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Application of Synthetic Nanozeolite Sodalite in Drug Delivery

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ABSTRACT
In this study nanozeolite sodalite was synthesized from natural volcanic glass (perlite) as silica (Si) source and sodium aluminate as aluminium (Al) source without using any organic template. We use perlite as Si source because it is cost-effective and available source. These nanoparticles of synthesized zeolite were prepared at 170°C in stainless steel reactor with hydrothermal method. The synthesized nanozeolite was characterized by X-ray diffraction (XRD), fourier transform infrared (FTIR) and scanning electron microscopy (SEM) techniques. Chemical composition of perlite was determined by X-ray fluorescence (XRF).This nanozeolite was modified with cationic surfactant, hexadecyltrimethylammonium bromide (HDTMAB). In this study adsorption of cetirizine (Cet) as a model drug onto nanozeolite sodalite as a carrier of drug was investigated and Ultra Violet-Visible (UV-Vis) spectrophotometry was used for determination of concentrations of Cet at 230 nm. Adsorption characteristics of Cet on nanozeolite sodalite were examined at different times (0-6 h) and also the analysis was carried at three pH levels 4, 5 and 6. Finally three buffered solutions with different pH (1.2, 6.8 and 7.2) were selected for release medium and the temperature was precisely controlled at 37 ± 0.1°C.

***Key Words*:** Carrier, cetirizine, loading, release, modification, perlite.

INTRODUCTION

Nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they can be successfully used as delivery tools for currently available bioactive compounds (Suri *et al.*, 2007). Liposomes, solid lipids nanoparticles, dendrimers, polymers, silica materials, carbon materials, and magnetic nanoparticles are the examples of nanocarriers that have been tested as drug delivery systems (Wilczewska and Pavelic, 2012).

Several toxicological studies proved that zeolites such as natural clinoptilolite are nontoxic and safe materials for use in human and veterinary medicine (Kralj *et al.*, 2003). Zeolites are microporous crystalline aluminosilicates that contain alkaline metal ions and water molecules. They are based on a three-dimensional framework of SiO_4 and AlO_4 tetrahedral that results in an extended uniform network of channels and pores (Rimoli *et al.*, 2008). Zeolites have been extensively used in various industrial applications based on their properties to act as catalysts, ion exchangers, adsorbents, and detergent builders (Pavelic, 1980; Sersale, 1985; Naber *et al.*, 1994; Garces, 1999; Colella, 1999). By virtue of these unique properties, they can absorb large amounts of molecules both in the gas and in liquid phases, facilitate ion exchange, and act as molecular sieves (Kralj *et al.*, 2003).

Cetirizine (Cet), figure 1, is a long acting antihistamine with some mast-cell stabilizing activity which is known as 1-(2-(carboxymethyl) ethyl)-4-(4-chlorobenzhydryl) piperazinium dichloride (trade name Zyrtec) and widely used in the comprehensive management of allergic rhinitis, the symptoms of which include itching, sneezing and nasal congestion. Its molecular formula is $C_{21}H_{27}Cl_3N_2O_3$ and is rapidly absorbed with the gastrointestinal track after the oral administration (Haghighi *et al.*, 2013). The recommended dosage of cetirizine in adults and children over the age of 12 is one 10 mg tablet daily (Spencer *et al.*, 1993). To the best of our knowledge, so far there have been no reports on optimization for preparation of synthetic nanozeolite sodalite as a potential carrier for delivery of cetirizine and our synthesis method for nanozeolite sodalite is new.

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MATERIALS AND METHODS

Materials

Natural perlite as Si source was purchased from Afrazand Corporation. The source of perlite was from Semnan, Iran. Sodium aluminate as Al source was purchased from Prolab BDH. Cetirizine was obtained from Pro Ventus life corporation, india. Sodium dihydrogen phosphate and hexadecyltrimethylammonium bromide , all analytical grade, from Fluka (Munich, Germany), disodium hydrogen phosphate from Merck (Germany).

Equipment

X-ray diffraction (XRD) patterns were recorded on a Bruker AXS D8 Advance X-ray diffractometer (Bruker, Germany) with Cu Kα radiation (λ ¼ 1.5418 Å). Size distribution of nanozeolite was performed on scanning electron microscope (SEM). The FT-IR spectra (4000–400cm^{-1}) in KBr were recorded using an FT-IR spectrometer (Tensor 27-Bruker). UV-Vis spectrophotometer (Cambridge, UK) was used for determination of concentrations of drug.

Synthesis of nanozeolite

For synthesis of nanozeolite, 9.8g of perlite was dissolved in 100 ml alkaline solution of NaOH 0.215 M (solution A). The mixture was stirred for 4 hour at 100°C. Then, the mixture was filtered and the filtrate was used to synthesize nanozeolite. Then 0.768 g sodium aluminate was added to 15 ml distilled water which contained of 0.26 g NaOH (solution B). Then solution A was added to solution B with hard shaking. The mixture was heated at 170°C for 18 hours in stainless steel reactor. Chemical composition of perlite was determined by XRF and it includes: 79.79% w/w SiO_2, 10.66% Al_2O_3, 2.46% Na_2O, 4.67% K_2O, 0.06% MnO, 0.67% Fe_2O_3, 0.20% MgO, 0.01% P_2O_5, 0.04% SO_3, 1.34% CaO, 0.10% TiO_2, 1.31% L.O.I.

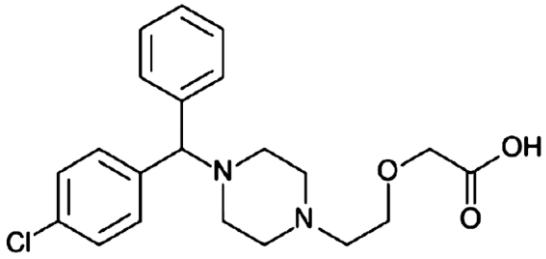

Figure 1: Chemical structure of cetirizine.

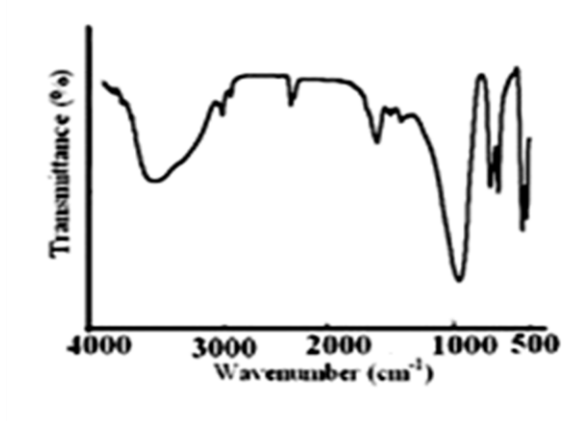

Figure 2: FT-IR spectrum of the synthesized nanozeolite sodalite.

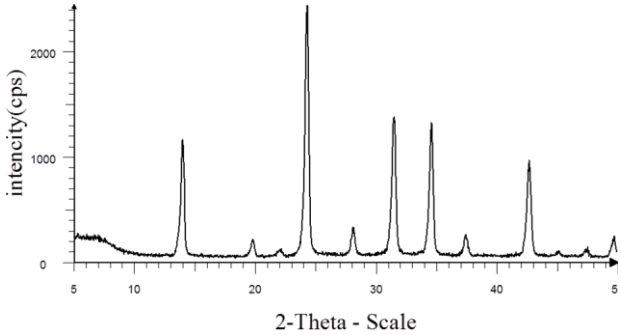

Figure 3: The XRD pattern of the synthesized nanozeolite sodalite.

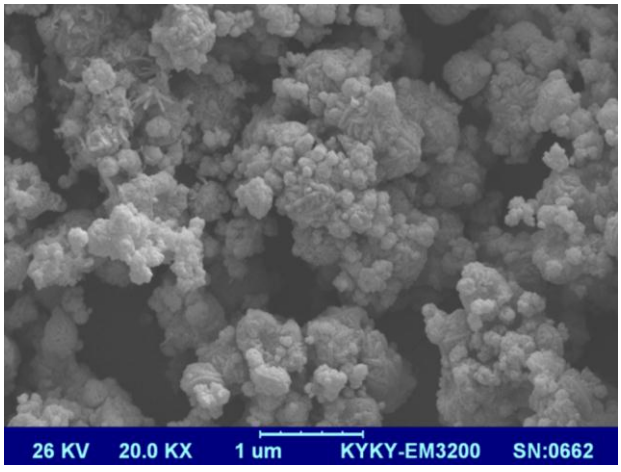

Figure 4: SEM image of synthesized nanozeolite sodalite.

Modification of nanozeolite

Due to the net negative charge on the framework, nanozeolites usually have little or no affinity for anions and exhibit low adsorption for organics in aqueous solution. To change the surface properties, one modification method widely employed is to use organic surfactants (Wang and Peng, 2010). Adsorption ability of modified nanozeolite was already proven for Cetirizine. To prepare the modified nanozeolite, 200 mg of synthetic nanozeolite sodalite was added to 50-mL aqueous solution of the cationic surfactant (HDTMAB) at concentration (10mmol/L) in polyethylene bottle. The sample was stirred for 24 h at room temperature. The suspension was centrifuged at 10000 rpm for 15 min. Surface-modified sample was then washed with excess amounts of water until no foam was formed by shaking the supernatant. The prepared modified nanozeolite was air-dried for 72 h (Nezamzadeh-Ejhieh and Tavakoli-Ghinani, 2014).

Drug loading

Tests determining adsorption of Cet by prepared modified nanozeolite was carried out in batch experiments at room temperature. Stock solution of the drug in the concentration 100 mg/L in three phosphate buffer solutions at pH 4, 5 and 6 were prepared. Note that the adsorption of drug was favored at pH< pH_{ZPC} (pH at the potential of zero charge) (Mall *et al.*, 2006). pH_{ZPC} measured using the pH drift method (Lopez-Ramon *et al.*, 1999). The pH 4 is under pH_{ZPC} and pH 6 is above pH_{ZPC} for nanozeolite. Then 200 mg of modified nanozeolite was soaked with 25 ml of each 3 buffer drug solutions under continuous stirring at 250 rpm at room temperature. After different times the sample was centrifuged 15 min at 10000 rpm. Supernatant was used for determination of the drug. The initial and final concentration of drug was determined by UV-Vis spectrophotometer (Krajišnik *et al.*, 2011).

In-vitro drug release

In-vitro release studies were performed in simulated body conditions according to references (Yang *et al.*, 2006; Liu *et al.*, 2013) with slight modification. Three buffered solutions with different pH 1.2 (stomach), 6.8 (intestine) and 7.2 (blood) were selected for release medium and the temperature was precisely controlled at 37°C. Cet loading into the nanozeolite was achieved as follows: 1 g of modified nanozeolite sodalite was soaked at pH 4 for 120 min, at room temperature, under continuous stirring and in 100 ml solution of 100 ppm of Cet. Then the solution was filtered and the solid was air-dried for 24 h.

Then, 200 mg of Cet loaded modified nanozeolite sodalite as a nanocarrier was immersed into 20 mL of each buffered solution with magnetic stirring. After 2, 4 and 6 hours the samples were centrifuged 15 min at 10000 rpm. Supernatants were used for determination of the drug. The initial and final concentrations of drug were determined by UV-Vis spectrophotometer.

RESULTS AND DISCUSSION

Characterization

FT-IR spectrum of the synthesized nanozeolite is illustrated in (figure 2). The original assignments of the main IR bands were as follows: internal tetrahedral 1250-920 cm^{-1}, pore opening vibrations; 1150–1050 cm^{-1}, double ring 650-500 cm^{-1}. The most important peak in the region from 500 to 600 cm^{-1} is related to the presence of the double ring (D_4R) that is characteristic in the nanozeolites (Breck, 1974). Sharp peaks corresponding to the water deformation mode at ~1650 cm^{-1} and 3500 cm^{-1} appears in the spectra.

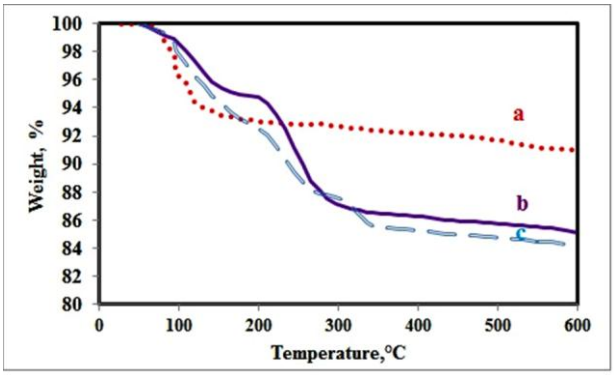

Figure 5: TGA thermograms of nanozeolite sodalite (a), modified nanozeolite sodalite (b) and modified nanozeolite sodalite with drug loaded (c).

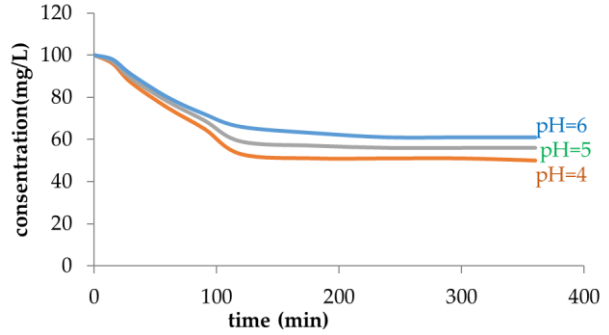

Figure 6: Effect of time and pH on the adsorption of Cetirizine.

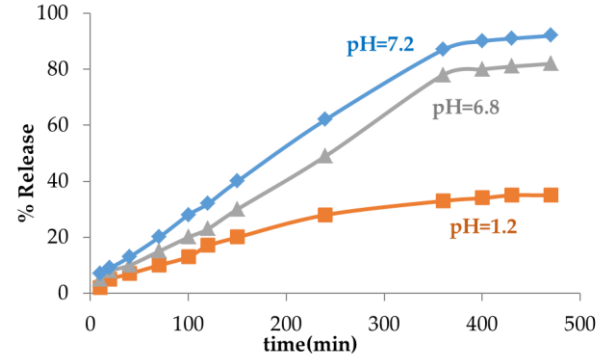

Figure 7: Cetirizine release profiles in different pH (1.2, 6.8 and 7.2) at 37 °C.

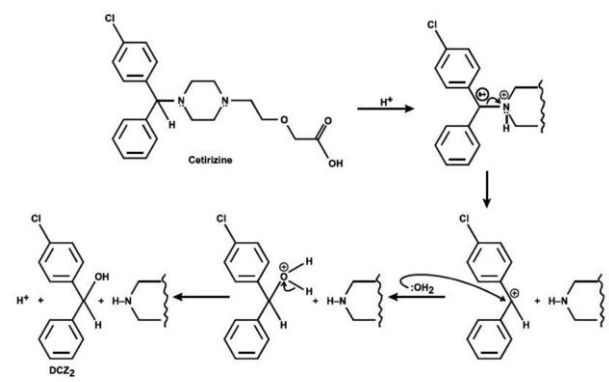

Figure 8: Degradation of Cetirizine in acidic solution.

The XRD pattern of the synthesized sample is shown in (figure 3). According atlas of zeolite framework types and comparison this pattern with mother pattern indicated that this synthesized sample has the structure of nanozeolite sodalite (Treacy and Higgins, 2001).

The SEM image of the particles is shown in figure 4, which shows the morphology of synthesized zeolite with small particle size in range of 30-81 nm.

Thermogravimetry analysis

Figure 5 shows TGA thermograms of nanozeolite sodalite (a), modified nanozeolite sodalite (b) and modified nanozeolite sodalite with drug loaded (c). The TGA profile (c) has three peaks of mass loss at 100, 220 and 260°C, respectively assigned to the loss of water by the nanozeolite, the thermal decomposition of surfactant and removal of drug.

Loading and release studies

The drug concentration in aqueous phase was determined spectrophotometrically at 230 nm and it was calculated from the difference between the initial and final concentration in the aqueous supernatant after the equilibrium. The amount of drug adsorbed onto modified zeolite, q_t (mg/g) at time t was calculated using following equation:

$$q_t = \frac{(C_0 - C_T)V}{M}$$

where C_0 (mg/L) is the initial adsorbate concentration, V(L) the volume of the drug solution in the flask, C_T(mg/L) the drug concentration after time t and M (g) is the mass of dry adsorbent that was used (Bhakta and Munekage, 2011; Hameed *et al.*, 2009), adsorption results are shown in figure 6.

In order to investigate the potential of using nanocarrier as drug carrier, its release behavior was evaluated in three different buffered solutions with pH 1.2, 6, 8 and 7.2 at 37 °C and in-vitro release profiles of it was shown in figure 7. Results show the release of drug, increases with pH and so a drug moves down the gastrointestinal tract from the stomach to the intestine, its release will increase.

According to the proposed mechanism of degradation of Cetirizine leading to DCZ_2 (Chlorophenyl benzyl alcohol) (Kaur *et al.*, 2014), in acidic solution (stomach), the amount of Cet is reduced (figure 8).

CONCLUSION

Our study displays that perlite is a suitable Si source for preparing of nanozeolite sodalite and this method is very fast and easy. Adsorption of Cetirizine on surface of modified nanozeolite sodalite was successful. The study on the nanozeolite discussed here demonstrates that this structure can be used effectively for carrier drug applications. This carrier can reduce toxicity and enhance therapeutic efficacy of drug, also can control release of drug in body.

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