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Enhanced release of poorly water-soluble drugs from synergy between mesoporous magnesium carbonate and polymers

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ABSTRACT

The need to combat poor water solubility has increased interest in supersaturating drug delivery systems. In this study, amorphous mesoporous magnesium carbonate (MMC) was used as a drug carrier to achieve supersaturation of tolfenamic acid and rimonabant, two drug compounds with low aqueous solubility. The potential synergy between MMC and hydroxypropyl methylcellulose (HPMC), a polymer commonly included as a precipitation inhibitor in drug delivery systems, was explored with the aim of extending the time that high supersaturation levels were maintained. Release was studied under physiological conditions using USP-2 dissolution baths. A new small-scale method was developed to enable measurement of the initial drug release occurring when the MMC is immersed in the water phase. It was shown that MMC and HPMC together resulted in significant supersaturation and that the polymer enabled both the achievement of a higher API concentration and extension of the supersaturation period. The new small-scale release method showed that the release was linearly increasing with the dose and that similar release rates were observed for the two model compounds. It was hence concluded that the MMC release was diffusion limited for the compounds explored.

1. Introduction

Limitations in the water solubility of active pharmaceutical ingredients (APIs) is an increasing problem; around 75% of the drugs under development and 40% of marketed drugs are poorly water-soluble (Di et al., 2012; Jia, 2005; Williams et al., 2013). Because intestinal absorption of an API is strongly affected by its solubility and dissolution rate, poor aqueous solubility can result in low bioavailability when the drug is taken orally (Amidon et al., 1995). Several methods of increasing the solubility and dissolution rate of poorly water soluble APIs are under investigation; among these are supersaturating drug delivery systems (SDDSs) (Brouwers et al., 2009; Fong et al., 2016). Supersaturation is achieved in these formulations through a process that can be explained by the so-called spring and parachute model. In short, the substance is delivered in a high energy form which is rapidly dissolved, creating a spring effect that results in a supersaturated solution. However, supersaturation is a metastable state and once the system starts to equilibrate, precipitation will take place. To hinder the precipitation and stabilize and maintain supersaturation, a "parachute" can be added (Brouwers et al., 2009). This is typically achieved through addition of a polymer which interacts with the API to prevent nucleation and/or crystal growth. Commonly used polymers include polyvinyl pyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG) (Brouwers et al., 2009; Overhoff et al., 2008; Rawlinson et al., 2007). Organic polymers have been used in conceptually different SDDSs, including amorphous solid dispersions (ASDs) (Brouwers et al., 2009), supersaturating lipid-based formulations (Hauss, 2007), silica-based systems (Wang et al., 2015), and nano-drug systems (Brouwers et al., 2009). Although the mechanisms involved in achieving supersaturation are different for these formulations, they all have the potential to increase the bioavailability of poorly water-soluble drugs. In a recent meta-analysis which investigated SDDSs as a means of enhancing oral bioavailability, it was shown that ASDs have attracted the greatest interest in recent years in terms of the number of scientific publications (Fong et al., 2016). However, that analysis also showed that when comparing the different SDDSs, nano-drug systems

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were the ones that resulted in the highest increases in in vivo bioavailability.

Advances in nanotechnology have also resulted in new tools for stabilizing amorphous pharmaceutical compounds in nanoporous matrices after Nakai et al. realized the potential of incorporating drug compounds in porous materials in 1984 (Nakai et al., 1984). The crystallization of APIs can be suppressed when they are loaded into the pores of mesoporous carrier materials, i.e. those with pore diameters between 2 and 50 nm. The main reason for this is that the pores provide geometric constraint, which changes the nucleation mechanisms and kinetics of the loaded compounds (Nakai et al., 1989; Rengarajan et al., 2008). For example, mesoporous silica carrier materials have been suggested as stabilizers for drug molecules (Bra's et al., 2011; Chen et al., 2009; Wang et al., 2012). However, high manufacturing costs due to the need for expensive templating agents and the high temperatures used to remove them and, in some cases, even the use of toxic surfactants as pore-forming templates have limited the widespread application of these materials (Gérardin et al., 2013). In contrast to the production issues associated with mesoporous silica, a mesoporous structure can be produced from calcium carbonate, which is one of the materials "generally recognized as safe" (GRAS) by the FDA, using a simple, low cost method. It has been shown that the resultant structure successfully stabilizes the poorly water-soluble compound celecoxib in its amorphous form (Forsgren et al., 2013a). However, this mesoporous material is not sufficiently stable in a moist environment to be useful for pharmaceutical applications. Recently, a novel amorphous mesoporous magnesium carbonate (MMC) material, commercialized as Upsalite®, was synthesized. MMC has been produced with a narrow pore diameter distribution, centered at approximately 5 nm, and has an extensive surface area (Forsgren et al., 2013b; Frykstrand et al., 2014). As magnesium carbonate is also a GRAS-listed material, MMC is an ideal candidate for pharmaceutical applications; in fact it has already been shown to suppress the crystallization of several poorly water-soluble drugs (Zhang et al., 2014, 2015, 2016). The aim of the study described in this paper was to explore whether MMC in combination with HPMC can be used as a drug delivery system to both induce and prolong the supersaturation of two model compounds, namely tolfenamic acid (TOL; a weak acid belonging to non-steroidal anti-inflammatory substances) and rimonabant (RIM; a weak base which was used to treat obesity before its recent withdrawal). Both of these compounds have poor aqueous solubility and relatively high lipophilicity.

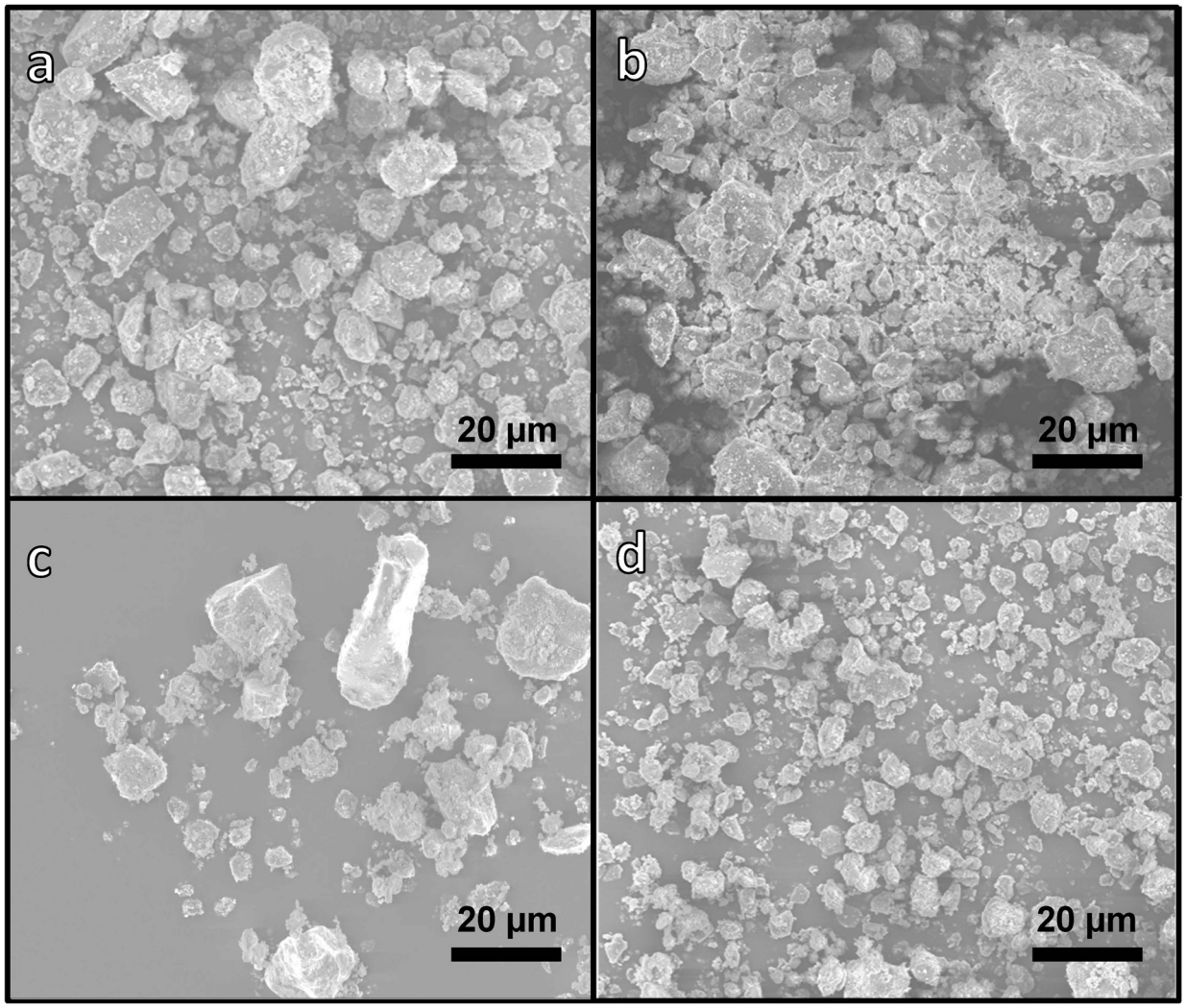

Fig. 1. Scanning electron microscopy images of mesoporous magnesium carbonate (MMC) prior to loading tolfenamic acid (TOL) (a), MMC-TOL (b), MMC prior to loading rimonabant (RIM) (c) and MMC-RIM (d). Scale bar: 20 µm.