Aminopropyl groups of the functionalized Mobil Crystalline Material 41 as a carrier for controlled diclofenac sodium and piroxicam delivery

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INTRODUCTION

Mesoporous silica is a promising mineral material with a high pore volume, large surface area, nanometer pore diameter (2–50 nm), good biocompatibility, thermal/chemical stability, ease of preparation, ease of...
functionalization, and adjustable pore diameter, making it a good candidate for controlled/sustained drug delivery and in new biomedical applications, such as tissue engineering and biological imaging.\(^1\)\(^\text{2}\) Due to its tunable nature, MCM-41 can assume different morphologies, such as worm shapes, crescent-like shapes, gyroids, hexagonal plates, spheres, rods, discs, and particles, so it is the most suitable choice for drug delivery, sensing, adsorption/separation, and acts as a catalyst and optically active material, among the mesoporous materials.\(^3\)

The variable effects of different types of surfactant on MCM-41 have been employed to obtain different pore sizes to investigate ibuprofen delivery. The profiles of drug release illustrate that the method of drug loading is effective for release, but that the type of surfactant has no effect on it.\(^4\) Functionalization of MCM-41 with aminopropyl groups with two methods of functionalization has also been employed to control the ibuprofen release. In addition, the method of functionalization has been varied: MCM-41 is directly synthesized using aminopropyl groups (Method I), while in the Method II, in the first step it was calcined and then synthesized using aminopropyl group. The rate of drug delivery through Method II is slower than that through Method I.\(^5\)\(^\text{6}\) In vitro assays of phosphorous functionalized MCM-41 showed a bioactive response after 13 days, but there was no evidence of bioactivity even after 2 months for pure MCM-41. Popova \textit{et al.} have synthesized amino carboxylic MCM-41 in two steps. The MCM-41 was first reacted with 3-amo-propyltriethoxysilane and then modified by succinic anhydride in toluene. \textit{In vitro} release of sulfadiazine illustrated that the rate of release from functionalized MCM-41 was slower than that from pure MCM-41. MCM-41-NH\(_2\)-COOH had no cytotoxicity to the human colon carcinoma cell line (Caco-2).\(^7\) In another study on the Caco-2 cell line, Heikkilä \textit{et al.} found that the effects of pure MCM-41 on carcinoma cells were diminished cell metabolism, increased apoptotic signaling, and weakened cell membrane integrity, and it was concluded that the use of an oral formulation must be avoided for the smallest microparticles.\(^8\) Vysockálová \textit{et al.} have functionalized MCM-41 through amino, chloro, and oxo groups and showed that the pure MCM-41 and functionalized MCM-41 with oxo groups have the slowest dissolution of acetylsalicylic acid \textit{in vitro} release.\(^9\) Furthermore, pure MCM-41 and functionalized MCM-41 have been utilized as sustained and controlled delivery systems for ibuprofen,\(^1\)\(^\text{10}\) aspirin,\(^1\)\(^\text{11}\) indomethacin,\(^1\)\(^\text{12}\) furosemide,\(^1\)\(^\text{13}\) cisplatin,\(^1\)\(^\text{14}\) mesalazine (5-acetylsalicylic acid),\(^1\)\(^\text{15}\) acetylsalicylic acid,\(^1\)\(^\text{16}\) and 5-Fu and famotidine.\(^1\)\(^\text{17}\) In the present research, MCM-41 was synthesized through sol–gel procedure and functionalized with aminopropyl groups. The physicochemical properties of MCM-41 were studied through particle size analysis (PSA), infrared spectroscopy (IR), transmission electron microscopy (TEM), scanning electron microscopy (SEM), and carbon–hydrogen–nitrogen (CHN) analysis. Diclofenac sodium and piroxicam, nonsteroidal anti-inflammatory drugs that also have analgesic and anti-fever effects, were loaded into the MCM-41 matrix, and a study of the \textit{in vitro} release was performed in simulated gastrointestinal medium. Drug loading was performed using the filtration and solvent evaporation methods. Furthermore, the drug-loading capacity was determined by ultraviolet (UV) spectroscopy, IR, X-ray diffraction (XRD), and Brunauer–Emmett–Teller (BET) analysis.

**MATERIALS AND METHODS**

**Materials**

Tetraethoxysilane, 3-aminopropyltrimethoxysilane, and hexadecyltrimethyl-ammonium bromide (CTAB) were supplied by Sigma–Aldrich (Darmstadt, Germany). Piroxicam and diclofenac sodium were provided by Sobhan Darou Co (Rasht, Iran). All other chemical materials were purchased from Merek (Darmstadt, Germany).

**Preparation of Mobil Crystalline Material 41**

MCM-41 was synthesized via sol–gel procedure as follows: at first, 2.5 ml tetraethoxysilane was added to the surfactant solution (0.5 g CTAB in 250 ml distilled water) containing 3.5 ml NaOH solution (2 M) and stirred for 30 min. The resulting gel was stirred for 24 h at 80°C. Next, 50 mL ethanol and 4 ml of HCl were added to the gel and stirred for 24 h at 70°C. Finally, the mixture was centrifuged at 8500 rpm (6785 relative centrifugal force) for 15 min. The precipitate was washed using deionized water in triplicate and dried at room temperature overnight. The particle sizes, zeta potential, and polydispersity index (PDI) were measured through PSA, and the particle size was also confirmed by TEM.

**Amine-functionalized Mobil Crystalline Material 41 particles**

The mixture of 2 g MCM-41, 70 ml toluene, and 0.35 ml 3-aminopropyl triethoxysilane was added into a stainless steel vessel and was refluxed at 20°C for 15 h. Finally, the aminopropyl-functionalized MCM-41 obtained was passed through the filter and washed with ethanol 96% and dried at 80°C for 8 h. The presence of the amino propyl in MCM-41 was confirmed by Fourier transform infrared (FTIR) and CHN tests.
Drug loading

Drug loading by filtration method (Method A)

For drug loading through Method A, 2.5 g matrixes (pure MCM-41 or functionalized MCM-41) containing 1 g diclofenac sodium or piroxicam powders were stirred in 300 ml acidic methanol (10% v/v) for 48 h at 600 rpm. After that, the resulting products were passed through 0.2-µm polyester filter, and the residual solvent was removed at vacuum condition at 30°C for 30 min using a rotary evaporator. The filtrates were maintained in dry place until use. The drug-loading content (LC) and loading efficiency (LE) of the matrices were measured using the following formulas:[1,2]

\[
LC\% = \frac{\text{Mass of drug loaded in the matrix}}{\text{Mass of matrixes}} \quad (1)
\]

\[
LE\% = \frac{\text{Mass of drug loaded in the matrix}}{\text{Mass of drug initially used}} \quad (2)
\]

Drug loading by solvent evaporation method (Method B)

In this method, the filtration stage was not carried out and the rest of the process was similar to Method A. The acidic methanol was evaporated using a hot plate stirrer at 55°C for 48 h.

Physicochemical characterization

FTIR and CHN analyses were used to ensure that the aminopropyl was placed on the surface of the matrices. Furthermore, UV spectroscopy, XRD, BET, and FTIR analyses were used to ensure that the drug was loaded in the matrices.

For FTIR, a 20-mg sample (drug, matrixes, and matrices containing drugs) was blended with 40-mg KBr in a mortar and then PerkinElmer spectrometer (model 1000 (USA)) was used for analysis.

CHN analysis was used to determine the carbon (C), hydrogen (H), and nitrogen (N) elemental concentrations in functionalized MCM-41. Functionalization with aminopropyl was assessed based on the amount of nitrogen in the matrix using a CHN analyzer (PerkinElmer 2400 Series II).[18]

Siemens-D5000 (UK) consisting of a PW3710 diffractometer and a X-ray tube (30 mA and 40 KV) with a copper anode from 5°–40° (diffraction angle 2θ) at a step size of 0.02° and a scanning rate of 4°/min radiation was used to obtain the XRD of the diclofenac sodium alone, the matrixes alone, and the matrixes containing diclofenac sodium.[19]

BET analysis through a Quantachrome Autosorb 1-MP using N\(_2\) adsorption was utilized to measure the surface area (m\(^2\)/g) of the matrixes alone and the matrixes containing drugs. The matrixes containing drugs were depleted at 60°C before analysis because the melting points of the drugs, namely diclofenac sodium and piroxicam were 283°C–285°C and 198°C–200°C, respectively.

The drug loading content through Method A within and on the surface of pure MCM-41 and functionalized MCM-41 was measured by UV spectroscopy. It was assumed that the drug loading content through Method B was 100% because the acidic methanol was evaporated and the entire content of the drug had been loaded into or onto the matrix. After filtration, the absorbance of the bottom solution was read. The absorption spectra of diclofenac sodium and piroxicam in the acidic methanol (10% v/v) were 302 and 332 nm, respectively, in terms of λ\(_{\text{max}}\). The different formulations’ abbreviations are listed in Table 1.

The particle sizes and size distributions of the matrixes were determined at a 90° scattering angle using a 4 mW He-Ne laser with 633 nm incident beam through dynamic light scattering (Malvern Zetasizer™ ZS, Malvern, UK).

TEM (Hitachi H-7000, Nissei Sangyo, USA) was used to determine the size of the matrixes. In practice, a dilute suspension of matrixes in distilled water (0.5 mg/mL) was prepared that was filtered and was observed at 80 kV. All measurements were performed in triplicate.

For the determination of the morphologies and sizes of pure MCM-41 and functionalized MCM-41 matrixes,[20] the SEM (LEO 1450, Germany) was used. Prior to imaging, the matrix samples were gold plated in order to investigate the surface structure.

Dissolution studies

To investigate the release of diclofenac sodium and piroxicam from the matrixes into simulated gastrointestinal medium from matrixes, a dissolution test apparatus was applied. The simulated gastric juice and simulated intestinal fluid containing HCl solution (pH = 1.5) and phosphate buffer at 0.2 M (pH = 6.8), respectively, were agitated at 100 rpm at 37°C. To prepare 1 L of phosphate buffer with a pH of 6.8 and a buffering capacity of 10, which could simulate the intestinal medium, salts of Na\(_2\)HPO\(_4\),2H\(_2\)O (0.838 g) and Na\(_2\)HPO\(_4\),12H\(_2\)O (1.656 g) were used. After washing and tuning the apparatus, 1000-ml dissolution medium was poured into each flask, and the drugs and matrixes containing drugs were subsequently separated poured into the flasks.

Sampling was performed using a peristaltic pump (Alitea, Sweden) at 0, 15, 30, 45, 60, 75, 90, 105, 120,
Figure 2: Fourier transform infrared analysis of the samples after amino functionalization (b, blue color) compared with before functionalization (a, black color).

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Table 1: Different formulations’ abbreviations

| Formulation name                                      | Symbol used |
|-------------------------------------------------------|-------------|
| Diclofenac sodium                                     | D           |
| Pure MCM-41                                           | M           |
| Functionalized MCM-41                                 | F           |
| Diclofenac sodium + pure MCM-41 + Method A            | D.M.A       |
| Diclofenac sodium + functionalized MCM-41 + Method A  | D.F.A       |
| Diclofenac sodium + pure MCM-41 + Method B            | D.M.B       |
| Diclofenac sodium + functionalized MCM-41 + Method B  | D.F.B       |
| Piroxicam                                             | P           |
| Piroxicam + pure MCM-41 + Method A                    | P.M.A       |
| Piroxicam + functionalized MCM-41 + Method A          | P.F.A       |
| Piroxicam + pure MCM-41 + Method B                    | P.M.B       |
| Piroxicam + functionalized MCM-41 + Method B          | P.F.B       |

Statistical analysis

The Food and Drug Administration Guidance for Industry Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products has recommended the difference factor ($f_1$) and a similarity factor ($f_2$) to assess the percentage similarity between two in vitro dissolution curves over all time points according to Eq (3) and Eq (4).\[^{[21,22]}\]

$$f_1 = \frac{\sum (R_t - T_t)}{\sum R_t} \times 100$$  \hspace{1cm} (3)

$$f_2 = 50 \log \left( 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{1.05} \times 100$$  \hspace{1cm} (4)

Where $T_t$ is the dissolution value of the test formulation at time $t$, $R_t$ is the dissolution value of the reference formulation at time $t$, and $n$ is the number of time points.\[^{[23]}\] The test and reference formulation curves could be equivalent when the $f_1$ values were up to 15 (0–15) and $f_2$ values were >50 (50–100).\[^{[24]}\]

RESULTS

The results for the particle size (Z-average), zeta potential (mV), and PDI of MCM-41 were 94.7 nm, –12.2 mV, and 0.192, respectively. Furthermore, the particle size was confirmed by TEM [Figure 1a] and SEM [Figure 1b].

The aminopropyl group of functionalized MCM-41 was confirmed by FTIR analysis, as shown in Figure 2. Furthermore, the amino propyl loading on MCM-41 was confirmed by the small peak for nitrogen in the functionalized MCM-41, identified using CHN analysis as shown in Figure 3.

The drug loading content was measured using UV spectroscopy within and on the surface of the matrixes.
The LC and LE results are tabulated in Table 2. According to the results of Table 3, the empty spaces of the matrixes were occupied at approximately 61% when the drug was loaded into the matrixes. During the loading of drug into the matrixes, the smooth surface and polyhedral shape of the matrixes [Figure 1b] were converted into an uneven surface, as shown in Figure 4a and b.

The maximum release values of diclofenac sodium and piroxicam (control) in the simulated gastric juice were 57.31% and 74.11%, respectively. After 150 min, the release values for matrixes containing diclofenac sodium and piroxicam were 0% and 10%, as shown in Figure 5a and b. The pure diclofenac sodium and piroxicam can be dissolved within 50 min, while for drugs with matrixes, drug was not released in this media. The maximum release value of both drugs from pure MCM-41 and functionalized MCM-41 after 150 min was 10%. Comparison between the dissolution profiles of formulations in the stomach-like medium was performed by computing the difference ($f_1$) and similarity ($f_2$) factors. All profiles of two drugs were different mutually except certain dissolution profiles for diclofenac sodium, including D.M.A versus D.M.B, D.M.A versus D.F.B, and D.M.B versus D.F.B, which were similar.

The maximum release values of diclofenac sodium and piroxicam (control) in the simulated intestinal fluid were 99.3% and 99.45%, respectively, after 30 min; while these values for matrixes containing diclofenac sodium and piroxicam were approximately 76% after 300 min [Figure 5c and d]. The dissolution curves of the formulations in the small intestine-like medium were compared by computing the difference ($f_1$) and similarity ($f_2$) factors. The curves for diclofenac sodium release, including D.F.A versus D.M.B; D.F.A versus D.F.B; D.F.A versus D.M.A; D.M.A versus D.M.B; and D.M.B versus D.F.B, and the curves for piroxicam release, including P.M.A versus P.M.B; P.M.A versus P.F.B; and P.M.B versus P.F.B, were found to be similar.

**DISCUSSION**

MCM-41 and functionalized MCM-41 as a mesoporous material were studied to verify their ability to encapsulate and release a nonsteroidal anti-inflammatory drug as diclofenac sodium and piroxicam. The results of TEM and SEM confirm that the method of synthesis was suitable because the PDI (0.15–0.4) showed that the nanomatrix (60–100 nm) had a suitable size distribution and a negative zeta potential due to the stability of MCM-41. The result of FTIR determined that the absorption bands at 3310 cm$^{-1}$ could be

![Figure 4: (a) Scanning electron microscopy images (×10,000) of D.F.A and (b) P.F.A](image-url)
Figure 5: (a) The profile of diclofenac sodium release in stomach-like media, (b) the profile of piroxicam release in stomach-like media, (c) the profile of diclofenac sodium release in small intestine-like media, (d) the profile of piroxicam release in small intestine-like media

The intensity of the peak. The spawning peaks in the curve were probably related to diclofenac sodium. The C = O groups in the molecule were indicated by FTIR that could be proved by the existence of diclofenac and piroxicam and their interactions in the matrixes. The stretching vibrational frequency of the silanol groups caused adsorption bands in the range of 3750 cm$^{-1}$–3000 cm$^{-1}$. A strong stretching band for the carbonyl group (C = O peak) in the infrared spectrum relating to the diclofenac sodium powder and the piroxicam was observed at a wave number of approximately 1700 cm$^{-1}$.[23] This carbonyl peak is one of the most useful infrared spectra and is often regarded as the first studied peak. The diclofenac sodium peak for C = O at wave numbers of 1696 and 1722 cm$^{-1}$ proves the presence of diclofenac sodium in the functionalized MCM-41 generated through Method A and Method B. In addition, the piroxicam peak for carbonyl at wave numbers of 1653 and 1652 cm$^{-1}$ proves the presence of piroxicam in the functionalized MCM-41 generated through Method A and Method B. The BET analysis indicating a significant decrease of surface area from matrix containing drugs was observed. The pores of matrixes have entrapped a huge amount of drug, rather than on the surface according to the results of TEM and SEM.[10] This conclusion was confirmed by dissolution studies.

The amount of release for diclofenac sodium and piroxicam was low because they have acidic pKa values and exist primarily in the unionized form in the stomach environment. Furthermore, uncharged MCM-41 can remain bound to these drugs in the simulated gastric media through hydrophobic interaction. It was concluded that these formulations can resist the release of drug from matrixes in the simulated gastric media, which supported our findings. It is worth mentioning that the rate of drug release was faster and more extensive for the formulations prepared by Method B in two release media (stomach-like and small intestine-like media) than prepared by Method A because the drug was placed on the surface of the matrixes through Method B. The drug release of matrixes was slow and continuous likely when compared to pure drug since the negatively charged surface of MCM-41 repelled the negatively charged drug in the simulated intestinal environment.

Rimoli et al.[25] and Khodaverdi et al.[23] have confirmed the results of drug release in the gastrointestinal media. Rimoli et al. showed that release of ketoprofen loaded into a carrier matrix is low in the stomach, whereas the drug can be dissolved in and released into the intestinal environment. Khodaverdi et al. indicated that ibuprofen and indomethacin cannot be released from a matrix in the stomach-like media, whereas these drugs can be released slowly and continuously in the small intestine-like media. The release of piroxicam from functionalized MCM-41 was slower than the release from pure MCM-41 in intestine-like medium because of
the formation of electrostatic bonds between piroxicam and the amino propyl groups of the functionalized MCM-41. However, in the case of diclofenac sodium, there was no significant difference between pure MCM-41 and functionalized MCM-41. The difference between piroxicam and diclofenac sodium was due to the high solubility of diclofenac sodium in the simulated intestinal medium (pH 6.8) which caused more rapid release from the matrices than for piroxicam.

CONCLUSION

MCM-41 was synthesized through sol–gel procedure and functionalized with aminopropyl groups and was investigated as a matrix for controlled release. Diclofenac sodium and piroxicam were loaded into pure MCM-41 and functionalized MCM-41 matrices, and a study of the in vitro release was performed in simulated gastrointestinal medium. Drug loading was performed using the filtration and solvent evaporation methods. Drug loading by the filtration method (Method A) is less than that by the solvent evaporation method (Method B), whereas the drug release of matrices prepared through Method A is slightly slower than the matrix through Method B. According to the dissolution tests of pure drugs (control sample) and matrix containing pure drugs (formulations), the pure diclofenac sodium and piroxicam were released more quickly than the drugs in the formulations in the simulated gastrointestinal environment. The release of piroxicam from functionalized matrices was slower than release from matrices in the simulated intestinal medium because of the formation of electrostatic bonds between piroxicam and the amine groups of the functionalized matrix. However, in the case of diclofenac sodium, there was no significant difference between the functionalized matrix and the pure matrix. The difference between piroxicam and diclofenac sodium was due to the high solubility of diclofenac sodium in the simulated intestinal medium (pH 6.8), which caused more rapid release from the matrices than for piroxicam.

Acknowledgments

This article is the result of a Pharm.D. thesis of Dr. Mina Ahmadi; we sincerely thank the Research Council of Mashhad University of Medical Sciences for providing the fund of this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mohammadzadeh M, Nourbakhsh MS, Khodaverdi E, Hadizadeh F, Omid Malayeri S. Enhanced loading and release of non-steroidal anti-inflammatory drugs from silica-based nanoparticle carriers. Chem Biol Drug Des 2016;88:370-9.
2. Tan SY, Ang CY, Li P, Yap QM, Zhao Y. Drug encapsulation and release by mesoporous silica nanoparticles: The effect of surface functional groups. Chemistry 2014;20:11276-82.
3. Liu Y, Gobbi J, Yin Y. Templated synthesis of nanostructured materials. Chem Soc Rev 2013;42:2610-53.
4. Vallet-Regi M, Ramila A, Del Real R, Pérez-Paquete J. A new property of MCM-41: Drug delivery system. Chem Mater 2001;13:308-11.
5. Horejšá J, Ramila A, Pérez-Paquete J, Vallet-Regi M. Influence of porosity size of MCM-41 matrices on drug delivery rate. Microporous Mesoporous Mater 2004;68:105-9.
6. Munoz B, Ramila A, Perez-Paquete J, Diaz I, Vallet-Regi M. MCM-41 organic modification as drug delivery rate regulator. Chem Mater 2003;15:500-3.
7. Popova MD, Szegedi A, Kolev IN, Mihály J, Tzankov BS, Mormekov GT, et al. Carboxylic modified spherical mesoporous silicas as drug delivery carriers. Int J Pharm 2012;436:778-85.
8. Heikkilä T, Santos HA, Kumar N, Murzin DY, Salonen J, Laaksonen T, et al. Cytotoxicity study of ordered mesoporous silica MCM-41 and SBA-15 microparticles on Caco-2 cells. Eur J Pharm Biopharm 2010;74:483-94.
9. Vyskočilová E, Luštíčková I, Machtová L, Červený L. Modified MCM-41 as a drug delivery system for acetylsalicylic acid. Solid State Sci 2014;38:85-9.
10. Manzano M, Aina V, Areán C, Balas V, Collilá M, et al. Studies on MCM-41 mesoporous silica for drug delivery: Effect of particle morphology and amine functionalization. Chem Eng J 2008;137:30-7.
11. Szegedi A, Popova M, Goshiev I, Mihály J. Effect of amine functionalization of spherical MCM-41 and SBA-15 on controlled drug release. J Solid State Chem 2011;184:1201-7.
12. Zeng W, Qian XF, Zhang YB, Yin J, Zhu ZK. Organic modified mesoporous MCM-41 through solvothermal process as drug delivery system. Mater Res Bull 2005;40:760-72.
13. Limnell T, Heikkilä T, Santos HA, Sistonen S, Hellström S, Laaksonen T, et al. Physicochemical stability of high indomethacin payload ordered mesoporous silica MCM-41 and SBA-15 microparticles. Int J Pharm 2011;416:242-51.
14. Ambrogi V, Petrioli L, Pagano G, Latterini L, Marmottini F, Ricci M, et al. MCM-41 for fuorescence dissolution improvement. Microporous Mesoporous Mater 2012;147:343-9.
15. Giri S, Trewny BG, Lin VS. Mesoporous silica nanomaterial-based biotechnological and biomedical delivery systems. Nanomedicine (Lond) 2007;2:99-111.
16. Popova M, Szegedi A, Yoncheva K, Konstantinov S, Petrova G, Aleksandrov H, et al. New method for preparation of delivery systems of poorly soluble drugs on the basis of functionalized mesoporous MCM-41 nanoparticles. Microporous Mesoporous Mater 2014;198:247-55.
17. Mathew A, Parambadath S, Park SS, Ha CS. Hydrophobically modified spherical MCM-41 as nanovale system for controlled drug delivery. Microporous Mesoporous Mater 2014;206:124-31.
18. Fukuda R, Ogawa H, Nagata T, Koike II. Direct determination of carbon and nitrogen contents of natural bacterial assemblages in marine environments Appl Environ Microbiol 1998;64:3352-8.
19. Khodaverdi E, Hadizadeh F, Tékie FS, Jalali A, Mohajeri SA, Ganji F. Preparation and analysis of a sustained drug delivery system by PLGA-PEG-PLGA triblock copolymers. Polym Bull 2012;69:429-38.
20. Sexton B, Smith T, Sanders J. Characterization of copper-exchanged Na-A, X and Y zeolites with X-ray photoelectron spectroscopy and transmission electron microscopy. J Electron Spectrosc Relat.
21. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123-33.

22. Peh KK, Wong CF. Application of similarity factor in development of controlled-release diltiazem tablet. Drug Dev Ind Pharm 2000;26:723-30.

23. Khodaverdi E, Honarmandi R, Alibolandi M, Baygi RR, Hadizadeh F, Zohuri G, et al. Evaluation of synthetic zeolites as oral delivery vehicle for anti-inflammatory drugs. Iran J Basic Med Sci 2014;17:337-43.

24. Emami J. In vitro – In vivo correlation: From theory to applications. J Pharm Pharm Sci 2006;9:169-89.

25. Rimoli MG, Rabaioli MR, Melisi D, Curcio A, Mondello S, Mirabelli R, et al. Synthetic zeolites as a new tool for drug delivery. J Biomed Mater Res A 2008;87:156-64.