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Application of hydroxypropyl methylcellulose as a protective agent against magnesium stearate induced crystallization of amorphous itraconazole

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ABSTRACT

Itraconazole is a fungicide drug which has low bioavailability due to its poor water solubility. Amorphous solid dispersion (ASD) is a tool that has the potential to greatly increase the dissolution rate and extent of compounds. In this work, the dissolution of tablets containing the ASD of itraconazole with either hydroxypropyl methylcellulose (HPMC) or vinylpyrrolidone-vinyl acetate copolymer (PVPVA) was compared in order to find a formulation which can prevent the drug from the precipitation caused by magnesium stearate. Formulations containing the PVPVA-based ASD with HPMC included in various forms could reach 90% dissolution in 2 h, while HPMC-based ASDs could release 100% of the drug. However, HPMC-based ASD had remarkably poor grindability and low bulk density, which limited its processability and applicability. The latter issue could be resolved by roller compacting the ASD, which significantly increases the bulk density and the flowability of the powder blends used for tableting. This roller compaction step might be a base for the industrial application of HPMC-based, electrospun ASDs.

1. Introduction

One of the most important challenges of the pharmaceutical industry is the poor water solubility of recently discovered drugs. Amorphous solid dispersion (ASD) has proved to be a useful tool for enhancing dissolution, and as a result, the bioavailability of these active pharmaceutical ingredients (APIs) (Chuah et al., 2014; Engers et al., 2010; Leuner and Dressman, 2000; Vasconcelos et al., 2007). Electrostatic spinning, which is a thoroughly discussed process, is a potent way of producing ASDs (Agarwal et al., 2013; Ghorani and Tucker, 2015; Nagy et al., 2012; Reneker et al., 2007; Reneker and Yarin, 2008; Yu et al., 2010; Yu et al., 2009a). Electrospun nanofibers gain their enhanced dissolution from the high specific area generated during the process (Balogh et al., 2014; Balogh et al., 2015a; Balogh et al., 2015b; Yu et al., 2009a; Yu et al., 2009b). A promising scaled-up electrospinning technology (high-speed electrospinning, HSES) has been recently developed (Nagy et al., 2015b), which can potentially produce several kilograms of ASDs in a day. HSES has been used to prepare ASDs for different formulations such as tablets (Démuth et al., 2016a) or drug-loaded straws (Farkas et al., 2018).

Itraconazole (ITR) is an orally active antifungal drug and its ability to bind to fungal cytochrome P-450 isozymes results in the inhibition of ergostherol synthesis, the perturbation of membrane-bound enzyme action, and membrane permeability (Grant and Clissold, 1989). ITR is a drug with remarkably weak aqueous solubility; therefore, it is a good candidate for the research of ASDs. Several articles have discussed that electrostatic spinning was a feasible way of preparing ASDs containing ITR and vinylpyrrolidone-vinyl acetate copolymer (PVPVA) or hydroxypropyl methylcellulose (HPMC) (Démuth et al., 2016b; Nagy et al., 2015a; Verreck et al., 2003a). However, the stability of the amorphous API can be obviously different in different polymer matrices; therefore, it is vital to choose the appropriate polymer to avoid suboptimal results (Ewing et al., 2014; Konno et al., 2008). One of the most important factors which determine the behavior of API-polymer systems is the presence of the various interactions (hydrophobic and hydrophilic interactions, hydrogen bond) between the API molecule and the polymer chains of the matrix (Huang and Dai, 2014; Meng et al., 2015; Ohara et al., 2005; Van Ngo et al., 2016). Polymers that can form hydrogen bonds with the API can protect the drug from crystallization during storage more effectively than those which cannot do so (Wegiel et al., 2013). The possibility of hydrogen bond formation does not only affect the physical stability but the dissolution behavior as well. For instance,

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HPMC can prevent the drug from precipitation, and thus better bioavailability can be realized than from dispersions without hydrogen bonds (Six et al., 2005). This cellulose derivative is able to form hydrogen bonds with ITR (oxo moiety of the drug and hydroxyl groups of the polymer), and therefore it is a promising choice as the polymer matrix of ASDs containing ITR. It has been found that HPMC can ensure good stability for ITR (keeping it perfectly amorphous for the investigated period of time, i.e. a year) due to the formation of strong secondary interaction with the drug. The crystallization of the API could be prevented for up to 12 months in electrospun nanofibers, even under harsh conditions e.g. 40 °C/75% relative humidity (Démuth et al., 2016b; Verreck et al., 2003b). Our recent research showed that an interaction between ITR and stearic acid (SA) can lead to the precipitation of the API during in vitro dissolution (Démuth et al., 2017b). However, it was also found that HPMC has the ability to prevent this phenomenon if it is applied as matrix in the ASD. To summarize, it can be stated that HPMC displays very beneficial properties with regards to the maintenance of the physical stability and good dissolution of amorphous drugs.

Conversion of nanofibers into conventional tablets is rarely discussed in the literature. There are only a few articles about the tableting of the materials produced by electrostatic spinning (Démuth et al., 2016a; Démuth et al., 2017a). In spite of their obviously advantageous behavior with respect to stability and dissolution, no study can be found discussing the downstream processing of HPMC-based, electrospun ASDs. In order to produce tablets, the challenging steps of fiber grinding and increase of the bulk density must be done. The goal of our work was two-fold. Firstly, the protective effect of HPMC was intended to be evaluated by comparing the in vitro dissolution profiles of different tablets containing PVPVA- and/or HPMC-based ASDs or PVPVA-based ASD and various forms of HPMC (tableting excipient or coating material). Furthermore, downstream processing of HPMC-based nanofibers with ITR was investigated to generate tablets.

2. Materials and methods

2.1. Materials

Itraconazole was given by Janssen Pharmaceutica N. V. (Beerse, Belgium). Hydroxypropyl-methylcellulose 2910 (HPMC) was supplied by Aqualon, Hercules (Zwijndrecht, the Netherlands). Mannitol (Pearlitol® 400DC) was a kind gift from Roquette Pharma (Lestrem, France). MgSt was obtained from Hungaropharma Ltd. (Budapest, Hungary). Aerosil® 200 was received from Evonik Industries (Hanau-Wolfgang, Germany). Microcrystalline cellulose (MCC, Vivapur® 200) was provided by JRS pharma (Rosenberg, Germany). PVPVA and Kollidon® CL were supported by BASF (Ludwigshafen, Germany). Organic solvents and the concentrated HCl solution were ordered from Merck Ltd. (Budapest, Hungary). Opadry OY-S-29019 was given by Colorcon (Chalfont, USA).

2.2. Preparation of ASD by electrospinning

ASDs were prepared by the HSES method as described in (Nagy et al., 2015a). The solution of ITR and the matrix polymers was loaded into the spinneret using a peristaltic pump at a rate of 91 mL/h. The rotational speed of the spinneret was 16,000 rpm. The electric tension between the spinneret and the collector (earthed aluminum sheet) was 30 kV. The collector-nozzle distance was set to 300 mm. In the case of ASD_HPMC, the solution used for HSES had a concentration of 0.125 g/mL (40% ITR, 60% HPMC), and the solvent was a 1:1 mixture of ethanol and dichloromethane. As for ASD_PVPVA, the concentration was 0.375 g/mL (40% ITR, 60% PVPVA), and the solvent was a 2:1 mixture of dichloromethane and ethanol.

In the case of ASD_PVPVA_HPMC, the composition had to be optimized. The investigated concentration of the solid materials was ranging from 0.125 g/mL to 0.25 g/mL, while ratios of the two solvents (dichloromethane and ethanol) and the two polymers (PVPVA and HPMC) were examined (1:1 or 2:1). The small amounts of the samples were prepared by the commonly used single needle electrospinning apparatus. The applied voltage was 30 kV, the solution was injected at a flow rate of 15 ml/h and the collector-nozzle distance was 300 mm.

2.3. Milling of the ASD

Two different methods were applied for grinding the fibers: hammer milling on an IKA MF10 equipment (rotational speed was set to 4000 rpm, and a sieve with 1 mm opening diameter was used), and pushing through a sieve with a hole size of 0.8 mm (according to our experience, this method gives very similar product as oscillational milling).

2.4. Modulated Differential Scanning Calorimetry (mDSC)

The DSC thermogram was recorded on a DSC Q2000 instrument (TA Instruments, Crawley, UK) by “Heat only” modulation mode, with a heating rate of 2 °C/min, an amplitude of 0.318 °C and a period of 60 s. Standard aluminum pans (TA instruments) were applied with crimping.

2.5. Scanning electron microscopy

Samples prepared by SNES and HSES were investigated with a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope. Each specimen was fixed with conductive double-sided carbon adhesive tape and sputter-coated with gold alloy prior to examination. The applied accelerating voltage was set to 15 kV.

2.6. Particle size distribution measurement

The particle size distribution of the HSES fibers was examined on a Malvern Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, UK) laser diffraction particle size analyzer (dynamic light scattering in solid state, i.e. without any solvent). About 1 g material was weighed, and a basket equipped with metal balls was placed after the sample tray to facilitate the disaggregation of particles.

2.7. Fourier-transform infrared (FTIR) spectroscopy

The FTIR spectra were recorded on a Bruker Tensor 37 type spectrometer (Ettlingen, Germany) equipped with deuterated triglycine sulfate detector. The samples were pressed into pastilles with KBr on a Camille OL95 type press (Manfredi, Turin, Italy). The region of 400 to 4000 cm^{-1} was investigated with 4 cm^{-1} resolution, while 16 scans were accumulated. Spectra were baseline corrected and normalized. Samples for FTIR examination were prepared as following: the two substances (HPMC and SA or HPMC and PVPVA) were dissolved in dichloromethane and a droplet of 0.1 N HCl solution was added to the mixture. Solutions were heated until complete dissolution while stirring and poured into a crystallizing dish. The solvent evaporated, and the sample was dried on air for a day.

2.8. Roller compaction of ASD

ASD was compacted on a QuickCompactor (Quick2000 Ltd., Tiszavasvári, Hungary). Feeder screw speed was set to 97 rpm, roll speed was 6 rpm, pressure was set to 80 bar, rotational speed of the granulator was 110 rpm, and a sieve with 1.2 mm size was used. The ASD with HPMC was compacted twice to generate satisfying enhancement of flowability and bulk density.