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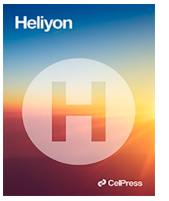

Research article

Encapsulation of a drug into electrospun fibers spun from water soluble polymers to control solubility and release

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ABSTRACT

Electrospun fibers prepared from water-soluble polymers (PVP, PVA, and HPMC) were loaded with pregabalin, a BCS I drug, to address its fast release and adverse effects. The drug dissolved partially (1.8–2.8 wt%) in the polymers, with excess pregabalin in crystalline form within the fibers. The solubility of the drug varied with the pH of the dissolution medium. Most of the drug encapsulated into the fibers during electrospinning, but some was lost due to technical reasons. PVP showed no impact on drug release, offering no benefit as a carrier. However, PVA-based fibers exhibited considerably slower release than the dissolution rate of the neat drug and also the release rate from fibers prepared from the other polymers. This indicates the potential of PVA for using it with pregabalin in practical drug formulations with improved release properties. The pH of the dissolution medium influenced solubility and release rate for specific polymers. Overall, the study highlights the importance of polymer selection and pH control in optimizing the release profile of pregabalin in enhanced drug delivery.

1. Introduction

Drugs can be administered to the patient in many ways, they can be given orally, by injections in various locations of the body (intravenously, intramuscularly, intrathecally, or subcutaneously), they can be placed under the tongue, inserted in the rectum, etc. The most preferred route, however, is oral administration for both the patient and the pharmaceutical company producing the drug [1,2]. The cooperation of the patient is the largest in the case of oral administration and this route offers large formulation flexibility for the producer. However, oral administration through liquids, capsules, or various tablets is often hindered by various factors including the physical-chemical properties of the drug, bad taste, or adverse effects [3–6]. The poor solubility of the drug is one of the main reasons for seeking diverse routes for the preparation of drug formulations, but permeability, controlled release or other reasons also demand the use of various ancillary components, agents, or preparation technologies [7,8].

Numerous approaches exist for enhancing the bioavailability of drugs. Since chemical methods involving the modification of the chemical structure of a drug [9,10] are seldom employed due to their complexity, expense, and inherent risks, physical methods are preferred generally. These include the reduction of particle size [11], the modification of crystallization conditions [12], the

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preparation of solid dispersions [13–15], and solubilization [16,17]. Different devices designed for controlled delivery and increased release rates have been developed as a result of these strategies, such as nanoparticles [18,19], membranes [20], and nanofibers [21–24]. These devices are produced from diverse materials, including both natural [21] and synthetic polymers [23], hydrogels [18,21,22], and composite materials [19,20,23].

Among the methods used, electrospinning is a frequently favored solution for formulating drugs with enhanced bioavailability. This technology is increasingly employed in medicine due to its advantages [25]. Electrospinning provides flexibility, formulation freedom, and often allows for precise control of release kinetics. While the technology itself is relatively straightforward, the characteristics of the resulting fibers depend on several factors such as the properties of the components and processing parameters like voltage, pump rate, and the distance to the collector [26]. Drug release from the fibers is influenced also by the interactions among the components, which can alter the form and location of the drug within the fibers thus affecting release kinetics [27,28]. Despite the many parameters influencing drug release, they also present opportunities to regulate solubility, dissolution rate, and other factors crucial for drug delivery and, ultimately, bioavailability.

Drugs are classified according to the Biopharmaceutics Classification System (BCS) into four categories. BCS IV drugs exhibit poor solubility and permeability, while BCS I drugs possess the opposite characteristics, making them the easiest to formulate. Pregabalin, also known as (S)-3-aminomethyl-5-methylhexanoic acid, is a BCS I drug utilized for its anticonvulsant, anti-hyperallergic, and anxiolytic effects by binding to the alpha-2-delta-1 proteins of voltage-dependent calcium channels in the central nervous system [29]. It is available as an immediate-release tablet, with a daily dosage ranging from 150 to 600 mg, administered two or three times daily [29,30]. Being a BCS I drug, one would wonder about the need for modified formulation technology, but pregabalin has at least two drawbacks: very fast release and adverse effects like sleepiness, dizziness and loss of consciousness. Consequently, several attempts have been made mainly to control release [31–34], but occasionally also to compensate or decrease its adverse effects [35]. The modified formulations used various polymers such as (hydroxypropyl) methyl cellulose (HPMC) and poly(methacrylic acid-co-methyl methacrylate), but also other components like oleic acid or polyethylene glycol [34]. Aydogan et al. [31] tried to prepare microspheres, while Qin et al. [33] developed a gastro-floating drug delivery system from pregabalin. No attempt has been made to use electrospinning to control the rate of release or compensate for the adverse effect of the drug.

Considering the drawbacks of pregabalin and the fact that electrospinning has not been used for its formulation yet, the objective of our investigation was to fabricate electrospun fibers utilizing three water-soluble polymers and assess their release characteristics. The chosen polymers, hydroxypropyl-methyl-cellulose (HPMC), polyvinyl-pyrrolidone (PVP), and polyvinyl-alcohol (PVA), are all approved and widely employed in the field of pharmaceutics. Electrospinning conditions were optimized in the study, and the morphology of the resulting fibers was characterized comprehensively. The form, location, and distribution of pregabalin within the fibers were examined using various methods. Subsequently, the release of the drug was investigated as a function of the pH of the dissolution medium. Release rate was modeled using the Noyes-Whitney equation, and the results were interpreted with practical application in mind.

2. Experimental

2.1. Materials

The pregabalin (Prega) used in the experiments was supplied by Egis Pharmaceutical PLC (Budapest, Hungary). Three water-soluble polymers were selected for the study. Hydroxypropyl-methyl-cellulose (Methocel E5, HPMC) was purchased from Colorcon Limited (Harleysville, PA, USA), polyvinyl-pyrrolidone (PVP) was obtained from Alfa Aesar, (Tewksbury, MA, USA) and polyvinyl-alcohol (Mowiflex LP, PVA) from Kuraray (Tokyo, Japan). The chemicals used for the preparation of solutions and buffers, i.e. disodium hydrogen phosphate dihydrate, anhydrous sodium dihydrogen phosphate, ethanol, methylene chloride, sodium hydroxide and hydrochloric acid (37 %) were purchased from Molar Chemicals, Hungary, while acetic acid from Merck (Darmstadt, Germany) and sodium acetate trihydrate from Reanal (Budapest, Hungary). All materials and chemicals were used as received.

2.2. Solutions

HPMC was dissolved in the 1:2 mass ratio mixture of ethanol and methylene chloride. 1 g polymer was dissolved in all three cases for electrospinning. Ethanol was used as a solvent for the preparation of PVP solutions. The concentration of the polymer changed between 20 and 50 wt% during the optimization of the electrospinning technology. PVA was dissolved in distilled water to prepare solutions containing the polymer at 15 wt%. In order to improve the quality of the fibers and find optimum conditions, water was replaced with 10, 20, 30 and 40 vol% ethanol. HPMC and PVP solutions were prepared by continuous stirring overnight. PVA could be dissolved at 70–90 °C in 20–30 min by intensive stirring. The active component, Prega, was dissolved in the solutions in various amounts depending on the quality of the fibers.

Release experiments were carried out in four media, in buffers with four different pH values. The solutions were prepared in a calibrated measuring vessel of 1000 ml capacity. The composition of the buffer solution of pH 4.0 and pH 6.8 was taken from the literature [34]. The solution with pH 1.2 was prepared with 5.26 ml concentrated (37 %) hydrochloric acid. The acetate buffer (pH 4.0) contained 4.7 ml concentrated (100 %) acetic acid, 2.45 g $C_2H_3O_2Na{\cdot}3H_2O$ and 2 ml 1 M NaOH solution. The phosphate buffer with pH 6.8 was produced from 6.12 g NaH_2PO_4, 8.72 g $Na_2HPO_4{\cdot}2H_2O$ and 2 ml 1 M NaOH solution. The pH of the solutions was checked with the help of a Metrohm 827 pH apparatus (Metrohm Ltd, Herisau, Switzerland) and was adjusted by adding the necessary amount of 1 M NaOH solution.

2.3. Electrospinning

Fibers were fabricated using the Spinsplit (Spinsplit LLC, Budapest, Hungary) electrospinning machine. Concentration, voltage, pump rate and the distance to the collector plate all depend on the characteristics of the solutions, i.e. on the combination of the polymer and solvent. The optimized parameters were different for the three polymers used. The time of fiber spinning changed between 5 and 60 min depending on the amount of fiber needed. The optimized composition of the fiber spinning solution and the electrospinning parameters are listed in Table 1.

2.4. Release experiments

Release experiments were carried out on 10 mg fiber containing 0.3–0.47 mg Prega. All measurements were done in triplicates. The standard deviation of the measurement was determined in each case. The fibers were placed into 100 ml solution and 2 ml samples were taken intermittently after various time intervals. The concentration of the drug in the samples was determined by UV–Vis spectrophotometry after calibration. Separate calibration curves were constructed for each of the four release media. After the determination of UV absorbance, the samples were replaced into the beaker containing the fibers. The experiments were carried out at room temperature without stirring. The kinetics of drug release was described quantitatively by the Noyes-Whitney equation [51]. The equation (Eq. (2)) was fitted to the amount of released drug by nonlinear regression using the Levenberg-Markquardt iteration algorithm. The iteration steps were done by using the Origin software (OriginPro 2018, Originlab Co., Northampton, MA, USA). The quality of the fit was characterized by the determination coefficient and the software determined the level of significance as well.

2.5. Characterization

2.5.1. Encapsulation

The encapsulation of the drug into the fibers was checked by Fourier transform infrared spectroscopy (FTIR). Spectra were recorded using a Bruker Tensor 27A (Bruker Corp., Billerica, MA, USA) apparatus in the wavelength range of 4000-400 cm^{-1} at 2 cm^{-1} resolution with 64 scans. Prega or the fibers cut into small pieces (2 mg) were mixed with KBR to prepare pastilles for the recording of the spectra. The spectra were evaluated using the Opus 2015 software. All spectra were recorded in triplicates. Encapsulation was checked also by dissolving 1.5 mg fibers containing the drug in 2 ml distilled water. The fibers were placed into capped glass vials and dissolved with stirring for 30 min to ensure complete dissolution. The amount of dissolved Prega was determined by UV–Vis spectrophotometry using a Unicam UV 500 type spectrophotometer (Unicam Ltd., Cambridge, UK) after calibration. The measurement was done in the wavelength range of 200–300 nm with 1 nm resolution and a scan rate of 240 mm/min. Experiments were run in triplicates.

2.5.2. Viscosity

The shear dependence of the polymer solution used for electrospinning was determined by rotational viscometry in the presence and absence of the drug. Rheological analysis was carried out using a rotational rheometer (Haake-Mars 60, Thermo Fisher Scientific, USA) in the cone-plate setup for solutions. The measurements were performed at 25 °C. The solutions were stirred constantly before the test.

2.5.3. Solubility

The solubility of the drug in the three polymers used as matrix was also determined by separate experiments. Increasing amounts of the drug was added to the solution of the polymer, the solution was poured into Petri dishes, the solvent was evaporated and then the characteristic absorbance of the drug was determined by UV–Vis spectrophotometry on the resulting films. Absorbance increased proportionally with the concentration of the dissolved drug, while above the solubility limit the drug precipitated, formed a separate phase and absorbance remained nearly constant. Solubility was determined from the intersection of the straight lines obtained for dissolved and phase separated drugs in the absorbance vs. concentration plot (see later in Fig. 2).

2.5.4. Structure

The crystalline structure of the components was studied by differential scanning calorimetry (DSC) and X-ray diffraction measurements (XRD). DSC measurements were done on 3–5 mg fibers or powder samples of the drug using a PerkinElmer DSC IC apparatus (PerkinElmer Inc., Waltham, MA, USA); samples were heated from 30 to 250 °C at the heating rate of 10 °C/min under N_2 purge, cooled down at the same rate and then heated again. XRD patterns were recorded using a Philips PW 1830 diffractometer (Philips N.V., Amsterdam, Netherlands). Measurements were carried out in the range of 2θ angles of 5–40° with 0.04° increments and 1 s/step rate at the accelerating voltage of 40 kV and exciting current of 35 mA.

Table 1
Composition of the fiber spinning solutions and the technological parameters used for electrospinning.

Polymer	Drug conc. (wt%)	Polymer conc. (wt%)	Voltage (kV)	Feeding rate (μl/s)	Collector distance (mm)
HPMC	3	10	18	0.5	100
PVA	5	15	15	0.2	140
PVP	5	40	18	0.5	125

2.5.5. Morphology

The morphology of the fibers was studied by digital optical (DOM) and scanning electron (SEM) microscopy. DOM micrographs were recorded using a Keyence VHX 5000 microscope (Keyence Corporation, Osaka, Japan) and they were used for the optimization of the electrospinning process as well as for the determination of fiber thickness. The diameter of at least 100 fibers was measured for each sample to determine average fiber thickness and its distribution. SEM micrographs were taken by using a JEOL JSM 6380LA (Jeol, Tokyo, Japan) scanning electron microscope (SEM) at the accelerating voltage of 15 kV.

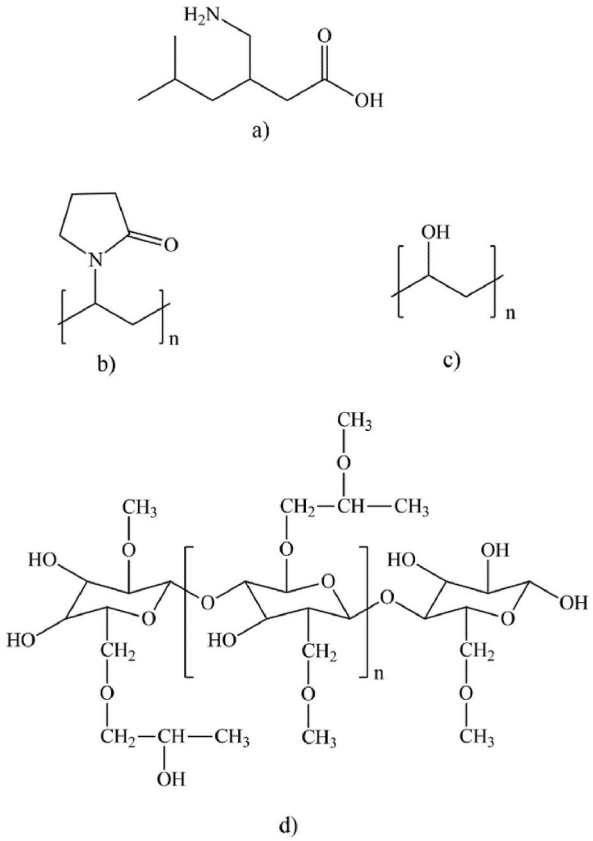
3. Results and discussion

The findings are discussed in several sections. The characteristics of the components influencing the preparation of electrospun fibers and the efficiency of drug release are considered initially. Subsequently, interactions and miscibility are analyzed, followed by the presentation of fiber characteristics. The subsequent section addresses the distribution of the drug within the fibers and its specific location. The final section presents the results of the drug release study, including quantitative analysis, along with notes on practical significance.

3.1. Component properties

The physical and chemical characteristics of the active components in drug formulations play an important role in their effect and efficiency. Pregabalin is a small molecule, an amino acid containing an amine and an acid group. The chemical structure of the molecule is presented in Scheme 1a. The drug is crystalline in its original form as shown by the SEM micrograph of Fig. 1a, but also by XRD (not shown here) and DSC measurements. According to the DSC melting curve presented in Fig. 1b, the melting point of the drug is 198.6 °C. Crystallinity usually hinders solubility, but pregabalin being a BCS I drug, dissolves easily in water. As shown by its chemical formula it can form hydrogen bonds, but it may take part also in electrostatic interactions, depending on the pH of the medium, of course.

The three water-soluble polymers selected for the study have a wide variety of chemical structures and functional groups as shown by Schemes 1b-d. All three of them are capable of forming hydrogen bonds either as hydrogen donors or acceptors, or both. Accordingly, strong interactions are expected to form among all components both in the spinning solution and in the final formulation. Besides their chemical structure, other factors also influence the efficiency of the polymers as carrier materials. PVA is crystalline,



Scheme 1. Chemical structure of the main components of drug containing electrospun fibers; a) pregabalin, b) PVP, c) PVA, d) HPMC.

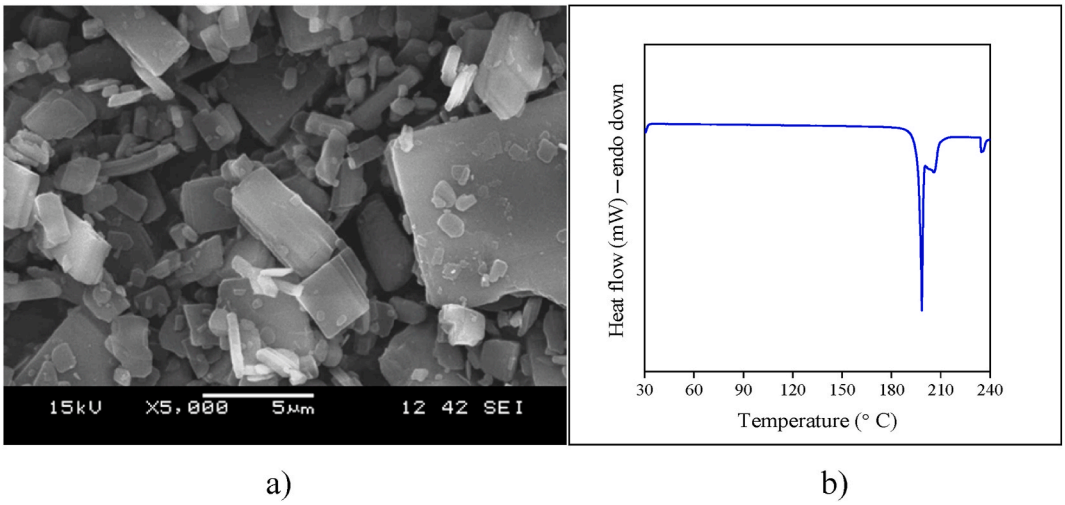


Fig. 1. Evidence for the crystalline structure of the drug (pregabalin) studied in this work; a) SEM micrograph, b) DSC melting curve.

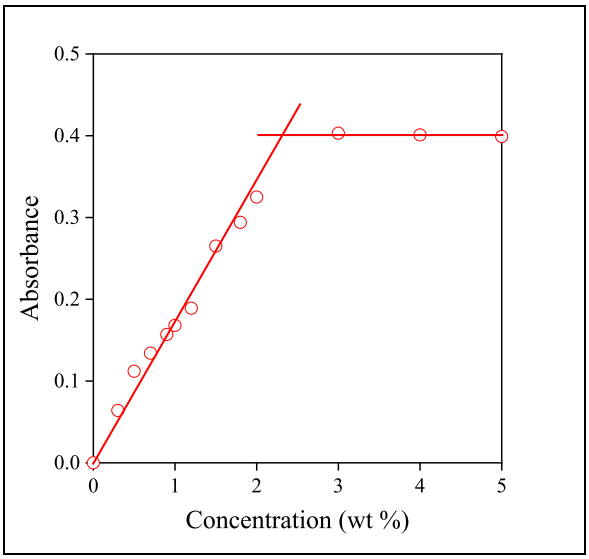


Fig. 2. Determination of the solubility of the drug in PVA by UV–Vis spectrophotometry.

while the other two polymers are amorphous. PVA fibers spun from a solution containing an organic solvent were shown to crystallize with time, which led to further phase separation and segregation of the active component within and outside the fibers [28]. Accordingly, interactions and solubility influence the structure of the final device, the distribution and form of the components, release rate and thus efficiency.

Table 2
Solubility parameters of the components calculated by Fedor's [36] approach and the solubility of the drug (pregabalin) in them.

Component	Solubility parameter, δ ($MPa^{1/2}$)	Solubility (wt%)
PVA	33.0	2.8 ± 0.03
PVP	26.0	2.4 ± 0.02
HPMC	28.6	1.8 ± 0.01
Pregabalin	21.0	–
Dichloromethane	20.2	0.1 ± 0.10
Ethanol	25.7	1.9 ± 0.03
Water	47.9	51.0 ± 0.13

3.2. Interactions, solubility

As mentioned in the previous section, interactions strongly influence the release and the efficiency of the formulation. The easiest way to estimate possible interactions is the comparison of the Hildebrand solubility parameter of the components. These are collected in Table 2 for the polymers, pregabalin and the solvents used for electrospinning. Quite surprisingly, apart from dichloromethane, pregabalin has the smallest solubility parameter indicating relative poor solubility in the polymers, but in most of the solvents as well. The comparison of the solubility parameters obtained for the various materials used in the study calls attention to the deficiency of the approach; Hildebrand solubility parameters cannot handle specific interactions very well.

The actual solubility of the drug in the polymer and in the solvents was also determined. The method for the former is demonstrated in Fig. 2. Increasing amounts of the active component are added to the polymer and the concentration of the drug is determined by UV–Vis spectrophotometry. Absorbance is proportional to the concentration of the dissolved drug up to the solubility limit, but does not change, or changes only slightly when the substance precipitates and forms a separate phase. According to the figure, the solubility of pregabalin in PVP is 2.6 wt%, which is relatively large, since much smaller solubilities were measured for polar, small molecular weight compounds, including drugs, in various polymers. Solubilities determined in this way are listed in the third column of Table 2. The solubility of the drug in the three polymers is very similar, covers the range of 1.8 and 2.8 wt%. Quite surprisingly, solubility is small in organic solvents and relatively large solubility was measured only in water (see Table 2).

In spite of the different solubility parameters, interactions develop between the drug and the polymers used for the spinning of the fibers. The shear dependence of the viscosity of the spinning solution is presented in Fig. 3. Because of the dissimilar chemical structure of the components, different concentrations and molecular weights, viscosities are quite different. The relatively large concentration of the polymers in the solution results in the interaction of the components, in the development of a network structure, shown by the change of viscosity at small shear rates. The shear dependence of PVA is the simplest; its viscosity is relatively small and shear dependence is weak. The behavior of PVP is very interesting; shearing results in the orientation of the molecules and increased interaction at intermediate shear rates. The interactions developing in the solution and shear dependence influence significantly the quality of the fibers, their diameter and its distribution. The interaction of the drug and the polymers is even more interesting. As the figure shows, the viscosity of the solution is smaller in the presence of the drug in all three cases, than in its absence. Obviously, polymer/drug interactions replace polymer/polymer interactions thus hindering structure formation and decreasing viscosity. Polymer/drug interactions may lead to slower drug release, an important issue in the case of pregabalin.

3.3. Fiber spinning and fiber characteristics

Fiber spinning, productivity and especially the quality of the fibers are determined by a large number of factors. The spinning technology must be optimized separately for each combination of polymer and drug. The main aspect of optimization is the quality of the fibers depending on concentrations and spinning parameters. Because of the interaction of the drug and the polymer in the spinning solution, drug content must be selected carefully. Drug content, polymer concentration, voltage, feeding rate and collector distance were the parameters optimized in our case. Optimized spinning parameters are listed in Table 1. Drug content should be as large as possible, but larger concentrations as those in Table 1 lead to improper fiber quality.

The quality of the fibers was excellent in the case of PVA and PVP and slightly worse for HPMC (Fig. 4); the fibers were more

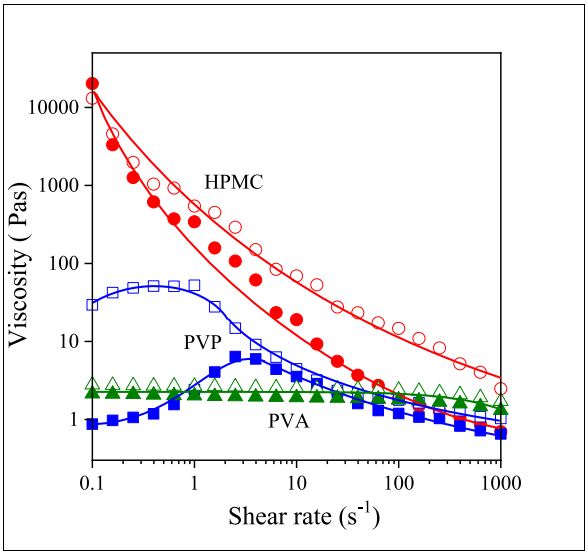


Fig. 3. Effect of the addition of the drug on the viscosity of the spinning solution. Symbols: (○,●) HPNC, (□,■) PVP, (△,▲) PVA; empty symbols: without the drug, full symbols: with drug.

irregular and their size distribution was wider in the latter polymer than in the other two cases. Fiber thickness influences considerably the rate of dissolution and thus the release of the drug. Accordingly, the diameter of the fibers and size distribution were determined and they are listed in Table 3. The presence of the drug influences fiber diameter only in the case of HPMC. The width of the distribution does not change upon the addition of the drug, except that it is slightly wider for PVP as shown in Fig. 5. The study of fiber morphology showed that the electrospun fibers containing the drug could be used as a potential delivery system.

Besides the shape and size of the fibers, the physical form of the components is also important for drug delivery. Although PVA is a crystalline polymer, the conditions of electrospinning do not allow its crystallization, all three polymers are amorphous in the fibers. On the other hand, the drug is originally crystalline as shown by Fig. 1. Crystalline drugs were shown to become amorphous when incorporated into electrospun fibers facilitating dissolution [37,38]. In the case of pregabalin, however, the undissolved drug forming a separate phase is crystalline as shown by Fig. 6 for PVP. Similar XRD traces were obtained also for the HPMC and PVA fibers containing the drug. The intensity of the crystalline reflections of the drug depended on drug content and the extent of solubility (see Table 1).

3.4. Location, distribution

According to the results presented above, the solubility of the drug is smaller in the polymer than the amount added in all three cases (see Tables 1 and **2**). Accordingly, some of the drug must form a separate phase in the device. Additionally, Fig. 6 proved unambiguously the presence of crystalline pregabalin in the fibers. FTIR spectroscopy provides a further proof for the presence of pregabalin in the electrospun fibers. FTIR spectra of pregabalin, PVA fibers and the PVA/pregabalin preparation are presented in Fig. 7. Pregabalin has several characteristic peaks including the NH_2 bending vibration appearing at 1550 cm^{-1}. This absorption band is clearly present also in the fibers containing the drug, which proves that the drug is encapsulated into the fibers produced by electrospinning. It is not completely clear, however, whether the drug is located within or among the fibers. Earlier research showed that depending on solubility and spinning conditions some of the drug could be located also among the fibers [37].

SEM micrographs might offer some indication about the location of the drug. Separate crystals have been observed to be located within [38], but also among the fibers [28]. In the present case, such unambiguous proof is not supplied by scanning electron microscopy. As Fig. 8 shows, fibers containing the drug have irregular surfaces, which might indicate the presence of particles within the fibers. Crystals have not been observed among the fibers for any of the three polymers, thus at least some of the drug must be located within the fibers. The degree of encapsulation was also determined in separate measurements and the results are presented in Table 4. As the results show, encapsulation is reasonable, values around 70–80 % were obtained for the three polymers. This amount includes all drug located both within and among the fibers. As shown earlier, the remaining drug might be lost during fiber spinning and the handling of the fibers [37,38].

3.5. Release

The final justification for the preparation of the electrospun device might be given by the release experiments. We cannot hope that the adverse effects of pregabalin are eliminated or compensated by the presence of a polymer, but the rate of release might be controlled in this way. The dissolution of the neat drug in various media is shown in Fig. 9. Although the extent of dissolution depends on pH that is not very surprising in view of the chemical structure of pregabalin (see Scheme 1a), the rate of release is very fast in all cases. For fast-release drug formulations, only a short time is spent within the safe but effective plasma concentration range before the need of re-dosing [39,40].

The time dependence of release is shown for two polymers in Fig. 10. The two polymers, PVP and HPMC behave differently. The

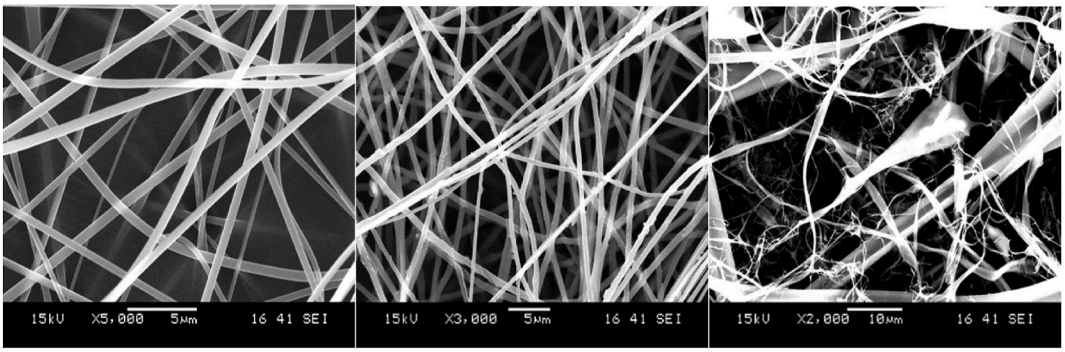


Fig. 4. SEM micrographs demonstrating the characteristics of the fibers; a) PVP, b) PVA, c) HPMC; the fibers contain the drug in the amount indicated in Table 1.

Table 3
Effect of the type of the polymer used and the presence of the drug on the characteristics of the electrospun fibers.

Polymer	Average fiber diameter (μm)	
	no drug	with drug
HPMC	2.7 ± 1.5	4.4 ± 0.9
PVA	1.5 ± 0.1	1.6 ± 0.3
PVP	2.9 ± 0.3	3.2 ± 0.2

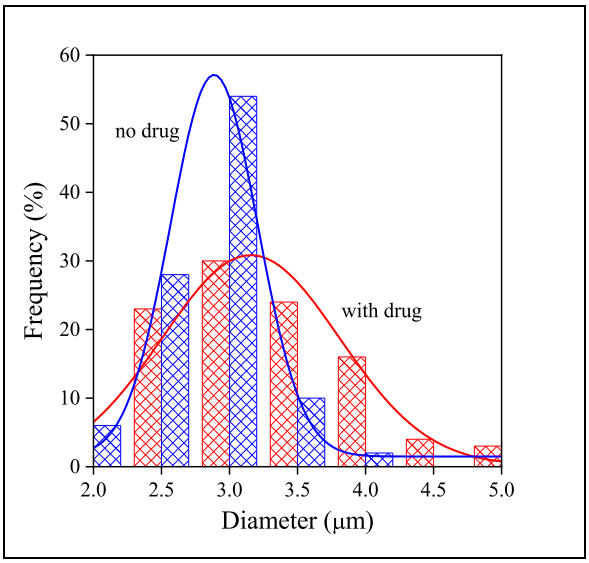


Fig. 5. Size (diameter) and size distribution of electrospun fibers produced from PVP. Effect of the presence of the drug.

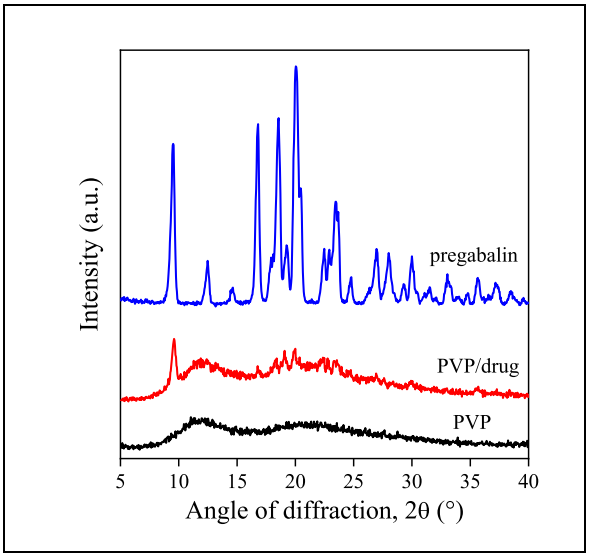


Fig. 6. XRD traces proving the presence of crystalline drug in electrospun PVP fibers; traces recorded on pregabalin, PVP and PVP/drug fibers.

rate of release and the released amount are completely independent of pH in the case of PVP, but both depend on pH to some extent for HPMC. PVA behaves very similarly to HPMC in the pH dependence of drug release. The chemical structure of the polymers used (see Scheme 1b-c) indicates that PVP behaves as an acceptor in hydrogen bonds, while the other two polymers are hydrogen donors. The difference in structure results in dissimilarities in interactions and in drug release behavior. The comparison of the dissolution profile

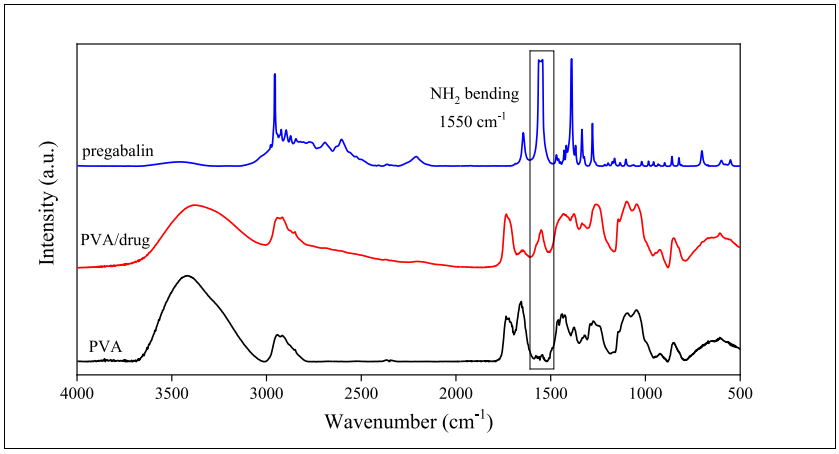


Fig. 7. Evidence for the encapsulation of the drug into the electrospun fibers; comparison of the FTIR spectrum of pregabalin, PVA and the PVA fibers containing the drug.

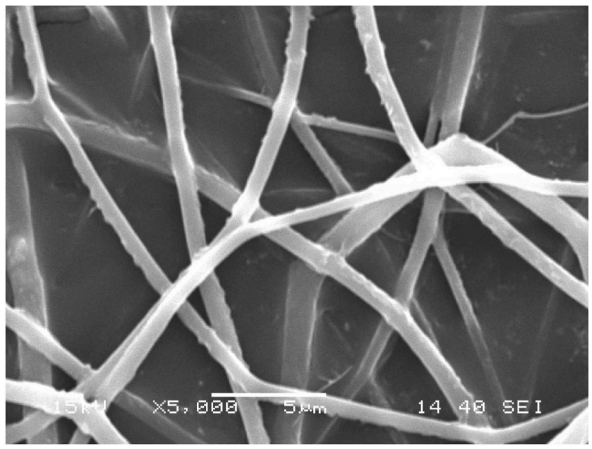


Fig. 8. Possible proof for the encapsulation of crystalline pregabalin into electrospun PVA fibers; SEM micrograph.

Table 4
Nominal drug content and the degree of encapsulation in the electrospun fibers prepared in the study.

Polymer	Nominal drug content (wt%)	Encapsulation (%)
HPMC	3.0	67.5 ± 0.9
PVA	5.0	78.7 ± 0.2
PVP	5.0	83.7 ± 0.4

of Prega and the release behavior of the fibers produced from the three polymers verifies these differences even further (Fig. 11). At pH = 7.2, the release from PVP and the dissolution of the neat drug proceed practically at the same rate, while both the released amount and the rate of release seems to be smaller for HPMC and PVA. While the preparation of electrospun fiber devices from PVP is not practical, one may consider using the other two polymers for the encapsulation of pregabalin.

The release profiles presented in Figs. 9–11 give a qualitative idea about solubility and release rate, but quantitative analysis facilitates evaluation and allows drawing conclusions that are more accurate. The release of pregabalin from the fibers may occur by two mechanisms: the diffusion of the drug from the fibers or the dissolution of the polymer. Many models exist for the description of diffusion but somewhat less for the quantitative analysis of dissolution. The fibers dissolve extremely fast, which in fact, caused some

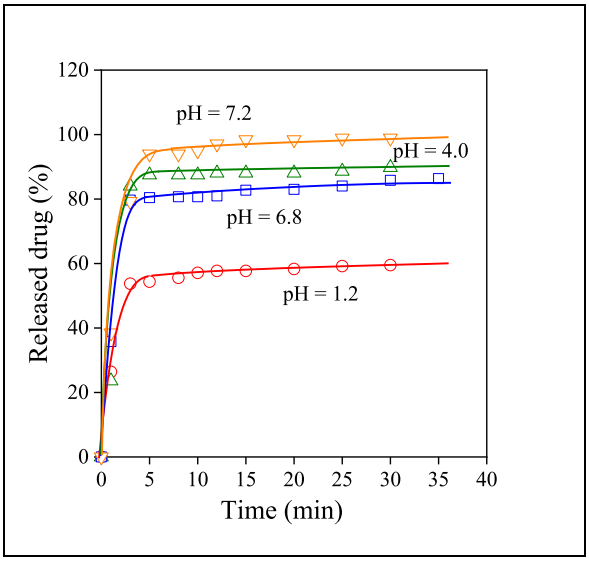


Fig. 9. Kinetics of the dissolution of neat pregabalin in buffers of various pH values. Symbols for pH: (○) 1.2, (□) 4.0, (△) 6.8, (▽) 7.2.

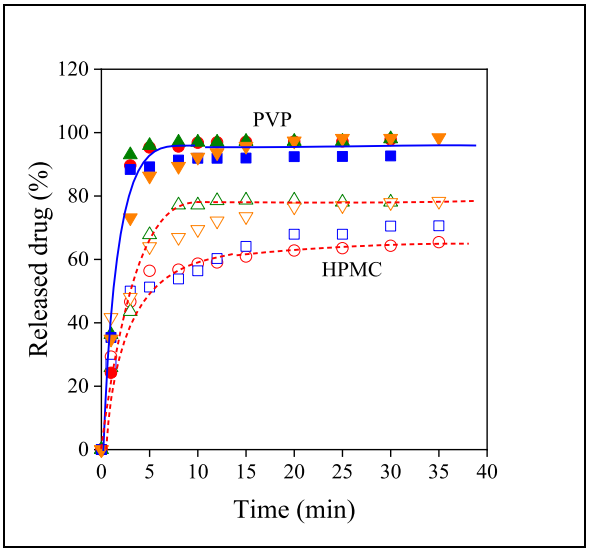


Fig. 10. Time dependence of drug release from electrospun PVP and HPMC fibers. Symbols are the same as in Fig. 9, empty symbols: HPMC, full symbols: PVP.

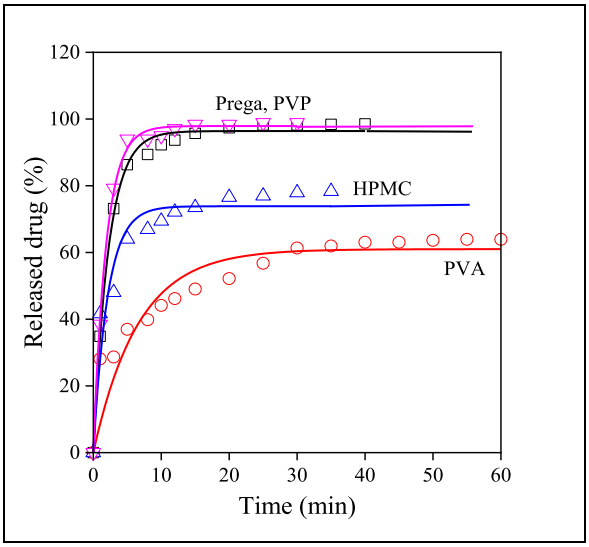


Fig. 11. Comparison of the release characteristics of electrospun polymer fibers at pH 7.2. Symbols: (○) PVA, (△) HPMC, (□) PVP, (▽) neat pregabalin.

practical problems, only a few points could be determined at short times during the release study. The very fast disappearance of the fibers indicate dissolution control, nevertheless diffusion models were also fitted to the experimental data for comparison and checking. Diffusion controlled release is often described by the zero-order [41], first order [41], power law [42,43], Peppas-Sahlin [44] and several other models [45–49]. Dissolution is modeled the most frequently by the Noyes-Whitney equation [50]. A proper diffusion model was also used to evaluate release kinetics [51]. The best fit was offered by the Noyes-Whitney equation and the diffusion model [51] but the fast disappearance of the fibers when immersed in the release medium indicated that release is probably not diffusion but dissolution controlled in our case thus confirming visual observation. We must call the attention here, though, that because of fast release and insufficient experimental data at short times, fitting was not always easy and unambiguous and occasionally other models gave better results than the Noyes-Whitney equation thus the exact mechanism of release could not be identified by modeling. Nevertheless, Eq. (2) was selected for further analysis and we are convinced that it is adequate for comparative purposes.

The Noyes-Whitney equation describes dissolution kinetics in the following way [52]

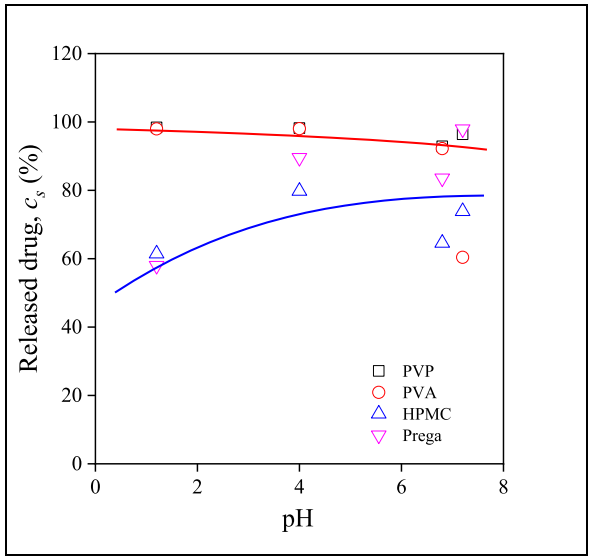
$$\frac{dc(t)}{dt} = \frac{A\,D}{V\,h}\,[c_s - c(t)] \tag{1}$$

where c is the concentration of the drug, t time, A surface area, D diffusion coefficient, V is the volume of the dissolution medium, h is the thickness of the diffusion layer and c_s solubility. The integration of the equation and rearrangement leads to

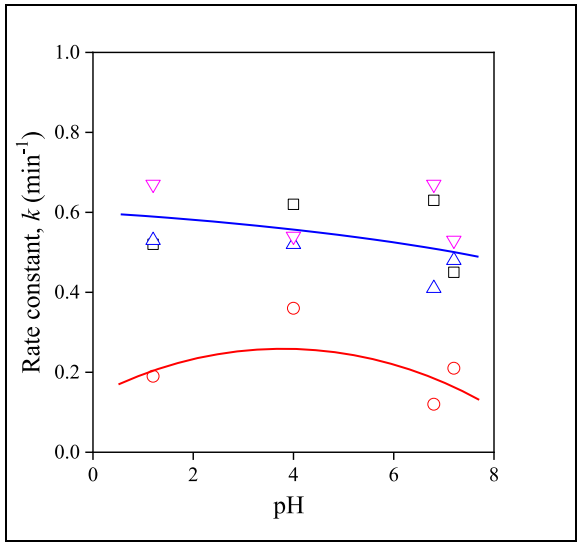
$$c(t) = c_s\,\left(1 - e^{-kt}\right) \tag{2}$$

where k contains the constants of **Eq. (1)**, i.e. $k = AD/Vh$ and corresponds to the overall rate of dissolution. **Eq. (2)** was fitted to all dissolution and release correlations to determine solubility (c_s) and the rate of dissolution (k).

The results of the calculations are presented in Fig. 12. The released amount is practically the same and it is close to 100 % for PVP and PVA (Fig. 12a). The amount of released drug practically does not depend on pH; a smaller value was obtained for PVA at pH 7.2, which might be a real effect, but might result also from experimental or fitting error. The dissolution of the neat drug was shown to depend on pH (Fig. 9), pH dependence is considerably smaller for the drug encapsulated into the fibers. The rate of release, which is much more important for practice, is similar for PVP and HPMC, but it is considerably slower in the case of PVA (Fig. 12b). The difference is significant, the release rate in PVA is less than one-third that of the dissolution rate of neat pregabalin thus the encapsulation of the drug into this polymer seems to be beneficial for practice. The release rate can be regulated further by the compression of fiber mats into disks and by the optimization of disk morphology [28].



a)



b)

Fig. 12. Kinetic parameters determined by the fitting of Eq. (2) to the time dependence of drug release for the three polymers and the neat drug. a) released drug, c_s, b) rate constant, k. Symbols: (○) PVA, (△) HPMC, (□) PVP, (▽) neat pregabalin.

4. Conclusions

Pregabalin, a BCS I drug has two drawbacks, adverse effects and very fast release. The second might be compensated by coating or proper formulation. The analysis of the polymers used for electrospinning and the components of the spinning solutions showed that all components interact with each other. Relatively large amount, 1.8–2.8 wt%, of the drug dissolves into the polymers and surplus pregabalin is located within the fibers in crystalline form. The solubility of the drug in the solvents used varies in a wide range and it depends on pH in the dissolution media used. Most of the drug is encapsulated into the fibers during electrospinning, but some of it is lost due to technological reasons. The majority of the encapsulated drug dissolves in most cases, but both solubility and release rate depend on pH for certain polymers. The three water-soluble polymers used for the production of the fibers can be divided into two groups. PVP does not influence the released amount or release rate, thus it does not offer any benefit as carrier for the drug. The release of the drug from PVA is much slower than from other polymers and slower than from the dissolution rate of the neat drug, thus it may be considered for the preparation of drug formulations for pregabalin.

CRediT authorship contribution statement

Lan Yi: Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Lemeng Shi:** Investigation, Formal analysis, Data curation. **János Móczó:** Software, Resources, Project administration, Methodology, Funding acquisition. **Béla Pukánszky:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lan Yi's support was provided by the Ministry for Innovation and Technology of Hungary. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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