Accepted Manuscript

Title: Electrospun fibers as potential carrier systems for enhanced drug release of perphenazine

Author: Giovanna Bruni Lauretta Maggi Loredana Tammaro Rosadele Di Lorenzo Valeria Friuli Sharon D'Aniello Mariarosa Maietta Vittorio Berbenni Chiara Milanese Alessandro Girella Amedeo Marini

PII: S0378-5173(16)30641-X
DOI: http://dx.doi.org/doi:10.1016/j.ijpharm.2016.07.011
Reference: IJP 15908

To appear in: *International Journal of Pharmaceutics*

Received date: 27-5-2016
Revised date: 6-7-2016
Accepted date: 8-7-2016

Please cite this article as: Bruni, Giovanna, Maggi, Lauretta, Tammaro, Loredana, Lorenzo, Rosadele Di, Friuli, Valeria, D'Aniello, Sharon, Maietta, Mariarosa, Berbenni, Vittorio, Milanese, Chiara, Girella, Alessandro, Marini, Amedeo, Electrospun fibers as potential carrier systems for enhanced drug release of perphenazine.International Journal of Pharmaceutics http://dx.doi.org/10.1016/j.ijpharm.2016.07.011

Electrospun fibers as potential carrier systems for enhanced drug release of perphenazine

Giovanna Bruni[a]*, Lauretta Maggi[b], Loredana Tammaro[c#], Rosadele Di Lorenzo[a], Valeria Friuli[b], Sharon D'Aniello[c], Mariarosa Maietta[a], Vittorio Berbenni[a], Chiara Milanese[a], Alessandro Girella[a], Amedeo Marini[a]

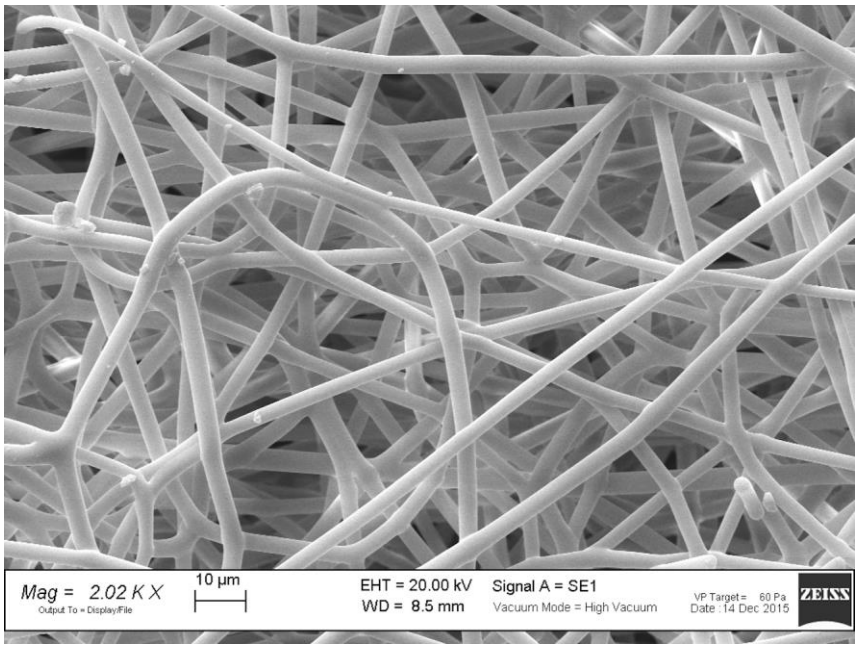
[a] C.S.G.I. - Department of Chemistry, Physical-Chemistry Section, University of Pavia, Viale Taramelli 16, 27100 Pavia, Italy.

[b] Department of Drug Sciences, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy.

[c] Industrial Engineering Department, University of Salerno, Via Giovanni Paolo II 132, 84084 Fisciano, Salerno, Italy.

Present address: ENEA (Italian National Agency for New Technologies, Energy and Sustainable Economic Development), Brindisi Research Center, S.S. 7 Appia km 706, 72100 Brindisi, Italy.

Graphical abstract



Abstract

Solubility represents an important challenge for formulation of drugs, because the therapeutic efficacy of a drug depends on the bioavailability and ultimately on its solubility. Low aqueous solubility is one of the main issues related with formulation design and development of new molecules. Many drug molecules present bioavailability problems due to their poor solubility. For this reason there is a great interest in the development of new carrier systems able to enhance the dissolution of poorly water-soluble drugs.

In this work, fibers containing an insoluble model drug and prepared by an electrospinning method, are proposed and evaluated to solve this problem. Two hydrophilic polymers, polyvinylpyrrolidone (Plasdone® K29/32) and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) were used to increase the water solubility of perphenazine.

The physico-chemical characterization suggests that the drug loaded in the fibers is in the amorphous state. Both polymeric carriers are effective to promote the drug dissolution rate in water, where this active pharmaceutical ingredient is insoluble, due to the fine dispersion of the drug into the polymeric matrices, obtained with this production technique. In fact, the dissolution profiles of the fibers, compared to the simple physical mixture of the two components, and to the reference commercial product Trilafon® 8 mg tablets, show that a

strong enhancement of the drug dissolution rate can be achieved with the electrospinning technique.

Keywords
Electrospinning, Perphenazine, Solubility, Dissolution rate, Polymeric drug carrier, Amorphous.

1. Introduction

The poor aqueous solubility and the low dissolution rate of many active pharmaceutical ingredients (API) is a limiting factor to their absorption after oral administration. This is particularly true for the drugs within class II of the Biopharmaceutical Classification System (BCS) (Amindon et al. 1995) whose number is always increasing. Solubility is one of the most important parameters to achieve suitable concentration of drug in systemic circulation for desired pharmacological response. Inadequate solubility or dissolution rate can significantly reduce both the rate and extent of drug absorption, deleteriously affecting oral bioavailability. Therefore an important goal of the pharmaceutical scientist in drug development is to discover ways of enhancing the solubility of poorly water-soluble drugs. A number of methodologies can be adapted to improve solubilization of poorly water soluble drug and further to improve its bioavailability, which include physical and chemical modifications of drug like micronization, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, use of surfactant, and so forth. Selection of a solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

One of the most innovative approaches is the loading of the drug in polymer fibers prepared by electrospinning (Bruni et al. 2015, Hamoria, et al. 2014, Paaver et al. 2015, Vrbata et al. 2014, Hu et al. 2014). This technique (Sharma et al. 2014, Sill et al. 2008) can be used to prepare continuous fibers with diameters ranging from tens of nanometers to several micrometers. In the process of electrospinning, a polymer solution, which may contain a drug, is pumped through a syringe nozzle connected to a high-voltage power supply that causes a cone-shaped deformation of the drop of polymer solution (Taylor cone) formed at the tip of the nozzle. Once the strength of electric field exceeds a threshold value, the electrostatic force on the deformed polymer drop can overcome the surface tension and thus a liquid jet is

formed and directed toward a metal collector. As the liquid jet is continuously elongated and the solvent is evaporated, ultrafine solid fibers are collected as final product.

The dissolution kinetics of the drug from the fibers is influenced by the physical state of the drug and the type of the polymer that forms the fibers. In most cases, the drug embedded in the fibers obtained by electrospinning of a polymeric solution is in an amorphous phase or molecularly dispersed since its molecules have no time to undergo crystallization due to the fast solvent evaporation (Lopez et al. 2014, Verreck et al. 2003, Seif et al. 2015). In other cases, drug crystals may grow on the surface of the fibers (Brettmann et al. 2013, Zenga et al. 2005, Kim et al. 2014).

In this study, fibers loaded with perphenazine (*P*) were prepared by electrospinning. To increase the dissolution rate of this drug, two different polymers were used, Plasdone® K29/32 (polyvinylpyrrolidone with nominal molecular weight 58000; *PVP* in the following) and Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer with molecular weight in the range 90000-140000; *SOL* in the following) (Paaver et al. 2014). Perphenazine, 2-chloro-10-[3-[1-(2-hydroxyethyl)-4-piperazinyl]propyl]phenothiazine (Scheme 1), a well known drug for the treatment of certain mental disorders such as schizophrenia and manic phase of bipolar disorder and for the control of severe nausea and vomiting in adults, is used as model drug (Hartung et al. 2005, Dahl 1998, Jin et al. 2010).

This molecule is soluble in chloroform and ethanol, but practically insoluble in water at neutral pH, while its solubility increases by lowering the pH. For this reason, its oral bioavailability could be influenced by the pH of the gastro-intestinal tract. The therapeutic doses are quite different: 2-4-8-12-32 mg daily, divided into three administrations. Frequently this drug needs dose adjustment to reduce side effects due to a large inter-individual pharmacokinetic variability (Jin et al 2010). In this work we choose the highest commercial dose of 8 mg, administered in tablets. The United States Pharmacopeia (USP) prescribes to perform the in vitro dissolution test in hydrochloric acid at pH=1 (United States Pharmacopeia (USP) 31 ed.). Indeed, this basic drug is much more soluble at low pH (empty stomach), but being administered three times daily, it is quite difficult to avoid after-meal administrations: the presence of food increases the pH of the gastric contents and this effect causes the perphenazine solubility to decrease and, as a consequence, the drug absorption could decrease as well.

PVP was selected because it is a highly hydrophilic and soluble excipient and, for this reason, it is able to enhance the drug-water interaction, while *SOL* is a graft copolymer with amphiphilic properties that is used to increase solubility and bioavailability of poorly soluble

drugs. It is generally recommended for the production of hot melt extrusion of drug-carrier systems, with excellent extrudability and easy processing (Djuris et al. 2013).

Scanning Electron Microscopy (SEM) was used to study the morphology of the fibers while Differential Scanning Calorimetry (DSC), Thermogravimetric analysis (TGA), Powder X-ray Diffraction (XRPD), Fourier Infrared Spectroscopy (FT-IR) were used to define the solid phase of the drug in the fibers and possible interactions between components.

The dissolution rate of perphenazine from the fibers was tested both in deionised water and in 0.1 N hydrochloric acid (pH=1) and compared to the simple drug-polymer physical mixtures. A commercial dosage form, Trilafon® tablets 8 mg, was used as reference.

2. Materials and Methods

2.1. *Materials and preparation of solutions*

Perphenazine (*P*) was kindly supplied by Trifarma (Rozzano, Italy); Plasdone® K29/32 by GAF Chemical Corp. Wayne (New Jersey, USA) and Soluplus® by BASF SE (Ludwigshafen, Germany). All reagents were of analytical grade and were used without further purification. The commercial product Trilafon® 8 mg tablets by Schering Plough (Milan, Italy) was bought in a pharmacy and does not contain any particular excipient intended to promote drug solubility. It contains the following inactive ingredients: lactose, starch, pregelatinized starch, magnesium stearate, sucrose, calcium sulphate, tribasic calcium phosphate, acacia gum, gelatine, white wax, carnauba wax, butyl-p-hydroxybenzoate and dye, opalux no. AS7504 grey.

The physical mixtures of each polymer containing 10% (w/w) of drug (*P:PVPpm* and *P:SOLpm*, respectively) were prepared by mixing the properly weighed amounts of the components by a Turbula (W.A. Bachofen AG, Basel, Switzerland) at 96 rpm for 15 min.

The *PVP* and *SOL* solutions for collecting electrospun fibers were prepared by dissolving the neat polymer in hot chloroform (35-40°C) at 20% (w/w) concentration and stirring for about 2h.

The polymer solutions including perphenazine were prepared by first dissolving the drug in hot chloroform and then adding the polymer under stirring for about 2h at a weight ratio drug/polymer of 1:9. The final concentration of the polymer in chloroform solution was 20% (w/w) for both polymer systems. The drug-loaded fibers were coded as *P:PVPel* and *P:SOLel* for *PVP* and *SOL*, respectively.

2.2. Electrospinning process

A climate-controlled electrospinning apparatus EC-CLI (IME Technologies, Geldrop, The Netherlands) was used for fabrication of all fibers. A series of experiments were carried out varying the electrospinning parameters to optimize the process. The applied electrical potentials ranged between 15 and 29 kV, the collection distance set from 10 to 30 cm, the feeding rate selected from 0.5 and 3.0 mL/h for Plasdone® system and from 1.0 to 1.5 mL/h for Soluplus® system.

The collected fibers were placed in a vacuum oven overnight to fully eliminate any residual solvent, then stored over silica gel in a dryer.

The fibers were analysed after manual milling of the fibrous fleeces in an agate mortar.

2.3. Scanning electron microscopy

A Zeiss EVO MA10 (Carl Zeiss, Oberkochen, Germany) was used to analyse the morphology of the fibers. The samples were gold-sputter coated under argon to render them electrically conductive prior to microscopy. The average diameter was determined by measuring the diameters of the fibers in SEM microphotographs, using the JMicroVision image analysis software.

2.4. X-ray powder diffraction

XRPD measurements were performed using a D5005 Bruker diffractometer (Karlsruhe, Germany) (CuKα radiation, $\lambda(K\alpha_1)$ = 1.54056 Å; voltage of 40 kV and current of 40 mA) equipped with a θ-θ vertical goniometer, Ni filter, monochromator, and scintillator counter. The patterns were recorded at room temperature in step scan mode (step size: 0.015°, counting time: 5 s per step) in the $5 < 2\theta° < 30$ angular range.

2.5. Infrared spectroscopy

FT-IR spectra were obtained using a Nicolet FT-IR iS10 Spectrometer (Nicolet, Madison, WI, USA) equipped with ATR (Attenuated Total Reflectance) sampling accessory (Smart iTR with ZnSe plate) by co-adding 256 scans in the 4000–650 cm^{-1} range with resolution set at 4 cm^{-1}.

2.6. Thermal analysis

Thermal characterization was carried out using a TGA Q2000 IR apparatus and a DSC Q2000 apparatus both interfaced with a TA 5000 data station (TA Instruments, New Castle, DE, USA). The DSC instrument was calibrated using ultrapure (99.999%) indium (melting point = 156.6

°C; ΔH = 28.54 $J \cdot g^{-1}$) as standard. The calorimetric measurements were performed in open standard aluminium pans under nitrogen flow (45 $mL \cdot min^{-1}$) at 5 $K \cdot min^{-1}$. All data from thermal measurements are the average of three or more experiments.

2.7. Dissolution test

The in vitro dissolution tests were performed using the USP Apparatus 2, paddle, 100 rpm (Erweka DT-D6, Dusseldorf, Germany), in 1000 ml of deionized water or 0.1 N hydrochloric acid (pH = 1.0) at 37 °C, (n=6). A weighed amount of the different samples, corresponding to a content of 8 mg of drug, was filled into hard gelatine capsules and put in the dissolution vessels. The cumulative amount of drug dissolved was determined at wavelength λ = 307 nm by a UV spectrophotometer (Lambda 25 UV Winlab V6 software, Perkin-Elmer, Monza, Italy) equipped with an automated sampler and connected to a PC for data processing. Trilafon® 8 mg tablets were tested in the same conditions and considered as reference.

3. Results and discussion

3.1. Influence of relevant process parameters on the homogeneity of the resulting electrospun fibers

In the present study, the best polymer–solvent combination for electrospinning of neat fibers and fibers loaded with Perphenazine was found to be 20% (w/w) concentration of both PVP and SOL polymers in chloroform.

A series of experiments were carried out varying the solution flow rate from 0.5 to 2.0 mL/h for electrospinning of PVP. The micrographs for the different fibrous samples investigated are shown in Figure S1 in the Supporting Information. Fibers produced with the highest flow rate (2.0 mL/h) show a not uniform morphology with a broad distribution of the fiber diameters (Figure S1a). In contrast, uniform fiber shapes with similar thicknesses along the fiber and almost bead-free morphologies were found for samples where a lower value of flow rate (0.5 mL/h) has been applied. At high applied voltage (25/-4KV and 21/-4KV) no fibers have been collected at flow rate of 0.5 mL/h. Decreasing the value to 14/-4KV, an uniform fibrous, almost bead-free structure was obtained (Figure S2). As shown in Figure S3, by increasing the needle-collector distance from 10 to 20 cm, the fiber morphology displays a worsening and therefore no more experiments have been carried out at distance higher than 20 cm.

The different process parameters were also optimized for Soloplus fibers. Experiments were performed decreasing the applied voltage from 25/-4 to 13/-4 kV and increasing the needle-

collector distance from 10 to 20 cm. SOL fibers produced with the lowest voltage (13/-4 kV) and the lowest distance (10cm) tended to form regular fibers as depicted in Figure 1c.

The combination of voltage, flow rate and distance that yielded the optimal nanofibers in the present electrospinning procedure was found to be 14/-4 kV, 0.5 mL/h and 10 cm, respectively, for PVP, and 21/-4 kV, 1.0 mL/h and 10 cm, respectively, for SOL.

These results are summarized in Table 1 including fibers loaded with P.

3.2. Physico-chemical characterization of the selected fibers

3.2.1. Microscopic analysis

SEM images of *PVP* and *SOL* unloaded and drug-loaded fibers are given in Figure 1. The fibers of all samples are randomly distributed and have smooth surfaces. In the drug-loaded fibers no isolated particles are visible, indicating that the drug is homogeneously dispersed into the polymer and a solid dispersion of the two components has been created. Indeed, this behaviour is expected since the drug is completely dissolved in the solvent and, during the electrospinning process, the fast solvent evaporation does not allow its crystallization. The drug solidifies molecularly dispersed in the polymer without the possibility to create long-range order. This behaviour is confirmed by the experimental evidence described in the following paragraphs.

For each sample, 200-300 fibers were tested to determine the diameter distribution. The data have been fitted according to normal-log distribution (eq. 1).

$$y = a \cdot \exp[-0.5(\ln x/x_0)/b^2] \qquad \text{eq. 1}$$

In Figure 2 the histograms of the diameter distribution and the curves of normal-log distribution are reported together with the mean value x_0, the standard deviation b, and the a coefficient. The parameters of the size distribution are reported in Table 2. It is evident that the mean size of the *PVP* fibers becomes significantly bigger when perphenazine is loaded.

Such increase is less evident in the *P:SOL* fibers probably because the *SOL* fibers show a larger diameter than the *PVP* fibers even before drug loading. The increase of the fibers diameter upon addition of drug is a common behaviour often met in literature. It could be due to changes in solution viscosity and electrical conductivity. An increase in solution viscosity and a decrease in the charge density on the surface of the electrospun jet result in larger fiber size (Paavera et al. 2015).

The milling process is quite efficient to achieve a low diameter to length ratio (Figure 3) so the particle size of the samples can be considered of the same order of magnitude of the fibers diameter.

3.2.2. X-ray powder diffraction

The characteristic peaks of perphenazine at angles of 2θ = 8.45, 13.95, 14.77, 18.39, 18.62, 20.48, 23.59, 25.17 and 25,62° are present in the XRPD pattern of the pure drug (Figure 4a), as expected for the crystalline compound, and are still visible, overlapping the broad band characteristic of the amorphous polymer, in the patterns of the physical mixtures *P:PVPpm* and *P:SOLpm* (Figure 4b-e), although with low intensity in agreement with the systems composition. On the contrary, the patterns of the fibers *P:PVPel* and *P:SOLel* (figure 4c-f) show only the broad band of the polymer (Figure 4d-g). In these systems the peaks of perphenazine are not visible not even when the counting time is high (20 s per step). This experimental evidence supports the idea that the drug is amorphous in both fibers.

3.2.3. Spectroscopic analysis

The FT-IR spectra of pure perphenazine, its physical mixtures with each polymer and drug loaded and unloaded electrospun fibers are shown in Figure 5.

As expected, considering the system composition, the spectra of the two physical mixtures show domination of the polymer's bands. Only the strongest absorptions of the drug not overlapping those of the polymers are visible. Among these, in the spectra of *P:PVPel* only the peak at 1562 cm^{-1} (aromatic ring stretching) can be seen while in *P:SOLel* only the peaks at 1564 cm^{-1}, at 1454 cm^{-1} (aromatic ring stretching) and at 755 cm^{-1} (C-H out of plane bending for ortho-disubstituted ring) are visible. The disappearance of several signals characteristic of perphenazine suggests that in the fibers the drug molecule changes its conformation and its vibration properties as a consequence of an interaction with the polymer. This interaction is a proof of a good compatibility between perphenazine and PVP.

3.2.4. Thermal analysis

The TG curves of all the fibers (not reported) show a low initial mass loss due to water removal (adsorbed from environment) followed by a decomposition step that in the case of *PVPel* and *P:PVPel* begins after 120 °C, while for *SOLel* and *P:SOLel* begins at 150 °C.

In the DSC curve of perphenazine, only a sharp single endothermic peak at T_{onset} 96.6 °C (ΔH = 83.4 $J \cdot g^{-1}$) which corresponds to the drug melting (Figure 6, curve a) is present. *PVPel* and

SOLel do not show thermal event in the same range of perphenazine (Figure 6, curve d-g). The DSC curves of the drug:polymer physical mixtures show the melting peak of the drug at 96.1 °C with enthalpy change corresponding to 10% of the typical value measured for the pure drug, in agreement with the composition of the systems (Figure 6, curve b-e). This evidence supports the idea that the Turbula mixing parameters result in homogeneous physical mixtures. The same peak is absent in the DSC curve of *P:PVPel* and *P:SOLel* (Figure 6, curve c-f) confirming that the drug in the fibers is amorphous. Measurements with ramp from -70 °C did not allowed to evidence possible glass transitions probably because the drug is too dilute in the fibers polymer.

The physico chemical behaviour of the fibers does not change after their storing under silica gel in a dryer for at least three months.

3.3. In vitro dissolution test

The solubility of *P* was measured in a previous work (Bruni et al. 2012) and is strongly pH-dependent: 2.08 g/L at pH=1 and 0.035 g/L in deionised water. As expected, all the samples show fast and complete dissolution in few minutes when tested in 0.1 N hydrochloric acid, pH=1 (data not reported). This medium simulates the fasted state, but in presence of food the pH of the gastric contents increases. In water, at neutral pH, the dissolution rate of this drug is strongly reduced: less than 40% of the dose is solubilised in 60 min and thus available for absorption (Figure 7). Simply mixing *PVP* with *P* does not produce any significant improvement of the drug dissolution rate. The commercial product Trilafon® shows just a slightly faster drug delivery in this medium, reaching 50% of drug released in one hour. On the contrary, *P:PVPel* fibers show a rapid and complete delivery of the drug in about 15 min. This result can be explained by the particular production method that causes drug amorphization and, at the same time, a fine dispersion in the carrier system.

The optimal performances of the electrospun fibers were also confirmed by the samples based on the SOL polymer, *P:SOLel* (Figure 8).

Soluplus® is an amphiphilic molecule and, for this reason, it is able to further enhance the drug dissolution rate even by simply mixing the two substances. In fact, also the *P:SOLpm* sample shows faster dissolution rate compared to the drug alone and to the reference Trilafon®, but only about 83 % of *P* dose is completely solubilised after 60 min with a dissolution rate much slower compared to the *P:SOLel* fibers.

As for *P:PVPel,* the drug-loaded *SOL* fibers show a rapid delivery of *P*, that is completed in about 30 min. Probably when the rate of dissolution of the two products reach the maximum, the differences between the two carriers are flattened.

4. Conclusions

Two polymeric carrier systems with Plasdone® (*PVP*) and Soluplus® (*SOL*), for the improvement of the water solubility of perphenazine (*P*), were prepared by electospinning and compared to the physical mixtures. The dissolution profiles showed that at neutral pH, *PVP* is not effective in improving drug dissolution rate from the physical mixture, while the amphiphilic product *SOL* is able to enhance the drug solubilisation even from the simple drug-polymer mixture, but only to a limited extent. Both carriers are most effective when used to produce fibers by electrospinning. In fact, the polymeric fibers containing *P* show a fast and complete drug dissolution in about 20-30 min, even at pH 7 where the drug is insoluble. This result can be explained by the physico-chemical characterization that shows how the particular production method causes drug amorphization, but also by the presence of the polymeric carrier and the molecular dispersion of the API in the electrospun matrices.

References

1) Amindon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413-420.

2) Bruni, G., Maggi, L., Tammaro, L., Canobbio, A., Di Lorenzo, R., D'Aniello, S., Domenighini, C., Berbenni, V., Milanese, C., Marini, A., 2015. Fabrication, physico-chemical, and pharmaceutical characterization of budesonide-loaded electrospun fibers for drug targeting to the colon. J. Pharm. Sci., 104, 3798-3803.

3) Hamoria, M., Yoshimatsua, S., Hukuchia, Y., Shimizua, Y., Fukushimab, K., Sugiokab, N., Nishimuraa, A., Shibata, N., 2014. Preparation and pharmaceutical evaluation of nano-fiber matrix supported drug delivery system using the solvent-based electrospinning method. Int. J. Pharm. 464, 243-251.

4) Paaver, U., Heinämäki, J., Laidmäe, I., Lust, A., Kozlova, J., Sillaste, E., Kirsimäe, K., Veski, P., Kogermann, K., 2015. Electrospun nanofibers as a potential controlled-release solid dispersion system for poorly water-soluble drugs. Int. J. Pharm., 479, 252-260.

5) Vrbata, P., Berka, P., Stránská, D., Doležal, P., Lázníček, M., 2014. Electrospinning of diosmin from aqueous solutions for improved dissolution and oral absorption. Int. J. Pharm. 473, 407-413.

6) Hu, X., Liu, S., Zhou, G., Huang, Y., Xie, Z., Jing, X., 2014. Electrospinning of polymeric nanofibers for drug delivery applications. J. Control Release, 185, 12-21.

7) Sharma, R., Singh, H., Joshi, M., Sharma, A., Garg, T., Goyal, A.K., Rath, G., 2014. Recent advances in polymeric electrospun. Crit. Rev. Ther. Drug Carrier Syst. 31, 187-217.

8) Sill, T.J., von Recum, H.A., 2008. Electrospinning: Applications in drug delivery and tissue engineering. Biomaterials 29, 1989-2006.

9) Lopez, F.L., Shearman, G.C., Gaisford, S., Williams, G.R., 2014. Amorphous formulations of indomethacin and griseofulvin prepared by electrospinning. Mol. Pharm. 11, 4327-4338.

10) Verreck, G., Chun, I., Peeters, J., Rosenblatt, J., Brewster, M.E., 2003. Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. Pharm. Res. 20, 810-817.

11) Seif, S., Franzen, L., Windbergs, M., 2015. Overcoming drug crystallization in electrospun fibers – Elucidating key parameters and developing strategies for drug delivery. Int. J. Pharm. 478, 390-397.

12) Brettmann, B.K., Cheng, K., Myerson, A.S., Trout, B.L., 2013. Electrospun formulations containing crystalline active pharmaceutical ingredients. Pharm. Res. 30, 238-246.

13) Zenga, J., Yanga, L., Liang, Q., Zhang, X., Guan, H., Xu, X., Chen, X., Jing, X., 2005. Influence of the drug compatibility with polymer solution on the release kinetics of electrospun fiber formulation. J. Control. Release 105, 43-51.

14) Kim, T.G., Lee, D.S., Park, T.G., 2014. Controlled protein release from electrospun biodegradable fiber mesh composed of poly(epsilon-caprolactone) and poly(ethylene oxide). Int. J. Pharm. 338, 276-283.

15) Paaver, U., Tamm, I., Laidmäe, I., Lust, A., Kirsimäe, K., Veski, P., Kogermann, K., Heinämäki, J., 2014. Soluplus graft copolymer: potential novel carrier polymer in electrospinning of nanofibrous drug delivery systems for wound therapy. BioMed. Res. Int. 1-7.

16) Hartung, B., Wada, M., Laux, G., Leucht, S., 2005. Perphenazine for schizophrenia. Cochrane Database Syst. Rev. 1, CD003443, DOI: 10.1002/14651858.

17) Dahl, S.G., 1998. Pharmacokinetics of neuroleptic drugs and the utility of plasma level monitoring. Psychopharmacol. Ser. 5, 34-46.

18) Jin, Y., Pollok, B.G., Coley, K., Miller, D., Marder, S., Florian, J., Schneider, L., Lieberman, J., Kirshner, M., Bies, R.R., 2010. Population pharmacokinetics of pephenazine in schizopherenia patents from CATIE: impact of race and smoking. J. Clin. Pharmacol, 50, 73-80.

19) United States Pharmacopeia (USP) 31 ed., 2965-2967.

20) Djuris, J., Nikolakakis, I., Ibric, S., Djuric, Z., Kachrimanis, K., 2013. Preparation of Carbamazepine-Soluplus solid dispersion by hot-melt extrusion, and prediction of drug-polymer miscibility by thermodynamic model fitting. Eur. J. Pharm. Biopharm. 84, 228–237.

21) Paavera, U., Heinämäkia, I., Laidmäea, I., Lusta, A., Kozlovab, J., Sillastea, E., Kirsimäec, K., Veskia, P., Kogermanna, K., 2015. Electrospun nanofibers as a potential controlled-release solid dispersion system for poorly water-soluble drugs. Int. J. Pharm. 479, 252–260.

22) Bruni, G., Maietta, M., Maggi, L., Bini, M., Capsoni, D., Ferrari, S., Boiocchi, M., Berbenni, V., Milanese, C., Marini, A., 2012. Perphenazine–fumaric acid salts with improved solubility: preparation, physico-chemical characterization and in vitro dissolution. Cryst. Eng. Comm., 14, 6035-6044.

Legend of figures

Figure 1. SEM micrographs of *PVPel* (a), *P:PVPel* (b), *SOLel* (c) and *P:SOLel* (d).

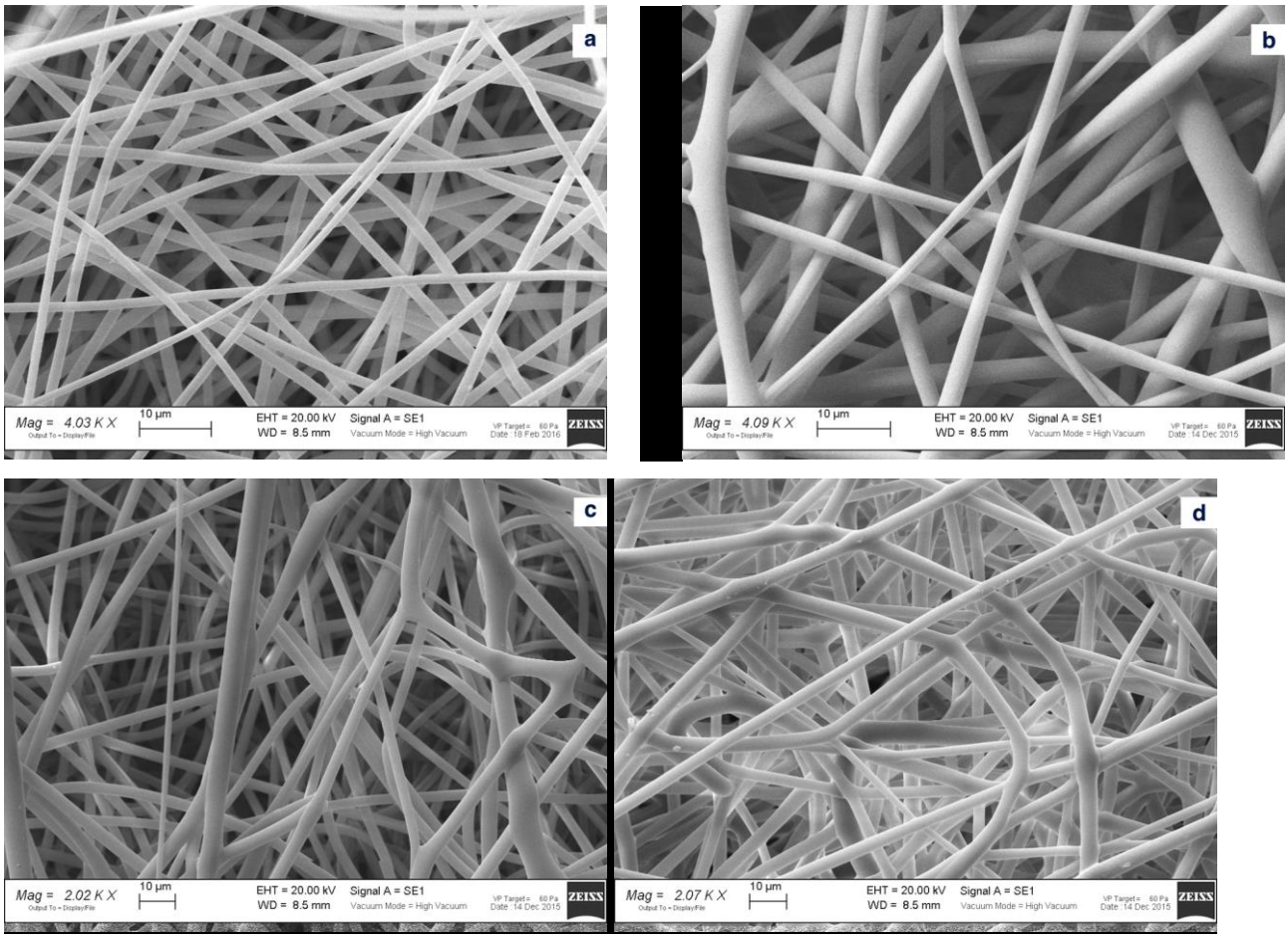


Figure 2. Histogram of the fiber diameter distribution and curve of normal-log distribution, mean value, standard deviation and regression coefficient for *PVPel* (a), *P:PVPel* (b), SOLel (c) and *P:SOLel* (d).

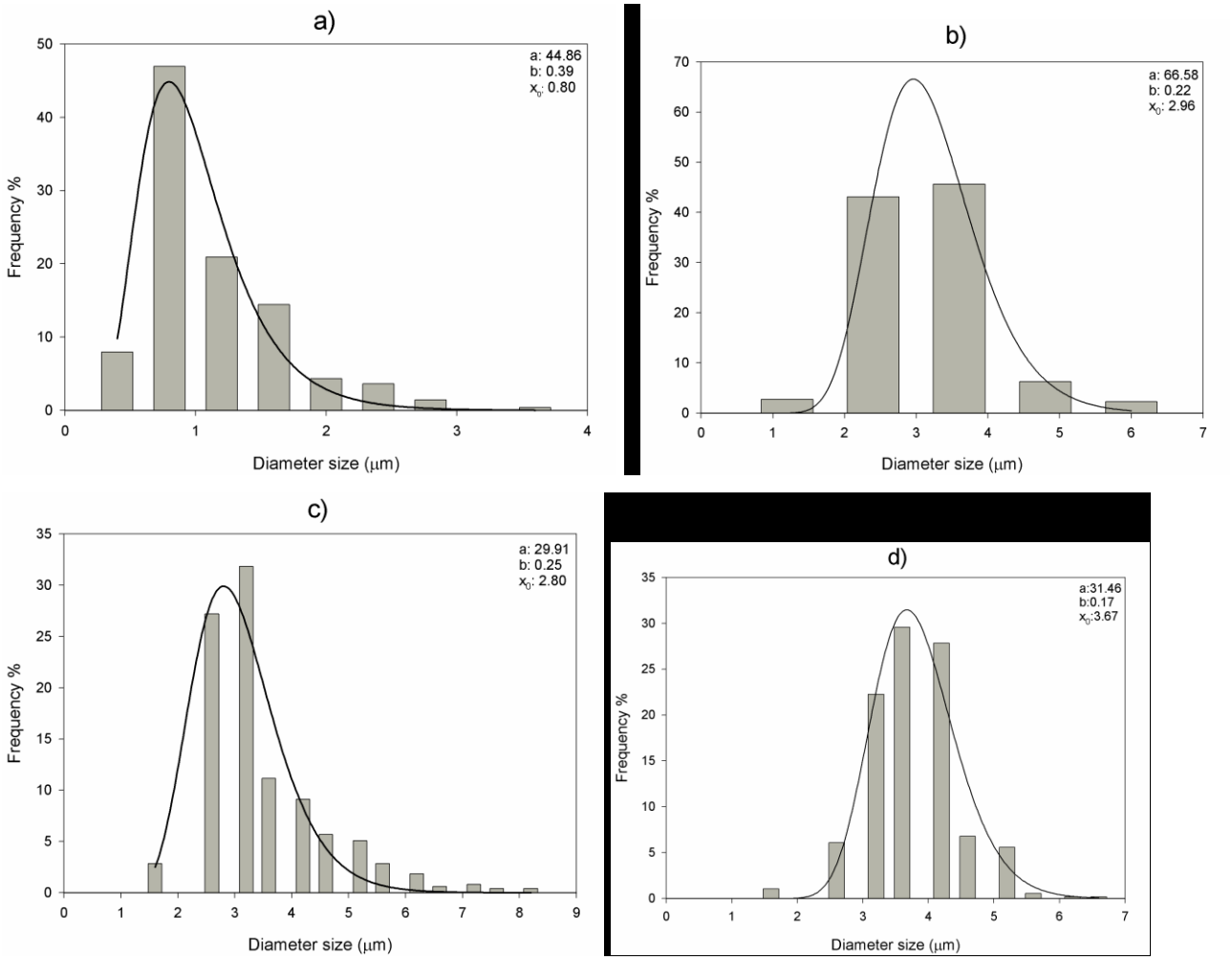


Figure 3. SEM micrographs of the *P:PVPel* (a), and *P:SOLel* (b) samples after milling.

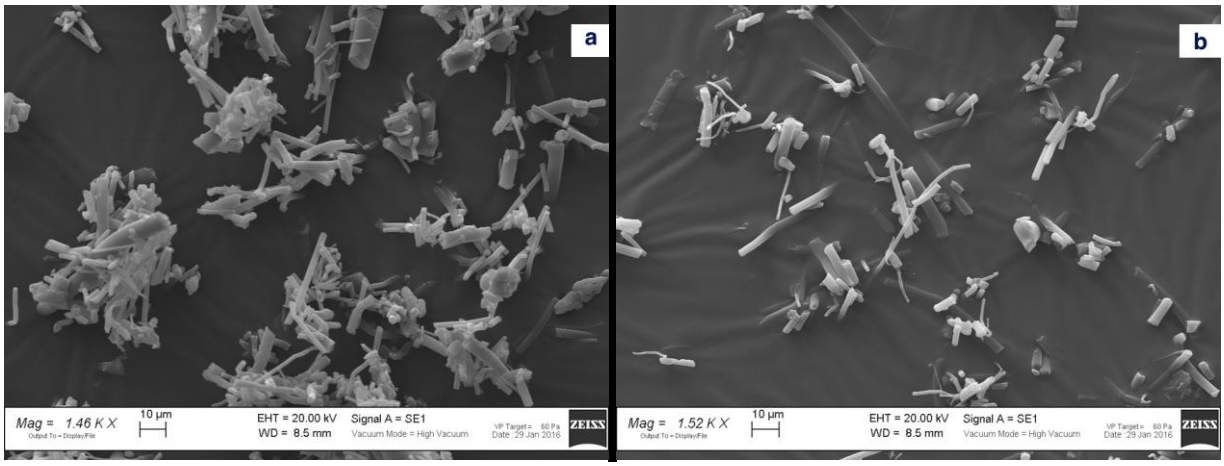


Figure 4. X-ray patterns of *P* (a), *P:PVPpm* (b), *P:PVPel* (c), *PVPel* (d), *P:SOLpm* (e), *P:SOLel* (f), *SOLel* (g).

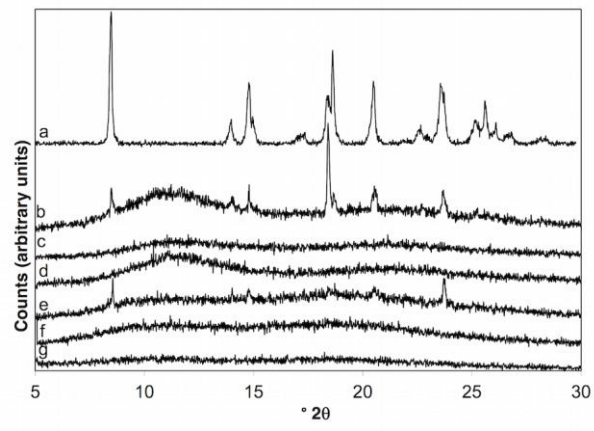


Figure 5. FT-IR spectra of *P* (a), *P:PVPpm* (b), *P:PVPel* (c), *PVPel* (d), *P:SOLpm* (e), *P:SOLel* (f), *SOLel* (g).

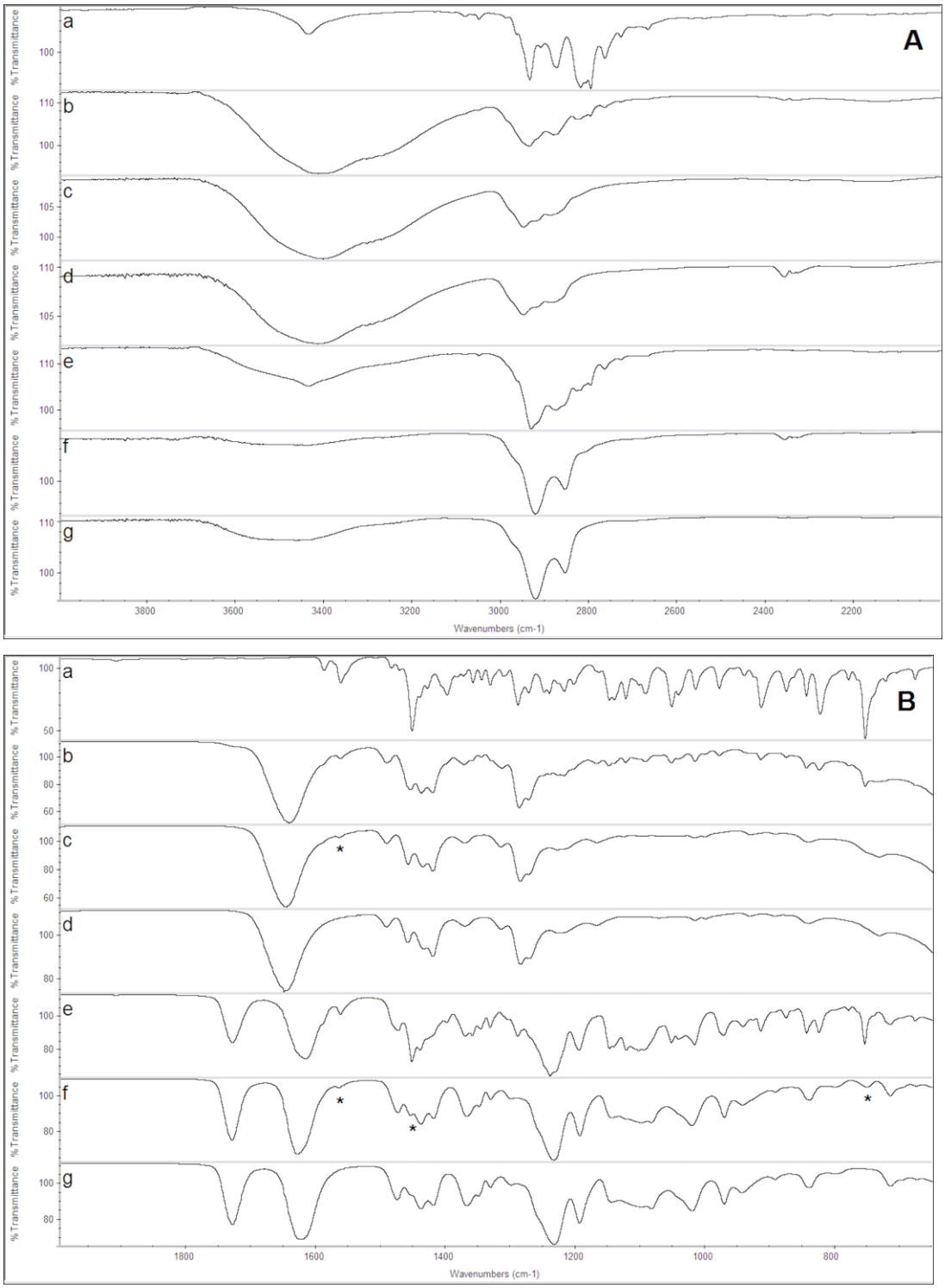


Figure 6. DSC curves of *P* (a), *P:PVPpm* (b), *P:PVPel* (c), *PVPel* (d), *P:SOLpm* (e), *P:SOLel* (f), *SOLel* (g).

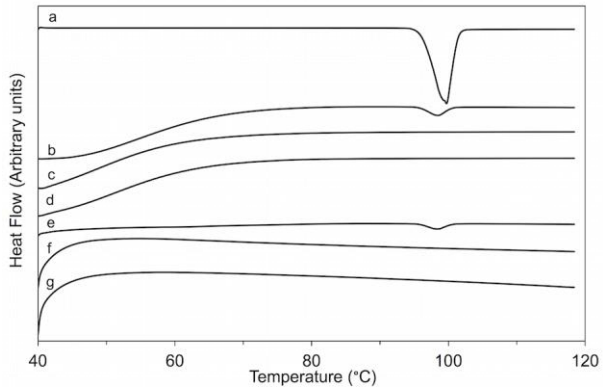


Figure 7. Perphenazine dissolution rate in water compared to physical mixture and electrospun fibers with *PVP*. Trilafon® tablets is the commercial reference. The content is always 8 mg of drug.

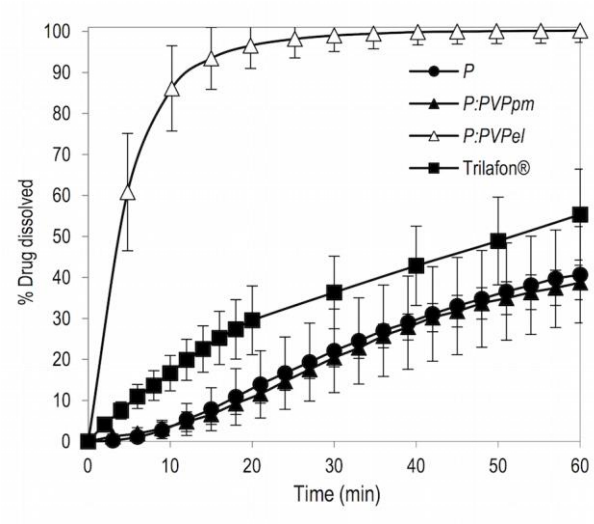
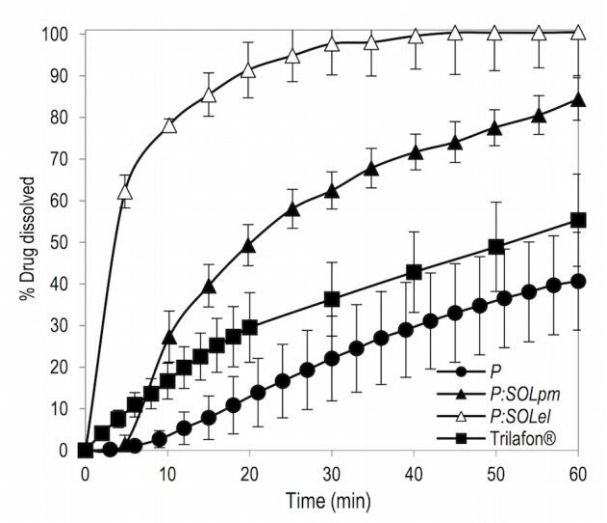


Figure 8. Perphenazine dissolution rate in water compared to physical mixture and electrospun fibers with Soluplus®, *SOL*. Trilafon® tablets is the commercial reference. The content is always 8 mg of drug.



Scheme 1. Molecular structure of perphenazine.

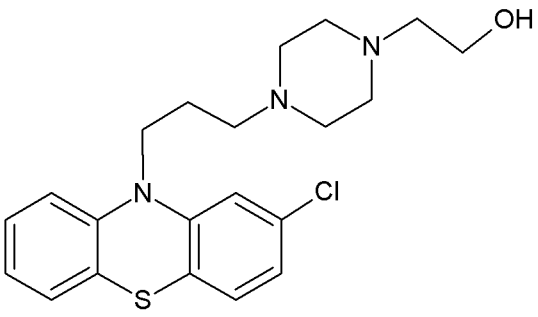


Table 1. Composition and processing conditions for fabrication of electrospun fibers (solvent chloroform, polymer solution concentration 20% (w/w), temperature 24°C, relative humidity 35%)

Sample	*PVP* (w/w)	*SOL* (w/w)	*P* (w/w)	Collector voltage (kV)	Needle voltage (kV)	Feeding rate (mL/h)	Needle-collector distance (cm)	Needle diameter (mm)
PVPel	100	-	-	-4	14	0.5	10	0.8
P:PVPel	90	-	10	-4	14	0.5	10	0.8
SOLel	-	100	-	-4	21	1.0	10	0.8
P:SOLel	-	90	10	-4	21	1.0	10	0.8

Table 2. Percentile values of the electrospun fibers diameters: d(0.1), d(0.5) and d(0.9) are the fractions of fibers having the reported size or lower.

Sample	d(0.1) μm	d(0.5) μm	d(0.9) μm
PVPel	0.57	0.93	1.53
P:PVPel	2.31	3.09	4.12
SOLel	2.17	2.99	4.13
P:SOLel	3.04	3.77	4.67