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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.

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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.

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