



POSTER PRESENTATIONS

RazelTM) that maintained steady flow rate. A high voltage on the needle was achieved by connection to a voltage generator (model HVG-P60-R-EU, Linari Engineering s.r.l. Italy). Planar collector covered with aluminium foil was placed 15 cm from the needle, flow rate was set on 0,7070 ml/h and applied voltage was 15 kV.

SEM characterisation of nanofibers

Nanofibers were characterised with SEM, 235 Supra 35VP-24-13, Carl Zeiss, Germany, operated at an accelerating voltage of 1 kV.

RESULTS AND DISCUSSION

Our results show that by increasing the concentration of PVA the viscosity increase, as well as elastic and plastic modulus (Fig. 1). The increase in viscosity is due to greater numbers of chain entanglements, which is also the reason for more homogenous and beads-free nanofiber morphology (Fig. 2). Therefore, the sufficient number of entanglements between chains is crucial for stabilization of electrospun jet (3). From Fig. 2 it can be observed that only concentrations above 8% (viscosity values above 0,27 Pas) possess sufficient number of entanglements for stabilisation and beads free nanofibers formation.

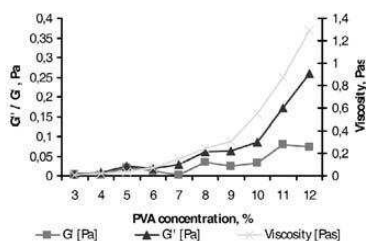


Fig. 1: Loss modulus, storage modulus and viscosity as function of polymer concentration

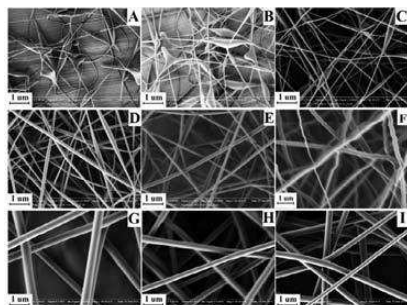


Fig. 2: SEM images of electrospun nanofibers: A-4% PVA, B-5% PVA, C-6% PVA, D-7% PVA, E-8% PVA, F-9% PVA, G-10% PVA, H-11% PVA, I-12% PVA, at 15 kV, flow rate 0,7070 ml/h and collector to needle distance 15 cm

Additionally we found out that increased polymer concentration resulted in thicker fiber diameter (Fig. 3). This can also be explained by increased number of entanglements between molecules, which reduce the thinning of the jet under the influence of applied voltage.

We also studied the correlation between elastic and plastic modulus and stabilization of the electrospun jet. Plastic modulus is a fraction of the energy that will be lost during loading system, while the elastic modulus represents the fraction of energy that will be stored. Measurements showed that both modulus increased with increased polymer concentration. It was determined that for efficient stabilization of the jet a considerable value of elastic module is needed, which ensures that the entanglements between

the chains are maintained during the flight of electrospun jet to the collector. Fig. 1 and 2 show that the sufficient values of G' for beaded free nanofibers formation are above 0,02 Pa. As a result of lower values of G' beaded nanofibers are formed. Additionally, in our opinion interfacial rheological properties of polymeric solutions have an essential role for nanofibers formation, what will be discussed further.

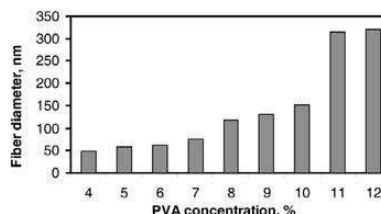


Fig. 3: Fiber diameter as a function of polymer concentration

CONCLUSIONS

It can be concluded that understanding the viscosity and elastic modulus can partially predict the successfulness of electrospinning. Our results show that at concentrations above 10 % viscosity begins to rise vigorously as well as the diameter of nanofiber.

The results enable the integration of chemical and physical aspects of polymer solutions and have a powerful impact on the rational design of suitable nanofibers for tissue engineering applications.

REFERENCES

1. Rošić R, Kocbek P, Baumgartner S, Kristl J. Electrospun hydroxyethyl cellulose nanofibers: the relationship between structure and process. *J. Drug Del. Sci. Tech.* 2011; In Press/Alì SL.
2. Beachley V, Wen X. Polymer nanofibrous structures: Fabrication, biofunctionalisation and cell interactions. *Progress in Polymer Science*, 35; 2010: 868-892
3. Gupta P, Elkins C, Long T, Garth L, Wilkes: Electrospinning of linear homopolymers of poly(methyl methacrylate): exploring relationships between fiber formation, viscosity, molecular weight and concentration in a good solvent, *Polymer* 2005; 46,4799-4810

NANOFIBROUS DRUG DELIVERY SYSTEMS FOR ENHANCED DISSOLUTION PREPARED BY ELECTROSPINNING

Z. K. Nagy^{1*}, A. Balogh¹, I. Wagner¹, P. Sótí¹, H. Pataki¹, K. Molnár², G. Marosi¹

¹ Budapest University of Technology and Economics, Department of Organic Chemistry and Technology, 1111 Budapest Budafoki út 8, Hungary; ² Budapest University of Technology and Economics, Department of Polymer Engineering, 1111 Budapest Műegyetem rkp 3, Hungary

INTRODUCTION

One of the largest challenges in the field of pharmaceutical technology is the enhancement of drug release from orally taken solid dosage forms as most of recently developed APIs are poorly soluble in water (1). Electrostatic spinning is a remarkably simple and efficient technique to generate water soluble polymeric fibers in submicron scale from polymer solutions (or melts) applying high electric voltage (2). Co-solution of polymer and API can be electrospun as well. This process, resulting in very fast drying, is advantageous from the formulation point of view of sensitive drugs. Generally the drying step is faster than 0.1 sec owing to the huge surface area formed during the spinning process and that it works in ambient temperature. Because of the ultra-fast drying there is no time for agglomeration or arrangement (recrystallization) of API molecules, thus, amorphous material is collected embedded in amorphous water soluble



polymer (PVP, PVA, PEG). Huge surface, amorphous physical state and water soluble polymer matrix are very promising to achieve adequate dissolution of poorly water soluble drugs (3). Bioavailability of drugs or drug candidates with good permeability and low water solubility (BCS II) is mainly dependent on the speed of dissolution step, thus, dissolution enhancement is often required (4). The aim of this work was to investigate solvent electrospinning and melt electrospinning techniques for improvement of the dissolution of drugs with poor water solubility. Electrospinning techniques were compared to melt-extrusion method. Isodimensional micro- and nanoparticles were also prepared using solvent-based electrospinning method. To map the industrial feasibility of electrospinning different types of solvent and melt electrospinning scaling-up capabilities were examined.

MATERIALS AND METHODS

Materials

Polyvinyl alcohol (PVA), purchased from Fluka (Buchs, Switzerland, molecular weight: 31000 Da), polyvinyl pyrrolidone (PVP) with two different chain lengths (molecular weight: PVP K12: 2500 Da, PVP K30: 50000 Da), kindly provided by BASF (Ludwigshafen, Germany) and Eudragit EPO was supplied by Evonik (Essen, Germany). Spironolactone was used as model drug and it was originated from Sigma-Aldrich (Budapest, Hungary).

Electrostatic spinning process

The electrostatic spinner used for the experiments was equipped with NT-35 High Voltage DC Supply (MA2000, Nagykanizsa, Hungary). The electrical potential applied on the spinneret electrode was adjusted during the experiments between 10-35 kV. Distance of the spinneret and the collector was 15 cm and the experiments were performed at room temperature (25 °C). Polymer solutions were dosed by SEP-10S Plus type syringe pump (Aitecs, Vilnius, Lithuania).

In vitro dissolution

The dissolution studies were performed by Erweka DT6 dissolution tester (Erweka, Heusenstamm, Germany). Concentrations of the collected samples were measured by Hewlett Packard 8452A type UV spectrophotometer.

RESULTS AND DISCUSSION

Morphology studies

According to microscopic investigations diameters of fibers were mainly in the submicron range (300-700 nm) in the case of Eudragit E-ethanol system (Fig 1). However, diameters of some thicker fibers were around 1 µm.

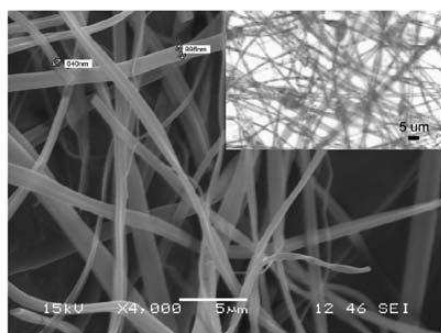


Fig. 1: SEM and optical microscopic images of EudragitE nanofibers loaded with 20 w/w % API

Fibers obtained by electrospinning of PVP-ethanol based systems had similar diameter distribution. In the case of melt electrospinning diameters of the fibers were significantly thicker (few microns).

Physical state of the API in the fibers and in the extrudates was examined by X-ray diffractometer (PANalytical X'pert Pro MDP).

Fig. 2 shows that successful amorphization of spironolactone was achieved using PVPK12 as a polymer matrix. Similar to PVPK12 XRD results amorphous systems were formed using the other polymers in all cases. Raman map of electrospun Eudragit E - spironolactone (20 %) fibers acquired by Raman-microscope (Horiba Jobin Yvon, LabRam) showed practically perfect distribution of spironolactone forming a solid solution which was confirmed by differential scanning calorimetric results. Spironolactone acted as a plasticizer since it lowered the glass transition temperature of Eudragit E.

Dissolution of spironolactone from the prepared solid forms were significantly faster owing to the successful amorphization of spironolactone, the increased wetting of spironolactone caused by polymer matrix and the formed huge surface area in the case of the electrospun ultrathin fibers.

Nanofibrous mat based orally dissolving web (ODW) technology was also successfully utilized for topical delivery. Scaling-up ideas of electrospinning applied in the textile industry are very promising for pharmaceutical applications as well.

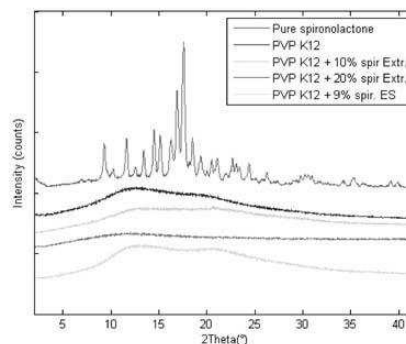


Fig. 2: X-ray diffractograms of PVPK12 based samples

ACKNOWLEDGEMENTS

This research was supported by OTKA Research Fund (code K76346), ERA Chemistry (code NN 82426) and New Hungary Development Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002).

REFERENCES

1. Keszler GM, Makara GM. The influence of lead discovery strategies on the properties of drug candidates. *Nature Reviews Drug Discovery*, 2009; 8: 203-212.
2. Nagy ZK, Nyúl K, Wagner I, Molnár K, Marosi G. Electrospun water soluble polymer mat for ultrafast release of Donepezil HCl. *Express Polymer Letters*, 2010; 4: 763-772.
3. Nagy ZK, Saucieu M, Nyúl K, Rodier E, Vajna B, Marosi G, Fages J. Use of supercritical CO₂-aided and conventional melt extrusion for enhancing the dissolution rate of an active pharmaceutical ingredient. *Polymers for Advanced Technologies*. 2011; Article in Press, doi: 10.1002/pat.1991
4. Patyi G, Bódis A, Antal I, Vajna B, Nagy Z, Marosi G. Thermal and spectroscopic analysis of inclusion complex of spironolactone prepared by evaporation and hot melt methods. *Journal of Thermal Analysis and Calorimetry*, 2010; 102: 349-355.