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Note

Effect of ion complexants on the iontophoresis of salbutamol

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Abstract

Small inorganic ions in transdermal systems can competitively reduce the iontophoretic delivery of the target drug. Crown ether sequesters Na^+ and its inclusion into salbutamol sulphate solutions (containing varying amounts of NaCl) produced a small increase in salbutamol flux. PEG 400, which has been reported to interact with cations such as Na^+, caused a slight decrease in flux. Possibly any enhancement is outweighed by complexation of PEG with salbutamol cations and/or the increase in vehicle viscosity.

Keywords: Iontophoresis; Salbutamol; Polyethylene glycol; Crown ether; Complexation

1. Introduction

During iontophoretic delivery of drugs there is the possibility that other ions present in the device might be transported preferentially. This is particularly a problem for cationic drugs where there is competition between the transport of the drug and small univalent ions such as sodium. This is evident, for example, in experiments on the iontophoretic delivery of nicotine, where increasing sodium chloride concentration decreases nicotine delivery (Brand and Guy, 1995). Small cationic species are often present in the delivery system as pH buffers or tonicity adjusters.

Thus if the mobility of the sodium cations can be reduced it may be possible to make iontophoresis more efficient. Complexation of Na^+ by crown ethers is well documented and therefore we investigated if the presence of such a sequestering agent would influence the transport of the model cationic drug salbutamol. It was recognised that crown ethers could not be used pharmaceutically. Addition of PEG 400 to the salbutamol donor solution was therefore also studied since there are reports that polyethylene glycols interact with cations such as Na^+ (Lundberg et al., 1966).

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2. Materials and methods

Salbutamol sulphate was purchased from Sigma and HPLC grade acetonitrile was from Rathburn. 15 crown–5 ether was obtained from Fisons and all other reagents were from BDH. All glass Franz-type diffusion cells were used, the donor compartment contained approximately 1.5 ml, the receptor chamber approximately 2.5 ml and the cross-sectional area was 1 cm^2. The receptor chamber of the cell was thermostated at 37°C.

Salbutamol was analysed using HPLC. Briefly, a C_{18} 10 μm 25 × 0.4 cm column was used with a mobile phase acetonitrile: pH 4 buffer (65:35). The pH 4 buffer was made with 0.05 M dihydrogen potassium phosphate adjusted to the correct pH with orthophosphoric acid. A flow rate of 0.8 ml/min gave a retention time of 3.5 min (u.v. detection was at 275 nm).

The receptor medium was pH 7.4 phosphate buffered saline (PBS). Samples were taken at a series of pre-determined times up to 24 h and immediately replaced by fresh PBS. Silver/silver chloride electrodes were used with the cathode being placed in the receptor medium.

Full thickness human abdominal skin was used and an iontophoretic current maintained at 300 mA/cm^2. The concentration of salbutamol in the donor phase was 4 mg/ml and the experiments examined the effect of addition of sodium chloride with and without 15 crown–5 ether or PEG 400. The experiments were conducted in triplicate.

Penetration of salbutamol sulphate without an iontophoretic current applied was barely detectable.

3. Results and discussion

The first series of experiments examined the effect of sodium chloride on the permeation rate of the salbutamol sulphate. The results are shown in Fig. 1. The presence of small concentrations of sodium chloride (5 mM) has an imperceptible effect on the salbutamol flux. This is, at first sight, surprising since there are very similar molar concentrations of the salbutamol and Na^+. It is possible that the amounts of Na^+ added are insignificant in relation to the endogenous Na^+ that is present in the full thickness skin.

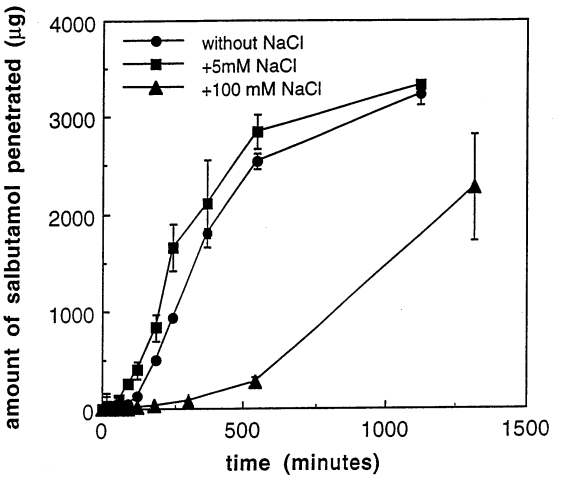

Fig. 1. The influence of sodium chloride concentration on the iontophoresis of salbutamol through full thickness human skin.

Increasing the NaCl concentration to 100 mM has a marked effect in reducing the salbutamol flux. These results are comparable to those found for the iontophoresis of nicotine across hairless mouse skin (Brand and Guy, 1995).

In order to monitor the effect of complexation, equimolar amounts of the crown ether were added to the donor medium. The results are shown in

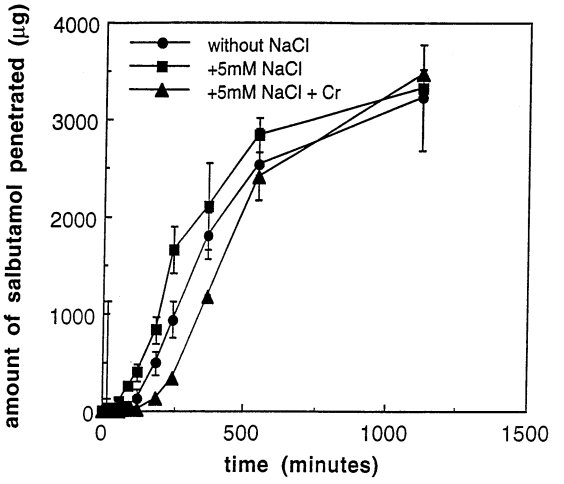

Fig. 2. The effect of 5 mM crown on the penetration of salbutamol in the presence of 5 mM NaCl.

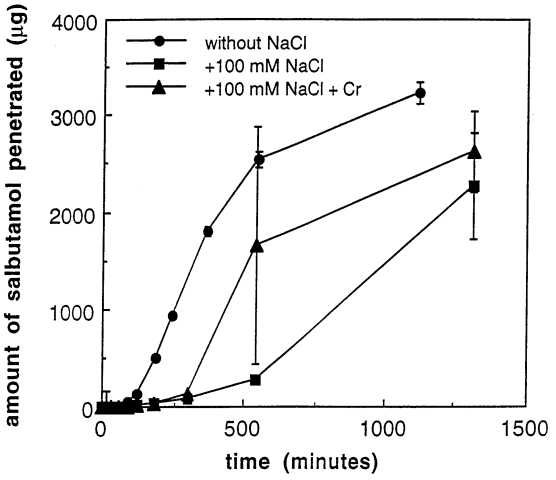

Fig. 3. The effect of 100 mM crown on the penetration of salbutamol in the presence of 0.1 M NaCl.

Figs. 2 and 3. At the lower NaCl concentrations the presence of either the sodium chloride or the combined sodium chloride plus crown ether has little impact on the salbutamol permeation.

At the higher salt concentrations, it is seen that the presence of the crown ether has a marked influence on the salbutamol flux but does not restore it to the value when no NaCl is present. However the results indicate that if appropriate complexants for sodium can be identified they can improve iontophoresis efficiency.

A pharmaceutically acceptable excipient, PEG 400, was examined to investigate its ability to enhance salbutamol flux. Previous reports have shown that PEGs are capable of forming association with Na^+ and it was thought that this effect might mimic the action of the crown ether. Fig. 4 shows the results for low NaCl concentrations. Equimolar PEG concentrations do not increase the permeation of the salbutamol. Indeed, there is an indication that PEG may be retarding absorption, since the effect was more marked at higher PEG concentrations. The exact mechanisms for this are unclear but it is possible that a complex has been formed between the PEG and the salbutamol. Alternatively, the absolute viscosity of the donor phase may be becoming a limiting factor.

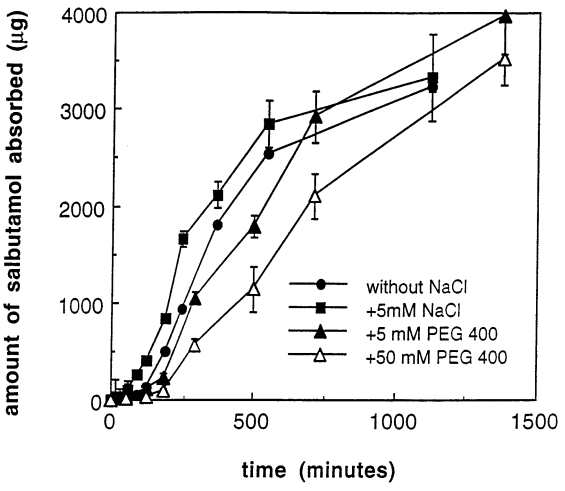

Fig. 4. The effect of 5 and 50 mM PEG 400 on the penetration of salbutamol in the presence of 5 mM NaCl.

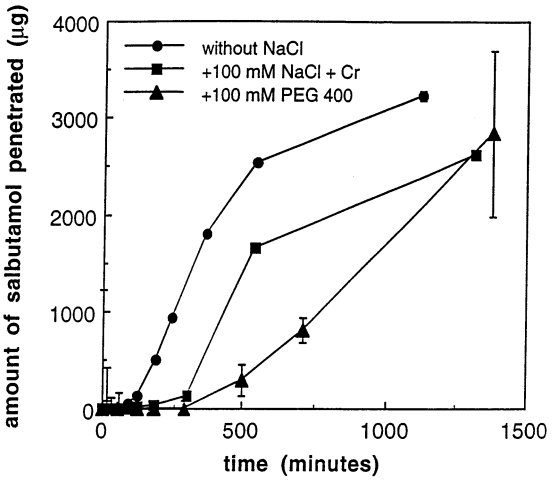

Fig. 5. The effect of 100 mM crown or PEG 400 on the penetration of salbutamol in the presence of 100 mM NaCl.

Fig. 5 shows the results at higher sodium chloride concentrations. PEG had no influence on the penetration of salbutamol. It is probable that under the conditions used the complex between the PEG and Na^+ is not sufficiently strong and under the influence of a potential the Na^+ ions move independently of the PEG.

References

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