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Investigation of downstream processing of electrospun nanoamorphous solid dispersions

Summary of Ph.D. dissertation

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1 INTRODUCTION

The appearance and spread of poorly water-soluble drugs in the contemporary discovery pipelines, which is mainly due to the application of high-throughput screenings[1], pose a large challenge to pharmaceutical experts. According to calculations, 40% of all approved drugs and 70% of new entities belong to the Biopharmaceutical Classification System II class (poor solubility, good permeability).[2] These drugs usually do not possess sufficient bioavailability due to their weak solubility, which can hinder their commercialization. Amorphous solid dispersions (ASDs) have emerged as a viable solution for tackling solubility issues related to newly discovered drugs. With ASDs, it can be possible to make these biologically potent, precious active pharmaceutical ingredients (APIs) suitable for administration, i.e. to invent formulations that enable good dissolution and bioavailability. Therefore, it is not a surprise that the number of marketed ASDs is increasing.[3]

The processes of spray-drying and melt extrusion for preparation of ASDs have been examined thoroughly and have become well-described with years. The majority of the marketed ASDs are manufactured by either of these technologies although drawbacks are also present. A promising method to manufacture ASDs with advantageous properties is electrostatic spinning (ES). The huge surface area of nanofibers, low energy consumption, the application of concentrated solutions (thus not a large volume of volatile solvent is evaporated), ability to easily form solid solutions, and the possibility for continuous production can be brought up as advantages for ES. However, ES is not employed in the pharmaceutical industry yet, probably due to the lack of an applicable scaled-up technology and knowledge of stability of fibers and downstream processing.

Several machines capable of manufacturing fibers at large scale exist on the market. The most developed one is probably the Nanospider™ equipment. However, the so-called 'free surface' electrospinning is feasible with this instrument, which is not compatible with the pharmaceutical industry and utilized mainly to prepare filters. Mass production of drug loaded nanofibers is still an obscure area.

Not many papers are discussing post-manufacturing investigations of electrospun ASDs such as stability or downstream processing although these are also inevitable.

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[1] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Adv. Drug Deliv. Rev.*, 23 (1997) 3–25.

[2] T. Takagi, C. Ramachandran, M. Bermejo, S. Yamashita, L.X. Yu, G.L. Amidon, A Provisional Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan, *Mol. Pharm.*, 3 (2006) 631-643.

[3] Y. He, C. Ho, Amorphous Solid Dispersions: Utilization and Challenges in Drug Discovery and Development, *J. Pharm. Sci.*, 104 (2015) 3237-3258.

Only several works discussing the physical stability of drug-loaded nanofibers can found. These usually do not give a comprehensive overview of the stability and the samples are investigated for not more than 6 months (since the main objective of the study is not the stability study).

The conversion of ASDs to applicable formulations such as tablets or capsules is rarely studied in detail in spite of their importance.[4] However, several challenges can arise with ASD prepared by different technologies, e.g. low bulk density and weak flowability of blends[5] (spray drying and ES) or poor compressibility of glassy particles[6] (melt extrusion), which should be investigated thoroughly.

There has been no published work scrutinizing downstream processing of electrospun fibers, mainly due to lack of available large amounts of them. Grinding and blending with excipients are inevitable steps to make the fibrous ASD suitable for compression. A pre-compression step such as dry granulation might be necessary to compensate the possible weak flowability and low bulk density of the fibers. To conclude, it is of a great interest to establish the fund of converting electrospun ASDs, which own advantageous characteristics, to tablet formulations.

After surveying the current 'state of the art' related to ASDs and electrospun materials, main objectives of the experimental work could be set up:

- characterizing electrospun fibers prepared by high-speed electrospinning (HSES), a scaled-up fiber spinning technology; in addition, compare the characteristics of these fibers to those fabricated by small-scale single needle electrospinning, and performing thorough, detailed stability tests of the amorphous API;
- converting electrospun nanoamorphous SDs into an industrially applicable formulation, practically immediate-release film-coated tablets; investigating the stability of amorphous API in tablets;
- studying the dissolution from tablets, comparing it to the dissolution of neat fibers, and providing an explanation for the incidental differences;
- examining the possibility to monitor the drug content and content uniformity in tablets containing electrospun ASD with near-infrared (NIR) and Raman spectroscopy.

[4] A.T.M. Serajuddin, Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs, *J. Pharm. Sci.*, 88 (1999) 1058-1066.

[5] A. Singh, G. Van den Mooter, Spray drying formulation of amorphous solid dispersions, *Adv. Drug Deliv. Rev.*, 100 (2016) 27-50.

[6] F. Zhang, J. W. McGinity, Properties of Sustained-Release Tablets Prepared by Hot-Melt Extrusion, *Pharm. Dev. Technol.*, 4 (1999) 241-250.

2 METHODS

2.1 Sample preparation

Single needle electrospinning (SNES)

The small-scale preparation of API containing nanofibers was performed by single needle electrospinning setup consisting of a nozzle with an inner diameter of 0.5 mm, a high voltage direct current supply, and a syringe pump.

High-speed electrospinning (HSES)

The large-scale manufacturing of electrospun ASDs was carried out by HSES developed in our research group. The main difference in the setup in comparison with SNES was the spinning part, which was a rotating, stainless steel spinneret in the case of HSES.

Preparation of tablets

Tablets were compressed on three different presses throughout the experimental work: Huxley Bertram hydraulic compaction simulator (compression profiles: Courtoy Modul S press), Dott Bonapace CPR-6 eccentric tablet press, and Kambert KMP-8 table top rotary press.

Film coating

Tablet cores were coated in a Glatt coating machine equipped with a perforated drum.

Storage of samples

Samples were stored in a Binder KBF 720 climate chamber.

2.2 Characterization methods

Traditional and modulated differential scanning calorimetry (DSC)

Samples were analyzed on a TA Instruments Q2000 DSC apparatus.

X-ray powder diffraction (XRPD)

Diffraction patterns were recorded on a PANalytical X'pert Pro MDP X-ray diffractometer.

Scanning electron microscopy (SEM)

Two different SEM machines were employed for investigations: a JEOL 6380LVa type scanning electron microscope and a Phenom Pro instrument.

Dynamic vapor sorption (DVS)

DVS isotherms were recorded on a DVS Intrinsic instrument.

In vitro dissolution testing

Dissolution of samples was studied on a Pharmatest PTWS600 dissolution tester coupled with an Agilent 8453 UV-Vis spectrophotometer in on-line mode.

Raman mapping

A Labram-type Raman instrument of Horiba Jobin-Yvon coupled with external 785 nm diode laser source and Olympus BX-40 optical microscope was employed.

Characterization of powders and tablets

Commonly measured attributes were determined to characterize tableting blends (particle size distribution, bulk density, tapped density, angle of repose, and true density) and tablets (hardness, disintegration time, friability).

High-performance liquid chromatography

The content of impurities was measured on an Agilent 1200 series RP-HPLC system coupled with a UV detector.

Polarized light microscopy

Carl Zeiss Jena Amplival polarized light microscope equipped with a 12,5x objective was applied.

Solution nuclear magnetic resonance (NMR) spectroscopy

^{1}H NMR spectra were recorded on a Bruker DRX-500 instrument.

Elemental analysis

Magnesium content determination was carried out by energy dispersive X-ray spectrometry (EOL6380LVa type SEM) and inductively coupled plasma optical emission spectrometry (Labtest Plasmalab ICP-spectrometer).

Solid state NMR spectroscopy

^{13}C CPMAS NMR spectra were recorded on a Varian NMR System 600 MHz spectrometer (14.1 T, ^{13}C 150.8 MHz) equipped with a 3.2 mm HXY probehead.

Raman spectrometry (drug content determination)

Tablets were examined on a Kaiser RXN2 Hybrid Analyzer.

Near-infrared (NIR) spectrometry (drug content determination)

NIR spectra acquisitions were performed on a Bruker Optics MPA™ FT-NIR spectrometer.

3 RESULTS

Electrospinning of two APIs and the subsequent downstream processings were studied in this work. In the first part, itraconazole (ITR) was formulated into ASDs with vinylpyrrolidone-vinyl acetate copolymer (PVPVA64, ASD_PVPVA64) and hydroxypropyl methylcellulose (HPMC, ASD_HPMC). Scaling-up and stability of these dispersions were investigated. After that, conversion of ASD_PVPV64 into immediate-release tablets is discussed in detail along with an excipient-induced crystallization of the dissolving drug. Last but not least, ES and downstream processing

of flubendazole-based ASD is also presented (applied matrices: hydroxypropyl-ß-cyclodextrin (HPßCD) and polyvinylpyrrolidone (PVP) K90).

3.1 High-speed electrospinning (HSES)

The scaled up ES technology, HSES, was compared to SNES, spray drying (SD) and film casting (FC). For both ES methods, a 7.5-fold more concentrated solution could be applied than for SD, which is of great interest with solvent technologies to reduce the evaporated organic solvents. For HSES, a 10-fold higher flow rate and 60-fold higher productivity (dry product) could be achieved in comparison with SD. Furthermore, owing to their huge surface area, electrospun nanofibers released ITR much faster than spray dried particles or cast film (*Figure 1*).

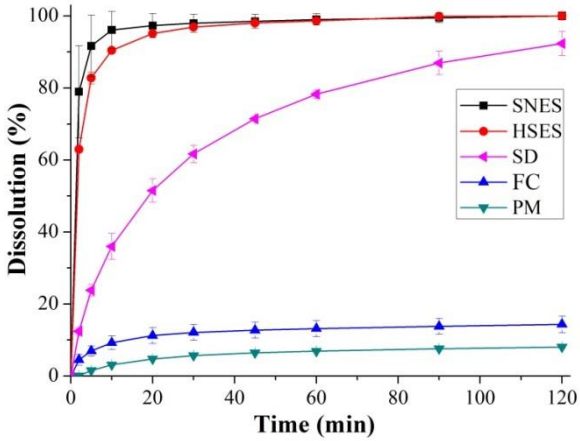

Figure 1 *Dissolution profiles of ITR from PVPVA64-based ASDs prepared by different technologies (n=3). HSES=high-speed electrospinning, SNES=single needle electrospinning, SD=spray drying, FC=film casting, PM=physical mixture.*

3.2 Stability of electrospun ASDs

The behavior of ASD_PVPVA64 under increasing humidity was studied with dynamic vapor sorption both at 25 and 40 °C. Based on the sorption isotherms, good physical stability (i.e. no phase separation) could be predicted for this ASD at 25 °C/60% relative humidity (RH), which was proven by a short-term stability test. Harsh conditions (40 °C and 75% RH), on the other hand, induced phase separation and crystallization of the amorphous API.

Long-term stability of nanofibers containing ITR and either PVPVA64 or HPMC was carried out according to the International Harmonization Conference guidelines, samples were stored at 25 °C/60% RH (closed holder) and 40 °C/75% RH (open holder). The nanofibers prepared by HSES can be viewed in *Figure 2*.

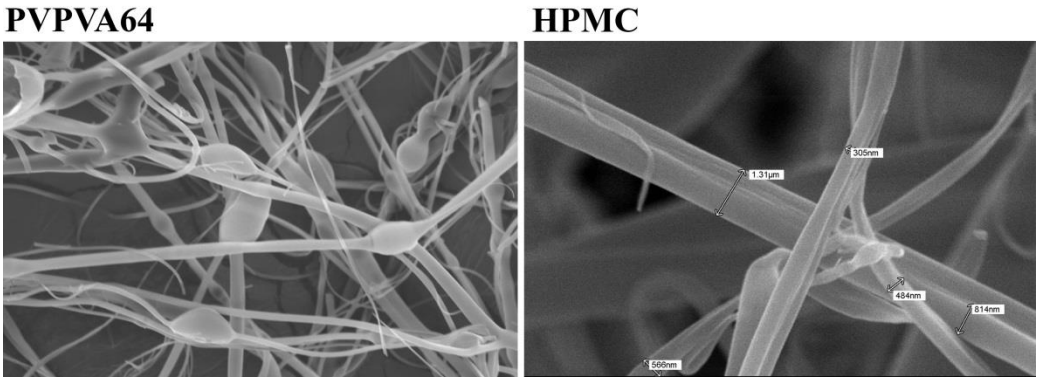

Figure 2 *SEM images of electrospun nanofibers with ITR and either PVPVA64 or HPMC*

After one year of storage, dissolution of ASD_PVPVA64 did not change significantly, the complete and fast release remained (*Figure 3*). A slight deceleration could be observed with ASD_HPMC after storage, which is presumably due to the rearrangement of the drug in the polymer matrix (additional hydrogen bonds could be formed).

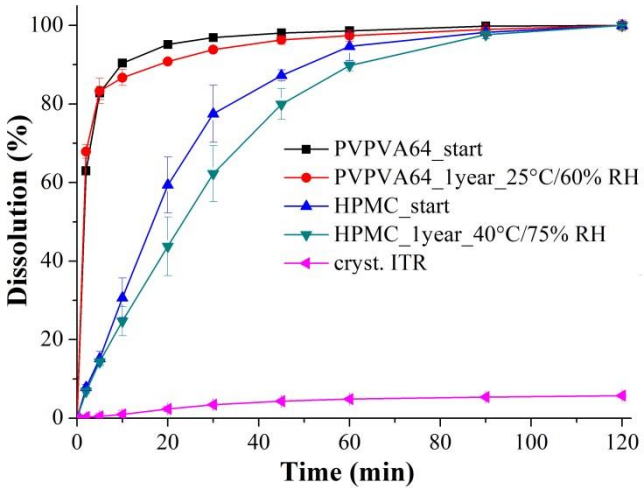

Figure 3 *Dissolution of ITR from electrospun ASDs, prepared by HSES, after production and one year of storage (n=3).*

3.3 Downstream processing of ASD_PVPVA64 to generate tablet formulation

Oscillatory milling was found applicable to make the fibers suitable for blending with excipients. After mixing, the electrospun ASD interestingly was prone to cover the structured microcrystalline cellulose particles in the powder according to the SEM images (but not mannitol that possesses a flat surface). This was also observed in tablets. The tableting blends had fair to poor flowability, but it did not seem impossible to carry out the downstream process with them.

The area of tableting of electrospun materials has not been investigated before this work was begun. Therefore, design of experiments approach was applied to systematically study the behavior of this ASD. Compression was performed on a compaction simulator to generate precise and analogous compression profiles. The setup of the experimental design and the measured attributes of the tablets can be seen

in *Table 1*.

Table 1 *The experimental design and the measured attributes of the tablets (n=3)*

Batch	Fillers fraction (%)*	Compression force (kN)	Tensile strength (N/mm^2)	Disintegration time (s)	Friability (%)
F_71.4_3	71.4	3.0	0.67±0.08	98±9	1.09
F_71.4_4.5	71.4	4.5	1.37±0.10	289±80	-
F_71.4_6	71.4	6.0	2.23±0.03	832±56	0.08
F_74.6_3	74.6	3.0	0.60±0.01	38±4	-
F_74.6_4.5	74.6	4.5	1.20±0.05	226±24	0.34
F_74.6_6	74.6	6.0	1.96±0.12	343±105	-
F_77.8_3	77.8	3.0	0.52±0.02	25±4	1.01
F_77.8_4.5	77.8	4.5	1.03±0.03	93±12	-
F_77.8_6	77.8	6.0	1.84±0.09	363±15	0.02
Optimized tablets (OT)	76.25	6.0	1.94±0.04	337±36	-

$*(\frac{m_{fillers}}{m_{fillers}+m_{ASD}}) \cdot 100$

The obtained values for every measured attribute belonged to the usual pharmaceutical ranges. Optimization was also carried out, and the optimum was found at 76.25% fillers fraction and 6 kN compression force.

3.4 Magnesium stearate-induced crystallization

After production of appropriate tablets, it was of interest whether good dissolution could be maintained with tablets. Interestingly, tablets released only ~80% of ITR despite the 100% dissolution of pure ASD (even at higher, 100 mg dose). No reference was found in the literature to explain this type of decrease in dissolution extent. Hence, it was our objective to provide an explanation for this phenomenon. It was also included in our goals to enhance this dissolution beyond 95%.

Magnesium stearate (MgSt) is known for its hydrophobicity that can deteriorate dissolution of drugs. We determined that two factors modify the release of ITR: temperature and the MgSt content (the same relation applied for both: as they increased dissolution extent decreased). MgSt diminished the dissolution of ITR even if it was placed in a basket moving in the medium i.e. not in the tablet. The desired complete (>95%) dissolution could be achieved by the application of another lubricant (sodium stearyl fumarate, SSF) or if HPMC was used in the initial ASD. The summary of the observed dissolution profiles can be seen in *Figure 4*.

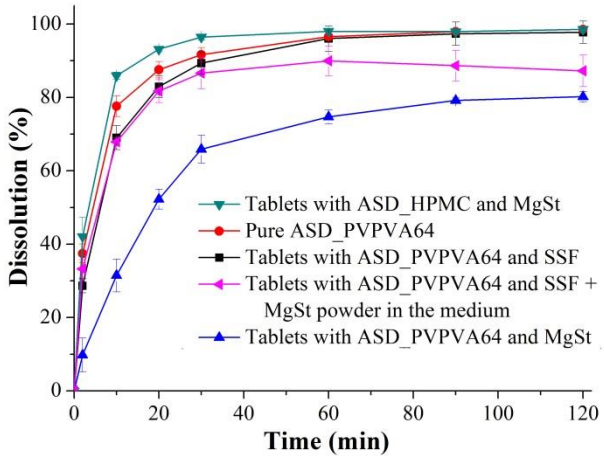

Figure 4 *Dissolution of ITR from different tablet formulations (n=3).*

It was feasible to filter a precipitated material from the dissolution medium of MgSt-based tablets (containing ASD_PVPVA64, mannitol, and MgSt in this case). Based on solution NMR spectra and elemental analysis, the filtrate consisted of ITR and stearic acid in a 1:1 ratio (no magnesium content could be noticed). Based on polarized light microscopy, XRPD analysis (*Figure 5a*) and solid state NMR spectroscopy, the material was crystalline but showed different nature than the aforementioned substances. Raman spectrometry (*Figure 5b*) indicated the interaction (possibly hydrogen bonding) between the triazole moiety of the drug and the carboxylic group of the acid (shift of the peak at 1612 cm^{-1} to 1562 cm^{-1}). Due to the hydrophobic nature of both substances, the association has a very low solubility decreasing the observed dissolution of ITR.

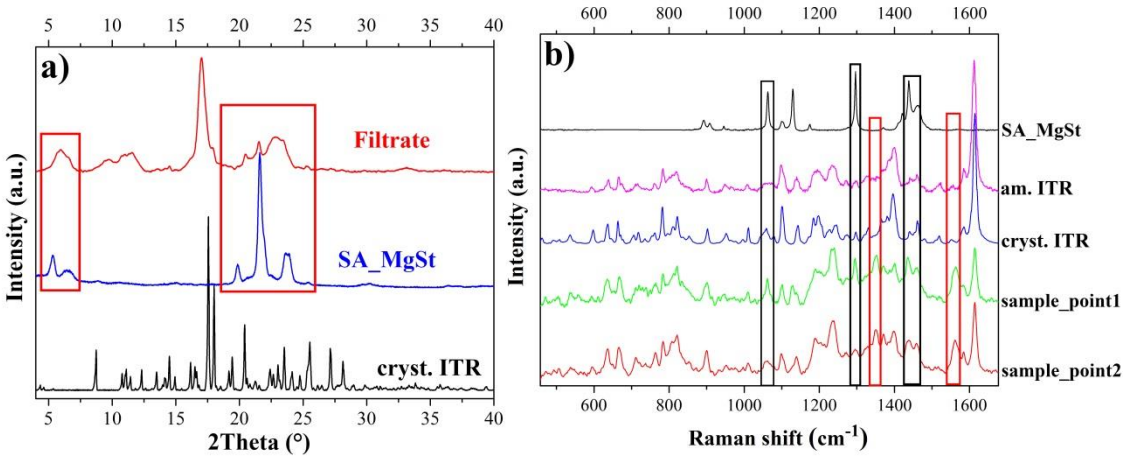

Figure 5 *XRPD diffractogram (a) and Raman spectrum (b) of the filtered ITR-stearic acid (SA) associate. SA_MgSt denotes the stearic acid reference sample prepared from MgSt.*

3.5 Long term stability of tablets containing ASD_PVPVA64

After finding the appropriate composition (with SSF), tablet preparation was feasible on a rotary press, and the obtained tablets were stored 25 °C/60% RH. The dissolution profile of ITR remained the same even after one year of storage. Furthermore, impurity content of ITR did not increase significantly in tablets in comparison with the pure

crystalline drug (crystalline: 0.46±0.04%, tablet: 0.54±0.10%). Film coating was feasible with these tablets containing electrospun ASD without any remarkable change in dissolution and purity.

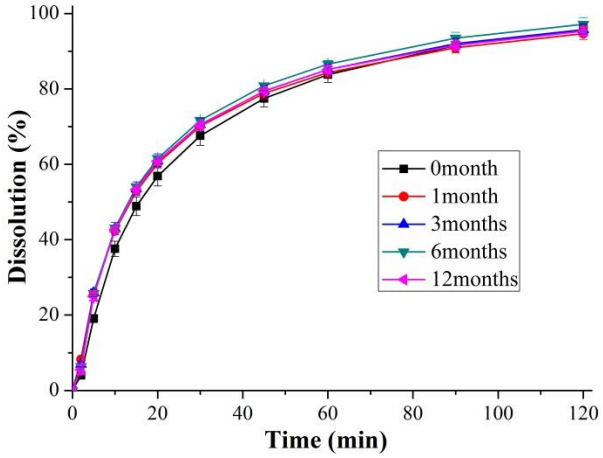

Figure 6 *Dissolution of ITR from tablets after production and storage at 25 °C/60% RH (open holder) (n=3).*

The feasibility of downstream processing with electrospun ASDs was generalized by the conversion of fibers containing FLU, HPßCD, and PVPK90 into directly compressed tablets. Fibers were manufactured by HSES in this case, too. Dissolution from tablets did not change significantly compared to the pure ASD. Drug content of the obtained tablets was investigated by the non-destructive NIR and Raman spectrometries, which were found to be precise, suitable techniques for this purpose.

4 THESES

1. Long-term physical stability of amorphous itraconazole (ITR) encapsulated in different nanofibers was determined, which has not been investigated earlier. ITR, as it was shown by DSC, XRPD, and Raman mapping, remained amorphous under different storage conditions in the electrospun nanofibers even after one year (PVPVA64: 25 °C/60% relative humidity (RH) and closed holder; HPMC: 40 °C/75% RH and open holder). We manufactured the fibrous nanoamorphous solid dispersions by a scaled-up fiber formation technology called high-speed electrospinning. High drug-loading fibers containing 40% ITR and 60% either PVPVA64 or HPMC were proven to have similar characteristics like those fibers prepared by single-needle electrospinning. Owing to the huge surface area of the fibers and the totally amorphous state of the incorporated drug, prepared fibers released it quickly and completely, even after one year of storage. [I, III]

2. The developed nanofibers (containing ITR and PVPVA64) were converted into conventional, immediate-release tablet cores and film coated tablets, both for the first time according to the literature. Design of experiments method was applied to optimize the tableting process (composition and compression force) on a

compaction simulator with regards to disintegration time and tensile strength. In spite of the large polymer content, we managed to fabricate fast disintegrating tablets (337±36 sec) while maintaining their high tensile strength (1.94±0.04 N/mm^2). The developed tablet composition with satisfying flowability was found to be suitable for scaled-up tableting on a rotary press. This first electrospinning-based formulation evaluated for scaled-up production possessed satisfying characteristics (weight variation, disintegration time, tensile strength and dissolution). Tablets could be film coated with aqueous suspension without any deterioration in dissolution. [II, IV, VI]

3. Dynamic vapor sorption (water uptake) isotherms showed no phase separation and predicted good stability of ITR in PVPVA64 matrix at 25 °C and 60% RH (open conditions). This was confirmed by a short-term stability test. Under these circumstances, glass transition temperature of the ASD remained the same for the investigated one month according to the modulated DSC measurements. The good and complete dissolution of ITR from tablets could be maintained after a year of storage at 25 °C and 60% RH. The active pharmaceutical ingredient remained chemically stable, according to the HPLC examinations after one year, measuring only 0.08% more contamination than with crystalline material (crystalline: 0.46±0.04%, tablet: 0.54±0.10%). [IV, VI]

4. We determined that the applied lubricant and the temperature could modify the extent of dissolution of amorphous ITR from tablets in pH=1.2 medium. 100% of the active pharmaceutical ingredient can be dissolved if the pure ASD is examined (both at 22 and 37 °C). Magnesium stearate as a tablet component decreased the dissolved amount of ITR and enabled a release of only ~80% of it from tablets. On the contrary, sodium stearyl fumarate (SSF) did not change the extent of dissolution of the initial ASD significantly, and tableting was feasible with it. Furthermore, it was proven that temperature could alter the dissolution extent: higher temperature (37 °C) induced a release of only ~80%, while at 22 °C more than 95% of ITR was dissolved. [IV]

5. We revealed the mechanism of precipitation of ITR, which was induced by magnesium stearate. It was proven that stearic acid deriving from the lubricant formed a crystalline associate with ITR, which is insoluble in the acidic dissolution medium. This phenomenon induced by magnesium stearate has never been described before. The chemical composition of this associate was confirmed by NMR and elemental analysis (energy dispersive X-ray and atomic emission

spectroscopies). A 1:1 ratio of ITR and stearic acid was observed with NMR spectroscopy. Physical characterization by X-ray powder diffractometry, solid state NMR spectroscopy, Raman mapping showed a distinctive state of this associated material compared to the relevant substances. The presence of hydrogen bonding between triazole moiety of ITR and the carboxyl group of stearic acid was proven by the shift of the peak belonging to the C=N bond in ITR from 1612 cm^{-1} to 1562 cm^{-1}. This disadvantageous crystallization phenomenon can be avoided by the application of improved compositions.

6. Electrospun flubendazole, with considerably improved bioavailability, was converted into tablet formulation by direct compression. The fast dissolution from tablets was more than threefold higher than from crystalline drug. Drug content uniformity was investigated by NIR and Raman spectrometries. Calibration models were built by partial least squares-genetic algorithm method. Root mean square error of cross validation values, which are dedicated to describing the accuracy of the models, were found to be 0.11% (Raman) and 0.10% (NIR). Therefore, NIR spectrometry provides a slightly more precise model, nonetheless, both of these spectrometries are suitable for monitoring the content uniformity of electrospun fiber-based tablets. [V]

5 APPLICATION OF THE RESULTS

ASDs are becoming more and more prominent in the pharmaceutical industry owing to their obvious advantages. An ASD preparation technology with the potentials to eliminate some known drawbacks of other methods and to introduce new material advantages, ES, was investigated in this work. Scaling-up of such technology and downstream processing of the obtained products, which were unknown before this work was begun, are always of great interest, both to academia and to the industry.

A significant part of this work was carried out in collaboration with Janssen Research and Development (Pharmaceutical Companies of Johnson & Johnson). Therefore, industrial utilization of the obtained results can certainly be foreseen in the future.

6 PUBLICATIONS

Publications related to the dissertation

Papers on which thesis findings are based:

I. Z. K. Nagy, A. Balogh, **B. Démuth**, H. Pataki, T. Vigh, B. Szabó, K. Molnár, B. T. Schmidt, P. Horák, G. Verreck, I. Van Assche, M. E. Brewster, High

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II. **B. Démuth**, Z. K. Nagy, A. Balogh, T. Vigh, G. Marosi, G. Verreck, I. Van Assche, M. E. Brewster, Downstream processing of polymer-based amorphous solid dispersions to generate tablet formulations, *Int. J. Pharm.*, 486 (2015), 268-286.
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III. **B. Démuth**, A. Farkas, H. Pataki, A. Balogh, B. Szabó, E. Borbás, P. L. Sóti, T. Vigh, É. Kiserdei, B. Farkas, J. Mensch, G. Verreck, I. Van Assche, G. Marosi, Z. K. Nagy, Detailed stability investigation of amorphous solid dispersions prepared by single-needle and high speed electrospinning, *Int. J. Pharm.*, 498 (2016), 234-244.
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V. T. Vigh, **B. Démuth**, A. Balogh, D. L. Galata, I. Van Assche, C. Mackie, M. Vialpando, B. Van Hove, P. Psathas, E. Borbás, H. Pataki, P. Boeykens, G. Marosi, G. Verreck, Z. K. Nagy, Oral bioavailability enhancement of flubendazole by developing nanofibrous solid dosage forms, *Drug Dev. Ind. Pharm.*, 43 (2017), 1126-1133.
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VI. **B. Démuth**, A. Farkas, B. Szabó, A. Balogh, B. Nagy, E. Vágó, T. Vigh, A. P. Tinke, Z. Kazsu, Á. Demeter, J. Bertels, J. Mensch, A. Van Dijck, G. Verreck, I. Van Assche, G. Marosi, Z. K. Nagy, Development and tableting of directly compressible powder from electrospun nanofibrous amorphous solid dispersion, *Adv. Powder Technol.*, 28 (2017), 1554-1563.
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IF: 3.994 C: 6

VIII. E. Borbás, B. Sinkó, O. Tsinman, K. Tsinman, É. Kiserdei, **B. Démuth**, A. Balogh, B. Bodák, A. Domokos, G. Dargó, G. T. Balogh, Z. K. Nagy, Investigation and Mathematical Description of the Real Driving Force of Passive Transport of Drug Molecules from Supersaturated Solutions, *Mol. Pharm.*, 13 (2016), 3816-3826.
IF: 4.440 C: 3

IX. A. Farkas, B. Nagy, **B. Démuth**, A. Balogh, H. Pataki, Z. K. Nagy, G. Marosi, Variable clustering and spectral angle mapper-orthogonal projection method for Raman mapping of compound detection in tablets, *J. Chemom.*, 31 (2017), e2861, 1-11.
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IF: 3,649 C: 0

Presentations related to the dissertation:

XII. Nagy Zs., Borbás E., Farkas B., **Démuth B.**: Elektrosztatikus szálképzés – az új ipari nanotechnológia? VII. Kerekasztal Konferencia, Magyar Kémikusok Egyesülete, Kristályosítási és Gyógyszerformulálási Szakosztály, May 16-17, **2014**.

XIII. **Démuth B.**, Nagy Zs., Marosi Gy.: Elektrosztatikusan szálképzett anyagok tablettázhatóságának vizsgálata kísérlettervezés segítségével, Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium ’15, September 17-18, **2015**.

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