Single and Multi-Layered Nanofibers for Rapid and Controlled Drug Delivery

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This paper introduces a new delivery system for rapid and controlled drug release. Mixture of hydrophilic, (poly vinyl alcohol, PVA, and randomly methylated β-cyclodextrin, RM β-CD), and hydrophobic (poly D,L-lactide, PLA, and poly D,L-lactide-co-glycoside, PLGA) polymers were electrospun to make a multi-layered/multi-component nanofiber mat. The release characteristics of the drug were modified using the layer by layer approach to help compensate the limitation of the individual materials. Incorporation of RM β-CD to the PVA solution was able to significantly decrease the degradation rate of the resulting fiber mat from a few weeks to a few seconds. Hydrophilic polymer mat (PVA-RM β-CD) can dissolve in the release media instantly and provide rapid release of the drug. This characteristic makes such carriers suitable as sublingual delivery systems in the treatment of acute disorders. Polyesters, PLA and PLGA, can control drug release *via* hydrolysis of the polymer and provide sustained and controlled release of the drug. Blends of these hydrophilic and hydrophobic polymers can effectively prolong drug release and decrease physiological toxicity resulting from fast release of drugs. These carriers may be suitable for the treatment of chronic disease where sustained release of the drug is required.

Key words nanofiber; drug delivery; poly D,L-lactide; poly D,L-lactide co-glycolide; randomly methylated β-cyclodextrin; poly vinyl alcohol

Polymeric drug delivery systems are able to improve therapeutic efficacy, reduce toxicity, and can be designed to control and prolong drug release by adjusting the degradation rate of the polymer.[1,2] Poly vinyl alcohol (PVA) is a biodegradable, hydrophilic polymer with distinct properties such as high degree of swelling, inherent non-toxicity and good biocompatibility.[3,4] Aliphatic polyesters such as poly (D,L-lactide) (PLA) and its copolymers with glycolic acid (PLGA) are biodegradable and biocompatible polymers with remarkably broad applications in sustained drug delivery.[5—7] Cyclodextrins (CDs) are a group of cyclic oligosaccharides. They are able to form inclusion complexes with lipophilic guest molecules which have been shown to improve aqueous solubility, dissolution rate and bioavailability of lipophilic drugs without decreasing the intrinsic ability of the lipophilic drug molecule to penetrate the biological membranes. Modified CDs, such as randomly methylated β-cyclodextrin (RM β-CD) have gained increasing popularity due to its improved water solubility and less toxicity as compared with the natural β-cyclodextrin.[8—10]

One of the approaches for modulating the release of drugs from a delivery system and changing the release kinetics over a period of time is to use blends of hydrophilic and hydrophobic polymers.[11]

Electrospinning utilizes high voltage source to produce nanoscale and microscale polymeric fibers with high surface area-to-volume ratio and porosity.[1,12,13] When the electrostatic charge exceeds the surface tension of the solution, the fiber jet travels from the syringe nozzle to the electrically charged ground collector and allows the solvent to evaporate, thus leading to the deposition of the non-woven solid polymer fiber on the surface of the metallic target collector. Multi-layered nanofiber mat is obtained by sequentially electrospinning the second polymer solution on the same target collector as the first polymer. This strategy helps to compensate the limitation of the individual polymers while the inherent advantage of both the polymers can be obtained in a single fiber mat.[14—17]

The aim of this work is the preparation of haloperidol loaded nanofiber *via* electrospinning of hydrophobic, PLA and PLGA, and hydrophilic polymers, PVA and RM β-CD. We intend to demonstrate that multi-component/multilayered polymeric mixture influence the physical and biological properties of electrospun fibers. The nanofiber morphology, structure, diameter of the polymeric nanofiber mats were investigated by field emission scanning electron microscopy (FESEM), and fourier transform infrared (FT-IR) measurements. The release characteristics of haloperidol from the drug-loaded fiber mats were investigated.

Experimental

Materials PLA (R 203H with inherent viscosity of 0.34 dl/g), PLGA (73 : 27 and 48 : 52) RG 503, RG 755S with inherent viscosity of 0.63 dl/g and 0.52 dl/g were a kind gift from Boehringer Ingelheim (Ingelheim, Germany). PVA Mw 70000—100000 and haloperidol were purchased from Sigma. RM β-CD (degree of substitution of about 1.8) was a gift from Wacker (Burghausen, Germany). All other reagents used were of analytical grade.

Electrospinning A weighed amount of PVA was dissolved in water to obtain 10% w/w solution, RM β-CD powder was added to the solution to obtain 0.5 M concentration. PLA, PLGA (48 : 52) and PLGA (72 : 28) solutions were prepared by dissolving the polymers in acetone at concentration of 35% w/w, 30% w/w and 30% w/w respectively. Haloperidol was kept at 2 mg/ml for all formulations as shown in Table 1.

Electrospinning was carried out using an adjustable DC power supply (RP50-1.25R/230DDPM, Gamma high voltage Research, U.S.A.) and a syringe pump (KD-100, KD scientific, Inc., U.S.A.) on which a 3 ml syringe was connected to a blunt gauge 26 stainless steel needle. A fixed voltage of 15 kV was applied across a distance of 15 cm between the tip of the syringe and the fiber collector. A constant flow rate of 2 ml/h was applied to all formulations. The depositions were performed at room temperature. Multi-layered fiber mats were obtained by fabricating the first polymer solution to form its individual layer and then the second polymer was electrospun on the same target collector as the first polymer (Fig. 1). The non-woven fabric was removed from the collector and was vacuum dried for a week at room temperature to remove residual solvent prior to usage.

Field Emission Scanning Electron Microscopy (FESEM) Electrospun fibers were sputter coated with platinum in an argon atmosphere using a sputter coater unit Jeol JFC-1600. The surface topography of the electrospun

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Table 1. Nanofiber Formulations

Formulation	Ingredients (% w/v)				
	PVA	RM β-CD	PLA	PLGA 48 : 52	PLGA 73 : 27
PVA	10	—	—	—	—
PVA-RM β-CD	10	50	—	—	—
PLA	—	—	35	—	—
PLGA 48 : 52	—	—	—	30	—
PLGA 73 : 27	—	—	—	—	30
PVA-RM β-CD+PLA	10	50	35	—	—
PVA-RM β-CD+PLGA 48 : 52	10	50	—	30	—
PVA-RM β-CD+PLGA 73 : 27	10	50	—	—	30

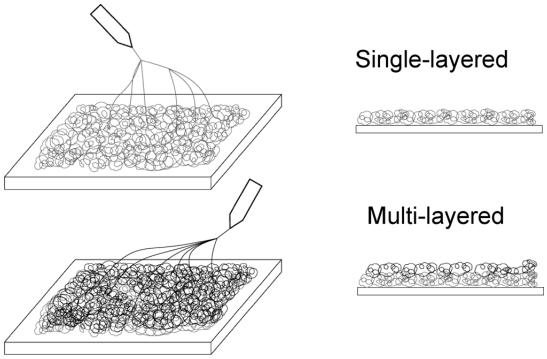

Fig. 1. Schematic Presentation of Single-Layered and Multi-Layered Nanofibers

fibers was assessed using a FESEM (Jeol JSM-6701F). Platinum-coated fibers were placed in the microscope chamber to which a high vacuum was applied. Surface morphological features were obtained in 5 kV accelerating voltage.

HPLC Analysis Haloperidol concentrations were quantified by HPLC from Agilent HP. The analysis was carried out using an Agilent column (5 μm, 4.6 mm×150 mm). Mobile phase was a 50 : 50 volume ratio of acetonitrile and 0.05 M phosphate buffer adjusted to pH 3 using phosphoric acid, flowing at a rate of 1 ml/min. UV detection at wave length 254 nm, injection volume 20 μl gave a retention time of 6 min. Standard solutions of (0.05—2 μg/ml) were prepared in aqueous solutions containing 0.03% w/v lactic acid.

Fourier Transform Infrared Measurements (FT-IR) FT-IR spectra of the polymeric nanofiber mats were taken with a Perkin Elmer (Spectrum 100) in the wavelength region 500—4000 cm^{-1} at room temperature. Samples were placed on KBr holder and mounted in the enclosed sample chamber, away from moisture to get their spectra.

Drug Release Profile Release studies were carried out in phosphate buffer saline pH 7.4 (PBS) solutions. Samples of the non-woven nanofibers (10 mg) were put in 15 ml plastic tubes and 10 ml release medium was added. The tubes were constantly moved at a speed of 75 rpm at 37 °C. At particular time interval, 1 ml samples were taken and an equal volume of fresh PBS was immediately added after each sampling. The amount of released haloperidol was determined *via* HPLC method.

Results and Discussion

Characterization of Nanofiber Figure 2 shows the FESEM image of the electrospun polymer fibers and a micrographic image of a typical nanofiber mat. The influence of the polymer type on the morphology of the resulting fibers was examined. All formulations presented a bead-free nanofibrous structure with wide ranges of fiber diameters. Haloperidol was encapsulated within the entire non-woven fiber mat and the FESEM images did not show any drug crystals. The large surface area of the fibers results in fast evaporation of the organic solvent which minimized the possibility of drug crystallization.[12)]

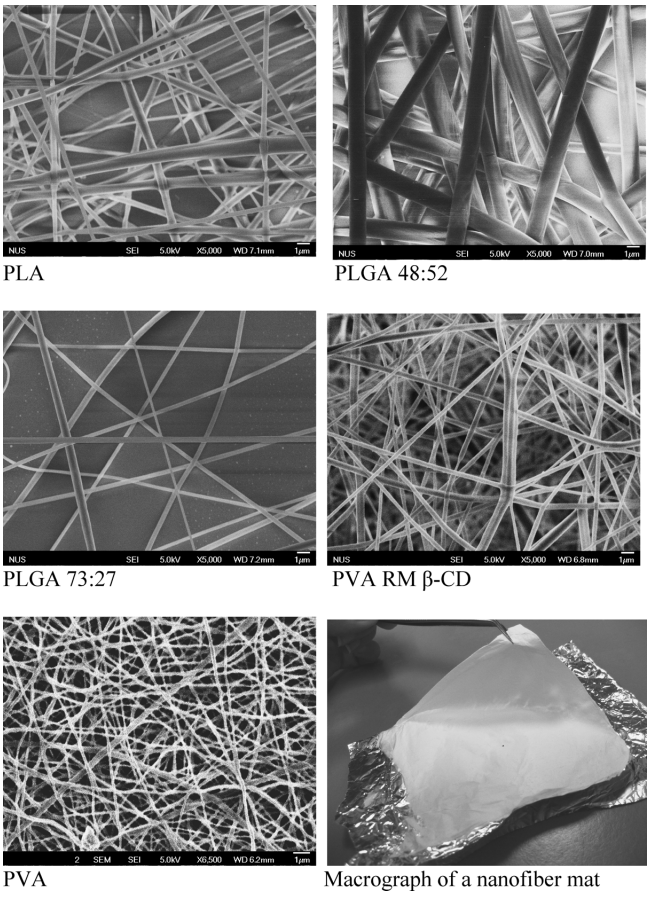

Fig. 2. FESEM Images of Single-Layered Haloperidol-Loaded Nanofibers and a Macrographic Image of a Typical Nanofiber Mat

FT-IR Studies FT-IR analysis was performed on PVA, PVA-RM β-CD, PLA and PLGA and the multilayered fiber mats (Fig. 3). From the FT-IR spectra of PLA and PLGA 48 : 52 and 73 : 27, it was observed that the C=O and C–O–C stretching peaks were detected at 1747 and 1090 cm^{-1} respectively. A peak at 1450 cm^{-1} is due to C–H stretching in methyl groups. It is known that the FT-IR peaks of PLA and PLGA are very similar with only some changes in the intensity of the C–O–C peaks.[18,19)]

For pure PVA, a broad band around 3336 cm^{-1} is attributed to the O–H stretching vibration of the hydroxyl group. The vibrational bands at 2942 and 1438 cm^{-1} represent the –CH stretching. The sharp peak band at 1095 cm^{-1} corre-

sponds to C–O–C symmetrical stretching present on the PVA backbone. There is a decline in the intensity of the –OH band when PVA is mixed with RM β-CD. It is clear that hydrogen abstraction occurred from PVA molecule in the presence of RM β-CD. Hydroxyl groups of the CD molecule oriented on the exterior of its cavity can easily form hydrogen bond with –OH groups of PVA.[20—22] This hydrogen bonding between CD and PVA may be responsible for the increased water solubility of the resulting fibers. FT-IR spectra for multi-layered fiber mats (Figs. 3c—e) show that the main characteristic absorption peaks of all the polymers appear at the same position which indicates that PVA, RM β-CD and PLA or PLGA are probably present in the resulting polymeric network formed.

***In Vitro* Drug Release** The release characteristics were carried out in phosphate buffer saline. The cumulative amount of the drug released from the drug-loaded fibers is illustrated in Fig. 4. Total drug content was determined prior to the release studies to calculate the release percentage of the actual haloperidol content of each fiber matrix.

Haloperidol release from PVA fibers was low, however PVA and RM β-CD electrospun fibers showed an immediate drug release as the fibers were rapidly dissolved within a few seconds upon contact with the aqueous medium. PVA dissolves in water at temperatures above 90 °C. Electrospun fibers of PVA have a disintegration time of a few weeks.[3] Results show that the addition of RM β-CD significantly decreased the disintegration time of the electrospun polymer from a few weeks to a few seconds. The increase in the solubility could be due to the formation of a hydrogen bond between PVA and RM β-CD as detected by the FT-IR spectra and 1 : 1 haloperidol–RM β-CD inclusion complex.[23]

In contrast, the PLA and PLGA fiber mat yielded a pronounced prolongation of drug release. Continuous controlled release of the drug was observed from fibers containing PLA or PLGA. The release of haloperidol from polyesters depends on their molecular weights, degree of crystallinity, glass transition temperature (T_g) and the ratio of glycolide to lactide of the polyesters. The glycolide unit can accelerate the degradation rate of the matrix and thus increase the drug release rate.[24]

From Fig. 4 it can be seen that PLA nanofiber mat had a lower drug release rate when compared to PLGA 73 : 27 and 48 : 52. This may be due to the slower degradation rate of the lactide unit when compared to glycoside. A stepwise drug release pattern was observed from PLGA 73 : 27 and 48 : 52, which may be due to the degradation of the glycoside unit followed by the lactide unit.

Multi-layered fiber mat containing both hydrophilic and hydrophobic polymers was able to provide an initial burst release to obtain the initial desired concentration of the drug followed by a degradation-dependent release from the fiber.

When used separately, PVA and RM β-CD fiber mats can be used in the treatment of acute disorders such as anaphylaxis and angina pectoris where the rapidly dissolved drug should immediately be absorbed in the systemic circulation from the buccal cavity before being swallowed by the patient.[25] Hydrophobic polymer mats can be used for the formulation with controlled release applications where prolonged action is required for the treatment of chronic diseases.

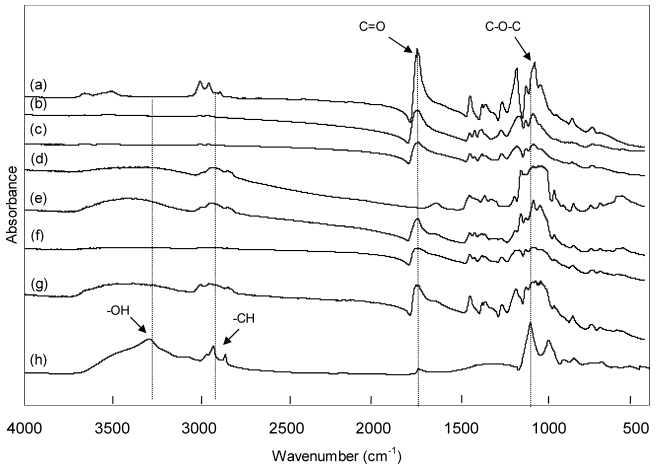

Fig. 3. FT-IR Spectra of (a) PLA, (b) PLGA 48 : 52, (c) PLGA 73 : 27, (d) PVA RM β-CD, (e) PVA RM β-CD and PLGA 48 : 52 (f) PVA RM β-CD and PLGA 73 : 27 (g) PVA RM β-CD and PLA, (h) PVA Nanofibers

Conclusion

The incorporation and sustained release of haloperidol from multilayered nanofibrous scaffolds were achieved without the loss of structure and bioactivity of the polymers. The release of haloperidol was shown to be affected by the hydrophilicity of the polymers, and we were able to modify the release profiles by blends of hydrophilic and hydrophobic polymers. Through this investigation we observed that

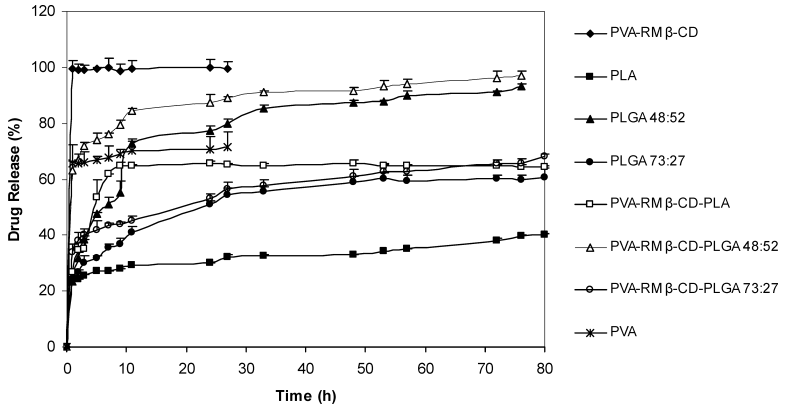

Fig. 4. *In Vitro* Release Profile of Haloperidol from Electrospun Fiber Mat in Phosphate Buffer Saline (pH 7.4) at Body Temperature (37 °C)

nanofibers may be suitable carriers for drug delivery. These polymeric nanofibers are easy to produce, do not require many excipients, sophisticated equipment nor time consuming techniques, as well as can be used to formulate products containing heat sensitive and low water soluble drugs.

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