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Synthesis of carbon nanostructures using hydrothermal method and investigation of its application in drug release control

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Abstract
A very important issue in the drug delivery system is to achieve a stable and resistant formulation in such a way that it greatly increases the effectiveness of the drug in the target tissue by circulating and releasing the drug at a certain time. With this aim, biodegradable polymers are used due to their availability, biodegradability, easy manufacturing, and nanoparticles to control the rate of drug release into the body. In this research, the synthesis of carbon nanostructure was carried out using carrot juice extract by hydrothermal method, and the suitable temperature for synthesis was investigated. The results showed that heating for 24 hours at a temperature of 180 ^{0}C is suitable. Then, polymer nanocomposites consisting of chitosan, gelatin, carbon nanostructure and tetracycline drug were prepared. The drug release from the prepared nanocomposites was investigated at different amounts of carbon nanostructure. The results showed that nanostructures coated with polymer lead to better drug delivery performance. FTIR, SEM and XRD were used to characterize the prepared carbon nanostructure. The optimal samples containing 0.015 g of carbon nanostructure showed the best performance compared to other samples in drug release.

Keywords: Drug release, Polymer nanocomposite, Tetracycline, Chitosan

1. Introduction

The common ways of drug release in the body, mainly through digestive (pills, capsules, syrup) and non-digestive (such as injections, eye drops, topical creams), are done at specific time intervals of drug consumption. In most of this behavior, the way the drug travels in the body is through crossing with the acidic environment of the stomach, passing through the tough connections of the cells of the intestinal wall, and entering the intrahepatic cycle, which is finally absorbed into the blood circulation [1-6]. Currently, most of the drugs reach their place of effect through traditional methods and systematic absorption, and with the loss of the drug during the passage through the digestive system, circulatory system and intermediate tissues, the drug dose is used more than the amount required for treatment. The targeted drug delivery process maintains the level of appropriate drug concentrations for a long time and reduces many limitations of conventional treatment such as the number of doses taken, the initial concentration of the drug, and the side effects caused by the spread of the drug in an uncertain systemic distribution [7-10]. Each targeted delivery system contains a drug, a carrier and a targeting ligand, in which the distribution of metabolism and cellular absorption is determined according to the physical, chemical and biological characteristics of the carrier and ligand. The design of the suitable ligand and carrier increases the efficiency of the drug in the diseased tissue and reduces the toxicity of the drug in other healthy tissues. Nowadays, oral polymer-controlled release technologies have been discussed economically and functionally in the development of drugs, which have improved the quality of life of patients by reducing the discomfort caused by continuous use of drugs.

The purpose of this paper is to synthesize drug structures containing carbon nanostructure to control the release of the tetracycline. Slowing down the release of tetracycline due to reducing its side effects by using carbon nanostructures and synthesis of optimal biocompatible nanocomposite as well as achieving a stable formulation are among the important goals of this paper. For this purpose, phosphate buffer (pH = 7.4) was used as release medium, similar to body condition.

2. Experimental

2.1. Materials and Methods

Chitosan was obtained from Sigma-Aldrich Company. Glycerin was made by Nima Gostar Chemical Industry Complex (NCIC). Phosphate buffer tablet (PBS) was purchased from Medicago AB Uppsala, Sweden.
A multi-wave ultrasonic generator (Bandeline MS 73), equipped with a converter/transducer and titanium oscillator, operating at 20 kHz with a maximum power output of 150 W was used for the ultrasonic irradiation.

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Scanning electron microscopy images were obtained using a LEO instrument (model 1455VP). XRD patterns were recorded by a Philips, X-ray diffractometer using Ni-filtered CuKα radiation. FT-IR spectra were recorded on Galaxy series FTIR5000 spectrophotometer.

2.2. Preparation of carbon nanostructures

The hydrothermal method is one of the most widely used bottom-up methods for the production of nanostructures, which has received much attention due to its cost-effectiveness. In this research, carrot juice extract has been used as a green material to prepare carbon nanostructure. For hydrothermal synthesis, first, 100 ml of carrot juice extract was poured into a 250 mL beaker and placed in the reactor, and after closing the reactor, it was placed in the oven for 24 hours at a temperature of 170 degrees Celsius to form the desired precipitate. After the reactor was cooled and brought to ambient temperature, the sediment formed was removed from the reactor and washed 4 to 5 times by ethanol and distilled water to separate and remove possible contamination. The remaining sediment was poured into a watch glass and placed at room temperature for a week.

2.3. Coating of carbon nanostructures with chitosan/gelatin

To prepare the coating of nanoparticles, first specific weight of carbon nanostructures was dispersed in 50 ml of acetic acid (1 wt%), then a specific amount of gelatin and chitosan as a coating agent was added. To improve the flexibility of pharmaceutical structures, 0.001 gr of glycerin was added to the solution.

2.4. Loading of tetracycline drug

After coating the desired nanostructures with gelatin and chitosan, tetracycline drug was loaded. For this purpose, 0.015 gr of tetracycline was weighed and dissolved in 10 ml of distilled water and then was added to the solution containing carbon nanostructures coated with gelatin and chitosan. The solution was homogenized for three hours on a stirrer at temperature of 70 ^{0}C and then was dried in a sheet form on a petri dish at temperature of 50 ^{0}C. The composition of the prepared samples is given in the Table 1.

Table 1: The composition of prepared samples

Sample	C_1	C_2	C_3	C_4
Tetracycline (gr)	0.0015	0.0015	0.0015	0.0015
Gelatin (gr)	0.1	0.1	0.1	0.1
Chitosan (gr)	0.4	0.4	0.4	0.4
Glycerin (gr)	0.001	0.001	0.001	0.001
Carbon nanostructure (gr)	0.01	0.015	0.02	0.05

2.5. Determination of drug concentration

In quantitative analysis, it is necessary to draw a calibration graph, which is a graph of absorbance values of standard samples according to drug concentration. The calibration graph resulting from the concentration plot is not linear in all concentrations, but several factors cause the calibration graph to become linear only in a certain range and follow Beer's law. For this purpose, solutions of sodium tetracycline with different concentrations were prepared and their absorbances were measured at the wavelength of 362 nm (λ_{max}).

2.6. Determining the amount of drug release

A certain amount of nanocomposite medicinal content was inserted in 50 ml of phosphate buffer (pH=7.4) at 37 ° C, and then the absorbance of the solution was measured by a spectrophotometer at 306 nm in a certain period of time. Using the standard absorption curve and the obtained equations, the concentration of drug in solution was calculated.

2.7. Swelling index

A specific number of nanocomposites was immersed in 50 ml of phosphate buffer and after 24 hours, it was centrifuged at 1500 rpm and its weight was compared with the original weight according to the equation (2):

$$Swelling\ index\ (\%) = \frac{Wt - Wd}{wt} \times 100 \quad (2)$$

W_t is the weight of the hydrated nanocomposite at time t and W_d is the dry weight.

3. Results and Discussion

3.1. Investigation of the FT-IR spectra of prepared carbon nanostructures

The FT-IR spectrum of carbon nanostructures in the range of 450-4000 cm^{-1} is shown in Fig. 1. The most important peaks in the obtained IR spectrum were observed in the following wavenumbers; the absorption bands

observed in the area of 3376 cm^{-1} are related to the strong stretching vibrations of the O-H bond. Also, the observed spectrum at 2925 cm^{-1} is related to C-H stretching vibration. The absorption band at 1703 cm^{-1} is related to C=O bond and the peak at 1380 cm^{-1} is related to C=C, and finally the absorption band 1211 cm^{-1} is related to the bending vibration of the C-H bond [11,12].

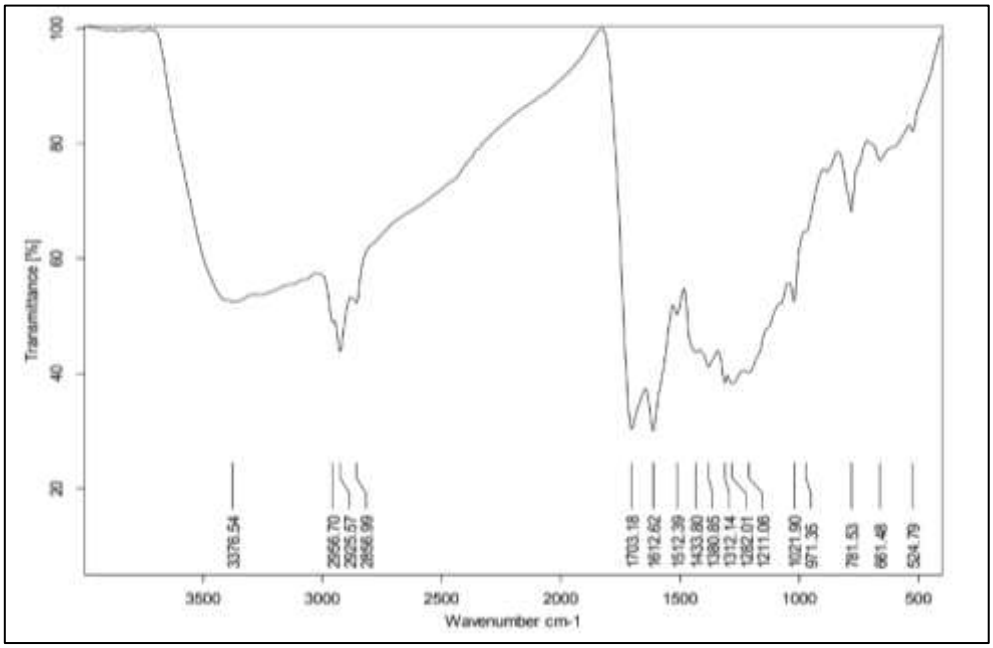

Fig. 1. FT-IR spectrum of prepared carbon nanostructures

3.2. XRD pattern of prepared carbon nanostructures

The XRD pattern of prepared carbon nanostructures is shown in Fig. 2. By investigation the XRD pattern of the carbon nanostructure, it was found that it has an amorphous structure.

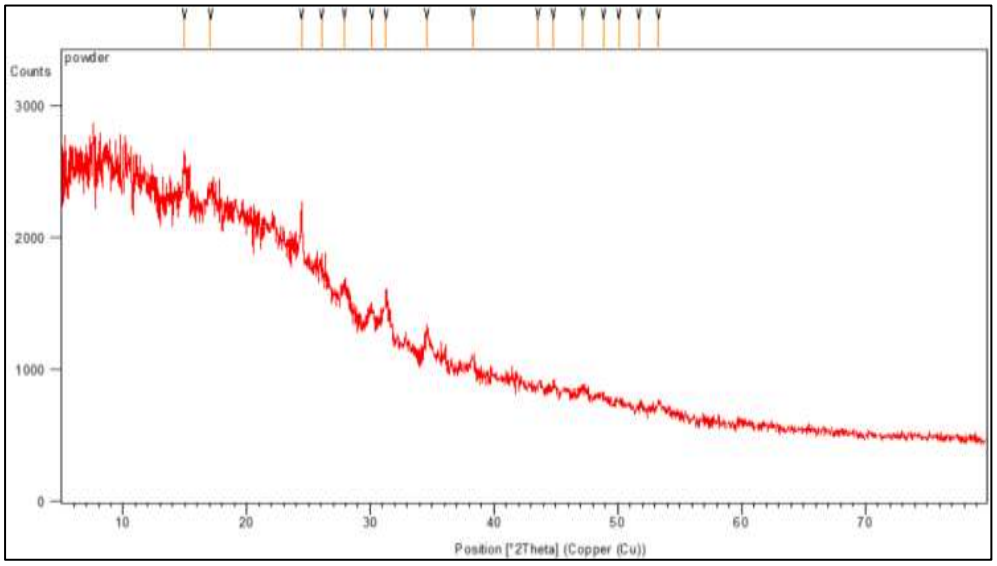

Fig. 2. The XRD pattern of prepared carbon nanostructures

3.3. SEM image of prepared carbon nanostructures

As it is clear from Fig. 3, the average size of prepared carbon nanostructures is below 100 nm, and the proper distribution of nanostructures can be clearly seen.

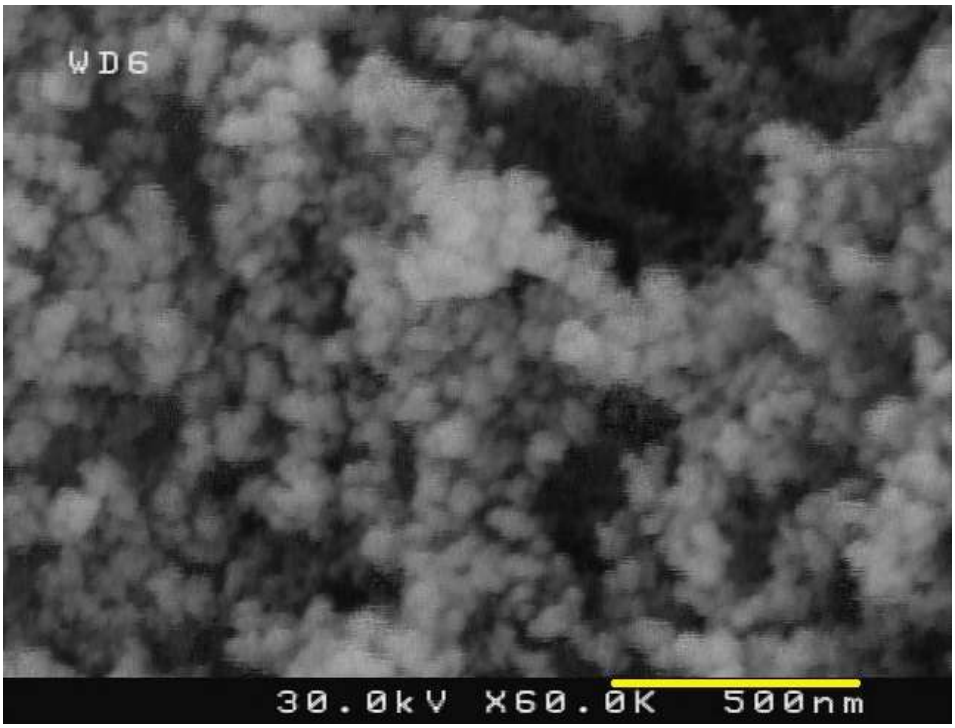

Fig. 3. SEM image of prepared carbon nanostructures

3.4. Results of drug release

In general, chitosan based biodegradable composites have a high potential for biological applications, because they are biocompatible and biodegradable. In addition, the suitable compatibility of chitosan-based matrices in living organisms has been proven [1, 3].

In this section, the release of tetracycline drug in the presence of gelatin and chitosan in phosphate buffer medium (pH=7.4) has been measured. Fig. 4 (a) and (b) are shown that the optimal sample is C_2 which had a more stable structure, suitable slope and controlled drug release. Therefore, the addition of nanostructure slows down the release of diclofenac.

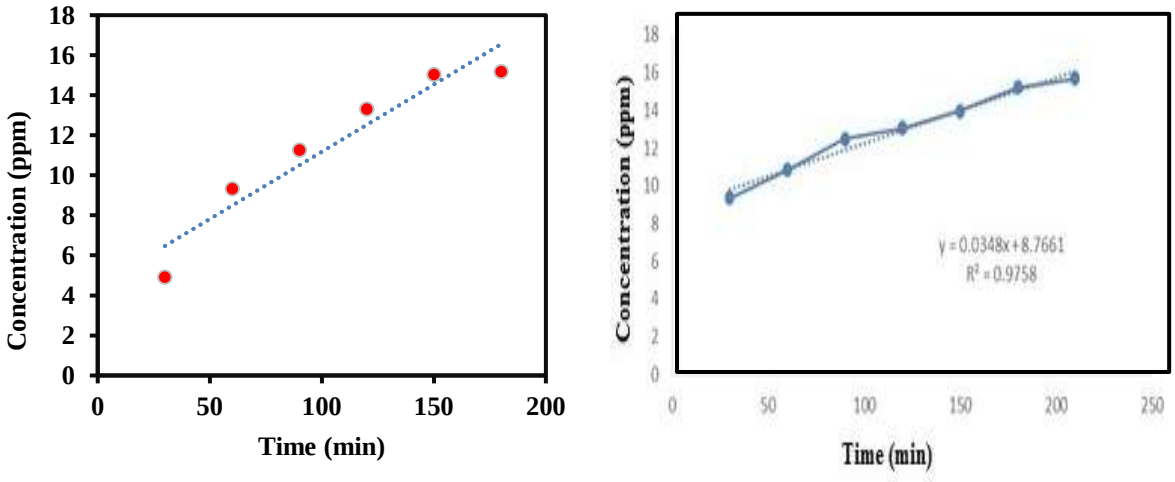

Fig. 4. (a) Drug release profile of prepared polymeric sample without carbon nanostructure, and (b) drug release profile of the nanocomposite sample (C_2)

3.5. Swelling index results

According to the results (Fig. 5), in the comparison between the polymer without nanoparticles and in the presence of carbon nanostructures, nanocomposites sample has lower swelling index. Thus, fewer amounts of water could penetrate inside the structure, which led to the release of fewer amounts of water-soluble tetracycline.

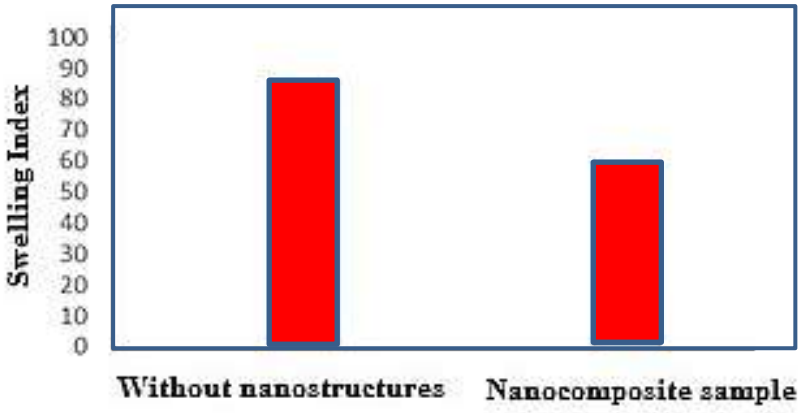

Fig. 5. The swelling of prepared samples

4. Conclusion

A very important issue in drug delivery systems is to achieve a stable formulation in a way that increases the effectiveness of the drug in the target tissue by circulating and releasing the drug at a certain time. The design and synthesis of an optimized nanostructure for use in drug delivery is of great importance. Chitosan and gelatin have suitable biocompatibility, which were used in this research as containing tetracycline drug to control drug release due to properties such as biodegradability, compatibility in human body environment and easy access. In the laboratory, solutions with a pH similar to human blood were prepared and the effect of different parameters on the tetracycline release was investigated. The obtained results showed that the presence of carbon nanostructures slows down the drug release over time.

Conflicts of Interest

The author declares no conflict of interest.

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