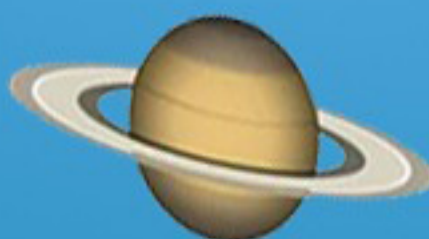
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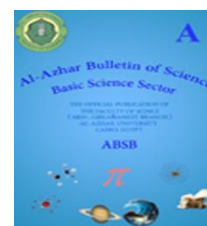
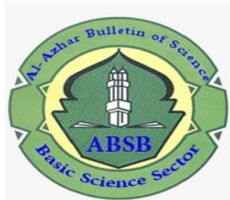
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PREPARATION, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF CHITOSAN-FATTY ACID DERIVATIVES AS A DRUG DELIVERY SYSTEM: INTERCALATION AND IN VITRO RELEASE OF CIPROFLOXACIN

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ABSTRACT

One of the most exciting areas of research in pharmaceutical sciences is the development of new delivery systems for controlled drug release. The main objective of this research focused on chitosan-fatty acid derivatized matrix for drug delivery. Saturated fatty acids (lauric acid and stearic acid) as well as unsaturated fatty acids (oleic acid and linoleic acid) are involved in this study which enhance the chemical properties of chitosan in drug delivery and enhance the permeability of ciprofloxacin drug compounds. The structure of the synthesized derivatives was characterized by Fourier transform infrared spectroscopy and X-ray diffraction. Intercalation and in vitro release of ciprofloxacin was investigated by UV spectrophotometrically. All the prepared chitosan derivatives showed a potent antimicrobial activity. It was observed that the release study of drug was maximum at the beginning and then released slowly. The initial burst release of drug may be due to the drug which exists on the surface of the film without being trapped efficiently. Chitosan linoleic ciprofloxacin composite (CS-Lin-CF) showed 52% drug release, chitosan stearic ciprofloxacin composite (CS-S-CF) showed 53.2% drug release and chitosan lauric ciprofloxacin composite (CS-L-CF) showed 63.1% drug release, chitosan oleic ciprofloxacin composite (CS-OI-CF) showed 79.1% drug release at 8 hours.

Keywords: Chitosan; Lauric acid; Stearic acid; Linoleic acid; Ciprofloxacin

1. INTRODUCTION

Regulated drug delivery systems in the field of pharmaceuticals have been of considerable importance over the last few decades to achieve efficient and targeted drug delivery and to minimize side effects. Particular attention has been paid to finding a way to control the rate of drug release by a carrier where the drug is dispersed or incorporated into an inert matrix [1]. Drug delivery research involves drug release from a dose in terms of drug uptake alteration technology, bioavailability enhancement, control methods for the absorption rate, optimization, and the ability to control the distribution of the drug within the body (drug targeting) [2,3]. Due to their biocompatibility, biodegradability, easy processing and repeatability, natural polymers are ideal drug carriers.

Chitin is the second most common biopolymer naturally occurring in the world (it is Available at Egyptian Knowledge Bank (EKP)

not soluble in aqueous acidic media) and is the main component of exoskeletal crustaceans such as crabs and shrimps [4]. It becomes soluble in aqueous acidic media when the deacetylation amount of chitin molecules approaches approximately 40 percent and is referred to as chitosan [4]. The latter is a co-polymer of units of glucosamine and N-acetylglucosamine bound by 1-4 glycosidic bonds [5]. A biocompatible, plentiful, biodegradable, non-toxic and renewable carbohydrate polymer [9] is defined as chitosan. It has various biological activities, including antimicrobial, antioxidant, immuno-enhancing [10] and antitumor activities [11]. Chitosan's biomedical applications include drug delivery, wound dressings, implant coatings, tissue engineering, and therapeutic agents' delivery systems [5-8].

In addition, many polycationic chitosan primary amines allow it to be easily modified by

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mixing with certain functional polymers. The continuing increase in interest in polymeric matrices for pharmaceutical formulation can be used as a treatment to minimize the concentration of plasma triacylglycerol and to reduce inflammation in patients with rheumatoid arthritis [12-15]. In addition, fatty acids are commonly used in cosmetics such as soaps, fat emulsions and liposomes, either alone or as part of complex lipids. Long-chain fatty acids [16] are known as surface-active anionic detergents and have a long history of more than eighty years of microbiology.

In general, the sensitivity of fatty acids is known to be a trait of gram-positive bacteria, with few gram-negative species susceptible [17,18]. The effective saturated fatty acids, capric acid, lauric acid and stearic acid, showed antimicrobial activity and controlled drug delivery [19-22]. Each hydrophobic chain length depends on the minimum inhibitory concentration (MIC) of saturated fatty acids. Chitosan stearic acid ciprofloxacin drug composite has been found to have the strongest antibacterial activity and drug release properties [23-27]. Unsaturated fatty acids such as linoleic acid and oleic acid are essential for good overall health. They are, respectively, omega-6 and omega-9 fatty acids. Our current study aims to examine the antimicrobial activities of saturated and unsaturated fatty acid as cross linker with chitosan and ciprofloxacin drug

against *S.aureus* and *E. coli*. and drug delivery applications of prepared composites.

2. EXPERIMENTAL

2.1 Materials

Chitosan (CS) (79% deacetylated) was obtained from exoskeleton of shrimp. saturated fatty acids (L, S), unsaturated fatty acids (OI, Lin), sodium hydroxide, acetic acid and glacial acetic acid were reagent grade and used as such. Ciprofloxacin drug (CF) was obtained from Hikma Pharma S.A.E Giza- Egypt.

2.2 Methods

2.2.1 Preparation of chitosan-fatty acid derivatives

To prepare (CS-L), (CS-S), (CS-OI) and (CS-Lin) derivatives. Individually, 10 mg of acids were added to chitosan (dissolved in 1% acetic acid) solution and stirred for 20 hours. They were then poured onto glass plates and air dried for 5 days.

2.2.2 Preparation of CS-fatty acid-drug composites

(CS-L-CF), (CS-S-CF), (CS-OI-CF) and (CS-Lin-CF) composites were prepared according to standard protocol. 1% chitosan solution (1% w/v glacial acetic acid) and ciprofloxacin drug in pure form (300 mg) was dissolved in minimum amount of water and gradually added to the chitosan solution with continuous stirring. The

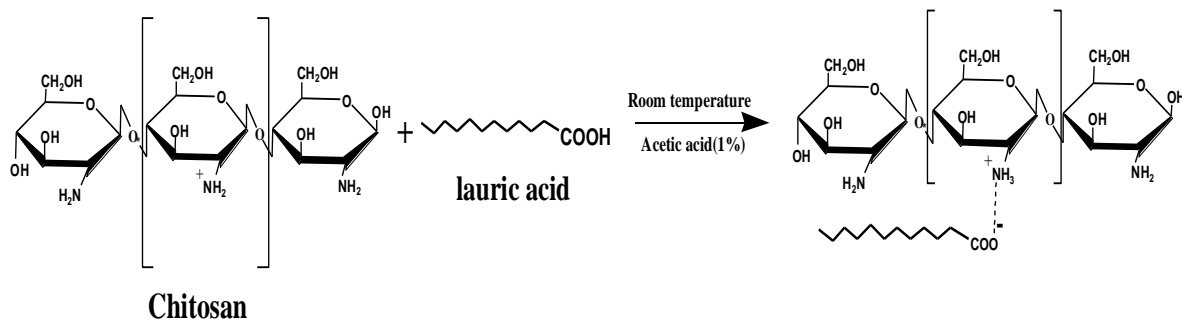


Fig. 1. Preparation of chitosan-lauric acid (n=10) derivative

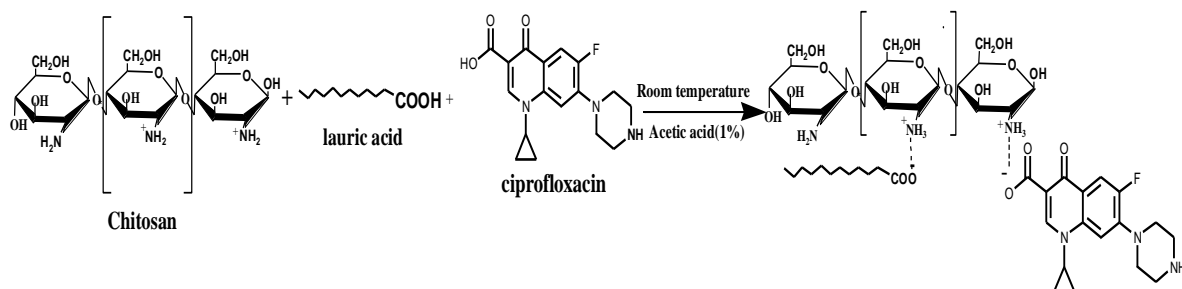


Fig. 2. Preparation of chitosan-lauric acid (n=10) drug composite

mixture was then stirred for 24h at room temperature to obtain the desired pro-drug. The drug loaded films were prepared by pouring and spreading the (CS-L-CF), (CS-S-CF), (CS-OI-CF) and (CS-Lin-CF) mixtures on glass plates and kept for two days at room temperature. After two days films were collected and used for further characterization and drug delivery study.

2.3 Measurements

2.3.1 FTIR analysis

IR spectra of chitosan and chitosan derivatives samples synthesized by solution casting method were recorded on a Perkin Elmer spectrophotometer (Spectrum RX1, Perkin Elmer, Singapore) using KBr pellet technique, in the range 4000-400 cm^{-1} , with a resolution of 2 cm^{-1} , using 4 scans per sample.

2.3.2 XRD analysis

Xray diffraction studies using Xray Powder Diffractometer (XRD – SHIMADZU XD – D1) using Nifiltered Cu K5-007 Xray radiation.

3. RESULTS AND DISCUSSION

3.1 Fourier Transform Infrared Spectroscopy (FTIR).

The FTIR spectrum of chitosan (CS) and fatty acids cross linked chitosan (CS-L), (CS-S), (CS-OI), (CS-Lin) is shown in Fig. 3. The characteristic peak of long-chain fatty acids was observed around 2928–2844 cm^{-1} [28]. The band at 1653 cm^{-1} refers to amide band for C-O stretch of acetyl group, 1593 cm^{-1} attributes amide band for N-H stretch. The band at 1375 cm^{-1} represents asymmetric C-H bending of CH_2 group and 1071 cm^{-1} skeletal vibration involving the linked C-O stretch of glucosamine residue [29]. The bands at 2919 cm^{-1} and 2850 cm^{-1} represent stretching vibrations of $-\text{CH}_2$ and $-\text{CH}_3$ and band at 1733 cm^{-1} for C= O stretching vibrations [30].

The band in 1750 to 1700 cm^{-1} represent the carbonyl C=O stretching. A broad peak at 1742 cm^{-1} (asymmetric stretching vibration of carboxylate) also indicates the inter chain or intermolecular ionic salt bonds, i.e., polyelectrolyte complex (PEC) between amino groups of chitosan and carboxyl groups of lauric acid. In other words, it was believed that PEC formation proceeded at the expense of electrostatic interaction between the positively charged amino groups of the chitosan and the negatively charged carboxyl groups on fatty acids.

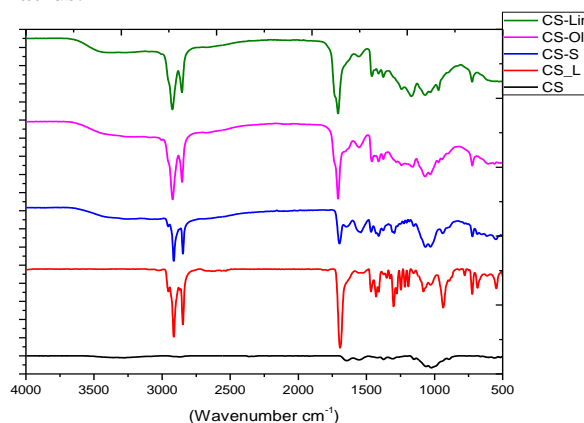


Fig. 3. (FTIR of chitosan (CS), chitosan-fatty acid derivatives (CS-L), (CS-S), (CS-OI) and(CS-Lin).

3.2 X ray diffraction (XRD)

The XRD pattern displayed in Fig. (4) shows regular lattice spacing of lauric acid crosslinked chitosan and lauric acid crosslinked chitosan - ciprofloxacin drug composite. The XRD pattern of lauric acid crosslinked chitosan shows sharp diffraction peaks at 16.2°, 21.4°, 23.8°, 39.4° and 46.3°. The peak of d-spacing 5.4 at $2\theta = 16.2^\circ$ is shifted to $2\theta = 18.0$ and new peak is formed at $2\theta = 12.1$ in the XRD pattern of lauric acid crosslinked chitosan -ciprofloxacin drug composite. This is proved the intercalation of ciprofloxacin drug between chitosan-lauric acid

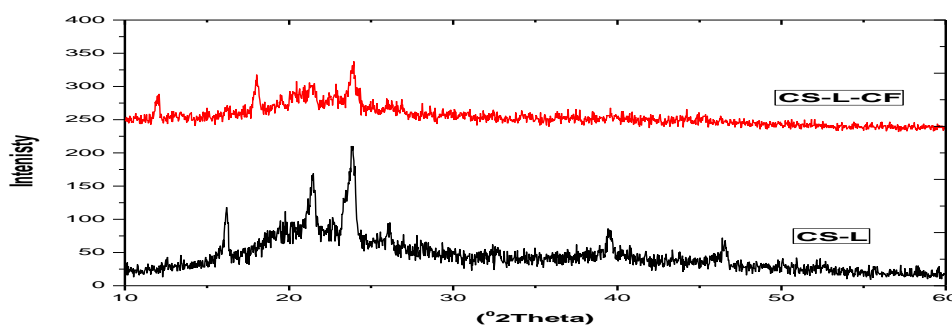


Fig. 4. The XRD spectrum of chitosan- lauric (CS-L) and chitosan-lauric- ciprofloxacin composite (CS-L-CF)

layers. The XRD pattern of lauric acid crosslinked chitosan -ciprofloxacin drug composite shows sharp diffraction peaks at 12.1° , 18.0° , 20.9° and 23.9° .

Fig. (5) shows XRD pattern for stearic acid crosslinked chitosan and stearic acid crosslinked chitosan -ciprofloxacin drug composite. The XRD pattern of stearic acid crosslinked chitosan shows two sharp diffraction peaks at 21.3° and 23.6° while stearic acid crosslinked chitosan -ciprofloxacin drug composite Shows sharp peaks at 11.9° , 21.3° , 23.6° and 26.6° . This proved the intercalation of ciprofloxacin drug between chitosan-stearic acid layers.

Fig. (6) shows XRD pattern for oleic acid crosslinked chitosan and oleic acid crosslinked chitosan -ciprofloxacin drug composite. The XRD pattern of oleic acid crosslinked chitosan shows one broad peaks at $2\theta = 19.6^\circ$ it may be due to the formation of an amorphous material which can be attributed to the intermolecular interaction

between chitosan and oleic acid within the films [42]. Oleic acid crosslinked chitosan-ciprofloxacin drug composite shows peaks at 10.7° , 19.6° , 25.3° and 32.7° which indicate the formation of drug composite.

Fig. (7) shows XRD pattern for linoleic acid crosslinked chitosan and linoleic acid crosslinked chitosan-ciprofloxacin drug composite. The XRD pattern of linoleic acid crosslinked chitosan shows one broad peak at $2\theta = 18.8^\circ$. due to the formation of an amorphous material. Linoleic acid crosslinked chitosan -ciprofloxacin drug composite shows peaks at 10.9° , 18.8° , 25.2° and 26.7° indicating that the crosslinking agent is molecularly dispersed in the polymer matrix which should assist to retard the delivery of the drug. The XRD pattern of CS-OI and CS-Lin drug composite displays an amorphous form, which may participate in pharmaceutical applications [43-45].

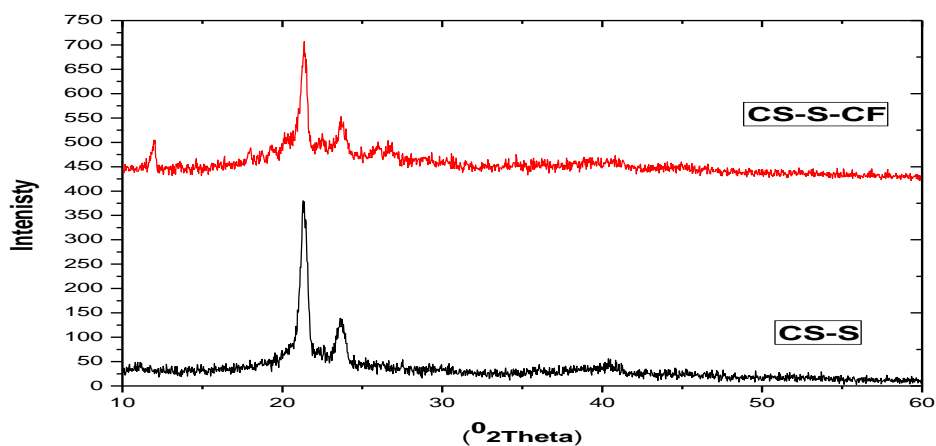


Fig. 5. The XRD spectrum of chitosan- stearic (CS-S) and chitosan-stearic-ciprofloxacin composite (CS-S-CF)

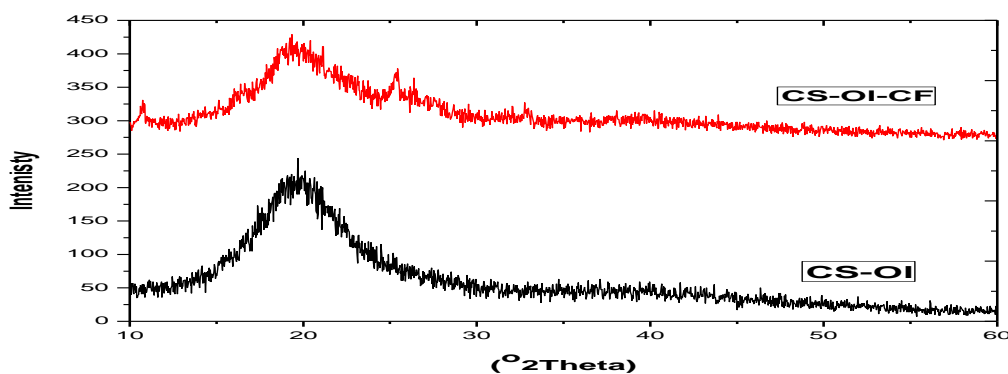


Fig. 6. The XRD spectrum of chitosan-oleic(CS-OI) and chitosan-oleic-ciprofloxacin composite (CS-OI-CF)

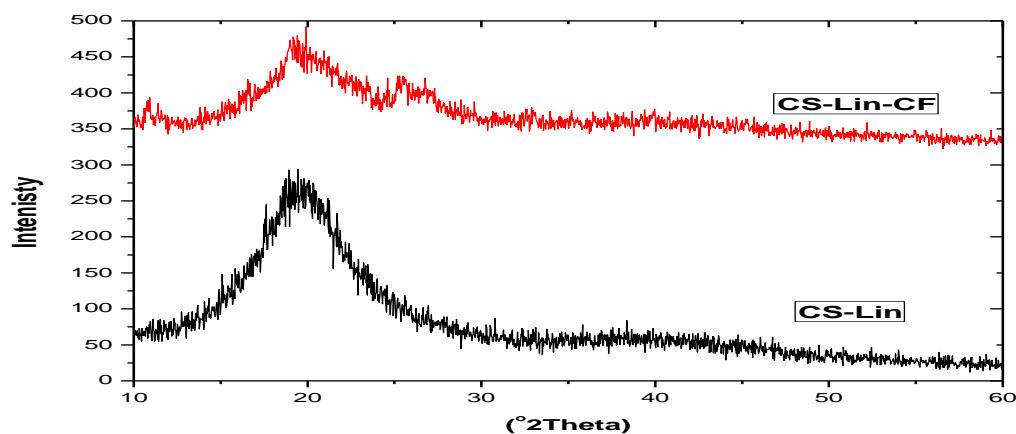


Fig. 7. The XRD spectrum of chitosan- linoleic (CS-Lin)and chitosan- linoleic- ciprofloxacin composite (CS-Lin-CF)

Antibacterial activity

Inhibitory effect of (CS-L), (CS-S), (CS-OI) and (CS-Lin), as well as (CS-L-CF) composite, (CS-S-CF) composite, (CS-OI-CF) composite and (CS-Lin-CF) composite against microbial strains *E.coli*, and *S.aereus* are shown in Fig. 8. The measurement of inhibitory effect was made based on a clear zone surrounding circular film strips [31]. Measurement of clear zone diameter includes diameter of film strips. Therefore, the values were always higher than the diameter of film strips whenever clearing zone is present. If there is no clear zone neighboring, it is assumed that there is no inhibitory zone, and furthermore, the diameter was obtained as zero [32-34]. In this study ciprofloxacin drug (CF), (CS-L), (CS-S), (CS-OI) and (CS-Lin), for *E.coli* measured as zero, no inhibition zone is observed. The antibacterial inhibition zone for (CS-L-CF) composite, (CS-S-CF) composite, (CS-OI-CF) composite and (CS-Lin-CF) composite against different microbial strain *E.coli* measured as 45,40,40 and 30 mm, respectively. This inhibition zone against different microbial cultures proves that CS-L-CF, CS-S-CF, CS-OI-CF, and CS-Lin-CF composites had a higher antibacterial activity. The antibacterial inhibition zone for ciprofloxacin drug, chitosan-lauric acid, chitosan stearic acid, chitosan oleic acid and chitosan linoleic acid against microbial strain *S. aureus* measured as 30, 40, 20, 25 and 20 mm, respectively. While the antibacterial inhibition zone for (CS-L-CF) composite, (CS-S-CF) composite, (CS-OI-CF) composite and (CS-Lin-CF) composite measured

as 60 , 35 , 40 and 45 mm, respectively. It shows that all composites prepared have better antibacterial activity. There are three reactive functional groups of chitosan (amino group at the C2 position of each deacetylated unit and hydroxyl group at the C6 and C3 positions) that can easily be subjected to chemical derivatization, enabling mechanical and solubility properties to be manipulated to improve their biocompatibility.

It is an antimicrobial biopolymer and Interaction between positively charged chitin/chitosan molecules and negatively charged microbial cell membranes is the most suitable mechanism for its antimicrobial activity. In this model, the interaction between the protonated NH_3^+ groups and the negative residues is mediated by electrostatic forces, possibly by competing with Ca^{2+} for electronegative membrane surface sites. This electrostatic activity results in two-fold interference: (i) by promoting changes in the characteristics of the membrane wall permeability, thus inducing internal osmotic imbalances and thereby inhibiting the development of microorganisms; and (ii) by hydrolysis of peptidoglycans in the wall of the microorganism leading to leakage of intracellular electrolytes such as potassium ions and other protein constituents of low molecular weight (e.g. proteins, nucleic acids, glucose and dehydrogenase lactate) [35-39]. Ciprofloxacin is a fluoroquinolone antibiotic which is highly active against both gram-positive and gram-negative bacteria. It is a commonly used urinary tract infection antibiotic that interacts with bacterial

topoisomerases, leading to the formation of oxidative radicals and to the death of bacterial cells. The mechanism of antibacterial activity of quinolone, such as ciprofloxacin, involves preventing the unwinding and duplicating of the DNA of bacteria [40]. Therefore, quinolone-enzyme-DNA complexes are produced, leading to the production of cell poisons and cell death [41].

The protonated amine group of chitosan and carboxylate anion of fatty acid forms polyelectrolyte complex (PEC), hence increasing its antibacterial activity. When ciprofloxacin drug binds with this PEC, the overall antimicrobial activity increases possibly due to the synergistic effect of the chitosan, fatty acid, and ciprofloxacin drug. Antibacterial assessment results of both bacteria are shown in Table 1.

Table 1. Antibacterial assement against *E. Coli* and *S.aureus*

Sample ID	Inhibitory zone against <i>E.coli</i> (mm)	Inhibitory zone against <i>S.aureus</i> (mm)
Ciprofloxacin	non	30
CS-L	non	40
CS-S	non	20
CS-OI	non	25
CS-Lin	non	20
CS-L-CF	45	60
CS-S-CF	40	35
CS-OI-CF	40	40
CS-Lin-CF	30	45

Where: (CS-L) chitosan-lauric acid, (CS-S) chitosan-stearic acid, (CS-OI) chitosan-oleic acid, (CS-Lin) chitosan - linoleic acid, (CS-L-CF) chitosan-lauric acid-ciprofloxacin composite, (CS-S-CF) chitosan-stearic acid-ciprofloxacin composite, (CS-OI-CF) chitosan-oleic acid-ciprofloxacin composite and (CS-Lin-CF) chitosan-linoleic acid-ciprofloxacin composite.

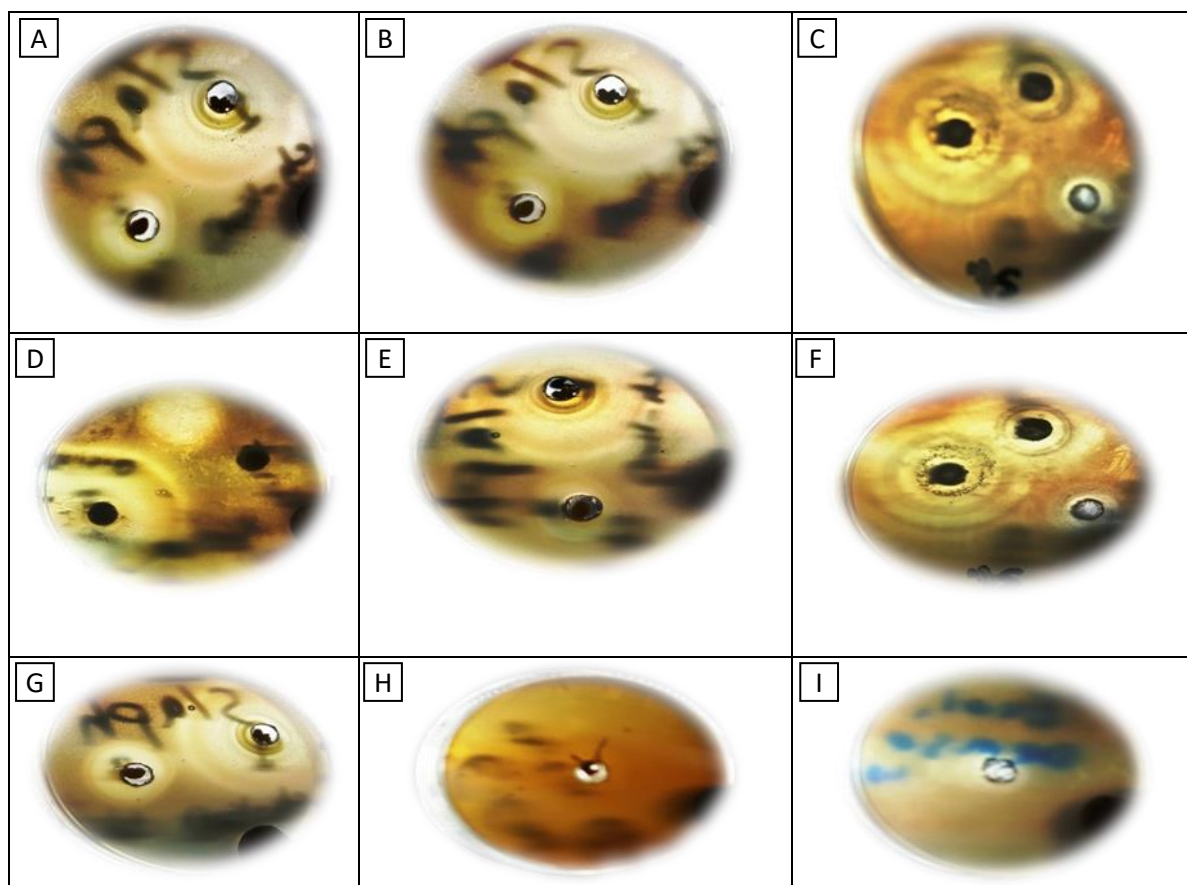


Fig. 8. Antibacterial activity of (CS-L) and (CS-L-CF) (A), (CS-S) and (CS-S-CF) (B), (CS-OI) and (CS-OI-CF) (E), (CS-Lin) and (CS-Lin-CF) (G), (CF) (D) against *S. aureus*, (CS-L-CF) and (CS-S-CF) (C), (CS-OI-CF) and (CS-Lin-CF) (F), (CS-L) (H), (CS-S) (I) against *E. coli*.

In vitro drug release

The drug release profile of CS-L-CF, CS-S-CF, CS-OI-CF and CS-Lin-CF drug composites in phosphate buffer solution (pH 7.4) was measured using an UV spectrophotometer at 291 nm (Fig.9) [46]. CS-L-CF composite shows 63.1% drug release, CS-S-CF composite shows 53.2% drug release, CS-OI-CF composite shows 79.1% drug release and CS-Lin-CF composite shows 52% drug release at 8 h. New biopolymer films are developed for the release study of drugs that can be used for external applications in pharmaceuticals. Modified chitosan films have stronger physical properties and mechanical strength compared to chitosan films. Drug release study of modified chitosan films were compared, and it was observed that CS-S-CF composite shows better release profile than CS-L-CF composite and

CS-Lin-CF composite shows better release profile than CS-OI-CF composite films, because of bulky drug interaction during the formation of polyelectrolyte complex (PEC) and the presence of conjugated double bond.

The ciprofloxacin drug follows a regular pattern of release in chitosan-fatty acid drug composite. At first hour, it shows a burst release of nearly 26.2%, 21.9%, 42.2% and 20.2% for CS-L-CF, CS-S-CF, CS-OI-CF and CS-Lin-CF, respectively. Then drug release becomes steady and slow in all cases.

The release of ciprofloxacin from chitosan-fatty acid derivatives took place by measuring absorbance at different times (every hour) and it was found that absorbance was increased with time, by Beer Lamberts Law. All data is reported in table (2).

Table 2. Release of ciprofloxacin drug from chitosan-fatty acid derivatives

Time (hr)	Absorbance			
	CS-L-CF	CS-S-CF	CS-OI-CF	CS-Lin-CF
1	0.2192	0.1496	0.3373	0.0730
2	0.2939	0.2145	0.4594	0.0957
3	0.3210	0.2336	0.5002	0.1078
4	0.3810	0.2881	0.5278	0.1278
5	0.4264	0.3138	0.5588	0.1581
6	0.4525	0.3249	0.5894	0.1648
7	0.4811	0.3335	0.6211	0.1748
8	0.5200	0.3635	0.6317	0.1896

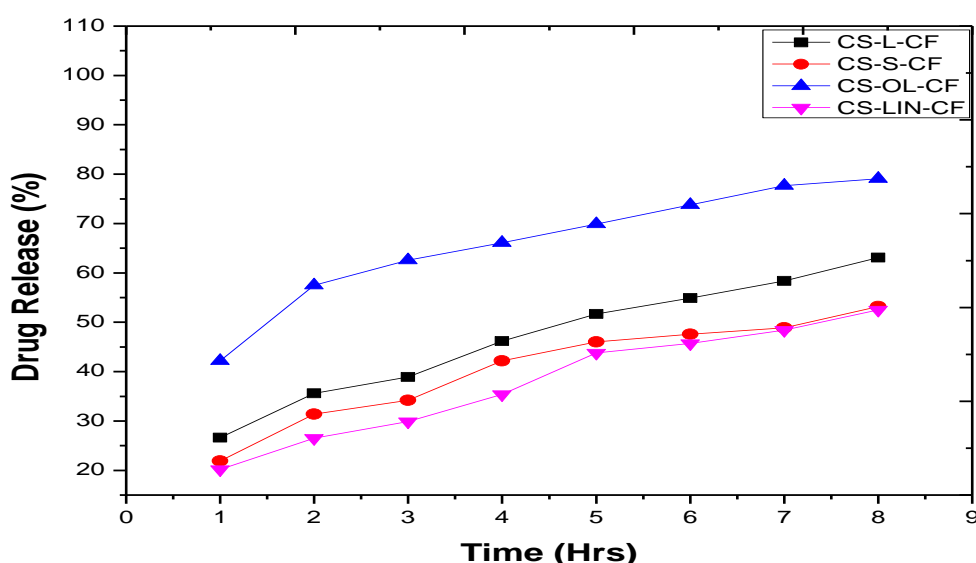


Fig. 9. Drug release profile of chitosan- lauric-ciprofloxacin composite (CS-L-CF), chitosan- stearic-ciprofloxacin composite(CS-S-CF), chitosan- oleic- ciprofloxacin composite (CS-OI-CF),chitosan- linoleic-ciprofloxacin omposite (CS-Lin-CF).

CONCLUSIONS:

The release of ciprofloxacin from the chitosan-fatty acid drug composites were evaluated. The result shows an efficient biocompatible carrier for drug delivery. IR spectra of CS-L, CS-S, CS-OI and CS-Lin have indicated the poly electrolyte complex (PEC) formation amid fatty acid and chitosan. The XRD study indicates that fatty acids and ciprofloxacin particles are well distributed into chitosan. All drug composites prepared exhibits superior antimicrobial activity against *E. coli* and *S.aureus*. All properties make CS-L- CF, CS-S-CF, CS-OI-CF and CS-Lin-CF composites as an effective candidate for controlled drug delivery and introduce a new dimension for biomedical use.

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التحضير والتوصيف والنشاط المضاد للميكروبات لمشتقات الشيتوزان / الاحماض الدهنية كنظام توصيل دوائى: التداخل والإفراج عن سيبروفلوكساسين في المختبر

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المخلص العربى

يعد تطوير أنظمة توصيل جديدة للإفراج المنظم عن الأدوية أحد أكثر مجالات الدراسة إثارة للاهتمام في العلوم الصيدلانية. الهدف الرئيسي من هذا البحث هو استخدام مشتقات حمض الشيتوزان الدهنية لإيصال الدواء. تشارك الأحماض الدهنية المشبعة (حمض اللوريك وحمض الاستياريك) وكذلك الأحماض الدهنية غير المشبعة (حمض الأوليك وحمض اللينوليك) في هذه الدراسة التي تعزز الخواص الكيميائية للشيتوزان في توصيل الأدوية وتعزز نفاذية مركبات دواء سيبروفلوكساسين. كما ان المركبات التي تم تحضيرها قد تم اثبات كونها باستخدام الأشعة تحت الحمراء وحيود الأشعة السينية وكذلك باستخدام الأشعة فوق البنفسجية. أظهرت جميع مشتقات الشيتوزان المحضرة نشاطاً قوياً كمضاد للميكروبات. كما لوحظ أن الإفراج عن الدواء كان بحد أقصى في البداية ثم تم إطلاقه ببطء. قد يكون الإطلاق الأولي للدواء بسبب الدواء الموجود على سطح الفيلم دون أن يتم حصره بكفاءة. أظهر مركب الشيتوزان لينوليك سيبروفلوكساسين إطلاق دواء بنسبة 52%. كما أظهر مركب الشيتوزان استياريك سيبروفلوكساسين إطلاقاً للدواء بنسبة 53.2%. بينما أظهر مركب الشيتوزان لوريك سيبروفلوكساسين إطلاق دواء بنسبة 63.1%. وأخيراً أظهر مركب الشيتوزان أوليك سيبروفلوكساسين إطلاق دواء بنسبة 79.1% في 8 ساعات.