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Journal of Applied Chemical Research, 18, 1, 26-40 (2024)

Investigation of the Potential of Adsorption and Drug Delivery Application of the Duloxetine Antipsychotic by using its Molecular Imprinted Polymer

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(Received 05 May 2023; Final revised received 18 Aug. 2023)

Abstract

The synthesis and application of a molecular imprinted polymer (MIP) as a carrier for drug delivery of Duloxetine (DUL) antipsychotic was investigated. Mimicking the natural receptors of DUL drug by synthesizing its MIP would lead to formation of some special active sites, which make able the MIP to accept only this special medicinal compound. Therefore, this MIP, which has been templated by DUL, could selectively absorb the molecules of DUL from the mediums in certain conditions and could release those chemical species in another place with different conditions. This MIP with its artificial receptors could be applied as a carrier for drug delivery applications and sustained released tablets. In order to synthesize this MIP based carrier, the precipitation polymerization method was applied. Also, methacrylic acid (MAA; as the functional monomer), 2,2-azobisissobutyronitrile (AIBN; as the initiator), and ethylene glycol dimethacrylate (EGDMA; as the cross-linker), were applied to obtain this sorbent. Moreover, the release kinetics of the drug was investigated by HPLC system, which was shown to be fitted with the Higuchi expression pattern at least at 5.8, and 6.8 pHs. Finally, the results revealed that the synthesized MIP is able to be used in formulation of the sustained released tablets.

Keywords: Duloxetine, Molecular imprinted polymer, Release, Drug delivery, HPLC-UV.

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Introduction

One of the most important antipsychotic medicines which have been applied for treatment of some of the mental illnesses such as bipolar disorder, schizophrenia, and depression, is Duloxetine (DUL) compound [1]. This active pharmaceutical ingredient (API) acts as a player for restoring the balance of some specified messengers or neurotransmitters in the central nervous system (CNS), which are improving the thinking, the mood, and the behavior [2]. Moreover, it works to block the serotonin receptors and dopamine terminals as two of the most important neurotransmitters [3]. The wide application of this compound, encouraged the formulators to develop different types of formulations such as slow release tablets, and oral suspensions in commercial scales [4].

The release rate of the drugs (into the blood or other target organs), which are being optimized via different approaches, has always been important for pharmaceutical chemistry experts. It is more important when the bioavailability and the release rate of a medicinal compound is high; while, the half-life and the dosage of that drug for the body is lower [5].

For this reason, several methods have been designed to regulate the release rate of the drugs. The slow-release tablets [6], the osmotic pumps [7], molecular imprinted polymers (MIP) [8], liquid crystals [9] and sol-gels [10] are of those methods.

Between several designed drug delivery approaches, MIP, these synthetic polymers that mimic the structure of the natural receptors, are of the most important achievements of the molecular imprinting technology (MIT). These special composites are recently developed as suitable candidates for drug delivery systems [11].

In such release models, the composites are formed in the presence of a drug as a molecular template (Figure 1) to mimic the structure of the real drug receptors. After formation of the polymer, the composite is washed for several times to make the substrates of the MIP, free of the templates. Thus, the whole structure of the composite will be full of billions of free sites, which would accept that guests molecules for further drug delivery (DD) applications [12].

Moreover, those composites could be applied as stationary phases for chromatography columns packing [13], nano sized sorbents [14], and nano actuators [15], biosensors [16], and nano drug delivery vehicles [17]. Beside the valuable experimental works, there are numerous theoretical reports that investigate the guest-host interactions of the receptors and chemical species in molecular and atomic scales [18-21].

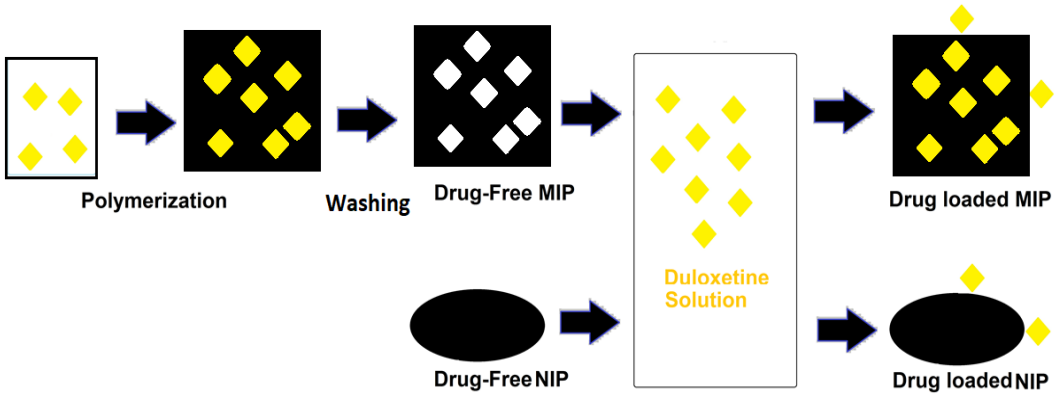

Figure 1. Synthesis and absorption process of DUL by MIP host compared to non-imprinted polymer (NIP) as reference

Based on the above-mentioned debates, we have used the DUL drug as the molecular template for synthesizing the MIP. The scanning electron microscopy (SEM) was used for morphology studies of the synthesized polymers. The drug adsorption/release process of the composites and those abilities for in vitro release were investigated by using the high-performance liquid chromatography (HPLC) [22-25]. Indeed, the principle of this study was to evaluate the drug release behavior of MIP by using different types of kinetic patterns and to understand its mechanism. The results of the study have indicated that using the MIP is more suitable compared to NIP. Moreover, those results have shown that the MIP could be applied as a vehicle for drug delivery at least in the case of DUL API.

Experimental

Materials and reagents

All chemicals were analytical grade. The ultra-pure water was being prepared by a Milli-Q purification system (Millipore, Bedford, MA, USA). The chemical reagents and solvents containing methacrylic acid (MAA), N,N-dimethyl formamide (DMF), ethylene glycol dimethacrylate (EGDMA), and 2,2-azobisissobutyronitrile (AIBN), were purchased from Sigma-Aldrich. Moreover, monobasic potassium phosphate (KH_2PO_4), and acetonitrile were obtained from the Merck Chemical Company. In addition, DUL API was prepared from other commercial sources.

Instrumentation

The Shimadzu Prominence HPLC system (Shimadzu Corporation, Kyoto, Japan) having a LC-20AD pump, a DGU-20A degassing agent, a SPD-20A UV-Vis detector, and a CTO-20A column oven, were applied for the analyses. In addition, the Lab-Solutions software version 5.51 was used for the data analysis and the other related processes. In addition, a end-capped (250×4.6) mm, 5µm C18 liquid chromatography column was applied for the assaying the concentration of DUL. Also, a CHZ-82 constant temperature water bath oscillator (Fuhua Instrument Co. Lid., China), a CR3i centrifuge (Thermo Fisher Scientific Inc., USA), a Spectrum 100 FT-IR spectrometer (PerkinElmer Co., Ltd., USA), a FEI Quanta 200 scanning electron microscope (Thermo Fisher Scientific, Netherland), a KQ2200B sonic device with frequency and temperature controller (Kunshan Ultrosonic Instrument Co., Ltd., China) were being applied for the required tasks. Finally, a ZRS-8G dissolution tester (Tianda Tianfa Technology Co., Ltd., China) was applied for the release analyses.

Preparation of MIP

Both of the synthesized polymers containing the NIP (as the reference) and MIP (as the main cases of study) were obtained *via* the precipitation polymerization approach, and also by the UV photo polymerization, respectively. Thus, at the first step, 1mmol of DUL was dissolved in a 50 ml of DMF as solvent. Next, 4 mmol of MAA, 20 mmol of EGDMA, and 0.347 mmol of AIBN were added to the mixture, respectively. Then, those were putted under ultrasonic waves for about 10 min. Subsequently; the mixture was purged by nitrogen atmosphere for 15 min [18,19,26]. The prepared granules were then powdered by grinding with a mortar. It should be mentioned that the NIP (as a reference sorbent) was synthesized under the identical conditions without the use of DUL as the template molecule. The schematic procedure for obtaining the MIP is presented in Figure 1. At the final stage, the granules were grinded by a mortar for about 20 minutes to give a nano-sized powder with average particle sizes lower than 100 nm.

Characterization of the MIP composite

SEM analysis

The surface morphology studies of the MIP was performed by using the SEM which its photographs were taken with a FEI ESEM QUANTA 200(USA). The surfaces and the cross-sections of the MIP and NIP were obtained by conductive deposition of the gold layers on the samples in the vacuum chamber. Figure 2 represents the SEM image of the polymers. In addition,

the sample morphologies were recorded under the SEM scanning at the voltage of 25 kV, respectively.

FT-IR analysis

The FT-IR spectra of the MIP and the NIP (as the reference sorbent) were prepared by the FT-IR analyzer. To do this, certain portions of the NIP and the MIP powders (about 5 mg) along with a 100 mg powder of KBr were mixed and grind accordingly. Then, the powder mixtures were pressed into 1 mm pellets. The produced pellets were measured respectively on the Spectrum 100 FT-IR spectrometers. The FT-IR spectra of the NIP and the MIP were plotted by recording from 400 to 400 cm^{-1} with a resolution of 2 cm^{-1} using a pellet of KBr as the blank.

Moisture Absorption

Before the analysis is begun, both of the MIP, and NIP (as reference) granules were dried for about three days at room temperature. Next, to evaluate the swelling capacity of the polymers, those were weighted and were then placed in a buffer at pH = 1.2, 5, 5.8,6.8 for about 24 hours at room temperature. Then, those were replaced from the buffer and the surfaces of composites were completely dried before weighting. The degree of swelling of the composites was reached, via Equation 1:

$$\text{Moisture Absorption} = \left(\frac{(W2-W1)}{W1}\right)*100 \quad \text{Equation (1)}$$

Where, W_1, W_2 are the MIP weights before, and after the swelling processes, respectively.

Data analysis

To study the mechanism of transportation of DUL by the polymers, four diffusion models containing the zero order, the first order, the Higuchi patterns and Korsmeyer-Pappas were used. The kinetic investigations were performed by plotting the cumulative values of the drug (in percents) per time (in hours). The correlation coefficient (r) for each kinetic pattern was performed to determine the pattern that was fitted:

The zero order model (concentration per time)

$Q= Q_0+K_0t$ Equation (2)

Higuchi's kinetic model (concentration per square root of time);

$Q_t/Q_0=K_H\, t^{1/2}$ Equation (3)

First order pattern (logarithm of the concentration per time);

$\text{Log } Q_t= \log Q\, K_t$ Equation (4)

Korsmeyer-Pappas Equation:

$$\text{Log } (M_t/M_\infty) = \text{Log } k + n \text{ Log } t \quad \text{Equation (5)}$$

Where Q_t is amount of diffused (mg) drug per time t (h), Q_0 is initial amount in donor compartment (µg). K_0 is the zero order constant (µg h^{-1}), K_1 is first order constant (µg h^{-1}), and also K_H is Higuchi's constant (µg $h^{1/2}$). The correlation coefficients (r) for each of the kinetic models were prepared to determine the patterns that were fitted with those.

Adsorption experiments

For the adsorption experiments, 10.0 mg parts of the MIP as well as the NIP were suspended in 1 ml of the phosphate buffer and 10.0 mL solutions of DUL (65 µg/ml) at different ranges of pHs for a time period between 5min – 60 min were mixed. Then, the sample solutions were filtered by micro membranes, and the amount of the drug in filtrate was calculated by HPLC according to the procedure describe in the HPLC section. The binding capacity of the NIP and the MIP and those selectivity factors were obtained by Eq. (6) and Eq. (7), respectively.

$$Qt = (C_0\text{-}C_t)V/m \quad \text{Equation (6)}$$

$$\alpha = Q_{MIP}/Q_{NIP} \quad \text{Equation (7)}$$

where Q_t (µmol/g) represents the adsorption capacity in different times, C_0 (mmol/L) is the initial concentration of DUL, the Ct (mmol/L) represents the concentration of DUL at the time t, V (in Liter) is the volume of the initial DUL solution, and m is the mass of the NIP or the MIP (in g). Finally, α represents the selectivity factor of the NIP to the MIP, Q_{NIP} (µmol/g) is the adsorption capacity of the NIP, and Q_{MIP} (µmol/g) is the adsorption capacity of the MIP.

The release experiments

To investigate the release kinetics of the DUL drug from the polymer, 10 mg of each of MIP, and NIP was mixed by 1 ml of solution A for about 40 minutes (where solution A was a 65 µg ml^{-1} of the DUL stock solution which was diluted to 10 ml with buffer at pH=6). Then, the mixture was centrifuged for about 10 minutes at 4000 RPM. Next, the supernatant was passed through a Syringe head filter. Then, it was injected to the HPLC-UV system. Also, the precipitate of the centrifuge was washed with the deionized water and was then centrifuged again. After that, the precipitate was dissolved by 5 ml of pH=1.2, 5, 5.8, and 6.8 buffers. The mixtures were then Shaked at 37 ºC. Next, 3 ml of the solutions were injected to the HPLC-UV instrument at 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 minutes, to give the release curves.

HPLC method

The chromatographic determination of the concentration and the release rate of DUL from the polymers was carried out by the Shimadzu HPLC system occupied with a UV/VIS detector set at

210 nm. The LC separation was carried out by a C18 (4.6 mm, 15cm, 3.5 μm) liquid chromatography column. The injection volume was 10 μL, the flow rate was 1 ml/min and the column temperature was fixed at 25°C (room temperature) by the column oven. An isocratic method was applied for the elusion and the mobile-phase was phosphate buffer (pH =2.5) / 1- propanol/ACN (13:17:70) v/v percentage Where, the buffer was prepared by dissolving the 10 mM of monobasic potassium phosphate in 1 liter of purified water set at pH of 2.5 by phosphoric acid [22,23].

Results and discussion

Structural characterization of the MIP

FT-IR spectroscopic analysis

The FT-IR spectra of the DUL drug free-MIP, and the DUL loaded MIP, were presented in Figure 2. The DUL-free-MIP represented strong absorption peaks at *ν*C=O (stretching)=1724.94 cm^{-1}, *ν*C-O (stretching)=1251.85 cm^{-1}, and *ν*O-H (stretching)= 3050.34 cm^{-1}, due to OH bonds, as well as carboxyl groups from the MAA (functional monomer), and EGDMA (cross-linking agent).

By comparison, after loading the DUL molecule on the MIP, the absorption peaks of C=O, C-O, and O-H, peaks, shifted to 1722.61 cm^{-1}, 1245.61 cm^{-1}, and 3048.45 cm^{-1}, respectively. On the other hand, the absorption peak of the O-H bond was increased and strengthened at 3631.31 cm^{-1} in the DUL loaded MIP, which revealed about the formation of a hydrogen bond between DUL and the MIP.

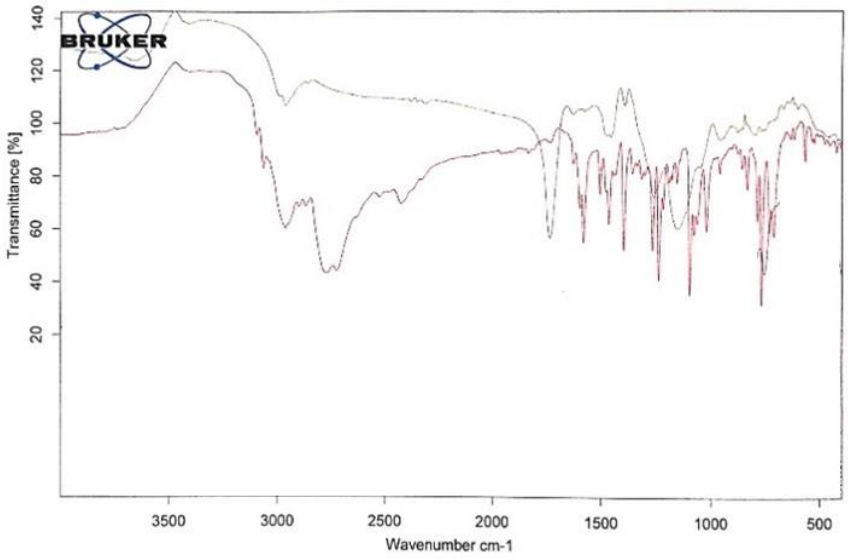

Figure 2. The FT-IR spectra of MIP (A; black line), DUL -drug loaded MIP (B; red line).

Physiochemical properties of MIP composite

The results of swelling analyses indicated that the amount of this parameter (in percentage) for MIP is about 80%; while, its amount for NIP is only about 49%. It has confirmed that the amount of swilling increases by rising the pH from 1.2 to 6.8. also, the results indicate that the amount of swelling form MIP are more than that of NIP (Table 1).

Table 1. The relation between the pH changes, and the type of polymer with swelling.

Polymer	**W_1 (g)**	**W_2 (g)**	**%Swelling**	**pH**
MIP	0.01	0.0520	80	6.8
NIP	0.01	0.0198	49	6.8
MIP	0.01	0.0410	75	5.8
NIP	0.01	0.0139	28	5.8
MIP	0.01	0.0240	58	5.0
NIP	0.01	0.0131	23	◦.0
MIP	0.01	0.0195	48	1.2
NIP	0.01	0.0110	9	1.2

Morphological structure analysis

As presented in Figure 3, both the surfaces of MIP, as well as NIP are scanned by applying the SEM photographs. These figures confirm that both NIP and MIP particles have spherical morphologies and almost uniform structures. In addition, the results confirmed that the average particle sizes are lower than 100 nm at least in one dimension, both for NIP, and MIP. In the other hand, the SEM images, which were presented here, show the uniform and regular texture of the synthesized nanocomposites. Moreover, there is not a considerable difference between the MIP, and NIP in view of the surface morphology. Therefore, loading the DUL on those polymers or using it as the molecular template for synthesizing of MIP does not lead to considerable changes on their surface morphology. Finally, the oligomerization of the composites is observed in different parts of the images. Such happening might be due to the tendency for oligomerization and increase in surface reactivity in the nano scale processing.

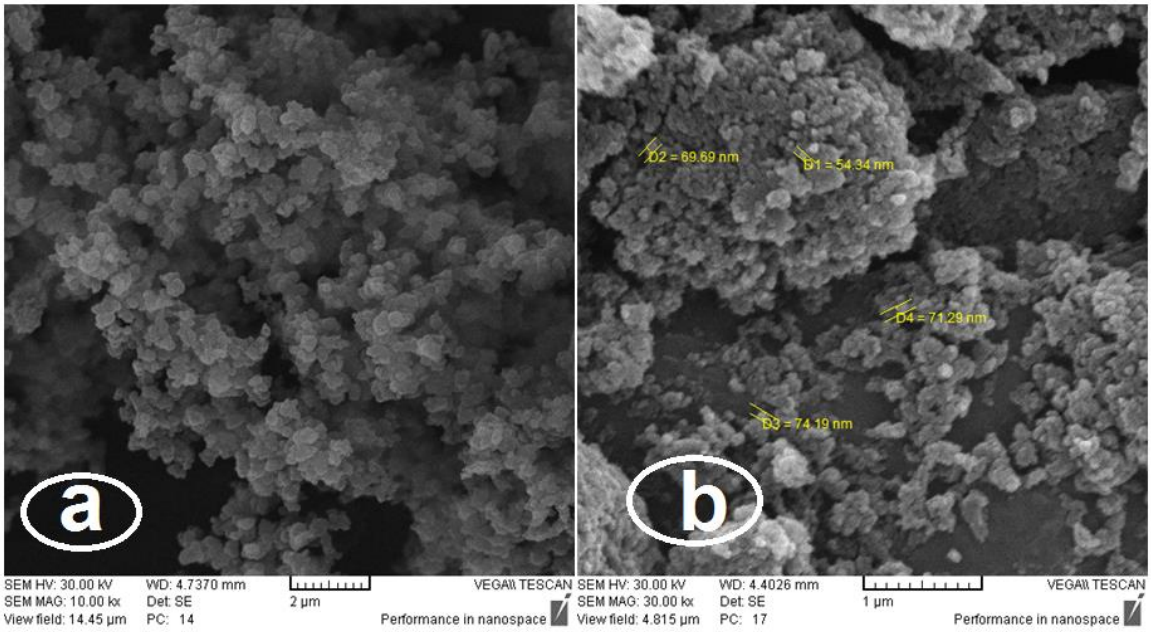

Figure 3. The SEM images of NIP nano particles (a), and MIP nano particles (b).

Release experiments

The kinetics of the release process of the drug from the composites was studied based on four models of the zero and, the first-orders, the Higuchi and the Korsmir-Papas. The data prepared from those models were evaluated based on the correlation coefficient (R^2) parameter. The release mechanism of the DUL drug from MIP was presented in this section. Investigation of this mechanism has been done by probing the drug release kinetics which was reached by plotting different kinetic patterns containing the zero, and the first orders, the Higuchi, and the Korsmeyer-Pappas models (Figure 4).

The linearity of the curves which were plotted in Figure 4, and the data presented in Table 2, confirm that the kinetic of the drug release from MIP follows the Higuchi kinetics at least in pHs of 5.8 , 6.8.

Moreover, the value of "n" parameter in the Korsmeyer-Pappas equation were 0.974, and 0.949, in pHs of 5.8, and 6.8, respectively. Those values show that the release kinetic follows the non-fickian diffusion, which might be the result to the combination of swelling and erosion of sorbent matrix.

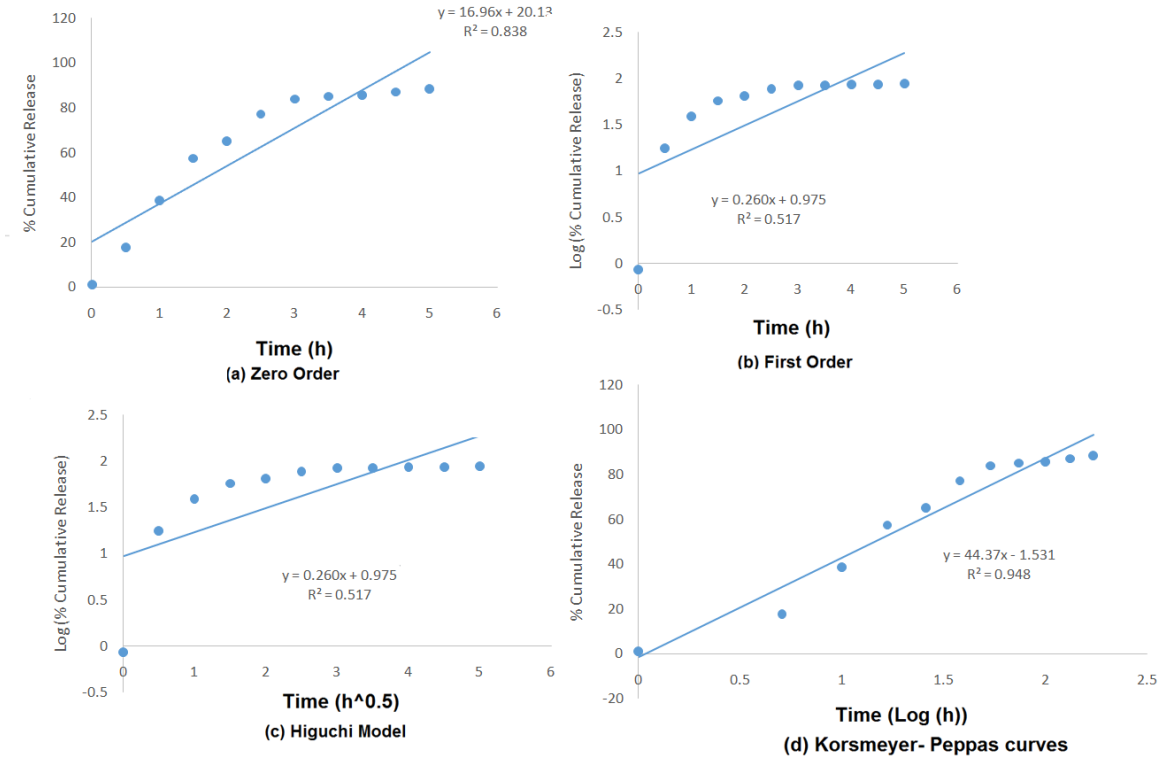

Figure 4. The zero order (a), the first order (b), the Higuchi model (c), and the Korsmeyer- Peppas (d) curves for the DUL release from MIP.

Table 2. The release kinetic studies of the release of the drug from the MIP.

pH	Zero order		First order		Higuchi		Korsemeyer -Peppas	
	K	R^2	K	R^2	K	R^2	N	R^2
5.8	10.488	0.859	-0.435	0.569	27.447	0.974	19.706	0.939
6.8	16.969	0.838	-0.601	0.517	44.37	0.949	0.311	0.915

Conclusions

The main advantage of using the MIP for drug delivery application in the case of DUL was that the release rate of the DUL drug (loaded on MIP) was slower than that of NIP (the reference sorbent). Moreover, the linearity of the curves confirm that the kinetic of the drug release from MIP follows the Higuchi kinetic model at least in pHs of 5.8 , 6.8. In addition, the value of n parameter in the Higuchi equation were 0.974, and 0.949, in pHs of 5.8, and 6.8, respectively; showing that the release kinetic follows the non-fickian diffusion, which might be the result to the combination of swelling and erosion of sorbent matrix.

Finally, it is suggested that in the future works, researchers investigate the suitability of making a transdermal patch formulation of this MIP by using a bacterial cellulose. Another suggestion is that the in vivo experiments will be performed on the effectiveness of this MIP in real biological conditions.

Acknowledgment

The authors are grateful to Science and Research Branch of Islamic Azad University for all kinds of their supports.

Declaration of Interests

The authors declare that there is no conflict of interests.

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