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Fast-Dissolving Atorvastatin and Amlodipine Combination Electrospun Fibers

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Abstract

Fixed-combination pharmaceutical forms offer the advantage of simple, reliable administration of two different active substances. This study aimed to develop atorvastatin- and amlodipine-containing polymer-based fibrous sheets at a 1:4 dose ratio for fast disintegration, enhancing elderly patient compliance. Polyvinylpyrrolidone-based polymer dispersion was embedded with two active ingredients via solubilization with polysorbate 80. The dispersions were described by pH, conductivity, and texture analysis. The fibrous sheets were characterized by morphology, disintegration, and dissolution. The single-jet electrospun fibers had an average diameter of 588 ± 190 nm. Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) results suggest the amorphization of the active substances. Disintegration was very fast, with a measured time under 3 s. The API release occurs in a burst, with complete dissolution achieved within the first 5 min. The fixed-dose combination fibrous sheets offer a possible fast-delivery system for future buccal administration in elderly patients.

Keywords: polymer-based fibers; PVP; atorvastatin; amlodipine; fixed-dose combination; electrospinning; burst dissolution

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1. Introduction

Atorvastatin (ATOR) is a lipid-lowering statin. By inhibiting the endogenous production of cholesterol in the liver, statins reduce abnormal cholesterol and lipid levels and ultimately reduce the risk of cardiovascular disease. In terms of its mechanism of action, it competitively inhibits the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate. This conversion is a critical metabolic reaction involved in the production of low-density lipoprotein (LDL) and very low-density lipoprotein. Therefore, it is an early rate-limiting step in cholesterol

biosynthesis [1,2]. Atorvastatin and other statins are considered first-line treatments for dyslipidemia and are also useful for their numerous pleiotropic effects [3,4]. Due to its structural properties, atorvastatin is practically insoluble in water (0.00063 mg/mL) and is classified as Biopharmaceutics Classification System (BCS) class II, characterized by low solubility and good permeability [5–7].

Amlodipine (AMLO) is a dihydropyridine calcium channel blocker used to treat hypertension and angina. It specifically inhibits the L-type Ca^{2+} channel at the plasma membrane, which mediates action potentials in smooth muscle. Consequently, it reduces Ca^{2+} entry into the cell, producing a significant vasodilatory effect in the arterial system. Amlodipine is a long-acting dihydropyridine (plasma half-life of 35–50 h), allowing once-daily administration, a favorable feature for tolerability in chronic therapy.

A fixed-dose combination of atorvastatin and amlodipine is available as tablets in a 1:4 dose ratio (1 tablet contains 5 mg amlodipine and 20 mg atorvastatin). The combination of active ingredients promotes patient comfort, a very important aspect of chronic treatment, thereby making drug therapy more tolerable over time [8–10].

A combination of drugs for concomitant hypertension and hypercholesterolemia offers clinical benefits, including reduced risk of cardiovascular death, acute myocardial infarction, stroke, and coronary intervention, as well as enhanced drug adherence [11–14].

Micro- and nanofibers are synthetic nanotechnological materials fabricated using various nanotechnological methods, with diameters of a few hundred nanometers. Due to their nanoscale, these products exhibit a large specific surface area. This drug carrier disintegrates and disperses rapidly, ensuring rapid release of the active ingredient and increased bioavailability. Electrospinning is considered a scalable, cost-effective, and reasonably automated technique for preparing fibers, allowing easy manipulation of the composition and properties of fibers [15–17]. Polyvinylpyrrolidone, as a fiber-forming polymer, can be characterized by an amorphous nature, biocompatibility, and water solubility. For nanofiber formation, the conditions were studied between 7 and 33 w/w%, combined with metallic oxides, in solvents like water, ethanol, dichloromethane, and N-dimethylformamide [18–20]. Drug-loaded PVP-based fibers under proper electrospinning conditions result in smooth, non-beaded, and non-porous surface fibers with fast disintegration [21]. Polysorbate 80, or Tween 80, is a well-known non-ionic solubility enhancer that works by forming micelles. For low-solubility drug molecules, it increases apparent solubility by sheltering the drug inside the micelle's oil-like core, while the hydrophilic polyoxyethylene chains face the solvent [22].

Atorvastatin and nifedipine coaxial electrospun nanofibers were developed for buccal administration in geriatric patients to improve convenience [21]. Atorvastatin-loaded core–shell fibers were studied for intravascular treatment of brain aneurysms [23]. It was already shown that atorvastatin, in combination with polycaprolactone as a drug-delivery system, enhances the wound-healing capacity of atorvastatin [24]. Atorvastatin-loaded collagen-silver nanoparticle-coated polycaprolactone fibers manufactured by electrospinning could serve as a promising wound-dressing platform for the effective treatment of diabetic wounds [25].

This study aims to obtain and characterize single-jet electrospun fibrous sheets of atorvastatin and amlodipine (combined) as potential novel drug formulations for geriatric patients.

2. Materials and Methods

2.1. Materials

Atorvastatin calcium was provided by Morepen Laboratories, New Delhi, India, amlodipine maleate by Glochem Industries Ltd., Telangana, India, ethanol by Chemical Com-

pany, Iasi, Romania, methanol by Adra Chim Srl, Bucharest, Romania, Tween 80 by Sigma Aldrich, Taufkirchen, Germany, Povidone K29/32 by GAF Chemicals, Parsippany, NJ, USA, sodium chloride by Brenntag, Chiajna, Romania, potassium phosphate monobasic and sodium phosphate dibasic by Lachner, Budapest, Hungary, acetonitrile by Honeywell, Seetze, Germany.

2.2. Methods

2.2.1. Preparation of Fibrous Sheets

As the first step in the electrospinning process, we prepared four polymer dispersions: ATOR alone, AMLO alone, and both in methanol, ethanol, Tween 80, and Povidone K29/32 (w/v). A blank or unloaded dispersion without an active substance was also prepared.

The main goal of this research was to produce fibrous sheets containing a 1:4 weight ratio of AMLO and ATOR. Due to the poor solubility of the active ingredients in water (atorvastatin—0.00063 mg/mL [26], amlodipine—0.0074 mg/mL [27]), it was necessary to dissolve them in ethyl alcohol. ATOR (0.2 g) and AMLO (0.05 g) were dissolved under continuous stirring (at a speed of 500 rpm) on a JK SMS HS magnetic stirrer (JKI, Shanghai, China) in a methanol (5 mL) and ethanol (10 mL) mixture with Tween 80 (1.25 g). After the solution was formed, Povidone was added and stirred at 1000 rpm at room temperature (20 ± 2 °C) for 40 min using the same equipment.

The theoretical drug load was calculated based on the weight of non-volatile components (10 mg of fibers containing 307 µg ATOR and 76 µg AMLO). Fibrous sheets were packed in aluminum foil and a plastic container and stored at room temperature in a desiccator with silica gel. From the composition, 3 independent batches were prepared. Fiber mats were prepared using an eSpin Tube system (SpinSplit, Budapest, Hungary) under the following conditions: 15 cm needle-to-collector distance (mechanically controlled), 25 kV tension, and a flow rate of 2 mL/h, using a G21 needle with an ID of 0.8 mm. The electrospinning was conducted at ambient temperature (20 ± 2 °C) and humidity (30–60%).

2.2.2. pH, Conductivity, and Viscosity Measurement of the Dispersion

The pH measurement was performed using a Consort C831 digital pH meter at 20 ± 2 °C. 0.5 g of the polymer dispersion was diluted with 20 mL of ultra-filtered water to determine the pH. Conductivity was recorded in mS. Viscosity was measured with a Fungilab Visco lead adv. Apparatus (FUNGILAB S.A., Esplugues de Llobregat (Barcelona), Spain), using spindle R3, at 100 rpm, at 20 ± 2 °C. Values are presented as mean and standard deviation ($n = 3$).

2.2.3. Texture Analysis of the Dispersion

Texture analysis was performed on the polymer dispersions. Dispersions were placed in a 3.8 cm diameter crucible, and a TPA (Texture Profile Analysis) cycle comprising two consecutive Compression/Tension cycles was initiated on a Texture Analyzer TX 700 (Lamy Rheology, Champagne au Mont d'Or, France) using a spherical probe. The analysis parameters were a speed of 0.5 mm/s, an initial force of 1 g, a distance of 4 mm, and a time between cycles of 5 s.

2.2.4. Fiber Morphology by Optical and Scanning Electron Microscopy (SEM)

Fibrous sheets were photographed with an optical microscope (Bresser LCD Micro 5 MP) at 10× and 40× magnification.

The fiber diameter was determined. SEM images were collected using a JEOL JSM-5200 electron microscope (JEOL, Tokyo, Japan) at an accelerating voltage of 10 kV. The fibrous

sheets were examined in their original state, without sputter coating. The average fiber diameter was calculated using 100 fibers measured randomly from three SEM photos of different parts of each sample, with a magnification of 5000×. The open-source ImageJ version 1.45 (National Institutes of Health, Bethesda, MD, USA) software was used to perform the measurements.

2.2.5. Disintegration Test

Weighted samples of 20 mg were placed in a Petri dish containing 15 mL of distilled water and artificial saliva, and the time to disintegration was measured ($n = 3$).

2.2.6. Differential Scanning Calorimetry (DSC)

The test was performed using a Shimadzu DSC-60 (Shimadzu, Kyoto, Japan) apparatus over the temperature range 30–300 °C at a heating rate of 5 °C/min under air (oxygen present). An amount of 5 mg of the sample was weighed out on an analytical balance and sealed in a 40 µL aluminum vessel. Al_2O_3 was used as a reference material. The curves were evaluated with the device's own software (version 2.1).

Binary 1:1 weight ratio physical mixtures of amlodipine and Povidone, atorvastatin and Povidone, and amlodipine and atorvastatin completed the sample list.

2.2.7. Fourier Transform Infrared Spectroscopy (FT-IR)

A Thermo Scientific Nicolet 380 Spectrometer (Waltham, MA, USA) was used to record spectra of the samples (powdered nanofibers and active ingredients). The measurements were performed over the spectral range 4000–400 cm^{-1} with a resolution of 4 cm^{-1}. The measurements were performed at room temperature by pressing 1 mg of the sample into a 100 mg KBr pellet using a hydraulic press. The FT-IR spectra were analyzed using the device's in-house software (OMNIC Lite, version 7.1).

2.2.8. Determination of Drug Content and Dissolution Study by HPLC Method

To determine the active-ingredient content of the nanofibers, an HPLC-UV system (Thermo Finnigan Surveyor, San Jose, CA, USA and ChromQuest 4.0 software, version 4.2) was used, employing a Waters Symmetry C18 5 µm column (4.6 mm × 150 mm) as the stationary phase. The mobile phase consisted of 10 mM phosphate buffer (pH 2.5) and acetonitrile (ACN), with a flow rate of 1 mL/min and a gradient elution (ACN: 0–3.1 min, 35%; 3.1–10 min, 55%; 10.1–13 min, 35%). Detection was performed at 237 nm. The chromatographic column was maintained at room temperature; the injection volume was 20 µL.

To measure the active ingredient content, 10 mg of nanofibers were weighed on an analytical balance and dissolved in 50 mL of purified water under ultrasonic assistance (Isolab, Laborgeräte GmbH, Eschau, Germany). The resulting solution was filtered, diluted with water, and the drug content was determined using the aforementioned HPLC method. The drug content was quantified against a standard calibration curve of peak area versus concentration.

The dissolution test was performed using a Biobase BK-RC3 apparatus (BIOBASE Group, Jinan, China), with 15 mg of sample in 100 mL of distilled water at 37 °C, stirred at 50 rpm with a rotating paddle. Samples were collected at 5 min intervals for 30 min for all three nanofiber formulations containing active ingredients (Atorvastatin, Amlodipine, and Atorvastatin plus Amlodipine). For each measurement, we used three parallel samples.

2.2.9. Statistical Analysis

All data are presented as mean ± standard deviation (SD). Statistical analyses were conducted using one-way analysis of variance (ANOVA) and Tukey's post hoc test. A

p-value < 0.05 was considered significant. All statistical analyses were performed using GraphPad Prism software (version 10.1, Dotmatics, Boston, MA, USA).

3. Results and Discussion

3.1. pH and Conductivity of the Dispersions

The measured pH values are acidic and above three; the exact data are summarized in Table 1.

Table 1. pH and conductivity values for the dispersions (D).

Sample	pH ± SD	Viscosity (mPas) ± SD	Conductivity (mS) ± SD
DBlank	3.28 ± 0.21	99.7± 8.6	18.25 ± 0.91
DATOR	3.84 ± 0.14	129.0 ± 15.2	42.0 ± 3.37
DAMLO	3.17 ± 0.12	130.3 ± 11.6	47.7 ± 4.16
DATOR + AMLO	3.61 ± 0.28	135.9 ± 12.8	61.0± 4.81

All dispersions had acidic pH. Adding atorvastatin increased the pH, whereas amlodipine decreased it compared with the blank. The pH of the dispersion containing the combined active ingredient is between the pH of the dispersion containing the two active ingredients.

Conductivity increased with the addition of the active ingredients. This change can be explained by the fact that they were added to the mixture as salts (atorvastatin calcium and amlodipine maleate). In the dispersion containing the combined active ingredients, the change relative to the blank is the greatest.

Viscosity increased after dissolving the active substances in the polymer solution; the highest value was measured for the dispersion containing both ATOR and AMLO. A similar viscosity value (114 mPas) was reported for PVP K29/32 at a concentration of 30% (w/w) [28].

3.2. Texture Analysis of the Dispersions

Table 2 shows the TPA results for the dispersions (using two consecutive Compression/Tension cycles).

Table 2. Results of texture analysis.

Sample	Max Force 1 (g) ± SD	Max Force 2 (g) ± SD	Min Force (g) ± SD	Cohesivity ± SD	Adhesion (mJ) ± SD	Elasticity ± SD
DBlank	8.8 ± 0.74	9.1 ± 0.82	−3.1 ± 0.26	0.83 ± 0.07	11.2 ± 1.02	0.33 ± 0.02
DATOR	9.6 ± 0.90	8.8 ± 0.59	−2.7 ± 0.22	0.79 ± 0.05	8.4 ± 0.78	0.33 ± 0.03
DAMLO	8.8 ± 0.61	9.0 ± 0.93	−2.8 ± 0.29	0.91 ± 0.08	7.6 ± 0.74	0.33± 0.03
DATOR + AMLO	8.4 ± 0.92	9.0± 0.72	−2.5± 0.16	0.90± 0.07	6.8 ± 0.59	0.33± 0.02

During the texture analysis, elasticity remained constant, and adhesiveness was relatively low. Cohesiveness is lowest for the atorvastatin dispersion and highest for the amlodipine dispersion, likely due to differences in chemical structure and intermolecular forces. Adhesion decreases with the incorporation of active substances compared with that of a polymer dispersion. For a fast disintegration drug delivery system, low adhesiveness is preferred.

3.3. Fiber Morphology by Optical and Scanning Electron Microscopy (SEM)

The produced fibers (F) were first examined with a microscope. The following images (Figure 1) were taken with 10× and 40× magnification:

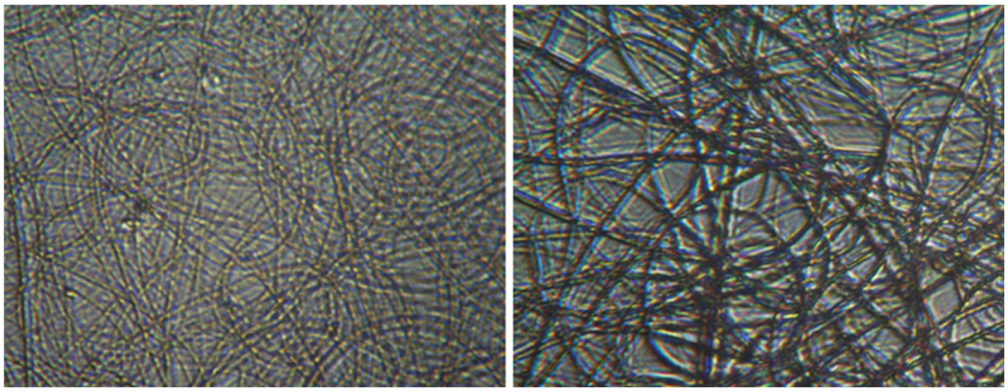


Figure 1. Images of FATOR + AMLO nanofibers taken with an optical microscope (using magnification of 10X and 40X).

The SEM images show smooth-surfaced, droplet-free fibers (Figure 2).

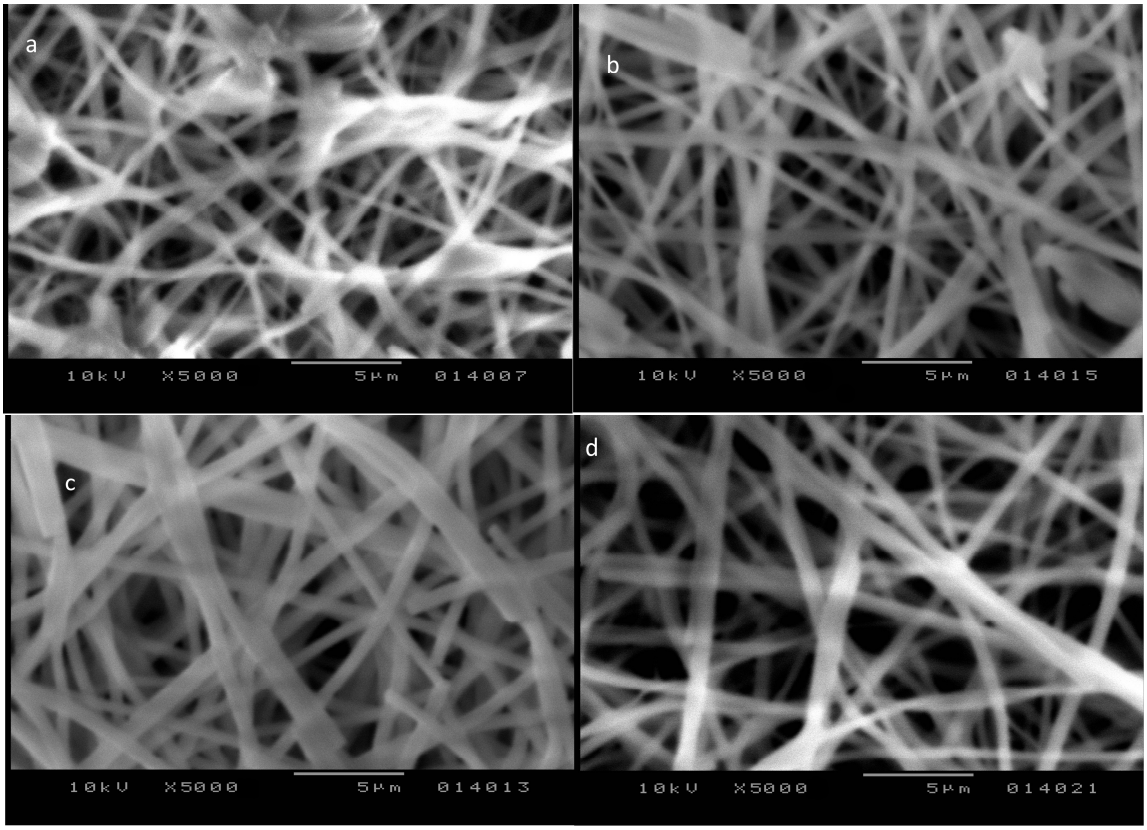


Figure 2. SEM images (blank—(**a**), FATOR—(**b**), FAMLO—(**c**), FATOR + AMLO—(**d**)).

The nanofibers, as measured by scanning electron microscopy, are in the nanometer range, with average diameters of 426–647 nm. The nanofiber without the active ingredient has the smallest diameter, and the nanofiber containing amlodipine has the largest. Compared to the blank nanofiber, the diameter of those containing the active ingredient is significantly larger. The combined active-ingredient fiber has a diameter of 588 ± 190 nm, indicating that it lies between the two single-ingredient fibers (Figure 3).

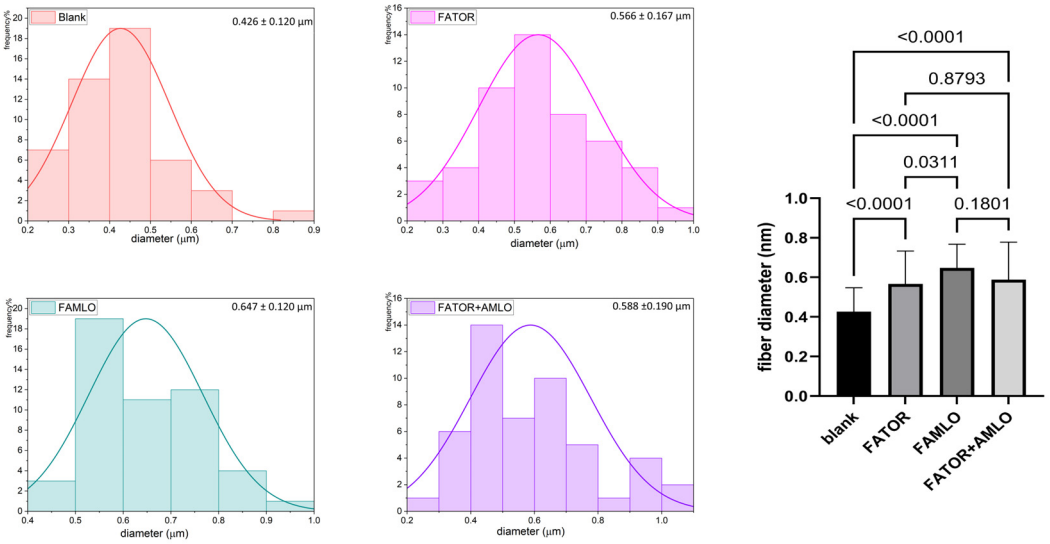


Figure 3. Histograms of the four fibrous samples and the results of statistical analysis (the numbers represent *p*-values).

Conductivity influences fiber diameter; the solutions' conductivity values increased monotonically with increasing salt content [29]. Combining ATOR and AMLO at 61.0 mS yields a fiber diameter of 588 ± 190 nm.

Statistically significant differences in fiber diameter were observed between blank and all three active substance-containing fibers. The fiber diameter difference between the combined and single-drug fibers was not statistically significant.

3.4. Disintegration Time

Disintegration in water was very fast, with all disintegration times under 3 s (FATOR 1.49 ± 0.12 s, FAMLO 2.24 ± 0.19 s, FAMLO + ATOR 2.36 ± 0.24 s, blank 1.28 ± 0.01 s). In a study, amlodipine and valsartan PVP-based nanofibers showed complete disintegration times under 3 s [29]. Nifedipine and atorvastatin core–shell nanofibers, for buccal administration in geriatric patients, presented a disintegration time under 12 s [21].

3.5. Differential Scanning Calorimetry Measurement

The DSC curve (Figure 4) shows the melting of the active ingredient, ATOR, at 162.03 °C, as evidenced by a sharp endothermic peak. Povidone, an amorphous polymer, does not exhibit a sharp melting point; the DSC curve shows a broad endothermic peak below 100 °C, attributed to water loss. The melting peak is absent in the atorvastatin-containing nanofiber, suggesting that the active ingredient is fully embedded within the nanofiber or that atorvastatin undergoes amorphization.

For amlodipine, a sharp endothermic peak is observed at 174.5 °C. In this case, only a broad peak characteristic of Povidone is visible on the nanofiber curve (below 100 °C), indicating that the active ingredient is fully embedded in the nanofiber.

In the physical mixture (PMATOR + AMLO), endothermic peaks appear between 167.01 and 173.2 °C but are shifted relative to those of the pure crystalline active ingredients. The fiber curve shows no prominent peaks (Table 3).

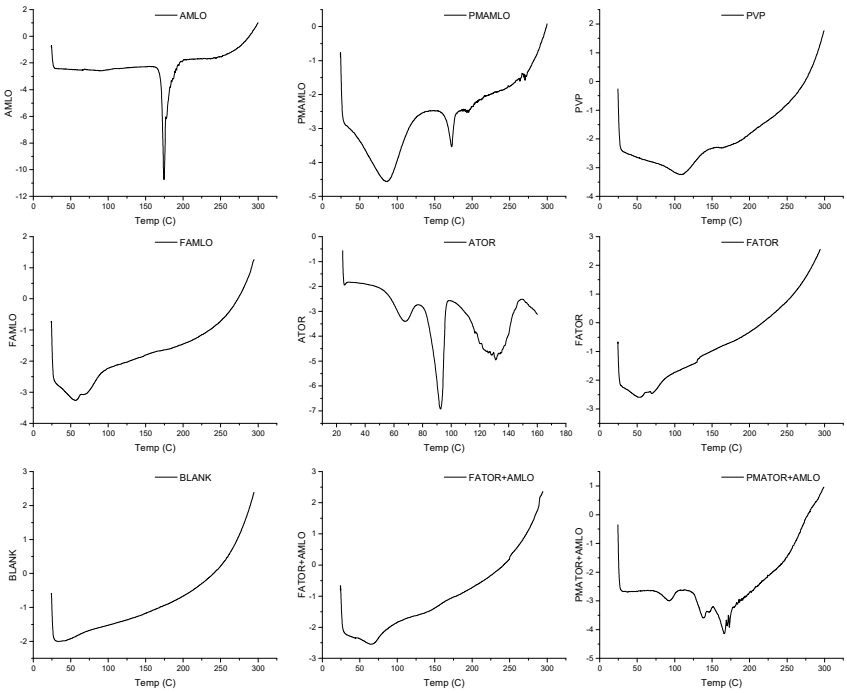


Figure 4. DSC thermograms of ATOR, Povidone K29/32, Blank fibers, AMLO, FAMLO, FTOR, FATOR + AMLO.

Table 3. Normalized DSC thermograms of the tested samples.

Sample	T (°C)	Δ (J/g)
AMLO	174.50	−10.74
FAMLO	61.48	−3.26
ATOR	162.03	−6.92
FATOR	57.80	−2.59
PMATOR + AMLO	167.01	−4.14
FATOR + AMLO	70.13	−2.55
Blank	38.53	−2.00
Povidone K29/32	106.99	−3.24

The DSC curve of the nanofibers shows no melting peaks characteristic of pure crystalline active ingredients.

3.6. Fourier Transform Infrared Spectroscopy

Figure 5 shows the infrared spectra of the pure active ingredients and the fibers.

The FTIR spectrum of ATOR showed O–H stretching at 3252 cm^{-1}, characteristic bands at 1649.95 cm^{-1} (asymmetric C = O stretching), 1511 cm^{-1} (symmetric C = O stretching), 1216 cm^{-1} (C–N stretching/C–O stretching), and between 1580 and 1438 cm^{-1} (C–C ring stretching), hydrogen bond stretching (–OH group at 3668.59 cm^{-1}), and amine group stretching (–N–H at 3365.122 cm^{-1}), which is in agreement with Alshaya et al. [21].

The IR spectrum of AMLO shows characteristic C=O stretches at 1690.02 cm^{-1} and a C-O-C asymmetric stretch at 1106 cm^{-1}. Other bands are present at 1040.44 cm^{-1} (NH_3 wagging), at 847.15 cm^{-1} (-C-O in-plane bending), and at 763.11 cm^{-1} and 740.7 cm^{-1} (N-H vibrations) [30].

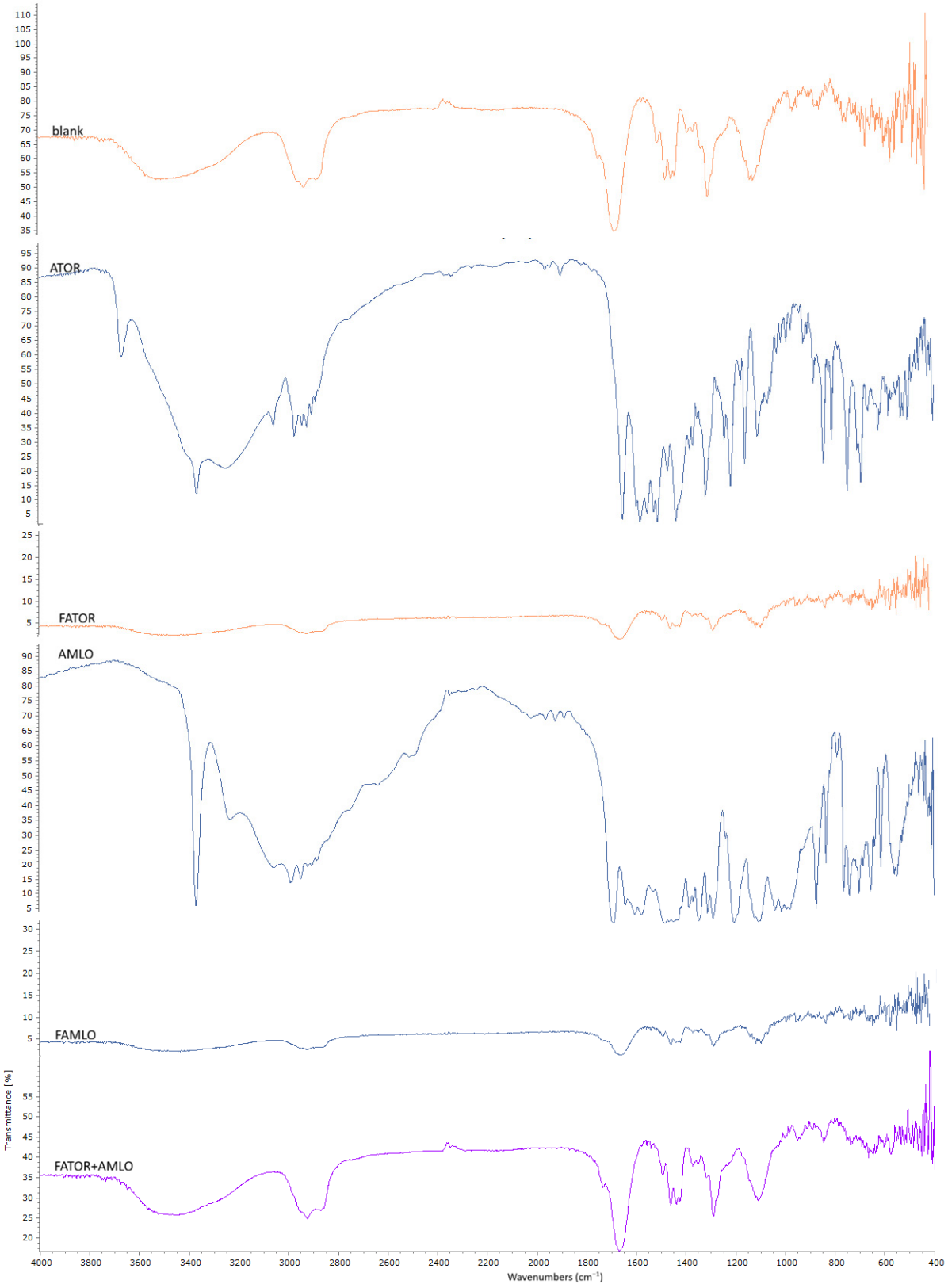


Figure 5. Infrared spectra of the pure active ingredients and the fibers.

The carbonyl group gives rise to characteristic bands at 1668 cm^{-1} in the blank and Plasdone spectra.

The infrared spectrum of the fibers containing one or even two active ingredients is very close to the spectrum of the blank fiber. The characteristic absorption peaks of atorvastatin and amlodipine do not appear in it.

3.7. Active Ingredient Content and Dissolution Study

Figure 6 presents the calibration curves used to measure the two active ingredients.

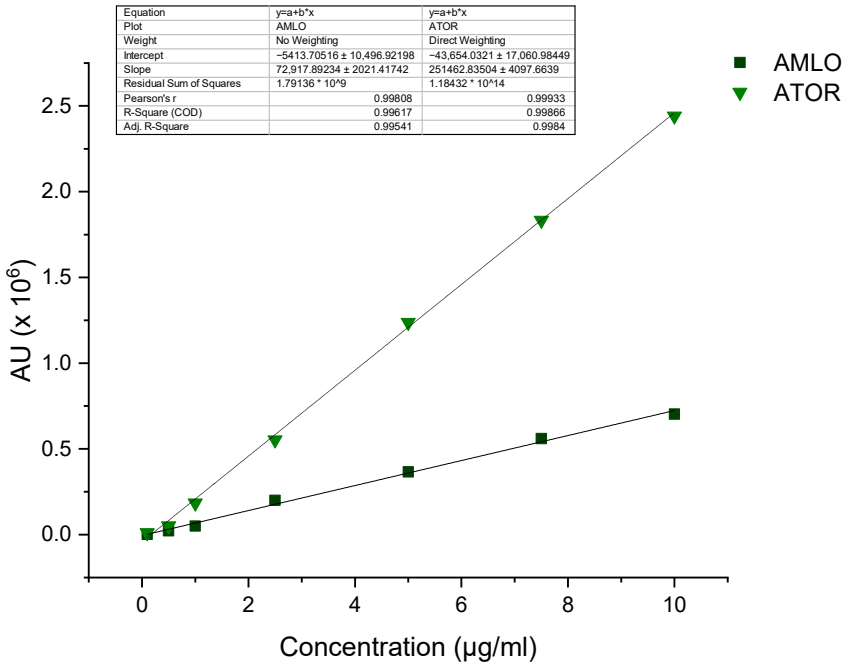


Figure 6. Calibration curves of the tested active ingredients.

As can be seen from the calibration curves, the linearity range is 0.1–10 µg/mL for both active ingredients. The residuals are randomly distributed around the zero line.

The peaks of the measured standard solution (1 µg/mL amlodipine and atorvastatin) measured with the method used are shown in the figure (Figure 7) below.

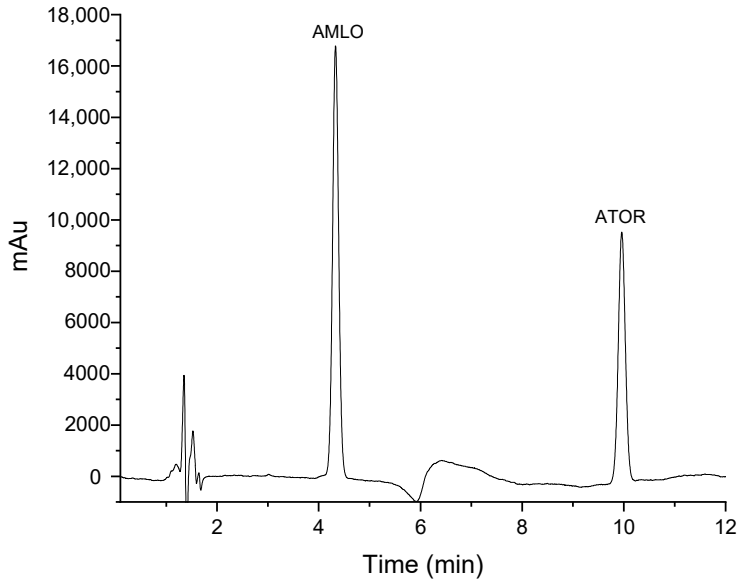
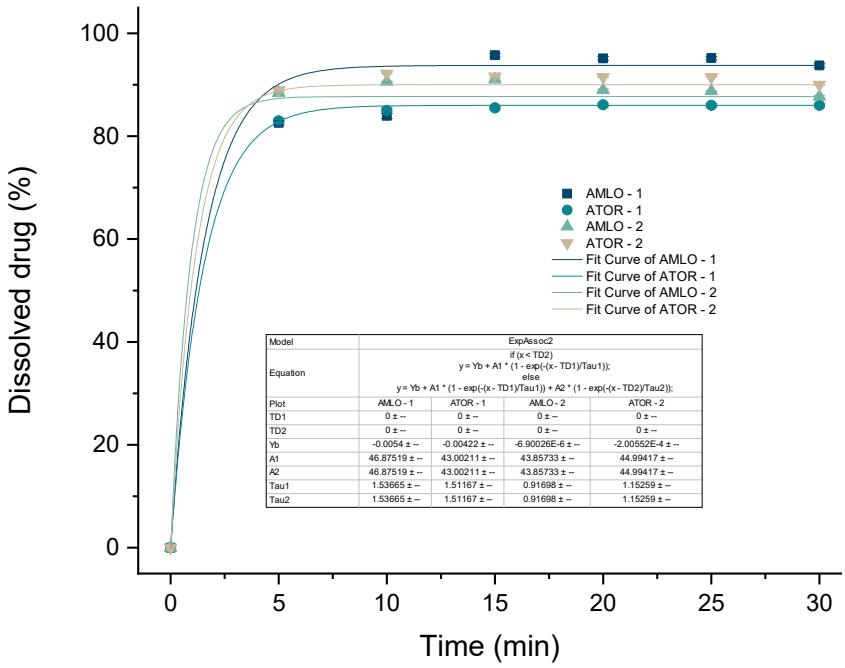


Figure 7. Chromatogram of a standard solution (1 µg/mL).

The retention time of atorvastatin is 9.95 ± 0.1 min, whereas that of amlodipine is 4.3 ± 0.09 min.

Regarding the active ingredient content of the fibers, 10 mg of FATOR + AMLO contains 77.1 µg of AMLO and 250.5 µg of ATOR, representing deviations of +1.44% and −18.40% from the theoretical values (signed relative errors), respectively.

Figure 8 shows the dissolution curves of the tested fibers (containing the active ingredient individually and the fiber containing both active ingredients).



Model	ExpAssoc2			

Equation	if (x < TD2)
	y = Yb + A1 * (1 - exp(-(x - TD1)/Tau1));
	else
	y = Yb + A1 * (1 - exp(-(x - TD1)/Tau1)) + A2 * (1 - exp(-(x - TD2)/Tau2));			

Plot	AMLO - 1	ATOR - 1	AMLO - 2	ATOR - 2
TD1	0 ± --	0 ± --	0 ± --	0 ± --
TD2	0 ± --	0 ± --	0 ± --	0 ± --
Yb	-0.0054 ± --	-0.00422 ± --	-6.90026E-6 ± --	-2.00552E-4 ± --
A1	46.87519 ± --	43.00211 ± --	43.85733 ± --	44.99417 ± --
A2	46.87519 ± --	43.00211 ± --	43.85733 ± --	44.99417 ± --
Tau1	1.53665 ± --	1.51167 ± --	0.91698 ± --	1.15259 ± --
Tau2	1.53665 ± --	1.51167 ± --	0.91698 ± --	1.15259 ± --

Figure 8. Results of the dissolution test: AMLO—1: amlodipine from FAMLO, AMLO—2: amlodipine from FAMLO + ATOR, ATOR—1: atorvastatin from FATOR, ATOR—2: atorvastatin from FAMLO + ATOR.

As the graphs show, dissolution is fast; the embedded active ingredient is practically released after 5 min. This is consistent with the short disintegration time and meets expectations.

Compared to atorvastatin fibers from previous studies, which presented burst release in the first minutes of the dissolution test (above 80% in the first 10 min), our fibers release the API more rapidly, with 90% released within 5 min [21]. Amlodipine and nifedipine fibers released over 90% of amlodipine within 120 s [30], a similar release to our findings.

4. Conclusions

In chronic treatment, a combined active-ingredient pharmaceutical formulation becomes more tolerable over time and more convenient for the patient. In this context, polymer-based fibers, through rapid disintegration, promote rapid drug release for both active ingredients.

Polymer dispersions were successfully prepared by solubilizing both of the APIs. DSC and FT-IR results show possible amorphization of AMLO and ATOR in the PVP nanofibres.

Fibers were smooth and homogeneous, presenting a random arrangement, with diameters between 426 and 547 nm.

The fibrous sheets disintegrated extremely quickly, with a measured time under 3 s. The API is released in a burst, with full dissolution occurring within the first 5 min.

Study limitations include limited formulation space (only polymer concentration, voltage, and speed were investigated), small-scale production, and an in vitro focus of the experiments. Future work should include in vivo assessment, and bioavailability enhancements remain to be confirmed.

The fixed-dose combination fibrous sheets present a potential fast-delivery system for future buccal administration in elderly patients.

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Abbreviations

The following abbreviations are used in this manuscript:

AMLO	Amlodipine
ATOR	Atorvastatin
DAMLO	Dispersion of amlodipine
DATOR	Dispersion of atorvastatin
DAMLO + ATOR	Dispersion of amlodipine and atorvastatin
BCS	Biopharmaceutical Classification System
FAMLO	Fiber containing amlodipine
FATOR	Fiber containing atorvastatin
FAMLO + ATOR	Fiber containing amlodipine and atorvastatin
PAMLO + ATOR	Physical mixture of amlodipine and atorvastatin
PVP	Polyvinyl pyrrolidone
API	Active pharmaceutical ingredient
DSC	Differential Scanning Calorimetry
FTIR	Fourier-transformed infrared spectroscopy

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