行政院國家科學委員會補助專題研究計畫成果報告

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※ 凝膠配方特性對電穿孔經皮輸藥影響之研究 ※
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執行期間：90 年 8 月 01 日至 91 年 07 月 31 日

計畫主持人：宋國峻教授
共同主持人：
計畫參與人員：

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執行單位：嘉南藥理科技大學藥學系

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行政院國家科學委員會專題研究計畫成果報告

凝膠配方特性對電穿孔經皮輸藥影響之研究

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摘要

本計畫主要目的乃在探討電穿孔及離子電透入法對 nalbuphine prodrug 由凝膠配方中經皮輸藥之影響。

Abstract

The aim of this study was to assess the effects of iontophoresis as well as electroporation on transdermal delivery of nalbuphine and its prodrugs from various hydrogel formulations.

Keywords: Nalbuphine; Prodrugs; Transdermal delivery; Iontophoresis; Electroporation; Hydrogel

Introduction

Nalbuphine (NA) is a narcotic analgesic used in the treatment of both acute and chronic pain. It is a potent analgesic with relatively low side effects. In order to maintain the blood nalbuphine concentration and to improve the patient compliance and therapeutic effectiveness in pain management, a series of nalbuphine prodrugs have been synthesized. The pharmacokinetic and biopharmaceutic characteristics of NA and its prodrugs suggest the practicality of transdermal route. Nalbuphine benzoate (NAB) and sebacoyl dinalbuphine ester (SDN) are relatively novel synthetic prodrugs of NA which prolongs its duration of action. Due to the various functional groups and structures of these prodrugs, the molecular size and lipophilicity and thus the skin permeation characteristics can be significantly different

Electrically-assisted delivery by iontophoresis or electroporation will provide a further advantage of programming the dose in proportion to the level of therapy desired. Drug in solution is not readily amenable to incorporate into an iontophoretic device. To circumvent this, hydrogel formulations prepared by polymers is needed to resolve this problem. The goal of this study was to assess the skin permeation of NA, NAB and SDN from formulations made with two types of hydrogels, including hydroxypropyl cellulose (HPC) and carboxymethyl cellulose (CMC).

Results and discussion

Transdermal permeation of NA, NAB and SDN from HPC hydrogels

The skin permeation of NA and its prodrugs from pH4 buffer with or without cellulose polymers was investigated. The permeation profiles for HPC hydrogels are shown in Fig.1. No significant difference (t-test, $p>0.05$) was observed between the flux of NA, NAB and SDN from pH4 buffer and 2.5% HPC hydrogels. This may suggest that the cross-linkage structure formed by HPC after hydration did not interact with NA and its prodrugs. For a specific dose of drug, varying the polymer concentration is probably the most efficient way to adapt the release characteristics of the formulation to a specific criterion. The passive diffusion of NA and NAB decreased significantly (t-test, $p<0.05$) as the HPC concentration increased from 2.5% to 5.0% (Fig.1 (A)(B)). The ability of a hydrogel system to serve as a reservoir for drug delivery is markedly influenced by the macro- and micro-rheological properties of the gel matrix. Viscosity is the most widely utilized reference for the characterization of polymer structure, although it is not sufficiently comprehensive for full determination of hydrogel strength. The viscosity increases drastically with the HPC concentration. This is a general rule for increasing the proportion of polymer, which

would cause a more rigid structure of gels and decrease the rate of drug release.

Application of electrically-assisted methods greatly increased the permeation of NA and its prodrugs from 2.5% HPC hydrogels (Fig.1). The same as passive diffusion, the addition of 2.5% HPC in buffer did not influence the permeation of NA and its prodrugs in the electric field. The flux of NA and SDN was significantly reduced by the increase of HPC concentration from 2.5% to 5.0%, which was similar to the condition of passive diffusion. Hydrogel viscosity is a parameter that can affect iontophoretic delivery since Waldens' Rule states that the' product of viscosity and molar conductance is a constant. An increase in viscosity should lead to a decrease in ionic mobility and iontophoretic permeation. However, this phenomenon was not observed in the NAB permeation from HPC hydrogels by combining iontophoresis and electroporation. It is our opinion that the increase of polymer concentration also decreases the proportions of buffer solution, which result in the reduction of the current density carried by the buffer species. NAB may be more sensitive to this effect.

The permeation of NA and its prodrugs from 5% HPC with different MW is compared as shown in Table 1. Low MW HPC did not hinder the permeation of NA, NAB and SDN by either passive diffusion or electrically-assisted enhancement because there was no significant difference (t-test, $p > 0.05$) between the flux of drugs from buffer and hydrogel with 5% HPC with low MW. The viscosity of 5% HPC with low MW was only 17.63±0.60 cps$\times^{-2}$ which was much lower than that of high MW. The great discrepancy of viscosity made the significant difference (t-test, $p < 0.05$) between flux of NA from low and high MW HPC. However, no significant difference (t-test, $p > 0.05$) was observed in the flux of NAB and SDN from these two HPC hydrogels by passive diffusion. This phenomenon was consistent with the result in Fig.1which demonstrated that increase in HPC concentration resulted in the higher viscosity of gel matrix and lower skin permeation of NA but not NAB and SDN. The result indicates that the passive permeation process of NA was consistent with vehicle-controlled mechanism but not skin-controlled mechanism, since the viscosity of hydrogels will play an important role in controlling the release of the drug if the diffusion of drug through the polymer matrix is a rate determining step. On the other hand, the prodrugs – NAB and SDN showed a skin-controlled mechanism which was opposite to NA.

Transdermal permeation of NA, NAB and SDN from CMC hydrogels

The anionic CMC is one of the synthetic water-soluble cellulose largely used as matrix for drug delivery systems. The results of the NA, NAB and SDN permeation by passive diffusion and electric field from CMC hydrogels are summarized in Fig.2. The results indicate that CMC had significant effects on the amount of drug across skin. The addition of 2.5% CMC did not influence the passive permeation (t-test, $p > 0.05$) of both NA and NAB as compared to the pH4 buffer vehicles (Fig.2 (A)(B)). The increase of CMC concentration from 2.5% to 5.0% significantly reduced the passive permeation of NA and NAB (t-test, $p < 0.05$). SDN still showed no cumulative amount in passive diffusion no matter what the donor vehicles were.

The transport of NA and its prodrugs was largely decreased by the presence of CMC after application of iontophoresis combined with electroporation (Fig.2). CMC is an ionized polymer with the counterion of sodium salt (Na^+). The low permeation in CMC hydrogels could be due to the competition of drug ions and Na^+ for the applied current. A part of current would be carried by Na^+ with relatively high mobilities, so that the residual fraction of applied current was carried by NA and its prodrugs. The reduction of flux after addition of CMC was greater for NA as compared to its prodrugs. Furthermore, only NA showed a significant decrease (t-test, $p < 0.05$) of flux when increasing the CMC concentration from 2.5% to 5.0% among three compounds tested. This may again indicate that NA was more

sensitive to the competitive effect in electric field.

References

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Assessment of progress

The results of this study have been written in a manuscript to be published in a journal as a research article.

Fig. 1

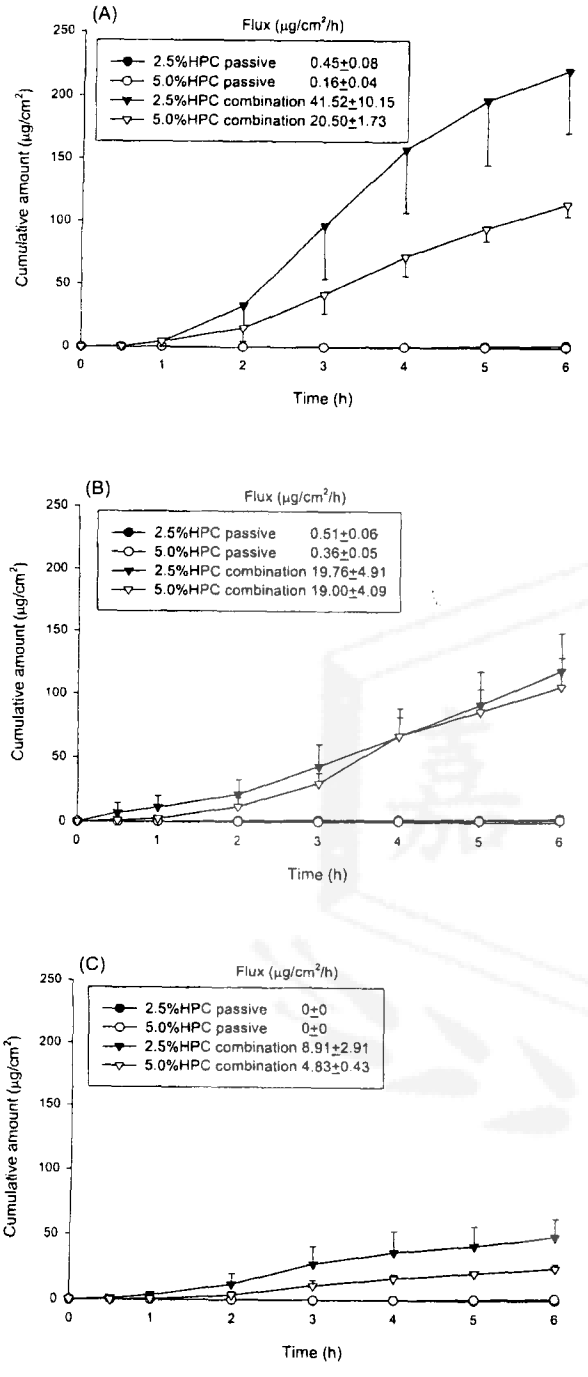

Fig. 2

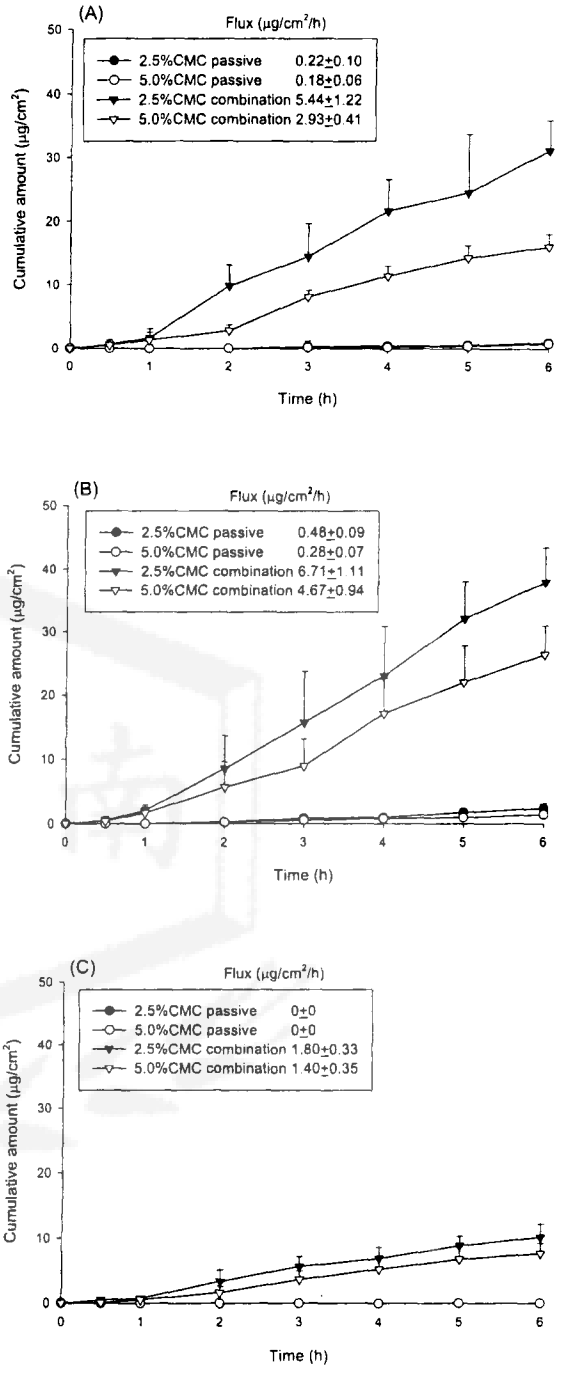

Table 1. The flux (μg/cm²/h) of nalbuphine from nalbuphine and its prodrugs in HPC hydrogels Of low and high molecular weight (MW)

Condition	Compound	Low MW HPC	High MW HPC
Passive diffusion	Nalbuphine	0.32±0.07	0.16±0.04
	N. Benzoate	0.35±0.06	0.36±0.05
	Dinalbuphine	0	0
Iontophoresis+Electroporation	Nalbuphine	30.55±3.56	20.50±1.73
	N. Benzoate	24.25±5.66	19.00±4.09
	Dinalbuphine	5.17±1.32	4.83±0.43