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Electrospun water soluble polymer mat for ultrafast release of Donepezil HCl

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Abstract. Electrostatic spinning (Electrospinning, ES) was applied to prepare Donepezil HCl loaded nanofibers as a potential orally dissolving dosage form. Electrospinning of water solutions of different polymers were performed in order to fabricate a consistent and removable web on the collector with ultra-fast dissolution in water based media. Poly(vinyl-alcohol) of low molecular weight was found to be the most appropriate for this purpose. Morphology of the prepared nanofibers was characterized by scanning electron microscope as a function of viscosity and drug content. Diameters of the fibers were between 100 and 300 nm with narrow distribution. *In vitro* drug release of the webs was immediate (less than 30 s) after immersion independently of their drug content owing to the formed huge surface area, while cast films with the same compositions and commercial tablets needed 30 min or more for complete dissolution. The developed technology for the preparation of orally dissolving web (ODW) formulations is a promising way for producing effective and acceptable dosage forms for children, older people and patients with dysphagia.

Keywords: *nanomaterials, electrospinning, drug delivery, orally dissolving web (ODW), ultrafast dissolution*

1. Introduction

Peroral administration of APIs (Active Pharmaceutical Ingredients) is the most preferred route in drug therapy especially if the patient compliance aspects are considered. Peroral delivery includes orally dissolving dosage forms, which are in the focus of numerous industrial research and development activities owing to their advantages such as:

– instant drug release and rapid onset action (e.g. against migraine);
– site-specific effect (e.g. sore throat);
– buccal adsorption, avoidance of first pass effect;
– improved oral bioavailability;
– acceptable for patients with swallowing difficulties (e.g. dysphagia, pediatric or geriatric patient, mental disorders, emesis, motion sickness);
– not requiring mastication or water;
– chance for reformulation of existing drugs (product life-cycle management, market competition).

More traditional oral formulations such as syrups and drops have some considerable disadvantages. Stability of drugs in liquids is generally much less than in solid forms due to the higher reactivity of substances in liquid phase [1]. Furthermore, the dose precision of liquid formulations is mostly imperfect. These disadvantages led the European Medicines Agency (EMEA) to recommend the development of solid dosage forms instead of oral liquid dosage forms [2].

The orally disintegrating tablet formulation (ODT) [3] meets the EMEA recommendation. Administration of ODTs is easy and there is no need to swal-

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low large particles or water. The required disintegration time of ODTs has to be less than 30 s which needs much care during the manufacturing. Compression force and hardness of the tablet are critical parameters of manufacturing of ODTs. If the compression force is too high the disintegration time increases over the established limit. In contrast, if the compression force is low the mechanical properties of the tablet will be weak, leading to fragile and brittle tablets of weak resistance against mechanical shocks during manufacturing, storage, packaging, transportation and intake. Another type of ODTs produced by freeze-drying is often very porous, brittle and fragile.

The most recent researches in the field of orally dissolving solid dosage forms have been dealing with oral thin film technology (OTF) which is a relatively new area of interest regarding the oral administration. The first commercial success of oral thin films appeared in the United States (Listerine PocketPaks). Nowadays several products, manufactured by this technology, reached the market or are in the clinical phase of development (Listerine PocketPaks, BioEnvelop, MonoSol Rx, BioFilm, Snoreeze, Triaminic, RapidFilm [4], Ora-Film [5]).

OTFs have some advantages over ODTs. The mechanical properties of the films are better than those of ODTs due to their flexibility. OTFs have higher surface to contact with the saliva and the dissolution can be faster. However oral thin films often contain ingredients insoluble in water such as microcrystalline cellulose to promote disintegration. Insoluble particles can be inconvenient for patients and furthermore they have to be swallowed.

Electrostatic spinning (Electrospinning, ES) is a dynamically developing technology which has been primarily applied in the textile/filtration industry. The ES technology is based on the impact of high electric field on polymer solutions generating polymer fibers in the submicron scale when the electric forces overcome the surface tension. The setup consist of a solution feeder and a high voltage power supply which is connected to a spinneret and a collector electrode. Usually the latter one is grounded. The solution on the spinneret electrode forms a droplet which can interact with electrostatic field. The droplet gains a cone-shape and thin jet can emerge from the tip of the cone. Fibers are drawn by electrostatic forces between the two electrodes and the solvent evaporates, resulting in solid nanofibers. The prepared non-woven web is removable from the grounded collector as a sheet. There are numerous promising research activities in various relevant areas such as composites [6–11], sterile filtration [12], wound dressing [13, 14], wound healing [15], tissue engineering [16–19] and semiconductors [20]. This technique is relatively new in the field of medical industry and ES is quite slightly known in pharmaceutical technology, where most of the relevant papers deal with sustained drug release [21]. Immediate release from nonwoven system of electrospun nanofibers (called mat or web generally) has been published only in some cases [22–25]. Consequently the reviews dealing with fast dissolving oral dosage forms such as OTFs, and ODTs missed to mention this technology [3, 5, 26–28].

Formation of non-woven tissues of the nanofibers, owing to their huge surface area, is a promising way to develop oral fast-dissolving dosage forms and the electrostatic spinning can be a capable technology for manufacturing such formulations. The wide versatility of the polymers available for this purpose supports this idea. Papers dealing with immediate release from electrospun mat applied organic solvents during their electrospinning process [22–25].

The aim of this work was to investigate applicability of organic solvent free electrostatic spinning method to produce orally dissolving formulation (ODW = Orally Dissolving Web) using a water soluble model drug. Donepezil HCl, administered against Alzheimer's disease, was chosen as an example because its ODT formulation is available on the market (Aricept ODT, Eisai) and its OTF formulation, developed using Rapidfilm technology (LabTec), is under clinical testing.

2. Materials and methods

2.1. Materials

The model drug Donepezil HCl (Figure 1) was kindly provided by Richter Plc (Budapest, Hungary).

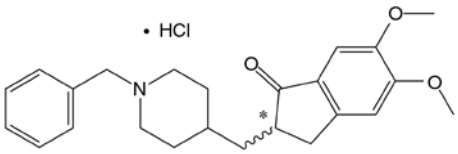

Figure 1. Chemical structure of Donepezil HCl

Poly(vinyl-alcohol) (M_w = 31 000 Da), purchased from Fluka (Buchs, Switzerland), PVA-PEG graft copolymer of Kollicoat IR type (BASF, Ludwigshafen, Germany) and Pharmacoat 606 HPMC hydroxypropylmethylcellulose (Shin-Etsu, Tokyo, Japan), were used as polymer matrices.

2.2. Preparation of solutions

The polymer was added into 10 ml purified water and stirred by ARE magnetic stirrer (VELP Scientifica, Usmate, Italy) at 600 rpm and 50°C till the complete dissolution. The API was dissolved in the solution of the polymer (magnetic stirrer, 600 rpm, 25°C). The compositions of PVA based solutions are presented in Table 1.

Table 1. Composition of PVA based solutions

Samples		PVA	Water	Do
Number	Referred as	[g]	[ml]	[g]
1	PVA 10%	1.11	10	0
2	PVA 15%	1.76	10	0
3	PVA 20%	2.50	10	0
4	PVA:Do 5:1	2.50	10	0.50
5	PVA:Do 2:1	2.50	10	1.25

2.3. Electrostatic spinning process

The electrostatic spinner used for the experiments was equipped with NT-35 High Voltage DC Supply (MA2000, Nagykanizsa, Hungary). The utilized electrical potential on the spinneret electrode was between 10–35 kV which was adjusted during the experiments. A grounded aluminium plate covered with aluminium foil or thin PVA film was used as collector. The 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 syringe pump (Aitecs, Vilnius, Lithuania). Electrospinning process was repeated 2 times to investigate the repeatability in the case of the drug containing compositions. Samples (equivalent to 10 mg Donepezil HCl) were cut from 3 different places of the collected web and were assayed by dissolution test. The weights of the cut PVA:Do 5:1 and PVA:Do 2:1 samples were ~60 and ~30 mg, respectively.

2.4. Rheological measurements

Viscosity of the solutions was determined by AR 2000 Rotational Rheometer (TA Instruments, New Castle, USA) in a parallel plate configuration. The upper moved portion was a 40 mm diameter stainless steel plate. The lower portion was a Peltier plate covered by Teflon and the applied gap between the plates was 0.5 mm. The temperature of the solutions was adjusted to 25°C by the Peltier thermoelement. The viscosities were measured at torques increased logarithmically from 10 to 1000 μNm·Pa. The viscosities shown in the Table 2 are the average of 10 measured values at different torques (no significant changes were estimated as a function of the torque).

2.5. Conductivity tests

Conductivity of the solutions was measured using a Radelkis OK-102/1 conductivity meter (Radelkis, Budapest, Hungary). The electrode was immersed into the solution and the measurement was carried out at 25°C. The results given in Table 2 represent the average of 3 parallel measurements.

2.6. Scanning electron microscopy (SEM)

Morphology of the samples was investigated by a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope. Each specimen was fixed by conductive double sided carbon adhesive tape and sputtered by gold (using JEOL 1200 instrument) in order to avoid electrostatic charging.

Table 2. Viscosity and conductivity of the solutions at 25°C

Sample	Viscosity [Pa·s] (n=10)	Standard deviation [Pa·s]	Conductivity [mS/cm] (n=3)	Standard deviation [mS/cm]
Water	0.00088	0.00026	0.023	0.002
PVA 10%	0.02590	0.00140	0.760	0.050
PVA 15%	0.10900	0.00800	0.940	0.040
PVA 20%	0.39500	0.01500	1.040	0.060
PVA:Do 5:1	0.40900	0.01100	3.700	0.110
PVA:Do 2:1	0.52100	0.01700	7.500	0.110

2.7. Film casting

Donepezil HCl containing PVA films (PVA:Do 5:1 and 2:1) were also prepared by casting method to compare the dissolution rate of electrospun mats and cast films. PVA was dissolved in purified water with magnetic stirrer at 50°C and 600 rpm (ARE Magnetic Stirrer, VELP Scientifica, Usmate, Italy). After the complete dissolution of the polymer Donepezil HCl was added into the solution at room temperature (25°C). Then the solution of the polymer and the drug was cast into square silicone moulds (4×100×100 mm). After evaporation of the water (room temperature, 3 days) the films were removed and stored at room temperature. The thicknesses of the prepared films were between 100 and 110 μm measured by Pro-Max electronic digital caliper (NSK, Tokyo, Japan). For dissolution tests squared films were cut equivalent to 10 mg Donepezil HCl.

2.8. *In vitro* drug dissolution measurement

The dissolution studies were performed by Erweka DT6 dissolution tester (USP II apparatus, Erweka, Heusenstamm, Germany). 3-3 samples were investigated from the two parallel electrospinning process in the cases of PVA:Do 5:1 and PVA:Do 2:1. Electropun samples to 10 mg Donepezil HCl were placed in the dissolution vessel containing 900 ml distilled water maintained at 37±0.5°C and stirred at 50 rpm. Samples (5 ml) were collected after 0.5, 1, 1.5, 2, 2.5, 5, 10, 15, 20 and 30 minutes and were analyzed by Hewlett-Packard HP 8452A UV-VIS spectrophotometer (Palo Alto,USA) using diode array detector at 272 nm. Concentration of Donepezil HCl in the collected samples could be easily calculated with the help of the calibration curve of pure Donepezil HCl in water (since PVA has no detectable absorbance at this wavelength).
For comparison 3 parallel samples of cast films (10 mg Donepezil HCl) with same composition as electrospun samples and six commercial Aricept peroral tablets (10 mg Donepezil HCl) were assayed. The collected liquid samples were filtrated through 0,22 μm membrane in the case of tablets.

2.9. Modeling oral dissolution

5 ml purified water was poured in a Petri dish (d = 5 cm). Electrospun samples were placed onto the surface of the water by a clip. The weight of the samples was ~60 mg for electrospun PVA placebo, while ~30 and ~60 mg for electrospun PVA:Do 2:1 and electrospun PVA:Do 5:1 respectively. Dissolution (disappearance) was investigated visually and the time of disappearance was measured. Six parallel assays were carried out on each composition (electrospun PVA placebo, electrospun PVA:Do 5:1 and electrospun PVA:Do 2:1).
In vivo dissolution (disappearance) test was also performed by electrospun PVA placebo. Electrospun samples (60 mg) were placed onto the tongue of a volunteer and the time of disappearance of the web was measured. Six parallel tests were performed.

3. Results and discussion

3.1. Selection of the polymer

Different polymers were applied to prepare adequate web for fast dissolution. The compared polymers were as follows: PVA, HPMC, PVA-PEG graft copolymer. The first characteristic of these polymers to be taken into consideration was their solubility and dissolution. For the purposes of present application the polymer has to be soluble in the water based medium of salvia and the dissolution time has to be as short as possible. The polymers applicable for pharmaceutical purposes are quite limited due to the stringent regulations. Several water soluble and insoluble polymers are applied by filmcoating technology, which is a rapidly developing part of pharmaceutical industry. In the most cases tablet coatings have to dissolve rapidly to avoid any delay in the action of APIs. Thus polymer components of fast dissolving filmcoatings are good candidates to develop orally dissolving systems.
Donepezil HCl has appropriate water solubility therefore the preferred solvent for electrospinning was pure water. Sequences of polymer water solutions of different concentrations were tested by the electrospinning apparatus. It was found that the selected type of cellulose derivate (see in the 2.1) is not adaptable for preparing suitable web for oral dissolution at any concentration in water. The experiments performed by water solutions of PVA-PEG graft copolymer were more successful but separated non fibrous particles were found as a result on the collector when the concentration was

≤ 20 w/w%. (At higher concentration there was not any utilizable material on the collector.) In the case when separated particles are formed instead of fibers the method is called electrospraying. With this process fine particles are readily producible but it is not the subject of this paper.

PVA solutions resulted promising fibrous web at various concentrations therefore further investigations were performed using PVA-based systems.

3.2. Morphology of the electrospun poly(vinyl-alcohol) webs

The morphology of the electrospun products as a function of the concentration of the polymer solution was examined by SEM. Varying the concentration of PVA solution in course of the electrospinning process beaded-fibers were gained at 10 w/w% while at higher concentrations (15, 20%) fibers of different thickness were formed owing to the increased viscosity and higher entanglement of the polymer chains. The concentration of 20 w/w% was found to be optimal for getting stabile structure of discrete fibres (Figure 2).

The structure shown in Figure 2c was expected to be important both from the diffusion and dissolution point of view. The drug diffusion in solid polymer matrix and consequently its crystal-growing process can be hindered, keeping them in nanocrystal range, when the discrete fibers are obtained. (No three-dimensional diffusion can occur.) Concerning the dissolution it was expected that not only faster dissolution rate of nanocrystals, enclosed in the fibers, can be achieved (owing to the higher surface area), but the total solubility can be higher as well comparing to large particles. The chance for it is based on the enhanced angle of curvature of the fine fibers resulting in higher surface energy, which in turn modifies the equilibrium solubility. (The particle size effect on the solubility is significant in the nanorange, while above several microns it is negligible.) Enhanced solubility influences the bioavailability of the drug substantially.

Diameter of the fibers and the beads was determined by the aid of the software provided by the SEM analyzer. Particle size of the beads was around 1 μm (see in Figure 2a) and the diameter of the fibers was in the range of hundred nanometers.

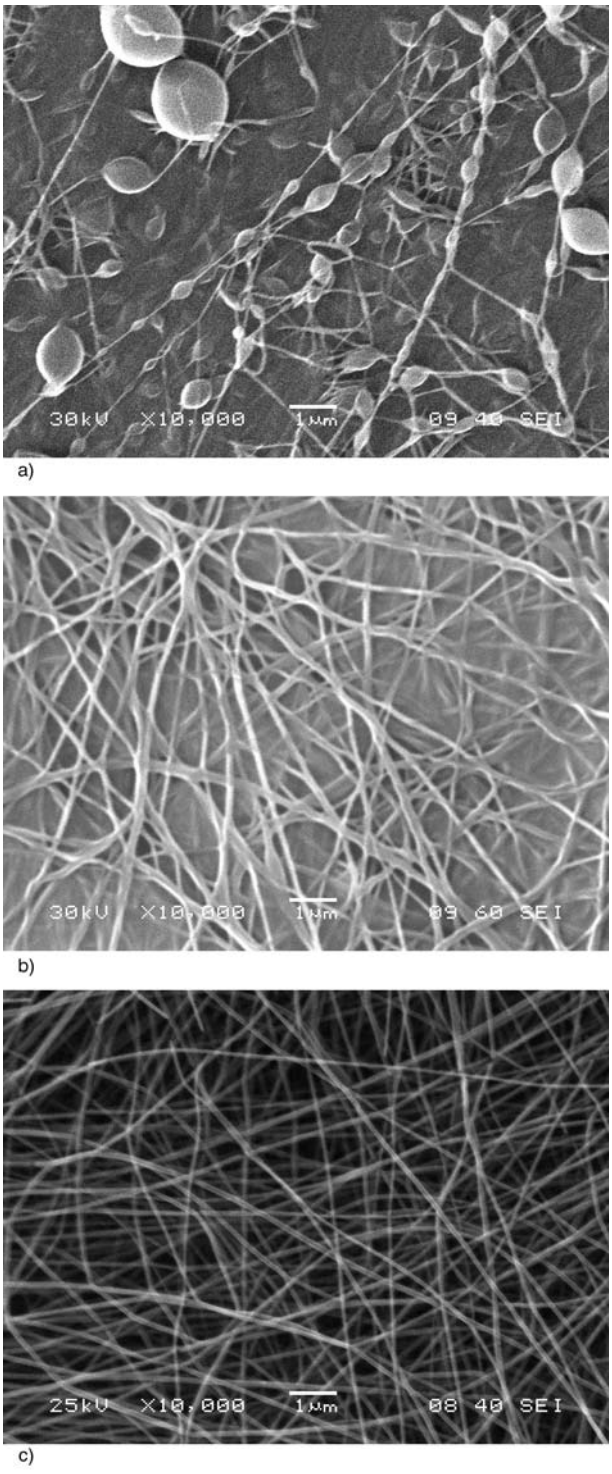

Figure 2. Scanning electron microscopic (SEM) images of PVA water solutions (magnification: 10 000×): a) PVA 10%, b) PVA 15%, c) PVA 20%

The mean fiber diameter of the electrospun PVA 20 w/w% solution was between 100–130 nm according to Figure 3. These very thin fibers have huge enough surface area to increase the dissolution rate significantly.

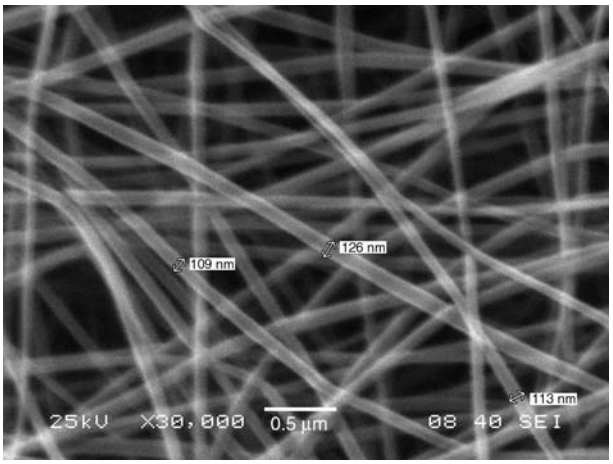

Figure 3. Scanning electron microscopic image of electrospun PVA 20% water solution (magnification 30 000×)

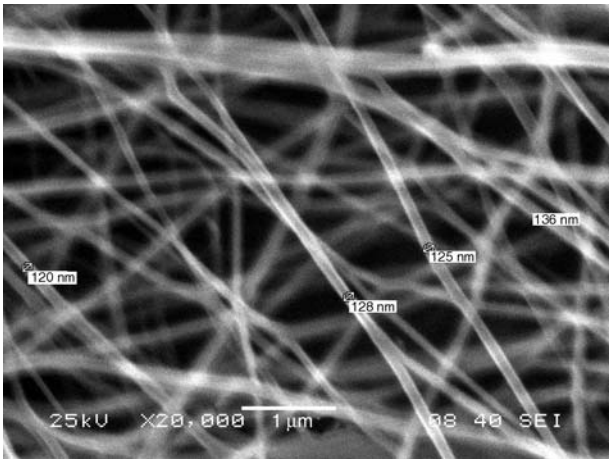

Figure 4. Scanning electron microscopic image of electrospun PVA:Do 5:1 (magnification 20 000×)

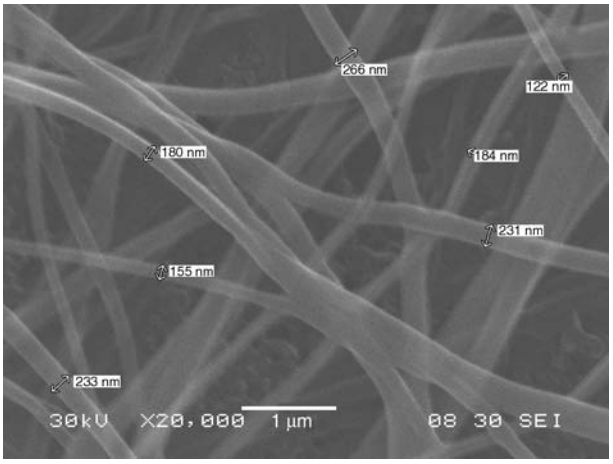

Figure 5. Scanning electron microscopic image of electrospun PVA:DO 2:1 (magnification 20 000×)

3.3. Morphology of the drug-containing electrospun fibers

Addition of Donepezil HCl (PVA:Do, 5:1) into the solution of PVA does not have significant effect on the technology and on the diameter. The mean diameter was between 100–150 nm (Figure 4). When the polymer drug ratio was increased up to 33 w/w% (PVA:Do, 2:1) the diameter of the electrospun fibers increased slightly, but it still not exceeding the 300 nm (Figure 5).

3.4. Rheology and conductivity of solutions

The entanglement of PVA chains depends on the PVA concentration of the aqueous solutions, which consequently determines its rheological behaviour during the electrospinning process. Addition 10 and 20 w/w% of PVA into water leads to 30 and 450 times higher viscosity respectively than the viscosity of pure water (Table 2). At low polymer concentration (≤10 w/w%) there is not enough entanglement between the polymer chains for increasing the viscosity and thus maintaining a uniform fiber stream that is the reason why beads or beaded fibers are formed during the electrostatic spinning [29]. Increased entanglement of PVA chains and consequently increased viscosity in the case of ~20 w/w% concentration results in stable fibrous morphology.

The viscosity of PVA 20% solution was not affected significantly by addition 4 w/w% Donepezil HCl and diameters of electrospun fibers did not changed noticeably. (Donepezil HCl of 4w/w% in the solution means (after the evaporation of water) ~16.7 w/w% in the solid electrospun product.) Increasing the Donepezil HCl concentration up to 10 w/w% in the PVA-water solution (33 w/w% in the solid product) leads to slightly increased viscosity and somewhat enlarged fiber thickness. It is concluded that the presence of the small Donepezil HCl molecules has a minor effect on the viscosity in this range of concentration.

However, the effect Donepezil HCl from the point of view of the conductivity is considerable. Addition of Donepezil HCl into the PVA solution increased the conductivity significantly as given in Table 2. Baumgarten [30] found that increasing of conductivity of the acrylic polymer solution decreased the diameter of fibers due to the stronger interaction between the solution and the electric field. However, according to our finding, the increased conductivity raised the viscosity of the solution slightly and the viscosity (and increased dry solid content) influenced the diameter of fibers

more significantly than the effect of increased conductivity.

3.5. Drug dissolution investigation

The prepared drug loaded samples of described morphology were considered promising for oral dissolution because of good water solubility of the applied fiber-forming polymer and the huge surface of the formed fibers. PVAs of high molecular weight were applied earlier in electrospinning for controlling and sustaining drug release through gel formation [31]. However, in this work the instant dissolution was the aim therefore PVA of low molecular weight (31 000 Da) was selected having moderate tendency for gel formation.

Figures 6 and 7 show the drug release profiles of electrospun webs, cast films with the same composition and commercial tablets. (Data of the samples from the two parallel electrospinning processes are represented in one plot because there were no significant differences between the samples collected from these processes.)

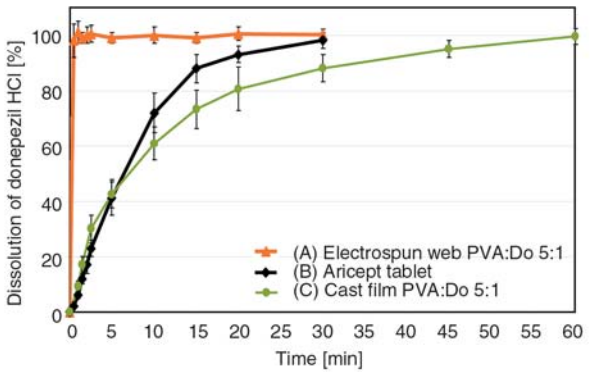

Figure 6. *In vitro* dissolution of Donepezil HCl (dose 10 mg, 900 ml distilled water, 50 rpm, 37°C): (A) Electrospun web of PVA-Do ratio 5:1 (n = 6), (B) Commercial Aricept tablet (dose 10 mg, n = 6), (C) Cast film of PVA-Do ratio 5:1 (n = 3)

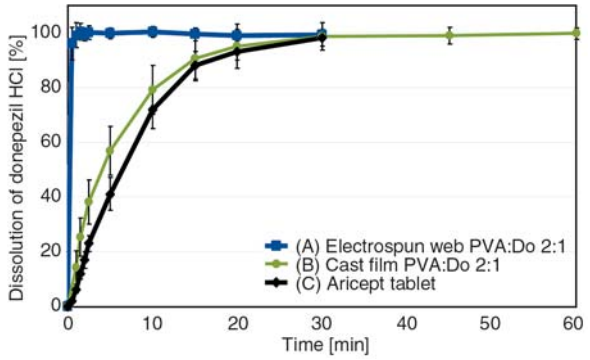

Figure 7. *In vitro* dissolution of Donepezil HCl (dose 10 mg, 900 ml distilled water, 50 rpm, 37°C): (A) Electrospun web of PVA-Do ratio 2:1 (n = 6), (B) Cast film of PVA-Do ratio 2:1 (n = 3), (C) Commercial Aricept tablet (dose 10 mg, n = 6)

The considerable difference between the rates of dissolution of different samples is well recognizable.

Dissolution of cast films was dependent of their drug content. Drug release of PVA:Do 2:1 cast films was significantly faster than that of PVA:Do 5:1. Probably Donepezil HCl as a small molecule with good water solubility can get easily into the solution phase, while PVA as a macromolecule dissolves slower if its long polymer chains are less plasticized by the drug molecules allowing larger extent of entanglement, inter- and intramolecular H-bonds. It means that PVA has retardant effect excepting the case when formation of extremely huge surface area decreases the value of bulk of entangled structure.

The electrospun webs, independently of their drug concentration, were dissolved immediately after immersion in dissolution media owing to the formed huge surface area. The correlation of surface area and dissolution rate, corresponding to the Noyes and Whitney equation [32], is described by Equation (1):

$$\frac{dC}{dt} = \frac{D \cdot A \cdot (C_s - C_t)}{h \cdot V} \tag{1}$$

where dC/dt is the dissolution rate, D, the diffusion coefficient, A, the surface area exposed to the dissolution media, h, the diffusion layer thickness, V, the volume of the dissolution media, C_s, the saturation solubility of the drug and C_t, the drug concentration at time t.

The equation shows that the dissolution rate is directly proportional to the surface area exposed to the dissolution media.

Modeling of oral dissolution of electrospun webs showed similar results as the standard USP II dissolution method. The disappearance time of the samples was 13±6 s, 11±4 s, 6±3 s for electrospun PVA placebo, electrospun PVA:Do 5:1 and electrospun PVA:Do 2:1, respectively. Time of disappearance increased slightly in the function of decreasing drug content but all electrospun samples fulfilled the requirement of fast dissolution (<30 s). *In vivo* assays were carried out using electrospun PVA placebo which had the longest dissolution

time of electrospun samples. The average disappearance time of the webs on the volunteers tongue was 9±6 s. The obtained results confirmed the possible applicability of electrospun PVA webs for oral dissolving dosage forms.

Electrospinning provides a very effective tool to increase the surface area and thus speed up the dissolution rate. Future perspectives of the way of administration of electrospun webs are considered quite wide. Owing to the variability of electrospinning process the physical properties of the electrospun web can be tailored to the requirements of certain applications. If it has proper physical behaviors (tensile strength, rigidity, … etc.) it can be used simply by cut out the area of adequate dosage from non-woven fabric produced. In all cases the uniform thickness of the web has to be ensured. Another possibility is application of a flat biocompatible solid carrier which can be the collector during the electrospinning. It can be conductive or non-conductive material as well. For demonstration PVA film (M_w = 31 000 Da) plasticized with polyethyleneglycol (PEG, M_w = 4000 Da) was used as collector during the electrospinning and the obtained double-layer structure was easy to handle and could be administered readily (Figure 8).

For industrial application of orally dissolving webs larger scale production has to be available. Scaling-up of electrospinning process is in the focus of several researches. Nowadays there are some promising systems available, such as Nanospider technology (Elmarco, Czech Republic). The 10 kg/day PVA web production capacity of this method means more than 100 000 units/day (if the dosage is 10 mg and one drug unit is 100 mg), which can fulfill the requirements of the pharmaceutical industry.

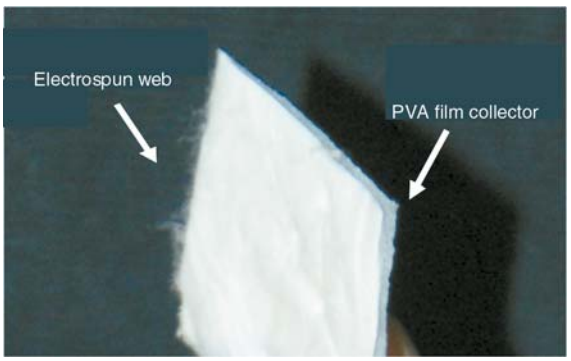

Figure 8. Image of nanofibrous web (PVA:Do 5:1) electrospun onto PVA film

4. Conclusions

Orally dissolving drug delivery systems have increasing attention in industrial and academic field too. Donepezil HCl, administered generally against Alzheimer's disease, was introduced into PVA solution and fabricated to nanofibers by electrospinning. Owing to the formed huge surface area the drug release was found immediate from the fibers. The developed method needs very low energy input and works at ambient temperature. This technology might be suitable for industrial scaling up owing to the recent rapid development of industrial electrospinning technology mainly in the textile and filtration industry [33]. The prepared PVA based nanofibrous orally dissolving web (ODW) formulation is a promising way for producing acceptable and effective dosage forms for children, older people, patients with dysphagia and so on.

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