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ScienceDirect
International Journal of Pharmaceutics 343 (2007) 141–147
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Surface chemistry and pore size affect carrier properties of mesoporous silicon microparticles

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Received 31 January 2007; received in revised form 7 May 2007; accepted 9 May 2007
Available online 16 May 2007

Abstract

Six different types of mesoporous silicon microparticles were prepared to evaluate the effect of surface treatment and pore sizes on their properties as drug carriers. The studied porous silicon particles were as-anodized, thermally carbonized (TCPSi) and thermally oxidized (TOPSi) in addition to three novel ones: annealed TCPSi, annealed TOPSi and thermally hydrocarbonized porous silicon (THCPSi). Drug dissolution at pH 5.5 and physical and chemical stabilities after 3 months of storage were used as experimental models to investigate the loaded particles. Loading degrees of ibuprofen in the particles were determined by several methods before and after storage, and the results were in good agreement with each other. Loading improved the dissolution rate of ibuprofen in all the studied cases, while the hydrophilic TCPSi material resulted in the fastest dissolution and the most stable mesoporous microparticles. The release profiles of ibuprofen did not change markedly during storage. The effect of storage on the loading degrees of the other PSi microparticles than the unstable (easily oxidized) as-anodized porous silicon was not notable.

Keywords: Porous silicon; Microparticles; Carrier properties; Drug loading; Drug release; Surface treated silicon

1. Introduction

Porous silicon (PSi) in different forms, like particles and films, has been under extensive interest for its favorable properties in varied applications (Salonen et al., 2000a) ever since Canham (1990) revealed that PSi exhibits photoluminescence. The first approaches concerned mostly the light emitting properties of PSi (Fauchet et al., 1995) followed by interest in PSi usage as sensor material (Björkqvist et al., 2003) and in other technologies (Stewart and Buriak, 2000). Applications of porous silicon as a carrier of drugs have later emerged (Foraker et al., 2003; Salonen et al., 2005a; Vaccari et al., 2006), and different kinds of organic molecules have been loaded into ordered (meso)porous structures (Vallet-Regí et al., 2001; Anglin et al., 2004; DeLouise and Miller, 2005; Vallet-Regí, 2006).

When considered as drug carrier, the obtained degree of loading has been found to depend on the properties of both the microparticles and the loaded substances as well as on the loading solutions (Anglin et al., 2004; Salonen et al., 2005a; Vallet-Regí, 2006). These properties have an effect also on the rate of dissolution of the molecules out of the particles as well as on the possible dissolution and stability of the supporting matrix. It has been shown that PSi as such, without any chemical modifications on its surface is not stable even at room temperature (Salonen et al., 1997). This has lead to the development of different stabilizing surface treatments (Stewart and Buriak, 2000; Björkqvist et al., 2003; Salonen et al., 2004; Schwartz et al., 2005). By selecting a proper treatment also the hydrophobicity/-philicity of the particles can be modified, which in turn has an effect on what kind of materials best match the pores. The specific carrier properties may also be modulated through the pore size of the PSi, as its potential utility as dissolution enhancing carrier is based on the assumption that the confined space of the

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doi:10.1016/j.ijpharm.2007.05.010

pores prevents crystallization of the loaded drug (Salonen et al., 2005a).

The objective of this work was to study the effects of surface chemistry and pore size (surface area and pore volume) on the carrier properties of mesoporous silicon microparticles. These characteristics include properties like the attainable loading degree, dissolution, and stability of the loaded substance. Differences in the stabilization methods of the particle surface may have a significant effect on the process and outcome of drug loading, as indicated by earlier results (Salonen et al., 2005a). In this study, the effect of surface treatment and pore size of PSi on the drug release and stability was studied by preparing pairs of particle types with a difference either in the surface treatment or pore size. Ibuprofen was chosen as a model compound because of its relatively poor aqueous solubility, and the novel mesoporous silicon microparticles were introduced as potential dissolution enhancer candidates. The dissolution of ibuprofen was studied in a buffer solution at pH 5.5, which was selected according to the previous results showing that the impact of loading into mesoporous silicon microparticles on ibuprofen dissolution was the highest at that pH (Salonen et al., 2005a). Several physical methods and HPLC assay of extracted samples were used to determine the loading degree immediately after preparation and after 3 months of storage at 30 °C. Dissolution behaviour of ibuprofen from the loaded particles was also studied after the storage.

2. Materials and methods

2.1. Materials

Silicon wafers Si (1 0 0), of p^+-type with resistivity values of 0.015–0.025 Ω were used in the preparation of porous silicon (PSi). The PSi was prepared by anodizing the wafers in an HF (38%)–ethanol mixture (HF:EtOH, 1:1); the process was performed in darkness. A current density of 50 mA/cm^2 was used to obtain a porosity of about 60%. Free-standing films were obtained by abruptly increasing the current. Ibuprofen was purchased from Sigma–Aldrich and used as received. Pure ibuprofen used in dissolution experiments as a standard was sieved with a 400 mesh sieve to obtain particle size <38 μm to correspond with the size distribution of the used silicon microparticles.

2.2. Production and loading of porous silicon microparticles

Porous silicon (PSi) microparticles of four different surface chemistries were studied: as-anodized PSi (Si–H_x termination), thermally carbonized PSi (TCPSi), thermally hydrocarbonized PSi (THCPSi) and thermally oxidized PSi (TOPSi) were prepared as described earlier (Salonen et al., 2004, 2005a). As-anodized microparticles were obtained by ball-milling the free-standing porous silicon films and sieving with a 400 mesh sieve to obtain particles <38 μm. Prior to further surface treatment, annealing of the as-anodized PSi was used to obtain batches of carbonized (annTCPSi) and oxidized (annTOPSi) particles of different pore sizes. Treatment of PSi at high temperature in inert atmosphere (N_2) leads to pore coalescence, and this can be used to increase the pore size (Björkqvist et al., 2006). In this study, treatment at 820 °C increased the average pore size of the as-anodized PSi from 12.9 nm to about 43 nm.

Before the surface was carbonized to obtain TCPSi, annTCPSi or THCPSi, the microparticles were treated with the 1:1 HF:EtOH solution to replace the oxidized surface formed during milling (hydrogen termination). A Teflon membrane filter of pore size 1 μm (Whatman Ltd.) was used to filter the pre-treated microparticles from the HF:EtOH solution. After that, a two-step thermal carbonization process was used to form a stabilizing SiC-terminated surface on the particles (TCPSi). THCPSi particles were prepared with continuous acetylene flush and at lower temperature than the carbonization for TCPSi. In THCPSi, there are some hydrogen atoms left on the surface (Salonen et al., 2004), while the TCPSi surface is completely free of hydrogen and, thus, hydrophilic. Thermal oxidation does not require the previously described hydrogenating process with HF:EtOH solution. Instead, thermal oxidation was performed directly after the sieving and annealing processes to obtain TOPSi and annTOPSi particles, respectively.

Drug loading was performed at room temperature using ibuprofen in EtOH at 800 mg/ml. The microparticles (100–150 mg) were closed for 1 h in 3 ml glass ampoules with 1–1.5 ml of loading solution, which was occasionally stirred during loading. After the loading, the microparticles were vacuum filtered from the solution using pre-described Teflon membrane filters. Solvent was removed by drying the microparticles on the membrane filters in a constant temperature oven for 1 h at 65 °C. Quantification of drug load was performed as soon as possible after the loading, and is expressed as $m_{drug}/(m_{drug} + m_{particle}) \times 100\%$. A part of the prepared batches of the loaded particles were stored (30 °C, 56% relative humidity) for 3 months, after which the loading degrees were determined again (no further treatments on the particles) by both physical and chemical (HPLC) methods.

2.3. Physical characterization of the microparticles and determination of drug load

The samples were characterized utilizing thermogravimetry (TG; TGA 7, PerkinElmer, 10 °C/min, N_2 gas purge), differential scanning calorimetry (DSC; Pyris Diamond DSC, PerkinElmer, 2 °C/min, N_2 gas purge), helium pycnometry (AccuPyc 1330, Micromeritics) and N_2 ad/desorption studies (TriStar 3000, Micromeritics). The pore size values were calculated utilizing BET and BJH theories. Details and rationale on the use of TG, DSC, He pycnometry and N_2 ad/desorption to determine drug loadings have been reported previously (Lehto et al., 2005; Salonen et al., 2005a,b). FTIR studies were carried out using a Spectrum BX II (PerkinElmer) with a horizontal ATR accessory (MIRacle, Pike Technology, Inc.). The resolution was 4 cm^{-1} in all the measurements. The total drug load was also determined by HPLC from extracted samples according to Ref. (Salonen et al., 2005a). These drug load values were

used as a basis for the calculation of % released of ibuprofen in the dissolution experiments.

2.4. Dissolution experiments

The dissolution experiments of the fresh and for the 3 months stored ibuprofen loaded mesoporous silicon microparticles were performed in buffered (10 mM MES) Hanks balanced salt solution (HBSS) at pH 5.5 at +37 °C with orbital shaking of 75 rpm. Transwell® cell culture inserts (polycarbonate membrane, pore size of 0.4 μm, 4.7 cm^2 area; Corning Costar Corp., Cambridge, MA, USA) and six-well plates were utilized as donor and acceptor compartments, respectively. The protocol of the dissolution experiments has been described earlier (Salonen et al., 2005a). All the experiments were performed at least in triplicate ($n = 3$–6) over 150 min, and performed under thermodynamical sink conditions in terms of solubility. The samples were analyzed by HPLC to determine the cumulative amount of ibuprofen released versus time. Dissolution of the sieved (<38 μm) ibuprofen at pH 5.5 was used as an external control to PSi loaded ibuprofen.

2.5. HPLC analysis

Ibuprofen concentrations in the samples were analyzed by HPLC (Waters Millennium, Milford, USA) using a Waters 486 Tunable Absorbance Detector, a Waters 717 Plus Autosampler, and a Waters 510 pump. The mobile phase during determination ($\lambda = 222$ nm, retention time 6.3 min) consisted of acetonitrile and 0.03% phosphoric acid (50:50). A μBondapak C18 reversed-phase column (300 mm × 3.9 mm; 10 μm) with a μBondapak C18 guard column (Waters, USA) was used with a flow rate of 2 ml/min and samples were injected using 20 μl injection volumes.

3. Results and discussion

Dissolution of the sieved (<38 μm) ibuprofen at pH 5.5 was used as an external control in all the experiments. Loading into the mesoporous PSi microparticles clearly improved the dissolution rate of ibuprofen in all the cases (see the chapters below). Because of the small pore size (Table 1), ibuprofen maintains the non-crystalline form inside the pores and, thus, dissolves faster. Also, the high surface area of the particles (Table 1) enhances the dissolution rate of poorly soluble compounds like ibuprofen.

Table 1
Surface area (A_s), pore diameter (d_p) and pore volume (V_p) of microparticles

	A_s, (m^2/g)	d_p (nm)	V_p (cm^3/g)
as-anodized	253.5	12.9	1.33
TCPS1	246.2	15.1	0.956
AnnTCPSi	58.9	46.5	0.631
TOPSi	222.4	8.53	0.624
AnnTOPSl	71.5	40.7	0.671

3.1. Properties of the mesoporous silicon microparticles

Six batches of differently treated silicon microparticles were compared. Three of them are novel, presenting treatments that have not been introduced in the context of drug carriers before. The particles varied in their surface chemistry, pore volume, pore area and pore diameter (Table 1). Due to the native oxidation, the as-anodized particles contained hydrophobic, easily oxidizing hydrogen atoms on the surface (Salonen et al., 1997). They have the largest pore volume and area of all the studied particles (Table 1). TCPSi and TOPSi particles have a hydrophilic surface, which in the TCPSi is chemically more stable than in the as-anodized PSi or TOPSi (Salonen et al., 2000b, 2002). This property makes the TCPSi a preferred PSi-type for drug loading (hypothesis). Annealing results in larger pores in the particles, but at the same time, it melts some pores together in the process of coarsening and, thus, result in a smaller overall pore volume (Table 1). For small molecules the pores of the annealed particles may even be too large if fast release of the amorphous drug is the desired effect. The larger pores may enable ibuprofen crystallization, although the diffusion of drug molecule is faster in the larger pores, which might lead to slower release rates. The optimal pore size would be the largest possible still preventing the crystallization of the loaded drug.

On the other hand, the annealed particles may provide an ideal carrier material for larger molecules. Because annealing is performed before the surface treatment, it does not affect the hydrophilic properties of the particles. When this treatment was done before the thermal carbonizing and thermal oxidizing, novel PSi types were attained, which give the loaded substance more space to get ordered in the pores while the total pore volume remains nearly the same or lower than that of the un-annealed counterpart (Table 1). A major difference between the prepared two pairs of particles is that the pore volume of TCPSi is about 1.5 times that of the annealed one, while annealing of TOPSi on the contrary increased the pore volume mariginally (8%).

The third novel PSi particle introduced in this paper, THCPSi, is more hydrophobic than TCPSi because of the hydrogen atoms left on the surface. Thermally hydrocarbonized particles were difficult to handle: they did not wet properly and generated electrical charges that caused adherence to preparation vessels and weighing instruments. Because of these properties and inconsistent dissolution behavior of the THCPSi particles loaded with ibuprofen, only preliminary experiments and measurements were performed with THCPSi. The hydrophobicity of THCPSi, as well as of the as-anodized PSi particles, was revealed in practice when the aqueous buffer solution was added on top of them in the dissolution experiments. Due to the poor wetting properties, most of the particles floated on the surface of the liquid. All the other particle types wetted immediately and were easy to handle.

3.2. Loading degrees

In addition to the extraction method (analysis by HPLC), the total drug load was also determined by several physical methods in order to obtain information on both the loading degree and

Table 2
Extent of drug loading (%, w/w) determined from different PSi microparticles before and after storage utilizing different methods

Particle	TG[a]	TG[b]	DSC[a,c]	DSC[b,c]	Pycnometry[a]	HPLC[a]	HPLC[b]	Average load[a,d] ±S.D.	Theoretical max load[e]	Theoretical max load[f]
as-anodized PSi	33.2	34.7	0.2	0.2	31.5	40.7	29.7	36.8 ± 4.8	51.6	59.8
TCPSi	34.7	33.1	0.1	0.4	27.6	30.3	31.9	30.9 ± 3.6	43.3	51.7
AnnTCPSi	41.3	43.8	u	u	38.5	38.9	38.1	39.6 ± 1.5	33.5	41.4
TOPSi	33.8	36.8	6.9	10.5	38.2	37.6	31.6	36.5 ± 2.4	33.3	41.1
AnnTOPSi	34.2	34.1	u	u	29.6	28.8	29.9	30.9 ± 2.9	34.9	42.9
THCPSi	32.9	–	3.6	–	–	30.9	–	31.9	–	–

u, unclear melting peaks; –, not detected.
[a] Before storage.
[b] After storage.
[c] Crystalling substance found on the surface of the microparticles.
[d] Average load is a mean value of TG, pycnometry and HPLC results.
[e] Theoretical maximum load, when pores are filled with loading solution 800 mg/ml.
[f] Theoretical maximum load = $(V_p \times \rho$ ibuprofen$)/(1\ g + V_p \times \rho$ ibuprofen); ρ ibuprofen = 1.118 g cm^{-3}.

physical state of the loaded ibuprofen (Table 2). After storing the particles, the degree of drug load was again measured by TG, DSC and HPLC. For the annealed particles, the overlapping of ibuprofen melting peaks in the heat flow curves made the interpreting of the DSC measurements impossible. The other results were in good agreement with each other, even though there were some differences between the results determined by different methods, the basis of which has been discussed in previous papers (e.g. Salonen et al., 2005a). Theoretical maximum load of ibuprofen inside the particles was determined by two methods based on pore volume: (1) by calculating how much ibuprofen would go into the pores by simply filling the pores with the loading solution (800 mg/ml ibuprofen) and (2) by utilizing the density of crystalline ibuprofen. The latter presents the highest possible theoretical maximum load and overestimates the real situation with the density of crystalline ibuprofen versus the density of amorphous ibuprofen inside the pores.

The average load obtained in annTCPSi and TOPSi particles was even higher than the theoretical maximum load when the pores are filled with loading solution (Table 2). This suggests that annTCPSi and TOPSi particles attract ibuprofen to accumulate inside the pores of the particles instead of the loading solution. A similar phenomenon has previously been observed when griseofulvin was loaded into TCPSi particles from an ethanol loading solution (Salonen et al., 2005a). This type of behavior would diminish the need of high concentrations in the loading solution and would therefore be highly desirable. The loading degree of all the particles is at least 60% of the highest possible theoretical maximum load.

Storage affected most the loading degree of the as-anodized PSi, which decreased from 40.7% to 29.7% (quantified by HPLC) in extracted samples. To clarify the origin of the decreased drug load, ibuprofen was extracted from the pores after the storage to obtain drug-free empty particles, which were thereafter measured with FTIR. A clear evidence of oxidation of the as-anodized PSi could be observed in the FTIR spectra measured after the ibuprofen extraction compared to those obtained before the loading (Fig. 1). A strong broad peak above 1000 cm^{-1} arisen after the storage verifies the growth of oxide on the surface. Also, the decrease of the three Si–Hx peaks above 2000 cm^{-1} indicates oxidation. In addition to the reduction of the pore size, the pore wall oxidation could cause degradation of the loaded ibuprofen (Caviglioli et al., 2002), although this was not seen in the HPLC-chromatograms of this study. Although no traces of ibuprofen reacted with the as-anodized PSi could be found in the FTIR spectra of the particles, the loaded ibuprofen had most likely oxidized the pore walls and degraded to some extent by the reaction. However, as a range of different end products may result from the ibuprofen oxidation (Caviglioli et al., 2002), the individual concentrations may be too low to be discerned in the FTIR data. The other five particle types were measured likewise with FTIR, and no traces of changes in any materials (PSi particles, ibuprofen) were detected.

The effect of storage on the overall loading degrees of the other PSi microparticles was not notable. Interestingly, the crystallized substance found on the surface of TOPSi particles increased 3.6% units during the storage, while there was practically no change in the amount of crystallized ibuprofen in the case of TCPSi. The effect could not be observed in the annTOPSi due to the above-mentioned problems in the interpretation of DSC curves, but the phenomenon may be due to the better chemical stability of TCPSi compared to TOPSi, as

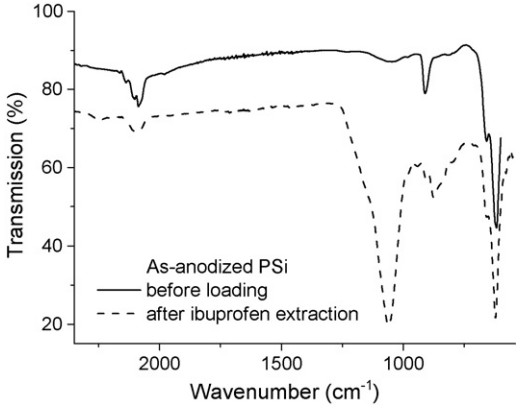

Fig. 1. FTIR spectra of the as-anodized PSi measured before the loading (solid) and after the ibuprofen extraction done after storage (3 months, +30 °C, RH 56%; dashed).

discussed in chapter 3.1. The total amount of ibuprofen determined with HPLC was slightly decreased in the case of TOPSi during the storage. Although the thermally oxidized surface is more stable than the as-anodized hydrogen terminated surface, it has been found to be chemically reactive in certain chemical environments (Salonen et al., 2007).

3.3. PSi particles as dissolution enhancing carriers

Dissolution from all the used silicon microparticles was faster than that of the unloaded ibuprofen at pH 5.5 (Fig. 2). Thermally carbonized particles (TCPSi) resulted in a markedly faster dissolution of ibuprofen than the other silicon microparticles used. At pH 5.5, the slope of the ibuprofen dissolution from the TCPSi was 2.8 times that of the free ibuprofen (Table 3). The small pore size of TCPSi particles, which leads to a decreased level of order of ibuprofen molecules, and the stabilizing surface treatment could both affect positively the dissolution of ibuprofen. It is known that disordered/amorphous material dissolves faster than its crystalline counterpart (Hancock and Parks, 2000). In addition, the hydrophilic TCPSi particles resulted in the most reproducible results, which further increases their value as a conceivable drug delivery vehicle. It has been shown previously (Salonen et al., 2005a) that loading into TCPSi particles diminishes also the pH dependency of ibuprofen dissolution rate. As compared to the other particles, the pore volume of TCPSi is 70% of the as-anodized PSi, and since the surface is hydrophilic, the interior of the particle wets more easily compared to the as-anodized PSi with larger pore volume but slower dissolution rate. TOPSi is also hydrophilic like TCPSi, but higher proportion of the ibuprofen loaded into TOPSi resides in crystalline form on the particle surface than in the case of TCPSi. Thus, the effects of poor wetting and higher portion of ibuprofen on the external surface of the loaded particles results in the attenuated dissolution properties, but also the physical state of the structure of ibuprofen inside the particles is a major factor affecting the dissolution rate.

Table 3
Slope of the first 30 min dissolution of ibuprofen before and after storage ± S.D. at pH 5.5

	Before	After
Free	0.44 ± 0.12	–
as-anodized	0.90 ± 0.23	0.84 ± 0.07
TCPSi	1.24 ± 0.05	0.93 ± 0.24
AnnTCPSi	0.58 ± 0.05	0.30 ± 0.08
TOPSi	0.77 ± 0.03	0.63 ± 0.06
AnnTOPSi	0.79 ± 0.06	0.76 ± 0.13

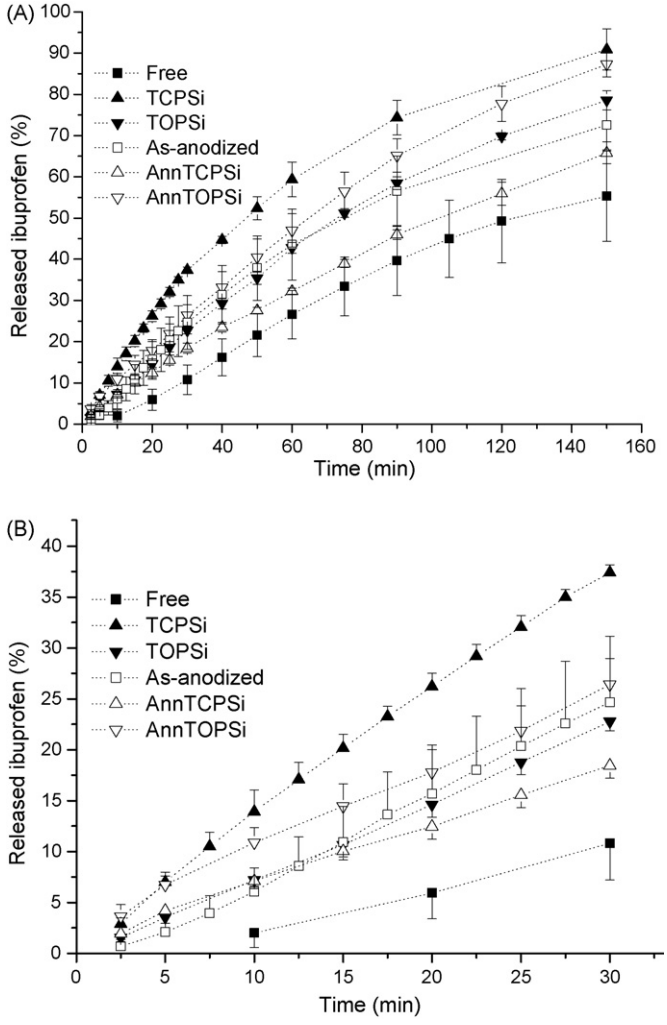

Fig. 2. Dissolution profiles of loaded and unloaded (free) ibuprofen in HBSS at pH 5.5, + 37 °C (A) before storage (n = 3–6, mean ± S.D.) and (B) enlargement of the first 30 min.

When the effect of pore size on ibuprofen dissolution was studied, two pairs of particles were compared. The particles of each pair had the same surface treatment, i.e. thermal carbonization or thermal oxidation, but different pore dimensions (Table 1). Annealing the samples before the surface treatment resulted in threefold to fivefold changes in the pore diameters and surface areas, so that in the annealed samples the diameters were larger and the areas smaller than in the un-annealed particles. Interestingly, the pore volume of TCPSi was 1.5 times the volume of the annealed one, while the volume of TOPSi was even slightly smaller than that of the annealed one. When TCPSi, TOPSi and their annealed counterparts were compared, it seemed that not only the pore size affected the release rate but also the surface chemistry had a role in it. Although TCPSi showed the fastest release rate of all the studied particles (Fig. 2), ibuprofen release was clearly slower in the case of annTCPSi. In annTOPSi the pore size is quite close to that of annTCPSi, but instead of slower release rate, annTOPSi showed faster release rates compared to TOPSi. Although the pore sizes in TCPSi and TOPSi were different, this indicates clearly that the surface chemistry affects the release rate. Based on the previous DSC measurements, the oxidized PSi surface has been found to prevent the crystallization of loaded ibuprofen better than the carbonized surface. In the DSC measurements, a larger portion of crystallized ibuprofen has been detected from TCPSi than from TOPSi particles with the same pore sizes. Obviously this is affecting the release rate too. If the crystalline portion was clearly larger in annTCPSi than in annTOPSi, the release rate

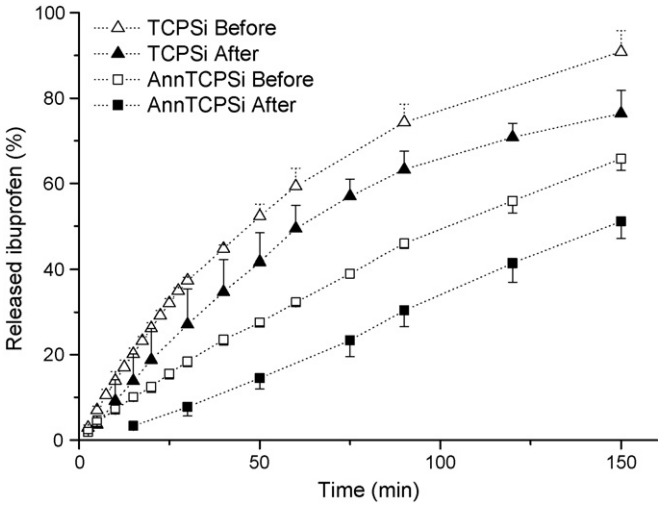

Fig. 3. Dissolution profiles of ibuprofen loaded into AnnTCPSi and TCPSi before (open symbols) and after (solid symbols) storage (3 months, +30 °C, RH 56%) in HBSS at pH 5.5, +37 °C ($n = 3$, mean ± S.D.).

would be slower from annTCPSi. But, if the crystalline portion remains similar, the fastest release rate would be obtained from the particles with the largest pores. This rationale also explains why the annTOPSi showed a faster release rate than TOPSi.

The hydrophobic particles, as-anodized PSi and THCPSi, resulted in the largest variability of the dissolution profiles. This is possibly due to unequal wetting of the inner parts of the particles, which results in unequal release rate of the ibuprofen out of the particle. Due to the erratic dissolution behavior of THCPSi-loaded ibuprofen as well as problems in repeatability due to the difficulties in handling and wetting, THCPSi results have not been presented in the figures. Due to these poor carrier properties, THCPSi was also excluded from the characterization and dissolution experiments after storage.

Comparison of the degrees of drug loading before and after the 3-month storage (Table 3) showed that the amount of ibuprofen in the particles was not remarkably changed due to the storage, with the exception of as-anodized PSi (see Section 3.2). The differences between ibuprofen dissolution from the differently treated PSi particles were not as clear as before storage, but the release rate from the TCPSi was still the fastest. After storage, the slope of the ibuprofen dissolution from the TCPSi was 2.1 times that of the free ibuprofen (Table 3). Some differences can be seen when the release curves from TCPSi and annTCPSi particles are compared before and after storage (Fig. 3). AnnTCPSi produced the largest change in dissolution before and after storage, although the particles still remained quite stable during the experiments. The other three particle types produced TCPSi-like changes in the release rates before and after storage. Overall, the ability of the PSi particles to improve dissolution remains also after storage and no evidence of chemical changes of ibuprofen were observed during the 3 months in the pores of surface treated PSi microparticles. This is a very important feature when considering the delivery of poorly soluble drugs with PSi carriers.

4. Conclusions

Loading and release properties of the studied untreated, as-anodized porous silicon and the thermally carbonized or oxidized PSi as well as their annealed counterparts show that surface chemistry and pore size affect the dissolution enhancing properties and stability of these particles. Of the surface treated particles, the ability of TCPSi microparticles to improve the dissolution of ibuprofen was the highest and the enhancement effect was maintained after the 3 months storage at 30 °C. As-anodized PSi was found unsuitable for drug delivery purposes due to its instability (oxidation). In the future, more experiments are needed to find out what kind of drugs and particles make the best combinations; whether the aim is to control (sustain) or improve (fasten) the dissolution rate of drugs.

Acknowledgements

The authors thank Ms. E. Piitulainen for technical assistance with HPLC analyses. Financial support was provided by the Academy of Finland (Grant 211048, HUMALA).

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