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Preparation and Evaluation of Calcium Deficient Hydroxyapatite Powder/Sodium Silicate Composition for Sustained Drug Delivery of Poorly Soluble and Low-Dose Drugs

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Abstract

The main goal of this study is to prepare and develop sustained drug delivery system for carrying poorly soluble and low-dose drugs. The drug delivery system combines three components: calcium deficient hydroxyapatite (CDHAp), sodium silicate and vitamin C, which blended together to form solid tablets exhibiting optimal characteristics as drug carriers. CDHAp was prepared via co-precipitation method using calcium hydroxide and phosphoric acid. For in-vitro drug release study, the Atenolol was used as a model for hypertensive drugs to evaluate the drug release behavior from the tablets. The characteristics of CDHAP and its drug delivery composite were analyzed using conventional techniques. The results revealed that synthetic microsized CDHAp having grain sizes less than 50 μm with pure hydroxyapatite (HAp) phase. The fabricated tablets showed a dense structure with good compressive strength while in-vitro release test revealed an adequate control release behavior of Atenolol. The results indicated that CDHAp and its composite can be promised economic carriers for poorly soluble and low-dose drugs.

Keywords: *Calcium deficient hydroxyapatite, Sodium silicate, Drug delivery, atenolol.*

1. Introduction

The last two decade have witnessed unprecedented progress in developing adequate sustained release drug delivery systems for poorly soluble and low dosed drugs [12][9]. Poorly soluble drug such as Atenolol, selective β1 receptor antagonist, is widely used in medicine as antihypertensive drug, treats high blood pressure, and as antianginal drug, treats chest pain [1]. The main challenge for administration atenolol via conventional routes is its poor water solubility, 60 g/L [4]. Atenolol effectiveness is strongly dependant on the drug solubility that affecting the oral bioavailability of atenolol, and on the formulation stability [14]. In addition to poor solubility, there are still many challenges in designing optimum carriers for atenolol such as chemical durablity and stability against corrosive stomach fluids, uniform drug distribution within the solid tablets, and oral bioavailability upon administration [6]. Drug delivery systems based on synthetic ceramics such as calcium phosphate have been frequently used due to their suitable biological and physical properties [2]. However, there is still a clinical need for using and test new biomaterials working as adequate drug delivery systems that have ability to carry poorly soluble and low dosed drugs such as atenolol. Therefore, the purpose of the present study is employing calcium deficient hydroxyapatite (CDHAp) as useful drug carrier, in view of the fact it has a similar chemical composition similar to inorganic part of bones, biological hydroxyapatite. Thus, the main objective of the present study is to fabricate a new carrier composition comprising CDHAp, sodium silicate and Vitamin C for sustained release of active pharmaceutical agents. The components of CDHAp are safe materials; CDHAp is nontoxic, biodegradable, biocompatible, and biosorbent [8]. Also, composition of CDHAp make it has enough chemical durability and stability against corrosive stomach fluids [13]. In addition, pure hydroxyapatite (HAp) is frequently used as a carrier for loading active drugs such as Metoprolol, antihypertensive drug, and Ibuprofen, anti-inflammatory drug [15]. Recently, low concentration solutions of sodium silicate were safely used as pH regulator and as a binder in cements and cosmetic applications [3][5]. Also, blending CDHAp, as a carrier, with chemically bonded compound, sodium silicate, can increase the amount of drug incorporation; enhance the mechanical strength and the chemical stability of the drug delivery system [7]. For drug delivery application, the high alkalinity of compound is regulated using safe acidifying agents such as citric acid, ascorbic acid, or butyric acid [11]. Ascorbic acid, vitamin C, that has various health benefits [10]. Consequently, the aim of this study was to design and fabricate new drug carriers based on CDHAp, sodium silicate and ascorbic acid (vitamin C) for administering low-dose drugs such as atenolol. For this purpose, the CDHAp was synthetic from natural bone using hydrothermal technique. Then the drug delivery composite tablets were fabricated by using three components: CDHAp as a carrier, sodium silicate solution as a binder, and ascorbic acid as a buffering agent. The

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conventional techniques such as XRD, FT-IR, and SEM were used to characterize the structure and morphology of the products. The mechanical and friability, and *in-vitro* drug release testing were achieved on the fabricated tablets.

2. Materials and methods

2.1 Preparation of calcium deficient hydroxyapatite

CDHAp was synthesized using medical grade of calcium hydroxide ($Ca(OH)_2$) and phosphoric acid (H_3PO_4), Adwic, El-nasr Chemical Co., Cairo, Egypt. In a typical procedure, 0.3 M aqueous solution of H_3PO_4 was to dropwisely added to 0.45 M aqueous suspension of $Ca(OH)_2$ at 40 °C under magnetic stirring to maintain Ca/P molar ratio constant at 1.5. Then the mixture was heated at 80 °C for 30 min, filtered, washed and dried overnight at 80 °C.

2.2 Fabrication of CDHAp powder/sodium silicate/vitamin C (CSV) composite tablets

The CDHAp based composite tablets were fabricated by blending CDHAp with sodium silicate and vitamin C. 3.0 ml of aqueous solution containing 300 mg of sodium silicate (Adwic, El-nasr Chemical Co., Cairo, Egypt) was prepared at room temperature. Then 300 mg of atenolol (a gift from Jedco International Pharmaceutical Co.,Cairo, Egypt) particles was mixed with sodium silicate solution under constant stirring. The slurry was prepared by adding a mixture containing about 3.0 g of CDHAp and 1.5 ml 20% vitamin C (Adwic, El-nasr Chemical Co., Cairo, Egypt) solution to the with the previous solution at room temperature and under homogeneous blending to accelerate hardening of the composite and to regulate the pH value. The mold was divided into 10 tablets, and then was set to dry and harden at room temperature. The average weight of each tablet was about 350 mg.

2.3 Characterization of the CDHAp and CSV composite tablets

The CDHAp and its drug delivery composite were characterized using conventional methods and tests such as X-ray powder diffraction (XRD), Fourier transformed infrared spectrum (FT-IR), scanning electron microscopy (SEM), friability test, and compressive mechanical tests. The crystalline structure of CDHAp and the composite tablets were characterized by XRD on a Philips PW 1840 diffractometer with CuK_α radiation of 1.5406 Å at 40 kV and 30 mA. The 2θ values were set in the range of 10 to 60° to investigate all significant peaks of the materials. Peaks on the X-ray patterns recorded for HAp samples were labeled by referring to the X-ray spectrum data obtained from the Powder Diffraction File (PDF) from Joint Committee on Powder Diffraction (JCPDS). The FT-IR was obtained with Perkin-Elmer-1600 using KBr pellet technique for the range 4,000 and 400 cm^{-1}. The morphologies and microstructures of the resultant products were examined by SEM using a JEOL 6400 electron microscope operating at 15kV of electron acceleration voltage. The friability test was performed by TA-100 friabilator (ERWEKA, Hainburg, Germany). 20 tablets for the composite were weighted and rotated at velocity 25 rev/min per 5 min. The Compressive mechanical tests were performed on the composites tablets. Six of the composites tablets with dimensions of (1.5 mm height × 8 mm diameter) were used for compression strength tests. The tests were conducted at room temperature; using An Instron 4302 mechanical tester with 10kN load cells and a crosshead speed of 20 mm/min.

2.4 Drug release study from CDHAp based composite tablets

Atenolol release tests from the CDHAp based composite tablets were performed at 37 °C in 600 ml of 0.1N HCl solutions. The tablets were immersed in the dissolution medium, and then stirred at a constant speed. The samples were collected at different time points. Atenolol concentration in the sampled release fluid was measured on an UV/Vis spectrometer (Unico-2800) at wavelength of 274 nm. All experiments were done in 6 replicates and the mean values were reported. The errors shown in the graph represented the standard deviation of the percentage release as calculated from the 6 replicates.

3. Results and discussion

3.1 Characterization of CDHAp powder

Fig.1 shows the XRD pattern of synthetic CDHAp and CSV composite tablets. XRD pattern of CDHAP, (Fig.1a), exhibits its crystalline structure with pure HAp phase as compared to standard HAp structure [JCPDS card No. 74-0874]. The main peak sets at 2θ values of 31.7° was for reflection (211). The synthetic CDHAp is pure where no peaks for other calcium phosphate or

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calcium carbonate compounds were detected. Fig.1b shows the XRD patterns of the CSV composite tablets produced by blending CDHAp with sodium silicate and vitamin C. Addition of sodium silicate and vitamin C has no effect on XRD pattern of the composite tablets. The XRD patterns revealed presence of a single phase structure indicating that the dominant phase in the composite is the HAp phase. The reason for absence XRD peaks belonging sodium silicate can attribute to its disability to crystallize in addition to its small weight within the composite; the weight ratio of CDHAp/sodium silicate was 10. It suggested that no chemical reaction occurred between the CDHAp and sodium silicate powder. CSV composite exhibited a strong main peak at 2θ values of 31.7° and distinctive reflections identical to that of CDHAp.

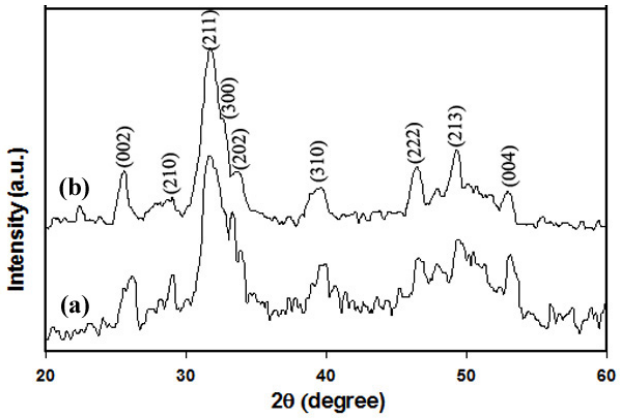

Fig.1 XRD patterns of synthetic CDHAp (a) and CSV composite (b).

FT-IR analysis, Fig.2, was applied to investigate the main chemical groups that characterize CDHAp and CSV composite compound such as PO_4^{-3}, -OH, Si-O, and CO_3^{-2}. Fig. 2 (a) shows FT-IR spectrum for CDHAp where there are four distinctive absorption bands for PO_4^{-3} ions that presented at 572, 600 and 1045 cm^{-1} and belonged HAp. The FT-IR spectrum for CSV composite produced by mixing CDHAp sodium silicate and vitamin C is shown in Fig.2 (b). As comparing with FT-IR spectra for CDHAp, Fig.2, new absorption peaks that attributed to the vibrational modes of SiO_3 group appeared at 960, 900 and 415 cm^{-1}.

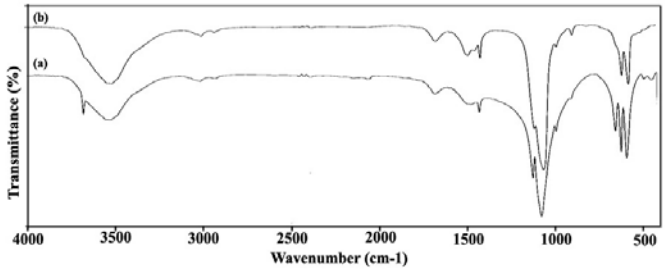

Fig.2 FT-IR spectra of synthetic CDHAp (a) and CSV composite (b).

The morphology and size of CDHAp particles synthetic from natural bone were characterized by SEM, Fig.3. SEM analysis of the powders reveals CDHAp powder with grai sizes less than 50 μm, Fig.3(a). These results of XRD, FT-IR and SEM reveal successful extracting of CDHAp. Fig.3 (b) shows SEM image of CSV composite tablets produced by mixing CDHAp with sodium silicate and vitamin C. SEM analysis of the broken tablets revealed a dense structure composed of tiny CDHAp particles.

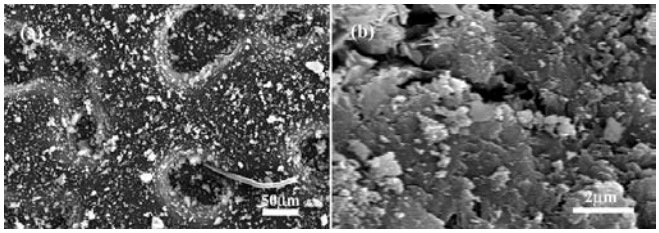

Fig.3 SEM images of synthetic CDHAp (a) and CSV composite (b).

3.2 Drug release from CSV composite tablets

The CSV composites have a complete hardening after 30 min. the dense CSV tablets showed very low friability, less than 0.1%. The compressive strength of the dense CSV composite tablets was 40 ± 0.5 MPa that is considered as optimal value for drug delivery application. The behavior drug release from CSV composite tablets can be explained by an action of the surface erosion mechanism where the HSC composites degrade and disappear from the surface. Fig.4 shows the cumulative atenolol release from CSV composite tablets, each contains 30 mg of atenolol, carried out at 37 °C in 0.1N HCl solutions. The drug release behavior for CSV tablets did not show a burst release indicating a highly binding nature of CDHAp particles in the tablets with sodium silicate. Atenolol release from CSV composite tablets after 60 min was approximately 82% while the complete release of the atenolol was achieved within 210 min (100%). The CSV composite tablets have found to be a promised candidate as low-dose drug carrier.

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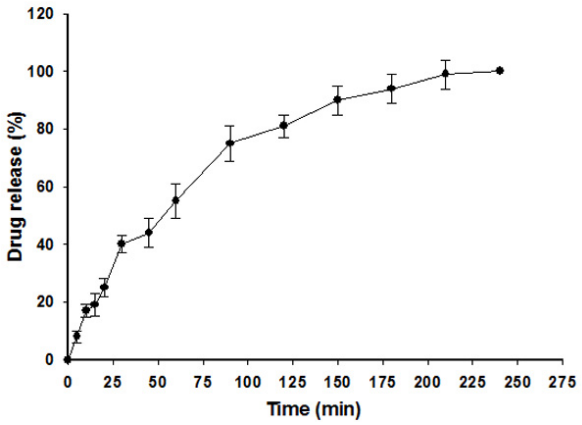

Fig.4. Drug release from the CSV composite tablets containing 30 mg atenolol.

4. Conclusions

In this study, degradable controlled drug delivery system was developed as effective an alternative carrier for low-dose oral drug such as atenolol, anti-hypertensive low-dose drug. For preparing the raw material, CDHAp was synthetic by using co-precipitation method. The CSV composite tablets were designed by combining CDHAp powder with sodium silicate and vitamin C. CDHAp was pure and had grain sizes less than 50 μm while CSV composite was found to have dense surface and exhibited high mechanical strength, 40 ± 0.5 MPa, with low friability, less than 0.1%. In-vitro release test of atenolol drug from CSV tablets confirmed their effectiveness as drug carriers. In summary, the present study has demonstrated the possibility of using CDHAp as economic raw materials as for developing sustained drug delivery systems for of poorly soluble and low-dose drugs

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