Budapest University of Technology and Economics

Department of Organic Chemistry and Technology

George A. Olah Doctoral School

Development of low dose formulations using electrospinning and continuous granulation technologies

Summary of Ph.D. dissertation

Author: Gergő Fülöp

Supervisor: Dr. Zsombor K. Nagy

Co-supervisor: Dr. György J. Marosi

FirePharma Research Group

Department of Organic Chemistry and Technology

Budapest, Hungary

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1. Introduction

In recent decades, the pharmaceutical industry has been working intensively on adopting new, innovative Continuous Manufacturing (CM) process steps in order to increase their overall effectiveness and final product quality of their medicines. CM has numerous benefits compared to traditional batch production methods, such as significant cost-reduction, lower ecological footprint, faster and more economic transition from small scale to production scale, which are all realized by maintaining a higher level of control throughout production[1].

Adopting CM technologies is challenging in its own right, but the development of specialized dosage forms, such as low-dose drug formulations present additional tasks to solve. In these compositions, the concentration of the Active Pharmaceutical Ingredient (API) is $\leq 2\%$[2], contributing to the fact that the formulation is predominantly made up of the applied excipients. As a result, characteristic challenges of low-dose drug product development can be listed as:

- Meeting the Content Uniformity (CU) requirements
- Chemical instability during storage
- Instability due to physical transformation of the API during manufacture or storage
- API loss during production
- Potential incompatibility with the high rate of excipients in the formulation

To tackle this problem, we have chosen two continuous manufacturing platforms for our purposes. The first one was a Twin-Screw Granulator (TSG) commonly adopted in numerous CM production lines[3], that was operated as a Twin-Screw Wet Granulator (TSWG). Although, the adoption of TSWG in low-dose formulations is still at its infancy demonstrated by the low number of publications[4], the advantages of this unique technology, e.g., continuous operation and potentially more efficient homogenization characteristics are definitely worth further investigation. The produced wet granules were intended to be processed via classical batch and CM downstream steps and ultimately to be compressed into low-dose tablets with an industrial tablet press.

The other selected piece of equipment was a scaled-up electrospinning (ES) device called

[1] Badman, C.; Cooney, C.L.; Florence, A.; Konstantinov, K.; Krumme, M.; Mascia, S.; Nasr, M.; Trout, B.L. Why We Need Continuous Pharmaceutical Manufacturing and How to Make It Happen. *Journal of pharmaceutical sciences* **2019**, *108*, 3521-3523

[2] European Medicines Agency, Guideline on process validation for finished products – information and data to be provided in regulatory submissions **2016,** EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1

[3] Seem, T.C.; Rowson, N.A.; Ingram, A.; Huang, Z.; Yu, S.; de Matas, M.; Gabbott, I.; Reynolds, G.K. Twin screw granulation — A literature review. *Powder Technology* **2015**, *276*, 89-102

[4] Van Melkebeke, B.; Vervaet, C.; Remon, J.P. Validation of a continuous granulation process using a twin-screw extruder. *International journal of pharmaceutics* **2008**, *356*, 224-230

high-speed electrospinning (HSES)[5], capable of producing nanofibers with an increased output (~450 g/h), that ultimately contain the processed API in an amorphous form resulting in an amorphous solid dispersion (ASD). Due to the significantly increased surface area and the amorphous state of these products, ASDs have superior dissolution properties compared to the traditional crystalline counterparts. The benefits of ES may also be exploited for the goal of producing low-dose drug products, since it is comparable to other micronization techniques due to production of the nano/micron-sized fibers[6]. Consequently, achieving acceptable CU in final formulations is simpler. Additionally, the quantity of a low-dose ASD to be processed is considerably larger compared to a micronized API, therefore the chance of potential drug loss during production is much smaller. At the same time, once the low amount of API is formulated into an ASD, its potency may increase due to its increased bioavailability ultimately leading to a final lower dose requirement. In our investigations, the manufactured fibers were designed to be blended with excipients and ultimately to be compressed into low-dose tablets.

API homogeneity of the produced solid dosage forms was planned to be investigated via multiple methods, such as UV-Vis spectrometry, High-Performance Liquid Chromatography (HPLC), and Raman mapping. Along with these analytical measuring techniques, the essential requirements for ideal content uniformity, such as proper settings of technological parameters and appropriate choice of complementary equipment was also intended to be inspected. Consequently, the main objectives of the experimental work can be set up as:

- Manufacture homogeneous low-dose tablets containing an electrospun substance prepared by HSES; assess the requirements of API homogeneity
    - apply fibers with 1% loading of model drug Carvedilol with PVPVA64 as a fiber forming polymer,
    - preparation of final blends to be acquired via DC and tableting on an industrial rotary press,
    - set dose of the API to 50 μg (0.05 m/m%),
    - evaluate API homogeneity by UV-Vis and Raman microspectrometry.
- Prepare homogeneous low-dose tablets based on continuous Twin-Screw Wet

[5] Nagy, Z.K.; Balogh, A.; Demuth, B.; Pataki, H.; Vigh, T.; Szabo, B.; Molnar, K.; Schmidt, B.T.; Horak, P.; Marosi, G., et al. High speed electrospinning for scaled-up production of amorphous solid dispersion of itraconazole. *International journal of pharmaceutics* **2015**, *480*, 137-142

[6] Casian, T.; Borbás, E.; Ilyés, K.; Démuth, B.; Farkas, A.; Rapi, Z.; Bogdan, C.; Iurian, S.; Toma, V.; Știufiuc, R., et al. Electrospun amorphous solid dispersions of meloxicam: Influence of polymer type and downstream processing to orodispersible dosage forms. *International journal of pharmaceutics* **2019**, *569*, 118593

Granulation (TSWG); ascertain the requirements of API homogeneity

- develop a production line composed of TSWG, Fluid-Bed Drying (FBD), sieving, and tableting,
- adopt Carvedilol as the model API with a dose of 30 μg (0.035 m/m%),
- measure API homogeneity by High-Performance Liquid Chromatography (HPLC),
- evaluate the potential application of various liquid-dosing units based on real-time balance measurements.

- Produce homogeneous low-dose tablets formulated by the following manufacturing line: TSWG, Continuous Fluid-Bed Drying (CFBD), Continuous Sieving (CS), and tableting
  - evaluate the applicability of a fully integrated TSWG-CFBD-CS granule production line for low-dose products,
  - use Carvedilol as the model API with a dose of 50 μg (0.05 m/m%),
  - measure API homogeneity by High-Performance Liquid Chromatography (HPLC),
  - perform scale-up experiments,
  - compare the efficiency of the CM production line to a traditional batch single pot granulator/dryer based on granule characteristics.

2. Methods

2.1 ES-based tablet formulation

Sample preparation

Single needle electrospinning (SNES)

The small-scale production of Carvedilol (CAR) containing fibers were carried by a single needle electrospinning setup consisting of a nozzle, a high voltage direct current supply and a syringe pump.

High-Speed Electrospinning (HSES)

The increased production of the API containing fibers were executed by the HSES equipment developed in our research group. The solution was dosed by a syringe pump, while a rotating spinneret under high voltage direct supply produced the electrospun material.

Low-Shear and High-Shear Homogenization

Homogenizations were carried out in plastic bags (low-shear mixing, LSM) or in a Diosna P-06 high-shear mixer (HSM).

Tableting

Tableting was performed on a Piccola tablet rotary press (Riva, Aldershot, UK) machine using 8 tablet dies with 6 mm diameter and no markings.

Characterization methods

Tablet physical tests

The compressed tablets were evaluated by standard tests, such as tablet weight, thickness, hardness, friability measurement and time of disintegration.

Content Uniformity Analysis

Content uniformity (CU) of 10 randomly selected tablets was measured UV-Vis spectrometry.

Sieve Analysis

Sieve analyses were made on the pure ES material and the final powder mixtures by a Fritsch Analysette 3 Pro Vibratory Sieve Shaker (Idar-Oberstein, Germany).

Raman microspectrometry

Raman spectrometry was performed using a Horiba Jobin-Yvon LabRAM-type microspectrometer.

2.2 TSWG-based tablet formulation

Sample preparation

Granule production

Granulation experiments were conducted in a continuous twin-screw granulator (TS16, Quick 2000 Ltd, Hungary) operated in wet granulation mode.

A gravimetric feeder (Brabender Technologie, Duisburg, Germany) was adopted in order to dispense the solid pre-blend of starch and lactose into the Twin-Screw Granulator (TSG). The granulation liquid (CAR-PVPK30-ethanolic solution) was dosed into the device using a peristaltic pump (Watson-Marlow 120U, Wilmington, MA, USA) or a syringe pump (SEP-10S Plus, Aitecs, Vilnius, Lithuania) or a piston pump (JASCO PU-980, Hachioji, Japan).

The prepared wet granules were then subsequently dried in a lab-scale fluid bed dryer (Aeromatic Strea-1, Düsseldorf, Germany) and lastly passed through a hand sieve.

Tableting

The powder mixtures were compressed into tablets on a Piccola tablet rotary press (Riva, Aldershot, UK) equipped with concave punches of 6 mm diameter and no markings.

Characterization methods

Tablet physical tests

The compressed tablets were evaluated by standard tests, such as tablet weight, thickness, hardness, friability measurement and time of disintegration.

Particle size distribution (PSD) measurements

The Particle Size Distribution (PSD) measurements were measured by a Malvern Mastersizer 2000 laser diffraction device (Malvern Pananalytical, Malvern, UK) in solid-state.

Content Uniformity Analysis

Content uniformity (CU) of 10 randomly selected tablets was determined by High-Performance Liquid Chromatography (HPLC).

Measurement of the liquid addition rate of different pumps

In these experiments, the granulating liquid was fed from a bottle to a plastic glass. The plastic glass was placed on a Sartorius MC-1 AC 210 P analytical balance (Göttingen, Germany) connected to a laptop. The laptop received the mass recorded on the balance in real-time and calculated the correspondent mass flow.

2.3. TSWG-CFBD-CS-based tablet formulation

Sample preparation

Granule production

Granule production was carried out on a fully continuous TSWG-Continuous Fluid Bed Drying (CFBD)-Continuous Sieving (CS) manufacturing line. Wet granulation experiments were conducted in a multifunctional continuous twin-screw equipment (TS16, Quick 2000 Ltd, Hungary) operated in wet granulation mode.

A gravimetric feeder (Brabender Technologie, Duisburg, Germany) was adopted to dispense the solid pre-blend of starch and lactose into the Twin-Screw Granulator (TSG) with a standard

feed rate of 1 kg/h. The granulation liquid (PVPK30 and CAR were dissolved in 2 v/v % acetic acid solution) was dosed into the device using a peristaltic pump (Watson-Marlow 120U, Wilmington, MA, USA) or a piston pump (JASCO PU-980, Hachioji, Japan).

Upon completion, the wet granules were dried in a horizontal fluid bed dryer (Quick 2000 Ltd, Hungary).

Dried granules were directly transported into the sieving device, where large agglomerates were broken down.

Scale-up trials

Scale-up experiments were carried out by increasing the powder feed rate to 3 kg/h and later to 10 kg/h. The higher feeding rate was achieved by using a vibratory conveying feeder (Fritsch Laborette 24, Idar-Oberstein, Germany) operated in volumetric discharge mode.

Reference batch granule production

Reference high-shear granulations were carried out in a small-scale batch granulator (Mi-Mi-Pro, ProCepT, Zelzate, Belgium). The excipients were placed into the granulator, where they were granulated by a dropwise addition of the granulating liquid dosed by a peristaltic pump (Watson-Marlow 120U, Wilmington, MA, USA). When all of the liquid was added to the mixture, the kneading phase was carried out. Subsequently, the wet granules were dried by applying vacuum and microwave energy and lastly passed through a hand sieve.

Tableting

The powder mixtures compressed into tablets on a Piccola tablet rotary press (Riva, Aldershot, UK) equipped with concave punches of 6 mm diameter and no markings.

Characterization methods

Tablet physical tests

The compressed tablets were evaluated by standard tests, such as tablet weight, thickness, hardness, friability measurement and time of disintegration.

Particle size distribution (PSD) measurements

The Particle Size Distribution (PSD) measurements were measured by a Horiba LA-960 laser diffraction device (Horiba Ltd, Kyoto, Japan) by solid dispersing.

Content Uniformity (CU) and Blend Uniformity (BU) analysis

CU and BU were determined by High-Performance Liquid Chromatography (HPLC).

Ten randomly chosen tablets (CU) or granules (BU) with the sum weight of 1 individual tablet (100 mg) collected ten times from different locations of the powder bed were evaluated.

3. Results

This thesis mainly focuses on evaluating the homogeneity requirements of various low-dose tablet formulations manufactured by different CM platforms. In the first part, a low-dose tablet formulation containing electrospun fibers produced by HSES is discussed. API homogeneity was measured by UV-Vis spectrometry and final powder mixture homogeneity was evaluated by sieve analysis.

In the next section, a low-dose tablet composition incorporating granules manufactured by a TSWG technology is detailed. API homogeneity was measured with HPLC and later pumps with different operating principles were characterized via real-time balance measurements.

In the final chapter, a low-dose tablet formulation containing granules produced by a fully integrated TSWG-CFBD-CS (Twin-Screw Wet Granulation-Continuous Fluid Bed Drying-Continuous Sieving) manufacturing line is investigated. API content and homogeneity of the produced batches were evaluated by CU (Content Uniformity) analysis. In the next step, scale-up experiments with increased feed rate (3 and 10 kg/h) were carried out and lastly, a reference batch (one-pot high-shear granulation, drying, and sieving) trial was also executed to compare the efficiency of the CM line with traditional batch manufacturing methods.

3.1 ES-based low-dose tablet formulation

3.1.1. Production of ES tablet batches

CAR containing fibers were manufactured via HSES and SNES. The production of the ES samples is shown in Table 1.

Table 1 *Comparison of the details of manufacturing using SNES and HSES*

Sample	Production method	Applied solvent	Dissolved PVPVA64 and CAR (99:1) in 10 mL of solvent (g)	Flow rate (ml/h)	Productivity for dried material (g/h)
PVPVA64 + 1% CAR SNES	Single-needle electrospinning	96% EtOH	4.00	6	1.8
PVPVA64 + 1% CAR HSES	High-speed electrospinning	96% EtOH	4.00	750	225

By applying HSES it was possible to increase our productivity 125-fold in regard to the

dried product compared to the SNES technique. Once the fibers were obtained, tablets were prepared by adopting a direct compression (DC) technology for which only plastic bags, a high-shear mixer, and a tablet rotary press were required. Overall, 6 batches were produced 4 of which contained ES product. Two were manually homogenized in plastic bags emulating industrial container homogenization and the other two were homogenized in an HSM. The final two batches contained crystalline carvedilol serving as a reference. One was homogenized in LSM conditions and the other by HSM. The batch characteristics are detailed in Table 2.

Table 2 *Batch characteristics and their physical test results (A and B are repetitions of the same technology)*

Characteristics	**LSM reference**	**HSM reference**	**LSM HSES Batch A**	**LSM HSES Batch B**	**HSM HSES Batch A**	**HSM HSES Batch B**
API type	Crystalline CAR	Crystalline CAR	Electrospun CAR	Electrospun CAR	Electrospun CAR	Electrospun CAR
Method of homogenization	Manual (LSM)	High-shear (HSM)	Manual (LSM)	Manual (LSM)	High-shear (HSM)	High-shear (HSM)
Weight (mg)	99.9 ± 0.5	99.2 ± 0.7	99.2 ± 0.8	100.2 ± 0.7	100.9 ± 1.0	99.8 ± 1.1
Thickness (mm)	3.08 ± 0.44	3.02 ± 0.54	3.06 ± 0.69	3.04 ± 0.57	3.05 ± 0.60	3.03 ± 0.52
Hardness (N)	64.3 ± 7.62	69.2 ± 6.22	60.6 ± 5.67	63.8 ± 7.51	68.6 ± 5.11	62.7 ± 6.71
Diameter (mm)	5.97 ± 0.19	5.95 ± 0.22	5.97 ± 0.27	5.98 ± 0.17	5.99 ± 0.29	5.97 ± 0.21
Friability (%)	0.21	0.31	0.39	0.25	0.20	0.27
Disintegration (s)	84 ± 25	95 ± 32	103 ± 29	119 ± 37	138 ± 42	125 ±35

Once the homogenizations were carried out, the mixtures were compressed into tablets using a tablet rotary press without any problems. Physical tablet tests were carried out to evaluate the oral dosage forms. The summary of the results is detailed in Table 2.

According to the acquired results, all batches had roughly the same properties without any unacceptable data. Friability was well below the 1% limit, while disintegration was easily achieved within 15 (Ph. Eur.) or 30 (USP) minutes both criteria set by the Pharmacopeias.

3.1.2. Investigation of API homogeneity via CU measurements

The summary of the measured average API contents and their homogeneity are detailed in Table 3.

Table 3 *CU results of the ES tablet batches*

Sample number	**Carvedilol (%)**					
	LSM Reference	HSM Reference	LSM ES A	LSM ES A	HSM ES A	HSM ES B
Average	98.76	97.68	94.19	93.21	97.63	96.71
SD (%)	7.43	4.65	9.50	6.80	2.04	2.49

RSD	7.52	5.13	10.08	7.30	2.09	2.58

The batches containing crystalline carvedilol yielded expected results with acceptable API content and high RSD values. This phenomenon could not be solved even in the HSM since SD and RSD values were still too high, 4.65 and 5.13 respectively. Out of the ES samples, the batches homogenized in HSM proved to be much better than the LSM tablets homogenized in plastic bags under low-shear conditions.

3.1.3. Results of sieve analysis

In order to clarify the deviations between the LSM and HSM, sieve analysis was selected as an alternative method. A total weight of 25 g (the equivalent of 250 tablets) of LSM and HSM final powder mixtures along with the pure fibers were investigated, whose results are shown in Table 4. Both LSM and HSM tablets are mainly (more than 90%) made up of lactose and microcrystalline cellulose tableting materials, whose average particle sizes are 150 and 130 μm respectively.

Table 4 *Sieve analysis results (the mixtures contain 5% ES material)*

Sieve size (μm)	Pure ES material (g)	LSM Final Powder Mixture (g)	HSM Final Powder Mixture (g)
355	13.80 (55.2%)	0.22 (0.88%)	0.02 (0.08%)
180	1.61 (6.4%)	5.02 (20.1%)	5.41 (21.6%)
90	1.03 (4.1%)	9.22 (36.9%)	9.35 (37.4%)
sub 90	8.56 (34.3%)	10.54 (42.12%)	10.22 (40.92%)

According to the measured sieve fractions, HSM homogenization was able to decrease the quantity of the 355 μm portion by more than ten times compared to LSM mixing. This is crucial since the bulk of the pure electrospun materials were recovered on this sieve and, more importantly for complete homogenization, particle sizes should be as close to each other as possible to avoid segregation[7]. Based on these results, the high-performance impeller and chopper blades present in the HSM can further reduce the average particle sizes (due to high shear forces) of the fibrous materials, thus superior blending with excipients can be achieved. These aforementioned >355 μm fractions were also evaluated by Raman spectroscopy to look for traces of electrospun substance. The spectra are shown in Figure 1.

[7] Williams, J.C. The segregation of particulate materials. A review. *Powder Technology* **1976**, *15*, 245-251

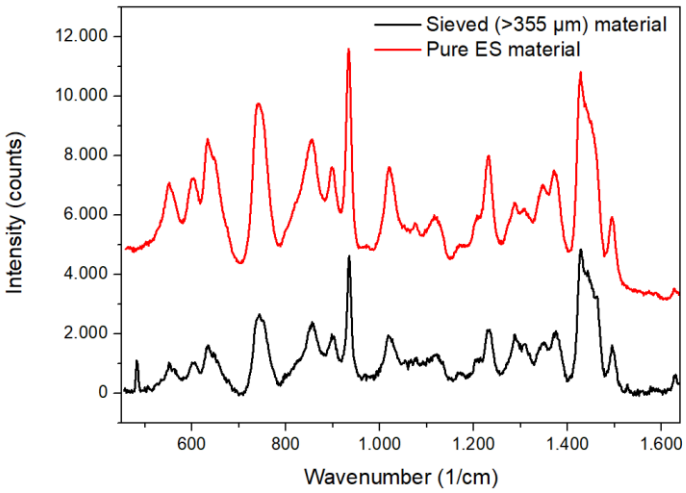

Figure 1 *Raman spectra taken of pure ES (red) and sieved (black) material of the >355 µm fraction*

According to the recorded spectra, the signal of the sieved >355 µm material is almost identical to the spectrum of the starting ES material ultimately confirming that the API containing polymer was detected in the sieved mixture. Conclusively, this contributed to higher inhomogeneity among LSM tablets compared to HSM tablets. This outcome can be linked to Table 3 where the high SD and RSD values of the LSM tablets validate these findings.

This outcome proves that the high-shear mixer coupled with the direct compression technology should be the first method of choice when proper homogenization of electrospun samples is required.

3.2 TSWG-based low-dose tablet formulation

3.2.1 Production of tablet batches

Initially, placebo tests were carried out to determine the most suitable TSWG technology for the low-dose experiments. Out of these trials, our initial run of dissolving the binder PVPK30 in the granulating liquid proved to be best according to our PSD measurements and tablet physical tests. These are shown in Figure 2 and Table 5, respectively. Prior to granulation, the desired range was determined to be between 90 and 1000 μm following sieving with a unimodal distribution[8].

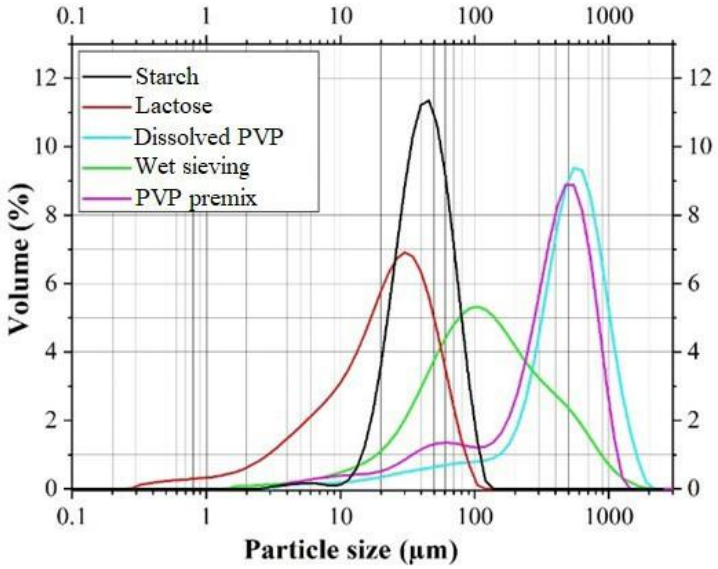

Figure 2 *Particle Size Distribution results based on laser diffraction measurements following sieving (0.8 mm)*

Granulation carried out with the initial dissolved PVP settings produced high-quality granules with a unimodal distribution profile. The premixing of PVP caused a slight increase of fines indicating that the binder was unable to blend perfectly with the excipients resulting in an incomplete granulation, while the implementation of wet sieving produced great amounts of fines.

Two of the discussed three kinds of granules were selected to be compressed into final dosage forms for further investigation. The batches manufactured with the dissolved PVP and the PVP premix were selected and processed accordingly. Upon completion of the final powder mixtures, the blends were compressed into tablets and their characteristics were measured and evaluated.

[8] Shekunov, B.; Chattopadhyay, P.; Tong, H.; Chow, A. Particle Size Analysis in Pharmaceutics: Principles, Methods and Applications. *Pharmaceutical research* **2007**, *24*, 203-227

Table 5 *Physical test results of the placebo tablets compressed from granules prepared by TSWG*

Compression force (kN)	**4**	**6**	**8**	**10**	**4**	**6**	**8**	**10**
Granule production	Dissolved PVP	Dissolved PVP	Dissolved PVP	Dissolved PVP	Premixed PVP	Premixed PVP	Premixed PVP	Premixed PVP
Weight (mg)	83.4±0.6	83.9±0.7	83.9±0.7	83.4±0.8	86.7±0.8	88.4±0.4	84.0±0.4	83.8±0.5
Hardness (N)	75±7	101±13	134±13	136±10	87±10	127±12	134±9	143±5
Friability (%)	0.248	0.282	0.26	0.292	0.360	0.352	0.324	0.415
Disintegration (s)	115±43	131±39	164±32	196±64	126±32	129±45	168±30	119±75

According to the results, the batches containing PVP in premix produced slightly stronger tablets with the same compression force, while the average time of disintegration was approximately identical. Tablets produced with the dissolved binder had significantly lower friability at all compression forces, which can be attributed to the enhanced binding ability of PVP in a solution, but the possibility of reaching the maximum limit of 1 % was never at risk.

3.2.2 Evaluation of API homogeneity via CU measurements

In accordance with the preliminary placebo tablet results, the initial dissolved PVP settings were selected to manufacture the CAR-containing batches with the TSWG technology. As CAR was dissolved in the ethanol, the adequacy of the applied pump was examined. During these experiments, three pumps with different working principles (peristaltic pump, syringe pump, piston pump) were evaluated on the outcome of success in CAR homogeneity. API content of the final dosage forms was measured and their RSD was subsequently calculated. These are shown in Figure 3.

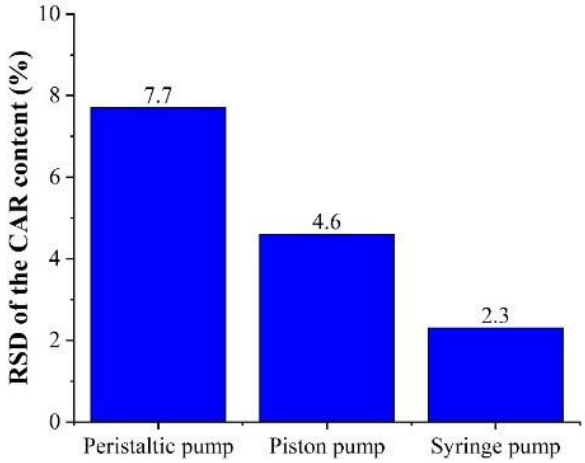

Figure 3 *Relative Standard Deviation of the CAR content in tablets (granules were made with*

different pumps)

According to the results, the adoption of the peristaltic pump produced the highest RSD values due to the apparent pulsating flow observed throughout the operation. As opposed to the peristaltic pump, syringe and piston pump ensured lower RSDs of the CAR content. It seems obvious that the type of pump has a significant effect on the homogeneity of the API. It can be claimed that when the API is dissolved in the granulating liquid, the successful result of the most important CQA (Content Uniformity) of low-dose products can be linked to the liquid dosing rate (and thus, the type of the pump) as the most important correspondent CPP.

3.2.3 Investigation of pump properties – the dosing profiles

In order to compare the different pumps, the liquid addition rate of the three applied types was measured. The recorded rate for one minute in the case of each pump is shown in Figure 4.

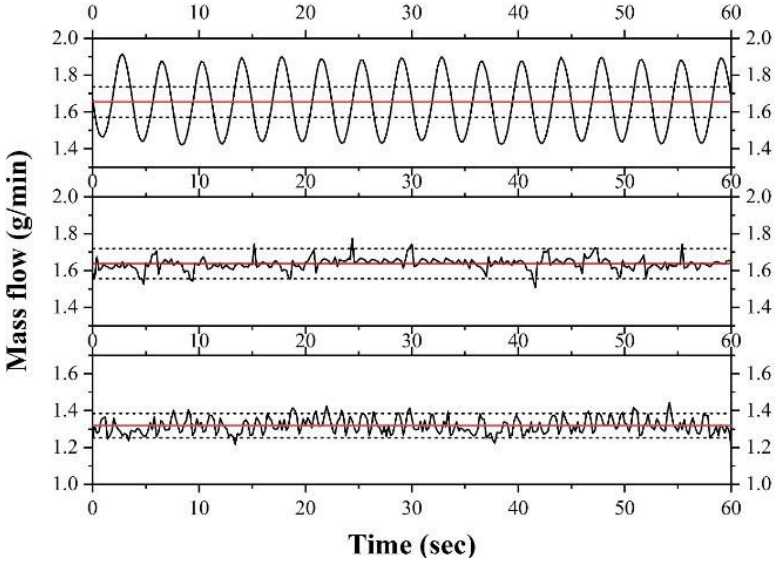

Figure 4 *Liquid dosing rates of (a) peristaltic pump (b) piston pump (c) syringe pump (red lines denote the average mass flow values while the dashed lines mark the ±5 % deviation)*

Not surprisingly, the least consistent dosing was demonstrated by the peristaltic pump showing a sinusoidal profile (RSD of the mass flow: 10 %). By adopting the piston pump, more consistent dosing of the ethanolic solution was achieved (RSD: 5.6 %). A very steady dispensing of the liquid was realizable with the syringe pump (RSD: 3.4 %). Consequently, the application of the latter two pumps is recommended when homogeneity of the liquid (and possibly, the dissolved drug) distribution is of great importance.

When the RSD values of the mass flows belonging to the different pumps are compared to the RSD values of the drug content in tablets, a good correlation can be found as shown in Figure 5.

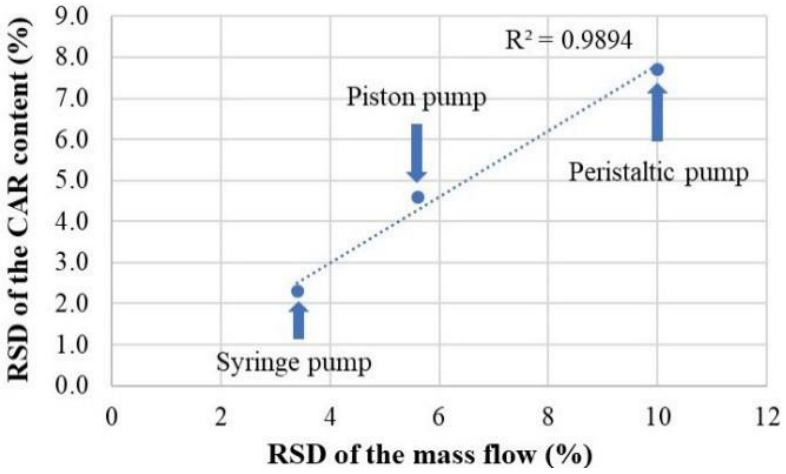

Figure 5 *Correlation between RSD values of mass flows and of CAR content*

The linear correlation means that based on the measurement of the liquid flow rate (as CPP), the Content Uniformity (as CQA) can be estimated in this case.

Based on these profiles achieved through simple trials, the applicability of certain pumps in future granulation experiments could be evaluated.

3.3 TSWG-CFBD-CS-based low-dose tablet formulation

3.3.1 Production of tablet batches

In order to maximize the production rate and minimize the energy consumption of the CM line, the minimal Liquid-to-Solid (L/S) ratio required for granulation was determined. By doing so, the amount of water needed to be evaporated throughout the drying phase can be lowered, thus increasing the overall efficiency of the whole unit.

Subsequently, PSDs of the produced placebo and API containing granules were determined and the results are shown in Figure 6a (placebo) and 6b (CAR).

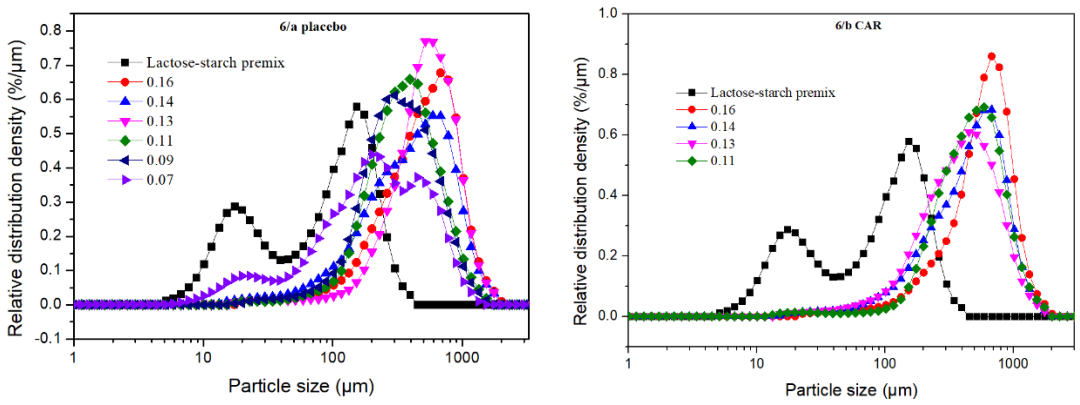

Figure 6a, b *PSD results of the lactose-starch premix and the manufactured granules with different L/S ratios from 0.07 to 0.16 (placebo) and 0.11 to 0.16 (CAR) according to laser diffraction measurements*

PSD requirements were set in accordance with the previously discussed TSWG-based tablet formulation meaning that the initial goal was to manufacture granules in the size range of 90-1000 μm with a unimodal size distribution.

According to the acquired results, all granulations except for the lowest applied L/S ratio produced unimodal PSDs along with particle sizes in the hundred-microns. The trial with the lowest L/S ratio resulted in increased amounts of fines and overall a bimodal distribution indicating the insufficient quantity of granulation liquid in the process. By adding the low-dose APIs to the process, the resulting average particle sizes did not differ significantly from the placebo runs of the same L/S ratio.

Out of all produced granules, only the low-dose CAR containing ones (L/S ratio of 0.11-0.16) were selected for tableting in order to investigate the homogeneity characteristics of the low-dose API in the final solid oral dosage forms. The results are detailed in Table 6.

Table 6 *Physical test results of the low-dose tablets compressed from granules prepared by the integrated CM line*

L/S ratio	Main compression force (kN)	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Friability (%)	Disintegration (s)
0.16	5	99.6±1.4	3.13±0.03	5.98±0.01	69±6	0.32	129±30
0.14	5	101.2±1.3	3.19±0.02	5.99±0.01	66±7	0.26	127±34
0.13	5	100.4±1.0	3.21±0.02	5.99±0.01	59±6	0.34	118±28
0.11	5	101.2±0.8	3.28±0.02	5.97±0.01	50±4	0.22	90±28

According to the acquired data, all batches yielded very similar results demonstrating the good compressibility of the produced granules independent of the applied L/S ratio.

3.3.2 Assessment of low-dose API homogeneity via CU measurements

To efficiently produce homogeneous low-dose tablets, the same principle was applied as in the previously discussed TSWG-based formulation leading to the adoption of a pulse-free liquid dosing unit (piston pump), while the minuscule amount of API was dissolved in the granulating liquid.

API contents of the CAR containing tablet batches were measured and the corresponding SD, Relative SD (RSD), and Acceptance Value (AV) values were calculated. The results are shown in Table 7.

Table 7 *Content Uniformity of the low-dose CAR tablets*

L/S ratio	Mean CAR content (%)	SD (%)	RSD	AV
0.16	94.0	2.82	3.0	11.3
0.14	89.4	0.99	1.1	11.5
0.13	96.8	1.95	2.0	6.4
0.11	96.4	1.02	1.1	4.6

Based on the results, the application of the L/S ratio of 0.11 yielded the best overall outcome shown by the lowest AV value[9], which is not only beneficial from a maximum drying efficiency standpoint, but also from meeting the content uniformity requirements.

3.3.3 Investigation of scale-up and blend uniformity results

Subsequently, scale-up trials were carried out by increasing the feed rates to 3 kg/h and later 10 kg/h with the same L/S ratio of 0.11.

PSD results incorporating the previous 1 kg/h trial and the starting lactose-starch premix are shown in Figure 7.

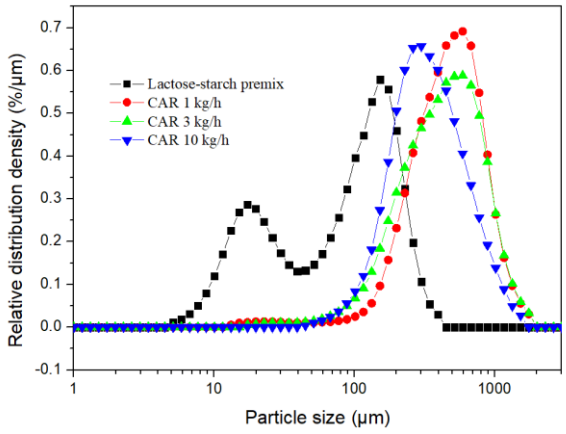

Figure 7 *PSD results of the lactose-starch premix and the manufactured granules with different feed rates according to laser diffraction measurements*

Based on the outcome of the acquired results, successful particle size enlargement was achieved for all granulation experiments. In the case of the 10 kg/h run, a small decrease in granule size was observed attributing to the apparent increase in barrel fill level[10].

Subsequently, the manufactured granules were not compressed into final dosage forms, and therefore blend uniformity measurements were initiated to assess API homogeneity. The

[9] US Pharmacopeia. Uniformity of Dosage Units/Content Uniformity. Available online: http://www.drugfuture.com/Pharmacopoeia/usp35/PDF/0420-0423%20[905]%20UNIFORMITY%20OF%20DOSAGE%20UNITS.pdf

[10] Lute, V.S.; Dhenge, M.R.; Salman, D.A. Twin Screw Granulation: An Investigation of the Effect of Barrel Fill Level. *Pharmaceutics* **2018**, *10*

measured CAR content and the calculated SD and RSD values are shown in Table 8.

Table 8 *Blend Uniformity of the low-dose CAR granules prepared by an increased feed rate of 3 kg/h and 10 kg/h based on HPLC measurements*

Feed ate	L/S ratio	Mean API content (%)	SD (%)	RSD
3 kg/h	0.11	92.2	1.68	1.8
10 kg/h	0.11	95.4	1.41	1.5

According to the results the requirements of blend uniformity[11] were successfully met for both runs.

All in all, the integrated continuous granulation-drying-sieving line is capable of manufacturing adequate granules in the productivity range of 1-10 kg/h without major optimization work.

3.3.4 Production of reference batch granules and blend uniformity results

Lastly, granules fabricated by High-shear granulation were prepared in order to compare the efficiency (granule quality, API homogeneity) of the two technologies by applying the same L/S ratio of 0.11.

Upon completion, the PSD results of the granules produced by both platforms were measured. These are shown in Figure 8 along with the results of the previous 1 kg/h trial and the starting lactose-starch premix.

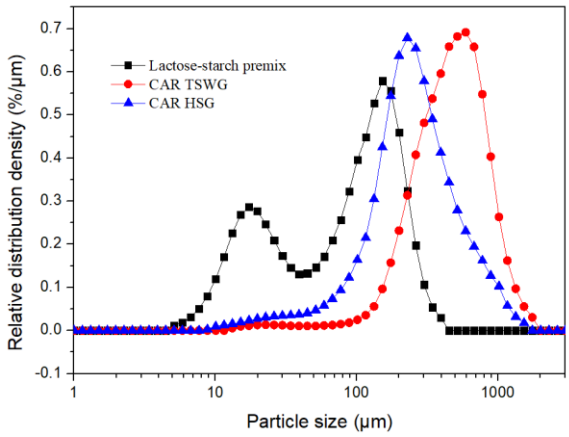

Figure 8 *PSD results of the lactose-starch premix and the manufactured granules with TSWG and HSG according to laser diffraction measurements*

[11] G Boehm, J.C., J Dietrick, L Foust, T Garcia, M Gavini, L Gelber, J Geoffry, J Hoblitzell, P Jimenez, G; Mergen, F.M., J Planchard, J Prescott, J Timmermens, and N Takiar. The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends. Available online: https://www.researchgate.net/profile/Loren_Gelber/publication/8959625_The_use_of_stratified_sampling_of_blend_and_dosage_units_to_demonstrate_adequacy_of_mix_for_powder_blends/links/0c9605315eb4b2a2c8000000.pdf

Based on the measured data, the produced granules from high-shear granulation were noticeably smaller compared to the TSWG granules confirming the superiority of the CM equipment in terms of liquid (and consequently binder) distribution.

The manufactured granules by HSG were not compressed into final dosage forms so the API homogeneity was investigated by blend uniformity analysis. In addition, to assess CAR homogeneity on a deeper level, both the TSWG and HSG granules were manually sieved to multiple size fractions. The measured API content and the calculated SD and RSD values are listed in Table 9.

Table 9 *Blend Uniformity of the low-dose CAR granules produced HSG and TSWG based on HPLC measurements*

	Particle size	**API content (%)**	**SD (%)**	**RSD**
	<100 µm	98.2	1.6	1.6
	100-300 µm	89.5	0.9	1
TSWG	300-500 µm	95.1	1.3	1.4
	500 µm<	99.0	0.6	0.6
	BUA	95.8	1.2	1.3
	<100 µm	45.4	0.5	1.1
	100-300 µm	69.6	1.9	2.7
HSG	300-500 µm	121.1	1.4	1.2
	500 µm<	166.5	1.8	1.1
	BUA	82.5	3.7	4.5

According to the results, TSWG was found superior both in terms of API content and homogeneity in the size fractions and BUA results. The TSWG samples met the BUA requirements with minimal loss of potency even in the size fractions, while the HSG granules were clearly overpotent in the larger size fractions and also failed to meet the BUA requirements.

4. Theses

1. We could produce the first homogeneous low-dose (µg) tablet batches from electrospun amorphous solid dispersions (ASD) based on a scaled-up electrospinning technology. The electrospun fibers were manufactured by high-speed electrospinning (HSES), while the subsequent blending and tableting process steps were carried out by adopting traditional industrial equipment. Batch size was set to 8000 tablets and the corresponding physical (weight uniformity, hardness, friability and time of disintegration) and chemical (content uniformity) results all met the requirements set by the Pharmacopeias. Based on the applied production rate of the HSES equipment,

electrospun fibers sufficient for the production of 45.000 low-dose tablets/hour could be manufactured [**1**].

2. We determined that the extent of the applied shear force throughout homogenization steps with electrospun materials is of great importance. We have shown that by applying low shear force mixing, the homogeneity of the active pharmaceutical ingredient (API) in the ES product was inadequate indicated by the high relative standard deviation (RSD) values. However, selection of high-shear blenders, exhibiting greater shear force on the processed materials by adopting appropriate impeller and chopper elements, resulted in excellent homogeneity levels even in the investigated low-dose ASD containing formulations [**1**].
3. By adopting sieve analysis and Raman microspectrometry, we proved that the cause of inhomogeneity in the ASD containing powder blends prepared by low-shear mixing (LSM) is the presence of large fiber aggregates (> 355 μm). The implementation of high-shear mixing (HSM) resulted in their complete disintegration and disappearance, thus low-dose tablets with acceptable content uniformity could be prepared [**1**].
4. We managed to manufacture tablet batches in the μg dose range based on continuous wet granulation for the first time. Granulations were achieved by adopting a twin-screw wet granulator, while tableting was carried in an industrial rotary tablet press. We have shown, that since the applied API was dissolved in the granulating liquid, the primary requirement in realizing acceptable API homogeneity and thus content uniformity is the adequate, consistent feeding profile of the applied liquid dosing unit [**2**].
5. We developed a fully integrated continuous manufacturing (CM) technology line for the production of ultralow-dose (μg) highly homogeneous granules comprising of twin-screw granulation, continuous vibratory fluid bed drying and continuous sieving/milling for the first time. To characterize the process dynamics of the production line, the residence time distribution (RTD) model was recorded. The CM technology was also compared to regular batch high-shear granulation resulting in its superiority by providing a lower L/S ratio for successful granulation. The prepared granules were later compressed into tablets with a batch size of 5000 and the corresponding physical (weight uniformity, hardness, friability and time of disintegration) and chemical (content uniformity) results all met the requirements set

by the Pharmacopeias [**3**,4,5].

6. The integrated continuous production of low-dose granules meeting industrial market demands was achieved for the first time. We proved, that the increase of output from 1 kg/h to 10 kg/h does not necessitate the adoption of an alternate manufacturing line, and thus the production of the model API containing tablets with an average weight of 100 mg, sufficient for 100.000 tablets/hour can be realized without the risk of scale-up. Granules prepared this way met all the physical (PSD, bulk/tapped density, flowability) and chemical (assay, homogeneity) requirements set by the Pharmacopeias [**3**,4,5].

5. Application of the results

Incorporating new, more efficient technologies such as CM into the manufacture of pharmaceuticals has always been one of the key driving forces of the industry. However, even with the appearance of multiple FDA-approved CM products on the market, the shift from the traditional batch processes to the more advanced CM methods is still at an early phase. Nonetheless, as it was shown in this thesis by various examples, this daunting step towards this shift is indeed worth taking. This is especially true for low-dose products, since it has the potential to assist in a lot of challenges characteristic of batch processes.

A significant portion of this work was executed in collaboration with Gedeon Richter Formulation Development (Gedeon Richter Ltd., Budapest, Hungary). Therefore, potential utilization of the results can certainly be foreseen in the future.

6. Publications

In journals with impact factor

Publications on which thesis findings are based:

1. **G. Fülöp**; A. Balogh; B. Farkas; A. Farkas; B. Szabó; B. Démuth; E. Borbás; Z. K. Nagy; G. Marosi, **2018**, Homogenization of Amorphous Solid Dispersions Prepared by Electrospinning in Low-Dose Tablet Formulation, *Pharmaceutics* 10(3), IF: 4.421; C: 6; https://doi.org/10.3390/pharmaceutics10030114
2. B. Démuth; **G. Fülöp**; M. Kovács; L. Madarász; M. Ficzere; Á. Köte; B. Szabó; B. Nagy; A. Balogh; K. Csorba; G. Kaszás; T. Nagy; A. Bódis; G. Marosi; Z. K. Nagy, **2020**, Continuous Manufacturing of Homogeneous Ultralow-Dose Granules by Twin-Screw Wet Granulation, *Periodica Polytechnica Chemical Engineering*, IF: 1.368; C:

3; https://doi.org/10.3311/PPch.14972

3. **G. Fülöp;** A. Domokos; D. Galata; E. Szabó; M. Gyürkés; B. Szabó; A. Farkas; L. Madarász; B. Démuth; T. Lendér; T. Nagy; D. Kovacs-Kiss; F. Van der Gucht; G. Marosi; Z. K. Nagy, **2020**, Integrated Twin-Screw Wet Granulation, Continuous Vibrational Fluid Drying and Milling: A fully continuous powder to granule line, *International Journal of Pharmaceutics*, IF: 4.845; C: 3; https://doi.org/10.1016/j.ijpharm.2020.120126

Further, related publications:

4. L. Madarász; Á. Köte; M. Gyürkés; A. Farkas; B. Hambalkó; H. Pataki; **G. Fülöp**; G. Marosi; L. Lengyel; T. Casian; K. Csorba; Z. K. Nagy, **2020**, Videometric mass flow control: A new method for real-time measurement and feedback control of powder micro-feeding based on image analysis, *International Journal of Pharmaceutics*, 580, 119223, IF: 4.845; C: 4; https://doi.org/10.1016/j.ijpharm.2020.119223
5. A. Domokos; É. Pusztai; L. Madarász; B. Nagy; M. Gyürkés; A. Farkas; **G. Fülöp**; T. Casian; B. Szilágyi; Z. K. Nagy, **2021**, Combination of PAT and mechanistic modeling tools in a fully continuous powder to granule line: rapid and deep process understanding, *Powder Technology*, IF: 4.142; C: 0; https://doi.org/10.1016/j.powtec.2021.04.059

Oral presentations (in Hungarian):

6. **G. Fülöp**; G. Kaszás; T. Nagy; B. Démuth; B. Nagy; Z. K. Nagy; G. Marosi, Folyamatos nedves granulálás gyógyszeripari bevezetésének lehetőségei, *Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium*, Szeged, **2017**. szeptember 11-12.
7. **G. Fülöp**; A. Balogh; B. Farkas; A. Farkas; B. Szabó; B. Démuth; E. Borbás; Z. K. Nagy; G. Marosi, Elektrosztatikusan szálképzett amorf szilárd diszperzió homogenizálása alacsony dózisú tabletta formulációban, *Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium*, Szeged, **2018.** szeptember 6-7.
8. **G. Fülöp**; B. Démuth, Új, folyamatos technológiákkal előállított köztitermékek homogenitásának biztosítása alacsony dózisú tabletta formulációkban, *Clauder Ottó Emlékverseny*, Budapest, **2018**. november 22-23.
9. **G. Fülöp**; B. Démuth; G. Kaszás; T. Nagy; Z. K. Nagy; G. Marosi, Homogén, kis dózisú tabletta formuláció előállítása folyamatos nedves granuláláson alapuló technológia alkalmazásával, *Gyógyszertechnológiai és Ipari Gyógyszerészeti*

Konferencia, Siófok, **2019.** szeptember 26-28.