Al-Khwarizmi Engineering Journal, Vol. 15, No. 1, March, (2019)
P.P. 117- 124

Al-Khwarizmi Engineering Journal

Experimental Study of Drug Delivery system for Prednisolone Loaded and Released by Mesoporous Silica MCM-41

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(Received 17 May 2018; accepted 26 June 2018)
https://doi.org/10.22153/kej.2019.06.004

Abstract

In the present study, nanoporous material type MCM-41 was prepared by the sol-gel technique and was used as a carrier for prednisolone (PRD) drug delivery. The structural properties of mesoporous were fully characterized by X-ray diffraction (XRD), N_2 adsorption /desorption and Fourier-transform infrared (FTIR). The mass transfer in term of adsorption process (loading) and desorption process (releasing) properties were investigated. The maximum drug loading efficiency was equal to 38% and 47.5% at different concentrations. The PRD released was prudently studied in water media of pH 6.8 simulated body fluid (SBF) in according to "United State Pharmacopeia (USP38)". The results proved that the release of prednisolone from MCM-41 was (69.4%) after 24 hr. The data of the released PRD was found to be submitted to a Korsmeyer–Peppas model.

Keywords: *Drug delivery, Kinetics model, MCM-41, Prednisolone.*

1. Introduction

Growing interests have been drawn to the application of mesoporous silica particles (MSPs) as drug delivery carriers [1]. In covenant with The International Union of Pure and Applied Chemistry (IUPAC) commendation, order mesoporous has a uniform and adjustable pore size of (2–50) nm [2]. Mesoporous silica has many advantages such as large surface area, tunable pore size, controlled the morphology and the size of the particles, large pore volumes, uniform porosity, stable aqueous dispersion make them promising materials for the preparation of delivery systems of bioactive molecules [3,4]. In addition to good chemical and thermal stability, morphology control, and surface functionalization, the applications of the silica materials in the biological systems can be considered as key potential candidates and controlled drug delivery [5]. The attention of many scientists have been attracted to the MCM-41 as drug delivery vehicles [6], because they feature by large pore volume, large surface area, highly ordered structure, tunable nanometer pores and ‘‘non-cytotoxic’’ properties [7].

In addition, silanol groups on both the internal and the external surface, which makes it simple to be modified and more interaction between these carrier and drug molecules leading high drug loading [8]. The amount released and loaded of the drug is directly related to the pore volume and pore size of mesoporous materials [9]. MCM-41 nanoparticles are effective and controllable delivery systems for biomedical applications [10,11]. Cavallaro et al. [12] have studied mesoporous as a carrier for drug delivery systems. Ibuprofen, diflunisal, and naproxen are used as anti-inflammatory agents. The release of drugs was also achieved at simulating gastrointestinal fluids. The proposed of release data that the matrix offering clever potential as a system for the modification of the released drug. Qu et al. [13] lately studied on the MCM-41 as a carrier for

captopril as water soluble drug delivery. the (BET) area and hydrophilicity and hydrophobicity of the surface of mesoporous silica is related by the amount of drug loading, whereas profile of the released drug can be controlled by tailoring pore size and the properties of the surface.

The focus of this paper on the preparation and characterization of MCM-41and used for the loading of prednisolone (PRD). The contact time effect on the efficiency of drug loading was studied. The release of PRD from water media of pH 6.8 was studied as well. Immunosuppressant and anti-inflammatory drug such as prednisolone (PRD), which is a synthetic corticosteroid drug, is particularly effective at different conditions such as inflammatory bowel diseases (IBD), inflammation (swelling), severe allergies, adrenal problems, arthritis, asthma and cancers which have been treated by the use of PRD. Side effect such as toxic is a result of prolonged absorption of the drugs from intestine which is caused by the large and frequent doses of PRD for a long period. This is why a specific delivery of drugs should be developed to be delivered to the disease parts. Additionally, according to the biopharmaceutics, prednisolone is a class II substance which is a poorly water soluble drug [14]. Fig.1 represented the 2D structure of prednisolone drug.

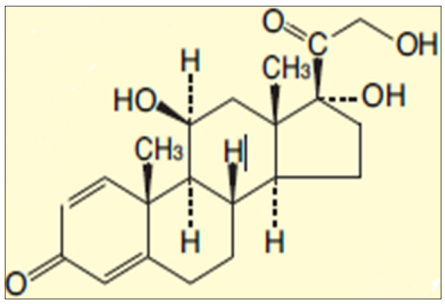

Fig. 1. The 2D structure of PRD [15].

2. Experimental

2.1 Chemicals

Cetyl trimethyammonium bromide $CH_3(CH2)_{15}N(Br)$ $(CH3)_{3,}$ (M_w=364.45 g/mol) and Tetraethyl orthosilicate (TEOS) were purchased from Sigma Aldrich. Sodium hydroxide (NaOH) from BDH England. Prednisolone was purchased from Al KINDI Company for Pharmaceutical Industries in Iraq. no further purification of all chemical reagents that used.

2.2 Synthesis of MCM-41Mesoporous

MCM-41 was prepared by sol-gel process**.** TEOS was used as silica precursor and CTAB was the structure directing agent (SDA). First, 1.01 g of CTAB was dissolved in mixture containing NaOH with a weight of 0.34 g and 30 mL of deionized water. Then, drop by drop of the added TEOS to the mixture with weight about 5.78 g under 1h of stirring at ambient temperature and the homogeneous mixture output was crystallized under constant hydrothermal conditions (110 °C) in an autoclave for 96 h. The solid product obtained by filtration process was washed with DI water to remove the partial surfactant. Then, the obtained solid was dried at 40 °C overnight and calcination was performed at 550 C° for 6 h to remove the surfactant, template, and then, MCM-41 was obtained [16].

2.3 Characterization

The X-ray pattern was used to discovery the crystalline structure, to distinguish crystalline phases, locating and to determine structural properties of MCM-41 with 2θ in the range 0° to 10° with scan rate 2(deg/min). The source of the X-ray radiation was Cu Kα (λ =1 .541Å). By using the equations a_o=2d100/√3 and nλ=2dsinθ the unit cell and d-spacing factors were obtained. Nitrogen adsorption-desorption isotherms were measured at −195.777°C using desorption analyzer [Type: ASAP 2020 600, Origin: USA]. The sample was degassed for 6 h at 200 C° under vacuum. By following the (BET) method, the BET surface area of the prepared sample was calculated in the 0.05 and 0.35 range of relative pressures. At P/P_o=0.98186, the adsorbed amount of liquid nitrogen taken from the adsorption branch of the N_2 isotherm allowing to calculate the total pore volume of the synthesized MCM-41. The thickness of the pore wall (W_t) can be calculated from the difference between unit cell parameter (a_o) and diameter of the pore (D_p) . The morphology of MCM-41 was characterized by scanning electron microscopy (SEM), accomplished on a TE SCAN (Model VEGA ш). The (FTIR) infrared spectra of the powder sample recorded at ambient condition in transmission mode in the range of 4,000 to 400 cm^{-1} at 4 cm^{-1} resolution regions using (Bruker–Tensor 27/ Germany).

2.4 Prednisolone Loading

A certain amount of MCM-41 was added to 50ml of PRD concentration 20 mg/l, and then positioned on a shaker at 500 rpm and ambient condition (25ºC) for 24 h to reach the state of equilibrium. The Prednisolone loaded MCM-41 (PRD@ MCM-41) was thereafter centrifugation for 30 min at 5000 rpm and drug supernatant was withdrawn by syringe filter type (0.22µ) into quartz for measurement the concentration of drug by UV_Vis spectrophotometer, by monitoring the major peak at 247nm, which relates to the absorption maximum of PRD. The quantity of loaded PRD was measured by UV–Vis spectrophotometer after deducting the quantity found in the supernatant from the amount of PRD present before the addition of the MCM-41. By using the following equation, the efficiency of drug loading was estimated [17]:

$$\text{Drug Loading(DL)}(\%) = \frac{M_2 - M_1}{M_3} \times 100 \quad \ldots (1)$$

2.5 Prednisolone Release

The dissolution study of the PRD released from MCM-41was done in Al KINDI Company for Pharmaceutical Industries using dissolution tester (USP) TDT-08L (Jar test) by following the United State Pharmacopeia (USP38). The certain quantity of (PRD@MCM-41) was soaked in 900 ml of water media with pH 6.8 and stirring (50 rpm) at 37 ˚C using an incubator in order to simulate body temperature. At given time intervals, the suspension was withdrawn by syringe filter type (0.22µ) into a quartz cuvette. By using UV–Vis spectrophotometer at 247 nm the amount of PRD released was measured. The percentage of PRD released was estimated using the following equation [18]:

$$\text{Release}\% = \frac{\text{The weight of drug in solution}}{\text{The weight of drug in MCM}-41} \times 100 \quad \ldots (2)$$

3. Results and Discussion

3.1 X-Ray Diffraction Pattern

XRD pattern of MCM-41sample is explained in Fig. 2, shows at about 2θ° of 2.86° and considered as an intense diffraction peak (1 0 0) and two additional higher order peaks (hkl) (1 1 0, 2 0 0) with lower intensities at 4.4°, 5° respectively. These two peaks indicate the formation of a hexagonal structure [19]. The position of the first peak, (1 0 0), allows direct determination of the unit cell parameter between adjacent tubes using $a_0 = (2*d100/\sqrt{3})$ [20]. The calculated d_{100} and a_o values are given in Table 1.

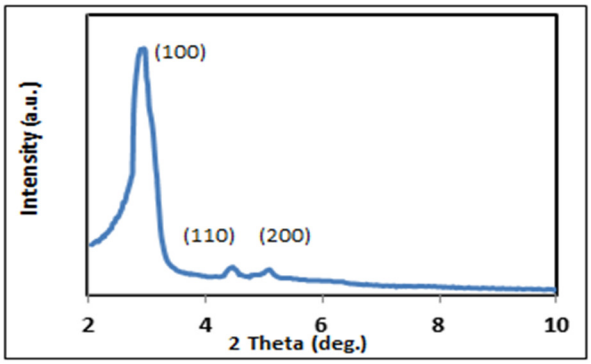

Fig. 2. XRD pattern for MCM-41.

3.2 FTIR Spectra

Fig. 3. shown spectra of the infrared of the MCM-41. The blue peaks around 1234 and 1086 cm^{-1} are attributed to the asymmetric stretching of Si–O–Si groups. Additionally, broad and weak bands at 970 cm^{-1} were indexed to the symmetric stretching vibration of Si–OH moieties presented in the pore channels. The broad peak around 3440 cm^{-1} is due to O–H stretching of water which was associated with O–H bending at 1680 and 1630 cm^{-1}. The absorption bands at 463 cm^{-1} were corresponding to the bending vibration of Si–O–Si. The absorption band at 1474 cm^{-1} which assigned to C-H stretching vibration of the alkyle group and the corresponding bending mode of C–H was observed at 2362 cm^{-1} [20].

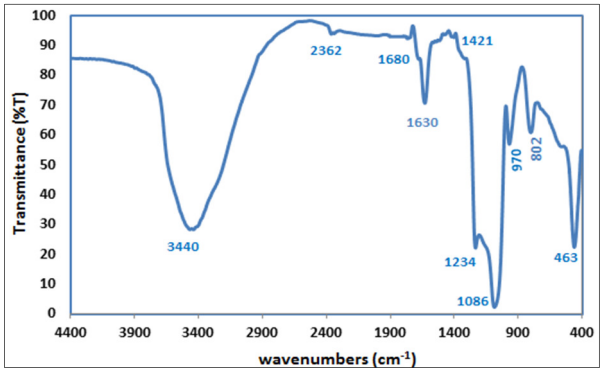

Fig. 3. FTIR for MCM-41.

Table 1,
The Structure properties of MCM-41.

material	d_{100}[a] (nm)	a_o[b] (nm)	D_p (nm)	W_t[c] (nm)	V_p[d](cm^3/g)	S_{BET}[e](m^2/g)
MCM-41	3.35	3.868	2.06	1.808	0.691	1340

[a] d-Spacing of (100) reflection
[b] Unit cell constant, $a_o=2d100/\sqrt{3}$
[c] The thickness of the pore wall calculated by the difference (a_o _ Dp)
[d] at $p/p_0=0.9818$ of N_2 volume adsorbed the total pore volume was taken
[e] in the linear part of the BET plot, the BET surface area was calculated

3.3 Scanning Electron Microscopy (SEM)

The SEM images of MCM-41as shown in Fig.4 indicate the presences of agglomerate spherical particles that are a feature of mesoporous materials. The SEM images obviously showed that the MCM-41 particles had a sphere shape and have smooth surfaces [21].

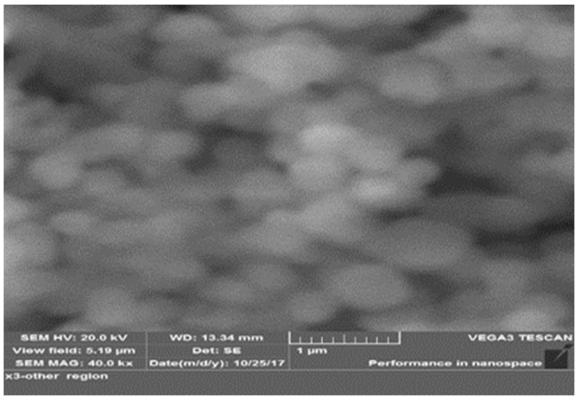

Fig. 4. SEM for MCM-41.

3.4 Prednisolone Loading

The contact time effect on the loading of drug efficiency of PRD was studied at a various concentration of PRD (Co=10 and 20 mg/l) as shown in Fig. 5. The drug loading efficiency of PRD is fast within the first 24 h of contact time and when 48 h the loading doesn't vary extremely. This could be illustrated that an oversized range of existing mesopore sites is accessible for the loading at the beginning. It was also suggested that a strong attractive force transpired between the PRD molecules and also the MCM-41 and with an increase in time of contact, the remaining available mesopore sites are tough to be occupied because of saturation. This might ensue to the lacking number of available loading sites at the end of the loading process, therefore the efficiency of loading continued nearly constant [19].

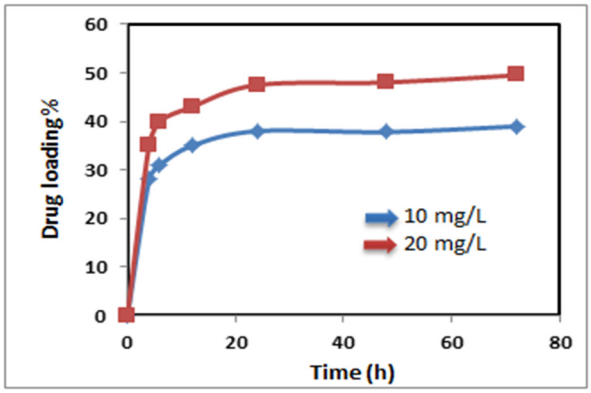

Fig. 5. Concentration-time dependence on loading uptake of PRD by MCM-41.

3.5 Release of Prednisolone

The dissolution analysis is a vital study for improvement and control of quality of the drug. The release of PRD from MCM-41sample was done at pH value of 6.8 with water media according to the "United State Pharmacopeia (USP38)". The drug release behavior of PRD drug was studied in water media with value of pH 6.8 at body temperature (35°C). An UV_vis spectrometer was used to measure the PRD release. The percentage of PRD released from the synthesized MCM-41 in water media of pH 6.8 according to United State Pharmacopeia (USP38) is displayed in Fig. 6. At the beginning of the dissolution, the concentration gradient between surfaces of the MCM-41 and in the bulk media was large leading to small percent of released PRD. Then, the PRD release has gradually increased with increasing in the time of dissolution until equilibrium was reached. This is due to the increasing in the concentration of H+ at pH 6.8and therefore the bond of the hydrogen strengthened between PRD and active sites of MCM-41. The cumulative release quantity of PRD form MCM-41 could reach up to 69.4% after 24 h.

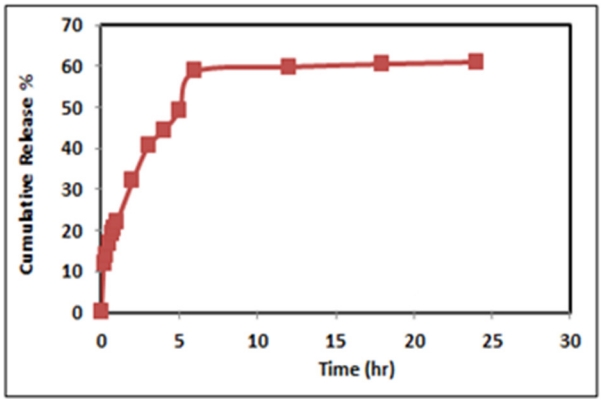

Fig. 6. The release profile of PRD in water media of pH 6.8.

3.6 kinetic Release of Prednisolone

Different kinetic models like, the first order, Higuchi, Korsmeyer-Peppas, and Weibull models were used to evaluate the mechanism of the PRD release. To determine the transport mechanism of drug, the exponent of diffusion (n) was estimated from Korsmeyer-Peppas model, the Fickian diffusion was characterized when the value of n ≤ 0.5 and the anomalous mechanism was characterized when the value of n from $0.5 - 1$.

First order:

$$\log(100 - W) = \log 100 - K_1 t \quad \ldots (3)$$

Higuchi kinetics: $W = K_H t^{\frac{1}{2}}$ … (4)

Korsmeyer – peppas model: $\frac{Mt}{M\infty} = Kt^n$ … (5)

Weibull : $\text{Log}[-\ln(1-f)] = m \log t - \ln t_o \ldots$ (6)

Where: W is the cumulative percentage release, f is the cumulative quantity fraction of PRD released and K_1, K_H, and m are the rate constants of PRD released of first order, Higuchi, and Weibull models, Mt/M∞ is the fraction of PRD released in the media of dissolution, K is a constant, which include structural properties and geometric of the drug. To study the kinetic mechanism of PRD release, the obtained PRD data were fitted with equations from (3-6) motioned above. All kinetics released was calculated from the linear plots for PRD released from MCM-41and as shown in Fig. 7. The rate constants of PRD released was measured and summarized in Table 2. A good linear fit of the released data from Korsmeyer-Peppas model was obtained.

Table 2,
Release kinetic parameters of PRD released from MCM-41.

		First order		Higuchi		Weibull		Korsmeyer- Peppas		
media	**pH**	**K_1 (h^{-1})**	**R^2**	**K_H ($\%h^{1/2}$)**	**R^2**	**m**	**R^2**	**K n (h^{-n})**	**n**	**R^2**
water	6.8	0.012	0.7232	29.583	0.9379	0.32	0.964	0.2769	0.662	0.966

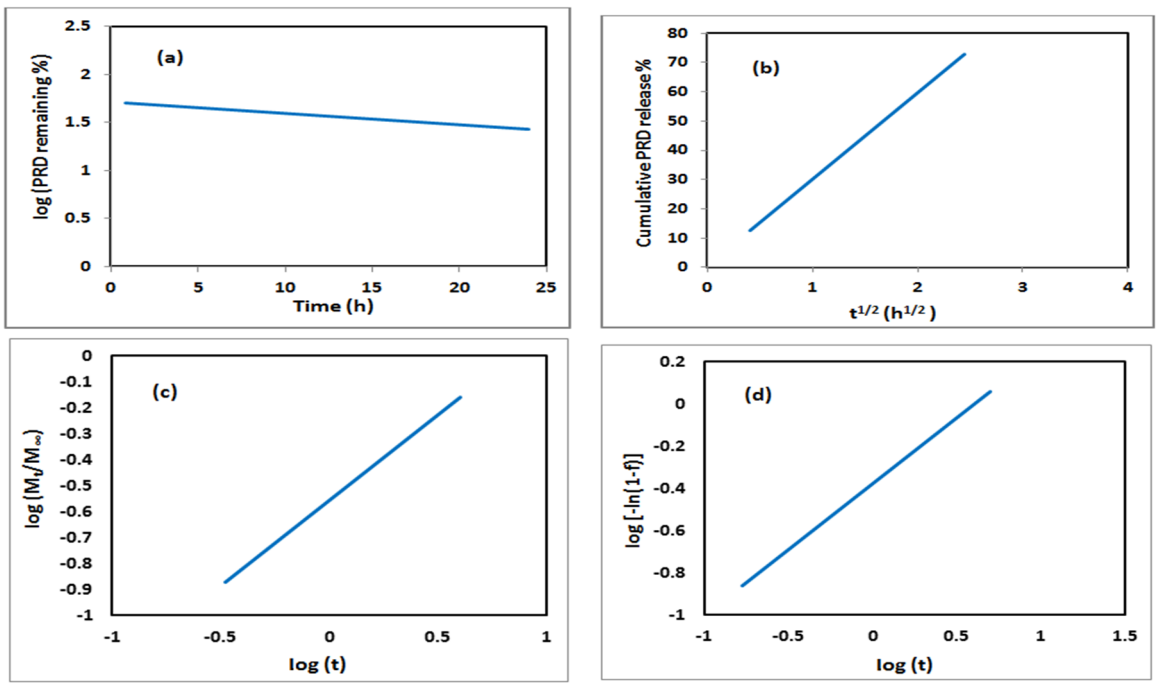

Fig. 7. Kinetic release of PRD for (a) first order, (b) Higuchi model, (c) Korsmeyer-Peppas, and (d) Weibull models.

4. Conclusions

MCM-41with high surface area was prepared successfully by the conventional method and used as drug delivery naocarrier. PRD was introduced in the MCM-41sample. Maximum loading efficiency (38% and 47.5%) was attained at different PRD concentration of (10 and 20) mg/L. The PRD release was investigated at water media with pH (6.8). The time of PRD release was 24 hr. The release kinetics of PRD from MCM-41 is fully qualified by a Korsmeyer-Peppas model. The release mechanism follows the non-Fickian mechanism for water media of pH 6.8.

Abbreviations

MSPs	Mesoporous Silica Particles
IUPAC	International Pure and Applied Chemistry
MCM	Mobil Composite Materials
PRD	Prednisolone
SEM	Scanning Electron Microscopy
SBF	Simulated body fluid
IBD	Inflammatory Bowel Diseases
CTAB	Cetyltrimethyl ammonium bromide
SDA	Structure directing agent
TEOS	Tetraethyl Orthosilicate
BET	Brunauer – Emmett – Teller
Dp	Pore Diameter

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دراسة تجريبية لنظام توصيل دواء البريدنيزولون المحمل والمحرر من قبل السليكا MCM-41

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الخلاصة

في هذه الدراسة ، حضرت المادة النانوية نوع MCM-41 وساطة تقنية sol-gel واستخدمت ناقلا لتوصيل دواء ريدنيزولون. خصائص هيكل المادة النانوية تم توصيفها الكامل عن طريق حيود الأشعة السينية (XRD) ، N_2 امتزاز / الامتصاص و جهاز مطياف الاشعة تحت الحمراء FTIR . تم تحقيق خصائص انتقال الكتلة في عملية الامتزاز (التحميل) و عكس عملية الامتزاز (التحرر) .كانت كفاءة تحميل الدواء القصوى (٣٨ ٪ و ٤٧,٥ ٪) في تراكيز مختلفة .تمت دراسة تحرر دواء البردنيزولون عناية في الوسط المائي من سوائل الجسم المحاكية (SBF)عند الا الهيدروجيني ذي القيمة ٦,٨ وعلى وفق الولايات المتحدة للأدوية ووجد أن تحرر دواء ريدنيزولون من MCM-41 كان (٦٩,٤ ٪) بعد ٢٤ ساعة .بانات تحرر PRD وجدت انها تخضع لمعادلة Korsmeyer – Peppas.