Journal of Materials Chemistry B

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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ARTICLE

Influence of the Structural and Textural Properties of Ordered Mesoporous Materials and Hierarchical Zeolitic Supports on the Controlled Release of Methylprednisolone Hemisuccinate

Cite this: DOI: 10.1039/x0xx00000x

Received ooth January 2012
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

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To alleviate the chronic inflammation, nasal obstruction, and loss of sense of smell that produces the rhinosinusitis disease, ordered mesoporous materials and hierarchical zeolites could be used for slow and sustained corticoid (methylprednisolone hemisuccinate conjugate) release. The correlations between delivery performance of methylprednisolone hemisuccinate and the physicochemical properties of carriers' release systems, including pore mesostructure, texture and size, and surface chemistry, have been well established. Different two-dimensional (2-D) and three-dimensional (3-D) mesostructured materials (MCM-41, SBA-15, expanded SBA-15, FDU-12, and SBA-16) were employed. In addition, for the first time and to the best of our knowledge, materials based on hierarchical zeolites with additional mesoporosity (h-ZSM-5 and h-BETA zeolites) were also tested. In particular, two materials (3-D cubic mesoporous silica SBA-16 and hierarchical Beta zeolite) have been probed as potential candidates, exhibiting high drug adsorption capacities and additionally slow drug release rate, which is the most favourable way of drug release in the particular rhinosinusitis application. Solid-state ^{1}H-^{29}Si HETCOR NMR analyses confirm the strong interactions of the drug with the surface of h-BETA and 3-D SBA-16 materials, via hydrogen bonding of carboxylic, ketone, and aliphatic moieties of the methylprednisolone hemisuccinate at surface silanol sites. Given the remarkable release performance, it is expected that 3-D mesoporous silica SBA-16 and hierarchical Beta zeolite are attractive for current applications in nasal inflammation treatments. The drug release rate can be further retarded by decreasing the pH at around 4.6, more attraction forces being detected as proved by zeta-potential measurements. Therefore, a slower deliverance trend of methylprednisolone hemisuccinate has been observed for all the materials, being more intense in the case of SBA-15 and SBA-16.

Introduction

Traditional systems for drug release imply that the supplied active molecules rapidly increase its concentration in plasma to exponentially decay as the drug is excreted and/or metabolised. The drawback of these systems consists in their inability to control either the release rate or site-specific administration, providing immediate and rapid drug liberation. The therapeutic level of drug in the blood is located between the overdose concentration in which the drug concentration is toxic and insufficient doses in which the treatment is incomplete or not effective. In these systems, the way to maintain an adequate therapeutic level of drug over a prolonged period of time is frequent administration. In addition, the usually increment of the dosage makes the drug concentration fluctuates greatly, reaching toxic effects.[1,2] Controlled delivery systems of drugs have been developed to solve these problems because they control the rate and period of drug delivery and also target specific areas of the body. Therefore, these systems increase therapeutic efficacy, reducing side effects and patient's disorders.

The rate of use silica nanoparticle materials as drug carriers with controllable release has increased significantly in recent years because of the versatility and stability of these mesoporous matrixes. Since 2001, when the MCM-41 material was first proposed for drug delivery system, materials based on silica have been studied as drug carriers and release devices.[3]

Mesoporous siliceous materials have unique physicochemical properties, which permit their utilisation as potential drug carriers: (a) an ordered pore network, which is very homogeneous in size and allows control of drug loading and release kinetics; (b) a high pore volume to accommodate the required amount of pharmaceutical products; (c) a high surface area, implying a high potential for drug adsorption; (d) external surface silanol-groups able to easily promote functionalisation and therefore allow better control over drug loading and release; and finally, (e) in vivo biological compatibility.[4–15]
Adsorption and release of drugs is based on physical drug-silica support interactions. Parameters related to the material surface, pore size, geometry, pore connectivity, and possible reactions of the silica support with the surrounding environment are some of the many factors to consider in the design of drug delivery systems.[2]
The pore diameter determines the size of the drug molecule that can be adsorbed in the mesopores.[4,5] When the molecule is smaller than the mesoporous cavity, the drug is confined inside the mesopores. On the other hand, when the drug molecule is larger than the pore diameter, the adsorption only takes place on the external surface of the material. In the case of the surface area, the higher the surface area, the greater the amount of adsorbed drugs. If the molecule to be loaded is much smaller than the pore diameter, most of the drug molecules will not be retained within the pores because only some of them may interact directly with the pore walls, while the rest would be released. With regard to the pore volume, high values favour large drug loadings. Respecting the modification of the drug-silica support interactions by organic modification, the high density of silanol groups on the surface permits the functionalisation of the mesoporous silica by reaction with organosilane compounds.[13,14] The organic groups are able to interact with drug molecules usually through noncovalent interactions (electrostatic interaction, van der Waals forces, hydrogen bonding, and hydrophobic interaction), although covalent bonds with ester groups have also been described.[15] In general, the effectiveness of these systems to control the delivered dose depends not only on the amount of drug accommodated in their pores but also critically on the release kinetics, which largely depends of the aforementioned parameters.
Corticoids are a variety of hormones from the group of steroids produced by the adrenal glands cortex. They all consist of the same basic structure formed by three hexane rings and one pentane ring and different end-chain functionalities—such as amino, carboxyl, phosphate, and others—that provide it with potential pharmacological action in several applications. Methylprednisolone is one of the most used and effective corticoids. This corticoid presents immunosuppressive and anti-inflammatory properties. Its administration relieves inflammation (swelling, heat, redness, and pain) and is involved in the treatment of arthritis; skin disorders; blood, kidney, eye, thyroid, and intestinal disorders (e.g., colitis); severe allergies; and asthma. Methylprednisolone is also used as palliative treatment in certain types of cancer, such as leukaemia and lymphomas.
A particular application is based on the treatment of rhinosinusitis. This is a disease of the nasal mucosa that is accompanied by acute or chronic inflammation from various causes. Although it is not a serious disease, the life quality of patients is significantly affected, mainly by nasal obstruction and loss of sense of smell. Moreover, this illness exhibits a high prevalence (between 4% and 8%) in the general population. Oral administration has been the conventional treatment in chronic rhinosinusitis. The fundamental problem of this pathway is the lower bioavailability of the active ingredient due to limitations in the stomach absorption and higher hepatic metabolism. This results in a shorter duration of the pharmacological effect. To overcome this limitation, the utilisation of mesoporous nanoparticles opens a door to control the corticoid release as a function of time and desired dose. Thus, theoretically, the intended effect of decreasing or avoiding side effects would already be achieved. Therefore, an interesting optional treatment in chronic sinusitis, with or without nasal polyposis, is open to study.[16] Herein, in the present research work, the immobilisation of corticoids (methylprednisolone hemisuccinate) is carried out over different silica-based materials to evaluate the influence of structural and textural properties, by adjusting the internal hollow mesopores, on corticoids release kinetics. Mesoporous silica materials with different structures (MCM-41, SBA-15, expanded SBA-15, FDU-12, and SBA-16) are studied. Degradability of mesoporous silica nanoparticles affected by different factors, such as surface modification, crystallinity, morphology, and particle size, among others, is in dispute. Therefore, in this investigation, novel materials based on hierarchical zeolites with additional mesoporosity have proved as drug delivery substance. The higher stability associated to their crystalline framework have been explored for the first time in this application to the very best of our knowledge.

Experimental

Materials synthesis

The synthesis of mesoporous and zeolitic materials was accomplished by using the methods described previously and illustrated in the Supporting Information Materials synthesis S1†.[17–24]

Characterisation

XRD patterns of the different samples were obtained with a Philips X´PERT MPD diffractometer using CuKα radiation. Both low- and wide-angle X-ray patterns were collected in order to characterise the mesoscopic ordering and the zeolite crystallinity of the samples, respectively.
The textural properties of the mesoporous materials were obtained by nitrogen adsorption-desorption isotherms at -196ºC. The calcined mesostructured samples were measured with a Micromeritics TriStar 3000 instrument. Before the measurement, the pure silica samples were outgassed under vacuum at 300ºC. Loaded drug carriers were outgassed at 100ºC under vacuum. Surface areas were calculated by applying the Brunauer-Emmett-Teller (BET) equation. Cylindrical pore geometry was assumed for the calculation of the mesopore size distribution using the BJH model. Argon adsorption-desorption isotherms at -186ºC were also recorded for the zeolite samples using an autosorb instrument (Quantachrome). Previously, the samples were outgassed under vacuum at 300ºC and 100ºC, without and with loaded drug, respectively. The surface area was also determined by applying the BET equation. The pore size distributions were calculated using the adsorption branch of the argon isotherms by applying the NLDFT model (Quantachrome).[25] This model was useful for estimating the contribution of both types of porosities (micro and meso) to the pore volume and surface area of the hierarchical materials.

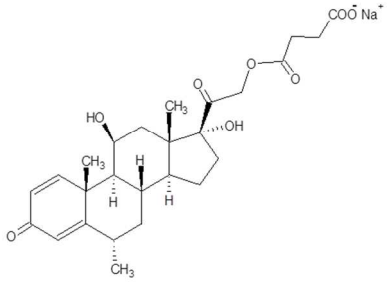
Transmission electron microscopic (TEM) images were obtained by means of a Philips Tecnai 20 microscope operated at 200 kV, with thermoionic gun and LaB6 filament, 2.7 Å resolution and ±70° tilt of the sample. For TEM measurements, the samples were prepared by dispersing the powder in acetone, followed by dispersing and drying on carbon film on a Cu grid.

Solid-state ^{13}C and ^{29}Si MAS NMR experiments were performed on a Varian Infinity 400-MHz spectrometer fitted with a 9.4-T magnet. These nuclei resonate at 100.53 and 79.41 MHz, respectively. An H/X 7.5-mm MAS probe and ZrO_2 rotors spinning at 6 kHz were used. On CP experiments, the cross-polarisation time was determined to guarantee the total proton polarisation verifying the Hartmann–Hahn condition. For ^{13}C acquisition, $\pi/2$ pulse, number of scans, repetition delay, and contact time were 4.25 μs, 2,000 scans, 3 s, and 1 ms, respectively. The ^{29}Si CP experiments were performed for 3,000 scans, $\pi/2$ pulse of 3.5 μs and 15 s of repetition time, while the contact period was 10 ms (as cross-polarisation depends upon heteronuclear dipolar interaction, the greater the distance, the larger the cross-polarisation time). ^{13}C and ^{29}Si chemical shifts were externally referenced to adamantane and tetramethylsilane, respectively.

Solid-state two-dimensional (2-D) $^{29}Si\{^1H\}$ heteronuclear chemical shift correlation (HETCOR) NMR experiments were performed on a Varian Infinity 400 MHz NMR fitted with a 9.4-T magnet, operating at XX and 79.41 MHz for ^1H and ^{29}Si, respectively. 4-mm TXY MAS probe was spinning at 8 KHz. Experiments were conducted at room temperature under magic-angle spinning (MAS) conditions at 8 kHz by using a 4-mm TXY MAS probe spinning with 4.0-mm zirconia rotors. It was employed an X-H heteronuclear correlation with Lee-Goldburg ^1H decoupling during X fid to avoid spin diffusion. The HETCOR technique allows different dipole-dipole-coupled moieties to be differentiated and identified by spreading their chemical shifts into a 2-D frequency map. The HETCOR experiment is similar to standard cross-polarisation magic-angle spinning (CP-MAS) NMR, with the key exception that the ^1H magnetisation is allowed to evolve for an incremented evolution time period t1 prior to magnetisation transfer to heteronuclei, such as ^{13}C or ^{29}Si, whose responses are measured directly during the detection period t2. Double Fourier transformation converts the time domain signal S(t1, t2) into the frequency domain F(ω1,ω2), which is typically presented as a 2-D contour plot spectrum. For the $^{29}Si\{^1H\}$ HETCOR experiments, a 6.8 μs 90º pulse, followed by a 2-ms contact time, was used for cross-polarisation. A total of 768 acquisitions with a 2-s recycle delay were collected for 128 t1 increments. The ^1H and ^{29}Si chemical shifts were referenced to tetramethylsilane. All 2-D HETCOR spectra are presented with contour levels shown to 20% of full intensity.

Corticoid loading

Methylprednisolone hemisuccinate (Scheme 1) was loaded into the SiO_2 meso and microporous materials by two different impregnation methods from a highly concentrated solution of the drug. On one hand, for the solvent adsorption methodology, the different micro/mesoporous materials (200 mg) were added to a solution of methylprednisolone hemisuccinate (10 and 25 mg) in water (1 mL). This suspension was vigorously stirred over three days at room temperature while the evaporation of water was prevented. The materials were dried at 70ºC overnight. In addition, the methylprednisolone hemisuccinate was added to the supports by incipient wetness impregnation of an aqueous solution containing methylprednisolone hemisuccinate with 10 and 25 mg/mL concentrations. The impregnated solids were dried overnight at 70°C. The determination of the methylprednisolone hemisuccinate loading in the material was carried out by thermogravimetric (TGA) analyses using a Star system Mettler thermobalance, as well as elemental microanalyses in a Vario EL III apparatus. The temperature range of the corticoid degradation was also studied through TG analyses (Supporting Information Fig. S1†). Focusing on the pure corticoid, the main weight loss was centred in the range 180ºC–500ºC. Below 100ºC, a small weight loss, associated with the adsorbed water by the drug, was detected. These results imply that the overnight drying step at 70ºC is far from the starting degradation temperature of the corticoid, therefore remaining unmodified for the release experiments.



Scheme 1. Chemical structure of the methylprednisolone hemisuccinate corticoid

In vitro drug release essay

Sterilised dialysis bags with dialyzer molecular-weight cutoff 10,000 Da were used to carry out the drug release experiments. These dialysis bags were pretreated prior to use as follows: They were fully immersed into 50% aqueous solution of ethanol and boiled for 1 h, then washed with water up to 40ºC for another hour. Finally, the dialysis bag was immersed in 100 mL of the simulated body fluid to be used later for the release experiments for 2 hours in order to stabilise them. Phosphate buffered saline (PBS) of pH = 7.4 and acetic buffer solutions (ABS) of pH = 4.5 were used as the drug release media to simulate normal blood/tissues and tumour environments.

The silica sample (0.1 g) with the drug adsorbed (10 mg) was dispersed into 2-mL release media, and then the solutions were placed into pretreated dialysis bags. The sealed dialysis bags were put into bottles, and then 100-mL release media were added. These bottles were shaken at a speed of 100 rpm at 37°C under a sealed condition. At certain time intervals, 1 mL of the release media was taken out for measuring the released drug concentrations by the UV-vis absorption technique and was then returned to the original release media. The concentrations of the released drug were calculated using the Beer–Lambert law according to the absorbance of the release media at 248 nm, which is the characteristic adsorption wavelength for the methylprednisolone molecule.

Each experiment (drug adsorption and release steps) was carried out thrice to calculate the standard error bar. The standard deviation was less than 5%, indicating the reproducibility of the results.

Results and discussion

Different methods and ionic and nonionic surfactants were employed to obtain the purely siliceous materials used as drug carriers. Thus, MCM-41 and SBA-15 were produced using cationic CTAB and triblock copolymer P123, respectively. These structures displayed hexagonally close-packed cylindrical pore channels. The TEM images (Supporting Information Fig. S2†) show the typical hexagonal structures along the channel system and parallel stripes if viewed perpendicular to channel directions. Both materials disclose uniform pore sizes of 27.4 and 89.4 Å, respectively. Pore expanded SBA-15 was obtained adding triisopropylbenzene as an organic swelling agent. The pore size was enlarged up to 232.5 Å. SBA-16 and FDU-12, having cubic mesostructures, were synthesised using acidic triblock copolymer F127. FDU-12 presents a cubic mesostructure with a large cavity size of 111.4 Å, while SBA-16 has a body-centred cubic mesostructure with pore sizes of 45.1 Å. The XRD patterns, N_2 sorption isotherms, and pore size distributions of the mesoporous materials are shown in Supporting Information (Supporting Information Fig. S3, S4, and S5†), indicating highly ordered 2-D mesostructured materials with hexagonal symmetry and mesoporous materials with three-dimensional (3-D) cage-type pores.

Table 1. Physicochemical properties of the ordered mesoporous silica materials and hierarchical zeolites

Sample	S_{BET}[a] (m^2/g)	D_p[b] (Å)	V_p[c] (cm^3/g)	k[d] (s^{-1})	Zeta potential (mV)	
					pH = 7.4	pH = 4.6
Pure MP					-23.0	-19.4
MCM-41	828.37	27.4	0.756	0.00498		
FDU-12	553.64	111.4	0.74	0.00569		
SBA-15	573.14	89.4	0.97	0.00487	-19.3	-4.11
SBA-16	801.41	45.1	0.55	0.00422	-12.7	-6.43
SBA-exp	454.84	232.5	1.16	0.00606		
Amorphous silica	266.8	100–400	1.81	0.00881		
ZSM-5	417 (87)[e]	--	0.48 (0.21)[f]	0.00283		
h-ZSM-5	499 (254)[e]	20–90	0.56 (0.15)[f]	0.00247	-17.3	-16.2
BETA	599 (87)[e]	--	0.44 (0.30)[f]	0.00183		
h- BETA	712 (287)[e]	15–70	0.69 (0.26)[f]	0.00179	-21.9	-19.6

[a] BET surface area determined from the N_2 or Ar adsorption isotherms. [b] Pore size distribution. [c] Pore volume. [d] Release kinetic constant. [e] External surface area in brackets. [f] Micropore volume in brackets. BET surface area and pore size distribution are depicted in Supporting Information Fig. 3 and 4.†

On the other hand, hierarchical zeolites with MFI and BEA structures were synthesised. These zeolitic materials possess a secondary porosity, in addition to the typical zeolite micropores. Therefore, the hierarchical zeolites display an enhanced accessibility that may lead to improve the amount of drug loading, avoiding the steric and/or diffusional limitations that experiment the standard zeolites when diffusing bulky species inside. The method here employed for the preparation of hierarchical zeolites is based on the crystallisation of silanised protozeolitic units. The incorporation of the seed silanisation agent (SSA) hinders the growth of the zeolite crystals and prevents their further aggregation. The materials obtained applying this strategy show high non-microporous surface area, as they consist of ultra-small zeolite nanounits with an additional porosity in the supermicro-mesopore regions generated by the silanisation agents.[26] The Ar sorption measurements indicate that three adsorptions take place. At low relative pressure, the filling of the micropores occurs. At intermediate relative pressure, the presence of the additional secondary porosity is evidenced by a significant adsorption. Finally, at high relative pressures, the presence of intercrystalline porosity is observed. The pore size distribution derived from the NLDFT model displays a clear peak corresponding to the zeolites micropores and, also, a second peak placed in the range 20–80 Å, associated to the extra porosity generated by the addition of the organosilane (Supporting Information Fig. S5†). Wide-angle XRD patterns of these materials show the typical diffractograms corresponding to the MFI and BEA zeolite structures (Supporting Information Fig. S3†). According to the Scherrer law for powder XRD, the increase in the peak width, measured at half height, is indicative of a reduction in the crystal size. Therefore, a decrease in the size of the crystalline domains is produced with the incorporation of the SSA.

The textural properties (BET surface area, mesopore diameter, and total pore volume) of the employed mesoporous and zeolitic materials, determined from the N_2 and Ar isotherms, are summarised in Table 1. Moreover, TEM images (Supporting Information Fig. S2†) display the nanoparticle features exhibited by all the materials.

In addition, the corticoid drug adsorption data on mesoporous silica and hierarchical zeolites adsorbents are summarised in Table S1†, including the adsorption efficiency. The corticoid adsorption was carried out through two methods: the incipient wetness method and a classical approach of adsorption from a solution. Three different drug concentrations of 10, 15, and 25 mg/mL were used. Considering the results of the corticoid amount adsorbed on each support, it is evident that the incipient wetness method incorporates higher drug amounts at low concentrations, while at higher initial corticoid loads, both methods reach similar concentrations, likely to be near the support saturation. Similar results were indistinctly obtained using either elemental microanalyses or TGA (Supporting Information Table S1†). Using lower drug concentrations, the real adsorbed amount nearly reaches the values of the initial concentration, and hence, higher load efficiencies are obtained. Thus, the loading technique selected was the incipient wetness method. In general, mesoporous and zeolitic materials achieve a high MP-loading efficiency, between 70% and 100% (Supporting Information Table S1†). Consequently, it has chosen 10 mg/mL (i.e., the lowest concentration). Taking into account the yield results obtained for the lowest drug concentration, the materials with highest incorporated corticoid are the expanded SBA-15 and amorphous silica. Expanded SBA-15 possesses the largest pore diameter; hence, a higher amount of methylprednisolone hemisuccinate may be accommodated inside their pores. Respecting the zeolitic materials, Beta zeolite shows superior drug amounts loading than ZSM-5. The enhanced BET surface area of the former material and the additional mesoporous channels permit reaching a similar yield as the mesoporous MCM-41 material.

The effect of adsorption retention in each support will be further studied in terms of release kinetics.

To assess the incorporation of the corticoid onto the materials' framework, different analyses were employed, as shown in Figure 1. Thus, by means of CP-MAS ^{13}C solid-state NMR, the qualitative identification of pure methylprednisolone hemisuccinate molecule was performed. Its subsequent adsorption on MCM-41 material was also studied by solid-state ^{13}C CP-MAS NMR.

Spectrum peaks show coincidence with that of the pure drug, corroborating the inclusion of the drug molecules on this sample. Nevertheless, the carbon nucleus environments for the adsorbed drug are narrower than those of the pure methylprednisolone hemisuccinate without diffusion impediments. This effect may be accounted for the incremented motion of the drug encapsulated inside the pores, as consequence of a reorientation or reordering of the molecules. The confinement inside the mesopores seems to promote a loss of the drug crystallinity. Therefore, drug becomes more mobile within the inorganic support, which is indicative that the solid state is not the predominant form inside the pores, but an amorphous-like state, which may facilitate a better dissolution on the simulated body fluid.[12, 27–29]

To prove the incorporation of the drug not only over the external surface but also inside the pores, N_2 adsorption-desorption analyses were carried out. Supporting Information Fig. S4† displays the isotherms before and after drug loading. After methylprednisolone hemisuccinate encapsulation, the N_2 volume adsorbed in the pores experiences a remarkable reduction, which demonstrates the access of the corticoid inside the pores. Over zeolitic materials, the amount of adsorbed argon presented similar behaviour compared with the mesoporous material, except standard ZSM-5 zeolite, in which the access of methylprednisolone hemisuccinate molecules within the zeolite channels is significantly hindered, being mainly adsorbed over the external surface. The N_2 and argon volume decline is also noticed at high relative pressures, confirming that the drug is also incorporated over the external surface.

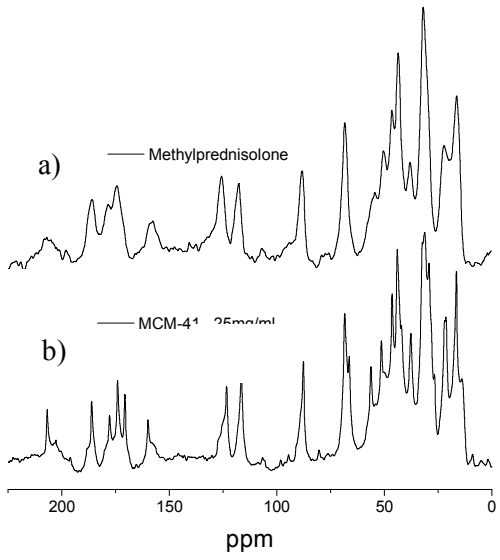


Figure 1. Solid-state ^{13}C NMR spectrum of (a) pure methylprednisolone hemisuccinate and (b) methylprednisolone hemisuccinate load onto mesoporous MCM-41 material

For the methylprednisolone hemisuccinate releasing test, the drug-loaded nanoparticles were soaked in simulated body fluids (SBF) at 37ºC. The cumulative release of methylprednisolone hemisuccinate from both ordered mesoporous materials and hierarchical zeolites was calculated. The release percentage of the samples was plotted against the release time, and the results are shown in Figures 2 and 3 for ordered mesoporous silica materials and hierarchical zeolites, respectively.

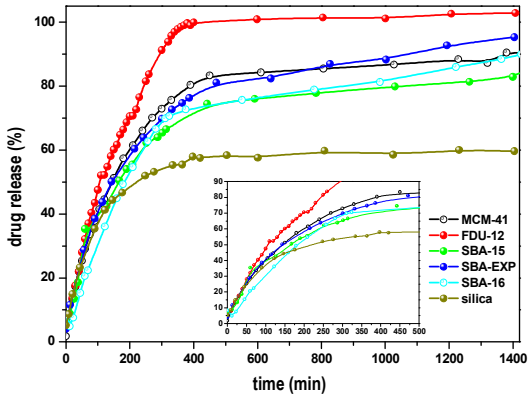


Figure 2. Methylprednisolone hemisuccinate release percentages as a function of release time by using the ordered mesoporous silica materials as carriers

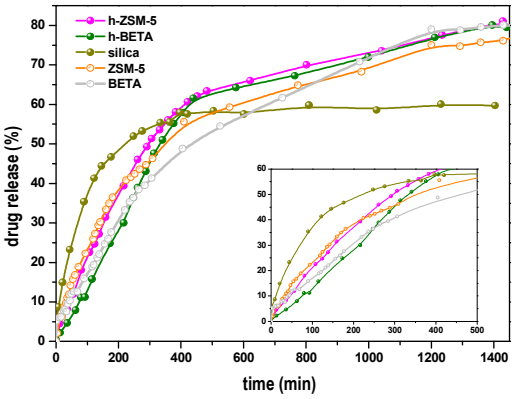


Figure 3. Methylprednisolone hemisuccinate release percentages as a function of release time by using the hierarchical zeolites as carriers

An initial release burst from the carriers occurs in the first 200–400 min, depending on the material, due to desorption of the methylprednisolone hemisuccinate located either on the external surface or near the channel mouth of the support. To quantify the release rate in the early stages, before the drug-sustained delivery is reached, the derivative of the release corticoid concentration with respect to the time was performed. Thus, the release kinetic constant in this initial period was determined, and the results are displayed in Table 1. Initial first-step burst release displays some hints about the behaviour

of the carriers. Thus, hierarchical Beta zeolite exhibits the lowest release kinetic constant of the corticoid, as displayed in Table 1 and in Figure 3. The hierarchical porosity of this support, constituted by the zeolitic micropores (around 6.5 Å) and the additional extra-mesoporosity, with a mean pore size diameter around 30 Å, exerts a constrained effect over the drug. The latter is the main reason that could explain the stronger interaction of support-drug and hence the more durable retention behaviour of this material, which is the most favourable way of drug release in the particular rhinosinusitis application. Another synergetic effect to be taken into account is the aluminium content. Al species present in the hierarchical zeolites reduce the electronegative charge between the methylprednisolone hemisuccinate and surface carrier, which consequently retards the corticosteroid release.[30] Hierarchical ZSM-5 zeolite also displays an initial slow release rate, lower than the mesoporous materials. However, the parent Beta zeolite used as reference, without any hierarchical porosity, releases the drug more slowly than h-ZSM-5 zeolite. Drug molecules with molecular size dimension of ~13.7 × ~5.6 Å (Supporting Information Scheme S1†) are able to partially diffuse into the Beta zeolite micropores, which is in agreement with the better result obtained for this material in comparison with h-ZSM-5. Then the release rate becomes relatively slow, because the delivered methylprednisolone hemisuccinate should diffuse from the inside of the channels. After more than 24 hours, drug release is rather slow until most of the encapsulated corticoid desorbs, following a sustained trend of methylprednisolone hemisuccinate release. Nevertheless, the curve profile of this second step indicates, for most of the materials, that the total release is not reached along the time range studied, which satisfies the requirements of corticoid long-term release for rhinosinusitis medical treatment.

Regarding the ordered mesoporous materials, the slowest release rate in the early stages was displayed by the 3-D cubic mesostructured SBA-16. This mesostructured material has a body-centred cubic of spherical cages with pore sizes of ~45 Å, which represents a rather adjustable pore to the molecular dimension of methylprednisolone hemisuccinate. Moreover, SBA-16 possesses a rather remarkable surface area of 801 m^2/g, which permits a suitable methylprednisolone hemisuccinate loading. Both combined features slow down the release rate of the corticosteroid and make the material a potential candidate to be employed as drug carrier. Opposite, 3-D cubic mesostructured FDU-12 displays a complete burst release at 400 min. The large pore size, 111.4 Å, besides its 3-D channels connecting system, facilitates the faster corticoid diffusion through the silica pores, assisting the express drug delivery. Also, 2-D mesostructured materials, MCM-41, SBA-15, and pore-expanded SBA-15 present a similar tendency, with a faster release than SBA-16 in the first stage. As shown in the Supporting Information Fig. S6†, the influence of the pore volume is not a determinant parameter on the drug loading efficiency as no clear trend is observed.

The explanation of the fastest initial first-step burst release of the commercial silica is based on the methylprednisolone hemisuccinate location either on the external surface or near its large channel mouth. However, the commercial silica retains around 40 wt% of the model drug. Based on the low mesoscopic order, together with the wide pore size distribution (100–400 Å), a probable reason to explain this fact may be the presence of diffusional problems that experiment the corticoid through the more internal heterogeneous channels. Another explanation could be related to the number of the surface silanol sites –OH. In the commercial silica, the number is around 4.6 OH. nm^{-2}, clearly higher than those of the mesostructured materials (around 3.8 and 3.0 OH. nm^{-2} in the case of SBA-15 and MCM-41 materials, respectively), which causes the drug to remain more retained in the vicinity of these hydroxyl groups. Although the result could be interesting to slow down the delivery and to improve the drug release control, the low BET surface area commercial silica, which is one-third lower than those of the mesostructured and hierarchical zeolites materials, leads to a sensitive decrease of the drug payload.

In order to assess the previous stated different interactions of the carriers' silanol sites with the drug, solid-state ^1H-^{29}Si HETCOR NMR analyses were accomplished. To identify the origin of the signals in Figure 4, cross-polarisation (CP) 2-D heteronuclear correlation (HETCOR) experiments were performed: magnetisation is transferred from abundant nuclei (^1H) to nonabundant ones ^{29}Si through space (i.e., via the heteronuclear ^1H-X dipolar interaction with ^{29}Si nucleus). Such experiments give information about the proximity between drug protons and the different silanol species of the silica materials, because the dipolar interaction depends on the inverse of the distance between ^1H and X nuclei.[12,31] There are two main regions in the ^1H spectra, corresponding to the aliphatic and aromatic methylprednisolone hemisuccinate drug, that ranges from 0 to 5 ppm and 5 to 7 ppm, respectively. The experiments give a clear correlation between the silicon species from the inorganic carriers (Q^2, Q^3, and Q^4 species) and the corticoid protons at 5–7 ppm. These signals could be assigned not only to the corticoid aromatic groups but also to the silica protons coming from either the adsorbed water or silanols groups, which distort the information to be extracted. Nevertheless, signals in the range 0–2 ppm, which certainly correspond to the aliphatic protons of the corticoid, are clearly correlated with the silicon species from the matrix. The strongest interactions, indicating more proximity between protons and the silicon nucleus, are found for hierarchical Beta zeolite, confirming the slowest release rate results obtained by this material in the delivery experiments. Hierarchical ZSM-5 zeolite also shows strong interactions, corroborating also the previous results. In addition, the presence of Al species, in tetrahedral positions, makes the zeolite more hydrophilic, increasing the electrostatic interactions between the zeolite silicon and aluminium nucleus with methylprednisolone hemisuccinate molecules. Regarding the ordered mesoporous materials, noticeable differences are established. Thus, the intensities of the drug aliphatic proton signals corresponding to 3-D cubic mesostructured SBA-16 are visibly stronger than those of the 2-D SBA-15 material, confirming again the results of the release experiments—that is, its slower delivery rate as consequence of the corticosteroid drug stronger adsorption with the distinct silicon Q^n species.

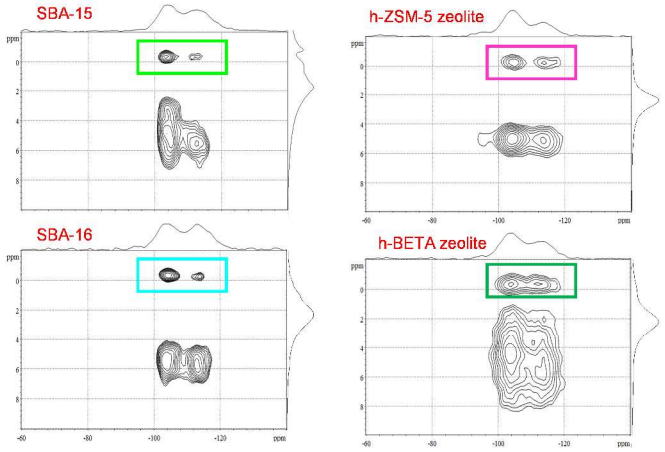


Figure 4. Solid-state ^{1}H-^{29}Si HETCOR NMR spectra of methylprednisolone hemisuccinate confined in mesoporous and hierarchical zeolitic materials and the corresponding ^{1}H and ^{29}Si projections

In order to better understand the release behaviour of methylprednisolone hemisuccinate from the carrier silica nanoparticles and establish the relationship between the pH and the adsorption capacity, experiments at different pH levels (7.4 and 4.6) were performed to study the corticoid release. The release percentage was plotted against the release time for the same samples included in the NMR study (SBA-15 and SBA-16 ordered mesoporous materials and h-ZSM-5 and h-BETA hierarchical zeolites), the results being shown in Figure 5. It demonstrates that the more acidic the pH is, a slower methylprednisolone hemisuccinate release is occurring. At neutral 7.4 pH, the sustained release starts at around 24 h, while at more acidic 4.6 pH, the release is delayed and takes up to 5–6 days to reach the continued release. Zeta-potential measurements (Table 1) show that the surface of all these adsorbates has an overall negative charge at the two tested pH. In addition, because of the carboxyl group's protonation, methylprednisolone hemisuccinate also becomes electronegatively charged in the studied pH range, as indicated in Table 1. Nevertheless, at lower pH, the electronegatively charged surface chemistry of the silica materials decreases; hence, more attraction forces between the drug and the materials walls are envisaged. At lower acidic pH, the total surface of the silica materials is more protonated, and therefore, the electrostatic interactions between the negatively charged methylprednisolone hemisuccinate carboxylic groups and the carrier are stronger.[32,33,34] This facilitates that the drug release slows down.

As displayed in Figure 5, there is a gradual slower methylprednisolone hemisuccinate release the more acidic the pH is, and thereby a better drug delivery control may be exerted. Therefore, a higher electrostatic attraction between the adsorbents and corticoid leads to an increase of adsorption affinity. Moreover, the difference between curve release profiles at the two pH levels is more pronounced for SBA-15 and SBA-16 materials than for hierarchical zeolites. The explanation for this result relies on the small zeta-potential divergence displayed by the hierarchical zeolites at the two studied pH, which is considerably lower than those exhibited by ordered mesoporous materials.

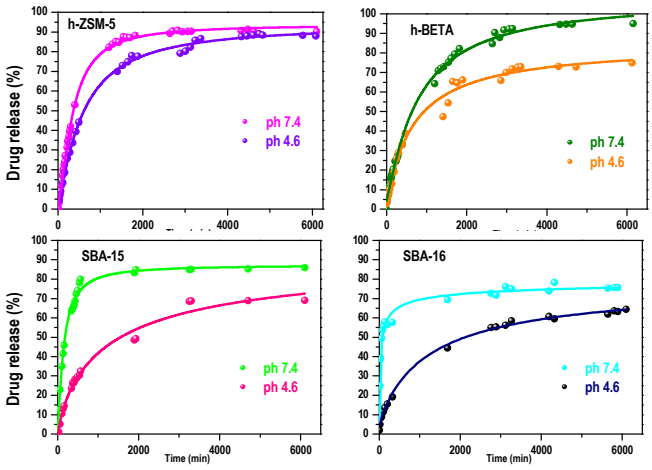


Figure 5. Methylprednisolone hemisuccinate release from different types of ordered mesoporous materials and hierarchical zeolite adsorbents, at 7.4 and 4.6 pH

Conclusions

The results here reported have demonstrated that the uptake of methylprednisolone hemisuccinate in mesoporous and hierarchical zeolites silica nanoparticles can be regulated by the different structural and textural properties of the ordered mesoporous materials and hierarchical zeolites used as supports. An adequate combination of surface area, pore diameter, pore volume, and cross channels is a key factor in designing effective drug delivery vehicles. Hierarchical Beta zeolite exhibits the lowest corticoid release rate in the early stages, as a consequence of the adjusted mesopore size diameter to the molecular dimension of the corticoid and also by its diffusion through the zeolitic micropores. These features increase the drug–surface carrier interaction, and therefore the higher drug adsorption of this material. The introduction of aluminium to substitute some of the silicon species in the framework can reduce the electronegatively charged drug surface, which constitutes an additional synergetic effect to retard the corticosteroid release. Among the ordered mesoporous materials, SBA-16 exhibits the slowest release rate, as a consequence of two combined factors: the pore size and the remarkable surface area. These results are the most favourable way of drug release in the particular rhinosinusitis application.

Solid-state ^{1}H-^{29}Si HETCOR NMR analyses confirm the previous results, showing the presence of stronger drug-surface interactions and, therefore, higher proximity between the drug and the silica silanol species, in the case of hierarchical Beta zeolite and 3-D cubic mesostructured SBA-16 materials. This observation confirms the lower release kinetic constant obtained by these materials in the drug delivery experiments, in the early stages, as consequence of the enhanced adsorption of the drug over the silica surface.

The experimental results show that slower corticoid release capacities are exhibited at lower pH values—therefore, the most favourable way of drug release in the particular rhinosinusitis application. Zeta-potential measurements prove that adsorption enhancement has direct connection with electrostatic interactions between methylprednisolone hemisuccinate molecules and the nanoparticles surface. As the pH decreases, a decline of the electronegative repulsions results in attraction between the methylprednisolone hemisuccinate molecules and the carrier surface. Consequently, the drug release rate slows down, with the results being more marked in the case of ordered mesostructured SBA-15 and SBA-16 materials.

Acknowledgements

The financial support of the Spanish government (CTQ2008-05909/PPQ and CTQ2011-22707) is gratefully acknowledged.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Materials synthesis, Structure of methylprednisolone hemisuccinate molecule, TEM images, XRD, N_2 adsorption isotherms and pore size distribution of materials, and Corticoid drug adsorption data on adsorbents]. See DOI: 10.1039/b000000x/

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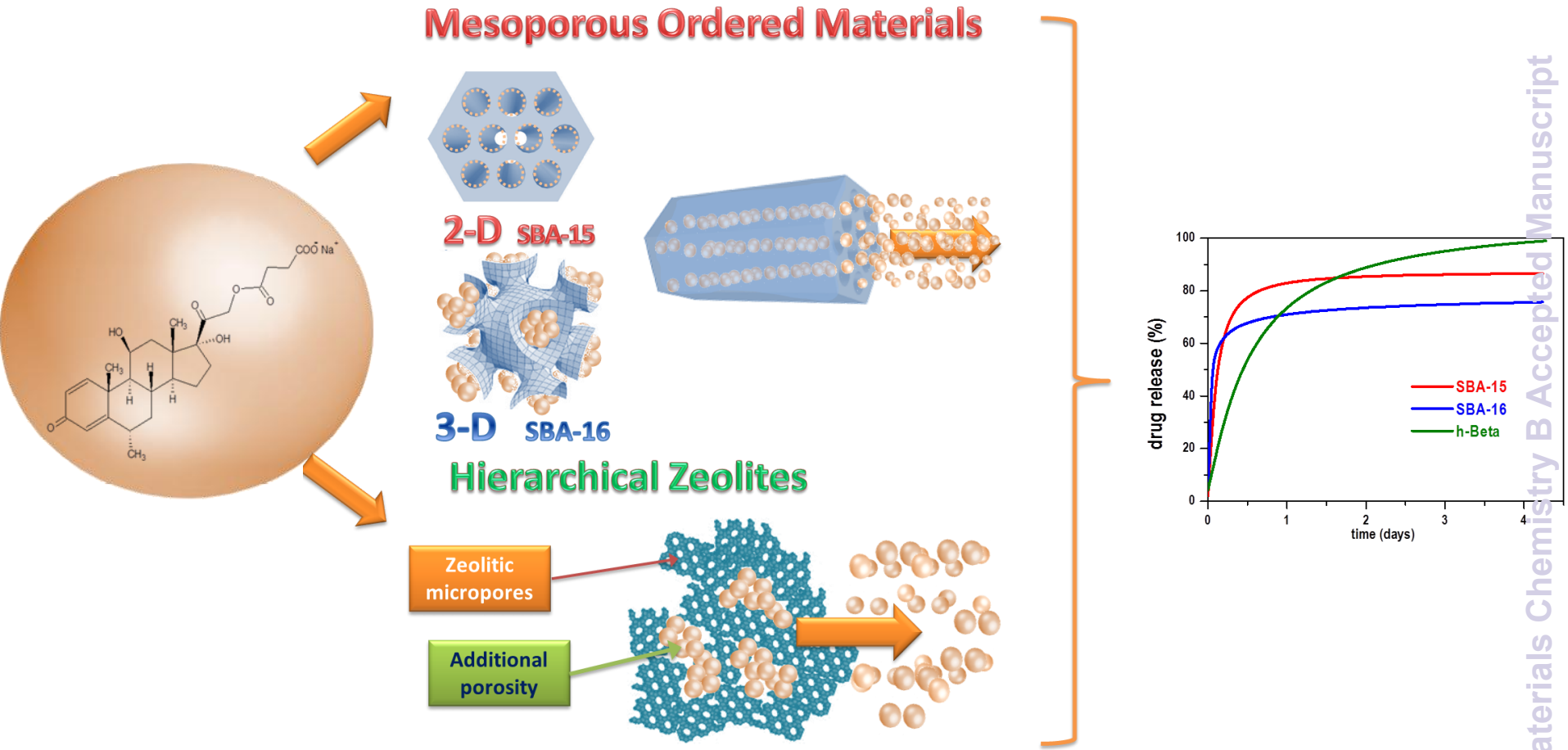

Influence of structural and textural properties of mesostructured siliceous and hierarchical zeolite materials in designing effective drug delivery vehicles