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Release of cortisol from propylene glycol monostearate--ethoxylated stearyl alcohol films

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RELEASE OF CORTISOL FROM PROPYLENE GLYCOL MONOSTEARATE - ETHOXYLATED STEARYL ALCOHOL FILMS

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ABSTRACT

In the present study, propylene glycol monostearate (PGM), ethoxylated stearyl alcohol (ESA) and combination thereof have been investigated for their film-forming potential. The wettability, strength, and integrity of the films were evaluated by measuing the contact angles and modulus of elasticity. The films of mixed composition had smaller contact angle than the films of either component. The modulus of elasticity of all films tested was in the range of 0.19 - 0.40 Kg/cm^2. A series of experiments were conducted in vitro to study the effect of changes in film composition, drug concentration and rate of agitation on cortisol release. Films of varying compositions containing 10 to 20% w/w ESA with corresponding decrease in PGM concentration with 4% w/w cortisol were found to release from 15 to 90% of cortisol during 12 hour period. Unidirectional drug release from all film matrices was found to follow first-order kinetic profile over first five hours of drug release. The examination of Q versus $t^{\frac{1}{2}}$ plots (granular matrix) revealed linearity for first five hours of drug release but curvilinear effect beyond. First-order release rate constant was found to increase linearly with rate of agitation.

ACKNOWLEDGEMENTS

I would like to express my deep appreciation to Dr. Ravindra C. Vasavada for his encouragement and guidance throughout this study. My appreciation is also due to Dr. Madhukar Chaubal and Dr. Hershel Frye for their patience and help. I would like to thank Dr. Richard Jones of Syntex Research, Palo Alto, California for his consideration.

I wish to dedicate this thesis to my wife and my parents without whose encouragement and support this would not have been possible.

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INTRODUCTION

The application of a drug dispersed in an inert matrix to achieve controlled relase has drawn great attention from researchers for the past two decades. This concept has been demonstrated to offer several advantages over conventional dosage forms. Less frequent dosing with prolonged action formulations, compared to the regular-release equivalent, is an important advantage. Patient acceptability was found to be another important consideration. Furthermore, a prolonged action mechanism may produce a more constant blood level of drug over a desired period of time resulting in fewer side effects. Also, the predictable control over rate and extent of absorption, and a possible decrease in the total dose of the drug are important benefits generally unavailable from the regular-release dosage forms. More recently, this method has been suggested for achieving controlled release of drugs in ophthalmic (1) and dermatologic practice (2,3), buccal absorption (4), and formulation of long-acting implants (5,6).

In the field of topical drug delivery systems, great interest has developed regarding the use of medicated polymeric films. Films of this type can be utilized as creams, solutions, aerosols, or lotions to achieve percutaneous absorption

of a therapeutically active substance. A variety of polymeric film-forming delivery systems have been investigated to achieve controlled drug release over a desired period of time (6,7), and for attaining other pharmaceutical objectives such as improving topical drug penetration by increasing hydration of skin by occlusion (8), and imparting wash and wear resistance to the site of application.

In the case of percutaneous absorption where skin serves as a natural barrier, the therapeutically active substance must reach the skin surface at an adequate rate from the vehicle to ensure optimal penetration. In other words, if the vehicle is a thin film, it is a prerequisite for the drug to be released from the film in order to attain the therapeutic objectives. Sciarra and Gidwani (3) pointed out that the nature of the film had significant effect on the release of drug suggesting that film properties must be taken into consideration. The film former should be inert and incapable of complexation with the drug. The film should remain intact and continuous at the site of application. The film surface in contact with the skin should have balanced hydrophilic-lipophilic characteristics to ensure uniform contact with the skin secretions, namely sweat and sebum. Continuous and uniform wetting of the film surface by the skin secretions would ensure more predictable and constant drug release. The moisture vapor transmission characteristics of film-forming systems might also deserve consideration in view of the importance of hydration of

stratum corneum in improving topical absorption of drugs.

Several polymeric substances have been studied for their film-forming characteristics and potential application in topical dosage forms (2,5,9). However, nonpolymeric substances do not appear to have been fully explored. Lanolin alcohol has been recently shown to form isolatable films on mercury substrate (10, 11). The release kinetics and *in vitro* skin penetration of triamcinolone acetonide from lanolin alcohol-ethyl cellulose films were also investigated in these studies. The potential application of such film compositions was further confirmed by Khan (12). Effective utilization of potential nonpolymeric film formers holds several promising features. The toxicologic hazards associated with monomeric impurities present in high molecular weight polymers could be minimized. Nonpolymeric materials are easy to manipulate and compound. They can be washed off from the skin by soap and water. Moreover, nonpolymeric substances can be obtained with relative ease in a state of more definable composition.

In the present study, propylene glycol monostearate and ethoxylated stearyl alcohol have been investigated for their film-forming characteristics. A preliminary evaluation of these potential film formers was conducted by measuring the solubilities in water, isopropyl alcohol, and ethyl alcohol. The film-forming ability and integrity of the films have been demonstrated by casting the films on mercury substrate

and isolating the films therefrom. The wettability characteristics of the film surface were evaluated by measuring the contact angles against water. The strength and elastic properties of the thin films were determined by measuring the hardness and modulus of elasticity at a given film thickness.

This work also describes the kinetics of drug release from selected compositions of thin films with varying proportions of propylene glycol monostearate and ethoxylated stearyl alcohol. For the purpose of these studies, cortisol was chosen as the model drug in view of its wide acceptability as an anti-inflammatory agent in topical dosage forms and demonstrated potential application in sustained release preparations (13,14).

THEORY

In the present study a film-forming delivery system composed of propylene glycol monostearate and ethoxylated stearyl alcohol has been examined. Cortisol is assumed to be uniformly dispersed as solid in the film matrix, and the solubility of cortisol in propylene glycol monostearate or ethoxylated stearyl alcohol is assumed as negligible.

Theoretical treatments of the mechanism of drug release from inert film matrices containing dispersed drug in solid phase assume that the rate controlling step is in the applied film, therefore, the skin properties can be ignored. Concentration gradient, if any, is assumed to occur in the vehicle and the skin can be regarded as a perfect sink. Because of the great resistance of the intact skin only a negligible concentration gradient may develop in the applied film in the direction normal to the skin surface. The concentration of the penetrating substance in the skin is essentially zero because of rapid dissipation into deeper tissues. For these systems, drug concentration in the vehicle, diffusion coefficient of the drug molecule in the vehicle, and solubility of the drug in the same are the important factors.

Based upon the assumptions mentioned above, Higuchi (5) has derived quantitative relationships governing such

situations. Two mechanisms of drug release from such delivery systems having unidirectional leaching or extraction from a simple planar surface have been proposed (16).

(i) release from a planar system having drug dispersed in a homogeneous matrix.

(ii) release from a planar system having durg dispersed in a granular matrix.

Drug Release from a Planar System Having a Homogeneous Matrix:

The extraction of the drug is a simple diffusional process through and from an enveloping, homogeneous matrix. The drug is presumed to go successively from the crystal surfaces into the uniform matrix and out into the bathing solvent which in turn acts as a perfect sink. The amount of total drug released from such a system could be determined by the relationship

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

where:

Q = the amount of drug released after time t per unit exposed area,

D = the diffusivity of the drug in the homogeneous matrix media,

A = the total amount of drug present in the matrix per unit volume, and

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

Drug Release from a Planar System Having a Granular Matrix:

The drug is leached by the bathing fluid which is able to enter the matrix phase through pores, cracks, and intergranular spaces. The drug is presumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with the extracting solvent. Intragranular diffusion is assumed to be negligible. Equation 1 was modified for this type of release where diffusion can occur.

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

where:

Q = the amount of drug released after time t per unit exposed area,

D = the diffusivity of the drug in the permeating fluid,

T = the tortuosity factor of the capillary system,

A = the total amount of drug present in the matrix per unit volume,

C_s = the solubility of the drug in the permeating fluid, and

ε = the porosity of the matrix.

The apparent solubility of the drug in the total system per unit volume is decreased by the porosity factor. The tortuosity factor is introduced to correct for the lengthened diffusional path caused by the necessary lateral excursions.

Both equations are based on the existence of pseudo steady state condition during the release process and on the assumption that the drug particles are quite small relative to the average distance of diffusion and are uniformly distributed in the matrix. The equations would be essentially valid for systems in which A is greater than C_s or εC_s by a factor of three or four.

Although the two equations are for different mechanisms, they both describe drug release as being linear with the square root of time:

$$Q = Kt^{\frac{1}{2}} \qquad \text{(Eq. 3)}$$

where K is the release rate constant. For a homogeneous matrix system:

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

For a granular matrix system:

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

These relationships have been confirmed experimentally by a number of workers using plastic and wax matrixes (9, 17-21).

A first order release mechanism based on the Whitney-Noyes equation is also considered as possible for this type of drug delivery systems. Sciarra and Gidwani (2) explained that the release of gentian violet from various plastic matrixes and different desorbing media followed this release model.

The first order release mechanism in which the release rate is proportional to the amount of drug left in the matrix can be shown as:

$$\log(Q_o - Q) = \frac{-kt}{2.303} + \log Q_o \qquad \text{(Eq. 6)}$$

where:

Q_o = the initial amount of drug present per unit area of the film,

Q = the amount of drug released per unit area at time t, and

k = the first order rate constant.

In this study the data for the release of cortisol from different film compositions were analyzed to determine which mechanism might be operative.

Recently a new model for drug release from thin films has been proposed. The model treats the drug-containing film matrix and the skin as a bilayer membrane system. The drug is assumed to diffuse through each layer by a time-dependent non-steady state process. This model has been successfully applied to the release of triamcinolone acetonide from a film containing lanolin alcohol, ethyl cellulose, and propylene glycol (22).

EXPERIMENTAL

Materials

Film Formers:

1. Propylene Glycol Monostearate (PGM), NF (Ruger Chemical Co. Inc., Irvington, NY)
2. Ethoxylated Stearyl Alcohol (ESA), (Volpo S.20^{R}, Croda Inc., New York, NY, Ethoxyl content of 20 moles).

Model Drug:

1. Cortisol (CO), USP (Lot #0712833, Amend Drug & Chemical Co. Inc., Irvington, NJ)

Solvent:

1. Ethyl Alcohol, USP (Commercial Solvents Co., Agnew, CA)
2. Isopropyl Alcohol, NF (Mallinckrodt, Inc., St. Louis, MO)

Solubility Studies

The solubilities of the film forming materials were determined in water, isopropyl alcohol, and ethyl alcohol at room temperature ($22^{o} \pm 0.5^{o}C$). About 6 to 7 g of the film former was added to 20 ml of each solvent in 50-ml flasks with screw caps. A teflon-coated magnetic bar was placed in each flask prior to capping it tightly. The flasks were supported by holders at a distance of 1.5 cm from the

motor and constant temperature was maintained throughout the stirring process for 48 hours.

The stirring was stopped prior to sampling and the undissolved portion was allowed to settle. An aliquot was filtered using a glass funnel with filter paper. Two milliliters of filtrate were pipetted in a preweighed petri dish and dried in a drying oven at 50^{o} for one hour. The petri dish was then left in a desicator for 24 hours at room temperature and weighed again. The solubility was calculated from the weight change of the petri dish. All studies were conducted in duplicate.

Preparation of Films for Initial Screening

For preliminary screening, all films were prepared from a 5% (w/v) solution (or suspension in the case of propylene glycol monostearate). The required amount of a film forming agent was added to ethyl alcohol contained in a volumetric flask equipped with a magnetic stirring bar and contents were stirred for 24 hours with the flask tightly capped.

The films were cast using the mercury substrate technique. Three milliliters of solution or suspension was poured on the surface of mercury contained in a 50x10 mm[1] glass petri dish, which was then partially covered with its lid. This helps to control the solvent evaporation rate and reduce the blistering of the surface of the deposited film.

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[1] 50 mm in diameter and 10 mm in depth.

The solvent was allowed to evaporate overnight. The film formation can easily be noted by observing the mercury substrate after complete solvent evaporation. The film preparation was carried out in a humidity controlled room at 25^{o} and 40% relative humidity. Preliminary trials were carried out to establish time for complete evaporation.

The resulting films were carefully removed from the mercury substrate and were individually stored between sheets of weighing paper inside a desicator over anhydrous calcium chloride

Minimum isolatable film thicknesses were determined by measuring the intact film thicknesses isolated from mercury substrate cast with reducing amounts (2.5 ml, 2 ml, 1.5 ml, and 1 ml) of solution or suspension.

Contact Angle Measurements

Films for contact angle measurements were cast on glass slides. A 25x75 mm slide was placed in a 100x15 mm glass petri dish. Mercury was poured onto the dish sufficient enough to surround the slide and to ensure that mercury surface was higher than the surface of the slide. The solution (or suspension) of a film former was poured on the slide. The surrounding mercury made it possible to hold the film solution on the glass slide. The solvent was allowed to evaporate for 24 hours in a humidity controlled room as described above to ensure good film formation.

The slide was lifted after complete evaporation of the solvent and was ready for contact angle measurements. The

film-coated slide was placed on an adjustable platform kept perfectly horizontal by means of a leveling device. A water drop of 1 µl was applied on the film using a microburette and was allowed to stand for 60 seconds to reach equilibrium before reading the contact angle. Contact angle was measured using a Reflective Goniometer[2] fitted with a protractor scale and an objective lens (magnification x3). The entire unit was mounted on an adjustable stand. The hairline of the protractor eyepiece was adjusted to coincide with the surface of the film, and the intersection of the two hairlines was fixed at the film-water-air triple interface. The verticle hairline was then adjusted to make a tangent to the liquid-air interface. With this baseline adjustment completed in sixty seconds, the contact angle was read directly from the scale.

Solid surfaces are nonhomogeneous and their surface energies are not evenly distributed. Therefore, the measurement of contact angles was taken at five points on each test film. The mean value based upon five drops was calculated in this study. Contact angle here is in reality only an apparent value, however, it should be emphasized that these measurements are valid and provide a useful method of comparing the wetting abilities of the different films studied.

Determination of Hardness and Modulus of Elasticity

For the determination of hardness and modulus of

[2]Kernco Instruments Co. Inc., El Paso, Texas.

elasticity, the solutions (or suspensions) of the film formers were prepared exactly as before. The film hardness was determined on film cast on a polished aluminum plate (20x20 cm) using a Multiple Clearance Applicator[3] producing a wet film thickness of about 1 mm. The Multiple Clearance Applicator has a dimension of 10.2x10.2x1 cm. It permits eight different thicknesses for the formation of films ranging from 5 to 50 mils, a mil thickness being equivalent to 25 μm.

The plate was dried in a humidity controlled room at 25° and 40% relative humidity. The dry film thickness was determined using a Minitector thickness measuring gauge (Model-N)[4]. It is necessary to zero the instrument on the same aluminum plate before each reading. The instrument was regularly calibrated using the standard foils provided with the instrument.

Film hardness was determined using an automatic Sward Hardness Rocker.[4] This instrument has been used for measuring the hardness of paint films (23) and to determine the Sward Hardness of some polymeric films (2) intended for pharmaceutical applications.

The automatic rocker is fitted with a shutter that crosses a focused beam of light which provides automatic counting. The number of rocks is the result of the total number of oscillations given by the automatic counter multiplied by two. Before each measurement, the rocker was

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

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

calibrated to show 100 rocks in 60 seconds on the standard polished glass plate. The glass plate was then replaced by the film-coated aluminum plate and the rocker was set in motion. The number of rocks was measured by the average of three determinations rounded off to the nearest whole number. All measurements were made at room temperature.

Modulus of elasticity E was calculated from the Sward Hardness R (number of rocks of the rocker on the test film):

$$E = \frac{KR^3}{T^3} \qquad \text{(Eq. 7)}$$

The values of constant K, for different thicknesses T, were obtained by plotting the different T values against standard K values on a semi-logarithmic paper. The standard values of K for different thicknesses are shown below (23):

Thickness	K
0.0012"	1.73×10^{-9}
0.0024"	2.1×10^{-8}
0.004"	1.3×10^{-7}
0.125"	2.5×10^{-2}

The precision of Sward Hardness reading is affected by large variations in temperature and the roughness of the film surface (23).

Determination of Drug Release Kinetics

The films were cast from a freshly prepared suspension containing 6.6% w/v solids (drug plus film formers),

using ethyl alcohol as the solvent. Ethoxylated stearyl alcohol and cortisol were added in required quantities to ethyl alcohol and were allowed to dissolve completely by stirring for a sufficient amount of time (approx. one hour). Propylene glycol monostearate was then added and stirring continued for another 24 hours to obtain a uniform dispersion. The stirring was stopped before samples were drawn. Three milliliters of this suspension was pipetted[5] into a preweighed, glass petri dish and was allowed to spread evenly across the bottom (60 mm in diameter) by gentle shaking.

The petri dish was partially covered and kept on a level surface for at least 24 hours to ensure slow and uniform evaporation of solvent. Complete evaporation was confirmed by weighing the petri dish to a constant weight. The film-coated petri dish was stored in a desiccator for at least 24 hours prior to the release study. Various film compositions prepared and investigated during the course of this study are listed in Table I.

Following the procedures previously developed in this laboratory (10), the release studies were conducted in a dissolution assembly (Figures 1 and 2) with dissolution flasks replaced by 1000 ml flat bottomed glass beakers, and the dissolution basket assemblies replaced by stainless steel stirrers with a propeller of 45 mm diameter. Three hundred ml of distilled water were added carefully to each beaker

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[5] Pipetman ^{R}, Model p-5000D, Woburn, MA.

Table I. Compositions of the Films Studied[a]

Film No.	Propylene Glycol Monostearate (PGM)	Ethoxylated Stearyl Alcohol (ESA)	Cortisol (CO)
1	0	96	4
2	96	0	4
3	94	2	4
4	92	4	4
5	90	6	4
6	88	8	4
7	86	10	4
8	85	11	4
9	84	12	4
10	83	13	4
11	82	14	4
12	81	15	4
13	80	16	4
14	79	17	4
15	78	18	4
16	77	19	4
17	76	20	4
18	82.85	14.15	3
19	83.71	14.29	2
20	84.56	14.44	1

Table I. (continued)

Film No.	Propylene Glycol Monostearate (PGM)	Ethxylated Stearyl Alcohol (ESA)	Cortisol (CO)
21	81.84	15.16	3
22	82.69	15.31	2
23	83.53	15.47	1

[a]Percent w/w based upon weight of the drug films.

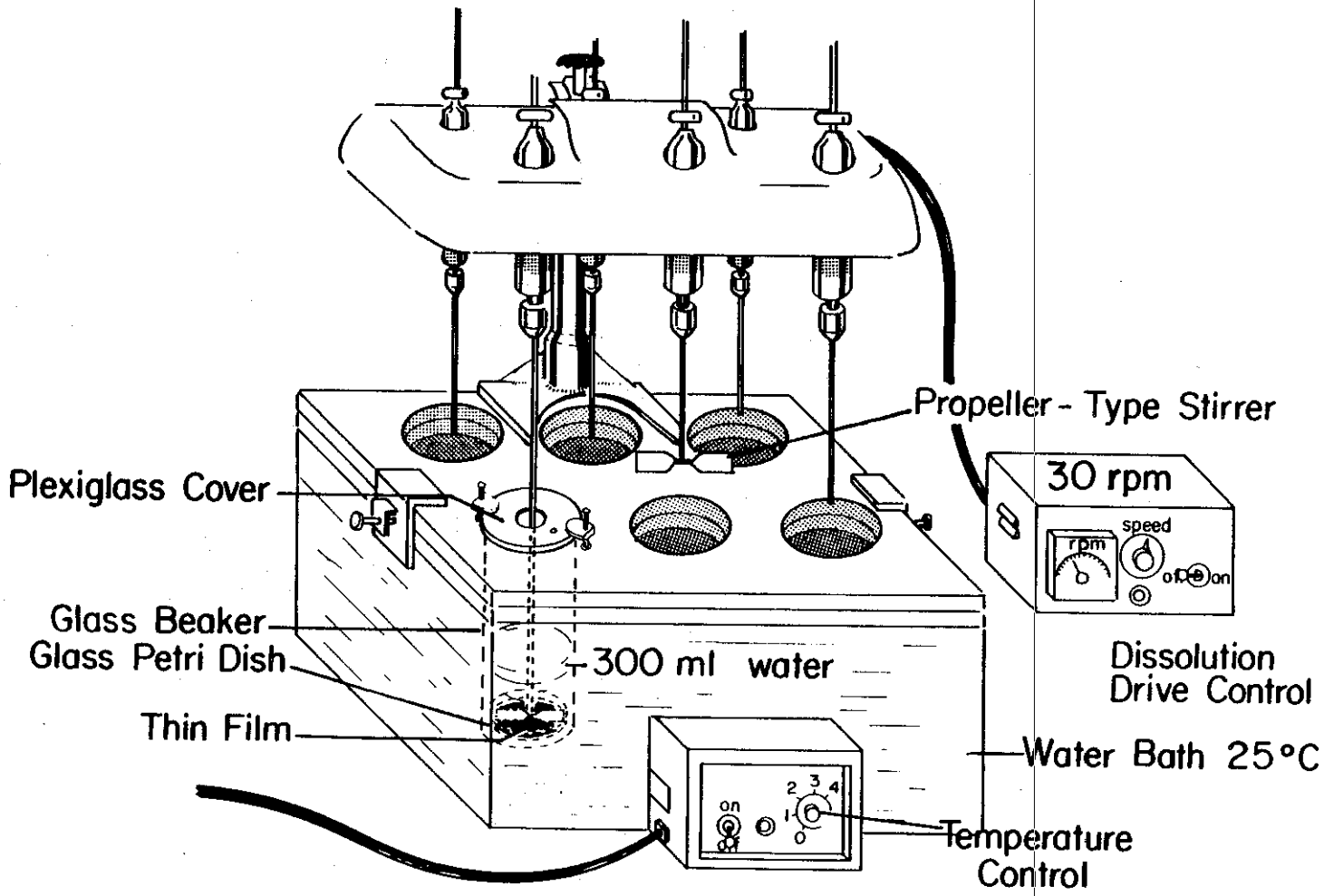

Figure I. Apparatus used for *In Vitro* release studies

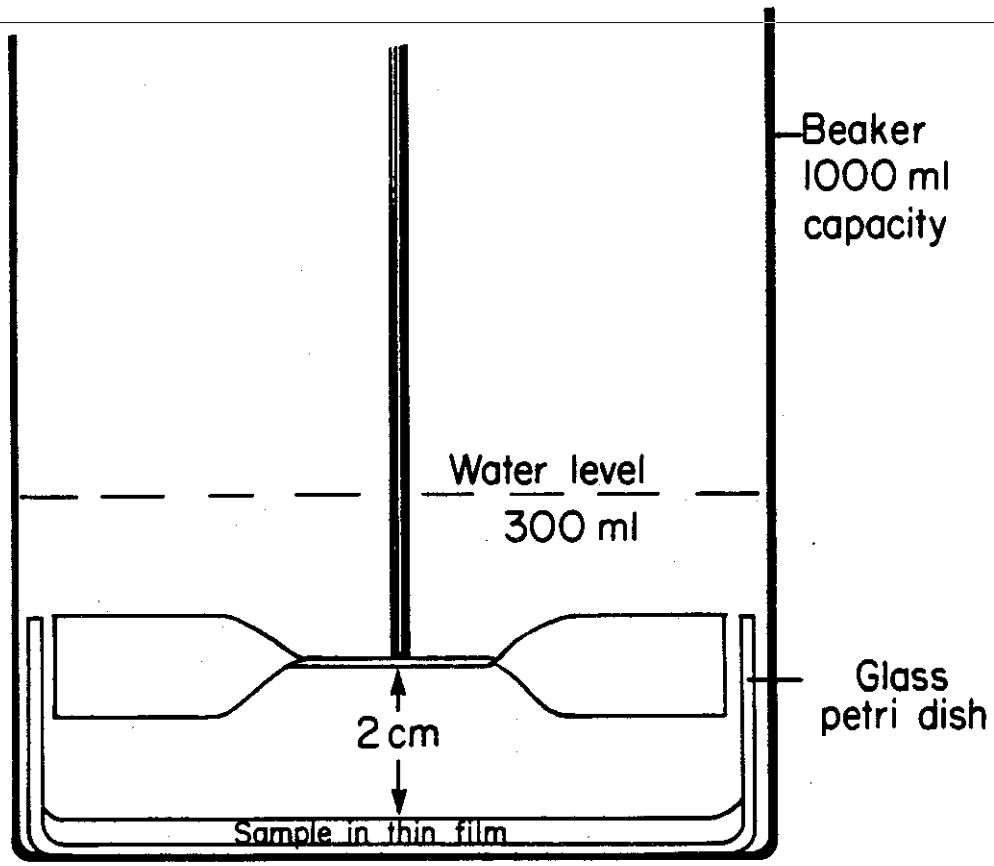

Figure 2. Enlarged view of experimental beaker

with a film-coated petri dish on the bottom. The distilled water was previously equilibrated at 25°. The stirring was maintained at 30 rpm and the water bath at 25° ± 0.5°.

Three ml samples were drawn[6] at appropriate time intervals over a 12 hour period. Each sample was pipetted into a glass test tube and analyzed spectrophotometrically at 242 nm.[7]

The volume of each sample removed (3 ml) from the release cell was replaced by an equal volume of water previously equilibrated at 25°. A cumulative correction was made to determine the total amount released according to the following formula (24):

$$C_n = C_m + \frac{3}{300} \times \sum_{s=1}^{n-1} C_s \qquad \text{(Eq. 8)}$$

where

C_m = the spectrophotometrically measured concentration,

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

n-1 = the total volume of all samples removed prior to the sample being measured, and

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

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[6] Pipetman ®, Model p-5000D, Woburn, MA.

[7] Bausch and Lamb, Spectronic 710.

The unidirectional release of the drug was assured by good adhesion of the film to the petri dish. No evidence of peeling or breaking of the films was observed during and at the termination of the experiments. The release data were calculated with the aid of a standard curve (Figure 3). All release studies were conducted in duplicate at room temperature.

The effect of agitation rate on the drug release was studied using Film No. 12 (Table I) at 25°. Drug release was investigated at the stirring rates of 10, 30, 50, and 80 revolutions per minute.

To estimate the degree of reproducibility of sample withdrawals from suspension prior to filming casting, a simple method was developed.

The selected composition was 82% w/w propylene glycol monostearate, 15% w/w ethoxylated stearyl alcohol, and 3% w/w cortisol. Five films were prpeared in the glass petri dish exactly in the same manner as the films for release study. Each film was placed in a beaker containing 300 ml distilled water and was stirred vigorously at 60° for 24 hours to assure complete dissolution of cortisol.

Films without cortisol, but containing the same amount of propylene glycol monostearate and ethoxylated stearyl alcohol were used as control in this experiment.

The solution was filtered with a 0.22 μm filter paper.[8] The first 5 ml of filtrate was rejected due to the

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

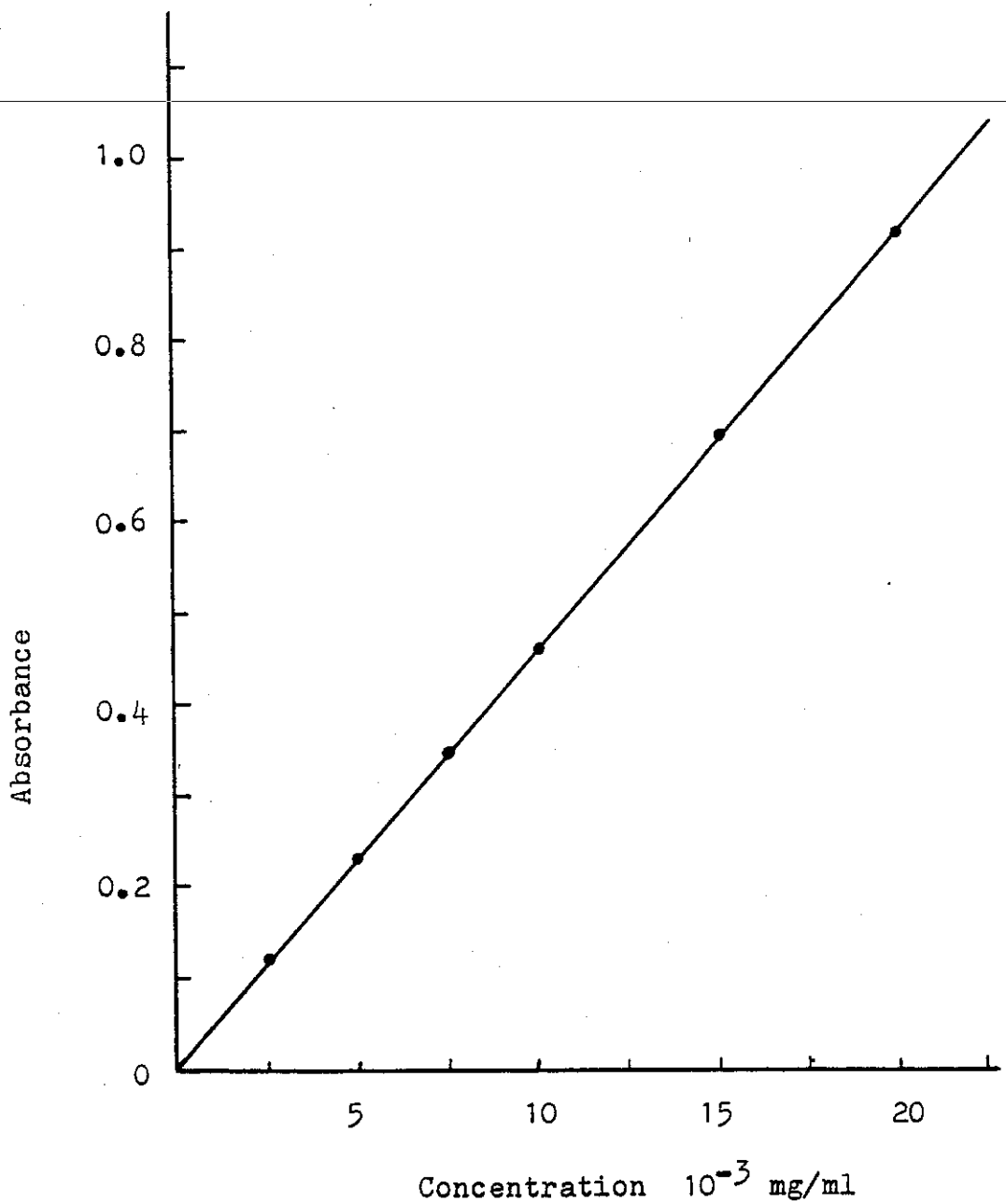

Figure 3. Standard curve for Cortisol

adsorption of the steroid to the filter paper (25). The concentration of cortisol in the solvent was determined using a spectrophotometer and the Beer's law plot prepared in this concentration range. The data is presented in Table II.

Table II. Degree of Variation Between the Film Weight and its Cortisol Content

Trial No.	Film[a] Weight mg	Absorbance	Actual Cortisol Content in Film mg	Expected Cortisol[b] Content in Film mg	Variation[c] Between Actual and Expected
1	207.6	0.943	6.15	6.23	1.3%
2	196.9	0.913	5.94	5.91	0.5%
3	196.3	0.908	5.91	5.89	0.3%
4	201.4	0.928	6.06	6.04	0.3%
5	203.2	0.929	6.06	6.10	0.7%

[a]Film composition of 82% w/w propylene glycol monostearate, 15% w/w ethoxylated stearyl alcohol, and 3% w/w cortisol.

[b]Expected cortisol content was calculated from the weight of film.

[c]Mean, 0.62 $\pm$ 0.41%

RESULTS AND DISCUSSION

The solubilities of film-forming agents were determined in water, isopropyl alcohol, and ethyl alcohol at $22^{\circ} \pm 0.5^{\circ}C$. Table III shows that the solubility of ethoxylated stearyl alcohol was greater than 15% in all three solvents. Propylene glycol monostearate was found to form a uniform and stable suspension in all three solvents. Since propylene glycol monostearate is a mixture of the propylene glycol mono- and diesters of stearic and palmitic acids, the solubility of propylene glycol monostearate is reported in Table III simply as a reference.

Film Preparation

Attempts to prepare isolatable thin films of propylene glycol monostearate from clear solutions were unsuccessful. All propylene glycol monostearate films, including those of mixed composition with ethoxylated stearyl alcohol, were cast from suspension. Ethoxylated stearyl alcohol films could be cast readily from its solution in ethyl alcohol.

The consistency of withdrawals and uniformity of suspensions prior to film preparation was checked. The data in Table II show a mean variation of 0.62% between actual and expected cortisol content during five trials.

Table III. Solubilities of Film Formers[a]

Film Former	Solvent		
	Water	Isopropyl Alcohol	Ethyl Alcohol
Propylene Glycol Monostearate	0.02	5.89	5.75
Ethoxylated Stearyl Alcohol	>15	>15	>15

[a]Expressed in grams per 100 ml.

Film Characteristics

Both propylene glycol monostearate and ethoxylated stearyl alcohol were found to form thin films isolatable from the mercury substrate individually and together as mixed compositions. All films, regardless of composition, were translucent and flexible with smooth but slightly tacky surfaces. Film characteristics of selected film compositions are described in Table IV.

a) Contact Angle:

The contact angles of propylene glycol monostearate-ethoxylated stearyl alcohol films were found to be smaller than those of either propylene glycol monostearate films or ethoxylated stearyl alcohol films. This may be due to increased wettability and hydrophilicity of the film surface and lowered film-water interfacial tension caused by incorportion of ethoxylated stearyl alcohol. The significant decrease in contact angle suggested a uniform distribution of ethoxylated stearyl alcohol molecules in the matrix of propylene glycol monostearate molecules with polar groups of either in close proximity at the film surface. Thus, incorporation of ethoxylated stearyl alcohol into propylene glycol monostearate films would be expected to favor the release of cortisol from such film compositions baring any drug-surfactant interaction especially in view of very high aqueous solubility of ethoxylated stearyl alcohol. The

Table IV. Physical Properties of Selected Propylene Glycol Monostearate-Ethoxylated Stearyl Alcohol Films

Film Composition[a]	Contact[b] Angle	Isolatable[c] Thickness µm	Film Property
100 : 0	28.7 ± 1.7	48.0 ± 3.2	Slightly Tacky, Translucent
0 : 100	58.3 ± 1.5	59.8 ± 2.7	Slightly Tacky, Translucent
90 : 10	20.0 ± 1.6	28.2 ± 2.4	Slightly Tacky, Translucent
85 : 15	19.8 ± 1.8	28.0 ± 2.2	Slightly Tacky, Translucent
80 : 20	19.4 ± 2.9	28.4 ± 2.1	Slightly Tacky, Translucent

[a]Expressed as propylene glycol monostearate : ethoxylated stearyl alcohol ratio, % w/w.

[b]Expressed as mean ± standard deviation of 5 readings.

[c]Expressed as mean ± standard deviation of 5 measurements.

increase in the content of ethoxylated stearyl alcohol from 10% to 20% w/w did not alter the contact angle of the film significantly.

b) Insolatable Film Thickness:

The minimum isolatable film thickness of propylene glycol monostearate-ethoxylated stearyl alcohol films was considerably smaller than that of either propylene glycol monostearate films or ethoxylated stearyl alcohol films (Table IV). The improved film strength and integrity as judged by the minimum isolatable film thickness might be due to more efficient arrangement, orientation, and packing of molecules in the films of mixed composition. Increase in the content of ethoxylated stearyl alcohol from 10 to 20% w/w did not result in corresponding improvement in minimum isolatable thicknesses of the films.

c) Modulus of Elasticity:

The results of Sward hardness and modulus of elasticity determination are reported in Table V. The variation of dry film thickness (maximum variation 1.6×10^{-4} inches or 4.06×10^{-4} cm) was minimized to ensure comparable results of modulus of elasticity. Relatively low values of modulus of elasticity obtained for all films might be attributed to the slight tackiness of the films. The inclusion of ethoxylated stearyl alcohol in the propylene glycol monostearate films did not have substantial effect on the modulus

Table V. Sward Hardness and Modulus of Elasticity of Selected Propylene Glycol Monostearate-Ethoxylated Stearyl Alcohol Films.

Film Composition[a]	Mean Dry Film Thickness ($\times 10^3$)[b] inches	Constant for a Given Thickness $K_t \times 10^{10}$	Sward[c] Hardness rocks (R)	Modulus of Elasticity (E), psi(Kg/cm^2)
100 : 0	0.433	0.58	2	5.72 (0.40)
0 : 100	0.307	0.10	2	2.76 (0.19)
90 : 10	0.465	0.68	2	5.41 (0.38)
80 : 20	0.346	0.21	2	4.06 (0.29)

[a]Expressed as propylene glycol monostearate : ethoxylated stearyl alcohol ratio, % w/w.

[b]Expressed as mean of five measurements.

[c]Expressed as mean of three measurements rounded to the nearest whole number.

of elasticity perhaps due to associated tackiness.

Release Kinetics

The release of cortisol from films containing varying proportions of propylene glycol monostearate and ethoxylated stearyl alcohol was investigated to study the effect of film composition, drug concentration, and agitation. These results have been further analyzed and interpreted to gain additional insight into the drug release mechanism.

a) Effect of Film Composition:

As anticipated, films containing only propylene glycol monostearate as the film former did not release significant amounts of cortisol in the aqueous medium over a twelve hour period due to relative insolubility of the film former in water (Table VI). On the other hand, films of ethoxylated stearyl alcohol were found to release their entire cortisol content within about 30 minutes (Table VII). The film and its drug content were found to have dissolved completely during this period.

Films of mixed composition containing varying proportions of the two film formers could be expected to show drug release profile somewhere between the two aforementioned extremes. The compositions of all films investigated for drug release are listed in Table I. Initial trial runs were conducted with various films containing 4% w/w cortisol, and increasing ethoxylated stearyl alcohol from 0% to 10% w/w

Table VI. Release of Cortisol from Propylene Glycol Monostearate Films (Film No. 2)

Time min.	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q^a$ mg/cm^2
60	0.014	0.86	0.069	0.002	0.280
120	0.015	0.95	0.076	0.003	0.279
240	0.017	1.15	0.092	0.003	0.279
360	0.019	1.32	0.105	0.004	0.278
480	0.020	1.41	0.112	0.004	0.278
600	0.021	1.53	0.122	0.004	0.278
720	0.022	1.62	0.129	0.005	0.277

^aQ_o = 0.282 mg/cm^2

Table VII. Release of Cortisol from Ethoxylated Stearyl Alcohol Films (Film No. 1)

Time min.	Absorbance	% Drug Released	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q^a$ mg/cm^2
5	0.143	11.56	0.915	0.032	0.248
10	0.863	71.09	5.628	0.199	0.081
15	1.197	99.39	7.868	0.278	0.002
20	1.188	99.62	7.886	0.279	0.001
25	1.178	99.76	7.897	0.279	0.001
30	1.169	99.98	7.916	0.280	0.000

$^aQ_o = 0.280\ mg/cm^2$

with a corresponding decrease of propylene glycol monostearate concentration (Tables VIII-XII). A trend towards gradual but small increase in the release rate of cortisol was evident. The film No. 7 containing 10% w/w ethoxylated stearyl alcohol was found to release approximately 15% of the drug contained in the film at the end of twelve hours (Table XII). Therefore, interest is mainly focused on drug release from film compositions containing 10% w/w or more ethoxylated stearyl alcohol.

Several films containing 4% w/w cortisol and starting from 10% w/w of ethoxylated stearyl alcohol with an increment of 1% w/w and a proportionately decreasing amount of propylene glycol monostearate were investigated (Tables XIII-XXII). The cumulative cortisol released at each time interval over twelve hour period was found to increase as the proportion of ethoxylated stearyl alcohol in the film increased from 10 to 20% w/w (Figures 4 and 5). The cumulative drug release *versus* time profiles for films No. 7 through 17 revealed an interesting curvature effect. For films No. 7, 8, 9, and 10, the release rate was found to increase with time, resulting in a gradually rising curve. The effect was more easily discernible after 5 hours. On the other hand, release rate declined with time for films No. 12-17 as evidenced by the subtle but definite reversal in the shape of the curves. This interesting behavior could be explained as follows: Following the relatively rapid

Table VIII. Release of Cortisol from Film No. 3[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
60	0.012	0.72	0.057	0.002	0.278
120	0.013	0.87	0.069	0.002	0.278
240	0.015	1.10	0.087	0.003	0.277
360	0.017	1.39	0.110	0.004	0.276
480	0.018	1.58	0.125	0.004	0.276
600	0.020	1.86	0.147	0.005	0.275
720	0.021	2.07	0.164	0.006	0.274

[a] PGM : ESA : CO = 94:2:4

[b] Q_o = 0.280 mg/cm^2

Table IX. Release of Cortisol from Film No. 4[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
60	0.015	0.93	0.075	0.003	0.283
120	0.017	1.21	0.098	0.003	0.283
240	0.022	1.73	0.140	0.005	0.281
360	0.026	2.18	0.176	0.006	0.280
480	0.030	2.69	0.218	0.008	0.278
600	0.034	3.24	0.262	0.009	0.277
720	0.038	3.82	0.309	0.011	0.275

[a] PGM:ESA:CO = 92:4:4

[b] Q_o = 0.286 mg/cm^2

Table X. Release of Cortisol from Film No. 5[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
60	0.015	0.93	0.075	0.003	0.281
120	0.017	1.22	0.098	0.003	0.281
240	0.023	1.82	0.146	0.005	0.279
360	0.028	2.39	0.192	0.007	0.277
480	0.034	3.08	0.247	0.009	0.275
600	0.040	3.81	0.306	0.011	0.273
720	0.046	4.59	0.369	0.013	0.271

[a] PGM:ESA:CO = 90:6:4

[b] Q_o = 0.284 mg/cm^2

Table XI. Release of Cortisol from Film No. 6[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
60	0.018	1.21	0.096	0.003	0.278
120	0.026	2.01	0.160	0.006	0.275
240	0.033	2.65	0.210	0.007	0.274
360	0.043	3.86	0.306	0.011	0.270
480	0.054	5.09	0.404	0.014	0.267
600	0.069	6.76	0.536	0.019	0.262
720	0.090	9.00	0.714	0.025	0.256

[a] PGM:ESA:CO = 88:8:4

[b] Q_o = 0.281 mg/cm^2

Table XII. Release of Cortisol from Film No. 7[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.024	1.67	0.135	0.005	0.281
60	0.027	1.91	0.154	0.005	0.281
90	0.030	2.19	0.177	0.006	0.280
120	0.033	2.48	0.200	0.007	0.279
180	0.042	3.21	0.259	0.009	0.277
240	0.055	4.32	0.349	0.012	0.274
300	0.066	5.21	0.421	0.015	0.271
360	0.081	6.49	0.524	0.018	0.267
420	0.095	7.70	0.622	0.022	0.264
480	0.109	8.89	0.718	0.025	0.260
540	0.125	10.27	0.830	0.029	0.256
600	0.142	11.75	0.949	0.034	0.252
660	0.159	13.23	1.069	0.038	0.248
720	0.177	14.84	1.199	0.042	0.243

[a] PGM:ESA:CO = 86:10:4

[b] Q_o = 0.286 mg/cm^2

Table XIII. Release of Cortisol from Film No. 8[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.032	2.42	0.186	0.007	0.265
60	0.036	2.80	0.215	0.008	0.264
90	0.038	2.98	0.229	0.008	0.264
120	0.044	3.55	0.273	0.010	0.262
180	0.054	4.41	0.339	0.012	0.260
240	0.063	5.23	0.402	0.014	0.258
300	0.077	6.49	0.499	0.018	0.254
360	0.090	7.65	0.588	0.021	0.251
420	0.104	8.89	0.684	0.024	0.248
480	0.119	10.27	0.790	0.028	0.244
540	0.135	11.74	0.903	0.032	0.240
600	0.151	13.22	1.017	0.036	0.236
660	0.165	14.56	1.120	0.040	0.232
720	0.182	16.15	1.242	0.044	0.228

[a] PGM:ESA:CO = 85:11:4

[b] Q_o = 0.272 mg/cm^2

Table XIV. Release of Cortisol from Film No. 9[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.050	3.97	0.306	0.011	0.262
60	0.056	4.51	0.348	0.012	0.260
90	0.060	4.86	0.375	0.013	0.259
120	0.069	5.69	0.439	0.016	0.257
180	0.086	7.19	0.554	0.020	0.253
240	0.105	8.88	0.685	0.024	0.249
300	0.127	10.84	0.836	0.030	0.243
360	0.149	12.81	0.988	0.035	0.238
420	0.170	14.70	1.133	0.040	0.233
480	0.193	16.82	1.297	0.046	0.227
540	0.214	18.73	1.444	0.051	0.222
600	0.238	20.97	1.617	0.057	0.216
660	9.258	22.84	1.761	0.062	0.211
720	0.281	25.05	1.931	0.068	0.205

[a] PGM:ESA:CO = 84:12:4

[b] Q_o = 0.273 mg/cm^2

Table XV. Release of Cortisol from Film No. 10[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.058	5.12	0.417	0.015	0.273
60	0.064	5.65	0.460	0.016	0.272
90	0.070	6.19	0.504	0.018	0.270
120	0.077	6.81	0.554	0.020	0.268
180	0.097	10.07	0.820	0.029	0.259
240	0.127	13.19	1.074	0.038	0.250
300	0.168	17.01	1.385	0.049	0.239
360	0.211	19.79	1.611	0.057	0.231
420	0.261	22.22	1.809	0.049	0.239
480	0.309	25.70	2.092	0.074	0.214
540	0.373	28.48	2.318	0.082	0.206
600	0.442	31.61	2.573	0.091	0.197
660	0.509	34.39	2.799	0.099	0.189
720	0.575	39.59	3.223	0.114	0.174

[a] PGM:ESA:CO = 83:13:4

[b] Q_o = 0.288 mg/cm^2

Table XVI. Release of Cortisol from Film No. 11[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	Q_o-Q[b] mg/cm^2
30	0.069	5.55	0.429	0.015	0.259
60	0.088	7.23	0.559	0.020	0.254
90	0.106	8.82	0.682	0.024	0.250
120	0.129	10.85	0.839	0.030	0.244
180	0.176	14.95	1.156	0.041	0.233
240	0.223	19.06	1.473	0.052	0.222
300	0.270	23.23	1.796	0.064	0.210
360	0.315	27.26	2.107	0.075	0.199
420	0.361	31.40	2.427	0.086	0.188
480	0.402	35.19	2.720	0.096	0.178
540	0.442	38.90	3.007	0.106	0.168
600	0.485	42.92	3.318	0.117	0.157
660	0.518	46.13	3.566	0.126	0.148
720	0.556	49.75	3.846	0.136	0.138

[a]PGM:ESA:CO = 82:14:4

[b]Q_o = 0.274 mg/cm^2

Table XVII. Release of Cortisol from Film No. 12[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.097	7.57	0.612	0.022	0.264
60	0.144	11.47	0.927	0.033	0.253
90	0.187	15.07	1.218	0.043	0.243
120	0.224	18.29	1.478	0.052	0.234
180	0.293	23.97	1.937	0.069	0.217
240	0.362	29.78	2.406	0.085	0.201
300	0.421	34.85	2.816	0.100	0.186
360	0.480	39.98	3.230	0.114	0.172
420	0.535	44.81	3.621	0.128	0.158
480	0.582	49.03	3.962	0.140	0.146
540	0.630	53.40	4.315	0.153	0.133
600	0.676	57.62	4.656	0.165	0.121
660	0.716	61.44	4.964	0.176	0.110
720	0.759	65.47	5.290	0.187	0.099

[a]PGM:ESA:CO = 81:15:4

[b]Q_o = 0.286 mg/cm^2

Table XVIII. Release of Cortisol from Film No. 13[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Release mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.082	6.15	0.509	0.018	0.275
60	0.098	7.52	0.622	0.022	0.271
90	0.144	11.28	0.933	0.033	0.260
120	0.186	14.70	1.216	0.043	0.250
180	0.280	22.22	1.838	0.065	0.228
240	0.354	28.37	2.346	0.083	0.210
300	0.415	33.49	2.770	0.098	0.195
360	0.498	40.34	3.336	0.118	0.175
420	0.545	44.44	3.675	0.130	0.163
480	0.604	49.56	4.099	0.145	0.148
540	0.663	54.69	4.523	0.163	0.133
600	0.717	59.48	4.919	0.174	0.119
660	0.757	63.24	5.230	0.185	0.108
720	0.801	67.34	5.569	0.197	0.096

[a] PGM:ESA:CO = 80:16:4

[b] Q_o = 0.293 mg/cm^2

Table XIX. Release of Cortisol from Film No. 14[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.089	6.69	0.561	0.020	0.277
60	0.139	10.66	0.894	0.032	0.265
90	0.189	14.66	1.230	0.044	0.253
120	0.244	19.09	1.602	0.057	0.240
180	0.351	27.62	2.317	0.082	0.215
240	0.458	36.26	3.042	0.108	0.189
300	0.542	43.16	3.621	0.128	0.169
360	0.628	50.26	4.217	0.149	0.148
420	0.715	57.54	4.828	0.171	0.126
480	0.779	63.11	5.295	0.187	0.110
540	0.840	68.47	5.745	0.203	0.094
600	0.896	73.49	6.166	0.218	0.079
660	0.947	78.18	6.559	0.232	0.065
720	0.977	81.20	6.813	0.241	0.056

[a]PGM:ESA:CO = 79:17:4

[b]Q_o = 0.297 mg/cm^2

Table XX. Release of Cortisol from Film No. 15[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.101	8.42	0.693	0.023	0.268
60	0.174	13.62	1.122	0.040	0.251
90	0.229	18.14	1.493	0.053	0.238
120	0.300	23.97	1.973	0.070	0.221
180	0.403	32.41	2.667	0.094	0.197
240	0.489	39.43	3.254	0.115	0.176
300	0.563	45.83	3.772	0.133	0.158
360	0.633	51.82	4.265	0.151	0.140
420	0.693	57.10	4.699	0.166	0.125
480	0.780	64.58	5.315	0.188	0.103
540	0.817	69.31	5.704	0.202	0.089
600	0.894	74.87	6.162	0.218	0.073
660	0.952	80.21	6.601	0.233	0.058
720	0.998	84.61	6.963	0.246	0.045

[a]PGM:ESA:CO = 78:18:4

[b]Q_o = 0.281 mg/cm^2

Table XXI. Release of Cortisol from Film No. 16[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.115	9.37	0.729	0.026	0.249
60	0.177	14.70	1.144	0.040	0.235
90	0.255	21.40	1.665	0.059	0.216
120	0.334	28.24	2.197	0.078	0.197
180	0.452	38.47	2.993	0.106	0.169
240	0.567	48.48	3.772	0.133	0.142
300	0.667	57.40	4.466	0.158	0.117
360	0.760	65.75	5.115	0.181	0.094
420	0.834	72.63	5.651	0.200	0.075
480	0.892	78.19	6.083	0.215	0.060
540	0.941	83.06	6.462	0.229	0.046
600	0.982	87.28	6.790	0.240	0.035
660	1.013	90.48	7.039	0.249	0.026
720	1.020	91.93	7.152	0.253	0.022

[a] PGM:ESA:CO = 77:19:4

[b] Q_o = 0.275 mg/cm^2

Table XXII. Release of Cortisol from Film No. 17[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.122	9.89	0.777	0.027	0.251
60	0.199	16.40	1.289	0.046	0.232
90	0.271	22.56	1.773	0.063	0.215
120	0.352	29.50	2.319	0.082	0.196
180	0.469	39.57	3.110	0.110	0.168
240	0.585	49.61	3.899	0.138	0.140
300	0.676	57.65	4.531	0.160	0.118
360	0.768	65.88	5.178	0.183	0.095
420	0.844	72.85	5.726	0.203	0.075
480	0.906	78.70	6.186	0.219	0.059
540	0.958	83.77	6.584	0.233	0.045
600	0.999	87.99	6.916	0.245	0.033
660	1.018	90.38	7.104	0.251	0.027
720	1.031	92.33	7.257	0.257	0.021

[a] PGM:ESA:CO = 76:20:4

[b] Q_o = 0.278 mg/cm^2

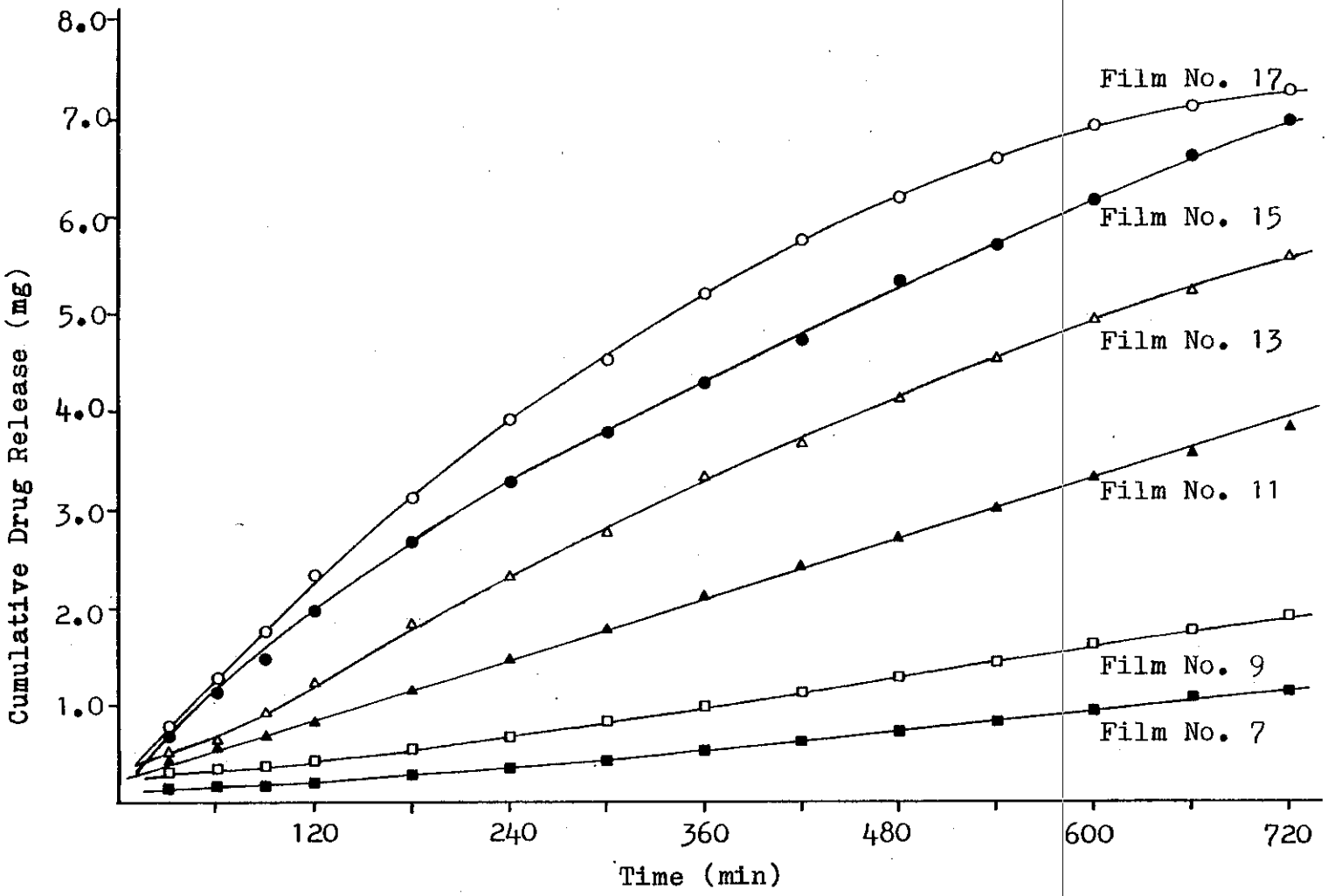

Figure 4. Cumulative Drug Release from Various Propylene Glycol Monostearate-Ethoxylated Stearyl Alcohol Films

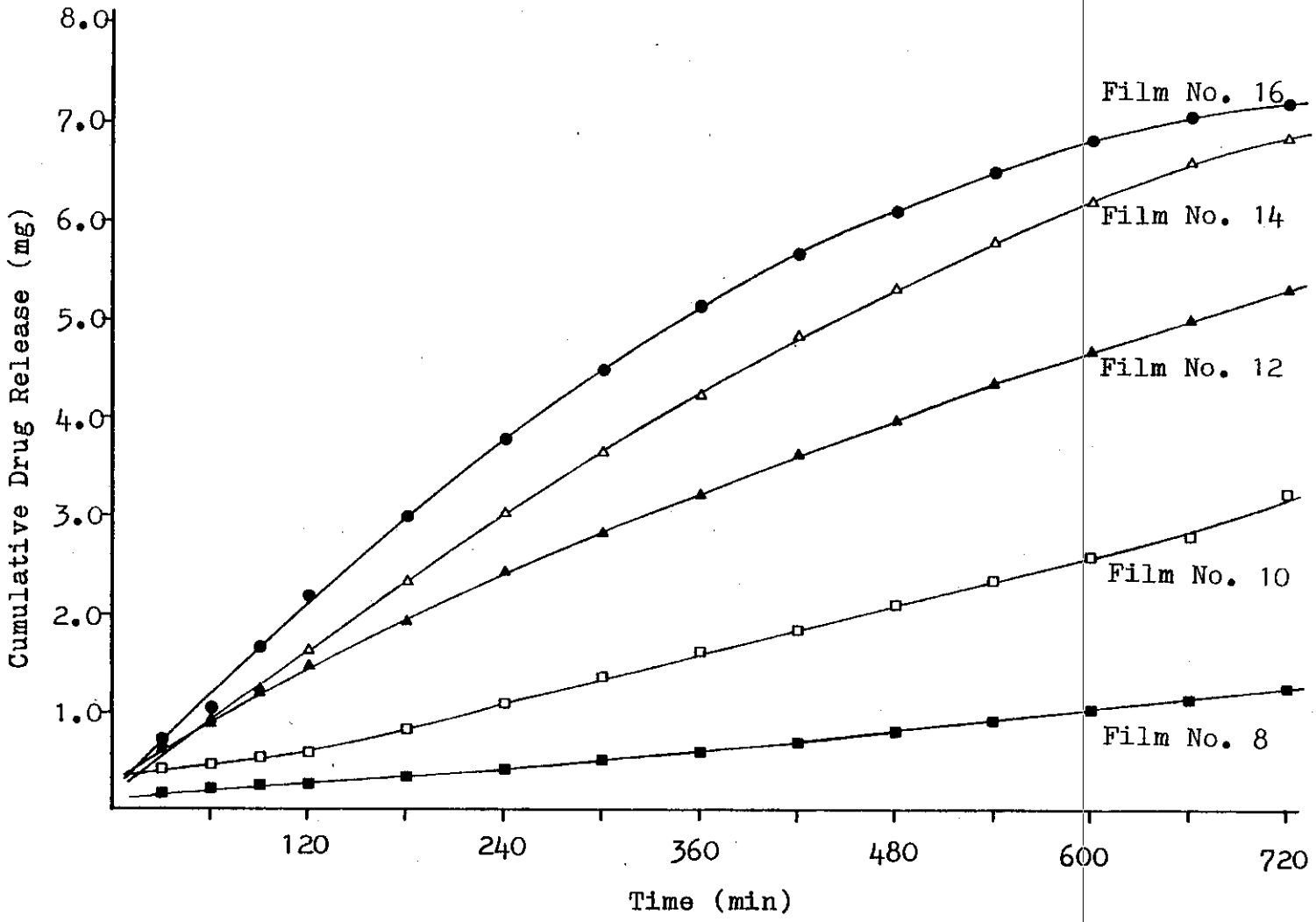

Figure 5. Cumulative Drug Release from Various Propylene Glycol Monostearate-Ethoxylated Stearyl Alcohol Films

dissolution from the film surface, continuing dissolution of ethoxylated stearyl alcohol from deep within the film matrix increased the porosity of the film, thereby increasing the surface area available for contact between the drug in the film and the dissolution medium, thus accounting for a gradually increasing release rate with time for each of the films No. 7,8,9, and 10. The rate of drug release throughout the observed release period was low enough that drug concentration in the film did not become a rate-limiting factor. The ethoxylated stearyl alcohol content and rate of drug release from films No. 7,8,9, and 10 were such that drug concentration at the film interface with dissolution medium was not appreciably altered. However, as the proportion of ethoxylated stearyl alcohol in the films increased further, such as films No. 12-17, the resulting high rate of drug release served to deplete the drug from the films rather rapidly. This was evidenced by the gradual leveling tendency of the curves due to declining rates of drug release from each of these films. A close examination of Figure 4 revealed that drug release profile for film No. 11 containing 14% w/w ethoxylated stearyl alcohol was nearly linear for 10 hours with a slight tendency to level off during the last two hours of drug release period. This suggested that various factors such as declining ethoxylated stearyl alcohol content of the films, increasing surface area of contact between drug and the dissolution medium, and the declining concentration of the drug at the film interface were in a state of dynamic equilibrium for the 10 hour

duration of the release period providing a constant rate of drug release from film No. 11. The rising curvature of the drug release versus time profiles for films No. 7,8,9, and 10 might be due to predominating influence of increases in surface area of contact between drug molecules and dissolution medium while declining curvatures of films No. 12-17 were more likely due to predominating influence of drug depletion in the films.

The release data obtained in this study were examined by both Higuchi's model and first-order mechanism. Observed data were analyzed and interpreted to test the fitness of either model. The correlation coefficients for the best statistical lines and lag times (time intercept extrapolated to Q=0) were used as the major criteria for evaluation.

The first order rate plots (Figures 6 and 7) confirmed our earlier analysis based upon plots of cumulative amount of drug released versus time. All firms included in the study demonstrated good first-order release profile for first five hours of drug release (correlation coefficients, 0.990-0.999). Divergence from the first-order relationship was noted as the ethoxylated stearyl alcohol: propylene glycol monostearate ratio increased. The drug release from films No. 7 and 8 appeared to follow first-order profile for the entire twelve hour period of study. Divergence from linearity was first noted after the 11-hour data point for films No. 9 and 10, and after 10 hour data point for films

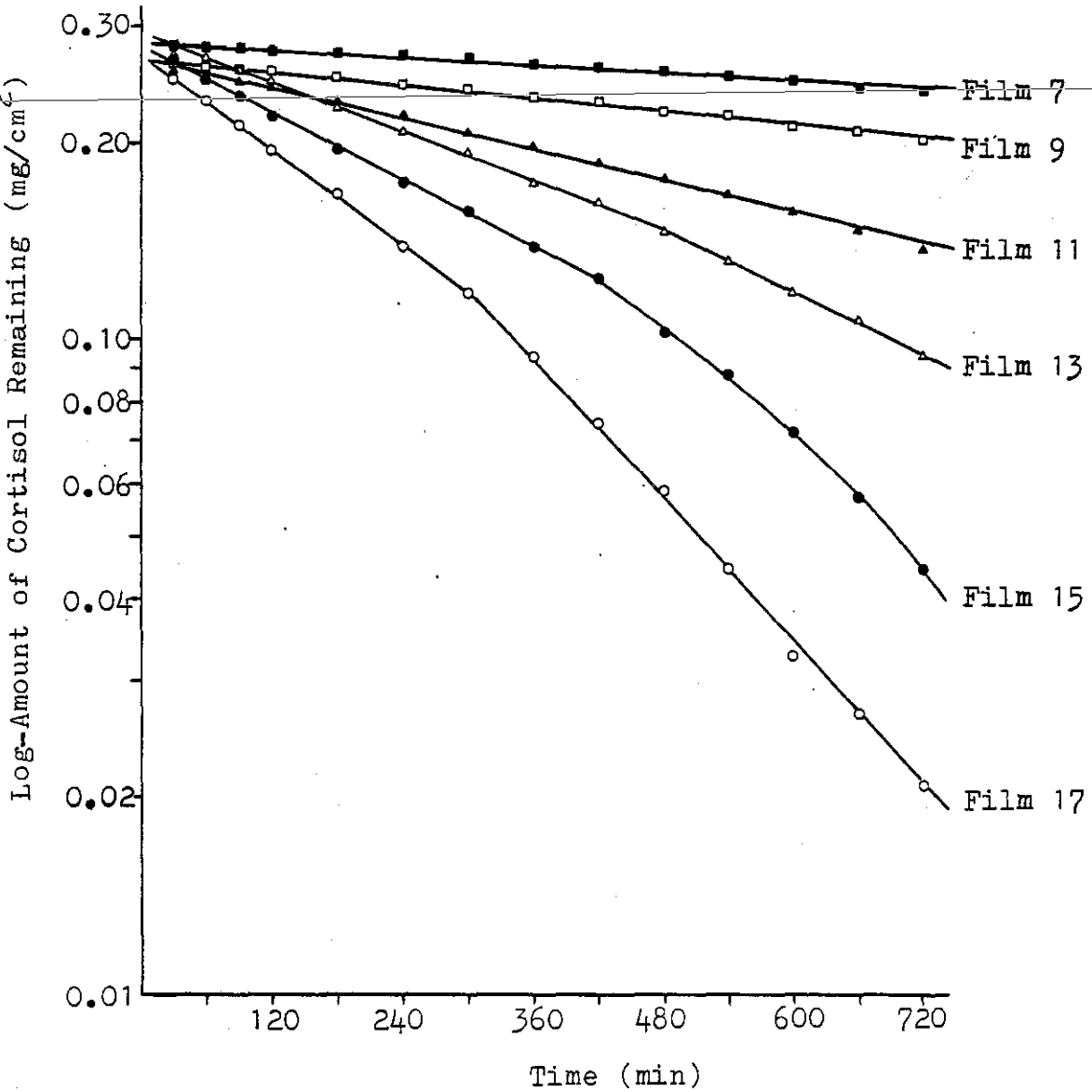

Figure 6. First-order Plots of Cortisol Release

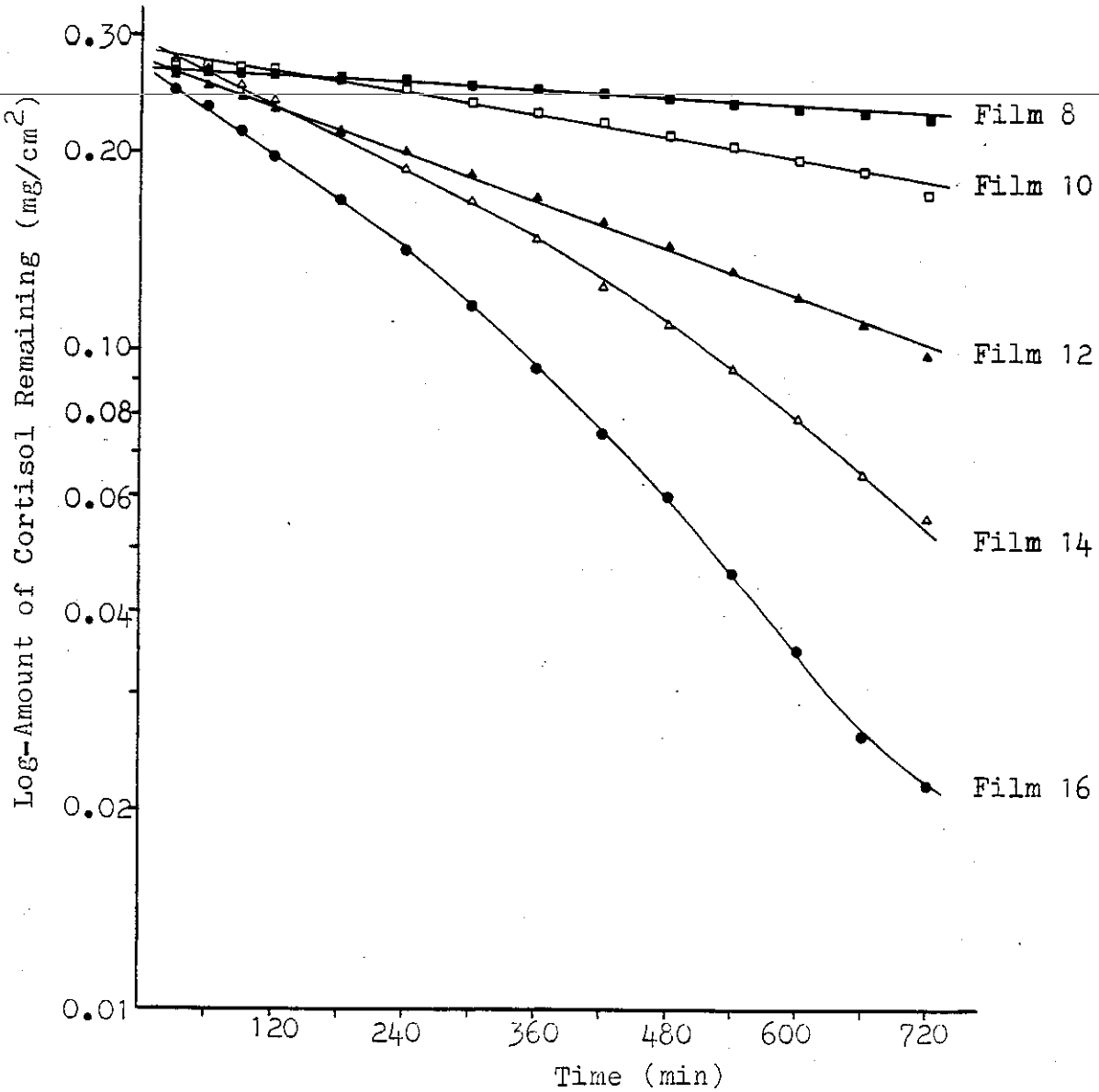

Figure 7. First-order Plots of Cortisol Release

No. 11 and 12. The duration for which the slope remained constant decreased as the ethoxylated stearyl alcohol : propylene glycol monostearate ratio in the film increased. The films No. 16 and 17 followed first-order profile for the minimum duration of about 4-5 hours. These observations have served to confirm that dynamics of release process changed as the ethoxylated stearyl alcohol : propylene glycol monostearate ratio was altered. For most cases, the lag times were no more than several minutes (Table XXIII). The negative lag times might be attributed to the immediate release of the drug present on the film surface. Varying amounts of cortisol present on the film surface might account for the magnitude of the lag times. The first-order release rate constants (Table XXIII) increased about 13-fold (0.21 to 2.8 per minute) as the ethoxylated stearyl alcohol content of the film was increased from 10 to 20% w/w (ethoxylated stearyl alcohol:propylene glycol monostearate ratio changed from 1.16 to 2.63). This increase was approximately linear for films No. 7-17 (Figure 8).

Cortisol release data for films No. 7 through 17 were also analyzed to test compliance with Higuchi's model which predicts a linear relationship between amount of drug released per unit area (Q) and square root of time (t)

$$Q = Kt^{\frac{1}{2}} \qquad \text{(Eq. 3)}$$

Table XXIII. First-order Treatment of Data for the Release of Cortisol.

Film No.	Film Composition[a]	% Drug Release After 12 Hours	Release Rate Constant (kx1000) min^{-1}	Lag Time min	Correlation Coefficient
7	86:10:4	14.84	0.211	4.84	0.990
8	85:11:4	16.15	0.218	-41.58	0.991
9	84:12:4	25.05	0.356	-49.01	0.995
10	83:13:4	39.59	0.635	-5.08	0.992
11	82:14:4	49.75	0.906	-6.84	0.998
12	81:15:4	65.47	1.392	-18.10	0.999
13	80:16:4	67.34	1.410	1.00	0.999
14	79:17:4	81.20	1.912	2.84	0.999
15	78:18:4	84.61	1.951	-16.37	0.999
16	77:19:4	91.93	2.709	-1.76	0.999
17	76:20:4	92.33	2.803	-4.00	0.999

[a]Proportion of propylene glycol monostearate, ethoxylated stearyl alcohol and cortisol expressed as % w/w.

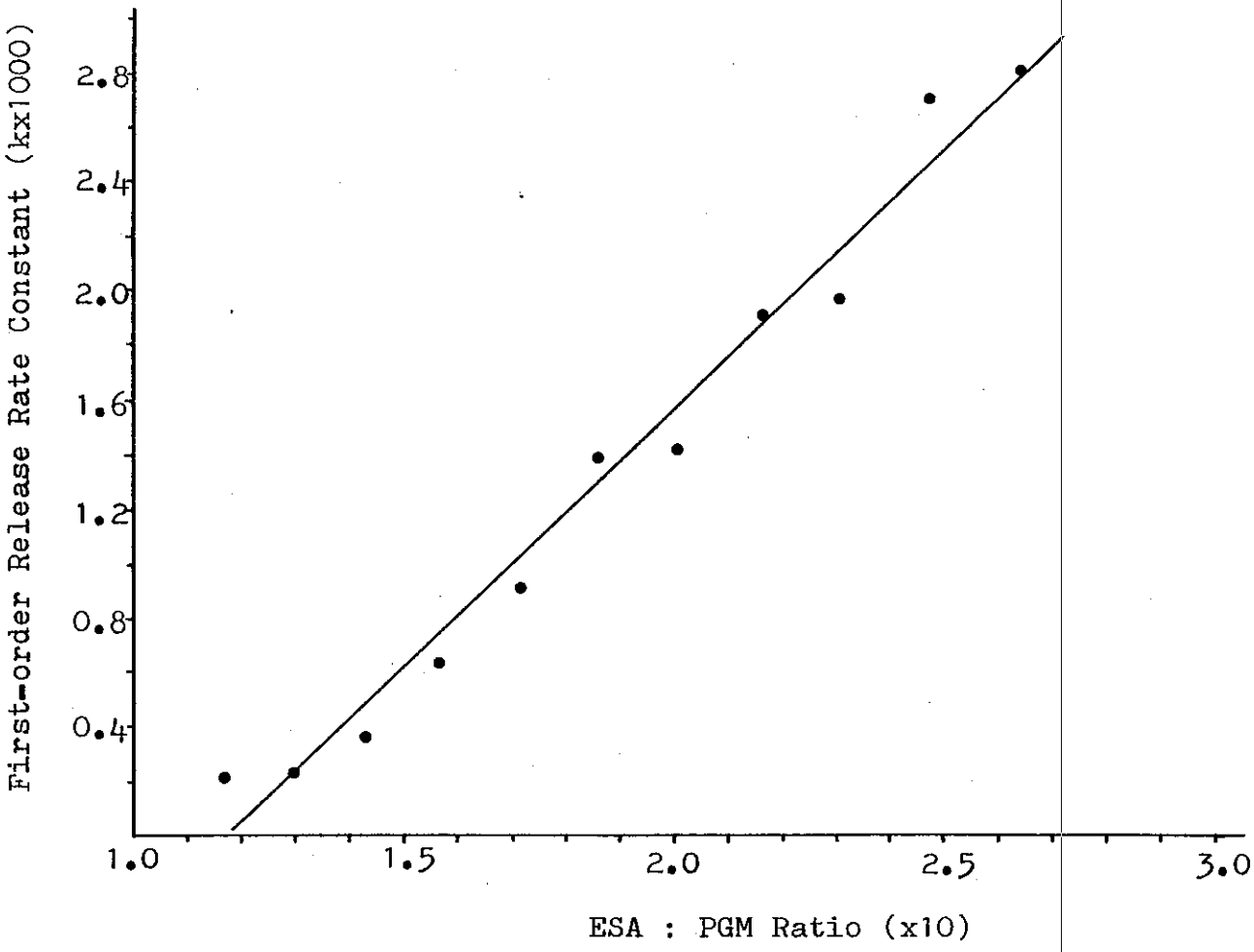

Figure 8. First-order Release Rate Constant As a Function of Film Composition

for either homogeneous or granular film matrix. Since solubility of cortisol could be assumed to be negligible in the film compositions investigated, Equation 2 describing the drug release from a granular matrix might be more applicable.

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

Since solubility of cortisol in water is 0.28 mg/ml at 25° (26), even at maximum release, drug concentration in the dissolution medium never exceeded beyond 10% of the reported drug solubility, thus ensuring near perfect sink conditions. It could not be readily ascertained whether total amount of drug present in the matrix per unit volume (A) was at least 3-4 times greater than the product of porosity (ε) and solubility of the drug in the permeating fluid (C_s) as required by Higuchi's model for granular matrix. However, based upon the observation that films of mixed composition had more compact packing of molecules, it might be assumed that porosity of the films was extremely low at least initially, thus ensuring $A >> \varepsilon C_s$ in the early stages of the study. Careful examination of Q <u>versus</u> $t^{\frac{1}{2}}$ plots (Figures 9 and 10) revealed a distinct curvilinear effect for all film compositions rather than predicted straight lines. The deviation from the Higuchi model could possibly be due to rapid dissolution of ethoxylated stearyl alcohol even though it did not constitute more than 20% of the film matrix. Higuchi's model does not account for such complications arising from erosion of the film matrix.

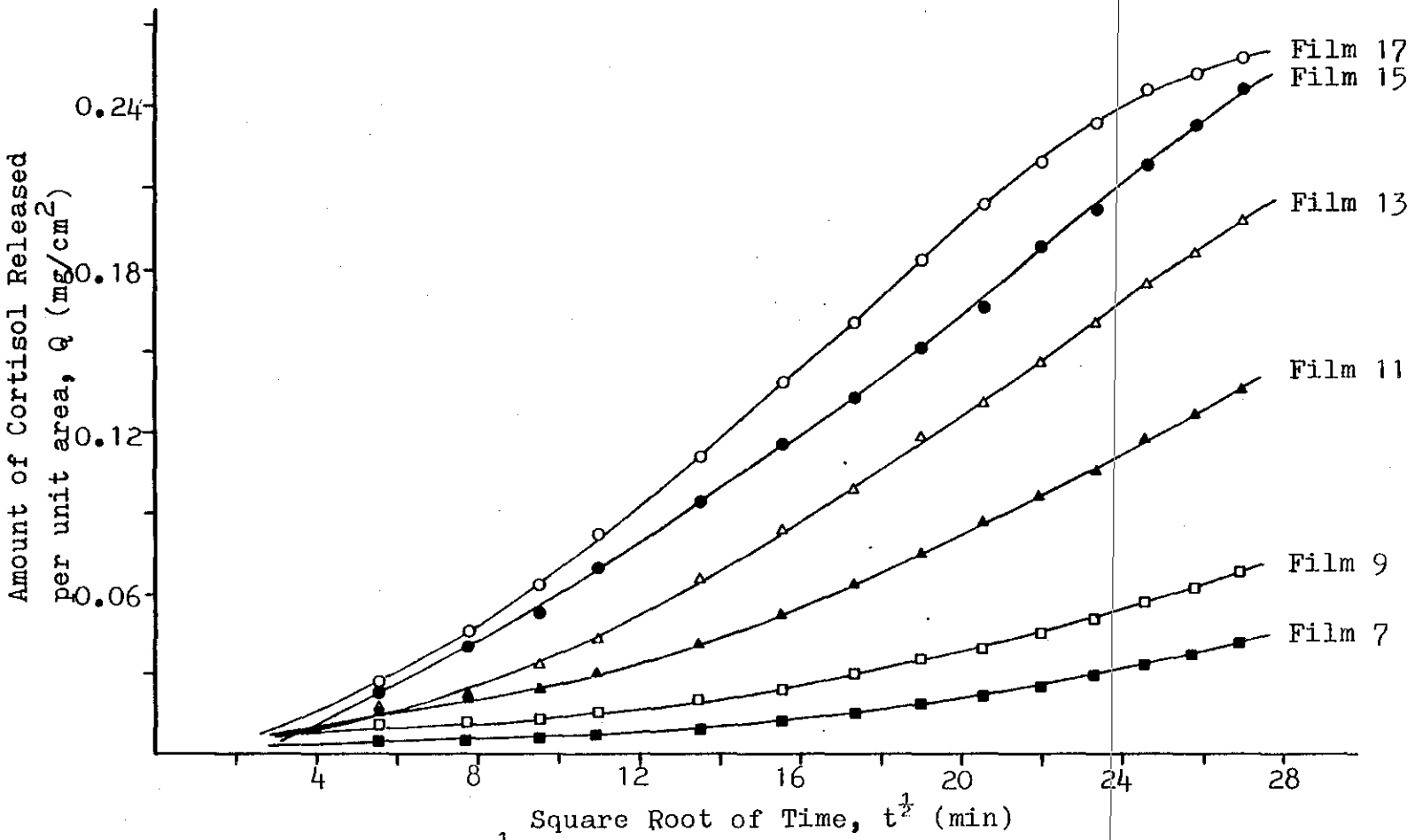

Figure 9. Q versus $t^{\frac{1}{2}}$ Plots of Cortisol Release

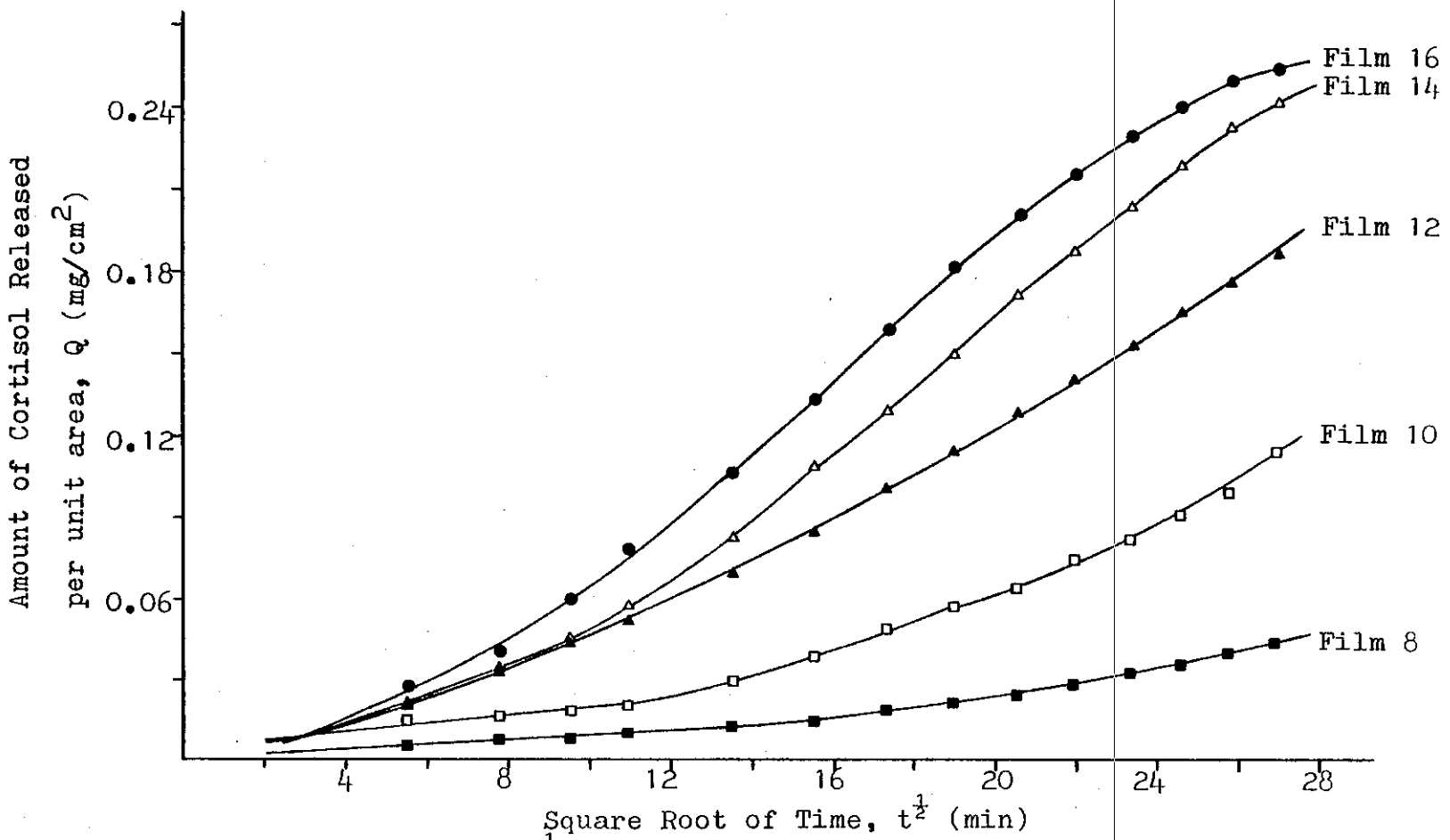

Figure 10. Q versus $t^{\frac{1}{2}}$ Plots of Cortisol Release

Effect of Drug Concentration

Film No. 11 (PGM:ESA:CO = 82:14:4) and No. 12 (PGM: ESA:CO = 81:15:4) were selected for evaluating the effects of changes in drug concentration on release behavior. The drug concentration was varied from 1 to 4% w/w with corresponding adjustment of propylene glycol monostearate and ethoxylated stearyl alcohol content such that PGM:ESA ratio remained constant at a value of 5.86 for variations of film 11 and at 5.4 for corresponding variations of film 12. The release data are presented in Figure 11 and Tables XXIV-XXVII for congeners of film 11 (film 18, 19, and 20), and in Figure 12 and Tables XXVIII-XXXI for varients of film 12 (film 21, 22, and 23).

The rate controlling effects of changes in drug concentration over the duration of release period were most apparent when drug content of the film was lowered to 1% w/w. This could be seen as the changing curvature of the drug release profile in Figures 11 and 12 for films 20 and 23, respectively. First-order plots (Figures 13 and 14) further confirmed this finding. The data in Tables XXVII and XXXI revealed that first-order rate constant remained nearly constant between the drug concentration range of 3 to 4% w/w but the rate constant increased as the drug concentration dropped below 3% w/w. The sharp increase in release rate constant (k) when drug concentration was lowered from 2 to 1% w/w further confirmed the complexity of the

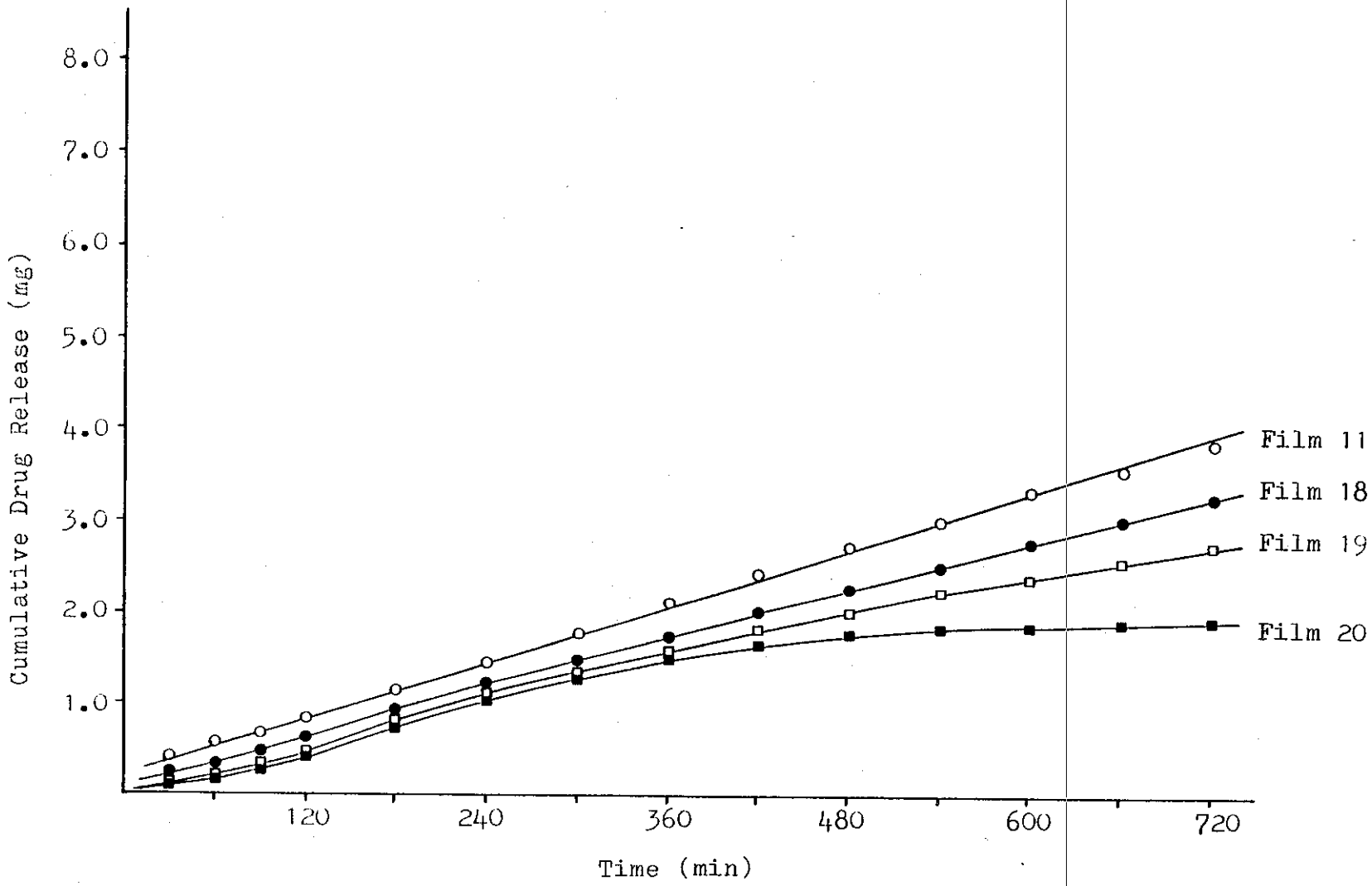

Figure 11. Cumulative Drug Release versus Time: Effect of Change in Drug Concentration

Table XXIV. Release of Cortisol from Film No. 18[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.039	3.88	0.234	0.008	0.205
60	0.054	5.56	0.335	0.012	0.201
90	0.074	7.75	0.467	0.017	0.196
120	0.098	10.42	0.628	0.022	0.191
180	0.143	15.45	0.931	0.033	0.180
240	0.183	19.94	1.201	0.042	0.171
300	0.224	24.57	1.480	0.052	0.161
360	0.261	28.78	1.734	0.061	0.152
420	0.299	33.25	2.003	0.071	0.142
480	0.334	37.35	2.250	0.080	0.133
540	0.370	41.65	2.509	0.089	0.124
600	0.404	45.73	2.755	0.097	0.116
660	0.439	49.95	3.009	0.106	0.107
720	0.472	54.00	3.253	0.115	0.098

[a] PGM:ESA:CO = 82.85:14.15:3

[b] Q_o = 0.213 mg/cm^2

Table XXV. Release of Cortisol from Film No. 19[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.019	2.56	0.102	0.004	0.137
60	0.032	4.76	0.190	0.007	0.134
90	0.050	7.74	0.309	0.011	0.130
120	0.078	12.40	0.495	0.018	0.123
180	0.126	20.34	0.812	0.029	0.112
240	0.163	26.63	1.063	0.038	0.103
300	0.205	33.79	1.349	0.048	0.093
360	0.234	38.85	1.551	0.055	0.086
420	0.270	45.17	1.803	0.064	0.077
480	0.298	50.18	2.003	0.071	0.070
540	0.330	55.84	2.229	0.079	0.062
600	0.351	59.82	2.388	0.084	0.057
660	0.375	64.30	2.567	0.091	0.050
720	0.397	68.51	2.735	0.097	0.044

[a] PGM:ESA:CO = 83.71:14.29:2

[b] Q_o = 0.141 mg/cm^2

Table XXVI. Release of Cortisol from Film No. 20[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.018	4.77	0.096	0.003	0.068
60	0.029	8.39	0.169	0.006	0.065
90	0.047	14.30	0.288	0.010	0.061
120	0.070	21.90	0.441	0.016	0.055
180	0.115	36.69	0.739	0.026	0.045
240	0.160	51.79	1.043	0.037	0.034
300	0.196	63.90	1.287	0.046	0.025
360	0.225	73.93	1.489	0.053	0.018
420	0.248	82.22	1.656	0.059	0.012
480	0.261	87.19	1.756	0.062	0.009
540	0.268	90.27	1.818	0.064	0.007
600	0.271	92.16	1.856	0.066	0.005
660	0.275	94.24	1.898	0.067	0.004
720	0.279	96.47	1.943	0.069	0.002

[a] PGM:ESA:CO = 84.56:14.44:1

[b] Q_o = 0.071 mg/cm^2

Table XXVII. Effect of Drug Concentration
First-Order Treatment of Data for the Release of Cortisol

PGM:ESA Ratio w/w%	Drug Concentration w/w%	$kx10^3$ min^{-1}	Correlation Coefficient r
84.56 : 14.44	1	2.334	0.983
83.71 : 14.29	2	1.473	0.997
82.85 : 14.15	3	0.905	0.999
82.00 : 14.00	4	0.906	0.998

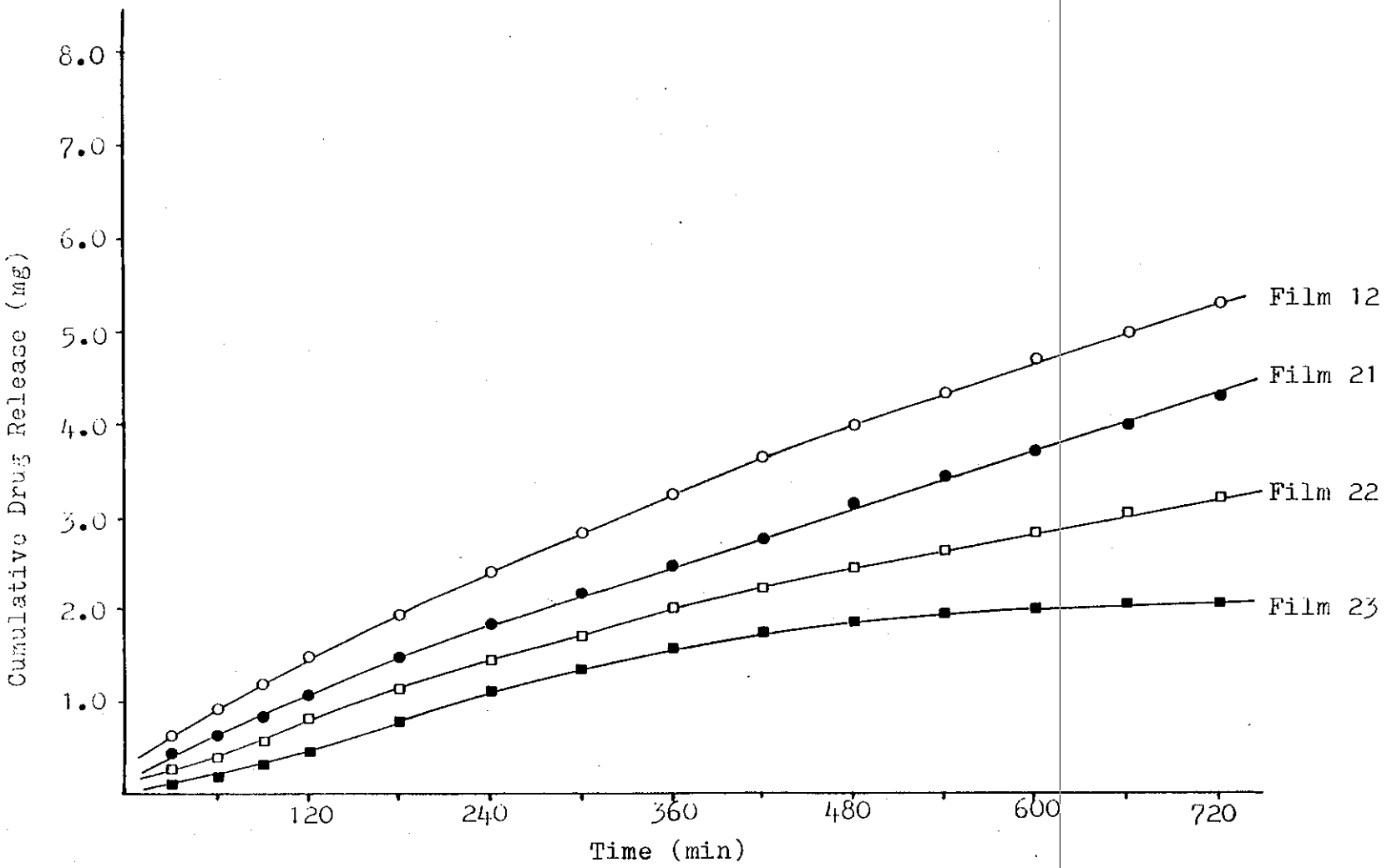

Figure 12. Cumulative Drug Release versus Time: Effect of Change in Drug Concentration

Table XXVIII. Release of Cortisol from Film No. 21[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.069	7.15	0.429	0.015	0.197
60	0.099	10.51	0.631	0.022	0.190
90	0.130	13.97	0.838	0.030	0.182
120	0.162	17.60	1.056	0.037	0.175
180	0.179	24.62	1.477	0.052	0.160
240	0.278	30.65	1.839	0.065	0.147
300	0.326	36.25	2.175	0.077	0.135
360	0.366	40.90	2.454	0.087	0.125
420	0.408	45.85	2.751	0.097	0.115
480	0.461	52.03	3.122	0.110	0.102
540	0.499	56.68	3.401	0.120	0.092
600	0.539	61.62	3.697	0.131	0.081
660	0.572	66.25	3.975	0.141	0.071
720	0.618	71.42	4.285	0.152	0.060

[a] PGM:ESA:CO = 81.84:15.16:3

[b] Q_o = 0.211 mg/cm^2

Table XXIX. Release of Cortisol from Film No. 22[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	Q_o-Q[b] mg/cm^2
30	0.043	6.35	0.258	0.009	0.135
60	0.063	9.68	0.393	0.014	0.130
90	0.088	13.84	0.562	0.020	0.124
120	0.127	20.18	0.820	0.029	0.115
180	0.173	27.86	1.131	0.040	0.104
240	0.215	34.85	1.415	0.050	0.094
300	0.256	41.77	1.696	0.060	0.084
360	0.300	49.43	2.007	0.071	0.073
420	0.332	55.00	2.233	0.079	0.065
480	0.359	59.90	2.432	0.086	0.058
540	0.386	64.75	2.629	0.093	0.051
600	0.410	69.19	2.809	0.099	0.045
660	0.440	74.68	3.032	0.107	0.037
720	0.460	78.72	3.196	0.113	0.031

[a]PGM:ESA:CO = 82.69:15.31:2

[b]Q_o = 0.144 mg/cm^2

Table XXX. Release of Cortisol from Film No. 23[a]

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q$[b] mg/cm^2
30	0.202	5.18	0.108	0.004	0.070
60	0.031	8.82	0.184	0.007	0.067
90	0.050	14.68	0.306	0.011	0.063
120	0.074	22.45	0.468	0.017	0.057
180	0.119	36.79	0.767	0.027	0.047
240	0.168	52.71	1.099	0.039	0.035
300	0.204	64.36	1.341	0.047	0.027
360	0.233	74.29	1.549	0.055	0.019
420	0.260	83.35	1.739	0.061	0.013
480	0.274	88.63	1.848	0.065	0.009
540	0.283	92.23	1.923	0.068	0.006
600	0.288	94.67	1.974	0.070	0.004
660	0.292	96.74	2.017	0.071	0.003
720	0.295	98.51	2.054	0.073	0.001

[a] PGM:ESA:CO = 83.53:15.47:1

[b] Q_o = 0.074

Table XXXI. Effect of Drug Concentration
First-Order Treatment of Data for the Release of Cortisol

PGM:ESA Ratio w/w%	Drug Concentration w/w%	$kx10^3$ min^{-1}	Correlation Coefficient r
83.53 : 15.47	1	2.260	0.983
82.69 : 15.31	2	1.785	0.998
81.84 : 15.16	3	1.413	0.999
81.00 : 15.00	4	1.392	0.999

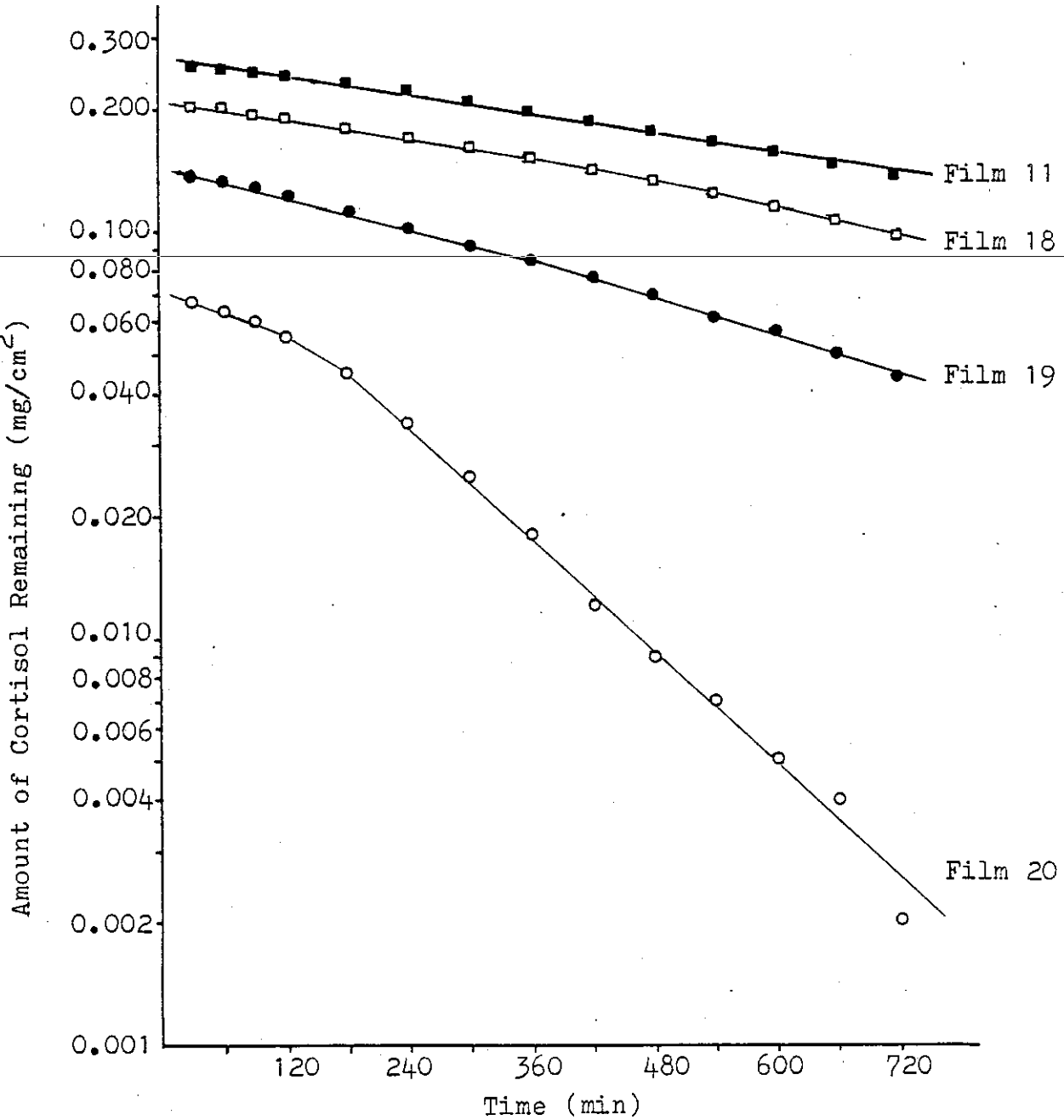

Figure 13. First-order Plots of Cortisol Release from Film 11 and Its Variants

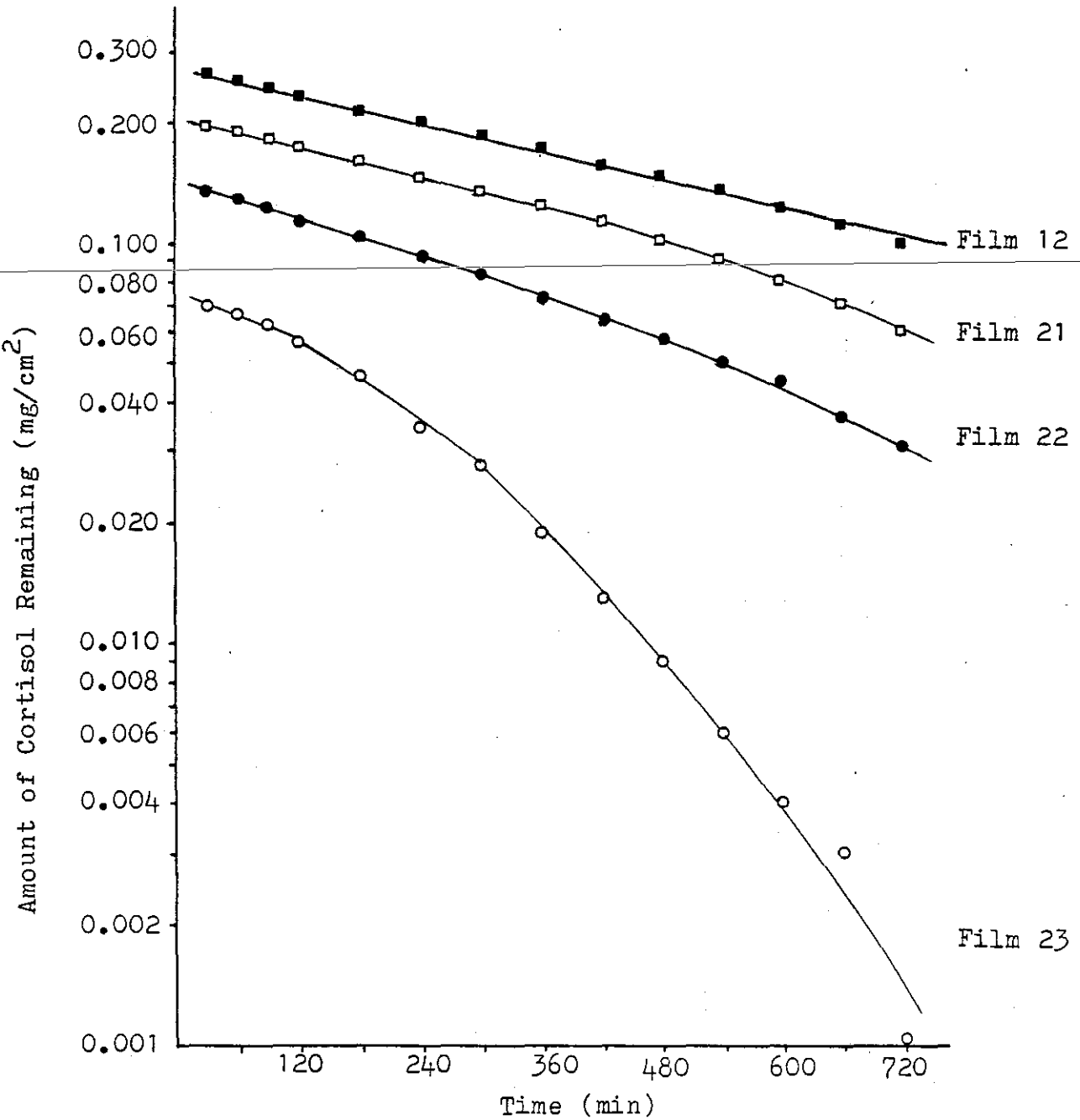

Figure 14. First-order Plots of Cortisol Release from Film 12 and Its Variants

release mechanism. What is the effect of increasing drug content in films beyond 4% w/w? What is the relationship between drug concentration of films and PGM:ESA ratio, particularly for films with 10% w/w or less ethoxylated stearyl alcohol? Additional studies are warranted to answer these questions and explain the drug release mechanism.

Effect of Agitation Rate

The film composition of 81% w/w propylene glycol monostearate, 15% w/w ethoxylated stearyl alcohol, and 4% w/w cortisol was selected (Film No. 12, Table I), and the release studies were conducted at the agitation speeds of 10, 30, 50, and 80 revolutions per minute. This experiment was carried out in the same dissolution apparatus described earlier (Figure 1). The cortisol release from the film was found to follow first-order profile at four rates of agitation investigated (Table XXXII, XXXIII, XXXIV, XXXV). The plot of release rate constants versus agitation speeds is shown in Figure 15. The release rate constant increased about two-fold as agitation speed increased from 10 to 80 rpm.

An empirical equation suggested by Wurster and Taylor (27) described the relationship between rate constant and agitation speed for dissolution of drugs.

$$K = a\ (N)^{b} \qquad \text{(Eq. 8)}$$

Table XXXII. Release of Cortisol from Film No. 12 at Agitation Speed of 10 rpm

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q^a$ mg/cm^2
30	0.094	7.43	0.594	0.021	0.262
60	0.137	11.00	0.879	0.031	0.252
90	0.178	14.49	1.158	0.041	0.242
120	0.214	17.56	1.403	0.050	0.233
180	0.277	22.92	1.831	0.065	0.218
240	0.335	27.87	2.227	0.079	0.204
300	0.391	32.77	2.618	0.093	0.190
360	0.447	37.66	3.009	0.106	0.177
420	0.484	40.83	3.262	0.115	0.168
480	0.520	43.99	3.515	0.124	0.159
540	0.563	47.95	3.831	0.136	0.147
600	0.609	52.17	4.168	0.147	0.136
660	0.645	55.63	4.445	0.157	0.126
720	0.681	59.09	4.721	0.167	0.116

[a] Q_o = 0.283 mg/cm^2

Table XXXIII. Release of Cortisol from Film No. 12 at Agitation Speed of 50 rpm

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q^a$ mg/cm^2
30	0.087	6.95	0.546	0.019	0.259
60	0.151	12.35	0.971	0.034	0.244
90	0.189	15.65	1.230	0.044	0.234
120	0.226	18.89	1.485	0.053	0.225
180	0.295	24.81	1.950	0.069	0.209
240	0.362	30.62	2.407	0.085	0.193
300	0.431	36.68	2.883	0.102	0.176
360	0.494	42.26	3.322	0.118	0.160
420	0.557	47.94	3.768	0.133	0.145
480	0.604	52.29	4.110	0.145	0.133
540	0.659	57.37	4.509	0.159	0.119
600	0.701	61.42	4.828	0.171	0.107
660	0.743	65.48	5.147	0.182	0.096
720	0.781	69.26	5.444	0.193	0.085

[a] $Q_o = 0.278\ mg/cm^2$

Table XXXIV. Release of Cortisol from Film No. 12 at Agitation Speed of 80 rpm

Time min.	Absorbance	% Drug Release	Cumulative Amount Released mg	Q mg/cm^2	$Q_o - Q^a$ mg/cm^2
30	0.084	6.61	0.528	0.018	0.264
60	0.150	12.08	0.965	0.034	0.249
90	0.186	15.13	1.209	0.043	0.240
120	0.229	18.81	1.503	0.053	0.230
180	0.311	25.72	2.055	0.073	0.210
240	0.406	33.74	2.696	0.095	0.188
300	0.479	40.08	3.202	0.113	0.170
360	0.544	45.76	3.656	0.129	0.154
420	0.620	52.43	4.189	0.149	0.135
480	0.690	58.67	4.688	0.166	0.117
540	0.754	64.46	5.150	0.182	0.101
600	0.805	69.27	5.535	0.196	0.087
660	0.860	74.43	5.947	0.210	0.073
720	0.912	79.37	6.342	0.224	0.059

$^aQ_o = 0.283\ mg/cm^2$

Table XXXV. First-order Treatment of Data for the Effect of Agitation on Cortisol Release from Film No. 12

Agitation Speed rpm	% Drug Release After 12 Hours	Release Rate Constant (kx1000) min^{-1}	Lag Time min	Correlation Coefficient r
10	59.09	1.146	-43.56	0.999
30	65.47	1.392	-18.10	0.999
50	69.26	1.571	-6.70	0.998
80	79.37	2.073	27.52	0.992

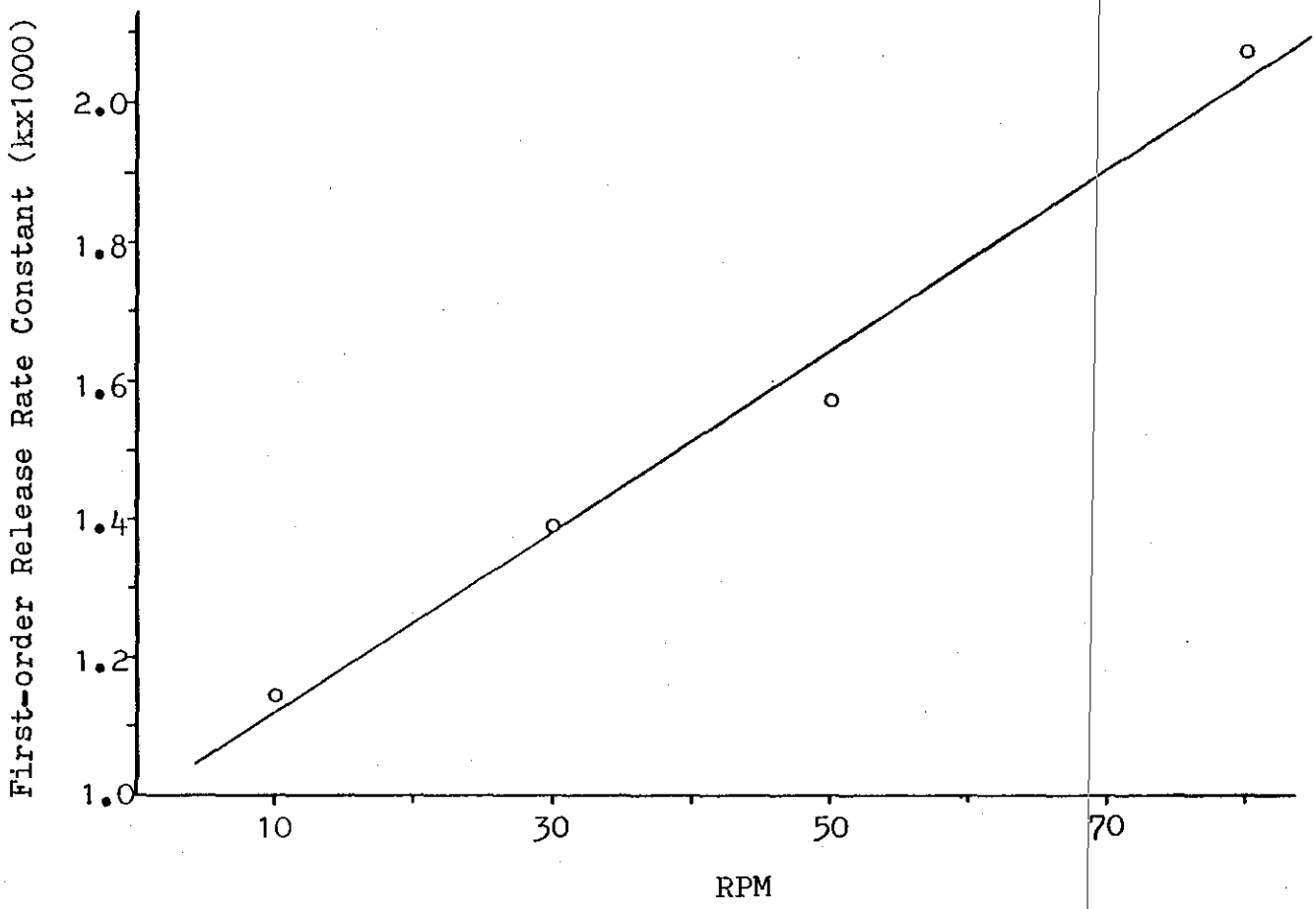

Figure 15. Correlation Between Drug Release and Stirring Rate

where, K = reaction rate,

a = constant,

N = agitation or stirring rate, and

b = constant.

The value of b was predicted to be 1 or near 1 if the reaction was diffusion controlled. The reactions controlled by the rate of interfacial reaction would not be affected by the agitation intensity and b should approach zero. If both processes were influential in the control of the rate, b should vary between zero and 1 if a sufficiently wide range of agitation intensities were employed. The value of b calculated from the data using the following relationship (Equation 9) derived from Equation 8 was

$$\frac{K_1}{K_2} = \left(\frac{N_1}{N_2}\right)^b \qquad \text{(Eq. 9)}$$

found to be 0.393 suggesting that drug release was not simple diffusion-controlled process and possibly other interfacial factors were involved. This analysis is in agreement with conclusions derived elsewhere in this study based upon a thorough analysis of drug release profiles from films of varying compositions.

Clinical Potential

Zero-order drug release from long-acting controlled drug delivery systems is a highly desirable attribute. This investigation has shown that by appropriate manipulation of ethoxylated stearyl alcohol : propylene glycol monostearate

ratio and the drug concentration in the film, a long-acting topical drug delivery system for cortisol with constant (pseudo-zero-order) release profile can be potentially developed. The film No. 11 containing 82% w/w propylene glycol monostearate, 14% w/w ethoxylated stearyl alcohol, and 4% w/w cortisol has been shown to have a constant drug release rate for 10 hours, and may have a promising clinical potential. Conceivably, this film could also serve as a vehicle for controlled release of other drugs as well.

SUMMARY AND CONCLUSION

In this study, several experiments were conducted for the initial screening of the characteristics of propylene glycol monostearate and ethoxylated stearyl alcohol films.

The data obtained from the preliminary evaluation suggested that the suitable combination of the two film formers might provide a means of controlling the rate and extent of release of cortisol over a prolonged period. The results of this study have demonstrated controlled release of cortisol from several compositions of films containing varying proportions of propylene glycol monostearate and ethoxylated stearyl alcohol. An important finding of this study is that film No. 11 containing 82% w/w propylene glycol monostearate, 14% w/w ethoxylated stearyl alcohol, and 4% w/w cortisol provides constant release rate for nearly 10 hours.

The release data were analyzed and interpreted to test if mechanism of drug release followed Higuchi's model or some other mechanism. The release of cortisol from propylene glycol monostearate-ethoxylated stearyl alcohol films was found to be a complex process rather than a simple diffusion or leaching of drug from the films. The potential clinical application of the film No. 11 with constant release rate profile for cortisol deserves further study.

Propylene glycol monostearate-ethoxylated stearyl alcohol films may offer promising potential for delivery of other drugs as well. Although this investigation has emphasized topical application of the films, such compositions and the underlying concepts deserve further study with respect to other routes of drug delivery.

REFERENCES

1. S. P. Loucas, and H. M. Haddad, J. Pharm. Sci., 61, 985 (1972)

2. J. J. Sciarra, and R. N. Gidwani, J. Soc. Cosmet. Chem., 21, 667 (1970)

3. J. J. Sciarra, and R. N. Gidwani, J. Pharm. Sci., 61, 754 (1972)

4. N. Applezweig, U. S. pat., 3,536,809 (1970)

5. T. J. Roseman, and W. I. Higuchi, J. Pharm. Sci., 59, 353 (1970)

6. J. H. R. Woodland, S. Yolles, D. A. Blake, M. Helrich, and F. J. Meyer, J. Med. Chem., 16, 897 (1973)

7. M. Luongo, J. J. Sciarra, and C. O. Ward, J. Pharm. Sci., 63, 1376 (1974)

8. A. W. McKenzie, and R. B. Stoughton, Arch. Dermatol., 86, 608 (1962)

9. S. Borodkin, and F. E. Tucker, J. Pharm. Sci., 63, 1359 (1974)

10. B. V. Iyer, and R. C. Vasavada, J. Pharm. Sci., 68, 782 (1979)

11. B. V. Iyer, and R. C. Vasavada, Int. J. Pharm., 3, 247 (1979)

12. A. R. Khan, B. V. Iyer, R. Cirreli, and R. V. Vasavada, "Release of Salicylic Acid from Lanolin Alcohol-Ethyl Cellulose Films," Abstracts, APhA Academy of Pharmaceutical Sciences, 25th National Meeting, 10, 94 (1980)

13. F. A. Kincl, G. Benagiano, and I. Angee, Steroids, 11, 673 (1968)

14. P. J. Dziuk, and B. Cook, Endocrinology, 78, 208 (1966)

15. T. Higuchi, J. Soc. Cosmet. Chem., 11, 85 (1960)

16. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963)

17. S. J. Desai, A. P. Simonelli, and W. I. Higuchi, J. Pharm. Sci., 54, 1459 (1965)

18. J. B. Schwartz, A. P. Simonelli, and W. I. Higuchi, J. Pharm. Sci., 57, 274 (1968)

19. J. B. Schwartz, A. P. Simonelli, and W. I. Higuchi, J. Pharm. Sci., 57, 278 (1968)

20. P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, J. Pharm. Sci., 56, 1542 (1967)

21. P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, J. Pharm. Sci., 56, 1548 (1967)

22. J. L. Fox, and B. V. Iyer, Abstracts, APhA Academy of Pharmaceutical Sciences 25th National Meeting, 10, 86 (1980)

23. R. A. Cass, J. Paint Technol., 38, 281 (1966)

24. J. J. Sciarra, and S. P. Patel, J. Pharm. Sci., 65, 1519 (1976)

25. W. L. Chiou, Can. J. Pharm. Sci., 10, 112 (1975)

26. "The Merck Index," Ninth Edition, Merck & Co., Inc., Rahway, NJ, p. 630 (1976)

27. D. E. Wurster, and P. W. Taylor, J. Pharm. Sci., 54, 169 (1965)