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Research paper

Release of naltrexone on buccal mucosa: Permeation studies, histological aspects and matrix system design

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Abstract

Transbuccal drug delivery has got several well-known advantages especially with respect to peroral way. Since a major limitation in buccal drug delivery could be the low permeability of the epithelium, the aptitude of NLX to penetrate the mucosal barrier was assessed. *Ex vivo* permeation across porcine buccal mucosa 800 μm thick was investigated using Franz type diffusion cells and compared with in vitro data previously obtained by reconstituted human oral epithelium 100 μm thick. Both fluxes (Js) and permeability coefficients (K_p) are in accordance, using either buffer solution simulating saliva or natural human saliva. Permeation was evaluated also in presence of chemical enhancers or iontophoresis. No significant differences in penetration rate were observed using chemical enhancers; in contrast, Js and K_p were extensively affected by application of electric fields. Tablets, designed for Naltrexone hydrochloride (NLX) administration on buccal mucosa, were developed and prepared by direct compression of drug loaded (56%) poly-octylcyanocrylate (poly-OCA) matrices. NLX is slowly discharged from buccal tablets following Higuchian kinetic. Histologically, no signs of flogosis ascribable to NLX and/or poly-OCA were observed, while cytoarchitectural changes due to iontophoresis were detected. Buccal tablets containing NLX may represent a potential alternative dosage form in addiction management.

Keywords: Transbuccal permeation; Porcine buccal mucosa; Iontophoresis; Naltrexone hydrochloride; Poly-octylcyanoacrylate matrices; Buccal tablets

1. Introduction

Buccal administration of drugs is a valid alternative to the peroral one since drugs directly diffuse into the systemic circulation. In particular, it is advantageous for those drugs that encounter degradation in the gastrointestinal tract or severe hepatic first-pass metabolism and require the administration of large doses to reach effective therapeutic levels in the target site [1,2]. Among the epithelial tissues, the buccal mucosa offers good performance for local/systemic pharmacological actions because of its permeability. Buccal drug delivery specifically refers to the delivery of drugs within/through buccal mucosa [3]. Buccal administration could be an alternative, non-invasive delivery route also for Naltrexone hydrochloride (NLX).

In formerly opioid dependent patients who have undergone detoxification, NLX is often used to assist relapse prevention also called ''Narcotic Antagonist Treatment Using Naltrexone'' [4]. Clinical pharmacology studies demonstrated that oral NLX at 50, 100 and 150 mg effectively blocks the physiological and subjective effects of parenterally administered heroin, hydromorphone or morphine for 24, 48 and 72 h, respectively [5]. It has been reported that the maintenance of blood NLX concentrations of at least 1 ng mL^{-1} provides prevention of overdoses for

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approximately 3 months [4,5]. A reduced number of opioid overdoses were also observed 7–12 months post treatment [6,7]. Recently, NLX has been approved also for alcoholism treatment, to stop the alcohol cravings during early days of abstinence from alcohol [8].

Usually, NLX is taken *per os* as conventional capsules or tablets either daily or three times a week for a sustained period of time and, as it is not addicting, itself has no subjective effects or potential for abuse. Following peroral administration, NLX is rapidly and quite completely absorbed (about 96%) from the gastrointestinal tract but the drug undergoes a significant first-pass effect [9]. Thus hepatic metabolism (>98% metabolized) will result in having a very low drug concentration in the brain [10].

Although peroral NLX is effective in treating alcohol and opiate dependencies, fluctuating plasma levels and a variety of adverse reactions to the medication limit its efficacy [11–13]. By delivering efficiently the drug through buccal mucosa the hepatic first-pass metabolism should be reduced; as a consequence, low drug doses could be administered and side effects minimized.

In this study we developed a new formulation of tablets suitable for the administration of NLX on buccal mucosa. Since a major limitation in the development of a buccal drug delivery device could be the low permeability of the buccal mucosa, the aptitude of NLX to penetrate the barrier was preliminarily evaluated.

To assess drug permeability, buccal mucosa from various animals (rabbits, dogs, monkeys, hamsters and pigs) as well as cultured tissues like reconstituted human oral epithelium have been used as models for human mucosa. However, when compared to the other animal models, porcine buccal mucosa has been considered the most representative model for human tissue as it is non-keratinised like human buccal mucosa [14].

Similar to other mucosal membrane, the buccal mucosa has disadvantages as well. Low drug bioavailability due to low mucosal membrane permeability, relatively small surface area available for absorption and poor retention of the drug and/or drug formulation at the site of absorption are the major limitations. These restrictions could be successfully altered using chemical penetration enhancers [15]. As NLX is a hydrophilic molecule, electrically charged at physiological pH ($pK_a = 8.1$ at 37 °C) also iontophoresis could be used to promote movement through the mucosal membrane [16,17].

Using reconstituted human oral epithelium, as *in vitro* model, we demonstrated that NLX well permeates the membrane [18]. Nevertheless, the cultured tissue is about 100 μm thick, whereas the epithelium of the human buccal mucosa is 500–800 μm thick [19,20]. Accordingly, our previous data on NLX permeation through reconstituted human oral epithelium [18] need further validation on a more thick tissue.

In this paper the aptitude of NLX to penetrate porcine buccal mucosa and reach therapeutical steady-state plasma concentrations following buccal administration is reported. The NLX diffusional behaviour through porcine mucosa is compared with that observed through the cultured tissue model [18].

Since the drug, the formulation components and the electric field could damage the structure of the biological tissue, we studied also the effects of their application on histology of porcine buccal mucosa.

2. Materials and methods

2.1. Materials

Naltrexone hydrochloride (NLX), USP grade, was purchased from Sun Pharmaceutical Industries LTD (Cujart, India) and 2-octylcyanoacrylate (2-OCA) from GluStich Inc. (Delta, Canada). Sodium dehydrocholate (NaDHC), EDTA disodium salt (NaEDTA) and trisodium citrate dihydrate (TNaC) were from Polichimica s.r.l. (Bologna, Italy). As simulated non-enzymatic plasma a phosphate buffered saline (PBS) Ca^{2+} and Mg^{2+} free solution, pH 7.4, was used. It was prepared by dissolving KH_2PO_4 (0.144 g), anhydrous Na_2HPO_4 (0.795 g) and NaCl (9.0 g) in 1 L of distilled water [18]. Buffer solution simulating saliva (pH 6.8) was prepared by dissolving NaCl (0.126 g), KCl (0.964 g), KSCN (0.189 g), KH_2PO_4 (0.655 g), and urea (0.200 g) in 1 L of distilled water [21]. All components of buffer solutions were from Sigma–Aldrich (Milano, Italy). Natural human saliva (pH 6.8) was obtained from a healthy donor without any conditioning habits i.e. smoking, alcohol, coffee drinking or any other further habit able to alter its composition.

Unstimulated mixed saliva was collected from one of the authors who, after overnight fasting, first brushed his teeth and thoroughly rinsed the mouth using only deionized water, then sat in a relaxed position with the head in a slightly-inclined forward position, allowing saliva to accumulate on the floor of the mouth. The first few millilitres of saliva were discarded. The accumulated saliva was then withdrawn using disposable sterile plastic pipettes until about 1.5 mL had been collected. The samples of saliva were not further handled to evaluate the drug behaviour in environmental conditions similar to those of the administration site.

All chemicals and solvents were of analytical grade and were used without further purification. All other reagents for cell culture were obtained from Sigma and solutions were prepared in endotoxin-free water.

2.2. Methods

2.2.1. Ex vivo permeation of NLX throughout porcine buccal mucosa

Mucosal specimens were obtained from tissue removed from the vestibular area of retromolar trigone of freshly slaughtered domestic pigs. After sampling, all specimens were immediately placed in a refrigerated transport box and transferred to laboratory within 1 h. Excesses of