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Development of Innovative Drug Delivery Systems Using Continuous Pharmaceutical Technologies

Theses of PhD dissertation

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2012

1. Introduction and aims

Importance of the drug formulation developments in the pharmaceutical industry is rapidly increasing partly due to economic factors and partly to the changing tendencies of drug candidates and marketed drugs (namely most of them are poorly water soluble and the ratio of sensitive biodrugs is increasing). Notable economic factors are as follows: decreasing number of blockbuster drugs, increasing drug research and development costs, globalization of the drug market and stringent governmental price control, which are resulting in intense competition and growing generic market share. The need for reduction of production costs initiates new research activities to develop pharmaceutical manufacturing technologies with decreased time and energy consumption. Continuous pharmaceutical production is a promising way to achieve these aims.

Thus, during the present research work continuous processes, technologies were used and developed to tackle the formulation challenges of the poorly water soluble active pharmaceutical ingredients (APIs) and biotech drugs.

The importance of melt extrusion as a continuous technology for dissolution enhancement of poorly water soluble APIs is rapidly growing according to the literature and to some newly marketed drugs produced this way. Application of **supercritical CO_2-aided melt extrusion** is a promising new direction of pharmaceutical technology, however among the few publications in this field only one former paper deals with dissolution enhancement [1].

The situation is similar in case of electrospinning, which is also a continuous technology and based on theoretical considerations, it is suitable to enhance the dissolution. Nevertheless, in the only article published prior to this doctoral work only a moderate dissolution improvement was achieved in comparison with film casting and melt extrusion [2].

Increasing number of biopharmaceuticals leads to proportionally growing demand for the development gentle formulation processes. One of the most challenging tasks is **drying and solid formulation of biodrugs**. According to the current industrial practice the freeze drying (lyophilization) is the most common method applied for this purpose, however this technology is extremely time- and energy consuming. Electrospinning is a promising

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continuous technology for gentle drying of biodrugs due to the immediate solvent evaporation at room temperature, thus investigating the capabilities of this technique to replace the expensive lyophilization method for drying biopharmaceuticals is of great importance.

According to the conclusions of the literature survey and based on the trends and challenges in the pharmaceutical industry the **main aims of the research work** were as follows:

- Investigation of the possibility to apply supercritical CO_2-aided extrusion in the pharmaceutical technology to improve the dissolution of poorly water soluble drugs in comparison with melt extrusion.
- Investigation of the applicability of electrostatic spinning for dissolution improvement, achieving fast buccal dissolution in comparison with melt extrusion and film casting.
- Investigation of the applicability of electrostatic spinning for drying and solid formulation of biopharmaceuticals.

During the development of new technologies, drug formulations and drug delivery systems high priority was given to the industrial feasibility of the proposed manufacturing technologies.

2. Applied methods

Experimental methods

Melt extrusion

Minilab Haake Rheomex CTW5 twin screw extruder

Melt extrusion coupled with supercritical CO_2 extrusion

SCAMEX Rheoscam single screw extruder

ISCO 260D superctritical CO_2 pump

Electrostatic spinning

MA2000 NT-35 high voltage DC supply

Aitecs SEP-10S syringe pump

Schlick spraying head

Laboratory scale Nanospider^{TM} equipment

Characterization methods

Rheology

TA Instruments AR2000 rotational rheometer

Scanning electron microscopy and energy dispersive spectrometry

JEOL JSM-6380LA scanning electron microscope

JEOL 1200 gold coater

Differential scanning calorimetry (DSC)

Setaram DSC92 differential scanning calorimeter

Fourier transform infrared spectrometry (FTIR)

Bruker Tensor 37 Fourier transform infrared spectrometer

Raman microspectrometry

Horiba Jobin Yvon LabRAM Raman-microscope

Transmission Raman spectrometry

Horiba Jobin Yvon Accura transmission Raman spectrometer

X-ray powder diffraction (XRPD)

PANalytical X'Pert Pro MPD X-ray powder diffractometer

In vitro dissolution

Erweka DT6 dissolution tester

Capillary electrophoresis

Agilent $HP^{3D}CE$ capillary electrophoresis equipment

3. Theses

1. Micro- and nanofibres were prepared the first time by electrospinning of polyvinyl caprolactam/polyethylene glycol/polyvinyl acetate graft copolymer, which could be used as drug delivery system. This way the dissolution of poorly water-soluble spironolactone could be significantly improved (from >8 hours to 10 min), owing to the efficient amorphization and enhanced specific surface area. The detection of crystalline drug traces nearby amorphous majority could be performed with higher sensitivity by transmission and micro-Raman spectrometry than by other methods (XRPD, DSC) [3].

2. Supercritical CO_2-assisted extrusion and Eudragit E matrix was successfully applied for improving the dissolution of carvedilol of poor water solubility from several hours to 5 minutes. The polymer matrix, of good solubility below pH 5 in aqueous medium, promoted the amorphization and homogeneous distribution efficiently. The experiments lead to the conclusion that the temperature of the extrusion can be decreased, the productivity can be increased and residence time can be reduced this way owing to the detected significant plasticizing effect of supercritical CO_2. Additionally the CO_2, released from the product, contributes to the increase the surface area, which accelerates the dissolution [4,17].

3. New fabric-type drug delivery system, consisting of submicron-size fibers, could be produced using Eudragit E matrix, which allowed the reduction of the dissolution time of antihypertensive carvedilol to 1 minute exceeding the performance of extrudates. The result was ascribed to the large surface area of the submicron-size fibres and the stabile amorphous structure [5,22].

4. Drug delivery system of sudden dissolution, independent of the pH of dissolving medium, could be developed by combined application of electrospinning and PVP K30 polymer matrix. Instantaneously soluble carvedilol formulation and concentrated carvedilol solution (exceeding many times the solubility of carvedilol) can be prepared this way. This system is appropriate for producing orally dissolving solid dosage form of drugs [2,7,20,21].

5. New straw-type dosage form was prepared and verified by using PVP-based nanofibrous drug delivery system, from which more than the 91% of the drug releases in the first 20 ml liquid, drawn across the straw, and the whole drug amount leaves the straw in the first 40 ml (of the drawn liquid). This new dosage form combines several advantages of solid and liquid pharmaceuticals, such as controlled dose, fast therapeutic effect and good patient compliance [2].

6. PVA-montmorillonite (MMT) based film-coating system could be prepared and applied successfully, which provides both good water vapour-barrier effect and rapid dissolution. The outstanding vapour-barrier activity of the coating is ascribed to the diffusion-restricting effect of the montmorillonite. Optimizing the amount of MMT the formation of water sensitive pharmaceuticals of enhanced stability and rapid disintegration became feasible [1].

7. Rapid dissolution of donepezil HCl, used against Alzheimer disease, could be ensured by PVA-based nanofibrous drug carrier system prepared by electrospinning method. The rapid dissolution is explained by the presence of water soluble polymer of relatively low molecular mass, the efficient amorphization and the high surface area, which was verified by several analytical methods (e.g. SEM, XRPD, Raman microspectrometry). The crystallization could be restricted up to min. 12 months, which shows the large diffusion- restricting capability of the nanofibres [6].

8. Network of electrospun nanofibres containing Lactobacillus acidophilus probiotic bacteria could be prepared from polymer solutions. Large amount of Lactobacillus acidophilus

bacteria of reproduction capability survived the process. In the cases of PVP K30 and PVP K90 the numbers of viable bacteria per gram are 400 and 600 million respectively, while with PVA this number achieved 1 billion. Each nanofibrous product, kept at 7°C, preserved 10 million viable Lactobacillus acidophilus per gram regardless of the type of the applied polymer. (It is comparable with the surviving ratio achievable using the costly freeze drying process.). The pharmaceuticals developed according to this process can be applied efficiently for the treatment of bacterialis vaginosis [2,7,21].

4. Industrial feasibility of the achieved results

Considering the experimental results and the current pharmaceutical industrial practice the industrial scale production of the developed drug delivery systems, prepared by melt extrusion or supercritical CO_2-assisted melt extrusion, are expected to be readily achievable.

In the field of original drug research and development, where samples of lower amount are needed, nanofibrous drug delivery systems can be manufactured in sufficient amounts, even by using laboratory electrospinning equipment with one capillary spinneret, for accomplishment of numerous examinations (such as toxicology test, bioavailability test, in-vitro dissolution test, amorphization, formation of solid solution, etc.). Such utilization of our electrospinning results has already been realized in several cases in cooperation with industrial partners, and the spreading of electrospinning technology is anticipated in laboratories of original drug research and development.

Next stage is the investigation of scale-up and industrial scale mass production. According to our experiments and the literature survey the output of nanofiber production can reach and exceed 10 kg/day rate which can be high enough to fulfil the quantity requirements of numerous pharmaceutical products at industrial scale. Probably, the developed fibrous dosage forms can be manufactured at industrial scale by coupling the fiber formation step with the existing manufacturing and packaging steps of buccal film or patch production.

Industrial scale production of patient-friendly fibrous dosage forms can result in significant break-through in the field of electrospinning and pharmaceutical technology, which could open up new drug delivery opportunities in case of small molecules and biopharmaceuticals as well.

5. Publications related to the dissertation

Patents

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