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In-vitro characterization of buccal iontophoresis: the case of sumatriptan succinate

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ABSTRACT

Buccal administration of sumatriptan succinate might be an interesting alternative to the present administration routes, due to its non-invasiveness and rapid onset of action, but because of its low permeability, a permeation enhancement strategy is required. The aim of this work was then to study, *in-vitro*, buccal iontophoresis of sumatriptan succinate.

Permeation experiments were performed *in-vitro* across pig esophageal epithelium, a recently proposed model of human buccal mucosa, using vertical diffusion cells. The iontophoretic behavior of the tissue was characterized by measuring its isoelectric point (Na^+ transport number and the electroosmotic flow of acetaminophen determination) and by evaluating tissue integrity after current application.

The results obtained confirm the usefulness of pig esophageal epithelium as an *in-vitro* model membrane for buccal drug delivery. The application of iontophoresis increased sumatriptan transport, proportionally to the current density applied, without tissue damage: electrotransport was the predominant mechanism.

Integrating the results of the present work with literature data on the transport of other molecules across the buccal mucosa and across the skin, we can draw a general conclusion: the difference in passive transport across buccal mucosa and across the skin is influenced by permeant lipophilicity and by the penetration pathway.

Finally, buccal iontophoretic administration of sumatriptan allows to administer 6 mg of the drug in 1 h, representing a promising alternative to the current administration routes.

1. Introduction

Sumatriptan succinate is a 5-HT1 receptor agonist, currently used for the treatment of migraine. It is usually administered orally, but for patients with nausea or vomiting, current treatment guidelines recommend the use of non-oral formulations, such as nasal (Pierce et al., 2013). Additionally a quick onset of the therapeutic effect is required, because the efficacy of the treatment is much higher if the drug is administered immediately after the attack (Femenia-Font et al., 2005b).

A sumatriptan nasal formulation is commercially available for the systemic noninvasive administration of the drug, although its bioavailability is low, approximately 15%, and the maximum plasma concentration is reached after 60–90 min (Femenia-Font et al., 2005b).

The transdermal administration of sumatriptan has also been deeply investigated, in particular with the application of iontophoresis, to achieve a sufficiently rapid effect: the molecule is positively charged at physiological pH values, so anodal iontophoresis can be used (Vrbata et al., 2013). This research led to the approval by the FDA, in 2013, of the first transdermal single use iontophoretic patch containing sumatriptan (Zecuity®, NuPathe Inc. Conshohocken, USA) for the treatment of acute migraine in adults. It delivers 6.5 mg of the drug over a 4 h period, a time period still quite long to treat an acute migraine attack.

The buccal route might be an interesting alternative, due to its non-invasiveness and rapid onset of action. In fact, the buccal mucosa is a potential site for systemic drug administration with distinct advantages over more traditional routes. Among others, its non-invasiveness and accessibility, the possibility to bypass the

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first pass effect and the GI degradation, the rapid drug uptake and improved patient's compliance.

Recently, the sublingual administration of sumatriptan was explored, through the development of orodispersible formulations (Tayel et al., 2016a, 2016b). When tested *in-vivo* in comparison with the reference oral formulation Imitrex®, the sublingual film (Tayel et al., 2016a) showed comparable C_{max} and AUC values, but a significantly shorter t_{max} (15 min *vs* 2 h); however, this t_{max} difference was not present when the sublingual tablet was used (2 h *vs* 2.5 h) (Tayel et al., 2016b). One of the drawback of sublingual dosage forms is the rapid removal of the drug from the sublingual area by the saliva, leading to a short residence time in the oral cavity. On the contrary, the buccal mucosa (cheek or gingival areas) is less subject to washout by the saliva and can therefore guarantee a longer contact time.

The major limitations of buccal administration are the relatively small absorption area and the barrier properties of the tissue, both reducing the amount of drug that can be absorbed. Preliminary studies on sumatriptan buccal delivery showed that the drug exhibits low permeability across buccal mucosa (Shidhaye et al., 2008; Vrbata et al., 2013), suggesting that a chemical or physical permeation enhancer is required. The most common physical enhancement method to improve drug transport across biological membranes is iontophoresis, a technique that has been shown to improve the buccal delivery of atenolol HCl (Jacobsen, 2001), lidocaine HCl, nicotine and diltiazem HCl (Hu et al., 2011b), ondansetron (Hu et al., 2011a) and some macromolecules (Patel et al., 2013a, 2013b). Owing to the positive results obtained with the application of iontophoresis to sumatriptan transdermal administration, iontophoresis appears to be a promising approach to improve sumatriptan permeation across the buccal mucosa.

In general, iontophoresis enhances drug delivery across a biological membrane by two main mechanisms, electrorepulsion and electroosmosis. The former is strictly related to the charge of the permeant, while the latter is a convective solvent flow caused by ion movement when an electric field is applied across a charged porous membrane. The relative importance of the two mechanisms depends on the physicochemical and electrical properties of the membrane and the permeant (Guy et al., 2000). Molecules with high charge density (ratio between charge and molecular weight) are transported primarily by electrorepulsion, while neutral or low charge density molecules are less sensitive to the direct effect of the electric field (Pikal, 2001). Electroosmosis is a solvent flow that results from the net negative charge that some biological membranes, such as the skin, support at physiological pH (Burnette and Ongipattanakul, 1987). The application of an electrical potential gradient across a charged membrane produces a convective solvent flow in the direction of the counter-ion transport (Guy et al., 2000): if the membrane is negatively charged (such are most of biological barriers) it assists the transport from anode to cathode and the membrane itself is defined permselective.

Porcine buccal mucosa is frequently used as model barrier of human mucosa because of their similarity in terms of structure, biochemistry and permeability (Shojaei, 1998). However, even though the availability of porcine tissue is higher than that of human tissue, it is often damaged by mastication and difficult to isolate from the underlying muscular tissue (Diaz del Consuelo et al., 2005c). Porcine esophageal mucosa has been proposed as an alternative permeability barrier: its structure and lipid composition are similar to that of the buccal tissue (Diaz del Consuelo et al., 2005b, 2005c), its isolation from the underlying tissues is simpler, its surface is larger and its integrity is guaranteed. Moreover, the proposed model has been used in comparative permeability studies involving fentanyl (Diaz del Consuelo et al., 2005a, 2007), carbamazepine, triamcinolone acetonide (Caon and Simoes, 2011) and nicotine (Kanjanabat and Pongjanyakul, 2011; Kanjanakawinkul et al., 2013; Pongjanyakul and Suksri, 2009) and gave satisfactory results.

The permselectivity of porcine buccal tissue has already been determined (Moscicka-Studzinska et al., 2009) but the same information is not available for esophageal epithelium. Thus, the aim of this work was to study the buccal iontophoretic transport. Because pig esophageal epithelium is a relatively new and only partially characterized model, a specific objective of this work was the determination of the isoelectric point of pig esophageal epithelium by measuring Na^+ transport number and the electroosmotic flow of acetaminophen. For the same reason, the integrity of tissue after current application was evaluated.

For comparison purposes, the permeability of a model drug (lidocaine hydrochloride), in passive and iontophoretic conditions, was determined and compared with that obtained across pig buccal mucosa. Finally, the iontophoretic transport of sumatriptan succinate was characterized in termed of current density dependence.

2. Experimental

2.1. Materials

Acetaminophen (AAP) was from ACEF (Fiorenzuola d'Arda, I). Sumatriptan succinate was a kind gift of GlaxoSmithKline Manifacturing SpA (S. Polo di Torrile, I). Lidocaine hydrochloride was a gift of Lisapharma SpA (Erba, I), HEPES, 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid, was from Sigma-Aldrich (St. Louis, MO, USA).

All other reagents were of analytical grade.

2.2. Tissue sample preparation

Pig esophageal epithelium was prepared according to (Diaz del Consuelo et al., 2005c). The esophageal mucosa was separated from the outer muscle layer with a scalpel and the epithelium was peeled off from the connective tissue after immersion in distilled water at 60 °C for 60 s. Samples obtained were frozen until use, that occurred within 3 months.

2.3. Measurement of the sodium transport number (t_{Na+})

The sodium transport number was determined using horizontal diffusion cells with permeation area of 0.2 cm^2 (Nicoli et al., 2003) and pig esophageal epithelium as barrier. The chamber facing the luminal side of the epithelium was filled with 4 ml of NaCl 0.1 M while the solution bathing the basal side of the tissue was NaCl 1 M (4 ml). Both solutions were prepared using 25 mM HEPES as buffer, and the pH was adjusted to the desired value using NaOH 0.1 M or HCl 0.1 M. Ag/AgCl electrodes, connected to a digital multimeter, were introduced into the chambers and after a period of equilibration, the potential value was registered. This value was corrected by subtracting the electrode potential to obtain the membrane potential.

The t_{Na+} was calculated from membrane potential using the following equation:

$$t_{Na+} = 0.5 + (FV_m/2\ RT\ ln(C_1 - C_2)) \quad (1)$$

where F is the Faraday's constant (C/mol), C_1 is the NaCl concentration (M) at the basal side of the epithelium, C_2 the NaCl concentration (M) at the luminal side of the epithelium, R is the universal gas constant (J/mol K), T is the absolute temperature (K) and V_m is the membrane potential (mV).