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Expert Review

Electrospun Nanofibers in Oral Drug Delivery

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Abstract. In order to enhance the delivery of drugs with limited absorption due to poor solubility/dissolution, approaches are being developed to improve the dissolution rates and solubility of drug molecules. These approaches include identification of water-soluble salts of parent drugs, preparation of stable amorphous drug formulations, inclusion of solubility-enhancing agents in the dosage form, and particle size reduction. Technologies to reduce drug particle size to sub-micrometer range are being applied to product development more frequently. Electrospinning is being considered as one of the technologies which can produce nanosized drugs incorporated in polymeric nanofibers. *In vitro* and *in vivo* studies have demonstrated that the release rates of drugs from these nanofiber formulations are enhanced compared to those from original drug substance. This technology has the potential to be used for enhancing the oral delivery of poorly soluble drugs.

KEY WORDS: bioavailability; drug delivery; electrospinning; nanofiber; solubility.

INTRODUCTION

With the advent of combinatorial chemistry and high throughput screening, a great majority of the drug candidates selected for development are highly hydrophobic, exhibiting poor or negligible water solubility. As a result, the oral absorption of these drugs is often limited by their poor solubility or slow dissolution in the human gastrointestinal contents (1). In order to enhance the oral absorption of such poorly water-soluble drugs by increasing their dissolution rates, several formulation strategies, such as salt formation (2), complexation (3), particle size reduction (4), prodrug (5), micellization (6), and solid dispersions (7), are being extensively studied in the pharmaceutical industry.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size (8). Consequently, methods of making finely divided drugs have been studied, and efforts have been made to control the size and size distribution of drug particles in pharmaceutical compositions. Wet milling is the preferred method to produce sub-micron particles. Motoyama *et al.* (9) described a solid drug pulverized in an aqueous solution of a water-soluble high molecular weight polymer using a wet grinding machine, resulting in the formation of finely divided drug particles ranging from 500 nm or less to 5 microns in diameter. Liversidge *et al.* (10–12) improved the wet milling process to produce free flowing crystalline drug substances having particle sizes lower than 400 nm. This wet milling technology (Nanocrystal® of Elan Pharmaceuticals) was successfully applied for enhancing the oral bioavailability of several products, including Sirolimus, which is marketed by Wyeth as Rapamune®, Tricor® from Abbott, Megace® ES from Par Pharmaceutical, and Emend® from Merck.

Rapamune®, Tricor®, and Megace® ES (13,14) are reformulations of existing products as nanoparticulate drug formulations for various reasons. In the case of Rapamune®, the original formulation was an oral suspension which required storage under refrigerated conditions and reconstitution using a syringe for dosing accuracy. Nanoparticulate reformulation with enhanced oral bioavailability facilitiated the switch from an oral suspension to a simple tablet, thereby improving patient compliance, convenience and acceptability. Megesterol acetate, which is a poorly water-soluble compound, was administered as an oral suspension. This oral suspension was a thick viscous liquid that was difficult to swallow. It had to be taken with food, and for patients with little or no appetite, having to take with food was a significant problem. Moreover, the patient had to take 24 mL as a daily dose. By applying the Nanocrystal technology, the exposure was increased requiring a much lower dose, 5 mL as opposed to 24 mL. Moreover, the Nanocrystal formulation minimized the Fed/Fast variability, thereby removing the "to be administered with food" product label. This much-improved Nanocrystal formulation of megesterol acetate is marketed as Megace® ES. For fenofibrate, the reformulation as Nanocrystal formulation (TriCor®) allowed more flexible dosing regime and reduced the Fed/Fast variability.

Another approach for improving dissolution rate is based on polymer-drug solid dispersions (7,15). Solid dispersions may be defined as the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state

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prepared either by the melting method, the solvent method or the melting-solvent method. Solid dispersions are classified into five major categories: (1) simple eutectic mixtures (2) solid solutions, (3) glass solutions of suspensions, (4) amorphous precipitation of a drug in a crystalline carrier, and (5) any combination of these groups. Two currently used methods of forming solid dispersions are fusion and solvent methods. In the fusion method, the drug and the carrier are melted to above either the melting (softening) point of the higher melting (softening) component or, in some cases, to above the melting point of the lower melting component, provided the other non-melted component has good solubility in the former. The fused mixture is rapidly quenched and pulverized to produce free flowing powders for capsule filling or tabletting. The fusion process requires both the drug and exicipient to be thermally stable at the processing temperature. In the solvent method, the drug and carrier are dissolved in one or more miscible organic solvents to form a solution. Removal of the organic solvent(s) is accomplished by any one or a combination of methods, such as solvent evaporation, precipitation by a non-solvent, freeze drying, spray drying, and spray congealing. Among the several drawbacks of the solvent method are use of large volumes of organic solvents, presence of residual organic solvents in the resultant formulation, and collection, recycling and/or disposal of organic solvents.

Solid dispersions of poorly soluble drugs prepared by both the fusion and solvent methods usually exhibit higher dissolution rates than their crystalline counterpart (7). However, the dissolution rate of the drug may potentially be hindered by dissolution of the carrier, usually a high molecular weight polymer. Therefore, solid dispersions are usually prepared from low or moderate molecular weight polymers.

Electrospinning, also referred to as electrostatic spinning, is a process of producing fibers with diameters in the range of 100 nm (16). The process consists of applying a high voltage direct current to a polymer solution or melt to produce a polymer jet. As the jet travels in air, the jet is elongated under repulsive electrostatic force to produce nanofibers. This process has been described in literature since the 1930s (17).

A variety of polymers, both natural and synthetic, have been electrospun under appropriate conditions to produce nanofibers (18). Different applications have been suggested for these electrospun nanofibers, such as air filters, molecular composites, vascular grafts, wound dressings and scaffolds for tissue engineering (19).

Our interest (20,21) in electrospinning stems from its ability to produce nanoparticulate drug-embedded nanofibers which can enhance the dissolution rate of drugs with poor water solubility. Electrospinning of solutions of drugs in polymers is expected to generate nanofibers having very large surface area. This extremely high surface area has profound influence on the bioavailability of a poorly soluble drug, since it is known that the increased surface area can lead to increased dissolution rate. A suitable dosage form, such as oral or parenteral, including aerosols, may be designed by judicious selection of polymeric carriers in terms of their physico-chemical properties as well as their regulatory status. Other pharmaceutically acceptable excipients may be included to ameliorate the stabilization and/or de-agglomeration of the drug nanoparticles. Electrospun pharmaceutical dosage forms may be designed to provide rapid, immediate, delayed, or modified dissolution, with sustained and /or pulsatile release characteristics.

Since the filing of patent applications (20,21) by GlaxoSmithKline (GSK), Verreck *et al.* have reported the application of electrospinning to oral and transdermal delivery of poorly soluble drugs (22,23). In their first report, Verreck *et al.* reported on the electrospinning of itraconazole, a poorly soluble drug, in combination with hydroxypropylmethylcellulose (HPMC), from dichloromethane/ethanol solutions (22). Characterization of these nanofibers by differential scanning calorimeter (DSC) showed the drug to be present in the amorphous form. Moreover, *in vitro* release of itraconazole from the nanofibers was found to be dependent on the drug/polymer ratio and fiber diameter. In a second report (23), Verreck *et al.* described the electrospinning of itraconazole and ketanserin in a non-biodegradable matrix, such as segmented polyurethane, so as to improve the transdermal delivery of these poorly soluble drugs. It was shown that these two drugs exist in the amorphous state in the polyurethane nanofibers. The rate of drug release from the nanofibers depended on the drug/polymer ratio. Since these initial publications, there have been several reports on electrospun fibers containing drugs (24).

This review focuses on the evaluation of electrospinning technology undertaken at GSK with various poorly soluble drug/polymer combinations. It is to be recognized at the very outset that in order to obtain nanoparticulate drug-laden polymer nanofibers, it is imperative that electrospinning be carried out from a homogeneous solution. This homogeneous solution of the drug in a polymer can be produced either in melt- or solvent-(s)-based solution. For a melt-based system, the drug has to exhibit good thermal stability by itself and in the polymer matrix at the processing conditions. For a solvent-based system, it is desirable that the polymer of choice be soluble in the same organic solvent as the drug, or in another miscible organic solvent. As the drug substance is electrospun from polymer-based homogeneous solutions, one has to be concerned about the crystallinity, degree of crystallinity, and polymorphism of the drug. Despite these considerations, it would be interesting to evaluate this novel and emerging technology to address pharmaceutical problems, as this is a low energy-intensive technology.

Among the various combinations studied, this review focuses on three different poorly soluble drugs, electrospun from solvent-based solutions of two types of polymers: semi-crystalline and amorphous. This review demonstrates how the drug morphology can be manipulated in the electrospun fibers by the proper selection of drug/polymer combinations:

1) First example describes the electrospinning of nabumetone/polyethylene oxide combination wherein the drug loading was systematically increased, and the effect of drug loading on the morphology of the electrospun fibers was studied.
2) Second example demonstrates how the selection of the polymer matrix can influence the morphology of another poorly soluble drug, Compound I.
3) Third example discusses the electrospinning of Compound II with a pH-sensitive polymer to produce a targeted drug release system.

ELECTROSPINNING OF DRUGS USING A SEMI-CRYSTALLINE POLYMER

High molecular weight polyethylene oxide is a water-soluble polymer commonly used by the pharmaceutical industry for the preparation of oral controlled-release formulations. It is a semi-crystalline polymer, which has a crystalline melting point at 60°C and a glass transition temperature (Tg) at −70°C. It is commercially available from Dow Chemicals under the trade name POLYOX, with various molecular weights ranging from 100 K to 7,000 K exhibiting increasing viscosities. Selection of POLYOX with appropriate molecular weight is important both in terms of electrospinning as well as for the release of the drugs from the electrospun fibers.

Nabumetone is a non-acidic, non-steroidal, anti-inflammatory drug (NSAID) marketed by GSK under the trade name Relafen®. Nabumetone is a prodrug (see Fig. 1 for chemical structure) which is metabolized to the active form (6 methoxy-2-naphylacetic acid) following absorption. This active metabolite has a mean terminal half-life of approximately 24 h, allowing once daily dosing. However, nabumetone has poor solubility in water. This poor solubility and the consequent reduction in absorption rate is claimed to be responsible for the slow onset of action of nabumetone in humans (25). It was hypothesized that the absorption rate of nabumetone could be improved by reducing the particle size.

Electrospinning is being evaluated as a viable alternative to the wet milling process which is currently used for producing nanoparticulate suspensions of poorly soluble drugs. During the wet milling process, the crystalline drug is usually suspended in an aqueous solution of polymeric carrier in the presence of a surfactant (26). In contrast, a homogenous solution of the poorly soluble drug/polymer in a suitable solvent is required for producing nanoparticulate drug-embedded polymer nanofiber by the electrospinning process. Accordingly, a homogenous solution of nabumetone/POLYOX prepared in a mixture of acetonitrile and water is used. This solution was transferred to a 25 mL glass vessel (Fig. 2) with a 0.03 mm capillary outlet at the bottom and two inlets, one was for applying a positive Helium pressure and the other for introducing the electrode which was connected to the positive terminal of a high voltage power supply (ModelD-ES30P/M692, Gamma High Voltage Research Inc. FL). The ground from the high voltage power supply was connected to a drum, covered with aluminum foil, an rotated at speed of 50–60 rpm. The solution was continuously fed to the orifice of the capillary tube by adjusting the pressure of Helium gas applied on the vessel through one of the openings in the round-bottom flask. The selection of the capillary diameter, the pressure of the helium gas, the applied voltage and the distance of the collection drum from the tip of the capillary were carefully adjusted to facilitate continuous formation and deposition of the fibers, without the formation of large droplets of the solution, which might simply fall off.

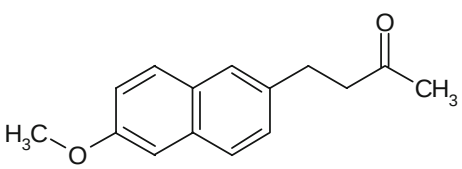

Fig. 1. Structure of nabumetone.

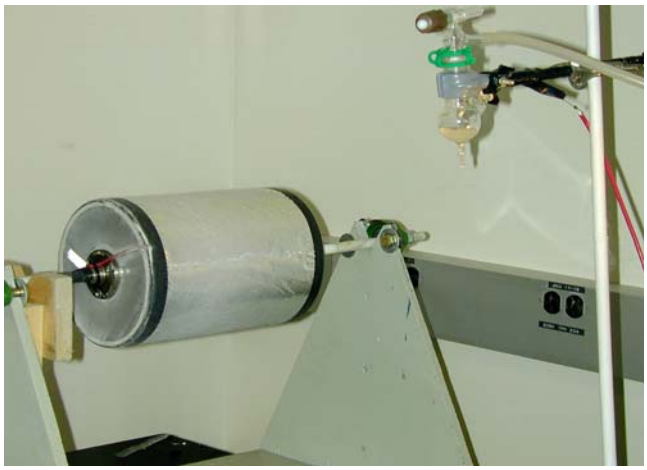

Fig. 2. Laboratory set up for electrospinning.

As shown in Table I, POLYOX solutions containing up to 84% of nabumetone were electrospun by selecting higher molecular weight polymer, thereby compensating for the decreased viscosity resulting from the higher drug content. It was found that POLYOX WSRN 3000, having a molecular weight of 400 K, was appropriate for producing nanofibers containing nabumetone incorporated up to 61%, whereas for higher nabumetone content, POLYOX WSR-1105, which has a molecular weight of 900 K, was the most suitable polymer matrix. In addition to drugs, other additives, such as surfactants, were also included in the medium for electrospining. Tween 80, Sodium dodecyl sulfate (SDS), Pluronic F68 and Vitamin E-TPGS (TPGS) were among the various surfactants used.

Fiber Morphology by SEM

The morphology of the electrospun fibers was studied using a Hitachi S/3500N electron microscope without gold coating. Electrospun POLYOX (Fig. 3A) had a uniform distribution of nanofibers with fiber diameter in the order of 100–300 nm.

When POLYOX was electrospun in the presence of 36% (w/w) nabumetone and other excipients, the fibers became heterogeneous, and diameter of the fibers increased up to 2 microns (Fig. 3B). As the drug content was further increased to about 74%, the fiber diameter was about 2–4 microns, and the fiber exhibited a morphology which suggested the presence of drug crystals on the fibers (Fig. 3C).

Thermal Properties

Nabumetone is a crystalline drug, which, when examined by modulated differential scanning calorimeter (MDSC), exhibited a melting endotherm at 79.6°C with an associated enthalpy of 135.5 J/g. A typical thermogram of electrospun fibers of POLYOX containing 79% (w/w) nabumetone is shown in Fig. 4. It exhibited two distinct melting endotherms at 48.1 and 73.5°C.

Table II summarizes the thermal behavior of a series of POLYOX fibers containing 29 to 84% (w/w) of nabumetone. The melting point of the first endotherm varied from 48–58°C based on the nanofiber composition, while the enthalpies

Table I. Compositions for Electrospinning of Nabumetone

Expt. #	Nabumetone content		POLYOX		Surfactant		Yield (g)
	Initial [a] (g)	Final [b] (%)	Type	Weight (g)	Type	Quantity	
1	0.5	29.0	400 K	1.5	Tween 80	0.1 mL	ND [c]
2	0.8	30.1	400 K	1.5	Tween 80	0.2 mL	2.2
3	0.8	35.9	400 K	0.75	Tween 80	0.2 mL	1.2
4	1.2	52.1	400 K	0.75	Tween 80	0.2 mL	1.2
5	0.9	61.3	WSR N-3000	0.3	Tween 80	0.1 mL	0.9
6	2.0	82.8	WSR-1105	0.4	SDS	0.1 g	2.1
7	2.0	84.4	WSR-1105	0.4	Pluronic	0.05 g	2.1
8	2.0	81.2	WSR-1105	0.4	TPGS	0.1 g	2.0

[a] present in the electrospinning medium
[b] present in the fibers, as determined by HPLC
[c] not determined

associated with this endotherm increased with POLYOX content. Therefore, this first endotherm can be attributed to the melting of POLYOX. This was further confirmed by performing the MDSC of POLYOX under identical conditions. POLYOX had a melting transition at 62°C with an enthalpy of 169.1 J/g. The second endotherm for formulations with high nabumetone content (84%) was at 75.3°C, with an associated enthalpy of 82.6 J/g. As the nabumetone content decreased to 35.9%, the melting point decreased to 64°C. Below 35.9% of nabumetone, this melting endotherm disappeared completely. Therefore, the second melting endotherm can be attributed to the presence of crystalline nabumetone present in the nanofibers. All nanofiber compositions containing less than 35.9% nabumetone exhibited a single melting endotherm. This may be either due to the formation of an eutectic mixture of POLYOX and nabumetone at some composition below 35.9% of nabumetone or due to the formation of an amorphous state during electrospinning.

The depression in the melting point of nabumetone with increasing POLYOX concentration is suggestive of a good drug/polymer miscibility, which is facilitated by the lower melting point (62°C) of POLYOX compared to nabumetone (79.6°C). Therefore, while nabumetone undergoes melting, it forms a miscible blend with the liquid polymer. A similar depression of the melting point has been reported for solid dispersions containing griseofulvin or tolbutamide with polyethylene glycol (27). Marsac *et al*. (28) observed significant melting point depressions in the cases of nifedipine or felodipine when prepared as solid dispersions with polyvinylpyrrolidone. Although the extent of depression depends on the volume fraction of the polymer, it may not be linear at all concentrations, due to the concentration dependence of the interaction parameter. This melting point depression for crystalline drug/polymer systems was theoretically explained using the Flory-Huggins theory.

In Vitro Drug Release

The *in vitro* dissolution of electrospun fibers containing various levels of nabumetone was studied using a modified USP 4 dissolution system. This system consisted of a stirred small volume cell through which water (dissolution medium) was pumped at 5 mL/min for a duration of 40 min. An in-line UV detector analyzed the dissolved nabumetone in the medium, while the undissolved material was retained in the cell using a 220 nm filter. The whole system was maintained in a thermostated chamber set at 37°C.

The raw dissolution profiles obtained were normalized with respect to nanoparticulate nabumetone produced by a wet bead milling technique (26). Fig. 5 compares the normalized dissolution profiles of various electrospun fibers to the unmilled nabumetone as well as nanoparticulate nabumetone. As expected, the unmilled nabumetone exhibited slow dissolution rate, with less than 10% of the drug dissolved in 40 min. The electrospun material had relatively faster dissolution rate than the nanoparticulate material.

Even though the average diameter of the electrospun fibers containing 80% nabumetone was 4 microns, these fibers had slightly higher dissolution profiles compared to the nanoparticulate drug. This unexpected high dissolution rate might be due to the presence of various surfactants in the fibers. Therefore, the influence of various surfactants, such as sodium dodecylsulfate, Pluronic F68, Tween 80 and TPGS, on electrospinning, as well as the dissolution of the resultant fibers, was studied. Electrospinning studies showed that the presence of various surfactants did not adversely affect fiber formation or fiber characteristics.

Among all the surfactants studied, TPGS provided the fastest dissolution rate for nabumetone. In order to ascertain whether the superior dissolution profile observed in TPGS containing electrospun fibers was truly due to electrospinning, a non-electrospun formulation containing TPGS, nabumetone and POLYOX was prepared and evaluated. As seen in Fig. 5, the dissolution profile of this formulation is similar to that of the unmilled material, thereby attesting to the fact that the enhanced dissolution rates observed were due to electrospinning.

ELECTROSPINNING OF DRUGS USING AMORPHOUS POLYMERS

Among the various polymeric excipients (29) present in FDA-approved oral formulations, synthetic polymers are attractive, since they have well-defined molecular weights and hence physico-chemical characteristics. POLYOX, poly-

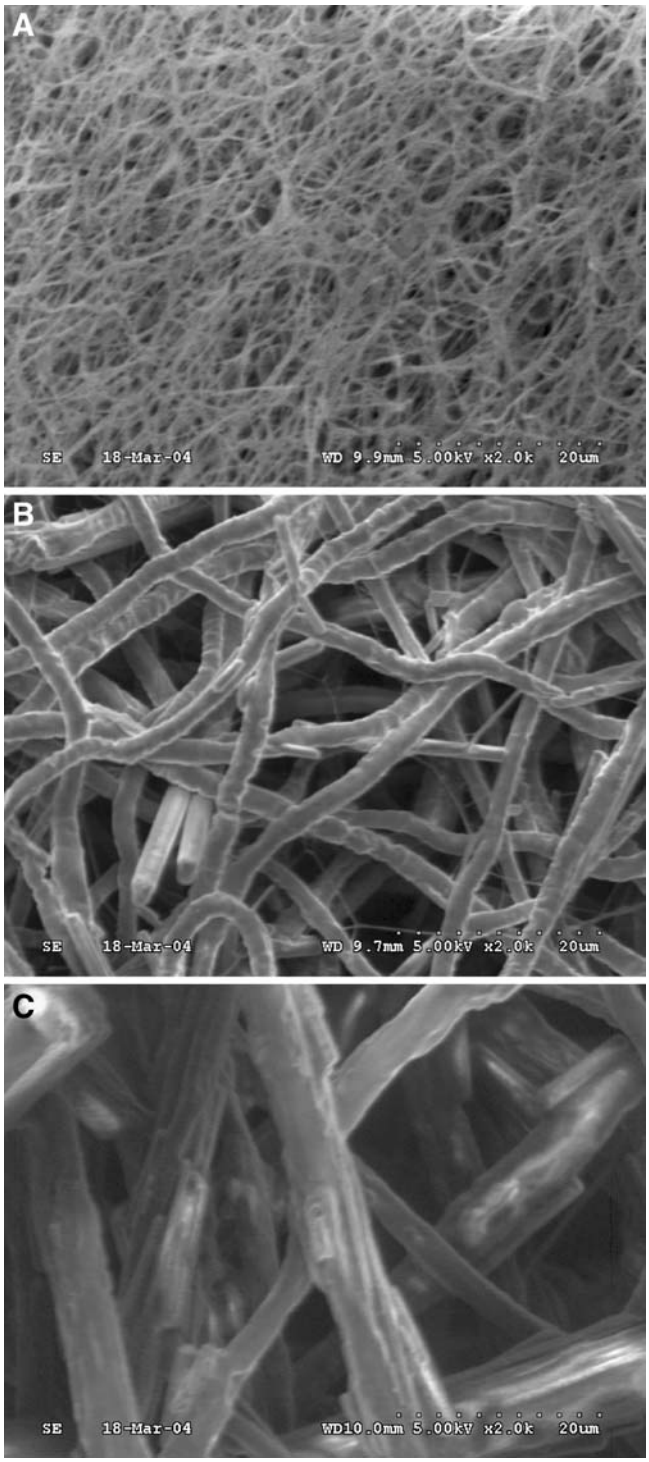

Fig. 3. SEM of (**A**) electrospun POLYOX, (**B**) and (**C**) electrospun POLYOX containing 36% and 74% nabumetone respectively.

vinylpyrrolidone (PVP), polyvinylpyrrolidone-co-polyvinylacetate (PVP-co-PVAc), polyvinylalcohol (PVA), and methacrylic acid esters are examples of such pharmaceutically acceptable synthetic polymers. Except for POLYOX, other polymers are amorphous in nature. PVP and its copolymer with polyvinylacetate are frequently used in pharmaceutical formulations for the preparation of solid dispersions containing amorphous drug (30). Drugs in the amorphous state are known to exhibit enhanced dissolution rates compared to their crystalline counterparts. However, since the amorphous state is an unstable high energy state, it tends to revert to the more stable crystalline state. If the crystallization were to occur during long-term storage, the dissolution profile and the *in-vivo* performance of the drug product could be compromised during storage.

In order to achieve stabilization of the amorphous drug in such a polymer-based formulation, it has been suggested that the glass transition temperature (Tg) of the formulation should be at least 10–20°C higher than the storage temperature. The formulations are stable below the glass transition temperature, since molecular mobility is constrained in the glassy state. Based on these considerations, PVP and its copolymers are excellent choices for stabilizing the amorphous state of the drug substance, since PVP by itself has an elevated glass transition of 163°C. Therefore, a homogeneous blend of the amorphous drug with PVP will have a higher glass transition temperature. Moreover, the formation of homogeneous blend between drug and PVP is facilitated by specific interactions, such as hydrogen bonding, complexation, etc., due to the presence of the carbonyl group in the repeating unit of PVP.

Based on the same considerations described above, POLYOX is not suitable for stabilization of amorphous drug formulations. POLYOX is a semicrystaline polymer with a low Tg of−60°C. Therefore, a formulation of POLYOX with amorphous drug substance will also have a low Tg, which means the molecular mobility is not curtailed at the storage condition, leading to the crystallization of the amorphous drug. Moreover, the crystallization of the amorphous drug is facilitated by the presence of crystalline domains of POLYOX acting as nuclei for crystallization. Furthermore, the chemical structure of POLYOX, unlike PVP, is not conducive to any specific interaction between the drug and POLYOX.

Eudragits are a class of copolymers of methacrylic esters marketed by Evonik Industries. The type and nature of substituents on these methacrylic esters are manipulated to achieve pH-dependent solubility in water. Since the pH of human gastrointestinal tract (GI) increases from 1–3 in the stomach to 5–7 in the lower part of the GI tract, these pH-dependent Eudragit polymers are used in the pharmaceutical industry to target the delivery of drugs to various parts of the GI tract. For example, Eudragit L100-55 is a 1:1 copolymer of methacrylic acid and ethyl acrylate, which is only soluble in water above pH 5.5. Eudragit L100-55 is used for coating of tablets containing drugs which can irritate the lining of the stomach. Eudragit L100-55 forms an acid-insoluble coating, preventing the drug release in the stomach. However, when this coated tablet reaches the lower GI tract where the pH is higher than 5.5, the coating dissolves, leading to the release of the drug. Eudragit L100-55 has a Tg around 107°C. Therefore, Eudragit L100-55 can be used to prepare stable amorphous drug formulations, since the Tg of such formulations will be above the storage temperature.

Compound I

Compound I is a poorly water-soluble compound. The intestinal permeability of Compound I was determined to be high using human intestinal cell line, Caco-2. Compound I,

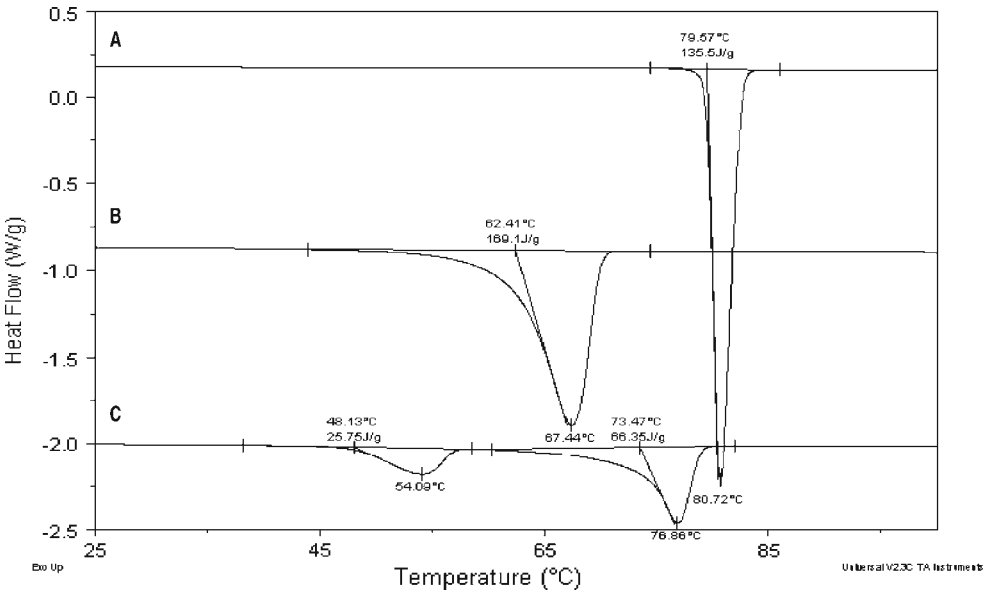

Fig. 4. DSC thermograms of (**A**) nabumetone, (**B**) POLYOX, and (**C**) electrospun nabumetone / POLYOX fibers.

when dosed as a solution formulation, gave high oral bioavailability in pre-clinical species. However, the oral absorption for Compound I was significantly lower when dosed as a solid dosage form in the same species. These results, together with the poor solubility of this Compound (1 μg/mL at pH 7), suggest that the oral absorption of Compound I may be limited by its dissolution rate.

Electrospinning studies of Compound I were performed to demonstrate how the morphology of the drug is dependent on the polymer matrix used. PVP and POLYOX were the two polymers selected for this study. Compound I is soluble in tetrahydrofuran (THF). Electrospinning of Compound I with PVP and Kolloidon VA64 (trade name for polyvinylpyrrolidone-co-polyvinyl acetate marketed by BASF) was performed from solutions of a mixture of THF and ethyl alcohol, as summarized in Table III. The drug content in the electrospun fibers was determined by an HPLC method. Electrospinning of Compound I in the presence of POLYOX was performed from a mixture of THF and acetonitrile. In all cases, the drug content was approximately 40% (w/w). Two of the PVP formulations contained either Tween 80 or TPGS as surfactants. These surfactants were included to study their influence on *in vitro* dissolution profiles.

In Vitro Dissolution Rates of Electrospun Compound I

In vitro dissolution rates of electrospun fiber formulations containing Compound I were determined using 0.1 M HCl as the dissolution medium. The equipment used for this procedure is a modified USP 4, the major differences being 1) low volume cell, 2) stirred cell, and 3) retaining filters which are adequate for retaining sub-micron material. The flow rate was 5 mL/min for 40 min, corresponding to a total dissolution volume of 200 mL.

A non-milled lot of Compound I was used for comparison. As shown in Table IV, the electrospun formulations have much faster rates of dissolution compared to the non-milled drug substance. Electrospun formulations containing surfactants exhibited faster dissolution rates than those without them. Formulation with TPGS as surfactant had a faster rate of dissolution than the one with Tween 80.

Table II. Thermal Properties of Electrospun POLYOX Fibers Containing Nabumetone

Expt. #	Nabumetone content [a](%)	POLYOX		Nabumetone	
		M.P (°C)	ΔH (J/g)	M.P (°C)	ΔH (J/g)
8	81.2	49.4	22.2	75	80
7	84.4	51.6	22.1	75.3	82.6
6	82.8	50.5	19.9	75.3	88.5
5	61.3	48.2	34.3	69.9	49.8
4	52.1	53.3	56.4	71.1	27.0
3	35.9	53.5	69.1	64.1	7.4
2	30.1	57.7	115.1	none	none
1	29.0	55.6	94.5	none	none

[a] Nabumetone content determined by HPLC.

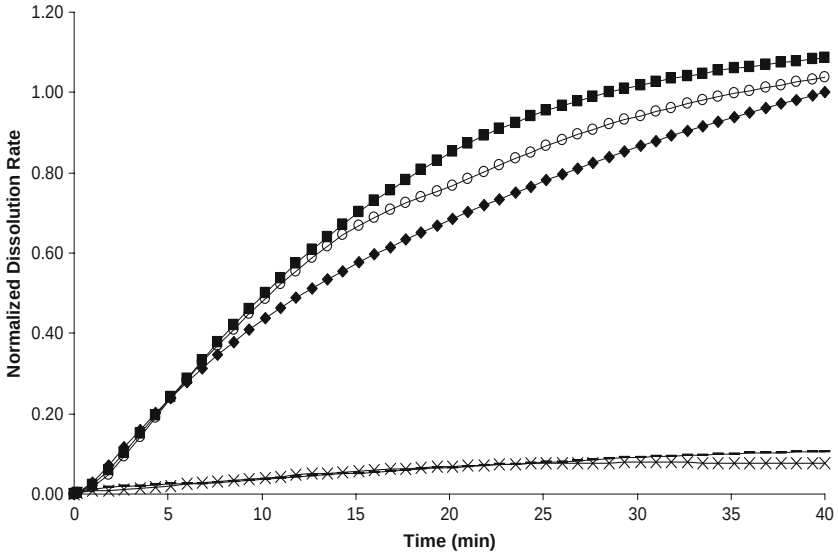

Fig. 5. Normalized dissolution rates of, (■) electrospun nabumetone (68.8% nabumetone, POLYOX 23.6%, TPGS 3.8% and Tween80 3.8%), (○) electrospun nabumetone (81% nabumetone, POLYOX 14% and TPGS 5%), (♦) nanoparticulate nabumetone (80% w/w), (X) unmilled nabumetone mixture (81% nabumetone, POLYOX 14% and TPGS 5%), (–) unmilled nabumetone (100%).

Thermal Behavior of Electrospun Fibers of Compound I

When examined by DSC, Compound I exhibited a crystalline melting point at 160.7°C. Electrospun fibers of Compound I (40% w/w) with POLYOX exhibited two distinct melting transitions (see Fig. 6). The concentration (40% w/w) and purity of Compound I in the fibers were determined by HPLC. The first melting at 54.7°C corresponds to that of POLYOX, whereas the second melting transition at 120.8°C might be that of Compound I. The lowering of melting transition of Compound I in the fibers could be due to its miscibility with POLYOX or due to the presence of surfactants. The presence of crystalline Compound I in the POLYOX fiber was also verified by XRPD. However, it is not clear from the XRPD data whether there is a change in the morphology of Compound I as a result of electrospinning, which might have also accounted for the lowering of melting transition. Also, the crystallinity of Compound I in POLYOX fibers was found to increase on storage.

Electrospun fibers of Compound I in PVP did not exhibit any melting transition (see Fig. 6). Instead, it has a single glass transition (Tg) at 63.5°C, indicating that the formulation is a uniform blend between PVP and Compound I. This Tg value also suggests that these formulations will preserve Compound I in the amorphous state when stored at room temperature. This was confirmed by studying the XRPD of electrospun fibers stored at 25°C. Fig. 7 shows that Compound I in electrospun PVP fibers is amorphous, and it did not develop any crystallinity when stored at 25°C for at least 120 days.

In Vivo Testing of Electrospun Fibers of Compound I

Results from *in vitro* dissolution studies using the modified USP4 flow-through dissolution method indicated that the dissolution rate of electrospun Compound I fiber was faster than that of non-milled Compound I (See Fig. 8). However, the dissolution rate of Compound I from the nano-milled formulation was significantly faster than the dissolution rate of Compound I from the nano-fibers. The nano-milled Compound I contained approximately 70% drug along with 20% Pluronic and 10% PVP. The slow dissolution rate of Compound I from the electrospun fibers may be due to the higher amount of PVP and the absence of surfactants in the formulation.

Table III. Compositions for Electrospinning of Compound I

Ingredients	Formulation 1	Formulation 2	Formulation 3	Formulation 4	Formulation 5
Compound I	400 mg	400	400	1 g	2 g
THF	2 ml	2 ml	2 ml	2.5 ml	5 ml
PVP	600 mg	550 mg	550	none	none
KolloidonVA64	none	none	none	1.5 g	3 g
Ethanol	10 ml	10 ml	10 ml	10 ml	20 ml
Surfactant	none	Tween 80/ 50 mg	TPGS/ 50 mg	none	none
Yield	900 mg	850 mg	860 mg	2.3 g	4.4 g
Drug content (%)[a]	36.7	36.6	39.9	40.0	39.1

[a] determined by HPLC

Table IV. *In Vitro* Dissolution of Electrospun Fibers Containing Compound I

Formulation	Drug content (%)	% Drug dissolved			
		10 min	20 min	30 min	40 min
Compound I	99.5	3.8	6.3	8.5	10.7
#1	36.7	15.7	30.1	43.8	59.1
#2	36.6	24.8	42.6	58.8	69.9
#3	39.9	19.6	44.9	62.8	75.9
#4	40.0	19.8	31.1	41.1	50.1
#5	39.1	26.2	40.2	52.0	60.3

In order to evaluate the effect of compression on the rate of dissolution of Compound I from the fibers, pellets were made by compressing the nano-fibers using a Caver Press at 5,600 pounds or 3 tons for 10 s. The dissolution rate of Compound I from these pellets was determined to be similar to its dissolution rate from electrospun fibers (see Fig. 8). According to DSC, Compound I remained in the amorphous state in the compressed pellet.

An *in vivo* study was conducted using four different formulations: (1) electrospun Compound I fibers, (2) pellets from electrospun fibers, (3) wet bead milled (D50 1-1.5 micrometer) and (4) non-milled Compound I. Each of the four formulations was dosed at 5 mg/kg in four fasted adult male beagle dogs. Plasma samples were collected at 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600 and 1,440 min, and the amount of Compound I was determined by LC/MS/MS. The plasma-time profiles were then used to estimate the pharmacokinetic parameters (mean ± SD) of Compound I. These pharmacokinetic parameters are listed in Table V. It can be seen from Table V that the absorption of Compound I formulated in the wet bead milled formulation gave the best level of exposure followed by the electrospun fibers, pellets of electrospun fibers, and non-milled formulation. The average AUC values for electrospun fibers of Compound I were similar to those obtained for pellets of electrospun fibers. The Cmax values for Compound I were variable, ranging from 0.729 μg/mL to 3.69 μg/mL for electrospun fibers, and from 0.871 μg/mL to 2.47 μg/mL for pellets of electrospun Compound I fibers. There was no correlation between an individual animal and either low or high Cmax values. The Tmax values were also variable, ranging from 120 min to 600 min for electrospun Compound I fibers and from 480 min to 600 min for the corresponding pellets. From the data, it can be concluded that the oral absorption of Compound I was highest from the wet bead milled formulation, followed by electrospun fibers, pellets, and then the non-milled formulation.

The oral absorption of Compound I from electrospun fibers was inferior to that from the nano-milled Compound I. These results are consistent with the observed rank order of rates of release of Compound I from these formulations in the *in vitro* dissolution experiments. These data suggest that the composition and processing conditions need to be refined in order to achieve better dissolution profiles and in turn better *in vivo* performance. The SEM of electrospun fibers used in this *in vivo* evaluation, Fig. 9, shows that the fiber diameter can be further refined, which may aid in enhancing the *in vitro* dissolution and hence the oral exposure.

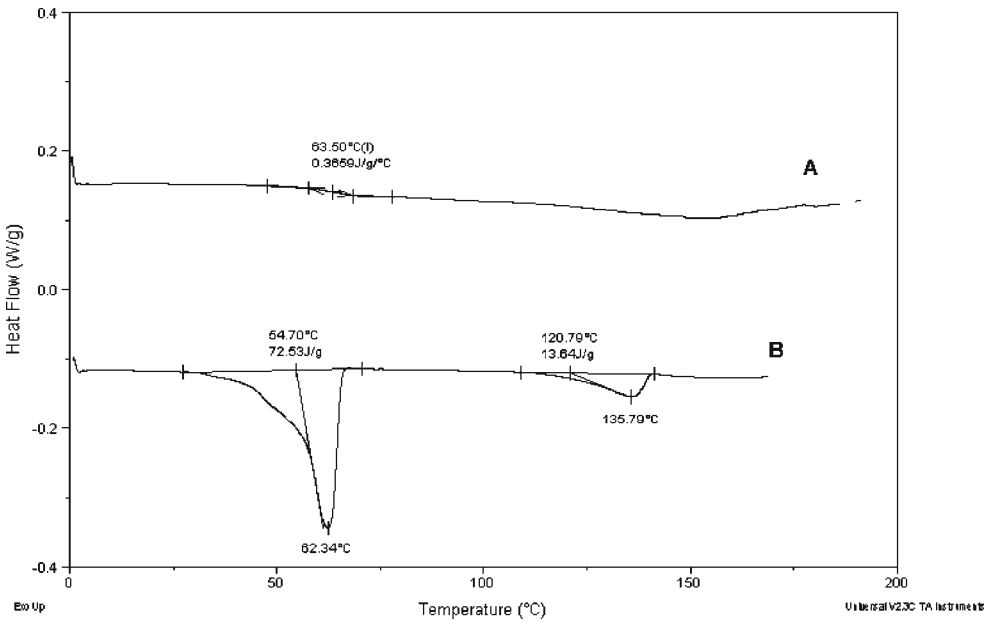

Fig. 6. DSC thermograms of Compound I electrospun in **A**) PVP matrix and **B**) POLYOX matrix.

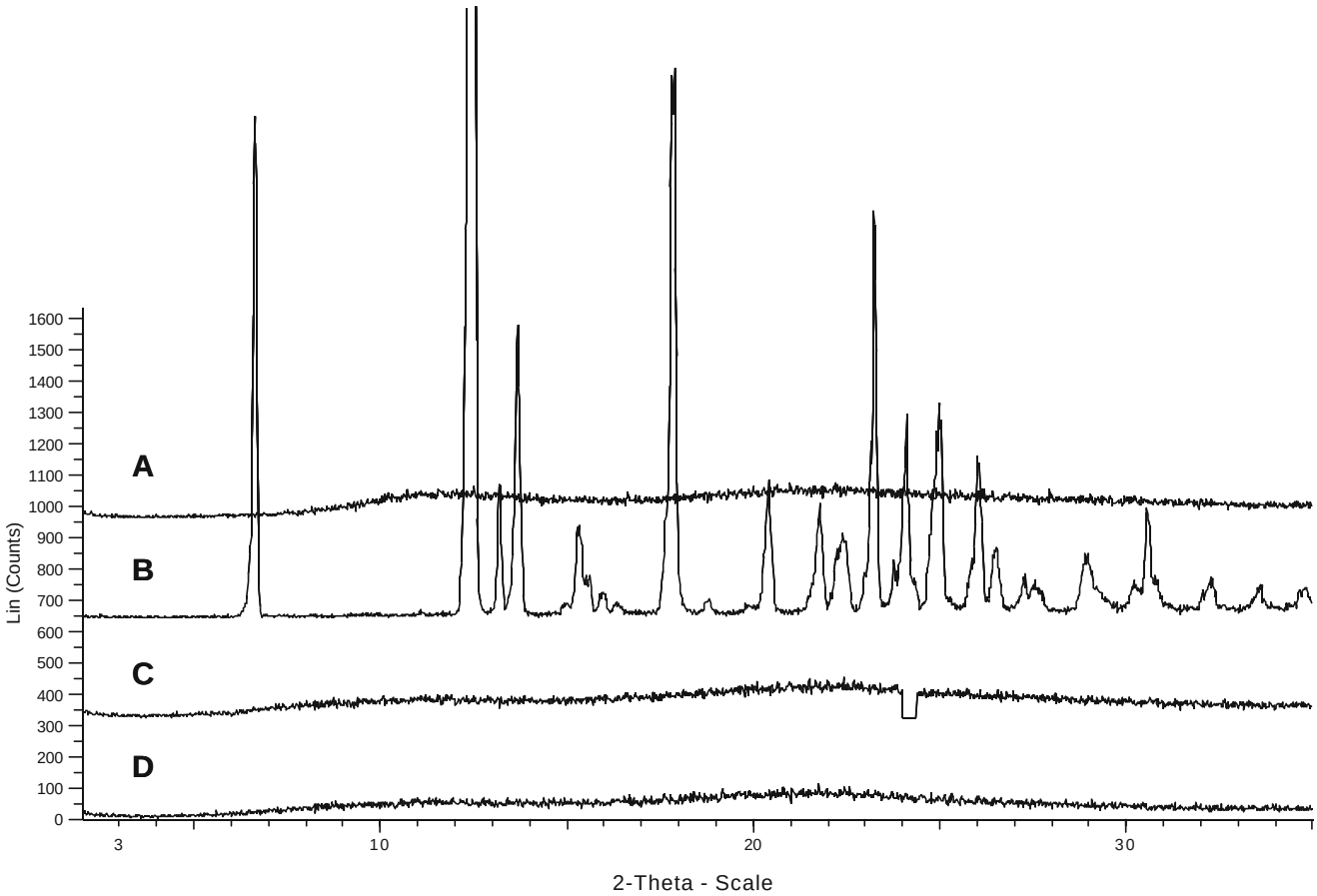

Fig. 7. XRPD of (**A**) PVP, (**B**) Compound I, (**C**) Compound I electrospun in PVP matrix stored for 120 days and (**D**) Compound I electrospun in PVP matrix (as prepared).

Compound II

In addition to producing formulations to enhance the *in vivo* release rates of poorly soluble drugs, the electrospinning technology can also be used to encapsulate drugs in different types of polymers to provide various release rates and profiles *in vivo*. One example of this application is demonstrated using a poorly water-soluble drug (Compound II). This compound has less than 0.5μg/mL solubility in water. In order to select a suitable solvent for the electrospinning of Compound II, a visual solubility screen of this compound in various solvents was conducted. It was found that Compound II has greater than 30 mg/mL solubility in methylene chloride. Therefore, methylene chloride was chosen as the primary solvent for the electrospinning of Compound II.

Electrospinning of Compound II was performed in two different polymer matrices: POLYOX, which is a semi-crystalline polymer, and Eudragit L100-55, which is an amorphous polymer. Eudragit L100-55 is insoluble in water below pH 5, but soluble above it. Therefore, Eudragit L100-55 can be used to target the delivery of Compound II to the lower part of the GI tract. Moreover, since the Tg of Eudragit L100-55 is 105°C, it can be used to prepare amorphous solid dispersions of Compound II. Electrospinning of Compound II in POLYOX was performed to demonstrate that the morphology of this compound depends on the polymer matrix.

Electrospun POLYOX fibers containing 38% (w/w) of Compound II were prepared from solutions in methylene chloride and acetonitrile (see Table VI for compositions used). Tween 80 at 0.4% (w/w) was also present in the electrospinning medium. Electrospun Eudragit L100-55 fibers containing 40% (w/w) of Compound II were prepared from methylene chloride/ ethanol mixtures.

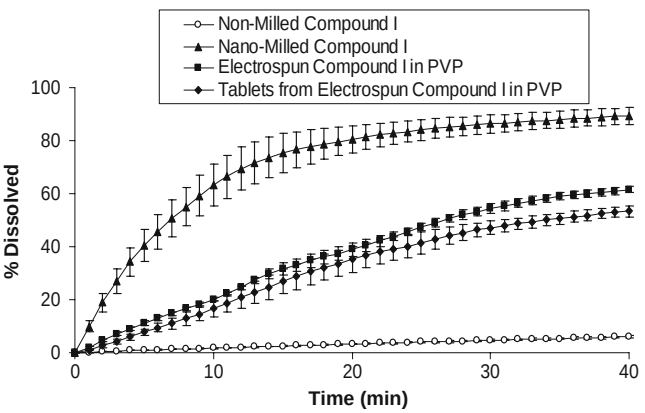

Fig. 8. Percent of Compound I dissolved from nano-milled, non-milled Compound I, electrospun Compound I fiber and pellet from electrospun Compound I fiber.

Table V. Pharmacokinetic Parameters Determined Following the Oral Administration of Various Formulations in Beagle Dogs

Formulation	Dose (mg/kg)	Cmax (μg/ml)	Tmax (min)	AUC_{0-t} (min·μg/ml)
Electrospun Compound I fibers	5.09±0.03	1.86±1.35	356.3±272.8	1076.0±662.2
Pellets of electrospun Compound I fibers	5.11±0.05	1.35±0.75	531.8±59.8	770.5±363.3
Wet bead milled Compound I	5.43±0.76	2.15±0.669	278.3±307.5	1654.0±1354.8
Non-milled Compound I	5	0.398±0.064	320±249.8	340.0±136.1

Fig. 10A shows the SEM of electrospun POLYOX containing 38% of Compound II. The fiber diameter varies from 500 to 750 nm. The fibers exhibited an unusual beaded morphology, which could be due to the presence of crystalline Compound II. When the electrospun Eudragit L100-55 fibers of Compound II were examined under SEM, there was no beaded structure (see Fig. 10B). The fiber diameter of these Eudragit L100-55 fibers ranged from 500–900 nm.

Thermal Properties of Electrospun Fibers of Compound II

As expected, Compound II exhibited a crystalline melting transition when electrospun in a POLYOX matrix. Fig. 11 shows the DSC thermograms of the fibers obtained from both POLYOX (A) and Eudragit L100-55 (B). POLYOX fibers had two melting transitions: the first at 62°C corresponded to the melting of POLYOX, whereas the second transition at 109.6°C was due to the melting of crystalline Compound II present in these fibers. Compound II itself exhibited a melting transition at 136°C.

The Eudragit L100-55 fibers of Compound II did not have any crystalline melting transitions, confirming the fact that Compound II existed in an amorphous state. This formulation exhibited a Tg at 59.5°C, which suggested that the amorphous Compound II present in this formulation will not develop crystallinity during storage at 25°C.

In Vitro Dissolution of Electrospun Fibers of Compound II

In order to discern and demonstrate the role of Eudragit L100-55 polymer in preventing the release of Compound II at low pH, the flow through *in vitro* dissolutions of electrospun Compound II were studied at two different pH values: 1 and 7.5. The pH 1 media contained 0.1 N HCl, whereas pH 7.5 buffer contained 10 mM sodium phosphate at pH 7.5, 2.7 mM potassium chloride and 137 mM sodium chloride. For comparison, non-milled and nano-milled Compound II (obtained by wet bead milling) were included in the study. Fig. 12(A) shows the dissolution profiles of various formulations tested at pH 1. Electrospun Compound II in POLYOX matrix, when tested at pH 1, exhibited an enhanced dissolution profile similar to nano-milled formulation. This data confirms the presence of nanoparticulate drug in the electrospun POLYOX matrix. The dissolution rate of Compound II from Eudragit L100-55 fibers was extremely slow (below 2.5% at 40 min), which was comparable to that obtained from non-milled Compound II (see Table VII for a comparison of dissolution rates performed in various buffers). Since Compound II exists in the amorphous form, it was expected to release faster than its non-milled counterpart. However, results indicate that Compound II is completely encapsulated in the polymer, and, hence, dissolution of polymer becomes the rate-limiting step.

The dissolution profiles of the same formulations tested in pH 7.5 buffer are shown in Fig. 12(B). Electrospun formulation of Compound II in Eudragit L100-55 showed the fastest dissolution rate. This is due to the solubility of Eudragit L100-55 at pH7.5 and the presence of Compound II in the amorphous form. Other formulations, such as the non-milled, nano-milled and POLYOX-based electrospun fibers, containing crystalline Compound II had less than 5% dissolution in 40 min. This may be due to the poor solubility of crystalline Compound II at pH 7.5 (less than 0.3μg/mL). These results clearly demonstrate that electrospinning can be used to encapsulate drugs in various polymer matrices to provide the desired release rates.

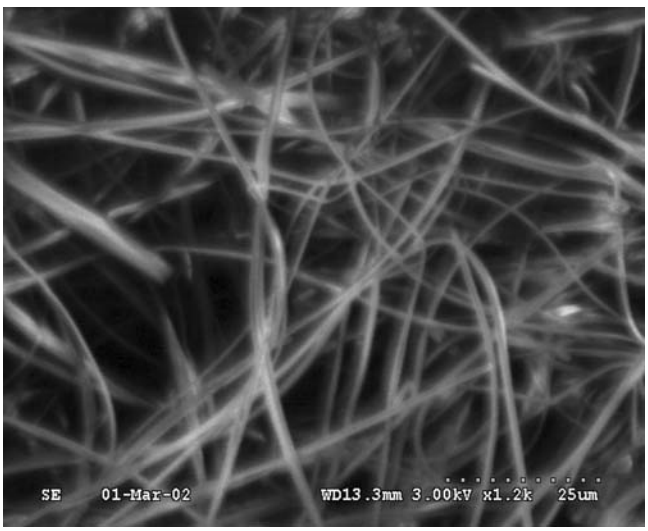

Fig. 9. SEM of Electrospun Compound I in PVP matrix.

Table VI. Compositions for Electrospinning of Compound II

Ingredients	Formulation 1	Formulation 2
Compound II	3.0 g	0.5 g
Eudragit L100-55	4.5 g	None
PEO WSR900K	none	0.7 g
Tween 80	0.1 g	0.05 g
Methylene Chloride	15 mL	2.5 mL
Ethanol	22 mL	22 mL
Acetonitrile	None	15 mL
Yield	5.2 g	0.8 g
Drug content (%)[a]	38.6	37.6

[a] determined by HPLC

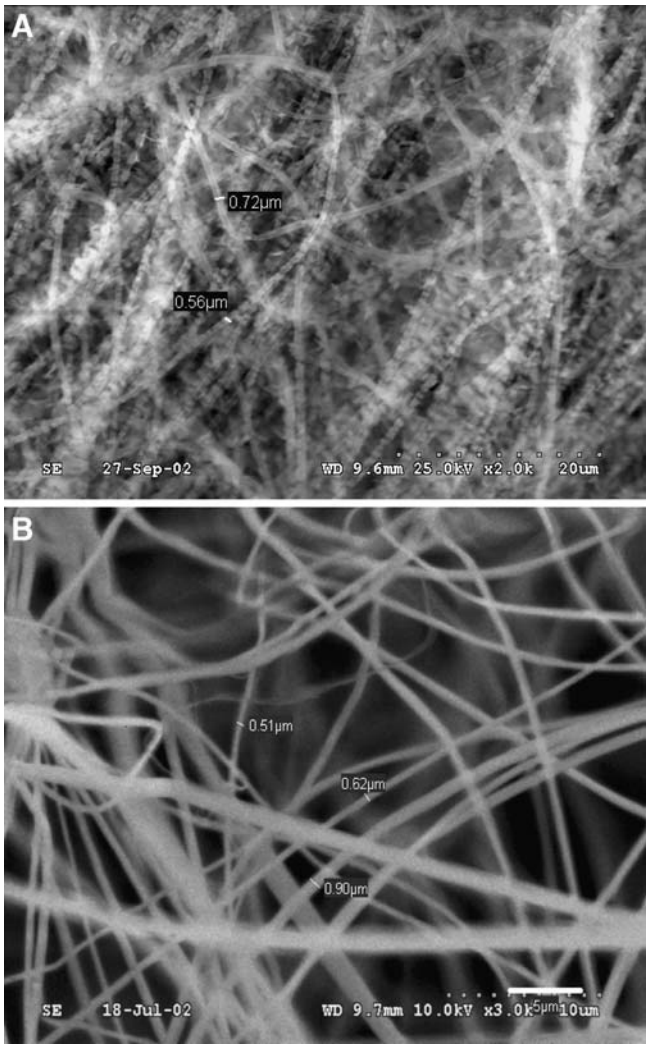

Fig. 10. SEM of electrospun Compound II in POLYOX (**A**) and Eudragit L100-55 (**B**).

CONCLUSION

In this review we demonstrated that poorly soluble drugs can be incorporated during electrospinning process to produce electrospun fibers. The drug loading in these electrospun fibers was as high as 84%. The release rate of the drug from the electrospun fibers was comparable to or even superior to that from nanoparticulate drug prepared by the wet milling technique. The selection of the polymer matrix had a tremendous influence on the morphology of the drug as well as on the site of drug release. POLYOX, a semicrystalline polymer, produced electrospun fibers containing crystalline drug. Amorphous polymers, such as PVP and Eudragit, produced drugs in amorphous form, which were stable under the room temperature storage condition. Moreover, use of Eudragit L100-55 resulted in a drug-encapsulated electrospun fiber which did not release the drug at low pH, and hence this system can be used for the targeted delivery of drugs.

The *in vivo* exposure of the Compound I from electrospun fibers was inferior to the wet bead milled nanoparticulate formulation, which was anticipated from their *in vitro* release behavior. Therefore, the formulations and process for electrospinning need to be optimized to produce fibers having dissolution rates comparable to the nanoparticles. There are several avenues for formulation optimization, including polymer selection and its molecular weight, drug loading, nature and amount of surfactants. Process optimization studies may entail voltage used and solution feed rate. The goal of the optimization studies would be to improve the fiber diameter and hence the *in vitro* dissolution, leading to better exposure.

Electrospinning is an emerging technology, and its application to drug formulations and product development would require further studies. Consideration should be given to the design of a patient-compliant dosage form. Scale up and commercial production are other challenges which need

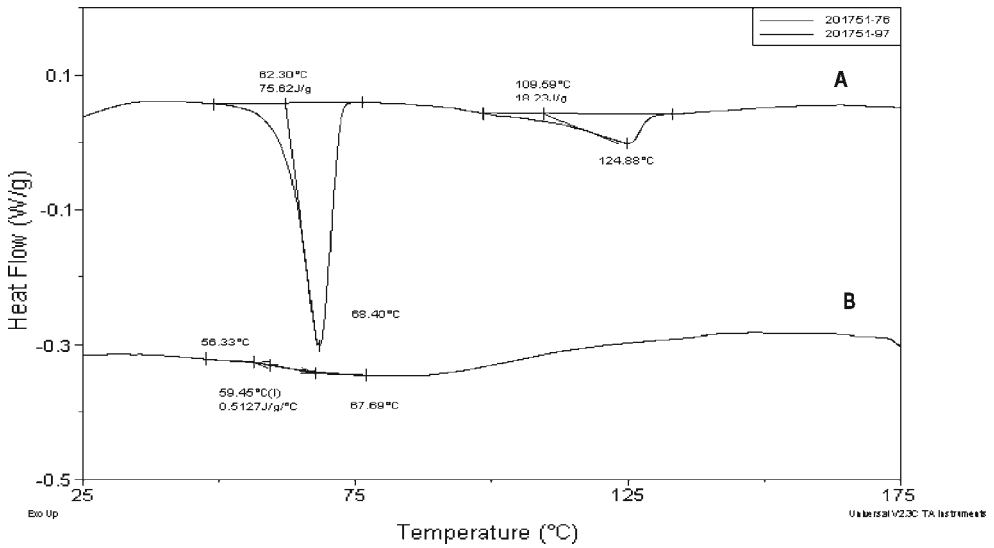

Fig. 11. DSC thermograms of compound II electrospun in presence of (**A**) POLYOX and (**B**) Eudragit L100-55.

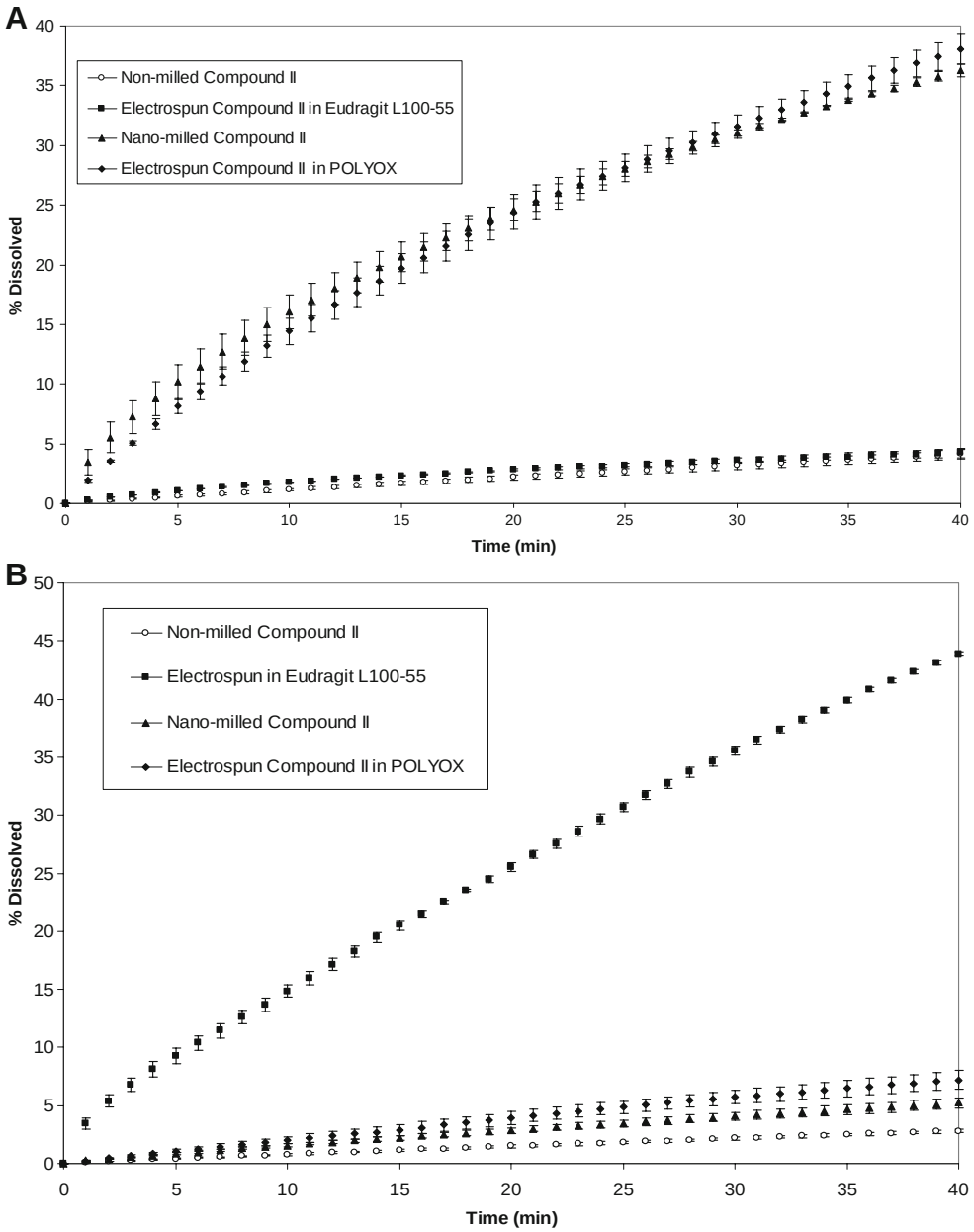

Fig. 12. *In vitro* dissolution profiles of Compound II at pH 1 (**A**) and at pH 7.5 (**B**).

Table VII. Summary of *In Vitro* Dissolution Profiles of Compound I & II Under Various Conditions

Formulation			Dissolution medium	% Drug dissolved			
API	Polymer	Drug content [a] (w/w %)		10 min	20 min	30 min	40 min
Compound I	PVP	39.1	pH1	26.2	40.2	52	60.3
Compound II	POLYOX	37.6	pH1	14.4	24.4	31.6	38.1
			pH 7.5	2.1	3.9	5.7	7.2
	Eudragit 100-55	38.6	pH1	1.8	2.8	3.6	4.2
			pH 7.5	14.8	25.5	35.6	43.9

[a] determined by HPLC

to be addressed. Storage stability of the electrospun fibers in such a dosage form need to be investigated. Other avenues which need further consideration are process safety, and presence of residual organic solvents.

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