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Collagen membrane controlled transdermal delivery of propranolol hydrochloride

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Abstract

Membrane permeation controlled-transdermal delivery systems for propranolol hydrochloride were developed using collagen membranes as rate-controlling membranes. Collagen extracted from fetal calf skin was used for this purpose. The ability of the transdermal devices to deliver the drug while supported on rabbit pinna skin was evaluated by conducting in vitro studies using modified Franz diffusion cells. The drug release profiles show that the drug delivery is well controlled by the devices. The drug release rate from the devices was found to depend on the permeability of the membrane used.

Keywords: Collagen membrane; Propranolol hydrochloride; Transdermal delivery

Collagen remains as the most exploited biopolymer for various biomedical applications. The membrane-forming property of collagen, particularly, finds many applications in biomedical and pharmaceutical fields. Collagen membranes have wide application today, particularly for wound/burn cover dressings (Doillon and Silver, 1986, Estelle et al., 1991) and for ophthalmic uses (Phinney et al., 1988, Sawusch et al., 1989, Gussler et al., 1990). Collagen membranes have not been well exploited for their potential application in the controlled transdermal drug delivery systems even though they have favorable physico-chemical and permeability properties needed for this application. In the present investigation, collagen membranes with different permeability properties were prepared and used to fabricate transdermal delivery systems for propranolol hydrochloride (prop-HCl). In the transdermal devices, these membranes were assigned to do the key role of controlling the rate of delivery of the drug.

Soluble collagen was extracted from fetal calf skin by a procedure standardized in our laboratory which is a slight modification of the method reported by Weiss and Elstow, 1983. After extraction, collagen was made telopeptide-poor by pepsin treatment. Collagen membranes were prepared by solvent evaporation technique by two methods. In one method (solution casting), 1%

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collagen solution in 0.5 N acetic acid was directly poured onto a clean rimmed perspex plate and allowed to dry at 4°C to form membranes. The membranes formed were neutralized with aqueous sodium hydroxide (1% w/v), washed thoroughly with distilled water and dried. In another method (gel-casting), collagen solution [0.5% (w/v) in 0.5M acetic acid] was neutralized by adding dilute aqueous sodium hydroxide solution. Glutaraldehyde was added to this dispersion and the contents were immediately poured onto a rimmed perspex plate. A thick uniformly spread gel was formed and it was allowed to dry at room temperature (27°C) in a dust free atmosphere to form highly porous membrane. This membrane was extensively washed with distilled water to remove residual glutaraldehyde. The washout was assayed for glutaraldehyde and washing was repeated until no trace of glutaraldehyde was detected in the washout. To assess the suitability of the membranes for transdermal application, the membranes prepared by both the methods were extensively characterized by scanning electron microscopy, thermogravimetric analysis, differential scanning calorimetry, tensile strength and equilibrium swelling studies, and their permeability properties for prop-HCl were evaluated by permeation studies (data not given).

A series of in vitro skin permeation studies for prop-HCl were carried out on rabbit pinna skin using various vehicles and skin penetration enhancers to achieve the degree of percutaneous absorption of the drug required for its therapeutic action, before fabricating the transdermal devices. It was found that propylene glycol and cineole are a good vehicle and penetration enhancer, respectively, for prop-HCl; hence, they were used for formulation enhancement in the present study.

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, 1995) 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, 1995). The drug reservoir consisted of a chitosan gel which contained propanolol dissolved in the vehicle propylene glycol along with the penetration enhancer, cineole. The devices possessed a surface area of 1.7 cm^2 for drug release and they were designed for daily use.

Freshly excised rabbit pinna skin was used for the evaluation of in vitro drug release profiles from transdermal devices. 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. A system employing three modified Franz glass diffusion cells were used for the present study. Normal saline containing 0.2M sodium azide was used as the receiver medium. 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 using a magnetic stirrer. At a predetermined time, samples were withdrawn from the receivers and replaced with fresh saline at 37°C. The samples were assayed for prop-HCl spectrophotometrically at 290 nm using a Shimadzu–UV 2100S instrument.

Fig. 1 shows the in vitro release profiles of propanolol from transdermal devices fabricated with collagen membranes. The devices fabricated with uncrosslinked solution-cast membrane released about 6.3 mg of drug in a near zero order fashion within 24 h. On the other hand, the devices fabricated with gel-cast crosslinked membrane released about 9.3 mg of drug in a near zero order fashion within 24 h. The higher drug release rate from the latter device may be attributed to the higher permeability coefficient of the membrane owing to its higher porosity.

Generally synthetic polymeric membranes are used to fabricate transdermal drug delivery systems. Biopolymeric membranes like collagen membrane are very good candidates for applying as rate-controlling membranes in transdermal drug delivery systems. Their permeability is easy to tailor and they are also highly biocompatible (Gilbert et al., 1988., Weadock et al., 1986, Wang et al., 1994). The present study demonstrates that collagen membranes could be successfully used to

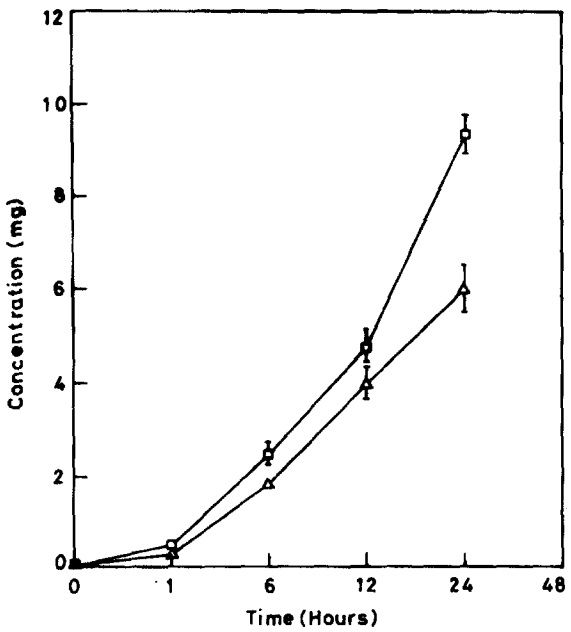

Fig. 1. In vitro release of propranolol hydrochloride from transdermal devices fabricated with collagen membranes. Solution cast membrane (△); gel cast membrane (□); values are mean ± S.D. (n = 6).

fabricate transdermal drug-delivery systems. By using this body-friendly natural polymer for transdermal application, some of the device-associated adverse skin reactions commonly encountered with the transdermal devices fabricated with synthetic polymers could be avoided.

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