APPLICABILITY OF ROTARY SPUN HYDROXYPROPYL CELLULOSE MICROFIBERS FOR THE FORMULATION OF ORODISPERSIBLE TABLETS OF POORLY SOLUBLE DRUGS

Ph.D. thesis

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Introduction

One of the most troublesome issues of modern pharmacy is that the pharmaceutical development must face the ever increasing proportion of actives of undesired physicochemical characteristics. Approximately, 70 % of new chemical entities and 30 % of the marketed drugs belong to Biopharmaceutical Classification System Class II, thus these drugs possess poor aqueous solubility and good membrane permeability. This phenomenon can be traced back to the high throughput screening and the superiority of potency enhancement over ADME (absorption-distribution-metabolism-excretion) feature optimization. The most important biopharmaceutical consequence of poor aqueous solubility is the low oral bioavailability, however difficulties in dosing, high interindividual variability and diminished patient compliance could be mentioned, as well.

Formulation scientists have been concerned about this issue for several decades, and a huge number of scientific papers are available addressing this issue. Although, a particular attention has been paid to chemical methods, e.g. pH adjustment, salt formation, complexation or prodrug strategy, the physical methods have been gained a notable popularity. The main approaches of the physical methods are the particle size reduction, the amorphous drug dispersions and the solid solutions. The effect of particle size reduction on solubility can be exploited in formulations only if the particle radius is below 1 μm, according to the Ostwald-Freundlich equation.

Amorphous drug dispersions are multicomponent systems comprising an amorphous active ingredient in a carrier that is usually a polymer, in which the active ingredient forms amorphous clusters. These systems containing poorly soluble drug in a metastable state possessing an apparent solubility greater than that of the initial drug. Solid solutions are solutions comprising a solid solute in a solid solvent, hence the solute is molecularly dispersed resulting in the formation of a homogenous amorphous phase. By reason of the molecular dispersion, solid solutions represent the pinnacle of the amorphous formulations, since this approach takes advantage of particle size reduction and amorphous conversion as much as possible.

Over the past few decades polymeric micro- and nanofibers have emerged as one of the most popular formulation pathways. These systems combine favorable properties such as

high specific area-to-volume ratio, high porosity, the possibility to keep drugs in an amorphous state, and an extracellular matrix-like structure. Polymeric fibers offer a suitable approach for formulations for tissue engineering, controlled release and solubility/dissolution enhancement purposes.

Different techniques are capable for the production of micro- and nanofibers. The most widespread applied method is electrospinning, in which fiber formation is induced by the high voltage applied on the sample loaded in a syringe equipped with a needle. Other techniques, such as blow spinning or high speed rotary spinning are also frequently used. In high speed rotary spinning, a viscoelastic polymeric solution or melt is put into a rotating reservoir, which has small wall orifices on its wall and is driven by a controlled engine. A revolution speed is achieved that is large enough to develop a centrifugal force capable to overcome capillary forces, thus the polymeric sample is pressed through the orifices.

Finally, the lengthening jet will solidify upon solvent evaporation and rapid cooling. This method also produces continuous fibers. Beyond the driving force, one of the most important difference from electrospinning, that this method typically employs more concentrated polymeric solutions

Aims

The objectives of my work were as follows:

- Enrichment of the range of polymers capable for high speed rotary spinning, by selecting a pharmaceutical polymer, namely hydroxypropyl cellulose (HPC) for high speed rotary spinning that have not been reported to be rotary spun so far.
- Conducting preformulation studies with HPCs of different average molecular weights in order to establish critical and optimal concentrations for fiber formation. The investigation of the impact of textural-rheological properties on fiber characteristics.
- By means of the exploitation of HPC’s versatile solubility features (soluble both in water and ethanol), the preparation of drug loaded microfibers incorporating actives selected from BCS class II.

- Physicochemical and supramolecular characterization of drug loaded microfibers with a particular attention to the crystalline-amorphous transition.
- Formulation of a solid oral dosage form, *i.e.* orodispersible tablets from processed drug loaded microfibers for the dissolution enhancement of incorporated actives and for highlighting the inherent possibilities of oral administration of fibers.
- To obtain information on physicochemical stability of drug loaded fibers using accelerated stability test.

Methods

Two hydroxypropyl celluloles of different average molecular weights were selected for fiber formation (Klucel® EXF Pharm and ELF Pharm, M_w 80,000 and 40,000 respectively). Applying these polymers, aqueous gels were prepared at room temperature for the preformulation studies. In case of Klucel® EXF aqueous gels were prepared in the concentration range of 38-52% w/w, and Klucel ELF gels were prepared between 42-60% w/w with an increment of 2% w/w. These gels were used in the fiber formation process with high speed rotary spinning (rotational speed of 10,500 rpm), and were subjected to texture analysis (CT3 texture analyzer, Brookfield Engineering Laboratories). In the course of texture analysis adhesiveness values were measured, by recording the load-distance curve of the probe immersing and ascending back to its initial position. The adhesiveness is the total negative area of the load-distance curve. Fiber morphology was monitored using optical transmission and reflection microscopes (Bresser LCD Micro type; and Nikon SMZ 1000 type optical microscope). Average fiber diameters and percentage yields were also calculated. Percentage yield was calculated as follows:

$$Yield\ \% = \frac{m_{fiber}}{m_{gel}c_{polymer}}100 \qquad (1)$$

where m_{fiber} is the weight of the fibers prepared from a gel of a weight of m_{gel} and a concentration of $c_{polymer}$.

The outcomes of the preformulation study were the critical and optimal fiber formation concentrations.

Drug loaded microfibers were prepared from Klucel® ELF Pharm gels of 50% w/w using a model drug and carvedilol. 100 mg/ml drug stock solutions contained citric acid monohydrate (model drug: 60 mg/ml, carvedilol: 52 mg/ml) as a hydrotropic agent, and a hydroalcoholic mixture was used as solvent.

The prepared microfibers were subjected to morphological evaluation using optical and scanning electron microscopy (Bresser LCD Micro type optical microscope, Amray 1830-D4 scanning electron microscope). Average fiber diameters were determined, and average drug contents were measured by UV-Vis spectroscopy (Agilent 8453 UV-Vis for model drug and Jasco 530 UV–Vis spectrophotometer for carvedilol) in 0.1 M hydrochloric acid solutions. In case of model drug X-ray patterns (X'Pert Pro diffractometer) and ortho-positronium lifetimes (positron annihilation lifetime spectroscopy, PALS, BaF2 /XP2020Q detectors and Ortec® electronics) were recorded. With respect to carvedilol microfibers thermograms (Seiko Exstar 6000/6200), X-ray patterns, FTIR spectra (Jasco FT/IR-4200 spectrophotometer) and ortho-positronium lifetimes were determined.

Drug loaded microfibers were further processed; thus microfibers were milled (Gorenje SMK 150 B), sieved (mesh sieve, nominal wire diameter of 320 μm). Particle size of milled components were determined by laser scattering particle size distribution measurement (LA-950V2 Horiba Co.). Distribution span values were calculated to characterize the width of the distributions based on Eq. (2):

$$Span = \frac{D_{90\%} - D_{10\%}}{D_{50\%}} \quad (2)$$

where $D_{10\%}$, $D_{50\%}$ and $D_{90\%}$ are the particle diameters at 10, 50 and 90% of the cumulative particles undersize plot. The results are the averages of five parallel measurements.

Milled microfibers were combined with common tableting excipients and the mixture was homogenized in a Turbula (T2F model; Willey A Bachofen AG) at 23 rpm for 30 min in a cylindrical container. The excipients of the orally disintegrating tablets were as follows: microcrystalline cellulose (Vivapur® 102 MCC) as filler and disintegrant, mannitol (Mannogem® EZ; for model drug) or spray-dried lactose monohydrate (Flowlac®100; for carvedilol) as filler, milled poly(ethylene glycol) 1500 (Macrogol 1500; for model drug)

or magnesium stearate (Ph.Eur.; for carvedilol) as lubricant, equimolar mixture of milled citric acid anhydrate (Ph. Eur.), and sodium bicarbonate (Ph. Eur.) as effervescent agent and croscarmellose sodium (Vivasol®) as superdisintegrant agent.

Orodispersible tablets containing 10 mg drug were prepared by direct compression technique using a single-punch tableting machine (Diaf TM20), with a shallow concave round punch of 13.5 mm.

Tablet parameters, including hardness (8M, Dr. Schleuniger Pharmatron), friability (Erweka friability tester TAP) and in vitro disintegration time (Erweka Disintegration Tester ZT 4 using 900 ml demineralized water at 37±2 °C) were determined according to the pharmacopoeial requirements.

Orodispersible tablets were examined in a Hanson SR8-Plus (Hanson Research) type dissolution tester equipped with rotating paddles at 37±1 °C, with a rotation speed of 50 rpm. Solution of hydrochloric acid of pH 1.0 (Ph. Eur. 8.), phosphate buffer of pH 4.5 (Ph. Eur. 8.) and phosphate buffer of pH 6.8 (Ph. Eur. 8.) were applied as dissolution media (the volume was 500 ml). The drug content of the samples was determined by UV-Vis spectroscopy (Agilent 8453 UV-Vis for model drug and Jasco 530 UV–Vis spectrophotometer for carvedilol).

Difference (f_1) and similarity (f_2) factors were calculated for the mathematical comparison of drug release profiles:

$$f_1 = \frac{\sum_{t=1}^{n'} |R_t - T_t|}{\sum_{t=1}^{n'} R_t} \times 100 \quad (3)$$

$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n'} (R_t - T_t)^2}{n'}}} \right) \quad (4)$$

where n is the number of time points, R_t is the dissolution value of the reference sample at time t (compressed physical mixture), and T_t is the dissolution value of the test sample (microfiber based formula) at time t.

Freshly prepared carvedilol loaded microfibers were transferred into sealed snapcap vials. Afterwards, the samples were placed in stability chamber (Sanyo type 022) and

maintained at 40 ± 2°C /75 ± 5% RH for 4 weeks. Samples subjected to stability test were analyzed by means of differential scanning calorimetry, X-ray diffractometry, and ATR-FTIR spectroscopy and positron annihilation lifetime spectroscopy (PALS).

Results

- Based on the literature review it was the first time that suitability of two different HPCs (Klucel® EXF and ELF) for high speed rotary spinning with the aim of producing polymer microfibers was demonstrated.
- Novel experimental set-up was introduced to the preformulation studies of high speed rotary spinning; the method was capable to mimic the conditions (elongation of the viscoelastic solution) of the spinning process. Thus a relationship was found between adhesiveness and spinnability; the lower the adhesiveness the better the spinnability. The novel application of textural analysis was first demonstrated for the characterization of spinnability.
- Unique shape of adhesiveness curves of the investigated HPCs was related to the concentration dependent liquid crystalline structure of the aqueous gels. This findings is in strong agreement with previous literature reports.
- The tracking of fiber formation; the determination of critical minimum, maximum and the optimum fiber forming concentrations could be easily established using the combination of microscopic evaluation, monitoring of process yield and textural characterization.
- It was the first reported that drug loaded microfibers were prepared via high speed rotary spinning using actives of BCS class II applying a novel approach. The high speed rotary spinning of polymer gels containing drugs dissolved resulted in the formation of an amorphous drug delivery system and in the supramolecular ordering of polymer chains.
- The fiber formation was successfully carried out without the employment of any harm solvent. Weak basic feature of drugs could be circumvented by the application of hydroalcoholic solvent mixture and citric acid.
- It was first described that fibrous structure of drug loaded microfibers can be retained after milling by rotary knife grinder.

- Novel orodispersible tablets, containing milled microfibers possessing satisfying features in terms of mechanical properties and in vitro disintegration were prepared. The combination of milled drug loaded microfibers with common tableting excipients enabled the preparation of orodispersible tablets by direct compression.
- The novelty of the work was the pH independent (in the pH range of 1.0-6.8), rapid and complete drug dissolution from microfiber based orodispersible tablets. Explanation of these observations were the high specific surface of microfibers, amorphous state of active ingredient, the acidic microenvironmental modulator effect of citric acid in the polymer-drug complex and the rapid disintegration of the compressed tablets.
- It was the first time, to the best to our knowledge, that physicochemical stability related data on rotary spun drug loaded microfibers was reported. Physicochemical stability of drug loaded microfibers is still a challenge and is influenced by several factors. Carvedilol loaded microfibers exhibited good stress tolerance capacity. Despite all of these, partial recrystallization took place by the end of the storage.

Conclusion

Polymeric microfibers possess a series of pharmaceutically beneficial properties, therefore it is worth the effort to explore their applicability in the formulation of various dosage forms with different drug delivery purposes. In this work, the suitability of hydroxypropyl cellulose of two different molecular weights for high speed rotary spinning was demonstrated by conducting prefomulation studies. It was shown that the combination of adhesiveness measurement, morphological evaluation and the monitoring of process yield is an effective way to establish critical and optimal fiber formation concentrations. Drug loaded microfibers were prepared and it was demonstrated that during the fiber formation process supramolecular ordering of polymeric chains and crystalline amorphous transition of the incorporated drug took place. Microfiber based orodispersible tablets were manufactured and exhibited rapid, complete and pH-independent release properties. Accelerated stability tests indicated a good stress tolerance capacity of carvedilol loaded microfibers, however as a result of the stress conditions a partial recrystallization occurred.

List of original publications

Papers connected to the Ph.D. thesis

1. **Szabó, P**., Kállai-Szabó, B., Kállai-Szabó, N., Sebe, I., Zelkó, R. (2014) Preparation of hydroxypropyl cellulose microfibers by high-speed rotary spinning and prediction of the fiber-forming properties of hydroxypropyl cellulose gels by texture analysis. Cellulose, 21: 4419-4427.
2. **Szabó, P.**, Kállai-Szabó, B., Sebe, I., Zelkó, R. (2014) Preformulation study of fiber formation and formulation of drug-loaded microfiber based orodispersible tablets for in vitro dissolution enhancement. International Journal of Pharmaceutics, 477: 643-649.
3. **Szabó, P**., Sebe, I., Stiedl, B., Kállai-Szabó, B., Zelkó, R. (2015) Tracking of crystalline-amorphous transition of carvedilol in rotary spun microfibers and their formulation to orodispersible tablets for in vitro dissolution enhancement. Journal of Pharmaceutical and Biomedical Analysis, 115: 359-367.
4. **Szabó, P**., Zelkó, R. (2015) Formulation and Stability Aspects of Nanosized Solid Drug Delivery Systems. Current Pharmaceutical Design, 21: 3148-3157.

Other publications

1. Sebe, I., Bodai, Z., Eke, Z., Kallai-Szabó, B., **Szabó, P.**, Zelkó, R. (2014) Comparison of directly compressed vitamin B12 tablets prepared from micronized rotary-spun microfibers and cast films. Drug Development and Industrial Pharmacy, 1-5.
2. Sebe, I., **Szabó, P.**, Kállai-Szabó, B., Zelkó, R. (2015) Incorporating small molecules or biologics into nanofibers for optimized drug release: A review. International Journal of Pharmaceutics, 494: 516-530.
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5. Kovács, G., Varga, D., Sebe, I., Hajdú, M., **Szabó, P.**, Ostorházi, E., Antal, I. Korszerű tartósítási módszer fejlesztése magisztrálisan előállítható műkönnyhöz. Acta Pharmaceutica Hungarica 4: 139-143.