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Synthesis and characterization of surface-modified poly (lactide-co-glycolide) nanoparticles by chitosan molecules for on-demand drug delivery applications

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ABSTRACT

One of the most considerable therapeutic systems for delivery of drugs across from the blood–brain barrier is nanoparticulate drug delivery systems. In this study, in order to obtain desired surface morphology and particle size for the delivery of drugs to the brain, the effectiveness of chitosan (CS) coating on the surface of poly (lactide-co-glycolide) (PLGA) nanoparticles (NPs) as a potential carrier for drug delivery, was investigated. In addition, strong electrostatic interaction occur between CS molecular chains and PLGA NPs. According to the results, by increasing the percentage of the CS (by adding 0.1g CS the average size of PLGA particles became<100 nm). The average nanoparticle size is decreased and this main feature of PLGA NPs makes them promising candidates for brain drug delivery.

Keywords: *PLGA nanoparticles, chitosan, modification, drug delivery.*

1. INTRODUCTION

Recently, one of the most challenging subject for researchers is the delivery of drugs to the brain, since this tissue benefits from a very efficient protective barrier, [1] numerous drug delivery systems such as; liposomes, emulsions, micelles, and polymeric micro/nanoparticles, have shown good potential for controlling the rate and duration of drug delivery, targeting the drug to specific cells or tissues. To overcome this limitation for transferring the drugs to the brain researchers utilized various nano carries, among these nano carriers, polymeric nanoparticles (NPs) are promising candidates because they are capable of opening the tight junctions of the blood–brain barrier [2]. Indeed, many important impermeable drugs can be passed through this barrier after being incorporated into polymeric NPs. As these polymeric NPs, can be dissolved, entrapped, encapsulated, adsorbed, attached or chemically coupled, the new area of research has been developed [3]. Among various of biopolymers, poly (lactide-co-glycolide) (PLGA) is used in a host of Food and Drug Administration (FDA) approved therapeutic devices, [4] due to its biodegradability and biocompatibility, also it is one of the most biodegradable polymers that has been used recently in this area owing to its small size and chemical nature, it is capable of opening the tight junctions of the blood–brain barrier [5]. On the other hand, the main impediment of PLGA NPs is their non-specific NPs-cells and NPs-proteins interaction which leads to drug accumulation in nontarget tissues [6, 7]. In addition, they are low on suitable functional groups that would allow efficient covalent conjugation with bioactive ligands. To overcome these limitations, physical and chemical surface modification of PLGA NPs has been developed [8]. Several polycations have been developed to modify surface of PLGA NPs including polyethyleneimine, cetyltrimethylamonium bromide, poly(2-dimethyl-amino) ethyl methacrylate didodecyl dimethyl ammonium bromide and some biopolymers such as chitosan (CS) can overcome several of these existing drawbacks [9].

CS has been one of the most attractive biopolymers due to its remarkable properties such as; biocompatibility, biodegradability and antibacterial activity. CS is a linear polysaccharide that derived by deacetylation of chitin [10, 11]. It is viewed as a good surface modifying based on its characteristics. The chemical structure of CS is shown in Figure 1.

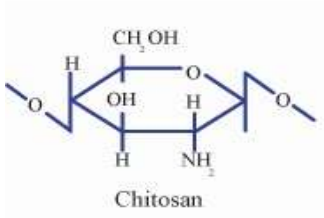


Figure 1. Schematic of chemical structure of CS.

Cs has a positive charge in acidic solutions according to the presence of protonated amino groups along its backbone. In contrast, the cell surfaces usually have negative charge. Hence, CS coated NPs can be targeted to the surfaces of cancer cells. The CS coating on the surface of NPs can also considerably decreases the initial burst of drug release from the NPs, without affecting other parts of the release [12].

In this work, the physicochemical properties of surface modification of PLGA NPs such as; particle size, morphology, and their molecular interactions with CS was studied.

2. EXPERIMENTAL SECTION

2.1. Modification of PLGA NPs surface by chitosan.

To obtain surface modification firstly, 50 mg of PLGA (50:50, Resomer-RG 503H; Boehringer Ingelheim) was dissolved in 1 mL of dichloromethane under magnetic stringing. Different percentage (0.03, 0.05, and 0.1g) of CS (medium molecular weight of 190000–310000, Orbital Pharma Co. [Hebei, China]) was separately dissolved in 1ml acetic acid (98%, Merck). After that CS solution slowly added to PLGA solution.

2.2. Characterization.

2.2.1. Morphology and particle size.

The morphology and particle size of synthesized samples were measured by scanning electron microscope (SEM, Philips XL30) that operated at the acceleration voltage of 15 kV.

2.2.2. Chemical bonding.

The Fourier transform infrared (FTIR-Bomem MB series) analysis was used to characterize the presence of specific chemical groups in CS and PLGA particles. Furthermore, it showed the interaction between CS and PLGA NPs.

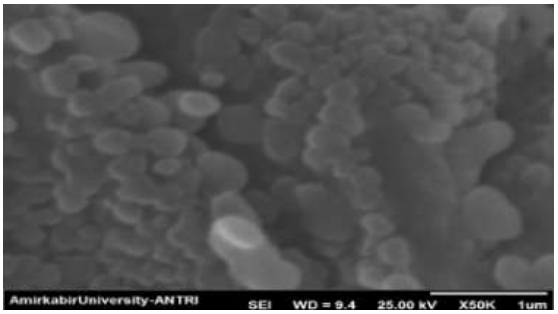
2.3. Statistical analysis.

All the experiments were performed in fifth replicate. The results were given as means ± standard error (SE). Statistical analysis was performed by using One-way ANOVA and Tukey test with significance reported when $P < 0.05$. Also for investigation of group normalizing, Kolmogorov–Smirnov test was used.

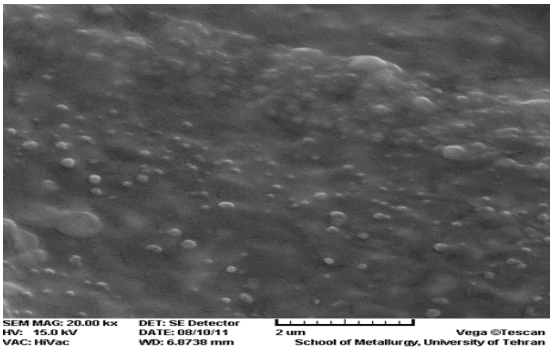
3. RESULTS SECTION

3.1. Morphology and particle size study.

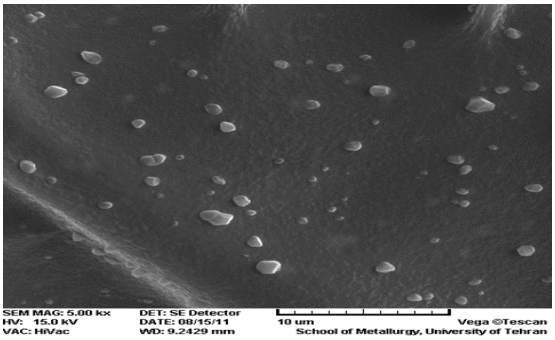
As shown in Figure 2 when various percentages of CS was added to PLGA NPs formulation as a surface modifying agent, it shows the effects of CS interaction on the surface morphology and particle size of the PLGA NPs.



a) PLGA NPs+0.1g CS



b) PLGA NPs+0.05g CS



c) PLGA NPs+0.03g CS

Figure 2. SEM micrographs of the synthesized samples containing (0.03, 0.05 and 0.1 g CS).

The SEM micrographs show that average size of PLGA-NPs modified with different percentages of CS is in the range of 100 to 400 nm. As illustrated in Figure 3 since, PLGA NPs containing small amounts of CS (e.g., 0.03g) had an average particle size 800 nm (Figure 2c) [2]. But by adding more amounts of CS to the synthesis media made a substantial reduction in particle size, as shown in Figure 3 in 0.1% CS the PLGA NPs average size is around 100 nm. In other words, Figure 2a-c show that modifying PLGA NPs with CS decrease the size particles significantly which causes the most advantages of using NPs for drug delivery to the brain. According to their size, NPs penetrate into even small capillaries and are taken up within cells results an efficient drug accumulation at the targeted sites (i.e. brain) in the body [6].

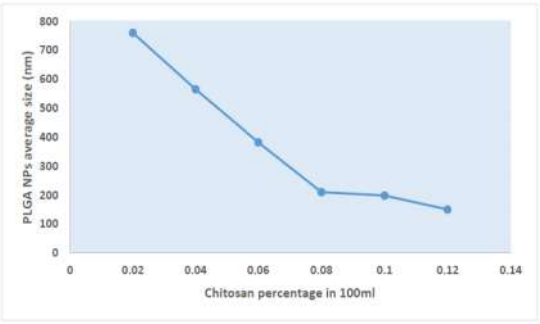


Figure 3. PLGA NPs average size (nm).

3.2. Chemical bonding.

FTIR method was used for better understanding of the surface chemistry of the synthesized samples, as shown in Figure 4. The FTIR analysis displayed the presence of the specific functional groups of both the PLGA polymer material and the CS molecules on the particle surfaces. The CS surface-modified samples clearly showed the major characteristic peaks around (850-1200) cm^{-1} related to the repeating saccharide unit of CS. By adding CS to PLGA NPs, a clear difference both in the shape and intensity of the absorption peaks of the PLGA particles was shown (Figure 4). The samples containing different percentages of CS (0.03, 0.05, and 0.1 g) showed the characteristic absorption peaks corresponding to both CS and PLGA molecules.

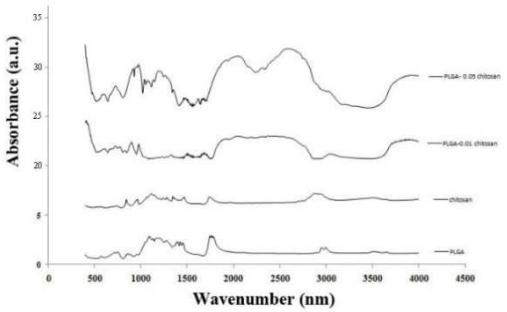


Figure 4. FTIR spectra of the PLGA, CS and CS/PLGA NPs.

The main bands appearing in CS spectrum were due to stretching vibrations of OH groups at (2700-3200) cm^{-1} that are overlapped to the stretching vibration of N-H groups. The peak was observed at 2878 cm^{-1} corresponding to C-H band in CH_2 symmetric and asymmetric stretching vibration. In addition, the strong absorption peaks at (1425-1384) cm^{-1} and 1325 cm^{-1} have been reported as a methylene and methyl groups, respectively. Absorption in the range of (1600-1656) cm^{-1} was related to the vibrations of carbonyl bands (C=O) in a secondary amide group. Moreover, all the synthesized PLGA/CS samples showed the main peaks corresponding to the functional groups of the PLGA chemical structure, such as -CH, $-CH_2$, $-CH_3$ (2800–3000 cm^{-1}), carbonyl -C=O (1700–1800 cm^{-1}), C-O (1000– 1200 cm^{-1}), ethyl - CH_2 (1400–14700 cm^{-1}), methyl $-CH_3$ (1200–1300 cm^{-1}) and -OH stretching vibrations (3400–3700 cm^{-1}) [2,11]. The remarkable difference between the synthesized particles occurred in the region of 3000–3400 cm^{-1}, due to the absorption feature for CS modification. In other words, increasing the amount of CS; decreased the absorbance due to the OH stretch bands of CS that were used to form chemical bands to the NPs. The covalent conjugation of CS molecules onto the PLGA molecules by the formation of an amide bond was confirmed by observing the bands around (1746 – 1510) cm^{-1}, corresponding to the amide I and II bands, respectively. As shown in Figure 4, Amide I and II bands were not observed when higher amounts of CS were adsorbed onto the particles [2,6]. Further addition of CS decreased the absorbance in this area, indicating the more absorption of CS molecules onto the surface of the PLGA NPs. According to the electrostatic interaction between negatively charged drugs with the $–NH_2$ groups of CS on the surface could be very useful for drug encapsulation, as these groups offer a potential carrier for drug delivery. Thus, this modification could be enabled the PLGA NPs as promising candidates for brain drug delivery.

4. CONCLUSIONS

In this research, the effectiveness of CS as surfaces modifier for the preparation of PLGA NPs with desired properties was investigated. According to the results, further addition of CS to synthesized PLGA NPs caused to obtain the smallest particles in the range of nanometers (nm) below 100nm. Based on the particle size, CS-coated PLGA NPs, the modifying PLGA NPs are promising candidates for brain drug delivery. NPs interpenetrate into even small capillaries and are taken up within cells results an effectual drug accumulation at the targeted areas in the body. Moreover, based on strong electrostatic interaction that occur between negatively charged drugs and cationic groups of CS, these groups offer a potential carrier for drug delivery.

Thus, the surface modification of NPs can be a useful method for achieving controlled and targeted release of active agents over a prolonged period to the brain.

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