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In this project we intended to integrate fiber formation techniques into the pharmaceutical process lines which includes the development of new fiber formation methods and to merge these techniques into continuous pharmaceutical manufacturing.

In the first year of our research high yield alternating current electrospinning was used for the first time to process HPMCAS - an important pharmaceutical cellulose ether - into nanofibers for dissolution enhancement [1]. A pH-dependent fibrous drug-delivery system was also developed based on Eudragit® FS using both direct and alternating current electrospinning for the first time with this polymer [2].

The most important result of the second year of our research was finalizing the development of our continuous model system (CMS) and publishing the results [3]. The CMS is able to synthetize and subsequently formulate the drug substance into a solid formulation in a fully continuous manner. We could achieve this for the first time in the benchtop size range by exploiting the advantages of electrospinning. The formulation module of the CMS was successfully used with another drug [4]. Due to the well-designed system the residual solvent content as well as the effect of secondary drying could be also investigated which were important parts of the project.

The success of fiber formation methods mostly depends on the suitability of the developed fibrous formulations for the patients. Various efforts have been made to resolve the great challenge of poorly water-soluble drugs. We discovered during the development of continuous tablet production based on an electrospun material that itraconazole – a poorly soluble antifungal agent – precipitates due to magnesium stearate and it could be resolved by replacing the lubricant [5]. In an international cooperation we investigated the formulation of flubendazole – another poorly soluble antifungal drug – using high speed electrospinning as a scaled-up method [6].

Our further works involved technology related pharmaceutical advancements. The aforementioned intraconazole-loaded polymeric nanofibers were direct compressed into tablets by the addition of free flowing excipients [7]. Direct compression can be easily integrated into a continuous production line due to its simplicity, therefore we investigated further the homogenization of the fibrous material with tableting excipients for the challenging production of ultra-low dose tablets [8]. We participated in another international cooperation about 3D printing which resembles the fiber spinning techniques [9]. Basically 3D printing is the controlled deposition of a thin molten polymeric liquid jet, and this method may be used for continuous tablet production of arbitrary shape and type. We also took advantage of the variable 3D arrangement of the electrospun material when the fibrous mats were loaded into plastic straws enabling ultrafast drug liberation especially for pediatric use [10]. Finally, our experiences with fiber-based tablets were molded into a concept of a continuous system involving spinning and subsequent grinding of the fibers, then homogenization and lastly tableting, all these with real-time analytical support [11].

In the last year of the research project we developed a nanofibrous orally dissolving formulation containing a poorly soluble drug at the pH of the stomach as part of an ongoing international cooperation [12]. A related work was published about the fusion of the results of four independent analytical methods investigating nanofibers with the same drug [13]. Besides these, our investigations regarding the development of fiber formation techniques persistently continued and as a side project a brief review article about continuous pharmaceutical

manufacturing was also published in Gyógyszerészet [14]. Continuous manufacturing was also the main principle during our extrusion-based wet granulation project where the target dose of the final tablets was set to the ultra-low range [15] similarly to our earlier work [8]. Meanwhile the throughput of alternating current electrospinning could be elevated approximately twenty times using a so called corona spinneret for the preparation of fast dissolving nanofibrous products [16]. It should be noted that the productivity of novel alternating current electrospinning with the same corona spinneret was several times higher than that of traditional direct current electrospinning. Thereafter the main focus of our research was to consider the change of the frequency and the waveform of alternating current high voltage and investigate their effect on alternating current electrospinning. The related results are being summarized in an upcoming publication [17].
To sum it up, we could exceed the expected number of publications ("2 articles with impact factor") during the three-year long period of the project since 14 articles have been published in journals with impact factor related to the original programme. Besides these, I participated in the creation of two other research paper not related to the project [18,19]. The cumulative impact factor of the listed and accepted articles is 56.263.

[1] A. Balogh, B. Farkas, Á. Pálvölgyi, A. Domokos, B. Démuth, G. Marosi, Z.K. Nagy, Novel alternating current electrospinning of hydroxypropylmethylcellulose acetate succinate (HPMCAS) nanofibers for dissolution enhancement: the importance of solution conductivity, J. Pharm. Sci. 106 (2017) 1634–1643.
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[2] A. Balogh, B. Farkas, A. Domokos, A. Farkas, B. Démuth, E. Borbás, B. Nagy, G. Marosi, Z.K. Nagy, Controlled-release solid dispersions of Eudragit ® FS 100 and poorly soluble spironolactone prepared by electrospinning and melt extrusion, Eur. Polym. J. 95 (2017) 406–417.
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[3] A. Balogh, A. Domokos, B. Farkas, A. Farkas, Z. Rapi, D. Kiss, Z. Nyiri, Z. Eke, G. Szarka, R. Örkényi, B. Mátravölgyi, F. Faigl, G. Marosi, Z.K. Nagy, Continuous End-to-End Production of Solid Drug Dosage Forms: Coupling Flow Synthesis and Formulation by Electrospinning, Chem. Eng. J. 350 (2018) 290–299.
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[4] A. Domokos, A. Balogh, D. Dénes; G. Nyerges, L. Ződi, B. Farkas, G. Marosi, Z.K. Nagy, Continuous manufacturing of orally dissolving webs containing a poorly soluble drug via electrospinning, Eur. J. Pharm. Sci. 130 (2019) 130: 91-99.
IF: 3.466

[5] B. Démuth, D.L. Galata, E. Szabó, B. Nagy, A. Farkas, A. Balogh, E. Hirsch, H. Pataki, Z. Rapi, L. Bezúr, T. Vigh, G. Verreck, Z. Szalay, Demeter, G. Marosi, Z.K. Nagy, Investigation of Deteriorated Dissolution of Amorphous Itraconazole: Description of Incompatibility with Magnesium Stearate and Possible Solutions, Mol. Pharm. 14 (2017) 3927–3934.
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[6] 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. (2017) 1–8.
IF: 2.295

[7] B. Démuth, A. Farkas, B. Szabó, A. Balogh, B. Nagy, E. Vágó, T. Vigh, A.P. Tinke, Z. Kazsu, 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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[8] G. Fülöp, A. Balogh, B. Farkas, A. Farkas, B. Szabó, B. Démuth, E. Borbás, Z.K. Nagy, G. Marosi, Homogenization of amorphous solid dispersions prepared by electrospinning in low-dose tablet formulation, Pharmaceutics. 10 (2018).
IF: 3.746

[9] K. Ilyés, N.K. Kovács, A. Balogh, E. Borbás, B. Farkas, T. Casian, G. Marosi, I. Tomuta, Z.K. Nagy, The 3D-FDM printability assessment in terms of pharmaceutical polymers / polymeric blends, Eur. J. Pharm. Sci. 129 (2019) 110-123.
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[12] T. Casian, E. Borbás, K. Ilyés, B. Démuth, A. Farkas, Z. Rapi, C. Bogdan, S. Iurian, V. Toma, R. Stiufiuc, B. Farkas, A. Balogh, G. Marosi, I. Tomută, Z.K. Nagy, Electrospun amorphous solid dispersions of meloxicam: influence of polymer type and downstream processing to orodispersible dosage forms, Int. J. Pharm. 569 (2019) 118593.
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[13] T. Casian, A. Farkas, K. Ilyés, B. Démuth, E. Borbás, L. Madarász, Z. Rapi, B. Farkas, A. Balogh, A. Domokos, G. Marosi, I. Tomută, Z.K. Nagy, Data fusion strategies for performance improvement of a Process Analytical Technology platform consisting of four instruments: An electrospinning case study, Int. J. Pharm. 567 (2019) 1-13.
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[14] A. Balogh, Innovatív megoldások a folyamatos készítménygyártásban, Gyógyszerészet 63 (2019) 267-273.
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[15] G. Fülöp, B. Démuth, M. Kovács, L. Madarász, M. Ficzere, B. Szabó, B. Nagy, A. Balogh, K. Csorba, G. Kaszás, A. Bódis, G. Marosi, Nagy Z.K., Continuous manufacturing of homogeneous ultralow-dose granules by twin-screw wet granulation, Periodica Polytechnica Chemical Engineering, BÍRÁLAT ALATT
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[16] B. Farkas, A. Balogh, R. Cselkó, K. Molnár, A. Farkas, E. Borbás, G. Marosi, Z.K. Nagy, Corona Alternating Current Electrospinning: A combined approach for increasing the productivity of electrospinning, Int. J. Pharm 561 (2019) 219-227.
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[17] B. Farkas, A. Balogh, A. Farkas, E. Szabó, G. Madarász, J. Madarász, G. Marosi, Z.K. Nagy, Frequency and waveform dependence of alternating current electrospinning and their use for dissolution enhancement, MANUSCRIPT

Az ösztöndíjhoz közvetlenül nem kapcsolódó cikkek:
[18] G. Varró, L. Hegedűs, A. Simon, A. Balogh, A. Grün, I. Leveles, B.G. Vértessy, I. Kádas, The First Enantioselective Total Synthesis of (−)-trans-Dihydronarciclasine, J. Nat. Prod. 80 (2017) 1909–1917.
IF: 3.280

[19] E. Borbás, Z.K. Nagy, B. Nagy, A. Balogh, B. Farkas, O. Tsinman, K. Tsinman, B. Sinkó, The effect of formulation additives on in vitro dissolution-absorption profile and in vivo bioavailability of telmisartan from brand and generic formulations, Eur. J. Pharm. Sci. 114 (2018).
IF: 3.466

The cumulative impact factor of the accepted articles during the project period: 56.263.