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Silica particles with three levels of porosity for efficient melt amorphisation of drugs

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ABSTRACT

Silica particles with a unique multi-level pore structure have been prepared in order to enable efficient melt-in amorphisation of pharmaceutical substances. The dissolution rate of drugs with a low aqueous solubility can be enhanced by their conversion from a crystalline to an amorphous form. In order to avoid spontaneous re-crystallisation over time, the amorphous form must be stabilised, in this case by melt-in sorption into a porous carrier. To stabilise the amorphous state, pore diameters not exceeding approximately ten times the equivalent molecular diameter are required. However, since the permeability of porous media scales with the square of the mean pore diameter, carrier particles with pores in the nanometer range suffer from slow melt-in rates. Therefore, silica particles with a novel multi-level porous structure have been proposed in this work. The particles combine a central hollow cavity, a network of conducting macro-pores for enhanced transport rate, and a mesoporous matrix for efficient stabilisation of the amorphous state. The particles were prepared by the hydrolysis of TEOS using a soft-templating method with octylamine. We show that by systematically modulating the hydrolysis rate by the presence of ethanol (a reaction by-product), particles with the desired pore structure, particle size and morphology can be formed. Furthermore, we demonstrate their superior transport properties during melt sorption, high drug loading capacity and the ability to stabilise the amorphous state of a drug.

1. Introduction

Mesoporous SiO_2 micro- and nano-particles have a diverse range of industrial and scientific applications including adsorption, catalysis, humidity control and drug delivery [1–4]. Recently, the utilisation of silica particles in oral drug delivery as carriers capable of preserving the amorphous state of active pharmaceutical ingredients (APIs) has been explored with high hopes of developing a universal method for formulating poorly soluble APIs [5–10]. The oral bioavailability of many APIs is limited by the low aqueous solubility of their thermodynamically most stable crystalline forms. The formation of metastable solid-state forms such as amorphous solid dispersions is therefore pursued in order to enhance the kinetic solubility of the APIs. Apart from the commonly used approach of API amorphisation using a polymer matrix [11], API loading into porous inorganic carriers represents a viable alternative [12]. This approach makes use of changes in the state behaviour of API molecules confined to the mesopores [13].

Methods for API loading into porous carrier particles include processes such as equilibrium solvent sorption, incipient wetness sorption, melt loading and supercritical fluid impregnation [9]. The incipient wetness and the equilibrium solvent sorption methods require the dissolution of the API in an organic solvent [14,15]. The solution is then soaked into the porous carrier particles and the solvent is dried off. However, the removal of solvents from mesoporous materials is a time-consuming, energy-intensive process often requiring vacuum drying due to strict limits on the residual solvent concentration in pharmaceutical products [16]. Supercritical fluid impregnation is problematic due to the usually low solubility of APIs in the supercritical CO_2 and also due to the high costs of the technology [17]. For thermally stable APIs that do not decompose or degrade when heated above their melting point temperature, these disadvantages can potentially be avoided by melt loading since no solvent is required and therefore no dissolution and drying steps need to occur. Moreover, the process can be carried out in standard pharmaceutical equipment (fluidised beds).

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Table 1
The reactant amounts and ethanol-water ratios used.

sample	OA (ml)	TEOS (ml)	EtOH (ml)	H_2O (ml)	ratio	HNO_3 (ml)
SiRef	10.0	10.0	0.0	100	0	0.2
SiEtOH_1:5	2.5	2.5	5.00	25	1:5	0.0
SiEtOH_1:4	2.5	2.5	6.25	25	1:4	0.0
SiEtOH_1:3	2.5	2.5	8.33	25	1:3	0.0
SiEtOH_1:2	2.5	2.5	12.50	25	1:2	0.0
SiEtOH_1:1	2.5	2.5	25.00	25	1:1	0.0

The process involves temporary heating of a mixture of the API and the carrier particles above the melting point of the API, after which the molten API is drawn by capillary forces into the porous structure of the carrier, where it solidifies after cooling [18]. If the pore diameter is sufficiently small (not exceeding approximately ten times the equivalent molecular diameter of the API), the amorphous state can be preserved over extended periods of time.

However, it can be challenging to get the molten API efficiently and uniformly distributed in the mesopores due to a combination of the high viscosity of the melt and the topologically complex, tortuous character of the pore network [19,20]. As a consequence, the API may preferentially deposit on the external surface of the carrier particles where it can later recrystallise due to lack of spatial confinement, rendering the amorphisation process ineffective. This problem could be mitigated by developing a material with a hierarchical porous structure, which would allow the viscous melt to flow more readily into the pores. The problem of optimum flow distribution to a given volume can be conceptually addressed by the constructal theory [21,22] and generally leads to structures involving hierarchical or bi-modal pore networks. For example, in the field of heterogeneous catalysis, porous particles with a bi-modal pore size distribution have been proposed to avoid diffusion limitations [23–25].

Silica particles with a defined porous structure can be synthesised by templating methods [26–28]. The combination of emulsion-based or soft templating methods with a controlled rate of silica precipitation makes it possible to customise the pore architecture and even produce particles with multiple levels of porosity [29–32]. In the present work, we report the synthesis and textural characterisation of novel silica carrier particles with three levels of porosity, consisting of a central hollow cavity, a macroporous shell for enhanced transport rate of the API melt, and a mesoporous matrix for efficient stabilisation of the amorphous state. These particles are shown to give superior melt-in rates compared to a reference mesoporous material without the macropores, combined with the ability to maintain a poorly soluble API (ibuprofen) in the amorphous state at drug loadings as high as 50% by weight.

2. Experimental methods

2.1. Materials

Tetraetoxysilane (TEOS, > 99%) and octylamine (OA, > 99%) were purchased from Sigma-Aldrich, nitric acid (HNO_3, 65%) and ethanol (99.9%) were purchased from Penta chemicals. Ibuprofen was kindly provided by Zentiva, k.s. All chemicals were used as received.

2.2. Synthesis of silica particles

As a reference material, hollow-core mesoporous silica particles without a hierarchical pore structure have been prepared. These particles were produced by a modified octylamine-templated synthesis route [26,32], which proceeds as follows: 10 ml of octylamine was mixed with 10 ml of TEOS in a 200 ml PTFE beaker and the mixture was stirred for 3 min (PTFE magnetic stirring rod 25 × 5 mm at 800 rpm). Under constant stirring, 100 ml of water acidified with 0.2 ml of nitric acid was rapidly added to the mixture and stirred for 3 min. The resulting particles were collected using centrifugation (Rotor TA 15-6-50, 6000 rpm, 3 min) and then washed by acetone-ethanol mixture 1:1 (v/v) three times. The washed particles were dried and calcined (using a 6-hour temperature ramp from 20 °C to 600 °C followed by 6 h at 600 °C). Particles prepared using this method will be denoted as “SiRef”.

To prepare particles with a hierarchical pore structure, a similar procedure to the one described above was used. The only difference was that instead of using acidified water, mixtures of water and ethanol at systematically varying ratios were used, as specified in Table 1. Due to the different amounts of added ethanol, the absolute volume of the reaction mixture varied as well. Particles prepared using this method were denoted depending on the ethanol-water ratio used as “SiEtOH_1:1”, “SiEtOH_1:3” and so on (cf. Table 1). The TEOS conversion was evaluated according to the reaction stoichiometry as

$$X = \frac{m_{SiO_2}}{m_{TEOS}} \frac{M_{w,TEOS}}{M_{w,SiO_2}} \quad (1)$$

where m_{SiO2} is the final mass of recovered silica particles (after drying and calcining), m_{TEOS} is the initial mass of TEOS used for the synthesis, and $M_{w,i}$ are the molar weights of the substances.

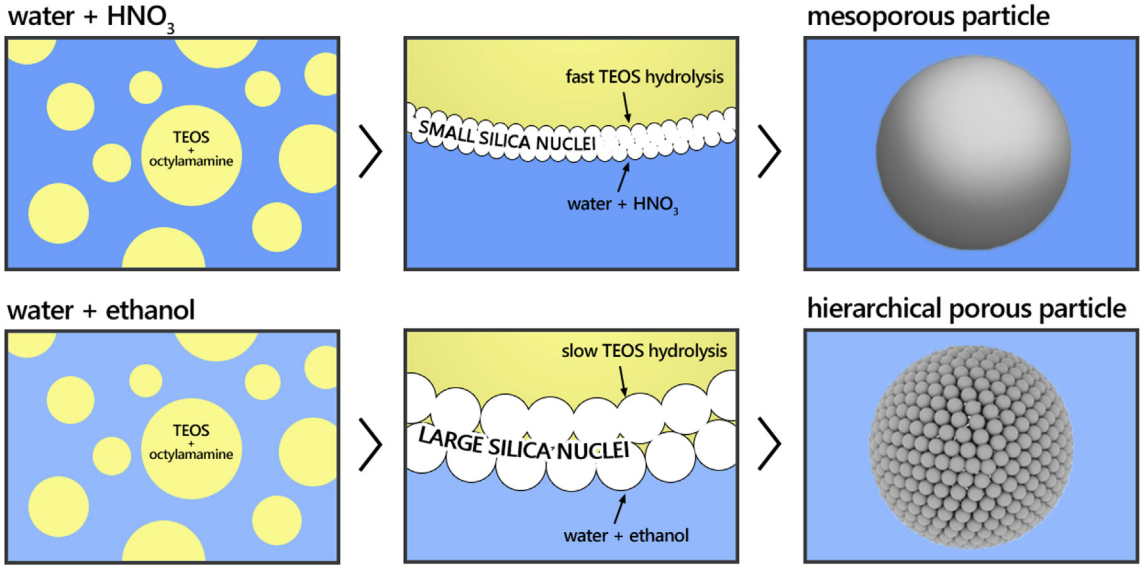

Fig. 1. Scheme of the particle formation mechanism for the original synthesis (top tow) and the synthesis in the presence of ethanol (bottom row).