BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
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Application of Continuous Technologies to Manufacture Solid Dispersions of Active Pharmaceutical Ingredients

PhD Thesis Summary

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1 Introduction

While it is beyond doubt that the authorised pharmaceutical products on the market meet the strict quality requirements, the cost of quality is very high, more than 20%; quality deviates in a broad range compared to the narrow approval limits, and in some cases the rejection rate can reach even 50%. Thus, the manufacturing processes in this industry cannot be called efficient by far; asset utilisation is also only 30–40%. Furthermore, rising costs outpaced the development of new pharmaceuticals and real market growth. As 36% of the expenses in the industry are spent on production, reduction of quality costs could result in an increase in competitive advantage. Replacing the traditionally used batch processes with continuous technologies can bring notable cost-cut in research, development and manufacture.

2 Literature Review, Aims

Continuous processing

Recently, innovation in pharmaceutical manufacturing has been strongly promoted by the regulatory authorities and researched by the industry (e.g. by Pfizer, Novartis and GSK). As part of this trend, continuous technologies will most likely gain ground in this field in the coming years, because they are in general less time-varying, less interconnected with uncertainties and hence better understood than batch technologies; furthermore, they are more cost-effective in respect of labour, more reliable and may reduce capital investment[1]. They are easier to monitor and automate, and deliver constant product quality.

The continuous processes during which solid dispersions are formed, i.e. an active pharmaceutical ingredient (API) is dispersed and, if necessary, amorphised of in an inert solid carrier (e.g. by melt extrusion or electrospinning) have proved to be effective for dissolution control (enhancement or prolonging of dissolution, and site-specific dissolution), which can often enhance bioavailability[2]. The dissolution enhancement of poorly water-soluble drugs requires special attention, because 70–90% of the new chemical entities belong to this group. However, in order to harvest the benefits of solid dispersions, one must mitigate the limitations of these novel continuous technologies, or improve several disadvantageous properties of the manufactured products (Table 1).

Melt extrusion

Melt extrusion is a high-throughput and solvent-free process, in which high drug loads are usually achievable without problems. At the same time, amorphisation by dissolution mechanism can take a longer time, and processing of heat-sensitive APIs has been reported to result in partial decomposition[3,4], the degree of which is most likely in connection with temperature and residence time.

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[1] K. Plumb, *Chem. Eng. Res. Des.* **83** (2005) 730–738.

[2] C. Leuner, *Eur. J. Pharm. Biopharm.* **50** (2000) 47–60.

[3] M.M. Crowley, F. Zhang, M.A. Repka, S. Thumma, S.B. Upadhye, S. Kumar Battu, J.W. McGinity, C. Martin, *Drug Dev. Ind. Pharm.* **33** (2007) 909–926.

[4] C. Capone, L. Di Landro, F. Inzoli, M. Penco, L. Sartore, *Polym. Eng. Sci.* **47** (2007) 1813–1819.

It is, therefore, important to investigate in what way process parameters influence amorphisation and degradation.

A beneficial way of reducing heat stress during extrusion is the reversible plasticisation achieved by use of supercritical carbon dioxide, which can also allow productivity to be increased. In spite of the promising advantages, such as the enlargement of specific surface area, utilisation of this technique for the experimental production of immediate-release solid dosage forms has been slight up to now[5,6,7].

Melt extrusion can be even more time-effective and economical if multiple properties can be adjusted at the same time. By developing gastro-retentive *and* sustained-release solid dosage forms, such as mucoadhesive formulations, absorption rate can be made less time-varying. Even bioavailability enhancement can be achieved for APIs with a short absorption window.

Electrostatic spinning

The main advantages of electrospinning in comparison with conventional melt extrusion are the high specific surface area generated (which can largely contribute to immediate release), the total and rapid amorphisation, and the low temperature of operation. At the same time, a high load of lipophilic drugs can prevent immediate dissolution by worsening wettability. As a further disadvantage, the fast dissolution of a poorly water soluble compound can result in subsequent precipitation because of local supersaturation.

When capsules or tablets are to be the final dosage forms, downstream processing of continuously produced electrospun nanofibres would include a milling step. This requirement makes the majority of the so far developed experimental nanoweb formulations ineligible for further processing. Therefore, there is a high need for matrices that can be milled or ground without pre-treatment and at the same time ensure the wanted dissolution profile.

Table 1. Comparison of melt extrusion and electrospinning regarding important process characteristics and product properties

	Melt extrusion	Electrospinning
Processing		
Heat stress	• Notable	✓ None
Use of solvents	✓ Solvent-free	• Solvent-based
Product properties		
High drug load	✓ Possible	• Wettability issues
Specific surface area	• Usually low	✓ High
Amorphisation	• Sometimes partial	✓ Usually total
Grindability	✓ Usually good	• Usually poor

[5] Z.K. Nagy, M. Sauceau, K. Nyúl, E. Rodier, B. Vajna, G. Marosi, J. Fages, *Polym. Adv. Technol.* **23** (2012) 909–918.

[6] G. Verreck, A. Decorte, K. Heymans, J. Adriaensen, D. Cleeren, A. Jacobs, D. Liu, D. Tomasko, A. Arien, J. Peeters, P. Rombaut, G. Van den Mooter, M.E. Brewster, *Eur. J. Pharm. Sci.* **26** (2005) 349–358.

[7] G. Verreck, A. Decorte, K. Heymans, J. Adriaensen, D. Liu, D.L. Tomasko, A. Arien, J. Peeters, P. Rombaut, G. Van den Mooter, M.E. Brewster, *J. Supercrit. Fluids* **40** (2007) 153–162.

Novel ways of physical and chemical characterisation

Monitoring of electrospinning and melt extrusion usually does not include the physical and chemical characterisation of the processed solid dispersions. There have been successful attempts very recently to equip instruments with appropriate probes[8,9], but the range of analytical techniques must be widened to get a clear picture of the benefits and applicability of each technique. Investigation of in-line or on-line applicable techniques is of high importance, taking the Process Analytical Technology guidelines of the Food and Drug Administration (FDA) into account.

In accordance with the literature survey, the following series of experiments were planned:

1. development of **mucoadhesive and at the same time release-prolonging melt extruded dosage forms** of trimetazidine 2HCl on polyacrylic acid/polyethylene oxide/polyethylene glycol basis according to a simplex lattice experimental design
2. melt extrusion of immediate-release spironolactone/Eudragit E solid dispersions according to a factorial experimental design so that the applicability of **transmission Raman spectrometry** for the characterisation of the **purity and residual crystallinity** of solid dispersions can be examined and so that the **influence of process parameters on amorphisation and drug degradation** can be evaluated based on the Raman estimations
3. foaming of spironolactone/Eudragit E solid dispersions in order to investigate the feasibility of **supercritical-fluid melt extrusion technology**, the **relationship between process parameters and foam structure** and the reduction of drug degradation
4. **polymer-free electrospinning** of the poorly water soluble drug spironolactone with hydroxypropyl-β-cyclodextrin (HPβCD) for dissolution enhancement, without heat stress
5. preparation of well wettable polyvinyl pyrrolidone (PVP) nanofibres using HPβCD as additive, and thereby **accelerating the dissolution of** formulations of **high drug load** and **preventing precipitation after the fast dissolution**
6. development of **grindable electrospun solid dosage forms** for flubendazole on HPβCD basis followed by **scale-up**

[8] L. Saerens, L. Dierickx, B. Lenain, C. Vervaet, J.P. Remon, T. De Beer, *Eur. J. Pharm. Biopharm.* **77** (2011) 158–163.

[9] L. Saerens, L. Dierickx, T. Quinten, P. Adriaensens, R. Carleer, C. Vervaet, J.P. Remon, T. De Beer, *Eur. J. Pharm. Biopharm.* **81** (2012) 230–237.

3 Experimental and Characterisation Methods

Electrospinning

- syringe pump (SEP-10S Plus, Aitecs, Vilnius, Lithuania)
- high voltage supply (NT-35 High Voltage DC Supply, MA 2000, Nagykanizsa, Hungary)

Melt extrusion

HAAKE MiniLab II (Thermo-Haake, Karlsruhe, Germany)

Supercritical-fluid melt extrusion

A modified single-screw extruder (SCAMEX, Crosne, France)
Pressure bearing syringe pump (260D, ISCO, Lincoln, NE, USA)

Scanning electron microscopy (SEM)

JEOL 6380LVa (JEOL, Tokyo, Japan)

Foam porosity

Helium pycnometry (AccuPYC 1330, Micromeritics, Norcross, GA, USA)
Size and mass measurements

High performance liquid chromatography (HPLC)

Agilent 1200 series HPLC, Alltech® Inertsil ODS-2 column, Agilent Eclipse XDB-C18 5 μm (4.6 mm × 150 mm) column, Agilent 6130 Quadrupole MS system (Santa Clara, CA, USA)

Differential scanning calorimetry (DSC)

Setaram DSC 92 instrument (Caluire, France)
TA Q2000 instrument (New Castle, DE, USA)

Powder X-ray diffraction (PXRD)

PANalytical X'pert Pro MPD X-ray diffractometer (Almelo, Netherlands)

Transmission Raman spectrometry (TRS)

AccuRA spetrometer (Horiba Jobin Yvon, Longjumeau, France)

Confocal Raman mapping (CRM)

Horiba Jobin-Yvon LabRAM system coupled with an Olympus BX-40 optical microscope (Horiba Jobin Yvon, Longjumeau, France)

Chemometrical evaluation of Raman spectra and maps

LabSpec 5.41 software (Horiba Jobin Yvon, Longjumeau, France)

***In vitro* drug dissolution testing**

- Erweka DT6 instrument (Erweka, Heusenstamm, Germany) and a Hewlett-Packard HP 8452A UV-VIS spectrophotometer (Palo Alto, USA)
- PTWS 600 instrument (Pharma Test Apparatebau AG, Hainburg, Germany) coupled with a Hewlett-Packard HP 8453G UV-VIS spectrophotometer (Palo Alto, USA)

Rat pharmacokinetics

Male Sprague-Dawley® rats

Three-point bending

Q800 (TA Instruments, New Castle, DE, USA) dynamic mechanical analyser

Measurement of mucoadhesion

AR2000 rheometer (TA Instruments, New Castle, DE, USA)

4 Results

Melt extrusion was applied for the first time to develop matrix formulations of the anti-anginal drug trimetazidine 2HCl (TMZ). These prolonged dissolution and were mucoadhesive at the same time. The formulations were intended to make administration safer. The mixture of partially cross-linked polyacrylic acid (Carbopol® 971), polyethylene oxide (POLYOX™ WSR N-12K) and polyethylene glycol 20,000 Da proved to be a robust polymer system, which enabled the matrix composition to be changed in wide ranges and hence functional properties to be adjusted.

The matrix composition was varied according to a simplex-lattice experimental design. The drug-release-prolonging effect of the different matrices was examined *in vitro*. While the crystalline TMZ starting material dissolved very fast in acidic medium, the drug release was remarkably retarded from the solid-dispersion-based tablets (>10 h). As the PXRD tests showed that the active pharmaceutical ingredient (API) did not undergo polymorphic transformation during processing, this sustained-release behaviour could be ascribed to the matrix of the extrudates alone. The low degree of amorphisation could also be explained with solubility parameter calculations, performed according to Hoftyzer and Van Krevelen. The Carbopol percentage had clearly the greatest (retarding) effect on dissolution. The composition dependence of dissolution efficiency was statistically described by regression.

The mucoadhesion of the melt-extruded formulations and the non-processed starting materials was measured by tensile testing after bringing compressed discs of formulations in contact with wet mucin/microcrystalline cellulose discs. Surprisingly, the work of adhesion was significantly higher in some cases than what could be expected from the mucoadhesion of the polymer components. Similarly to dissolution efficiency, adhesion was also found to be adjustable by modifying the matrix composition. Assuming the goal that the highest possible mucoadhesion and the slowest possible drug release are to achieve, a compromise is necessary when the optimum composition is to be determined, because of the dissimilar dependence of these properties on the ratio of matrix polymers.

Another widely-explored application of melt extrusion is the amorphisation of poorly water-soluble drug compounds, which can solve the bioavailability issues of BCS[10] II-classified APIs, for example several steroidal drugs. When extruded together with Eudragit E (an eligible fast-dissolving matrix), prednisolone could be totally amorphised according to PXRD neither at 130 °C, nor at 150 °C with a drug loading of 10%. Only when the drug load was reduced to 5% could the drug be dissolved in the melt completely. When spironolactone was extruded with the same matrix, a residence time of 2.75 min was enough at 150 °C to achieve full amorphisation even with a drug load of 10%. This observation regarding the different behaviour of the two APIs was confirmed by the theoretic calculations of miscibility performed using the method of Hoftyzer and Van Krevelen.

As it had not been investigated with a broad experimental design yet in what way process parameters influence amorphisation in the dissolution (or solubilisation) regime, spironolactone/Eudragit E solid dispersions were prepared according to a factorial experimental design consisting of 54 (2×3^3) points. By varying the process parameters it was investigated systematically how temperature (110, 130 and 150 °C), residence time (2.75, 11.00 and 24.75 min) and screw speed (20 and 40 rpm), and drug load (10, 20 and 30%) affected the extent of amorphisation. The processing temperature, residence time and drug load had notable, while shear rate (screw speed) had no or minor influence on amorphisation in the investigated ranges. In the case of some selected fully amorphised samples no significant crystallisation could be observed by PXRD in 3 and 6 months.

The degree of crystallinity had a notable effect on *in vitro* dissolution. Three-minute release was achieved in the case of a solid solution, and the samples containing the drug partially in its crystalline form also showed improved dissolution. While more than 95% of the spironolactone content of each solid dispersion was dissolved in 60 min, the pure crystalline drug dissolved very slowly in the acidic medium.

The HPLC examinations of selected extrudates showed, however, that spironolactone underwent degradation to some extent during extrusion. The main decomposition product was canrenone by far, regardless of the applied process parameters. The amounts of further impurities were negligible. Dramatic improvement could be achieved in purity at 130 °C simply by increasing the screw speed and using the extruder in flush mode (i.e. without cycling the melt). Using a speed of 200 rpm instead of 20 rpm resulted in a 1.12 mol% canrenone content, which already met the requirements.

It was assumed that during the processing of the spironolactone/Eudragit E extruded systems, a certain molar percentage of the drug became amorphous without degradation (x_a), another percentage degraded (x_d), while the rest of the drug remained crystalline (x_c). It was demonstrated by the analysis of the 27 extrudates prepared at 20 rpm screw speed that transmission Raman spectrometry (TRS) together with chemometric data processing (the method of classical least squares) is an appropriate tool for the quick estimation of residual drug crystallinity (x_c) and the degree of drug degradation (x_d). Confocal Raman mapping was also performed for comparison, but it took 8–10 h per sample, while TRS delivered a bulk spectrum for each extrudate within 1 min. A linear relationship was found between the two Raman techniques in respect of the x_c and x_d values. When comparing the canrenone/spironolactone mole ratios obtained by HPLC with the Raman score ratios of canrenone to spironolactone, also a linear relationship was found. Furthermore, Raman spectrometry could be applied to predict the glass-

[10] Biopharmaceutics Classification System

transition temperature (T_g) of the formulations from the estimated x_c and x_d values. The prediction, which was based on a Raman–DSC calibration resembling the empirical Fox equation, was found to be highly accurate. The estimation of the glass transition temperature of polymer-based systems can provide useful information about physical stability.

In accordance with the principles of Quality by Design, the critical product attributes x_c, x_a and x_d calculated from the Raman data were matched to the experimental points inside the space of experiments. The relationship between the extrusion process parameters and x_c as well as x_d was statistically established, and the significant effects and interactions were determined. This allows one to understand the behaviour of the spironolactone/Eudragit E system during melt extrusion.

In the scaled-up melt extrusion of the spironolactone/Eudragit E system the minimum temperature of extrusion could be lowered from 130 to 110 °C at a high melt throughput when supercritical carbon dioxide ($scCO_2$) was used as a reversible plasticiser. This way the impurity content of the formulations could be decreased. As a physical blowing agent, $scCO_2$ increased the specific surface area of the extrudates remarkably. This and the formation of highly amorphous solid dispersions enabled >90% drug release in 2–5 min in acidic medium. Our experiments showed that an increase in porosity leads to a significant advantage in dissolution. Thus, the relationship between the process parameters and the foam structure was expedient to be studied. Lowering of processing temperature and increasing of melt throughput were found to have significant positive effects on foam structure. By optimisation high porosity (87–92%) and even submicronic cell walls could be reached (Fig. 1). It was found that the chemical quality of the drug substance can also largely influence cell density. While the order of magnitude of cell density was 10^4 cm^{-3} and porosity was typically 75–85% when 10% spironolactone was extruded, these were 10^6 cm^{-3} and 50–60% when 10% prednisolone was dispersed in the amorphous polymer matrix instead of spironolactone under the same conditions. The wall thickness of the cells did not differ notably, but cell diameters of prednisolone foams deviated around 50 μm, in contrast to the 200–300 μm cells observed in the case of spironolactone.

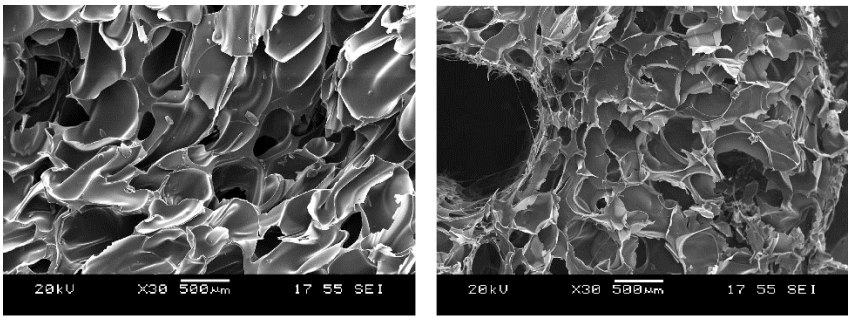

Fig. 1. SEM images of 10% spironolactone/90% Eudragit E solid foams with porosities of (A) 75% and (B) 92%

The heat-stress free formulation of spironolactone was realised using electrospinning. The wettability-worsening effect of the lipophilic drug was counterbalanced by a well wettable carrier system. Twenty and even 40% spironolactone was embedded into nanofibrous matrices consisting of polyvinylpyrrolidone (PVP) K90, hydroxypropyl-β-cyclodextrin (HPβCD) or their mixtures at various

excipient ratios. DSC, PXRD and TRS showed that the API was totally amorphised in all the formulations, owing to the rapid solvent (ethanol) evaporation.

When the matrix was PVP K90 alone, fibre diameters of 100 to 300 nm were measured using scanning electron microscopy, and the dissolution rate was remarkably increased compared to that of crystalline spironolactone. On the other hand, a part of the released spironolactone precipitated as slowly dissolving crystalline particles because of local supersaturation. This could be prevented by using 15% or more HPβCD besides PVP (Fig. 2). The width of the HPβCD-containing PVP fibres was found to be slightly greater and varied between 200 and 500 nm. When comparing the dissolution from the microfibres that had HPβCD/spironolactone mass ratios of 2:2, 3:2, 4:2 and 8:2, the dissolution-accelerating effect of HPβCD was well observable. When increasing spironolactone content to 40%, dissolution rate became slightly lower, but 95% of the drug could be dissolved in 90 min.

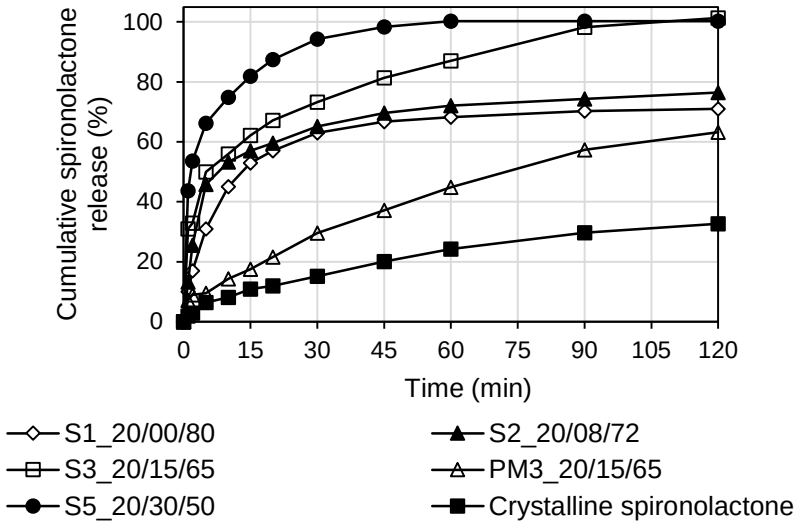

Fig. 2. Dissolution curves of crystalline spironolactone, a physical mixture (PM) and fibrous formulations at a dose of 25 mg in 900 ml of water. (Naming: Sample number_API% / HPβCD% / PVP%)

While fibre manufacturing from polymers is common, it was shown for the first time that a dissolution-enhancing drug-containing microfibrous amorphous solid dosage form can be produced solely on HPβCD basis, without using any polymeric excipient. The HPβCD fibres were prepared using a volatile and authorised organic solvent (ethanol). These fibres were thicker (with diameters between 1 and 5 μm), but ensured spironolactone release (>90%) in one minute. A further benefit of the polymer-free electrospun web is its excellent grindability. This enables its easy conversion into tablets, which are a conventional and popular dosage form.

The dissolution and bioavailability of the anthelminthic flubendazole was enhanced by electrospinning for the first time. The fibrous solid dosage forms based on PVP and HPβCD were completely amorphous. Flubendazole would be eligible to treat onchocerciasis, elephantiasis and loiasis when administered systemically, but its crystalline form is practically not absorbed. This is why nanofibres containing 10 and 20% API were developed, with which the release of a 40 mg dose could be

achieved within 15 minutes in contrast to the crystalline API, only a few milligrams of which could be dissolved in 900 ml of a pH 1 medium in 2 h. A notable implication of the therapeutic feasibility of the amorphous system is the increased plasma concentration in rats in contrast to the practically non-absorbable crystalline flubendazole (Fig. 3)[11]. The fibrous systems were completely amorphous according to DSC and PXRD. No crystallisation was observed in the samples in 1 month, 3 and 5 months.

The HPβCD/flubendazole mass ratio could be increased up to 4:1, which was already enough to obtain grindable fibrous mats, which is a technological advantage. The grindable nature of the fibres aids downstream processing, such as milling and tableting. Furthermore, a 250-fold increase could be achieved (from 0.24 g/h to approx. 60 g/h) in productivity when the manufacturing process was scaled up from the single-needle setup. Scale-up did not affect fibre morphology notably; fibre diameters were less than 500 nm.

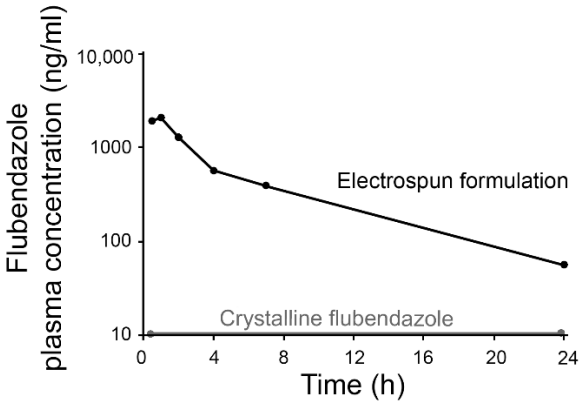

Fig. 3. Plasma levels of flubendazole after a 20 mg/kg dose was administered as a 10%-API-containing nanospun dispersion (FLU_CD_7) and as crystalline drug substance by gavage in 0.5% HPMC with the vehicle containing 2 mg/ml drug

[11] All animal studies were completed under appropriate national and international guidelines.

5 Thesis Findings

1. A novel release-prolonging and at the same time gastroretentive matrix system was developed for drugs of short half-life. The continuously melt processed matrix consisted of partially cross-linked polyacrylic acid, polyethylene oxide and polyethylene glycol. Using this carrier, trimetazidine dihydrochloride was formulated by melt extrusion for the first time, by which its release was prolonged for more than 10 hours. By optimising matrix composition according to a simplex-lattice design it was shown that melt processing can create synergism between the polymers regarding mucoadhesion [xviii, xxv].
2. It was proven that a rapid (< 1 min) non-invasive estimation of residual crystallinity, purity and glass-transition temperature is possible using transmission Raman spectrometry in the case of amorphous solid dispersions. (These can improve the bioavailability of poorly dissolving drugs.) With spironolactone being the model compound, correlation was found between the estimation results obtained by the rapid transmission Raman spectrometry and the off-line confocal Raman mapping technique. The achieved results prove that transmission Raman spectrometry can be used as a tool in process control [i].
3. In the case of spironolactone, a model of the compounds that partly degrade during melt processing, the relationship between melt extrusion process parameters and the degree of amorphisation as well as purity was established and statistically described by use of a factorial experimental design. By identifying the subspace of process parameters inside which full amorphisation could be reached, a 3-minute release of spironolactone was ensured, while in the case of the crystalline drug not more than 60% dissolved in one hour [i].
4. It was proven that degradation of melt extruded spironolactone can be reduced even in a scaled-up process by using supercritical carbon dioxide as a reversible plasticiser. The canrenone content (impurity) of the formulations could be reduced by enabling processing this way even at a 20 °C lower temperature at a high throughput [iii, xi, xii].
5. A relationship was established between the process parameters of pharmaceutical supercritical-fluid extrusion (processing temperature and melt throughput) and the foam structure. By optimisation very high porosity (92%) could be achieved in the case of spironolactone solid foams, and that was proven to have significant (accelerating) influence on dissolution rate. Examining the way in which chemical quality of the drug substance affects foam structure, cell density was found to be two orders of magnitude higher when prednisolone was dispersed in the amorphous polymer matrix instead of spironolactone (under the same conditions) [iii, xi, xii].
6. It was shown for the first time that dissolution enhancement of drugs can be achieved by electrostatic spinning of a microfibrous amorphous solid dosage form solely on 2-hydroxypropyl-β-cyclodextrin basis, without the use of any polymeric excipients. The resulting system was proven to potentiate one-minute drug release of spironolactone (>90%). The rapid drug dissolution makes the process feasible to produce orally disintegrating fibrous dosage forms too [ii].

7. High (20% and 40%) drug loads could be achieved when spironolactone was electrospun into fast-dissolving amorphous nanowebs of poly(*N*-vinyl pyrrolidone) and 2-hydroxypropyl-β-cyclodextrin matrix. It was proven that the presence of the well wettable complexing agent in the formulation is necessary to avoid the crystallisation of the drug in the dissolution medium after an ultrafast release [ii].
8. The bioavailability of the anthelminthic flubendazole was remarkably enhanced (in comparison with its pure crystals) in the form of an electrospun fibrous and completely amorphous solid formulation of poly(*N*-vinyl pyrrolidone) and 2-hydroxypropyl-β-cyclodextrin matrix. The thus produced flubendazole formulation is anticipated to be active against onchocerciasis, elephantiasis and loiasis. The bioavailability enhancement is based on the considerably improved dissolution. The release of a dose of 40 mg could be achieved within 15 minutes. Increased blood concentration was measured in rats in contrast to the practically non-absorbable crystalline flubendazole. Furthermore, a technological advantage was also realised owing to the easy-to-grind nature of the fibres [xxi,xxii].

6 Applicability of Results

Our results showed through the example of trimetazidine 2HCl-containing systems that multiple desirable formulation properties such as mucoadhesion and sustained-release can be ensured at the same time by melt extrusion. A Hungarian pharmaceutical company has already been considering the introduction of similar melt-extrusion-based formulations.

Having purchased a twin-screw extruder, another manufacturer, Richter Gedeon Nyrt, already utilises the relationships established between the extrusion parameters of the spironolactone/Eudragit E solid dispersions and residual drug crystallinity as well as drug degradation. A systematic investigation of pharmaceutical melt extrusion processes, as it was carried out in this work, can help determining design space boundaries in Quality-by-Design-based manufacturing. Supercritical-fluid melt extrusion is also being considered by the company, in which the investigated process parameter dependency of the characteristics of API-containing foams will help understanding the foaming processes.

Raman spectrometry, which was demonstrated in this work to be able to estimate the residual drug crystallinity and drug degradation inside solid formulations, is currently in use at Richter Gedeon for material characterisation. Beyond the benefits that are already exploitable using the backscattering Raman setup, transmission Raman spectrometry can make possible even real-time monitoring. Process control is also expected to be feasible based on the analytical signal.

Johnson & Johnson have committed themselves to eliminate or control 10 neglected tropical diseases by 2020[12]. The bioavailability enhancement of flubendazole achieved by electrospinning PVP/HPβCD-based amorphous nanofibres allow targeting ocular, dermal and lymphatic sites of tropical worm infection. The high throughput ensured and the grindable nature of the fibres make the technology industrially feasible.

[12] S.A. Silber, *Neglected Tropical Diseases – Not Neglected by Johnson & Johnson*, http://www.blogjnj.com/2013/01/neglected-tropical-diseases-not-neglected-by-jj/ (accessed: 11.05.2015)

7 Publications

Related scientific articles

In impact factor journals:

[i] T. Vigh, G. Drávavölgyi, P.L. Sóti, H. Pataki, T. Igricz, I. Wagner, B. Vajna, J. Madarász, G. Marosi, Z.K. Nagy, *Predicting final product properties of melt extruded solid dispersions from process parameters using Raman spectrometry.*, J. Pharm. Biomed. Anal. **98** (2014) 166–177. IF: 2.83, I: 4

[ii] T. Vigh, T. Horváthová, A. Balogh, P.L. Sóti, G. Drávavölgyi, Z.K. Nagy, G. Marosi, *Polymer-free and polyvinylpirrolidone-based electrospun solid dosage forms for drug dissolution enhancement*, Eur. J. Pharm. Sci. **49** (2013) 595–602. IF: 3.01, I: 18

[iii] T. Vigh, M. Sauceau, J. Fages, E. Rodier, I. Wagner, P.L. Sóti, G. Marosi, Z.K. Nagy, *Effect of supercritical CO_2 plasticization on the degradation and residual crystallinity of melt-extruded spironolactone*, Polym. Adv. Technol. **25** (2014) 1135–1144. IF: 1.96, I: 1

[iv] 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. IF: 3.79

[v] P.L. Sóti, Z.K. Nagy, G. Serneels, B. Vajna, A. Farkas, F. Van der Gucht, P. Fekete, T. Vigh, I. Wagner, A. Balogh, H. Pataki, G. Mező, G. Marosi, *Preparation and comparison of spray dried and electrospun bioresorbable drug delivery systems*, Eur. Polym. J. (2015) doi: 10.1016/j.eurpolymj.2015.03.035 IF: 3.24, I: 1

[vi] Z.K. Nagy, A. Balogh, B. Démuth, H. Pataki, T. Vigh, B. Szabó, K. Molnár, B.T. Schmidt, P. Horák, G. Marosi, G. Verreck, I. Van Assche, M.E. Brewster, *High speed electrospinning for scaled-up production of amorphous solid dispersion of itraconazole*, Int. J. Pharm. **480** (2015) 137–142. IF: 3.79, I: 2

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