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Diffusion-Controlled Drug Release From the Mesoporous Magnesium Carbonate Upsalite®

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ABSTRACT

In vitro drug release from well-defined particle-size fractions of the mesoporous magnesium carbonate material Upsalite® was investigated in detail using ibuprofen, a biopharmaceutics classification system class II drug, as the model compound. The weight of loaded drug corresponded to 30% of the weight of the carrier and the pores were filled to approximately 80%. The incorporated ibuprofen was found to be in an amorphous state and was physisorbed, rather than chemisorbed, to the surfaces of the pore walls. In contrast to ibuprofen in mesoporous silica, there was no detectable drug on the outer surface of the carrier particles. Two ibuprofen doses were loaded into Upsalite® particles with size fractions ranging from 25 μm to more than 200 μm. The initial release rate was controlled by the particle size; the dissolution rate of the loaded ibuprofen during this period was more than four times faster than that of the crystalline drug. An extended-release period of about 24 h followed the initial rapid-release period. The features of this extended-release period were dependent on the total drug concentration in the release medium. Detailed analysis of the diffusion of ibuprofen in Upsalite® provided the ibuprofen diffusion coefficient (9.8×10^{-8} cm^2/s), the constrictivity of the diffusion process (0.47) and the tortuosity of the carrier (15). This relatively high tortuosity value indicates that Upsalite® can be used not only to enhance the dissolution rate of poorly soluble drugs but also as a carrier in sustained-release applications by using larger particle sizes or even pellets of the material.

Introduction

Poor solubility of a drug in the intestinal fluid can lead to a low intestinal concentration of the dissolved active pharmaceutical ingredient (API) and, hence, a low plasma concentration after oral administration. As a result, the desired therapeutic effect of the API will be low or even nonexistent. Poor solubility also increases the time to onset of action for the API. The solubility of drugs in the gastrointestinal tract is described by the biopharmaceutics classification system (BCS), which relates solubility to the pH gradient of the gastrointestinal tract and the dose of the compound. Poorly soluble compounds are classified as BCS II or IV compounds, defined as those for which the total oral dose cannot be dissolved in 250 mL in the pH interval 1–6.8 [European Medicines Agency guideline] or 1–7.5 (US Food and Drug Administration (FDA) guideline). The absorption of BCS II and IV compounds may be limited by solubility and/or dissolution rate; up to 90% of compounds in the drug discovery pipeline are currently estimated to belong to these two classes.[1] For these drug candidates, poor aqueous solubility and a slow dissolution rate in gastrointestinal fluids are likely to be limiting factors for their commercialization.[2,3] Therefore, improving the bioavailability of such drug candidates by enhancing their dissolution rate and thereby facilitating absorption during the limited time available during intestinal transit is one of the most challenging issues in the pharmaceutical industry.

Over the last two decades, there has been an increasing interest in the amorphous state of poorly soluble drugs, mainly because of the higher apparent solubility of the amorphous state than its crystalline counterpart. The resulting increase in apparent solubility may be translated to a faster onset of action and, potentially, increased bioavailability of the API.[4–6] However, as the amorphous form is inherently metastable, there is always the risk of recrystallization to the more energetically favorable crystal form.[7]

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Nanostructured materials in life science applications have opened up the possibility of suppressing the crystallization of amorphous, poorly soluble drugs; this can be achieved by incorporating them into mesoporous nanostructures (i.e., particles with pore diameters between 2 and 50 nm).[7-10]

In our previous work, the novel mesoporous and amorphous material Upsalite® was investigated as a phase stabilizer of amorphous ibuprofen to increase its dissolution rate.[11-14] Upsalite® consists of magnesium carbonate ($MgCO_3$) that is "generally recognized as safe" by the FDA. It has a large specific surface area (typically 300-800 cm^2/g) and a narrow pore-size distribution (usually 6-8 nm), and these material properties have been associated with high loading of ibuprofen (30%) and suppressed crystallization.[14] However, in that study, the particle size of Upsalite® was not controlled and, hence, the impact of the particle size distribution on the behavior of this new material as a drug delivery vehicle could not be explored. This study was therefore undertaken to further investigate the potential of Upsalite® as a new drug delivery vehicle for facilitating the safe oral delivery of poorly soluble APIs. In order to obtain more detailed information about the drug delivery properties of Upsalite®, the release of ibuprofen from samples with defined particle sizes was analyzed by challenging the release medium using two ibuprofen doses, both below the saturation limit of the free drug. We hypothesized that these different size fractions could be used to tune the release profile of the drug, potentially allowing Upsalite® to be used as a universal carrier for immediate-, extended-, controlled-, and sustained-release applications. This study also provided information on the diffusion coefficient of ibuprofen, and the tortuosity and constrictivity related to diffusion, in the mesopores of Upsalite®.

Materials and Methods

Materials

Magnesium oxide (MgO) and ibuprofen were obtained from Sigma–Aldrich (Stockholm, Sweden). More than 90% of the as-received ibuprofen particles were between 100 and 75 μm in diameter, as determined by sieving. Methanol and ethanol were purchased from VWR International (Spånga, Sweden). CO_2 was obtained from AirLiquide (Sundbyberg, Sweden). All chemicals were used as received.

Sample Preparation

Synthesis of Upsalite®

Upsalite® was synthesized as described previously.[11] Briefly, 170 g of MgO and 2.5 L CH_3OH were mixed in a 5L Ecoclave pressure reactor from Büchi (BÜCHI Labortechnik AG, Flawil, Switzerland) at a stirring speed of 500 rpm. The reaction was carried out at 55°C and 3 bar CO_2 pressure. After a reaction time of 4 days, the temperature was decreased to room temperature and the reactor was depressurized. The product was dried at 75°C in a vacuum oven (VO 150 EA; MSL Technoven, Lissone, Italy) for 2 days and then calcined at 250°C for 12 h in the oven (Heraeus Oven T6; Heraeus, Hanau, Germany) to remove all the organic intermediates formed in the reaction. After calcination, a white particulate material was obtained.

Grinding and Sieving of Upsalite®

After calcination, the material was ground in a Planetary Ball Mill (Restch PM 100; Restch, Haan, Germany) to reduce the particle size. Thereafter, five sieves—200, 100, 75, 50, and 25 μm (Retsch GmbH Test Sieve; Restch)—were used to separate the ground material into samples containing particles in controlled size ranges: >200, 200–100, 100–75, 75–50, and 50–25 μm. Three sample batches, Upsalite®-Large (particle size > 200 μm), Upsalite®-Medium (particle size 100–75 μm), and Upsalite®-Small (particle size 50-25 μm), were selected as drug delivery vehicles and further characterized.

Drug Loading Procedure

Ibuprofen was incorporated into the Upsalite® samples via solvent evaporation. A 24 mg/mL ibuprofen solution was obtained by dissolving 6 g ibuprofen in 250 mL ethanol. Three grams of each Upsalite® sample was added to 55 mL of the ibuprofen–ethanol solution. The mixtures containing the Upsalite® samples and the ibuprofen–ethanol solution were placed on an orbital shaker (100 rpm) at room temperature to allow the ibuprofen to diffuse into the Upsalite® particles. After 24 h of shaking, the solvent was removed by evaporation at 35°C and the ibuprofen-loaded samples were left to dry in a vacuum oven at 70°C. Three types of ibuprofen-loaded sample were thus synthesized: Upsalite®-IBU-Large, Upsalite®-IBU- Medium, and Upsalite®-IBU-Small, in accordance with the size of the Upsalite® carrier particles.

Characterization

Unless otherwise stated, the characterization methods described below were employed for analyzing as-received ibuprofen, as-synthesized and unsieved Upsalite®, and all Upsalite®-IBU samples.

Powder X-Ray Diffraction

X-ray diffraction (XRD) analyses were carried out in a Bruker D8 (Bruker, Bremen, Germany) Twin-Twin instrument (45 kV and 40 mA) with $Cu_{K\alpha}$ radiation ($\lambda = 0.154$ nm). The samples were ground in a mortar and put on silicon zero background sample holders prior to analysis. The patterns were obtained using a standard powder analysis set-up in the 2θ range 10°–70°, with a step size of 0.02° and 38 s measuring time per step. EVA 11.0.0.3 software (Bruker) was used to interpret the data.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FT-IR) studies were carried out in a Bruker FT-IR Tensor 27 spectrometer (Bruker) with a single-reflection diamond attenuated total reflectance (ATR) accessory (A225/Q Platinum ATR; Bruker) at room temperature. A background scan was acquired before scanning the powder samples. All FTIR spectra were collected at a spectrum resolution of 4 cm^{-1} over the range of 4000–400 cm^{-1} with 50 scans. The results were processed using OPUS 7.0 software.

Specific Surface Area

Nitrogen gas sorption isotherms were recorded on as-synthesized and sieved Upsalite® as well as on all Upsalite®-IBU samples at −196°C in an ASAP 2020 instrument from Micromeritics (Norcross, GA). Prior to analysis, all samples were degassed for 12 h. The degassing temperature was 90°C for the as-synthesized Upsalite® samples, whereas the Upsalite®-IBU samples were degassed at 65°C. A lower temperature was used in the latter process to avoid melting the ibuprofen, which occurs at 78°C for the as-received drug.[15] The specific surface area (SSA) was calculated using the multipoint Brunauer–Emmett–Teller (BET) method for adsorption values in the relative pressure range between 0.05 and 0.30, whereas the pore size distribution was calculated based on the density functional theory method using the model for nitrogen at −196°C.[12,16] The total pore volume was obtained from single point adsorption at a relative pressure $P/P_0 \approx 1$. These values, including the errors of the SSA values, were all calculated using ASAP 2020 (Micromeritics) software.

Thermal Gravimetric Analysis

Thermal gravimetric analysis (TGA) analysis was employed to assess the amount of ibuprofen loaded into Upsalite® using a SDTA851e TGA instrument (Mettler Toldeo, Greifensee, Switzerland), under airflow in an inert aluminum cup. The samples were heated from room temperature to 600°C at a heating rate of 5°C/min. Measurements were analyzed using Mettler-Toledo STARe Software DB v9.00.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analysis was performed on a DSC Q2000 instrument from TA Instruments (Sollentuna, Sweden) using Exstar software. Samples of 3.5–5.5 mg were weighed into 5 mm aluminum pans and sealed by a press. Samples were first cooled to −35°C for stabilization and then heated to 150°C at a heating rate of 3°C/min. Indium (156.6°C and 28.4 mJ/mg) was used to calibrate the temperature scale and the enthalpic response.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) images of the samples were recorded before and after ibuprofen loading using a Leo 1550 FEG microscope (Zeiss, Oberkochen, Germany) equipped with an in-lens detector. A thin gold/palladium layer was sputtered onto the samples prior to analysis to avoid charging them. The analysis was performed at 1.5 kV acceleration voltage.

Drug Release Measurement

Low-Concentration Drug Release

The release of ibuprofen was measured in a USP-2 dissolution bath (Sotax AT7 Smart; Sotax AG, Aesch, Switzerland). Samples with a total ibuprofen content of 20 mg were placed in vessels containing 500 mL phosphate buffer (pH 6.8, 37°C, 50 rpm). Aliquots of 3 mL were withdrawn from each vessel at regular intervals for 120 min with an additional withdrawal after 24 h and the ibuprofen concentration in the liquid samples was analyzed using UV/visual absorbance recordings at 219.4 nm (1650PC; Shimadzu Corporation, Kyoto, Japan). Prior to UV analysis, samples were filtered through 0.2 μm nylon membrane filters (Whatman, Dassel, Germany). Measurements were made in triplicate on as-received ibuprofen and all Upsalite®-IBU samples. The mean concentrations and corresponding standard deviations were calculated.

To examine the mechanism of ibuprofen release from Upsalite®, the release data were fitted to the semiempirical Korsmeyer–Peppas equation[16,17]:

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t/M_∞ is the fraction of the drug released at time t, k is a kinetic constant, and n is the diffusional exponent characteristic of the release mechanism.

High-Concentration Drug Release

To assess the drug release profile at different concentrations, the above procedure was also carried out using a three times higher ibuprofen concentration in the release medium. Hence, the only difference was that 200 mg of Upsalite®-IBU sample, containing 60 mg of ibuprofen, was added to the 500 mL phosphate buffer (pH 6.8). This led to a significantly higher concentration of ibuprofen in the release medium and the samples therefore had to be diluted prior to analysis. The release profile was compared with that of the same amount of as-received ibuprofen. All measurements were performed in triplicate and the mean concentrations and standard deviations were calculated.

Results and Discussion

XRD, DSC, TGA, FTIR, and SEM Analyses

The detailed results from XRD, DCS, TGA, and FTIR measurements are presented in the Supporting Information. The data confirm those from our previous work showing that the Upsalite® synthesis and the drug loading procedures are reproducable.[15] Briefly, it was found that (1) ibuprofen incorporated in Upsalite® is in a state lacking long-range order, that is, the crystalline structure of ibuprofen is lost when loaded to Upsalite® (Figs. S1 and S2); (2) the ibuprofen concentrations in the Upsalite®-IBU-Large, -Medium, and -Small samples were 30.1, 29.2, and 30.6 wt%, respectively, which is in good agreement with the amount of ibuprofen of approximately 30 wt% used in the loading procedure (Fig. S3); and (3) ibuprofen was physisorbed rather than chemisorbed to the surface of the pore walls in Upsalite® (Fig. S4). SEM analysis found no structural differences between the loaded and unloaded samples (Fig. 1).

Nitrogen Analysis

The BET surface areas and pore volumes of the studied samples are given in Table 1, whereas the pore size distributions are displayed in Figure 2. As expected, the Upsalite® surface area, pore volume, and average pore size (represented by the pore size corresponding to the maximum value of the differential pore volume) are reduced after ibuprofen is loaded. The amount of ibuprofen inside the pores was estimated from the decreases in pore volume of approximately 0.503, 0.506, and 0.550 cm^3/g for the Upsalite®-Large, -Medium, and -Small samples, respectively, after loading. The theoretical molecular volume of ibuprofen (0.437 nm^3) was used to calculate the amount of ibuprofen in the samples as: 28.4 wt% (Upsalite®-Large), 28.6 wt% (Upsalite®-Medium), and 31.1 wt% (Upsalite®-Small). These values are in good agreement with the ibuprofen content of the samples found from the TGA analysis and thus give further support to the conclusion that only an insignificant amount of the drug, if any, resides on the outer surface of the Upsalite® particles. The reduction in pore volume further shows that approximately 80% of the accessible pore volume in Upsalite® is filled with ibuprofen after the loading step.

In addition, the nitrogen adsorption data showed that the large and medium-sized as-synthesized particles had similar surface areas, average pore sizes, and volumes, whereas the small particles had a smaller surface area, a somewhat larger average pore size, and a greater pore volume. The explanation for this increase in pore volume and pore size, and the reduced surface area of the smallest particles, probably lies in the drying of the gel in the synthesis step and the subsequent milling. Regions in the dried gel with a slightly higher porosity than the average value were probably more likely to break and thus form smaller particles than regions of lower porosity.

Further, the observation that the average pore size was reduced by approximately 1 nm when the large- and medium- sized Upsalite® particles were loaded with ibuprofen (particles of which have a diameter of ~1 nm), whereas the corresponding reduction was approximately 2 nm for the small particles is fully in line with the finding that the extent of loading was similar for all particles, whereas the accessible surface area was smaller for the small particles. Possible distribution patterns for ibuprofen molecules on the pore walls in the different samples, which are in agreement with the above findings, are illustrated in Figure 3.

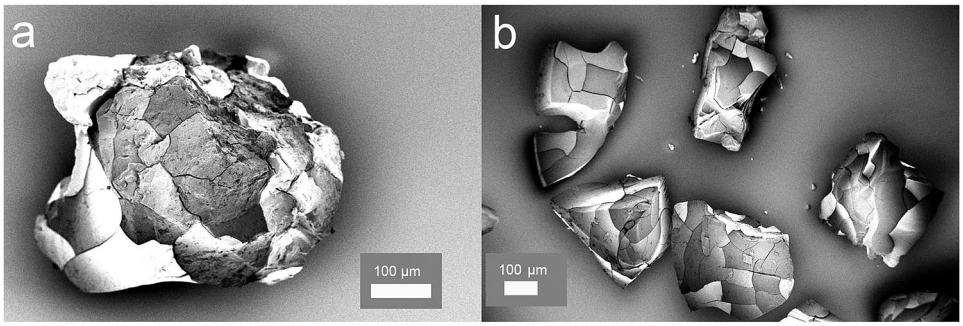

Figure 1. Scanning electron microscopy image of an Upsalite® particle showing the same irregular structure when (a) unloaded and (b) loaded with ibuprofen.

Dissolution Profile

The dissolution profile of as-received ibuprofen along with the ibuprofen release curves from the different Upsalite® samples are displayed in Figure 4. The values on the left y-axis are given as percentages of the total amounts of ibuprofen present in the dissolution vessel (in free form or inside the Upsalite® carrier) and, for all release curves, 100% corresponds to an ibuprofen concentration of 40 mg/L, as indicated by the left y-axis.

The initial dissolution rate of the crystalline, as-received ibuprofen was considerably lower than the release rate of the amorphous drug from the Upsalite® batches of varying particle size. For the crystalline ibuprofen, the lattice energy is the limiting factor for dissolution as hydration is expected to be good at the pH of the dissolution medium used.[18] As seen from the dissolution profile, only approximately 21% of the added crystalline, 100–75 μm-sized ibuprofen particles dissolved within the first 10 min, and after 60 min, only approximately 61% had dissolved, whereas approximately 86%, 70%, and 36% of the ibuprofen were released from the Upsalite®-IBU-Small, -Medium, and -Large sample types, respectively, after the first 10 min. This clearly shows that not only can Upsalite® act as a stabilizer for amorphous ibuprofen, thus encouraging a significantly enhanced ibuprofen dissolution rate, but the release profile can also be tuned to obtain the desired properties for the formulation by carefully selecting the size of the particles used for delivery.

In addition to the above, the rate of drug release from the drug-loaded samples was significantly decreased after the initial rapid-release period of approximately 14, 18, and 52 min for the Upsalite®-IBU-Small, -Medium, and -Large samples, respectively, at which point approximately 88%, 79%, and 70% of the loaded ibuprofen had been released. After reaching this plateau on the release curves, it took a total of 24 h to reach release values of approximately 87%–98% from the samples under study. A reasonable explanation for the slow-release region could be that the carboxylic groups of the ibuprofen molecules interacted with hydroxyl groups on the Upsalite® pore wall surface remaining after synthesis.[13] A similar hydrogen bond interaction between the carboxylic group on ibuprofen and silanol groups on the pore walls of mesoporous silica has been hypothesized to cause the experimentally observed plateau in ibuprofen release from mesoporous silica. The slow release of drug from that material extends over several days.[19] The slow- release period from Upsalite® being significantly shorter than that from mesoporous silica indicates that the interaction between the drug and the carrier is weaker than that obtained with silica.

To obtain further insight into the mechanism of drug release from the Upsalite® particles, the possibility of performing a Korsmeyer–Peppas analysis of the release data was investigated. The Korsmeyer–Peppas equation (1) is valid only for the first approximately 60% of the released drug.[20] In the case of nonswelling systems such as Upsalite®, this analysis can be employed to discriminate between Fickian diffusion, non-Fickian (anomalous) diffusion, and zero-order release mechanisms; for a monodispersed sample of spherical particles, an n-value of 0.43 or lower represents Fickian or quasi-Fickian diffusion, whereas an n-value of 1.0 represents a zero-order release mechanism. Any n-value between 0.43 and 1.0 represents some combination of release mechanisms or non-Fickian transport.[20] It was found that the first seven data points in the ibuprofen release curve from Upsalite®-IBU-Large, representing release of up to approximately 60% of the loaded drug, obtained an n-value of 0.36 ($R^2 > 0.99$). Hence, release from this particle-size fraction of Upsalite® is diffusion controlled. This value also indicates that this sample type had somewhat nonuniform particle size distribution.[20] This was expected, as the Upsalite®-IBU-Large sample was sieved to contain particles larger than 200 μm but with an unidentified upper limit in size. For the smaller Upsalite® particles loaded with ibuprofen, Upsalite®-IBU-Medium and -Small, the initial release was so rapid that the data points below 60% release were too few to allow reliable analysis. However, the diffusion-controlled release mechanism was also confirmed for these particles when the release for the three samples was compared; the smaller the particles, the shorter the diffusion pathway, which evidently leads to faster release. Hence, the dissolution rate of the drug inside the porous structure of Upsalite® is much greater than the diffusion rate and does not limit the release of the drug.

To assess the drug release profile from the Upsalite® particles with different drug concentrations, the above measurements were repeated at three times the ibuprofen concentration in the release medium. Figure 5 shows the first 500 min of the release curve. For all release curves, 100% corresponds to an ibuprofen concentration of 120 mg/L. Figure 5 indicates that the Upsalite®-IBU samples released an almost identical proportion ofthe incorporated drug during the initial rapid release period (of ~14, 18, and 52 min for the Upsalite®-IBU-Small, - Medium, and -Large samples, respectively) just as when the release medium was challenged with a lower

Table 1
Specific Surface Area and Total Pore Volume of the Samples Under Study

Samples	Surface Area (m^2/g)	Pore Volume (cm^3/g)
Upsalite®-Large	399 ± 1.81	0.623
Upsalite®-IBU-Large	128 ± 0.55	0.120
Upsalite®-Medium	406 ± 2.57	0.651
Upsalite®-IBU-Medium	129 ± 0.75	0.145
Upsalite®-Small	327 ± 1.34	0.729
Upsalite®-IBU-Small	136 ± 0.63	0.179

The values are based on single measurements and the errors were obtained using the ASAP 2020 (Micromeritics) software.

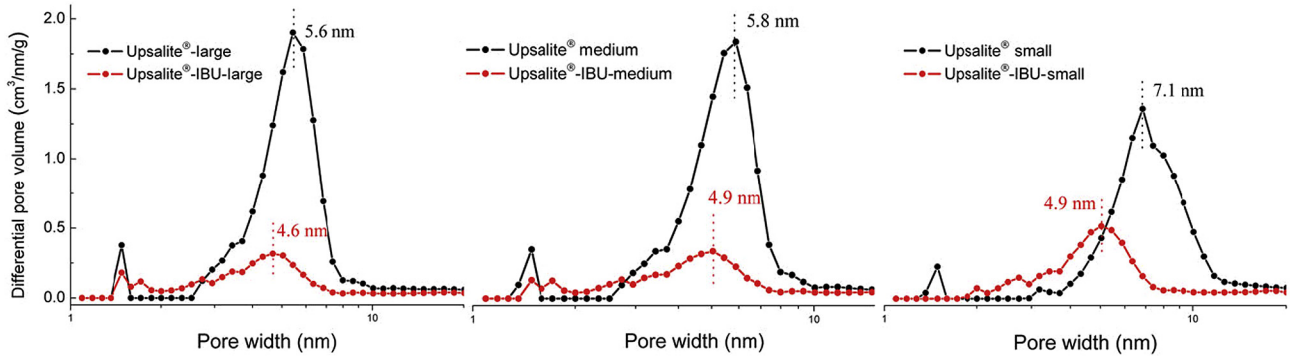

Figure 2. Pore size distributions, presented as the differential pore volume, for the as-synthesized Upsalite® and the Upsalite®-IBU samples. The pore sizes corresponding to the maximum value of the differential pore volume are indicated for each sample.

ibuprofen concentration (Fig. 4). This was expected, as both experimental settings were performed under sink conditions. The total amount of ibuprofen loaded in both experiments was less than 10% of the solubility of ibuprofen, which was determined as 2.15 mg/mL, in agreement with previous reports.[21] After the initial release period, the release profile for three times higher drug load differed significantly from that with the lower concentration. Instead of immediately entering a plateau-like, slow-release period, the concentration of released ibuprofen in the dissolution medium reached a peak and then began to decrease before the slow-release period started. We therefore increased the time period for two of the samples to obtain more data for interpretation of this phenomenon but currently we can only speculate about the origin of this behavior. After 24 h, the concentration of ibuprofen released from the Upsalite®-IBU-Small sample was 82.3 mg/L, that is, there was no increase in the released concentration over the time period between 500 min (8.3 h) and 24 h for this sample. The crystalline ibuprofen sample, on the contrary, continued to dissolve slowly; the concentration was 51.6 mg/L after 24 h and 108 mg/L after 48 h. As no redissolution of the ibuprofen that was released from Upsalite® was observed, and the studies were performed under sink conditions, we speculate that the decrease in concentration observed for the small particle size fraction was more a consequence of crystallization on the surface of the Upsalite® particles than of crystallization occurring in solution. The threefold higher drug load also meant that there was three times the quantity of Upsalite® particles in the solution compared with what was used in the low drug load studies. Hence, a much larger surface area of Upsalite® was in direct contact with the medium. The trend showing that the effect of the particle size fraction on the drop in concentration was reduced when the particles increased in size from small through medium to large also supports this theory, as the surface area in contact with the medium decreased as the particle size of the drug-loaded Upsalite® increased. Finally, the small particles were rapidly releasing ibuprofen and it is likely that higher local concentrations of ibuprofen existed close to the Upsalite® particle surface, thus further driving nucleation of ibuprofen on the surface of Upsalite®. Ongoing studies are now exploring whether physically or chemically adsorbed ibuprofen can be detected on the surfaces of Upsalite® after completion of the release experiment; these studies are also addressing the extent to which such a phenomenon could be dependent on the physicochemical properties of the drug.

An interesting observation can be made from the linear curve fit to a plot of the time at which the maximum for each release curve was reached versus the square of the approximated average distance the ibuprofen molecule had to travel inside the carrier particle before being released into the dissolution medium. If one

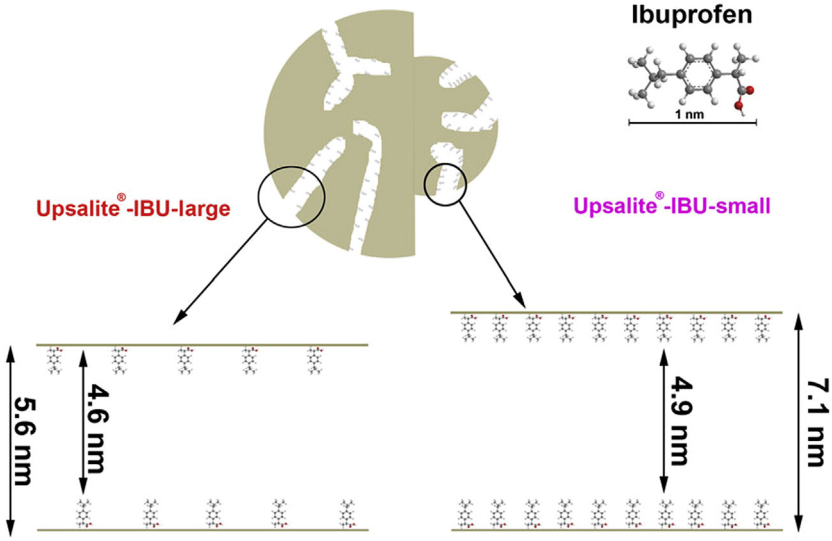

Figure 3. Illustration of the possible distribution of ibuprofen molecules on the pore walls of the Upsalite® samples under study.

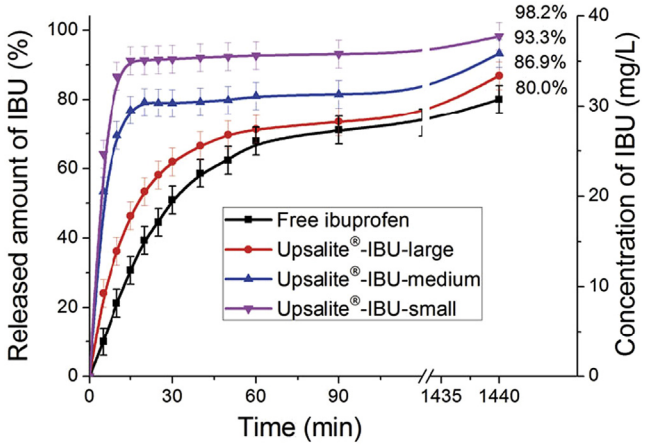

Figure 4. Dissolution of as-received ibuprofen and ibuprofen released from the different Upsalite® samples. The symbols represent the measurement times, whereas the solid lines are guides for the eye. The percentage numbers in the upper right corner of the graph state the dissolved/released amounts of ibuprofen after 24 h (i.e., 1440 min).

assumes that this distance is in the order of half the radius of the particles (i.e., ~10, 22, and 50 μm for the Upsalite®-IBU-Small, -Medium, and -Large particles, respectively), such a curve fit ($R > 0.99$) attains a slope of approximately 5.1×10^6 s/cm^2. The time t that it takes for a molecule to travel a distance X in a diffusion process characterized by an effective diffusion coefficient D_e can be expressed as:

$$t = \frac{X^2}{2D_e} \tag{2}$$

which gives a D_e for the release process of 9.8×10^{-8} cm^2/s. This value is about 1.5 orders of magnitude lower than the diffusion coefficient D for free ibuprofen in a phosphate buffer (5.5×10^{-6} cm^2/s) and four orders of magnitude larger than the effective diffusion coefficient for ibuprofen from 100 μm amorphous microporous silica spheres with pore diameters smaller than 2 nm (9.8×10^{-12} cm^2/s).[22,23] Two interesting conclusions can be drawn from this observation: (1) the initial part of the release of ibuprofen

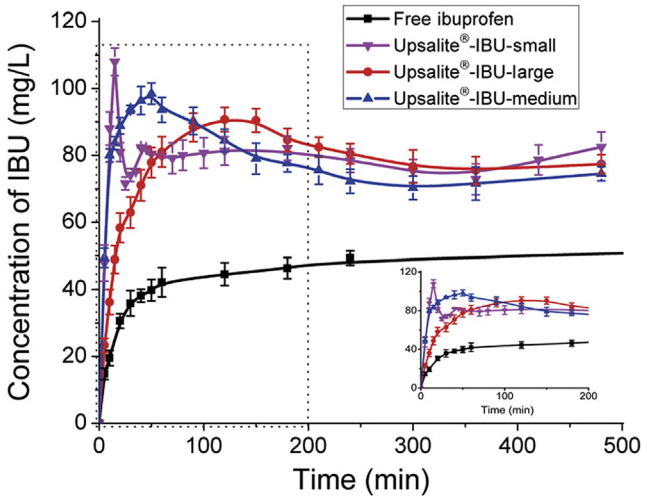

Figure 5. Ibuprofen release from the Upsalite® samples at three times the ibuprofen content in the dissolution vessel compared with that in the experiments shown in Figure 4. The first 200 min of the release is magnified in the inset.

from Upsalite® is indeed diffusion limited; and (2) the ratio between the constrictivity δ and the tortuosity τ for the Upsalite® carriers is approximately 0.03. The latter follows from the fact that[24]:

$$D_e = \frac{D\varepsilon_t\delta}{\tau} \tag{3}$$

where ε_t is the porosity available for diffusive transport, which can be estimated as 0.67 for Upsalite®, as the pore volume is approximately 0.7 cm^3/g (Table 1), and the density of anhydrous magnesium carbonate is 2.958 g/cm^3 $\left(\frac{0.7}{0.7+1/2.958} = 0.67\right)$.[25]

In the above-mentioned equation, the tortuosity relates the actual distance a molecule has to diffuse between two different points in a porous medium to the straight line distance between these two points and is, thus, a measure of the degree of "winding" of the diffusion path (note that, in the older literature, $\sqrt{\tau}$ is sometimes denoted as the tortuosity). For homogeneous, macroporous, isotropic media, τ is normally between 1 and 3.[26] For mesoporous materials, the actual physical significance of the tortuosity can be debated but, regardless, it expresses an effective coefficient of resistance against diffusion. Tortuosity values slightly above 20 have been reported for mesoporous structures of γ-alumina and silica.[27] Further, the constrictivity accounts for the slowing down of diffusion caused by small pores and narrow pore throats in a porous medium and it is, thus, a characteristic of the so-called bottleneck effect.[28] Four empirical equations relating the constrictivity to the ratio of the diameter of the diffusing molecule to the pore diameter have been developed; these vary with the nature of the diffusing molecule and the porous medium in which diffusion occurs.[29-32] By applying all four of these equations to the diffusion of ibuprofen in Upsalite®, using an ibuprofen diameter of 1 nm and an Upsalite® pore diameter of 6 nm, a constrictivity value between 0.46 and 0.48 was obtained. This, in turn, gave a tortuosity value for the pore system in Upsalite® of about 15, significantly higher than tortuosity values reported for macro-porous media but somewhat lower than, although in the same order of magnitude as, the values for the γ-alumina and silica mesoporous materials mentioned above.[27]

Conclusions

In vitro drug release from defined particle size fractions of the mesoporous magnesium carbonate material Upsalite® was investigated in detail using the BCS class II drug ibuprofen as a model compound. The release medium was challenged with two ibuprofen doses loaded into Upsalite® particles with size distributions ranging from 25 μm to more than 200 μm.

The particles were loaded with approximately 30 wt % of ibuprofen, corresponding to approximately 80% filling of the pores, as determined by TGA and nitrogen adsorption. The release measurements showed that the initial release rate could be controlled by selection of different Upsalite® particle sizes. The particle size range explored in this study resulted in a release of ibuprofen that was four times higher than that for crystalline ibuprofen. After the initial rapid drug release, an extended-release period followed for about 24 h, with features dependent on the total drug concentration in the release medium. These features allowed for detailed analysis of the diffusion of ibuprofen in Upsalite®, giving values for the ibuprofen diffusion coefficient, the constrictivity of the diffusion process, and the tortuosity of the carrier of about 9.8×10^{-8} cm^2/s, 0.47 and 15, respectively. The results of this study show that Upsalite® can act as a stabilizer for amorphous ibuprofen, thus significantly enhancing the dissolution rate of the drug. Further, Upsalite® can be used to tune the release profile to obtain the

desired properties for the formulation simply by carefully selecting the size of the particles used for delivery. Finally, the relatively high tortuosity value obtained for Upsalite® demonstrates that the material could also be used as a carrier for sustained-release applications by using larger particle size fractions or even pellets of the material.

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