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Mesoporous Silica Nanoparticles as a System for Ciprofloxacin Drug Delivery; Kinetic of Adsorption and Releasing

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Abstract:

Mesoporous silica (MPS) nanoparticle was prepared as carriers for drug delivery systems by sol–gel method from sodium silicate as inexpensive precursor of silica and Cocamidopropyl betaine (CABP) as template. The silica particles were characterized by SEM, TEM, AFM, XRD, and N2adsorption–desorption isotherms. The results show that the MPS particle in the nanorange (40-80 nm) with average diameter equal to 62.15 nm has rods particle morphology, specific surface area is 1096.122 m^2/g, pore volume 0.900 cm^3/g, with average pore diameter 2.902 nm, which can serve as efficient carriers for drugs. The adsorption kinetic of Ciprofloxacin (CIP) drug was studied and the data were analyzed and found to match well with pseudo-first order kinetic model. The CIP drug-loaded mesoporous silica (CIP-mSiO2) nanoparticles has capacity of about 16.3 mg drug/ mg $mSiO_2$ were achieved, and capable of releasing 26% and 98.6% of their drug content after 90 min in water and PBS solution(pH,7.4) respectively. In-vitro controlled release studies of CIP in Simulated Body Fluid were carried out under stirring conditions. A study on release kinetics and mechanism using Koresmeyer-Pepps model, first order kinetic, and kopcha model shows that the Korsmeyer-Peppas and Kopcha models, both conform more closely to the release data.

Key words: Adsorption kinetic, Ciprofloxacin, Mesoporous silica, Release kinetic.

Introduction

Among the materials which may have widespread potential as drug carriers such as colloidal systems, liposomes, micro emulsion, *etc*. (1-4), mesoporous silica (MPS) have some engaging properties, for example large pore volume and surface area, narrow pore size range, chemically inert and allowing easier functionalization of their surface (5, 6) which make them an attractive drug carrier and its release.

In 2001, MPS was first reported as a drug delivery system and in which they loaded ibuprofen drug into the mesoporous of MPS which exhibited high drug loading capacity and sustained drug release (7). An amphiphilic molecules modified with amino acid were used as drug model and the loading on MPS containing a cage and cylindrical pore. The controlled release from its carrier has been also studied (8). A novel mesoporous silica nanoparticles as a carrier for Ibuprofen drug was synthesized and the release kinetics was evaluated. The results show that the synthesized carrier exhibited high loading and a very good release rate (9).

The feasibility of loading rifampin as a drug model into prepared mesoporous silica nanoparticles was determined using methanol, water, and dimethyl sulfoxide solvents in adsorption experiments to load rifampin within the mesoporous. The loading results show that methanol was the best solvent, providing a drug loading efficiency of 52 % and capable of releasing 95% after 24 h using buffer phosphate saline BPS (pH=7.4) (10). The loading and release of two anticancer drugs 5-fluorouracil and 7-hydroxycoumarin from MCM-48 nanoparticles were investigated and the results show that loading capacities of 5-fluorouracil and 7-hydroxycoumarin onto the nanoparticles of about 24 and 14 % were achieved, respectively (11). MPS nanoparticles have diameters in the range of a few hundred nanometers and two pore structures were synthesized , loaded with doxorubicin drug, and the release into a buffer solution was studied to

determine the pore structure and type of MPS nanoparticles effect (12, 13).

The aim of this study is to synthesize MPS silica nanoparticles with a large surface area, high pore volume and regular distribution of pore sizes and to characterize the prepared $mSiO_2$ particles using different techniques. Ciprofloxacin (CIP) drug was selected as a model drug to study the kinetics of loading and of releasing in water and buffer solution.

Materials and methods

Sodium silicate (14% NaOH, 27% SiO_2 w/w) as silica precursor and Cocamidopropyl betaine (CABP) as template were obtained from the state company of vegetable oils – Iraq. Ciprofloxacin (CIP), as an antibiotic, molar mass 367.8 g/mol, λ_{max} at 277nm is purchased from DSM with purity 98%. Figure 1 shows its structure,

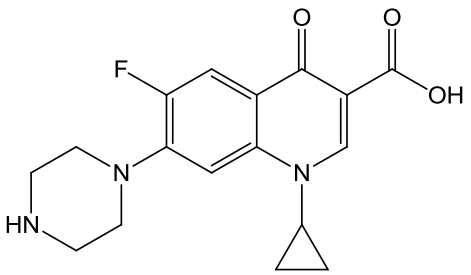

Figure 1. Chemical structure of Ciprofloxacin drug

Characterization

The prepared mesoporous silica was characterized by field emission scanning electron microscopy (FE-SEM), energy-dispersive X-ray spectroscopy (SEM; Oxford instruments model SEM: S-3200N). The isotherms of N_2adsorption-desorption at 77 K were determined using Autosorb-1 Quantachrome Instrument (Quantachrome Instruments, Boynton Beach, FL, USA). The particle size and particle size distributions were analyzed using Atomic Force Microscopy (AFM) SPMAA 3000, Advanced Angestrum Inc., USA. The XRD patterns were obtained with a Rigaku diffractometer using Cu Kα (λ = 0.154 nm) radiation.

Preparation of Mesoporous Silica

Firstly, 12 g of (CAPB) were dissolved in 150 mL of distilled water and 17mL of H_2SO_4 (1M) were added. Then, 3.5g of sodium silicate dissolved in 150 ml of distilled water were added drop by drop to the mixture from burette for 3 hours. The formed white precipitate was separated by filtration and washed with water after aging at 80 °C for one day. After drying at 80 °C, the calcination was performed at 600 °C for 4 hours to remove the surfactant.

Adsorption Kinetic Procedure

The kinetic study of CIP adsorption on $mSiO_2$ adsorbent was performed by mixing the amount of adsorbents (0.05 g) with 100 mL of CIP (20 mg/L) solution in 250 mL flask. The shaking was performed using thermostatic shaker bath at the temperature 289 K. At various time intervals, a sample was pipetted and the absorbance at maximum wavelength 277 nm was measured to determine the concentration. The amount of drug adsorbed was determined by the equation:

$$\mathbf{q_e} = \frac{(\mathbf{C_0} - \mathbf{C_e})\,\boldsymbol{v}}{\boldsymbol{w}} \quad (1)$$

Where q_e is the equilibrium adsorption capacity of CIP adsorbed on unit mass of the adsorbent (mg /g), C_0 is the initial concentration of CIP drug (mg L^{-1}), C_e the CIP equilibrium concentration respectively, W (g) is the weight of adsorbent, and (v) is the volume of CIP solution.

Drug Loading

CIP was loaded inside MPS by synthetic method previously reported (14)**.** 0.03 g of MPS was suspended in 5 mL of drug solution (concentration equal to100 mg/mL) and stirred for 24 hours. The CIP loaded MPS (CIP-$mSiO_2$) was centrifuged and the precipitate washed several times with water. Then CIP-$mSiO_2$ was dried at 80 °C.

In Vitro Drug Release

The prepared CIP-$mSiO_2$ sample was immersed in 100 mL of water or phosphate buffered saline (PBS, pH = 7.4) under slow stirring at 37.5 °C. At selected time intervals, aliquots (1 mL) were removed from the mixture solution, the amount of CIP released was estimated by the UV–Vis absorption spectra of the aliquots.

Results and Discussion:

The SEM technique was used to study morphology of $mSiO_2$surface and to determine the particle size and the size distribution. Figure 2a shows the SEM images of MPS.

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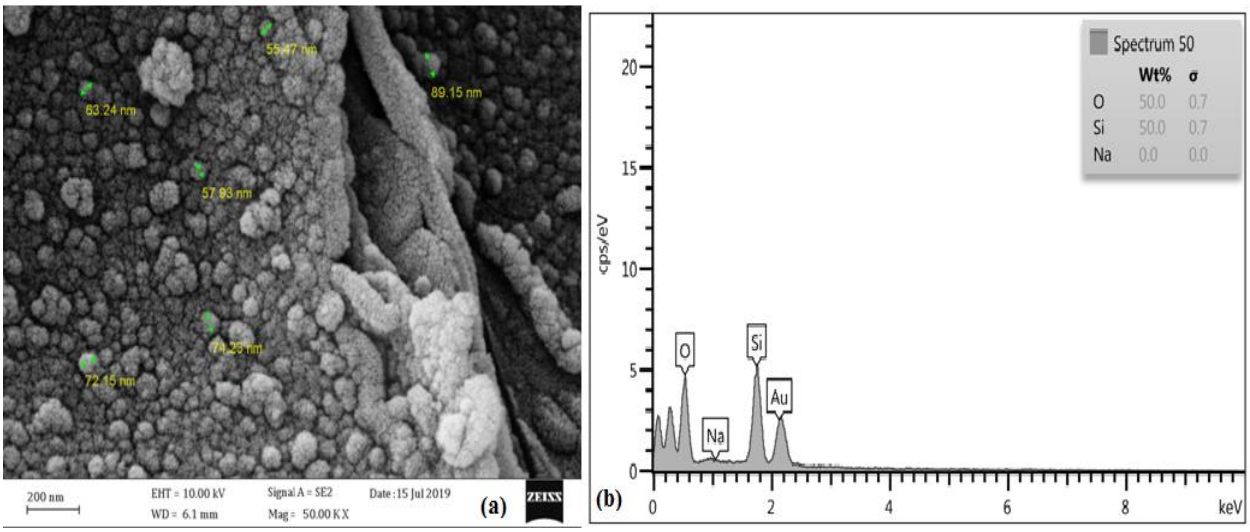

Figure 2. a) SEM image; b) EDX image of m SiO_2.

It is revealed from the images that particles morphology is almost rod type. The range of the particles size is from (89.15-55.45) nm. It means that the particles size is smaller than 100 nm with relatively uniform size distribution. Figure 2b of EDX spectrum shows the presence of silicon and oxygen with zero percent of Na, which confirms that the sodium ion is completely removed from the prepared $mSiO_2$ by washing and no other impurities are present.

Fig. 3 shows the TEM images of $mSiO_2$.

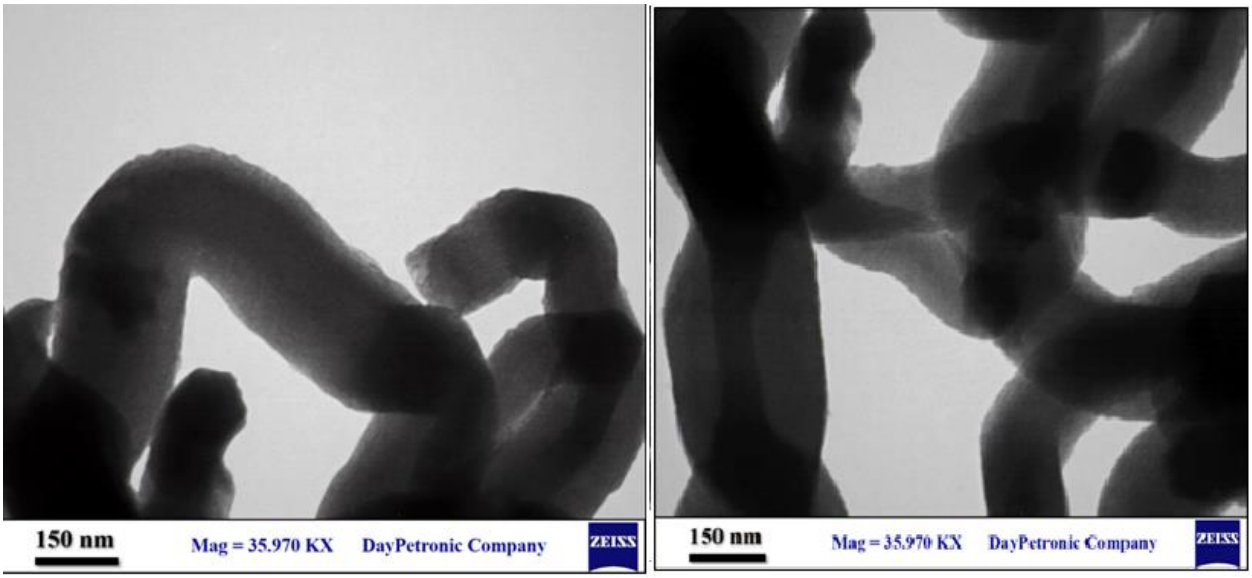

Figure 3. The TEM images mSiO2

TEM images show that the size of mSiO2 particles varies form 80 - 150 nm and confirms the rod shape. They also show the porous structure is produced and the pores are visible in the images.

Figure 4 illustrated the isotherm and pore size distribution for nitrogen adsorption-desorption on $mSiO_2$ adsorbent.

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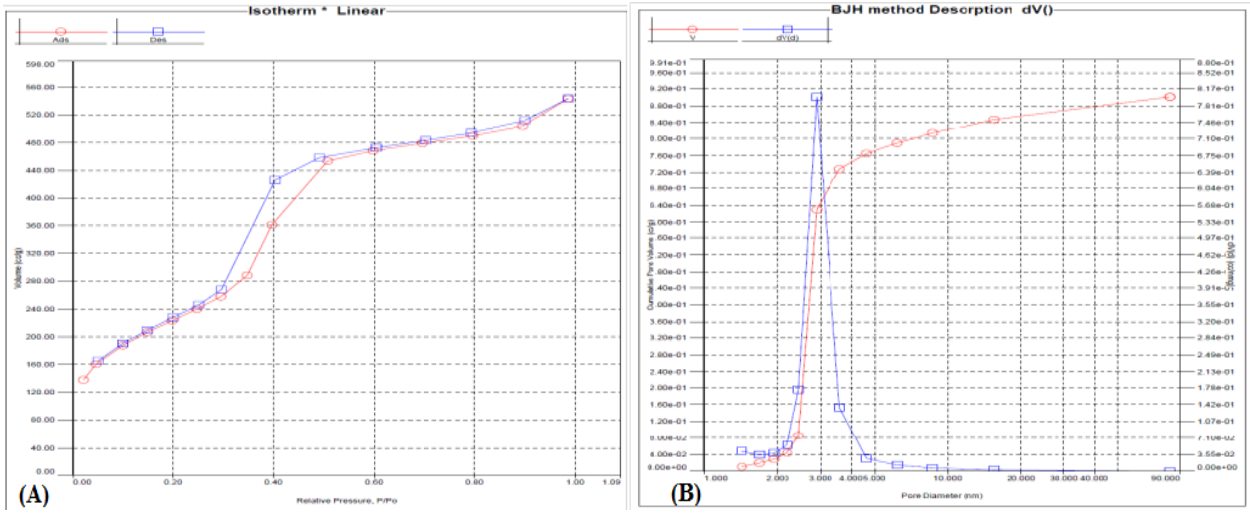

Figure 4. A) N2 adsorption-desorption isotherm, B) the pore size distribution.

The obtained isotherm is typical type -IV isotherm and has H2 type hysteresis loop which indicates the formation of mesoporous with ink bottle type pores. The measured Brunauer-Emmett-Teller (BET) surface area and Barrett-Joyner-Halenda (BJH) pore diameter and pore volume are listed in the Table 1.

Table 1. The surface area and pore properties of mSiO2

Sample	S_{BET} (m^2/g)	Pore Volume (cc/g)	BJH(nm)
$mSiO_2$	1096.122	0.900	2.902

The results of Table 1 show that MPS has very high surface area(S_{BET})and large pore volume and narrow range pore size distribution with 2.902 nm average pore size. The size of nano particle and rod type of MPS particles were confirmed by AFM technique as depicts in Fig. 5. The obtained results of particle size distribution in Fig. 5b show that it is in the range 40 - 80 nm and the average diameter is 62.15 nm.

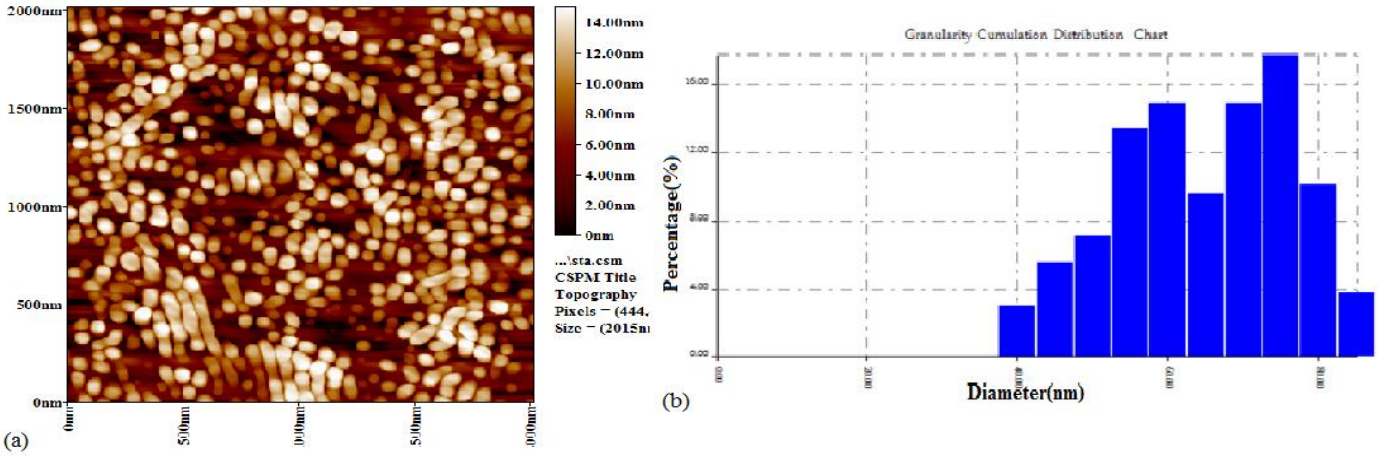

Figure 5. a) AFM image; and b) Histogram of Granularity Distribution for $mSiO_2$

The XRD (Fig. 6) of the prepared mesoporous silica shows a main peak at 2θ angle in the range of 1.5 -3° which reveals long range ordering of the mesoporous in the MPS, and in agreement with the literature-reported data (14, 15).

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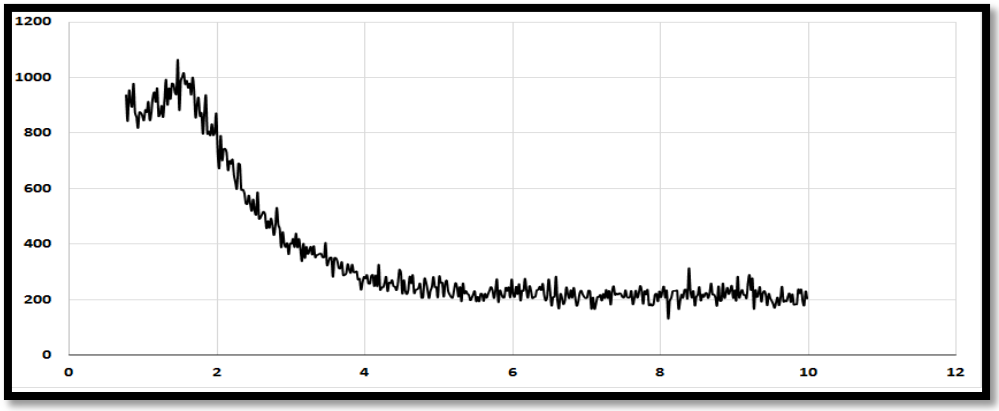

Figure 6. XRD pattern of the prepared mesoporous silica

Kinetics of Drug Adsorption

Lagergren-first-order (16, 17), pseudo-second order (18), and intr-aparticle diffusion (19) models are applied to investigate the adsorption kinetic behavior of CIP (20 mg/L) onto MPS adsorbent. The equations of the three models are as follows:

$$\ln (q_e - q_t) = \ln q_e - k_1 t \quad (2)$$

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{1}{q_e} t \quad (3)$$

$$q_t = K_D t^{1/2} + c \quad (4)$$

Where k_1 (min^{-1}), k_2 (g mg^{-1} min^{-1}), and k_D (mg g^{-1} $min^{-1/2}$) are the rate constants of the pseudo-first order, pseudo-second order, and intra-particle diffusion kinetics respectively. q_e and q_t are amounts of CIP adsorbed on the surface of the adsorbent at equilibrium and at any time (mg g^{-1}) respectively, C is constant. Initial adsorption rate (h) was calculated from the equation :- $h = k_2 q_e^2$. The kinetics parameters obtained from slope and intercept of the plots in Fig. 7 are shown in Table 2.

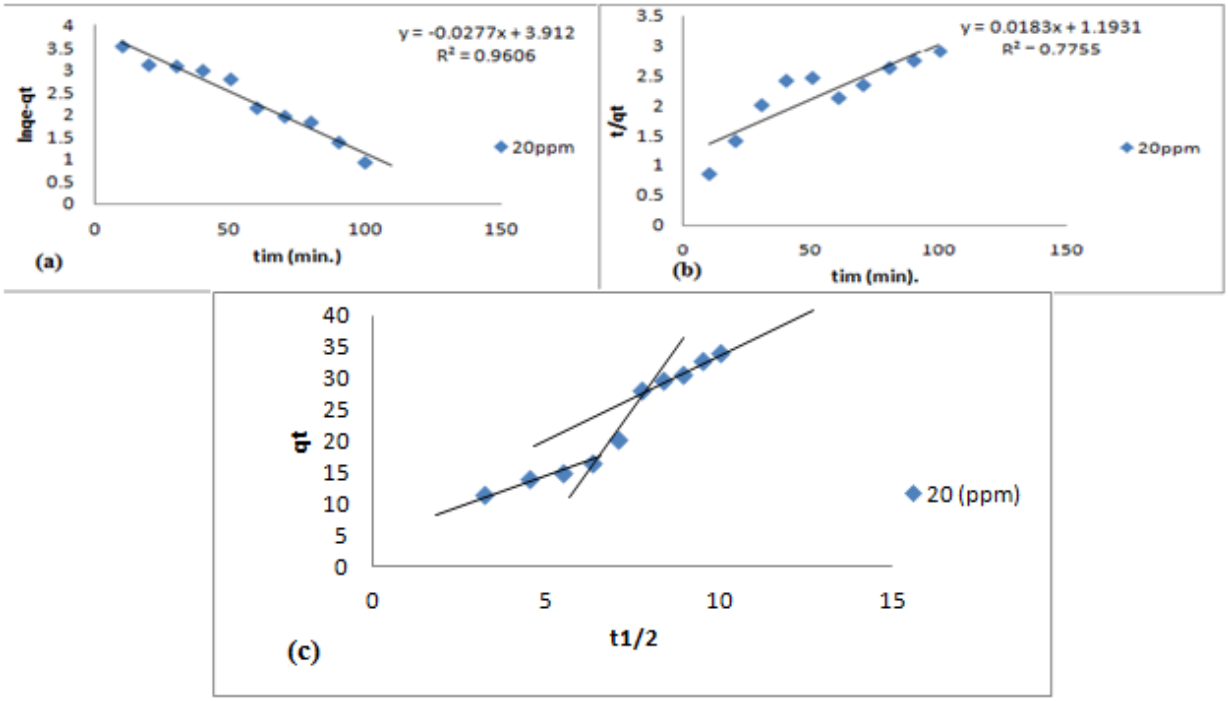

Figure 7. The linear plots of the three kinetics models; a) pseudo-first order b) pseudo- second order c) intraparticle diffusion.

Table 2.The kinetics parameters of the adsorption of CIP drug on $mSiO_2$.

q_e	pseudo-first -order			pseudo-second –order					intrapartical diffusion				
(exp.)	q_e(calc) (mg/g)	K_1 $(min)^{-1}$	R^2	q_e(calc). (mg/g)	K_2 (mg min^{-1})	h (mg g^{-1} min^{-1})	R^2	$K_{D(1)}$ (mg g^{-1} min^{-2})	R^2	$K_{D(2)}$ (mg g^{-1} min^{-2})	R^2	$K_{D(3)}$ (mg g^{-1} min^{-2})	R^2
36.783	49.99	0.0277	0.963	54.644	0.00040	1.005	0.775	1.492	0.965	8.069	0.946	2.785	0.978

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From the correlation coefficient (R^2) values presented in Table 2, it can be seen that the adsorption perfectly complies with pseudo first order model. Also, it can be seen from the plot of intra-particle diffusion model, the adsorption of CIP drug onto $mSiO_2$adsorbent was controlled by three stages. The first linear portion is attributed to the diffusion of CIP molecules from bulk toward adsorbent. The second linear portion corresponds to intra-particle diffusion. The third linear portion is the diffusion inside small pores and then the equilibrium is established. If the data shows multi-linear plots and do not pass through the origin, the rate determining step is not only intra-particle diffusion but two or more other steps are involved (20, 21).

Kinetic of Drug Releasing

The amount of drug loaded in MPS samples has been calculated using the weight of CIP in the 5ml of solution, the weight of CIP in the solution after impregnation, and the weight of the MPS sample .The calculated amounts of CIP loaded in the samples was 16.3 mg drug/mg sample. The concentrations of CIP drug released into the media (water or PBS buffer) were determined using a calibration curve in water or PBS buffer at pH 7.4. Figure 8 shows the CIP drug release from $mSiO_2$ carrier into the two media.

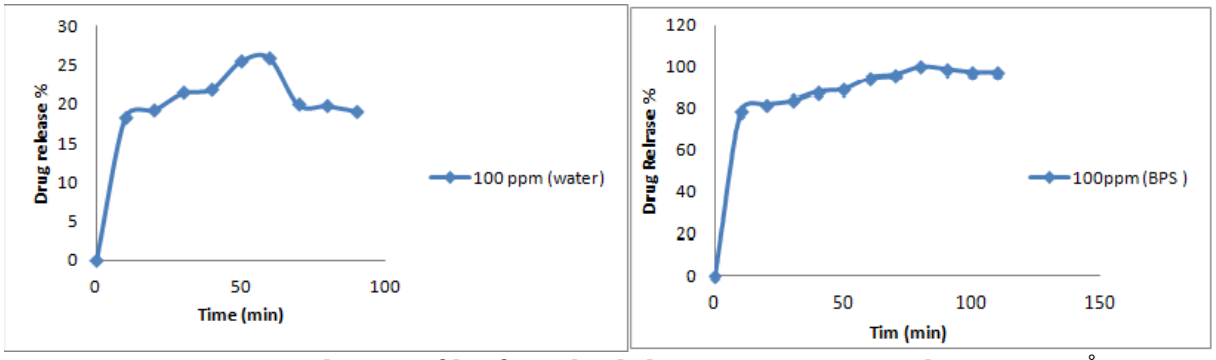

Figure 8. Release profile of CIP loaded mSiO2 in (a) water, (b) PBS at 37 ˚C.

To study the mechanism and kinetics of the CIP drug release, the data obtained were fitted to three models as follow:

$$M_t/ M_\infty = k_{K\text{-}P}t^n \quad (5)$$

$$M_t/ M_\infty = 1 - e^{-k t} \quad (6)$$

$$M_t = At^{1/2} + Bt \quad (7)$$

The first model (equation 5) is the Korsmeyer - Peppas (22), where M_t is the amount of CIP released at time t in minutes, M_∞ is the loaded amount of CIP in $mSiO_2$ particles, $k_{K\text{-}P}$ is a kinetic constant related to host-guest pair, and n is related to the host shape and drug release mechanism. The second model(equation 6) is the first order kinetic release model, where k is the first order rate constant. The third model (equation 7) is Kopcha model (11, 23), where A is the contribution of diffusion and B is the contribution of erosion. The fit are shown in Figs. 9 and 10 for releasing of CIP in water and PBS respectively, while the results obtained are listed in Table 3.

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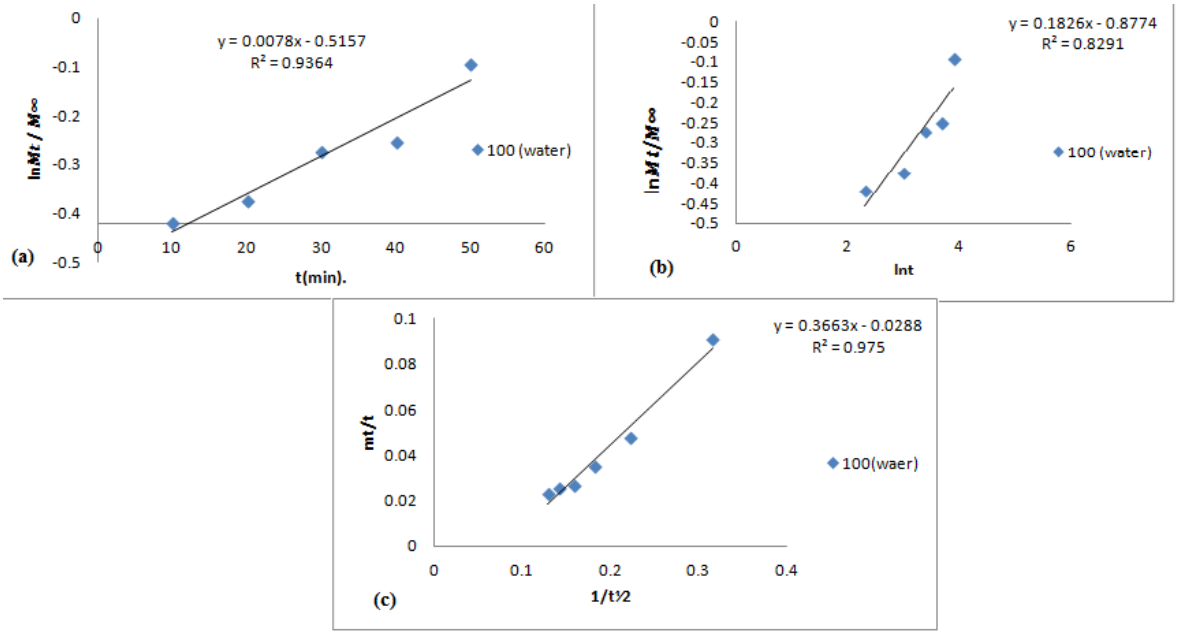

Figure 9. The linear plots of three kinetics releasing models; a) Korsmeyer - Peppas b) psedo-first order c) Kopcha, for CIP releasing in water.

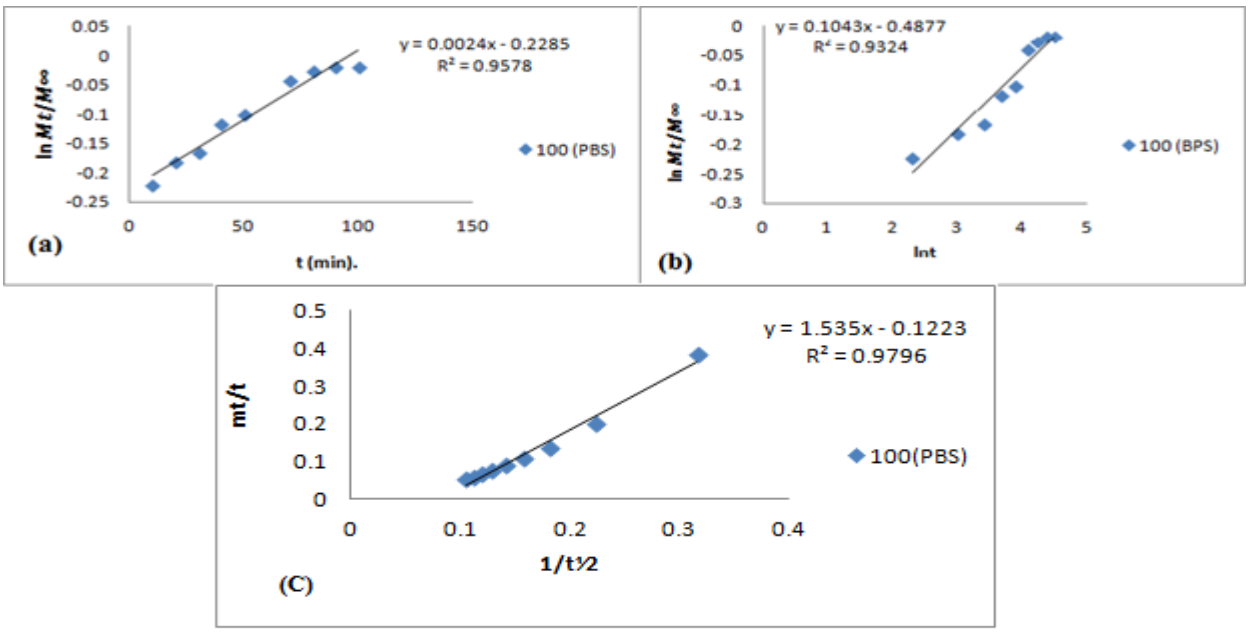

Figure 10. The linear plots of three kinetics releasing models; a) the Korsmeyer-Peppas b) the psedo-first order c) the Kopcha model, for CIP releasing in PBS.

Table 3.The kinetics parameters of the adsorption of CIP drug on $mSiO_2$.

model	Korsmeyer-Peppas			Pseudo-first –order		Kopcha model		
parameters	n	K_1	R^2	K	R^2	A	B	R^2
(PBS)	0.1043	1.6285	0.9578	0.0024	0.9324	1.535	0.1223	0.9769
(Water)	0.1826	2.404	0.99365	0.0078	0.829	0.366	0.028	0.975

It can be observed from Figs. 9 and 10 and Table 3, that both Korsmeyer-Peppas and Kopcha models fit more closely to the obtained data and the first order kinetic release model shows the poorest fit to the data in both cases. The two fitted parameters for Korsmeyer-Peppas model are the kinetic parameter k and exponential term n. Since the obtained value of n in the two cases are smaller than the range (0.43 and 0.85), the particle of drug carrier is not a spherical shape and the mechanism of drug releasing is diffusion (24). In Kopcha model, If A/B ≥ 1 the diffusion is predominates, but if A/B < 1, the erosion predominates (11). The media is greater than 1(12.55 for PBS, and13.071for

water medium) which indicate that the dominate mechanism is diffusion.

Conclusions:

The foregoing results of this study confirm the synthesis of mesoporous silica nanoparticle as carriers for CIP drug delivery systems by sol–gel method. The prepared sample has average diameter equal to 62.15 nm, rods particle morphology, specific surface area 1096.122 m^2/g, pore volume 0.900 cm^3/g, and average pore diameter 2.902 nm. The CIP drug-loaded mesoporous silica nanoparticles have capacity of about 16.3 mg drug/ mg $mSiO_2$ and capable of releasing 26% and 98.6% of their drug content after 90 min in water and PBS solution(pH,7.4) respectively. A study on release kinetics shows that the Korsmeyer-Peppas and Kopcha models, both conform more closely to the release data.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

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الحبيبات النانوية للسليكا متوسطة المسام كنظام لتوصيل الدواء سيبروفلوكساسين ; حركيات الامتزاز والازالة

ايناس عبد الحسين خضير **سمير حكيم كريم**

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الخلاصة:

حضرت السليكا متوسطة المسام ذات الحبيبات النانوية كحامل في نقل الدواء بواسطة طريقة sol-gel باستخدام سلكيات الصوديوم كمصدر رخيص للسليكا والمادة الفعالة سطحياً cocamidopropyl betaine شخصت حبيبات السليكا باستخدام التقنيات XRD-AFM-TEM-SEM و ايزوثيرمات امتزاز – امتزاز غاز النيتروجين ، واثبتت النتائج ان الحبيبات هي من النوع النانوي ضمن المدىnm (80-40) كمعدل 62.15 نانوميتر وعلى شكل قضبان ويملك مساحة سطحية تساوي 1096.122 متر^2/ غم وحجم مساحة مقداره 0.9 سم^3/غم مع معدل قطر مسام يساوي 2.902 نانومتر، مما يؤهلها لتكون حاملة للدواء بكفاءة. درست حركيات امتزاز الدواء سيبروفلوكساسين (ciprofloxacin) ثم حللت النتائج ووجد انها تنطبق جيداً مع معادلة المرتبة الاولى الكاذبة وكانت سعة تحميل الدواء على حبيبات السليكا النانوية بمقدار 16.3ملغم دواء لكل ملغم سليكا وكذلك نسبة ازالة مقدارها 26% و 98.6% من الدواء المحمل بعد مرور 90 دقيقة في الوسط المائي ومحلول الفوسفات بفر سلاين (PBS) ذو الاس الهيدروجيني pH=7.4 على التوالي أجريت عمليات حركيات الازالة في كلا المحلولين (الماء ومحلول البفر) تحت التحريك وباستخدام معادلاتKorsmeyer-Peppass وحركيات المرتبة الاولى وKopcha ودلت النتائج على ان معادلتي Korsmeyer-Peppas و Kopcha هي الاكثر انطباقاً.

الكلمات المفتاحيه: الامتزاز الحركي، سيبروفلوكساسين، متوسطة المسام، سيلكا، حركيات الامتزاز