Developing and scaling up fast-dissolving electrospun formulations based on poly(vinylpyrrolidone) and ketoprofen

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Abstract: Poly(vinyl pyrrolidone) (PVP) electrospun fibers loaded with ketoprofen were fabricated in this work as potential fast dissolving drug delivery systems (DDSs) for oral delivery. By changing the processing parameters and collector geometry it was possible to increase the throughput rate from 1 to 20 mL/h. The fibers all took the shape of cylinders and had smooth surfaces. They comprise amorphous solid dispersions of drug-in-polymer, with very high drug encapsulation efficiencies (100%). With a low drug loading (9.09% w/w) the electrospun materials could disintegrate quickly and accelerate the dissolution profile of ketoprofen under non-sink conditions representative of the oral cavity. However, at higher loadings (23.08% w/w), this benefit is no longer realized, indicating that there is a maximum drug loading above which the dissolution-enhancing properties of the amorphous form and the hydrophilic PVP carrier cease to be effective. After storage under ambient conditions (19-21 °C, relative humidity 30-40%) for 4 weeks, the formulations remained amorphous, with no significant change in the drug release properties. Very similar behaviour in terms of drug release and storage stability was seen regardless of the throughput rate used for fiber fabrication, showing the potential to rapidly produce large amounts of high-performing material.

Keywords: electrospinning, PVP, ketoprofen, oral fast dissolving drug delivery system

1. Introduction

Fast-dissolving drug-delivery systems (FD-DDSs) were first developed in the late 1970s [1]. These formulations can either dissolve or disintegrate rapidly in the oral cavity, without the need to drink water [2]. FD-DDSs have attracted great interest from the pharmaceutical industry due to their benefits of improved patient compliance, increased bioavailability [3] and rapid onset of action [4]. Several forms of FD-DDSs have been developed including tablets [2] and films [1], and there are already products on the market including Feldene® fast dissolving tablets (manufactured by Pfizer, these contain the non-steroidal anti-inflammatory drug piroxicam) and Donepezil® rapid dissolving films (manufactured by Labtec Pharma for treating Alzheimer's disease).

Among the various types of FD-DDSs, sublingual films have attracted particular attention [10]. However, such films have several limitations. For example, as the sublingual site has a relatively small area, the released drug could be washed away by saliva before it can permeate the sublingual membrane. Involuntary swallowing of liquids could lead to the drug entering the gastrointestinal

tract [7]. Taste-masking is also a challenge [8]. That said, sublingual films have significant advantages as an oral administration system for patients with swallowing or digestion problems, including pediatric and geriatric patients [9], given their ease of administration, avoidance of first-pass effects, and rapid onset of action [10].

The literature reports a range of approaches to fabricate thin films for rapid drug release: for instance, solvent casting, semi-solid casting, hot melt extrusion, solid dispersion extrusion and rolling [3, 11, 13-15]. In recent years, electrospinning has been proposed as an alternative way to develop fast-release thin films. Electrospinning uses electrical energy to solidify a polymer solution. The latter is loaded into a syringe fitted with a metal needle (the spinneret), and a high voltage power supply is employed to provide a high potential difference between the spinneret and a grounded collector. The polymer solution is infused through the spinneret at a controlled rate using a syringe pump [16]. As the polymer solution leaves the spinneret, the usually spherical droplet is deformed into a conical shape (the Taylor cone) owing to the electrical charge it carries. A charged jet is ejected from the Taylor cone, and then undergoes a series of bending and whipping motions as it travels to the collector. As a result of this drawing under the electric field the solvent evaporates rapidly, leading to the deposition of solid fibers on the collector [17]. Electrospinning has been shown to have great promise in the development of drug delivery systems because of the resultant fibers having advantageous properties including high surface area, high porosity, and high drug encapsulation efficiency [18-20].

Ketoprofen (Figure 1a) is a non-steroidal anti-inflammatory drug which can control pain and inflammation in rheumatic diseases [21]. Its main side effect is gastric irritation. In addition, ketoprofen's poor solubility in water (0.01% w/w, pH=7) restricts its oral, topical and parenteral applications [22]. Electrospun fibers typically comprise amorphous solid dispersions, and thus ketoprofen loaded fibers have the potential to overcome the solubility issue. Several authors have explored electrospun fibers containing ketoprofen and based on hydrophilic polymers [*e.g.* poly(vinyl pyrrolidone) {PVP}, poly(vinyl alcohol)] to increase the dissolution rate and water solubility of the drug [21, 23-24]. However, most research is performed at the bench-top scale, which normally employs flow rates of 1 to 2mL/h and a static flat-plate collector. Such experiments have low production yields (a maximum of ca. 5 g of solid product per day).

In order to increase production efficiency to cater to industrial pharmaceutical manufacturing, higher throughput is required [25]. In the laboratory, this is typically achieved by using a rotating collector and a rastering needle. For instance, Zhao and co-workers [26] used a metal rotating drum as the collector and successfully made polymer fibers at a solution flow rate of 7 mL/h. In other work, Ding and his team [42] fabricated poly(vinyl alcohol) (PVA) and cellulose acetate (CA) fibers with a feeding speed of 114 and 138 mL/h respectively. Such scale-up of traditional electrospinning usually involves an increase in the spinning voltage. To move to even higher throughput, a needleless approach is usually employed. For instance, Molnar and Nagy [12] scaled-up electrospinning to a PVP solution feed rate of 120 mL/h with a rotating spinneret and conveyer belt collector. Szabó et al. [51] scaled up the electrospinning of poly(vinyl pyrrolidone vinyl alcohol) to a flow rate of 200 mL/h. Some other methods to scale up electrospinning include the application of alternating current instead of direct current, and work reported by Balogh et al.[6] used this approach to process a Eudragit® E PO solution at 40 mL/h. Most recently, Farkas et al.[43] combined the needleless approach and alternating current electrospinning to reach a flow rate of 1200 mL/h.

This paper reports a study looking at how increases in electrospinning throughput affect the

properties and functional performance of PVP fibers loaded with ketoprofen. The release profiles of formulations with different drug loadings are further explored. PVP (Figure 1b) is a hydrophilic polymer widely used as a matrix for preparing solid dispersions to increase the dissolution rate of drugs with poor water solubility [27-28]. It is biocompatible [29] with muco-adhesive properties [30], and has been applied to fabricate solid dispersions for fast drug release in a number of studies in the literature [31, 44-45]. A series of PVP-based fibers loaded with ketoprofen was prepared, fully characterized, and drug release from them explored in detail.

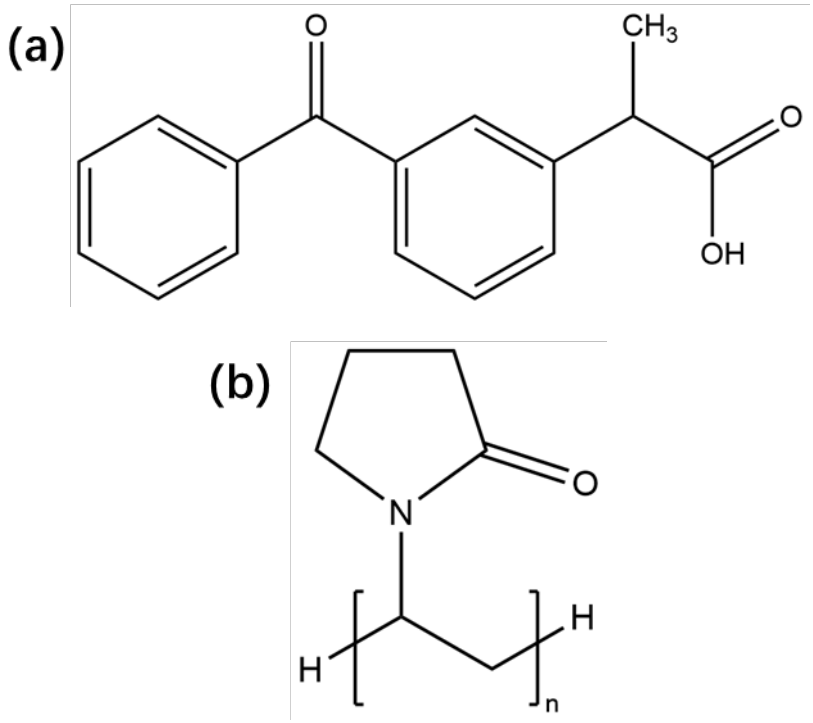


Figure 1. Chemical structures of (a) ketoprofen; (b) PVP.

2. Materials and methods

2.1 Materials

Ketoprofen (≥98%, CAS No. 22071-15-4) was purchased from LKT Laboratories, Inc (UK). PVP (K60, average Mw=360,000, CAS No. 9003-39-8) was sourced from Sigma–Aldrich (UK). All other chemicals were of analytical grade and used as provided.

2.2 Preparation of spinning solutions

Anhydrous ethanol, widely used for electrospinning [32], was selected as the spinning solvent since ketoprofen is freely soluble in ethanol [23]. The concentration of PVP was fixed at 10% w/v while different concentrations of ketoprofen were added (Table 1). The solutions were subject to mechanical stirring overnight at room temperature to ensure complete dissolution. As a control, a physical mixture of PVP and ketoprofen was prepared (Table 1).

Table 1. Compositions of electrospinning solutions, fibers, and the physical mixture.

Concentration	Formulation			
	F0	F1	F2	PM
Spinning solutions (% w/v)				
Ketoprofen	0	1	3	-
PVP	10	10	10	-
Solid fibers (% w/w)				
Ketoprofen	0	9.09	23.08	-
PVP	100	90.91	76.92	-
Physical mixture (% w/w)				
Ketoprofen	-	-	-	9.09
PVP	-	-	-	90.91

2.3 Fabrication of electrospun fibers

2.3.1 Bench-top electrospinning

The polymer solution was loaded into a plastic syringe (5 mL, Terumo, UK) fitted with a metal spinneret (21G, 0.51 mm inner diameter, Nordson EFD, UK). A high voltage power DC supply (HCP35-35,000, FuG Elektronik, Germany) was employed to generate an electric field, with the positive electrode connected to the spinneret and the grounded electrode connected to a staticF metal plate collector (14.7 × 20 cm, covered with aluminum foil). An electrical potential was created across the distance between the spinneret tip and the metal collector, with a syringe pump (78-9100C, Cole-Parmer, UK) feeding the polymer solution at a certain flow rate. A photograph of the experimental set-up is given in the Supplementary Information, Figure S1a. Initial optimization was carried out to identify suitable processing parameters, leading to the conditions summarized in Table 2. Electrospinning was carried out under ambient conditions (19-21 °C, relative humidity 30-40 %).

Table 2. Parameters for bench-top electrospinning

Formulation – flow rate (mL/h)	Voltage (kV)	Spinneret-collector distance (cm)
F0-1	8	15
F1-1	10	15
F2-1	10	15
F0-2	8	10
F1-2	10	10
F2-2	10	10

2.3.2 Scaled-up electrospinning

The fabrication of fibers was conducted in a NEU-BM electrospinning instrument (Shenzhen Tongli Micro-nano Technology Co., Ltd., China). Unlike in bench-top electrospinning, a rotating metal drum (diameter 100 mm, length 250 mm) was used as the collector (see Figure S1b and Figure 2). The rotation speed was 300 rpm. The spinneret rastered with a scanning speed of 50

mm/s over a range of 20 cm. The inner diameter of the spinneret was 0.51 mm. The syringe was placed on a pump (TL-F6, Shenzhen Tongli Micro-nano Technology Co., Ltd., China) and connected to the spinneret with polytetrafluoroethylene tubing. The full details of the processing parameters are shown in Table 3. The temperature and relative humidity were controlled at 28-30 °C and 20-25 % using the inbuilt controls in the NEU-BM instrument.

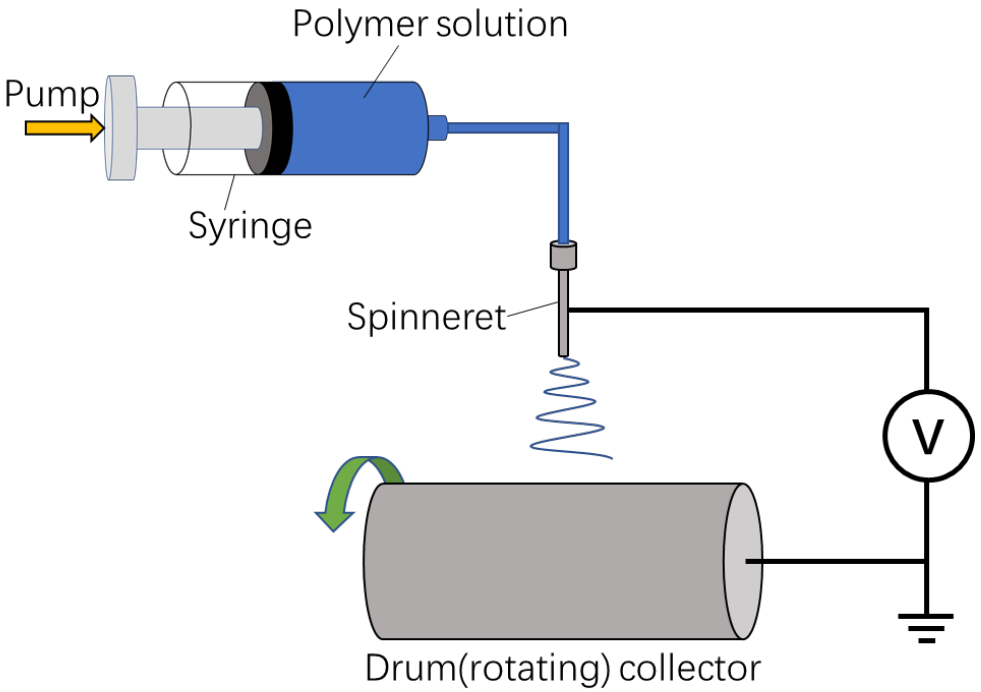


Figure 2. Schematic image of electrospinning on the NEU-BM instrument

Table 3. Parameters for high-speed electrospinning

Formulation - Flow rate (mL/h)	Voltage (kV)	Spinneret-collector distance (cm)
F0-10	21	10
F1-10	25	10
F2-10	25	10
F0-20	31	10
F1-20	35	10
F2-20	35	10

2.4 Characterization

2.4.1 Morphology

A bench-top scanning electron microscope (SEM; Phenom ProX, Thermo Fisher Scientific, USA) was employed to study the morphology of the electrospun fibers. Samples were gold sputter-coated to render them electrically conductive before images were taken at an excitation voltage of 5 kV. The average fiber size was analyzed by measuring diameters at 100 points in SEM images, and results are reported as mean ± standard deviation (SD).

2.4.2 X-ray diffraction

A MiniFlex 600 diffractometer (RigaKu, Japan) supplied with Cu Ka radiation (λ = 1.5148 Å; 40 mV, 15 mA) was employed to collect X-ray diffraction (XRD) patterns over the 2θ range 3°-35°.

2.4.3 Differential scanning calorimetry

A Q2000 calorimeter (TA Instruments, USA) was used to obtain differential scanning calorimetry (DSC) data. Samples (ca. 5 mg) were placed into Tzero aluminum pans (TA Instruments, USA) and heated from 30-200 °C at a rate of 10 °C/min. The machine was purged continuously with nitrogen purge during measurements, at a flow rate of 50mL/min.

2.4.4 Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) spectroscopy was carried out with a Spectrum 100 FTIR spectrometer (PerkinElmer, USA). The scanning range was 4000-650 cm^{-1} and the resolution set at 1 cm^{-1}.

2.5 Wetting assays

Samples containing 3 mg ketoprofen were prepared for the drug loaded fibers, while for the blank F0-X formulations the sample mass was fixed at 30 mg. These were placed in a Petri dish with 15 mL simulated saliva (prepared by adding NaCl (8.00 g), KH_2PO_4 (0.19 g), and Na_2HPO_4 (2.38 g) to 1 L of distilled water; pH=6.8 [32]) which was pre-heated to 37 °C. The disintegration of the material was recorded with a digital camera (Q, Leica, Germany) at 60 frames/s.

2.6 Drug loading

Samples containing 1.5 mg of ketoprofen were completely dissolved in 10 mL of anhydrous ethanol at room temperature. The drug concentration was quantified at 290 nm using a UV spectrophotometer (Cary 100, Agilent, USA). The experiment was conducted in triplicate and results are reported as mean ± SD.

2.7 Dissolution tests

Dissolution studies were performed using a slightly modified method from the literature [32]. A sample containing 3 mg ketoprofen was placed in a 7cm diameter Petri dish with 15 mL of simulated saliva pre-heated to 37 °C. A 1 cm long magnetic stirrer was placed in the Petri dish and a multipoint stirrer (CimarecTM iPoly 15, ThermoScientific, UK) used to stir the solution at 150 rpm. The temperature was maintained at 37 ± 1 °C. At pre-determined time points, 200 µL of the supernatant was removed from the Petri dish and replaced with 200 µL of pre-heated simulated saliva. The supernatants taken were diluted with simulated saliva to 1 mL and analyzed at 296 nm with a UV spectrophotometer (Cary 100, Agilent, USA). The experiment was conducted in triplicate and results are reported as mean ± SD. The recorded solubility of ketoprofen is 0.1 mg/mL at pH=7) [22], while the maximum drug concentration which could be attained here was 0.2 mg/mL. The dissolution tests were thus not under sink conditions, but instead were designed to more closely mimic what might realistically happen in the oral cavity.

2.8 Stability studies

Samples were kept at ambient conditions (19 – 21 °C, relative humidity 30-40 %) for 4 weeks. The aged fibers were then characterized by XRD and DSC as detailed in Sections 2.4.2 and 2.4.3. Dissolution tests (Section 2.7) were also repeated, again in triplicate.

3. Results and discussion

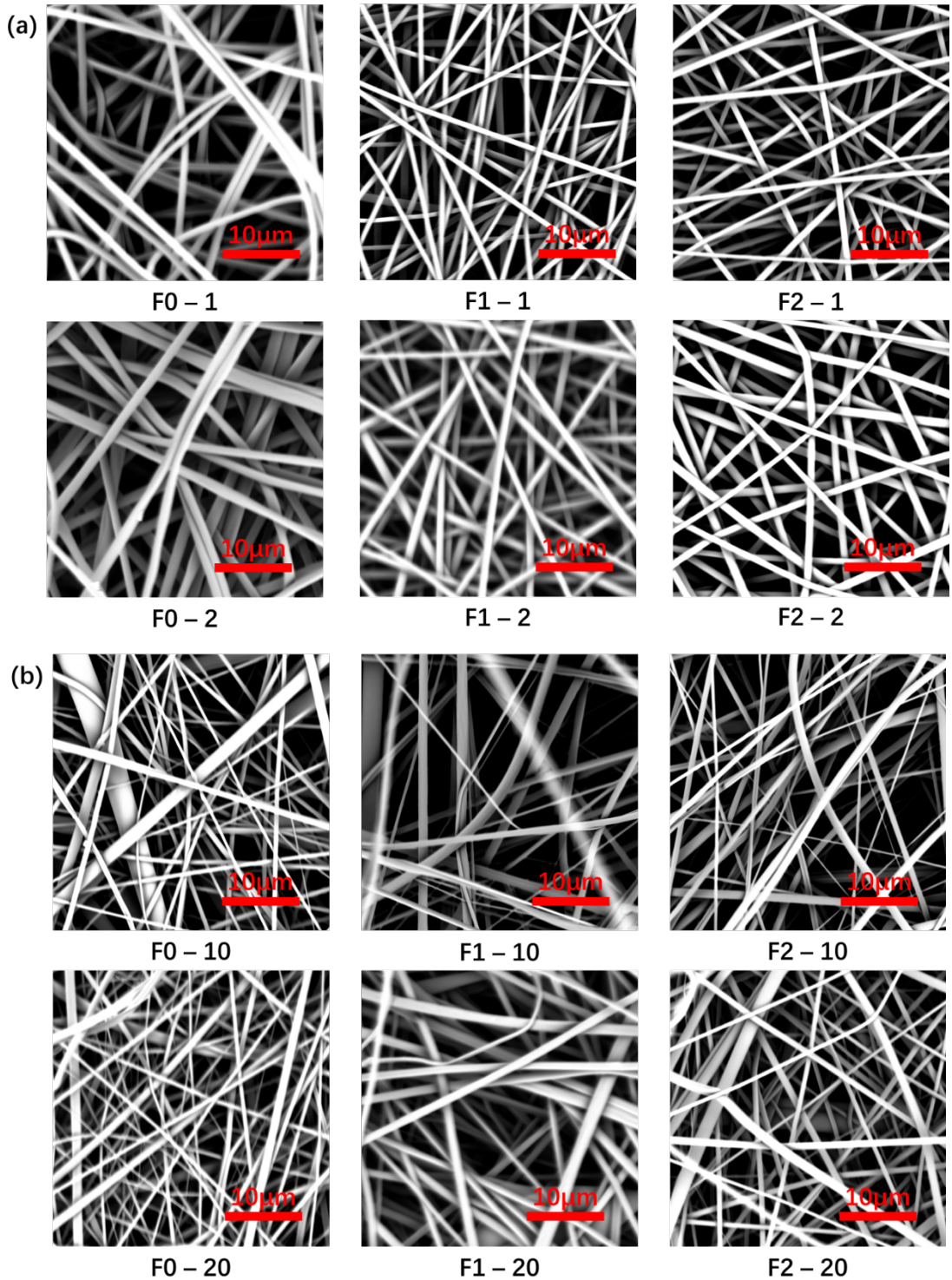
3.1 Electrospinning

The PVP/ketoprofen ethanolic solutions (Table 1) were all clear. Initial optimization experiments were performed to select suitable electrospinning parameters (data not shown). The optimum values are presented in Tables 2 and 3. It can be see that the addition of ketoprofen to the polymer solutions leads to an increase in the applied voltage being required in order to ensure a stable spinning process and form solid fibers. An increase in the electric field gradient is also needed when increasing the flow rate: a reduction in the spinneret to collector distance from 15 to 10 cm was needed when moving from 1 to 2 mL/h on the bench top apparatus. Similarly, on the NEU-BM instrument the voltage applied needed to be raised from 21-25 to 31-35 kV as the flow rate increased from 10 to 20 mL/h. A series of formulations were successfully prepared as detailed in Tables 2 and 3.

3.2 Fiber morphology

SEM images of the polymer/active pharmaceutical ingredient (API) electrospun fibers are shown in Figure 3a,b. It can be observed from the images that the fibers are all cylindrical in shape. No bead-on-string morphology is visible and there are no surface particles present, implying a homogenous encapsulation of API. The fibers are oriented randomly. The diameters of the fibers are summarized in Table 4 (histograms of the fiber diameter distribution can be found in the Supplementary Information, Figure S2). For bench-top electrospinning, the diameters were 1.01 ± 0.14 µm (1 mL/h, F0-1); 0.76 ± 0.10 µm (F1-1); 0.79 ± 0.09 µm (F1-2); 1.21 ± 0.13 µm (2 mL/h, F0-2); 1.00 ± 0.13 µm (F1-2); and 0.93 ± 0.11 µm (F2-2) respectively. It can be concluded from the data that for bench-top electrospinning, as the spinning flow rate increased from 1 mL/h to 2 mL/h, there was an increase in the fiber diameter (Figure 3c).

With the scaled-up electrospinning, the fiber diameters were 0.66 ± 0.44 µm (10 mL/h, F0-10); 0.71 ± 0.33 µm (F1-10); 0.65 ± 0.18 µm (F2-10); 0.64 ± 0.15 µm (20 mL/h, F0-20); 0.83 ± 0.18 µm (F1-20); and 0.69 ± 0.24 µm (F2-20) respectively (Table 4). As can be seen in Figure 3c, when moving from bench-top scale to the NEU-BM instrument, the fiber diameter decreased markedly [46]. This is because although the spinning flow rate increased significantly over the benchtop experiment (2 → 10 mL/h), there was also an increase in the spinning voltage (Tables 2,3) and a change in collector geometry (from a flat plate collector in bench-top spinning to a rotating mandrel in the NEU-BM instrument; see Figure S1 and Figure 2). The additional drawing mediated by the higher voltage and/or rotating collector clearly outweighs the greater solute dispensing rate. When the spinning flow rate was increased from 10 to 20 mL/h on the NEU-BM instrument, a slight increase in the fiber diameter was observed for the drug loaded materials (Figure 3c).


(a)
10μm
F0 – 1
F1 – 1
F2 – 1
F0 – 2
F1 – 2
F2 – 2
(b)
F0 – 10
F1 – 10
F2 – 10
F0 – 20
F1 – 20
F2 – 20

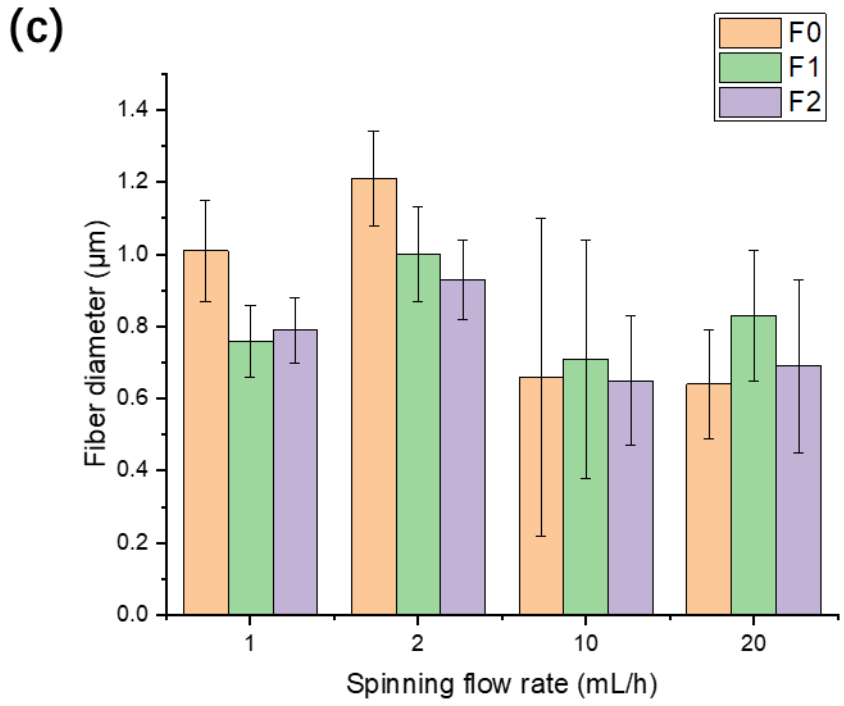


Figure 3. SEM images of electrospun PVP/ketoprofen fibers and the fiber diameter distribution. (a) bench-top electrospinning; (b) NEU-BM instrument; (c) fiber diameter distribution.

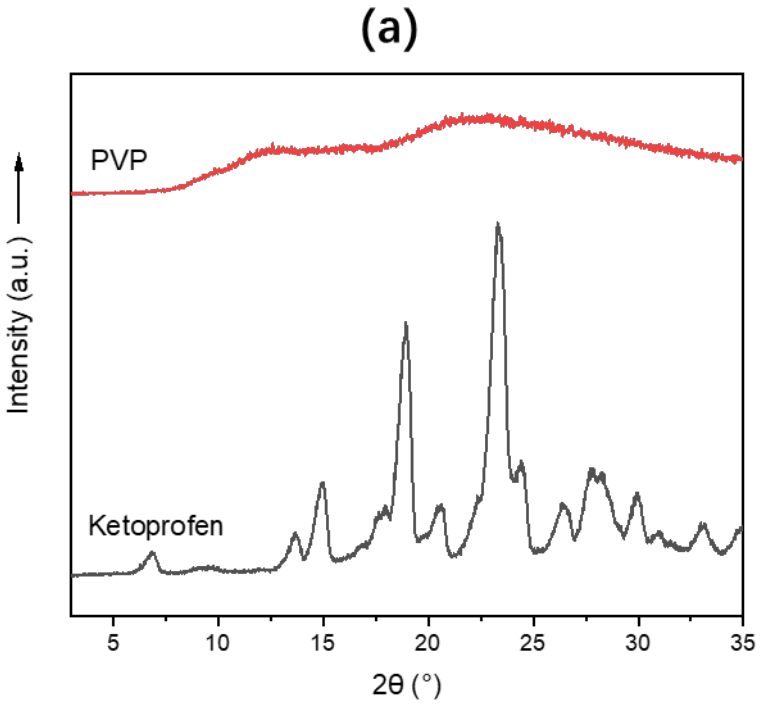
Table 4. Average diameters of the formulations prepared at different flow rates

Formulation - flow rate (mL/h)	Diameter (µm, mean ± SD)
F0-1	1.01 ± 0.14
F1-1	0.76 ± 0.10
F2-1	0.79 ± 0.09
F0-2	1.21 ± 0.13
F1-2	1.00 ± 0.13
F2-2	0.93 ± 0.11
F0-10	0.66 ± 0.44
F1-10	0.71 ± 0.33
F2-10	0.65 ± 0.18
F0-20	0.64 ± 0.15
F1-20	0.83 ± 0.18
F2-20	0.69 ± 0.24

3.3 X-ray diffraction

XRD was conducted to examine the physical form of the electrospun materials. XRD patterns of the raw materials (Figure 4a) reveal ketoprofen to be a crystalline material with numerous sharp

Bragg reflections in the diffraction pattern [33]. PVP displays only a broad halo in XRD, confirming it to be amorphous, as is well established in the literature [34]. Regardless of the flow rate used for spinning, all the fibers are amorphous, with no Bragg reflections visible in their XRD patterns (Figure 4b,c). There were broad humps at around 10 and 17° in the XRD patterns of the electrospun fibers (Figure 4b,c), which arise from the coating on the sample holder used for measurements and the high porosity of the electrospun materials [32] making background signals visible. All the fibers thus comprise amorphous solid dispersions of drug in polymer, which agrees with the literature [43].



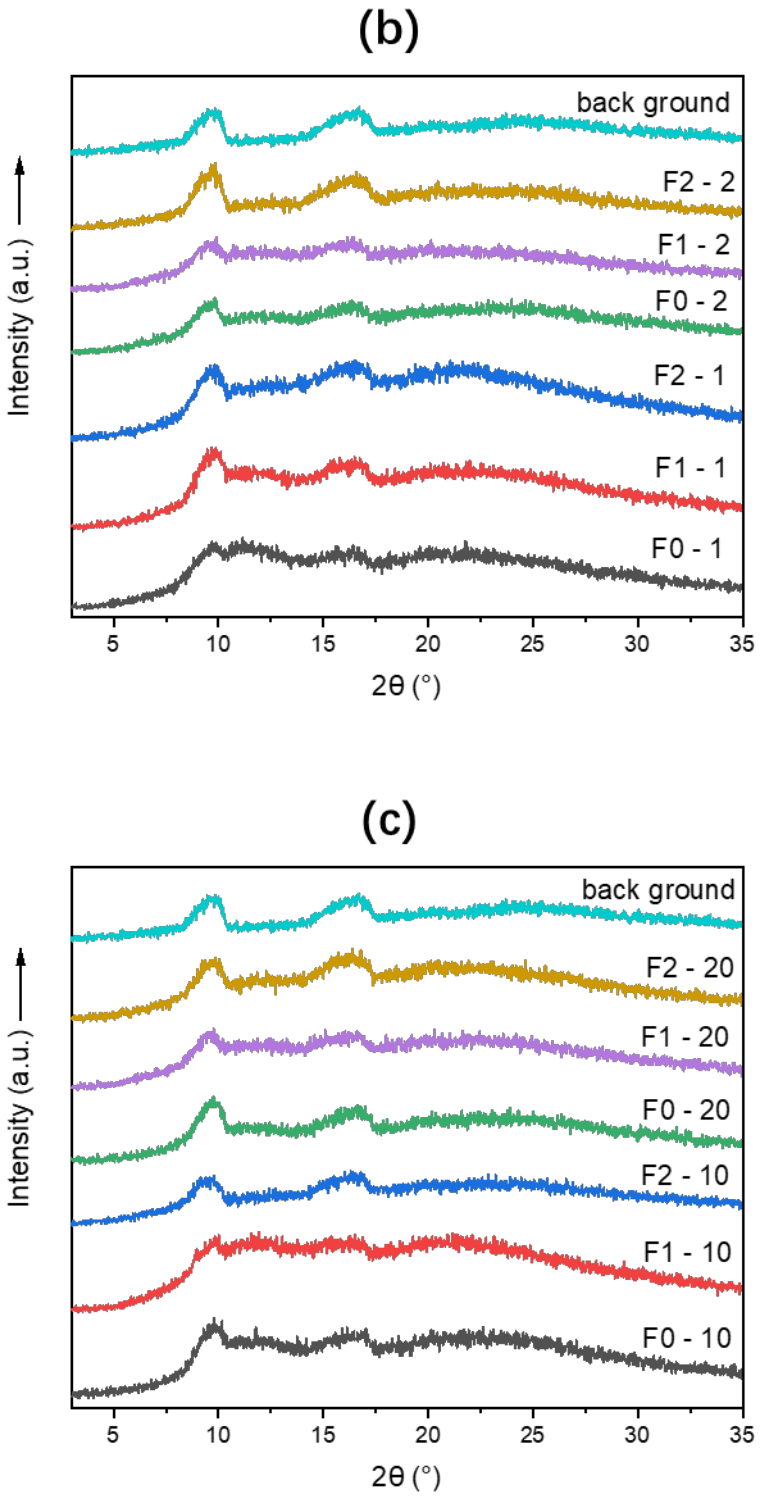


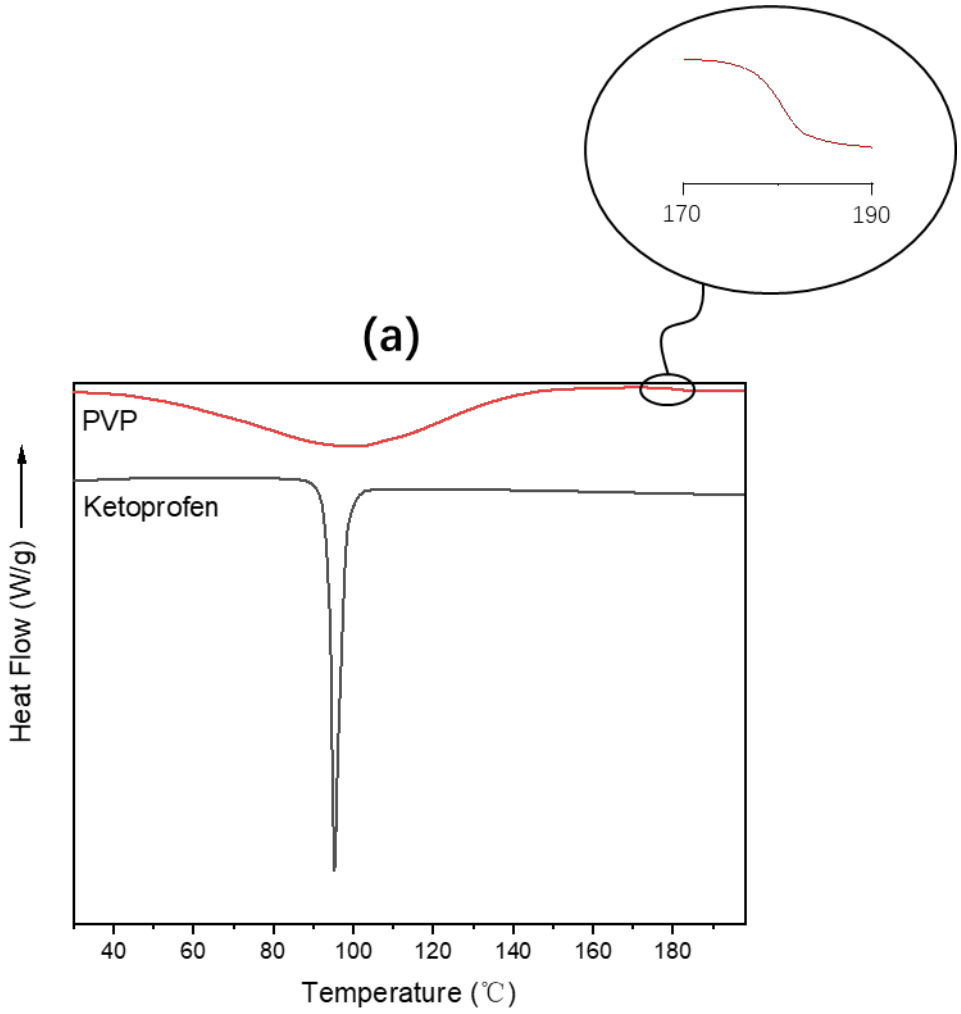
Figure 4. XRD patterns of (a) raw materials and electrospun fibers prepared on (b) the benchtop apparatus, and (c) the NEU-BM instrument.

3.4 Differential scanning calorimetry

It could be observed from DSC (Figure 5a) that ketoprofen has a sharp endothermic peak at 95.3°C, which corresponds to melting. This close to the recorded melting point (T_{peak} = 96.8 °C) [35].

The PVP DSC trace (Figure 5a) showed a broad endothermic curve running from room temperature to ca. 140 °C, corresponding to loss of adsorbed water. There is no melting point, suggesting the polymer to be amorphous [36]. Similarly for the fibers, the DSC thermograms only contain broad endothermic events (water loss) and no melting points are observed (Figure 5b,c). These observations concur with those from XRD, and confirm the fibers to comprise amorphous solid dispersions (ASDs) [23]. There was a slight decrease of the broad endotherm's peak temperature as the drug loading increased, which has also been observed by other groups [23].

The PVP thermogram shows a baseline shift at around 180°C arising from the glass transition (T_g), which is similar to other T_g values reported in the literature (170-180°C) [47]. The T_g values for the fibers are harder to see, and there is the potential for this to overlap with the decomposition of ketoprofen, reported to occur at 206 °C [57]. The recorded glass transition temperature of ketoprofen is −3°C [37]. Therefore, as the mass fraction of ketoprofen increases, a decrease in the glass transition temperature is expected [49]. This is not completely obvious from the data, but in general this does hold true. For example, as shown in Figure 5c, the onset of the glass transition of F1-10 was 180 °C, while for F2-10 this arises at 176 °C.



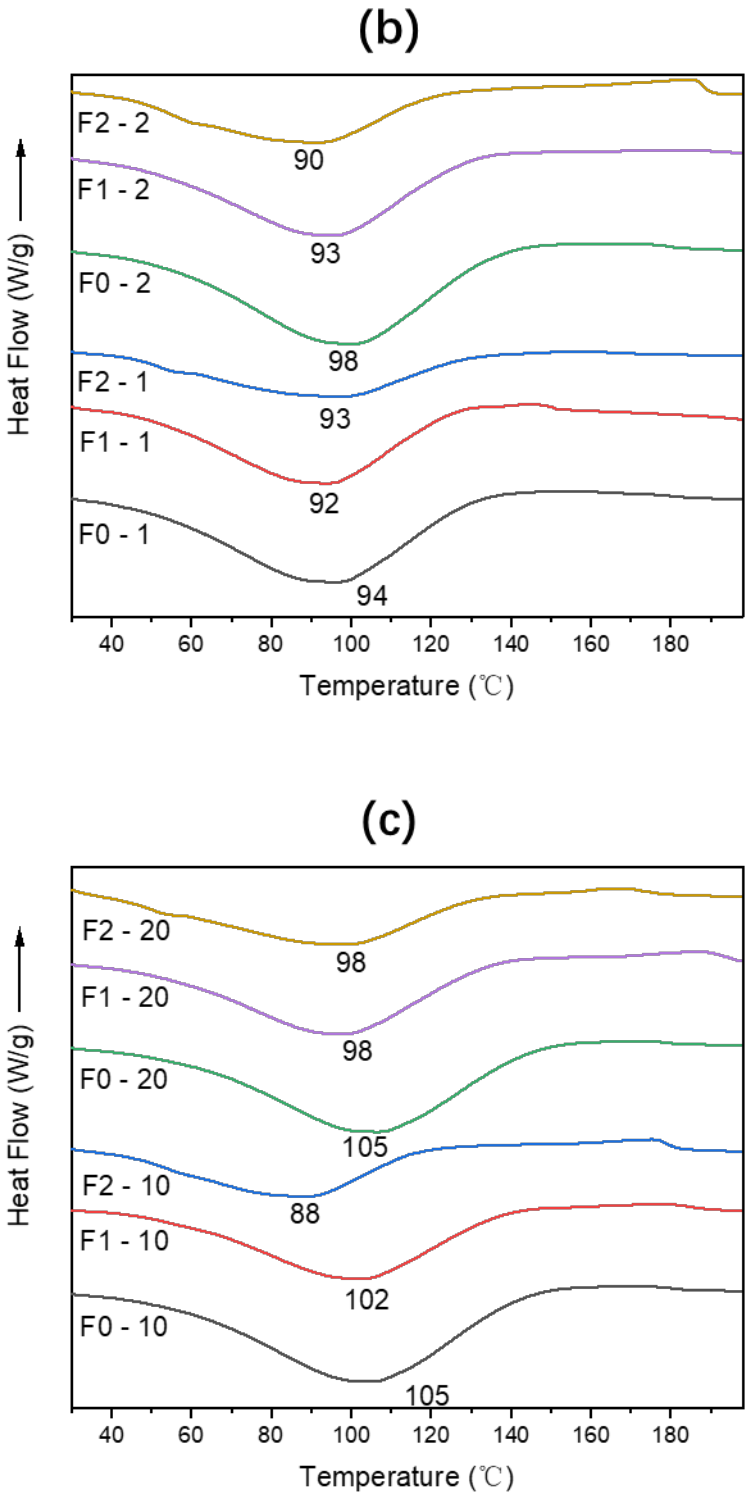
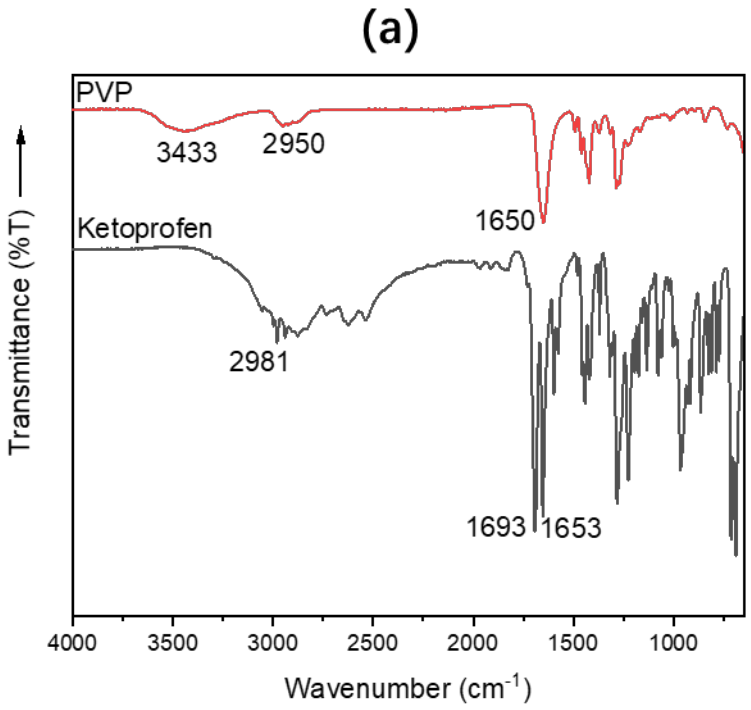


Figure 5. DSC data for (a) the raw materials and fibers prepared using (a) the benchtop apparatus and (c) the NEU-BM instrument.

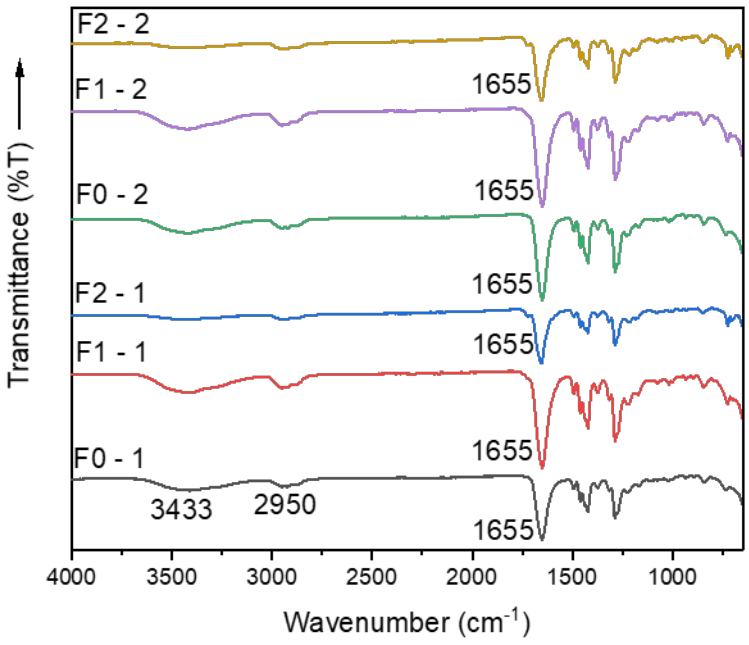
3.5 Infrared spectroscopy

FTIR spectra of the raw materials and electrospun fibers are given in Figure 6. PVP (Figure 6a) shows a broad band centered at ~3430 cm^{-1} representing O-H stretching, which confirmed the

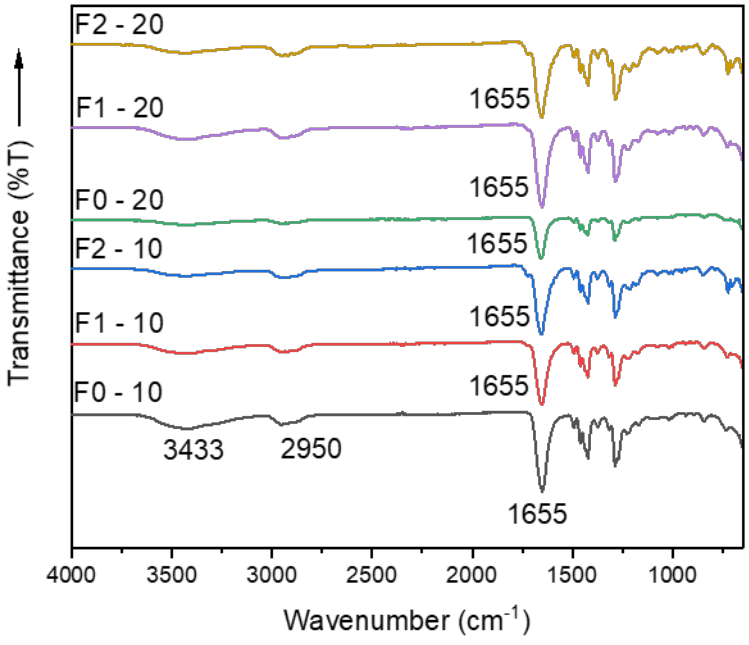
presence of water. The peak at ~2950 cm^{-1} is due to the stretching vibration of C-H groups, and the well-defined sharp peak at ~1650 cm^{-1} arises from C=O stretching. These findings are consistent with the literature [23]. For ketoprofen (Figure 6a), the signal at ~2981 cm^{-1} is attributed to C-H stretching. The two well-defined peaks at ~1693 cm^{-1} and ~1653 cm^{-1} are due to C=O stretching. The former corresponds to the C(=O)OH stretch in the dimeric carboxylic acid units that form the building blocks of crystalline ketoprofen, and the latter is the ketonic C=O [37]. The carboxylic acid stretch at 1693 cm^{-1} cannot be seen in the spectra of the fibers (Figure 6b,c). This phenomenon can be attributed to the absence of ketoprofen dimers after electrospinning, and hydrogen bonding between ketoprofen and PVP molecules [38]. In the higher drug loading F2 formulations a new signal at ~1725 cm^{-1} is visible (Figure 6d), which corresponds to the stretching vibration of the carboxylic acid C=O stretch in isolated ketoprofen molecules. The rapid drying which occurs during electrospinning and the possibility for ketoprofen molecules to interact with PVP through hydrogen bonding prevents dimer formation and crystallization [39], resulting in ASDs [23,48].



(b)


F2 - 2
F1 - 2
F0 - 2
F2 - 1
F1 - 1
F0 - 1
1655
3433
2950
Transmittance (%T)
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)

(c)


F2 - 20
F1 - 20
F0 - 20
F2 - 10
F1 - 10
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Transmittance (%T)
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Wavenumber (cm-1)

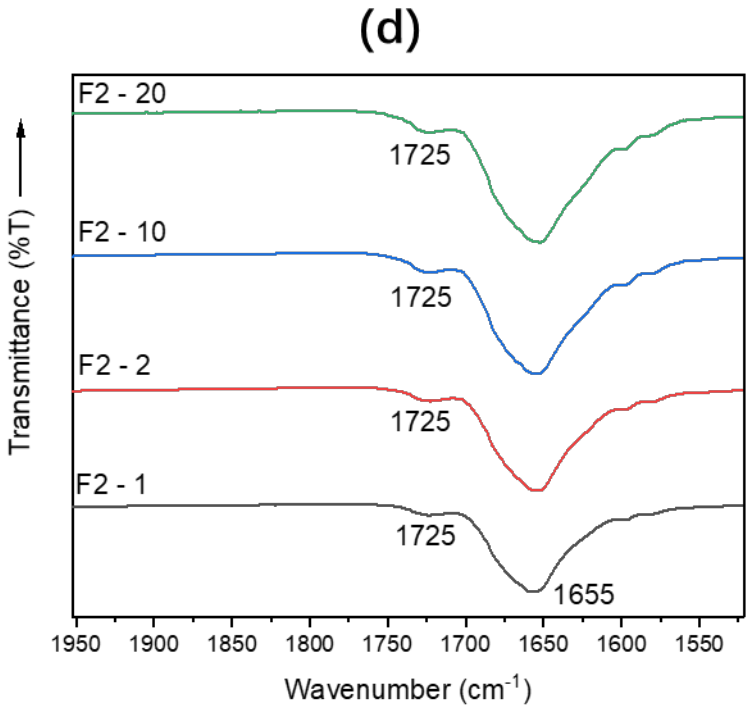

Figure 6. FTIR spectra of (a) raw materials, (b) fibers prepared at 1 and 2 mL/h, and (c) fibers prepared at 10 and 20 mL/h, with (d) an enlargement of the carboxylate region for the F2 formulations.

3.6 Drug loading

All the fiber formulations could be fully dissolved in ethanol, and the resultant solutions were analyzed by UV spectroscopy. The results are given in Table 5. In all cases, the loading of ketoprofen is close to the theoretical loading, confirming no losses during spinning. The ketoprofen content in each formulation was found to be slightly larger than the theoretical loading. It was also greater than the reports in the literature for similar systems, which suggest an actual drug loading of 95-97% of the theoretical value [49]. These differences are not believed to be significant. A possible explanation for this could be small amounts of polymer loss during the preparation of solutions.

Table 5. The encapsulation efficiency (EE) of the electrospun fibers. EE% = 100 x actual loading/theoretical loading.

Formulation - flow rate (mL/h)	EE (%, mean ± SD)
F1-1	110.3 ± 3.5
F2-1	105.1 ± 8.7
F1-2	104.5 ± 4.9
F2-2	107.3 ± 6.4
F1-10	104.3 ± 2.5
F2-10	109.6 ± 4.4
F1-20	102.1 ± 4.2
F2-20	108.8 ± 1.0

3.7 Wetting assays and dissolution studies

Stills from videos taken during disintegration of the fibers are shown in Figure 7 and Figure S3 . These experiments were performed in 15 mL of simulated saliva, in order to provide a reasonable mimic of what would occur in the oral cavity if the fibers were administered as oral films. The pure PVP F0 formulations disintegrated completely within approximately 500 ms (Figure 7a, Figure S3a, d, g). Upon the addition of ketoprofen, the F1 systems (9.09% w/w drug) disintegrated into small fragments within 60 s (Figure 7b, Figure S3b, e, h). As the drug loading climbed, disintegration slowed and the F2 materials (23.08% w/w ketoprofen) had not fully disintegrated after 60 s (Figure 7c, Figure S3c, f, i). Some literature reports [36, 50] have observed drug-loaded PVP electrospun mats to disintegrate in 10-15 s, markedly quicker than the times obtained here with high drug loadings. This can partly be explained because the experiments here were not done under sink conditions (samples containing 3 mg ketoprofen were tested in 15 mL simulated saliva) and thus an increase in disintegration time could be expected over other reports in the literature. Augmenting this effect are the properties of ketoprofen itself: it has log P = 3.12 [52], and thus is a lipophilic drug [53], with solubility of 0.01% w/w at pH=7 [22]. Thus, disintegration is slower than in previous studies using more soluble active ingredients.

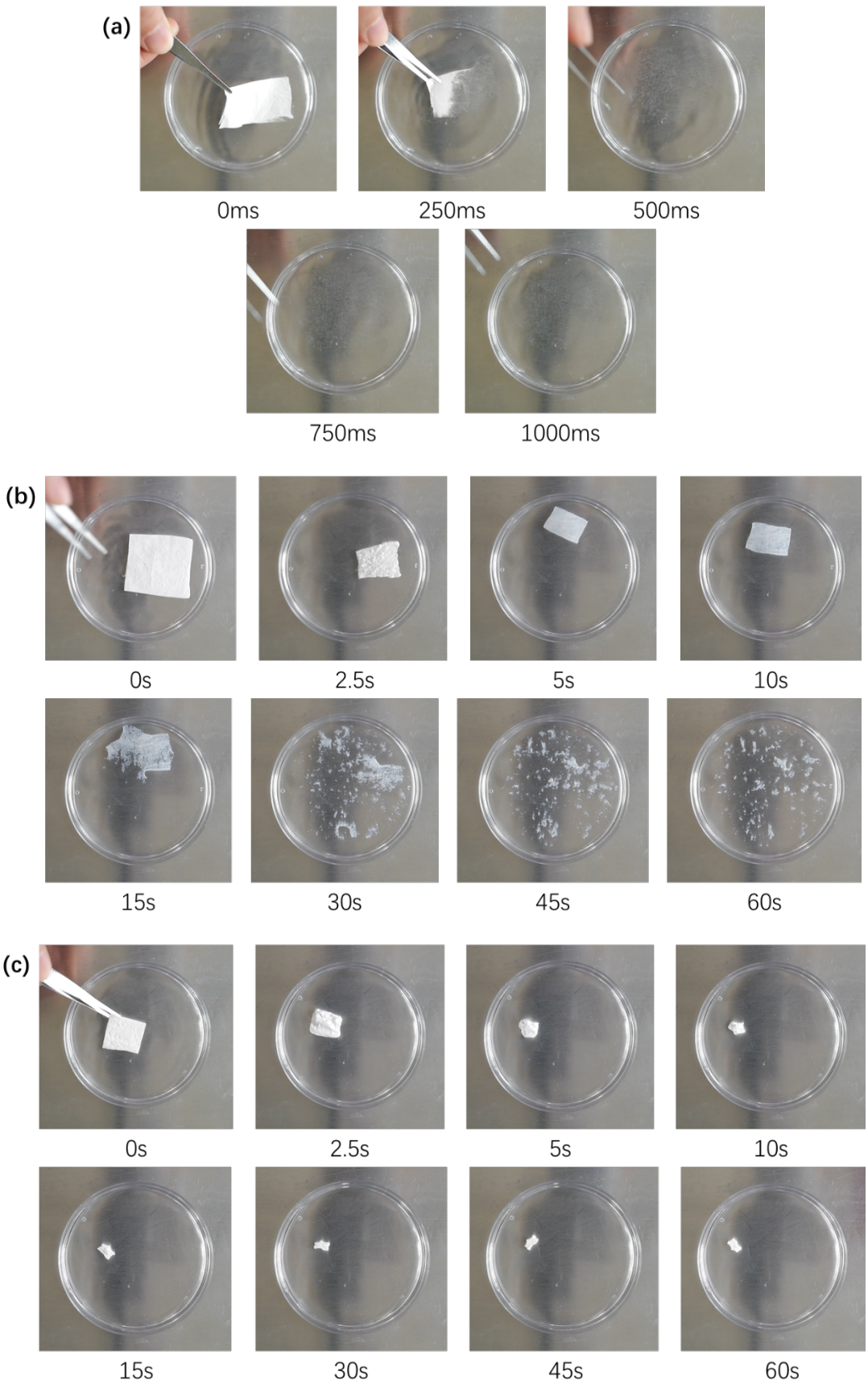

Figure 7. Camera images of the disintegration of polymer/API electrospun fibers. (a) F0-20; (b) F1-20; (c) F2–20.

In vitro ketoprofen release profiles are given in Figure 8a. The low-loading F1 systems release 75-85 % of the incorporated ketoprofen in 6 mins (F1-1: 81.9 ± 7.1 %; F1-2: 75.6 ± 4.3 %; F1-10: 85.6 ± 4.5 %; F1-20: 81.4 ± 2.5 %). However, formulation F2 only releases 30-40 % of the drug loading in this time period (F2-1: 40.9 ± 7.6%; F2-2: 38.0 ± 1.0 %; F2-10: 34.0 ± 7.7 %; F2-20: 38.9 ± 6.1%). The physical mixture (ketoprofen 9.09%, PVP 90.91%) released 49.0 ± 1.4 % of the ketoprofen content within 6 mins. Samples containing 3 mg ketoprofen were tested in 15 mL simulated saliva, while the solubility of ketoprofen is 0.01% w/w, pH=7 [22]. Thus, these experiments were not under sink conditions. Fast dissolution of formulation F1 (>75% in 6 min) was observed with all production rates and fibers from both the benchtop apparatus and the NEU-BM instrument; the scaling-up of the electrospinning process therefore did not reduce the rate or extent of drug release from the polymer fibers. However, there were slight changes in the release amount from the F1 recipe with the systems prepared at different flow rates. This is thought to be because of fiber diameter differences: as the fiber diameter decreased, the release amount increased (see Figure 8b), which is consistent with the literature [5, 60].

Previous work by Yu et al. [23] generated PVP/ketoprofen fibers and observed complete drug release within 30 s. Other researchers [50] have fabricated electrospun fibers based on hydrophilic polymers with bench-top electrospinning (1.25mL/h), and noted 95% drug release within 8 mins. Similar systems prepared with scaled-up electrospinning (60 – 1200 mL/h) also gave a burst release of 95% in 5 min [43]. The drug release experiments in all these reports in the literature were performed under sink conditions, however. Thus, the slower drug release noted in this work is expected to be a result of the different experimental set-ups used for dissolution studies, rather than the inherent properties of the fibers. The observation of drug release rates being constant for both benchtop and scaled-up electrospun PVP fibers is consistent with the literature (which in both cases noted 90-95% release in 5-10 min under sink conditions [43, 56]).

It is clear that with the low-drug loaded F1 systems forming an ASD of ketoprofen increases the dissolution rate of the drug compared to the physical mixture. This is a result of the molecular dispersion of the drug in the polymer, the large surface area of the electrospun fibers, and the hydrophilicity of PVP [23]. When the electrospun fibers come into contact with the dissolution medium, the PVP polymer dissolves quickly and ketoprofen is released into the medium simultaneously. This can be described as a “polymer-controlled” release process [40].

However, when the drug loading was raised in formulation F2 there was slower release than obtained with the physical mixture. This drug-dependent profile has also been observed by other groups [38]. At low drug loading, the material disintegrates into fragments quickly before dissolving into the solution, while at high drug loading, the material swells but no particles break off. A possible explanation for this type of dissolution profile with high drug loading was suggested by Higuchi et al. [41]. These authors proposed that a gel-like drug-rich layer was formed on the surface of the material which hindered further dissolution. This is also consistent with the disintegration data in Figure 7c and Figure S3c, f, i.

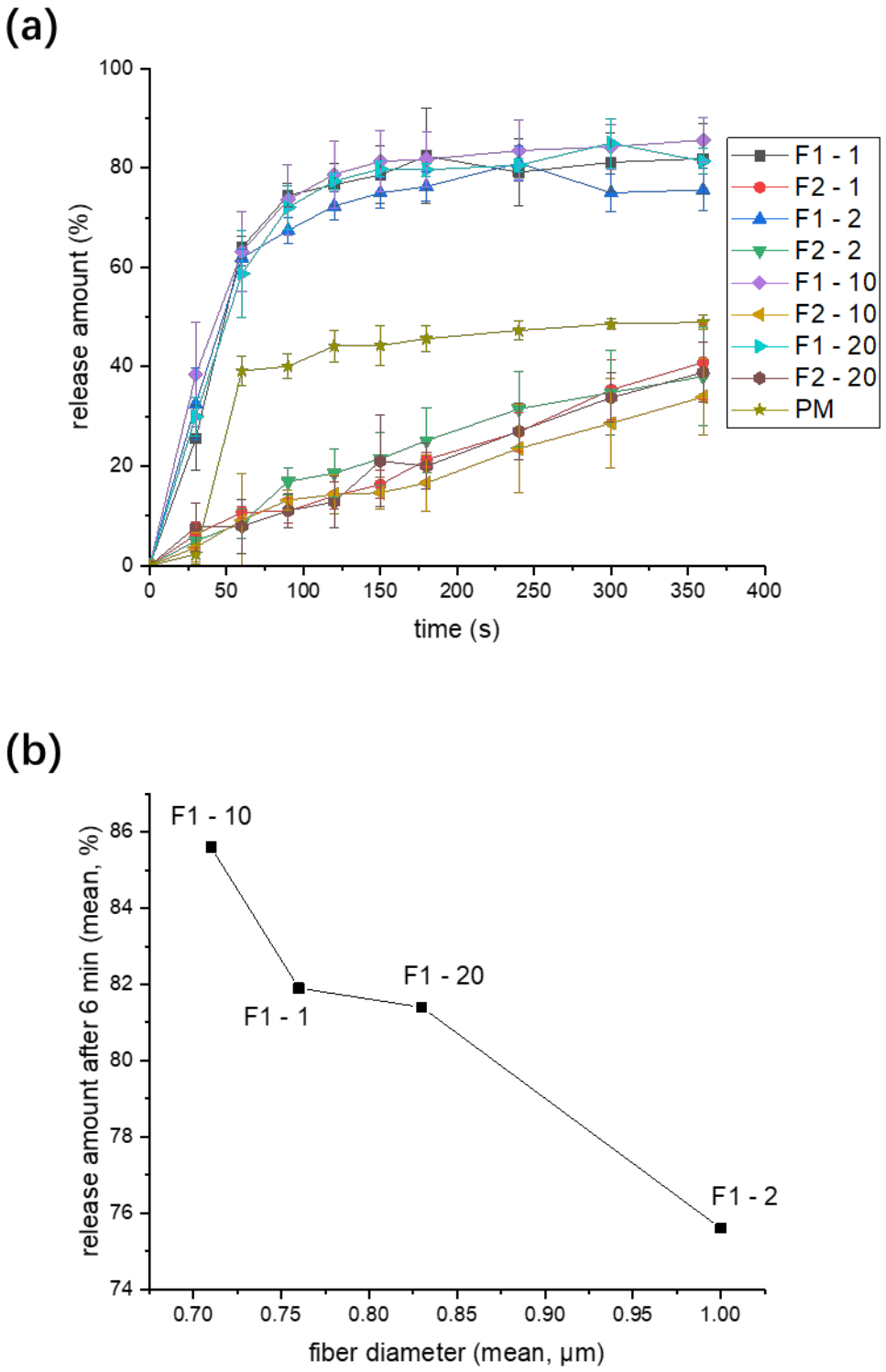

Figure 8. (a) *In vitro* dissolution profiles of electrospun fibers of F1, F2 and PM with different spinning flow rate. Results are given as mean ± SD. (b) The relationship between release amount and fiber diameter for the F1 formulations.

3.9 Stability studies

XRD patterns for formulations aged for 4 weeks are given in Figure 9 and Figure S4. The patterns are all the same regardless of the flow rate, showing only broad haloes and suggesting that the fibers remained amorphous after storage. The humps at around 10° and 17° arise from the sample holder used and the high porosity of the fiber mat [32].

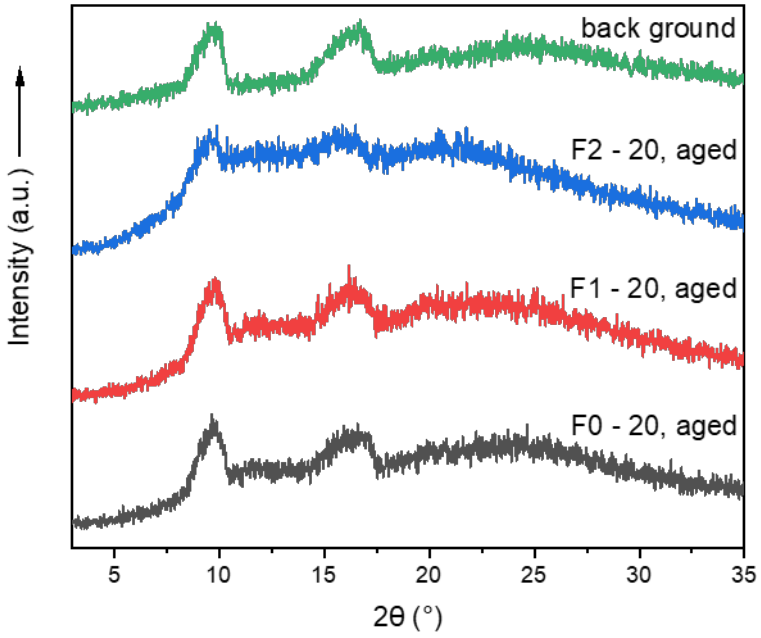

Figure 9. XRD patterns of selected polymer/ketoprofen fibers after storage for 4 weeks.

DSC traces of the aged materials (Figure 10 and Figure S5) show only broad endothermic peaks arising from the loss of adsorbed water, and the glass transition of PVP. No sharp endothermic peaks were visible, confirming the findings from XRD: the aged electrospun fibers remain amorphous.

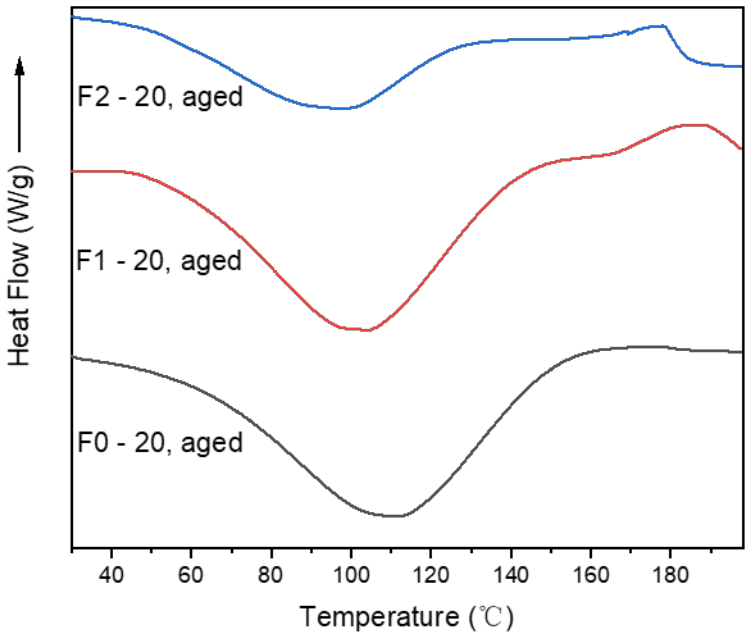

Figure 10. DSC traces selected fibers after storage for 4 weeks.

Figure 11 and Figure S6 illustrate the *in vitro* dissolution profiles of the electrospun polymer/ketoprofen fibers after storage. The aged F1 formulations release 75-90 % of their ketoprofen loading within 6 mins (F1-1: 81.8 ± 3.0 %; F1-2: 79.4 ± 1.8 %; F1-10: 87.8 ± 6.3 %; F1-20: 85.6 ± 2.7%), and the release profiles are identical to those obtained with the fresh samples (see Figure S6).

Considering the aged F2 systems, the materials could release 25-40 % of their ketoprofen cargo in 6 mins (F2-1: 36.9 ± 10.8 %; F2-2: 27.3 ± 4.3 %; F2-10: 31.1 ± 5.0% ; F2-20: 27.7 ± 4.8%). Compared to the fresh samples, there is a slight decrease in the amount of drug release in 6 min after aging (Figure S6), which might be because these high drug loading samples contain both molecular ketoprofen and also amorphous drug particles. Thus, during the dissolution process, slower release is seen as some time is required for the amorphous drug clusters to dissolve. Upon storage, the mass fraction of amorphous nanodrug clusters increased, which decreased the amount of drug released in 6 min [28, 40].

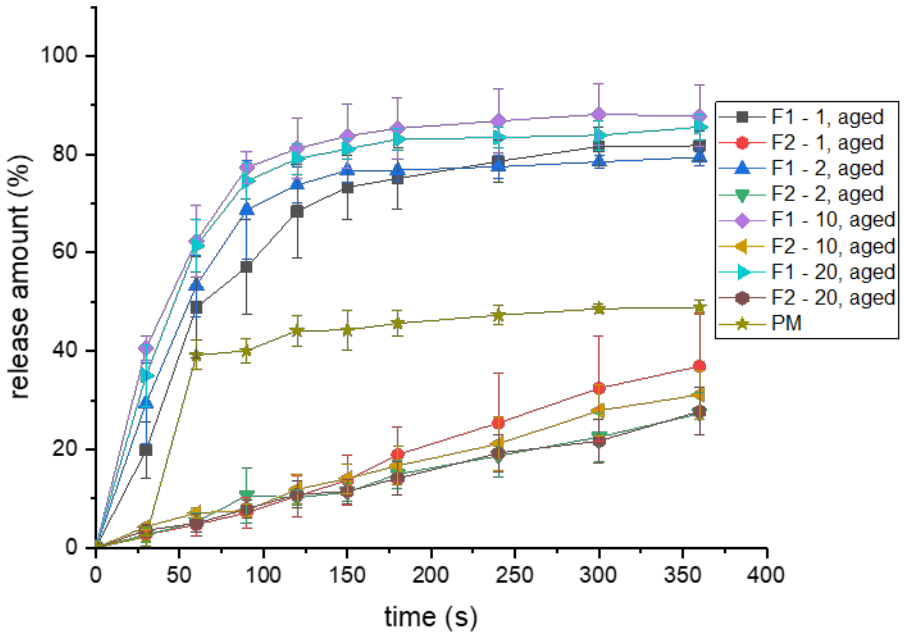

Figure 11. *In vitro* dissolution profiles of the aged electrospun formulations. Results are given as mean ± SD.

Overall, the electrospun PVP/ketoprofen fibers remained amorphous after storage for 4 weeks. In the case of F1 they also had *in vitro* drug release profiles very similar to the fresh materials. The F2 formulations were observed to give a slight decrease in the release amount after storage.

In this work, different drug loadings were observed to lead to different release profiles, with materials with low drug loading (F1, ketoprofen 9.09%, PVP 90.91% w/w) releasing drug quickly while the higher drug loading fibers (F2, ketoprofen 23.08%, PVP 76.92%) showed much slower release. Formulation F1 has great potential as a fast dissolving drug delivery system for oral absorption as it can disintegrate quickly and accelerate the dissolution profile of ketoprofen. However, there must be a maximum loading of ketoprofen in PVP electrospun fibers which permits such fast release, which is likely to lie between 9.09 and 23.08% w/w. The scale-up of electrospinning (1, 2 mL/h → 10, 20 mL/h) did not markedly affect the release speed, and the fibers with the smallest diameter (F1 prepared at 10 mL/h) gave the most rapid drug release.

Other groups fabricating fast release drug delivery systems using scaled-up electrospinning techniques with hydrophilic polymers have also reported that dissolution profiles are unaffected by scale up (90-95% release in 5-10 min, under sink conditions [43, 56]). Thus, industrial quantities of material can be prepared without compromising quality. The British National Formulary suggests a ketoprofen dose of 100–200 mg once daily for adults. The loading of F1 was 9.09%, so 1.1-2.2g of formulation F1 would be needed per day. However, oral administration of ketoprofen leads to an absolute bioavailability of approximately 81-85% [59], but because sublingual route could avoid the first-pass metabolism effect, the daily required dose could be reduced to perhaps 800 mg. This quantity of fibers is a relatively large amount, but could in theory be applied in the mouth. 800 mg would require ca. 0.5 h to prepare at 20 mL/h however, meaning that further scale up will be

needed to make an industrially viable amount of material. There are a wide range of other poorly-soluble drugs with similar dosages (e.g. ibuprofen, indomethacin, diclofenac), and the electrospinning approach can similarly be applied to these APIs to yield fast dissolving drug delivery systems for rapid relief of symptoms.

4. Conclusions

In this study, electrospun polymer fibers were fabricated using poly(vinylpyrrolidone) as a fast-dissolving polymer matrix, loaded with ketoprofen as a model active pharmaceutical ingredient (API). Experiments were performed to increase the production flow rate from bench-top scale (1, 2 mL/h) to greater throughput (10, 20 mL/h) using a rotating metal drum as the collector. Scanning electron microscopy revealed that the fibers generated at all four flow rates using three formulations [F0 (100% PVP), F1 (PVP 90.91%, ketoprofen 9.09% w/w), F2 (PVP 76.92%, ketoprofen 23.08% w/w)] had smooth surfaces and average diameters ranging between 0.6 and 1.2 µm. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) analyses demonstrated all the formulations to comprise amorphous solid dispersions. Fourier transform infrared (FTIR) spectroscopy showed that there was hydrogen bonding between PVP and ketoprofen molecules, which could help stabilize the molecular distribution of the drug in the polymer carrier. The encapsulation efficiencies for all formulations were essentially 100% of the theoretical loading. The F1 formulations prepared at all flow rates could disintegrate quickly and increase the dissolution rate of ketoprofen in simulated saliva. However, this benefit was not seen with the higher drug-loaded F2 systems, indicating that there is a maximum concentration above which there is no benefit in dissolution enhancement. After storage under ambient conditions (19-21 °C, relative humidity 30-40%) for 4 weeks, XRD and DSC data showed that the polymer fibers and the drug loaded systems all remained amorphous, and the dissolution profiles do not show any significant changes from those with the fresh formulations.

5. Supplementary information

Supplementary information available: Figure S1 (Photographs of bench-top and NEU-BM electrospinning setup), Figure S2 (Histograms of the fiber diameter distribution), Figure S3 (Camera images showing the disintegration of the electrospun fibers), Figure S4 (XRD patterns of the electrospun polymer/API fibers after storage for 4 weeks), Figure S5 (DSC traces of the electrospun polymer/API fibers after storage for 4 weeks) and Figure S6 (*In vitro* dissolution profiles of electrospun polymer/ketoprofen fibers before and after storage for 4 weeks).

5. Acknowledgements

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7. Research data

Data can be accessed by request to the corresponding author.

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