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Development and Characterization of Membrane for Local Delivery of Cephalexin

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Laminated films composed of drug-containing reservoir layer and drug-free membrane were prepared. Zero-order drug release with lag time was achieved by laminating drug-free film onto the reservoir layer, while burst effect was observed on cast-on film. The rate controlling membrane was either attached to or cast directly into the reservoir. The release rate was independent on the reservoir composition but dependent on the composition of rate-controlling membrane. In growth inhibitory test of cephalexin from Eudragit RS film to *Streptococcus Mutans*, the disk even after release test for 72 hours showed more bacterial growth inhibition than that of control. Permeation of drug through rat skin was proportional to the HPC fraction in the film. We could control the release of cephalexin from the film by changing the fraction of Eudragit RS, HPC and DEP content. Consequently, Eudragit RS/HPC film was found to be very effective system for local delivery of drugs.

key words : Cephalexin, Percutaneous, Transdermal, Local, Delivery, Eudragit, Hydroxypropylcellulose

INTRODUCTION

Incorporation of drug in inert polymer films during their manufacturing is a possible method of achieving controlled release. Such products can be used to topical, oral and other routes of administration (Donbrow and Friedman, 1975). This method has long been favored for the preparation of sustained release tablet for oral ingestion (Kaplan, 1965). More recently, the concept has been suggested for other uses such as catheters coated with antibiotic-impregnated polymers, prolongation of the release of pilocarpine in eye administration (Loucas and Haddad, 1972), long-term buccal absorption of drugs (Applezweig, 1970), dermatological applications (Chien *et al.*, 1988) and long-acting implants (Roseman and Higuchi, 1970). Local drug delivery by using biocompatible polymers has been developed for the treatment of periodontitis for many years and has been proved to be an effective method to control the bacterial flora of the pocket without adverse effect.

This type of drug delivery system can be adapted to transdermal therapy. For many decades, the skin has been commonly used as the site for the administration of dermatological drugs to achieve a localized pharmacological action. It is exemplified by the use of hydrocortisone for dermatitis, benzoylperoxide for acne and neomycin for superficial infection (Kastrup and Boyd, 1983). Most recently, there is an increasing recognition that the skin can also serve as the port of administration for systemically active drugs. It is exemplified by the transdermal administration of nitroglycerin for the treatment of angina pectoris (Shaw *et al.*, 1976), scopolamine for the prevention of motion sickness (Armstrong and Marks, 1980) and estradiol for the medication of postmenopause (Sitrikware *et al.*, 1980).

Poly(meth)acrylates can be used in various ways to develop oral formulations with controlled release (Okor and Obi, 1990; Goto *et al.*, 1985). Hydroxypropylcellulose is soluble in water below 40°C, gastrointestinal fluids and many polar organic solvents. Eudragit RS alone forms a very brittle film. Combination of both polymers was tried to alter the drug release pattern and to yield a flexible film. To improve the film characteristics, plasticizers such as diethylphthalate (DEP) and dibutylphthalate (DBP) were used.

The effects of adhesion method of rate-controlling membranes such as cast-on or lamination were studied. Cephalexin, gram negative and positive antibiotics, was selected as a model drug to study the

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drug release and the skin permeation. Growth inhibitory activity of cephalexin from different disks and percutaneous permeation rate of cephalexin through rat skin from different matrix film were studied. The purpose of this study was to investigate the release from the laminated films composed of HPC and Eudragit-RS and to examine the possibility of use as carrier for local delivery and transdermal drug delivery system.

MATERIALS AND METHODS

Materials

Cephalexin was purchased from Donghwa Pharm. Co. Ltd. and hydroxypropylcellulose was from Ilyang Pharm. Co. Ltd. (Korea). Eudragit-RS was purchased from Roehm Pharm. Co. (Germany). Brain heart infusion (BHI) broth was from Difco. Lab. and methanol was HPLC grade from Fisher Scientific Co. (U.S.A.).

Film preparation

Six percents solution (polymer and plasticizer) was prepared by dissolving hydroxypropylcellulose (HPC) and Eudragit RS in methanol-acetone (8 : 2) with vigorous stirring. After standing for 24 hours, the solution was poured onto the plate coated with a teflon and allowed to evaporate at room temperature for 24 hours and the prepared films were removed carefully from the plate. Drug content was calculated from the weight ratio of drug and polymer used. The thickness of the films was determined using micrometer. The laminated films were prepared either by wetting one side of the rate-controlling membrane with methanol : acetone (8 : 2) and then pressing it immediately onto the reservoir layer or by casting solution forming the rate-controlling membrane directly onto the dried reservoir layer.

Determination of antimicrobial activity

Bacterial strain used in this study was *Streptococcus mutans* ATCC OMZ 176. This strain was cultured in BHI broth (Difco) at 37°C incubator for 16 hours.

Assay of growth inhibitory activity by disk diffusion method

The inhibitory activity of casting films against *Streptococcus mutans* was assayed by the disk diffusion method. The film (Eudragit-RS: HPC : DEP=6 : 3 : 1, one-fourth inch in diameter) containing 12.5% cephalexin that had been released in a dissolution tester for 1, 2 and 3 days was placed on the nutrient agar plates that had been seeded with *Streptococcus mutans*. The plates were then incubated at 37°C for 16 hours and the inhibition zones were measured.

Percutaneous absorption

A square section of the abdominal skin was obtained from a male rat and an epidermal membrane was prepared by heat separation method (Southwell and Barry, 1983; Cooper, 1984; Aungst *et al.*, 1990; Durrheim *et al.*, 1980). Franz diffusion cell was used for *in vitro* permeation study. A glass plate was used for blocking the stratum corneum side of the skin. The half cell opening was 2.00 cm in diameter, providing a 3.14 cm^2 effective contact area between the skin and the bulk solution of 20 ml. The two parts of the cell were held together by a clamp. The reservoir was warmed to 37°C with circulating water jacket and the receptor side was stirred continuously at 120 rpm. The entire volume was removed at the various sampling times and was replaced with fresh saline solution. The permeation amount was calculated from the cephalexin concentration multiplied by the reservoir volume.

HPLC determination of cephalexin

The liquid chromatography was equipped with a UV detector set at 262 nm and a 3.9×300 mm stainless steel column prepacked with octadecylsilane chemically bonded on totally porous silica. The mobile phase was composed of 30% methanol-70% 0.01 M sodium acetate aqueous solution. Chromatography was performed at ambient temperature and samples were eluted at a flow rate of 1.5 ml/min. Fifty microliters of solution at suitable intervals were injected with the flow stopped. Peak heights were measured and the concentrations were calculated from the calibration curves obtained daily.

RESULTS AND DISCUSSION

Drug release

Drug release from film containing dispersed drug could be changed from linearity with the square root of time to linearity with time (zero order) by laminating a membrane layer to the releasing surface. This effect was demonstrated in many such laminated film (Borodokin and Tucker, 1974; Borodokin and Tucker, 1975; Bodmeir and Paeratakul, 1990).

Fig. 1 shows the drug release from films containing dispersed drug with and without membrane layers. Lamination of a membrane layer to film containing dispersed drug results in slower drug release as well as a change in kinetics due to the barrier nature of the membrane layer. This does not mean that all lam-

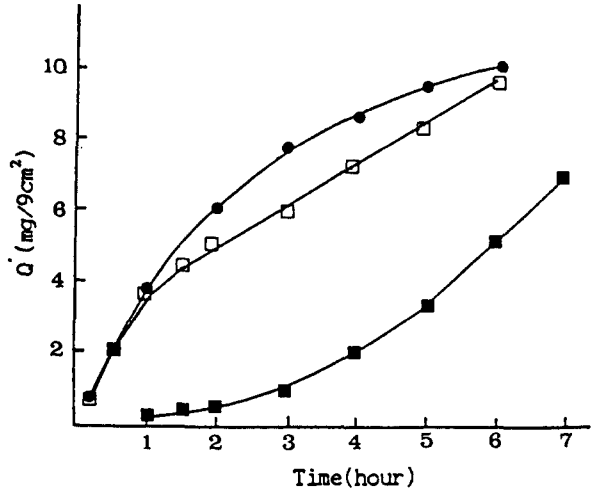

Fig. 1. Effect of lamination method on the drug release of cephalexin from films of cephalexin (17%)/Eud : HPC : DEP (5 : 4 : 1)-Eud : HPC : DEP (5 : 4 : 1) membranes. □, cast-on; ■, laminated; ●, no membrane

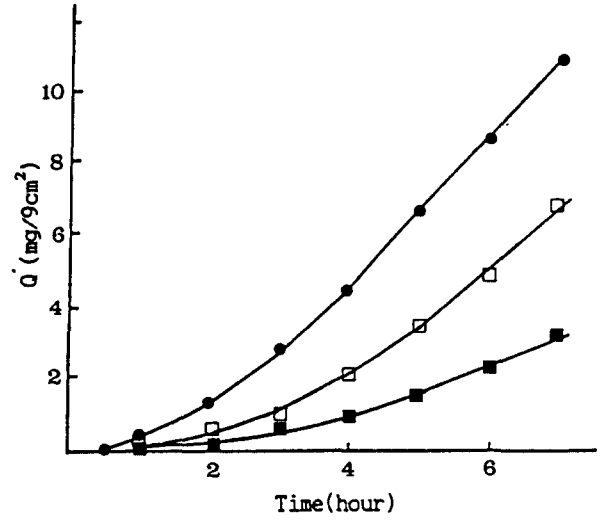

Fig. 2. Effect of different rate-controlling membrane made by lamination on the drug release from cephalexin 17%(w/w)/Eud : HPC : DEP (5 : 4 : 1)-Eud : HPC : DEP laminates. ●, 2 : 7 : 1; □, 5 : 4 : 1; ■, 7 : 2 : 1

inated films must release drug at slower rates than nonlaminated films but that different release patterns can be fabricated.

Lamination method

Zero order or constant drug release could be obtained by laminating a second, drug-free membrane onto the reservoir. The method of lamination had a pronounced effect on the drug release pattern. The rate-controlling membrane was either laminated on to the drug supplier layer by wetting it with solvent used and pressing it onto the reservoir or polymer solution forming the membrane was cast directly onto the

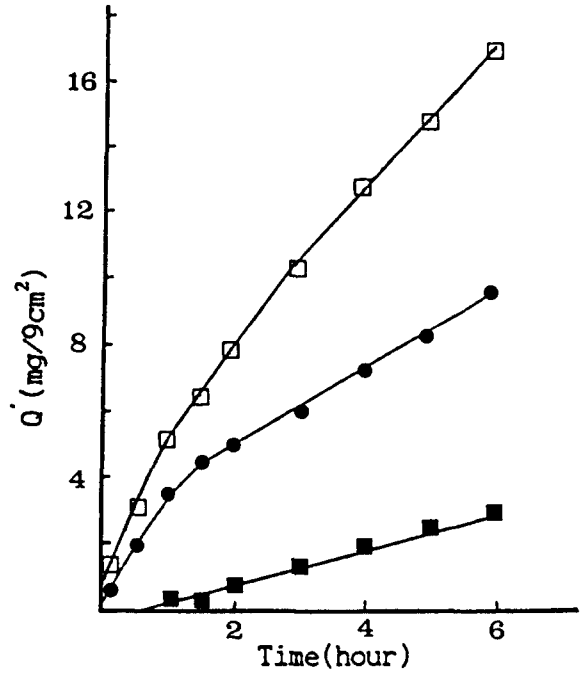

Fig. 3. Effect of different rate-controlling membrane made by cast-on method on the drug release from cephalexin (17%)/Eud : HPC : DEP (5 : 4 : 1)-Eud : HPC : DEP laminates. □, 2 : 7 : 1; ●, 5 : 4 : 1; ■, 7 : 2 : 1

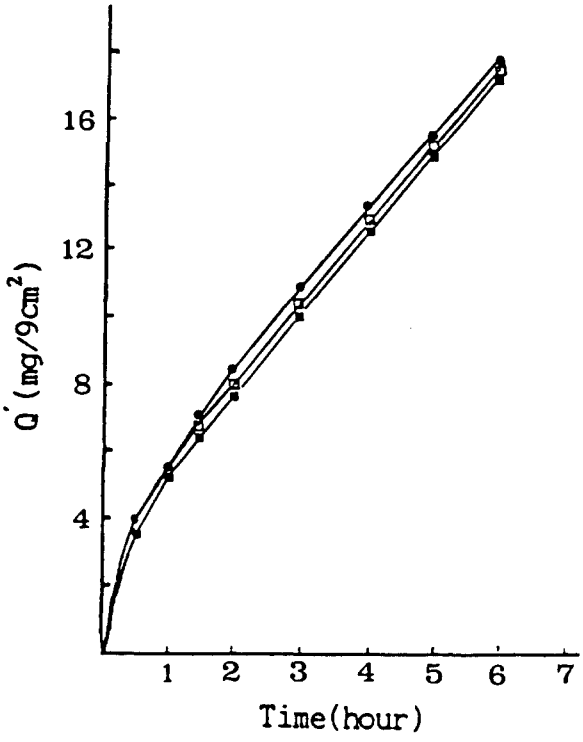

Fig. 4. Effect of different reservoir compositions on the drug release from cephalexin (17%)/Eud:HPC:DEP-Eud : HPC : DEP (3 : 6 : 1) laminates. ●, 2 : 7 : 1; □, 5 : 4 : 1; ■, 7 : 2 : 1

reservoir layer. Zero order release was obtained by both methods in hours. First method of lamination

Table I. Diameter of inhibition zone produced by EUD : HPC : DEP (6 : 3 : 1) disk containing 12.5% (w/w) cephalexin after release test

Release time (hr)	0	6	12	24	36	48	72	control
diameter (mm) (Mean±SE)	32.4±0.85	30.0±0.92	27.9±1.28	24.6±1.68	21.0±1.56	18.0±0.15	12.8±0.51	12.00

results in long lag time (Fig. 2) and cast-on method results in an initial rapid drug release (Fig. 3). Negative lag times indicated that the rapid exit of drug could stem from the presence of drug in the rate-controlling membrane. Drug might be extracted from the reservoir layer into the membrane layer during drying. The cast-on method may be useful to overcome the lag time and to increase the initial release of drug. The adhesion of the two layers in laminates prepared by the cast-on method was strong.

Polymer ratio in membrane

The effects of changing polymer ratio on drug release was investigated. A hydrophilic polymer, HPC, was added at various ratios to the rate controlling membrane. The addition of HPC in the membrane layer increased the release rate (Fig. 2 and 3). The increase in drug release with increasing proportion of the HPC could be explained with the swelling of HPC which results in increase of water permeability into the film. The hydration of the hydrophilic polymer caused the lag times to decrease with increasing HPC ratio. As shown in Fig. 4, varying the concentration of HPC in the drug reservoir layer did not affect the drug release. The drug release in the laminated film was controlled by the membrane layer.

Antimicrobial activity of films

Growth inhibitory activity of cephalexin from Eudragit RS film on *Streptococcus mutans* is shown in Table I. There are significant differences between blank matrix and matrices that had been released for 1 and 2 days but only slight difference was observed when released for 3 days. The disk after release test for 72 hours showed bacterial growth inhibition. The longer was the release time, the smaller were the diameters of growth inhibitory zones to *Streptococcus mutans* and that there is no growth inhibitory activity in blank disk (Table I). Therefore, this matrix could be adapted for the treatment of periodontitis instead of oral administration.

Percutaneous absorption

Fig. 5 shows *in vitro* percutaneous absorption of cephalexin from the matrix in rat skin. The results of the skin permeation studies indicate that cephalexin penetrates through the abdominal skin of the rat at a

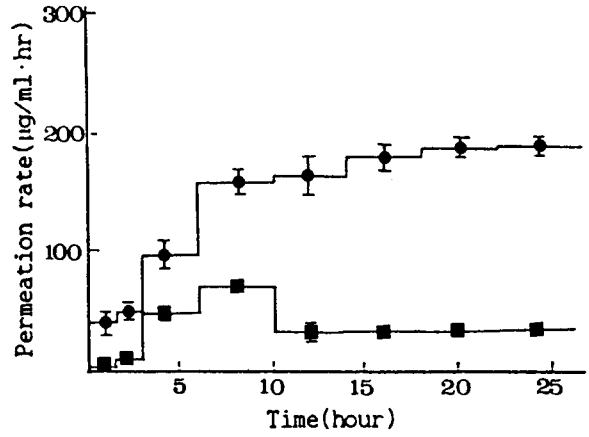

Fig. 5. Percutaneous permeation rate of cephalexin through rat skin from different matrix film containing 12.5% cephalexin. ■, Eud : HPC : DEP (5 : 4 : 1); ●, Eud : HPC : DEP (3 : 6 : 1)

rate profile. The pattern of transport in Eudragit RS/HPC (5 : 4) and Eudragit RS/HPC (3 : 6) film was different from each other. Steady state was achieved, after burst effect, in Eudragit RS/HPC (5 : 4) film and the flux of drug was gradually increased in Eudragit RS/HPC (3 : 6) film. After burst release at early stage, zero-order drug release has been obtained since eight hours. Burst effect results from drug release at the surface of matrix.

Excised rat skin has been used in studies on percutaneous absorption of drugs, because of its readily availability, although it differs significantly from human skin. The penetration of drug through skin was increased with HPC fraction in the film. The transport of drug through skin was controlled by the change of the film composition.

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