嘉南藥理科技大學專題研究計畫成果報告

計畫名稱

Development of hydrogels for transdermal buprenorphine delivery

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Buprenorphine is a morphine-like drug with partial agonist activity at the μ-opiate receptor and antagonist activity at the κ-opiate receptor. It is approximately 25～30 times more potent than morphine and has been widely used in the treatment of acute and chronic pain. Its half-life after parenteral administration was estimated to be 3～5 h and the recommended dosing frequency was 3~4 times each day. The orally administered buprenorphine was reported to undergo extensive first-pass effect, with only 10～15% of bioavailability. Thus, in order to circumvent those unfavored biopharmaceutical characteristics and to improve therapeutic effectiveness in pain management, the development of controlled release or alternative delivery systems for buprenorphine are desirable.

In the present study, the major goal is to evaluate the use of hydrogels as vehicles for buprenorphine transdermal systems, the effects of various hydrogel polymers on transdermal permeation kinetics of buprenorphine will also examined.

Various polymer based on CMCNa, $CMCNH_4$, and chitosan were utilized to formulate hydrogels as the vehicles for buprenorphine transdermal delivery. There was no statistically significant differences among the flux and lag time of buprenorphine from three hydrogel formulations via passive diffusion (ANOVA test, $p > 0.05$). Moreover, the permeation fluxes as well as lag times from the vehicles of pH 5 buffer solution and hydrogels were also similar, suggesting that the diffusion of buprenorphine was not hindered by hydrated polymer structure formed.

The magnitude of viscosity before in vitro experiments was in the order of chitosan $>$ $CMCNH_4$ $>$ CMCNa. The viscosity of buprenorphine hydrogels was slightly reduced after performing 8h of passive diffusion experiments and no statistically significant difference was observed (t-test, $p > 0.05$). The viscosity of the polymer matrices showed no impact on the permeation, indicating that the passive permeation of buprenorphine was the skin-controlled mechanism but not vehicle-controlled

mechanism, since the viscosity of hydrogels will play an important role in controlling the permeation of buprenorphine if diffusion of drug through the polymer matrix is the rate determining step.

The results also indicate that hydrogel composotion had significant effects on the permeation rate of buprenorphine via iontophoresis. The flux of buprenorphine for various vehicles increased in the order of chitosan $>$ $CMCNH_4$ $>$ CMCNa (t-test, $p < 0.05$). The flux of buprenorphine from chitosan hydrogel was also higher than that from pH 5 buffer solution (t-test, $p < 0.05$) Except for the polymer backbone, the major difference between composition of chitosan hydrogels and other hydrogel vehicles was that its aqueous phase was 5% lactic acid but not pH 5 buffer. The chitosan thus possess positive charge. Since the ionic mobility is opposite to its size (molal volume or molecular weight)under applying iontophoreses, the high molecular weight of chitosan polymer thus could not act as a strong competitive ion for permeation. On the contrary, the repulsion force between the positively charged buprenorphine and chitosan vehicle may increase the drug permeation.

The application of iontophoresis also caused a great reduction of viscosity in chitosan hydrogels, however, similar phenomenon was not observed in CMC hydrogels. The anode electrode in the donor may drive the positively charged chitosan and the rheological behavior which could influence subsequent drug release . In the present study, the application of electric field may collapse of the chitosan network and subsequently enhancing drug release rate. The charge repulsion between buprenorphine and chitosan as well as viscosity reduction of chitosan vehicles contribute to the higher buprenorphine permeation rates.

The skin permeatiom of buprenorphine by iontophoresis from different counterions of CMC hydrogels was also compared. The counterions of CMC polymer may also compete with buprenorphine for permeation. Since the radius of $–Na^+$ was smaller

than $-NH_4^+$ and buprenorphine, $-Na^+$ may show the higher mobility. As a result, the enhancement effect of buprenorphine permeation by iontophoresis was significantly lowered from CMCNa vehicle than from $CMCNH_4$ vehicle.

Although the viscosity of chitosan hydrogels was also significantly reduced (t-test, $p < 0.05$) after electroporation, a slight increase (1.63-fold) in buprenorphine flux was observed from chitosan hydrogels via electroporation. Similar as the results from buffer solution, the combined iontophoresis and electroporation did not further increase flux of buprenorphine by iontophoresis. However, the lag time for drug permeation was significantly reduced (t-test, $p < 0.05$) after combining the two electrically-assisted methods. The results again demonstrate that the application of electroporation has limited influence for the permeation of buprenorphine from hydrogels.