Research Article

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Development, characterization, and in vitro evaluation of adhesive fibrous mat for mucosal propranolol delivery

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Abstract: This research focuses on the synthesis and adhesive properties of mucoadhesive mats, prepared with poly (vinylic alcohol) as a base polymer for the oromucosal release of propranolol (PRO) by the electrospinning technique. The nanofibrous mats were evaluated by scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy, thermogravimetric analysis, and differential scanning calorimetry; in vitro drug entrapment efficiency, degradation time, and adhesion studies were performed. SEM images of the electrospun mats show the correct formation of fibers with a variable diameter and porosity.

Keywords: electrospinning, poly(vinyl alcohol), nanofiber, propranolol, drug delivery, oromucosal

1 Introduction

Hemangiomas in children are the most common group of benign tumors in infancy due to uncontrolled reproduction of endothelial cells, producing permanent esthetic deformations, and in serious cases affecting vital functions (1–3).

Treatment is individualized, depending on morphology, size, localization, and growth rate of the lesion. Nowadays, several treatments have been used orally, such as corticoids, and others such as interferon, timolol and propranolol (PRO) intravenously (4,5). Among these, PRO is the most studied therapeutic option in recent years, thanks to the fact that it has been effective in cutaneous, hepatic, and respiratory tract hemangiomas, both before and after the proliferative phase (6,7).

PRO, a non-selective beta (β)-blocker, has been used orally or intravenously for the treatment of high blood pressure, hemangiomas, migraine headaches, and to prevent future heart problems in those with angina pectoris, among others (8,9). Hence, PRO was proposed as a first-line treatment due to its effectiveness, low cost, and safety in pediatric use (10–12).
Innovation of the pharmaceutical industry has led to the development of numerous technologies in terms of drug administration, creating new and improved drug delivery systems such as implantable, transdermal, transmucosal, and oral administration systems (13–17). Although most drugs are administered in the form of tablets and capsules, it is estimated that about 28% of the general population has frequent problems swallowing medications, especially toddler patients or older adults (18–21). Furthermore, commercial presentations of PRO for pediatric patients are not widely available. For instance, some hospitals administer PRO as an extemporaneous syrup prepared just before administrating it to patients. This approach may be associated with the administration of incorrect doses (22).

To overcome these problems, researchers in the pharmaceutical field have created oral dissolving films and mats, which also have the advantage of providing exact doses (23–25).

Given the growing demand for new and improved materials for the production of drug delivery systems, electrospun nanofibers have attracted attention. This fibrous matrix provides a potential solution to the current challenges in the biomedical field, where drugs can be loaded by “entrainment” and released through nanofibers’ degradation (26–29). The fiber flexibility formed by electrospinning a polymer solution is important to achieve interpenetration between the mucoadhesive fibers chains and the mucins present in the mucosa of the tissue where it will be applied (30,31).

To date, studies have been reported where poly(vinyl alcohol) (PVA) is used as a base polymer for scaffolds fabrication through the electrospinning technique, both as homopolymer and as copolymer. PVA has been proved as an excellent biomaterial candidate for the design of drug release systems, thanks to its properties such as non-toxicity, biocompatibility, among others (32,33). In addition to these properties, PVA has attracted attention to drug release through fibrous systems produced by the electrospinning technique, where disintegration time, amount of drug released, and adhesive properties of the system are key factors (34–36).

The main objective of this work is to produce an adhesive oral mat, through the electrospinning technique with PVA as a delivery polymer, containing PRO as a controlled dose drug for topical and systemic treatment of hemangiomas in geriatric/pediatric patients. The resulting mats were characterized by scanning electron microscopy (SEM), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FTIR) techniques in order to identify the chemical composition, thermal behavior as well as the correct incorporation of the drug. We also evaluated disintegration time, amount of drug released, and adhesive properties of the system.

2 Materials and methods

2.1 Materials

PVA (Product #: 341584, CAS: 9002-89-5, MW: 89.000 to 98.000, hydrolysis of 98–99%) was obtained from Sigma-Aldrich. PRO hydrochloride (Product #: PR140, CAS: 318-98-9) was purchased from Spectrum Chemical. Deionized water (DW) and methanol (Mt) were used to prepare all polymer solutions. All reagents were used without any pre-treatment. Human fibroblast HFF-1 cells (ATCC-SCRC-1401) were purchased from the American Type Culture Collection (ATCC), Dulbecco’s modified Eagle’s medium (DMEM) and fetal bovine serum (FBS) were from BenchMark, Gemini Bio Products, and penicillin-streptomycin was purchased from Sigma-Aldrich. TOX1 in vitro toxicology assay kit was purchased from Sigma-Aldrich and 96-well plate reader was from Thermo Scientific.

2.2 Preparation of Electrospun mats

A PVA 10% (w/w) solution was prepared by dissolving the polymer in a DW/Mt mixture (1:1) at 80°C under constant stirring until a homogeneous solution was obtained. The polymeric solution was left to rest overnight to remove bubbles. Subsequently, the solution was loaded with 10% (w/w) PRO (PRO 10) and 15% PRO (PRO 15) under stirring at room temperature.

The polymeric solutions were poured into a 3 mL syringe attached to an 8 cm metallic needle with an 18-needle gauge. A collector wrapped in aluminum foil was used for fiber collection. Afterward, the blend solution was electrospun at a 20 kV voltage and 15 cm distance collector/needle. After the electrospinning process, the resulting scaffold was folded up to 1 cm × 1 cm to minimize drug losses. In the end, scaffolds were left overnight under vacuum, for removal of the solvent residue.

2.3 SEM

The morphological appearance of the electrospun mat samples was observed with a JEOL JSM-7600F Schottky
Field Emission SEM with an acceleration voltage of 20 kV. Fiber mats were placed on a metallic plate and covered it with a gold layer using an assisted deposition. The images with a magnification of 10,000× were examined through ImageJ software for the measurement of fiber diameters, and diameter distributions as described by Ameer et al. (37).

2.4 FTIR spectroscopy

In order to chemically analyze polymeric scaffolds, FTIR spectra were recorded. The attenuated total reflectance–fourier transform infrared-Thermo Scientific Nicolet 6700 equipment was used to perform the chemical analysis, electrospun scaffolds were scanned at wavelengths between 4,000 and 400 cm⁻¹, and each measurement consisted of 32 scans.

2.5 Thermal properties (TGA, DSC)

In order to evaluate thermal stability and the degradation temperature of fibrous membranes, TGA and DSC measurements were performed on an TA instruments simultaneous differential thermogravimetric analyzer (SDT), model Q600 V20.9. Ten milligram samples of pure and blend materials were placed on a platinum pan and weight loss data were collected, in the temperature range of 20–600°C at a heating rate of 10°C.min⁻¹ in a nitrogen atmosphere. The resulting data were analyzed by the software Universal V4.5A TA Instruments.

2.6 In vitro drug entrapment efficiency

Electrospun-loaded nanofibers were carefully peeled from the aluminum foil and weighed using a digital balance. The total mass of the released drug was assessed by quantifying the cumulative PRO release from the electrospun mats, using a HACH DR 6000 UV-Vis spectrophotometer at a wavelength of 290 nm. The loaded scaffolds were immersed in 50 mL of DW at 37°C under continuous stirring for 2 h; subsequently the solutions were centrifuged for 5 min at 4,000 rpm for fiber sedimentation and filtered to remove polymer residues through Whatman® syringe filters (pore size: 0.45 µm). The cumulative drug release was calculated using Eq. 1 as suggested by Adepu et al. (38):

\[
\text{Total mass of drug release on nanofibers} \times 100 \quad (1)
\]

\[
\frac{\text{Mass of total drug added}}{\text{Mass of total drug added}}
\]

2.7 In vitro disintegration time

To determine the disintegration time, 10 mg of fibrous mats were placed on a phosphate buffer moistened membrane at pH 6.8, 37°C (aiming to mimic the moisture on the oromucosal tissue) placed on a Petri dish. The time was recorded in a continuous shooting mode with a CANON PC1304; the total disintegration was observed by visual inspection of footage, in accordance with Tonglairoum et al. (39). Experiments were conducted in triplicate.

2.8 Ex vivo mucoadhesive properties

An adhesive test was conducted, evaluating forces to detach the adhesive mats from the mucosal tissue. A Brookfield CT3 Texture Analyzer fitted with a cylindrical probe was used to carry out the test according to Khutoryanskiy (40). Rabbit small intestinal specimens were obtained from the abdominal cavity of a rabbit. Longitudinal incisions were made along a small intestinal segment to expose the mucosal tissue, subsequently were cut into small portions (6 cm). Mucosal specimens were washed with phosphate buffer solution (pH 6.8) at 37 ± 5°C. The mucosal tissue was mounted on Mucoadhesion Test Fixture TA-MA and submerged in phosphate buffer at constant stirring. Adhesive mats were attached to a cylindrical probe using a double-sided tape (Figure 1). Both parts made contact for 30 s applying a force of 1 N. Detachment force (DF) data were obtained.

2.9 MTT cytotoxicity test

HFF-1 cells were cultured in the DMEM supplemented with 15% FBS, 1% penicillin/streptomycin, 1% L-glutamine, and 1.5 g.L⁻¹ sodium bicarbonate under incubation conditions of 5% CO₂ atmosphere, 37°C, and 95% humidity. Subcultures were done each time that culture confluence reached 80%. For cell viability determination, disks of 0.3 cm² from each sample material were cut and sterilized by UV radiation for 15 min. Then, disks were soaked in 100 µL of fresh DMEM for 1 h and placed into a 96-well plate. After this, 1 x 10³ HFF-1 cells per well were seeded on the top of each disc to assure direct contact with the fibrous scaffolds. After 24 h incubation, cell viability was assessed with the TOX1 assay kit based on the MTT reagent reduction. Dimethyl sulfoxide was used as a positive control of cell viability, which induces total cell death. Cell survival
negative control was achieved by incubating the cells in DMEM. Experiments were conducted independently in triplicate. Absorbance measurement of MTT reduction was achieved with a 96-well plate reader at 570 and 690 nm. Absorbance results from the negative control (cell media) were used as 100% of cell survival, and survival percentage of each treatment was calculated with \( \% \text{growth} = \frac{AT}{AC} \times 100 \), where AT is the absorbance of treated cells, and AC is the absorbance of control cells. Experiments were performed independently in a threefold manner with internal triplicates (41).

3 Results and discussion

3.1 Morphology and porosity of nanofibrous mats

To create the electrospun scaffolds, PRO was added to the PVA base solution; subsequently, electrospinning parameters were optimized to obtain adequate features for the polymer blends, 10% and 15%. Fiber morphology and diameter distribution are illustrated in Figure 2.

Electrospinning conditions led to the production of smooth and homogenous and not beaded nanofibers in pure PVA (Figure 2a); similar findings were made by Park et al. (42). The resulting fibrous mats present a fiber diameter variation from 110 to 350 nm. SEM images prove that fiber formation is not affected by PRO incorporation into the solution (43). However, PVA/PRO fibers do not have a homogeneous fiber diameter and present an amorphous and rough appearance with some beads present due to crystalline drug on the surface of the mat, as also observed by Tonglairoum et al. (44). The fiber diameter in PRO 10 (Figure 2b) varies from 110 to 760 nm, while PRO 15 (Figure 2c) fibers exhibit the same morphology as the previous blend, but with variations in the diameter of the fibers ranging from 120 to 730 nm.

SEM images (10,000×) were used to calculate the scaffold porosity ratio, porosity, and mean diameter and are presented in Table 1. According to porosity calculations, it can be observed that the addition of PRO into the solutions increases the fiber diameter while the porosity slightly decreases; this is related to the number of wide diameter fibers predominant in the loaded mats (45).

The histograms of fiber diameter distributions show that both blends at 10% and 15% exhibited a considerable diameter variation. Meanwhile, pure PVA has a smaller variation (Figure 2b and c). The fiber population for PVA exhibited a single peak with a normal distribution (Figure 2a), consistent with the fiber uniformity observed in SEM images, while both PRO scaffolds have a more significant variation, especially PRO 15. On the other hand, SEM images prove that PRO incorporation does not affect fiber formation while fiber diameter increases (46).

3.2 FTIR analyses

FTIR analyses were carried out to verify the drug incorporation into fibrous scaffolds as well as possible interactions between its components. Figure 3 depicts the FTIR spectra of pristine materials and blends. In the pure PVA spectra (Figure 3a), a broad band at 3,281 cm\(^{-1}\) corresponding to hydroxyl groups (–OH) was observed; next to it, at 2,931 cm\(^{-1}\), a short band that could be attributed to asymmetric methylene group (–CH\(_2\)) stretching was found; and the peak at 1,633 cm\(^{-1}\) was ascribed to C=O stretching (47,48). In the pure PRO spectra (Figure 3b), two short bands at 3,272 and 2,936 cm\(^{-1}\) could be seen that were assigned to hydroxyl groups (–OH) and N–H stretching on secondary amine; a characteristic peak for aromatic ring stretching could also be seen at 1,456 and 1,401 cm\(^{-1}\); a peak at 1,103 cm\(^{-1}\) was visualized as well and linked to an aryl alkyl ether (C–O–C) stretching; likewise, the peaks at 798 and 767 cm\(^{-1}\) were associated with substituted naphthylene and C–H bond out of the plane (49,50).

Both fibrous PRO-loaded mats (Figure 3c and d) exhibit a merge of hydroxyl group bands (–OH) from PVA and PRO, which had a decreased intensity and broader than that of pure compounds at ~3,280 cm\(^{-1}\). At the same time, characteristic peaks from PRO are present in the blend electrospun material, which seem to be more
prominent at higher concentrations (indicated in red boxes) for the presence of aromatic ring and aryl alkyl ether, despite its low concentration in the scaffold, demonstrating the presence and integration of PRO on PVA fibrous scaffolds.

### 3.3 Thermal properties

After thermal data were obtained, it can be seen in the TGA curve (Figure 4b) that PRO exhibits thermal stability and there is no mass loss until approximately 200°C; it also presents a single mass loss step between 275°C and 345°C attributed to polymer degradation, showing
complete degradation at 345°C with a mass loss of 99.76% of the initial data. It was also perceived that all samples containing PVA exhibit a char residue above 450°C, as found on pure PVA mats since PVA is a semicrystalline polymer (51, 52). It is worth noticing that the PRO-loaded scaffolds started to degrade at temperatures lower than that of the pure PVA; this temperature decreases as the PRO quantity increases in the electrospun fiber mats.

Figure 4a illustrates DSC thermograms, and all electrospun scaffolds show that a first degradation stage (50–60°C) occurred due to the presence of moisture and solvent residues. On pure PVA, a sharp endothermic peak is observed at about 227°C, assigned as a melting point (Tm) which is also seen in previous reports (53). On the other hand, pure PRO powder exhibits a large and sharp endothermic peak at 165°C, which also agrees with the reported data for melting point (54). This peak is shifted to approximately 161°C on blended polymer mats. Also,
in loaded fibers, the characteristic peak of PVA is displaced 20°C to 207°C, which is attributed to an interaction between PVA and PRO. Both polymeric blends exhibit the melting temperatures from both PVA and PRO, consistent with the data reported by other authors for immiscible blends (55). Further, good thermal stability can be observed for UV and heat sterilization without affecting fiber’s morphology, molecular weight, or thermal properties of electrospun mats according to Horakova et al. (56).

3.4 In vitro drug entrapment efficiency

In vitro drug mass recovery was evaluated after 2 h degradation of the PRO-loaded polymeric mats. After dissolution, the total drug content was quantified at both concentrations; small drug amounts were expected to be lost during the process due to uncollected fibers from the electrospinning device and debris in the syringe. According to the results, the total PRO released was 89% and 88% for PRO 10 and PRO 15 dissolved scaffolds, respectively. Recovery percentage was acceptable according to Perez-Gonzalez et al. (57). Drug recovery proportions indicate an adequate erosion and degradation of the fibrous matrices, despite the possible loss of drug in the electrospinning process due to uncollected fibers and loss of solution when passing it from container to the syringe (58).

3.5 In vitro disintegration time

The polymeric scaffolds of PVA were evaluated (Figure 5), and it was observed that the unloaded scaffold disintegrated completely within 15 min, congruent with other data reported (59). Meanwhile, PRO-loaded scaffold disintegrates in 22 min, and morphological changes are depicted in Figure 5. Hence, the time lengthening can be attributed to the presence of the drug particles. Disintegration time differences can be attributed to the fiber diameter since PVA unloaded mats have a smaller fiber diameter than PRO-loaded ones, providing a greater surface area to be in contact with the moistened membrane.

3.6 Ex vivo mucoadhesive properties

Pure PVA and PVA/PRO blend materials were tested for adhesive work to find a relation between the PRO content and adhesive capacity. It has been established that by increasing the surface area of the material, the adhesive capacity is increased due to interpenetration in the mucosa; it has also been documented that fibrous matrices have this outcome (60). Figure 6 exhibit DFs, adhesive bond strengths, and mucoadhesive strengths of pure PVA and PVA/PRO electrospun scaffolds. DFs were 4.01 ± 0.8 and 3.93 ± 0.3 N for PVA and PVA/PRO, respectively. The

Figure 5: Evaluation of in vitro disintegration time.
mucoadhesive strengths were found to be 409 ± 82 g for pure PVA and 401 ± 36 g for loaded fibers; the adhesive bond strengths were 4.1 and 4.0 N·cm⁻² for PVA and PVA/PRO, respectively. These adhesive characteristics exhibited by both mats are considered as good mucoadhesive properties in accordance with Garg et al. (61). The results obtained above indicate that the PRO content does not affect the adhesive capacity of the mats; similar findings were observed by Kraisit et al. (62).

3.7 MTT cytotoxicity test

In this study, cytotoxities of PVA mats and PRO-loaded scaffolds were tested. As can be seen in Figure 7, PVA fibers with and without drugs did not display any important cytotoxicity in HFF-1 human fibroblast cells. PVA fiber showed the highest proliferation rate, even better than the unexposed cells (104%). PVA is a well-known biocompatible polymer, which does not alter the growth of several cell lines such as 3T3 mouse fibroblast (63), HFF-1 human fibroblast cells (64), Hemsc cells (65), NIH 3T fibroblast cell (66), among others. In most of the cited studies, pure PVA fibers present an unaltered proliferation rate due to the high adhesion rate in PVA fiber with cell membrane proteins, thanks to their higher hydrophilicities and smoothness of the fiber (66).

Moreover, matrix properties, such as hydrophobicity/hydrophilicity, surface morphology, mechanical strength, stiffness, molecular structure, and surface functional groups, affect the cell attachment and proliferation on scaffolds (66), which indicate that randomly distributed fibers are better for cell viability such as our scaffolds.

Huang et al. reported that the interaction between fibroblast cell membrane receptors and ligands located on the fiber surface is usually the initial step in the formation of cell-matrix adhesion. The same study claimed that in long-term cultivation (after 7 days of cultivation the fibroblast proliferation was upgraded over 50% of the unexposed cells) suggested that PVA fibers do not show any negative influence on cell proliferation (63).

In the case of PRO-loaded PVA fibers, a slight decrease in the cell proliferation was detected, where it can be observed that as the PRO concentration increases on the fibers cell survival is reduced (PRO10 97% and PRO15 83%, respectively) (Figure 7), consistent with the literature where HemSC (hemangioma stem cells) cell proliferation decreases when the PRO concentration increased (64). Notwithstanding, Wang et al. reported that PRO at low concentrations demonstrated no significant influence on cell proliferation and highest PRO concentrations led to cell death; PRO decreases the expression of β receptors, affecting the rate of apoptosis and cell cycle distribution (67). However, PRO is reported as a high safety and tolerated drug, used in clinical practice for over 40 years as a first-line oral medication for infantile hemangioma (68).

4 Conclusion

In summary, an adhesive and dissolvable PVA delivery system was fabricated, successfully incorporating a reproducible amount of PRO as a potential oromucosal delivery system for pediatric use. FTIR analysis proves the correct incorporation of the drug into the polymeric matrix. Fiber
distribution shows a variation in the fiber diameter influenced by concentrations of PRO, which increases with drug concentration under laboratory conditions. The TGA curve confirms the presence of PRO in the electrospun scaffolds and presents excellent thermal stability. After 4 h of disintegration, adhesive mats are formed and an adequate amount of PRO is released, improving the bioavailability of the drug at the delivery site; supporting this, the adhesion test shows that it is an effective mucoadhesive system. In vitro cytotoxicity test proves low or null cytotoxicity and good initial biocompatibility for all the tested fiber mats. Overall, this research suggests that electrospun PVA/PRO mats are promising alternative for PRO delivery to the oral mucosa in pediatric patients, although further “in vivo” biocompatibility studies are required.

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