Original Article

Trends in Pharmaceutical Sciences and Technologies 2025: 11(2): 143-152.

Atorvastatin loaded PVA/alginate fibers as a potential wound dressing

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Abstract

Wound healing is a complex process that involves cellular and biochemical aspects. Many effective methods and formulations for wound healing have been reported in the studies. Hydrogels containing biodegradable and biocompatible polymers have shown significant effectiveness in wound healing process. Atorvastatin, an effective drug in the wound healing process, accelerates healing through impacting on various stages. In this study, a fiber was formed of two biocompatible polymers, sodium alginate and polyvinyl alcohol, with an optimized concentration of 1.2% and 10%, respectively. The drug was added to the initial polymer solution at a concentration of 1% and was simultaneously electrospun. Glutaraldehyde was used as cross-linker to enhance the physical characteristics of fiber. The fibers were subjected to strength and release assays. The prepared fiber exhibited smooth and uniform three-dimensional structure with proper strength. Atorvastatin was released within 30 minutes. Based on the results obtained, the proposed fiber could potentially be used in wound dressing membranes.

Keywords: Atorvastatin, Electrospinning, Polyvinyl alcohol, Sodium alginate

Please cite this article as: Ahmadi F, Mohammadi A, Parhizkar E. Atorvastatin loaded PVA/alginate fibers as a potential wound dressing. Trends in Pharmaceutical Sciences and Technologies. 2025;11(2):143-152 doi: 10.30476/tips.2025.106250.1290

1. Introduction

Wound healing is an intricate biological process encompassing several fundamental stages: hemostasis, inflammation, proliferation, and remodeling. Several factors can impact this process, such as wound severity, age, nutrition, oxygenation, and overall health status (1, 2).

Statins are principally recognized for reducing cholesterol levels through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA). These medications have also been researched for their potential impacts on wound healing (3-5).

The relationship between statins and wound healing lies in the anti-inflammatory effects of statins, which create an optimal healing environment for wounds. Statins also aid in the delivery of nutrients and oxygen to healing tissues. Wounds leave the skin susceptible to microbial contamination, which can escalate tissue damage and inflammation, leading to delays in the healing process. The antimicrobial properties of statins could potentially lower the risk of infection (6). While statins may offer potential benefits in wound healing; they are not suitable candidates for topical delivery. Their lipophilicity poses some challenges their skin permeability. There are various types of wound healing bases and dressings, each designed for a specific type of wounds (5, 7, 8). One of the most intriguing dressings is hydrogels, which provide moisture to dry wounds due to their high water content,

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Received: 16/01/2025; Accepted: 01/03/2025

Table 1. Variables of electrospinning process.

Na Alg Concentration (%w/v)	PVA Concentration (%w/v)	Voltage (KV)	Collector and Solution Bath Distance (cm)
1, 1.2, 1.5, 2	8, 8.5, 9, 9.5, 10	15, 20, 25, 30	8, 10, 12

and consequently stimulates tissue proliferation. Ideal hydrogel dressings are biocompatible, capable of strong adhesion to tissues, and ensuring adequate coverage of the wound site to prevent microbial entry. They also degrade over time without leaving any additional tissue behind (9-12).

Electrospinning is an innovating technique that has garnered significant attention in the field of wound healing. Various polymers and materials can be utilized to create dressings. The prepared scaffolds possess a high surface area, mimic the natural extracellular matrix, and retain a moist environment (12-15). Electrospun scaffolds can be infused with diverse drugs like growth factors or antimicrobial agents for chronic and surgical wounds, burns, and skin grafts. These drugs can be released in a controlled manner, fostering a conducive environment for cell growth, tissue regeneration, and infection prevention. Customized fibers with varying diameters, porosity, and mechanical properties can be tailored based on polymer types, solvents, and processing parameters (15-18).

The main objective of this study was to optimize, prepare, and evaluate electrospun fibers loaded with atorvastatin as a potential dressing for wound healing. Polyvinyl alcohol (PVA) and sodium alginate (Na Alg) were utilized as hydrogel polymers, and the fibers were subjected to different characterization tests including strength and release.

2. Methods and Materials

2.1. Materials

Poly vinyl alcohol (PVA, Mw 80000) and Sodium alginate (Na Alg) (medium viscosity) were obtained from Sigma (Germany). Glutaraldehyde and ethanol 96% were purchased from Hamoon Teb (Iran). Atorvastatin was gifted from Sobhan Co. (Iran). Other materials and reagents were of analytical grade.

2.2. Preparation of electrospun fibers

2.2.1. Optimization of variables

The electrospinning process was performed using an electrospinning machine (Nano Javan Saanat Co., Iran). Technical specifications such as voltage of the power supply, and distance between the collector and the polymer solution bath could affect the mechanical properties of the fiber. Polymer concentration is another critical factor in electrospinning procedure. These variables (Table 1) were optimized and the final solution was prepared as follows: briefly, PVA and Na Alg powders were dissolved in distilled water at a temperature of 85±5 °C for 24 hours to obtain a viscous solution mixture. The prepared solution was loaded into the 500 mL tank in a constant optimized distance with the collector wrapped with a piece of aluminum foil. Different voltage of the device and the distance between the collector and polymer solution bath were also optimized (Table 1). At the end of the process, the electrospun fiber was detached from the aluminum foil and dried at room temperature for 48 hours.

2.2.2. Cross-linking

The optimized fibers were cross-linked using glutaraldehyde vapor at room temperature for 24 h. Then, the fiber was heated at 40°C for 12 hours to remove any residue of glutaraldehyde.

2.3. Preparation of drug loaded electruspun fibers

Due to the low water solubility of atorvastatin, a two-bath solution method was utilized for electrospinning. In this method, a bath contained the drug; dissolved in 5 mL ethanol was mixed with PVA solution, while the other bath contained Na Alg solution. Both solutions were spun simultaneously, resulting

in the formation of drug-loaded fibers. The final concentration of atorvastatin in the total volume of the solutions was 1% w/v. Concentrations of Na Alg and PVA were optimized, as detailed in section 2.2.1. A constant operation speed of 30 rpm and an optimized voltage of 30 kV were applied to conduct the electrospinning process. Cross-linking was performed according to the method outlined in 2.2.2.

2.4. Characterization of fiber

2.4.1. Weight evaluation

The dried base and drug loaded fibers were cut into 2×2 cm pieces and weighed precisely before and after cross-linking. All experiments were performed in triplicate.

2.4.2. Dissolution of fibers

Fiber (base and drug loaded) portions (4 cm^2) were placed in beakers with 20 mL distilled water, then let stand at room temperature. The time required for the complete dissolution of the fibers (complete disappearance of the fiber) was measured. All tests were carried out in triplicate.

2.4.3. Determination of tensile strength of fibers

The mechanical properties of drug loaded fibers (before and after cross-linking) were evaluated using a texture analyzer (model CT3, Brookfield, USA) with a 10-kg load cell. Fiber strips in the constant dimension (10×1 cm) were held between two clamps positioned at a distance of 8 cm. The strips were pulled at a rate of 0.1 mm/s by the force of 10 mN. Measurements were run in triplicate. Three mechanical properties, peak load (mN), deformation at peak load (cm) and Work (mJ) were reported for the fibers (11, 19, 20).

2.4.4. Scanning electron microscopy observation

The morphology of the fibers (base and drug loaded) was analyzed via a scanning electron microscope (SEM, TESCA, Czech Republic). Samples were sputtered with a thin layer of gold and then analyzed by SEM.

2.5. Drug release from electrospun fibers

2.5.1. Atorvastatin Analysis

Atorvastatin analysis was performed using a validated UV-Spectrophotometry method (UV-vis spectrophotometer (T80, Germany)) which determined atorvastatin amount at the maximum wavelength without interfering with other materials. Different atorvastatin concentrations (10, 8, 6, 4 and 2 µg/ml) were prepared in phosphate buffer pH 6: ethanol (25:75) using serial dilution technique. All concentrations were prepared in three different days and each concentration was tested triplicate. Calibration curve was validated for linearity, intraday and inter-day precision, accuracy, limit of detection (LOD) and limit of quantitation (LOQ).

2.5.2. In Vitro Release Study

In vitro release of atorvastatin from the fiber was evaluated by a diffusion cell. Diffusion cell was filled with phosphate buffer pH 6: ethanol (6:1), as dissolution medium. Whole collection was maintained at 37±1 °C and a magnetic bar stirred the receptor medium at 100 rpm to avoid diffusion layer effects. Samples were withdrawn at defined intervals and the amount of atorvastatin was determined using the analysis method (19, 21).

3. Results and discussion

3.1. Evaluation of variables

As previously mentioned, effect of various concentrations of PVA and Na Alg was examined in the fiber formation process. As illustrated in Table 2, the formation of fibers and the uniformity of the electrospun fiber were found to be dependent on the polymer concentration. Solutions containing PVA at concentrations of 8.5, 9, and 9.5, and Na Alg at concentrations of 1.2 and 1.5, resulted in the formation of fibers. However, only homogeneous fibers with acceptable spinneret dimen-

Table 2. Fiber forming at different concentrations

Sample No.	PVA (%w/v)	Na Alg (%w/v)	Film Formation	Homogeneity
1	10.0	2.0	-	-
2	9.5	1.5	+	-
3	9.5	1.2	+	+
4	9.0	1.2	+	-
5	8.5	1.5	+	-
6	8.0	1.5	-	-

sions were achieved at the concentrations of 9.5% PVA and 1.2% Na Alg. These concentrations were identified as the optimized levels for the rest of the study. This outcome aligns with findings from other studies (22-24).

The optimized voltage was 30 kV, and the collection plate was located at a fixed distance of 10 cm from the solution bath. Properly mixing the polymers results in reducing the trapped gas in the solution and improving the uniformity of the final fiber. PVA is one of the most extensively studied synthetic polymers that have been employed as wound dressings. PVA shows inadequate elasticity, which restricts its use alone as a wound dressing (22-24). Na Alg is a hydrophilic polymer that can absorb excess wound exudate; however, Na Alg aqueous solution is not readily electrospun into a fiber due to the high surface tension arise from electrical conductivity (16, 25). Blending Na Alg with other polymers such as PVA is an effective strategy to electrospin the fibers. The blend increases the mechanical strength and electrospinning possibility of Na Alg (25, 26). The use of prepared fibers made from blending PVA and Na Alg was limited due to the burst release of drugs. Glutaraldehyde, as a cross-linker, interacts with the hydroxyl groups of polymers and results in fibers with suitable mechanical strength and high stability; however, its cytotoxicity at high doses has been reported. Keeping fibers at higher temperatures reduces the amount of glutaraldehyde, and toxicity can be reduced via a reaction with glycine (27, 28). In many studies, calcium chloride, as a safe agent, has been used as a cross-linker (29-31); however, mechanical properties such as faster degradation and lower compressive strength of the prepared fibers have been also reported (31).

3.2. Drug loading into the fiber

Atorvastatin is only slightly soluble in distilled water and phosphate buffer (pH 7.4), but it is soluble in ethanol and methanol (11). On the other hand, Na Alg, made up of residues of D-mannuronic acid and L-guluronic acid, is almost insoluble in ethanol but is slowly dissolved in water to create a viscous colloidal solution. PVA is a water-soluble polymer that is slightly soluble in ethanol, requiring the mixture to be heated to about 90°C for dissolution. When mixing the drug solution with polymer blends, there is a risk of Na Alg sedimentation (32). To address this issue, the two-bath method was used to create drug-loaded fibers. In various studies, the use of organic solvents and simultaneous electrospinning has been reported (13-14). The method does not necessitate a specific solvent to prepare a blend solution that can dissolve various materials with different solubility. This technique has been employed for the co-delivery of multiple drug-loaded fibers (14).

3.3. Characteristics of fiber

The electrospun fibers possess an interconnected pore structure with a high surface area to volume ratio. The weight and dissolution of the fibers are documented in Table 3. It is evident that the sample weight increased post cross-linking. The increase in weight after crosslinking suggests the presence of glutaraldehyde in the fiber structure, which aligns

Table 3. Weight and dissolution of different fibers.

Sample		Weight (g)	Dissolution (Sec)
Fiber base	Before Cross-linking	0.013±0.001	178 ± 7
	After Cross-linking	0.036±0.001	440 ± 10
Drug loaded fiber	Before Cross-linking	0.006± 0.001	55 ± 5
	After Cross-linking	0.026± 0.001	540 ± 7

with findings from other studies (23-25).

3.3.1. Mechanical properties of the fibers

Mechanical properties of drug loaded fibers are reported in Table 4.

Peak load is the maximum load that sample sustains during the test. The final length at peak load is the increase in length at break or rupture. The final work indicates the amount of work needed to break or rupture the film. Cross-linking increased the mechanical strength of the fiber. Higher work was needed to rupture the fiber. The cross-linked film was more resistant to tension and lengthened by about 7 mm before rupture. However, the fiber before cross-linking was not elastic enough and ruptured immediately (Figure 1).

The load-bearing capacity of cross-linked fiber was lower compared to non-cross-linked fiber due to differences in the pattern of rupture. In non-cross-linked fiber, the rupture occurred suddenly, causing the entire width of the fiber to break rapidly under tension. However, in cross-linked fiber, the presence of glutaraldehyde led to increased interactions in the functional groups. When the fiber was stretched, it initially became thinner. Subsequently, some strands in the fiber were torn while others remained intact. After reaching a stretch upto 7 mm, the remaining strands were cut by a force of approximately 5000 mN. Consequently, the peak load in non-cross-linked fiber is associated with the entire width of the fiber, whereas in cross-linked fiber, it is

Table 4. Mechanical characteristics of drug loaded fiber before and after cross- linking.

Sample	Peak Load (mN)	Final Length at Peak Load (mm)	Final work (mJ)
Before Cross-linking	10460±96	1.37±0.12	12.24±1.22
After Cross-linking	5025±68	7.10±0.18	25.30±1.05

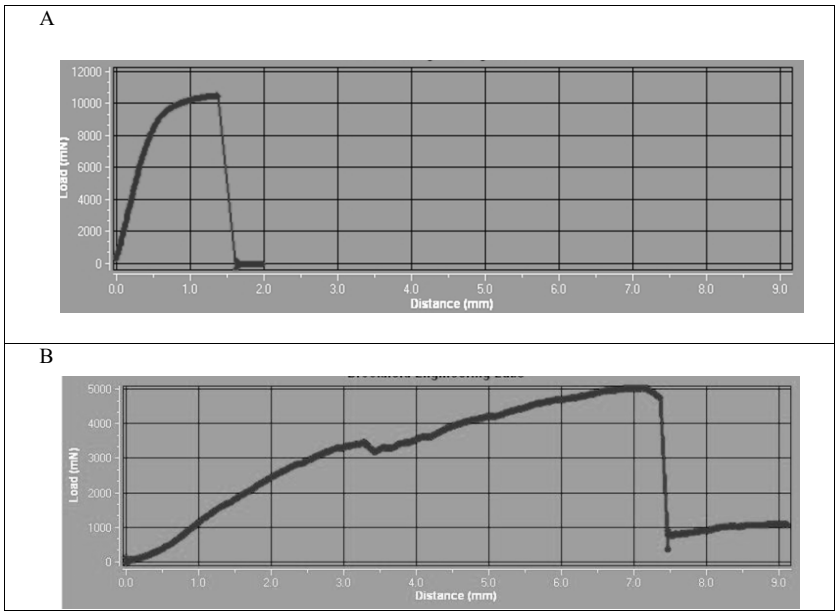

Figure 1. Load vs distance diagram of A) fiber before cross-linking B) fiber after cross-linking.

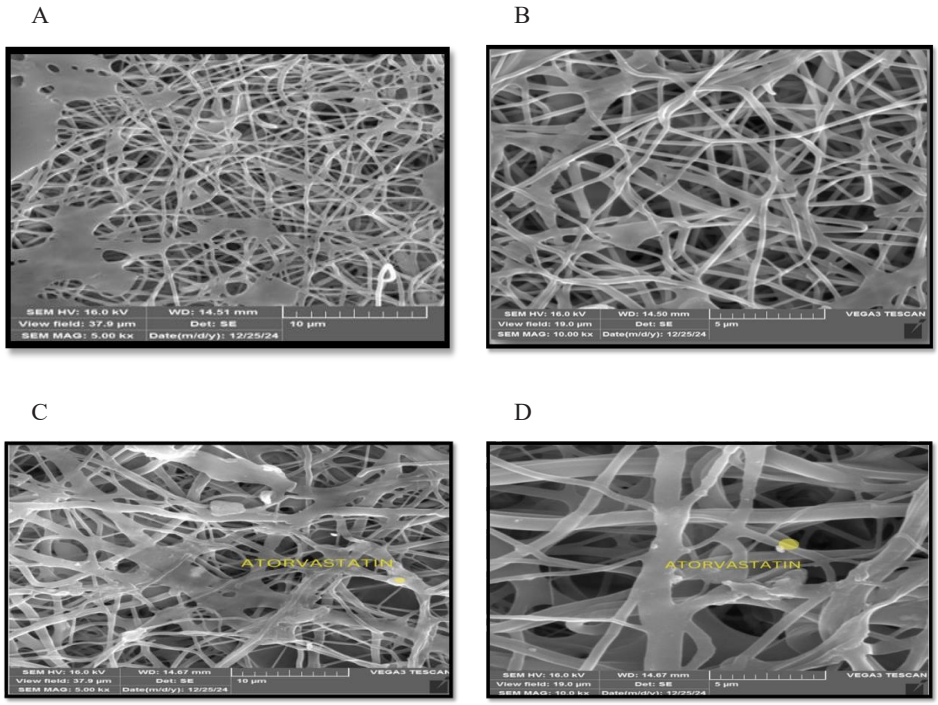

Figure 2. SEM image of base fiber (A and B) and drug loaded fiber (C and D) with 5 and 10× magnification respectively.

related to the partial strands of the fiber.

3.3.2. Morphology of fiber

The morphology of the fibers is shown in Figure 2. SEM results showed that smooth, bead-free, and randomly oriented fibers were successfully electrospun. Atorvastatin was loaded on the fiber and could be traced.

3.4. Drug release study

3.4.1. Atorvastatin analysis

Maximum wavelength of atorvastatin was 247 nm that is in accordance with other studies (11). Calibration curve data was constructed in the range of the expected concentrations of 2 to 10 µg/mL. Regression coefficient (r2) of the standard curve (0.9946) indicated linear relationship at selected range of atorvastatin concentrations. Precision, accuracy, LOD and LOQ are illustrated in Table 5, which are in the acceptable ranges.

3.4.2. In vitro drug release

As it is shown in Figure 3, almost 100% of atorvastatin was released in the first 30 minutes. After this time, all the fiber was dissolved and no fiber was seen in the diffusion cell. Release rate depends on many factors such as the thickness, and the surface area of the fiber, water solubility of the polymer and the crosslink percentage. By changing these parameters the rate may change significantly.

When the hydrophilic fibers are exposed to aqueous environment, the solvent penetrates into the pores; and dissolve the drug. Furthermore, the polymer chain swells and forms a gelatinous layer (3, 33). If the gel layer is thin, drug release is much faster. The

Table 5. Regression and validation parameters of calibration the analysis method of atorvastatin.

Equation	r^2	Precision% (Intraday)	Precision% (Interday)	Accuracy%	LOD (µg/mL)	LOQ (µg/mL)
y=0.0798x+0.0385	0.9946	97.93± 1.56	96.69± 2.36	99.76± 3.09	0.59	1.79

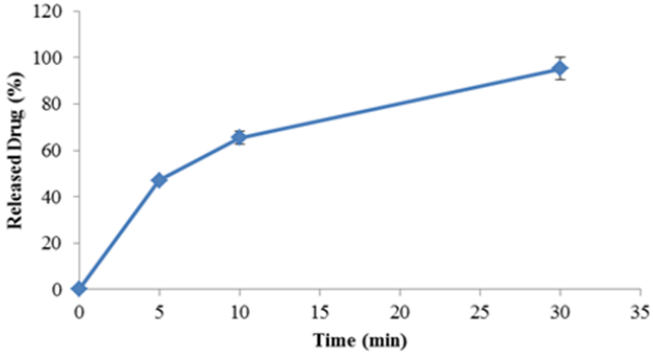

Figure 3. *In vitro* release of atorvastatin.

prepared fiber was a thin layer and the release pattern was predictable.

4. Conclusion

An ideal wound healing dressing must maintain a moist environment. Sodium alginate (Na Alg) is one of the most renowned polymers for absorbing wound exudates. This study assessed the possibility of electrospinning of Na Alg in combination with various ratios of polyvinyl alcohol (PVA). It was discovered that the Na Alg:PVA ratio significantly influenced fiber formation. Additionally, parameters like voltage and working distance were optimized for the study. PVA/ Na Alg electrospun fibers were produced using an all-aqueous electrospinning technique that subsequently treated with glutaraldehyde as a cross-linking agent. The addition of the cross-linking agent enhanced mechanical properties of the fibers and imparted elasticity to them. The fibers exhibited smooth and uniform three-dimensional structure. The drug atorvastatin, known for its effectiveness in wound healing, was electrospun concurrently with the polymers and detected in SEM analysis. This study suggests the application of PVA/ Na Alg electrospun fibers as scaffolds for wound healing that warrants further exploration in future research.

Acknowledgements

This study was the Pharm. D project of Ali Mohammadi and was financially supported by Shiraz University of Medical Sciences (Grant No. 28691).

Authors' Contributions

FA: Supervision, Project administration, Methodology, Formal analysis, Data curation, Visualization, review & editing.

AM: Project administration, Methodology, Formal analysis, Writing- original draft

EP: Supervision, Methodology, Formal analysis, Data curation, Writing – original draft, Visualization, Writing – review & editing.

Conflict of Interest

The authors declare that they have no conflict of interest.

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