Final report of OTKA PD-128241 project entitled ‘Innovative, continuous technologies for downstream processing of sensitive drugs’ (01/10/2018 – 31/08/2019)

In the first year of the project, twin-screw granulations were planned to be investigated. Besides that, work on electrospinning of cyclodextrins (platform technology for biomolecules) and compatibility studies of amorphous drugs has already been begun.

Twin-screw wet granulation (TSWG) has been gaining more and more ground in the pharmaceutical industry in the last few years due to its easy scalability, better process control and more homogeneous quality of the product. One area where TWSG has not been exploited yet is the low-dose products. We used this technology to simultaneously granulate and homogenize a drug with low dose. Based on our experiments, better homogeneity could be achieved with a pump with steady dosing of the liquid (as the drug was dissolved in the granulating liquid) such as syringe pump or piston pump. The disadvantageous distribution of the API with peristaltic pump was due to the pulsation of the liquid verified by real-time balance-based characterization of the pumps. The manuscript based on this work is currently prior to submission.

In-line monitoring of the critical quality attributes during TSWG such as particle size distribution and feedback control of the technology based on this are of great importance. For this purpose, we developed a process camera based image analysis from which particle size can be measured and particle size distribution can be calculated. Based on the measured particle size, the liquid-to-solid ratio could be changed to enhance the granulation to ensure the feedback control of the process. The published paper from this subject: L. Madarász *et al.*, *Int. J. Pharm.* 547 (2018) 360-367.

TSWG and twin-screw melt granulation of amorphous solid dispersions (ASDs) might be really important in the future as these materials sometimes have weak flowability and low bulk density. Both kinds of granulations were feasible with an electrospun ASD consisting of itraconazole and vinylpírrolidone and vinyl-acetate copolymer (PVPVA64) and good flowing granules could be obtained. However, tablets made from the granules did not release 100% of the drug, which might mean that the drug crystallized during the granulation. This was confirmed by modulated differential scanning calorimetry examinations. In the future, optimization of the processing parameters is needed to avoid crystallization and maintain advantageous dissolution.

Cyclodextrins are known to stabilize biomolecules. Electrospinning of sulfobutylether-ß-cyclodextrin with viscous aqueous solution was carried out during the last year. This can be a platform technology, the model API was voriconazole. The electrospun material had similar properties than the lyophilized product on the market; therefore, electrospinning can be considered as a continuous alternative to freeze drying. The published paper from this subject: P. Vass, B. Démuth* *et al., J. Control. Release* 298 (2019) 120-127.

As a continuation of a previously started work, the compatibility of amorphous itraconazole with magnesium stearate in the presence of PVPVA64 or hydroxypropyl methylcellulose (HPMC) was investigated. In contrast to PVPVA64, HPMC was able to ensure more advantageous dissolution of the drug owing to the forming interactions between the two substances. It was also shown that HPMC was the most effective when used as a matrix realizing complete dissolution (when used as an excipient or in the coating, release of ~90% was doable). The published paper from this subject: B. Démuth *et al., Eur. J. Pharm. Sci.* 121 (2018) 301-308.