

# Galantamine Delivery on Buccal Mucosa: Permeation Enhancement and Design of Matrix Tablets

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## Abstract

The most important feature in transbuccal drug delivery is the low drug passage through the buccal mucosa. In our previous work we demonstrated the aptitude of Galantamine to penetrate the buccal tissue. The collected data suggested that Galantamine passively crosses the membrane, but the calculated  $J_s$  and  $K_p$  values showed that the drug amount that crosses the membrane wasn't sufficient to assure blood therapeutic level. So, in this study, *ex vivo* permeation tests, using porcine buccal mucosa, were performed in presence of physical or chemical enhancers. No significant differences in penetration rate were observed using chemical enhancers as sodium dehydrocholate, EDTA disodium salt and trisodium citrate dihydrate; while,  $J_s$  and  $K_p$  were extensively affected by application of electric fields. Tablets, designed for Galantamine administration on buccal mucosa, were prepared by direct compression of drug loaded Eudragit<sup>®</sup> RS 100 matrices. When the tablets were coated with lipophilic material, Galantamine is slowly discharged from buccal tablets, following the Higuchian kinetic. Buccal tablets containing Galantamine may represent a potential alternative dosage form in Alzheimer management.

## Introduction

During the last two decades, transepithelial routes have been widely investigated by pharmaceutical researchers as alternative routes of delivery. Along with the various transepithelial sites available, the oral mucosa is the most convenient and accessible and, also, allows drug delivery for both local and systemic therapies (Giannola et al., 2008).

The buccal mucosa is generally well-accepted site for delivering systemically acting drugs mainly for the treatment of chronic diseases (Giannola et al., 2008; Giannola et al., 2007a; Giannola et al., 2007b).

Buccal administration could be an alternative, non-invasive delivery route also for Galantamine, widely used for treatment of Alzheimer's disease (AD).

AD is characterized by progressive decline in memory with impairment of at least one other cognitive function (Coyle and Kershaw, 2001; Heinrich and Teoh, 2004; Farlow, 2001). Galantamine is an allosteric potentiating ligand because it acts at a site on nicotinic acetylcholine (ACh) receptors (nAChR) that is different from the ACh-binding site. Galantamine appears to

enhance both pre- and post-synaptic nAChR function by making these receptors more sensitive to available ACh.

At present, Galantamine is available in the market as either tablets or oral solutions, and two daily oral administrations are required (Heinrich and Teoh, 2004; Migliaccio-Walle et al., 2003; Raskind et al., 2000; Erkinjuntti, 2002). Even if oral administration is convenient for most patients, some drawbacks have been described. In particular, effects of Galantamine on motor and evacuative functions when in contact with intestinal tissue have been experienced both *in vivo* and *in vitro*. Among the advantages of transmucosal delivery are the potential to avoid dose-limiting GI-mediated side effects such as nausea and vomiting, the most common adverse events leading to discontinuation of treatment. (Kays Leonard et al., 2007).

For these reasons, buccal administration of Galantamine could be helpful for the success of the therapy. The therapeutic efficacy of a drug administered by transbuccal route, following its application on this mucosa, mainly depends on its ability to penetrate the tissue fast enough to provide the required plasma concentrations, thus resulting in the desired pharmacological activity. In particular, given that the most important determinant of buccal delivery is the degree of permeability of the mucosa, in our previous work we demonstrated the aptitude of Galantamine to penetrate the buccal tissue. The collected data suggested that buccal mucosa does not block galantamine diffusion and the drug passively crosses the membrane (De Caro et al., 2008). However, taking into account the pharmacokinetic parameters of Galantamine (Clarke's, 2004) and the  $J_s$  and  $K_p$  values determined we calculated that these values are not sufficient to assure blood therapeutic level for Galantamine and the use of penetration enhancers was needed.

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.

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These restrictions could be successfully altered by using chemical promoters or physical enhancement method (Starokadomsky and Dubey, 2006; Williams and Barry, 2004). Chemical enhancers act mainly by transiently altering the permeability characteristics of the outer layer which forms the rate-limiting lipophilic barrier to absorption (Nicolazzo et al., 2005), whereas iontophoresis provides a physical mechanism to enhance the penetration of hydrophilic and charged molecules across the epithelial stratum by applying an electric fields (Kalia et al., 2004).

So, in this work preliminary we reported the study of Galantamine permeation enhancement by electric field or chemicals additives, using porcine buccal mucosa as membrane and Franz type diffusion cells as permeation model.

Many buccal dosage forms have been developed including toothpastes, mouthwashes, lozenges, gels, ointments, wafers, microparticles, chewing gums, lollipops, films, patches, tablets and some specialized devices. Conventional dosage forms exhibit some drawbacks; for example, the low bioavailability as a result of the washing effect of saliva and mechanical stresses.

Unconventional dosage forms allow control of the buccal environment, optimization of drug permeation and governance of the drug dissolution rate. Formulations able to prolong the drug residence time on the absorptive tissue offer great advantages in promoting transmucosal delivery for systemic therapies (Mundargi et al., 2007; Ciper and Bodmeier, 2006). Recent research on polymers has led to the development of several buccal delivery systems able to maintain a steady release of drug in the systemic circulation (Sudhakar et al., 2006; Diaz del Consuelo et al., 2007; Bruschi and de Freitas, 2005; Owens et al., 2005). Thanks to the lack of the transient spikes in drug concentration typical of daily multiple-dose regimens, these delivery systems decrease the risks of toxic side-effects. For efficient and prolonged release of drugs, these delivery systems must be in close contact with the mucosal membrane, which results in high concentration in a local area and high drug flux through the mucosa (Perioli et al., 2007; Prego et al., 2005).

In this study, we developed new formulations of tablets suitable for the administration of Galantamine on buccal mucosa.

## Materials and Method

### Materials

Galantamine hydrobromide (Galantamine), USP grade, was purchased from Biodar (Yavne, Israele), lauric acid from Sigma-Aldrich (Milano, Italia), glyceryl monostearate, sodium dehydrocholate (NaDHC), EDTA disodium salt (NaEDTA) and trisodium citrate dihydrate (TNaC) were from Polichimica s.r.l. (Bologna, Italy). Eudragit® RS-100 was kindly supplied by Rofarma s.r.l. (Gaggiano-Milano, Italy). Glyceryl tristearate was synthesized as previously described (Giannola and De Caro, 1997).

Phosphate buffered saline (PBS) Ca<sup>2+</sup> and Mg<sup>2+</sup> free solution, pH 7.4, was prepared by dissolving KH<sub>2</sub>PO<sub>4</sub> (0.144 g), anhydrous Na<sub>2</sub>HPO<sub>4</sub> (0.795 g) and NaCl (9.0 g) in 1 litre of distilled water.

Simulated saliva was prepared using a buffer solution (pH 6.8) containing NaCl (0.126 g), KCl (0.964 g) KSCN (0.189 g), KH<sub>2</sub>PO<sub>4</sub> (0.655 g), and urea (0.200 g) in 1 litre of distilled water

(Sudhakar et al., 2006). All components of buffer solutions were purchased from Sigma-Aldrich (Milano, Italy).

Unstimulated mixed saliva was collected from one of the Authors, 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 for cell culture were prepared in endotoxin-free water.

## Methods

### Ex vivo permeation studies

**Permeation of Galantamine throughout porcine buccal epithelium in presence of chemical enhancers:** The permeation kinetic throughout the porcine buccal mucosa was evaluated using Franz type diffusion cells. Mucosal specimens (kindly supplied by Pig Farm, Pioppo, Palermo) were obtained from tissue removed from two freshly slaughtered domestic pigs. After sampling, all specimens were immediately placed in a refrigerated transport box and transferred to the laboratory within 1h. Excesses of connective and adipose tissue were trimmed away until 0.8 ± 0.1 mm thick slides were obtained. Some specimens were used fresh; the remaining specimens were stored at -40°C for periods up to six months. The frozen specimens were equilibrated in PBS, (pH 7.4) for 1 h at room temperature to thaw completely prior to the start of experiments. To avoid damage of the epithelial surface, the mucosal samples were carefully cut to obtain suitable disks. These sections of mucosa were then mounted in the flow-through cell. Tissue disks were equilibrated for 1 h at 37 ± 0.5°C [Polimix EH 2 bath equipped with a constant-rate adjustable stirrer RECO® S5 (Kinematica, Switzerland)] adding PBS in both the donor and the acceptor compartment. This step was followed by the removal of PBS from the compartments.

In the donor compartment was then placed 1.0 ml of a solution of simulated saliva or natural human saliva containing 3 mg of Galantamine and 0.3 mg of chemical enhancer (NaDHC, NaEDTA, or TNaC). In the acceptor compartment was placed PBS (26 ml) and the temperature of equipment was maintained at 37 ± 0.5°C. At regular time intervals (30 min), samples were withdrawn (0.5 ml) from the acceptor compartment. To avoid saturation phenomena and maintain the "sink" conditions, the sample volume taken out was replaced by fresh fluid. Each experiment was carried out for six hours. Results are reported as means ± SD of six different experiments in which fractions of the same portion of tissue were used (P < 0.05).

The Galantamine transferred from the donor to the acceptor compartment was monitored spectrophotometrically (see Section 2.2.5.1).

The integrity of the mucosal tissue was monitored after each

permeability study as described before (De Caro et al., 2008).

**Iontophoretic permeation of Galantamine throughout porcine buccal epithelium:** In the donor chamber of the equipment described in Section 2.2.1.1 a silver electrode (active electrode) was placed for anode; in the acceptor chamber a silver chloride-coated silver electrode (reference electrode) was applied for cathode. Prior to chloridation, the silver electrode was dipped in distilled water, ethanol, fuming nitric acid and finally washed with distilled water. The electrode was then treated with 0.1 N HCl and a current of 1 mA was applied for 24 h using silver as cathode (Jacobsen, 2001). The distance between the electrodes and membrane was 5 mm. Current densities of 0.5, 1 and 2 mA/cm<sup>2</sup> (expressed per unit of crossing area of tissue) were applied to observe the effect of iontophoresis on permeation rate. Experiments were carried out in continuous current. In the donor chamber was placed 1.0 ml of a solution containing 3 mg of Galantamine in simulated saliva or natural human saliva. Withdrawals of samples were made as described in Section 2.2.1.1. Each experiment was carried out for six hours. Results are reported as means  $\pm$  SD of six different experiments in which fractions of the same portion of tissue were used ( $P < 0.05$ ).

The Galantamine transferred from the donor to the acceptor compartment was monitored spectrophotometrically (see Section 2.2.5.1).

The integrity of the mucosal tissue was monitored after each permeability study as described before (De Caro et al., 2008).

#### Preparation of drug loaded matrices

Solid dispersions (matrices) were prepared by the solvent evaporation method. Galantamine (0.125 g) was powdered, passed through a 100  $\mu$ m standard mesh wire stainless steel sieve and put in a porcelain mortar. To the powder the appropriate amount of Eudragit<sup>®</sup> RS-100 (0.125 g) was added. To the blend was added acetone (10 ml) to obtain a workable combination. The whole mixture was stirred with the pestle to obtain a uniform creamy mass. Grinding/mixing was continued until complete solvent evaporation has occurred. The residual mass was air-dried at room temperature for 24 h, and stored as free flowing material. The amount of Galantamine entrapped into the matrix was determined spectrophotometrically as described in section 2.2.5.2. The average drug content in the matrix was 48.8 % w/w.

#### Preparation of tablets

Before compression, the matrix (100 mg) was passed through a 100  $\mu$ m standard stainless steel sieve and mixed with glyceryl tristearate (25 mg). Tablets (13 mm diameter, 1.33 cm<sup>2</sup> surface and 1.10 mm thickness, weighing 125 mg) were obtained by direct compression (PerkinElmer IR Accessory, hydraulic, single die, Tableting Machine) (10 tons for 30 s) of the mixture using two flat-faced punches and a die.

Some batches of tablets were after that coated with lauric acid, glyceryl tristearate or glyceryl monostearate using the press-coating method and the same tableting machine (Janugade et al., 2009). Briefly, accurately weighed amounts (3 mg) of coating material were transferred in the die to make a powder bed; then the core tablet was placed manually at the center. An equivalent amount of barrier mixture was added into the die, and the content

was compressed at a pressure of 10 tons.

The coating material represents the 4.6% (w/w) of the final weight of tablet.

#### In vitro drug release from tablets

The drug release from tablets was assessed using a flow through system (HSG-IMIT, Villingen-Schwenningen, Germany) (Giannola et al., 2005). Briefly, the system consists of a buffer solution simulating saliva container (100 ml) from which liquid is forced to a release cell (volume 0.17 cm<sup>3</sup>). The flow rate of saliva was controlled by a peristaltic pump (Biorad econo pump, USA) and maintained constant (1.2 ml/h) during the experiments. In the cell, the salivary film wetting the pill is about 0.1 mm thick. During the flow through, saliva wets the drug loaded tablet embedded inside the cell. The wetted tablet releases the drug enriching saliva in Galantamine content. The temperature was controlled by submerging the cell and the saliva container in a thermostatted bath ( $37 \pm 0.5^\circ\text{C}$ ). The drug amount in the taken out saliva solution was quantitatively determined spectrophotometrically (see section 2.2.5.3.). Experiments were performed on six different batches and mean results were reported. The residual drug content in the tablets after release studies was determined for selected samples. The amount of drug released and the residual drug content matched the original drug content within 2-8%.

#### Drug assay

**Drug assay in permeation studies:** The cumulative amount of drug permeated through porcine buccal mucosa was calculated from the Galantamine concentration in the acceptor medium and plotted as a function of time. Each experiment was performed six times using six different samples of porcine buccal mucosa. Each data point on the plot represents the mean of the recorded values ( $P < 0.05$ ).

In all experiments the Galantamine transferred from the donor to the acceptor compartment was monitored spectrophotometrically (UV/VIS Shimadzu mod. 1700 Pharmaspec instrument) by measuring the drug that reached the acceptor fluid using the appropriate calibration curve and blank ( $\lambda_{\text{max}} = 288.2 \text{ nm}$ ,  $E_{1\%} = 0.0840$  in PBS, pH 7.4).

The UV absorption peak was highly reproducible and linearly related to concentration over a range 0.001-0.4 mg/ml. At testing concentrations, acceptor medium components used do not interfere significantly with the UV absorption of Galantamine. At testing concentrations, buffer components and used chemical enhancers do not interfere significantly with the drug UV absorption. The sensibility was less than 0.0001 mg/ml. Intraday and interday variations, observed during collection of experimental data, were lower than sensibility.

#### Drug content into the matrix

Aliquots of randomly selected matrices of each batch were accurately weighed ( $10.00 \pm 2.00 \text{ mg}$ ), transferred into 50 ml flask, sonicated and brought to volume with acetonitrile to solubilize both the drug and the polymer. Galantamine was quantified spectrophotometrically using the appropriate blank and calibration curve ( $\lambda_{\text{max}} = 291.0 \text{ nm}$ ,  $E_{1\%} = 0.0890$  in acetonitrile). The UV absorption peak was highly reproducible and linearly related to concentration over a range 0.001-0.4 mg/ml. At the

concentrations used, dissolved Eudragit® RS 100 does not interfere with the UV absorption of Galantamine.

### Drug assay in release studies

The drug released from the tablets in simulated saliva was quantitatively determined by UV spectrophotometric analysis at  $\lambda = 288.0$  nm using the appropriate blank and calibration curve ( $E_{1\%} = 0.0866$  in simulated saliva). The UV absorption peak was highly reproducible and linearly related to concentration over a range 0.001-0.4 mg/ml. At testing concentrations, buffer components do not interfere significantly with the UV absorption of Galantamine.

### Data analysis

The flux values ( $J_s$ ) across the membranes were calculated at the steady state per unit area by linear regression analysis of permeation data following the relationship:

$$J_s = \frac{Q_r}{A t} (\text{mg cm}^{-2} \text{ h}^{-1}) \quad (1)$$

where:  $Q_r$  is the quantity of galantamine which passes through the tissue into the receptor compartment (mg),  $A$  is the active cross-sectional area available for diffusion ( $\text{cm}^2$ ) and  $t$  is the time of exposure (h).

The permeability coefficient ( $K_p$ ) was then calculated by the relationship:

$$K_p = \frac{J_s}{C_d} (\text{cm h}^{-1}) \quad (2)$$

where:  $J_s$  is the flux calculated at the steady state ( $\text{mg cm}^{-2} \text{ h}^{-1}$ ),  $C_d$  is the drug concentration in the donor compartment ( $\text{mg cm}^{-3}$ ) (De Caro et al., 2008).

Flux and permeability coefficient values, obtained as average value of six replicated experiments, were reported with the standard deviations. All differences were statistically evaluated by the Student's  $t$ -test with the minimum levels of significance with  $P \leq 0.05$ .

All release data were elaborated according to (Vergnaud, 1993; Korsmeyer et al., 1983; Peppas and Sahlin, 1989) equations using Curve Expert program version 1.3. Linear or non-linear least squares fitting methods were used to determine the optimum values for the parameters present in each equation. Fittings were validated using  $\chi^2$  test and analysis of residuals.

### Results and Discussion

The most important limitation in the development of a buccal drug delivery device could be the low drug passage through the buccal mucosa, so we reported in previous work the aptitude of Galantamine penetrate the barrier using two permeation models. We measured drug fluxes and permeability coefficients of Galantamine throughout reconstituted human oral epithelium and domestic pig mucosa, in condition of simple diffusion process. No significant differences were observed using artificial saliva or natural human saliva as donor medium. Taking into account the different thickness of the two membrane models used, the data collected by *in vitro* and *ex vivo* experiments were in agreement and suggested that buccal mucosa does not block diffusion of Galantamine (De Caro et al., 2008).

Constant blood levels can be achieved when the rate of drug entry in the systemic circulation is equal to the rate of drug disappearance from the blood. As the drug declining is a first order process, its rate is equal to the product of the steady state concentration (maintenance dose) with the first order rate constant of elimination ( $K_e$ ) which can be calculated by the biological half-life of the drug. In other words:

Drug input rate = Drug output rate = Steady state concentration  $\times K_e$  where  $K_e = 0.693/t_{1/2}$ .

Taking into account the pharmacokinetic parameters of Galantamine ( $t_{1/2}$  in healthy man is about 7-8 h, clearance  $200 \text{ ml min}^{-1}$ , volume of distribution about 175 L and the concentration range is between 29-97 ng/ml and 42-137 ng/ml (Clarke's, 2004), we considered a therapeutic average blood concentration at steady state of 33.55 ng/ml and we predicted that at least  $2.9 \text{ ng ml}^{-1} \text{ h}^{-1}$  of Galantamine should permeate throughout the buccal mucosa to maintain the steady state levels. As the steady state flux ( $J_s$ ) across the porcine buccal mucosa was experienced as  $0.127 \pm 0.010 \text{ mg/cm}^2 \text{ h}$  (De Caro et al., 2008) and considering the distribution volume, we calculated that  $1 \text{ cm}^2$  of mucosal tissue is able to absorb  $0.73 \text{ ng ml}^{-1} \text{ h}^{-1}$ . As this value is not sufficient to assure blood therapeutic level for Galantamine, the use of penetration enhancers was needed.

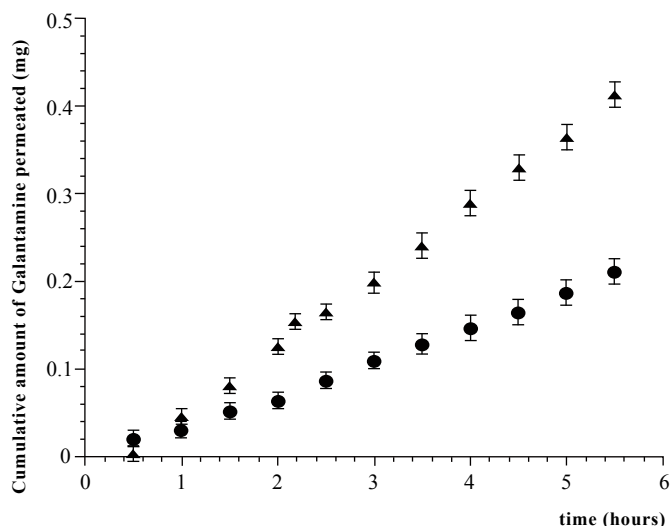
In this study, the enhancing effects of co-administration of chemical penetration enhancers, from different classes, on buccal penetration of Galantamine were investigated. Among different classes of penetration promoters, we chose sodium dehydrocholate (NaDHC), EDTA disodium salt (NaEDTA) and trisodium citrate dihydrate (TNaC): no significant modifications were observed in permeation rate of Galantamine through the porcine buccal mucosa, using both artificial and natural human saliva as donor medium. The chosen enhancers of the three classes gave the same results.

This result was probably due to physico-chemical properties of Galantamine hydrobromide that, prevailing at  $\text{pH} = 6.8$  the ionized form, could prefer the aqueous pathway as penetration route.

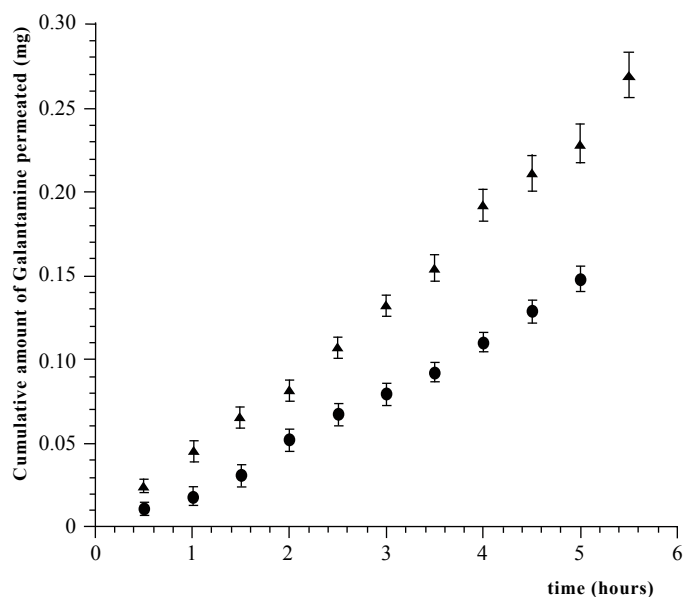
The application of electric field provides a physical mechanism to enhance the penetration of hydrophilic and charged molecules across the epithelial stratum (Kalia et al., 2004; Attia et al., 2004). The physico-chemical properties of Galantamine make this drug a suitable compound for iontophoretic movement through biological membranes. Since current density over  $2 \text{ mA/cm}^2$  causes severe cytophatic effects (Giannola et al., 2007b) we investigated the Galantamine permeation in presence of a current density of 0.5, 1.0 and  $2.0 \text{ mA/cm}^2$ .

The application of a current density of  $0.5 \text{ mA/cm}^2$  was not sufficient to appreciably enhance permeation, whereas a current density of  $1.0 \text{ mA/cm}^2$  or more determined a good improvement. Flux may be divided into the contributions of passage through the lipid matrix and through aqueous pores of the mucosal membrane (Kontturi and Murtomaki, 1996); iontophoresis enhances only the aqueous pathway. Accordingly, we attributed the permeability improvement to the increase of Galantamine movements in the membrane aqueous domain.

Figure 1 and Figure 2 show the amount of drug permeated *versus* time under iontophoresis with constant current of  $1.0 \text{ mA}$ /



**Figure 1:** Plot of cumulative amount of Galantamine permeated across porcine buccal mucosa under application of electric field *versus* time (● 1 mA/cm<sup>2</sup>; ▲ 2 mA/cm<sup>2</sup>), using buffer solution simulating saliva as donor medium and PBS simulating plasma as receptor phase. Values are presented as means ± SD (n = 6).



**Figure 2:** Plot of cumulative amount of Galantamine permeated across porcine buccal mucosa under application of electric field *versus* time (● 1 mA/cm<sup>2</sup>; ▲ 2 mA/cm<sup>2</sup>), using natural human saliva as donor medium and PBS simulating plasma as receptor phase. Values are presented as means ± SD (n = 6).

cm<sup>2</sup> and 2.0 mA/cm<sup>2</sup>, using, respectively, artificial and human saliva as donor medium: it is evident that the increase in electric field determines significant growing in the amount of drug permeated both using artificial and natural human saliva. The steady-state fluxes, the permeability coefficients and the enhancement ratio (ER) (ratio of the value of permeability coefficient of Galantamine under iontophoretic conditions to the value under passive diffusion) are listed in Table 1.

The results have to be evaluated considering that in this work we used saliva obtained from just one person.

The application of a current density of 1 mA/cm<sup>2</sup> could consent an absorption of about 1.8-2.1 ng/ml h *per* 1 cm<sup>2</sup> of mucosal tissue; this amount is not yet enough to ensure an adequate blood level of drug. Whereas, the therapeutic concentration is achieved with the application of a current density of 2 mA/cm<sup>2</sup>, that permit an absorption of 2.7- 2.9 ng/ml h *per* 1 cm<sup>2</sup> of mucosal tissue.

In the present study, we report also the development of tablets suitable for the administration of Galantamine on buccal mucosa. Tablets were prepared by direct compression of drug loaded Eudragit® RS 100 matrices used as a matrixing, low permeable, pH-independent, and insoluble agent. Before compression, to improve the lipophilicity and compressibility, glyceryl tristearate was added to the obtained matrix (ratio 1:4). The physical mixture was then compressed to obtain the desired tablets suitable for buccal administration, containing 39.0 % (w/w) of Galantamine.

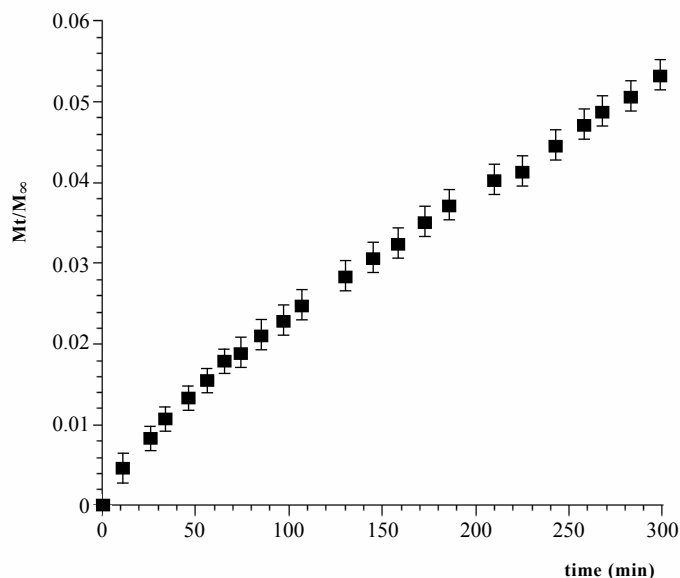
The Galantamine release from the tablets was evaluated using the apparatus previously described (Giannola et al., 2005) which complies with the saliva turnover in the buccal environment.

Experimental results showed that about 70% of the loaded Galantamine was released in 5 h. By extrapolation of data, complete exhaustion of the matrix tablet is obtained in about 8 h, corresponding to a release rate of about 6 mg/h.

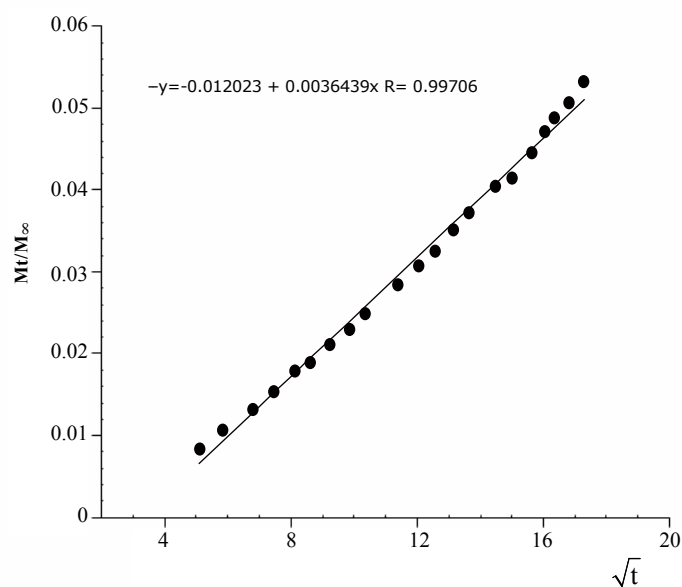
In order to reduce the release rate, the tablets were coated with different lipophilic materials, such as glyceryl tristearate, glyceryl monostearate and lauric acid. The glyceryl tristearate coated tablets release Galantamine with a too slow rate. On the other hand, the kinetic release pattern from tablets coated with gliceryl monostearate was not controlled and reproducible: this phenomenon is probably ascribable to unpredictable and no homogeneous hydrolysis reactions on the gliceryl monostearate film. The best results in terms of release rate and reproducibility were obtained when tablets were coated with the lauric acid (Figure 3).

Donor medium	Diffusion	Js (mg/cm <sup>2</sup> h)	Kp (cm/h)	ER
Simulated saliva	Simple	0.127 ± 0.010	0.042 ± 0.003	
	Iontophoretic (1mA/cm <sup>2</sup> )	0.370 ± 0.010	0.123 ± 0.003	2.91
	Iontophoretic (2mA/cm <sup>2</sup> )	0.511 ± 0.020	0.170 ± 0.006	4.02
Natural human saliva	Simple	0.127 ± 0.010	0.042 ± 0.003	
	Iontophoretic (1mA/cm <sup>2</sup> )	0.320 ± 0.010	0.106 ± 0.003	2.52
	Iontophoretic (2mA/cm <sup>2</sup> )	0.481 ± 0.020	0.160 ± 0.006	3.78

**Table 1:** Calculated steady-state flux values, permeability coefficients and enhancement ratios, for Galantamine permeation through porcine buccal mucosa with and without application of electric fields. Values are presented as means ± SD (n = 6). Donor phase was buffer solution simulating saliva or natural human saliva, receptor phase was PBS simulating plasma.



**Figure 3:** *In vitro* profile of drug release from lauric acid coated tablets prepared with Eudragit® RS-100 matrices loaded with Galantamine. Values are presented as means  $\pm$  SD (n = 6).



**Figure 4:** *In vitro* profile of dose fraction of Galantamine discharged against the root square of time.

The fraction of drug released from the lauric coated tablets *versus* time was plotted and the most common mathematical models used in dissolution analysis were fitted to our experimental data. The best fit was obtained using the equation  $Mt/M_{\infty} = kt^n$  (where  $Mt/M_{\infty}$  is the fraction of drug released at time  $t$  and  $k$  is the kinetic constant) setting  $n = 0.5$  (Higuchian behaviour) (Grassi and Grassi, 2005). This kinetic behaviour suggested that diffusion through the inert polymer matrix was the primary mechanism of dissolution: a linear trend was observed (correlation coefficient 0.997; standard error 0.0020) plotting  $Mt/M_{\infty}$  *vs*  $t^{1/2}$  (Figure 4).

The formulation of the matrix tablet was aimed to continuously release the drug in adequately amount to replace the same eliminated by the body.

Taking into account the above mentioned pharmacokinetics

parameters of Galantamine, we calculated that a drug discharge rate of 0.49 mg/h on buccal mucosa in presence of electric field could be sufficient to ensure the desired Galantamine plasma concentration (2.9 ng/ml h). By Galantamine release experiments from coated tablets we experienced a drug release rate of 0.59 mg/h. This flux value could be adequate to maintain therapeutic blood level.

This prediction takes into account drug losses due to facial movements, dilution, swallowing, intraindividual variations or other similar factors might occur as well.

The data suggested that the application of electric fields promotes drug diffusion through buccal mucosa. Both fluxes and permeability coefficients, in simulated saliva or in natural human saliva, increase significantly when the applied current density grows.

On the basis of these considerations we suppose that buccal mucosa could represent an alternative way of administration for Galantamine. The drug loaded Eudragit® RS 100 matrix tablets could be allocated in the "IntelliDrug device" (Scholz et al., 2008) next to the vestibular area of retromolar trigone, in intimate contact with the mucosa, so allowing the drug release with adequate rate to assure a sufficient drug concentration on absorptive surface; iontophoresis enhancement allows Galantamine to permeate buccal mucosa, so achieving and maintaining therapeutic blood levels. Anyhow, these assumptions should be verified on animal models.

This study is part of the European Project "Intellidrug: intraoral medicine delivery microsystem to treat addiction and chronic disease" (Sixth Framework, Project n° 002243 IST; www.intellidrug.org). This project has the aim to develop a buccal device for the controlled release of drugs. The high-tec mechatronic IntelliDrug device loaded with Galantamine matrix tablets could provide a new opportunity in management of AD.

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