Intermolecular Interactions and the Release Pattern of Electrospun Curcumin-Polyvinyl(pyrrrolidone) Fiber

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An electrospun fiber of polyvinyl(pyrrrolidone) (PVP)–Tween 20 (T20) with curcumin as the encapsulated drug has been developed. A study of intermolecular interactions was performed using Raman spectroscopy, Fourier transform infrared (FT-IR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD). The Raman and FT-IR studies showed that curcumin preferably interacted with T20 and altered PVP chain packing, as supported by XRD and physical stability data. The hydroxyl stretching band in PVP shifted to a lower wavenumber with higher intensity in the presence of curcumin and PVP, indicating that hydrogen bond formation is more intense in a curcumin or curcumin–T20 containing fiber. The thermal pattern of the fiber did not indicate phase separation. The conversion of curcumin into an amorphous state was confirmed by XRD analysis. An in vitro release study in phosphate buffer pH 6.8 showed that intermolecular interactions between each material influenced the drug release rate. However, low porosity was found to limit the hydrogen bond-mediated release.

Key words curcumin; fiber; electrospinning; interaction; porosity; polymeric drug delivery system

Curcumin is the major constituent of turmeric rhizome (Curcuma sp.). Curcumin has a number of demonstrated pharmacological effects, such as antioxidant, anti-inflammatory, anticancer, hepatoprotective, antimicrobial, and antiviral. Clinical trials have proven that curcumin is well tolerated by the body, with a maximum dose of 12g daily. Unfortunately, the efficacy of curcumin is limited by its poor solubility in water, as well as its instability under light, heat, and alkaline conditions. The solubility of curcumin in aqueous buffer (pH 5) is reported to be 11 ng/mL. Moreover, the absorption of curcumin in the gastrointestinal tract is very low, leading to poor bioavailability (in animals and humans). Therefore, designing an effective delivery system is necessary in order to address the limitations of curcumin use.

A wide range of drug delivery systems has been developed to improve the bioavailability of poorly soluble drugs, including fast-dissolving tablets, incorporation into a hydrophilic complex, micellization, and solid dispersion. Electrospinning, a technique of producing thin strands of fiber using high voltage, has opened up opportunities in the development of drug delivery systems. An optimized electrospinning process can produce nano-sized fibers. The high surface area and porosity of these electrospun fibers are advantageous in their use as carriers for poorly water-soluble drugs. Therefore, the incorporation of curcumin into an electrospun fiber is expected to improve its oral bioavailability.

Tailoring a suitable drug-loaded fiber requires careful selection of materials, in addition to an optimized production process and environment. Generally, the drug is mixed with a polymer solution to be spun into fiber. In the case of curcumin, one of the key factors is miscibility. In a miscible mixture of polymer and other materials, interactions such as hydrogen bonding, polyanion–polycation complex, dipole–dipole interaction, and electrostatic force occur. These must be taken into consideration, since intermolecular interactions can affect the entrapment and release kinetics of the encapsulated drug.

While research on molecular interactions in electrospun fibers is mainly linked to the fiber’s physical aspects (conductivity, viscosity, spinnability, tensile strength, and elongation), investigation into how intermolecular interactions in electrospun fibers affect the drug release profile is still lacking.

In this study, an electrospun fiber based on a nonionic hydrophilic polymer polyvinyl(pyrrrolidone) (PVP), with curcumin as the active compound, has been developed. A nonionic surfactant Tween 20 (T20) with a concentration exceeding critical micellar concentration (CMC) was added to the mixture. This study was designed to evaluate the interactions between each material in order to predict the influence of the molecular interactions on the characteristics of the fiber as well as the drug release profile.

MATERIALS AND METHODS

Materials Curcumin derived from Curcuma domestica (95% curcuminoid) was obtained from Phytochemindo Lestari, Indonesia. PVP (molecular weight (MW) 1500000) was obtained from Combiphar, Indonesia. T20 was purchased from SEPPIC, France. Ethanol 96% (Merck, Germany) and acetone

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Methods
Preparation of Polymer Mixture
A curcumin–polymer mixture was prepared fresh just prior to the spinning process. Into 5 mL of ethanol, 2% (w/v) of T20 was added and mixed using a magnetic stirrer. Various amounts of PVP were added under constant stirring, yielding final concentrations of 5–10% (w/v). The polymer was allowed to completely dissolve by moderate stirring for 3 h. The curcumin solution was prepared separately by dissolving curcumin powder in 5 mL of acetone. This curcumin solution was added drop-wise into the PVP solution, followed by moderate stirring for 3 h.

Electrospinning Process
The resulting polymer solution was loaded into a 10 mL syringe (inner diameter of 0.5 mm). The solution was discharged by a syringe pump with a feeding rate of 10 µL/min. The solution was electrosprun under an applied voltage of 19 kV, a tip-to-collector distance of 17 cm, and temperature and relative humidity at 30±1°C and 70±3%, respectively. The resulting fibers were collected on aluminium foil fixed on a rotating cylindrical collector.

Morphology and Size
The morphology and size of the fiber were analyzed by scanning electron microscope (SEM) JEOL JSM 6510 LV. The scanning was performed at 10 kV in a vacuum condition. The size distribution of the fibers was analyzed using Origin v. 8.1 Software.

Porosity
Porosity of the resulting fibers was determined by measuring the void area within SEM images using ImageJ software.

Raman Spectroscopy
Raman spectra of curcumin, T20, PVP fiber, PC7 fiber, and PCT7 fiber were recorded using a Bruker Senterra spectrometer. A diode laser was used as an excitation laser at a wavelength of 424 nm. Samples were mounted on a glass slide without any pre-treatment.

Fourier Transform Infrared (FT-IR) Spectroscopy
The prepared solutions subject to electrospraying are shown in Table 1. The solutions were completely miscible, clear and free of undissolved particles. Nozzle clogging occurred occasionally due to the high viscosity of the polymer and the rapid evaporation of the solvent. Fiber mats with dense packing were obtained and stored in a dry cabinet (30°C, relative humidity 50%).

Differential Scanning Calorimetry (DSC) Analysis
Thermal properties of the fibers were analyzed by a DSC method (Linseis DSC PT1000). The heating rate for DSC analysis was set at 10°C/min.

X-Ray Diffraction (XRD) Analysis
XRD pattern of the fibers was recorded using an XRD Diffractometer (Philips Analytical) with 2θ between 5 and 60, an applied voltage of 40 kV, and current of 30 mA.

In Vitro Release Study
The release study was performed using Dissolution Apparatus I USP (Hanson Research SR8 Plus). The release medium used in the experiment was a phosphate buffer (pH 6.8) with 0.5% (v/v) of T20. Fibers containing 3.5 mg of curcumin were placed in the basket and were then immersed in 400 mL of release medium. The experiment was conducted in triplicate with temperature maintained at 37°C and a steady revolution of 50 rpm. Aliquots of 3 mL were taken at 5, 10, 15, 30, 45, and 60 min, and were replaced by an equal volume of release medium. The amount of curcumin released was determined by UV-Visible Spectrophotometer at 424 nm.

RESULTS AND DISCUSSION

Electrospinning Process
The prepared solutions subjected to electrospinning are shown in Table 1. The solutions were incompletely miscible, clear and free of undissolved particles. Nozzle clogging occurred occasionally due to the high viscosity of the polymer and the rapid evaporation of the solvent. Fiber mats with dense packing were obtained and stored in a dry cabinet (30°C, relative humidity 50%).

Morphology
Both curcumin–PVP fiber (PC) and curcumin–PVP–T20 fiber (PCT) were uniform in shape, and were free from beads (Figs. 1, 2), indicating sufficient polymer concentration in the precursor solution for the electrospinning process. Sufficient polymer concentration is important in order to produce a continuous and beadless fiber, as well as to prevent electrospaying instead of electrospinning. The minimum concentration of PVP required in electrospinning varies, depending on MW. For instance, PVP with MW around 350000 can produce beadless fiber when used in a concentration of ≥10% (w/v), while only 7% (v/v) is required for PVP with a MW of 1300000. Beadless fibers are preferred since they provide a higher surface area to volume ratio and favorable mechanical properties.

The size distribution of the fiber (Figs. 1, 2) was rather broad. This was likely caused by the solvent. It has been reported that high electrical conductivity of the solvent results in a broad distribution of fiber size. The solvent used in this study was acetone–ethanol. Each of these solvents have high conductivity (more than 1×10−3 S/cm−1), and therefore they provide a higher surface area to volume ratio and favorable mechanical properties.

The presence of T20 did not seem to affect the size distribution. However, since electrospinning takes place when the electrostatic force of the solution exceeds the surface tension, the solution containing T20 is expected to result in branchy jets of varying thickness, which subsequently leads to a less uniform fiber.

The effect of PVP concentration on fiber diameter is displayed in Fig. 3a. It was found that higher PVP concentrations produced fibers of greater diameter. In fact, a PVP concentration above 7% (w/v) yielded fibers within a sub-micron to
micrometer range. Fiber diameter is strictly controlled by the viscosity of polymer, where the degree of chain entanglement is increased with higher viscosity, leading to the formation of a larger fiber diameter. The addition of T20 did not alter the shape of the fiber, but it did affect the diameter of the fiber.

Porosity In this study, the two-dimensional pore was described as a polygon encircled by fiber strands crossing from different angles. Figure 3b shows that porosity was reduced as fiber diameter decreased. Similar to the findings in this study, Kaur et al. and Varesano et al. reported that porosity was reduced as fiber size decreased. In any given area, the number of fiber strands that can occupy the space is higher when the fiber diameter is smaller. Consequently, the density per unit area is higher and the total area of polygons (uncovered area) is smaller with smaller diameter fibers. The lowest porosity was observed in PC5 (diameter 328.75 nm) at 6.28%. In contrast, the porosity of PCT10 (diameter 2.83 µm) was the highest, at 28.56%. High porosity indicates that the number of intermolecular bondings formed was low. Higher PVP concentration in the precursor solution of PCT10 has more available binding sites for other materials, resulting in fewer intermolecular interactions. Therefore, porosity increased in fibers with higher PVP concentrations.

It is important to consider the porosity of electrospun fibers since porosity can control the diffusion of a drug from the matrix. A slow release rate of paclitaxel from an electrospun fiber due to the low porosity of the fiber has been reported. Our findings also revealed that the fiber with the smallest porosity, PC5, had the slowest release rate.

Intermolecular Interaction
Raman and FT-IR Spectroscopy
Figure 4 shows the Raman spectra of pure curcumin, PC5 fiber and PCT5 fiber. Raman-active vibrational modes were clearly dominated by curcumin, with a subtle background.

Fig. 1. Morphology of Fiber Observed with SEM
PCT5 (a), PCT7 (b), and PCT10 (c). Magnification of all images were 5000×.
of PVP (in PC5 and PCT5) and Tween 20 (in PCT5). This indicates that curcumin was uniformly distributed within the polymer bundles inside the nanofiber. Peak assignment related to curcumin is displayed in Table 2. In general, peaks related to C–C bending, C–H bending, and C=O stretching occurred at higher wavenumbers in PC5 and PCT5. In contrast, C=C stretching shifted to lower wavenumbers in PC5 and PCT5. However, no difference in peak position was observed between PC5 and PCT5. Detailed information regarding intermolecular interactions between curcumin, PVP and T20 is described in our FT-IR study.

The infrared spectra of curcumin, T20, PVP, PC5 and PCT5 are shown in Fig. 5. A strong PVP background was noticed in the spectra of PVP fiber, PC5, and PCT5. The fact that curcumin absorbs strongly in Raman spectroscopy, but not in FT-IR spectroscopy, shows that curcumin is not dispersed along PVP chains. Instead, curcumin was dispersed between PVP chain bundles in the nanofibrils. The illustration of a nanofibril is shown in Fig. 6. Table 3 summarizes characteristic peaks of PVP in pure PVP fiber, PC5 and PCT5. We observed peak broadening over 3200–3700 cm\(^{-1}\). The intensity and width of the peak was in the following order: PCT5>PC5>PVP, indicating a stronger hydrogen bond formation in PC5 and PCT5. Curcumin also showed phenolic hydroxyl stretching at 3501 cm\(^{-1}\) (see Table 4). This peak might contribute to the formation of hydrogen bonding, since the intensity of the O–H band in PC5 was higher than that of PVP. An interesting spectral range was found between 2800 and 3000 cm\(^{-1}\). In the PVP spectrum the peaks were weak and broad, while with PC5 the peaks were sharper. In PCT5 the peaks were significantly well-defined. Thus, curcumin is thought to be a spacer between PVP polymer bundles in which the C–H bonds along the PVP chain were able to vibrate more freely. It was suggested that curcumin as a spacer

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Fig. 2. Morphology of Fiber Observed with SEM
PC5 (a), PC7 (b), and PC10 (c). Magnification of all images were 5000×.
resulted in molecular arrangement on a higher order in PC5 and PCT5. This finding is supported by XRD data in which the peak at the 2θ position of 11.66 in PVP shifted to 10.18 in PC5 and to 10.44 in PCT5 (this will be described later).

Pure curcumin demonstrated C=C stretching at 1601 cm⁻¹. This peak appeared as a shoulder next to a carbonyl stretching band of PVP around 1650 cm⁻¹ in PC5 and PCT5. The hygroscopic nature of pure PVP was indicated by a C=O stretching band at 1646 cm⁻¹. A number of studies have reported that a strong hydrogen bond is commonly indicated by the presence of a C=O stretching band below 1664 cm⁻¹. Other peaks exhibited by curcumin at 1490 and 1500 cm⁻¹ shifted to a higher wavenumber in the PC5 and PCT5 spectra, while the peak at 1424 was absent in PC5 and PCT5. Another characteristic demonstrated by curcumin is the formation of polaron band over 1600–3400 cm⁻¹ due to π–π stacking of C=C along the structural chain and benzene ring. This peak was absent in PC5 but present in PCT5, starting at 1701 cm⁻¹. Polaron occurs when stacked conjugated chains are present, resulting in higher interchain interaction.²⁹ It is then suggested that curcumin in PCT5 was incorporated and accumulated into a micellar structure with T20 as the outer layer. As supporting evidence, Tween 20 demonstrated a C=O stretching peak at 1734 cm⁻¹ (pure T20) and at 1730 cm⁻¹ (in PCT5). The prefer-

![Diagram](image1)

**Fig. 3.** Relationship between Polymer Concentration and Fiber Diameter (a), and Relationship between Fiber Diameter and Porosity (b)

![Diagram](image2)

**Table 2.** Raman Peak Assignment of Curcumin

<table>
<thead>
<tr>
<th>Raman shifts (cm⁻¹)</th>
<th>Vibrational mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure curcumin</td>
<td>PC5</td>
</tr>
<tr>
<td>961</td>
<td>971</td>
</tr>
<tr>
<td>1183</td>
<td>1187</td>
</tr>
<tr>
<td>1150</td>
<td>1161</td>
</tr>
<tr>
<td>1250</td>
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<tr>
<td>1600</td>
<td>1595</td>
</tr>
<tr>
<td>1625</td>
<td>1632</td>
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</tbody>
</table>

δ=in-plane bending; ν=stretching.

![Diagram](image3)

**Fig. 4.** Raman Spectra of Curcumin in Pure Curcumin, PC5, and PCT5
ence of curcumin to interact with T20 versus with PVP, due to micelle formation, is confirmed by a stability study, as will be fully explained later. After months of storage, PCT5 formed a brittle film with a strong indication of moisture adsorption by PVP. In contrast, PC5 did not undergo such physical change. The mesomeric structure of PVP allows for hydrogen bonded C=O groups between pyrrolidone rings in the presence of moisture, as indicated by an O–H stretching band in PVP, PC5, and PCT5 around 3200–3700 cm\(^{-1}\). In the case of PC5, the carbonyl groups in curcumin might mildly interact with hydrogen-bonded C=O in PVP. In PCT5 the carbonyl groups in curcumin had higher interaction with the hydroxyl groups in T20, since T20 is a proton donor in hydrogen bond formation. Consequently, the evidence of moisture uptake by C=O groups in PVP was more obvious.

**Thermal Profile** Thermograms of curcumin, PVP, PC and PCT fibers are displayed in Fig. 7a. The formulation of PC and PCT fibers used in DSC analysis were PC5 and PCT5. A
thermogram of pure curcumin showed an endothermic peak at 175.2°C, indicating the melting temperature \(T_m\) of curcumin in a crystalline state. The peak was not observed in the thermogram of PC and PCT, suggesting that all the ingredients were in a homogenous system. The peak was not observed in the thermogram of PC and PCT, suggesting that all the ingredients were in a homogenous system. The glass transition temperature \(T_g\) of pure PVP was observed at 178.73°C (Fig. 7b). A homogenous system in PC and PCT fiber is expected to result in a single \(T_g\). The \(T_g\) value can be predicted theoretically using the Gordon–Taylor equation (1),

\[
T_{gm} = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2}
\]

where \(T_{gm}\), \(T_{g1}\), and \(T_{g2}\) are the \(T_g\) of mixture, of compound 1, and of compound 2, respectively. The weights of compounds 1 and 2 are indicated by \(w_1\) and \(w_2\), respectively. Constant value, \(k\), is determined using the equation below,

\[
k = \frac{Q_1 T_{g1}}{Q_2 T_{g2}}
\]

where \(Q_1\) and \(Q_2\) are the densities of compounds 1 and 2. Tobyn et al.\(^{35}\) used these equations to determine the \(T_g\) of an amorphous drug–PVP binary system. In this study, the predicted \(T_g\) in PC fiber was approximately 164.14°C. This value should not differ significantly in PCT fiber.\(^{29}\) However, no \(T_g\) in the electrospun fiber was detected over a temperature range between 130 and 190°C, as shown in Fig. 7c. This might be due to the presence of a relaxation peak of the fiber, which resulted from mechanically-induced stress.\(^{36}\)

**Crystallinity** A crystallinity analysis was performed to confirm the data on intermolecular interactions and thermal analysis. The XRD patterns of individual components and their mixtures in an electrospun fiber are shown in Fig. 8. The formulations of PC and PCT fiber used in XRD analysis were PCs and PCT5. Pure curcumin powder showed characteristic patterns of a crystalline state between the 2\(\theta\) positions of 10° and 30°: intense peaks at 8.9°, 14.54°, 17.22°, 18.16°, and 23.34°.

### Table 3. FT-IR Peak Assignment of PVP

<table>
<thead>
<tr>
<th>FT-IR peaks (cm(^{-1}))</th>
<th>Vibrational mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure PVP</td>
<td>PC5</td>
</tr>
<tr>
<td>3396</td>
<td>3409</td>
</tr>
<tr>
<td>2950</td>
<td>2951</td>
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<td>2922</td>
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<tr>
<td>1017</td>
<td>—</td>
</tr>
<tr>
<td>933</td>
<td>933</td>
</tr>
<tr>
<td>843</td>
<td>844</td>
</tr>
<tr>
<td>572</td>
<td>576</td>
</tr>
</tbody>
</table>

\(δ\)=in-plane bending; \(ν\)=stretching; —=the peak was absent.

### Table 4. FT-IR Peak Assignment of Curcumin and T20

<table>
<thead>
<tr>
<th>FT-IR peaks of curcumin (cm(^{-1}))</th>
<th>Vibrational mode</th>
<th>FT-IR peaks of T20 (cm(^{-1}))</th>
<th>Vibrational mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure curcumin</td>
<td>PCS</td>
<td>PCT5</td>
<td>Pure T20</td>
</tr>
<tr>
<td>3501</td>
<td>*</td>
<td>*</td>
<td>ν(O–H)(^{25})</td>
</tr>
<tr>
<td>1601</td>
<td>1587</td>
<td>1588</td>
<td>ν(C=O)(^{25})</td>
</tr>
<tr>
<td>1508</td>
<td>1513</td>
<td>1513</td>
<td>ν(C=O), δ(CCC), δ(C–C=O)(^{22})</td>
</tr>
<tr>
<td>1424</td>
<td>—</td>
<td>—</td>
<td>ν(CCC), ν(CH) of aromatic ring, δ(COH) of enolic group, δ(CH) due to CH(_2)(^{32})</td>
</tr>
<tr>
<td>3478</td>
<td>*</td>
<td>*</td>
<td>ν(O–H)(^{33})</td>
</tr>
<tr>
<td>2919</td>
<td>—</td>
<td>2871</td>
<td>Asymmetric ν(CH(_2))(^{33})</td>
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<td>2862</td>
<td>—</td>
<td>2852</td>
<td>Symmetric ν(CH(_2))(^{33})</td>
</tr>
<tr>
<td>1734</td>
<td>—</td>
<td>1730</td>
<td>ν(C=O) of ether group(^{31})</td>
</tr>
<tr>
<td>1092</td>
<td>—</td>
<td>1125</td>
<td>ν(C–O) of ether group(^{34})</td>
</tr>
</tbody>
</table>

\(δ\)=in-plane bending; \(ν\)=stretching; —=the peak was absent; *=Overlapped with other peaks.
and 30° without diffraction peaks, illustrating an amorphous form of PVP. The presence of these two distinct haloes was observed in diffractograms of PC and PCT, confirming the presence of PVP. However, the intensities of these haloes were lower, where the area under curve value was 50% compared to 13% in pure PVP.

Interestingly, characteristic peaks for curcumin were absent in the diffractograms of PC and PCT fiber. This implies that curcumin was converted into an amorphous state. The underlying reason for the conversion was the electrospinning process and the use of an amorphous PVP polymer. During electrospinning, the solvent evaporated rapidly and the jet of polymer solution travelled through the high voltage environment in an incredibly short time, allowing no time for crystallization.\footnote{Zhang et al. stated that electrospinning delayed the crystallization of polymers owing to molecular stretching with high elongation while the molecule undergoes rapid solidification.\footnote{This corresponded with our results. An amorphous polymer such as PVP is known to be able to interact and convert drugs into an amorphous state.\footnote{The presence of T20 did not seem to significantly affect the molecular arrangement of either curcumin or PVP.}}}

The diffractogram of PVP, PC5, and PCT5 also provides information on how curcumin and T20 affect the chain packing of PVP. It was found that the peak at the 2θ position of around 12° in PVP shifted to 10.18° in PC5 and to 10.44° in PCT5. This might indicate a separation between PVP chain bundles in the nanofibrils of nanofiber strands due to curcumin–T20 micelles. The second peak at the 2θ position of around 20° in PVP diminished significantly in PC5 and PCT5. The ratio of the peaks at 20° to 10° in PVP was 1.17, while in PC5 and PCT5 the ratios were 0.49 and 0.45, respectively. This is thought to be the consequences of increased inter-bundle spacing, where PVP chain bundles were forced to rearrange into denser packing, which resulted in decreased inter-lamelar spacing. The possibility of curcumin-containing micelles forming between the PVP chain bundles has been previously suggested by our FT-IR study in which the C–H stretching of PVP was more intense in PC5 and PCT5, indicating that PVP chains were able to move freely due to the increase in space between chain bundles.

**Physical Stability**

The hygroscopic nature of PVP becomes the main challenge in maintaining the stability of PVP-based fibers. Pure PVP fibers completely lost their structure within three days under storage at 30±1°C (relative humidity 70±3%), despite being placed in an airtight container. PC5 and PCT5 fibers were stored under the same storage condi-

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**Fig. 8.** X-Ray Diffraction Patterns of Curcumin, PVP, PC Fiber, and PCT Fiber

**Fig. 9.** SEM Images of PC and PCT Fibers Following Twelve Month Storage at 30°C (5000× Magnification)

PC5 (a) and PCT5 (b) were initially in fiber form. After twelve months, PC5 fiber remained intact (c) while PCT5 fiber degraded and transformed into fractured film (d).
tion. Determination of the moisture content using thermogravimetric analysis showed that PC5 and PCT5 had moisture content of 1.03 and 1.01%, respectively. After twelve months, PCT5 formed a brittle film, while PC5 remained in its original form. SEM analysis of PC5 and PCT5 fibers was performed to observe morphological changes following twelve months of storage. The results are shown in Fig. 9. The findings in this stability study supported our analysis of intermolecular interaction, where the carbonyl groups in curcumin are thought to preferably interact with T20 instead of the hydrogen-bonded C=O in PVP. In contrast, all fibers stored in a dry cabinet (30±0.5°C, relative humidity of 50±0.5%) were relatively stable.

In Vitro Release Study In the current study, the fraction of curcumin released over time is shown in Fig. 10. The high surface area of electrospun fibers significantly enhanced the release rate of curcumin. In our previous study, a similar drug release study was conducted for pure curcumin powder. The results showed that less than 15% of curcumin was released within 1 h. By contrast, in this study, curcumin was completely released from the fiber within 1 h.

Generally, the release patterns of curcumin from fibers consisted of two phases, initiated by a burst release. This combination of two distinct release rates in drug-loaded electrospun fibers has been reported in a number of studies. The initial rapid release is due to structural characteristics of the electrospun fiber, which includes a high surface-to-volume ratio. This burst release was more pronounced in fibers with a higher diameter, as shown in Figs. 7b and c. A higher release rate was observed in fibers with a higher diameter. In PCT10 (average diameter 2.84 μm) and PCT7 (average diameter 1.15 μm), 100% release of curcumin occurred in less than 15 min. However, the amount of curcumin released in 15 min in PC7 was only 48%, while in PC10 it was 68%.

A significant increase in release rate was also suggested to be a result of intermolecular interaction between curcumin, hydrophilic PVP and amphiphilic T20. The presence of T20 in the electrospun fibers formed a hydrophobic interaction with curcumin, most likely in a micellar form. This is in accordance with the results of our study on intermolecular interaction by Raman spectroscopy, FT-IR spectroscopy, and XRD. In micellar form, Tween 20 interrupted the bond between curcumin and the fiber matrix, PVP. This interaction allowed for the effective release of curcumin into the medium. For instance, the release rate in PC10 was lower than in PCT7 and PCT10 because the drug release process in PCT7 and PCT10 was enhanced by the T20–curcumin interaction. However, findings in this study showed that such interaction did not necessarily enhance the release rate. Enhancement of the dissolution rate due to T20 was observed only in fibers with higher diameters.

Fig. 10. The Release Pattern of Curcumin in Electrospun Fiber
Comparison in all preparations (a), in relation to fiber diameter (b,c). The fiber in (b) contained T20, while fiber in (c) did not contain T20.
a PVP concentration of 7 and 10% (w/v) (PC7, PCT7, PC10, and PCT10). The release rate in PCT5 and PC5 differed only slightly despite the addition of T20 in PCT5. Thus, it was suggested that the characteristics of a fiber, such as its diameter and porosity, were attributed to this phenomenon.

The mechanism of drug release from a biodegradable polymer is a complex process governed by both polymer erosion/degradation and drug diffusion. In addition, numerous factors such as drug–carrier interaction, morphology of the matrix, porosity, and polymer concentration can influence the release profile. In fact, the interaction between drug and the matrix is a key factor affecting drug release. Although the hydrogen bond is a weak interaction, Hao and Li found that a substantially high number of hydrogen bond formations could decrease a drug’s release rate. The results of FT-IR analysis showed hydrogen bond formation between curcumin and PVP and between PVP and T20, and a hydrophobic interaction between curcumin and T20. The strength of these intermolecular interactions seemed to vary in each preparation, and affected the release pattern.

According to a study by Park et al., the release rate of a drug incorporated within an electrospun fiber was controlled by the porosity of the fiber. In highly porous fibers, drug diffusion is determined by the pores rather than by polymer erosion. The slower release in PCS5 and PCT5 can be attributed to low porosity, because the decrease in pore size results in reduced wettability of the fiber, limited mass transfer, and a lower water flux. Porosity has been reported to correlate with intermolecular interaction. In this study, the electrospinning of a higher concentration of PVP resulted in higher fiber diameter and porosity. At a higher PVP concentration, more available binding sites for other materials were available. Therefore, the number of intermolecular interactions formed was lower. This weak interaction subsequently led to a loose and porous fiber. Weber et al. reported that excessive intermolecular interactions, such as hydrogen bonds, resulted in low porosity. He found that hydrogen bond formation caused a reduction in the free volume of a polymeric matrix. Therefore, it can be concluded that intermolecular interactions can enhance the release rate, but excessive interaction could result in low porosity, which decreases the drug release rate. Furthermore, PVP is a non-ionic polymer which does not undergo repulsion when being spun into fiber. As a consequence, PVP fibers have a high packing density, instead of the fluffy structure of polymers with a surface charge. The compact structure of PVP fibers means a decrease in free volume, which can result in low water diffusivity. Thinner fibers have been reported to have a more compact structure. This could explain the phenomenon of the slower release rate of curcumin in fibers with a smaller diameter, since the release medium required more time to penetrate the compact structure of the fiber.

CONCLUSION

Successful drug loading into electrospun fibers requires a careful approach in order to produce the desired physicochemical properties, release characteristics, and stability. Curcumin-containing fibers have been successfully synthesized using an electrospinning method. Intermolecular interaction in the fiber has been shown to influence the physicochemical properties of the fiber and also the release rate. In this study, intermolecular interaction in the form of hydrogen bonding potentially enhanced rhw release profile. However, the results indicate that excessive interaction, which resulted in low porosity, was found to decrease the drug release rate. It is expected that the findings of this study may contribute information on the appropriate selection of matrix and other ingredients (such as surfactant) in accordance with the desired release profile of electrospun fiber-incorporated drugs. For instance, a non-ionic polymer is more suitable for electrospun fibers intended for immediate release, since it only forms weak electrostatic interactions with the other ingredients. Possible future directions of this research may include study of interactions with anionic or cationic surfactants using various spectroscopy methods and classical physicochemical methods.

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REFERENCES