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Release of salicylic acid from lanolin alcohol-ethyl cellulose films

Arshad Rahim Khan
University of the Pacific

RELEASE OF SALICYLIC ACID FROM LANOLIN ALCOHOL-ETHYL CELLULOSE FILMS

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Arshad Rahim Khan

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Arshad Rahim Khan

is approved for recommendation to the Committee on Graduate Studies, University of the Pacific.

Department Chairman or Dean:

Carl C. Russell

Thesis Committee:

Chairman

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Abstract of Thesis

In the present study lanolin alcohol films were investigated as potential drug delivery systems for the controlled release of salicylic acid. A series of experiments were conducted *in vitro* to study the release of salicylic acid from these films. The effect of changes in film composition and stirrer speed on drug release were examined. Seven film compositions with varying proportions of lanolin alcohol and ethyl cellulose were prepared over the ethyl cellulose concentrations of 0-30% w/w, while keeping the drug concentration at 2.5% w/w.

The release data obtained in this study were examined by the Q *vs* $t_{\frac{1}{2}}$ relationship and the first-order relationship. This was done to probe deeper into the underlying mechanism of drug release. Upon examination of the release data by the Q *vs* $t_{\frac{1}{2}}$ treatment, it was observed that the correlation coefficients were quite high and lag times were only slightly negative in agreement with the observed initial release data. In contrast, the first-order treatment of data showed somewhat lower correlation coefficients and very high negative lag times. These data strongly suggest that the unidirectional release of salicylic acid from the lanolin alcohol-ethyl cellulose films follows Higuchi's diffusion-controlled granular matrix model.

The release rate constant showed an initial increase with inclusion of ethyl cellulose followed by a sharp decline as the ethyl cellulose concentration was further increased reaching a minimum value at about 15-20 percent of ethyl cellulose. Further increases in the concentration of ethyl cellulose increased the rate of drug release with a tendency to level off at about 30 percent ethyl cellulose concentration.

The effect of stirring rate on the release rate constant showed that the rates of release of salicylic acid increased with increases in the stirring rate.

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INTRODUCTION

Topical drug therapy has been the subject of intensive research for over three decades. Workers have overcome many technical difficulties in this period of time and many theoretical and procedural breakthroughs have occurred. In the field of topical drug delivery systems, the industrial pharmacist is continually faced with the problem of developing an optimum vehicle for a particular therapeutic agent, consistent with the physical and chemical properties of the drug and the vehicle, and the nature of the skin to be treated.

The human skin functions as a protectant against the penetration of a wide variety of substances. The membranes of cells of the stratum corneum are structurally rigid and show a remarkable chemical resistance. Hydration of the stratum corneum is possibly the most important factor in skin penetration. McKenzie and Stoughton (1) have shown that penetration of corticosteroids may be increased a hundred-fold by occluding the site of application by a plastic barrier. While this technique effectively hydrates the stratum corneum, the enhanced activity can also be attributed (at least in part) to increased contact between vehicle and skin.

Vehicles have significant effects on the penetration

of substances through the skin (2). It has been shown that diffusion of the drug from the vehicle into the skin surface and subsequent penetration of the drug through the stratum corneum is a function of the partition coefficient of the drug between stratum corneum and vehicle and of the relative solubility of the drug in the vehicle (3, 4). The physical properties of the vehicle are important in determining the degree of occlusion produced.

The efficacy of various types of vehicles in aiding penetration has been explained on the basis of their effect on: (i) hydration of the stratum corneum; (ii) the activity of water in the stratum corneum, and (iii) the stratum corneum: vehicle partition co-efficient. Fatty substances produce a certain degree of occlusivity and induce hydration by sweat accumulation at the skin-vehicle interface (5). This effect can be further enhanced by covering with a plastic bandage.

The use of polymeric films with or without the incorporation of medicinal substances has attracted a great deal of attention in the field of cosmetics, pharmaceuticals, and dermatologicals. Films of this type may be applied as solutions, spray-on bandages, creams, or lotions to accomplish a variety of therapeutic or cosmetic objectives. The film-forming delivery systems may be formulated to achieve the controlled-drug delivery necessary to produce optimal therapeutic effect over a desired time course while minimizing the side effects (6).

Shertler (27) has formulated a film-forming preparation using polyacrylate and hydroxypropyl cellulose which is suitable for topical application of corticosteroids. Lang and Fang (7) have described the use of aqueous topical adhesives as spray-on bandages. More recently, Shaw et al. (8) have described a transdermal system which delivers the drug scopolamine at a rate that prevents motion-induced nausea, while minimizing other parasympatholytic effects of the drug. Enhanced therapeutic effect combined with predictable control over the rate and extent of absorption of the drug are some of the advantages offered by drugs incorporated in such delivery systems.

Skin disorders such as acne are often treated by agents which possess kerotolytic properties causing mild erythema and later peeling of the skin. The keratolytic properties of salicylic acid have been utilized in the treatment of acne and for removal of warts and corns. Incorporation of salicylic acid in a film-forming delivery system would insure prolonged contact of the drug with the area under treatment and thus may afford a more predictable and effective treatment.

Lanolin alcohol, a high molecular weight non-polymeric alcohol, has been recently studied for its film-forming potential (10, 11). It was reported that lanolin alcohol forms thin isolatable films on mercury substrates. Incorporation of small amounts of ethyl cellulose, a known film

former, and a plasticizer, such as propylene glycol, was found to give tack-free films of improved quality. Effective utilization of nonpolymeric substances such as lanolin alcohol in film-forming compositions holds considerable promise for a variety of reasons. Such delivery systems could be designed and formulated to provide sustained drug delivery. The potential hazard associated with monomeric impurities in the polymers are avoided. Nonpolymeric materials are easy to manipulate and compound. They can be washed from the skin with relative ease using soap and water. Nonpolymeric materials are also relatively easy to obtain in a state of definable composition. The potential clinical applications of film-forming properties of lanolin alcohol have not been fully explored even though it is a widely used ingredient in cosmetics and pharmaceutical preparations.

In this study, the <u>in vitro</u> release of salicylic acid (a known keratolytic agent) from lanolin alcohol-ethyl cellulose films has been examined. The effect of variation in lanolin alcohol-ethyl cellulose content on the release of the drug has been reported. The data have been analyzed to gain an insight as to the mechanism of drug release.

THEORY

In the present study a film-forming delivery system composed of lanolin alcohol and ethyl cellulose has been examined. Salicylic acid is assumed to be uniformly dispersed in the film matrix, and the solubility of salicylic acid in lanolin alcohol or ethyl cellulose is issumed to be negligible.

Theoretical treatments of the mechanism of drug release assume that diffusion of the drug from the vehicle is rate limiting, and therefore the properties of the skin can be ignored. It is assumed that all of the concentration gradient occurs in the applied phase and the skin can be regarded as a perfect sink. The concentration of the penetrating material in the skin is essentially zero because of rapid dissipation into deeper tissues.

These assumptions would be valid in cases involving absorption by injured skin or where highly insoluble, suspension-type ointments were used with large concentration gradients in the applied phase. Quantitative relationships governing such situations have been developed by T. Higuchi (12).

Two mechanisms of drug release from such diffusion-controlled systems have been considered (13).

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

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

Both mechanisms assumed unidirectional drug release.

Drug Release from a Planar System Having a Homogeneous Matrix

Here the drug is released by 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 into a bathing medium acting essentially as a perfect sink would be determined by the relationship:

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

where:

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

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:

Here, the drug is leached by the bathing fluid which is able to enter the drug-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 insignificant. For such systems Higuchi has proposed the following relationship:

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

where:

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

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

τ = 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.

For both Equations 1 and 2, the derivation is based on the existence of a 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.

Since the solubility of salicylic acid is assumed to be negligible in the lanolin alcohol-ethyl cellulose film, Equation 2, describing the relationship of drug release from a granular matrix, might be a more appropriate description of the drug release process. The C_s, therefore, would refer to the solubility of salicylic acid in the permeating fluid.

Although both equations, are for a different mechanism of drug release, 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 and

$$k_G = \sqrt{\frac{D\varepsilon}{\tau}\,(2A-\varepsilon C_s)C_s} \quad \text{(granular matrix)} \qquad \text{Eq. 4}$$

$$k_H = \sqrt{D\,(2A-C_s)\,C_s} \quad \text{(homogeneous matrix)} \qquad \text{Eq. 5}$$

In the present study the release of salicylic acid was examined to determine its conformity to the Q vs $t^{\frac{1}{2}}$ relationship.

A first-order release mechanism in which the release rate is proportional to the amount of drug remaining in the matrix might also be considered possible for the release of drugs from systems of this type (6, 9). This could be shown as:

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

where Q_o is the initial amount of drug present per unit area of the film, Q is the amount of drug present per unit area at time t and K is the first-order rate constant. The salicylic acid release data from the film will be examined to test this possibility.

EXPERIMENTAL

Materials

1. Lanolin Alcohol (Super Hartolan ^{R}, Croda Inc., New York, NY), melting point 61-64^{o}C.
2. Ethyl Cellulose N-50 (Hercules Inc., Wilmington, DE), ethoxyl content of 48.5.
3. Salicylic Acid, USP (Amend Drug and Chemical Company, Irvington, NJ).
4. Isopropanol NF (Mallinckrodt Chemical Works, St. Louis, MO) spectral grade.

Preparation of Solutions

Solutions containing appropriate amounts of lanolin alcohol and ethyl cellulose were prepared as shown in Table I. Ethyl cellulose was dissolved in a beaker containing 25 ml of isopropyl alcohol at 55-55^{o}C by sprinkling weighed amounts of ethyl cellulose onto isopropyl alcohol over a period of two hours. Magnetic stirring was employed throughout this time period. This procedure insured uniform dissolution and prevented formation of clumps. The required amount of lanolin alcohol was then dissolved in this solution by continued gentle stirring and warming. Prior to the addition of salicylic acid, the solution was cooled to room temperature.

Table I. Film Compositions Prepared.

Film No.	Lanolin Alcohol	Ethyl Cellulose	Salicylic Acid[a]
1	97.5	0.0	2.5
2	92.5	5.0	2.5
3	87.5	10.0	2.5
4	82.5	15.0	2.5
5	77.5	20.0	2.5
6	72.5	25.0	2.5
7	67.5	30.0	2.5

[a]Percent w/w based upon dry weight of the film.

The resulting solution was transferred to a 50 ml volumetric flask and allowed to stand for 24 hours before final volume was made up with isopropyl alcohol. All solutions were examined visually for undissolved or particulate matter. All seven films listed in Table I were prepared in an identical manner.

Preparation of Films

Two ml of a solution was pipetted onto a preweighed glass Petri dish (area = 18.1 cm^2), kept on a level surface in a temperature- and humidity-controlled room (18° C, 50% relative humidity). The Petri dishes were kept covered to minimize surface drafts and to allow slow and uniform evaporation. The evaporation process was usually completed in 48 hours.

The complete evaporation of the solvent was always confirmed by weighing the Petri dishes to a constant weight. The film-coated Petri dishes were stored in a desiccator containing anhydrous calcium chloride at least 24 hours prior to release studies. The unidirectional release of salicylic acid from the films was insured by good adherence of the film to the bottom of the Petri dishes as confirmed by frequent visual examinations during and at the termination of the experiment. No evidence of peeling was ever noted during the course of these studies.

Release Studies

The release studies were conducted in a dissolution

assembly (Figure 1) with the following modifications: the dissolution flasks were replaced by 1000-ml flat-bottomed polypropylene beakers and the dissolution basket assemblies were replaced by stainless steel stirrers with propeller diameters of 4.5 cm.

The film-coated Petri dishes were placed at the bottom of the beakers. The beakers were held in position by means of plexiglass discs with a central circular port for the stirrers and a small sampling port. The stirring assembly was set in position so that the stirring blade was approximately 3 cm above the film surface. Three hundred ml of preheated (37° C) distilled water was carefully added to each beaker, and the stirring was maintained at 40 rpm. The water bath in the assembly was maintained at 37 $\pm$ 0.5° C.

During the course of the release study, three-ml samples were drawn at definite time intervals over a period of 10 hours. The amount of the fluid withdrawn each time was replaced with an equal amount of distilled water to keep the volume constant. Each sample was stored in a small test tube until the end of the experiment, when all of the samples were analyzed spectrophotometrically at 297 nm.[1]

The release data were computed and analyzed with the help of a standard curve, Figure 1, appropriate corrections were applied for the samples withdrawn and media added. All release studies were conducted in triplicate, strict adherence

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[1]Bausch and Laumb Spectronic 710 UV vis.

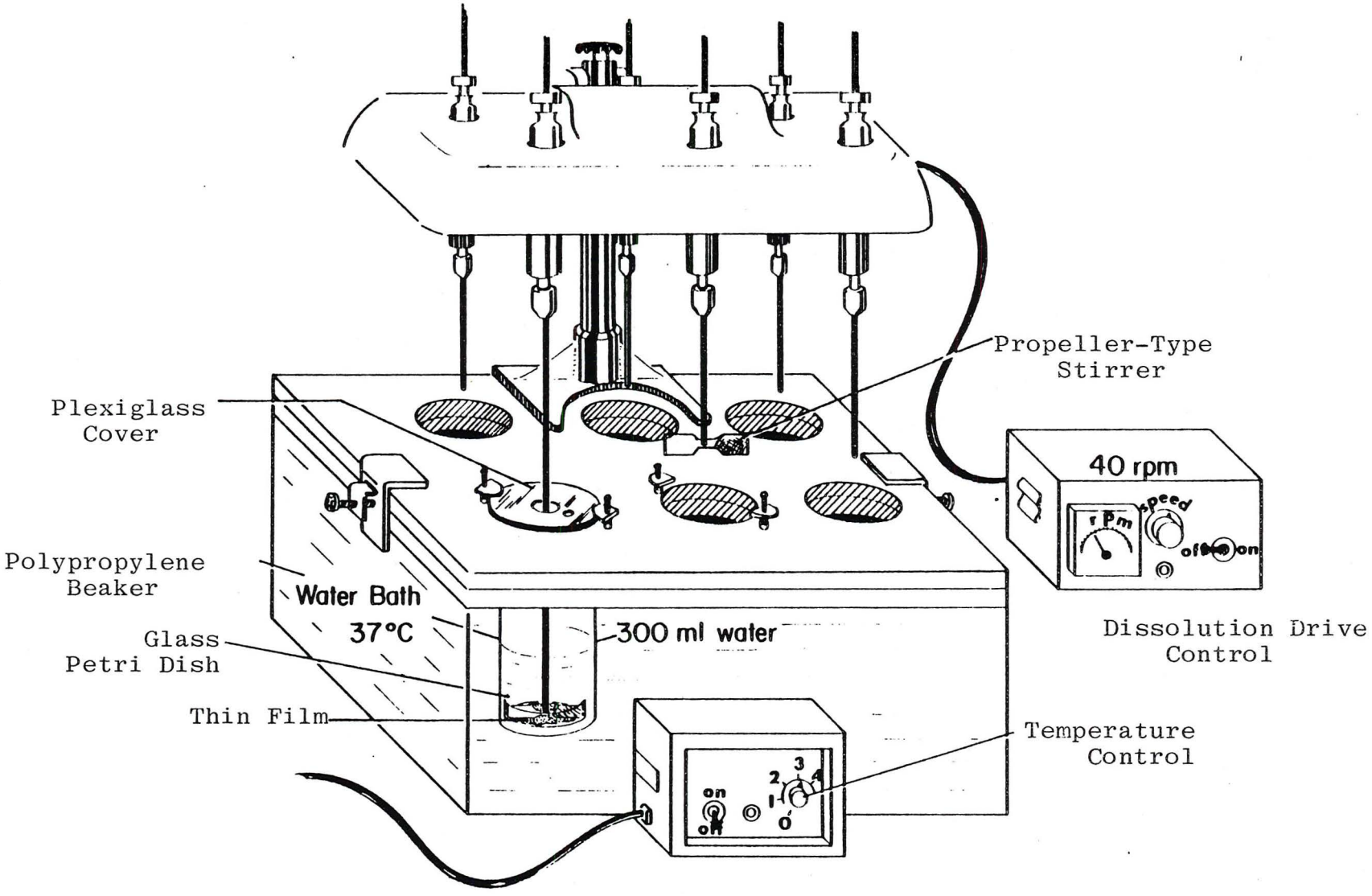

Figure 1. Apparatus Used for In Vitro Release Studies.

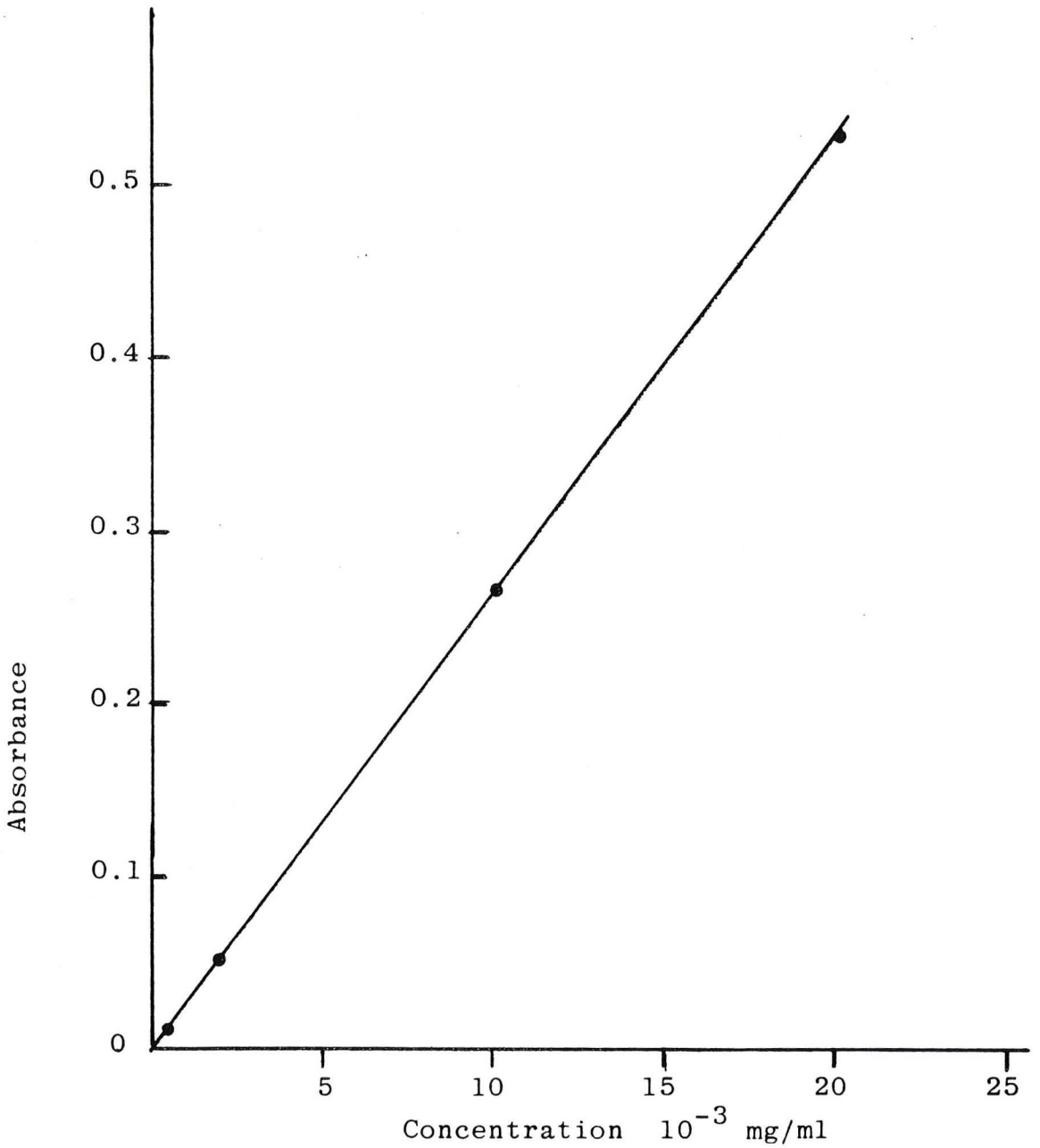

Figure 2. Standard curve for Salicylic Acid.

to established experimental protocol was practiced to insure high reproducibility.

The effect of change in stirring rates on drug release was also investigated. One composition of lanolin alcohol-ethyl cellulose film was selected (Film No. 4, Table I) and studies conducted. All other experimental parameters were kept constant, as drug release was examined at stirring rates of 20, 30, 40, 50, and 60 revolutions per minute. The data from these experiments were analyzed in the same manner as the previous studies.

RESULTS AND DISCUSSION

Evaluation of Films

In the present study, release of salicylic acid (2.5% w/w) from seven different compositions of films with varying ratios of lanolin alcohol and ethyl cellulose were examined.

As previously discussed, both Higuchi models (Eq. 1 and 2) describe drug release as being linear with the square root of time:

$$Q = kt^{\frac{1}{2}} \qquad \text{Eq. 3}$$

where, for the granular matrix:

$$k_G = \frac{D\varepsilon}{T}(2A - \varepsilon C_s)C_s \qquad \text{Eq. 4}$$

and for the homogeneous matrix:

$$k_H = D(2A - C_s)C_s \qquad \text{Eq. 5}$$

The validity of the relationship has since been confirmed experimentally by a number of workers (14,15).

Adherence of drug release to the Q versus $t^{\frac{1}{2}}$ relationship requires that the drug concentration in the depleted zone far exceeds the solution concentration at the interface ($A >> C_s$ or εC_s). In the systems studied, this criterion was satisfied (Table II).

Table II. Calculated Values for Selected Parameters.

Film No.	Density of Film[a] g/ml	Volume of Film ml	A mg/ml	C_s mg/ml	εC_s[b] mg/ml
1	0.992	0.202	24.812	0.0167	0.00179
2	1.012	0.205	25.324	0.0173	0.00174
3	1.032	0.192	25.813	0.0165	0.00185
4	1.052	0.186	26.300	0.0163	0.00183
5	1.072	0.181	26.828	0.0162	0.00181
6	1.092	0.176	27.300	0.0160	0.00179
7	1.112	0.181	27.828	0.0168	0.00188

[a]Based upon density (g/ml) of lanolin alcohol (0.98), ethyl cellulose (1.38) and salicylic acid (1.44).

[b]Porosity (ε) = 0.112; reported by Schwartz (16) for a wax matrix with 5% salicylic acid.

A first-order relationship with the release rate proportional to the concentration of drug remaining within the film might also be considered possible.

$$\ell n\ (Q_o - Q) = -kt + \ell n\ Q_o \qquad \text{Eq. 6}$$

Sciarra and Gidwani (9) reported that gentian violet, cetylpyridinium chloride, and benzalkonium chloride were released from various films by the first-order mechanism. Schwartz et al. (16) rigorously examined the drug release from wax matrices before concluding that the Higuchi model (Q versus $t^{\frac{1}{2}}$ relationship) provided a better fit than the first-order treatment of data.

The release data obtained in this study were examined by both methods with a view to probe deeper into the underlying mechanism of drug release. The correlation coefficients for the best statistical line and the lag time (time intercept extrapolated to Q = 0) were used as the principal criteria for evaluation.

Q versus $t^{\frac{1}{2}}$ treatment of data for the release of salicylic acid from matrices containing varying composition of lanolin alcohol and ethyl cellulose are shown in Tables III - IX and Figures 2 - 8, respectively.

The corresponding first order treatment of data is shown in Table X and Figure 9.

Upon examination of the release data obtained by the Q versus $t^{\frac{1}{2}}$ treatment, it was observed that the correlation

Table III. Release of Salicylic Acid from Film No. 1

Time min.	$t^{\frac{1}{2}}$	Absorbance	% Drug Release	Cummulative Amount Released mg	Q mg/cm^2
30	5.48	0.085	18.68	0.936	0.052
60	7.75	0.104	23.17	1.161	0.064
90	9.49	0.141	32.57	1.632	0.090
120	10.95	0.158	36.23	1.815	0.100
180	13.42	0.188	43.71	2.190	0.121
240	15.49	0.205	48.08	2.409	0.133
360	18.97	0.237	55.87	2.799	0.155
480	21.91	0.262	62.22	3.117	0.172
600	24.49	0.281	67.37	3.375	0.186

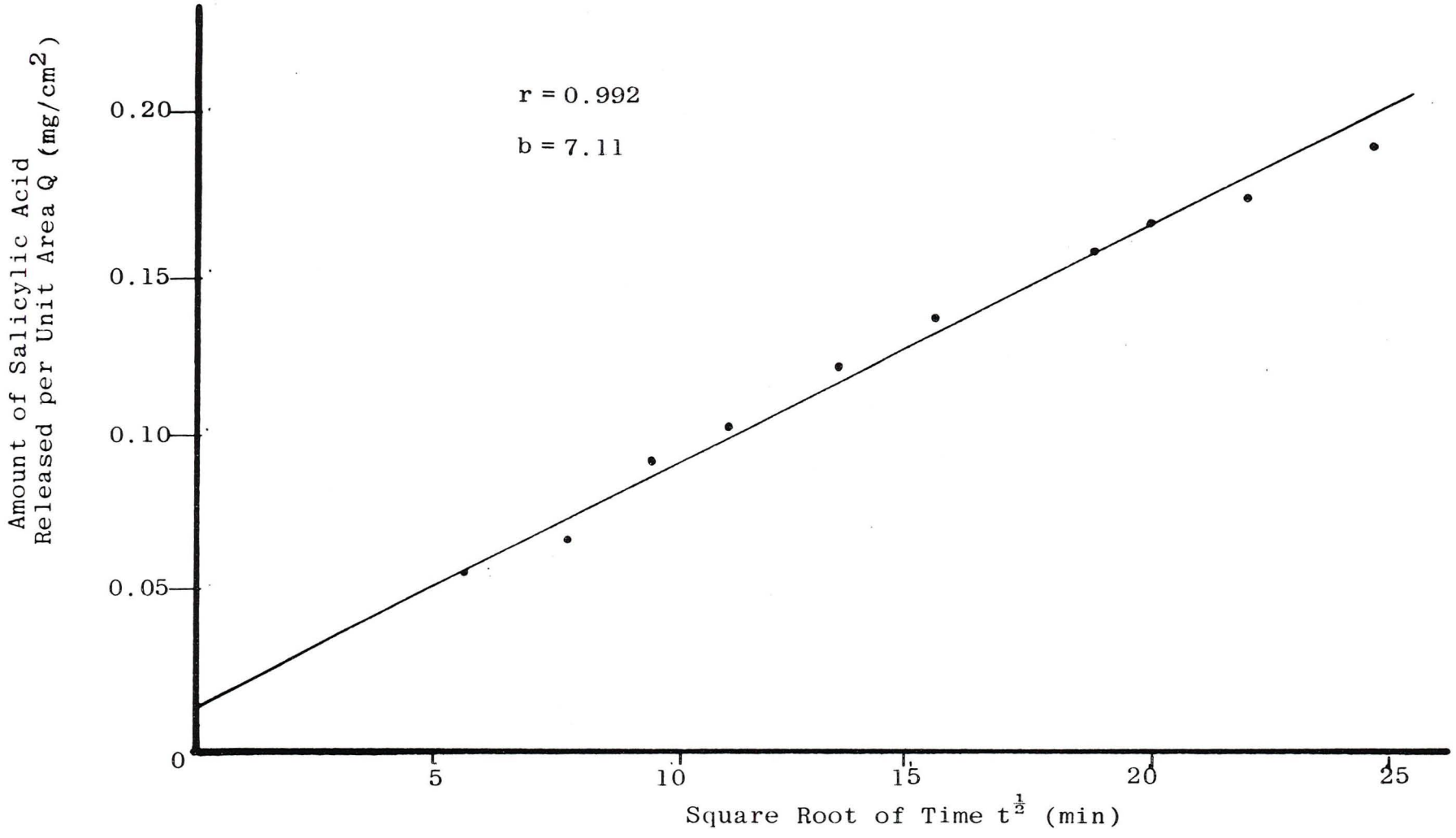

Figure 3. Release of Salicylic Acid from Film No. 1

Table IV. Release of Salicylic Acid from Film No. 2.

Time min.	$t^{\frac{1}{2}}$	Absorbance	% Drug Release	Cummulative Amount Released mg	Q mg/cm^2
30	5.48	0.078	16.56	0.858	0.047
60	7.75	0.105	22.76	1.179	0.065
90	9.49	0.147	32.37	1.677	0.093
120	10.95	0.162	35.96	1.863	0.103
180	13.42	0.198	44.41	2.301	0.127
240	15.49	0.219	49.68	2.574	0.142
360	18.97	0.252	57.38	2.973	0.164
480	21.91	0.276	63.52	3.291	0.182
600	24.49	0.296	68.50	3.549	0.196

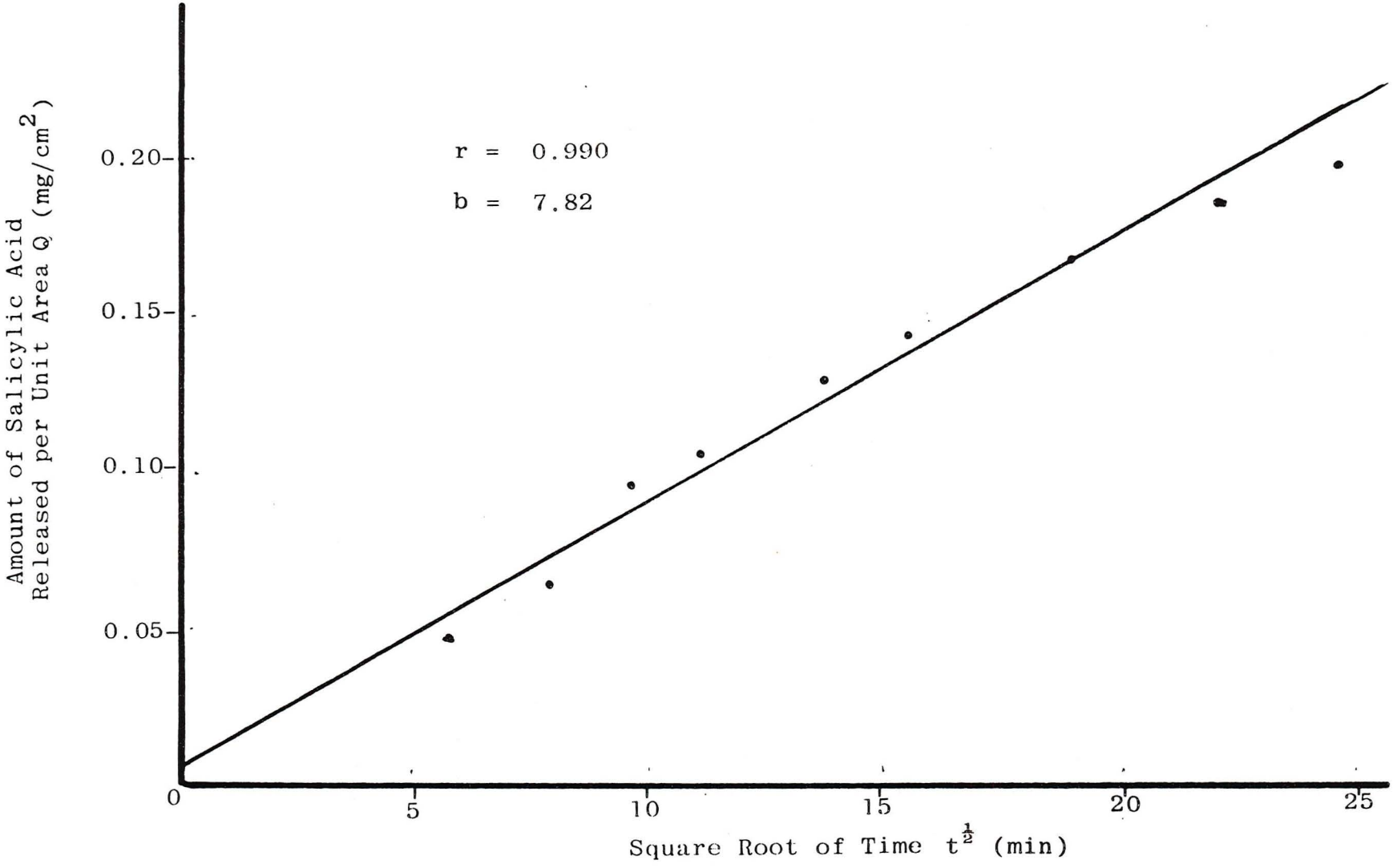

Figure 4. Release of Salicylic Acid from Film No. 2

Table V. Release of Salicylic Acid From Film No. 3.

Time min.	$t^{\frac{1}{2}}$	Absorbance	% Drug Release	Cummulative Amount Released mg	Q mg/cm^2
30	5.48	0.041	8.48	0.420	0.023
60	7.75	0.066	14.48	0.717	0.040
90	9.49	0.987	19.52	0.966	0.053
120	10.95	0.101	23.15	1.146	0.063
180	13.42	0.122	28.24	1.398	0.077
240	15.49	0.143	33.39	1.653	0.091
360	18.97	0.174	40.97	2.028	0.112
480	21.91	0.193	45.82	2.268	0.125
600	24.49	0.215	51.52	2.550	0.141

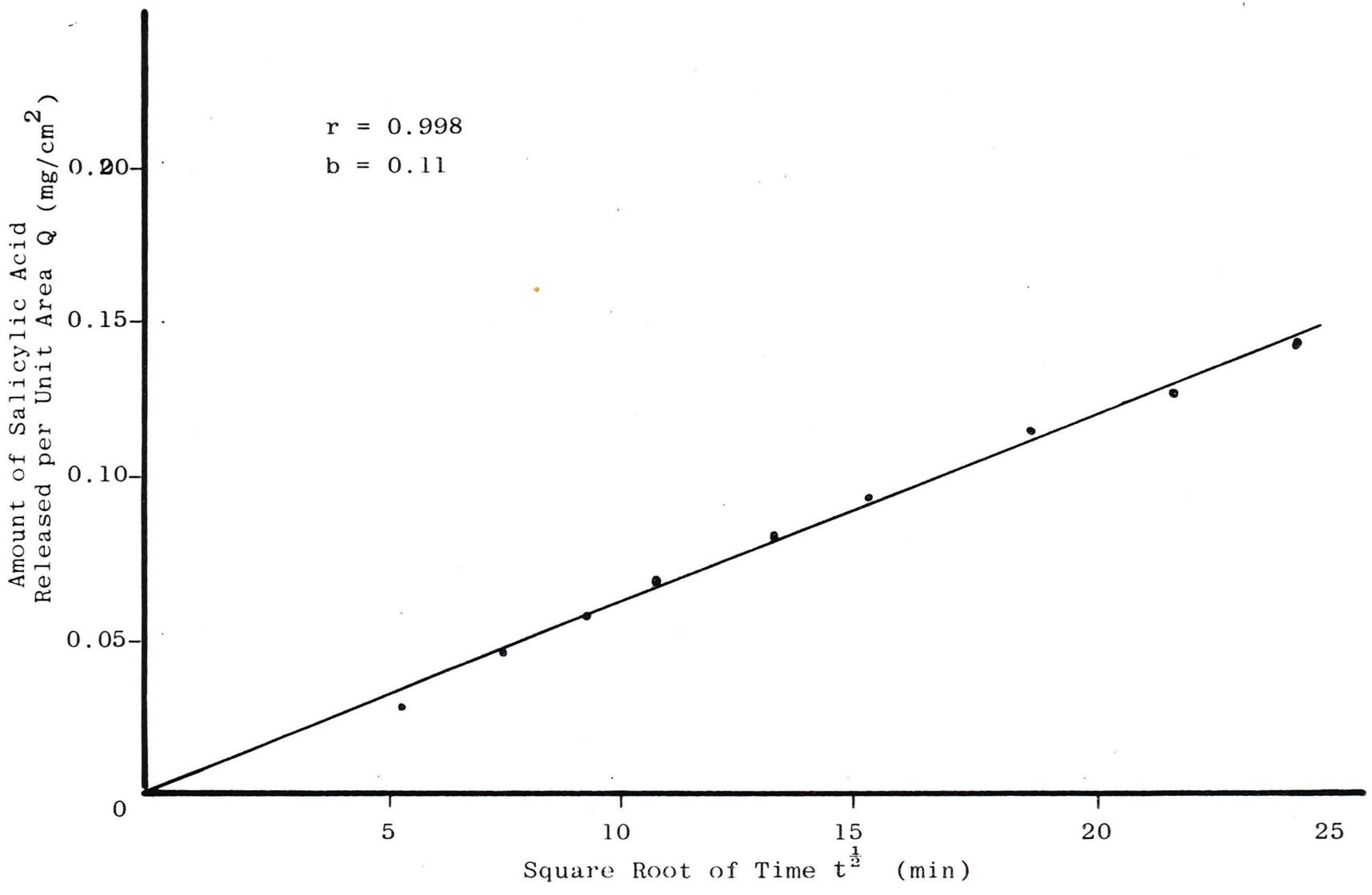

Figure 5. Release of Salicylic Acid from Film No. 3

Table VI. Release of Salicylic Acid From Film No. 4.

Time min.	$t^{\frac{1}{2}}$	Absorbance	% Drug Released	Cummulative Amount Released mg	Q mg/cm^2
30	5.48	0.028	5.51	0.270	0.015
60	7.75	0.057	12.49	0.612	0.034
90	9.49	0.068	15.25	0.747	0.041
120	10.95	0.085	19.35	0.948	0.052
180	13.42	0.105	24.43	1.197	0.066
240	15.49	0.124	29.09	1.425	0.079
360	18.97	0.141	36.64	1.746	0.097 0.960
480	21.91	0.174	41.58	2.037	0.113
600	24.49	0.195	46.91	2.298	0.127

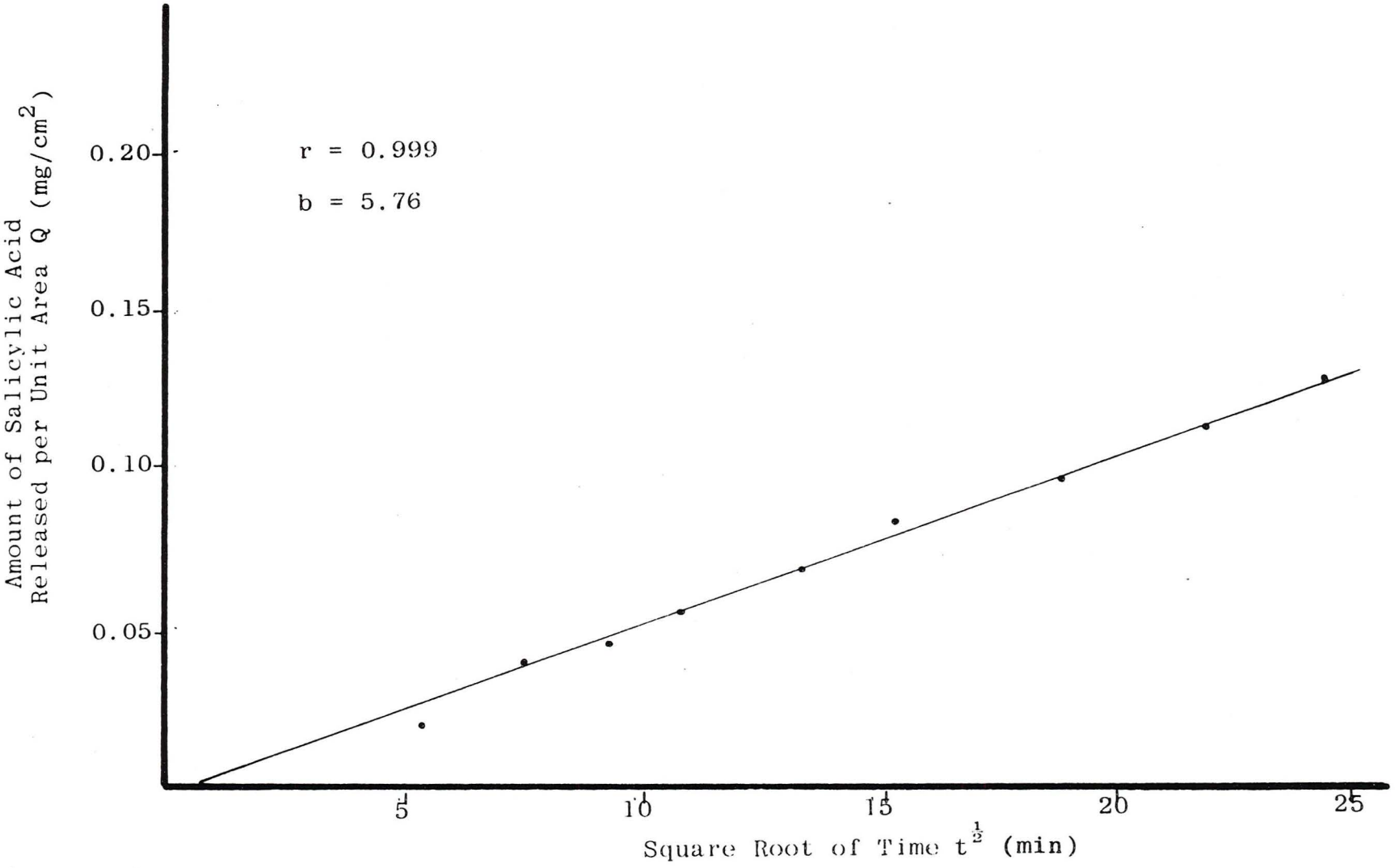

Figure 6. Release of Salicylic Acid from Film No. 4

Table VII. Release of Salicylic Acid From Film No. 5.

Time min.	$t^{\frac{1}{2}}$	Absorbance	% Drug Release	Cummulative Amount Released mg	Q mg/cm^2
30	5.48	0.048	10.39	0.504	0.028
60	7.75	0.073	16.39	0.795	0.044
90	9.49	0.091	20.90	1.014	0.056
120	10.95	0.103	24.00	1.164	0.064
180	13.42	0.130	30.67	1.488	0.082
240	15.49	0.148	35.31	1.713	0.095
360	18.97	0.175	42.12	2.043	0.113
480	21.91	0.192	46.75	2.268	0.125
600	24.49	0.203	49.72	2.412	0.133

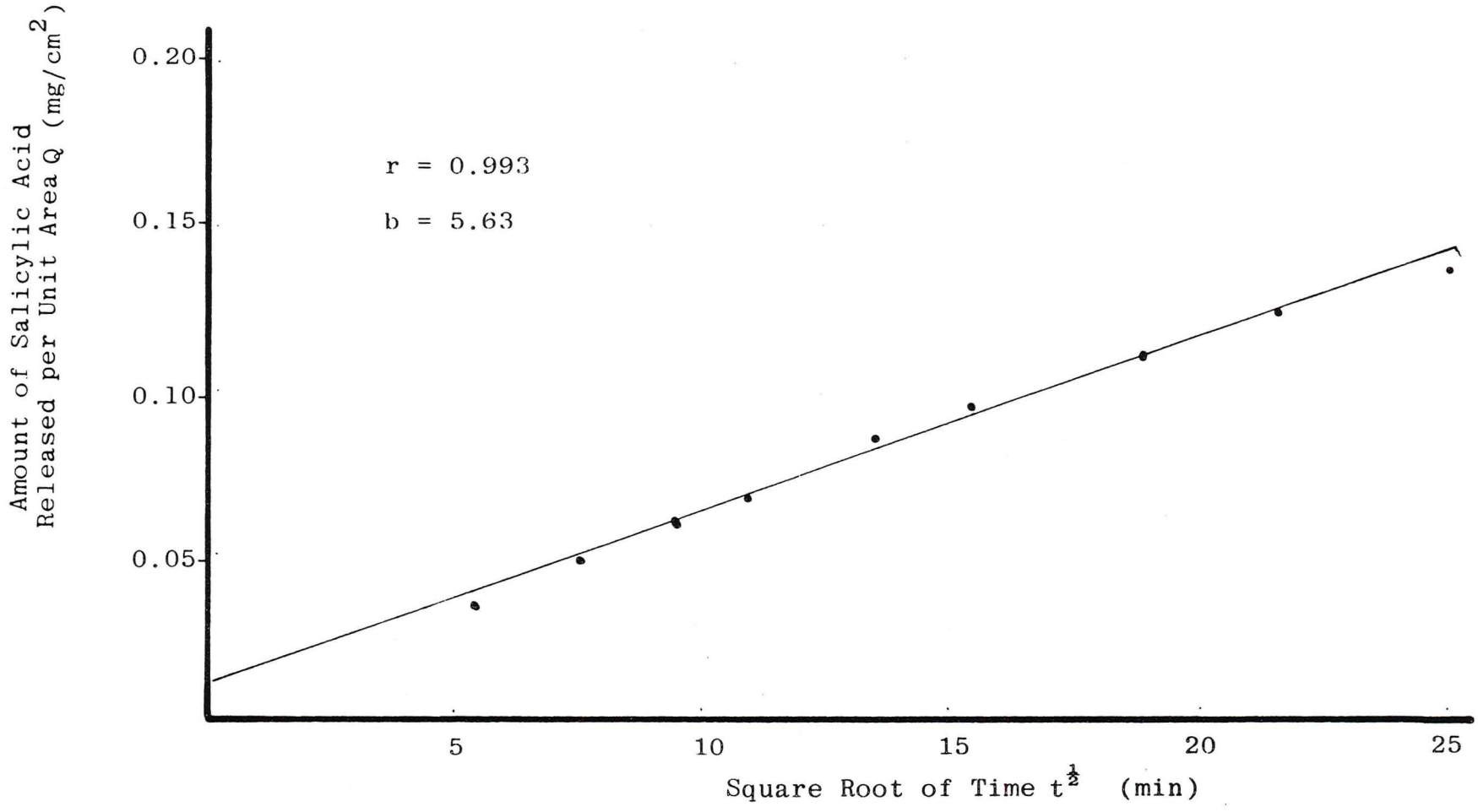

Figure 7. Release of Salicylic Acid from Film No. 5

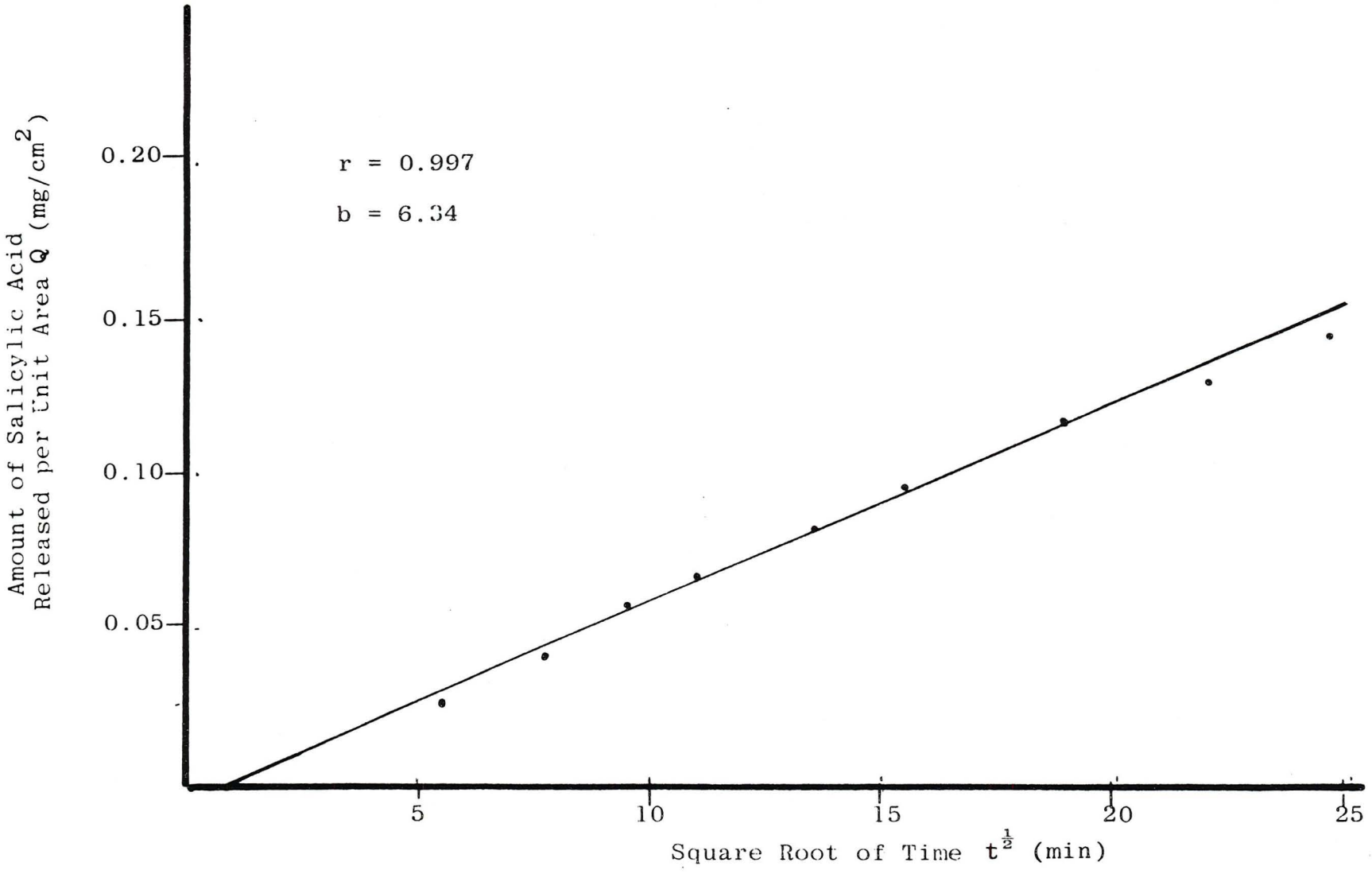

Figure 8. Release of Salicylic Acid from Film No. 6

Table VIII. Release of Salicylic Acid From Film No. 6.

Time min.	$t^{\frac{1}{2}}$	Absorbance	% Drug Release	Cummulative Amount Released mg	Q mg/cm^2
30	5.48	0.044	9.54	0.459	0.025
60	7.75	0.065	14.72	0.708	0.039
90	9.49	0.089	20.65	0.993	0.055
120	10.95	0.106	24.95	1.200	0.066
180	13.42	0.130	31.00	1.491	0.082
240	15.49	0.148	35.68	1.716	0.095
360	18.97	0.181	43.98	2.115	0.117
480	21.81	0.203	49.72	2.391	0.132
600	24.49	0.220	54.34	2.613	0.144

Table IX. Release of Salicylic Acid From Film No. 7.

Time min.	$t^{\frac{1}{2}}$	Absorbance	% Drug Release	Cummulative Amount Released mg	Q mg/cm^2
30	5.48	0.034	6.18	0.342	0.019
60	7.75	0.054	11.52	0.579	0.032
90	9.49	0.073	16.00	0.804	0.044
120	10.95	0.089	19.88	0.999	0.055
180	13.42	0.114	25.85	1.299	0.072
240	15.49	0.133	30.51	1.533	0.085
360	18.97	0.168	38.87	1.953	0.108
480	21.91	0.188	43.94	2.208	0.122
600	24.49	0.218	51.28	2.577	0.142

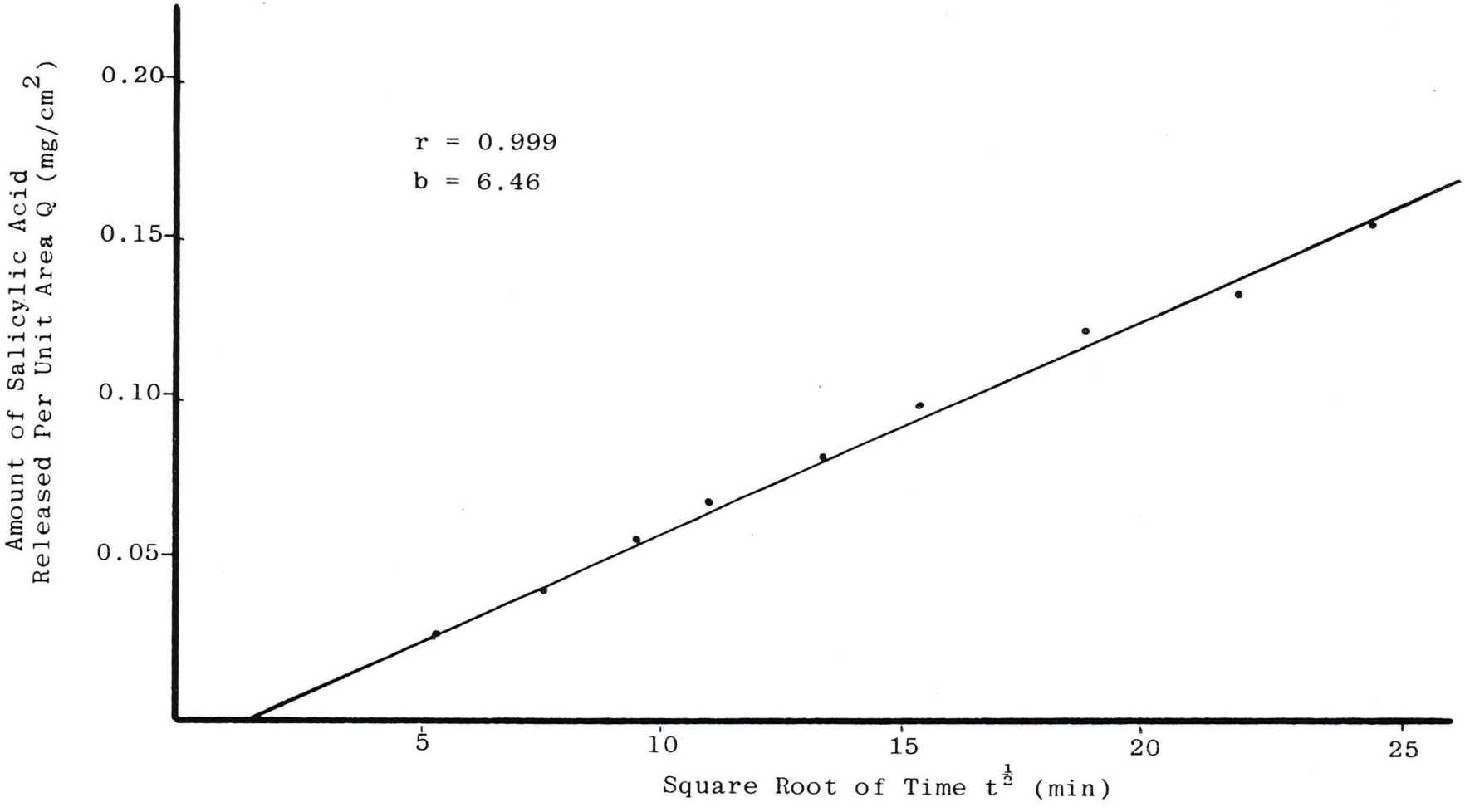

Figure 9. Release of Salicylic Acid from Film No. 7

Table X. First Order Treatment of Data for the Release of Salicylic Acid from Lanolin Alcohol and Ethyl Cellulose Films

Film No.	Film Composition[a]	Release Rate Constant (k) mg cm^{-2} $min^{-\frac{1}{2}}$	Lag Time min	Correlation Coefficient r
1	97.5 : 0 : 2.5	0.094	-149.1	0.987
2	92.5 : 5 : 2.5	0.099	-132.9	0.985
3	87.5 : 10 : 2.5	0.064	-106.4	0.988
4	82.5 : 15 : 2.5	0.057	-84.1	0.990
5	77.5 : 20 : 2.5	0.060	-144.3	0.978
6	72.5 : 25 : 2.5	0.071	-103.2	0.988
7	67.5 : 30 : 2.5	0.066	-62.8	0.994

[a]Proportion of lanolin alcohol, ethyl cellulose and salicylic acid expressed as % w/w.

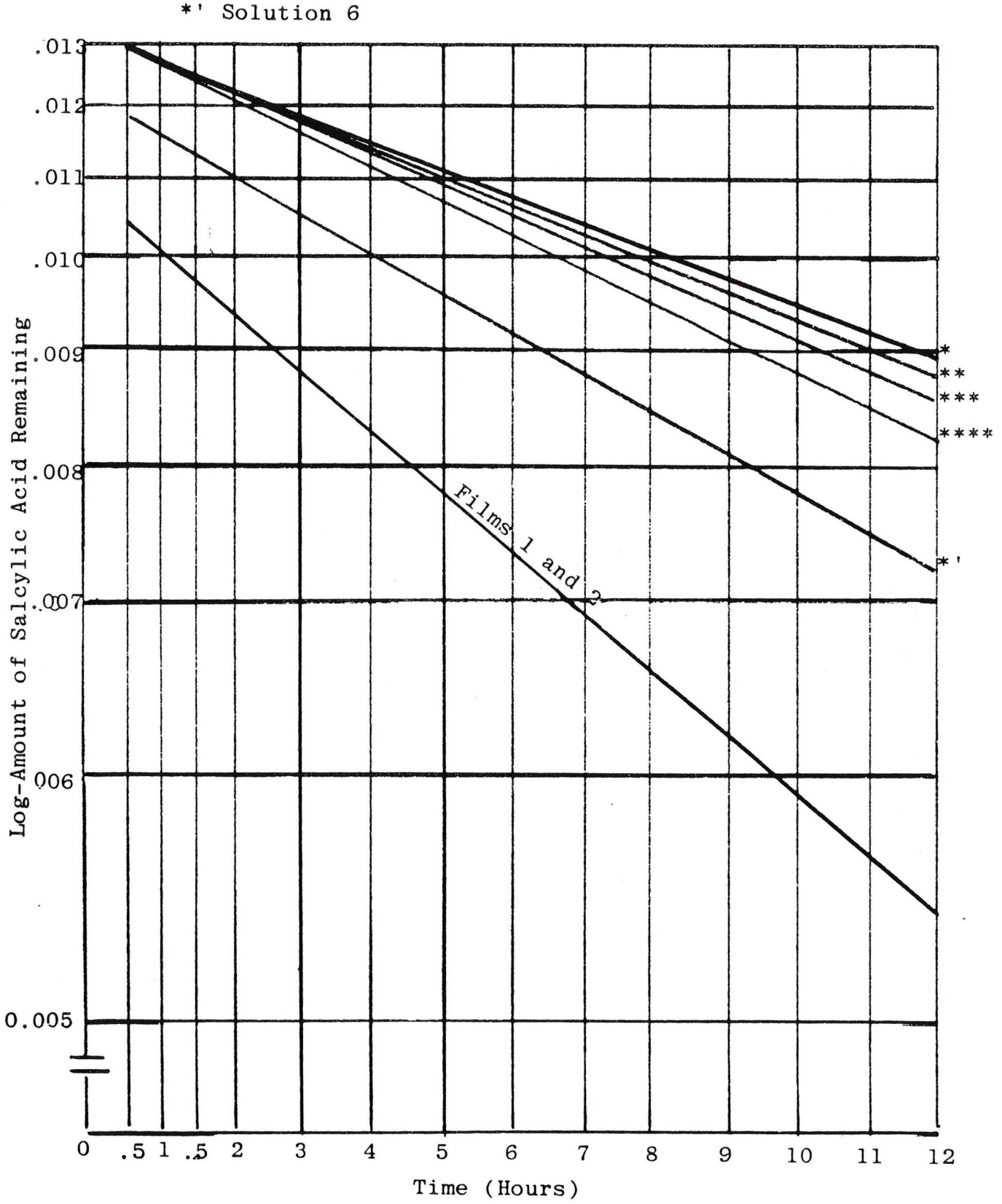

Figure 10. First Order, Release of Salicylic Acid.

Table XI. Q *versus* $t^{\frac{1}{2}}$ Treatment of Data for the Release of Salicylic Acid from Lanolin Alcohol and Ethyl Cellulose Films.

Film No.	Film Composition[a]	Release Rate Constant ($k \times 1000$) mg cm^{-2} $min^{-\frac{1}{2}}$	Lag Time min	Correlation Coefficient r
1	97.5 : 0 : 2.5	7.11	-6.47	0.992
2	92.5 : 5 : 2.5	7.82	-2.80	0.990
3	87.5 : 10 : 2.5	6.11	1.06	0.998
4	82.5 : 15 : 2.5	5.76	4.87	0.999
5	77.5 : 20 : 2.5	5.63	-0.15	0.993
6	72.5 : 25 : 2.5	6.34	0.97	0.997
7	67.5 : 30 : 2.5	6.46	6.43	0.999

[a]Proportion of lanolin alcohol, ethyl cellulose, and salicylic acid expressed as % w/w.

coefficients were quite high (0.990-0.999). Three film compositions, i.e., 1, 2, and 5, had negative lag times, but the values were relatively small. These negative lag times might be attributed to the immediate release of the drug present on the surface of the film, and the magnitude of the negative lag times might be related to the varying amounts of salicylic acid present on the film surface. The calculated release rate constant represents the steady-state region. The variation of rate constant as a function of the film composition is shown in Table XI and Figure 10. It was observed that the release rate increased at first with inclusion of ethyl cellulose and then declined sharply with increases in the ethyl cellulose concentration passing through a minimum value at about 15-20 percent of ethyl cellulose. Further increases in the concentration of ethyl cellulose (beyond 20% w/w) resulted in increased rate of drug release, with a tendency to level off at about 30 percent ethyl cellulose concentration.

During the first-order treatment of data, the correlation coefficients were high (0.978-0.994) but were not as high with the Higuchi model (0.990-0.999). All of the film compositions showed very high negative lag times (-62.8 to -149.1). These highly negative lag times might suggest significant release and dissolution of the drug from the film surface immediately upon contact with the dissolution medium. The release data, however, do not support this

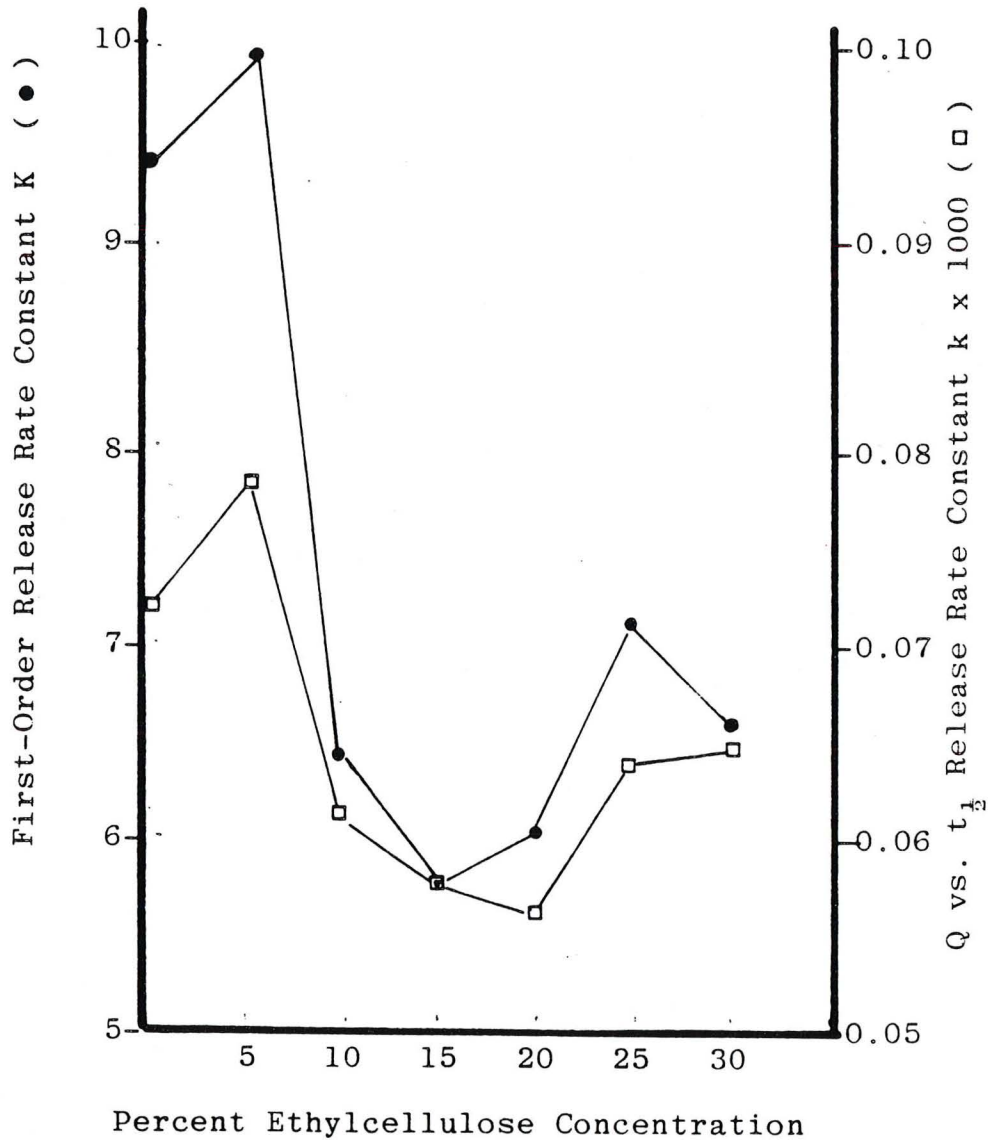

Figure 11. Effect of Vehicle Composition on Release Rate

interpretation (Tables III - IX). The plot of first-order rate constant versus the film composition (Figure 10) showed an analogous profile to that depicted by Higuchi model. This plot also revealed the minimum K value for films with about 15-20 percent ethyl cellulose concentration.

In the case of the first-order treatment, an initial curvature effect (Figure 9) was observed in the plot, suggesting that the initial release rate was much faster than the steady state region. This effect was not visible in the Q versus $t^{\frac{1}{2}}$ treatment (Figures 3-9). The high negative lag times, comparatively lower correlation coefficients and the initial curvature effect in the plot, all appear to discount the first-order relationship.

The high correlation coefficients, low lag times and linear plots for the Q versus $t^{\frac{1}{2}}$ treatment strongly suggest that the unidirectional release of salicylic acid from the lanolin alcohol-ethyl cellulose films follows Higuchi's diffusion-controlled granular matrix model.

Effect of Stirring Rate

The effect of stirring rate or agitation was studied as part of this study to delineate the primary process controlling drug release. The film containing 82.5 percent lanolin alcohol and 15 percent ethyl cellulose and 2.5 percent drug (Film No. 4) was selected and the release rates were examined at stirring speeds of 20, 30, 40, 50, and 60 revolutions per minute. The experiments were carried

out in the dissolution apparatus described earlier (Figure 1).

The data obtained in the present study were analyzed by both first-order method and the Q *versus* $t^{\frac{1}{2}}$ method. The release rate constants in both cases represent the steady state region. These results are shown in Table XII. The plot of release rate constants *versus* the stirring speeds is shown in Figure 11. It may be seen that the increases in the agitation speed resulted in higher release rates.

Wurster's (26) empirical relationship between rate constant and agitational speed has been shown to hold for dissolution of drugs. Equation No. 7 predicts a value of unity for the exponent, b

$$K = a\,(N)^{b} \qquad \text{Eq. 7}$$

where:

K = a reaction rate,

a = constant,

N = stirring or agitation rate, and

b = constant

for diffusion-controlled dissolution of drugs. The calculated value of b(0.427) fell considerably short of that. Two factors might account for this divergence:

(i) The diffusion of drug molecules from the film matrix is probably a considerably more complex process than dissolution of drug from tablets; and

Table XII. Effect of Stirring Rates on the Release of Salicylic Acid from Lanolin Alcohol-Ethyl Cellulose Films.

Film No.	Film Composition[a]	Stirring Speed rpm	First-Order, K min^{-1}	Q vs $t^{\frac{1}{2}}$ k x 1000 units
4	82.5 : 15 : 2.5	20	0.045	5.29
4	82.5 : 15 : 2.5	30	0.046	5.24
4	82.5 : 15 : 2.5	40	0.057	5.76
4	82.5 : 15 : 2.5	50	0.060	6.10
4	82.5 : 15 : 2.5	60	0.072	6.61

[a]Proportion of lanolin alcohol, ethyl cellulose and salicylic acid expressed as percent w/w.

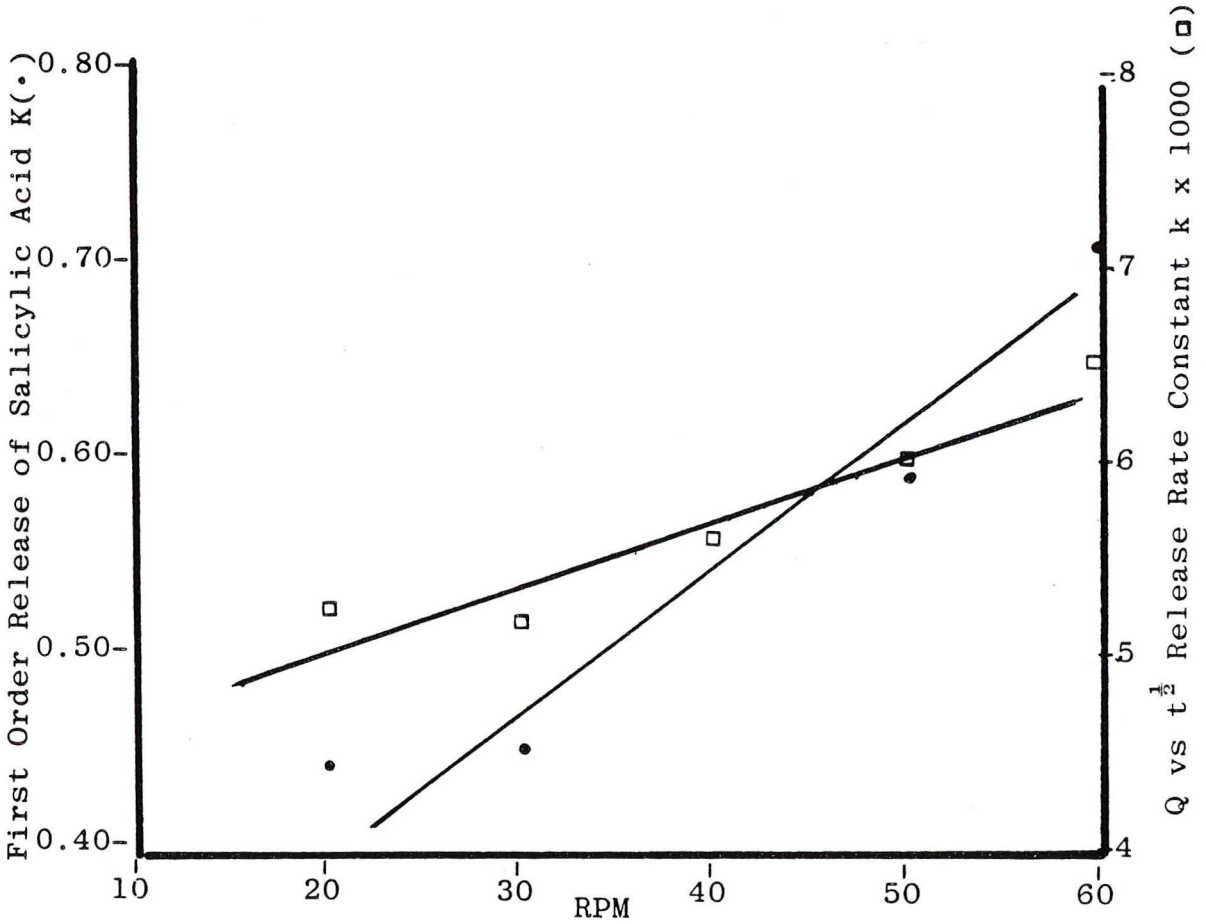

Figure 12. Correlation Between Drug Release and Stirring Rate

(ii) The range of agitational speeds studied in the investigation is relatively narrow.

Wurster's empirical relationship has been shown to hold over relatively wider range of speeds.

Further studies into this aspect are necessary to arrive at a more definitive conclusion.

Clinical Potential

The keratolytic properties of salicylic acid have been utilized mostly for the treatment of acne and the removal of warts and corns. The design and development of a long acting drug delivery system for such a drug should, therefore, include consideration of onset of action, rate of drug delivery to the site, and duration of action, besides other factors.

The film systems examined in this study are capable of providing prolonged release. On the basis of the data obtained, film number 2 would be expected to have the quickest onset and the fastest rate of release of all the films examined, while films with 15 - 20% ethyl cellulose would provide slow release. Proper selection of a film composition, however, must await precise determination of the rate of availability of salicylic acid required to produce a clinically significant effect and the duration of contact desired to achieve therapeutic benefit. Consequently, the amount of salicylic acid incorporated in these films may have to be adjusted to meet the desired criteria.

SUMMARY AND CONCLUSION

During the present investigation, the *in vitro* release of salicylic acid from seven film-forming vehicles containing varying proportions of lanolin alcohol and ethyl cellulose was investigated. The release studies were conducted with salicylic acid as the model drug suspended in the film matrix. The effects of change in the vehicle composition on the release profile were examined and the effects of variation in rates of agitation on one film were also studied.

The results of this investigation revealed that Higuchi's diffusion-controlled matrix model was an accurate representation of the mechanism of release prevalent here. The release rate constant was shown to increase initially with inclusion of ethyl cellulose and then to decline sharply as the ethyl cellulose concentration was increased, reaching a minimum value at about 15-20 percent of ethyl cellulose. Further increases in the concentration of ethyl cellulose (beyond 20 percent) increased the rate of drug release with a tendency to level off at about 30 percent ethyl cellulose concentration.

The effect of stirring rate on the release rate constants showed that the rates of release of salicylic acid increased with increases in the stirring rate.

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