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Collagen-chitosan composite membranes controlled transdermal delivery of nifedipine and propranolol hydrochloride

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Abstract

Membrane-permeation-controlled transdermal devices were fabricated for the controlled delivery of nifedipine and propranolol hydrochloride using composite membranes made of natural polymers chitosan and collagen. Devices were fabricated for a single application daily. The drug release profiles from these devices were evaluated in modified Franz glass diffusion cells using rabbit pinna skin. The data showed that the devices effectively controlled the transdermal delivery of both drugs.

Keywords: Collagen-chitosan composite membrane; Nifedipine; Propranolol hydrochloride; Transdermal delivery

Collagen membranes have been well exploited for various biomedical applications due to their excellent biocompatibility. Recently, we have demonstrated that collagen membranes could be successfully used for the fabrication of transdermal drug delivery systems (Thacharodi and Panduranga Rao, 1995a; in press). Transdermal devices made of collagen membranes promise many advantages over conventional transdermal patches. One major advantage of this system is that collagen membrane is very skin friendly and reduces skin damage. However, collagen membranes could not be used as such for an application without stabilizing it by crosslinking. If a conventional chemical crosslinking agent like glutaraldehyde is used to crosslink collagen, the residual crosslinking agent present in the membrane may cause some adverse side effect. It is possible to stabilize collagen with chitosan, a polycationic biopolymer which is also highly biocompatible and used for various biomedical applications (Hirano et al., 1990; Muzzarelli et al., 1994; Song et al., 1995). Collagen forms a stable composite with chitosan; also, collagen-chitosan composite membranes have favorable physicochemical properties needed for many biomedical applications (Taravel and Domard, 1995). We have reported earlier that the permeability properties of collagen-chitosan composite membranes are suitable for controlled drug delivery applications (Thacharodi and Pan-

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duranga Rao, 1995b). The physico-chemical and mechanical properties of these composite membranes were found to be suitable for transdermal application. In this paper, we have studied the usefulness of collagen-chitosan composite membranes for the development of a transdermal delivery system for the controlled delivery of a lipophilic drug, nifedipine, and a hydrophilic drug, propranolol hydrochloride (prop-HCl).

Telopeptide-poor soluble collagen was extracted form fetal calf skin as described earlier (Thacharodi and Panduranga Rao, 1995a). Collagen-chitosan composite membranes were prepared as follows: equal volumes of 0.5% (w/v) solutions of chitosan [a gift from Central Institute for Fisheries Technology (CIFT), India] and collagen prepared in 0.5 M acetic acid were mixed thoroughly over a vortex mixer. The resulting solution was allowed to stand at 4°C until all air bubbles had disappeared. The bubble free solution was then poured onto a rimmed perspex plate and allowed to dry at 4°C. The membranes thus obtained were neutralized by immersion in 1% aqueous NaOH for 30 min, washed thoroughly with distilled water and dried at 4°C. The membranes were stored in the refrigerator for further studies.

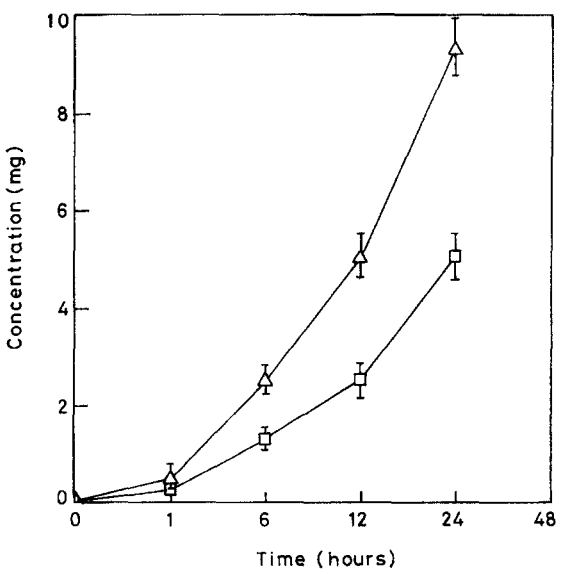

Fig. 1. In vitro release profiles of nifedipine and propranolol hydrochloride from transdermal devices made of collagen-chitosan composite membranes. Values are mean ± S.D. for three determinations. Nifedipine (△) and Prop-HCl (□).

A pressure sensitive adhesive consisting of a copolymer of 2-ethyl hexylacrylate and acrylic acid was synthesized by free radical initiated solution polymerization as reported earlier (Thacharodi and Panduranga Rao, 1995a) and used for the fabrication of transdermal devices.

Transdermal devices were fabricated by an adhesive sealing technique. The detail procedure of fabrication has been published elsewhere (Thacharodi and Panduranga Rao, 1995b). The drug reservoir for prop-HCl delivery devices consisted of a chitosan gel which contained prop-HCl dissolved in the vehicle propylene glycol and the penetration enhancer, cineole. The reservoir for nifedipine-delivering devices consisted of an alginate gel which contained nifedipine dissolved in 25% aqueous ethanol and penetration enhancer cinnamon oil (nifedipine solution containing cinnamon oil and calcium chloride was injected through an opening at the backing membrane made of aluminum coated with polyester into empty reservoir of the device, followed by the injection of sodium alginate solution). Calcium alginate gel with entrapped drug and enhancer was thus formed in situ within the reservoir and the opening at the backing was adhesive sealed). The usefulness of the penetration enhancer cinnamon oil for transdermal absorption of nifedipine has been reported earlier (Thacharodi and Panduranga Rao, 1994) and it has been reported that nifedipine, a highly light sensitive drug, could be rendered more stable if incorporated in alginate gel (Masaki and Teruko, 1990). The devices possessed a surface area of 1.7cm^2 for drug release and were designed for a single application daily. A system employing three modified Franz glass diffusion cells was used for the in vitro drug release study of the transdermal devices. Freshly-excised rabbit pinna skin was used for in vitro studies. The devices applied on the stratum corneum side of the pinna skin (one device on each skin) were mounted and clamped carefully between the receiver and donor compartments of diffusion cells with the device facing the donor side. Normal saline containing 0.2 M sodium azide and 40% aqueous ethanol were used as the receiver media for prop-HCl and nifedipine re-

spectively. The receivers were maintained at 37°C by circulating thermostatically-controlled water through a jacket surrounding each cell body and the receiver content was stirred continuously at controlled speed using a magnetic stirrer. At predetermined time, samples were withdrawn from the receivers and replaced with fresh receiver solutions at 37°C. The samples were assayed for prop-HCl and nifedipine spectrophotometrically at 290nm and 337nm, respectively, using a Shimadzu-UV 2100S instrument.

Fig. 1 Shows the in vitro release profiles of nifedipine and prop-HCl from transdermal devices. About 9.5 mg of nifedipine and 5 mg of prop-HCl were found to release from the devices through the full thickness skin in a near-zero order fashion for a period of 24 h after a very short initial lag time. This study clearly shows that collagen-chitosan composite membranes could be successfully used to fabricate transdermal devices for the delivery of both lipophilic and hydrophilic drugs. Since collagen/chitosan composite membrane is highly skin compatible, some of the device-associated adverse skin reactions of transdermal devices could be avoided.

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