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Original Research Paper

Development and tableting of directly compressible powder from electrospun nanofibrous amorphous solid dispersion

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ABSTRACT

This work was carried out to explore the unknown area of converting non-woven fibres, prepared by high speed electrospinning, into a directly compressible blend by mixing with excipients. An experimental design, with independent variables of compression force and fillers fraction, was realized to investigate tabletability of electrospun material (EM) and to produce hard tablets with appropriate disintegration time. The models proved to be adequate; fitted to the results and predicted values well for the optimal tablet, which was found to be at 76.25% fillers fraction and 6 kN compression force. Besides standard characterizations, distribution of EM was investigated by Raman mapping and scanning electron microscopy revealing the propensity of EM to cover the surface of microcrystalline cellulose and not of mannitol. These analytical tools were also found to be useful at investigating the possible formation of the so-called gelling polymer network in tablets. Scanning electron microscopic pictures of tablets confirmed the maintenance of fibrous structure after compression. The moisture absorption of EM under increasing humidity was studied by dynamic vapour sorption measurement, which suggested good physical stability at 25 °C and 60% relative humidity (corroborated by modulated DSC). These results demonstrate the feasibility of a pharmaceutically acceptable downstream processing for EMs.

1. Introduction

The challenge to make drug candidates of poor water solubility suitable for commercialisation has been investigated for decades. Several new ideas and technologies have been introduced in order to enhance the bioavailability of such active pharmaceutical ingredients (APIs). One of the most promising methods is the formation of amorphous solid dispersions (ASDs) [1–3] owing to the advantageous dissolution characteristics of the amorphous form of a drug. To prepare these dispersions melt extrusion and spray drying have emerged as the most important technologies and they are still vividly investigated [4–8]. There are already several products on the market containing ASD prepared by melt extrusion or spray drying [2]. This also means that their downstream processing techniques are developed [9] although in most cases many unique issues can emerge during downstream of the solid dispersion, which therefore needs to be investigated separately. For instance, it might be challenging to mill a melt extrudate [10] or sometimes the inherent poor compressibility of glassy or rubbery extrudates requires a lot of fillers during compression [11,12]. In case of spray dried dispersion the very low bulk density and the poor flowability (due to the small particle size) often pose challenge to experts of formulation [4,13]. A strategy has been developed recently to control and lower residual solvent content in spray-dried solid dispersion [14], which is of great importance of solvent technologies.

Tablets have obvious advantages over other formulations whereby they add up to 80% of all formulations. Thus, formulation of tablets is generally the first goal of a pharmaceutical company with a new API (considering the patient compliance, convenient storage, good mechanical properties and precise dosing) even if it

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might be very challenging (e.g. creation of free flowing powder, good compressibility). In case of ASD there is one extra, serious challenge: the maintenance of the physical stability of the amorphous API during the whole downstream processing and storage [9,15]. Granulation (especially wet granulation due to presence of water) can induce phase separation and recrystallization [16,17] of the API; therefore, direct compression is always the preferred route. However, phase separation upon compression has been also published [18,19]. Although the direct compression of ASDs might be very complex it was chosen in the present work for forming tablets from fibrous ASD.

Electrostatic spinning is a promising technology in the pharmaceutical industry for the production of ASDs for oral drug delivery [20–28] or other applications [29–31]. Just like the aforementioned two techniques (spray drying and melt extrusion), this is also a continuous technology [32,33]. Electrospinning, for pharmaceutical purposes, has been investigating since 2003 (wound healing and drug loaded nanofibres) [34,35]. Promising results in pharma industry compatible scaling-up of electrospinning have been achieved by creating high speed electrospinning [22,26]. However, the downstream process has still never been investigated thoroughly. According to the author's best knowledge, this is the first paper discussing a trial to convert an electrospun nanofibrous mat into a directly compressible powder to prepare tablets. The investigation of dynamic vapour sorption of EM (and the related modulated differential scanning calorimetry studies) was included as well as an experimental design to optimize disintegration time and tensile strength of tablets. Design of experiments approach is often applied to optimize pharmaceutical powders [36]. Furthermore, unique peculiarities of EM have been determined in blends and tablets with scanning electron microscopy and Raman mapping.

2. Materials and methods

2.1. Materials

Itraconazole (ITR), vinylpyrrolidone-vinyl acetate 6:4 copolymer (PVPVA64) and magnesium stearate were provided by Janssen Pharmaceutica (Beerse, Belgium). Aerosil® 200 was purchased from Evonik Industries (Essen, Germany). Microcrystalline cellulose (Vivapur® 200, MCC) was given by JRS Pharma (Rosenberg, Germany). Lactose (Tablettose® 80) was received from Meggle Pharma (Wasserburg, Germany). Mannitol (Pearlitol® 400DC) was a kind gift from Roquette Pharma (Lestrem, France). Kollidon® CL was supplied by BASF (Ludwigshafen, Germany).

2.2. Preparation of electrospun material (EM) by high speed electrospinning

The EM was prepared according to the description provided by Nagy et al. [26]. The high speed electrospinning of the solution of PVPVA64 (60%) and ITR (40%) in dichloromethane-ethanol (ratio is 2:1; 225 mg PVPVA64 and 150 mg ITR in 1 ml solvent mixture) was performed under the following conditions: 50 kV voltage, 40,000 rpm spinneret rotational speed, 1500 mL/h feeding rate, ambient temperature. Further information and the basic characterization can be found in the aforementioned article. Prior to further application the obtained sheet was passed through a sieve with 0.95 mm holes to make it suitable for blending.

2.3. Dynamic vapour sorption (DVS)

The DVS measurement was performed on a DVS Intrinsic instrument (Surface Measurement Systems, London, UK). The relative humidity (RH) was altered every hour by 10% from 0 up to 95%. The measurement was carried out on two different temperatures: 25 °C and 40 °C. Two sorption and desorption cycles were collected. The weight of the sample was measured continuously on a SMS UltraBalance™.

2.4. Modulated differential scanning calorimetry (mDSC)

The EM was analysed in 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 aluminium pans (TA instruments) were applied with crimping. Samples were kept in climate chambers at 25 °C/60% RH or 40 °C/75% RH in open holders for the stability test.

2.5. Experimental design for preparation of fast disintegrating tablets

Firstly, a 2^2 design was planned in order to study the compression behaviour of the EM. The compression force and the fillers fraction were selected as independent variables. The fraction of the fillers was calculated from the weight of the fillers and EM to highlight their ratio since it might have a significant effect on the formation of a gelling polymer network [9]. Levels of independent variables were selected based on preliminary experiments to achieve an appropriate range for dependent variables (disintegration time and tensile strength). Centrum point measurements were added to the design to check the adequacy. However, the fitted linear model was not adequate; hence the design was expanded to a 3^2 randomized full factorial design where quadratic effects can be introduced. Composition of tableting blends can be observed in Table 1, while levels of independent variables in Table 2. Tensile strength and disintegration time were chosen as dependent variables since these values can be measured rather precisely and independent variables might have a significant effect on them. Tensile strength was calculated from hardness as the following [37]:

$$T = \frac{2 \cdot H}{\pi \cdot t \cdot d} \quad (174)$$

where T is the tensile strength, H is hardness, t is thickness of the tablets, while d is the diameter of the punches and tablets (9.5 mm).

Three tablets were measured in each case (to obtain standard deviation and increase the reliability of the design) and individual results were evaluated with Statistica 12 (Tulsa, Oklahoma, USA). Every measurement was performed by one person to minimalize the error. Our purpose was to optimize the compression force and the composition for both dependent variables (low disintegration time, high tensile strength). Furthermore, it was intended to maintain the structure of the fibres in tablets as good dissolution properties can be attributed to this.

2.6. Preparation of blends

All excipients were pushed through a sieve with 0.95 mm holes prior to blending. Mixing was carried out with a Turbula® T2F shaker-mixer (Glenn Mills Inc., Clifton, NJ, USA) for 5 min (magnesium stearate was mixed separately after other excipients).

2.7. Characterization of blends

A granulometry study was carried out for two blends (presumably centre blend has intermediate characteristics). Bulk and tapped densities were determined with 100 g of the blends. Tapped density was measured after 1250 taps on an ERWEKA SVM 12 tapping volumeter (Heusenstamm, Germany). Also 100 g was applied for the sieve analysis. The used sieves: 1000 μm,