FINAL REPORT

Development of nanofiber production methods and new nanofiber-based drug delivery systems

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According to the determined work plan we performed our research work in the field of drug loaded nanofibers in the two-year period of the project. The main aim of this project was to map the technological/scientific capability and limitations of the promising high speed electrospinning method for producing new drug delivery systems with improved drug bioavailability and/or patient compliance.

Detailed aims described in the project proposal were as follows:

- comparison of single needle electrospinning and high speed electrospinning
- investigation and downstream processing of nanofibrous materials prepared by high speed electrospinning
- effect of the excipients on the membrane transport of the drug molecules formulated by electrospinning.

In the first year of the project according to the determined aims of the proposed project we compared the high speed electrospinning with single needle electrospinning for preparation of amorphous solid dispersions. We prepared carvedilol containing nanofibrous material using PVPK30 as polymer matrix and it was filled into plastic straws to test this new drug formulation possibility. In vitro dissolution studies revealed ultrafast drug release from the prepared fibrous formulations inserted into plastic straws. Based on the results the developed drug delivery system is suitable for storing the formulation in a solid dosage form and in situ turning it into liquid form when administered. (B. Farkas et al.: ***Medicated Straws Based on Electrospun Solid Dispersions***, Periodica Polytechnica Chemical Engineering, 2018).

Similarly high speed electrospinning and single needle electrospinning was compared in the case of spironolactone (model API) and PVPVA64 (polymer matrix). Single needle electrospinning was applied at first for screening the composition of the prepared ASDs. Scaling-up the selected polymer-drug combination was accomplished by high speed electrospinning, the productivity of which enabled investigation of downstream processing to generate tablet formulation. The steps of a potential continuous production line (fibre collection, grinding, feeding and tableting) proved to be feasible with the electrospun ASD without any sign of crystallization. If crystalline drug was added into the ASD containing tablets as impurity strictly monotonous decrease of drug dissolution was observed in the function of the crystalline drug content. The capabilities of the non-destructive Raman and near-infrared spectroscopies, as fast quality assurance tools, were compared to each other in quantifying of crystalline SPIR content in the prepared tablets. Later batch and continuous blending was investigated to obtain homogenous powder blends which might be a large

challenge in the case of low dose formulations (E. Szabó et al.: ***Scaled-up preparation of drug-loaded electrospun polymer fibres and investigation of their continuous processing to tablet form***, Express Polymer Letters, 2018; B. Nagy et al.: ***Spectroscopic characterization of tablet properties in a continuous powder blending and tableting process***, European Journal of Pharmaceutical Sciences, 2018; G. Fülöp et al.: ***Homogenization of Amorphous Solid Dispersions Prepared by Electrospinning in Low-Dose Tablet Formulation***, Pharmaceutics, 2018).

During this research period we investigated of the effect of magnesium stearate on the dissolution of itraconazole from nanofibrous formulations prepared by high speed electrospinning, grounding, blending and tableting. Incomplete dissolution of the tablets was noticed under the circumstances of the standard dissolution test, after which a precipitated material could be filtered. The filtrate consisted of ITR and stearic acid since no magnesium content was detectable in it. In parallel with dissolution, ITR forms an insoluble associate, stabilized by hydrogen bonding, with stearic acid deriving from magnesium stearate. This is why dissolution curves do not have the plateaus at 100%. Two ways are viable to tackle this issue: change the lubricant (with sodium stearyl fumarate >95% dissolution can be accomplished) or alter the polymer in the solid dispersion to a type being able to form hydrogen bonds with ITR e.g. hydroxypropyl methylcellulose (B. Démuth et al.: ***Investigation of deteriorated dissolution of amorphous itraconazole: Description of incompatibility with magnesium stearate and possible solutions***, Molecular pharmaceutics, 2018). Formulations containing the PVPVA-based ASD with HPMC included in various forms could reach 90% dissolution in 2 h, while HPMC-based ASDs could release 100% of the drug. However, HPMC-based ASD had remarkably poor grindability and low bulk density, which limited its processability and applicability. The latter issue could be resolved by roller compacting the ASD, which significantly increases the bulk density and the flowability of the powder blends used for tableting. This roller compaction step might be a base for the industrial application of HPMC-based, electrospun ASDs (B. Démuth et al.: ***Application of hydroxypropyl methylcellulose as a protective agent against magnesium stearate induced crystallization of amorphous itraconazole***, European Journal of Pharmaceutical Sciences, 2018).

The effect of formulation additives on membrane transport of drugs from supersaturated solutions were also investigated. The brand and four generic formulations of telmisartan, an antihypertensive drug, were used in in vitro simultaneous dissolution-absorption, investigating the effect of different formulation additives on dissolution and on absorption through an artificial membrane. The in vitro test was found to be sensitive enough to show even small differences between brand and generic formulations caused by the use of different excipients. By only changing the type of filler from sorbitol to mannitol in the formulation, the flux through the membrane was reduced by approximately 10%. Changing the salt forming agent as well resulted in approximately 20% of flux reduction compared to the brand formulation. This significant difference was clearly shown in the published in vivo results as well. The use of additional lactose monohydrate in the formulation also leads to approximately 10% reduction in flux. The results show that by changing excipients, the

dissolution of telmisartan was not altered significantly, but the flux through the membrane was found to be significantly changed.

These results pointed out the limitations of traditional USP dissolution tests and emphasized the importance of simultaneously measuring dissolution and absorption, which allows the complex effect of formulation excipients on both processes to be measured. Moreover, the in vivo predictive power of the simultaneous dissolution-absorption test was demonstrated by comparing the in vitro fluxes to in vivo bioequivalence study results (E. Borbás et al.: ***The effect of formulation additives on in vitro dissolution-absorption profile and in vivo bioavailability of telmisartan from brand and generic formulations***, European Journal of Pharmaceutical Sciences, 2018). Size exclusion membranes were also tested for transport measurements, where the aim was to investigate the driving force of membrane transport through these size-exclusion membranes and to provide a concentration-based mathematical description of it to evaluate whether it can be an alternative for lipophilic membranes in the formulation development of amorphous solid dispersions. Carvedilol, an antihypertensive drug, was chosen and formulated using solvent-based electrospinning to overcome the poor water solubility of the drug. Vinylpyrrolidone–vinyl acetate copolymer (PVPVA64) and Soluplus were used to create two different amorphous solid dispersions of the API. The load-dependent effect of the additives on dissolution and permeation through regenerated cellulose membrane was observed by a side-by-side diffusion cell, µFLUX. The solubilizing effect of the polymers was studied by carrying out thermodynamic solubility assays. The supersaturation ratio (SSR, defined as the ratio of dissolved amount of the drug to its thermodynamic solubility measured in exactly the same medium) was found to be the driving force of membrane transport in the case of size-exclusion membranes. Although the transport through lipophilic and size-exclusion membranes is mechanistically different, in both cases, the driving force of membrane transport in the presence of polymer additives was found to be the same. This finding may enable the use of size-exclusion membranes as an alternative to lipid membranes in formulation development of amorphous solid dispersions (E. Borbás et al.: ***Effect of formulation additives on drug transport through size-exclusion membranes***, Molecular pharmaceutics, 2018).

In the second year of the project according to the determined aims of the proposed project we compared the high speed electrospinning with single needle electrospinning for preparation of voriconazole loaded solid dispersions. The main achievements of the work were:

- continuous collection of drug-loaded fibers by a cyclone attached to the high-speed electrospinning machine is performed
- viscous aqueous solution of sulfobutylether-β-cyclodextrin can be electrospun with high production rate at room temperature

- voriconazole becomes molecularly dispersed in the cyclodextrin matrix during electrospinning, the product dissolves in 30 s
- scaled-up electrospinning of aqueous solutions at room temperature can be a viable, continuous alternative to freeze drying

Our results were published in a Journal of Controlled release (IF: 7.901). (P. Vass et al.: ***Continuous alternative to freeze drying: Manufacturing of cyclodextrin-based reconstitution powder from aqueous solution using scaled-up electrospinning***, Journal of Controlled Release, 2019). The published article is already highly cited (15 citations in 11 months).

In another study corona electrospinning and single needle electrospinning was compared in the case of spironolactone (model API) and PVPK90 (polymer matrix). Single needle electrospinning was applied at first for screening the composition of the prepared ASDs. Scaling-up the selected polymer-drug combination was accomplished by corona electrospinning (B. Farkas et al.: ***Corona alternating current electrospinning: A combined approach for increasing the productivity of electrospinning,*** International Journal of Pharmaceutics, 2019)

The capabilities of the non-destructive Raman, as fast quality assurance tools, were reviewed and tested for dissolution prediction. (B. Nagy et al.: ***SRaman Spectroscopy for Process Analytical Technologies of Pharmaceutical Secondary Manufacturing***, AAPS PharmSciTech, 2019; B. Nagy et al.: ***Application of artificial neural networks for Process Analytical Technology-based dissolution testing***, International Journal of Pharmaceutics, 2019).

During this research period we investigated of the electrospinning technology as a promising continuous alternative of freeze-drying for drying of biopharmaceuticals. At first, the state of art of the oral delivery of biopharmaceuticals was reviewed and published (P. Vass et al.: ***Drying technology strategies for colon-targeted oral delivery of biopharmaceuticals,*** Journal of Controlled Release, 2019). Later a promising, grindable placebo system was developed based on PVA polymer matrix after the testing of different sugars for aiding of the grinding. (E. Hirsch et al.: ***Electrospinning scale-up and formulation development of PVA nanofibers aiming oral delivery of biopharmaceuticals,*** Express Polymer Letters, 2019).

Last but not least a protein-type drug was dried by high speed electrospinning. The obtained fibers were grindable, and tablets were compressed after mixing the fibrous material with common tableting excipients (MCC, Mannitol, …). The protein was stable and bioactive after drying and in the tablets for one year. (P. Vass et al.: ***Scaled-Up Production and Tableting of Grindable Electrospun Fibers Containing a Protein-Type Drug,*** Pharmaceutics, 2019)

Cumulative impact factor of the published articles of this project: 58.215 (15 publications in international journals with impact factor, average impact factor: 3.881).