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Mesoporous silica nanoparticles facilitating the dissolution of poorly soluble drugs in orodispersible films

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ABSTRACT

Orodispersible films (ODF) are immediately dissolving/disintegrating intraoral dosage forms, presented as substitutes of conventional tablets or capsules to ease problems associated with swallowing. Efforts have been made to be able to exploit ODFs as dosage forms for poorly soluble drugs. In the last two decades, mesoporous silica nanoparticles (MSNs) have been extensively used in drug delivery applications to overcome solubility problems of drugs. The tunable features of MSNs make them suitable candidates as drug carriers and solubility enhancers. In this study, the feasibility of MSNs as a carrier of poorly soluble drugs, using prednisolone as a model drug, in ODFs was investigated. Our results revealed that the increased amount of MSNs in ODFs leads to shortening of the disintegration time of the films. Drug content investigations showed that low dose ODFs with prednisolone incorporation efficiencies higher than 80% could be produced. Furthermore, the prednisolone release profile from ODFs can be tuned with the incorporation of MSNs as drug carrier (MSN_{pred}). The MSN_{pred} incorporated ODFs yield with immediate release of drug from the ODF, whereby 90% of the prednisolone content could be released in the first minutes. By modifying the MSN_{pred} design with copolymer surface coating, prednisolone (cop-MSN_{pred}) release can be modulated into a two-step sustained release profile. To sum up, the MSNs platform does not only provide careful low dose incorporation into ODF with high efficiency, but it also aids in tuning the drug release profiles from ODFs.

1. Introduction

Oral drug administration is still considered the most convenient route for patients, known for the highest patient acceptability and high therapy compliance. Nevertheless, pediatrics, geriatrics, the mentally ill, the developmentally disabled, and uncooperative, nauseous patients experience difficulties in taking solid oral dosage forms (Hoffmann et al., 2011). Therefore, pharmaceutical companies have tremendous interest in developing alternative oral dosage forms that can alleviate the problems of swallowing (Slavkova and Breitkreutz, 2015).

Orodispersible films (ODF) are immediately dissolving/disintegrating intraoral dosage forms that could be regarded as substitutes for conventional tablets or capsules to ease the problem of swallowing. ODFs with the special features of being thin, available in various sizes and shapes, requiring neither water nor having the risk of choking can thus alleviate the problems associated with swallowing. In addition, ODFs are offering the possibility of individualization of the dose, which is an important means to achieve more precise medication and mitigate significant variability in drug response (Hoffmann et al., 2011; Peck, 2018). ODF provides release of the drug within seconds, and the drug is absorbed through the oral cavity and thus the first-pass metabolism can be avoided for some drugs, which may improve bioavailability (Bala et al., 2013).

ODFs are commonly used with water-soluble drugs, which are the easiest to formulate for fast dissolution and homogenous drug distribution. Despite the estimated 40% of approved drugs and nearly 90% of the drugs in the developmental pipeline consisting of poorly soluble molecules, they have not been formulated in the ODF dosage form due to their limits in dissolution and bioavailability (Kalepu and Nekkanti, 2015). Formulation approaches utilizing nanoparticles in combination with ODF dosage forms are conducted to address this issue, with benefits provided by the particle size reduction that can overcome the solubility limitation. In the literature, examples include formulations encompassing the embedding of nano-sized drug crystals in the film forming polymer during the manufacturing process or printing drug suspensions onto drug-free ODF templates (Shen et al., 2013; Steiner

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et al., 2017, 2016; Wickström et al., 2017; Zhang et al., 2015). In these formulations, however, the aggregation of the nanosized drug crystals is a major obstacle to achieving the expected gains of dissolution enhancement. Therefore, in the literature, sufficient particle stabilization methods by using polymers or surfactants have been investigated (Beck et al., 2013; Krull et al., 2015; Shen et al., 2013).

The solubility of poorly soluble drugs can be improved by physical, chemical, or other modifications of the drug molecules (Maleki et al., 2017). Mesoporous silica nanoparticles (MSNs) have been shown to be advantageous for enhancing the solubility of different drug molecules, which was recently also demonstrated in its first-in-man study (Bukara et al., 2016). MSNs possess unique properties, such as high specific surface area, high pore volume and appropriate pore sizes in the molecular range, ordered pore structures and silanol groups on their surfaces that can interact with a variety of drug molecules. MSNs can be successfully used as dissolution enhancers due to the confinement effect provided by the molecularly sized pores (in the range of 2–50 nm) to prevent the crystallization of loaded drug molecules. Further, the surface silanols can form hydrogen bonds with the drug molecules and, in the case of weak interactions, the adsorbed compound can be released as fast as single molecules (Maleki et al., 2017). Therefore, we believe that by loading poorly soluble drugs into the confined pores of MSNs, the obstacles due to the interaction between the drug crystals and ODF film forming polymer matrix and incompatibilities could be eliminated. This way, the limitations in the poorly soluble drug formulations of ODFs can be overcome, and better solubility and bioavailability of the drugs can be provided.

The objective of the present study is to develop MSNs-incorporated ODF formulations to provide enhanced drug (in the present case, the BCS class II drug prednisolone) dissolution and, therefore, potentially increase the bioavailability of poorly soluble drugs. Furthermore, we show that low dose drugs can be incorporated adequately into ODFs with the aid of MSNs. The incorporation of MSNs into poly(vinyl)alcohol based ODFs by embedding the MSNs into the polymeric matrix of ODFs was successfully carried out. The obtained results show that the disintegration time of ODFs can be decreased with the increased amount of MSNs in the ODF matrix. Low dose drug incorporation into ODFs with high efficiency can be prepared, and tuning of the drug release profiles from ODFs can be obtained.

2. Materials and methods

2.1. Materials

All the reagents used in MSNs synthesis were purchased from Sigma-Aldrich. For the orodispersible film preparations, polyvinyl alcohol4-88 (PVA, EMPROVE® exp, Merck, Germany), anhydrous glycerin (Sigma-Aldrich, Germany) and Milli-Q water were used. Prednisolone ≥99% (Sigma–Aldrich) was employed as the API to be incorporated into ODF.

2.2. Methods

2.2.1. Preparation and characterization of pristine and drug-loaded mesoporous silica nanoparticles (MSNs)

MCM-41 type MSNs were synthesized in basic aqueous solution with the addition of absolute ethanol (20 v/v%) as co-solvent. Cetyltrimethylammonium bromide (CTAB) and tetraethylorthosilicate (TEOS) were mixed to the basic aqueous reaction solution as structure-directing agent (SDA) and the silica source, respectively. The reaction was conducted overnight in a conical flask overnight with stirring at 33 °C. The molar composition of the synthesis solution was 1 TEOS: 1.2×10^{-2} CTAB: 0.31 NaOH: 71.8 EtOH: 1063.8 H_2O. After the overnight reaction, the SDA was removed by solvent extraction process three times in ethanolic NH_4NO_3 solution. The obtained MSNs were kept as dry powder form after extraction under vacuum. The hydrodynamic sizes and ζ-potential values of prepared MSNs were analyzed in HEPES buffer solution (25 mM, at pH 7.2). Furthermore, the morphology and porous structure of the MSNs were investigated with electron microscopy imaging.

In order to investigate the potential of MSNs as the drug carriers in the ODF, the drug loading capacity of MSNs was investigated. For this purpose, prednisolone was loaded into MSNs with the method optimized in our previous study (Martín et al., 2014). Briefly described: 20 mg of MSNs was mixed into different concentrations of 10 mL prednisolone-cyclohexane solutions (5, 10, 20, 50, 100 w/w% in respect to the particle mass). The suspension was kept overnight at room temperature under stirring. The next day, the prednisolone loaded MSNs were collected by centrifugation and the obtained samples were vacuum dried. Afterward, prednisolone elution was carried out in order to plot the prednisolone adsorption isotherm as a function of equilibrium concentration and to determine the highest prednisolone loading amount on MSNs. The adsorption isotherm of prednisolone is presented in Fig. S1. The prednisolone loaded MSNs with different drug loading degrees were abbreviated as MSN_{pred}, and starting prednisolone loading amounts with respect to MSNs were denoted as $MSN_{pred\ (20\ w/w\%)}$, $MSN_{pred\ (50\ w/w\%)}$, $MSN_{pred\ (100\ w/w\%)}$ later in this study.

The redispersibility of MSNs with different degrees of drug loading was investigated by measuring the hydrodynamic size and ζ-potential of MSNs suspensions in physiological buffer solution (HEPES 25 mM, pH 7.2) in order to decide the most appropriate drug loading degree for the handling during the preparations of ODF.

Furthermore, the MSN_{pred} with the optimal prednisolone loading degree was surface coated with the in-house-produced $mPEG_{high}$-PEI copolymer in order to improve MSNs dispersibility during the ODF incorporation process (Şen Karaman et al., 2014). The surface coating of MSNs was carried out via mixing of the copolymer with $MSN_{pred.}$ suspensions in HEPES with a 50 w/w% copolymer ratio with respect to MSNs. The copolymer adsorption process was carried out for 3 h at room temperature with mild stirring. After the adsorption process was accomplished, the particles were centrifuged and washed to get rid of excess and loosely adsorbed copolymers. The copolymer adsorbed $MSN_{pred.}$ samples are henceforth abbreviated as cop-$MSN_{pred.}$ later in the study. The success of copolymer adsorption was confirmed with the ζ-potential measurements.

2.2.2. Preparation of orodispersible films with/without MSNs

In this study, the solvent casting method was employed for the preparation of ODFs. The film former (PVA) and plasticizer (glycerin) were mixed in Milli-Q water for 2 h at 90 °C and left for homogenization overnight under stirring at room temperature. The composition of the film solution was adjusted to PVA 30%, glycerin 4%, and 66% water based on preliminary investigations. The film solution was subsequently poured onto a transparent foil and casted with the coating knife (Erichsen D-58675 Hemer/Westfalen) and casting thickness was adjusted to 500 µm.

After casting of the films, solvent evaporation at different temperatures (room temperature (RT), for 18 h, 40 °C and 60 °C for 4 h, as well as 80 °C for 2 h) were tried out in order to obtain ODFs according to the defined thickness range of 5–200 µm in the literature by using the most convenient method (i.e. time efficiency and uniformity) for the preparations (Anand Saharan, 2017).

The incorporation of MSNs into the ODF matrix was carried out by mixing the ready-made MSNs suspensions with the homogenized film former solution. Afterward, the formulation was stirred and sonicated until visual homogenization is obtained. The MSNs content was varied to be 0.1 w/w% and 0.5 w/w% relative to the PVA content. 0.1 w/w% MSN incorporated ODF and 0.5 MSN incorporated ODFs henceforth abbreviated as MSN(0.1 w/w%)-ODF and MSN(0.5 w/w%)-ODF Thus, in the case of a 100 g preparation, 150 mg and 30 mg MSNs were incorporated into film forming solution. After adjusting the preparation methods and investigating the characteristics of the ODFs, all the drug incorporated ODFs were prepared. In this approach, MSN_{pred} and cop-