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Bilayer chitosan-based patches for clobetasol transmucosal drug delivery in the oral cavity

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INTRODUCTION

Clobetasol proprionate (CP) is the most potent steroid currently available in the market, used only for dermatological application because of the very high lipophilicity (1). CP is also the standard of care for chronic, immune cell-mediated and autoimmune diseases of the oral cavity (1), where the environment is even more challenging because of the presence of salivary flow and muscular activity during speech and swallowing (2).

To date, a CP galenic preparation in form of gel is usually prescribed for oral lesions (2), but the ideal delivery system is still lacking and demanding.

AIM

- Development of chitosan (CS)-based, muco-adhesive, bilayer porous patches, electrophoretic deposition (EPD) in presence of ethanol solvent, for the topical delivery of CP
- Preclinical evaluation of the patches

METHOD

EPD of CS-CP bilayer patches: CP was used in 30% water + 70% ethanol bath (pH = 4.8, [CS MMW] = 1g L^{-1}, [CP] = 1g L^{-1}). Processing conditions were optimized to obtain CS/CP patches on Titanium plates (Ti, grade 2): square waves (100-75 V / Dc= 0.17 t= 5 min). The deposited patches (2x2 cm^2) were freeze-dried and stored at RT. CS bilayer patches were obtained by double step deposition: a first deposition starting from a solution containing only CS was performed and, after drying, a second layer was deposited starting from a CS solution with or without CP, namely CS-CP and CS respectively.

Morphological surface analysis: optical microscope and SEM analyses.

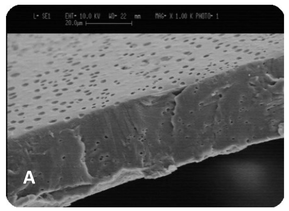
Swelling properties as percentage of water uptake: immersion of patches in 1 ml of Phosphate Buffer Solution (PBS) (pH=7.4) at room temperature.

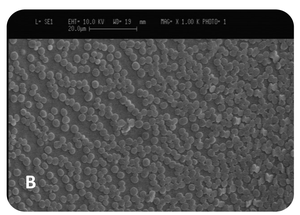
CP loading and release: liquid chromatography mass spectrometry (LC-MS).

Tissue-engineered oral mucosal model: oral mucosal models were obtained as previously described (3).

RESULTS

Morphological surface analysis: SEM images (Fig. 1A-C) showed patches with a homogeneous and defined porous structure. The two deposited layers were indistinguishable and stable also after immersion in PBS.





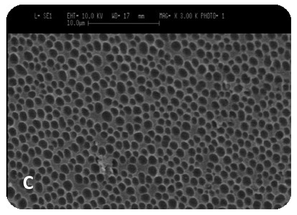


Fig.1A-B *Presence of amorphous CP on the CS-CP patch surface.* ***Fig.1C*** *The amorphous amorphous CP dissolved after washing the samples with PBS/ethanol solution, exposing the surface with a random microporosity.*

Swelling properties: The swelling data, in PBS (pH=7.4), of CS patches with and without CP are shown in Fig. 2A and 2B. Swelling tests revealed an absorption rate for CS and CS-CP samples of 346 ± 0.37% and 302 ± 0.81% respectively, as achieved after 3 hours from immersion.

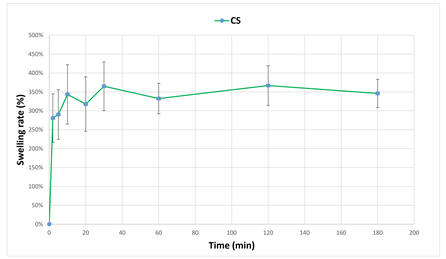


Fig.2A *Swelling of EPD bilayer Chitosan (CS) patch*

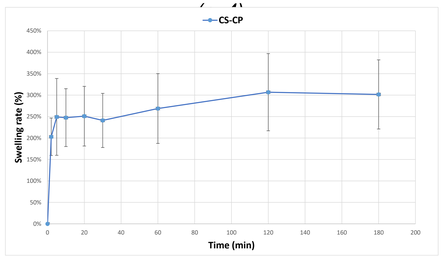


Fig.2B *Swelling of EPD bilayer Chitosan-Clobetasol (CS-CP) patch (n=8)*

CP loading and release: The LC-MS data showed that CP was successfully loaded at a concentration of 96.6 ±12.4 µg/mL. Fig.3 describes the releasing profile from CS-CP patches. The amount of drug released was about 40 µg/mL/patch, as achieved after 20 min.

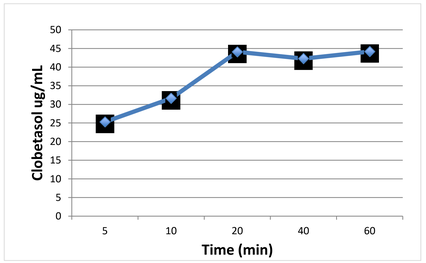


Fig.3 *Clobetasol release from CS-CP patches*

Tissue-engineered oral mucosal model for testing drug absorption and patch adhesion: the 3D model was successfully reproduced by coupling the cultivation of fibroblast and keratinocytes into dedicated tissue culture inserts. The reconstructed model displays both the basal fibroblast lower layer as well as the upper keratinized layer (Fig. 4).

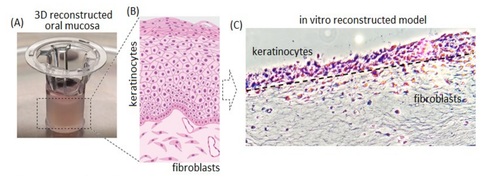


Fig.4A-C Tissue-engineered oral mucosal 3D model*. The histological examination shows both the basal fibroblast lower layer as well as the upper keratinized layer.*

CONCLUSIONS

- Bilayer CH-based patches can be successfully loaded in double layer using a highly lipophilic drug as CP, and regarded as a promising drug delivery system for the oral mucosa.
- The swelling properties, pivotal for mucoadhesion, and the drug release during time are confirmed.
- We developed a tissue engineered model of oral mucosa for further testing the patches in terms of cytotoxicity and drug permeation.

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