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Mesoporous silica material TUD-1 as a drug delivery system

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Abstract

For the first time the feasibility of siliceous mesoporous material TUD-1 (Technische Universiteit Delft) for drug delivery was studied. Model drug, ibuprofen, was adsorbed into TUD-1 mesopores via a soaking procedure. Characterizations with nitrogen adsorption, XRD, TG, HPLC and DSC demonstrated the successful inclusion of ibuprofen into TUD-1 host. The amount of ibuprofen adsorbed into the nanoreservoir of TUD-1 material was higher than reported for other mesoporous silica drug carriers (drug/carrier 49.5 wt.%). Drug release studies in vitro (HBSS buffer pH 5.5) demonstrated a fast and unrestricted liberation of ibuprofen, with 96% released at 210 min of the dissolution assay. The drug dissolution profile of TUD-1 material with the random, foam-like three-dimensional mesopore network and high accessibility to the dissolution medium was found to be much faster (kinetic constant $k = 10.7$) and more diffusion based (release constant $n = 0.64$) compared to a mesoporous MCM-41 material with smaller, unidirectional mesopore channels ($k = 4.7$, $n = 0.71$). Also, the mesoporous carriers were found to significantly increase the dissolution rate of ibuprofen, when compared to the pure crystalline form of the drug ($k = 0.6$, $n = 0.96$). TUD-1 was constituted as a potential drug delivery device with fast release property, with prospective applications in the formulation of poorly soluble drug compounds.

Keywords: Mesoporous silica TUD-1; Drug carrier; Drug loading; Drug delivery; Drug release

1. Introduction

Recently many reports have emerged on the application of synthetic mesoporous silica based materials as potential drug delivery systems. The tunable pore sizes in the mesopore range of 2–50 nm, high specific surface areas and large pore volumes of these materials provide interesting possibilities for the inclusion of molecules of therapeutic value. So far, the most often used mesoporous silica material based drug carrier has been the ordered hexagonal molecular sieve MCM-41, typically featuring large surface areas (>1000 m^2/g), high pore volumes (>0.7 cm^3/g) and a very uniform pore structure of unidirectional channels (pore diameter 2–3 nm) (Beck et al., 1992; Kresge et al., 1992b). MCM-41 has been applied with several different pharmaceutical compounds such as ibuprofen (Vallet-Regí et al., 2001; Babonneau et al., 2003; Muñoz et al., 2003; Andersson et al., 2004; Cavallaro et al., 2004; Charnay et al., 2004), vancomycin (Lai et al., 2003), model compound fluorescein (Fisher et al., 2003), diflunisal and naproxen (Cavallaro et al., 2004), hypocrellin A (Zhang et al., 2004), aspirin (Zeng et al., 2005) and for the inclusion of proteins with therapeutic use, such as cytochrome c and myoglobin (Deere et al., 2003). Fewer reports have emerged on the application of synthetic mesoporous silicas having interconnecting three-dimensional pore networks. One such reported silica material is the cubic ordered MCM-48 that has been applied for the immobilization of protein (Washmon-Kriel et al., 2000) as well as to the encapsulation of small molecule drugs (Izquierdo-Barba et al., 2005).

In the present paper, we report for the first time the application of a novel mesoporous silica material TUD-1 as a drug delivery vehicle. TUD-1 (Technische Universiteit Delft) is one of the new

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mesoporous materials (Jansen et al., 2001; Shan et al., 2005). The synthesis procedure of this mesoporous material is straightforward (one-pot) and cost-effective, because it is surfactant-free. TUD-1 is synthesized as siliceous, containing only biocompatible and biodegradable amorphous mesostructured silica. TUD-1 has a foam-like mesoporous structure, where the mesopores are randomly connected in three dimensions. The surface area of TUD-1 material typically lays in the 400–1000 m^2/g range, the pore volume varies from 0.5 up to 1.7 cm^3/g and the mesopore diameters can be tuned from 2.5 to 25 nm by varying the synthesis conditions (Jansen et al., 2001; Hamdy et al., 2005a,b; Shan et al., 2005). The novel random three-dimensional structure of TUD-1 gives rise to a high accessibility as well as interesting release characteristics for potential substrates of biological interest. Therefore, it was interesting to compare the drug release from the random mesoporous material TUD-1 and the ordered mesoporous material MCM-41, especially as to our knowledge, the comparison of the drug release characteristics of such materials has not been previously reported.

2. Experimental

2.1. Sample preparation

TUD-1 sample was synthesized by aging, drying, and calcining a homogeneous synthesis mixture consisting of a silicon alkoxide source such as tetraethyl orthosilicate (TEOS), and triethanolamine (TEA). In a typical synthesis procedure, a mixture of TEA (97%, ACROS) and H_2O was added dropwise into TEOS (98%, ACROS) while stirring. Finally, tetraethyl ammonium hydroxide (TEAOH, 35%, Aldrich) was added dropwise. After stirring for 2 h, a clear and pale yellow solution was obtained, with a molar ratio composition of $1SiO_2$:0.3TEAOH:1TEA:$11H_2O$. The mixture was aged at room temperature for 24 h, dried at 373 K for 24 h, hydrothermally treated in a stainless steel Teflon-lined autoclave for 4h, and then calcined at 873 K for 10 h. Synthesis of siliceous MCM-41 mesoporous molecular sieve was carried out in a 300 ml autoclave (Parr Instruments) using methods mentioned in references (Kresge et al., 1992a; Bernas et al., 2002) with some modifications. The reagents used in the synthesis were fumed silica (Aldrich), tetramethyl ammonium silicate (Sachem), sodium silicate (Merck), cetyltrimethyl ammonium bromide (Aldrich) and distilled water. A gel mixture was prepared and introduced in a 300 ml autoclave (Parr). The synthesis of MCM-41 was carried out in an oven at 373 K. After the completion of synthesis, the autoclave was quenched, and mesoporous material was filtered and washed with distilled water. Drying of the sample was carried out at 383 K for 12 h and calcination at 823 K for 10 h. The synthesized materials were ball milled and sieved to obtain microparticles with nominal size of <38 μm.

Ibuprofen (Sigma–Aldrich, USA) was selected as the model drug for loading into TUD-1 due to its suitable molecular size of 1.0 nm × 0.5 nm (Vallet-Regí et al., 2001) considering the pore diameter of both TUD-1 and MCM-41. Ibuprofen is a well-known non-steroidal anti-inflammatory drug (NSAID) with an analgesic property. Drug adsorption into the mesopores of TUD-1 (the procedure was similar for MCM-41) was realized via soaking the powdered mesoporous material in solution of ibuprofen and ethanol (concentration 700 mg/ml). Ethanol (99.5%, Primalco, Finland) was used as the loading solvent as it is safe, non-toxic and dissolves ibuprofen in large quantities. The carrier:drug ratio was 1:4.8 (w/w). The loading was performed in a closed container to prevent evaporation of ethanol for the total loading time of 20 h at ambient conditions, whereupon the sample was vacuum filtered through a teflon membrane filter with a 1 μm nominal pore size (Whatman Ltd., UK). The ibuprofen adsorbed on the exterior surfaces of the drug loaded microparticles was removed by washing the sample with 3 ml of ethanol. Finally, the sample was dried at 65 °C for 3 h.

2.2. Methods of sample characterization

Transmission electron microscopy (HR-TEM) was carried out on a CM30UT electron microscope (Philips, The Netherlands) with a field emission gun as the source of electrons operated at 300 kV. The XRD measurements were performed on a Bragg–Brentano $\theta/2\theta$ reflection geometry based PW1830/1820/1710 (Panalytical, The Netherlands) diffractometer using Ni filtered Cu Kα (40 kV/50 mA) radiation and $0.02^\circ\ s^{-1}$ step scan. The pore characteristics of the samples were studied using N_2 adsorption/desorption with TriStar 3000 gas adsorption analyzer (Micromeritics, USA) at 77 K. The samples were evacuated preceding the measurements using a VacPrep degasser (Micromeritics). The unloaded samples were evacuated at 250 °C for 23 h, while the ibuprofen loaded samples were evacuated for 23 h at room temperature. The pore characteristics were determined according to the BET and BJH theories from the adsorption branches of the isotherms. The density measurements were performed with He-pycnometry using AccuPyc 1330 apparatus (Micromeritics, USA). Thermogravimetric measurements were performed with a TGA-7 instrument (Perkin-Elmer, USA) with a heating rate of 10 °C/min under a N_2 gas purge of 40 ml/min. Differential scanning calorimetric analysis was carried out with a Pyris Diamond DSC (Perkin-Elmer) using a heating rate of 10 °C/min under a N_2 gas purge of 40 ml/min in 30 μl aluminum sample pans with pierced lids. The HPLC system (Waters Millennium, Milford, USA) consisted of a Waters 486 Tunable Absorbance Detector, a Waters 717 Plus Autosampler and a Waters 510 Pump. The mobile phase during determination of ibuprofen ($\lambda = 222$ nm, retention time = 5.6 min) consisted 50:50 of acetonitrile (Walkerburn, Scotland) and 0.03% phosphoric acid (Merck Darmstadt, Germany). A Bondapak C_{18} reversed-phase column (300 mm × 3.9 mm; 10 μm) with a C_{18} guard column (Waters, USA) was used with a flow rate of 2 ml/min. Injection volumes of 20 μl were used in all the experiments. Water was purified in an Alpha-Q water-purification system (Millipore, Molsheim, France). The total ibuprofen loads were determined by extracting 2 mg of the loaded microparticles in 10.0 ml of ethanol (99.5%) for 4 h with continuous magnetic stirring, after which the samples were filtrated and analysed by HPLC. Extracted drug loads were used as a basis for calculation of percentage-released in the dissolution experiments.

2.3. Drug dissolution and release rate experiments

Dissolution experiments were performed in buffered (10 mM MES/HEPES) Hank's balanced salt solution (HBSS) at pH 5.5 at +37 °C using orbital shaking (75 rpm). HBSS and HEPES solution were bought from Gibco Invitrogen Corp. (Life Technologies Ltd., Paisley, Scotland) and 2-(*N*-morpholino)-ethanesulfonic acid (MES) from Sigma–Aldrich (St. Louis, MO, USA). All of the dissolution experiments were performed under "sink conditions", meaning that amounts of compound determined in the acceptor compartment during individual sampling intervals did not exceed 10% of amounts in the donor compartment. Experiments were performed utilising Transwell cell culture inserts (polycarbonate membrane, pore size of 0.4 μm, area of 4.7 cm^2; Corning Costar Corp., Cambridge, MA, USA) and 6-well culture plates as donor and acceptor compartments, respectively. Amount of 2 mg of the ibuprofen loaded microparticles were weighed directly onto the filter inserts. Filter inserts (donor compartments) with ibuprofen loaded microparticles ($n = 3$) were placed on corresponding wells in a well plate (acceptor compartments), containing pre-warmed 2.75 ml HBSS/well and 1.5 ml of HBSS was added to the donor compartments. The samples were collected at several time points up to 210 min by moving the filter insert into a new well with fresh HBSS. At the end of the experiment, the content of the donor compartment was collected, absolute ethanol was added five times the volume of the donor to ensure the total dissolution of potentially remaining drug. The ibuprofen amount in the samples and the residual of the donor compartment were analysed by HPLC.

3. Results and discussion

3.1. Sample characterization

HR-TEM images of TUD-1 material (Fig. 1) showed a fully disordered (sponge-like) mesoporous structure characteristic for the material. The XRD pattern exhibited a single reflection with intensity maximum at 1.5° (2θ), indicating the meso-structured nature of the material (Fig. 2a). The result of the XRD and HR-TEM analysis were consistent, demonstrating the mesoporous property of TUD-1. The porosity of the samples were characterized by calculating the surface area, the total pore volume and the average pore diameter values from the nitrogen adsorption isotherms using the BET and BJH methods (Fig. 3; Table 1). The isotherms were typical type IV isotherms according to the IUPAC classification, characteristic for mesoporous materials, with the inflection of the capillary condensation observed at the p/p_0 values of 0.28 (MCM-41) and 0.72 (TUD-1) of the adsorption isotherms. The porosity-percentage was calculated from the measured density and the measured mesopore volume. Thermal analysis of TUD-1 material with DSC and TG did not exhibit any major thermal events, with only slight desorption of moisture from the sample detected under heating, indicative of the hydrophilic character. After ibuprofen loading the nitrogen sorption measurement of the sample clearly indicated a substantial pore filling of the mesoporous network of the microparticles (Fig. 3). The determined surface area and the total pore volume values (Table 1) dropped significantly (>90%) compared to the unloaded TUD-1 microparticles, reflected in the porosity of the material of only 6% after drug loading. The average pore size

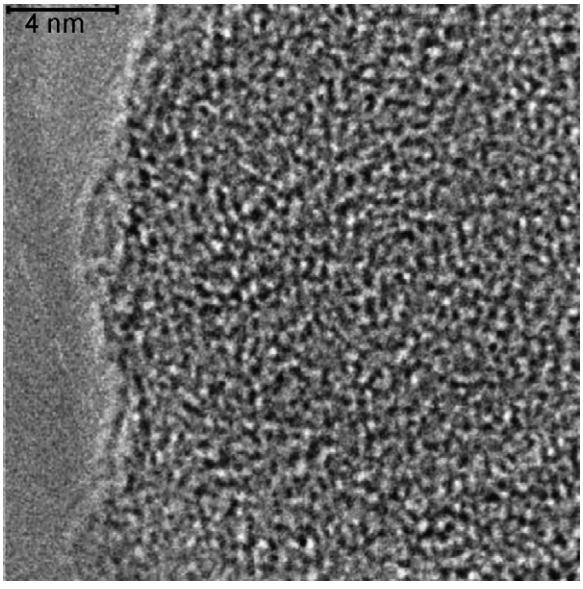

Fig. 1. HR-TEM image of mesoporous TUD-1 material.

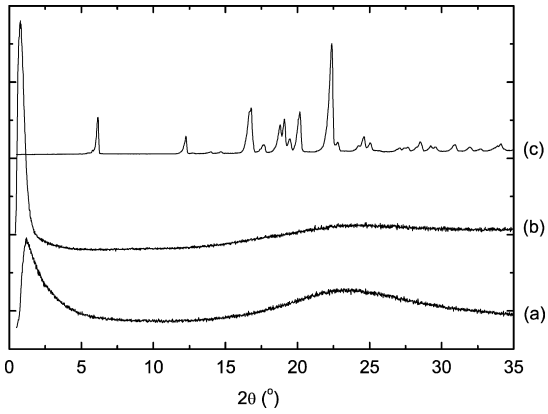

Fig. 2. XRD patterns for TUD-1 (a), ibuprofen loaded, washed TUD-1 (b) and ibuprofen, intensity scaled 1:10 (c).

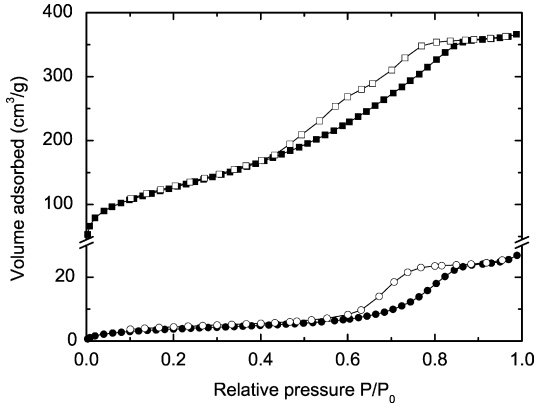

Fig. 3. N_2 adsorption/desorption isotherms for TUD-1 (■/□) and ibuprofen loaded non-washed TUD-1 (●/◯).

Table 1
Results of sample characterizations

Sample	TUD-1	TUD-1-ibu[a]	TUD-1-ibu[b]	MCM-41	MCM-41-ibu[b]
Surface area S_{BET} (m^2/g)	453	14	n/d	1063	n/d
Pore diameter D_{BJH} (nm)	4.9	9.9	n/d	2.6	n/d
Pore volume V_p (cm^3/g)	0.556	0.043	n/d	0.717	n/d
Density (g/cm^3)	2.30	1.49	2.04	2.55	n/d
Porosity (%)	56	6	n/d	65	n/d
Drug load ($wt.\%_{sample}$)[c,e]	–	33.1	19.6	–	20.8
Drug load ($wt.\%_{silica}$)[d,e]	–	49.5	24.4	–	26.6

[a] Before washing, maximum drug uptake.
[b] After washing, used in dissolution experiments.
[c] Drug loaded into the mesopores in relation to the total sample mass.
[d] Drug loaded into the mesopores in relation to the mass of carrier.
[e] Drug loaded into the mesopores quantified by combining TG/HPLC and DSC.

value increased due to the total filling of the smaller mesopores. The XRD pattern of the ibuprofen loaded TUD-1 exhibited the characteristic TUD-1 reflection at the low angle (Fig. 2b). Thus, no major degradation of the mesopore network of the TUD-1 microparticles had taken place during the drug loading. No peaks associated to the ibuprofen or other crystalline phases were detected.

3.2. Drug load quantification

The detection of crystalline ibuprofen in a loaded mesoporous sample can be associated to an unloaded, particle surface adsorbed drug portion (Charnay et al., 2004; Lehto et al., 2005; Salonen et al., 2005b). Thus, the absence of crystalline ibuprofen reflections in the XRD pattern of the loaded TUD-1 demonstrated that the washing had removed all of the surface loaded ibuprofen (Fig. 2b). The absence of crystalline ibuprofen was also confirmed with DSC. The ibuprofen load in the mesopores of TUD-1 was quantified using TG (Fig. 4) and HPLC with DSC according to the procedure introduced by Lehto and Salonen et al. (Lehto et al., 2005; Salonen et al., 2005a,b). The TG/HPLC analysis (mean value used) revealed a total ibuprofen loading of 45.6% for the ibuprofen loaded TUD-1 material before washing. After subtracting the surface loaded ibuprofen portion (quantified with DSC) from the total drug load, the actual amount of drug in the mesopores was found to be 33.1 wt.% (drug/total sample mass). It is noted that the achieved drug load value, corresponding to 49.5 wt.% of mass drug/carrier, is the highest ibuprofen load value reported for mesoporous silica drug carriers. The surface rinsed TUD-1 sample had a lower ibuprofen loading of 19.6 wt.% (Fig. 4b) because the surface rinsing also removed large portion of ibuprofen from the mesopores of the carrier in addition to the ibuprofen removed from the surface of the microparticles. The filled ibuprofen load and easy removal of drug indicated the high accessability of the TUD-1 mesopores, which was also evident in the subsequent drug release experiments.

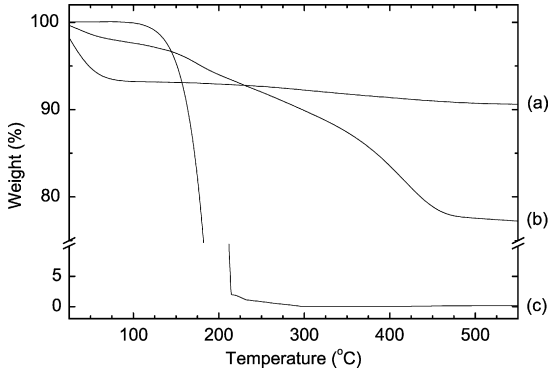

Fig. 4. Thermogravimetric curves for TUD-1 (a), ibuprofen loaded TUD-1, washed (b) and ibuprofen (c).

3.3. Drug release

The release of drugs from different mesoporous silica matrices has been found to be mainly diffusion controlled (Charnay et al., 2004; Andersson et al., 2004) modified by the same parameters as the drug adsorption process, i.e. the pore architecture (Andersson et al., 2004; Izquierdo-Barba et al., 2005) and the host–guest chemical interaction (Muñoz et al., 2003; Izquierdo-Barba et al., 2005), as well as the properties of the dissolution medium, such as pH (Cavallaro et al., 2004; Charnay et al., 2004; Salonen et al., 2005a), in combination with the dissolution properties of the loaded drug.

In the present study, the in vitro dissolution experiments were performed using Hank's Balanced Salt Solution buffer at pH 5.5 to mimic the conditions in the duodenum (beginning of the small intestine), which is one of the major sites of drug adsorption in the human gastro-intestinal tract for oral formulations. The dissolution profile of pure ibuprofen along with the ibuprofen release profiles from the TUD-1 and MCM-41 drug carriers are presented in Fig. 5. The drug loads of the samples used in the dissolution experiments were similar (TUD-1 19.6 wt.%, MCM-41 20.8 wt.%) and the total absence of the surface loaded drug was certified for both samples. No degradation of the loaded ibuprofen was detected according the HPLC analysis. The ibuprofen molecules were mainly weakly hydrogen bonded to the MCM-41 silica pore walls (Andersson et al., 2004), which was also assumed to be the case for the TUD-1 material as the composition of the material is the same, i.e. mesostructured amorphous silica. Therefore, the drug release from these materials was not

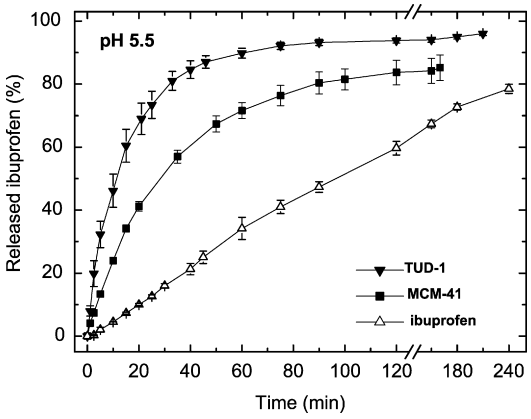

Fig. 5. Ibuprofen release from TUD-1, MCM-41 and the pure crystalline form at HBSS pH 5.5 medium.

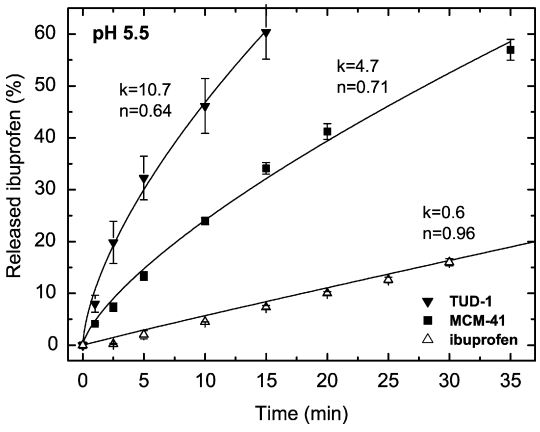

Fig. 6. The initial 60% of ibuprofen release at pH 5.5 fitted with the Korsmeyer–Peppas model $F = kt^n$.

expected to be differentiated by the chemical interaction of the ibuprofen molecules with the carrier but the different geometries of the mesopore networks.

The dissolution of ibuprofen is strongly affected by the pH of the dissolvent medium as it displays low aqueous solubility at acidic pH values below and close to its pK_a of 4.42 (Avdeef et al., 2000). Hence, the observed dissolution rate for the pure ibuprofen was quite low. The amount of dissolved ibuprofen in the HBSS buffer of pH 5.5 at typical sampling time of 45 min accumulated to 25%, while the release of 80% was not reached during the total experiment time of 240 min. Remarkably, the dissolution rate of ibuprofen released from the mesoporous carriers was approximately 2.5–3.5-fold faster (64–87% versus 25% release at 45 min of assay) compared to the dissolution rate of pure ibuprofen. The amount of dissolved ibuprofen in the HBSS buffer at typical sampling times of 20, 45 and 65 min accumulated to 68, 87 and 91% for TUD-1. Correspondingly, the amounts were 41, 64 and 73% for MCM-41. The required sampling time to reach 80% release from the TUD-1 material was 32 min, whereas the MCM-41 reached this level much later, at 89 min. The total amount of ibuprofen released at the end of the dissolution assay (160 min) was 94% for TUD-1, whereas MCM-41 reached a lower 85% release.

In order to compare the drug release characteristics of TUD-1 and MCM-41 the dissolution data was fitted with the Korsmeyer–Peppas equation

$$F = kt^n, \quad (1)$$

where F is the fractional release of drug, k the kinetic release constant incorporating structural and geometrical characteristics of the dosage form, t the elapsed time and n is the release exponent describing the drug release mechanism (Costa and Lobo, 2001). The release exponent $n = 0.5$ corresponds to a fully Fickian diffusion based transport of drug to the dissolution medium. In such case, the Korsmeyer–Peppas model would be reduced to the Higuchi equation $F = kt^{1/2}$, which has been previously found to describe the release of ibuprofen from different mesoporous silica carriers (Andersson et al., 2004; Izquierdo-Barba et al., 2005). The Korsmeyer–Peppas model fits to the ibuprofen release from the silica hosts and the pure ibuprofen are presented in Fig. 6. The model was found to describe the initial 60% ibuprofen release very well with high correlation coefficients ($R^2 > 0.99$) in all cases (as a short time approximation the Korsmeyer–Peppas model cannot be applied beyond the 60% release). The clearly faster release of ibuprofen from the TUD-1 carrier (kinetic constant $k = 10.7$) compared to MCM-41 ($k = 4.7$) demonstrated the unrestricted diffusion of the drug to the dissolution medium due to the high accessibility and stability of the TUD-1 mesopore network. The modelling of the dissolution curve of the pure crystalline form of ibuprofen confirmed the much slower release of drug ($k = 0.6$) compared to the mesoporous carriers.

The modelling of the Korsmeyer–Peppas exponent n revealed that the ibuprofen release mechanism of the TUD-1 material was more diffusion based ($n = 0.64$) than the MCM-41 material ($n = 0.71$). It was evident that the highly accessible nanoreservoir of the TUD-1 material provided a relatively unrestricted release of the drug, whereas the long and narrow mesopore pathways of the MCM-41 sterically hindered the free diffusion of ibuprofen from the mesopores. On the other hand, the dissolution mechanism of pure ibuprofen ($n = 0.96$) was close to a linear zero order type of release, typical for slow dissolving drugs. The results emphasized the improving effect of the mesoporous carriers on ibuprofen dissolution at the low pH conditions, where the dissolution of pure ibuprofen is otherwise slow.

4. Conclusions

The results of the study demonstrated the successful inclusion and then the release of a model API in the silica mesopores, realizing the potential property of TUD-1 as a drug delivery system for the first time. The highly accessible mesopore network allowed ibuprofen to adsorb into TUD-1 with very high efficiency and the amount of loaded drug exceeded the reported values for other biocompatible mesoporous silicas such as MCM-41 and MCM-48. The high drug uptake capacity of the TUD-1 nanoreservoir is an important property of the material as actual formulations (implants and tablets) are limited in volume. The drug release experiments in acidic dissolution medium mimick-

ing the conditions at the start of the small intestine demonstrated a rapid and close to a complete (96%) liberation of ibuprofen from TUD-1 host during 210 min, a realistic time frame considering the drug transit time of the small intestine (often cited as 200 min). Further, the TUD-1 host released the initial 60% of the drug very rapidly (15 min), which is ideal considering the very short compartmental drug transit time through the major drug adsorption window of the duodenum. The more restrictive pore characteristics of a typical MCM-41 material provided a much slower initial release of ibuprofen (60% release at 40 min), which may limit the bioavailability of the drug. Still, both of the mesoporous carriers released ibuprofen clearly faster than the pure form of the drug. The dissolution improvement was associated to the mesoporous carriers altering the solid state property of the loaded drug to the amorphous form, which typically dissolves faster compared to the crystalline form. The low pH conditions of the dissolution experiment were well suited to emphasize the improving effect provided by the mesoporous drug carriers to the dissolution profile of ibuprofen. In more neutral conditions ibuprofen is highly soluble by itself, thus the dissolution improvement offered by the mesoporous carriers is not expected to be as significant. However, considering practical applications the dissolution improvement evidenced at the low pH conditions mimicking the major drug absorption site in vivo is a very interesting property of the mesoporous drug carriers. Therefore, the high drug capacity and fast release kinetics present TUD-1 as a potential drug carrier for the formulation of poorly soluble drug compounds.

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