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Kinetics of Cephalexin Release from Eudragit–Hydroxypropylcellulose Membranes

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ABSTRACT

The release of cephalexin dispersed in films composed of different ratios of Eudragit-RS and hydroxypropylcellulose (HPC) was investigated. The results indicate that drug release from matrix follows a diffusion-controlled model, where the quantity released per unit area is proportional to the square roof of time. The release rate was found to be proportional to diethylphthalate (DEP) content, drug concentration, and HPC fraction in the film. Addition of plasticizer is indispensable for the improvement of film characteristics. The aggregation of drug particles was increased with DEP contents in film. The release rate was enhanced by adding the HPC to the rate-controlling membrane.

INTRODUCTION

Eudragit-RS is a copolymer synthesized from acrylic and methacrylic acid esters with low content of quaternary ammonium groups. Poly(meth)acrylates can be used in various ways to develop oral formulations with controlled release (1,2). This polymer is inert to the digestive tract, pH independent, impermeable to water, and capable of swelling and release of active ingredient by diffusion. 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 the two polymers not only alters drug release pattern from film, but also yields a flexible film. To improve the film characteristics, plasticizers such as diethylphthalate (DEP) and dibutylphthalate (DBP) were used.

Cephalexin was selected as a model drug to study the drug release. The purpose of this study was to investigate the drug release from a matrix composed of hy-

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droxypropylcellulose and Eudragit-RS, and to examine the possibility of use as carrier for a 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 from Roehm Pharm. Co. (Germany). All other chemicals were reagent grade and used as received.

Film Preparation. Six percent 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 hr, the solution was poured onto a plate coated with Teflon and allowed to evaporate at room temperature for 24 hr, and the prepared films were then carefully removed from the plate. Drug content was calculated from the weight ratio of drug and polymer used. The thickness of the films was determined using a micrometer.

In Vitro Dissolution Study. Square films (9 cm^2) were obtained from a selected portion of the cast film. A thin coating of high-vacuum silicone lubricant was applied to a glass plate. The film was carefully pressed into the plate, making sure that all edges adhered and no lubricant touched the exposed surface. Silicone lubricant was found superior to solvent-based adhesives by virtue of its noninteracting compatibility with the film. The slide was placed into a dissolution tester containing 500 ml of distilled water and the dissolution was determined at 37°C, 40 rpm. The samples were withdrawn at predetermined time intervals and assayed by a UV spectrophotometer at 262 nm. All experiments were repeated three times and mean values were obtained.

RESULTS AND DISCUSSION

Film Preparation

For the preparation of drug-containing polymeric films, drugs were dissolved in the polymer solution prior to casting. Drug and polymers were dissolved in methanol–acetone (80:20) mixture at concentration of 6% (w/v). The concentration of solute is very important in preparation of the polymer matrix. The solution was preserved at room temperature for 24 hr in order to enhance interpenetration of polymer particles. Upon drying, polymer solutions were converted into dry polymer films. Various research groups have studied the mechanism of film formation from polymer dispersions (3,4). The film formation occurs in three stages; (a) evaporation of organic solvent and concentration of polymer particles (chains); (b) deformation and coalescence of polymer particles; and (c) further fusion by interdiffusion of the polymeric molecules of adjacent polymer particles. The physical state of the drug in the dried film is dependent on the solubility of the drug in the polymer. A prerequisite for the successful preparation of the films was the compatibility of the dissolved drug and the polymer. Both polymers were compatible with the drug.

Kinetics of Drug Release

The release of drugs dispersed in thin films can be treated using Higuchi's equations for diffusion-controlled transport in a polymer matrix. In a planar homogeneous system, the following relationship holds:

$$Q = \{D(2A - C_s)C_s t\}^{1/2} \quad (1)$$

where Q is the amount of drug released per unit exposed area after time t, D is the diffusivity of the drug in the matrix, A is the initial drug concentration, and C_s is the drug solubility in the matrix. Higuchi later derived a similar relationship for planar release from a granular matrix system in which diffusion occurs through channels.

$$Q = \left[\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t\right]^{1/2} \quad (2)$$

where D and C_s refer to diffusivity and solubility in the permeability fluid, respectively, τ is the tortuosity of the matrix, and ε is the porosity of the matrix. Drug release from matrix systems follows either a square root of time relationship or more complex patterns according to the diffusional character of the system. One of the major objectives in the development of a controlled-release drug delivery system is to prepare devices which release drugs at a constant rate for extended periods of time. Zero-order or linear drug release can be obtained by laminating a drug-free membrane onto a drug reservoir layer. The drug supply layer serves as the reservoir that controls the duration of drug release, while the drug-free layer functions as the rate-controlling membrane (5,6).

In order to fit the drug release to the Q' versus $t^{1/2}$ relationship, the drug concentration in the undepleted zone should far exceed the solution concentration at the interface ($A \gg C_s$ or εC_s). A first-order relationship might be possible.

$$\log A' = \log A \frac{kt}{2.303} \quad (3)$$

where A' is the drug content of the film at time t. When experimental data were treated according to the diffusion-controlled model, the drug concentration increased linearly with the square root of time in all systems (Fig. 1). The release data obtained in this study were treated by both methods to ascertain which relationship gave the best fit (Fig. 2). The correlation coefficients for the best statistical lines were used as the principal criteria for evaluation. The data comparing the two treatments for different composition of films are shown in Table 1. The linear relationship obtained by plotting Q' versus $t^{1/2}$ generally gave correlation coefficients greater than 0.998; these were maintained throughout the whole experiments except for Eudragit-RS/HPC film (7:2).

Further evidence bearing upon the relative validity of these two models was obtained by utilizing the differential forms of their rate equations. For diffusional control, the release rate, dQ'/dt, is proportional to the reciprocal of Q', $1/Q'$, where Q' is the total drug amount released at a given time.

$$\frac{dQ'}{dt} = \frac{k'^2}{2Q'} \quad (4)$$

$$\frac{dQ'}{dt} = KA - KQ' \quad (5)$$

Release rates were determined by measuring the slopes of Q' versus time curves. When the release rates from Eudragit-RS/HPC film (5:4) were plotted as a function of Q' and $1/Q'$, linearity was obtained only in the latter case (Fig. 3 and Table 2), indicating that the process is diffusional. Experimentally, the linear diffusion model held up to 60–70% drug release, after which the rate decreased progressively. This deviation would be explained by the total exhaustion of solid drug phase from the film, subsequent to which the diffusion gradient would be first-order dependent on drug content.

The derivation of Q' versus $t^{1/2}$ relationship requires a constant concentration gradient through release. Therefore, the drug concentration in the medium must remain insignificant compared to its solubility. Experimental conditions used were easily met with the drug, where the maximum concentration that could be encountered with complete drug release was well below 1% of its solubility.

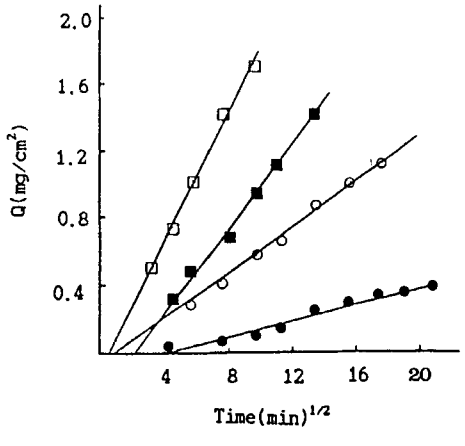

Figure 1. Drug release from the various ratio Eud/HPC films containing 10% (w/w) cephalexin. □, 1:8; ■, 3:6; ○, 5:4; ●, 7:2.

Effect of Polymer Ratio

Altering the HPC/Eudragit-RS ratio in the polymer mixture markedly affected the release rate (Fig. 4). The results showed an acceleration of the release rate with an increasing proportion of HPC in the polymer matrix.

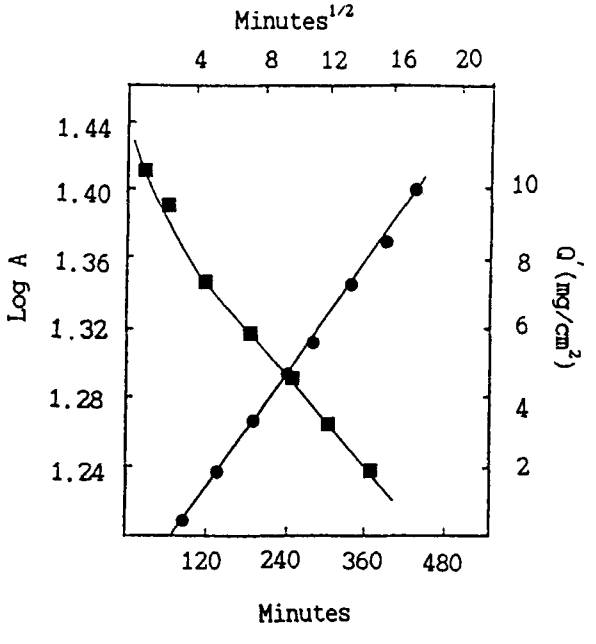

Figure 2. Comparison between first-order release treatment and Q' versus $t^{1/2}$ treatment from data of 5:4:1 ratio of Eud/HPC/DEP film containing 10% (w/w) cephalexin. ■, log A versus t; ●, Q' versus $t^{1/2}$.

Table 1

Comparison Between Linearization of Release Rate of Cephalexin from Eud/HPC Films Containing 10% (w/w) Cephalexin by First-Order and Diffusion-Control Treatments

	First-order Treatment			Diffusion-Control Treatment		
Eud/HPC Ratio (w/w)	K × 10^4 (min^{-1})	t_{lag} (min)	Correlation Coefficient	k' (mg/9 $cm^2/min^{1/2}$)	t_{lag} (min)	Correlation Coefficient
7:2	1.43	69.97	0.983	0.227	5.31	0.999
5:4	5.62	35.38	0.992	0.606	2.21	0.999
3:6	14.24	14.04	0.988	1.136	2.32	0.998
1:8	32.80	18.29	0.988	1.731	0.48	0.988

Note: Eud = Eudragit-RS.

The best explanation for the large k' changes with polymer ratio in terms of the parameters shown in Eqs. (1) and (2) would be through consideration of the hydrated film obtained upon immersion in the medium as a actual diffusion matrix. In terms of the homogeneous matrix system [Eq. (1)], the increasing k' values obtained with increasing HPC may occur primarily through high water permeability into the film in the more hydrophilic matrix. Alternatively, in terms of the granular matrix system [Eq. (2)], increased porosity ε and decreased tortuosity τ would accompany the greater hydration of films containing increasing ratios of HPC.

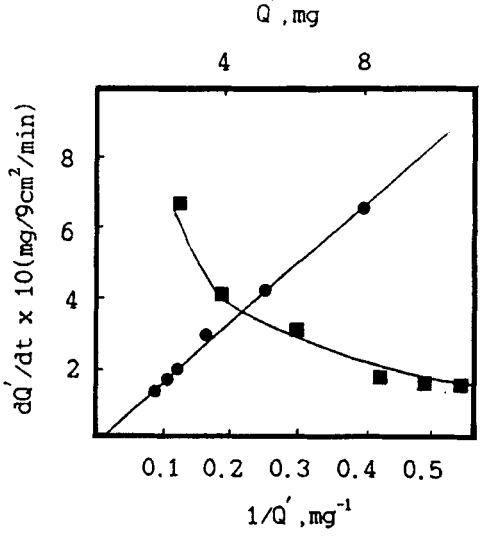

Figure 3. Comparison plots of release rate of cephalexin from Eud/HPC/DEP (5:4:1) film containing 10% (w/w) cephalexin against the amount of drug released (Q') and the reciprocal amount of drug released ($1/Q'$). ■, dQ'/dt versus Q'; ●, dQ'/dt versus $1/Q'$.

Effect of Plasticizer

The addition of plasticizer is indispensable in Eudragit-RS film, because pure Eudragit-RS film is very

Table 2

Comparison of Parameters of Linearity Obtained from Plots of Release Rates Against the Reciprocal Amount of Cephalexin Released ($1/Q'$) and the Amount (Q') of Cephalexin Released

Eud/HPC ratio (w/w)	Correlation Coefficient	
	Rate Versus Q'	Rate Versus $1/Q'$
7:2	0.928	0.997
5:4	0.926	0.996
3:6	0.965	0.996
1:8	0.974	0.996

Note: Eud-Eudragit-RS.

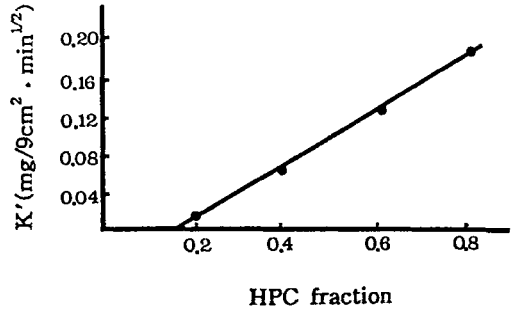

Figure 4. Relationship of the release rate constants of cephalexin to the HPC fraction.

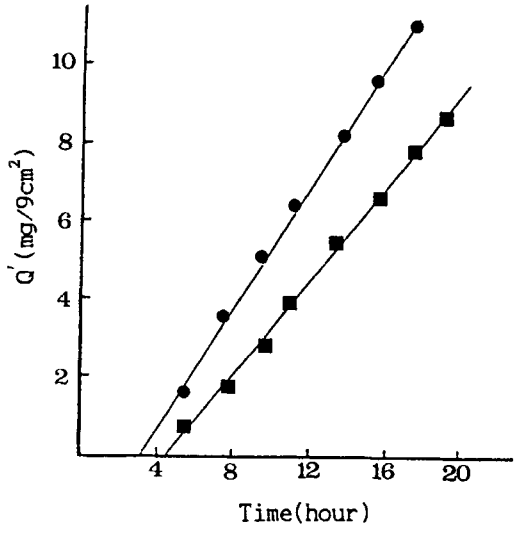

Figure 5. Effect of plasticizers on the release of cephalexin from Eud/HPC/plasticizer (6:3:1) films containing 12.5% (w/w) cephalexin. ●, 10% dibutylphthalate; ■, 10% diethylphthalate.

brittle. As a plasticizer, dibutylphthalate (DBP) or diethylphthalate (DEP) was selected. Addition of DBP was more effective for the release of drug than DEP (Fig. 5). It seems that hydrophobicity of DBP caused the aggregation of drug particles. The drug particles were uniformly dispersed in the films at no plasticizer or 10% (w/w), indicating that the drug was dissolved in the polymer matrix. But drug particles were aggregated at 20% concentration of plasticizer (Fig. 6).

The effect of increasing DEP at constant drug concentration was a marked increase in the release rate (Fig. 7). Addition of DEP increased the aggregation of drug particles and porosity of the film surface. The aggregation of drug particles increased the possibility of channel formation (Fig. 8). As a certain particle-occupied volume in the matrix leaches out, the void volume would be expected to be occupied by external solvent diffusing into the film. Upon exposure to an aqueous solvent, molecules can then leave the matrix through these particles and diffuse through the network of pores which is formed as water penetrates further into the system. Particles of drugs which are totally incarcerated by the polymer matrix will never be released if the polymer matrix is nondegradable. The release rate was increased with higher DEP fraction (Fig. 9).

Effect of Drug Concentration

The effect of drug concentration on the release rate was tested using four different concentrations, from

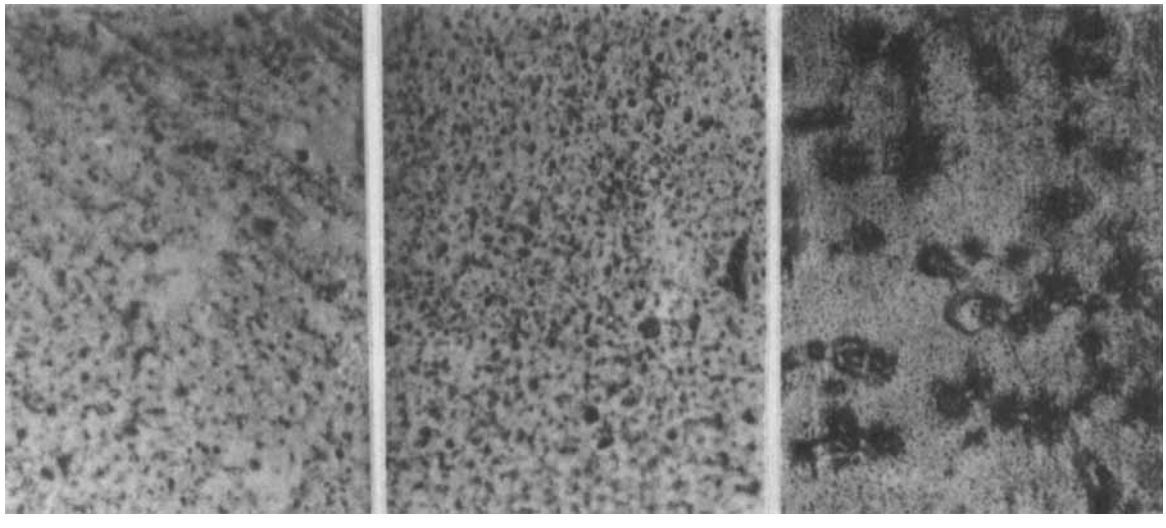

Figure 6. Microscopic photographs of DEP/HPC (5:4) films containing 12.5% cephalexin at different concentrations (w/w) of diethylphthalate before drug release (× 48). A, 0%; B, 10%; C, 20%.

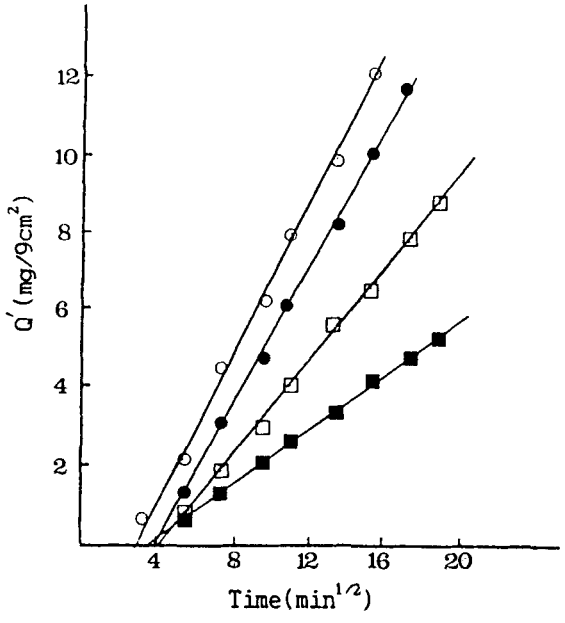

Figure 7. Drug release from Eud/HPC (6:3) films containing 12.5% cephalexin at different concentrations (w/w) of diethylphthalate. ■, 5%; □, 10%; ●, 15%; ○, 20%.

7.5% to 15% in Eudragit-RS/HPC films (5:4) (Fig. 10). The densities of Eudragit-RS, HPC, and cephalexin were 1.07, 0.89, and 0.928 g/ml, respectively. The weight per weight drug concentrations were converted to weight per volume (A values) concentrations. The k' versus A plots were slightly more linear ($r = 0.995$) than the k' versus $A^{1/2}$ plots ($r = 0.975$). This relationship is difficult to explain in terms of Eq. (1), where k' might be expected to be linear with the square root of drug concentration. However, it may be rationalized on the basis of the drug concentration effect on D and C_s through film hydration. A more plausible explanation may be made on the basis of Eq. (2) for a granular matrix system. By assuming that all matrix porosity necessary for the diffusion pathway is due to that vacated by the dispersed drug, ε may be equated to KA ($K = 1/\rho$). Assuming also that $2A >> \varepsilon C_s$ (Eq. 6) may be simplified:

$$k' = \left(\frac{DKC_s}{\tau}\right)^{1/2} A \tag{6}$$

The release rate constant would be proportional to the drug concentration (A) (Fig. 10).

CONCLUSIONS

The present investigation on Eudragit-RS/HPC films showed the following results.

1. The release of cephalexin from the matrix followed Higuchi's equation.
2. The quantity released per unit area was proportional to the square root of time.

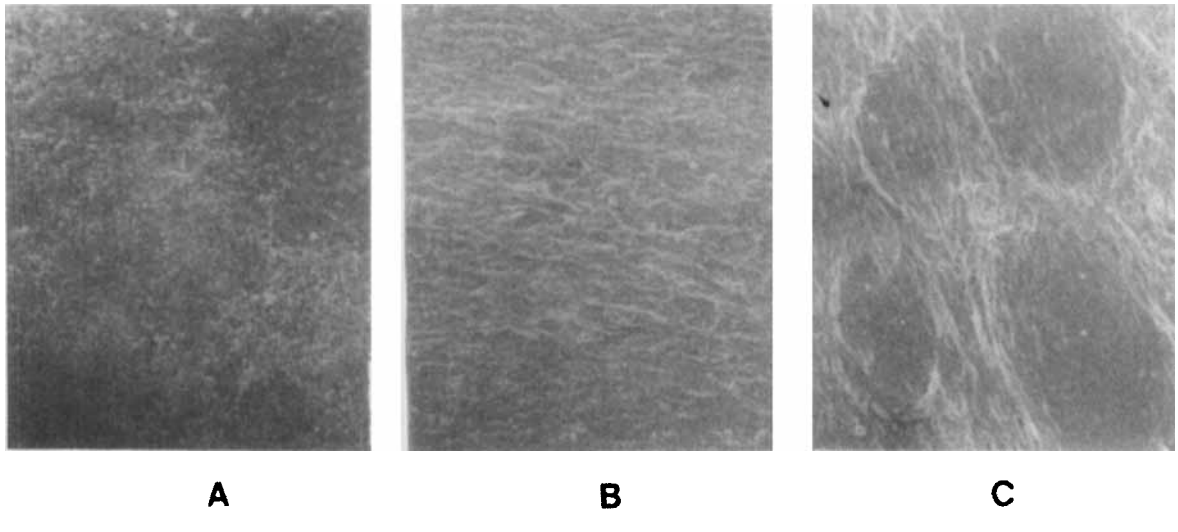

Figure 8. Scanning electron micrographs of Eud/HPC (5:4) films containing 12.5% cephalexin concentrations (w/w) of diethylphthalate after drug release for 8 hr (× 48). A, 0%; B, 10%; C, 20%.

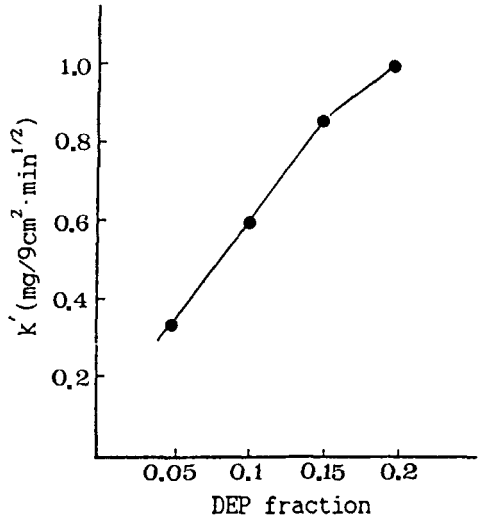

Figure 9. Effect of DEP concentrations on the release rate constants of cephalexin from Eud/HPC/DEP (6:3:1) films.

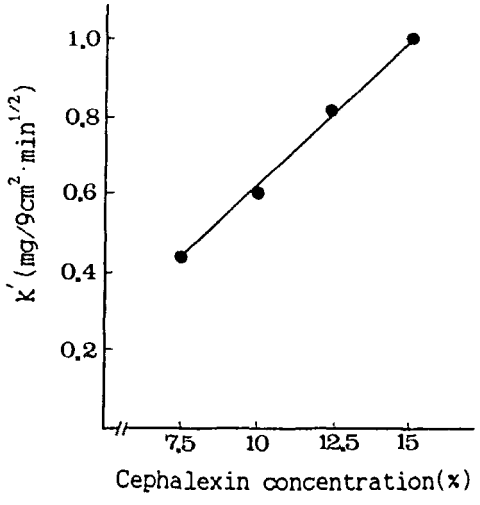

Figure 10. Relationship of the release rate constants to the loaded cephalexin concentration in Eud/HPC/DEP (5:4:1) films.

3. The release rate constant (k') was proportional to DEP content, drug concentration, and HPC fraction in the film.
4. Addition of plasticizer was indispensable for the improvement of film characteristics.

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