CHAPTER 6

Mesoporous Silica: An Alternative Diffusion Controlled Drug Delivery System

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Summary

Mesoscopically ordered mesoporous silica materials have attracted a wide interest since their discovery in the early 1990's due to their diverse potential applications areas; including catalysis, filtration and chromatography. Supramolecular surfactant aggregates are used as structure directing agents for inorganics during condensation, leading to mesoscopically ordered surfactant-inorganic composites. Porosity can be induced in the inorganic part by removal of the surfactant portion through thermal or chemical means. By controlling the synthesis conditions and choice of structure directing agents, the system can be engineered to fit numerous functions of preference. As the purely siliceous mesoporous materials have been shown to be biocompatible, or sometimes even bioactive, there is an increasing interest in this class of materials for applications in the field of bioceramics, especially as bone substitute materials. Furthermore, the highly organized porous silica matrix could be used as a potential controlled drug release system. Another attractive advantage is that amorphous silica is degradable in an aqueous solution, and thus problems related to the removal of the material after use can be avoided. In this article, a few of the most common forms of drug delivery mechanism from ceramic drug carrier systems are investigated. Furthermore, some examples are given on different mesoporous silica systems as drug delivery devices and how factors such as pore size, pore connectivity and surface affect the drug loading and the release (diffusion) rate.

KEYWORDS: bioceramics', mesoporous silica, drug delivery, ibuprofen, silica, diffusion controlled

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INTRODUCTION

During the last decades a diversity of polymer based pharmaceutical carrier systems have been developed as new means of controlling temporal or distributional (site-specific) drug delivery (1). Pharmaceutical controlling delivery systems offer numerous advantages compared to conventionally administrated drugs in dosage forms, such as improved efficiency and reduced toxicity (1). Conventional dosage forms have the disadvantage not to be able to control either the rate of drug delivery or the target area of drug administration and provide a rapid and an immediate drug release. Thus, frequent administration is necessary in order to maintain a therapeutic level, which in turn causes drug concentration in blood and tissues to fluctuate widely.

Polymeric cross-linked carrier matrices, such as hydrogels and supra-molecular polymer aggregates as well as different types of microencapsulation vehicles, are typical examples of common drug delivery devices (1-4). Controlled release systems are generally classified based on their physicochemical, pharmaceutical or clinical aspect. They can also be classified according to their release mechanism and preparation methods as follows (5):

- Physical systems, including diffusion controlled systems such as monolithic porous systems and biodegradable/bioerodable systems.
- Chemical systems, including immobilization of drugs.
- Biological systems, including gene therapy

Depending on the delivery system and the pharmaceutical in use, different release mechanisms are applied. However, there are three primary ways by which active agents can be released from such system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the system (a ceramic or polymer based matrix) that forms the controlled-release device. The diffusion can occur on a macroscopic scale—as through pores in the matrix—or on a molecular level, by passing between, for instance, polymer chains. The diffusion controlled release could be activated by several means, including ionic strength, pH and thermal, magnetic or chemical changes. Controlled release based on an eroding matrix (surface or bulk) allow diffusion of drug from the degrading system (5).

Temporal or distributional drug delivery could be beneficial when handling numerous classes of dugs, such as anti-inflammatory agents, antibiotics, chemotherapeutic drugs, steroids, hormones and vaccines, to mention a few (5,6). The ability to control over the drug delivery can be an important factor especially at times when traditional oral or injectable drug formulations are difficult to distribute. In some cases there might be a need of a slow release of a water soluble drug or a fast release of low-solubility drugs. It might also be convenient for drug delivery to specific sites, drug delivery using nanoparticulate systems, delivery of two or more agents with the same formulation, and also systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system should be inert or biodegradable, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.

MULTIFUNCTIONAL DRUG DELIVERY DEVICES - CERAMICS

The carrier system controlling the release of an active agent does not necessarily remain inert to the conditions surrounding the device. An active carrier system can sometimes be a part of an additional treatment in terms of contribution to the healing of the surrounding environment (tissue). In this category we find bioactive devices such as certain bone substitute materials used in the form of implants (screws, nails, plates etc.), fillers (beads, granules) or pastes. A desirable aspect of many bone-substitute materials is that there will be a possibility to simultaneously introduce *in situ* drug release in combination with the implant. The advantage of localized biodegradable therapy includes high, local drug concentration at the site of infection, as well as, obviation of the need for removal of the implant after treatment. Also, a controlled drug release from the implant would help minimize toxic side effects and further compliance problems that might occur due to prolonged oral antibiotic therapy (7,8).

A good example of this is when treating bone diseases due to osteomyelitis or osteosarcoma. It is then necessary to maintain a high concentration of drug at the site of infection for a sufficient period of time. An effective local concentration may not be achieved with a systemic administration of a drug (*e.g.* chemotherapeutic, antibiotic or chemobiotic), and surgical treatment as well as local administration of drug are often required. Local administration limits the adverse effects of systemic administration, and higher concentration

of medication reach to the targeted site, and the surgical procedure results in producing bone defects.

Some novel ceramic-based particulate systems for delivery and application of drug, such as antibiotics, growth factors and anticancer drug are claimed to have enhanced bioavailability, predictable therapeutic response and prolonged drug release time. Of particular interest are the biodegradable systems where controlled biodegradation ability is being biocompatible with tissues. Today's implant drug delivery devices are based on biodegradable polymers, such as polylactic acid (PLA) and polyglycolic acid (PGA) (9). At the same time, antibiotic-impregnated acrylic bone cement beads have been widely used for local administration of antibiotic and dead space management. Walenkamp et al. (10) reported that healing of osteomyelitis was achieved in 92 of 100 patients using gentamicin-impregnated PMMA bone cement beads. However, this implant material showed various problems, including the requirement for subsequent removal of the beads, thermal damage of the antibiotic, and poor antibiotic elution property. The amount of gentamicin, which is heat stable and released by the beads, does not exceed 25 % of the total amount implanted. The collagen-gentamicin sponge appears to be equally as popular as acrylic bone cement beads for the treatment of osteomyelitis. Although the sponge is biodegradable and does not need surgical removal, antibiotic release may last only four days. Thus, drug delivery system based on porous bioceramics in form of granules has been developed to fill the bone defect with antibiotic (11,12). However, the problem still remains of matching of drug release rate and biodegradation kinetics (13,14). In order to obtain the ultimate implant material, the chemical and phase compositions, the microstructure (pores size distribution and interconnectivity) and their biological behavior with a cellular component needs to be systematically studied. The objectives will be the sustainable for production in industry of new "smart" multifunctional materials with tailor-made functionalities, where these materials may be used to restore the viability of damaged tissues and/or organs in humans and drug delivery systems.

One new set of materials that have the potential to fulfill many of the criteria required for such a multifunctional system are sol-gel-derived silicon oxides (15-21). However, before going into further details about an example of these systems, models to describe the mechanism behind the drug release are discussed in brief.

DRUG DELIVERY MECHANISMS

There are several mathematical models to describe release mechanism of an active agent from a drug delivery system. To be able to describe or predict the release profile, knowledge of the type of system, and rate controlling mechanism is crucial. Amongst the typical controlled release system we find diffusion controlled devices (reservoir, membrane, or monolithic devices), chemically controlled (monolithic) systems, water penetration controlled (osmotic or swelling) systems and regulated (magnetic or chemical) systems (5). As we will concentrate on drug release from a porous ceramic matrix, the diffusion controlled release is of greatest interest and will be discussed in further detail.

DIFFUSION CONTROLLED DELIVERY SYSTEMS

A diffusion controlled release can be obtained by two different systems: monolithic devices and reservoir devices (membrane controlled devices).

In a monolithic device the drug is dispersed in a matrix and the release is controlled by diffusion from the system. The diffusion can occur on a macroscopic scale, either through pores in the ceramic (or polymer) matrix, or on a molecular level, by passing between polymer chains.

The solubility of a drug and its dissolution rate can significant influence on the drug release kinetics. If the drug is present in the matrix below its solubility limit it can be dissolved in a polymer matrix and if it is present above its solubility limit, it is dispersed. For a dispersed drug in a matrix it is assumed that the dissolution rate of the drug is minimal compared to the diffusion rate of the drug. When the dissolution rate is slower than the diffusion rate of the drug, the former will determine the release rate. These kinds of systems will follow a two-step process.

The release of a drug from a monolithic system is based on Fickian diffusion (5). The fractional release from a one-dimensional porous system can be described using Fick's second law (I). Fick's second law describes how the concentration within the diffusion volume changes with respect to time, and D is the diffusion coefficient and c is the concentration.

$$\frac{\partial c}{\partial t} = D \cdot \Delta c \qquad \text{(I)}$$

In a one-dimensional system, the release rate is proportional to the square root of time. For the first 60 % of released drug, the release correspond to the early time approximation of Fick's second law,

$$\frac{\partial M_t}{\partial t} = \sqrt{2M_0\left(\frac{D}{\pi l^2 t}\right)} \qquad \text{(II)}$$

Thereafter, the release kinetics follows the late time approximation (first order kinetics) according to:

$$\frac{\partial M_t}{\partial t} = \frac{8DM_0}{l^2}\exp\left(\frac{\pi^2 Dt}{l^2}\right) \qquad \text{(III)}$$

where l is the thickness of a slab, M_o is the total amount of drug dissolved in the system, and M_t is the amount released at time t. Here, the release rate is dependent on the diffusion length.

A first order linear release profile is generally obtained for a pharmaceutical released from a porous matrix. There are several mathematical models that can describe the various aspects of such systems. However, usually a simplified model is used to describe the systems in a first approximation. A good example of this is the Higuchi model (22,23). The Higuchi model could be applied for a spherical system or a planar surface. Studies showed that the time required to release 50% of the drug appeared to take 10% of the time required to dissolve the last trace of solid drug in the center of a spherical pellet (22). Higuchi discovered that the release of a drug from an insoluble matrix could be described as a square root of time dependent process based on Fickian diffusion as (5,23)

$$Q = \sqrt{(2A - C_s)DtC_s} \qquad \text{(V)}$$

where Q is the amount of drug released per unit of exposed area at time t, from a planar system having a homogeneous matrix, D is the diffusitivity of the drug in the homogeneous

matrix, A, the total amount of drug in the matrix per unit volume, and C_s, the solubility of the drug in the matrix. Equation (V) was originally applied for release of a dispersed drug from an ointment base. To avoid Higuchi's approximation of the "pseudo-steady-state", for which the limit of $A > C_s$, does not satisfactory predict the release kinetics for $A < C_s$ or even $A = C_s$, other models were developed, including the "exact analysis" (unsteady state) by Paul and McSpadden (VI).

$$Q = \sqrt{\left(2A - \frac{2}{3}C_s\right)C_s Dt} \qquad \text{(VI)}$$

The kinetics of a drug released from porous carrier materials can be described using a modification of the Higuchi model (22,23). According to this model, the release of a drug from an insoluble, porous carrier matrix can be described as a square root of time-dependent process based on Fickian diffusion. The release, Q, is related to following parameters as

$$Q = f(\varepsilon, \tau, t, C_s, A, D) \qquad \text{(IV)}$$

where ε is the fractional porosity (pore volume/total material volume), τ relates to the tortuosity factor that accounts for, or corrects for the additional distance a particle must travel due to its circuitous path within the matrix, t is the immersion time, C_s the solubility of the drug in the permeating fluid, A is the initial drug loading in the matrix, and D is describing the diffusion of the drug in the medium inside which the carrier is immersed.

For a leaching type mechanism, where there is diffusion through a porous system, factors that affect the diffusion path-length (τ) and the effective volume (ε) are considered, as

$$Q = \sqrt{\left[\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t\right]} = k_h\sqrt{t} \qquad \text{(VII)}$$

where k_H is the release rate constant for the Higuchi model. Thus, for a purely diffusion controlled process, the amount of drug released exhibit a linear relationship if plotted against the square root of time. The Higuchi equation is based on ideal diffusion conditions and is not

able to describe the true *in vitro* release situation for a degrading device. Here, the Higuchi relation provides merely a measure of the release rate constant.

RESERVOIR DEVICES – MEMBRANE CONTROLLED DIFFUSION

Reservoir devices are another example of controlled delivery systems, where the drug is encapsulated or present as a core within a polymer film or coat. The diffusion occurs through a membrane that controls the movement of the drug or solvent between two sides. Both the membrane permeability of the drug and the solvent as well as the geometry of the device determines the diffusion rate of molecules through the membrane. Modelling the release characteristics of reservoir devices as well as monolithic devices, in which the transport of the drug is by a solution-diffusion mechanism, involves a solution to Fick's second law (unsteady-state conditions, concentration dependent flux) for the valid boundary conditions. When the device contains dissolved drug, the rate of release decreases exponentially with time as the concentration of the drug within the device decreases (first order release). If, however, the active agent is in a saturated suspension, then the driving force for release is kept constant (zero order) until the device is no longer saturated. Alternatively the release-rate kinetics may be desorption controlled, and a function of the square root of time (5). The flux of a molecule traveling through the membrane is described by

$$J = \frac{k(C_1 - C_2)}{l} D \qquad \text{(VIII)}$$

where l is the membrane thickness, k is the partition coefficient and ΔC is the concentration on either side of the membrane. A system (slab or plane) having a constant activity reservoir maintains a constant concentration gradient across the membrane under steady state conditions as seen in Figure 1.

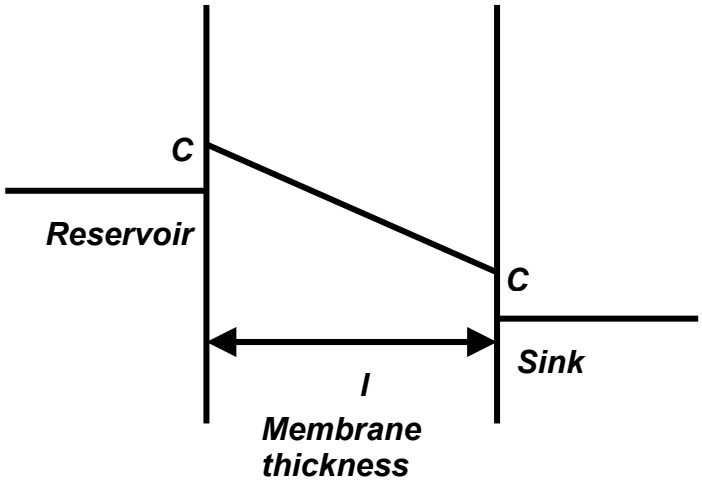

Figure 1. Schematic model for a membrane-reservoir system (5).

CONTROLLED DRUG RELEASE FROM ORDERED MICRO- AND MESOPOROUS SILICA MATRICES

How a porous ceramic will function as a carrier system for a pharmaceutical when it comes to both adsorption from and dissolution to a surrounding media, depends on several issues. Factors, such as adsorption properties (interactions between drug and matrix), pore size, pore connectivity, pore geometry and matrix reactions with surrounding media (dissolution properties) are just a few of the things to take into account when designing a controlled drug delivery system.

Mesoscopically ordered mesoporous silica materials have attracted a wide interest since their discovery in the early 1990's (24-28) due to their diverse potential applications areas; including catalysis, filtration and chromatography. Supramolecular surfactant aggregates are used as structure directing agents for inorganics during condensation, leading to mesoscopically ordered surfactant-inorganic composites. Porosity can be induced in the inorganic part by removal of the surfactant portion through thermal or chemical means (24,26,29,30). By controlling the synthesis conditions and choice of structure directing agents, the system can be engineered to fit numerous functions of preference.

The new group of mesoporous ordered materials was discovered independently by a Japanese group (27,28) and a group from Mobil Oil, USA (24-26). The Mobil Oil family of mesoporous materials were designated M41S, where the hexagonal MCM-41 was similar to the Japanese material designated FSM-16.

The first MCM-41 materials prepared by the Mobil Oil group were derived under alkaline synthesis conditions using an ionic surfactant (25,26). Characteristic of the Mobil Oil materials were the well defined ordered and large pores ranging from 1.5 to 10.0 nm with specific surface areas up to $1500 m^2/g$. By varying the synthesis conditions they obtained three different structures of the mesophase; a hexagonal phase (MCM-41, Mobil Composition of Matter 41), a cubic phase (MCM-48) or a lamellar phase (MCM-50) illustrated in Figure 2.

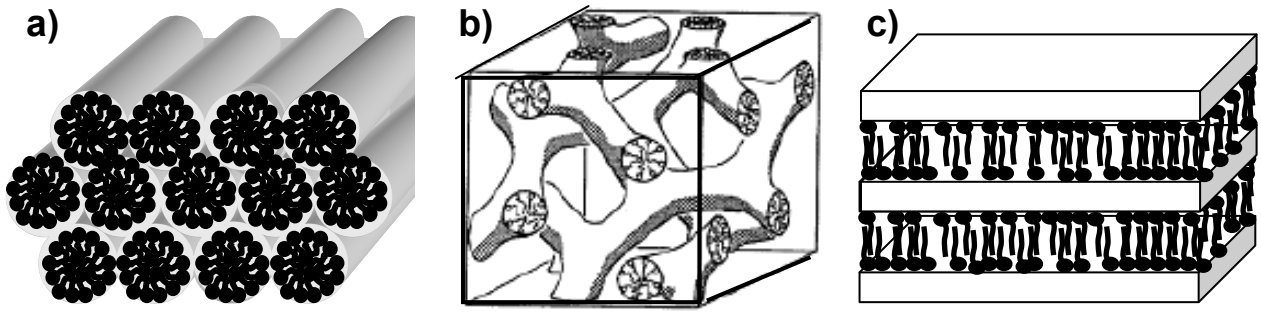

Figure 2. Mesophase structures of M41S: a) MCM-41, b) MCM-48[31] and c) MCM-50.

The formation of mesoporous materials with a variety of crystallographically well-defined frameworks has been realized via cooperative self-assembly including co-assembly of surfactants and silica into liquid crystalline structures.

Later, synthesis of mesoporous silica under acidic conditions was reported by Stucky and co-workers (pH < 2.0) (32,33). A similar material to M41S materials are the SBA materials, developed at the University of Santa Barbara (34,35). The SBA-15 material has similar features at that of MCM-41, but the pore walls are thicker, and the specific surface areas and specific pore volumes are usually smaller than of the M41S materials. Therefore, the mechanical and hydrothermal stability of these materials are better. Unlike the M41S materials, the SBA-15 material has microporous pore walls. However, SBA-15 has a well defined hexagonal symmetry similar to MCM-41.

As the purely siliceous mesoporous materials have been shown to be biocompatible, or sometimes even bioactive, there is an increasing interest in this class of materials for applications in the field of bioceramics, especially as bone substitute materials. Furthermore, the highly organized porous silica matrix could be used as a potential controlled drug release system. Another attractive advantage is that amorphous silica is degradable in an aqueous solution, and thus problems related to the removal of the material after use can be avoided.

Andersson *et. al.* (36) describes the use of calcined mesoporous silica materials as pharmaceutical carrier systems for controlled drug release. The drug release abilities were investigated on a series of M41S and SBA materials (Table 1). There are important

differences in the pore structure and pore connectivity between the studied materials. The MCM-41 and the SBA-3 type materials have straight one-dimensional cylindrical pores, while the SBA-1 materials have a 3D interconnected porosity, where close to spherical pores are connected through smaller windows. The c-MCM-41a material has also one-dimensional pores, but the cylinders are not straight but corrugated, which essentially is equal to a situation where larger pores are connected through smaller pore openings.

Ibuprofen, a common nonsteroidal anti-inflammatory pharmaceutical, was used as a model drug due to its size and possibility to interact with silanol groups present in the pore walls of the siliceous materials.

DRUG LOADING PROCEDURE

The impregnation process was performed according to one of the procedures described by Vallet-Regi *et al*. (15). Ibuprofen was dissolved in hexane (33mg/mL), and a pellet of the silica material (Table1) was soaked in the solution (33mg/mL silica/hexane) in a closed batch to prevent evaporation of the liquid. The impregnation time was set to 3 days. The drug-loaded disks were carefully washed with hexane to remove any adsorbed ibuprofen on the exterior surface. RAMAN spectroscopy (Bruker IFS66, Germany) and TGA-FT-IR (Bruker Equinox, Germany) were used in order to confirm complete evaporation of the hexane from the impregnated materials. The amount of incorporated ibuprofen was determined gravimetrically but also spectroscopically using a Perkin-Elmer UV-VIS-NIR spectrometer (Germany) reading at 273 nm measuring the amount absorbed from solution.

DRUG RELEASE PROCEDURES

The drug-loaded tablets were dried and immersed in simulated body fluid, SBF, for *in vitro* drug release studies (1mg ibuprofen/mL SBF) using static volumes. The release processes were followed spectroscopically.

The silica contents from the degrading matrices were measured using molybdenum blue as a tracer and the concentration were monitored by means of UV-VIS spectrophotometry (37).

IBUPROFEN ADSORPTION STUDIES

The studied materials are presented in Table 1, along with data for the original and ibuprofen impregnated materials.

The adsorption of ibuprofen from hexane was studied by determining adsorption isotherms for the different porous silica matrices (Fig. 3). The Langmuir isotherms are valid for monolayer adsorption and are obtained from equation (IX) (38),

$$\boldsymbol{m}\ (n/w) = [(\boldsymbol{m}/b)\ c_{eq}\ ] / [(\boldsymbol{m}/b)\ c_{eq} + 1] = [K_L\ c_{eq}]/[K_L\ c_{eq} + 1] \qquad \text{(IX)}.$$

where K_L is the Langmuir equilibrium constant. The constants $\boldsymbol{m}$ and b are obtained experimentally from the equation

$$c_{eq} / (n/w) = \boldsymbol{m}\ c_{eq} + b \qquad \text{(X)}.$$

Table 1: Lattice spacing, d_o; Specific surface area, *a*(BET); pore volume, *V*; pore diameter, *d*(BJH); for acid and alkaline synthesized silica materials. (Drug loaded matrices have been impregnated for 3 days in ibuprofen/hexane solution (33mg/mL).) * Determined from the adsorption branch.

Sample	Lattice Structure	Lattice Parameter d_o (nm)	Pore Diameter *d*(BJH) (nm)	Specific Surface Area *a*(BET) (m^2/g)	Pore Volume *V* (cm^3/g)
MCM-41	hexagonal	4.8	3.3	1200	1.0
MCM-41/ ibuprofen			2.6	370	0.2
MCM-41a	hexagonal	4.8	2.8	~1050	1.0
MCM-41a/ ibuprofen			2.3	450	0.2
c-MCM-41a	hexagonal	7.5	5.0*	650-800	1.0-1.2
c-MCM-41a/ ibuprofen			3.0	400-650	0.4-0.6
m SBA-3	hexagonal	3.8	2.6	>1000	1.0
m SBA-3/ ibuprofen			n.d.	440	0.35
μ SBA-3	hexagonal	3.0	1.7	>1000	0.51
μ SBA-3/ ibuprofen			n.d	220	0.11
SBA-1	cubic	6.9	1.8	>1000	0.54
SBA-1/ ibuprofen			n.d.	240	0.13

As seen from the isotherms (Fig. 3, left), the ibuprofen adsorption capacities differ extensively between the materials. The microporous materials showed the lowest (25 wt% for SBA-1 and μSBA-3) and the MCM-41 sample the highest (41 wt%) adsorption capacity calculated on a weight percentage basis. The other materials reached loading degrees around 30wt%.

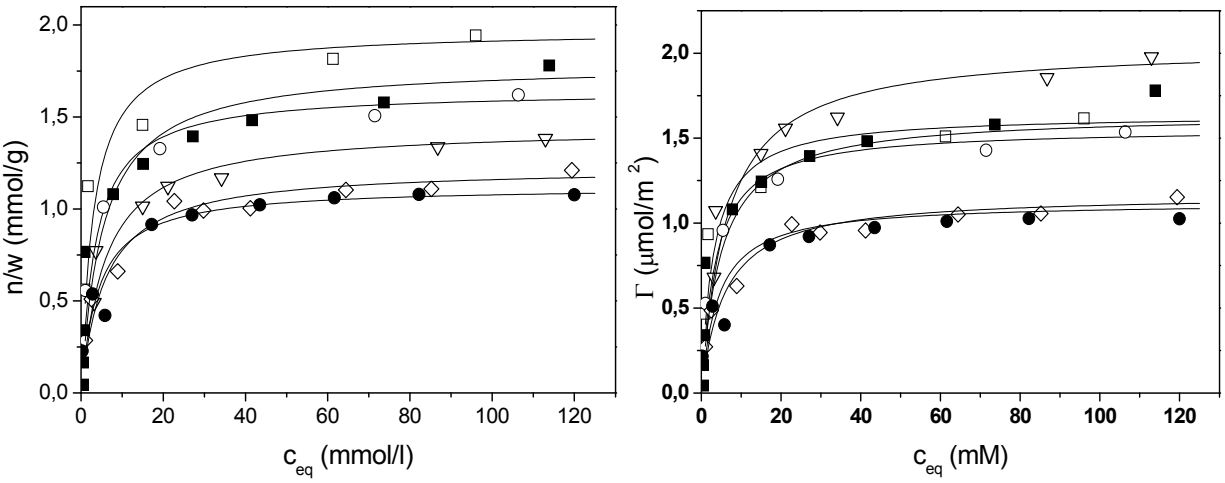

Figure 3. Adsorption isotherms of ibuprofen from hexane solution for the studied porous silica materials expressed as amount of adsorbed ibuprofen /g silica (left) and as the surface coverage Γ (amount of adsorbed ibuprofen /m^2) from solution (right). The surface area was determined using the BET-method. (□) MCM-41, (O) MCM-41a, (∇) c-MCM-41a, (■) mSBA-3, (◊) μSBA-1 and (●) μSBA-3.

The Langmuir isotherms can also be expressed as the amount ibuprofen adsorbed per unit specific surface area *a*(BET), *i.e.* the surface excess (moles per unit area of adsorbent), Γ, versus the equilibrium concentration, c_{eq}. The surface excess is based on *a*(BET) as

$$\Gamma = n/w \cdot a(\mathrm{BET})^{-1} \quad (\mu\mathrm{mol/m^2}) \qquad \text{(XI)}.$$

The adsorption isotherms in Fig. 3 (right) are divided into three separate groups, where the microporous materials possess the lowest adsorption capacity. The fairly low surface coverage for the microporous materials are probably due to the effects of size exclusion. With increasing ibuprofen loading, the adsorbing molecules experience steric hindrance when diffusing into small micropores that are less than double the length of a fully stretched ibuprofen molecule (~1 nm).

From the Langmuir adsorption isotherms one can conclude that the loading degree depends on especially two factors, such as the specific surface area *a*(BET) and also the pore size. Apart from these, also the density of surface silanol groups in the pore walls are thought to have an impact on the ibuprofen drug loading, since the pharmaceutical interact via hydrogen bonds with surface silanol groups located inside the pores.

The difference in surface concentration of ibuprofen has important implications for the release process, because the higher the ibuprofen surface loading the more hydrophobic the pores will become, which could affect the kinetics of water diffusion into the matrix.

IN VITRO DRUG RELEASE FROM MESOPOROUS AND MICROPOROUS SILICA

In vitro release studies were performed on the mesoporous siliceous materials and calcined pellets of the materials were immersed in SBF solutions (39,40). The ibuprofen concentrations were monitored in the solutions until all of the ibuprofen had diffused from the pellets.

Depending on the material characteristics a controlled release was observed for time periods reaching from 24 hours for the majority of ibuprofen incorporated in the MCM-41a material to above 400 hours for the catanionic c-MCM-41a (Fig. 4).

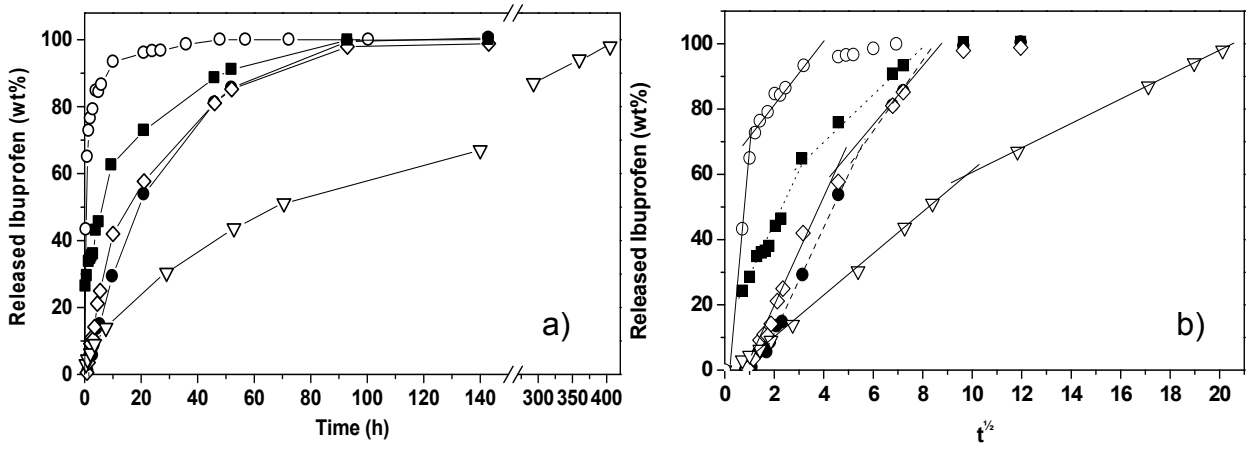

Figure 4: Ibuprofen release profiles for impregnated microporous and mesoporous materials in SBF at 37°C (a). Higuchi square root of time plot for the release of ibuprofen from the studied microporous and mesoporous materials (b). (O) MCM-41a, (▽) c-MCM-41a, (■) mSBA-3, (◊) μSBA-1 and (●) μSBA-3.

The microporous μSBA-3 and μSBA-1 materials and the mesoporous mSBA-3 material all display total release times in the range of 100 hours. The mSBA-3 exhibit a pronounced primary burst effect, corresponding to the intercept in Figure 4 a, where almost 20 wt% of the impregnated ibuprofen will be released within an hour.

The drug release kinetics of these systems can be described using the Highuchi model (22,23) since the release is a diffusion controlled process and the adsorbed are relatively small and uniformly distributed over the matrix. For a purely diffusion controlled process, the amount of drug released exhibits a linear relationship if plotted against the square root of time. However, the MCM-41a, mSBA-3, and μSBA-1 matrixes all display a two-step release (Fig. 4 b). The deviation from overall linearity is probably related to different dissolution rates of the silica matrixes.

In Figure 5, the silica dissolution rates from the studied silica matrixes are plotted against time. The rate of silica solubility is highest in the early stages, while the solubility rate decreases with time. This observation can be ascribed to the sink-type experiment and probably does not correspond to the dissolution rate *in vivo*. The silica dissolution rate is significant for all of the materials, which can be related to the fact that they were synthesized at room temperature (41). The silica dissolution rate is seemingly following the order of the drug release (Fig. 4) compared between the different materials. The more stable materials shown in the silica dissolution plot (Fig. 5), *i.e.* c-MCM-41a and μSBA-3, have less pronounced two steps in the Higuchi plot. A straight line in the Higuchi plot would correspond to a pure Higuchi type of diffusion-driven release for a carrier where no alteration of the matrix occurs on the time-scale of the release. Therefore, it can be concluded that the rate of silica solubility has an influence on the observed ibuprofen release rates.

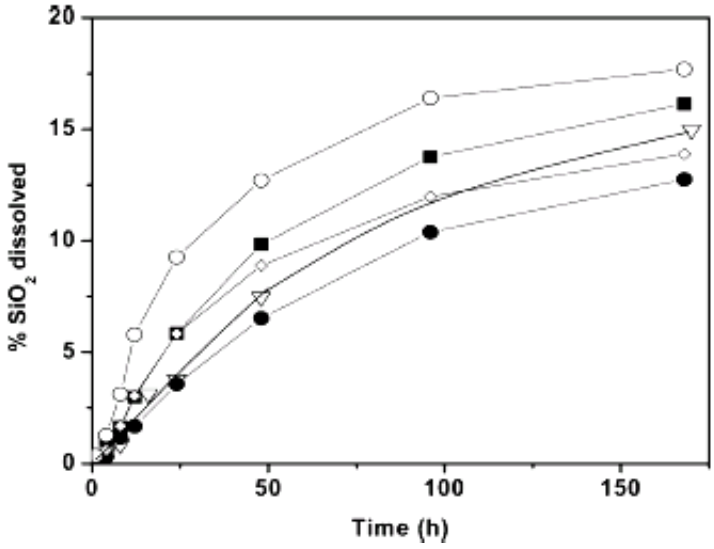

Figure 5. Amount of silica dissolved measured for ibuprofen containing tablets in SBF at 37°C. (O) MCM-41a, (▽) c-MCM-41a, (■) mSBA-3, (◊) μSBA-1 and (•) μSBA-3.

Other factors that are thought to influence on the ibuprofen diffusion rate is the primary and secondary particle size of the substrate, and also that the silica matrix is unlikely to dissolve in a homogeneous manner. The silica would preferentially dissolve from regions, from which the ibuprofen has been released, since the rate of silica dissolution was clearly slower for materials containing ibuprofen as compared to the pure substrates.

In order to exclude any influence of apatite formed on the silica surface during the *in vitro* drug release (42) also the calcium concentration was monitored from the SBF solution. It was found that no, or negligible, precipitation was observed for any of the ibuprofen loaded samples during the release period, which is why this effect can be excluded in this investigation. Although, for the pure matrix, before or after the release, a calcium-loss from SBF-solution was detected, indicating bioactivity and nucleation of hydroxyapatite.

CONCLUSION

In conclusion, the major factor contributing to the release of a drug from a porous ceramic matrix, such as the mesoporous silica matrix, is the pore size. This was especially seen for the materials exhibiting a 2D hexagonal structure with cylindrical pores, where the release rate increased in the order of μSBA-3 < mSBA-3 < MCM-41. The slow release rate seen from the c-MCM-41 material can be explained from its pore structure, as the material has corrugated, cage like pores, where the pore opening is very small. The slow release kinetics could also be explained by the more hydrophobic nature of the pore system due to the high drug loading, which leads to slower water penetration rates (43,44) in this sample.

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