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Alternating current electrospinning for preparation of fibrous drug delivery systems

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ABSTRACT

Alternating current electrospinning (ACES) was compared to direct current electrospinning (DCES) for the preparation of drug-loaded nanofibrous mats. It is generally considered that DCES is the solely technique to produce nanofibers using the electrostatic force from polymer solutions, however, less studied and also capable ACES provides further advantages such as increased specific productivities. A poorly water-soluble drug (carvedilol) was incorporated into the fibers based on three different polymeric matrices (an acid-soluble terpolymer (Eudragit® E), a base-soluble copolymer (Eudragit® L 100-55) and a nonionic homopolymer (polyvinylpyrrolidone K90)) to improve the dissolution of the weak base drug under different pH conditions. Morphology and fiber diameter evaluation showed similar electrospun fibers regardless the type of the high voltage and the major differences in feeding rates. The amorphous ACES and DCES fibers provided fast and total drug dissolutions in all cases. The presented results show that ACES can be a more feasible novel alternative to formulate fibers for drug delivery purposes.

1. Introduction

In the field of pharmaceutical technology solvent-based electrospinning represents one of the most multifarious drug delivery platforms in terms of preparing nanofibrous solid dispersions for controlled delivery of the active pharmaceutical ingredient (Démuth et al., 2015; Gordon et al., 2015; Nagy et al., 2012; Shi et al., 2015; Vrbata et al., 2014; Wang et al., 2015; Wu et al., 2015; Xie et al., 2014; Yu et al., 2009). Electrospun fibers with high surface area and amorphous drug content can be produced from polymer solutions under the drawing force of the electrostatic field in a gentle way (Nagy et al., 2014; Reneker et al., 2007). Researchers utilizing electrospinning in many areas use solely direct current (DC) high voltage sources to generate the electrostatic field (Li and Xia, 2004; Nagy et al., 2013). Accordingly, more significant modifications in the electrospinning method were mostly related to the spinneret (e.g., side-by-side (Gupta and Wilkes, 2003) or co- and triaxial electrospinning (Yu et al., 2015a,b)). In spite of that, replacing static DC high voltage to a dynamic alternating current (AC) high voltage also results in a similar electrostatic fiber formation but with significant differences. AC electrospinning (ACES) has been reported only for a very few cases (Kessick et al., 2004; Maheshwari and Chang, 2009; Sarkar et al., 2007) in contrast to the vast literature of DCES (Agarwal et al., 2013; He et al., 2010) and also the more discussed AC version of the analogous electrospraying technique (Chetwani et al., 2011).

Recently, Pokorny et al. (2014) have been pointed out that ACES forms a collectable fibrous aerogel (called fibrous plume, Fig. 1) without the need of a grounded counterpole. Another significant finding of that rediscovery work of ACES was that the throughput of single needle electrospinning could be multiplied when using ACES. Although notable efforts have been accomplished to increase the limited productivity of electrospinning including the combined method of high speed electrospinning (Nagy et al., 2015) or electroblowing (Balogh et al., 2015b) to prepare drug-loaded fibers, further advancements are required to meet the industrial demands considering the outstanding throughput rates of other fiber formation methods such as melt blowing (Balogh et al., 2015a; Luo et al., 2012). Therefore, ACES appears to be a promising new approach to improve the productivity of electrospinning at both

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Fig. 1. The nanofibrous plume generated during alternating current electrospinning without using a grounded collector (normal photographic image; Eudragit® L 100-55, 25 kV_{RMS}, 30 mL/h; see Section 2.3).

laboratory and industrial scales. Despite that, ACES has not been used earlier to prepare fibrous drug delivery systems.

There are only two water-soluble polymers having been applied earlier for ACES and which may be applicable for drug-loaded solid dispersions. Poly(ethylene oxide) has been used for ACES (Kessick et al., 2004), however, either the aqueous spinning solution or the semicrystalline structure of the polymer are not in favor of formulating amorphous solid dispersions containing a poorly water-soluble drug. Polyvinylpyrrolidone fibers have been also prepared using ACES (Maheshwari and Chang, 2009), nevertheless, at extremely low feeding rates (≤0.5 mL/h) and the grade of the polymer was not indicated in the referred paper.

In the work outlined in this paper, drug-loaded ACES fibers were prepared for the first time and compared to DCES fibers with a focus on increasing the throughput rate of ACES using the same spinneret geometry. The rationale behind the polymer selection for the electrospinning techniques was to improve the dissolution of the incorporated poorly water-soluble drug (carvedilol) under different pH conditions. Taking into account that the solubility of crystalline carvedilol sharply decreases with increasing pH (pK_a = 7.8) (Loftsson et al., 2008), ensuring fast drug release can be challenging especially in more basic media. Accelerated dissolution of the solid dispersion is easily achievable using ionic polymers due to the repulsion forces between the protonated or deprotonated functional groups. Therefore, we selected a cationic (Eudragit® E, E-EPO) and an anionic (Eudragit® L 100-55, E-L100-55) methacrylate copolymer exhibiting excellent dissolution properties in acidic and basic media, respectively. Nonionic high molecular weight polyvinylpyrrolidone (PVPK90) was also involved offering improved dissolution of the drug independently from the pH. Besides the morphological examination and fiber diameter evaluation, the amorphity of the drug in the fibrous solid dispersions as well as the release kinetics were investigated.

2. Materials and methods

2.1. Materials

Carvedilol (CAR, free base) from Sigma–Aldrich (Budapest, Hungary) with purity ≥99% was used as API. Eudragit® E PO (E-EPO) was kindly provided by Evonik (Darmstadt, Germany), which is a butylmethacrylate-(2-dimethylaminoethyl)-methachrylate-methylmethacrylate terpolymer (1:2:1) with an average molecular weight of 47 kDa. Polyvinylpyrrolidone K90 (PVPK90) was supplied by Sigma–Aldrich (Budapest, Hungary) and has an average molecular weight of 1 MDa. Eudragit® L 100-55 (E-L100-55) was also kindly provided by Evonik (Darmstadt, Germany), which is a poly(methacrylic acid-co-ethyl acrylate) copolymer (1:1) with an average molecular weight of 320 kDa. Absolute ethanol (≥99.8) was purchased from Molar Chemicals (Budapest, Hungary).

2.2. Direct current electrospinning (DCES)

The direct current solvent-based electrostatic spinner used for the experiments was equipped with NT-35 high voltage direct current supply (MA2000; Unitronik Ltd., Nagykanizsa, Hungary). The electrical potential applied on the spinneret electrode was 25 kV in all cases. A grounded aluminum plate covered with aluminum foil was used as collector. The distance of the spinneret and the collector was 20 cm and the experiments were performed at room temperature. Ethanolic solutions of the selected polymers and the drug were prepared for electrospinning using a magnetic stirrer (600 rpm, 50 °C), for applied optimal concentrations see Table 1. The solutions were dosed by a SEP-10S Plus type syringe pump (Aitecs, Vilnius, Lithuania) through a needle spinneret (1 mm ID, 2 mm OD) with a dosing rate of 5 mL/h.

2.3. Alternating current electrospinning (ACES)

The alternating current electrospinning experiments were conducted using a FME-24 voltage transformer (24,000 V/100 V ratio) (Transzvill Ltd., Budapest, Hungary) fed by a 0–230 V variable transformer. The electrical potential applied on the spinneret electrode was 25 kV (root mean square, RMS) at the frequency of the mains voltage (50 Hz). The sinusoidal AC high voltage was controlled by manual feedback using the variable transformer based on the measured output signal of a high voltage probe connected to the electrode. The polymer solutions, their preparations and concentrations were identical to those of used for DCES

Table 1
Details of preparation of carvedilol-loaded alternating current electrospun (ACES) and direct current electrospun (DCES) fibers.

Composition	Preparation method	Voltage (kV, root mean square)	Dissolved polymer in 10 mL pure EtOH (g)	Flow rate (mL/h)
E-EPO + 15% CAR	DCES	25	2.5	5
	ACES	25	2.5	40
PVPK90 + 15% CAR	DCES	25	0.5	5
	ACES	25	0.5	10
E-L100-55 + 15% CAR	DCES	25	1.25	5
	ACES	25	1.25	30

(Table 1.). The solutions were dosed by a SEP-10S Plus type syringe pump through the same spinneret applied for DCES. The dosing rates were increased gradually with 5 mL/h or 10 mL/h depending on the fiber forming ability of the polymer.

2.4. Scanning electron microscopy (SEM) and fiber diameter analysis

Morphology of the samples was investigated by a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope. Each specimen was fixed by conductive double-sided carbon adhesive tape and sputter-coated with gold prior to the examination. Applied accelerating voltage and working distance were 15–30 kV and 10 mm, respectively. A randomized fiber diameter determination method was used based on SEM imaging as described in our previous work (Balogh et al., 2015a).

2.5. Differential scanning calorimetry (DSC)

Differential scanning calorimetry measurements were carried out using a TA Instruments Q2000 DSC apparatus (New Castle, Delaware) (sample weight: ~2–3 mg, closed aluminium pan, 50 mL/min nitrogen purge gas). The temperature program consisted of an isothermal period, which lasted for 1 min at 25 °C, with subsequent linear heating from 25 °C to 200 °C at the rate of 10 °C/min. Purified indium standard was used to calibrate the instrument.

2.6. X-ray diffraction (XRD)

Powder X-ray diffraction patterns were recorded by a PANanalytical X'pert Pro MDP X-ray diffractometer (Almelo, The Netherlands) using Cu-Kα radiation (1.542 Å) and Ni filter. The applied voltage was 40 kV while the current was 30 mA. The untreated materials and the fibrous samples (multiple fibrous sheets gently compressed by hand) were analyzed for angles 2θ between 4° and 42°.

2.7. In vitro dissolution measurement

The dissolution studies were performed using a Pharmatest PTWS 600 dissolution tester (USP II apparatus (paddle); Hainburg, Germany). Samples equivalent to 12.5 mg of CAR were added directly in the dissolution vessel containing 900 mL dissolution liquid (0.1N HCl, pH 6.8 or pH 7.4 100 mM phosphate buffers prepared according to USP). Fibrous samples were used for dissolution tests as spun. The temperature was maintained at 37 ± 0.5 °C and stirred at 100 rpm. An on-line coupled Agilent 8453 UV–vis spectrophotometer (Palo Alto, California) was used to measure the concentration of dissolved CAR at a wavelength of 242 nm. Percentage of dissolution was readily calculated according to the calibration curves of carvedilol due to the lack of absorption peaks of the applied excipients in this range.

3. Results and discussion

3.1. Preparing fibers and increasing productivity

In order to compare ACES and DCES, first we attempted to prepare fibers setting a common dosing rate ordinary for DCES (5 mL/h). ACES and DCES could be performed from the same polymer solutions without the need of concentration adjustment, all three selected polymers are considered to be a good fiber former for electrospinning. While varying the high voltage during DCES does not affect significantly the formation of the fibers above a threshold voltage, the increasing AC voltage has a more visible effect on the movement of the flying fibrous plume. Since fiber formation of ACES is not affected by the presence of a grounded collector to our experience (collectorless operation), the

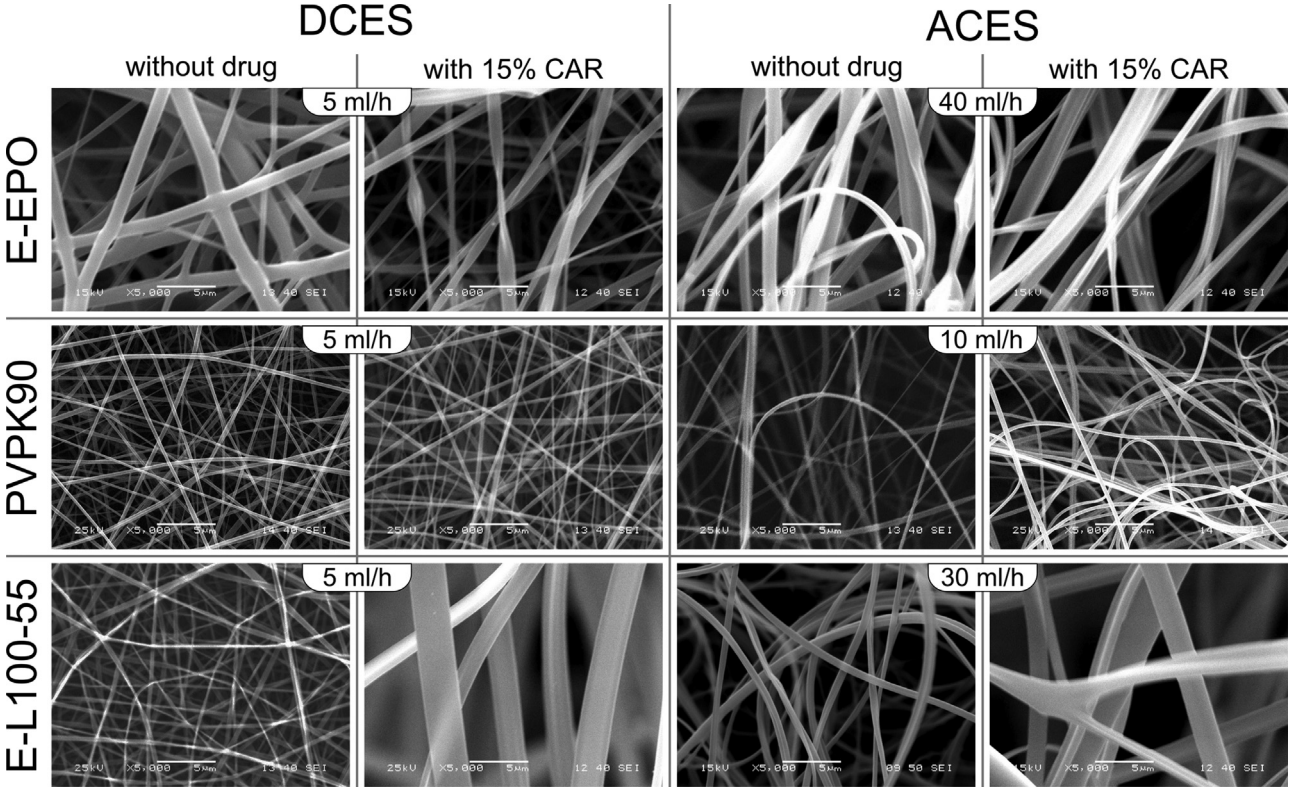

Fig. 2. Scanning microscopic images of Eudragit® E (E-EPO), polyvinylpyrrolidone K90 (PVPK90) and Eudragit® L 100-55 (E-L100-55) fibers with and without 15% carvedilol (CAR) content prepared by alternating current electrospinning (ACES) or direct current electrospinning (DCES). 5000× magnification in all cases.

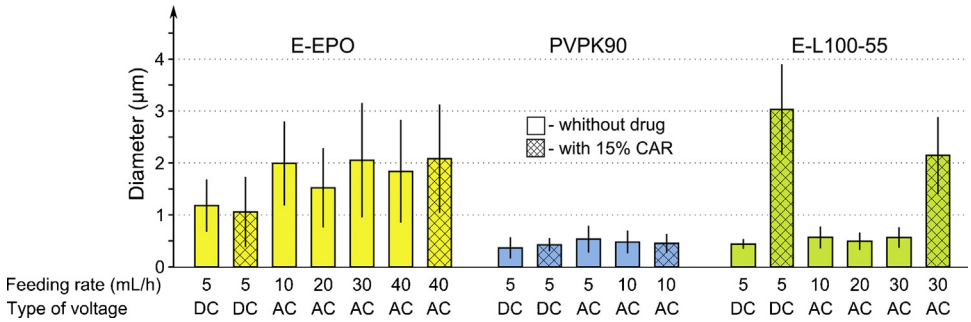

Fig. 3. Average diameters of placebo and drug-loaded alternating current (AC) and direct current (DC) electrosun fibers, the AC electrospun fibers were prepared at increased feeding rates. The error bars indicate the standard deviations ($n = 100$).

movement of the plume as a whole is suspected to be determined mainly by the electric wind surrounding the spinneret (Pokorny et al., 2014). The average velocity of the electric wind is proportional to the applied voltage (Robinson, 1961), thus, higher AC voltages also make a more stable stream of the generated fibers and collection is also easier due to the more focused plume. The selected 25 kV (root mean square) high voltage was found to be appropriate to readily prepare both AC and DC electrospun fibers.

The main advantage of ACES is the achievable increased productivities compared to DCES even with the same spinneret geometry. DCES generates usually one liquid jet from the charged cone-shaped polymer solution droplet on the tip of spinneret, thus, not higher than 5 mL/h feeding rate could be used for DCES. The dynamic effect of the periodic change (100 zero crosses per second) of the sinusoidal AC voltage results in multiple fiber sources on the surface of the polymer solution (Fig. 1) (Pokorny et al., 2014). Gradual increase in dosing rates was tested during ACES from the different polymer solutions with varying results. E-EPO was found to be excellent for ACES, eightfold increase in dosing rate could be reached (40 mL/h) with the same type of spinneret used for DCES. At feeding rates above 40 mL/h larger liquid droplets left sideways the spinneret (i.e., not into the fibrous plume) without turning into a fibrous material. Similar conclusions could be drawn when processing the E-L100-55 solution with ACES, a sixfold increase was registered and droplet formation could be observed above 30 mL/h. As opposed to the acrylic polymers, the dosing rate of the PVPK90 solution could be only doubled with ACES (10 mL/h). More intense feeding of the less concentrated optimal PVPK90 solution resulted in a not dried droplet content in the fibrous plume meaning that the flying fibers declined after a few seconds and collapsed due to the heavier wet contamination. At the end of the exploring process of ACES drug-loaded electrospun fibers were produced containing 15% carvedilol as API in all cases at the determined maximal feeding rates, the main details of the preparations are summarized in Table 1.

3.2. Fiber morphology and diameter analysis

The obtained fiber morphologies are shown in Fig. 2. The SEM images of the DCES samples confirm the good fiber formation abilities of the selected polymers even with 15% drug content, mainly bead-free fibers could be observed. The ACES at increased dosing rates also produced fibrous materials similar to the DC electrospun fibers in terms of diameters and quality.

Diameter analysis provided more details about the effects of the type of the voltage, the presence of the drug and increased throughput rates (Fig. 3). ACES of E-EPO yielded fibers with average diameters around 2 μm which was almost twice of that of DCES E-EPO fibers regardless drug loading or higher feeding rates. Nevertheless, the relative standard deviations remained between

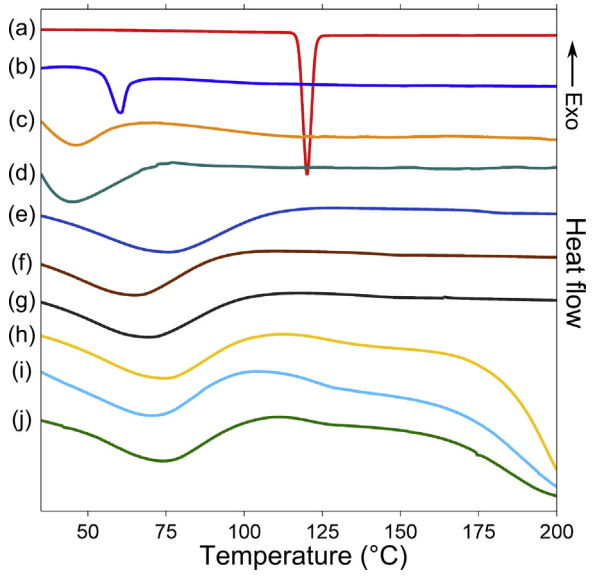

Fig. 4. Differential scanning calorimetry thermograms of (a) crystalline carvedilol, (b) pure E-EPO, (c) DC and (d) AC electrospun E-EPO + 15% CAR fibers, (e) pure PVPK90, (f) DC and (g) AC electrospun PVPK90 + 15% CAR fibers, (h) pure E-L100-55, (i) DC and (j) AC electrospun E-L100-55 + 15% CAR fibers.

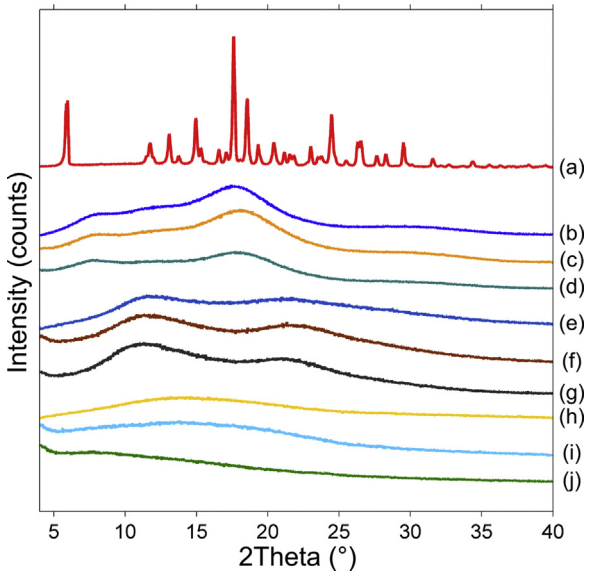

Fig. 5. X-ray diffraction patterns of (a) crystalline carvedilol, (b) pure E-EPO, (c) DC and (d) AC electrospun E-EPO + 15% CAR fibers, (e) pure PVPK90, (f) DC and (g) AC electrospun PVPK90 + 15% CAR fibers, (h) pure E-L100-55, (i) DC and (j) AC electrospun E-L100-55 + 15% CAR fibers.

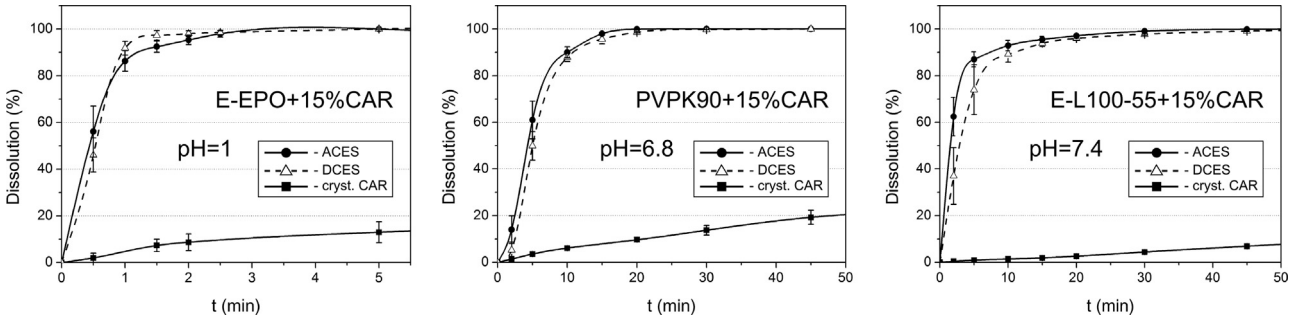

Fig. 6. Dissolution profiles of CAR [12.5 mg dosage, 900 mL, USP dissolution apparatus 2 (paddle), 100 rpm, 37 °C] from drug-loaded ACES and DCES fibers (as spun) and unprocessed crystalline CAR at selected pH. The error bars indicate the standard deviations ($n = 3$).

the 40–60% range and considerable amount of submicronic AC electrospun E-EPO fibers could be still observed. Practically only submicronic PVPK90-based fibers could be collected using DCES and ACES, average diameters varied around 400–500 nm with negligible effects of the drug and the doubled feeding rate during ACES. E-L100-55 also served as excellent fiber forming agent to prepare AC and DC electrospun fabrics with 500 nm average diameters, however, the drug-loaded E-L100-55 fibers were at least four times thicker in average than the placebo fibers. The reason of that remarkable difference may lie in the ionic interaction of the weak base drug and acidic E-L100-55 altering the spinning behavior of the copolymer.

3.3. Differential scanning calorimetry

In order to investigate the physical state of the API in the electrospun fibers DSC measurements were performed (Fig. 4).

The melting peak of crystalline CAR could be measured at 117 °C. ACES and DCES fibers did not contain crystalline traces of the drug according to the DSC thermograms. The glass transition of pure E-EPO is clearly observable around 60 °C combined with an endothermic overshoot. That overshoot of the E-EPO + 15% CAR fibers is wider and appears at lower temperatures due to the plasticizing effect of the drug (Balogh et al., 2014). PVPK90 and E-L100-55 polymers have glass transition temperatures of around 180 °C (Turner et al., 1985) and 120 °C (Andrews et al., 2008), respectively. Below 100 °C the wide endothermic peaks belong to the water loss. With drug loading these water loss endotherms shifted to lower temperatures in the case of the PVPK90 fibers presumably also because of the plasticizing effect of CAR. The thermograms of the E-L100-55 + 15% CAR fibers remained similar to that of the granular polymer, the weak humps around 130 °C can be attributed to the glass transition of the matrix. The endothermic declination of the curves of the E-L100-55 samples above 170 °C indicates the decomposition of the carboxylic functions of the side chains (Petereit and Weisbrod, 1999).

3.4. X-ray diffraction

X-ray diffraction was used to analyze the prepared fibers in regard of crystallinity of the drug the result of which is shown in Fig. 5.

The diffractogram of unprocessed CAR showed several intense peaks due to the regular crystalline structure. In contrast, the applied polymers did not reveal any diffraction phenomenon, only the amorphous background could be observed. The patterns of the drug-loaded fibers were similar to those of the pure polymers. The ultrafast drying of the polymeric fibers led to an amorphous form of the drug during DCES and also ACES even with multiple times higher feeding rates.

3.5. In vitro dissolution

The results of dissolution testing with the fibrous mats are presented in Fig. 6. AC and DC electrospun fibers exhibited very similar dissolution characteristics of the drug. The acid-soluble E-EPO-based fibers dissolved very quickly in pH 1 media, almost total drug release could be measured within 1 min as opposed to the slower dissolution of the crystalline drug. As expected, the dissolution of weak base crystalline CAR markedly decelerated at higher pH values. Despite that, fast release of the drug was observable with the well soluble PVPK90 matrix in pH 6.8 phosphate buffer, more than 85% of CAR was in the liquid phase after 10 mins. E-L100-55 + 15% CAR fibers enhanced the dissolution rate effectively in a pH 7.4 buffer partly due to the accelerated solvation of the self-repulsing ionized polymer chains similarly to the case of cationic E-EPO. Noteworthy that DC electrospun E-L100-55 fibers dissolved somewhat slower than the AC electrospun product. In general, electrospinning produces a sheet-like fibrous mat due to the attraction force toward the grounded collector at DCES and the sticky behavior of the fine filaments. AC electrospun E-L100-55 fibers tended to have a cotton-wool-like appearance also after storage and this low density macroscopic structure dissolved faster than an as spun sheet with tightly packed fibers.

4. Conclusions

ACES was investigated to prepare drug-loaded fibers for the first time to enhance the dissolution and compared to DC electrospun fibers. The selected ionic and neutral polymers could be readily electrospun with increased ACES feeding rates. The SEM images coupled with fiber diameter analysis revealed that switching to AC from DC high voltage doubled the average thickness of the E-EPO fibers while in the case of PVPK90 no such effect could be observed. The higher feeding rates during ACES also led to insignificant increase in the diameters of the fibers regardless the type of the polymer. However, drug-loaded E-L100-55 fibrous product had average diameters at least four times of those of the placebo E-L100-55 nanofibers presumably due to the ionic interaction of the drug and the polymer. The DSC and XRD results confirmed the amorphous form of the drug embedded into the electrospun fibers owing to the very fast drying of the fibrous solid dispersions. Appropriate polymeric matrices, high surface area and the well soluble amorphous form of the drug ensured fast release rates at both acidic and rather basic pH values. The promising results regarding the quick-dissolving ACES fabrics indicate feasibility for preparing fibrous drug delivery systems. Further exploitation of ACES may be expected in industrial scale up of electrostatic fiber formation techniques.

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