Investigation of Loading and Releasing of Losartan potassium based on mesoporous silica

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ABSTRACT

The use of controlled release drug maintains the optimal therapeutic concentration of the drug in the blood and increases the duration of activity in drugs with short half-lives. The purpose of this study was to identify and characterize porous silicate mesopores MCM-41 with the aim of obtaining a suitable drug carrier for the controlled release of losartan potassium. For this purpose, different samples of MCM-41 modified with acidic agents including citric acid, acetic acid and ascorbic acid were prepared and characterized by XRD and FTIR methods. In the next step, the drug loading of losartan potassium on modified MCM-41 was performed and the drug system was prepared. The results of drug loading showed that loading of losartan potassium in MCM-41 functionalized with ascorbic acid and citric acid was higher than other synthesized samples. The amount of losartan loaded in these carriers was 97.6% and 29.1% respectively. Also, the results of the drug release phase experiments showed that these carriers have the highest drug release.

Keywords: silicate mesopores, release control, losartan potassium, loading

1. Introduction

The set of methods used to distribute medicinal compounds to produce a therapeutic effect on the human or animal body is described. The earliest drug delivery systems were slow release systems that allowed for a steady and uniform plasma concentration of the drug for a certain period of time in the blood. In this way, the drug is embedded in the system and released into the body. The drug system then circulates through the bloodstream to the target tissue and releases the drug to work. In this method, the type of particle, the way the drug enters the body, and the way the drug is released is regulated by the type of disease, the type of drug and the organ involved. The focus of drug technology is to get the drug to the right place in the body at the right time and with the desired therapeutic effects. This technology has many benefits including: decrease drug use, reduce side effects of the drug because the drug only goes to a certain position and does not affect other organs, increased efficacy of the drug due to accumulation of the drug at the site of the lesion, reduce treatment duration and make treatment safer and more secure, increased patient satisfaction in receiving treatment, reduce costs, Other benefits of controlled drug release include: ability to maintain the drug concentration at a relatively constant level for a specified period, adjustable drug release rate depending on drug delivery site, ability to deliver multiple medications with one formulation, possible drug delivery in nanometers…[1].

Traditional drug delivery systems have virtually no control over the location and speed of drug release. Also the concentration of the drug in the blood is constantly changing and the efficacy of the drug is reduced and side effects are inevitable. With the advent of new drug delivery systems, it is possible to deliver the drugs to the target area in a controlled manner and with reduced side effects. So far, many materials have been studied as drug release systems, including biodegradable polymeric materials [2], ceramic materials such as hydroxyapatite [3-4] and calcium phosphates [5]. Most recently, mesoporous silica materials [6-7], have received the most attention. These compounds have a very large surface area and their cavities are adjustable. They also have a high level of functionality, thus providing an opportunity for the development of new drug delivery systems that can control the rate of drug loading and release through these properties of the compounds. In fact, the high porosity of mesoporous silicate materials allows biologically active molecules of varying size to settle in the cavities of these materials. In addition, the network of regular porosities of these compounds allows for a rapid loading and release rate. Also, since the adsorption of molecules on mesoporous compounds is a surface phenomenon, the high specificity of these substances also results in the absorption of more biologically active molecules. In addition, the development of stimulating and targeted drug delivery systems is one of the potentials of these substances. What is important in designing a drug release system is its biocompatibility and biodegradability [8-9]. MCM-41 as a member of the family of porous silicate compounds has very regular hexagonal channels. The diameter of the channels can be set between 1.5-10 nm. High surface area, large cavity volume and ideal biocompatibility make MCM-41 one of the best materials to carry many compounds so that it attracts a great deal of attention in the design of drug delivery systems. In this study, we first synthesized MCM-41 and identified it by different methods. We then modified it with ascorbic, acetic and citric acids and performed loading and release experiments with losartan potassium on different forms of MCM-41.

2. Experimental

2.1. Materials

Materials used for the synthesis of mesoporous MCM-41, cetyl trimethyl ammonium bromide (CTAB) were purified by 98% purity, sodium silicate and ethanol from Merk and 25% ammonia from Qatran Chemical Company. Acids used in the porous meso-correction process including ascorbic and citric acid were purchased from Merk and acetic acid from Qatran Chemical Company. Losartan potassium 100.6% purity was obtained from Damavand Drug Factory in Iran and phosphate buffered saline salts including monosodium phosphate and disodium phosphate from Merk Germany.

2.2. Synthesis of MCM-41

Pour a certain amount of CTAB into a balloon and add 120 ml of distilled water to dissolve. Then place the solution on an electric mixer and add 10.25 ml of 25% ammonia solution. Add 10 ml of ethanol to the above stirring solution and stir for another 30 minutes. Then add 7.5 ml of sodium silicate to the solution and stir for one hour. Then shake off the stirrer and remove the solution with a filter paper from the precipitate and the precipitate is washed several times with distilled water to neutralize. After being neutralized, transfer the precipitate to the oven to dry at 110 ºC for 24 hours. The sediment is transferred to the furnace for calcination. The oven temperature and time are set to 550 ºC and 5 hours, respectively. Finally the withe powder is synthesized MCM-41 [10].

2.3. Grafting of MCM-41 with acids

Ascorbic, citric and acetic acids are used to modify mesoporous silicate (MCM-41). Thus 1 g of MCM-41 is mixed with 20 ml of 0.6 M acid in an ultrasonic bath for 45 minutes. The solution is stirred with a stirrer for 45 minutes. The solution is placed in the oven at 50 ºC for 24 hours. After 24 hours the oven temperature rises to 120 ºC. After 90 minutes remove the precipitate from the oven and rinse with distilled water until neutralized. In the final step, the precipitate is placed in the oven for 70 hours at 70 ºC. This is the same for all three acids. Carriers modified with ascorbic acid MCM-41-As, modified with acetic acid MCM-41-Ac and modified with citric acid MCM-41-Ci.

2.4. Drug loading experiments

0.25 g of the carrier is poured into a jejunal balloon and 25 ml of losartan solution (0.5 mg/ml) is added to it. Put the balloon on an electric shaker in low light conditions and stir for 24 hours. After 24 hours the balloon is removed from the shaker and the solution is centrifuged and the precipitate is removed from the solution. This way the drug is loaded onto the carrier. To calculate the amount of drug absorbed by the carrier, the solution is taken from UV analysis after centrifugation. Also the centrifuge precipitate is the same carrier/drug that used for the release phase. The amount of drug absorbed by the carrier at the drug absorption stage is obtained from the following formula:

loading efficiency(W/W%)=(initial amount of drug-residual drug)/(initial amount of drug)×100

2.5. Drug release experiments

In the process of determining the amount of drug release from the drug-carrier system, the following is done: Dissolve 0.15 g of the precipitate from the adsorption step in a balloon and add 30 ml of phosphate buffer (pH= 7.4). The balloon is then incubated in an incubator shaker at 37 ºC for 17 hours in the absence of light. Then remove the balloon from the incubator and centrifuge the mixture inside it. UV analysis reveal the drug release rate from the carrier.

3. Results and discussion

3.1. Characterization of the samples

3.1.1. XRD investigation

Figure 1A shows the XRD spectrum of MCM-41. Figure 1B shows the XRD spectra of mesoporous synthesized pores in the 2θ range between 1.5-10º. The standard X-ray diffraction pattern of MCM-41 and its functionalized specimens show three peak indices that show a strong diffraction of the plate (100) at an angle of 2θ of about 2 degrees, reflecting the two-dimensional structural pattern of the six-facet synthesized meso materials and two peaks of less intensity correspond to plates (110) and (200) appearing at angles of 3.6 and 4.3 degrees indicating the high order of the meso-material of the synthesized. Comparison of the pattern obtained from the XRD spectra of the synthesized mesoporous in this study with the examples cited in the literature indicates that the mesoporous hexagonal structures are correctly synthesized and free from any defects [11]. After MCM-41 is operationalized, the peaks corresponding to the diffraction patterns of 100, 110 and 200 are less detectable, which can indicate both the success of the functionalization and the order of structure of the mesoporous material is retained after being functionalized. It can also be said that the decrease in peak intensity of 100 in the functionalized samples indicates the placement of functional groups within the main pores of the mesoporous material. In addition, the decrease in peak intensities is due to the decrease in the number of pores available due to the occupancy of the pores, and on the other hand, the peaks due to plate diffraction in the functionalized samples are shifted to higher 2θ, which this also confirms the connectivity of the functional groups.

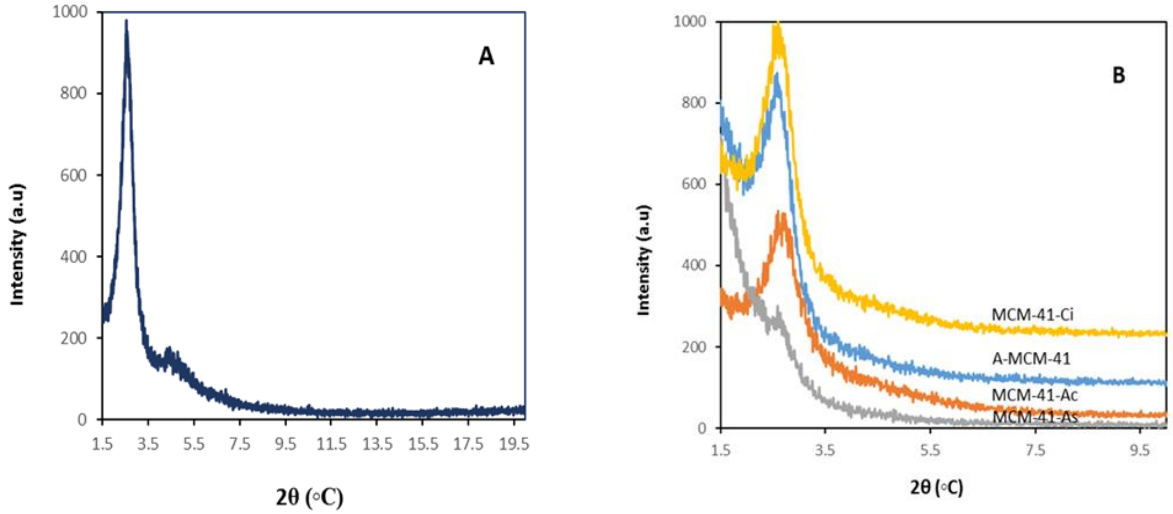
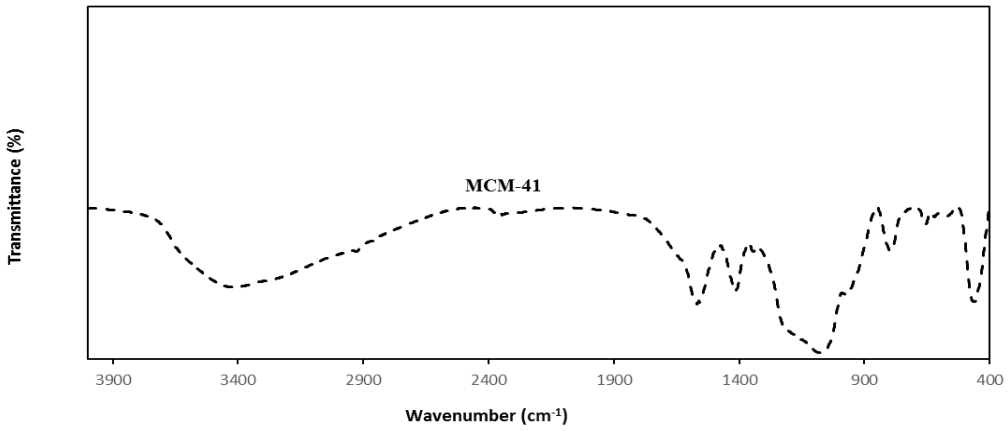


Fig1. XRD spectra of synthesized particles A) MCM-41, B) low angle spectrum of functionalized carriers

3.1.2. Investigation of FT-IR spectra

The FT-IR spectra of MCM-41 and its modified forms in the range 400-4000 cm^{-1} are shown in fig.2. For all samples, the peak observed at 3400 cm^{-1} is related to the tensile vibrations of the OH group and the water absorbed on the sample surface. The strong band observed at 1080 cm^{-1} has asymmetric tensile stress and the band at 1799 cm^{-1} has symmetric tensile Si-O-Si. Also the absorption spectrum observed at about 450 cm^{-1} can be attributed to the bending vibrations of the siloxane group (Si-O-Si) in the silicate compressed lattice. These three peaks are the major markers in mesoporous silicate materials indicating the successful synthesis of MCM-41 [12].



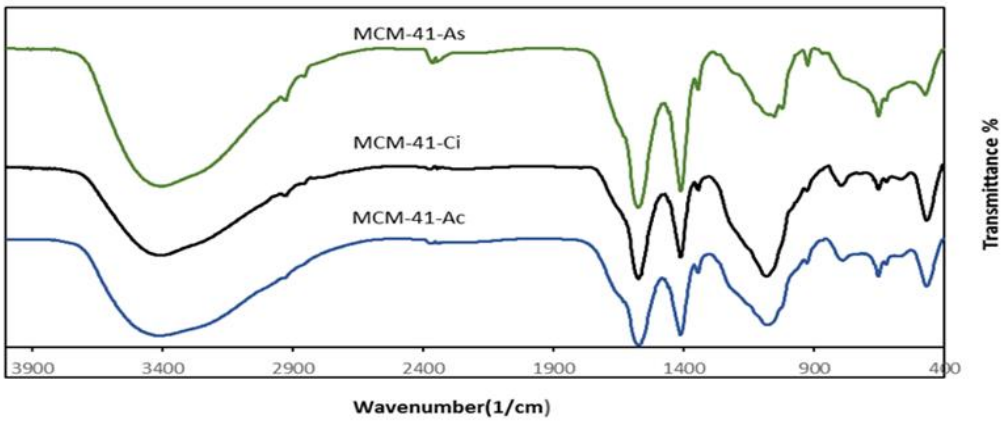


Fig.2. FT-IR spectra of the synthesized particles

3.2. Drug loading studies (The effect of carrier type on drug loading)

The effect of the types of carriers synthesized on the drug loading process is examined. At this stage 4 experiments were designed. Carriers were 0.25 g and solution of Losartan potassium 25 ml per balloon. Other test conditions such as contact time, shaker speed and light conditions were the same for all samples. The diagram for the experiments of this step is shown in figure 3. The results showed that MCM-41-Ci and MCM-41-As had the highest adsorption rates compared to other carriers.

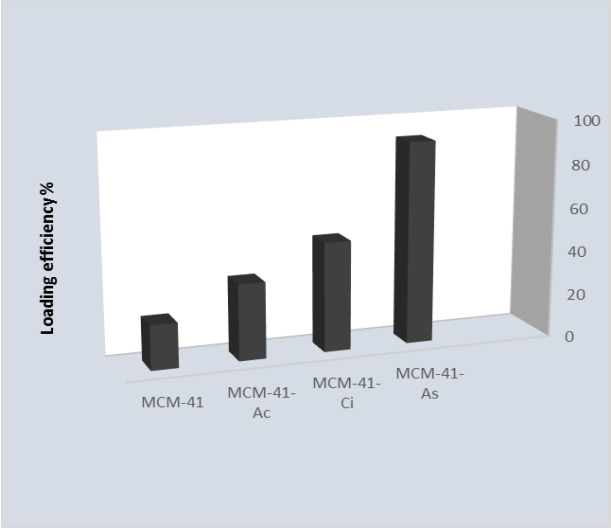


Figure 3. Chart loading of Losartan on synthesized carriers

3.3. Drug release studies (The effect of carrier type on drug release rate)

In order to investigate the effect of the type of carrier in the drug release phase, 4 experiments were designed in which all conditions are the same but in each test the type of carrier is changed to obtain the optimal carrier in the drug release phase. Diagrams of the effect of carrier type on the release of Losartan are shown in figure 4. As shown in the figure, the MCM-41-As and MCM-41-Ci carriers have better drug release performance than other carriers and have the highest drug release rates. Therefore, MCM-41-As and MCM-41-Ci carriers are selected as the optimal carriers in the drug release phase.

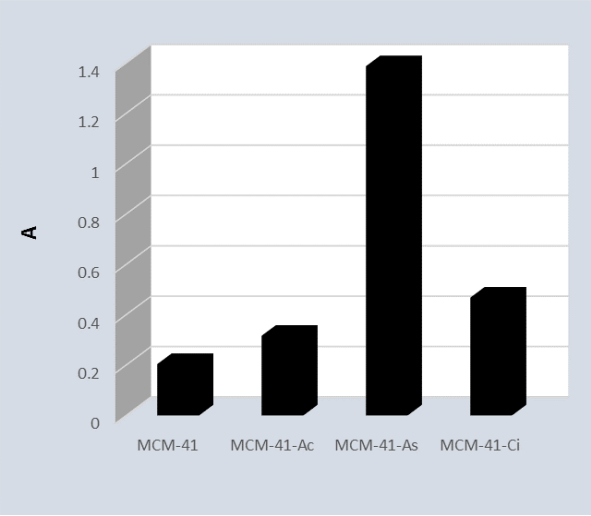


Figure 4. The effect of carrier type on drug release

4. Conclusion

In this study, MCM-41 silicate mesopor and its modified forms with acetic acid, citric acid and ascorbic acid were used as carriers for the drug Losartan Potassium. First, the effect of MCM-41 as well as its modified forms with different acids on the absorption and release of Losartan was investigated. The results of experiments performed in this study showed that MCM-41-As and MCM-41-Ci, compared to other samples synthesized in this study, performed better in adsorption of Losartan. After performing the adsorption test with optimal conditions, the percentage of drug uptake by MCM-41-As and MCM-41-Ci carriers is equal to 97.6%.and 29.1% respectively. Also, the rate of drug release from the carrier-drug system in these two carriers are the highest and equal to 79.1% and 57.1%, respectively.

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