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Research paper

A minitab formulation made from electrospun nanofibers

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ABSTRACT

The purpose of this study was to evaluate electrospun drug loaded nanofibers as a new matrix for minitab. Prednisone, a poorly water-soluble drug, was loaded into povidone (polyvinylpyrrolidone, PVP) nanofibers using the process of electrospinning. The drug-loaded nanofiber mat was compressed into minitab with a 2 mm diameter and a height of 2.63 ± 0.04 mm. SEM analysis of the minitab identified a nano-web structure with a nanofiber diameter in the range of 400–500 nm. The minitab met the requirements of the US Pharmacopeia with respect to content uniformity and friability. DSC and XRPD analysis of the minitab indicated that the drug-polymer mixture was a one-phase amorphous system. XRPD analysis of the drug loaded nanofiber mat after 10-months of storage at ambient temperature showed no evidence of recrystallization of the drug. Solubility and dissolution properties of the drug formulated into a nanofiber mat and minitab were evaluated. These results show that electrospun nanofibers may provide a useful matrix for the further development of minitabs.

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1. Introduction

Medicines are often oral solid dosages in the form of tablets, which are manufactured at industrial scale with high productivity, and reproducibility. This efficiency has led to lower prices and greater access to medicines for the world's population. Despite these benefits, solid oral dosage forms manufactured using conventional unit operation practices have limited dose flexibility, which needs to be addressed to fulfil the growing demand for personalized therapy. Personalized medicine aims at an individualized therapy specifically tailored to the requirements of an individual patient. Factors such as age, weight, height, race, gender, disease state, personal preferences and behaviour of the individual patient, are considered and translated in precisely tailored oral delivery forms to provide individualized therapy [1]. Patient populations which have greater needs of individualized therapy are paediatric and elderly patients [2–4]. Regulatory agencies and the WHO have incentivised the development of paediatric formulations that enable dose flexibility, easier administration and better acceptance by children [3,5,6].

To provide paediatric patients with their individual dose requirements, the current practice is to prepare an oral liquid suspension or to divide the tablet. Due to stability or drug solubility

issues, liquid oral dosage forms are limited [2]. Divisible tablets have inherent issues like difficulty with breaking, inaccuracy in dosing and loss of drug loaded mass [7]. A number of new technologies have emerged for improved dose flexibility and ease of swallowing; these include films, multi-particulates, chewable formulations and minitabs [8–10].

Minitabs are small solid tablets that have a diameter equal or smaller than 3 mm [11]. Studies have shown that young children from the age of 6 months are able to swallow single minitabs [12,13]. Under controlled trial conditions the acceptability and swallowability of multiple minitabs as a single dose was demonstrated in preschool-aged children [14]. These minitab dosage forms have been made by conventional direct compression of the active ingredient with appropriate excipients to form a tablet [11,15,16].

This study investigates the potential of drug loaded electrospun nanofiber as a new solid matrix for minitabs. Electrospinning is a simple, inexpensive and versatile process that produces polymeric nanofibers with diameters of a few nanometres to several micrometres [17]. These nanofibers are produced by an electrostatically driven jet of polymer solution or polymer melt. The electrospinning technique is described in more detail in several review articles [16,18]. Several advantages have been identified for using electrospun nanofibers for drug delivery systems; in particular, the high surface area and the high porosity of these nanostructures can facilitate fast-wetting, which promotes a rapid release of the drug. This wettability may be further enhanced by combining the

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drug with a hydrophilic polymer, such as povidone (polyvinylpyrrolidone, PVP). Moreover, drugs can be incorporated into electrospun nanofibers in an amorphous form which can be utilized to increase both apparent solubility and dissolution rate of the drug [17,19,20]. To date, electrospun nanofibers have been investigated as oral delivery devices in the form of nanofiber mats [21–24]. A major challenge for electrospinning technologies has been the scale-up of production. To date a range of different approaches have been investigated to increase production [25], however, for pharmaceutical production, electrospinning has yet to become reality. Recently a milestone was reached in the pharmaceutical field which demonstrated utilizing a rotating spinneret approach with drug loaded polymer nanofibers able to be produced with significantly higher productivity than the standard needle electrospinning setup [26]. With the possibility of pharmaceutical production electrospinning in the near future, the purpose of this study was to determine if minitables made from nanofibers have suitable properties for an oral dosage form. This was demonstrated by using electrospun PVP nanofibers loaded with the poorly water soluble drug, prednisone [27].

2. Materials and methods

2.1. Materials

Prednisone was purchased from Sigma Aldrich (Missouri, US) and povidone (polyvinylpyrrolidone, PVP, MW. 44,000) was purchased from VWR International (Poole, England). N,N-Dimethylacetamide 99.5% extra pure was obtained from Acros Organics (Geel, Belgium). Acetone, hydrochloric acid (fuming, 37%), methanol, and tetrahydrofuran were all of analytical grade and procured from Merck (Germany).

2.2. Electrospinning

Electrospinning solution was prepared by dissolving 0.8 g of PVP in a 2 ml mixture of acetone and dimethylacetamide (DMA) at 1:1 with stirring for 2 h at room temperature. At least one hour prior to electrospinning, prednisone (89 mg) was added to the polymer-solvent system under stirring to give a final drug loading mass of 10 % (w/w). The polymer drug solution was loaded into a 5 ml syringe with a 20-gauge needle and the needle was connected to the positive electrode of the high-voltage power supply (Bertain HVPS Series 230 power supply, Spellman, NY). The distance between needle tip and earthed rotating mandrel (diameter 30 cm and width 1.7 cm, 6 rpm) was 15 cm. Electrospinning was carried out under ambient conditions, using a voltage of 20 kV. The feed rate of the solution was controlled at 0.5 ml/h using a single syringe pump (200 syringe pump; Chemyx Stafford, TX, USA). The entire prepared volume (2 ml) of solution was electrospun. The collected electrospun mat was dried under vacuum overnight before further use.

2.3. Preparation of tablets

Nanofiber mat, approximately 0.6 cm in length and 10.50 mg in mass was placed into a 2 mm diameter standard flat faced punch. Using a single manual pellet press (No. 4350 CARVER, Wabash, Indiana, USA) the nanofiber mat was compressed into a minitab at a pressure of 10 MPa.

2.4. Scanning electron microscopy

The morphology of PVP nanofiber mat and minitables were analysed by field emission scanning electron microscopy (FESEM).

Sample was attached to a 10 mm aluminium stub, which was covered with 10 nm gold palladium in an Emitech K575X Peltier-cooled high resolution sputter coater with carbon coater attachment (EM Technologies, Kent, England). Samples were analysed in a 5 kV JEOL JSM-6700F field emission scanning electron microscope (JEOL, Tokyo, Japan). A high resolution image was achieved by a scanning electron detector with working distances of 5.8 and 6.4 mm.

2.5. Friability

Twenty minitables and 6 g of 3 mm glass beads were and placed into the friabilator (Copley Scientific, Nottingham, UK) [28]. The friabilator was rotated at 25 rpm for 100 revolutions. The minitables were collected and weighed, the percentage loss of the total weight was evaluated.

2.6. Tablet uniformity

The height of ten minitables were measured by using a vernier caliper. The weight of ten individual minitables was determined according to the harmonised monographs United States Pharmacopeia (USP) specifications (General Chapter: <905> Uniformity of dosage Units) and Ph.Eur. 2.9.40.

The average prednisone content of the unit dose was determined by dissolving each individual minitab in 50 mL of solution containing water (69% v/v), tetrahydrofuran (25% v/v) and methanol (6% v/v). To dissolve the prednisone, the suspension was shaken at 140 rpm overnight using a mechanical shaker (RATEK, Orbital mixer Incubator, Australia). A 1 mL of sample was taken, filtered through a 0.45 μ m syringe filter (Phenomenex, New Zealand) and analysed by UV/VIS spectroscopy (Ultrospec 2000, UV/Visible Spectrophotometer, Biotech Pharmacia, USA) at 242 nm. The amount of prednisone was determined by using a standard curve of prednisone.

2.7. Differential scanning calorimetry

Modulated temperature differential scanning calorimetry (MDSC) was performed using a Q100, TA Instruments-Waters LLC setup (New Castle, Delaware, USA) under dry nitrogen purge (50 mL/min nitrogen). The sample was weighed (3–4 mg) directly into an aluminium sample pan and hermetically sealed. The total heating rate was 5 °C/min, modulated with a 0.5 °C amplitude every 40 s and the temperature ranged from 40 °C to 300 °C.

2.8. X-ray powder diffraction

X-ray powder diffraction (XRPD) analysis was carried out using an X'Pert PRO X-ray diffractometer (PANalytical, the Netherlands; MPD PW3040/60 XRD; CuK α anode; λ = 1.541 Å). Samples were mounted on aluminium sample holders and scanned at 45 kV and 40 mA from 5 to 35° 2 θ using a scanning speed of 0.1285° min⁻¹ and a step size of 0.008°.

2.9. Solubility

Samples containing the equivalent of 5 mg prednisone, and in the form of powder, nanofiber mat or minitab, were added to 15 mL of simulated gastric fluid (0.1 M HCl). The suspensions were placed in a mechanical water bath (Grant Instruments Cambridge, UK) with a constant shaking rate of 100 strokes per min at 37 °C. At each time point, a 1 ml sample was taken and filtered through a 0.2 μ m nylon syringe filter (AXIVA Slichem Biotech, Delhi, India). The concentration of prednisone in solution was determined at 242 nm using a UV spectrometer (Ultrospec 2000, UV/Visible

Spectrophotometer, Biotech Pharmacia, US). The amount of prednisone was determined using a standard curve (in the range of 2–15 $\mu\text{g/mL}$) of prednisone prepared in 0.1 M HCl.

2.10. *In vitro* dissolution

In vitro dissolution studies were performed according to the USP (2011) basket method (Apparatus 1; USP <711> Dissolution) using a ZRS-8 dissolution tester (Tianda Tianfa Technology, China). Either five minitabets or a 50 mg nanofiber mat (equivalent to 5 mg of prednisone) was placed into a basket. The basket was rotated at a speed of 50 rpm in 750 mL of simulated gastric fluid (0.1 M HCl), which was equilibrated at $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$. At certain time points a 1 mL sample was withdrawn and filtered through a $0.2\text{ }\mu\text{m}$ nylon syringe filter (AXIVA Sicheem Biotech, Delhi, India) and the filtrate was analysed at 242 nm using a UV–VIS spectrometer (Ultrospec 2000, UV/Visible Spectrophotometer, Pharmacia Biotech, US).

3. Results

3.1. Physical properties of nanofiber mats and minitabets

PVP nanofibers containing prednisone loaded at 10% (w/w) were electrospun from a solution of PVP and prednisone in the solvent system of acetone and dimethylacetamide. SEM images of the PVP nanofiber and prednisone loaded PVP nanofiber mats are shown in Fig. 1. The images reveal that the nanofibers have a smooth surface without any formation of beads, and all formula-

tions had a similar nanofiber diameter range of approximately 400 to 500 nm. The nanofiber mat appeared off-white in colour. The nanofiber minitabets were prepared from the nanofiber mats by tableting in a manual press at a compression pressure of 10 MPa. Upon visual inspection, the minitabets appeared off-white in colour with a smooth surface and no visible cracks (Fig. 2a). SEM analysis of the minitabets surface (Fig. 2b) showed that some of the nanofibers at the surface have coalesced, while below the surface a nanofiber network structure can be observed with a similar average nanofiber diameter range (400–500 nm) as for the nanofiber mats.

The diameter of the minitabets was 2 mm (Fig. 3a) with a mean height of $2.63 \pm 0.04\text{ mm}$ (Fig. 3b) ($n = 10$). The mean drug content for 10 minitabets ranged from $0.93 \pm 0.06\text{ mg}$ (94–110 %) with a relative standard deviation (RSD) of 5.9%. This means the minitabets meet the standard pharmacopeia requirements of content uniformity of 85–115% and a RSD of less than or equal to 6.0% (USP 29, uniformity of dosage units 905). The mean weight of the minitabets was $10.12 \pm 0.18\text{ mg}$ ($n = 10$). The percentage mass lost during friability testing for the prednisone loaded minitabets when mixed with glass beads was 0.03% w/w.

To investigate the crystallinity of the prednisone in the nanofiber, X-ray powder diffraction (XRPD) measurements were undertaken. The presence of diffraction peaks in the XRPD diffractogram of prednisone powder (Fig. 4A) reveals that the drug is present as a crystalline material. The PVP nanofiber mat diffraction pattern (Fig. 4B) exhibits a diffuse diffraction halo, which indicates the polymer is amorphous. The diffraction pattern of the prednisone loaded nanofiber mat (Fig. 4C) and minitabets

Fig. 1. Scanning electron microscopy images; (A) PVP nanofiber mat, (B) PVP nanofiber mat containing prednisone ($\times 5500$).

Fig. 2. (A) PVP nanofiber minitabets containing prednisone. (B) Scanning electron microscopy image of the surface of PVP nanofiber minitabets containing prednisone ($\times 5500$).

Fig. 3. (A) Diameter and (B) height of PVP nanofiber minitab containing prednisone measured by a digital vernier calibre.

Fig. 4. X-ray powder diffractograms of (A) prednisone powder, (B) PVP nanofiber mat, (C) prednisone loaded PVP nanofiber mat, (D) prednisone loaded PVP nanofiber minitab and (E) prednisone loaded PVP nanofiber mat after 10-month storage at ambient temperature.

(Fig. 4D) also reveals that these fibres are in the amorphous phase before and after tableting.

Modulated temperature DSC analysis was performed to compare the phase-related solid-state behaviour of prednisone as a powder and in the nanofiber formulations (Fig. 5). The PVP powder did not show any melting endotherm over the temperature range studied due to the amorphous nature of this polymer and lack of crystallization during heating (Fig. 5A). The reversible heat flow thermogram featured a glass transition temperature (T_g) at 166.0 °C (midpoint), which is reasonably consistent with previous reports of 156 °C [29] and 162 °C [30].

DSC of the prednisone powder had a single sharp endothermic peak at 235 °C (onset) which corresponds to melting of the crystalline drug (Fig. 5B). The prednisone-loaded PVP nanofiber mat and minitab had no endothermic peaks indicating the transformation of the prednisone from crystalline to an amorphous state after electrospinning and remained in this state after tablet compression. The non-reversing endotherms observed with onsets of 157 and 136 °C for the prednisone loaded PVP nanofiber mat (Fig. 5C) and prednisone loaded PVP minitab (Fig. 5D) nanofiber respectively, can be attributed to water loss. The endotherm is observed over a broader temperature range for the minitab than for the uncompressed nanofiber mat, presumably due to the lower

specific surface area hindering water desorption. A single T_g was observed in the reversing signal at 161.3 °C and 140.0 °C for the uncompressed and minitab samples respectively. A T_g of 92.85 °C has been reported for pure amorphous prednisone [31]. The presence of a single T_g , intermediate between those of the pure amorphous drug and polymer, suggests that, in both cases, a single phase is present with molecular-level mixing of the drug within the polymer matrix. The difference between the T_g s of the two samples can be attributed to the influence of water: in the uncompressed sample water loss occurred while the sample was still in the glassy phase, and thus the T_g reflects that of the dry sample, while in the minitab, the water loss was sufficiently impeded to plasticise the sample such that T_g was lowered into the temperature range in which the water was still present.

3.2. Solubility

The solubility of prednisone in the powder form and when formulated into a nanofiber mat or minitab was evaluated as a function of time in 0.1 M HCl at 37 °C. Fig. 6 shows that the crystalline prednisone powder reached a steady state concentration of 0.16 mg/ml at the 4 h time point. The prednisone released from the nanofiber mat and minitab formulations reached a similar steady state concentration of approximately 0.23 mg/ml at the 2 h and 6 h time points, respectively.

3.3. Dissolution

The dissolution of the prednisone from nanofiber mat and minitab formulations under sink conditions was determined in 0.1 M HCl dissolution media. The dissolution profile for the nanofiber mat shows that 100% of the drug was released at the 5 min sampling time point (Fig. 7) while for the minitab dissolution profile showed 100% drug release at the 20 min sample point.

3.4. Physical stability

Following 10 months' storage of the prednisone loaded nanofiber mat at ambient conditions (20–30 °C; 20–30% RH) the mat was evaluated by XRPD measurement to determine if there were any changes in the physical state of the drug entrapped in the nanofiber over that time period. The XRPD diffraction pattern after storage showed an amorphous halo (Fig. 4E) with no formation of distinct peaks indicative of crystalline material.

Fig. 5. Modulated differential scanning calorimetry thermograms (total, reversing, non-reversing) of (A) PVP powder, (B) prednisone powder, (C) prednisone loaded PVP nanofiber mat and (D) prednisone loaded PVP minitab.

Fig. 6. Mean concentrations of prednisone in simulated gastric fluid (0.1 M HCl) at a constant shaking rate of 100 strokes per min at 37 °C from prednisone powder (open square), prednisone nanofiber mat (closed square) and prednisone loaded PVP minitab (triangle) with bars representing the SD of three experiments.

4. Discussion

Electrospun nanofiber is a nanotechnology-based approach which has been shown to enhance the bioavailability of drugs, in particular those with low aqueous solubility [32]. This work

investigates electrospun nanofiber matrices as a potential modern platform for oral minitab dosage forms which have advantages of dose flexibility and ease of swallowing over conventional tablets.

The poorly aqueous soluble drug, prednisone, was successfully incorporated into PVP nanofibers by the process of electrospinning

Fig. 7. Dissolution profiles of prednisone in simulated gastric fluid (0.1 M HCl) from PVP-prednisone nanofiber mat (square) and prednisone loaded PVP nanofiber minitables (triangle) with a bar represent mean SD of three experiments.

using an acetone and DMA solvent system. SEM of the collected mat showed a three-dimensional continuous nano-web structure, nanofibers had cylindrical morphology and were smooth without evidence of drug crystals or separate phases. The nanofibers with and without prednisone loading had a similar diameter range of between 400–500 nm. Prednisone existed in the nanofibers in the amorphous physical form molecularly dispersed in the polymer, as shown using DSC and XRPD. These findings are in agreement with other studies which demonstrated that poorly water soluble drugs entrapped into electrospun PVP are in the amorphous state [32–35].

Tablet compression of the prednisone loaded nanofiber mat at 10 MPa resulted in a minitab with a diameter of 2 mm and a height of 2.63 ± 0.04 mm. SEM analysis of the minitab surface showed a nanofiber network structure with coalescence of some nanofibers at the surface of the minitab. To measure the mechanical strength of the minitables, friability tests were performed. To correct for the low mass of minitables which will have lower mechanical stress applied, glass beads were added to the friabilator [28]. The friability for the prednisone loaded minitab when mixed with glass beads was 0.03% which is lower than maximum limit of 1% for a tablet with satisfactory mechanical resistance for handling and administration [36].

This low friability may be due to the nanofiber network structure in which the drug is molecularly dispersed which could provide good mechanical integrity to the minitab without the need for additional binding excipients. The observed low friability of the nanofiber-based minitables can be attributed to the excellent mechanical properties that has been observed in nanostructured biomaterials including electrospun nanofibers [37,38]. While strong specific and/or nonspecific intermolecular interactions form the basis for the low friability, further work is required to understanding the formulation and processing factors which influence the mechanical performance of the minitables, these factors include the chemical composition, tablet compression pressure, drug loading, and morphological features of the network structure.

The uniformity of a dosage unit can be evaluated either by measuring the content uniformity or the weight of the tested units. However for uncoated tablets containing 25 mg or less of a drug substance or comprising 25% or less, by weight, of the dosage unit the test for content uniformity is only required (Ph.Eur. 2.9.40 and USP <905> harmonized monographs). The drug content uniformity of the minitables passed the first test as the relative standard deviation (RSD) is less than 6% and no value was outside 85–115%.

Solubility experiments were performed as the aqueous solubility of a drug is a fundamental property affecting its absorption after oral administration. Solubility measurements in 0.1 M HCl showed that the formulation of prednisone in a PVP nanofiber increases its (apparent) solubility over the crystalline powder form of the drug. Prednisone nanofiber mat and minitab formulations reached a steady state concentration of the drug at approximately 0.23 mg/ml while that of the prednisone crystalline powder was approximately 0.16 mg/ml. An improved solubility of drug formulated into a nanofiber mat has been observed for a range of drugs and polymer carriers [21,19,39]. Although it is possible that solubilised PVP may be contributing to a limited increase in the thermodynamic solubility, the observed 'steady state' concentration is expected to be higher than any increase in the thermodynamic solubility and reflects the apparent/kinetic solubility of the amorphous drug (in the molecular dispersion), commonly referred to as the 'spring' effect. Over the 48 h period of analysis there was no reduction in concentration for the prednisone formulated in PVP nanofiber, this indicates that there is no process of recrystallization of the prednisone in saturated solution to reach the thermodynamic solubility. This is presumably due to the presence of PVP, which is known to be an effective crystallisation inhibitor in solution even at very low concentrations.

Dissolution tests verified that prednisone loaded PVP nanofiber mat and minitab formulations have immediate drug release properties. The nanofiber mat released 100% of the drug at the 5 min sampling time. Upon placing the drug loaded electrospun PVP mat into 0.1 M HCl the mat completely dissolved in less than 10 s. This rapid dissolution of the drug loaded nanofiber mat in media has been observed previously for PVP based nanofiber mats [33,35,40,41]. The fast dissolution rate for nanofiber mats has been attributed to a number of properties which include the hydrophilic nature of the polymer, absence of drug crystallinity, the high surface area of the nano-web matrix structure itself and the molecular dispersion of the drug [22]. DSC and XRPD analysis of the prednisone loaded nanofiber mat and minitab concurred that the drug was molecularly dispersed in an amorphous form. The dissolution release profile for the minitab showed a slower release of prednisone compared to that from the mat; 100% drug release was achieved at the 20 min time point. The slower drug release is presumably due to the lower specific surface area exposed to the media for the tablet form compared to the mat. Tableting pressure may influence the network porosity influencing the capacity of the dissolution media to diffuse into the tablet matrix.

The prednisone nanofiber mats showed promising stability after a 10-month storage period at ambient temperature and

humidity. XRPD measurements of the nanofiber mat after storage showed no signs of recrystallization or solid-state changes. The stability of the amorphous physical form observed here is in agreement with the work which observed that indomethacin in PVP nanofibers remained amorphous after up to 6 months' storage in a desiccator at 40 °C [34]. Due to the hygroscopic nature of PVP and the high surface area of the nanofiber matrix (especially prior to tablet manufacture), these minitabets will have a high potential for water sorption, which may have an influence on the long-term product stability. Future studies are required to determine the effect of water sorption on product stability and suitable protective packaging.

An important consideration in the development of an acceptable oral nanofiber dosage form is the amount residual organic solvent in the final product. Analyses will need to be performed on the nanofiber dosage form to check if amount of solvent in the final product does not exceed acceptable limits given by ICH Q3C guideline (Impurities: residual solvents). In this study, the solvent mixture of dimethylacetamide (DMA) and acetone was used for electrospinning, according to ICH Q3C guidelines DMA is a Class 2 solvent with a permitted daily exposure (PDE) of 10.9 mg/day and acetone a Class 3 solvent has a PDE of 50 mg or more per day. The amount of residual solvent in the final product will depend on the completeness of solvent evaporation from the nano-jets during electrospinning and subsequent vacuum drying of the nanofiber mat. Future work will require the analysis of the solvent in the final product to check if the amount of solvent does not exceed acceptable limits.

This work shows for the first time that a drug loaded electrospun nanofiber can provide a suitable matrix for a minitabets dosage form. For this technology to be adapted as a new platform for minitabets further studies are required to establish the manufacturability of these minitabets from nanofibers at a higher scale and speed. New techniques for large-scale manufacturing of nanofibers are being developed such as the centrifugal techniques (pressure gyration) [42]. These studies will identify whether tableting can be performed without the need for additional tableting excipients. The minitabets presented in this work were prepared by a manual press and did not require additional tableting excipients. A minitabets with a low burden of excipient would have advantages in particular for the administration to paediatric patients as excipients commonly regarded as safe may represent a safety risk for children [3].

5. Conclusion

The results obtained in this study demonstrated that drug loaded electrospun nanofibers can be used as a matrix for minitabets. The minitabets could be fabricated by compression of a drug loaded nanofiber mat consisting of only the drug and polymer. The nanofiber minitabets meet the standard pharmacopeia requirements of content uniformity and friability. The incorporation of poorly water-soluble drug prednisone into the nanofiber minitabets enhanced drug solubility and dissolution properties. These findings demonstrate that the unique drug delivery properties of nanofibers can be incorporated into a minitabets dosage form.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] J. Pardeike, D.M. Strohmeier, N. Schrödl, C. Voura, M. Gruber, J.G. Khinast, A. Zimmer, Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines, *Int. J. Pharm.* 420 (2011) 93–100, <http://dx.doi.org/10.1016/j.ijpharm.2011.08.033>.
- [2] J. Breitzkreutz, J. Boos, Paediatric and geriatric drug delivery, *Expert Opin. Drug Deliv.* 4 (2007) 37–45, <http://dx.doi.org/10.1517/17425247.4.1.37>.
- [3] A. Zajicek, M.J. Fossler, J.S. Barrett, J.H. Worthington, R. Ternik, G. Charkoftaki, S. Lum, J. Breitzkreutz, M. Baltezor, P. Macheras, M. Khan, S. Agharkar, D.D. MacLaren, A report from the pediatric formulations task force: perspectives on the state of child-friendly oral dosage forms, *AAPS J.* 15 (2013) 1072–1081, <http://dx.doi.org/10.1208/s12248-013-9511-5>.
- [4] T.B. Ernest, D.P. Elder, L.G. Martini, M. Roberts, J.L. Ford, Developing paediatric medicines: identifying the needs and recognizing the challenges, *J. Pharm. Pharmacol.* 59 (2007) 1043–1055, <http://dx.doi.org/10.1211/jpp.59.8.0001>.
- [5] P. Gauthier, J.-M. Cardot, Developing drugs for children and the adjustment of medication—is it a new challenge or an adaptation of past ideas?, *J. Pers. Med.* 1 (2011) 5–16, <http://dx.doi.org/10.3390/jpm1010005>.
- [6] D.A. van Riet-Nales, E.G.A.W. Römkens, A. Saint-Raymond, P. Kozarewicz, A.F.A. M. Schobben, T.C.G. Egberts, C.M.A. Rademaker, Oral medicines for children in the European paediatric investigation plans, *PLoS ONE* 9 (2014) e98348, <http://dx.doi.org/10.1371/journal.pone.0098348>.
- [7] E. van Santen, D.M. Barends, H.W. Frijlink, Breaking of scored tablets: a review, *Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Für Pharm. Verfahrenstechnik e.V.* 53 (2002) 139–145, <<http://www.ncbi.nlm.nih.gov/pubmed/11879995>> (accessed March 9, 2016).
- [8] F.L. Lopez, T.B. Ernest, C. Tuleu, M.O. Gul, Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms, *Expert Opin. Drug Deliv.* 12 (2015) 1727–1740, <http://dx.doi.org/10.1517/17425247.2015.1060218>.
- [9] M. Preis, Orally disintegrating films and mini-tablets—innovative dosage forms of choice for pediatric use, *AAPS PharmSciTech.* 16 (2015) 234–241, <http://dx.doi.org/10.1208/s12249-015-0313-1>.
- [10] A. Aleksovski, R. Dreu, M. Gašperlin, O. Planinšek, Mini-tablets: a contemporary system for oral drug delivery in targeted patient groups, *Expert Opin. Drug Deliv.* 12 (2015) 65–84, <http://dx.doi.org/10.1517/17425247.2014.951633>.
- [11] P. Lennartz, J.B. Mielck, Minitabletting: improving the compactability of paracetamol powder mixtures, *Int. J. Pharm.* 173 (1998) 75–85, [http://dx.doi.org/10.1016/S0378-5173\(98\)00206-3](http://dx.doi.org/10.1016/S0378-5173(98)00206-3).
- [12] N. Spomer, V. Klingmann, I. Stoltenberg, C. Lerch, T. Meissner, J. Breitzkreutz, Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study, *Arch. Dis. Child.* 97 (2012) 283–286, <http://dx.doi.org/10.1136/archdischild-2011-300958>.
- [13] V. Klingmann, N. Spomer, C. Lerch, I. Stoltenberg, C. Frömke, H.M. Bosse, J. Breitzkreutz, T. Meissner, Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children, *J. Pediatr.* 163 (2013) 1728–1732.e1, <http://dx.doi.org/10.1016/j.jpeds.2013.07.014>.
- [14] A. Kluk, M. Sznitowska, A. Brandt, K. Sznurkowska, K. Plata-Nazar, M. Mysliwiec, B. Kaminska, H. Kotłowska, Can preschool-aged children swallow several minitabets at a time? Results from a clinical pilot study, *Int. J. Pharm.* 485 (2015) 1–6, <http://dx.doi.org/10.1016/j.ijpharm.2015.02.068>.
- [15] H.M. Tawfeek, I.Y. Saleem, M. Roberts, Dissolution enhancement and formulation of rapid-release lornoxicam mini-tablets, *J. Pharm. Sci.* 103 (2014) 2470–2483, <http://dx.doi.org/10.1002/jps.24073>.
- [16] K.M. El-Say, T.A. Ahmed, M.F. Abdelbary, B.E. Ali, B.M. Aljaeidi, A.S. Zidan, Risperidone oral disintegrating mini-tablets: A robust-product for pediatrics, *Acta Pharm.* 65 (2015) 365–382, <http://dx.doi.org/10.1515/acph-2015-0038>.
- [17] A.J. Meinel, O. Germershaus, T. Luhmann, H.P. Merkle, L. Meinel, Electrospun matrices for localized drug delivery: current technologies and selected biomedical applications., *Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Für Pharm. Verfahrenstechnik e.V.* 81 (2012) 1–13, <http://dx.doi.org/10.1016/j.ejpb.2012.01.016>.
- [18] M. Hadjiargyrou, J.B. Chiu, Enhanced composite electrospun nanofiber scaffolds for use in drug delivery, *Expert Opin. Drug Deliv.* 5 (2008) 1093–1106, <http://dx.doi.org/10.1517/17425247.5.10.1093>.
- [19] M.V. Natu, H.C. de Sousa, M.H. Gil, Effects of drug solubility, state and loading on controlled release in biocomponent electrospun fibers, *Int. J. Pharm.* 397 (2010) 50–58, <http://dx.doi.org/10.1016/j.ijpharm.2010.06.045>.
- [20] S. Qi, D. Craig, Recent developments in micro- and nanofabrication techniques for the preparation of amorphous pharmaceutical dosage forms, *Adv. Drug Deliv. Rev.* (2016), <http://dx.doi.org/10.1016/j.addr.2016.01.003>.
- [21] D.-G. Yu, X.-F. Zhang, X.-X. Shen, C. Branford-White, L.-M. Zhu, The improvement of poorly water-soluble drug solubility through electrospun drug-loaded nanofibers, *Yao Xue Xue Bao.* 44 (2009) 1179–1182, <<http://www.ncbi.nlm.nih.gov/pubmed/20055145>> (accessed April 12, 2016).
- [22] F. Ignatious, L. Sun, C.-P. Lee, J. Baldoni, Electrospun nanofibers in oral drug delivery, *Pharm. Res.* 27 (2010) 576–588, <http://dx.doi.org/10.1007/s11095-010-0061-6>.
- [23] W. Samprasit, P. Akkaramongkolporn, T. Ngawhirunpat, T. Rojanarata, R. Kaomongkolgit, P. Opanasopit, Fast releasing oral electrospun PVP/CD nanofiber mats of taste-masked meloxicam, *Int. J. Pharm.* 487 (2015) 213–222, <http://dx.doi.org/10.1016/j.ijpharm.2015.04.044>.

- [24] T. Potrič, S. Baumgartner, R. Roškar, O. Planinšek, Z. Lavrič, J. Kristl, P. Kocbek, Electrospun polycaprolactone nanofibers as a potential oromucosal delivery system for poorly water-soluble drugs, *Eur. J. Pharm. Sci.* 75 (2015) 101–113, <http://dx.doi.org/10.1016/j.ejps.2015.04.004>.
- [25] L. Persano, A. Camposeo, C. Tekmen, D. Pisignano, Industrial upscaling of electrospinning and applications of polymer nanofibers: a review, *Macromol. Mater. Eng.* 298 (2013) 504–520, <http://dx.doi.org/10.1002/mame.201200290>.
- [26] Z.K. Nagy, A. Balogh, B. Démuth, H. Pataki, T. Vigh, B. Szabó, K. Molnár, B.T. Schmidt, P. Horák, G. Marosi, G. Verreck, I. Van Assche, M.E. Brewster, High speed electrospinning for scaled-up production of amorphous solid dispersion of itraconazole, *Int. J. Pharm.* 480 (2015) 137–142, <http://dx.doi.org/10.1016/j.ijpharm.2015.01.025>.
- [27] F. Ferrari, M. Bertoni, C.M. Bonferoni, S. Rossi, C. Caramella, G.K. Bolhuis, Dissolution enhancement of an insoluble drug by physical mixture with a superdisintegrant: optimization with a simplex lattice design, *Pharm. Dev. Technol.* 1 (1996) 159–164, <http://dx.doi.org/10.3109/10837459609029890>.
- [28] C. De Brabander, C. Vervae, L. Fiermans, J.P. Remon, Matrix mini-tablets based on starch/microcrystalline wax mixtures, *Int. J. Pharm.* 199 (2000) 195–203, [http://dx.doi.org/10.1016/S0378-5173\(00\)00383-5](http://dx.doi.org/10.1016/S0378-5173(00)00383-5).
- [29] T. Matsumoto, G. Zografi, Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization, *Pharm. Res.* 16 (1999) 1722–1728. <<http://www.ncbi.nlm.nih.gov/pubmed/10571278>> (accessed July 26, 2016).
- [30] R.J. Chokshi, N.H. Shah, H.K. Sandhu, A.W. Malick, H. Zia, Stabilization of low glass transition temperature indomethacin formulations: impact of polymer-type and its concentration, *J. Pharm. Sci.* 97 (2008) 2286–2298, <http://dx.doi.org/10.1002/jps.21174>.
- [31] A. Alzghoul, A. Alhalaweh, D. Mahlin, C.A.S. Bergström, Experimental and Computational Prediction of Glass Transition Temperature of Drugs, (n.d.). <http://dx.doi.org/10.1021/ci5004834>.
- [32] C. Wang, C. Ma, Z. Wu, H. Liang, P. Yan, J. Song, N. Ma, Q. Zhao, Enhanced bioavailability and anticancer effect of curcumin-loaded electrospun nanofiber. In vitro and in vivo study, *Nanoscale Res. Lett.* 10 (2015) 439, <http://dx.doi.org/10.1186/s11671-015-1146-2>.
- [33] D.-G. Yu, X.-F. Zhang, X.-X. Shen, C. Brandford-White, L.-M. Zhu, Ultrafine ibuprofen-loaded polyvinylpyrrolidone fiber mats using electrospinning, *Polym. Int.* 58 (2009) 1010–1013, <http://dx.doi.org/10.1002/pi.2629>.
- [34] B.K. Brettmann, A.S. Myerson, B.L. Trout, Solid-state nuclear magnetic resonance study of the physical stability of electrospun drug and polymer solid solutions, *J. Pharm. Sci.* 101 (2012) 2185–2193, <http://dx.doi.org/10.1002/jps.23107>.
- [35] F.L. Lopez, G.C. Shearman, S. Gaisford, G.R. Williams, Amorphous formulations of indomethacin and griseofulvin prepared by electrospinning, *Mol. Pharm.* 11 (2014) 4327–4338, <http://dx.doi.org/10.1021/mp500391y>.
- [36] I. Stoltenberg, J. Breitzkreutz, Orally disintegrating mini-tablets (ODMTs)—a novel solid oral dosage form for paediatric use, *Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Für Pharm. Verfahrenstechnik e.V.* 78 (2011) 462–469, <http://dx.doi.org/10.1016/j.ejpb.2011.02.005>.
- [37] S.-C. Wong, A. Baji, S. Leng, Effect of fiber diameter on tensile properties of electrospun poly(ϵ -caprolactone), *Polymer (Guildf)* 49 (2008) 4713–4722, <http://dx.doi.org/10.1016/j.polymer.2008.08.022>.
- [38] I. Greenfield, X. Sui, H.D. Wagner, Stiffness, Strength, and Toughness of Electrospun Nanofibers: Effect of Flow-Induced Molecular Orientation, (n.d.). <http://dx.doi.org/10.1021/acs.macromol.6b01204>.
- [39] Z.K. Nagy, A. Balogh, B. Vajna, A. Farkas, G. Patyi, A. Kramarics, G. Marosi, Comparison of electrospun and extruded Soluplus®-based solid dosage forms of improved dissolution, *J. Pharm. Sci.* 101 (2012) 322–332, <http://dx.doi.org/10.1002/jps.22731>.
- [40] J. Quan, Y. Yu, C. Branford-White, G.R. Williams, D.-G. Yu, W. Nie, L.-M. Zhu, Preparation of ultrafine fast-dissolving feruloyl-oleyl-glycerol-loaded polyvinylpyrrolidone fiber mats via electrospinning, *Colloids Surf. B. Biointerf.* 88 (2011) 304–309, <http://dx.doi.org/10.1016/j.colsurfb.2011.07.006>.
- [41] G. Verreck, I. Chun, J. Peeters, J. Rosenblatt, M.E. Brewster, Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning, *Pharm. Res.* 20 (2003) 810–817. <<http://www.ncbi.nlm.nih.gov/pubmed/12751639>> (accessed April 1, 2016).
- [42] S. Marano, S.A. Barker, B.T. Raimi-Abraham, S. Missaghi, A. Rajabi-Siahboomi, D.Q.M. Craig, Development of micro-fibrous solid dispersions of poorly water-soluble drugs in sucrose using temperature-controlled centrifugal spinning, *Eur. J. Pharm. Biopharm.* 103 (2016) 84–94, <http://dx.doi.org/10.1016/j.ejpb.2016.03.021>.