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Stabilisation of amorphous ibuprofen in Upsalite, a mesoporous magnesium carbonate, as an approach to increasing the aqueous solubility of poorly soluble drugs

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ABSTRACT

One attractive approach to increase the aqueous solubility and thus the bioavailability of poorly soluble drugs is to formulate them in their amorphous state since amorphous compounds generally exhibit higher apparent solubilities than their crystalline counterparts. In the current work, mesoporous magnesium carbonate was used to stabilise the amorphous state of the model substance ibuprofen. Crystallisation of the drug was completely supressed in the formulation, resulting in both a higher apparent solubility and a three times faster dissolution rate of the drug where the drug release was shown to be diffusion controlled. It was also shown that the formulation is stable for at least three months when stored at 75% relative humidity. The simple synthesis together with a high loading capacity and narrow pore size distribution of the mesoporous magnesium carbonate is foreseen to offer great advantages in formulations of poorly soluble drugs.

1. Introduction

Over recent decades, the poor aqueous solubility of many active pharmaceutical ingredients (APIs) has been one of the most challenging issues for the pharmaceutical industry. About 40% of newly marketed drugs have poor solubility and 80–90% of drug candidates in the R&D pipeline fail because of solubility problems (Babu and Nangia, 2011; Jia, 2005; Serajuddin, 1999). These drugs with poor aqueous solubility subsequently have low bioavailability, which can limit their therapeutic efficacy. To circumvent this problem, a number of different strategies have been developed, including crystalline salt formulations, API particle reduction, use of solubilisers, co-ground mixtures, and pro-drugs (Brouwers et al., 2009). The success of a formulation strategy depends on both the chemical nature of the drug and practical processing issues. For example, strongly acidic and basic substances can be formulated as salts while weak acids and bases cannot, whereas reduction of the API particle size can lead to build-up of static charges imposing handling difficulties for certain substances (He, 2009).

Since a high number of therapeutically promising, poorly soluble APIs never reach the patient due to lack of suitable formulation methods, there is still a high unmet need for new strategies in this area. One recently embarked on, and seemingly attractive, approach is to stabilise such APIs in their amorphous state since, despite the higher energy and metastability associated with this state, amorphous drugs generally exhibit higher apparent solubility than the crystalline form of the same substance (Brouwers et al., 2009; Galia et al., 1998; Xu et al., 2013). However, because of their metastable nature, amorphous APIs are driven by thermodynamics to crystallise, depending on factors like the glass transition temperature (T_g) and moisture content of the formulation (Yoshioka and Aso, 2007). Thus, the amorphous API needs to be stabilised in the formulation in order to prevent crystallisation. Typically, organic polymers like polyethylene glycol (PEG) and polyvinyl pyrroline (PVP) are used in solid dispersions for this purpose. The complex polymer network acts by reducing the mobility of the drug molecules (Konno et al., 2008; Rawlinson et al., 2007). However, this approach is associated with difficulties in the industrial manufacturing processes and problems with the chemical stability of the products (Qian et al., 2010; Taylor and Zografi, 1997).

Nonetheless, the emergence of nanotechnology in the last decades has provided novel solutions for drug delivery in most

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pharmaceutical formulation areas (Fadeel et al., 2010; Mihranyan et al., 2012), including the area targeting the stabilisation of amorphous APIs. It has been found that mesoporous structures (with pore diameters between 2 and 50 nm) are able to effectively suppress the crystallisation of amorphous substances via geometrical constraints, and also as a result of changes in nucleation mechanisms and kinetics inside the small pores and the interaction between the API and the pore walls (Rengarajan et al., 2008), which can induce a crystalline-to-amorphous phase transformation (Qian and Bogner, 2011). This effect is more pronounced on surfaces featuring high curvature and on those with permanent dipoles, which can induce polarization or form dipole–dipole interactions (Qian et al., 2011). The phenomenon was first observed in 1984 when Nakai et al. (Nakai et al., 1984) saw an anomaly in the melting endotherm and the X-ray diffraction pattern of organic compounds that were mixed together with controlled-pore glass beads. It was suggested that this anomaly was due to amorphisation of the organic molecules under study (i.e. benzoic acid), which had diffused into the voids between the glass beads and existed there in an amorphous state. It was later shown that this type of amorphisation is pronounced in pores with diameters smaller than 50 nm (Nakai et al., 1989). In 2001, the mesoporous silica MCM-41 was proposed as a drug delivery vehicle (Vallet-Regi et al., 2001) and since then different mesoporous silicas have been found useful for improving the solubility of several pharmaceutical compounds (such as itraconazole, atazanavir and ibuprofen (Bras et al., 2011; Heikkila et al., 2007; Mellaerts et al., 2007; Xia et al., 2012)) because of conservation of the amorphous state of the incorporated API. Recent publications have also shown good correlations between improved in vitro solubility and improvements in the bioavailability of drugs formulated in mesoporous materials (Wang et al., 2012; Xia et al., 2012). However, the mesoporous silica industry struggles with high manufacturing costs due to expensive silica sources and surfactants used in the fabrication, as well as environmental concerns related to the often toxic surfactants needed as pore-forming templates in the synthesis (Gerardin et al., 2013). Mesoporous silica is not yet available in bulk quantities and the price for MCM-41 available via e.g. Sigma–Aldrich is presently ~20,000 € kg^{-1} (2014)[1]. Mesoporous silicon produced via etching of crystalline silicon also appears to conserve amorphous APIs, but this type of material is also associated with high production costs and difficulties with large scale manufacturing (Xu et al., 2013).

In connection to the above, it should be pointed out that the mesoporous forms of silica and silicon should not be confused with colloidal silica based on aggregated nanoparticles forming rather fluffy structures. Whereas the latter is commonly used in pharmaceutical formulations as, e.g. anti-caking agent, adsorbent or disintegrant, it lacks the pore structure of the former and has not been shown to have the ability to work as solubility enhancers of poorly soluble substances.

As an alternative to mesoporous silica, we have recently proposed the use of a mesoporous type of vaterite (calcium carbonate) for the stabilisation of amorphous drugs (Forsgren et al., 2013a). The studied vaterite had a smaller pore volume and less well-defined pore size than mesoporous silica but is already listed as 'generally recognized as safe' (GRAS) by the FDA, and it can be produced from inexpensive raw materials in a simple synthetic process, which makes it an interesting drug stabiliser candidate. Vaterite had a stabilising effect on the incorporated amorphous API, which resulted in higher solubilities and faster dissolution rates for both celecoxib and ketokonazol (Forsgren et al., 2013a). However, the vaterite carrier proved to be unstable when exposed to humidity and complete suppression of crystallisation of the incorporated API was not obtained at higher drug loading levels. Other recent publications also show the possibility of using materials like mesoporous alumina and titanium zirconium oxide for the purpose of stabilising amorphous drugs (Kapoor et al., 2009; Wang et al., 2013), however, the FDA does not list these materials as GRAS, which is expected to complicate the route toward regulatory approval for such materials as pharmaceutical excipients.

Recently, we disclosed the synthesis and characterization of a novel mesoporous type of magnesium carbonate, named Upsalite, which can be synthesised using MgO, methanol and CO_2 as raw materials without using surfactants as pore-forming agents (Forsgren et al., 2013b; Frykstrand et al., 2014). Just like calcium carbonate, magnesium carbonate is also GRAS listed and the current work investigates the ability of Upsalite to enhance the solubility and at the same time provides high loading capacity and stability of poorly soluble APIs. Ibuprofen, a well-known, non-steroidal anti-inflammatory drug with limited aqueous solubility is used as model API in this study.

2. Materials and methods

2.1. Materials

Magnesium oxide (MgO) and ibuprofen (IBU) were obtained from Sigma–Aldrich, Sweden. Methanol and ethanol were purchased from VWR International, Sweden. CO_2 was obtained from AirLiquide, Sweden. All chemicals were used as received.

2.2. Synthesis of Upsalite

Upsalite was synthesised as described previously (Forsgren et al., 2013b; Frykstrand et al., 2014). Briefly, 170 g of MgO and 2.5 L CH_3OH were mixed at 500 rpm in a 5 L Ecoclave pressure reactor from Büchi. The reactor was pressurised with 3 bar CO_2 and the reaction was carried out at 55 °C. After four days, the temperature was lowered to room temperature and the reactor was depressurised. The product was dried at 75 °C in a vacuum oven for three days and then calcined at 250 °C for 6 h. Calcination is needed for complete decomposition of the organic intermediates formed in the reaction carried out in the pressure reactor (Frykstrand et al., 2014). When the calcination is performed at temperatures below 350 °C, magnesium carbonate is formed but at higher temperatures the carbonate will decompose into MgO and CO_2. After calcination, the obtained material was in the shape of white, centimetre sized particles that were grinded down to a smaller particle size using a mortar.

2.3. Drug loading procedure

IBU was incorporated into the Upsalite via a soaking method: 203.2 mg IBU was dissolved in 50 mL ethanol and then 642.7 mg of Upsalite was added to the solution. The mixture was placed on an orbital shaker at 100 rpm at room temperature for 24 h to allow for diffusion of IBU into the Upsalite. Subsequently, the suspension was dried in an oven at 70 °C to evaporate the solvent.

2.4. Characterisation

2.4.1. X-ray powder diffraction (XRD)

XRD analysis was performed with a D5000 diffractometer (40 kV, 40 mA, Siemens/Bruker) using Cu-Kα radiation (λ = 0.154 nm). Samples were ground in a mortar and put on silicon sample holders with zero background prior to analysis.

[1] www.sigmaaldrich.com on 22 Jan 2014.