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A preliminary study for the development and optimization by experimental design of an in vitro method for prediction of drug buccal absorption

Paola Mura, Serena Orlandini, Marzia Cirri, Francesca Maestrelli*, Natascia Mennini, Giada Casella, Sandra Furlanetto

Department of Chemistry, School of Human Health Sciences, Univ. of Florence, Italy

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Cholesterol CAS 57-88-5
L-α-Phosphatidylcholine CAS 8002-43-5
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ABSTRACT

The work was aimed at developing an in vitro method able to provide rapid and reliable evaluation of drug absorption through buccal mucosa. Absorption simulator apparatus endowed with an artificial membrane was purposely developed by experimental design. The apparent permeation coefficient (P_{app}) through excised porcine buccal mucosa of naproxen, selected as model drug, was the target value to obtain with the artificial membrane. The multivariate approach enabled systematic evaluation of the effect on the response (P_{app}) of simultaneous variations of the variables (kind of lipid components for support impregnation and relative amounts). A screening phase followed by a response-surface study allowed optimization of the lipid-mixture composition to obtain the desired P_{app} value, and definition of a design space where all mixture components combinations fulfilled the desired target at a fixed probability level. The method offers a useful tool for a quick screening in the early stages of drug discovery and/or in preformulation studies, improving efficiency and chance of success in the development of buccal delivery systems. Further studies with other model drugs are planned to confirm the buccal absorption predictive capacity of the developed membrane.

1. Introduction

Transmucosal buccal drug delivery has received increasing attention over the past two decades, considering the many advantages it offers over the classic oral route. In fact, in addition to being easily accessible, non-invasive, painless and very well accepted by patients, it provides a milder environment in terms of pH and enzyme activity and allows direct access to systemic circulation, avoiding pre-systemic elimination in the gastrointestinal tract and hepatic first-pass metabolism (Shojaei, 1998; Madhav et al., 2009; Patel et al., 2011). Moreover, the oral mucosa presents additional advantages such as rich vascularization, rapid cellular recovery, easy removal, if necessary, of the dosage form, and wide versatility in use in a broad range of therapies, being suitable for both local or systemic drug administration, and offering the possibility of both a rapid onset time, and/or a prolonged release, depending on the formulation design and on the site of application. In fact, the permeability of the oral mucosa decreases in the order sublingual > buccal > palatal and gingival (Madhav et al., 2009; Zhang et al., 2002). The least permeable keratinized areas of gingiva and hard palate are preferred when a local in situ delivery is desired. The most permeable area of sublingual mucosa is instead generally exploited in the treatment of acute disorders requiring a fast onset of action (Squier, 1991). However, its surface is constantly being washed by saliva and subjected to tongue activity, making it difficult to keep the dosage forms in prolonged contact with the mucosa. As a result, the relatively immobile buccal mucosa constitutes a more adequate site for the common retentive systems used for oral transmucosal drug delivery, and its relatively lower permeability is more suitable for formulations intended for sustained release action (Madhav et al., 2009).

The extensive research and continuous advances in drug delivery technology are progressively increasing the variety of drugs that can be delivered across the oral mucosa for the treatment of systemic diseases, including biological agents such as peptides, protein, genes and antibodies (Hearnden et al., 2012; Sattar et al., 2014).

Therefore, considering the increasing potential applications of this administration route, particularly for paediatric and geriatric patients, and the challenging in development of effective buccal dosage forms, there is a need for reliable in vitro methods allowing a rapid assessment of oral mucosa permeability of candidate drugs, and evaluation and optimization of their release from the delivery systems.

In fact, in addition to the poor drug permeability through the buccal

Abbreviations: NAP, naproxen; CHOL, cholesterol; PC, L-α-phosphatidylcholine; OCT, octanol; PHOS, phospholipid; SS, simulated saliva

* Corresponding author at: Department of Chemistry, Via Ugo Schiff 6, 0019 Sesto Fiorentino (Firenze), Italy.
E-mail address: francesca.maestrelli@unifi.it (F. Maestrelli).

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mucosa (Sattar et al., 2014; Campisi et al., 2010), the lack of such methods could be a further reason for the low number of oral transmucosal formulations successfully reaching the market.

The efficiency of buccal delivery is commonly evaluated in vitro by diffusion studies across freshly excised animal mucosa, being the porcine buccal mucosa the most frequently used, due to its greater resemblance with the human mucosa (Patel et al., 2012; Ceschel et al., 2002; Semalty et al., 2010; Figueiras et al., 2009). However, the use of animal mucosa has several drawbacks, including ethical issues, lack of full resemblance with human mucosa, difficult and time-consuming preparation, handling, and maintenance of freshly excised tissues, possibility of tissue damages, difficult of easy availability of mucosal tissues and, high sample to sample biological variability even within the same species (depending on age, sex, race, etc), with consequent poor reproducibility in permeation resultsWHO Dermal Absorption (WHO Dermal Absorption, 2006; Simon et al., 2016). These problems make the use of biological mucosa difficult for rapidly testing large numbers of drugs or drug formulations.

Alternatively, the use of buccal epithelial cell cultures has been proposed for a more accurate simulation of the human mucosa (Nicolazzo et al., 2008). Among the different cultured epithelial membranes proposed, the more commonly used is the TR146 cell line, originating from a human buccal carcinoma, eventually combined with an external layer of mucin and glycerol added to the epithelium surface (Nielsen, 2000; Teubl et al., 2013; Holm et al., 2013).

Such models may be very useful in assessing drug buccal permeability and metabolism and in studying the drug transport mechanisms at cellular or sub-cellular level. However, their use as a high throughput screening approach is limited by high costs associated with cell cultures, long cell growth cycles, possible risks of microbial contamination, and rather high inter-experimental and inter-laboratory variability (Teubl et al., 2013; Holm et al., 2013).

In vitro methods based on the use of artificial membranes as substitutes of the excised animal mucosa could represent an interesting alternative to both the above methods, in virtue of their greater simplicity, lower costs, shorter times of experiments and better reproducibility of results. In fact, considering that most of drugs are mainly absorbed by passive transport (Di et al., 2012), artificial membranes mimicking passive diffusion could provide a quick and reliable high throughput tool for assessing buccal drug absorption potential before in vivo studies (Obradovic et al., 2008; Khdair et al., 2013).

In this light, the purpose of this work was the setting up of an in vitro method for drug buccal absorption assessment, based on the use of an absorption simulator apparatus endowed with an artificial membrane specifically developed, able to provide a rapid and reliable prediction and evaluation of buccal drug absorption and overcome the problems and limitations associated with other currently used techniques. This method is mainly intended to provide aid in the development of new buccal delivery systems, allowing a rapid in vitro screening of their performance before clinical trials, and therefore reducing time and development costs; moreover it could also be used to evaluate the performance of marketed products which have been subjected to changes in components supplier, formulation or manufacturing, avoiding the need to perform new extensive studies for their approval (FDA, 1997; FDA, 2014).

Naproxen, a BCS Class II non-steroidal anti-inflammatory drug, was selected as model in this preliminary study, since its transport across biological membranes primarily occurs by passive transcellular diffusion (Lennernaas, 1998). The drug apparent permeation coefficient determined using freshly excised porcine buccal mucosa, was considered as the target value to be obtained with the artificial membrane. An experimental design methodology, based on an initial screening phase followed by a response surface study, was used to optimize the composition of the lipid mixture used for support impregnation, in order to achieve the desired target within a prefixed confidence interval. The multivariate approach allows a systematic evaluation of the effect of several variables on the selected response. The simultaneous variations of all the considered variables is performed according to experimental matrices, where the columns report the factors' values and the rows report the values that each factor has to assume in each experiment, i.e. the rows represent the experiments. In this way it is possible to calculate a regression model linking the considered factors to responses. Among the main advantages of this approach there are the possibility of detecting interactions between factors, to obtain a map of the variation of the response throughout the experimental domain and to consider simultaneously several responses. Experimental design represents a fundamental tool of Quality by Design approach, which is recommended by the recent International Conference on Harmonization Guidelines (ICH Harmonised Tripartite Guideline, 2009), and it enables the definition of the design space. The design space is represented by the multidimensional zone where the combination of the selected variables fulfills the required value for the response at a fixed probability level.

2. Materials and methods

2.1. Materials

Naproxen 98% ((S)-(+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid) (NAP), Cholesterol 99% (CHOL), potassium phosphate monobasic 99%, di-sodium hydrogen phosphate dodecahydrate 99%, Sodium chloride 99% and L-α-Phosphatidylcholine from egg yolk, 99% (PC) were from Sigma-Aldrich Chemie GmbH, Germany; Lipoid® E80 (obtained from egg yolk lecithin and containing 82% of phosphatidylcholine and 9% of phosphatidylethanolamine) was kindly donated by Lipoid GMBH (Ludwigshafen, Germany). (n)-Octanol 99% (OCT) was from Merck (Italy). Cellulose acetate-nitrate membrane pore size 0.025 µm and 0.22 µm, cellulose acetate membrane pore size 0.1 µm kindly supplied by Merck Millipore (Italy), cellulose acetate membrane pore size 0.2 µm donated by Sartorius Italia S.p.a. (Italy), cellulose nitrate and polyamide membrane pore size 0.2 µm gifted by Whatman were tested as inert support. Simulated saliva (SS) was prepared by dissolving 2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8 g NaCl in 1 L of distilled water, and pH adjusted at 6.75 (Mashru et al., 2005, Gohel et al., 2009). A pH 7.4 phosphate buffer solution (PBS) composed by 0.8 g/L Na_2HPO4, 0.15 g/L KH2PO4 and 9 g/L NaCl, was used as simulated plasma. The solvents used in high performance liquid chromatography (HPLC) procedures were of HPLC grade. All other reagents were of analytical grade.

2.2. HPLC assay of naproxen (NAP)

HPLC assay of NAP was carried out by a Merck Hitachi Elite Lachrom apparatus (Darmstadt, Germany) equipped with aL-2400 UV–vis spectrophotometric detector and a L-2130 isocratic pump. A Hibar Purospher® STAR RP-18E column (5 µm particle size; 150 mm × 4.6 mm) (Merck Hitachi (Darmstadt, Germany) was used as stationary phase. The mobile phase consisted of a mixture of 0.02 M phosphate buffer (adjusted to pH 3 with phosphoric acid), acetonitrile and methanol in a 40:10:50 (v/v) ratio and it was run through the column at a flow rate of 1 ml min^{-1}. UV detection was set at 230 nm. The injection volume was 20 µl and the column temperature 25 °C. The retention time of NAP under these experimental conditions was 7 min. A calibration curve in the 0.1–2.5 mg/l concentration range was prepared. The limit of detection (LOD) and the limit of quantification (LOQ) of the HPLC method represented the lowest amount of analyte which can be detected and the lowest amount of analyte which can be quantitatively determined with suitable precision and accuracy. LOD and LOQ values, determined as the concentration values that resulted in a signal-to-noise ratio of 3:1 and 10:1, were 0.02 mg/l and 0.07 mg/l, respectively

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