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FABRICATION OF POLYVINYL ALCOHOL NANOFIBROUS WEBS CONTAINING MOMETASONE FUROATE MONOHYDRATE AND MELATONIN LOADED SILICA XEROGELS FOR TOPICAL DRUG DELIVERY: *IN VITRO* RELEASE STUDY

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ABSTRACT: A key approach to the controlled release of bioactive molecules is the development of drug delivery systems that minimize side effects and precisely regulate drug release. A strategy for enhancing the drug release properties of drug delivery systems involves loading drugs into a carrier before their incorporation into the system. Xerogels can be utilized since they are porous, and can be synthesized through ambient pressure drying of precursor wet-gels, offering a cost-effective, facile, and sustainable approach. In this study, polyvinyl alcohol (PVA)/drug loaded-silica xerogel nanofibrous webs were fabricated via electrospinning. Xerogels were synthesized via sol-gel polymerization, loaded with mometasone furoate monohydrate and melatonin, then incorporated into PVA solutions and processed into PVA/xerogel/drug nanofibrous webs. The webs were characterized in terms of their morphological and chemical properties via scanning electron microscope and Fourier transform infrared spectrometer, respectively, and as well as drug release profiles. Morphological analysis confirmed the successful incorporation of drug-loaded xerogels within nanofibers without significant change in morphological structure, while chemical analysis identified distinct peaks corresponding to the specific bands of PVA, xerogel, and drugs. *In vitro* drug release studies demonstrated that the release of MLT was 50.289% ± 0.462% and 55.080% ± 2.955% for the 1:1 and 1:2 MLT: Xerogel formulations, respectively, whereas the control formulation (1:0 MLT: Xerogel) exhibited a release of 66.295% ± 3.293% at first 24h. The presence of xerogel resulted in a slower MLT release compared to the xerogel-free formulation. The findings highlight the potential of xerogel-incorporated nanofibrous webs as effective carriers for controlled topical drug delivery applications, i.e., wound dressing.

Keywords: Topical drug delivery system, xerogel, mometasone furoate monohydrate, melatonin, electrospinning, PVA

TOPİKAL İLAÇ SALIMI İÇİN MOMETAZON FUROAT MONOHIDRAT VE MELATONİN YÜKLÜ SİLİKA KSEROJEL İÇEREN POLİVİNİL ALKOL NANOLİF MEMBRAN ÜRETİMİ: *IN VITRO* SALIM ÇALIŞMASI

ÖZ: Biyolojik aktif moleküllerin kontrollü salımına yönelik temel yaklaşımlardan biri, yan etkileri en aza indirirken ilaç salımını hassas bir şekilde düzenleyen ilaç salım sistemlerinin geliştirilmesidir. İlaç salım sistemlerinin ilaç salım özelliklerini iyileştirmeye yönelik stratejilerden biri, ilaçların sistem içine dahil edilmeden önce bir taşıyıcıya yüklenmesidir. Gözenekli yapıları ve öncül ıslak jellerin ortam basıncında kurutulmasıyla sentezlenebilmeleri nedeniyle, kserojeller düşük maliyetli, kolay uygulanabilir ve sürdürülebilir bir yöntem sunarak ilaç taşıma sistemlerinde kullanılabilirler. Bu çalışmada, elektro-eğirme yöntemi kullanılarak polivinil alkol (PVA)/ilaç yüklü silika kserojel nanolif yüzeyler üretilmiştir. Kserojeller sol-jel polimerizasyonu yoluyla sentezlenmiş, mometazon furoat monohidrat ve melatonin ile yüklenmiş, ardından PVA çözeltilerine dahil edilerek PVA/kserojel/ilaç nanolif yüzeyler geliştirilmiştir. Üretilen yüzeylerin morfolojik ve kimyasal özellikleri sırasıyla taramalı elektron mikroskobu ve Fourier dönüşümlü kızılötesi spektrometresi ile karakterize edilmiş, ayrıca ilaç salım profilleri değerlendirilmiştir. Morfolojik analizler, ilaç yüklü kserojellerin nanoliflere başarılı bir şekilde entegre edildiğini ve morfolojik yapıda belirgin bir değişiklik olmadığını doğrulamıştır. Kimyasal analizler ise PVA, kserojel ve ilaçlara özgü belirgin piklerin varlığını göstermiştir. *In vitro* ilaç salım çalışmaları, 24 saat sonunda MLT salımının 1:1 ve 1:2 MLT:kserojel formülasyonları için sırasıyla %50.289 ± %0.462 ve %55.080 ± %2.955 olduğunu, kontrol formülasyonu (1:0 MLT:kserojel) için ise %66.295 ± %3.293 salım gerçekleştiğini göstermiştir. Kserojel varlığı, kserojel içermeyen formülasyona kıyasla MLT'nin daha yavaş salınmasını sağlamıştır. Elde edilen bulgular, kserojel içeren nanolifli ağların kontrollü topikal ilaç salımı uygulamaları, örneğin yara örtüleri, için etkili taşıyıcılar olarak potansiyelini ortaya koymaktadır.

Anahtar kelimeler: Topikal ilaç salım sistemi, kserojel, mometazon furoat monohidrat, melatonin, elektroeğirme, PVA

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1. INTRODUCTION

One of the leading strategies for delivering bioactive molecules involves the design of drug delivery systems that can precisely control drug release, have low side effects, and ensure high patient compliance. Topical drug delivery has gained attention due to its advantages such as ease of self-application, targeted drug delivery, reduced total dose, and minimized off-target side effects [1]. The extensive surface area of the skin presents a promising opportunity for drug delivery applications. Therefore, topical drug delivery systems need to be capable of penetrating the specific skin layers where the active pharmaceutical ingredient exerts its pharmacological effects. The absorption efficiency of drugs in topical drug delivery systems is largely determined by key factors, such as the physicochemical properties of the drug's bioactive composition, i.e., molecular weight, polarity, degree of hydrogen bonding, and surface charge [2].

Researchers have investigated the application of nanotechnology, particularly using nanofibers for drug delivery in topical and transdermal drug delivery systems [3]. Electrospinning is the most commonly employed method for nanofiber production due to its simplicity and cost-effectiveness. In this process, a polymer solution is introduced into a syringe pump and subsequently subjected to an electric field created between the nozzle tip and the metal collector. Once the applied voltage surpasses a critical threshold, a charged jet is emitted from the needle tip and directed toward the collector surface. As the jet moves, it undergoes stretching and thinning, while the solvent evaporates. The yielded fibers are deposited onto a flat or round metal collector. This method facilitates the fabrication of fibers with average diameters ranging from nanometers to micrometers [4]. Electrospun nanofibrous webs offer various desirable properties for drug delivery systems. For instance, nanofibrous webs can be produced from a wide variety of biobased, biodegradable, or biocompatible polymers, i.e., chitosan, gelatin, collagen, polylactide (PLA), polyglycolide (PGA), polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), poly(vinyl alcohol) (PVA), which are suitable for application in drug delivery systems [5]. Besides, nanofibrous webs can provide efficient delivery of both hydrophobic and hydrophilic drugs due to their high surface area-to-volume ratio and high loading capacity [6]. Additionally, the drug release profile can be tailored by modifying various factors, such as the polymer-to-drug ratio, fiber diameter, and porosity [7], allowing nanofibrous webs to achieve controlled drug release. PVA is a biocompatible, biodegradable and water-soluble synthetic polymer with good electrospinnability that has been widely studied in drug delivery and wound dressing applications [8-11]. In the study of Fathollahipour et al. [8], PVA/chitosan nanofibrous webs comprising gelation nanoparticles were fabricated as a dual drug delivery system. In another study [9], collagen/PVA nanofibrous webs were produced, then crosslinked using UV radiation or glutaraldehyde to strengthen the structure and reduce the extent of rapid drug release. Cui et al. [12] also reported that crosslinked PVA/chitosan nanofibers had a lower drug release rate and smaller amounts of drug burst release than those of PVA/chitosan nanofibers alone. In the study of Rahmani et al. [13], the nanofibrous webs of buprenorphine-loaded poly(vinyl pyrrolidone) (Bup/PVP) and buprenorphine-loaded PVA/PVP were fabricated for transdermal drug delivery. In the study of Açık et al. [14], organosoluble and quaternized PVA derivatives were developed by incorporating chloroacetyl chloride and quaternized ammonium groups into the main chain through esterification and nucleophilic substitution. Afterward, the model drug, naproxen sodium (NAP), was incorporated into a PVA polymer solution, and electrospun NAP-loaded PVA webs were fabricated to serve as potential drug carriers for controlled release. In another study [15], hydrophilic polyhexamethylene guanidine hydrochloride (PHGC) and hydrophobic indomethacin (Indo) were loaded into PVA and PCL nanofibers to fabricate antibacterial and anti-inflammatory PCL-Indo/PVA-PHGC wound dressing. In the study of Gutschmidt et al. [16], PVA/soy protein isolate nanofibrous webs were loaded with ketoprofen, and in order to improve drug release control, a tubular nanoparticle, sepiolite, was used as a secondary release control tool.

Extra drug carriers, i.e., nanoparticles, liposomes, hydrogels, aerogels, xerogels, are employed in drug release studies primarily to enhance drug delivery efficiency, control release kinetics, and protect the drug from degradation [17]. Aerogels are ultra-light, porous nanomaterials that have a complex three-dimensional structure [18]. There are various types of aerogels, including silica-based, metal oxide-based and carbon-based. Among these, silica (SiO_2) aerogels remain the most widely used due to their outstanding properties, such as low density, high porosity, large specific surface area, and very low thermal conductivity [18]. These unique features make them highly beneficial in various applications, including acoustic and thermal insulation [19], capacitors [20], solar energy collectors [21], sensors [22], and drug delivery systems [23]. However, the fabrication of aerogels requires supercritical drying technique, which is highly expensive, low in scalability and energy-intensive. Xerogels are also porous materials that can be synthesized via ambient pressure drying of any wet gel precursor, which is a cheaper, easier and more environment-friendly method. They have lower porosity and surface area than aerogels due to the drying difference; on the other hand, they have better mechanical stability and higher density compared to aerogels [24, 25]. Xerogels have been widely investigated for drug delivery applications. In a study of Zhou et al. [26], poly (ε-caprolactone)-chitosan-silica xerogel was used for tetracycline hydrochloride delivery, and the presence of silica in the xerogel notably improved the thermal stability while also providing favorable in vitro bioactivity and controlled drug release properties. In another study [27], an alginate-based xerogel was modified with g-poly (methacrylic acid) for insulin delivery, and a significant enhancement in the physical stability and good swelling properties were observed. Besides, more than 70 % of the loaded insulin was released from the xerogel in two days. In the study of Rafati et al. [28], a xerogel was produced from silica and poly(ethylene glycol) by a facile sol–gel route and showed

sustained release of an enrofloxacin antibiotic drug. In another study [29], silk fibroin-based xerogels were fabricated, and their potential for long-acting hormone estradiol delivery was evaluated. It was reported that a controlled drug release of up to 129 days from the xerogel was achieved, demonstrating the biopolymeric xerogel's potential for the sustained release of hydrophobic drugs.

A glucocorticoid anti-inflammatory drug, mometasone furoate monohydrate, is marketed as a topical formulation, such as creams, lotions, and ointments [30], for effectively reducing inflammation, swelling, redness, and itching. It is an intranasal corticosteroid that is highly lipophilic. In the study of Rivelli et al. [31], mometasone furoate-loaded PLGA nanofibers were fabricated, and they provided a controlled release of the drug for 60 days. Melatonin, a hydrophilic drug, has been shown to function as a shield against UV-induced skin damage, i.e., photodermatitis, due to its extensive antioxidant and radical scavenger capability, which was demonstrated by previous *in vitro* studies [32, 33]. In the study of Mirmajidi et al. [34], a three-layered nanofibrous wound dressing, i.e., chitosan-PCL/ PVA-melatonin/ chitosan-PCL was fabricated for controlled release of melatonin, and the three-layered wound dressing decreased burst release (45 %) and resulted in a sustained release of melatonin over 11 days. In another study [35], hydrophobic PLA and hydrophilic PVA polymers were used to fabricate electrospun nanofibers that incorporated melatonin at varying concentrations. PLA-based nanofibers exhibited a sustained drug release profile, whereas PVA-based nanofibers released the full melatonin load within 20 minutes. Furthermore, the inclusion of Tween® 80, a permeation enhancer, in PLA-based nanofibers resulted in more rapid dissolution, achieving complete release, along with a significant enhancement in swelling behavior, approximately 20-fold.

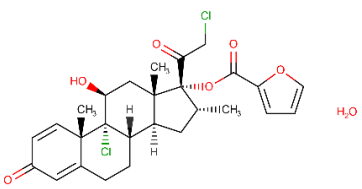
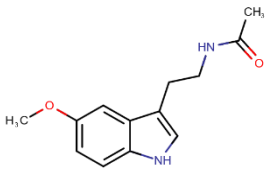
In the current study, we aimed to fabricate PVA/silica xerogel nanofibrous webs for topical drug delivery applications, i.e., wound dressing. Initially, SiO_2 xerogels were synthesized via sol-gel method, which were then loaded with two different types of drugs, namely hydrophobic mometasone furoate monohydrate and hydrophilic melatonin. The drug-loaded SiO_2 xerogels were incorporated into the electrospinning solution of PVA and electrospun into PVA/silica xerogel/drug nanofibrous webs. The drug release profiles of the resultant composite webs were investigated, and the drug release performance of the developed topical drug delivery systems with different hydrophilic characters was compared. Previous studies have indicated that silica xerogel is capable of carrying drugs for drug delivery [36], and to the best of our knowledge, it has not been integrated into nanofibrous webs for topical drug delivery or wound dressing applications. Therefore, this study aims to pioneer the integration of SiO_2 xerogel into nanofibrous webs for potential use in controlled drug release applications, and to contribute to the literature by analyzing the performance of SiO_2 xerogel as a potential drug carrier in nanofibrous webs, by comparing it to the performance of xerogel alone.

2. MATERIALS AND METHODS

2.1 Materials

A silica precursor tetramethyl orthosilicate (TMOS) (≥99%), methanol (≥99.8%), ammonium hydroxide (NH_4OH) solution (8-30 wt% in water), *N*,*N*-dimethylformamide (DMF, molecular weight: 73.09 g/mol, 99% purity), and polyvinyl alcohol (PVA, M_w 146,000-186,000) were supplied from Sigma Aldrich (USA). Distilled water was obtained from the Milli-Q ultrapure water system. Mometasone furoate monohydrate (MFM) was kindly provided by Abdi İbrahim Pharmaceuticals, Turkey. Melatonin powder was a kind gift from Swati Spentose PVT. Ltd. (India). All chemical solvents used were of analytical grade and were used without further purification.

Table 1. Properties of the drugs

Compound	Mometasone furoate monohydrate	Melatonin
Chemical Structure		
Chemical Formula	$C_{27}H_3{}_2Cl_2O_7$	$C_{13}H_{16}N_2O_2$
Log P	5.06	1.6
Molecular Weight	539.45	232.28
References	[37]	[38]

2.2. Preparation of SiO_2 Xerogel

Silica xerogel was synthesized via sol-gel method [39, 40]. TMOS was used as the silica precursor and was hydrolyzed in the presence of water to enable polymerization. Methanol was employed as a co-solvent, since it is miscible with both TMOS and water, facilitating their reaction. The NH_4OH solution was used as an alkaline catalyst to accelerate the reaction process. To maintain a straightforward synthesis, three separate solutions were prepared. Firstly, NH_4OH stock solution was prepared by adding 5.40 mL of concentrated NH_4OH to 1000 mL of distilled water. Secondly, the alkoxide solution was prepared by mixing 2.0 mL of TMOS with 2.0 mL of methanol. Thirdly, the catalyst solution, was prepared by combining 5.0 mL of the previously prepared NH_4OH stock solution with 2.0 mL of methanol. Finally, the sol-gel solution was obtained by stirring the catalyst solution and the alkoxide solution for 2 minutes. The sol solution was then poured into cylindrical mold with a diameter of 1.5 cm, to fully solidify. After solidification, solvent exchange was carried out with methanol at 25°C for every 24 hours for five times. Following the aging process, the sol-gel was dried at ambient temperature and the dried xerogel was ball-milled at a frequency of 30 Hz for approximately 20 minutes using an MTI Corporation SFM-1 ball milling device. Schematic illustration for the preparation of SiO_2 xerogel was given in Figure 1.

2.3. Preparation of the Drug-Loaded SiO_2 Xerogel/ PVA Polymer Solutions and Fabrication of Nanofibrous Webs via Electrospinning Method

The drugs were loaded after the synthesis of xerogel to avoid the risk of drug degradation due to temperature, organic solvents, and the ball-milling process. In order to load the drugs into the pores of the synthesized silica xerogel in powder form, the synthesized xerogel was dispersed in DMF. Subsequently, the drugs were added, and the mixture was stirred for 12 hours. Afterward, the mixture was stored under ambient conditions for three days to encapsulate the drugs in the pores of xerogel.

Separately, PVA was dissolved in water by magnetically stirring at 80°C for 30 minutes. To prevent the drugs from being damaged by heat, the PVA solutions were first cooled down to room temperature. The cooled PVA solutions were then mixed with the drug/xerogel mixture and stirred for 12 hours, and the final solutions (Table 2) were employed in the electrospinning device (Figure 1).

For the electrospinning process, a vertical electrospinning device (Inovenso Nanospinner24) was employed. The polymer solutions were fed into a 10-mL syringes, and standard syringe needles were used. Nanofibers were collected on a round collector rotating at a constant speed of 100 rpm. The tip-to-collector distance, voltage, and feed rate were set to 17 cm, 25 kV and 1.1 ml/h, respectively, at room temperature and ambient humidity.

Table 2. The formulations of polymer solutions for electrospinning process

Sample Code	Drug: Xerogel ratio	Drug type	Drug (g)	Xerogel (g)	DMF (g)	PVA (g)	Water (g)	Total (g)
1:0 MFM: xerogel (control sample)	1:0	MFM	0.01	-	0.95	0.896	8.144	10
1:1 MFM: xerogel	1:1	MFM	0.01	0.01	0.95	0.896	8.124	10
1:2 MFM: xerogel	1:2	MFM	0.01	0.02	0.95	0.896	8,134	10
1:0 MLT: xerogel (control sample)	1:0	MLT	0.01	-	0.95	0.896	8.144	10
1:1 MLT: xerogel	1:1	MLT	0.01	0.01	0.95	0.896	8.124	10
1:2 MLT: xerogel	1:2	MLT	0.01	0.02	0.95	0.896	8.134	10

*MFM: Mometasone furoate monohydrate, MLT: Melatonin

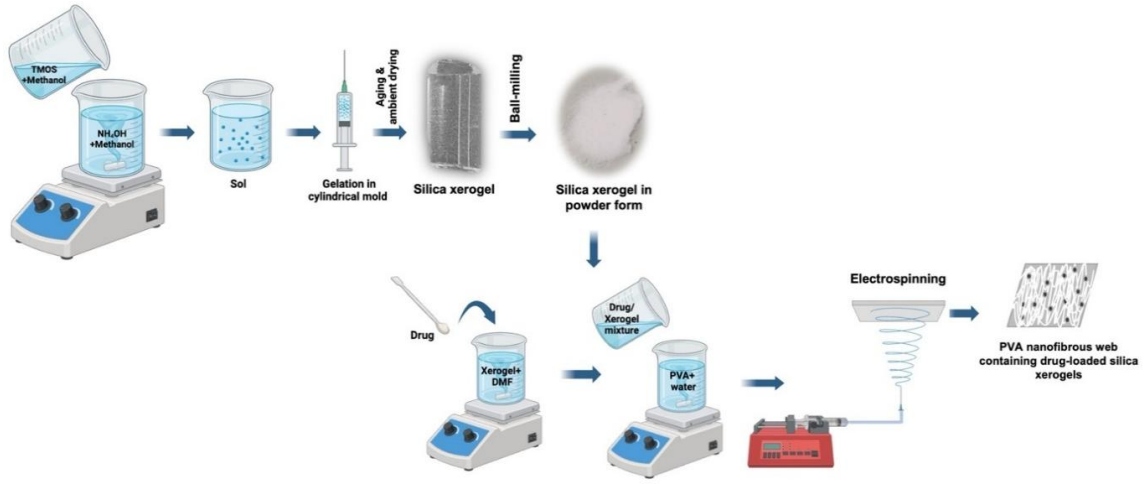


Figure 1. Schematic illustration for the preparation of SiO_2 xerogel and PVA nanofibrous webs containing drug-loaded SiO_2 xerogel

2.4. Morphological Analysis

A scanning electron microscope (SEM), Tescan Vega3, was utilized to conduct morphological analysis of nanofibrous webs at an operating voltage of 20.00 kV. Prior to SEM imaging, the nanofibrous webs were coated with gold (Au)/palladium (Pd) for 2 min using a Quorum Sputter Coater. ImageJ software was used for measuring the diameter of the nanofibers. A total of 100 measurements were taken, and the average fiber diameters (*<D>)* were reported.

2.5. Chemical Analysis

A Perkin Elmer Spectrum 65, Fourier transform infrared spectrometer (FT-IR-ATR), equipped with an IR source, a LiTaO3 detector and a KBr beam splitter, was used to investigate the chemical structure of the synthesized silica xerogel, drugs, and nanofibrous webs of PVA/drug and PVA/drug/ xerogel. The spectra were recorded within a 4000-500 cm^{-1} wavelength range, with 16 scans acquired at a 4 cm^{-1} resolution. The FT-IR data was normalized using OriginPro software.

2.6. *In vitro* Drug Release Study

In vitro release studies were conducted using Franz diffusion cells (PermeGear V6A Stirrer, Hellertown, USA) with a receptor volume of 14 mL and a diffusion area of 4.91 cm^2. The solubility of the drug in receptor medium was assessed to ensure its suitability for maintaining sink conditions throughout the study. A mixture of phosphate-buffered saline (PBS) (pH 7.4) and ethanol (50:50, v/v) was confirmed to provide sink conditions for MFM, with a solubility value of 271.62 µg/mL, and was used as the receptor medium for the *in vitro* release studies. For MLT; however, PBS (pH 7.4) was used as the receptor medium alone, as it adequately maintained sink conditions.

After the receptor phase was degassed in an ultrasonic bath, the cells were filled in a way that no air bubbles would form. A magnetic stirrer was placed in each cell and a dialysis membrane (MWCO 14 kDa, Sigma) was cut to the appropriate size and placed on the cells. Nanofiber formulations containing MFM or MLT as donor phase were weighed and placed precisely, and the study was started by covering the donor phase. The temperature was kept constant at 32±0.5°C (skin temperature) throughout the study, and a rotation speed of 500 rpm was applied.

For MFM, the samples were taken from the receptor phase as 1 mL at 0.5, 1, 2, 3, 4, 5, 6, 8, 24, and 30 hours and filtered through a 0.45 µm syringe tip membrane filter (PTFE), placed in vials, and 1 mL of fresh receptor medium was added to the cells after each sample. For MLT, the study was carried out by taking samples at 0.5, 1, 2, 3, 4, 5, 6, 8, 24 (day 1), 48 (day 2), 72 (day 3), and 96 (day 4) hours. Samples were analyzed by validated HPLC methods. *In vitro* drug release experiments were conducted at least three times.

2.7. HPLC Analysis

The validated High-Pressure Liquid Chromatography (HPLC) methods were used to determine drug concentrations in the samples. All analytical measurements were performed using a HPLC equipment with a PDA detector (Shimadzu Model LC 20AT, Kyoto, Japan). The other parameters for each drugs were given in Table 3.

3. RESULTS AND DISCUSSION

3.1. Morphological Structure of the Nanofibrous Webs

SEM images of PVA/melatonin-loaded xerogel and PVA/melatonin nanofibrous webs are presented in Figures 2 and 3, respectively. It was observed that PVA nanofibers with drug-loaded SiO_2 xerogel incorporation, as well as those with drug incorporation were fabricated successfully. Drug-loaded xerogels were detectable in the PVA nanofiber structure (Figure 2), while there was no significant difference in the morphology of PVA nanofibers with drug loading only (Figure 3). Additionally, the average fiber diameter of PVA/melatonin-loaded xerogel nanofibers was measured to be 194 ± 80 nm (Figure 2), while the average fiber diameter of PVA/melatonin nanofibers was 210 ± 95 nm (Figure 3), indicating that the incorporation of xerogel did not have a significant impact on the average fiber diameter.

Table 3. The HPLC method parameters of drugs

Parameters	MFM	MLT
Column	5-µm C18 Inertsil ODS-3 column (250 × 4.6 mm, GL Sciences, USA)	5-µm C18 Inertsil ODS-3 column (150 × 4.6 mm, GL Sciences, USA)
Mobile Phase	Mixture of methanol and water (80:20, v/v)	Mixture of acetonitrile and water (40:60, v/v)
Wavelength (nm)	248 nm	220 nm
Flow rate (mL/min)	1.0 mL/min	1.0 mL/min
Injection Volume (µL)	50 µl	100 µl
Column Temperature (^{0}C)	25 ^{0}C	30 ^{0}C
Retention Time	8 min	3 min
References	[41]	[42]

*MFM: Mometasone furoate monohydrate, MLT: Melatonin

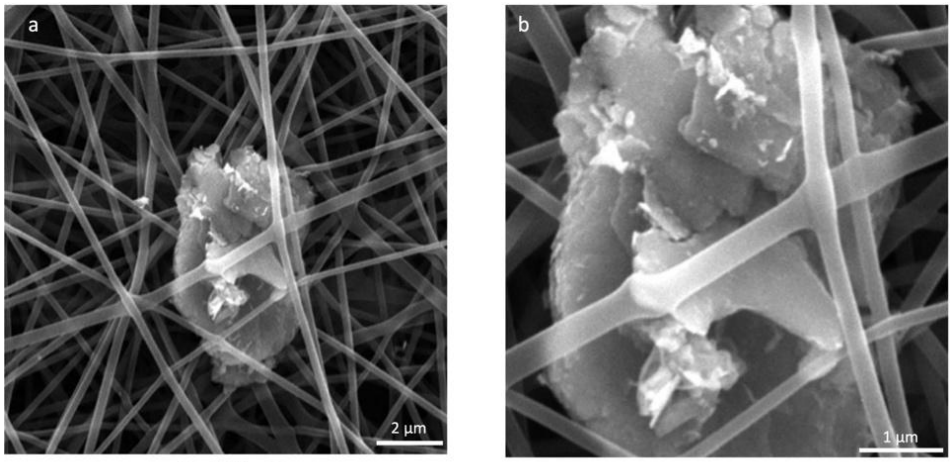


Figure 2. Melatonin-loaded silica xerogel in PVA nanofibrous webs at different magnifications, 10kX (a) and 25kX (b).

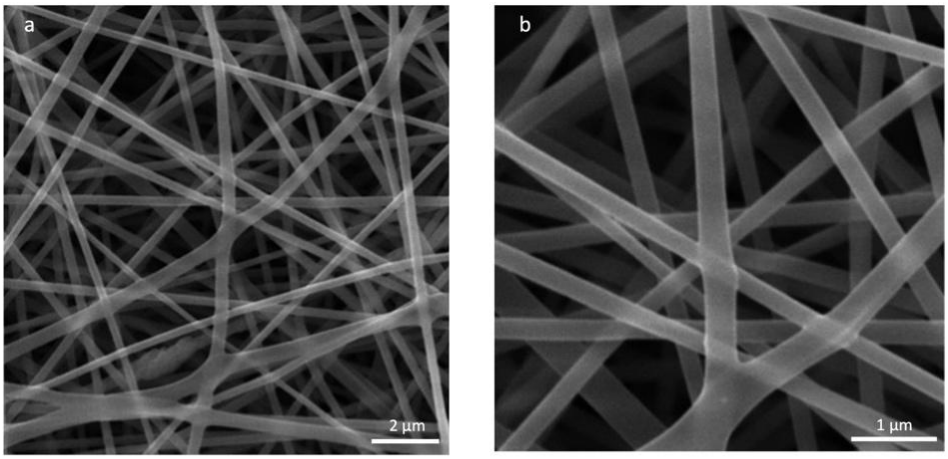


Figure 3. PVA/melatonin nanofibrous webs at different magnifications, 10kX (a) and 25kX (b)

3.2. Chemical Analysis of the Nanofibrous Webs

In order to demonstrate the presence of drug-loaded xerogels within the nanofibrous webs, nanofibrous webs comprising melatonin-loaded xerogels were chemically characterized via FT-IR analysis (Figure 4). In the FT-IR spectrum of PVA, a broad and strong peak of -O-H stretching was observed in the range of 3200-3600 cm^{-1}, along with peaks of -C-H stretching in the alkyl group in the range of 2800-3000 cm^{-1} [43]. The spectrum of melatonin showed a broad peak in the range of 2800-3000 cm^{-1}, indicating -C-H stretching of methyl groups. The carbonyl stretching of the amide group, -C=O stretching, showed a distinct peak at 1624.8 cm^{-1}. In the range of 1000-1300 cm^{-1}, peaks of -C-O stretching in alcohol groups were observed. Additionally, -O-H stretching of hydroxyl groups showed a broad and strong peak in the range of 3200-3600 cm^{-1} [44]. The characteristic peaks of xerogel, -Si-O-Si stretching, were observed in the range of 1000-1200 cm^{-1}, indicating the silica network structure in xerogel [45].

The control sample (PVA/melatonin nanofiber) showed a broad peak of -O-H stretching at 3290 cm^{-1}, due to hydroxyl groups from both PVA and melatonin. A strong peak of -C-H stretching was observed at 2900 cm^{-1}, indicating methylene groups. A peak at 1714 cm^{-1} was attributed to carbonyl -C=O stretching in PVA. Additionally, a peak at 1256 cm^{-1} was attributed to -C-O stretching in both melatonin and PVA. PVA/melatonin/xerogel nanofibers showed similar characteristic peaks to the PVA/melatonin nanofibers control sample. In addition, a -Si-O-Si stretching peak at 1091 cm^{-1} was observed, indicating the silica network structure due to the presence of xerogel. These results confirm that melatonin-loaded xerogel PVA nanofibers were successfully produced and chemically validated.

3.3. Drug Release Studies

The release of MFM from xerogel-PVA nanofiber webs (1:1 MFM:xerogel and 1:2 MFM:xerogel) and from PVA nanofibers alone (1:0 MFM:Xerogel) was monitored for up to 30 hours

(Figure 5). At the end of 30 hours, MFM release was 59.701% ± 7.766% and 87.249% ± 8.562% for formulations 1:1 MFM:xerogel and 1:2 MFM:Xerogel, respectively, while release from the control formulation (1:0 MFM:xerogel) was 30.146%. ± 1.905% MFM release kinetics from xerogel-PVA nanofibers followed Higuchi kinetics, indicating that drug release occurred by diffusion [46]. This finding is in accordance with the information that enhanced release rates are characteristic of nanoporous drug carriers, and this phenomenon is generally attributed to the ability of the nanostructure to suppress drug crystallization and to expose a large surface area of the drug to the aqueous elution medium [47]. The release of the lipophilic active substance was higher in the 1:2 MFM:Xerogel formulation, where the amount of xerogel in the system was higher.

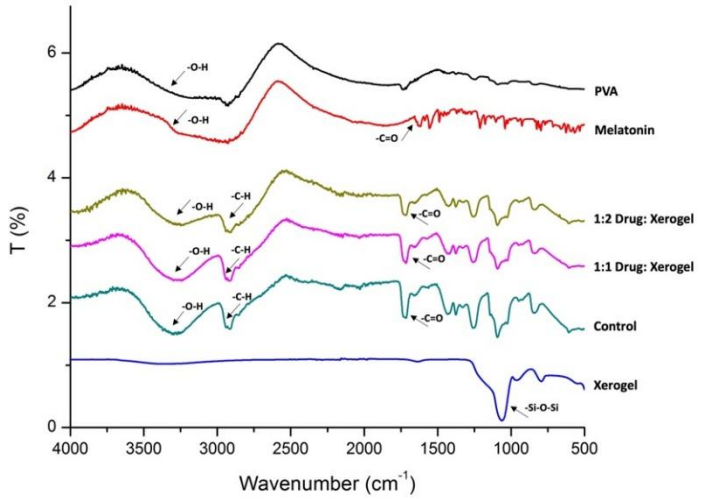


Figure 4. FT-IR spectra of the samples

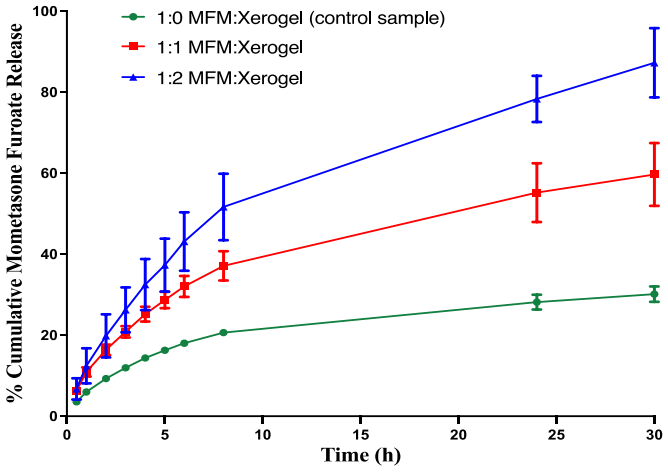


Figure 5. The cumulative release profiles of MFM from nanofibers

In vitro release studies, the receptor phase should be selected based on the physicochemical properties of the drug and the dosage form. The medium must provide sink conditions, meaning the solubility of the active ingredient in the selected medium should be at least three times the drug concentration at the end of the test [48]. MFM is a very lipophilic active substance (log P: 5.06), and ethanol was included in the receptor phase to maintain sink conditions. In the presence of ethanol, xerogel may have disintegrated more easily, facilitating the release of the lipophilic drug. MLT, on the other hand, is a hydrophilic model active substance (log P: 1.6), and several studies have reported drug release properties of MLT-loaded nanofibrous webs. Romeo et al. [35], investigated PVA and poly (lactic acid) (PLA) nanofiber inserts for ocular melatonin delivery. The scaffolds were prepared with and without the nonionic surfactant, Tween 80, resulting in different release rates. PLA nanofibers containing Tween 80 released the full amount of encapsulated MLT within 6 hours, whereas those produced without Tween 80 released only 40–55% of MLT by the end of 12 hours. PVA nanofibers exhibited very fast release, with Tween 80-containing PVA nanofibers releasing MLT in approximately 5 minutes. In their study, the receptor phase was PBS (pH 7.4), as in our study; however, the experimental setup based on a dissolution method in which nanofibrous samples were attached to a magnetic stirrer at 100 rpm, and 10 mL of fresh receptor phase was added to the medium after each sample collection [35]. This method differs significantly from the Franz diffusion cell method used in our study to evaluate the *in vitro* release performance of formulations intended for topical application to the skin. Similarly, Deng et al. [49] studied MLT-encapsulated silk fibroin electrospun nanofibers and found that approximately 42% of MLT was released within the first 24 hours. In another study, Mirmajidi et al. [34], developed and characterized crosslinked chitosan (Cs)-polycaprolactone (PCL)/ PVA-MLT/chitosan- PCL three-layer nanofiber wound dressings. The cumulative release of MLT from these three-layer wound dressings was evaluated, revealing an initial burst release of up to 51% of melatonin within the first 14 hours, followed by a very gradual, sustained release over 250 hours. Their findings suggested that differences in porosity, degradation rate, and hydrophobicity among the layers significantly influenced drug release.

The *in vitro* release data for MLT over 96 h is presented in Figure 6. At the 24 h mark, MLT release was 50.289% ± 0.462% and 55.080% ± 2.955% for the 1:1 MLT:xerogel and 1:2 MLT:xerogel formulations, respectively, while release from the control formulation (1:0 MLT:xerogel) was 66.295% ± 3.293%. This release profile remained consistent over the 96-hour period. The presence of xerogel in the nanofibrous formulations resulted in a slower MLT release compared to the xerogel-free formulation. However, no statistically significant difference was observed between the formulations containing xerogel at ratios of 1:1 and 1:2. Additionally, MLT release from all formulations followed Korsmeyer-Peppas kinetics, suggesting that drug release occurs through a combination of diffusion, polymer relaxation, and matrix erosion [50].

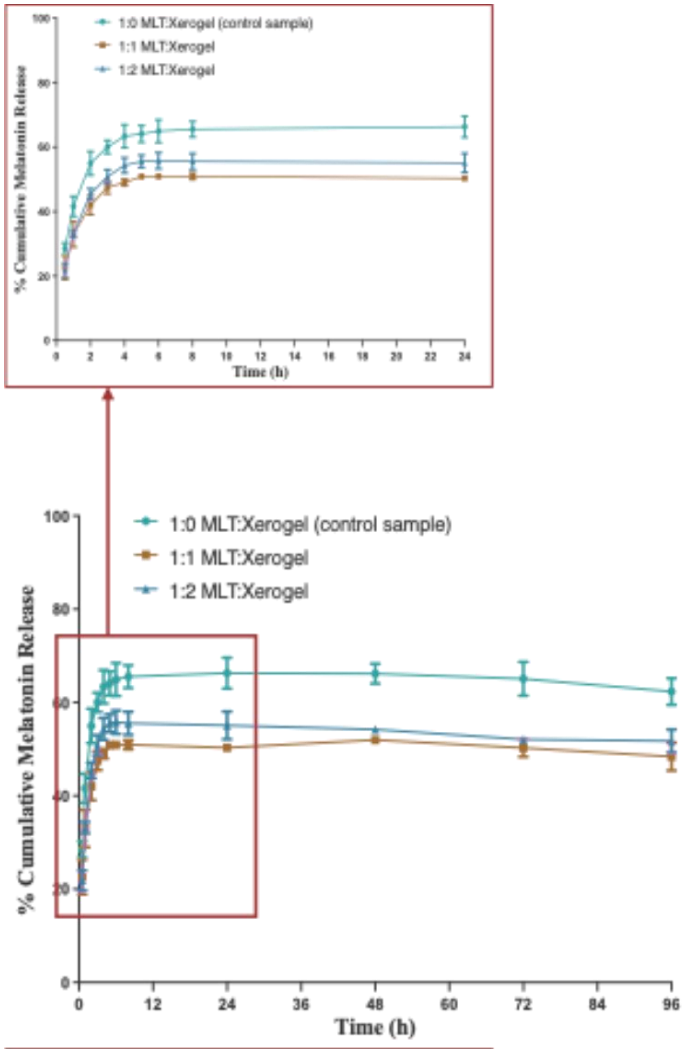


Figure 6. The cumulative release profile of the MLT from nanofibrous webs

4. CONCLUSION

This study shows the integration of drug-loaded silica xerogel into nanofibrous webs for potential use in controlled drug release applications for the first time. The incorporation of xerogels, loaded with hydrophilic melatonin, into PVA nanofibrous webs achieved successfully confirmed by morphological and chemical characterization, and xerogels maintained structural integrity while allowing the desired drug release behavior. The drug release study showed that at 24 hours, melatonin release was measured as 50.289% ± 0.462% and 55.080% ± 2.955% for the 1:1 and 1:2 MLT:xerogel formulations, respectively, whereas the control formulation (1:0 MLT:xerogel) exhibited a release of 66.295% ± 3.293%. This trend remained consistent throughout the 96-hour period. It was concluded that the incorporation of xerogel into the formulations led to a reduction in melatonin release compared to the xerogel-free formulation. The findings provide insights into the use of xerogels as a promising strategy for tailoring drug release properties in topical drug delivery systems, i.e., wound dressing. Our future studies will focus on investigating how varying polymer ratios influence the release behavior of model active ingredients with different physicochemical properties. This will involve adjusting the ratios of PVA:xerogel and drug:xerogel while enhancing drug loading. Additionally, we seek to deepen our understanding of xerogel-polymer interactions and their role in modulating the release of active substances with varying lipophilicities.

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