European Journal of Pharmaceutical Sciences 93 (2016) 468–474

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Supersaturation of poorly soluble drugs induced by mesoporous magnesium carbonate

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ARTICLE INFO

Article history:
Received 1 August 2016
Received in revised form 25 August 2016
Accepted 29 August 2016
Available online 31 August 2016

Keywords:
Mesoporous
Crystallinity suppression
Drug release
Kinetics
Magnesium carbonate
Supersaturation

ABSTRACT

This work investigates whether the solubility of poorly soluble compounds can be improved by using mesoporous magnesium carbonate (MMC) as the drug delivery system. A solvent evaporation method was used to load structurally diverse model drugs (celecoxib, cinnarizine and griseofulvin) into the pores of MMC. The drug-loaded carrier system was then characterized in terms of porosity, crystallinity, and release profiles by a variety of experimental techniques, including X-ray diffraction, nitrogen adsorption analysis, differential scanning calorimetry, infrared spectroscopy, UV absorption spectroscopy, and thermogravimetric analysis. All three drugs were in a non-crystalline state after loading into the pores of MMC. The concentrations of the drugs in solution over time (a measure of the release rates from loaded MMC) were higher than the corresponding concentrations (dissolution rates) of equal amounts of the crystalline drugs. The release rates were five (celecoxib), three (cinnarizine) and two times (griseofulvin) higher than the dissolution rates of their crystalline counterparts. Supersaturation release profiles were also observed; the areas under the concentration-time curves (0–240 min) were 25- (celecoxib), 5- (cinnarizine) and 2-fold (griseofulvin) greater than those of the crystalline drugs. Hence, MMC shows promise as a general drug delivery vehicle for increasing the bioavailability of compounds with dissolution rate- or solubility-limited absorption.

1. Introduction

About 70% of all new active pharmaceutical ingredients (APIs) emerging from the discovery pipelines of pharma companies are poorly soluble in water. Poorly water-soluble drugs typically have low oral bioavailability which can result in oral dosage forms not producing the expected therapeutic effect (Amidon et al., 1995; UFAD, 2000). The solubility of APIs is shown in the biopharmaceutics classification system (BCS), which is used to identify compounds that merit biowaivers based on their in vitro dissolution, solubility, and permeation of the gastrointestinal tract tissues (UFAD, 2003). The solubility of BCS class II and IV compounds is too low for the complete dosage form to be dissolved (Yu et al., 2002). However, since permeation is constantly occurring along the gastrointestinal tract, some of the compounds could be more accurately regarded as dissolution rate-limited rather than as solubility-limited (Lennernäs, 2007; Volpe, 2010; Yang et al., 2007). To identify whether increasing the dissolution rate of an API could significantly increase its absorption, Butler and Dressman introduced the developability classification system (DCS) in 2010 (Butler and Dressman, 2010). The criteria for measuring the intestinal permeability to the drugs are the same in the DCS as in the BCS, but the dissolution volume is changed to identify dissolution rate- or solubility-limited compounds (van Hoogevest et al., 2011).

The relationship between dissolution rate and solubility is given by the Noyes-Whitney equation (Noyes and Whitney, 1897):

$$\frac{dC}{dt} = \frac{AD(C_S - C)}{h} \quad (1)$$

where dC/dt is the rate of dissolution, A is the available surface area of the dissolving solid compound, D is the diffusion coefficient of the compound, C_S is the maximum concentration of the compound dissolved in a given volume of dissolution medium at equilibrium (i.e. its solubility), C is the concentration of the compound in the medium at time t, and h is the thickness of the boundary layer around the dissolving compound. If the volume of the dissolution medium is large enough, the concentration of the drug (C) will generally be much lower than the solubility (C_S). This is commonly described as the dissolution being performed under sink conditions, which allows Eq. (1) to be simplified to:

$$\frac{dC}{dt} = \frac{ADC_S}{h} = kC_S \quad (2)$$

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http://dx.doi.org/10.1016/j.ejps.2016.08.059
0928-0987/

In this case, the dissolution rate is proportional to the solubility, which explains why drugs with limited solubility (i.e., class II and IV drugs) normally have low dissolution rates. Consequently, increasing the solubility could improve the dissolution rate, and subsequently the bioavailability, of drugs with poor aqueous solubility (Brouwers et al., 2009; Stegemann et al., 2007; Vasconcelos et al., 2007).

To achieve this increased solubility, a number of formulation strategies have been developed. Recently, strategies such as using the salt of the drug, including a surfactant to improve solubilization, using microemulsion, self-emulsifying or liposomal drug delivery systems, reducing drug particle size, and using co-crystal, solid dispersion or amorphous forms of the drug has resulted in improved solubility (providing faster dissolution) and enhanced bioavailability for a significant number of poorly water-soluble drugs (Bikiaris, 2011; Merisko-Liversidge and Liversidge, 2011; Stegemann et al., 2007). All these strategies have their respective benefits and limitations and, since different APIs have different physiochemical properties, there is no universal solution.

One approach that has gained in popularity recently is to formulate the API in its amorphous state, since the apparent solubility of this physical form is greater than that of the crystalline counterpart (Babu and Nangia, 2011; Dahan et al., 2013; Frank et al., 2012; Serajuddin, 1999). However, the amorphous form is thermodynamically unstable and is prone to recrystallize to the more energetically favorable crystal form if it is not stabilized (Kaushal et al., 2004; Qian et al., 2012; Sinclair et al., 2011). Physical stabilization of the amorphous form has been achieved using organic polymers like hydroxypropyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP), since the polymer networks reduce the mobility of the drug molecule (Gupta et al., 2004; Konno et al., 2008; Qian et al., 2010). However, after addition of the polymer the chemical stability of the product may still be limited, with recrystallization as the result.

Mesoporous materials (i.e., with pore sizes between 2 and 50 nm) inhibit the crystallization of APIs and also provide long-term stability of the non-crystalline forms (Forsgren et al., 2013a; Frank et al., 2014). For example, the addition of mesoporous silica materials (such as SBA-15 and MCM-41) to the formulation has improved the solubility of several pharmaceutical compounds (Azais et al., 2006; Qian and Bogner, 2012; Shen et al., 2010; Shen et al., 2011; Aerts et al., 2011; Wang, 2009; Wang et al., 2012). Recently, we demonstrated that the novel, biocompatible, mesoporous magnesium carbonate (MMC) material (commercialized as Upsalite®), which has a narrow pore diameter distribution centered at ~5 nm and a high surface area (>400 m^2/g, dependent on production settings), can maintain loaded drug material in its non-crystalline form (Frykstrand et al., 2015; Zhang et al., 2014; Zhang et al., 2016). Unlike mesoporous silica, there is no requirement for organic surfactants during the synthesis of such MMC (Forsgren et al., 2013b; Frykstrand et al., 2014). When used as a drug carrier, MMC has been successfully loaded with a high proportion of ibuprofen (about 30% w/w) in its amorphous state and the loaded drug has been proven to be rapidly released into solution, resulting in a higher concentration than seen with crystalline ibuprofen (Zhang et al., 2014; Zhang et al., 2016).

To date, we have demonstrated the use of MMC as a delivery system for BCS II compounds ibuprofen (Zhang et al., 2014; Zhang et al., 2016) and itraconazole (Cheung et al., 2016). In this paper, we explore the more general applicability of MMC as a delivery system for poorly water-soluble compounds (Maity and B., 2015; UFAD, 2000). Three structurally diverse compounds were selected for this purpose (Table 1). We chose drugs with different protolytic functions (a weak base, a weak acid and a non-protolyte) and for which the solid state had varying impact on solubility and dissolution. The release of these compounds from the carrier system was studied after loading them in amounts that would result in concentrations below and above the saturation limit.

2. Materials and methods

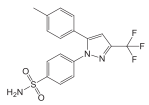
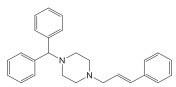
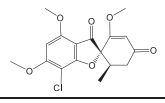
2.1. Materials

MMC (Upsalite®) was provided by Disruptive Materials AB, Sweden. Crystalline celecoxib was purchased from 3Way Pharm Inc., China, and crystalline cinnarizine and griseofulvin were purchased from Toronto Research Chemicals, Canada. Nylon membrane filters were purchased from Whatman, Germany. The purity of celecoxib, cinnarizine and griseofulvin was determined by HPLC to be 93%, 95% and 90%, respectively. Ethanol was purchased from VWR International, Sweden. Monobasic potassium phosphate and sodium hydroxide were purchased from Sigma-Aldrich. All chemicals were used as received.

2.1.1. Sample preparation and drug loading procedure

Before the drug loading procedure, the MMC was heated at 250 °C for 12 h to remove all organic intermediates formed during its synthesis. Each test compound was incorporated into the MMC via a solvent evaporation method. For celecoxib, 30 mg of the crystalline drug was dissolved in 50 ml ethanol before adding 500 mg MMC. The mixture was then placed on an orbital shaker (100 rpm) for 48 h at room temperature to allow the drug to diffuse into the MMC. Subsequently, the mixture was heated at 75 °C until the solvent was completely evaporated, after which the drug-loaded sample was left to dry at 85 °C for 24 h. Finally, the dried sample was ground and sieved to a particle size smaller than 100 μm (sample MMC-CEL). The same method was used for loading 95 mg cinnarizine and 90 mg griseofulvin into 1000 mg MMC, using 50 ml ethanol each (samples MMC-CIN and MMC-GRI, respectively).

Table 1
Physicochemical properties of celecoxib (acid), cinnarizine (base) and griseofulvin (non-ionizable).

Name	Chemical structure	logP[a]	pKa[a]	Molecular weight (g/mol)	Melting point (°C)[a]	Aqueous solubility (μg/ml)[b]
Celecoxib		3.9	11.1	381.4	160	1
Cinnarizine		5.6	7.5	368.5	118	<1
Griseofulvin		2.3	17.7	352.8	220	11

The following abbreviations are used: partition coefficient between octanol and water (logP), dissociation constant (pKa).
[a] logP, pKa and melting point were obtained from references Box and Comer (2008); Fagerberg et al. (2015), and Perlstein et al. (2014).
[b] Aqueous solubility values were obtained from references Forsgren et al. (2013a); Hedaya (2012), and Shahba et al. (2012).