 DOI: 10.1002/masy.200750720

IntelliDrug Implant for Medicine Delivery in Alzheimer's Disease Treatment

Aleksandra E. Moscicka, Kinga Czarnecka, Tomasz Ciach*

Summary: IntelliDrug it is a denture implant containing a reservoir with drug and making enable a galantamine transport via buccal mucosa by means of iontophoresis. The in vitro experimental studies on drug passive and iontophoretic transport through porcine buccal mucosa were carrying out in horizontal two-chamber permeation cell with silver electrodes. The drug mass flux was investigated. The influences of initial drug concentration and current density for transport velocity were defined.

Keywords: buccal mucosa; drug delivery system; galantamine; implant; iontophoresis

Introduction

The research on drug delivery systems has advanced considerably in recent years. It brings many improvements: the increase of drug transport efficiency, safety and convenience of treatment for suffering. Patients usually prefer oral rout of medicine delivery, however oral bioavailability is usually low and compounds are subjected to degradation in gastro-intestinal track or to hepatic first-pass metabolism. Other routes of administration are proposed such as nasal, pulmonary, transdermal or buccal.

The oral cavity is an attractive site for delivery of drugs. The non-keratinized surface of buccal which is highly vascularized enables local or systemic delivery of drugs. The buccal route is generally used in the treatment of chronic disease when the prolonged release of compound is required because this mucosa is resistant to irritation and damage. The disadvantage of buccal route is absorption area limitation, short time of exposure and washing effect of saliva.[1,2]

The Faculty of Chemical and Process Engineering, Warsaw University of Technology, ul. Warynskiego 1, 00-645 Warsaw, Poland
E-mail: moscicka@ichip.pw.edu.pl

IntelliDrug Project

IntelliDrug Project (''Intelligent Intraoral Medicine Delivery Micro-system to Treat Addiction and Chronic Diseases'') is aimed at developing controlled drug delivery system to provide an alternative approach for the treatment of opiate addiction and Alzheimer's disease and diabetes. IntelliDrug it is a denture implant containing a reservoir with drug and making enable a drug transport via buccal mucosa (Figure 1).

The IntelliDrug Project overcomes difficulties related to absorption through buccal mucosa and improves the drug transport by means of iontophoresis. Iontophoresis is the application of an electrical potential across the tissue that causes a movement of charged particle. It is a non-invasive and painless method applied for drugs transport through skin and transdermal diagnosis at present,[3–6] however it is very rarely using for non-keratinized tissue – buccal mucosa.[7]

The drug applies in IntelliDrug implant for treating Alzheimer's disease is galantamine · HBr. It is an acetylcholinesterase inhibitor and was approved by FDA for Alzheimer's treatment in 2001.[8] Following oral administration, galantamine is 100% bioavailable,[9] but this route has disadvantages. Alzheimer's disease is the most com-

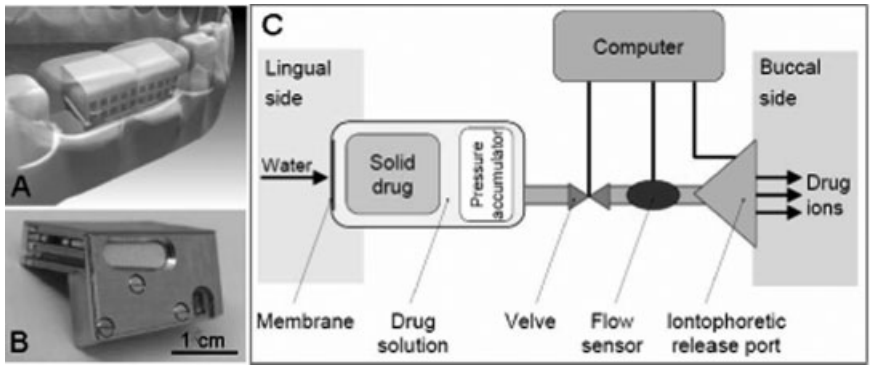

Figure 1.
IntelliDrug implant: A – location of implant, B – prototype without housing (denture), C – principle of operation.

mon cause of dementia. Sufferings have to take the medicine twice daily, but loss of memory very often makes impossible to do this by themselves. Additionally the oral administration of galantamine leads to some negative gastrointestinal side effects: bigger gastrointestinal tonus and peristaltic activity in the stomach and ileum, spastic reactions in the duodenum, acceleration of the evacuation kinetics.[10] It is advisable to work out new route of galantamine delivery and new formulation, especially that number of suffering from Alzheimer's disease is fast growing. In 2000, there were 4.5 million persons with this disease in the US population. By 2050, this number will increase to 13.2 million.[11]

Materials and Methods

The galantamine · HBr was received from Biodar Pharma LTD (Yavne, Israel). All other chemicals were of analytical grade. Phosphate-buffered saline (PBS) buffer consisted of 8.0 g sodium chloride, 0.2 g potassium chloride, 0.2 g potassium dihydrogen phosphate anhydrous, 2.32 g disodium hydrogen phosphate dodecahydrous in deionized water to 1000 ml. Artificial saliva buffer consisted of 0.55 g sodium bicarbonate, 0.09 g sodium chloride, 0.11 g calcium chloride, 0.82 g potassium dihydrogen phosphate anhydrous, 0.95 g potassium chloride in deionized water to 1000 ml.

Domestic pig buccal mucosa had been received from the local slaughter and was kept frozen. Each pieces of mucosa was used only in one measurement and all pieces came from one animal. The mucosa slice 2 mm thick was defrosted and washed in PBS buffer for 45 minutes before the experiment.

Ag/AgCl electrodes were used in research works. This type of electrodes is the most well-suited to iontophoresis, because the relatively high conductivity of silver chloride and avoids the sharp decreases in pH.[3,7,12] Silver wire 1 mm in diameter for electrodes came from Mennica Metali Szlachetnych LTD (Warsaw, Poland). Electrodes were prepared from 4 cm long pieces of wire, which were spiral twisted. Cathodes were electrochemically coated with chloride layer in solution of sodium chloride in water.

The iontophoretic and passive in vitro permeation studies were carried out in two-chamber horizontal cell at room temperature. The donor chamber had capacity of 4 ml, the acceptor chamber of 8 ml. The donor chamber was filled with galantamine solution in artificial saliva buffer. The acceptor chamber was filled with PBS buffer. Chambers had holes for inserting electrodes (anode in donor and cathode in acceptor chamber) and for sampling. The surface area of drug solution-mucosa-PBS buffer was 0.2 cm^2. The magnetic micro stirring bar (8×3 mm) was put in each chamber. The experimental set was put on magnetic

stirrer which was turning on before filling chambers with buffers.

Two milliliters of sample was collected from acceptor chamber at predetermined time intervals and replaced with the same volume of fresh PBS buffer. Direct current was applied since 45 minute of iontophoretic experiments.

Spectrophotometer BioMate 3 was used to analyse concentration of galantamine. Measurements were made at the wavelength of the maximum absorbance for galantamine solution in PBS buffer. At this wavelength it is possible to observe absorbance of compounds washed out to aqueous solutions from the buccal mucosa. These are substances naturally occur in the tissue. The presence of them in examined samples caused, that the measured absorbance was a sum of galantamine and these compounds absorbance. In order to determine the influence of the presence of compounds washed out from mucosa on received results the studies were performed in which the donor chamber instead of the solution of drug in artificial saliva buffer was filled with pure buffer (blank test). Read out samples absorbance was counted over according to calibration curve for galantamine receiving the apparent concentration of the drug in solution not-containing it.

Results and Discussion

All experiments are listed in Table 1, where are shown average mass fluxes after reaching the steady-state condition of transport process and the time of steady-state beginning.

Average apparent mass fluxes of passive transport blank test (Experiment no. 1) and iontophoretical transport blank tests (Experiments no. 8–10) have similar value of the order of 0.005 $mg \cdot min^{-1} \cdot cm^{-2}$.

This phenomenon is related to quantitative determination compounds washed out from mucosa which proved to be non-ionic, so electric field doesn't change the velocity of theirs transport. This conclusion enable to assumption that observed increase of mass flux during iontophoretic transport of galantamine is caused only by drug movement.

Passive transport of galantamine was tested only for saturated solution of drug in artificial saliva buffer (Experiment no. 2). Observed average mass flux was at level of blind test fluxes, what indicate that diffusion is slowly and applied method of measurement can't determine this value precisely.

The influence of initial donor concentration (Experiments no. 3–5) is showed at Figure 2. The increase of concentration

Table 1.
List of Experiments. Table include blank tests of diffusion and iontophoresis.

Experiment number	Current density	Initial donor concentration	Average mass flux[a)]	Delay of steady-state conditions[b)]
	$mA \cdot cm^{-2}$	$g \cdot L^{-1}$	$mg \cdot min^{-1} \cdot cm^{-2}$	min
1	0.0[c)]	0[d)]	0.005	<30
2	0.0	280	0.003	<30
3	1.0	280	0.075	105
4	1.0	30	0.042	145
5	1.0	15	0.036	195
6	1.5	15	0.067	255
7	2.0	15	0.093	180
8	1.0	0	0.007	0
9	1.5	0	0.005	0
10	2.0	0	0.004	0

a) For blank tests apparent mass flux.
b) The time since beginning of experiment for passive transport or since turning on current for iontophoretic transport.
c) Passive transport.
d) Blank test.

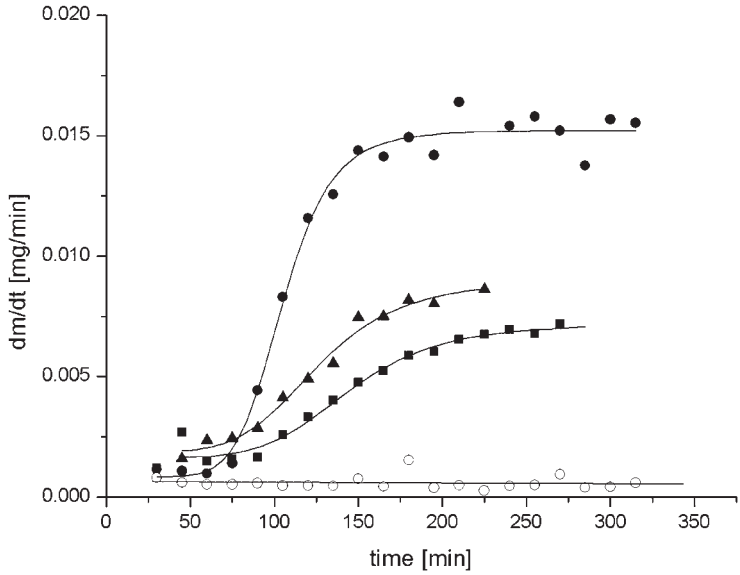

Figure 2.
Plot of mass flux profiles of galantamine permeated across porcine buccal mucosa – the initial donor concentration effect. Key: ● = 280 $g \cdot L^{-1}$, iontophoresis; ▲ = 30 $g \cdot L^{-1}$, iontophoresis; ■ = 15 $g \cdot L^{-1}$, iontophoresis; ○ = 280 $g \cdot L^{-1}$, passive delivery, 0.0 $mA \cdot cm^{-2}$. For iontophoresis the current was turn on at 45 minute of experiment, value of current density was 1.0 $mA \cdot cm^{-2}$.

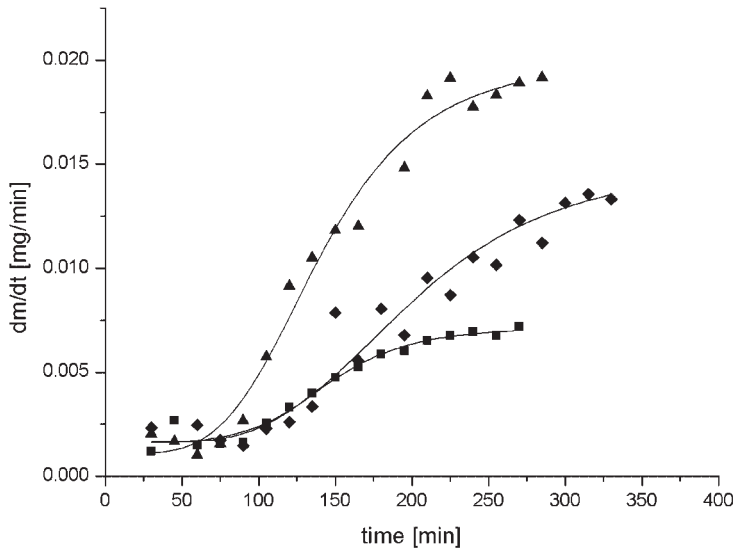

Figure 3.
Plot of mass flux profiles of galantamine permeated across porcine buccal mucosa – the current density effect. Key: ▲ = 2.0 $mA \cdot cm^{-2}$; ◆ = 1.5 $mA \cdot cm^{-2}$; ■ = 1.0 $mA \cdot cm^{-2}$. The current was turn on at 45 minute of experiment. The initial donor concentration was 15 $g \cdot L^{-1}$.

causes increase of mass flux, but it's not linear dependence.

The influence of current density (Experiments no. 5–7) is showed at Figure 3. The increase of current density causes increase of mass flux and this dependence is linear.

The delay of steady-state beginning of drug transport process is related to thickness of mucosa samples. The random of this parameter comes from even small difference of thickness and from diversification of tissue morphology.

Conclusion

Application of iontophoresis enables controlled release and increase of galantamine·HBr transport through buccal mucosa. Passive transport of drug from saturated solution was slower than $0.003\ mg \cdot min^{-1} \cdot cm^{-2}$. Using iontophoresis $1\ mA \cdot cm^{-2}$ and saturated solution reach mass flux $0.075\ mg \cdot min^{-1} \cdot cm^{-2}$. Applying current density $2.0\ mA \cdot cm^{-2}$ and galantamine concentration $15\ g \cdot L^{-1}$ reached a mass flux of $0.093\ mg \cdot min^{-1} \cdot cm^{-2}$.

Acknowledgements: This work is a part of IntelliDrug Project (project no. 002243) and was financially supported by European Commission, 6th Framework Programme.

[1] S. Rossi, et al., *DDT* **2005**, *2*, 59.
[2] J. A. J. Hoogstraate, et al., *PSTT* **1998**, *1*, 309.
[3] Y. N. Kalia, et al. *Adv. Drug Delivery Rev.* **2004**, *56*, 619.
[4] Y. Wang, et al., *EJPB* **2005**, *60*, 179.
[5] L. P. Ganagarossa, Sr., et al. *Int. J. Pharm.* **1995**, *123*, 159.
[6] V. Merino, et al., *TIBTECH* **1997**, *15*, 288.
[7] J. Jacobsen, *J. Controled Release* **2001**, *70*, 83.
[8] S. H. Ferris, *Clin. Ther.* **2001**, *23* [Suppl A], A3.
[9] M. R. Farlow, *Clin. Ther.* **2001**, *23* [Suppl A], A13.
[10] V. I. Turiiski, et al., *Eur. J. Pharmacol.* **2004**, *498*, 233.
[11] L. E. Hebert, et al., *Arch. Neurol.* **2004**, *61*, 802.
[12] C. Cullander, G. Rao, R. H. Guy, in: "*Prediction of Percutaneous Penetration*", R. K. Brain, V. J. James, K. A. Walters, Eds., University of California San Francisco, San Francisco **1993**, p. 381.

