ELECTRICALLY ENHANCED AND CONTROLLED DRUG DELIVERY THROUGH BUCCAL MUCOSA

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The majority of drugs is administrated orally. Patient compliance is very high with this administration route, but bioavailability is often low – from the reason of first pass hepatic effect (e.g. naltrexone HCl) and unpredictable – from variable absorption conditions in digestive system. This popular drug form may also lead to negative gastrointestinal side effects (e.g. galantamine HBr) or to cirrhosis additionally (1-4). Because patients usually don’t accept injections there is a necessity to work out efficient, painless drug administration technique which will provide a high bioavailability of active substance and reduce the side effects. There is a need to determine new route of administration and to work out therapeutic system which makes possible to optimize doses and provides an improvement of life comfort for sufferers.

The oral cavity is an attractive site for delivery of drugs. The non-keratinized surface of buccal which is highly vascularized 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 (5,6).

The increase the drug transfer through tissue and also keeping the control under this process may be reached by applying the iontophoresis – a process of drugs delivery under the influence of electric field. It is a noninvasive and painless method applied for local and systemic drugs delivery through skin and transdermal diagnosis (7-12). Enhancing drug transfer through non-keratinized tissue – buccal mucosa by means of iontophoresis is a new but augurs well route of drug delivery (13, 14). The aim of this work was to determine the possibility of transmucosal iontophoretic delivery of cationic drug and to investigate ex vivo galantamine HBr and naltrexone HCl administration via buccal mucosa by applying the iontophoresis and to define of initial donor drug concentration (in the presence and without of competitive cations) and current density influences on drug flux.

EXPERIMENTAL

Galantamine HBr and naltrexone HCl were received from Biodar Pharma Ltd. (Yavne, Israel). All chemicals were of analytical grade. Phosphate-buffered saline (PBS), pH 7.4, was prepared by dissolving KH2PO4 (0.2 g), anhydrous Na2HPO4 (0.92 g), NaCl (8.0 g) and KCl (0.2 g) in 1 L of distilled water. Artificial saliva buffer (ASB) consisted of: NaHCO3 (0.55 g), NaCl (0.09 g), CaCl2 (0.11 g), KH2PO4 (0.82 g), KCl (0.95 g) and distilled water to 1 L. Specific conductivity of distilled water at 22°C was 2.9×10−4 S m−1. Silver wire 1 mm in diameter for electrodes came from Mennica Metali Szlachetnych LTD (Poland). Domestic pig buccal had been received from the local slaughter (Sochaczew, Poland) and was kept deep-frozen. The buccal mucosa slice 0.2 cm thick was mechanically cut out using a scalpel, defrosted and washed in PBS for 45 min before inserting into measuring set.

The ex vivo iontophoresis through porcine buccal mucosa were conducted at room temperature in a horizontal two-chamber permeation cell with silver/silver chloride electrodes (15). Chambers contents were stirred to prevent concentration polarization. The donor was a galantamine HBr solution in ASB or naltrexone HCl in distilled water. The

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acceptor was a PBS. The drug concentration was monitored spectrophotometrically (UV-vis BioMate 3, Thermo). PBS and ASB components did not interfere significantly with the UV absorption of naltrexone HCl and galantamine HBr. Drug transfer rate was estimated as a molar flux.

RESULTS

For experiments with galantamine HBr (0.04 M), where in donor chamber were found competitive cations from ABS, the increase of current resulted in the increase of drug flux. It was a straight dependence in the range of 0.4 – 1.5 mA/cm², but over this range it deviated from a straight line. Results from experiments with the same drug, and where the current density was constant, showed that the drug flux was an exponential function of drug concentration in the presence of small inorganic cations, which came from a buffer (Figure 1).

For experiments with naltrexone HCl, where in donor chamber were only a drug cations, the drug flux was independent on drug concentration in whole range of drug solubility.

DISCUSSION AND CONCLUSION

Iontophoresis enables control and enhance drug delivery through buccal mucosa. The presented work shows that composition of donor solution had a considerably influence to efficiency of drug transport. It is possible to deliver a therapeutic dose of drug using the iontophoresis in spite of that the percentage current efficiency reached only the level of 2-10 % under the experimental conditions. The initial drug concentration and current density provide an easy way to control the rate of drug delivery. These results suggest possibility of design and construction of an introra oral implant for systemic controlled drug delivery.

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REFERENCES