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- In-line monitoring of the amorphous solid dispersion content was performed
- The prepared tablets passed the USP <905> content uniformity test
- Continuous manufacturing of milled electrospun materials to tablets proved feasible

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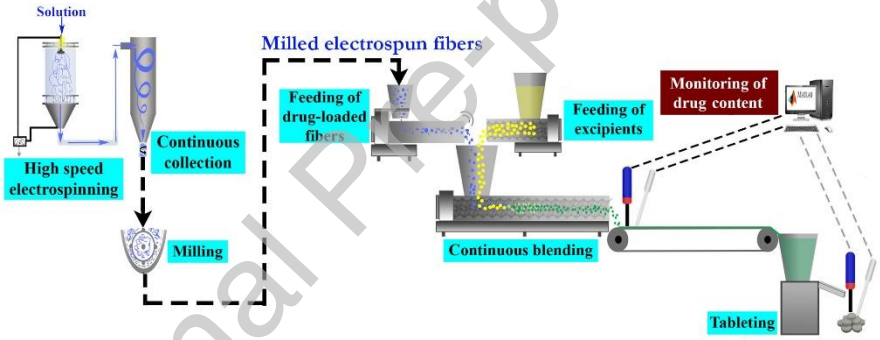
Graphical Abstract



Abstract

Electrospinning is a technology for manufacture of nano- and micro-sized fibers, which can enhance the dissolution properties of poorly water-soluble drugs. Tableting of electrospun fibers have been demonstrated in several studies, however, continuous manufacturing of tablets have not been realized yet. This research presents the first integrated continuous processing of milled drug-loaded electrospun materials to tablet form supplemented by process analytical tools for monitoring the active pharmaceutical ingredient (API) content. Electrospun fibers of an amorphous solid dispersion (ASD) of itraconazole and poly(vinylpyrrolidone-*co*-vinyl acetate) were produced using high speed electrospinning and afterwards milled. The milled fibers with an average fiber diameter of 1.6 ± 0.9 µm were continuously fed with a vibratory feeder into a twin-screw blender, which was integrated with a tableting machine to prepare tablets with ~ 10 kN compression force. The blend of fibers and excipients leaving the continuous blender was characterized with a bulk density of 0.43 g/cm^3 and proved to be suitable for direct tablet compression. The ASD content, and thus the API content was determined in-line before tableting and at-line after tableting using near-infrared and Raman spectroscopy. The prepared tablets fulfilled the USP <905> content uniformity requirement based on the API content of ten randomly selected tablets. This work highlights that combining the advantages of electrospinning (e.g. less solvent, fast and gentle drying, low energy consumption, and amorphous products with high specific surface area) and the continuous technologies opens a new and effective way in the field of manufacturing of the poorly water-soluble APIs.

Keywords:

amorphous solid dispersion, electrospinning, scale-up, continuous formulation, process analytical technologies, tablets

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1. Introduction

A large portion (up to 75%) of small molecule drug candidates in todayôs development portfolio has poor water solubility and is one of the main challenges in the pharmaceutical industry (Williams et al., 2013). Amorphous solid dispersions (ASDs) are a common technology and effective way to enhance the dissolution properties of poorly water-soluble molecules (Jermain et al., 2018; Pandi et al., 2020). Several techniques are known to prepare ASDs among which spray drying and hot-melt extrusion are the most typically used (Jermain et al., 2018; Pandi et al., 2020). However, electrospinning is also a very gentle and promising continuous method since it is capable of drying at ambient temperature and operates at atmospheric pressure (Yu et al., 2018). Furthermore, the energy consumption and the solvent needs during ES are favorable compared to the other solvent-based ASD preparation methods (Drosou et al., 2017; Kang et al., 2020; Levit et al., 2018; Sóti et al., 2015; Vass et al., 2019a). Although the mentioned advantages make the technique suitable for pharmaceutical applications, there are still some key challenges that need to be addressed.

Besides increasing the dissolution of the potential drug molecules, the development of the technologies and integration of continuous manufacturing (CM) processes is a hot topic nowadays in the pharmaceutical industry too. The marketed products prepared by CM and the increasing number of publications about CM show that continuous technologies get more and more attention in the pharmaceutical field (Burcham et al., 2018; Lawrence and Kopcha, 2017). Nonetheless, there are two FDA-approved CM medicines contain spray-dried samples, which indicate the opportunities in the simultaneous application of ASDs and CM (Szabó et al., 2019). Although spray drying is a widely used method with high productivity, only a few publications have been published relating to the CM of spray-dried materials to tablets (Adali et al., 2020; Hu et al., 2011; Vanhoorne et al., 2016). From the industry point of view, the two FDA-approved spray-dried material-loaded CM medicines confirm that the topic has great industrial relevance. Using CM in the case of other ASDs products might also be effective with respect to the practical application since a high volume of ASD-loaded products are manufactured year by year and the cost of production or the energy consumption can be reduced in this way (Burcham et al., 2018; Pandi et al., 2020). However, it is worth keeping in mind that the handling of products with poor flowability is a general challenge for tablet development and it is even more difficult during the CM of spray-dried samples or electrospun materials with low bulk densities (Al-Zoubi et al., 2021). Therefore, overcoming the flowability problems of critical materials such as active pharmaceutical ingredients (APIs)

or ASDs is a crucial part of continuous process development (Besenhard et al., 2016; Chattoraj and Sun, 2018; Pingali et al., 2009; Szabó et al., 2019).

In general, one of the most critical parts of continuous tablet preparation is the feeding because it has a great influence on the homogeneity and the content uniformity of the blend and later the tablets (Blackshields and Crean, 2018). Consequently, the feedability of materials with poor flow properties needs to be improved with different formulation techniques. In the case of APIs or poorly flowable excipients, the most common method is coating the given material with silica, which improves the flowability and thereby the performance of the feeding (Escotet-Espinoza et al., 2020; Kunnath et al., 2018; Mullarney et al., 2011). Besides, the feedability enhancement can also be done through equipment design, for instance via application of vibratory feeders since the danger of clogging, and electrostatic charging of the particles is less than in the case of the twin-screw feeders (Besenhard et al., 2016). However, not only accurate feeding but also effective blending is important to prepare appropriate tablets continuously. The homogeneity of the blend largely depends on the process parameters of the continuous blending thus the determination of the influencing factors is a significant element of the process development (Liu et al., 2018; Vanarase et al., 2013).

Furthermore, introducing the process analytical technology (PAT) principles, the drug content needs to be monitored during the continuous blending to produce good quality products. Besides, the use of in-line analytical methods may contribute to the feedback control of the processes, which is a critical part of CM systems (Nagy et al., 2017). To accomplish quick, real-time determination of the API content, different non-destructive in-line analytical tools must be applied (De Beer et al., 2011). A widely used method is the near-infrared (NIR) spectroscopy, which has been already used successfully in many continuous blending processes (Colón et al., 2014; Koller et al., 2011; Vanarase et al., 2010). Similar results can be achieved by Raman spectroscopy since the organic API molecules have strong signals in the Raman spectrum (Nagy et al., 2019; Vergote et al., 2004). The real-time monitoring of the homogeneity and drug content has an important role in the process development because the effect of different parameters can be followed continuously (Martínez et al., 2013).

CM of electrospun material containing tablets is a rarely researched area because the industrial relevant scaled-up production of API-loaded fibers has not yet spread. The commonly used single needle electrospinning apparatus has very low productivity, circa 0.01-1 g/h (Vass et al., 2019c); therefore, it of limited use for ASDs where production rates of double digit kg/h are typically required (Jermain et al., 2018; Pandi et al., 2020). To achieve

the necessary production rate, different electrospinning principles and equipment designs have been researched to increase the efficiency of the technology (Vass et al., 2019c). For instance, the multi-jet electrospinning utilizes more needles (Kumar et al., 2010), the free surface electrospinning methods are based on the curvature formation of the solution surface (Ahmed et al., 2020; Jiang and Qin, 2014), the alternating current electrospinning replaces the common used direct current techniques (Farkas et al., 2019; Kessick et al., 2004), and high speed electrospinning (HSES) takes the advantage of both electrostatic forces and centrifugal forces (Nagy et al., 2015). The latter can be very promising from the pharmaceutical application point of view since even a 450 g/h production rate is achievable and the technology is considered scale-able (Nagy et al., 2015) and is similar to rotary spray dryers, which are scale-able to large capacity (Masters, 1985).

The second main question relates to the conversion of the electrospun fibers into a final dosage form. Although preparing orally dissolving webs via electrospinning is an easy and possible solution for pharmaceutical usage (Balogh et al., 2018; Celebioglu and Uyar, 2019; Sipos et al., 2019), the manufacture of the most commonly used dosage forms of capsules and tablets using electrospun fibers is more complicated due to their physical properties such as low bulk density or the fibrous structure (Démuth et al., 2017). The tableting of the pure electrospun products seemed to be possible in lab-scale (Hamori et al., 2016) but an industrially relevant process requires the application of the appropriate downstream steps and the suitable excipients (Démuth et al., 2016; Vass et al., 2019b). Besides, coupling continuous processing steps to the electrospinning is also challenging since the electrospun products with low bulk density can cause difficulties during the feeding, blending and tableting (Szabó et al., 2018). Increasing the flow properties of fluffy fibers via milling is the key point for preparing tablets (Vass et al., 2019b).

The main goals of the current research were to investigate the continuous downstream processing of milled electrospun fibers to tablet form for the first time and to develop in-line analytical methods for determining the ASD content, and thus the API content in real-time. An integrated system consisting of continuous feeding, blending and tableting was tested for the continuous manufacture of electrospun materials. Furthermore, the comparison of two non-destructive, in-line analytical tools, namely NIR and Raman spectroscopy, was also performed to investigate their applicability during continuous downstream processing of electrospun samples. The development of a fully continuous manufacturing line using electrospinning coupled with the appropriate PAT tools might be very promising in the pharmaceutical industry for effective manufacture of ASDs.

2. Materials and methods

2.1. Materials

Itraconazole (ITR) and vinylpyrrolidone-vinyl acetate 6:4 copolymer (PVPVA64) were obtained from Janssen Pharmaceutica (Beerse, Belgium). Microcrystalline cellulose (Vivapur® 200) and sodium stearyl fumarate (Pruv®) were received from JRS Pharma (Rosenberg, Germany). Mannitol (Pearlitol® 400DC) was a kind gift from Roquette Pharma (Lestrem, France). Crosslinked polyvinylpyrrolidone (Kollidon® CL) was given by BASF (Ludwigshafen, Germany). Aerosil® 200 was supplied from Evonik Industries (Essen, Germany). Reagent grade dichloromethane and ethanol were purchased from Merck Ltd. (Budapest, Hungary).

2.2. High speed electrospinning (HSES)

Electrospinning of the ITR-loaded fibers was accomplished using HSES equipment, which was combined with a cyclone (Figure 1) (Vass et al., 2019a). A fan provided a constant 120 m^3/h gas flow rate in the system during the whole production period. The key element of the apparatus is the stainless steel, round-shaped spinneret with 36 orifices (d = 500 εm) on its edge. This spinneret is connected to a pneumatic air-bearing turbine to reach a high rotation speed. The rotation speed of the spinneret was set to 40000 rpm. The preparation of fibrous product was carried out at 25 °C ± 1°C and 45 ± 5% relative humidity, while the applied voltage was fixed at 40 kV. The solid material concentration of the investigated composition was 0.375 g/ml (consisted of 40% ITR and 60% PVPVA64) and the solids were dissolved in the mixture of dichloromethane:ethanol (volume ratio 2:1) (Nagy et al., 2015). The solution containing the drug and the polymer was fed with a built-in peristaltic pump (Watson－Marlow Fluid Technology Group, Budapest, Hungary) with a flow rate of 1000 mL/h.

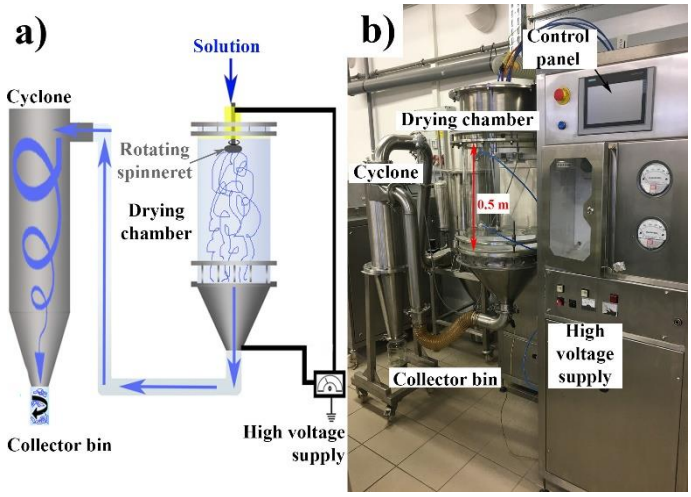

Fig. 1. Schematic drawing (a) and photo (b) of the applied high speed electrospinning (HSES) apparatus connected with a cyclone.

2.3. Milling of the electrospun product

A QUICKmill Lab multifunctional milling apparatus (Quick2000 Ltd., Tiszavasvári, Hungary) was used to reduce the fiber length to increase the bulk density and thereby to obtain a powder from the fibrous material with better flow properties (Section 3.1.). The equipment can be operated both in oscillating and conical milling mode depending on the applied grinding head. During this work, the oscillating mode was chosen due to its higher capacity and less material loss. A sieve with holes of 2.0 mm was used for the milling of the prepared electrospun sample. The milling rate was adjusted to 200 cycle/min, which resulted in circa 200 g/h milling capacity in the case of the investigated ITR-loaded fibrous system.

2.4. Characterization of the electrospun product

The basic characterization of the ITR-loaded electrospun material after milling was performed using differential scanning calorimetry, X-ray powder diffraction, in vitro dissolution testing, scanning electron microscopy, and laser diffraction measurements, as in our previous studies (Démuth et al., 2017; Démuth et al., 2018; Nagy et al., 2015). Non-milled fibers were investigated only by scanning electron microscopy since the non-milled samples cannot be examined by laser diffraction and the results of all the other measurements did not show any differences between the milled and non-milled samples according to prior experiences. Besides, the amount of the residual solvents is also a crucial factor during the application of solvent-based methods, which can examine well with headspace gas chromatography (Balogh et al., 2018). The method in the case of ITR-loaded fibers was similar than in one of our prior studies (Nagy et al., 2012). Our previous researches connected to the same composition showed that 700 ppm of ethanol and 300 ppm of dichloromethane

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