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Proceeding Paper

Electrospun Hyaluronan-Based Nanofibers with Mangiferin: Preparation, Morphology, and Drug Release Kinetics †

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Abstract: The rise in antibiotic-resistant bacterial infections is a major global health concern. The search for natural compounds that inhibit the growth of pathogens is becoming urgent. One such compound is mangiferin, a non-toxic polyphenolic compound derived mainly from *Mangifera indica*. In addition to antibacterial properties, it exhibits anticancer, antioxidant, immunomodulatory, analgesic and other activities. However, the clinical application of mangiferin is limited by poor solubility and bioavailability. This study describes mangiferin-loaded electrospun nanofibers based on high-molecular-weight hyaluronic acid. The nanofibers improve mangiferin delivery and possess favorable morphological characteristics and drug release kinetics, making them promising candidates for effective antibacterial dressings. This study found that an increase in the mangiferin content of the fibers led to an increase in the average diameter of the fibers. It was also found that nanofibers with different mangiferin content have similar release kinetics with an anomalous non-Fickian transport pattern: most of the mangiferin is released within 10–15 min.

Keywords: biologically active agent; biopolymer matrix; drug loading capacity; drug release kinetics; mangiferin; targeted drug delivery system

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1. Introduction

One of the major global healthcare problems is the strong increase in the spread of resistant bacterial infections [1]. To address this problem, numerous studies are being conducted worldwide to find alternative treatment options. One of these solutions is the use of natural biologically active agents derived from plants with antibacterial properties [2].

Mangiferin (Figure 1) is a non-toxic polyphenolic natural compound present in different plant families in various concentrations, but one of its main sources is *Mangifera indica* [3,4].

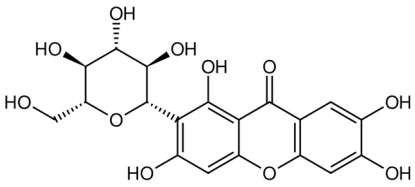

Figure 1. Structural formula of mangiferin.

Antibacterial studies have shown that mangiferin is able to inhibit the growth of pathogens from the ESKAPE group, except for the growth of *Acinetobacter baumannii* [5–10]. In addition to antibacterial properties, this polyphenolic compound has numerous pharmacological properties, including antioxidant, antiviral, antidiabetic, anticancer, immunomodulatory, hepatoprotective, analgesic, and anti-aging effects [11]. Therefore, mangiferin is a potent therapeutic agent, but its clinical application is limited due to its poor aqueous solubility (0.111 mg/mL) and bioavailability [12,13]. Various methods have been used to improve the efficacy of the bioactive compound, including the loading of mangiferin into polymeric transport systems [14]. Among such systems, films based on hydroxyethyl cellulose were studied. Such systems showed significant antimicrobial activity against Gram-positive bacteria [15]. Mangiferin was also loaded in core–shell hydrogel beads based on carrageenan and chitosan. The higher the mangiferin content in the beads, the higher the % of release efficiency [16]. In addition, electrospun fibers based on polyurethane and hydroxypropyl methyl cellulose loaded with mangiferin also showed high and dose-dependent antibacterial efficacy [17].

Biopolymer-based nanofibers have recently attracted attention due to their increasing application in the medical field [18–21]. Such materials are ideal for the use as wound dressings due to their biocompatibility, which results in fewer immunogenic reactions. Hyaluronic acid (HA) is a natural heteropolysaccharide, which, due to properties such as biodegradability, biocompatibility, and mucoadhesiveness, is widely used in targeted drug delivery as well as in various medical applications like ophthalmology, oncology, arthrology, regenerative medicine, and cosmetology [22]. Nanofibers based on this biopolymer promote cell adhesion and cell proliferation and can be used as wound dressings [23]. Moreover, hyaluronic acid nanofibers loaded with a natural compound like curcumin showed antibacterial activity against Gram-positive and Gram-negative bacteria [24].

This study describes the mangiferin-loaded electrospun nanofibers based on high-molecular-weight hyaluronic acid, their morphological characteristics, and the drug release kinetics of mangiferin from the polymer matrix into PBS with pH = 7.34.

2. Materials and Methods

2.1. Materials

Hyaluronic acid with molecular weight equal to 1.30 MDa was purchased from Rensin Chemicals Limited (Nanjing, China); mangiferin 98% was obtained from abcr GmbH (Karlsruhe, Germany); dimethyl sulfoxide (DMSO) 99.5% ACS TS 2635-114-44493179-08 was purchased from JSC EKOS-1 (Moscow, Russia); and distilled water GOST R 58144-2018 was obtained using a laboratory distilling apparatus.

2.2. Preparation of Polymer Solution

To prepare the polymer solution, hyaluronic acid was dissolved in binary (equivoluminal) solvent mixture consisting of distilled water/DMSO to obtain a spinning polymer solution with HA concentration equal to 1.9 wt.%. Mangiferin was added into a spinning solution with the weight ratios of HA to mangiferin as follows: 1:0, 25:1, 15:1, and 5:1.

2.3. Electrospinning

Nanofiber formation was performed using electrospinning equipment with the following technological parameters: applied voltage 28 kV, volume flow rate 2 mL/h, distance between electrodes 140 mm, temperature 22.0 ± 2.0 °C, and relative humidity 20.0–25.0%.

2.4. Determination of Morphology and Diameters of Nanofibers

A MIRA3 TESCAN scanning electronic microscope was used to accurately determine the morphology and size distribution of nanofibers. The scanning parameters were as follows: accelerating voltage 2.0 kV, SE detector, and working distance 15.17 mm.

2.5. Digital and Statistical Analysis

The digital analysis of photomicrographs and diameter measurement was conducted using the ImageJ program Version 1.54k (National Institutes of Health, Bethesda, MD, USA). Each nanofibrous sample was analyzed with 2–3 SEM photomicrographs, with 400 measurements taken in total. The diameter distribution was determined using OriginPro 2024b software (OriginLab Corporation, Northampton, MA, USA).

2.6. Drug Loading Capacity and Encapsulation Efficiency

Accurately weighed samples were dissolved in 10.0 mL of phosphate-buffered saline (PBS, pH 7.34). After total dissolution, the solution was filtered through a membrane filter with a pore size of 0.45 μm and analyzed using a UV spectrophotometer Lambda 1050 (PerkinElmer, Waltham, MA, USA) at 237 nm from the previously obtained calibration curve for mangiferin in the same media. The drug loading capacity (DL) and encapsulation efficiency (EE) were calculated using the formulae [25,26]:

$$DL = \frac{Amount\ of\ mangiferin\ in\ the\ HA-based\ nanofibers}{Amount\ of\ the\ HA-based\ nanofibers} \times 100 \quad (1)$$

$$EE = \frac{Amount\ of\ mangiferin\ in\ the\ HA-based\ nanofibers}{Amount\ of\ the\ initial\ mangiferin} \times 100 \quad (2)$$

For each mangiferin-loaded nanofiber, the determinations were carried out in triplicate and the results are presented with the standard deviation (SD).

2.7. Evaluation of Mangiferin Release Kinetics from Polymeric Nanofibers

Phosphate-buffered saline (pH 7.34) was used to analyze the kinetics of mangiferin release from hyaluronic acid-based fibers. An accurately weighted nanofibrous sample was immersed in 20 mL of PBS at 37.0 ± 1.0 °C with constant shaking at 100 rpm. An aliquot 1.0 mL was taken at predetermined intervals, and 1.0 mL of fresh PBS was added each time to maintain the total volume. If necessary, the samples were diluted 8–10 times. Spectrophotometry was performed similarly to the previous subsection. The experiment was performed three times for each sample.

To determine the kinetics release of mangiferin from polymeric nanofibers, the most common mathematical models were used, including zero-order, first-order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas, Peppas–Sahlin, and Weibull. The values of the kinetic parameters were obtained by the analysis of the experimental data in OriginPro 2019b (OriginLab Corporation, Northampton, MA, USA).

3. Results

3.1. Morphology of Electrospun Nanofibers

SEM microphotographs of drug-loaded nanofibers with various HA/mangiferin weight ratios are demonstrated in Figure 2.

The diameter distributions histograms of mangiferin-loaded nanofibers with HA/mangiferin weight ratios of 1:0, 25:1, 15:1, and 5:1 were obtained by ImageJ analysis of SEM photomicrographs and are depicted in Figure 3.

As shown in Figure 3, the minimum diameter, average diameter, and range of blank HA nanofibers are equal to 107 nm, 252 nm, and 291 nm, respectively. With increasing mangiferin concentration, the above-mentioned characteristics increase up to 152 nm, 291 nm, and 398 nm, respectively. Thus, the diameter distribution extension is detected. Nanofibers fabricated with a high content of mangiferin have a higher mean diameter in general. The sample with a HA/mangiferin weight ratio of 25:1 (Figure 3b) has a lower mean diameter than the blank nanofibers; however, the blank nanofibers have the lowest minimal and maximal diameters. Additionally, the samples of mangiferin-loaded fibers (HA/mangiferin 5:1) have a wider diameter distribution (397.9 nm, in comparison with

291.3 for blank nanofibers). Also, there is a tendency to form fibers of the same diameter in a narrow range of values when adding mangiferin.

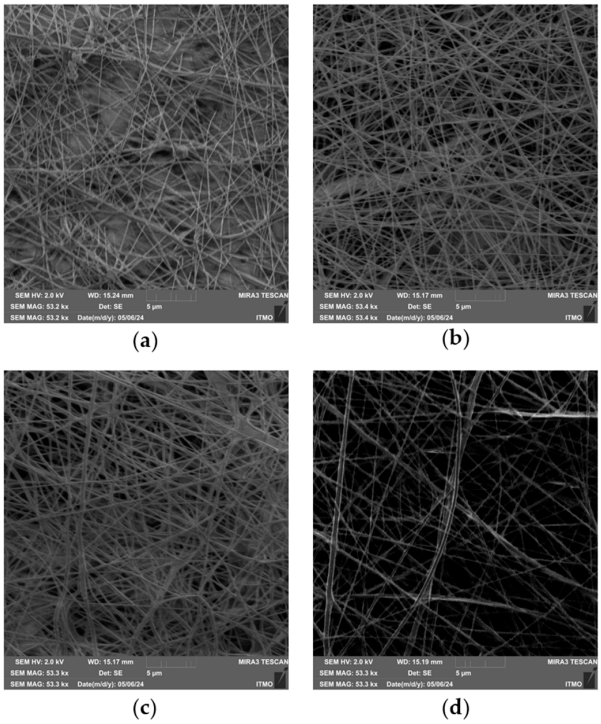

Figure 2. (**a**) SEM microphotographs of electrospun nanofibers: blank nanofibers; (**b**) mangiferin-loaded nanofibers (HA/mangiferin = 25:1); (**c**) mangiferin-loaded nanofibers (HA/mangiferin = 15:1); (**d**) mangiferin-loaded nanofibers (HA/mangiferin = 5:1).

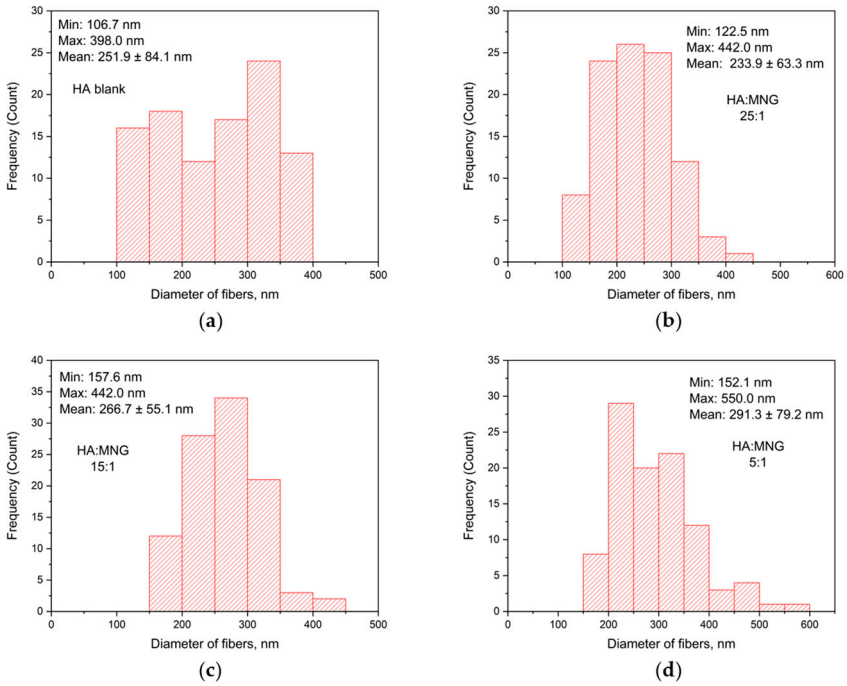

Figure 3. (**a**) Results of statistical analysis of fiber diameter: blank HA-nanofibers; (**b**) nanofibers containing hyaluronic acid/mangiferin = 25:1; (**c**) nanofibers containing hyaluronic acid/mangiferin = 15:1; (**d**) nanofibers containing hyaluronic acid/mangiferin = 5:1.

3.2. Drug Loading Capacity and Encapsulation Efficiency

The calculated drug loading capacity (DL) and encapsulation efficiency (EE) are demonstrated in Table 1.

Table 1. Experimentally determined and theoretical values of drug loading capacity and encapsulation efficiency. Data are presented for samples MNG:HA = 1:25; MNG:HA = 1:15; and MNG:HA = 1:5 (n = 3, ±SD).

Sample Name	Polymer Matrix Capacity, %		Encapsulation Efficiency, %	
	Theoretical	Experimental	Theoretical	Experimental
HA_25	3.85	2.78 ± 0.25	~100.0	71.49 ± 6.64
HA_15	6.25	5.82 ± 0.96	~100.0	85.79 ± 10.01
HA_5	16.67	14.74 ± 0.28	~100.0	81.68 ± 13.53

According to Table 1, the encapsulation efficiency of all samples has high value and exceeds the recommended level (70%) [27] in all cases. The polymer matrix capacity depended on the initial mangiferin amount and increased with the increase in mangiferin content.

3.3. Evaluation of Mangiferin Release Kinetics from Polymeric Nanofibers

The mangiferin release profiles into phosphate-buffered saline (pH 7.34) from HA-based electrospun nanofibers are depicted in Figure 4. The kinetic release had a similar profile regardless of the mangiferin content in the samples. Additionally, there was a burst effect: most of mangiferin was released in the first 10–15 min, and then we had a controlled or sustained release from 15 to 60 min. The fast initial release and further stable regime provide us with the possibility of rapid anti-inflammatory and antibacterial activity and could be used in modern medicine as a potential antibacterial wound dressing.

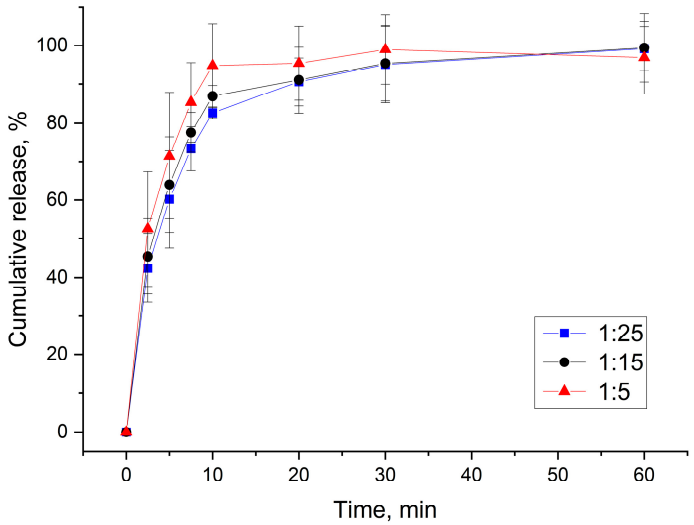

Figure 4. Results of an experiment on the release of mangiferin from hyaluronic acid fibers. Data are presented for samples MNG:HA = 1:25; MNG:HA = 1:15; and MNG:HA = 1:5.

The mechanism of mangiferin release from hyaluronic acid-based nanofibers can be analyzed by comparing the experimental data about mangiferin release with various mathematical models of drug release kinetics, including zero-order, first-order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas, Peppas–Sahlin, and Weibull models. These models were applied to the release profile of mangiferin from electrospun nanofibers. The results of the calculation of the key parameters are demonstrated in Table 2.

Table 2. Kinetic parameters of mangiferin release from nanofibers.

Model and Parameters		Sample Name		
		HA_25	**HA_15**	**HA_5**
Zero-order	K_0	0.03193	0.06394	0.18515
	R^2	0.47533	0.43284	0.38877
First-order	K_F	0.01051	0.0093	0.00666
	R^2	0.49673	0.4616	0.33961
Higuchi	K_H	0.4856	1.03552	2.60798
	R^2	0.54692	0.45556	0.22509
Hixson–Crowell	K_S	−0.01064	−0.02131	−0.04554
	R^2	0.47533	0.43284	0.32487
Korsmeyer–Peppas ($Q_t/Q_0 < 0.6$)	K_K	0.24052	0.25268	0.26158
	n	0.58171	0.60316	0.74067
	R^2	0.99456	0.99425	0.99933
Korsmeyer–Peppas (all data)	K_K	0.44886	0.48982	0.58548
	n	0.21271	0.19101	0.14669
	R^2	0.95284	0.94886	0.93256
Peppas–Sahlin	K_1	0.35698	0.4034	0.4807
	K_2	−0.03157	−0.04025	−0.05609
	m	0.46212	0.43404	0.41491
	R^2	0.98935	0.98412	0.98213
Weibull	α	0.2872	0.31206	0.32284
	β	0.74328	0.7571	0.88384
	R^2	0.99697	0.99451	0.99503

The Korsmeyer–Peppas (up to 60% released mangiferin), Peppas–Sahlin, and Weibull models are the most suitable mathematical descriptions of the mangiferin release kinetics from polymeric matrixes based on hyaluronic acid. The value of the diffusional exponent n in the Korsmeyer–Peppas model for all analyzed samples falls within the range $0.45 < n < 0.89$, that indicates an anomalous non-Fickian mechanism of mangiferin diffusion from the nanofibers [28,29]. Such an anomalous mechanism of mangiferin release in this case could be attributed to the hydrophilic nature of hyaluronic acid, the rapid swelling of the polymer matrix, and the similar orders of solvent diffusion rate and polymer relaxation rate [30].

In the Weibull equation, the parameter β characterizes the shape of the release curve. Thus, if $\beta = 1.0$, the release curve is exponential; if $\beta > 1.0$, it is sigmoidal; and in the case of $\beta < 1.0$, it is parabolic [31,32]. For the analyzed hyaluronic acid-based nanofibers, the shape parameter β is less than 1.0, which corresponds to the parabolic profile of the mangiferin release. In addition, the value $0.59 < \beta < 1.13$ for all samples indicates an anomalous non-Fickian transport pattern of mangiferin release from the nanofibers [33]. This model is flexible and allows us to describe complex systems, including those based on hydrophilic polymers that have the ability to swell during the release of biologically active agents loaded into the polymer matrix.

4. Conclusions

The demand for alternative substances with antimicrobial activity is growing due to the increasing resistance of pathogenic bacterial strains and bans on the use of antibiotics in agriculture. Mangiferin, in particular, being a natural compound, has antimicrobial,

antioxidant, and immunomodulatory properties. In our study, we embedded mangiferin in hyaluronic acid nanofibers obtained by electrospinning. It was found that increasing the concentration of mangiferin in the matrix led to an increase in the average diameter of the nanofibers. However, the difference between the largest and smallest fiber diameter did not exceed 25% of the smallest diameter. It is also possible that this effect is in part mediated by the particularities of the electrospinning method. The data from the mangiferin release experiment show that hyaluronic acid nanofibers release most of the mangiferin within 10–15 min, which makes it difficult to use such nanofibers as long-lasting matrices; however, they may be very useful for urgent medical treatment. Mangiferin release from the polymer nanofibers has an anomalous non-Fickian transport pattern. The data obtained can be used both for the further study of mangiferin and its properties and for the development of polymeric matrices for the delivery of drugs with prolonged action.

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