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Release of cortisol from lanolin alcohol-providone films

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RELEASE OF CORTISOL FROM LANOLIN ALCOHOL-POVIDONE FILMS

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ABSTRACT

In this study, lanolin alcohol as well as lanolin alcohol-povidone films (1:1.5) were investigated as a potential drug delivery system. The *in vitro* drug release from these films was studied in terms of the effect of agitation, film thickness and drug concentration.

The rate of release of Cortisol from lanolin alcohol films was not affected by the intensity of agitation. Moreover, the film matrix was found to remain essentially intact throughout the release process. Further analysis of the data revealed that Higuchi's diffusion-controlled granular matrix model explained the mechanism of Cortisol release from such films.

The results of drug release from lanolin alcohol-povidone films have shown that although Higuchi's release rate constant was found to be independent of film thickness, it was affected by the intensity of agitation, since the rate constant was found to increase as agitation speed was increased, especially at low speeds. In addition, povidone was found to leach out of the film matrix along with the drug. These factors, in conjunction with further analysis of the drug, explained the failure of this film system to conform to the matrix-controlled diffusion model. The release

rate of Cortisol from this film system was found to follow first-order dependence on drug concentration.

The drug was found to be completely insoluble in lanolin alcohol, and slightly soluble in povidone. Povidone was found to enhance the solubility of Cortisol in water.

ACKNOWLEDGMENTS

I would like to express my profound gratitude and deep appreciation to Dr. Ravindra C. Vasavada for his encouragement, constructive criticism, and guidance throughout all stages of this work. My thanks and appreciation are also due to Drs. Donald Y. Barker and Herschel Frye for their patience and help.

I would like to thank Mr. Rajesh Patel, my fellow graduate student, for his help during the course of this project. I am also grateful to Mrs. Sandy McNett-McGowan for her kind help with the preparation of this manuscript. Acknowledgments are also due to Mrs. Carol Sarnoff who typed this work.

Finally, I wish to dedicate this thesis to my parents, my wife Amal, and my country.

TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF TABLES
(continued)

LIST OF TABLES
(continued)

LIST OF FIGURES

LIST OF FIGURES
(continued)

LIST OF FIGURES
(continued)

INTRODUCTION

The use of drugs incorporated into an inert matrix to achieve controlled release has been under extensive research for the past few decades. Minimization of patient compliance problems through the use of prolonged action dosage forms is one of the major factors responsible for this interest. Another factor that has sparked interest in controlled delivery systems has been the rapid growth of polymer technology and its application to the solution of many biomedical problems. Many advantages can be obtained by the use of such controlled systems. For instance, it makes it possible to decrease the frequency with which the patient has to take the dosage, and to prolong the activity throughout the night so the patient is not disturbed during his sleep. Furthermore, fewer side effects could occur, when a constant blood level of the drug is maintained over a desired period of time. Numerous medical applications of such systems have been reported in dermatologic practice (1,2), opthalmic practice (3), vaginal devices (4-6), and long term buccal absorption of drugs (7).

A major function of the skin is the retardation of the diffusion and evaporation of water from within the body, except at the sweat glands. The stratum corneum is probably responsible for this retardation. Drugs may be applied to

the skin for a local effect, especially on the superficial layers of the epidermis. The drugs are incorporated into vehicles which adhere to the skin, allowing diffusion of drug molecules out of the vehicle into the epidermis. Hydration of the stratum corneum is probably the most important factor in enhancing the rate of skin penetration. The prevention of water loss by the application of occlusive plastic film in steroid treatment of different skin diseases leads to accumulation of larger amounts of water in the skin layer, and the subsequent enhancement of the applied steroid penetration (8-10). McKenzie and Stoughton (9) have increased the percutaneous absorption of corticosteroids by the occlusion of the skin surface with Saran Wrap®. The occlusion of the skin surface has resulted in a 100-fold difference in the absorption over simple topical application. Vehicles also play an important role in percutaneous absorption of several drugs. Poulsen et al. (11) have investigated the release of fluocinolone acetonide and its acetate ester from gelled propylene glycol-water vehicles. It was found that steroid release is a function of its concentration, solubility in the vehicles, and the partition coefficient between the vehicles and the receptor phase. Katz et al. (12), have observed that the structural changes which produce potent topical anti-inflammatory corticosteroids provided the physical properties necessary to achieve effective percutaneous absorption, and effective biological

activity. Coldman et al. (13) have enhanced the skin penetration of fluocinolide and fluocinolone acetonide from vehicles containing different proportions of isopropanol and propylene glycol. The incorporation of dimethylsulfoxide (14) and more recently, Azone® (15) into the dermatologic preparations have also been successfully shown to enhance drug penetration across the stratum corneum. Wester et al. (16) have noticed in the in vitro study in the Rhesus monkey that the level of absorption of hydrocortisone is significantly increased during long-term administration.

The use of polymers in controlled drug delivery systems has been the focus of interest in many pharmaceutical research laboratories. Sciarra and Gidwani (1,2) have shown that the nature of the films and their physical properties had a significant effect on the release of drugs, and on the application of such films as aerosol sprays. Loucas and Haddad (3) observed that by the use of ophthalmic flakes of pilocarpine alginate as a solid dosage form, the availability of pilocarpine in the cul-de-sac of albino rabbit's eyes, may be more uniform as a consequence of diminished diffusion through the gel matrix, in contrast to liquid dosage forms where the dose is immediately released into the conjunctival fluids. Chien et al., have taken advantage of the high permeability of silicone polymers to steroids in the development of vaginal devices in the shape of rings. The factors influencing the rate of release of ethynodiol diacetate from solid silicone

polymer vaginal devices were evaluated (4). Two types of release mechanisms, matrix-controlled and partition-controlled, were noticed when the release profiles of ethynodiol diacetate from these vaginal devices were followed daily in these systems (5). The solution-solubility dependency of the controlled release of the drug from such matrices was mathematically analyzed (6). Roseman and Higuchi (17) have studied the release of medroxyprogestrone acetate from a silicone rubber matrix *in vitro*. This study has suggested that the partition coefficient, diffusion coefficient, drug concentration within the polymer, and agitation conditions play important roles in the release process. In another study (18), Roseman found that the amount of four progesterone-type steroids, released from the same silicone matrix system was dependent upon the molecular structure of the steroid. Borodkin and Tucker (19) used an additive polymer, hydroxypropylcellulose, which was selected on the basis of hydrophillic properties to increase the rate of release of methyapyrilene hydrochloride, sodium pentobarbital, and salicylic acid dispersed in films composed of different ratios of hydroxypropylcellulose and polyvinyl acetate. The effect of a leachable component, polyethylene glycol, on ethyl cellulose films has been investigated (20). Luongo *et al*. (21) have attempted to formulate a topical spray-on bandage as an effective preparation for contaminated wounds. The results indicated that neomycin sulfate and triclosan

were released from ethylcellulose-polyamide resins films, and the spray-on bandages did reduce the degree of infection about the wound. Shaw et al. (22) have developed a trans-dermal therapeutic system for scopolamine. These systems were designed to deliver the drug at various rates to the skin surface, and hence to the systemic circulation. The different rates of scopolamine permeation through the skin were evaluated for their ability to prevent nausea and vomiting due to motion.

Lanolin alcohol*, a non-polymeric material, has been under investigation in our laboratories (23,24). It was observed that lanolin alcohol forms films which could be easily isolated from mercury substrate. The film-forming potential of lanolin alcohol was evaluated. The film characteristics were improved by the inclusion of ethyl cellulose. Triamcinolone acetonide was used as a model drug. The release kinetics from such a film system were reinvestigated and confirmed (25). The use of non-polymeric substances, such as lanolin alcohol, as film formers has many advantages:

a) they could be designed to provide sustained drug delivery.

b) hazards associated with monomeric impurities in polymer systems could be avoided.

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*Mixture of aliphatic alcohols, triterpenoid alcohols, and sterols, obtained by hydrolysis of lanolin.

c) films of these materials are easily washable from the skin without leaving any traces.

d) non-polymeric materials are easy to manipulate and formulate.

Because of its favorable physico-chemical properties and high degree of physiological tolerance, polyvinylpyrrolidone (PVP) is used for many different purposes in pharmacy and medicine. Both types of PVP, soluble and insoluble, are used in the pharmaceutical industry as film formers, tablet binders, thickeners, solubilizers, and tablet disintegrants. Dakkuri et al. (26), have utilized PVP as a channeling agent by its incorporation into a mixture of carnauba wax and stearyl alcohol by fusion and subsequent congealing. The results indicated that fusion is essential for channel formation. The addition of certain substances, ethyl cellulose and shellac, was found to eliminate the tackiness associated with PVP films due to the hygroscopicity of PVP (27).

Research background:

The continuing investigation about the potential of lanolin alcohol as a film-former has resulted in the development of a new film system of PVP-lanolin alcohol (28). Series of films of PVP and/or lanolin alcohol and Cortisol, a topical anti-inflammatory agent, as a model drug were prepared. It was observed that as the proportion of lanolin alcohol was increased in the films, they became translucent, flexible,

and could be more easily isolated. It was also noticed that both sward hardness and modulus of elasticity were significantly decreased by the increase in the proportion of lanolin alcohol. The wettability of PVP films was decreased by the incorporation of small amounts of lanolin alcohol, resulting in higher contact angles due to the hydrophobicity of lanolin alcohol. It was found that the rate of Cortisol release was markedly decreased with decreasing PVP content and increasing lanolin alcohol in the films. This work is a continuing research on the same system, PVP-lanolin alcohol films, to further investigate the mechanism by which Cortisol is released from such a film matrix. Two film compositions film #6 (film A), and film #9 (film B), have been chosen from the above-mentioned work to study the effect of different factors on drug release (Table I).

The diffusion of the drug from the film vehicle into the aqueous release medium in vitro has been studied. The concentration gradient occurs in the applied phase and the aqueous receptor fluid assumed to be a perfect sink since drug concentration attained at any given time was never more than 7.7% of the reported drug solubility (29) at $37^{o}C$.

According to the results of a theoretical analysis of the mathematical relationships concerning the rate of release of solid drugs dispersed in solid matrices, two mechanisms of drug release have been developed by Higuchi (30):

(I) Unidirectional drug release from a planar homogeneous matrix.

(II) Unidirectional drug release from a planar granular matrix.

(I) Unidirectional drug release from a planar homogeneous matrix:

In this mechanism, the drug is presumed to diffuse through and from the uniform homogeneous matrix, and out into the perfect sink which is the bathing solvent. The amount of drug released from such a system into the bathing medium would be determined by the following relationship:

$$Q = \sqrt{Dt\ (2A - C_s)\ C_s} \quad \ldots\ldots\ldots\ldots \text{(Eq. 1)}$$

Where:

Q is the amount of drug released after time t per unit exposed area.

D is the diffusivity of the drug in the homogeneous matrix media.

A is the total amount of drug present in the matrix per unit volume.

C_s is the solubility of the drug in the matrix substance.

(II) Unidirectional drug release from a planar granular matrix:

The drug is leached out from this matrix by the bathing fluid, which is able to go into the drug-matrix phase through pores, cracks, and intergranular spaces. By the slow dissolution

of the drug into the permeating fluid, the drug is assumed to diffuse through the channels and cracks. Higuchi's model (Eq. 1) has been modified for the effective volume where diffusion can occur and the effective diffusional path the following relationship has resulted:

$$Q = \sqrt{\frac{D\varepsilon}{T}(2A - \varepsilon C_s) C_s t} \quad \ldots\ldots\ldots \text{(Eq. 2)}$$

Where:

Q is the amount of drug released after time t per unit exposed area.

D is the diffusivity of the drug into the permeating fluid.

T is the tortuosity of the capillary system.

A is the total amount of drug present in the matrix per unit volume.

C_s is the solubility of the drug in the permeating fluid.

ε is the porosity of the matrix.

The derivation of both equations 1 and 2 (31) is based on the existence of a pseudo-steady state condition during the release process. It is also assumed that the drug particles are very small relative to the average distance of diffusion and are uniformly distributed in the matrix. It was also stated that these equations would be essentially valid for systems in which A is greater than C_s and εC_s by a factor of three or four.

Both equations describe drug release as being linear with square root of time:

$$Q = K\, t^{\frac{1}{2}} \quad \text{(Eq. 3)}$$

Where K is the release rate constant

$$K_H = \sqrt{D\,(2A - C_s)\,C_s} \quad \text{Homogeneous matrix} \quad \text{(Eq. 4)}$$

$$K_G = \sqrt{\frac{D\varepsilon}{T}\,(2A - \varepsilon C_s)\,C_s} \quad \text{Granular matrix.} \quad \text{(Eq. 5)}$$

In this study the release of Cortisol was examined to determine whether or not it obeys one of the Higuchi models.

EXPERIMENTAL

Materials:

1. Lanolin Alcohol (Super Hartolan, Croda Inc., New York, New York (Lot #72577).
2. Polyvinylpyrrolidone, Povidone ^{R}, K-30 (PVP) Matheson, Coleman & Bell, Manufacturing Chemists, Nortwood, Ohio.
3. Hydrocortisone (Cortisol ^{R}), Amend Drug & Chemical Co., Inc., Irvington, New Jersey (Lot #F16755 GO8).
4. Isopropyl Alcohol, U.S.P. (2-Propanol), J. T. Baker Chemical Co., Phillipsburg, New Jersey (Lot #215614).
5. Ethyl Acetate "Baker Analyzed" ^{R}, J. T. Baker Chemical Co., Phillipsburg, New Jersey (Lot #019002494).

Preparation of the Solution:

A solution containing the appropriate amounts of Povidone, Lanolin Alcohol and Cortisol (Table I) was prepared. The required quantities of the drug and film formers were dissolved in about 40 ml of isopropanol by gently heating it in a water bath at 50^{o}C. The solutions were checked by visual

examination, to ensure the absence of any suspended particles. The solutions were cooled to room temperature and then completely transferred into a 50-ml volumetric flask, with the aid of two washings. The volume was then adjusted to the mark.

Preparation of the Films:

All films were cast from a 10% (w/v) solution which contained the drug and film formers. Five ml of the solution was poured into aluminum petri dishes (Surface area 44.18 cm^2) using a Pipetman® pipette.[1] The dishes were kept on a level surface to ensure the uniform distribution of the solution, and films of even thickness. The dishes were partially covered to allow uniform evaporation of the solvent at room temperature. The solution was left to evaporate over 48 hours. The complete dryness of the films was confirmed by weighing the dishes to a constant weight. The film-coated petri dishes were stored in a desiccator containing anhydrous Calcium Sulphate, for about 24 hours prior to the release studies. The unidirectional release of Cortisol from the films was ensured by checking for the adherence of the film to the dish bottom throughout the release process.

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[1] Pipetman®, Model p-5000D, Woburn, Massachusetts.

Drug Release Studies:

The release studies were carried out using a dissolution assembly[2] (Figure 1), with the following modifications:

a) the flasks were replaced by 1000-ml bottomed polypropylene beakers.

b) the dissolution basket assemblies were replaced by stainless steel stirrers with a propeller of 4.5 cm diameter.

Three hundred ml of distilled water previously equilibrated at 37°C were added to each beaker, followed by the careful immersion of aluminum dishes with a test film adhered to the bottom. The agitation speed was maintained at 30 rpm throughout each experiment and the water bath temperature was kept at 37±0.5°C. The effect of the agitation speed on the release was studied at the stirring rates of 0, 10, 30, 60, 90, 150, and 210 rpm. Three ml of the sample were withdrawn at appropriate time intervals over 24 hours, and analyzed for Cortisol content. Each sample (3 ml) was replaced by an equal volume of distilled water in order to keep the total volume constant. A cumulative correction was made for the removed samples to determine the total amount released according to the following formula (32):

$$C_n = C_n \text{ meas.} + \frac{3}{300} \sum_{s=1}^{n-1} . (C_s \text{ meas.}) \quad \text{(Eq. 6)}$$

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[2] Hanson Research Corp., Northridge, California.

Where:

C_n meas. is the spectrophotometrically measured concentration.

C_n is the concentration of the nth sampling expected in the medium if previous samples had not been removed.

n-1 is the total volume of all samples removed prior to the sample being measured.

C_s meas. is the total of all spectrophotometrically measured concentrations at n-1 samples.

The Cortisol concentration in distilled water was determined by ultra violet spectrophotometry at wavelength 242 nm[3], and then by consulting the standard curve of Cortisol (Figure 3). All studies were conducted in duplicates.

Film Thickness Study:

Films of different thicknesses were prepared by the use of the mercury substrate technique (23, 24). 5ml, 7ml, 9ml, 11ml, and 13ml of the film-forming solution were poured on the surface of the mercury contained in the aluminum dishes, which then were partially covered with their lids. The partial covering of the dishes helped in controlling the rate of evaporation of the solvent, and prevented the blistering

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[3] Spectronic 710, Bausch and Lomb, Rochester, New York.

of the deposited films. The larger amounts needed a longer time (up to 7 days) to completely dry up, than the small amounts. The dry films were carefully removed from the mercury substrate and were individually stored between sheets of wax paper in a desiccator.

The film thickness was measured by means of a Minitector thickness measuring gauge (Model-N).[4] The instrument was calibrated using the standard foils provided with the instrument. Ten readings were recorded at different points of the film surface. An average of twenty readings on two films of the same composition was recorded, and the standard deviation was calculated (Table II).

Povidone Release Studies:

To test if the PVP was leached out from the film matrix, a series of films (placebo and medicated films) were prepared the same way as in the other studies. The weights of the drug films were determined. The release studies were carried out using the same technique and the same apparatus used in the drug release studies which were previously described. After running the experiment over 24 hours, the film-coated petri dishes were taken out of the dissolution medium and dried in an oven at 50°C. The complete dryness of the films was confirmed by weighing the dishes to a constant

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[4] Gardner Laboratory, Inc., Bethesda, Maryland.

Table I. Composition of films A and B.

Material	Film A	Film B
Povidone (% w/w)	58.5	0.00
Lanolin alcohol (% w/w)	39.0	97.5
Cortisol (% w/w)	2.5	2.5

Table II. Volumes of solution and the resulted film thickness.

Volume of Solution	Dry film thickness µm ± S.D.[a]
5 ml	93 ± 4.1
7 ml	138 ± 8.6
9 ml	219 ± 8.7
11 ml	317 ± 12.8
13 ml	409 ± 11.2

[a] Mean ± standard deviation of ten measurements in duplicates.

weight. Three ml of the bathing solution was withdrawn and analyzed spectrophotometrically to determine the amount of the drug released. The weight loss was determined and the amount of PVP leached out was calculated (Table III). The same experiment was performed using pure lanolin alcohol films to determine the possibility of dissolution of lanolin alcohol.

Solubility of Cortisol in the Film Matrix:

(I) Solubility of Cortisol in lanolin alcohol: First, the solubility of Cortisol in distilled water was determined by adding excess amounts of Cortisol to a known volume of water in 50-ml conical flask. A teflon-coated magnetic bar was placed in the flask prior to capping it tightly. The solution was left stirring for about 48 hours. The stirring was stopped prior to the sampling. An aliquot was filtered using 0.22 μm filter paper.[5] The first few mls of filtrate were discarded due to the adsorption of the steroid to the filter paper (33). After proper dilution, the concentration of Cortisol was determined as usual. About 1.1 gm of lanolin alcohol was melted in a preweighed 25-ml flask containing a known amount of Cortisol dissolved in 20 ml of distilled water (a saturated solution). A teflon-coated magnetic bar was placed in the flask, which was then capped and kept

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[5] Swinnex-25, Millipore Filter Corp., Bradford, MA.

in a water bath at 37°C, over a magnetic stirrer. The flask was supported by a holder at a distance of 2 cm from the bottom of the bath. The stirring was stopped after 96 hours. The lanolin alcohol was allowed to settle. An aliquot of the aqueous phase was filtered using a glass funnel with filter paper. One ml was pipetted into a 25-ml volumetric flask. The volume was adjusted to the mark. The drug concentration was measured spectrophotometrically as described before. The apparent solubility of the drug in lanolin alcohol was determined using the equation (Eq. 7).

(II) Solubility of Cortisol in PVP:

The solubility of Cortisol in ethyl acetate was determined the same way as in the experiment of the drug solubility in lanolin alcohol. One gm of PVP was suspended in a saturated solution of Cortisol in ethyl acetate in 50-ml conical flask, which was tightly capped and stirred magnetically. The stirring was stopped after 96 hours, and the PVP was allowed to settle. Ten ml of the filtered supernatant were pipetted into a 100-ml volumetric flask. The solvent was evaporated in an oven at 55°C. The residue was dissolved in distilled water, and the resulting solution was properly diluted. The apparent partition coefficient K_e was determined by the equation (Eq. 8) proposed by Chowhan et al. (34).

(A) Lanolin Alcohol-Water:

$$K_e = \frac{A_1/W_1}{A_w/W_w} = \frac{(A_w^1 - A_w)\, W_w}{A_w\, W_1} \quad \ldots\ldots \text{(Eq. 7)}$$

Where:

A_1 and A_w are the amounts of drug in lanolin alcohol and water respectively.

A_w^1 is the initial amount of drug in water.

W_1 and W_w are the weights of lanolin alcohol and water respectively.

(B) PVP-Ethyl Acetate:

$$K_e = \frac{A_p/W_p}{A_E/W_E} = \frac{(A_E^1 - A_E)\, W_E}{A_E\, W_P} \quad \ldots\ldots \text{(Eq. 8)}$$

Where:

A_p and A_E are the amounts of drug in PVP and ethyl acetate respectively.

A_E^1 is the initial amount of drug in ethyl acetate.

W_p and W_E are the weights of PVP and ethyl acetate respectively.

Since the effective partition coefficient relates to the drug concentration in the two phases near saturation, the apparent solubility of the drug in PVP or lanolin alcohol can be determined from the drug solubility in water or ethyl acetate, using the formula:

$$C_s^{p\ldots 1} = K_e \cdot C_s^{E\ldots w} \quad \ldots\ldots \text{(Eq. 9)}$$

Where:

$C_s^{p...1}$ is the apparent solubility in PVP or lanolin alcohol.

$C_s^{E...w}$ is the apparent solubility in ethyl acetate or water.

A control test was conducted using the same amount of Cortisol in 50 ml ethyl acetate. The whole experiment was carried out in duplicate.

Effect of PVP on Cortisol Solubility in Water:

Excess amounts of Cortisol were added to solutions of PVP in distilled water. The PVP concentrations were 1, 5, 10, 25, 30, and 40% (w/v), respectively. The solutions were kept in tightly covered beakers (Parafilm® was used) and stirred by means of stainless steel stirrers in the dissolution assembly described previously. The temperature was kept at $37 \pm 0.5^{\circ}C$ throughout the experiment. The stirring was stopped after 96 hours and the supernatants were filtered by means of 0.22 µm filter paper.[6] One ml of each solution was pipetted out and properly diluted. The concentration of the drug was measured as described previously. The whole study was conducted in duplicate.

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[6] Swinnex-25, Millipore Filter Corp., Bradford, MA.

Effect of Drug Concentration:

The effect of the concentration on the drug release rate was tested using film A. The drug concentration was varied while keeping the proportion of film formers constant. The Cortisol concentrations were 0.5, 1.5, 2.5, 5, 7.5, 8.5, and 10% (w/w), respectively. The stirring speed was maintained at 30 rpm and the temperature was kept at $37 \pm 0.5^{\circ}C$.

Table III. Composition of Lanolin Alcohol-PVP films at different Drug Concentrations (% w/w)

PVP	59.5	59.0	58.5	57.0	55.5	55.0	54.0
Lanolin Alcohol	40.0	39.5	39.0	38.0	37.0	36.5	36.0
Cortisol	0.5	1.5	2.5	5.0	7.5	8.5	10.0

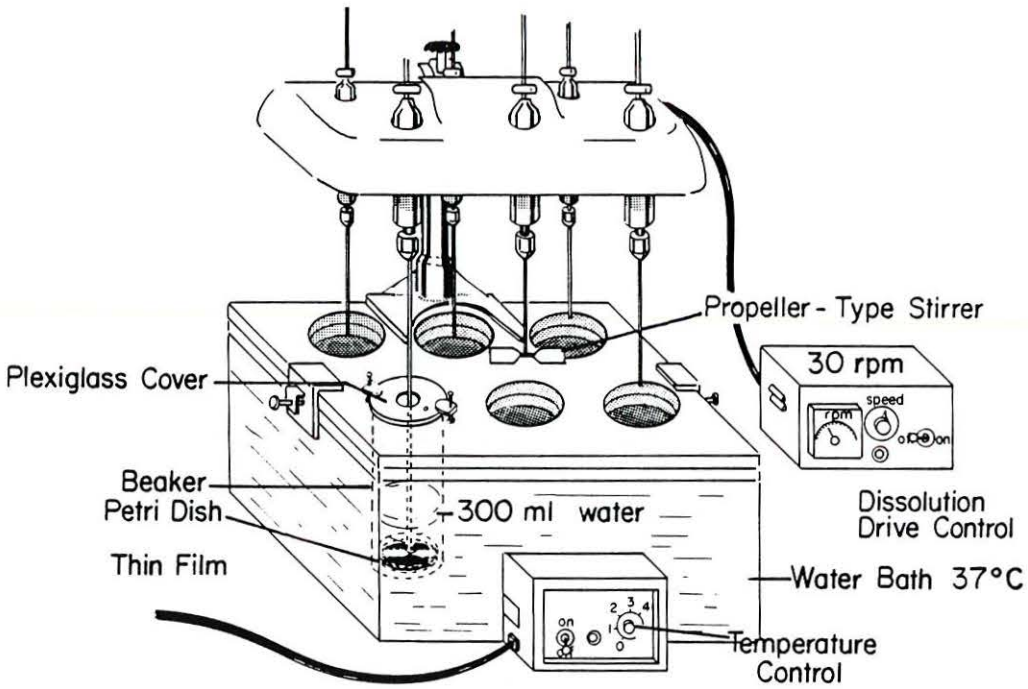

Figure 1. Apparatus used for <u>in vitro</u> release studies.

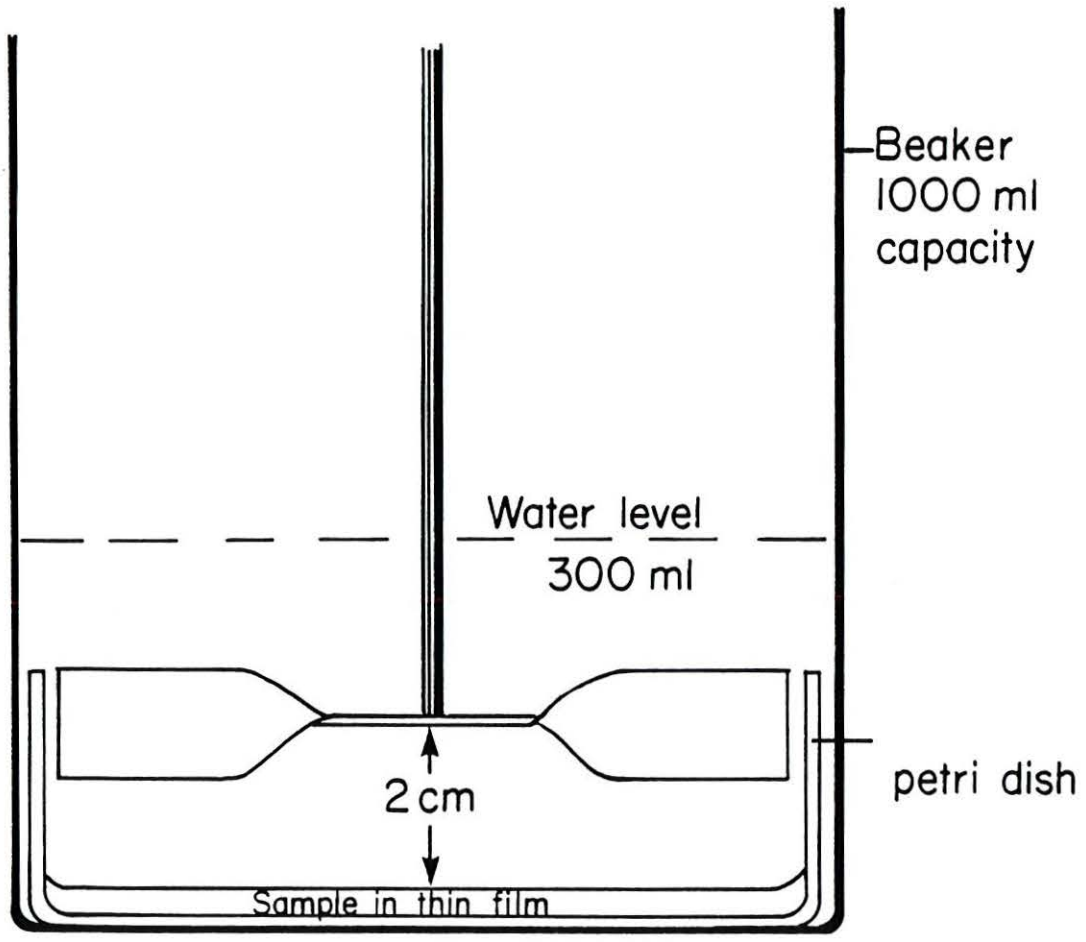

Figure 2. Enlarged view of experimental beaker.

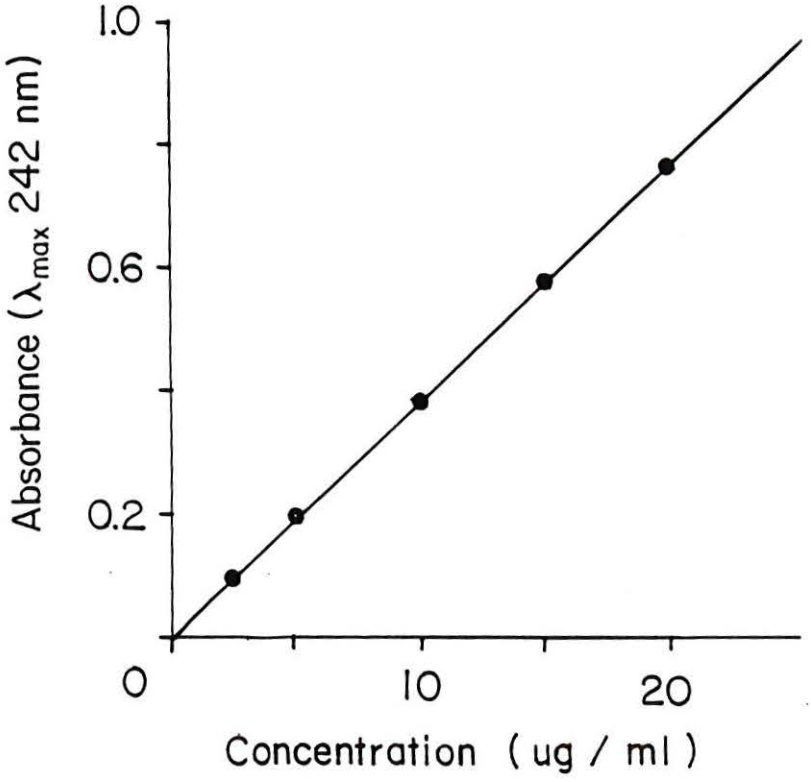

Figure 3. Standard curve for Cortisol.

RESULTS AND DISCUSSION

In this study, the release of Cortisol from lanolin alcohol and lanolin alcohol-PVP films (Table I) was investigated. The effects of agitation, film thickness and drug concentration on the rate of drug release have been carefully examined. The resulting drug release data were further analyzed and interpreted in order to gain additional insight into the drug release mechanims.

It was previously explained that the two Higuchi models (Eq. 1 and 2) describe drug release as being linear with the square root of time.

$$Q = K\, t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots \text{(Eq. 3)}$$

Where:

K is the release rate constant.

For a homogeneous matrix:

$$K_H = \sqrt{D\,(2A - C_s)\,C_s} \quad \ldots\ldots\ldots\ldots \text{(Eq. 4)}$$

and for a granular matrix system:

$$K_G = \sqrt{\frac{D\varepsilon}{T}\,(2A - C_s)\,C_s} \quad \ldots\ldots\ldots\ldots \text{(Eq. 5)}$$

The data have been analyzed to test the applicability of this mode.

Solubility of Cortisol in Film Matrix:

The solubility of Cortisol in the film matrix was examined. The results indicated that after 96 hours of continuous

stirring of Cortisol and lanolin alcohol in distilled water as described in the experimental section, Cortisol was completely insoluble in lanolin alcohol. Based on the solubility of Cortisol in ethyl acetate (3.2 mg/ml), and by the use of equations 8 and 9, the apparent solubility of Cortisol in PVP was calculated and found to be 6.34 mg/g. The attainment of equilibrium solubility in 96 hours was confirmed by the fact that there was no difference in absorbance between the samples analyzed at the end of 48 hours and 96 hours.

From the aforementioned results, it was shown that the initial drug concentration in the matrix, A (30,41 mg/cm^3), was greater than its solubility in the same matrix by more than four fold, ($A >> C_s$).

Effect of the Stirring Rate:

The effect of agitation was studied at stirring speeds of 0, 10, 30, 60, 90, 150, and 210 rpm at 37^oC. The data are shown in Tables IV - XVII and Figures 4 - 10.

Upon reviewing the effect of agitation on the release rate of the drug from film A (Tables XVIII - XIX), it was observed that there is a slight increase in the release rate constant with increasing agitation up to 60 rpm followed by a slight decline. This fact was observed with both the diffusion release rate and the first-order release rate constants. If the drug release from the film A followed the diffusional process which was matrix controlled, one

Table IV. Release of Cortisol from Unagitated Film A.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.075	4.6	0.570	0.013
60	0.103	6.4	0.795	0.018
90	0.127	7.9	0.992	0.022
120	0.153	9.7	1.208	0.027
180	0.211	13.4	1.676	0.038
240	0.264	16.9	2.110	0.048
300	0.285	18.4	2.295	0.052
360	0.346	22.4	2.795	0.063
420	0.357	23.3	2.912	0.066
480	0.395	25.9	3.239	0.073
540	0.414	27.3	3.417	0.077
600	0.449	29.8	3.726	0.084
660	0.472	31.6	3.944	0.089
720	0.507	34.0	4.254	0.096
1440	0.815	53.8	6.721	0.152

Table V. Release of Cortisol from Unagitated Film B.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.061	3.7	0.459	0.010
60	0.121	7.5	0.938	0.021
90	0.155	9.7	1.214	0.027
120	0.186	11.6	1.469	0.033
180	0.223	14.2	1.774	0.040
240	0.254	16.3	2.038	0.046
300	0.284	18.3	2.291	0.052
360	0.302	19.7	2.458	0.056
420	0.340	22.2	2.778	0.063
480	0.368	24.2	3.027	0.069
540	0.383	25.4	3.173	0.072
600	0.402	26.8	3.353	0.076
660	0.415	27.9	3.486	0.079
720	0.432	29.2	3.653	0.083
1440	0.602	40.2	5.025	0.114

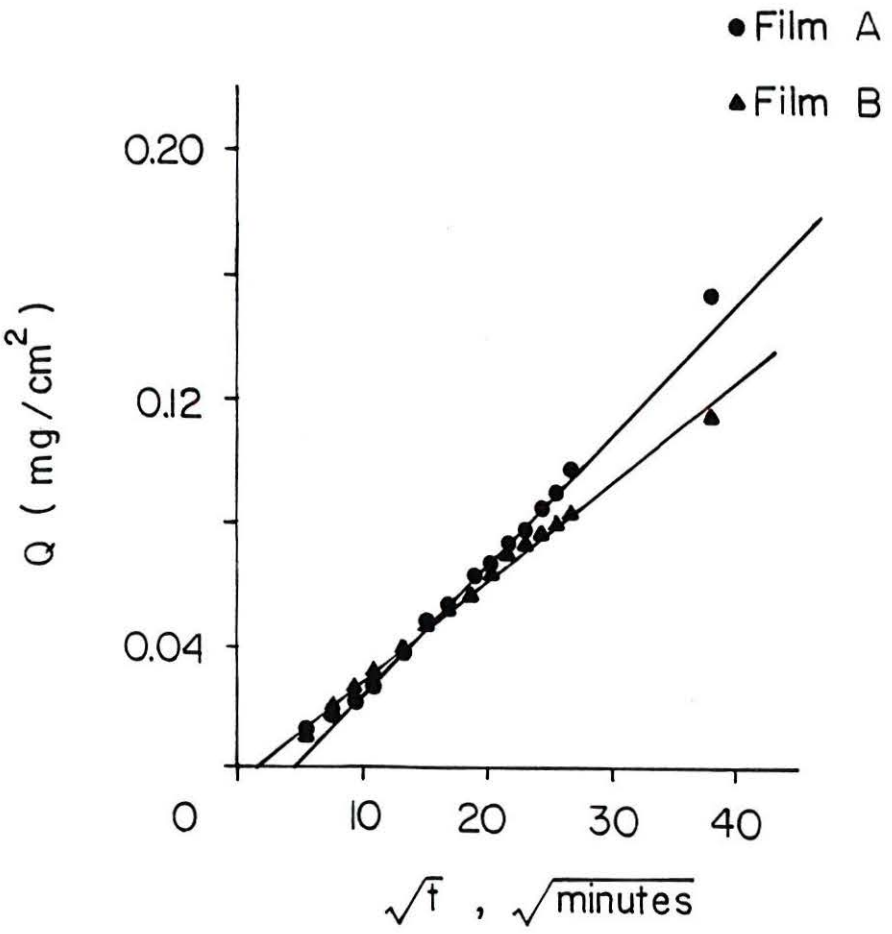

Figure 4. Release of Cortisol from Unagitated Films A and B.

Table VI. Release of Cortisol from Film A at Agitation Speed of 10 rpm.

Time (min)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.085	5.2	0.648	0.015
60	0.138	8.6	1.081	0.025
90	0.176	11.1	1.382	0.031
120	0.218	13.8	1.726	0.039
180	0.281	17.9	2.238	0.051
240	0.339	21.8	2.719	0.062
300	0.375	24.2	3.027	0.069
360	0.432	28.1	3.507	0.079
420	0.472	30.8	3.855	0.087
480	0.503	33.1	4.135	0.094
540	0.547	36.2	4.520	0.102
600	0.582	38.7	4.839	0.110
660	0.617	41.3	5.160	0.117
720	0.639	43.1	5.383	0.122
1440	0.518*	68.3	8.535	0.193

* Proper dilution was made.

Table VII. Release of Cortisol from Film B at Agitation Speed of 10 rpm.

Time (min)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q_2 mg/cm^2
30	0.075	3.8	0.48	0.011
60	0.112	6.0	0.743	0.017
90	0.150	8.0	1.02	0.023
120	0.183	10.0	1.26	0.028
180	0.224	12.5	1.57	0.035
240	0.263	15.0	1.84	0.042
300	0.287	16.0	2.03	0.046
360	0.314	18.0	2.24	0.051
420	0.329	19.0	2.37	0.054
480	0.353	20.0	2.56	0.058
540	0.361	21.0	2.64	0.060
600	0.386	22.7	2.84	0.064
660	0.393	23.0	2.91	0.066
720	0.410	24.0	3.06	0.069
1440	0.557	33.0	4.12	0.093

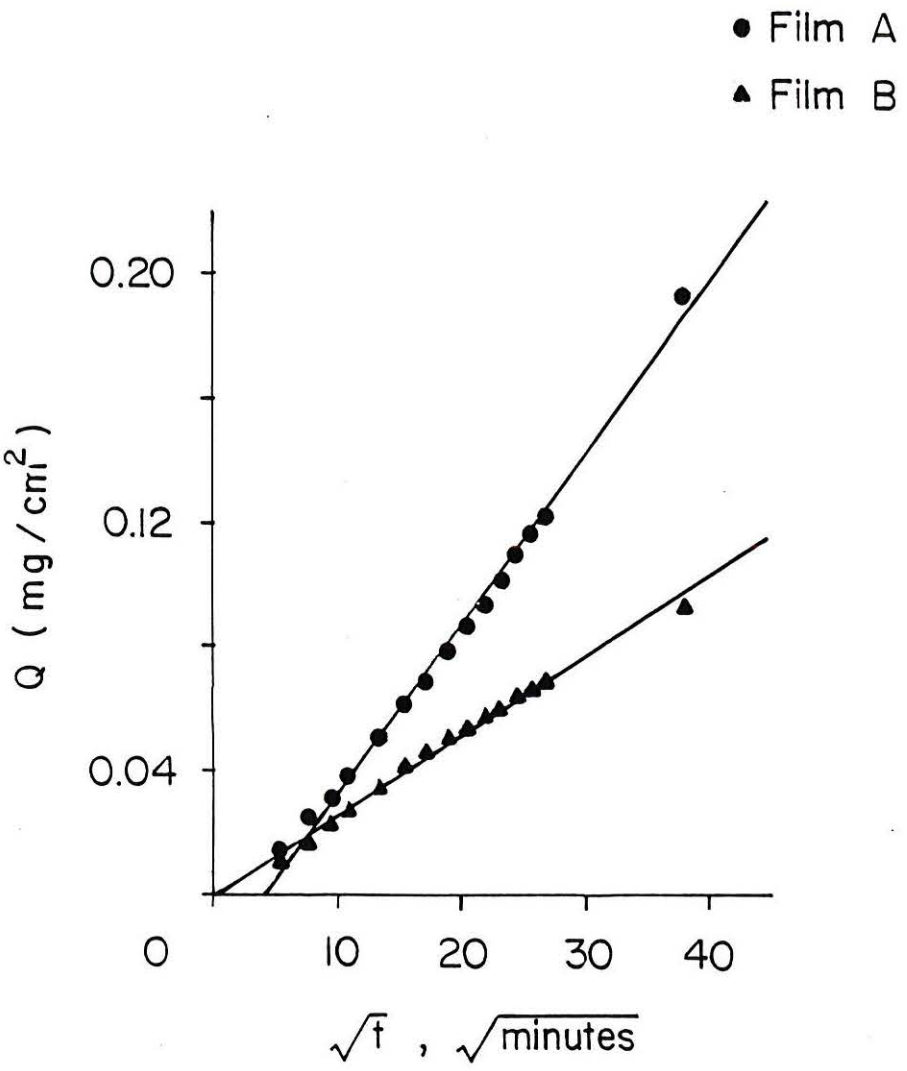

Figure 5. Release of Cortisol from Films A and B, at Agitation Speed 10 rpm.

Table VIII. Release of Cortisol from Film A at Agitation Speed of 30 rpm.

Time (min)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.086	5.3	0.657	0.015
60	0.113	7.0	0.877	0.020
90	0.155	9.7	1.215	0.028
120	0.186	11.8	1.470	0.033
180	0.249	15.9	1.983	0.044
240	0.298	19.0	2.386	0.054
300	0.369	23.7	2.967	0.067
360	0.400	25.9	3.242	0.073
420	0.447	29.0	3.643	0.082
480	0.493	32.0	4.041	0.091
540	0.547	36.0	4.502	0.102
600	0.582	38.6	4.821	0.109
660	0.624	41.6	5.200	0.118
720	0.647	43.4	5.428	0.123
1440	0.565*	74.1	9.262	0.210

* : Proper dilution was made.

Table IX. Release of Cortisol from Film B at Agitation Speed of 30 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.077	4.7	0.585	0.013
60	0.120	7.4	0.930	0.021
90	0.156	9.8	1.221	0.028
120	0.180	11.4	1.422	0.032
180	0.226	14.4	1.799	0.041
240	0.252	16.2	2.021	0.046
300	0.281	18.1	2.268	0.051
360	0.304	19.8	2.473	0.056
420	0.333	21.8	2.725	0.062
480	0.347	22.9	2.862	0.065
540	0.366	24.3	3.036	0.069
600	0.381	25.5	3.185	0.072
660	0.394	26.5	3.317	0.075
720	0.405	27.5	3.434	0.078
1440	0.558	37.4	4.669	0.106

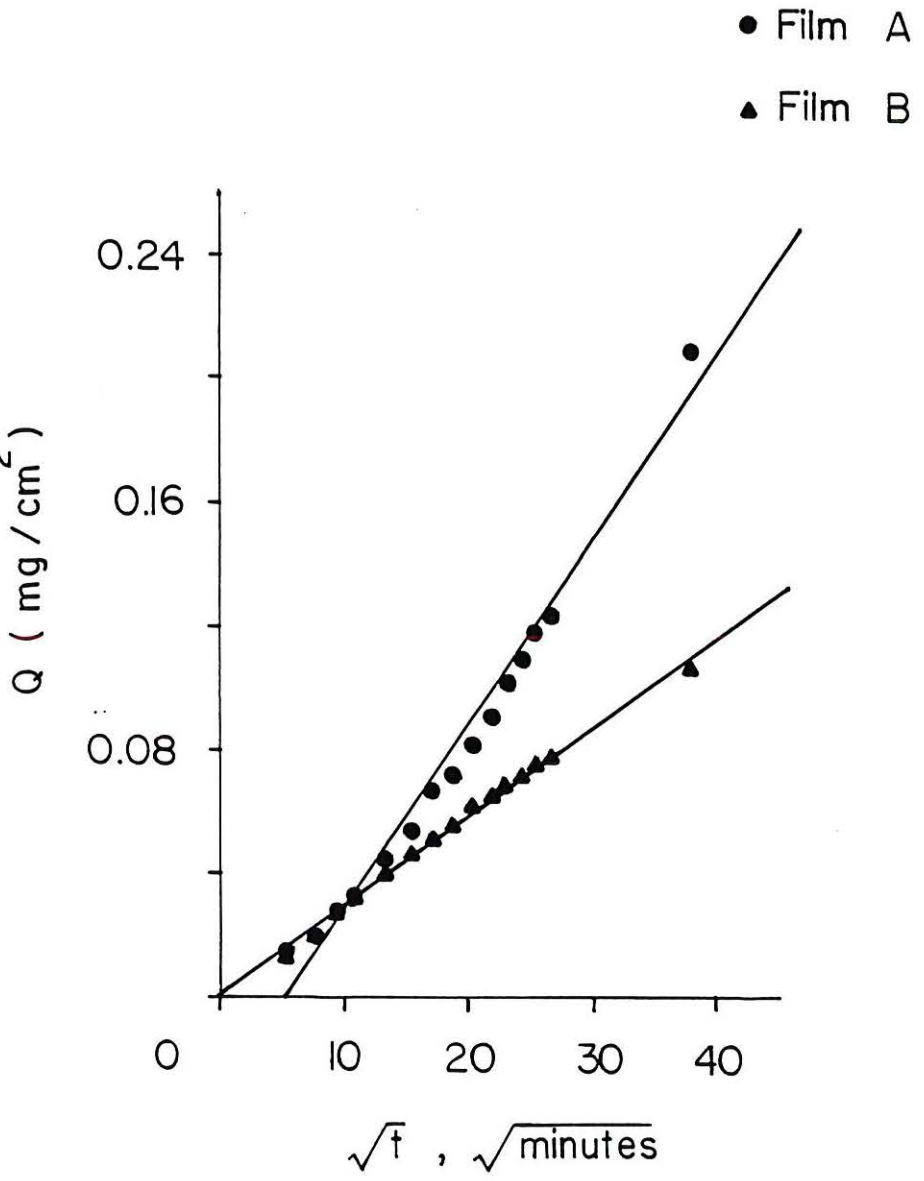

Figure 6. Release of Cortisol from Films A and B, at Agitation Speed 30 rpm.

Table X. Release of Cortisol from Film A at Agitation Speed of 60 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.106	6.5	0.813	0.018
60	0.170	10.6	1.325	0.030
90	0.230	14.5	1.812	0.041
120	0.270	17.2	2.145	0.049
180	0.356	22.7	2.841	0.064
240	0.418	26.8	3.355	0.076
300	0.475	30.7	3.838	0.087
360	0.531	34.5	4.316	0.098
420	0.589	38.5	4.817	0.109
480	0.636	41.6	5.232	0.118
540	0.679	45.0	5.621	0.127
600	0.727	48.4	6.052	0.136
660	0.758	50.8	6.352	0.144
720	0.805	54.2	6.781	0.153
1440	0.597*	79.1	9.889	0.224

* : Proper dilution was made.

Table XI. Release of Cortisol from Film B at Agitation Speed of 60 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.104	5.7	0.724	0.016
60	0.156	8.4	1.05	0.024
90	0.192	10.5	1.32	0.030
120	0.232	12.9	1.61	0.037
180	0.290	16.2	2.03	0.046
240	0.332	19.0	2.38	0.054
300	0.368	21.0	2.65	0.060
360	0.412	24.0	2.99	0.068
420	0.444	26.0	3.24	0.073
480	0.459	27.0	3.39	0.077
540	0.496	29.0	3.66	0.083
600	0.535	31.7	3.97	0.090
660	0.534	32.0	4.00	0.091
720	0.548	33.0	4.13	0.094
1440	0.792	47.0	5.88	0.133

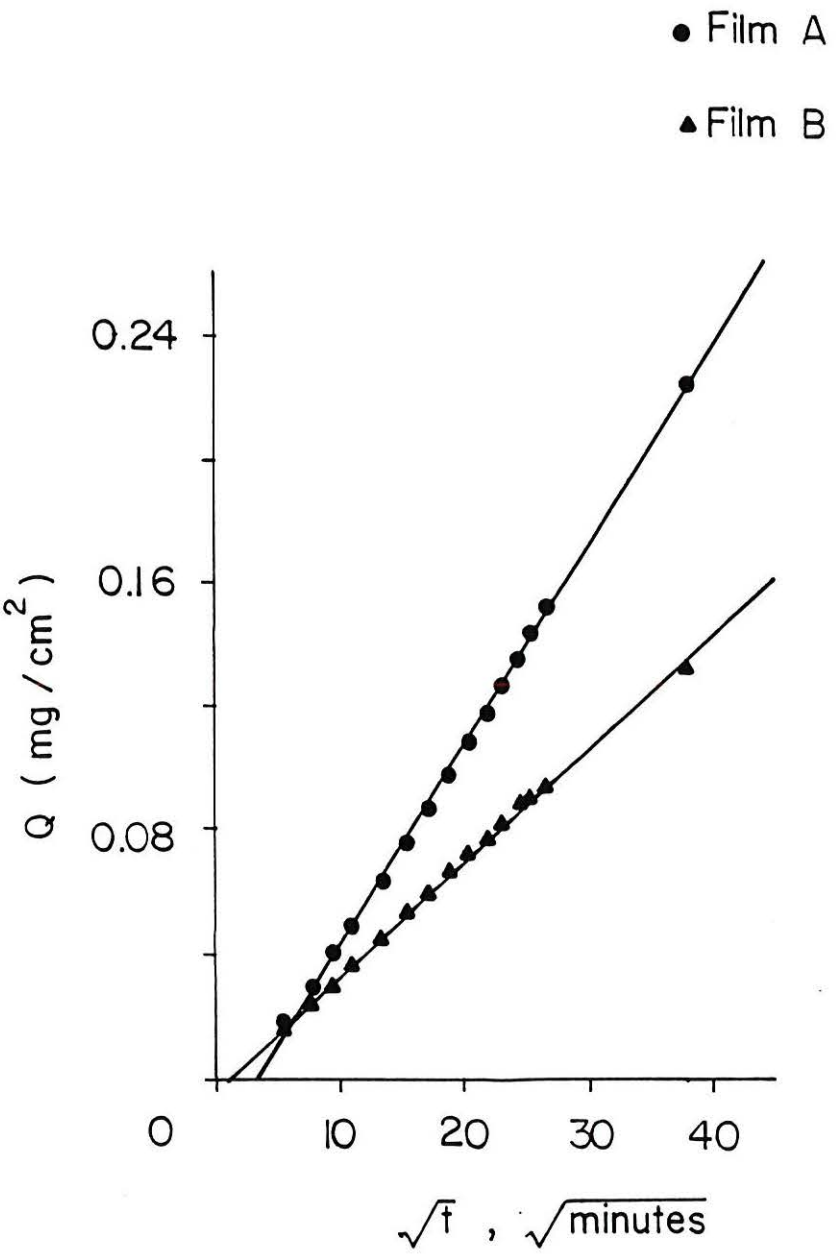

Figure 7. Release of Cortisol from Films A and B, at Agitation Speed 60 rpm.

Table XII. Release of Cortisol from Film A at Agitation Speed of 90 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.085	5.2	0.648	0.015
60	0.128	7.9	0.994	0.022
90	0.160	10.0	1.255	0.028
120	0.194	12.3	1.535	0.035
180	0.248	15.8	1.976	0.045
240	0.301	19.3	2.412	0.055
300	0.350	22.6	2.823	0.064
360	0.409	26.5	3.312	0.075
420	0.441	28.8	3.596	0.081
480	0.485	31.8	3.979	0.090
540	0.525	34.7	4.332	0.098
600	0.564	37.4	4.679	0.106
660	0.594	39.8	4.960	0.112
720	0.622	41.8	5.226	0.118
1440	0.517*	67.7	8.467	0.190

* : Proper dilution was made.

Table XIII. Release of Cortisol from Film B at Agitation Speed of 90 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.085	4.4	0.549	0.012
60	0.127	6.8	0.848	0.019
90	0.161	8.8	1.10	0.025
120	0.184	10.0	1.27	0.029
180	0.227	12.6	1.58	0.036
240	0.281	15.8	1.97	0.045
300	0.307	17.4	2.17	0.049
360	0.339	19.4	2.42	0.055
420	0.374	21.5	2.69	0.061
480	0.372	21.6	2.70	0.061
540	0.427	24.9	3.11	0.070
600	0.441	25.9	3.24	0.073
660	0.455	27.0	3.38	0.076
720	0.481	28.7	3.59	0.081
1440	0.693	40.7	5.09	0.115

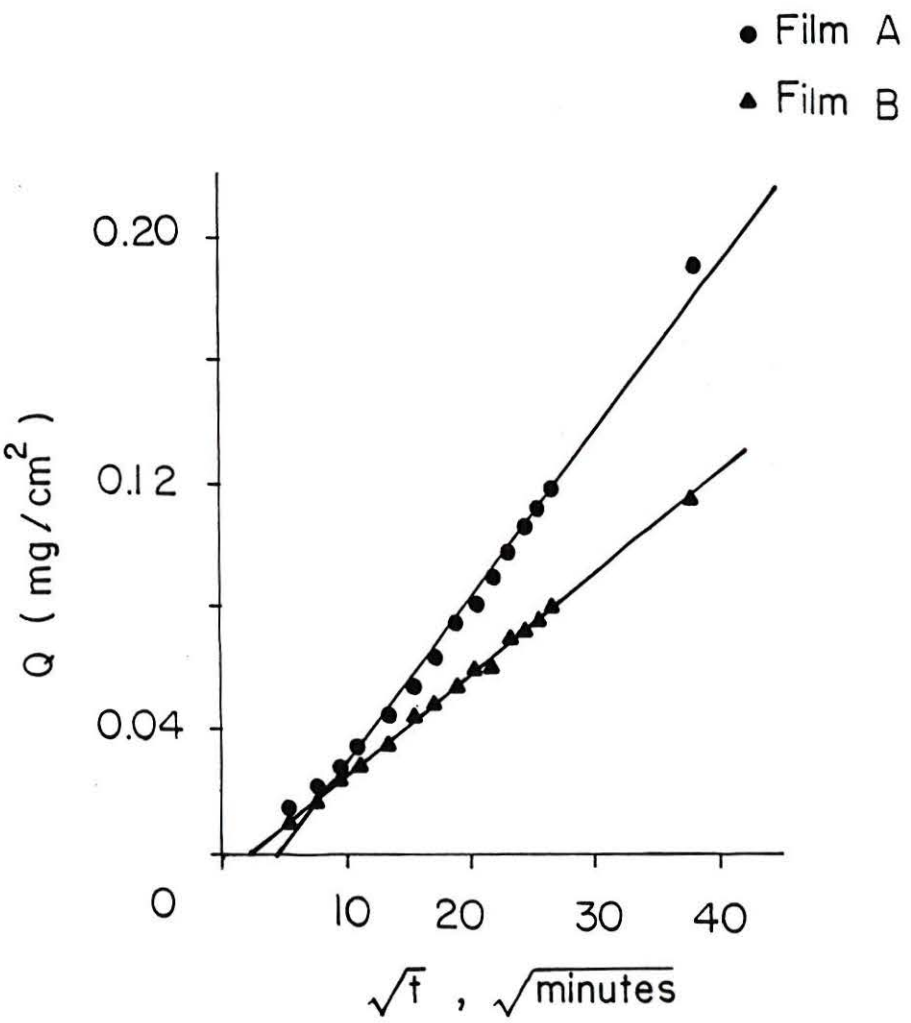

Figure 8. Release of Cortisol from Films A and B, at Agitation Speed 90 rpm.

Table XIV. Release of Cortisol from Film A at Agitation Speed of 150 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.084	5.1	0.642	0.015
60	0.127	7.7	0.966	0.022
90	0.155	9.7	1.216	0.028
120	0.188	11.9	1.486	0.034
180	0.240	15.3	1.912	0.043
240	0.290	18.6	2.323	0.053
300	0.342	22.1	2.757	0.062
360	0.383	24.8	3.105	0.070
420	0.423	27.6	3.450	0.078
480	0.462	30.3	3.789	0.086
540	0.499	32.9	4.116	0.093
600	0.536	35.6	4.449	0.101
660	0.562	37.6	4.695	0.106
720	0.596	40.0	5.010	0.113
1440	0.508*	66.4	8.306	0.188

* : Proper dilution was made.

Table XV. Release of Cortisol from Film B at Agitation Speed of 150 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.094	5.0	0.612	0.014
60	0.137	7.0	0.918	0.021
90	0.174	9.5	1.19	0.027
120	0.211	11.7	1.46	0.033
180	0.240	13.0	1.67	0.038
240	0.269	15.0	1.89	0.043
300	0.302	17.0	2.15	0.049
360	0.332	19.0	2.38	0.054
420	0.350	20.0	2.52	0.057
480	0.381	22.0	2.76	0.063
540	0.396	23.0	2.90	0.066
600	0.413	24.0	3.04	0.069
660	0.433	25.7	3.21	0.073
720	0.476	28.0	3.54	0.080
1440	0.664	39.0	4.89	0.111

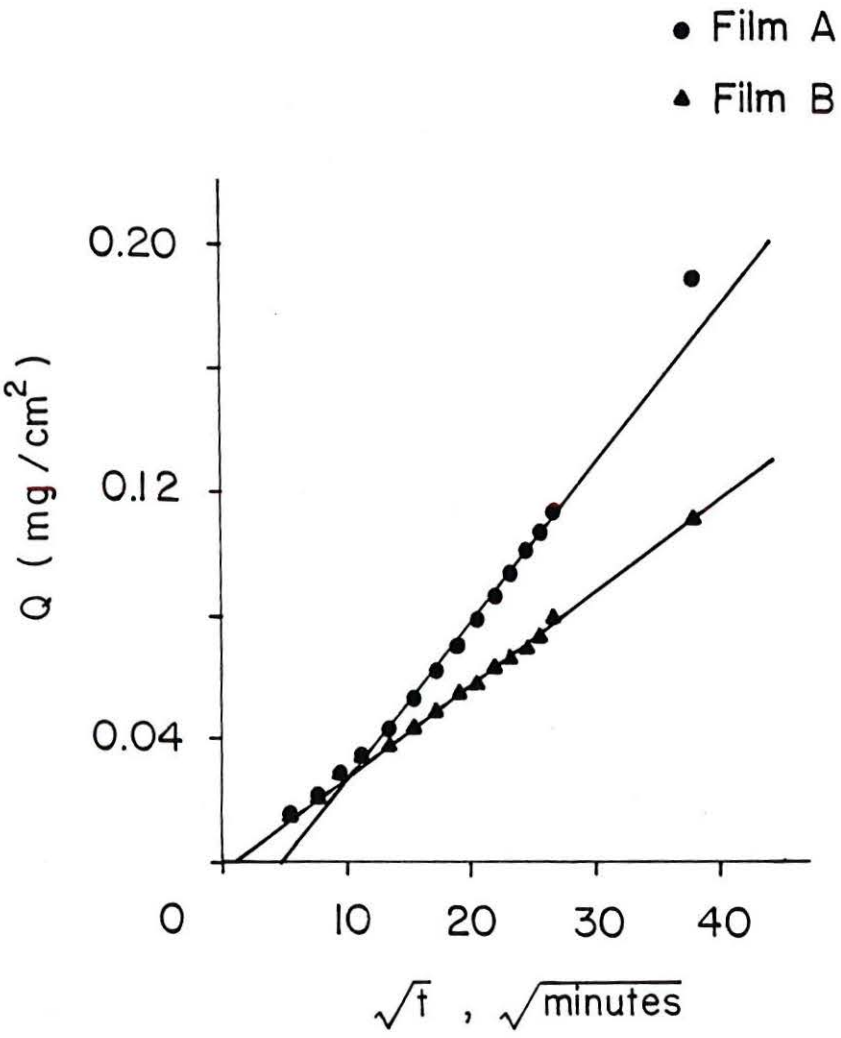

Figure 9. Release of Cortisol from Films A and B, at Agitation Speed 150 rpm.

Table XVI. Release of Cortisol from Film A at Agitation Speed of 210 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.084	5.0	0.642	0.015
60	0.125	7.8	0.969	0.022
90	0.149	9.3	1.168	0.026
120	0.181	11.5	1.432	0.032
180	0.232	14.8	1.848	0.042
240	0.282	18.0	2.259	0.051
300	0.320	20.6	2.581	0.058
360	0.358	23.2	2.906	0.066
420	0.396	25.8	3.231	0.073
480	0.431	28.3	3.538	0.080
540	0.469	31.0	3.871	0.088
600	0.504	33.5	4.184	0.095
660	0.528	35.3	4.413	0.100
720	0.575	38.6	4.823	0.109
1440	0.521*	68.2	8.522	0.193

* : Proper dilution was made.

Table XVII. Release of Cortisol from Film B at Agitation Speed of 210 rpm.

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.074	4.0	0.471	0.011
60	0.121	6.0	0.806	0.018
90	0.156	8.0	1.06	0.024
120	0.185	10.0	1.27	0.029
180	0.219	12.0	1.52	0.034
240	0.254	14.0	1.78	0.040
300	0.285	16.0	2.02	0.046
360	0.308	18.0	2.20	0.050
420	0.336	19.0	2.41	0.055
480	0.356	20.6	2.58	0.058
540	0.360	21.0	2.63	0.060
600	0.381	22.0	2.8	0.063
660	0.395	23.0	2.93	0.066
720	0.408	24.0	3.04	0.069
1440	0.556	33.0	4.11	0.093

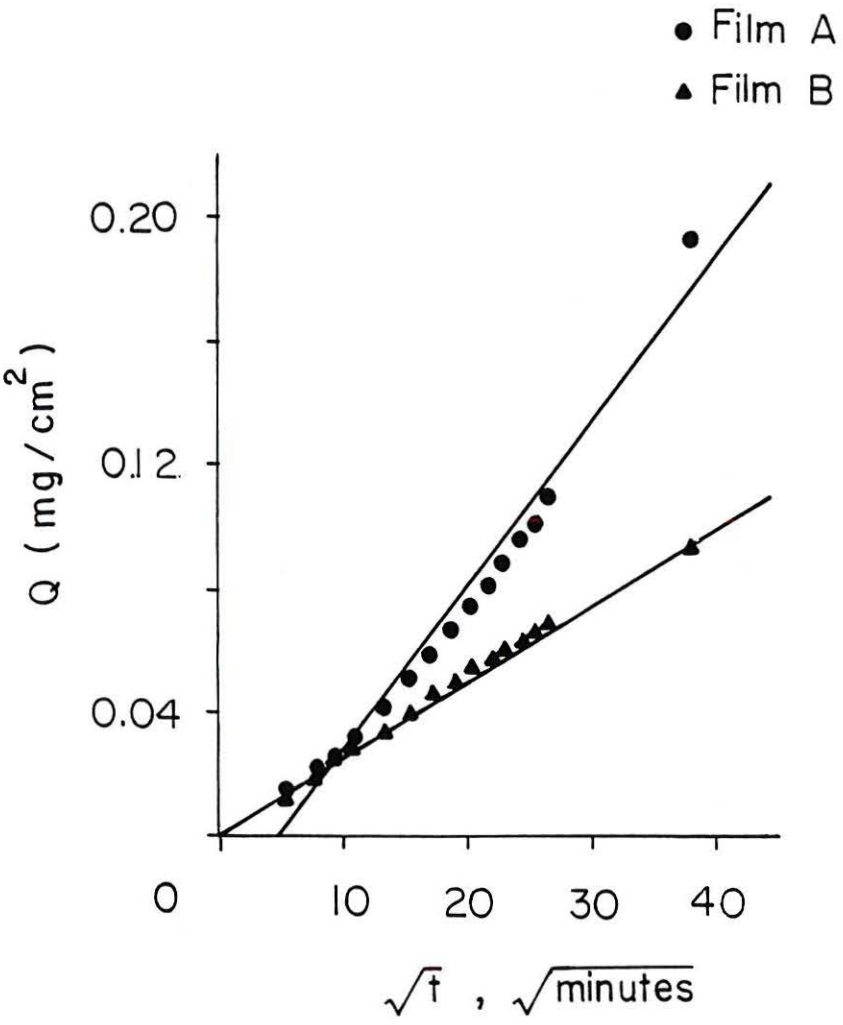

Figure 10. Release of Cortisol from Films A and B, at Agitation Speed 210 rpm.

Table XVIII. Q vs $t^{1/2}$ Treatment of Data for Release of Cortisol from Film A at Different Agitation Speeds.

Agitation Speed (rpm)	K x 10^{-3} (mg/cm^2 $min^{1/2}$)	Lag Time (min.)	Correlation Coefficient
Zero	4.2	20.3	0.995
10	5.4	16.0	0.997
30	5.9	26.9	0.989
60	6.4	12.3	0.999
90	5.3	20.9	0.994
150	5.0	25.0	0.991
210	5.2	25.0	0.981

Table XIX. First-order Treatment of Data for Release of Cortisol from Film A at Different Agitation Speeds.

Agitation Speed (rpm)	$k \times 10^{-3}$ ($min.^{-1}$)	Lag Time (min.)	Correlation Coefficient
Zero	0.517	0.6	0.998
10	0.750	2.4	0.999
30	0.883	-0.24	0.993
60	1.03	0.26	0.999
90	0.733	-2.2	0.999
150	0.717	0.66	0.998
210	0.733	-0.17	0.990

Table XX. Q vs $t^{1/2}$ Treatment of Data for the Release of Cortisol from Film B at Different Speeds.

Agitation Speed (rpm)	K x 10^{-3} (mg/cm^2 $min.^{1/2}$)	Lag Time (min.)	Correlation Coefficient
Zero	3.2	1.13	0.998
10	2.8	0.002	0.996
30	2.9	0.05	0.997
60	3.7	0.73	0.999
90	3.2	3.1	0.999
150	3.0	0.025	0.998
210	2.6	0.006	0.997

Table XXI. First-Order Treatment of Data for the Release of Cortisol from Film B at Different Speeds.

Agitation Speed (rpm)	$k \times 10^{-3}$ ($min.^{-1}$)	Lag Time (min.)	Correlation Coefficient
Zero	0.333	0.55	0.972
10	0.250	3.84	0.958
30	0.333	2.88	0.967
60	0.417	-10.2	0.980
90	0.333	0.6	0.983
150	0.317	1.6	0.999
210	0.250	-1.44	0.970

could expect the release rate to be independent of the agitational changes in the release medium. The results clearly show that at least at low agitational speeds, a surface diffusion layer-controlled release mechanism is operative rather than matrix-controlled diffusion.

As can be seen from Tables XVIII - XIX the correlation coefficient of the square root of the time plots is not as high as those of the corresponding first-order plots. Furthermore, the lag times (time intercept extrapolated to Q = O) of Q vs $t^{1/2}$ plots are much higher than those of the corresponding first-order plots.

Q vs $t^{1/2}$ treatment of the data for film B is shown in Table XX. The corresponding first-order treatment of the data is shown in Table XXI. It is clear that the linear square root of the time plots has high correlation coefficients; and the observed lag times were very small. More significiantly, the Higuchi constant K is independent of the change in agitation intensity. On the other hand, lower correlation coefficients and higher lag times were obtained with the first-order treatment of data.

Film Thickness Study:

Series of films (film A) of different thicknesses Table II were investigated for drug release at 37°C. The data is shown in Tables XXII - XXVI and the corresponding

Table XXII. Release of Cortisol at Film Thickness of 93 μm ± 4.6.[a]

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.086	5.3	0.657	0.015
60	0.113	7.0	0.877	0.020
90	0.155	9.7	1.215	0.028
120	0.186	11.8	1.470	0.033
180	0.249	15.9	1.983	0.044
240	0.298	19.0	2.386	0.054
300	0.369	23.7	2.967	0.067
360	0.400	25.7	3.242	0.073
420	0.447	29.0	3.643	0.082
480	0.493	32.0	4.041	0.091
540	0.547	36.0	4.502	0.102
600	0.582	38.6	4.821	0.109
660	0.624	41.6	5.200	0.118
720	0.647	43.4	5.428	0.123
1440	0.565[b]	74.1	9.262	0.210

a : Mean ± SD of ten measurements.

b : Proper dilution was made.

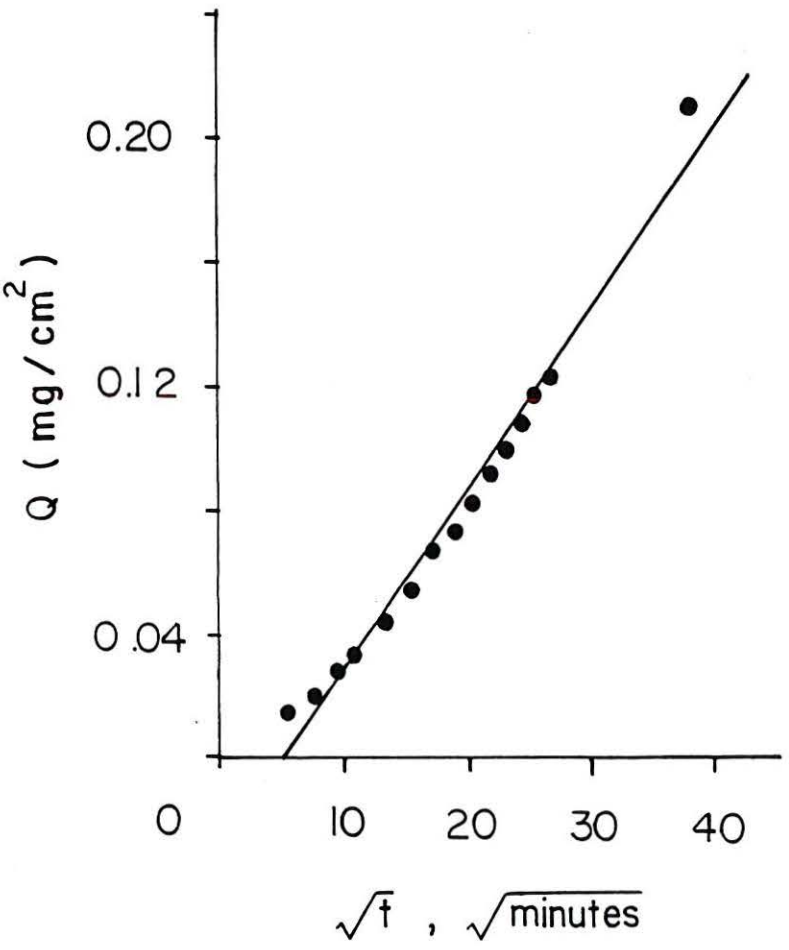

Figure 11. Release of Cortisol from Film A at Thickness of 93 μm.

Table XXIII. Release of Cortisol at Film Thickness of 138 µm ± 8.6.[a]

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.061	2.6	0.459	0.010
60	0.103	4.5	0.794	0.018
90	0.165	7.4	1.291	0.029
120	0.229	10.3	1.807	0.041
180	0.326	14.8	2.587	0.059
240	0.417	19.1	3.339	0.076
300	0.491	22.5	3.944	0.089
360	0.533	24.7	4.316	0.098
420	0.598	27.8	4.867	0.110
480	0.635	29.7	5.205	0.118
540	0.689	32.5	5.681	0.129
600	0.731	34.7	6.065	0.137
660	0.782	37.3	6.524	0.148
720	0.878	42.0	7.342	0.166
1440	0.665[b]	62.6	10.95	0.248

a : Mean ± SD of ten readings in duplicate.

b : Proper dilution was made.

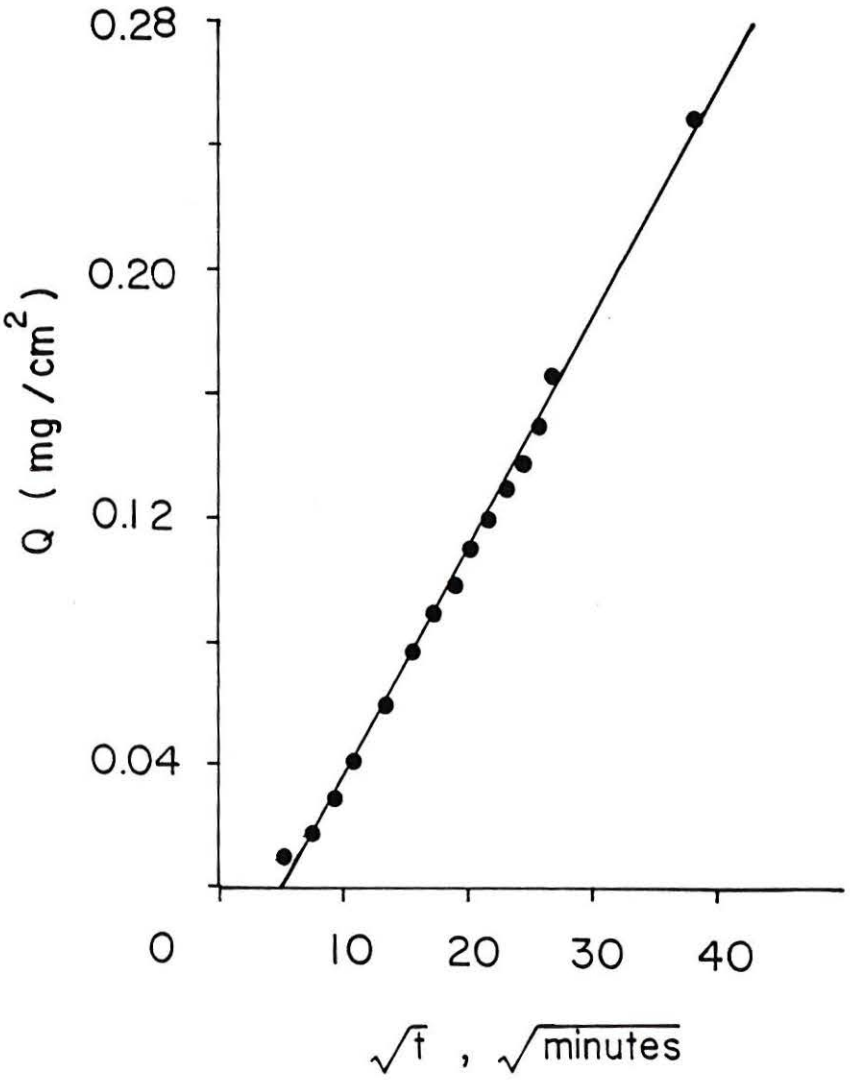

Figure 12. Release of Cortisol from Film A at Thickenss of 138 μm.

Table XXIV. Release of Cortisol at Film Thickness of 219 µm ± 8.7.[a]

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.069	2.2	0.498	0.011
60	0.123	4.2	0.953	0.022
90	0.189	6.6	1.482	0.034
120	0.214	7.5	1.694	0.038
180	0.309	10.9	2.458	0.056
240	0.424	15.1	3.388	0.077
300	0.470	16.8	3.781	0.086
360	0.539	19.4	4.361	0.099
420	0.578	20.9	4.712	0.107
480	0.635	23.1	5.205	0.118
540	0.697	25.5	5.743	0.130
600	0.729	26.9	6.05	0.137
660	0.765	28.4	6.389	0.145
720	0.809	30.2	6.797	0.154
1440	0.618[b]	44.9	10.11	0.229

a : Mean ± SD of ten readings in duplicate.

b : Proper dilution was made.

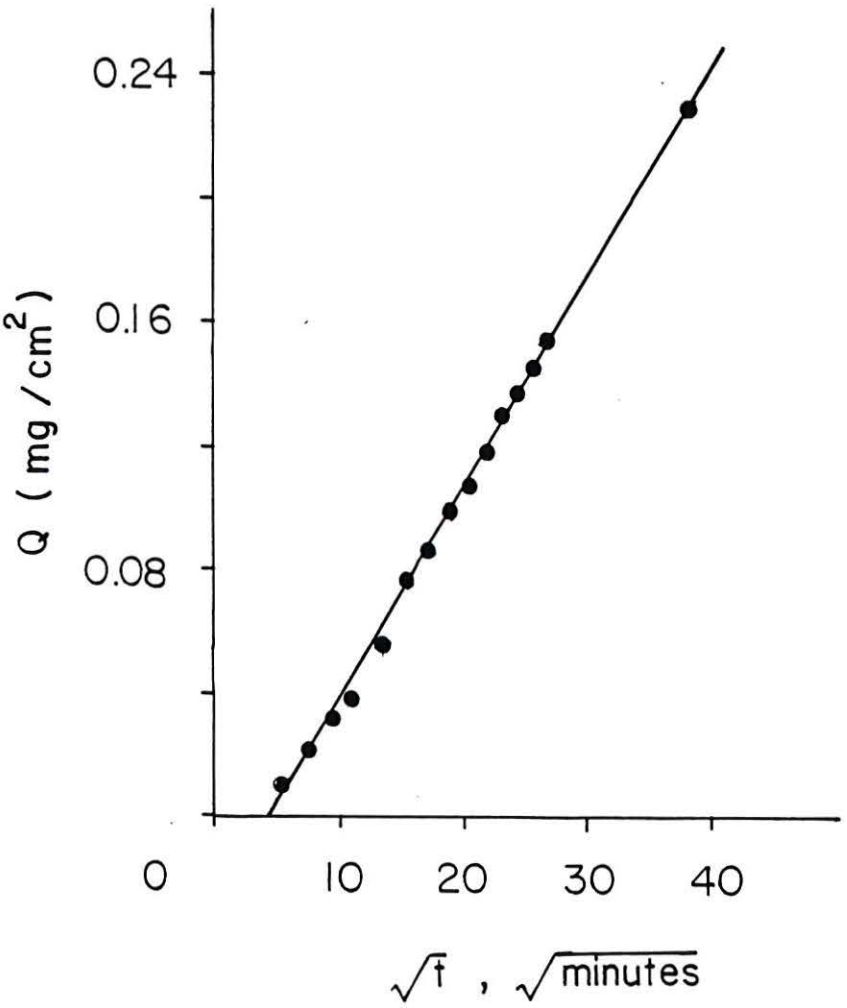

Figure 13. Release of Cortisol from Film A at Film Thickness of 219 µm.

Table XXV. Release of Cortisol at Film Thickness of 317 µm ± 12.8.[a]

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.079	2.2	0.60	0.014
60	0.141	4.0	1.095	0.025
90	0.192	5.5	1.508	0.034
120	0.222	6.4	1.760	0.040
180	0.307	8.9	2.446	0.055
240	0.400	11.6	3.202	0.072
300	0.483	14.1	3.885	0.088
360	0.550	16.2	4.450	0.101
420	0.612	18.1	4.982	0.113
480	0.660	19.7	5.408	0.122
540	0.703	21.1	5.799	0.131
600	0.725	21.9	6.025	0.136
660	0.766	23.3	6.406	0.145
720	0.439[b]	26.6	7.327	0.166
1440	0.640	38.4	10.56	0.239

a : Mean ± SD of ten readings in duplicates.

b : Proper dilutions were made.

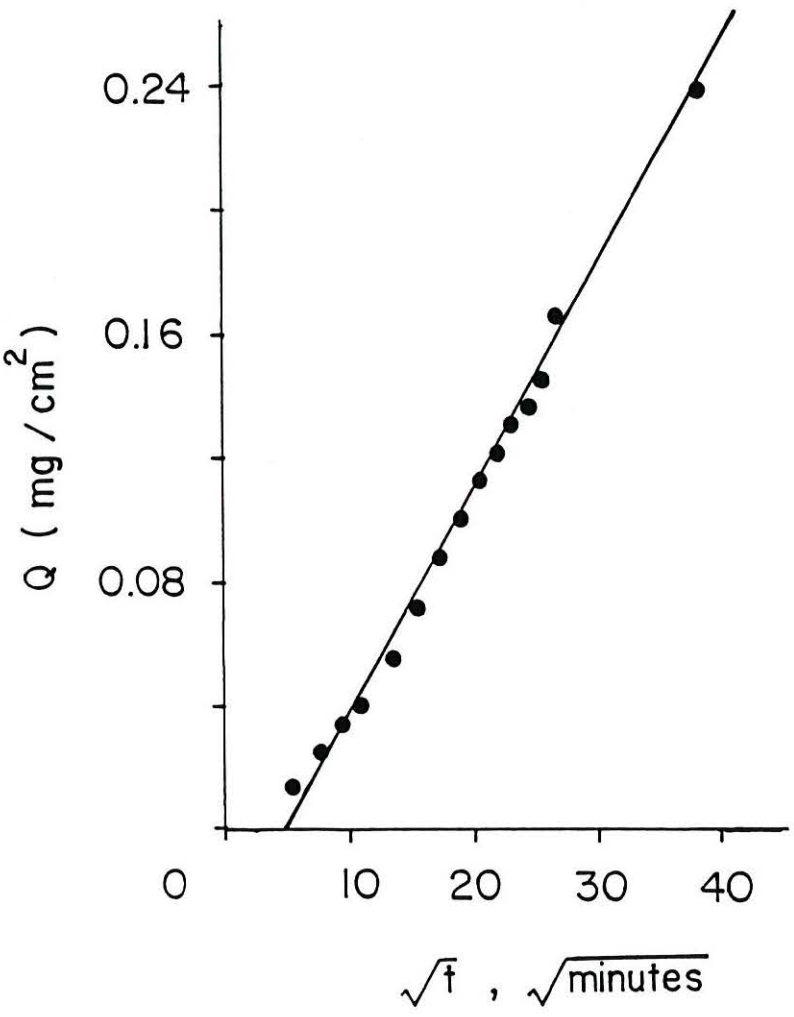

Figure 14. Release of Cortisol from Film A at Thickness of 317 μm.

Table XXVI. Release of Cortisol at Film Thickness of 409 µm ± 11.2.[a]

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.078	1.8	0.594	0.013
60	0.139	3.3	1.080	0.024
90	0.190	4.6	1.493	0.034
120	0.239	5.8	1.891	0.043
180	0.345	8.4	2.744	0.062
240	0.424	10.4	3.395	0.077
300	0.516	12.8	4.151	0.094
360	0.590	14.7	4.774	0.108
420	0.664	16.6	5.402	0.122
480	0.709	17.9	5.808	0.131
540	0.754	19.1	6.217	0.141
600	0.817	20.8	6.775	0.153
660	0.866	22.2	7.223	0.163
720	0.490[b]	25.1	8.170	0.185
1440	0.679	34.4	11.17	0.253

a : Mean ± SD of ten readings in duplicate.

b : Proper dilutions were made.

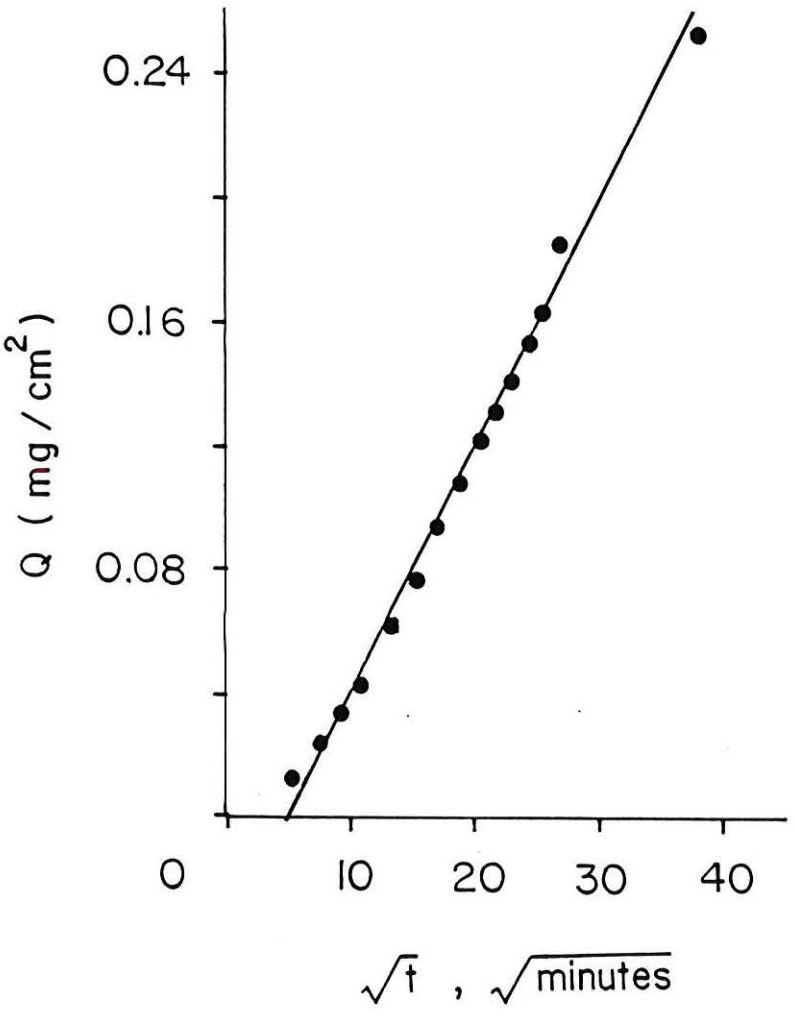

Figure 15. Release of Cortisol from Film A at Thickness of 409 µm.

plots in Figures 11 - 15. According to Higuchi's diffusion-controlled mechanism of drug release, the release rate constant K has the dimensions of weight per area per square root of time and should be independent of film thickness. The approximate constancy of K with varied film thickness is shown in Table XXVII.

It was reported (19, 20) that the film thickness does affect the duration of the drug release. The time required for the release of half of the amount of the drug present in the film, the product half-life ($t_{1/2}$), was shown to be related to the film thickness by the following relationship derived from Eq. 5:

$$t_{1/2} = \left(\frac{A\ h}{2K}\right)^2 \quad \ldots\ldots\ldots \text{(Eq. 10)}$$

Where:

A: Initial drug concentration in the film matrix.

h: Film thickness.

K: Release rate constant (Higuchi).

The results shown in Table XXVIII indicate that the $t_{1/2}$ values calculated by the first-order relationship:

$$t_{1/2} = \frac{0.693}{k} \quad \ldots\ldots\ldots\ldots\ldots\ldots \text{(Eq. 11)}$$

Where:

k is the first-order rate constant.

and much more accurate in the predicting the time for release of 50% of the original amount of the drug in the film. That is

Table XXVII. Q vs $t^{1/2}$ Treatment of Data for Release of Cortisol from Film A as a Function of Film Thickness.

Film thickness μm ± S.D.[a]	K x 10^{-3} (mg/cm^2 $min.^{1/2}$)	$t_{1/2}$ (min.)	
		Measured	Calculated
93 ± 4.1	5.9	870.3	574.4
138 ± 8.6	7.4	1024	683.1
219 ± 8.7	7.0	1722.3	1323.1
317 ± 12.8	7.1	2256.3	1922.9
409 ± 11.2	7.8	2601	2106.8

Table XXVIII. First-Order Treatment of Data of Release of Cortisol from Film A as a Function of Film Thickness.

Film thickness μm ± S.D.[a]	k x 10^{-3} ($min.^{-1}$)	$t_{1/2}$ (min.)	
		Measured	Calculated
93 ± 4.1	0.883	792	784.8
138 ± 8.6	0.667	1056	1039
219 ± 8.7	0.417	1716	1661.9
317 ± 12.8	0.333	2052	2081.1
409 ± 11.2	0.300	2328	2310

a : Mean ± standard deviation of ten measurements.

confirmed by the small variation between calculated and measured $t_{1/2}$ by first-order analysis (Table XXVIII). On the other hand, it is clear that this variation is very high. When $t_{1/2}$ is calculated by Q *vs* $t^{1/2}$ treatment Table XXVIII. The first-order rate constant k is dependent on film thickness.

PVP Release Studies:

Placebo and medicated films were prepared by the previously described technique and were tested for the loss of PVP during the drug release period at 37°C. As can be seen from Table XXIX, a significant amount of PVP was leached out from both the placebo and the medicated films. The loss of PVP was substantially greater from the medicated films than from the placebo. It would appear that the incorporation of Cortisol enhanced the loss of PVP.

Higuchi (30) suggested that the film matrix should remain intact throughout the release process in order to validate one of the Higuchi models. The presence of complications such as partial dissolution of the matrix substance, weakens the possibility of the application of either one of the two Higuchi models. The observed results and subsequent analysis are consistent with this expectation. Films of pure lanolin alcohol (Film B) were checked for the possibility of loss of lanolin alcohol in the dissolution medium. It is clear from Table XXX that a negligible

Table XXIX. Loss of PVP from Placebo and Medicated Film in the Bathing Fluid over 24 Hours.

Film	Weight of Dry Film mg	Weight of Dry Film After Release (24 hr) mg	Loss Weight mg	Amount of Cortisol Released mg	Amount of PVP Released mg	Original Amount of PVP mg	PVP Lost %
Placebo (I)	0.5096	0.4493	0.0603	-	0.0603	0.3058	19.7
Placebo (II)	0.5033	0.4389	0.0644	-	0.0644	0.3020	21.3
Mean	0.5065	0.4441	0.0624	-	0.0624	0.3039	20.5
A_I	0.4999	0.3914	0.1085	0.0085	0.10004	0.2924	34.2
BI	0.5021	0.3926	0.1095	0.0092	0.1003	0.2937	34.15
Mean	0.501	0.3920	0.109	0.0089	0.1002	0.2931	34.19

Table XXX. Loss of Lanolin Alcohol From Film B.

Film	Weight of Dry Film gm	Weight of Dry Film After Release Study (gm)	Amount Lost gm	Amount of Cortisol Lost (gm)	Amount of Lanolin Alcohol Lost (gm)	Original Amount of Lanolin Alcohol (gm)	Lanolin Alcohol Lost %
Film B_I	0.4869	0.4786	0.0083	0.0047	0.0036	0.4747	0.76
Film B_{II}	0.4822	0.4739	0.0083	0.0047	0.0036	0.4701	0.76
Mean	0.4846	0.4763	0.0083	0.0047	0.0036	0.4724	0.76

amount (0.8%) of the film matrix was lost during the release period.

Effect of PVP on Cortisol Solubility in Water:

The solubility of Cortisol in distilled water was determined at 25°C and at 37°C (Table XXXI). PVP was found to enhance the solubility of Hydrocortisone in water (Table XXXII and Figure 16). Simonelli et al. (35) have reported that co-precipitation of drugs with PVP can significantly increase the dissolution and the apparent solubility of a given drug. The results of another interesting report (36) have suggested that a high energy form of Cortisol, with an activity of 14-15 times that of the pure drug is present in the PVP-Cortisol co-precipitate. The formation of Cortisol-PVP co-precipitate is possible during the film preparation. Thus it would appear that both Cortisol and PVP influence each other's dissolution profile favorably.

Effect of Drug Concentration:

The effect of the change in drug concentration on the release rate constants K and k was investigated over a wide range of drug concentrations (0.5 - 10% w/w, Table III) at 37°C. The release data are shown in Tables XXXIII - XXXIX and Figures 17 - 23. Q vs $t^{1/2}$ treatments of data for drug release at various concentrations are shown in Table XXXX. The corresponding first-order treatments of data are shown in Table XXXXI. The first-order plots are shown in Figures 24 and 25. Although the square root of time plots have

Table XXXI. Solubility of Cortisol in Water at Different Temperatures.

	Solubility of Cortisol (mg/ml)	
	Reported	Experimental[c]
At 25°C	0.280[a]	0.298
At 37°C	0.543[b]	0.532

a : Reference (37)

b : Reference (29)

c : Mean of duplicate trials.

Table XXXII. Effect of PVP on Cortisol Solubility in Water.

PVP Concentration (% w/v)	Cortisol Solubility (mg/ml)[a]	
	at 25°C	at 37°C
1.0	0.520	0.540
5.0	0.622	0.707
10.0	0.720	0.958
25.0	0.985	1.60
30.0	1.250	1.72
40.0	1.310	2.3

a : mean of duplicate trials.

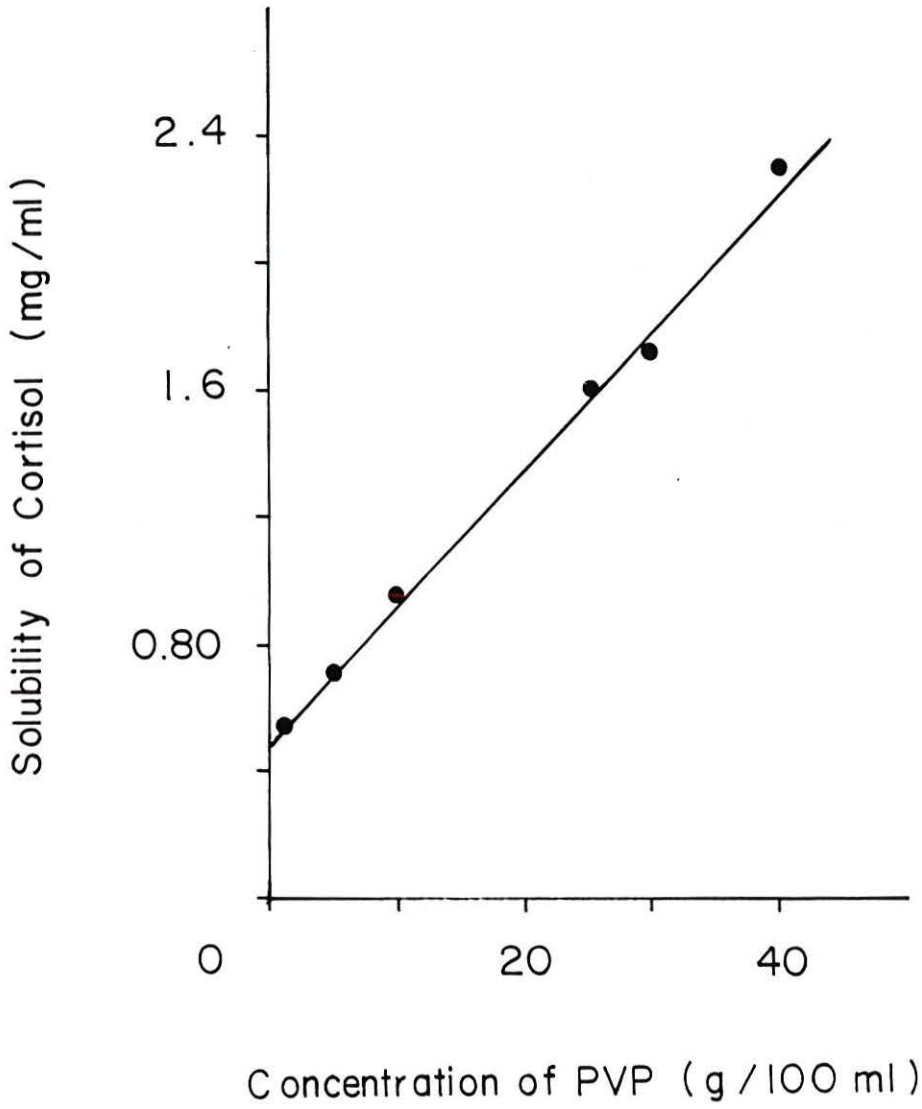

Figure 16. Effect of PVP on Cortisol Solubility in Water at 37°C.

Table XXXIII. Release of Cortisol at Concentration of 0.5% (w/w).

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.057	17.0	0.429	0.010
60	0.058	18.0	0.439	0.010
90	0.068	21.0	0.525	0.012
120	0.081	25.0	0.632	0.014
180	0.098	31.0	0.770	0.017
240	0.113	36.0	0.898	0.020
300	0.130	42.0	1.038	0.023
360	0.122	39.0	0.985	0.022
420	0.126	41.0	1.028	0.023
480	0.134	44.0	1.10	0.025
540	0.135	45.0	1.12	0.025
600	0.151	50.0	1.25	0.028
660	0.151	51.0	1.27	0.029
720	0.157	53.0	1.33	0.030
1440	0.248	82.0	2.05	0.046

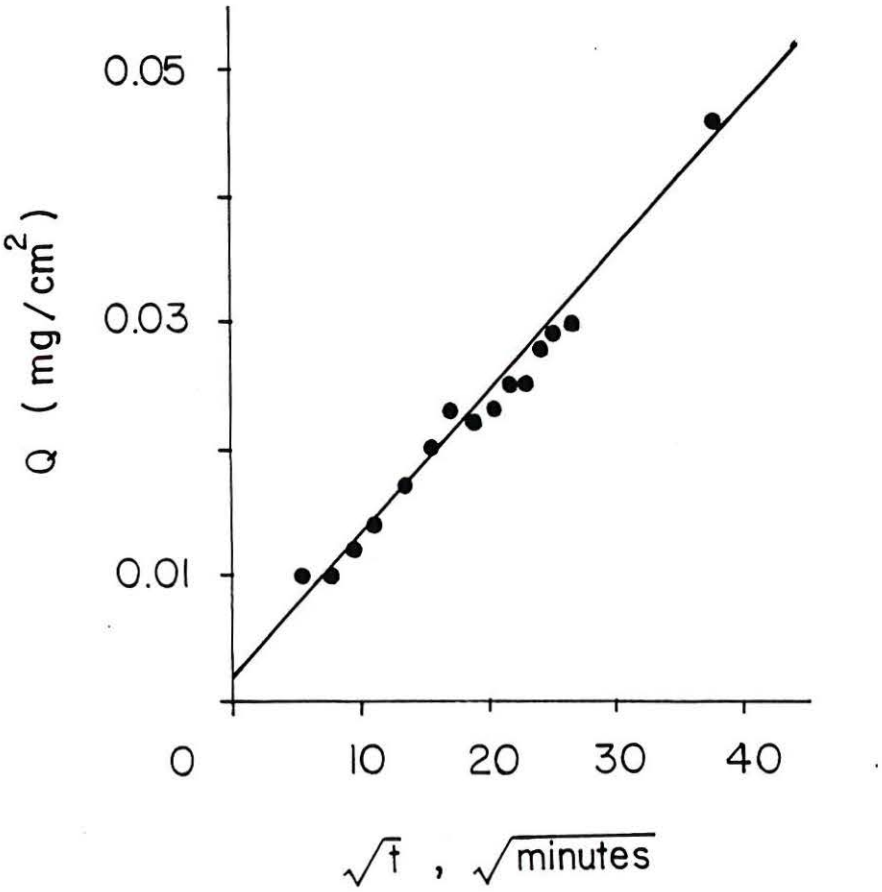

Figure 17. Release of Cortisol from Film A at Concentration of 0.5% (w/w).

Table XXXIV. Release of Cortisol at Concentration of 1.5% (w/w).

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.070	7.0	0.531	0.012
60	0.109	11.0	0.842	0.019
90	0.141	15.0	1.10	0.025
120	0.161	17.0	1.27	0.029
180	0.182	19.0	1.45	0.033
240	0.229	24.0	1.83	0.041
300	0.259	28.0	2.09	0.047
360	0.285	31.0	2.31	0.052
420	0.323	35.0	2.63	0.060
480	0.336	37.0	2.76	0.063
540	0.359	40.0	2.97	0.067
600	0.394	44.0	3.27	0.074
660	0.398	44.4	3.33	0.075
720	0.409	46.0	3.45	0.078
1440	0.629	70.0	5.22	0.118

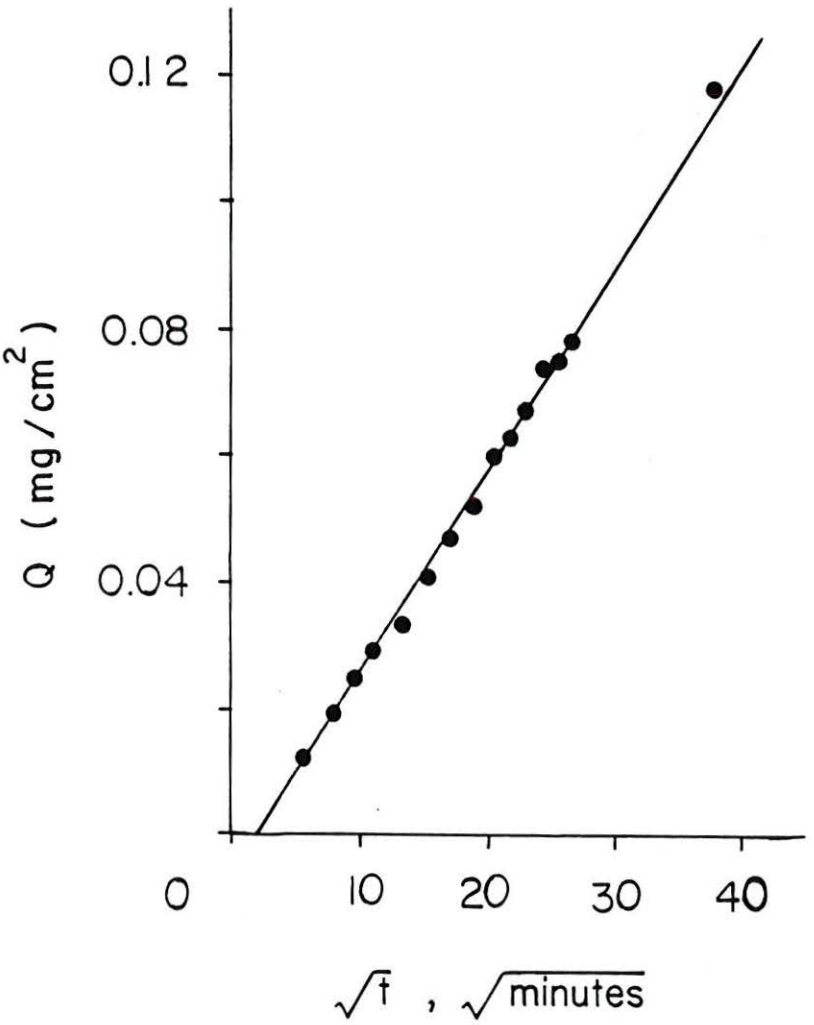

Figure 18. Release of Cortisol from Film A at Concentration of 1.5% (w/w).

Table XXXV. Release of Cortisol at Concentration of 2.5% (w/w).

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.086	5.3	0.657	0.015
60	0.113	7.0	0.877	0.020
90	0.155	9.7	1.215	0.028
120	0.186	11.8	1.470	0.033
180	0.249	15.9	1.983	0.044
240	0.298	19.0	2.386	0.054
300	0.369	23.7	2.967	0.067
360	0.400	25.7	3.242	0.073
420	0.447	29.0	3.643	0.082
480	0.493	32.0	4.041	0.091
540	0.547	36.0	4.502	0.102
600	0.582	38.6	4.821	0.109
660	0.624	41.6	5.200	0.118
720	0.647	43.4	5.428	0.123
1440	0.565*	74.1	9.262	0.210

* : Proper dilution was made.

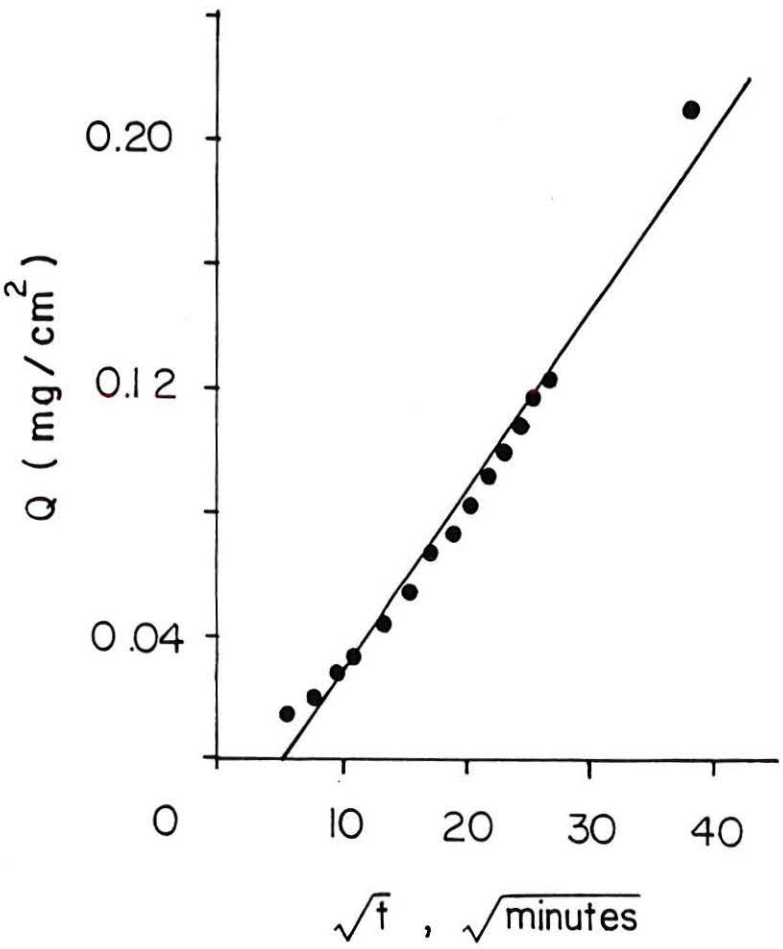

Figure 19. Release of Cortisol from Film A at Concentration of 2.5% (w/w).

Table XXXVI. Release of Cortisol at Concentration of 5% (w/w).

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.179	5.6	1.389	0.032
60	0.282	8.6	2.213	0.050
90	0.384	12.2	3.039	0.069
120	0.497	15.8	3.957	0.090
180	0.657	21.0	5.256	0.119
240	0.770	24.8	6.195	0.140
300	0.460*	29.7	7.417	0.168
360	0.514	33.4	8.341	0.189
420	0.559	36.5	9.134	0.207
480	0.606	39.8	9.960	0.225
540	0.665	43.9	10.98	0.249
600	0.456*	45.5	11.37	0.257
660	0.480	48.2	12.05	0.273
720	0.518	52.2	13.05	0.295
1440	0.651*	85.7	21.41	0.485

* : Proper dilutions were made.

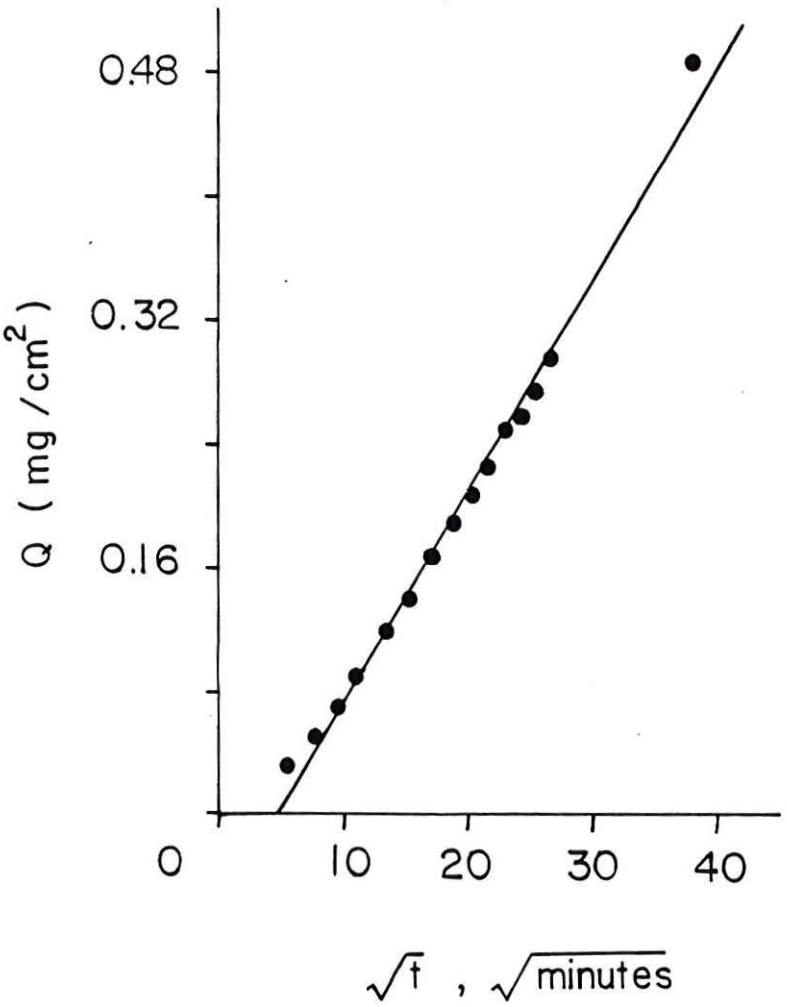

Figure 20. Release of Cortisol from Film A, at Concentration of 5% (w/w).

Table XXXVII. Release of Cortisol at Concentration of 7.5% (w/w).

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.620*	25.9	9.72	0.220
60	0.883	37.2	13.96	0.316
90	0.659*	41.9	15.73	0.356
120	0.667	42.9	16.08	0.364
180	0.713	46.2	17.32	0.392
240	0.758	49.5	18.56	0.420
300	0.788	51.8	19.44	0.440
360	0.821	54.4	20.41	0.462
420	0.869	56.0	21.74	0.492
480	0.875	58.9	22.09	0.500
540	0.901	61.0	22.89	0.518
600	0.874	59.4	22.27	0.504
660	0.722*	66.0	24.74	0.560
720	0.720	66.5	24.92	0.564
1440	0.876	80.1	30.04	0.680

* : Proper dilutions were made.

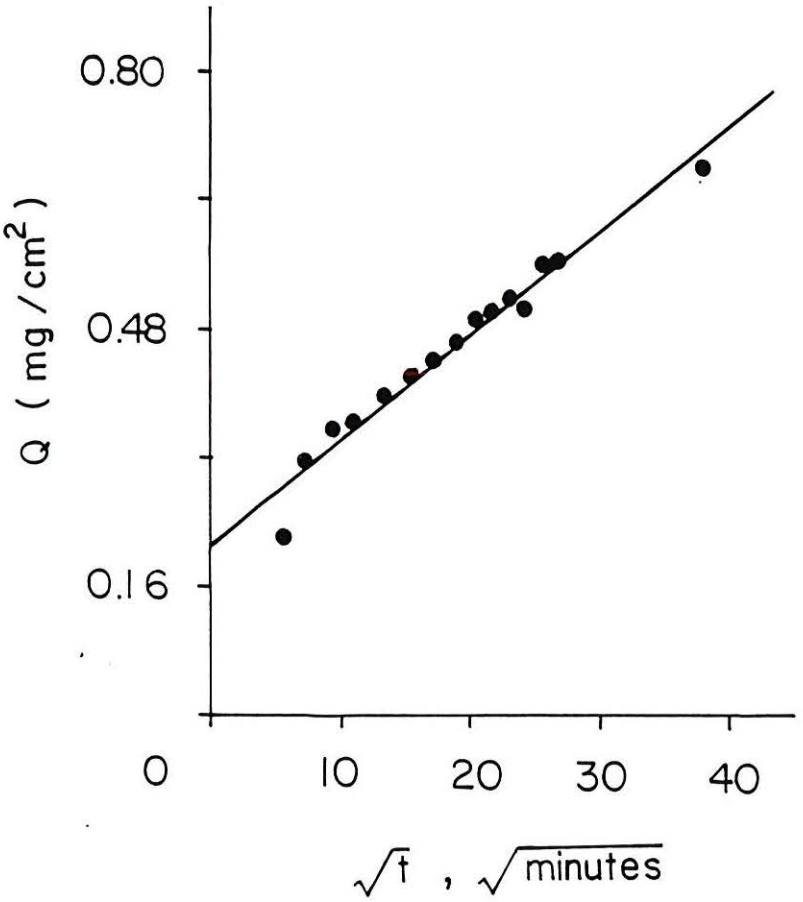

Figure 21. Release of Cortisol from Film A, at Concentration of 7.5% (w/w).

Table XXXVIII. Release of Cortisol at Concentration of 8.5% (w/w).

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.575*	21.2	9.012	0.203
60	0.581*	32.4	13.75	0.311
90	0.479*	35.8	15.23	0.345
120	0.410*	38.6	16.41	0.371
180	0.449	42.6	18.10	0.410
240	0.477	45.6	19.39	0.439
300	0.505	48.6	20.67	0.468
360	0.530	51.4	21.86	0.495
420	0.547	53.5	22.72	0.514
480	0.576	56.7	24.08	0.545
540	0.582	57.8	24.54	0.555
600	0.594	59.4	25.25	0.572
660	0.609	61.3	26.07	0.590
720	0.621	63.0	26.79	0.606
1440	0.638*	76.9	32.69	0.740

* : Proper dilutions were made.

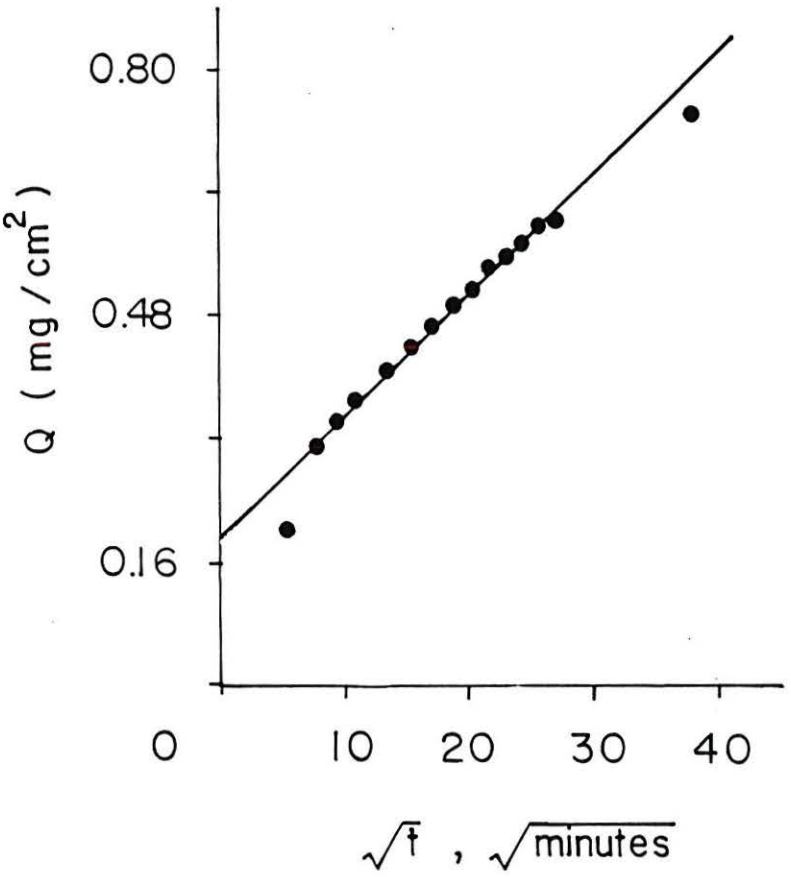

Figure 22. Release of Cortisol from Film A, at Concentration of 8.5% (w/w).

Table XXXIX. Release of Cortisol at Concentration of 10% (w/w).

Time (min.)	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2
30	0.899*	28.0	14.11	0.319
60	0.806*	38.4	19.19	0.434
90	0.642*	40.9	20.47	0.463
120	0.551*	44.2	22.12	0.501
180	0.588	47.6	23.79	0.538
240	0.615	50.2	25.08	0.568
300	0.627	51.6	25.79	0.584
360	0.645	53.5	26.75	0.605
420	0.667	55.7	27.87	0.631
480	0.690	58.1	29.04	0.657
540	0.711	60.3	30.14	0.682
600	0.721	61.6	30.81	0.697
660	0.734	63.2	31.60	0.715
720	0.750	65.0	32.52	0.736
1440	0.806*	82.7	41.35	0.936

* : Proper dilutions were made.

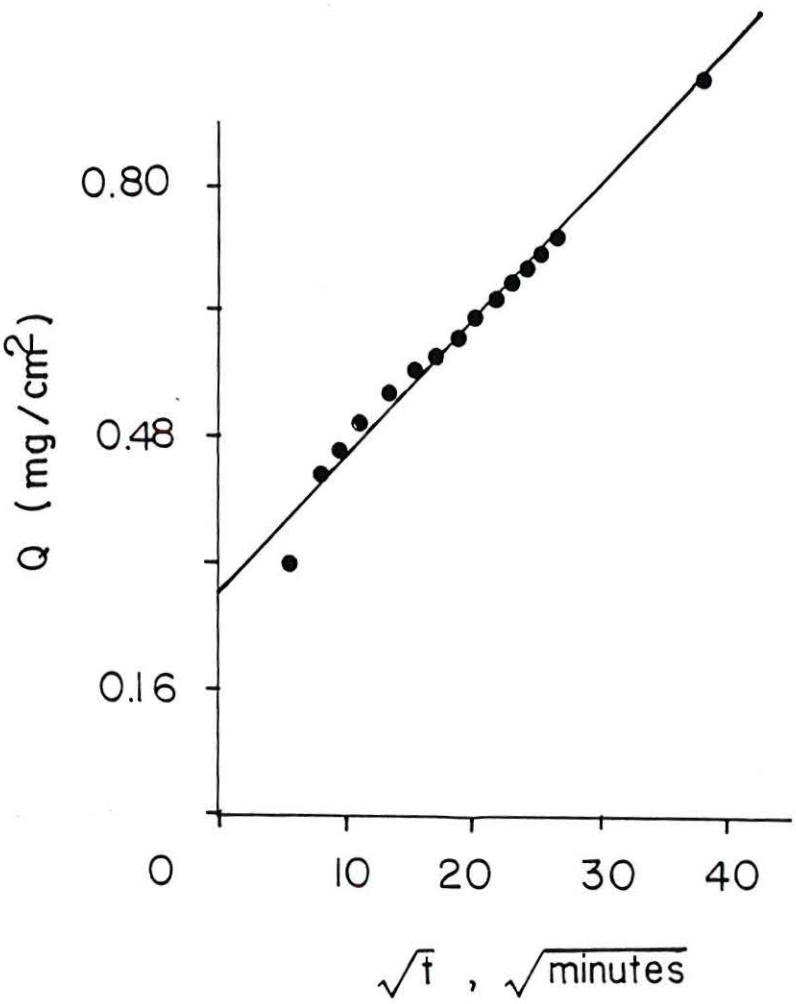

Figure 23. Release of Cortisol from Film A, at Concentration of 10% (w/w).

Table XXXX. Q vs $t^{1/2}$ Treatment of Data for Release of Cortisol from Film A at Different Drug Concentrations.

Drug Concentration (w/w)	K x 10^{-3} (mg/cm^2 $min.^{1/2}$)	Lag Time (min.)	Correlation Coefficient
0.5%	1.00	-7.2	0.992
1.5%	3.20	5.4	0.998
2.5%	5.9	26.9	0.989
5.0%	12.0	14.8	0.998
7.5%	13.0	-162.7	0.982
8.5%	16.0	-96.6	0.989
10.0%	17.0	-145.2	0.990

Table XXXXI. First-Order Treatment of Release Data of Cortisol from Film A at Different Drug Concentrations.

Drug Concentration (w/w)	$k \times 10^{-3}$ ($min.^{-1}$)	Lag Time (min.)	Correlation Coefficient
0.5%	0.883	4.56	0.992
1.5%	0.767	1.68	0.998
2.5%	0.883	-0.24	0.993
5.0%	0.950	0.38	0.998
7.5%	0.867	0.24	0.981
8.5%	0.817	-4.62	0.979
10.0%	0.917	-3.12	0.991

relatively high correlation coefficients. Table XXXX, the observed lag times were relatively high. The deviation from the origin became progressively worse with increasing drug concentration. On the other hand, relatively high correlation coefficients were also obtained for the first-order treatments of the release data. The calculated lag times were very small and the first-order rate constants were independent of drug concentration as was confirmed by the parallelism of the first-order plots (Figures 24 and 25). The films containing 7.5% w/w or more of Cortisol showed a significant burst effect due to the presence of the surface drug, while the films containing 5% w/w or less of Cortisol appear to release the drug more slowly initially.

From the studies conducted on film A, it has been described how Higuchi's release rate constant k was changing with the change in speed of agitation. Moreover, PVP has been found to leach out to the extent of 34%. A careful examination of Q vs $t^{1/2}$ plots seems to suggest a curvilinear relationship rather than the expected linearity. All this data appears to discount the possibility of a matrix-controlled diffusion theory to such a film system. Further evidence of the invalidity of this mechanism is that the rate of release is not inversely proportional to the total amount of the drug released, Q, as predicted by Eq. 12 which has been derived from Eq. 2:

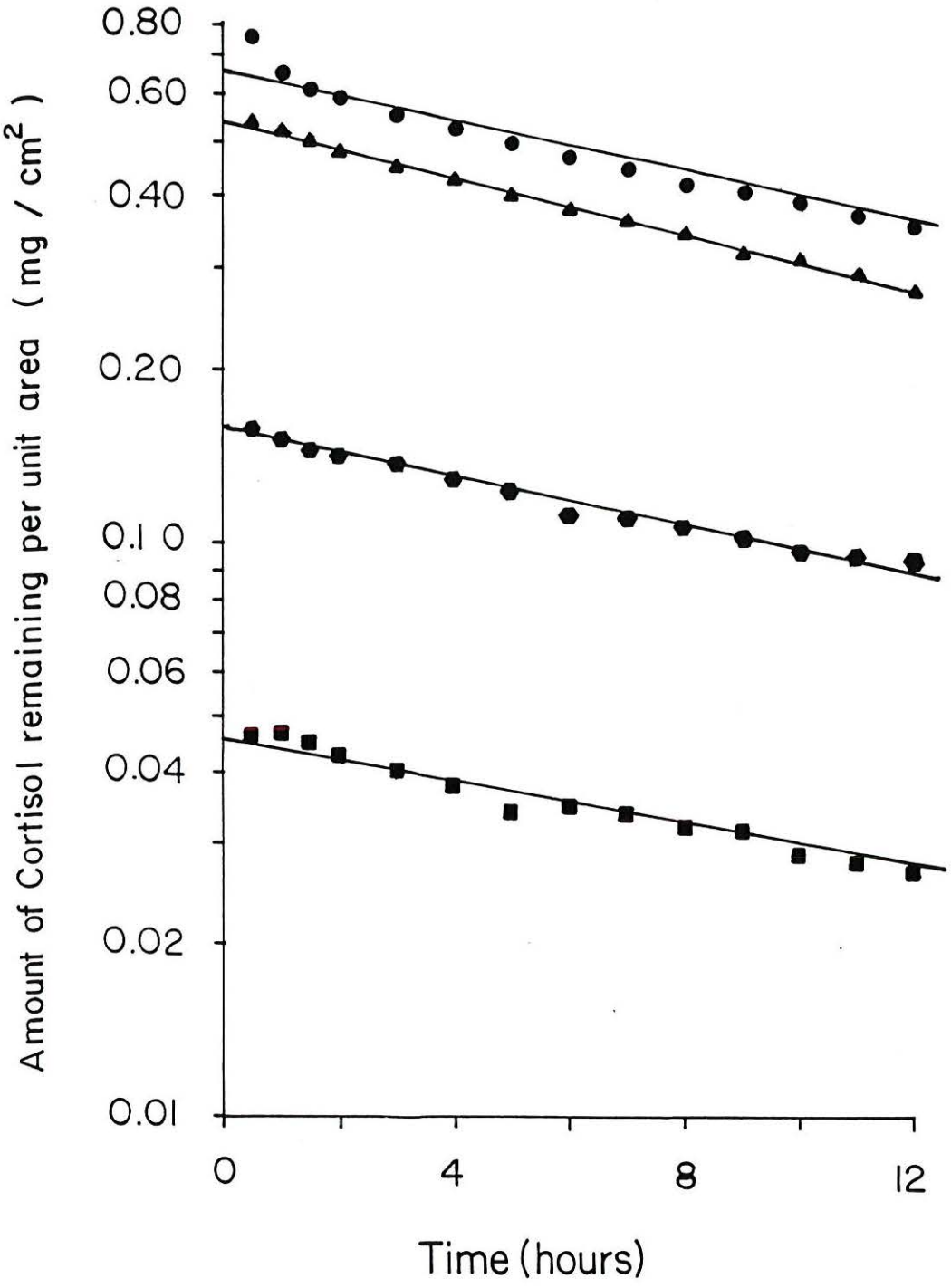

Figure 24. First-order plots of Cortisol, Release from Film A, at Concentrations of 0.5% (■), 1.5% (⬢), 5% (▲) and 8.5% w/w (●).

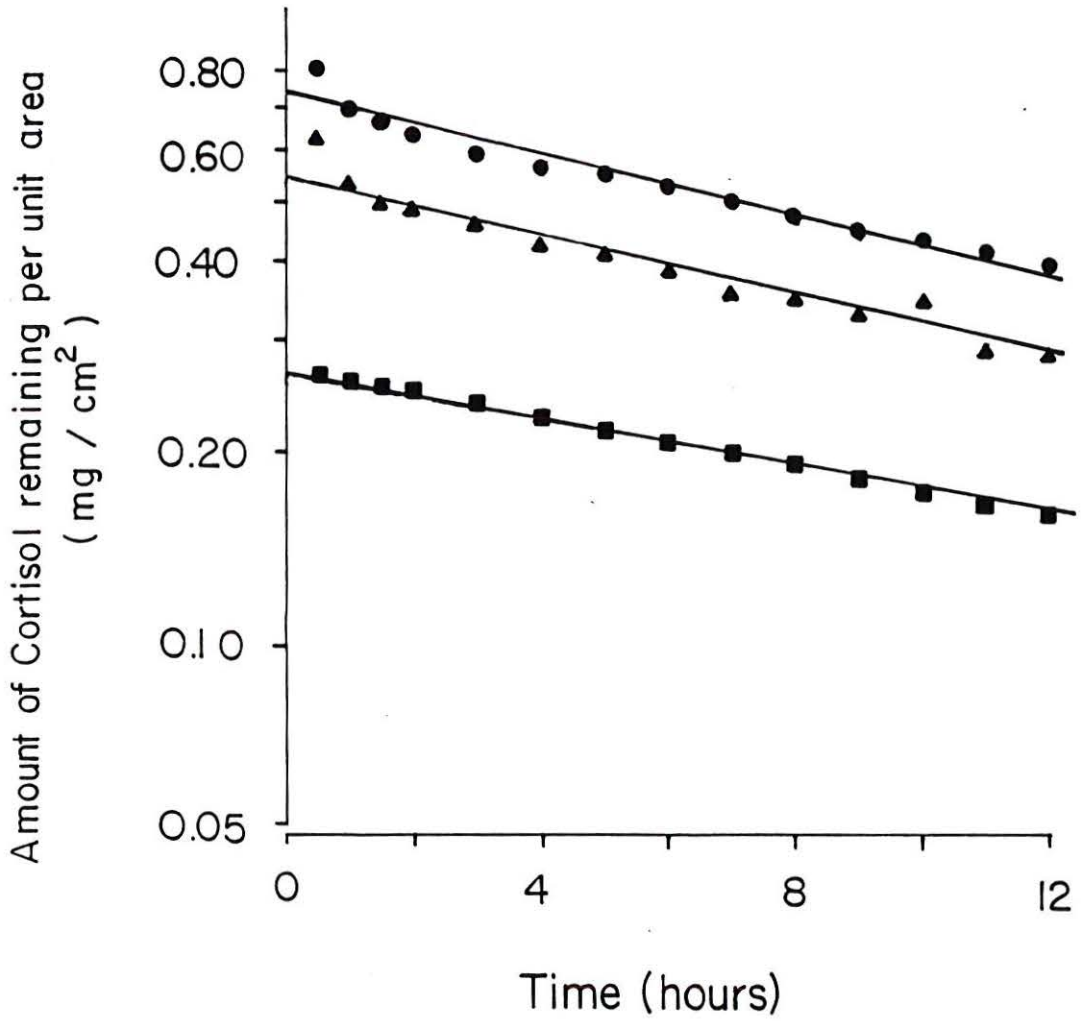

Figure 25. First-order Plots of Cortisol Release from Film A, at Concentrations of 2.5% (■), 7.5% (▲) and 10% w/w (●).

$$\frac{dQ}{dt} = \frac{K^2}{2Q} \quad \text{. . . . . (Eq. 12)}$$

The following first-order relationship

$$\log x = \log X - \frac{kt}{2.303} \quad \text{. . . . . (Eq. 13)}$$

Where:

x is the drug content of the film at time t. It predicts a direct proportionality between the rate of release and that any amount of drug released as suggested by the following equation:

$$\frac{dQ}{dt} = kX - kQ \quad \text{. . . . . (Eq. 14)}$$

When the rate of release is plotted as a function of Q, and 1/Q, linearity was not obtained with either one of the two mechanisms (Figure 26). Final evidence against the applicability of a matrix controlled diffusion mechanism is provided by plotting log Q vs log t, based on the logarithmic form of Eq. 15:

$$\log Q = \log K + 1/2 \log t \quad \text{. . . . . (Eq. 15)}$$

Such a plot should have a slope of 0.5. However, the observed slope was 0.70 (Figure 27). These findings suggest that the drug release rate from Film A does not follow the matrix-controlled diffusion model, but that a different mechanism might indeed be operative. Additional studies might be helpful in delineating the precise mechanism.

By reviewing the data obtained from the drug release profiles from Film B, it was observed that the matrix remained

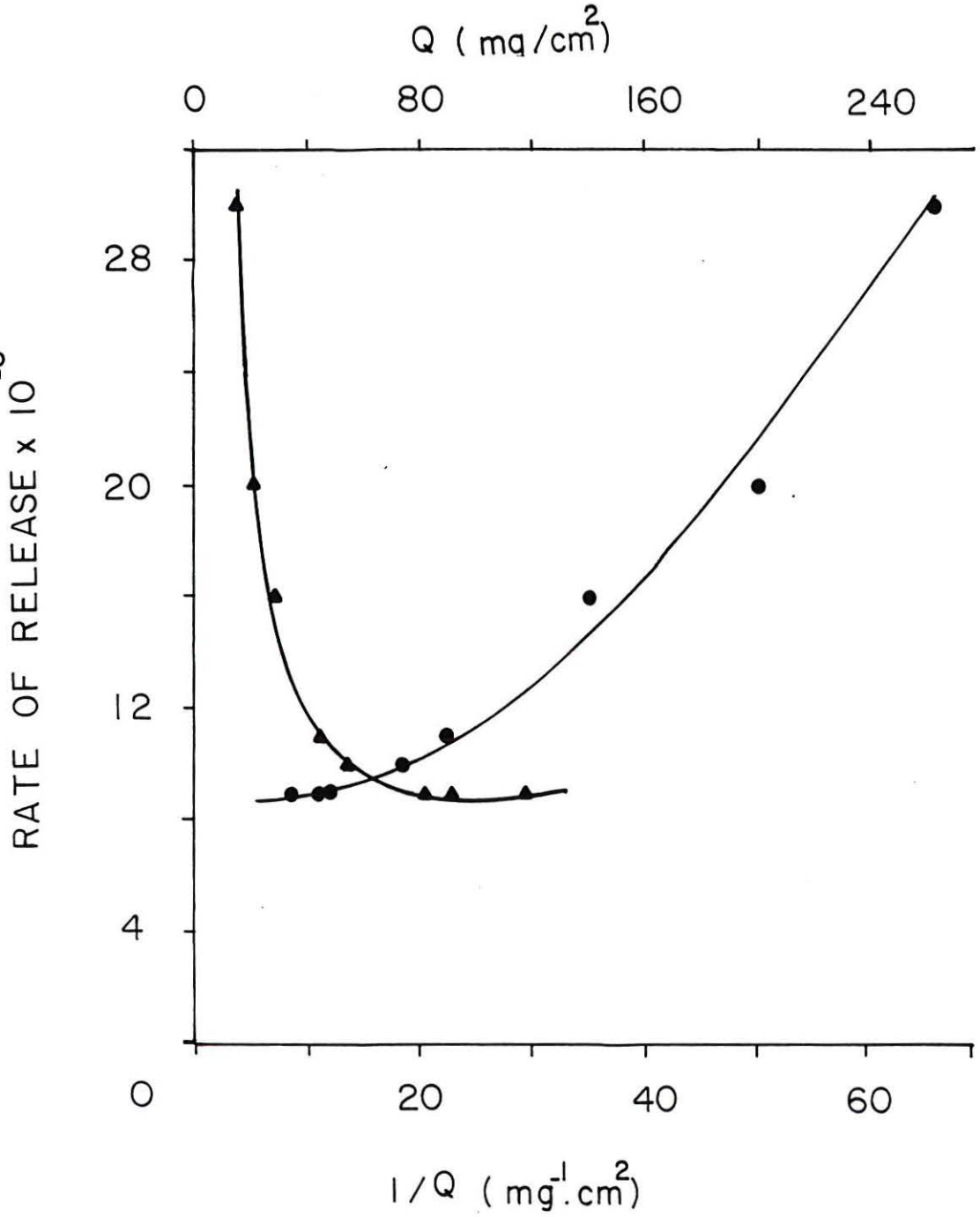

Figure 26. Plots of Release Rate of Cortisol from Film A Vs. the amount of drug release (Q) (▲) and the reciprocal of the amount of drug release (1/Q) (●).

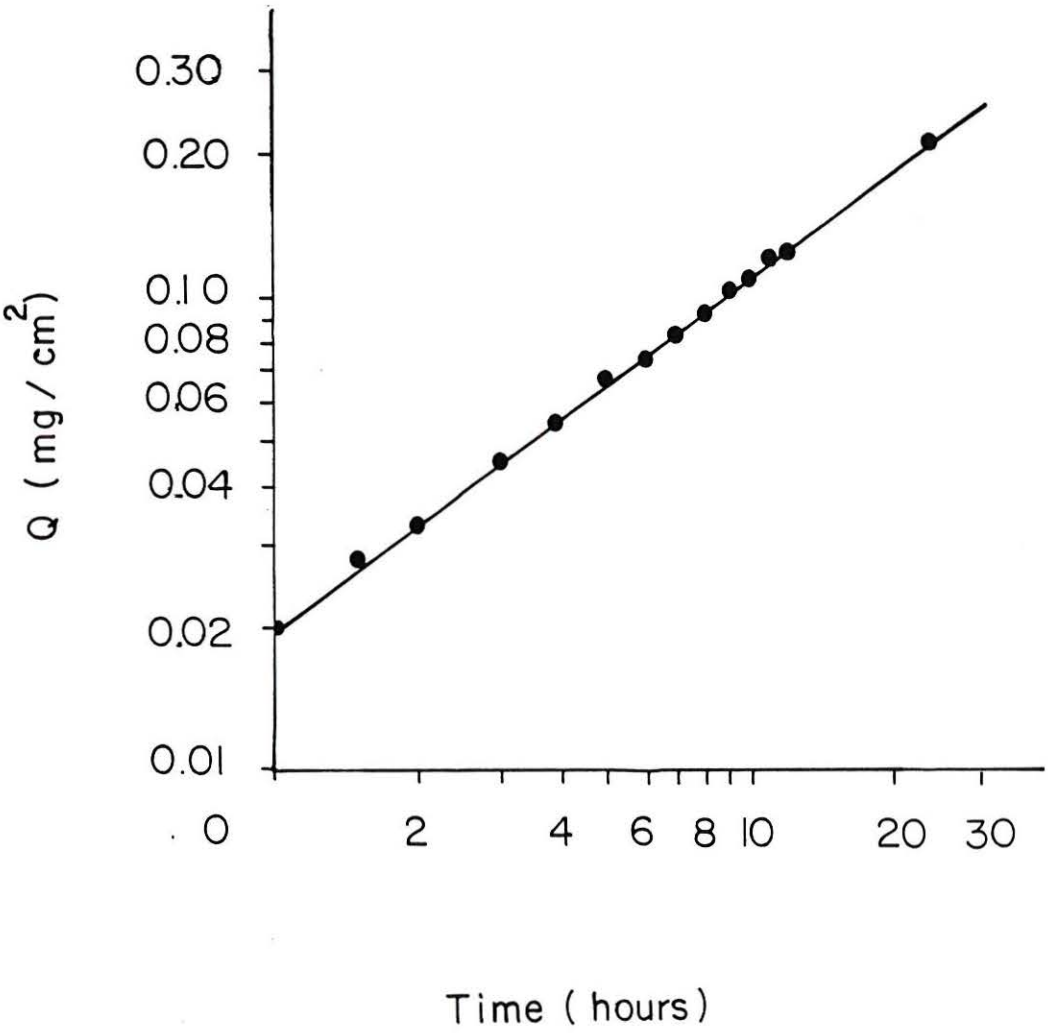

Figure 27. Relationship of log Q to log t, of Cortisol from Film A (slope = 0.70).

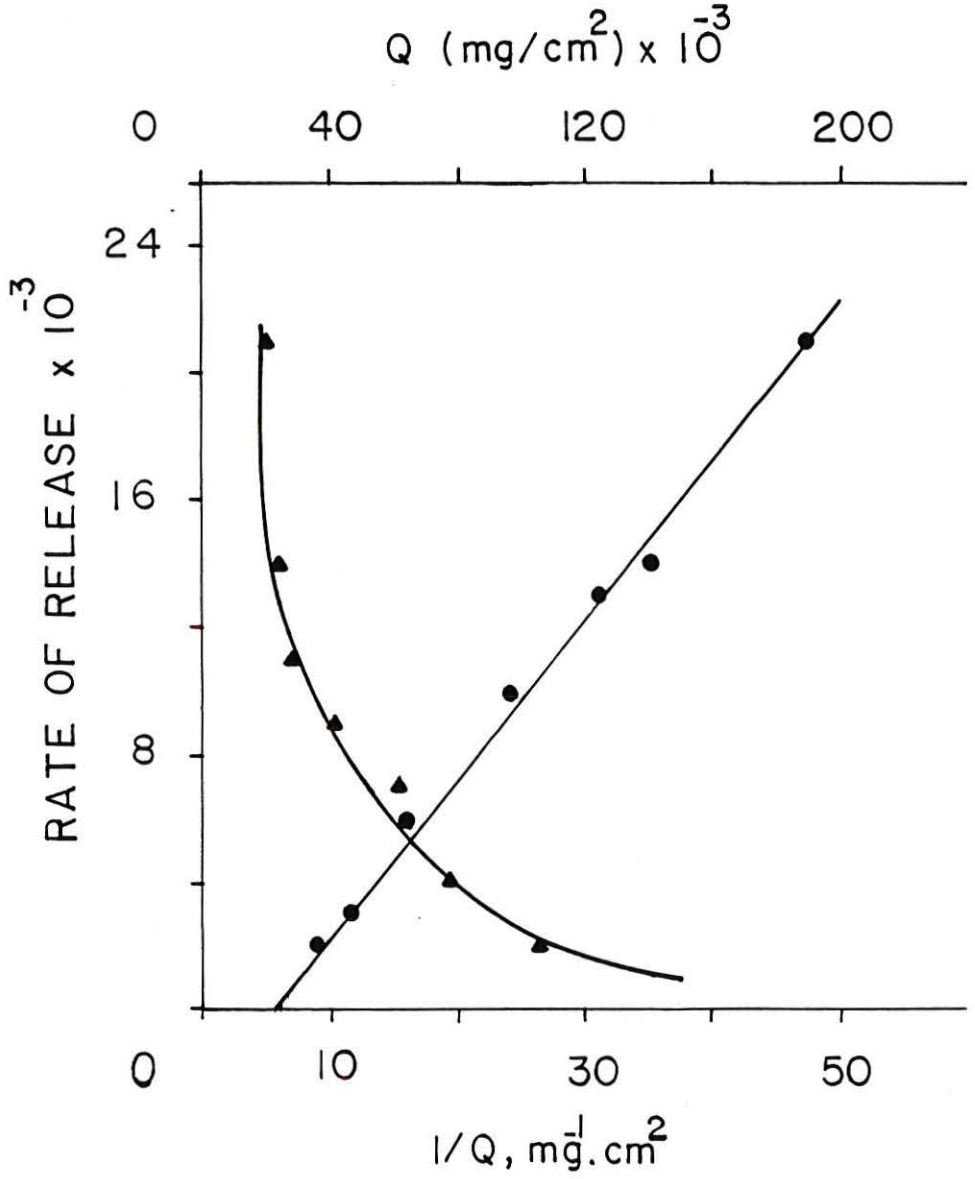

Figure 28. Plots of Release Rate of Cortisol from Film B, Against the Amount of Drug Release (Q) (●) and the Reciprocal of the Amount of Drug Release (1/Q) (▲).

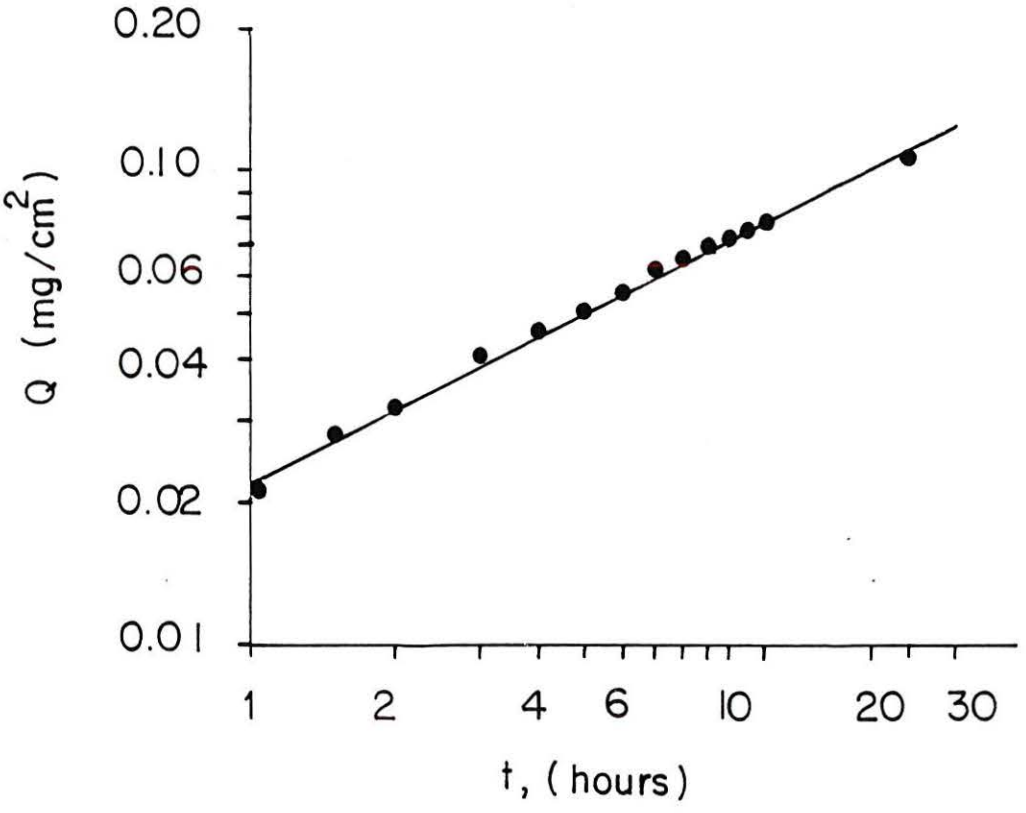

Figure 29. Relationship of log Q to log t, of Cortisol Release from Film B (slope = 0.53).

intact throughout the release process. The diffusion release rate constant remained unchanged over a wide range of agitation speeds. Furthermore, by plotting the rate of release vs Q and 1/Q, linearity was obtained only with 1/Q (Figure 28). In addition to that, a plot of log Q vs log t (Figure 29), had a slope of 0.53. These findings are in marked contrast to those for film A and serve to confirm the diffusion-controlled mechanism for film B.

Clinical Potential:

The controlled release of drugs from dosage forms is a highly desirable attribute. Former studies (28) have shown that pure povidone films released their entire Cortisol content in only 30 minutes. On the other hand, pure lanolin alcohol films released less than 50% of their Cortisol content over a period of 24 hours. The films containing varying proportions of these two film formers showed drug release profiles somewhere between these two extremes. The lanolin alcohol-PVP film system offers promising potential in the design of a controlled or time drug delivery system. The physiological tolerance towards Povidone has made this polymer very attractive for various applications in pharmacy and medicine. Although Cortisol was used as a model drug in this study, this delivery system could be adapted for other drugs as well. Although this work has emphasized topical application, the film system studied here could be used in the design of dosage forms intended for the other routes as well.

SUMMARY AND CONCLUSION

In vitro release of Cortisol from pure lanolin alcohol and lanolin alcohol-PVP films was investigated. The effect of agitation was studied on both types of films while the effect of drug concentration and film thickness was studied on lanolin alcohol-PVP films. Solubility of the drug in the film matrix was determined. The leaching of PVP from the film matrix and its effect on drug solubility in water was also studied.

The results of the investigations on lanolin alcohol films showed that the rate of drug release from these films was not affected by the intensity of agitation. Furthermore, the film matrix remained intact throughout the release process. Further analysis of the data revealed that Higuchi's diffusion-controlled granular (since Cortisol is found to be insoluble in lanolin alcohol) matrix model explained the mechanism of Cortisol release from these films.

The investigations of lanolin alcohol-PVP films have shown that although Higuchi's release rate constant was found to be independent of film thickness, it was affected by the intensity of agitation. In addition to that, PVP was found to diffuse out of the film matrix along with Cortisol. This explains the failure of this film system to conform

to the matrix-controlled diffusion model of Higuchi. The Cortisol rates show first-order dependence on drug concentration. The first-order rate constant was found to be independent of drug concentration. Further analysis of the data confirmed this conclusion.

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