

Design and Development of Electrospun Patch Platform Technology of the Delivery of Carvedilol in the Oral Mucosa

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Abstract: *Carvedilol, sold under the brand name Coreg among others, is a beta blocker medication, that may be prescribed for the treatment of high blood pressure (hypertension) and chronic heart failure with reduced ejection fraction (also known as HFrEF or systolic heart failure). Beta-blockers as a collective medication class are not recommended as routine first-line treatment of high blood pressure for all patients, due to evidence demonstrating less effective cardiovascular protection and a less favourable safety profile when compared to other classes of blood pressure-lowering medications. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery (such as oral, topical, intravenous, or intramuscular) is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Carvedilol is a therapeutic alternative on the World Health Organization's List of Essential Medicines. It is available as a generic medication.*

Keywords: Carvedilol Drug, Patch Technology, By Oral Mucosa

1. Introduction

The oral mucosa is the mucous membrane lining the inside of the mouth. It comprises stratified squamous epithelium, termed "oral epithelium", and an underlying connective tissue termed lamina propria. The oral cavity has sometimes been described as a mirror that reflects the health of the individual. Changes indicative of disease are seen as alterations in the oral mucosa lining the mouth, which can reveal systemic conditions, such as diabetes or vitamin deficiency, or the local effects of chronic tobacco or alcohol use. The oral mucosa tends to heal faster and with less scar formation compared to the skin. The underlying mechanism remains unknown, but research suggests that extracellular vesicles might be involved.

- 2) **Alveolar mucosa:** The lining between the buccal and labial mucosae. It is a brighter red, smooth, and shiny with many blood vessels, and is not connected to underlying tissue by rete pegs.
 - **Buccal mucosa**, the inside lining of the cheeks; part of the lining mucosa.
 - **Labial mucosa**, the inside lining of the lips; part of the lining mucosa.
- 3) **Masticatory mucosa:** Keratinized stratified squamous epithelium, found on the dorsum of the tongue, hard palate, and attached gingiva.
- 4) **Specialized mucosa**, specifically in the regions of the taste buds on lingual papillae on the dorsal surface of the tongue; contains nerve endings for general sensory reception and taste perception.

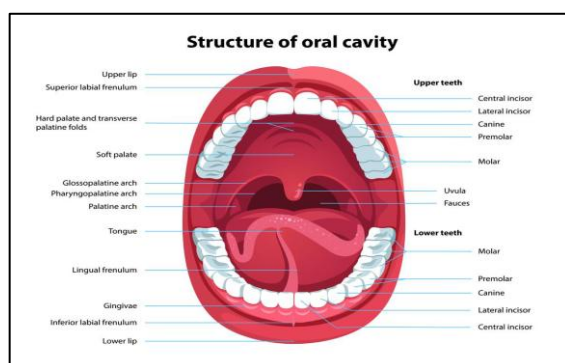


Figure: Structure of the oral mucosa

Classification:

Oral mucosa can be divided into three main categories based on function and histology:

- 1) **Lining mucosa:** Nonkeratinized stratified squamous epithelium, found almost everywhere else in the oral cavity, including the:

Structure

Schematic illustration of the layers found in keratinized oral mucosa that include a deeper lamina propria and basement membrane in-between and superficial layers of stratified squamous epithelium that include from deepest to most superficial:

- 1) Stratum Basales
- 2) Stratum Spinosum
- 3) Stratum Granulosum
- 4) Stratum Corneum

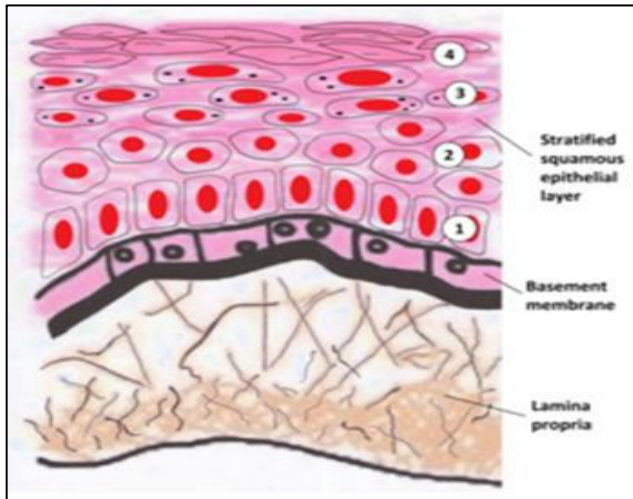


Figure: Structure of Skin Layer

Oral mucosa consists of two layers, the surface stratified squamous epithelium and the deeper lamina propria. In keratinized oral mucosa, the epithelium consists of four layers:

- Stratum basal (basal layer)
- Stratum, spinosum (prickle layer)
- Stratum granulosum (granular layer)
- Stratum corneum (keratinized layer)

In nonkeratinized epithelium, the two deep layers (basales and spinosum) remain the same but the outer layers are termed the intermediate and superficial layers.

Function:

- Mechanical stress is continuously placed on the oral environment by actions such as eating, drinking and talking.
- The mouth is also subject to sudden changes in temperature and pH meaning it must be able to adapt to change quickly.
- The mouth is the only place in the body which provides the sensation of taste.
- Due to these unique physiological features, the oral mucosa must fulfil a number of distinct functions.

Sensation:

- The oral mucosa is richly innervated, meaning it is a very good at sensing pain, touch, temperature and taste.
- A number of cranial nerves are involved in sensations in the mouth including trigeminal (V), facial (VII), glossopharyngeal (IX) and vagus (X) nerves.

Thermal regulation:

Although not significant in humans, some animals such as dogs rely on panting to regulate their temperature, as sweat glands are only present in their paws.

Clinical significance

Autoimmune

- 1) **Lichen planus:** A chronic inflammatory disease with different forms of oral presentations. The most classic appearance of lichen planus is the presence of white streaks in inner cheek, tongue, and gum.

- 2) **Graft-versus-host disease:** An autoimmune disease developed following bone marrow transplant in which its oral presentation is similar to lichen planus.
- 3) **Pemphigus vulgaris:** An autoimmune chronic disease with clinical presentation of formation of superficial and large blisters which then burst into ulcers on the skin or mucous membrane.

Traumatic

Frictional keratosis: This typically presents as white plaques on the oral mucosa due to mechanical trauma. When the cause of frictional keratosis is removed the white patch may resolve.

Sarcomas

Connective tissue malignancies, sarcomas, are rare in the oral mucosa. Osteosarcoma, chondrosarcoma arise in bone and cartilage, lymphoma in haematological disorders. The most common malignancies are carcinomas, overwhelmingly squamous cell carcinoma.

Routes of Administration:

- 1) **Buccal Mucosa (inner cheek):** Suitable for buccal administration.
- 2) **Labial Mucosa (inner lips):** Suitable for buccal drug administration.
- 3) **Sublingual Mucosa (under tongue):** Ideal for sublingual administration due to high permeability.
- 4) **Sublabial Mucosa (under lower lip):** Suitable for sublabial administration due to good vascularization.

Introduction Patch Platform Technology

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery (such as oral, topical, intravenous, or intramuscular) is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.



Figure: Microneedle Transdermal Patches

Hormonal patches:

Estrogen patches are sometimes prescribed to treat menopausal symptoms (as well as post-menopausal osteoporosis) and to transgender women as a type of hormone replacement therapy.

There Are Five Main Types of Transdermal Patches

- 1) **Single-layer drug-in-adhesive:** The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug.
- 2) **Multi-layer drug-in-adhesive:** The multi-layer drug-in-adhesive patch is similar to the single-layer system; the multi-layer system is different, however, in that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases).
- 3) **Reservoir:** Unlike the single-layer and multi-layer drug-in-adhesive systems, the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer.
- 4) **Matrix:** The matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer, partially overlaying it.

- 5) **Vapour patch:** In a vapour patch, the adhesive layer not only serves to adhere the various layers together but also to release vapour. Vapour patches release essential oils for up to 6 hours and are mainly used for decongestion.

Microneedle Patch Technology

Microneedle drug delivery

The microneedle patch (MNP) is a type of transdermal patch which retains the advantages, but reduces the disadvantages of basic transdermal patches. Embedding as many as 102–104 needles per square centimetre of patch, encapsulated or coated with intended drug, MNPs can easily pass skin tissue known as the stratum corneum which is roughly 20 μm in thickness, allowing up to the size of macromolecule to pass.

Micro-Needle Patches Drug Delivery

As mentioned earlier, MNPs deliver more efficient delivery compared to topical or oral intake. In drug delivery study,

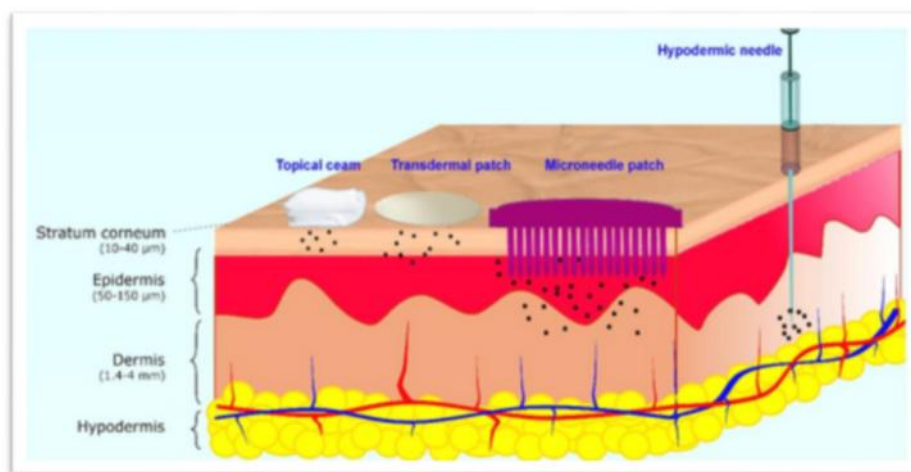


Figure: MNPs may puncture stratum corneum to deliver directly to the dermis layer

Table 1: Tissues Studied for MNPs Delivery:

Internal surface	External surface
Mouth	Skin
Gastrointestinal tract	Finger nail
Vagina	Eye
Vascular scalp	Wall
	anus

Types of Microneedle: There are many types of microneedle that are distinguished by the shape and other characteristics.

- 1) **Soluble or dissolvable MNPs:** One of the types of MNPs are water-soluble needles made out of soluble polymers or saccharide. However, dissolvable needles cannot efficiently deliver drugs to the dermal layer.
- 2) **Non-Soluble Or Dissolvable Mnp:** Other than dissolvable MNPs, needles can also be made out of metal or ceramic that will not dissolve in the body environment. These coated drug needles can deliver consistent concentration of drugs without the needles dissolving in the body.

Drug Profile and Polymers

A large proportion of new drug candidates present poor water solubility, whilst others also present a strong first-pass effect, limiting their use in potential medical therapies.

In light of this, researchers are focusing their efforts on searching for novel technologies and formulations that can aid to improve the bioavailability and solubility of these active pharmaceutical ingredients (APIs).

The delivery vehicle available for these systems are often manufactured in the form of adhesive gels, particulates, tablets, and more commonly as patches or films [5] which are mainly prepared by solvent casting, hot melt, and nanotechnology-based approaches, such as electrospinning.

2. Materials and Methods

1) Materials

S. No	Materials and Chemicals	Company Name
1.	Carvedilol (CVD)	J.K. Chemicals Pvt. Ltd. Valsad Gujrat, India.
2.	(PCL, Mw 80,000 Da)	Maoyi Industrial Pvt. Ltd. Mumbai, India
3.	Poly(DL-lactide) (PDLA 2.0 dl/g)	A.B. Enterprises Pvt. Ltd. Mumbai, India
4.	poly(3-hydroxybutyrate) (PHB P226, Mw 426,000 Da)	OLL Chem. Inc. Ahmadabad, Gujrat, india.
5.	Polyethylene oxide (PEO, Mw 200,000 Da)	Aritech Chemazon Pvt. Ltd. Haryana, India.
6.	polyvinylpyrrolidone (PVP)	Marinal Chemtech, Pvt. Ltd. New Delhi, India
7.	ethyl cellulose (EC, viscosity 22 cP, 5% in toluene/ethanol 80:20)	Panchmurat Chemicals Pvt. Ltd. Mumbai, India.
8.		Krishna Solvents, Pvt. Ltd. Hyderabad, India. JV Chemicals Pvt. Ltd. Bangaluru, India.
9.	Chloroform (ACS reagent, ≥99.8%)	Vibhor Chemicals Industries Pvt. Ltd. Kanpur, India.
10.	whilst methanol, ethanol (≥99%)	Stanlee India Petro Chem Pvt. Ltd. New Delhi, India
11.	acetone (≥98%)	Alpha Chemicals Pvt. Ltd. Mumbai, India.
12.	2,2,2-trifluoroethanol (TFE, ≥99%)	AB Enterprises Pvt. Ltd. Mumbai, India
13.	N,N,-dimethylformamide (DMF, ≥99.8%)	Gunjal Enterprises Pvt. Ltd. Ankeleswar, Gujrat, India.
14.	Electrospun Mat	Ceratattva Innotech Pvt. Ltd. Tamilnaidu, India.

2) Methods & Evaluation

Sample Fabrication:

a) Electrospinning and Cast Film Preparation:

For the electrospun mats, the electrospinning process was carried out in a high throughput Fluidnatek™ LE-100 equipped with a multi-emitter injector system from Ceratattva Innotech Pvt. Ltd. Tamilnaidu, India and an air-conditioned unit.

Table 2: Electrospinning parameters of polymeric solutions with and without CVD. V+ indicates voltage on the injector and V- indicates voltage on the collector

Sample	Polymer Matrix	Flow Rate (mL/h)	Voltage V+/V- (kV)	Needle-to Collector Distance (cm)
PCL	-	20	20/-20	30
PCL/CVD	PCL			
PHB	-	20	20/-5	25
PHB/CVD	PHB			
PDLA	-	15	20/-20	30
PDLA/CVD	PDLA			
Backnig layer	PCL	20	15/-2	15
Mucodhesive layer	PEO/PVP/EC	26	30/-20	28

To prepare the cast films loaded with CVD, the solutions were poured at a specific volume into glass Petri dishes and left to dry under controlled humidity and temperature overnight (20 °C and 40% R.H.).

b) Three-Layer Patch Fabrication:

To prepare the mucoadhesive patch, a three-layer patch structure was prepared using a conceptual design previously developed in our research group. The mucoadhesive layer made of PEO/PVP/EC and PHB with and without CVD electrospun fibers were first electrospun continuously layer by layer.

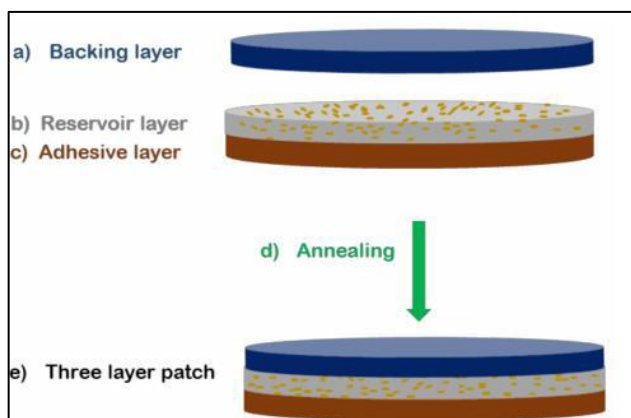


Figure: Diagram of multilayer drug delivery approach composed of PCL backing layer (blue),

Characterization

1) Fiber Morphology

The fiber morphology was analyzed by scanning electron microscopy (SEM) using a Thermoscientific Phenom XL with an electron beam acceleration of 5 kV.

Wide-Angle X-ray Scattering (WAXS):- Wide-angle X-ray scattering measurements were performed using a Bruker AXS D4 Endeavor diffractometer.

2) In Vitro Drug Release

Drug release was evaluated using an ultraviolet/visible spectrophotometer DINKO UV4000 (Barcelona, Spain). For this, membranes containing $157.23 \pm 0.01 \mu\text{g}/\text{cm}^2$ of CVD Nanomaterials 2022, 12, 438 6 of 16 were used. The release of CVD-loaded electrospun fibers into the medium was monitored by measuring the absorbance at 240 nm at predetermined times.

Evaluation of Transdermal Patches

The developed patches were evaluated by performing following tests

- 1) **Thickness:** Screw gauze was used for the determination of thickness of 10 selected patches.
- 2) **Uniformity of weight:** Uniformity of weight was calculated by weighing the patches on digital balance.
- 3) **Moisture content:** For moisture content, desiccator with fused calcium chloride was used.

- 4) **Moisture uptake:** For maintaining the 84% Humidity in desiccator, Potassium Chloride solution was placed in Desiccator.

Pharmacokinetic evaluation of patches on animals

Only 230 to 250 g weight of rats were selected and shaving on dorsal side was done. Rats were kept under observation before application of the transdermal patches to avoid any unwanted effect of shaving. Rats were kept completely fasted in this period of time. Three groups were prepared.

Group I was administered with drug Carvedilol orally (5 mg/kg), Group II was administered F6 formulation and group III was administered F7 formulation. The blood samples were taken out at various time intervals i. e. 2, 4 8 and 24 h. vials at -70°C. The drug plasma concentration was measured by reverse phase HPLC method.

Chromolith column was used (column length: 100 X 4.6 mm, 2 mm), flow rate was 1.5 ml/min, Methanol: Acetonitrile: Phosphate buffer pH 3.0 (45:25:30 v/v) was used as a mobile

phase. Injection of sample volume was 10 mL. and retention time was 5.5 min.

3. Results and Discussion

Physicochemical Solution Properties

It is well known that the physicochemical properties of polymer solutions play an important role in electrospinning processability and therefore in the final fiber morphology of the material. Additives such as surfactants, other polymers, and active ingredients can also affect the properties of the solution, modifying the processability of electrospinning.

Thus, the viscosity, surface tension, and conductivity of the solutions with and without CVD were measured and summarized in Table 3. Both viscosity and conductivity values increased with the addition of CVD, which could be due, on one hand, to the presence of more solid content in the solution and, on the other hand, to the presence of the ionic form

Table 3: Characterization of the prepared CVD and polymeric solutions in terms of conductivity ($\mu\text{S}/\text{cm}$), surface tension (mN/m), and viscosity (Cp)

Sample id	Polymer matrix	Polymer /api ratio (w/w)	Conductivity ($\mu\text{S}/\text{cm}$)	Viscosity (Cp)	Surface Tension (mN/m)
PCL	PCL	-	0.14 ± 0.01	328.5 8.3	46.7 4.9
PCL/CVD	-	90/10	0.59 0.10	346.3-7.4	30.1 2.0
PHB	PHB	-	10.80 0.20	369.4 16.7	47.2 1.9
PHB/CVD	-	90/10	33.68 0.80	410.4 6.3	25.7 0.6
PDLA	PDLA	-	0.36 0.01	46.3 3.3	31.2 1.3
PDLA/CVD	-	90/10	0.41 0.02	66.6 4.1	24.0 0.5

Fiber Morphology:

The CVD-loaded electrospun fibers prepared with different polyesters were analyzed by SEM (see Figure 2). The pristine PCL and PCL/CVD fibers presented a visible difference in morphology, with the pristine PCL fibers presenting large

porous beads across the fibrous material. The addition of CVD into electrospun PCL fibers resulted in uniform and smooth fibers, which may indicate that the presence of CVD promoted the elimination of beads, most likely due to a slight increase in viscosity and conductivity.

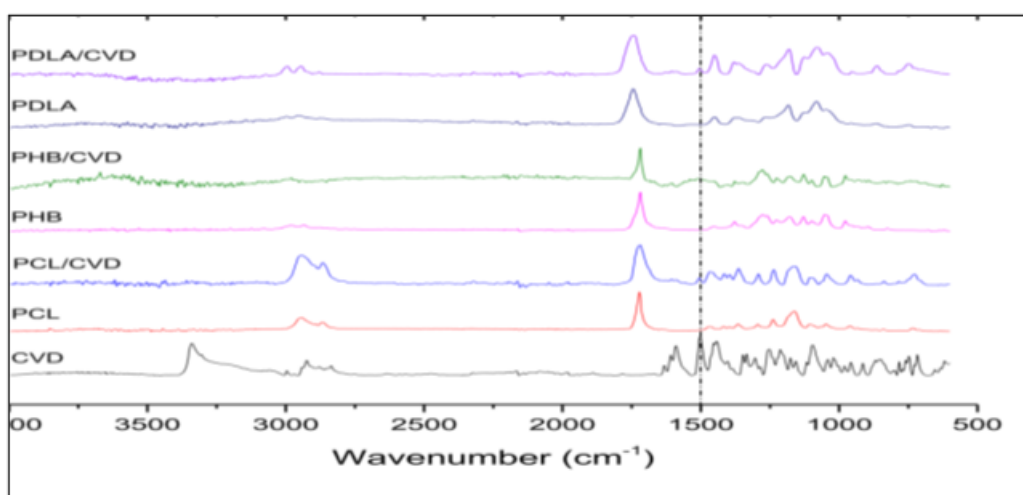


Figure: ATR-FTIR spectra of samples with different polymer matrices (PCL; PCL/CVD, PHB, PHB/CVD, PDLA; PDLA/CVD) and commercial CVD. For comparison, the C=C stretching bond in the aromatic ring of CVD has been highlighted with a dashed-dotted line.

Thermal Analysis (DSC)

Differential scanning calorimetry (DSC) was used to analyze the physical state of the drug and polymer in the electrospun fibers. Figure 4 shows the DSC data of the different electrospun polyesters with and without CVD as well as the thermal run for the commercial CVD. The thermogram of

CVD showed an endothermic peak around 116.2 C with a DHm of 98.10 J/g, revealing its crystalline nature. Additionally, differences in the polymer melting point were observed for the electrospun biopolymers in the presence of CVD. In the case of the pristine PCL and PCL/CVD fibers, there was a melting temperature (T_m) of 53.90.

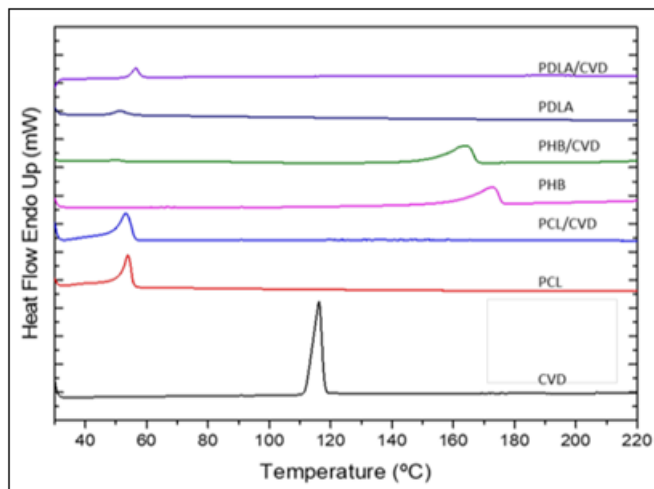


Figure: DSC thermograms of different polymer matrices with and without CVD (PCL; PCL/CVD; PHB, PHB/CVD; PDLA; PDLA/CVD) and the commercial CVD powder

In Vitro CVD Release Rate from Monolayers:

The theoretical CVD loading was set to 10 wt% in this study obtaining a ratio of 90:10 polymer:(API) in the fiber. To quantify the attained CVD loading present in the fibers, the samples were fully dissolved and measured by UV-Vis spectroscopy. The results indicated that the CVD loading in the fibers was 9.41 0.32% for PCL-CVD-loaded fibers, 10.45 0.39% for PHB fibers, and 10.11 0.54% for PDLA fibers.

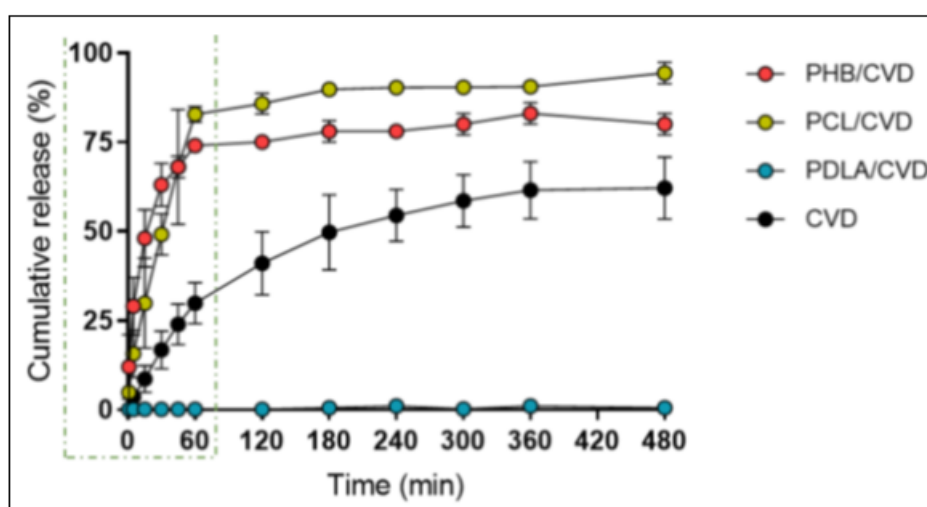


Figure (A) CVD release profiles from fibers PCL/CVD, PHB/CVD, PDLA/CVD, and from commercial CVD

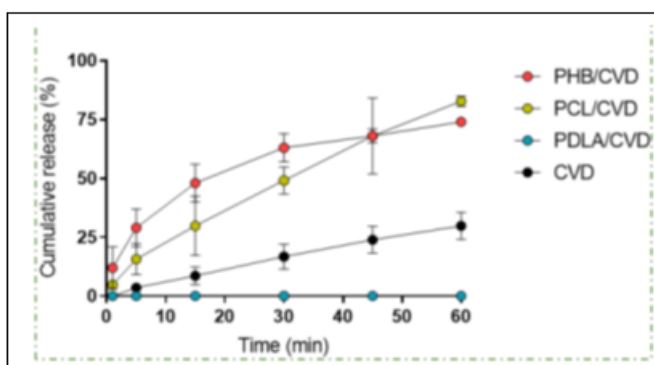


Figure (B): CVD release within the first hour. Graphs are presented as the mean S.D. (n = 3)

4. Conclusion

The work herein presented demonstrates the feasibility of using the nanofiber fabrication electrospinning technique as a solubility enhancer technology for poorly water-soluble drugs. Various biopolymers, such as PCL, PHB, and PDLA were fabricated to generate electrospun active monolayers to deliver directly to the oral mucosa poorly water-soluble drugs like CVD. The amorphous physical state of the encapsulated drug was confirmed by DSC and WAXS, whilst the ATR-

FTIR spectrum confirmed that CVD was compatible with the different biopolymers used.

Results of the drug release kinetics from the electrospun biopolymer monolayers suggested an enhancement in the release rate of CVD compared to the actual dissolution kinetics of the commercial pure CVD, except for the slow-releasing PDLA. Electrospun monolayers of PCL and PHB were also seen to release at a faster pace than their solvent cast counterparts. From these results, a multilayer patch approach with CVD-loaded PHB was selected and designed.

The obtained results indicate that electrospinning is further confirmed as a very promising technology to generate drug delivery platforms made of ultrathin fibers for poorly water-soluble drugs.

References

- [1] Nanci (2013). Ten Cate's Oral Histology. Elsevier. p. 280. Oral Manifestations of Systemic Diseases at eMedicine Squier, Christopher A.; Kremer, Mary J. (2001).

- [2] 2."Biology of Oral Mucosa and Esophagus". Journal of the National Cancer Institute. Monographs. 2001 (29): 7–15.
- [3] Mak, Karen (2009). "Scarless healing of oral mucosa is characterized by faster resolution of inflammation and control of myofibroblast action compared to skin wounds in the red Duroc pig model". Journal of Dermatological Science. 56 (3): 168–180.
- [4] Sjöqvist, Sebastian (2019). "Exosomes derived from clinical-grade oral mucosal epithelial cell sheets promote wound healing". Journal of Extracellular Vesicles. 8 (1) 1565264.
- [5] Chandra (1 January 2004). Textbook of Dental and Oral Histology and Embryology with MCQs. Jaypee Brothers Publishers. pp. 180–. ISBN 978-81-8061-238-1.
- [6] Lee, Jeong Woo; Prausnitz, Mark R. (May 7, 2018). "Drug delivery using microneedle patches: not just for skin". Expert Opinion on Drug Delivery. 15 (6): 541–543.
- [7] Li, Junwei; Zeng, Mingtao; Shan, Hu; Tong, Chunyi (August 23, 2017). "Microneedle Patches as Drug and Vaccine Delivery Platform". Current Medicinal Chemistry. 24 (22): 2413–2422.
- [8] Nachum Z, Shupak A, Gordon CR (2006). "Transdermal scopolamine for prevention of motion sickness: clinical pharmacokinetics45 (6): 543–66. \
- [9] Berner B, John VA (February 1994). "Pharmacokinetic characterisation of transdermal delivery systems". Clinical Pharmacokinetics. 26 (2): 121–34.
- [10] ADUBA JUNIOR., Donald C. et al. Semi-interpenetrating network (sIPN) gelatin nanofiber scaffolds for oral mucosal drug delivery. Acta Biomaterialia, v. 9, n. 5, p. 6576–6584, 2013.
- [11] ALAZAB, Mohamed et al. Sustainable Electrospinning of Nanoscale Fibres. Procedia Manufacturing, v. 12, p. 66-78, 2017.
- [12] AL-HAZEEM, Nabeel Zabar Abed. Nanofibersand Electrospinning Method. In: KYZAS, George Z. (ed.). Novel Nanomaterials: Synthesis and Applications. London: IntechOpen, 2018. chapter. 11.
- [13] ALKAHTANI, Manal E. et al. Fabrication and characterization of fast-dissolving films containing escitalopram/quetiapine for the treatment of major depressive disorder. Pharmaceutics, v. 13, n. 6, p. 891,2021.
- [14] Larrañeta, Eneko; Donnelly, Ryan F. (November 13, 2019). "Design andDevelopment of Liquid Drug Reservoirs for Microneedle Delivery of Poorly Soluble Drug Molecules". Pharmaceutics. 11 (11): 605.
- [15] Perioli, L.; Ambroggi, V.; Rubini, D.; Giovagnoli, S.; Ricci, M.; Blasi, P.; Rossi, C. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. J. Control. Release 2004, 95, 521–533.