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Keyphrases

Amines–spectroscopy review
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Mass spectrometry

Research Articles

Role of Wetting on the Rate of Drug Release from Inert Matrices

By PARVINDER SINGH*, SAURABH J. DESAI*, ANTHONY P. SIMONELLI, and WILLIAM I. HIGUCHI

This investigation has shown that matrix permeability and rates of permeation of the matrix by the solvent can individually limit drug release rates. This was found to be a function of the pore size distribution of the matrix and the permeation pressure of the release media defined by its surface tension and contact angle. Methods useful in separating the various roles of the above were developed and are presented. They include the correlation and use of external pressure, vacuum techniques, surface tension and contact angle measurements, and porosimeter data. The results have been used to develop models to illustrate the possible systems that can be encountered. Concepts such as rates of pore permeation, varying solubility dependence, and tortuosity are developed and applied to these models.

PREVIOUS release studies have indicated that the polyethylene matrix gave excellent results in the presence of surfactant (1). The experiments in water, however, gave comparatively poor results as release rates were very slow and apparent tortuosities very high. It was speculated at that time that polyethylene was hydrophobic in nature and that wetting was not fully achieved.

Studies involving the effect of increasing concentrations of dibasic potassium phosphate on salicylic acid release from polyethylene matrices surprisingly showed no rate increase due to potassium phosphate even though the solubility increased by a factor of 45. There was, however, a dramatic rate increase in the presence of surfactant, even though the solubility remained constant.

These studies prompted this investigation in order to further clarify the possible mechanisms which can be operative under various conditions.

EXPERIMENTAL

Release Rate Determinations—The general procedure used for investigating the release rates has been previously described (2). It was necessary, however, to redesign the apparatus to allow the pressure to be kept constant at different pressures, as illustrated in Fig. 1.

A water-jacketed (C) glass conical flask with 2

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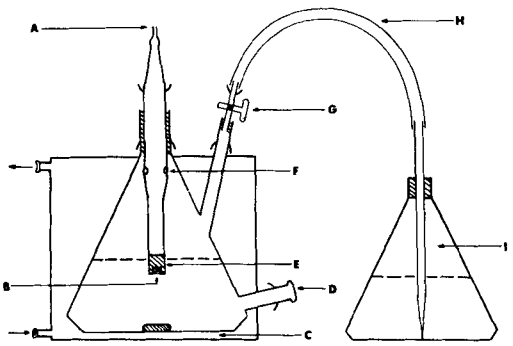

Fig. 1—Schematic diagram of the apparatus used to study release rates under positive net pressures.

side arms was used for these experiments. The tablet was mounted on a holder with a ground-glass joint to fit into the ground-glass necked conical flask. The lower part of the tube (E) was sealed to prevent hydrodynamic flow during the pressure experiments. The holder (A) was designed so that vacuum or pressure could be applied to its upper end and transmitted to the surface of the solvent by means of the lower openings (F).

Pressure was applied and maintained at a constant level by utilizing a tank of compressed nitrogen. To maintain a closed system when it was charged with solvent under vacuum conditions, the side arm (G) was connected by means of a tube (H) to a flask containing the solvent. Before vacuum was applied, the connecting tube (H) and stopcock bore (G) were completely flushed with the solvent to remove any entrapped air. A vacuum pressure of less than 0.1 mm. Hg was obtained to make certain all air was removed from the matrix before the solvent from the flask (I) was allowed to flow into the apparatus. The length of the tablet holder was sufficient to ensure that the tablet was not exposed to air, but was completely immersed in solvent prior to the release of the vacuum.

It should be emphasized that once the matrix is immersed in solvent, air can no longer enter the matrix, and a pressure differential of 1 Atm. remains on the system even though the vacuum is eliminated. Since this net solvent pressure of penetration is given by $P_{net} = P_{vacuum} + P_{external}$ it can be readily seen that each specific pressure can be achieved by many combinations of the above. For obvious technical reasons, however, the vacuum contribution was restricted to 1 Atm. pressure.

Samples were withdrawn using a 10-ml. syringe which was injected through a self-sealing multidose vial stopper (D). The sample outlet was placed so that it was always below the solvent level to prevent a change in pressure due to loss or addition of air to the system whenever fluid was removed or added.

Contact Angle Measurements—Contact angle measurements were made for all experiments reported in this study. The solutions used were made by dissolving enough drug in the solvent to provide a concentration equivalent to approximately 95% of its solubility in order to approximate the conditions existing in the matrix at the solvent front boundary.

The tablet was placed on an adjustable platform kept perfectly horizontal by means of a leveling device. A small drop of the test solution was placed on the tablet surface, and the contact angle was measured using a Gaertner[1] telemicroscope fitted with a protractor eyepiece and an objective lens (magnification 5×). The entire unit was mounted on an adjustable stand. The hairline of the protractor eyepiece was adjusted to coincide with the flat surface of the tablet, and the intersection of the two hairlines was fixed at the solid–liquid–air triple interface. With this baseline adjustment made, the reading on the protractor eyepiece was recorded. The eyepiece was then rotated until the horizontal hairline was made tangent to the liquid–air interface at the table surface. The angle difference between these two readings was equal to the contact angle used in these studies. These contact angles are not the contact angles in the classical sense because of the presence of capillaries and other heterogeneities on the surface. It should therefore be noted that the term contact angle, as referred to in the text, is in reality only an apparent value. However, it should also be emphasized that these measurements, and not the classical ones, are valid and provide a useful method of comparing the wetting tendencies of the different systems studied.

Other Parameters—The solubilities and diffusion coefficients were measured using methods reported earlier (3). The surface tension measurements were carried out using the Wilhelmy plate method (4). The solutions used were again made by dissolving enough drug in the solvent to provide a concentration equivalent to approximately 95% of its solubility.

RESULTS AND DISCUSSION

Water and Surfactant Data—As mentioned in the introduction, the release profile of salicylic acid from the polyethylene matrix was studied utilizing a wide range of dibasic potassium phosphate concentrations, thereby providing increasing solubilities. The results of these studies, along with the apparent solution–tablet contact angles, are presented in Table I. The expected slopes listed in the last column of Table I have been calculated using the 0.01 *M* K_2HPO_4 slope as the reference, and then calculating the release rates for the dibasic potassium phosphate systems based on the predicted square root of solubility dependence (2). It is clear that this dependence is not observed, as the experimental rates for the various systems studied are relatively constant and do not show the predicted five- to six-fold increase. This strongly indicates that the diffusion model is not applicable under the above conditions.

Examination of Table I further shows that for all these dibasic potassium phosphate solutions, the contact angles are extremely high (>90°), and reflect a nonwetting solid–liquid interface. This suggests that drug release may possibly be controlled by the rate of solvent penetration.

If this is true, the release rates should be considerably increased by reducing the contact angle to below 90°. Studies in water and 0.01% dioctyl

[1] Gaertner Scientific Corp., Chicago, Ill.

TABLE I—PARAMETERS CHARACTERIZING THE SALICYLIC ACID–POLYETHYLENE SYSTEM IN VARYING CONCENTRATIONS OF DIBASIC POTASSIUM PHOSPHATE IN WATER

Solvent, moles K_2HPO_4 in H_2O	θ, °	cos θ	γ, dyne/cm.	γ cos θ	$C_s \times 10^2$, Gm./ml.	$Q/t^{1/2} \times 10^5$ Exptl. Gm./sec.$^{1/2}$	$Q/t^{1/2} \times 10^5$ Expected[a] Gm./sec.$^{1/2}$
0.01	95	−0.105	60.0	−6.30	0.43	1.22	1.22
0.05	95	−0.105	59.3	−6.20	1.00	1.28	1.81
0.10	98	−0.156	59.0	−9.20	1.60	1.32	2.45
0.25	99	−0.174	58.3	−10.14	3.72	1.22	3.61
0.50	99	−0.174	57.0	−9.92	6.70	1.10	4.83
1.00	97	−0.139	56.7	−7.88	11.5	1.06	6.31

[a] The experimental slope with 0.01 *M* K_2HPO_4 used as reference.

TABLE II—PARAMETERS CHARACTERIZING THE SALICYLIC ACID–POLYETHYLENE SYSTEM IN VARYING CONCENTRATIONS OF DIBASIC POTASSIUM PHOSPHATE IN AOT SOLUTIONS

Solvent moles K_2HPO_4	% AOT	θ, °	cos θ	γ, dyne/cm.	γ cos θ	$C_s \times 10^2$, Gm./ml.	$Q/t^{1/2} \times 10^5$ Exptl. Gm./sec.$^{1/2}$	$Q/t^{1/2} \times 10^5$ Expected Gm./sec.$^{1/2}$	τ, Exptl.
...	...[a]	92	−0.052	60.4	−3.14	0.26	0.53	2.20	107
...	0.01	56	0.559	38.1	21.30	0.26	1.08	2.20	25
...	0.05	0	1.00	30.4	30.40	0.27	3.00	2.20	3.3
0.01	0.01	31	0.857	31.3	26.82	0.43	3.49	2.81	4.1
0.01	0.05	0	1.00	26.3	26.30	0.44	3.40	2.81	4.2
0.05	0.01	29	0.875	27.5	24.06	1.00	4.40	4.28	5.9
0.05	0.05	0	1.00	26.4	26.40	1.04	4.42	4.28	5.9
0.10	0.01	32	0.848	27.6	23.41	1.75	5.42	5.63	6.6
0.25	0.01	32	0.848	26.6	22.56	3.78	8.30	8.30[b]	6.0

[a] Data in this row refer to water as the solvent. [b] The experimental slope with 0.25 *M* K_2HPO_4 and 0.01% AOT used as reference.

sodium sulfosuccinate[2] (AOT) confirmed this. Release rate studies of 20% salicylic acid from a polyethylene matrix were then carried out in varying concentrations of dibasic potassium phosphate solutions containing 0.01% AOT.

Examination of the 0.01% AOT results shown in Table II demonstrate the desired increase in rates with increasing solubility. The rate shown by the solvent not containing any dibasic potassium phosphate, however, was considerably lower than expected. At the same time there was a seemingly concomitant higher contact angle and surface tension.

To investigate this effect further, the above studies were repeated using 0.05% AOT, and these results are also tabulated in Table II. Interestingly, the rates in dibasic potassium phosphate solutions did not change, but the water data show a dramatic increase. A comparison of the rates and their corresponding contact angles and surface tensions clearly shows a strong relationship. The rate was greatly increased when the contact angle was lowered from a value greater than 90° to either 56° or 31°. The surface tensions were also correspondingly lowered. The slope was not changed, however, when the angle was lowered from 31° to essentially 0°, but dramatically increased when the angle was lowered from 56°. At the same time the surface tension also remained constant when the contact angle was lowered from 31°, but decreased when the angle was lowered from 56° to 0°. This implies that the rate is either controlled by the surface tension or that an effective maximum wetting effect is achieved at a contact angle between 31° and 56°. This observation is also implied by the fact that only the solutions of contact angles equal to or greater than 56° significantly show slower rates. Lastly, the apparent tortuosity values also are reasonable for all solutions but those showing contact angles of 56° or greater, as seen by the water data showing values of 107, 25, and 3.3.

The nonsurfactant solutions of Table I, on the other hand, had high contact angles and surface tensions, indicating that in those systems solvent penetration into the matrix may have been the reason for nonconformity to the diffusion model.

It would be highly desirable at this point to determine the individual roles that surface tension and contact angles play in this regard. A study in which contact angle can be continuously varied while a relatively constant surface tension is maintained could shed light on these roles, and in this way the two effects could be separated. Polysorbate 80[3] provided such a system. A series of varying concentrations of polysorbate 80 was selected so that the contact angle decreased from 97° to 46° with little change in surface tension, with the hope of obtaining a varying rate of solvent penetration. Table III shows that the release rates of salicylic acid considerably increase with increasing concentration of polysorbate 80. Figure 2 and Table III indicate that the experimental rates show a strong relationship with the corresponding contact angle, but are relatively independent of the surface tension. A large effect is also demonstrated regarding the apparent tortuosities which decrease exponentially.

This strongly suggests that the contact angle or degree of wetting is more important than surface

[2] Marketed as Aerosol OT by the American Cyanamid Co., Wayne, N. J.

[3] Marketed as Tween 80 by Atlas Chemical Industries, Wilmington, Del.

TABLE III—PARAMETERS CHARACTERIZING THE SALICYLIC ACID–POLYETHYLENE SYSTEM AS A FUNCTION OF POLYSORBATE 80 CONCENTRATION

Solvent, 0.1 *M* K_2HPO_4 in % Polysorbate	$C_s \times 10^2$, Gm/ml.	θ, °	cos θ	γ, dyne/cm.	$\gamma \cos \theta$	$Q/t^{1/2} \times 10^5$ Gm./sec.$^{1/2}$	τ
0	1.69	98	−0.156	59.0	−9.20	1.32	111
0.001	1.62	97	−0.139	42.6	−5.92	1.60	75.8
0.005	1.62	93	−0.070	44.0	−3.08	1.94	51.6
0.01	1.62	87	+0.052	38.4	2.00	2.22	39.4
0.05	1.63	59	+0.515	38.2	19.67	4.26	10.7
0.10	1.62	46	+0.695	40.0	27.80	5.20	7.2
0.01% AOT	1.75	32	+0.848	27.6	23.41	5.42	6.6

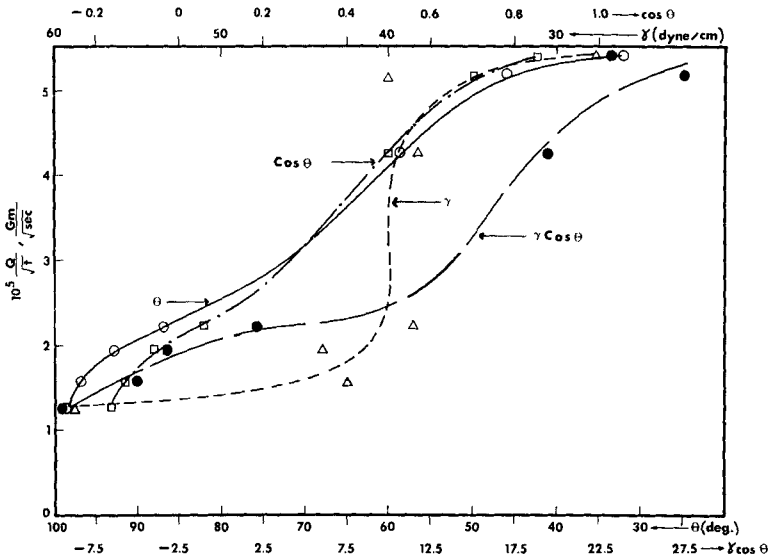

Fig. 2—Relationship between the release rates and the variables controlling penetration of the matrix.

tension in determining solvent penetration. In these studies, however, the surface tension was already considerably lower (40 dynes/cm.). The studies in water, listed in Table I, on the other hand, are involved with a high surface tension in addition to a high contact angle, and in this situation the contact angle may not be the more important factor. The contact angle effect, independent of the surface tension effect, can be studied by using a matrix which shows a moderate contact angle in water. It was found that a matrix made of 70% polyvinyl chloride (PVC) and 30% polyethylene satisfied these requirements, as it exhibited a wetting contact angle (~70°) in the presence of nonsurfactant solutions. The study of Table I, *i.e.*, by varying the solubility using dibasic sodium phosphate, was then repeated using this matrix. The data are tabulated in Table IV and show that despite the presence of high surface tension of a nonsurfactant solution, the rate is increased with increasing solubility, and low tortuosity values are obtained. This shows that the degree of wetting is the important factor controlling matrix permeability and is the reason that the solubility effect was not observed in the experiments of Table I.

TABLE IV—PARAMETERS CHARACTERIZING THE SALICYLIC ACID–POLYVINYL CHLORIDE–POLYETHYLENE SYSTEM IN VARYING CONCENTRATIONS OF DIBASIC SODIUM PHOSPHATE IN WATER

Solvent, moles Na_2HPO_4 in H_2O	$C_s \times 10^2$, Gm./ml.	$Q/t^{1/2} \times 10^5$ Exptl., Gm./sec.$^{1/2}$	$Q/t^{1/2} \times 10^5$ Expected., Gm./sec.$^{1/2}$	τ Exptl.
0	0.26	2.57	2.57[a]	6.0
0.10	1.00	6.00	6.37	6.8
0.25	3.70	10.6	9.70	5.0
0.50	6.60	12.6	13.0	5.8
0.75	9.10	13.0	15.2	7.2
1.00	11.5	13.5	17.1	8.1

[a] Reference.

Pressure Studies as a Function of Solubility—The question of whether the apparent wetting dependence is an all-or-nothing effect or whether it is a rate effect, however, has yet to be answered.

These roles of solvent penetration can be further investigated by applying external pressure to the system as its permeation rate will increase with an increase of external pressure on the solvent. In this way the role of the rate of solvent penetration can be illustrated.

With the above in mind, experiments utilizing water as the release medium were carried out. The results tabulated in Table V show the feasibility of this method as the rates indeed are significantly increased and the apparent tortuosities decreased by an increase in pressure, despite a constant solubility, surface tension, and contact angle. As a matter of fact, the release rates and tortuosities obtained at higher pressures were comparable to those obtained from the same system (no K_2HPO_4) in the presence of surfactant (see Table II), and

TABLE V—EFFECT OF PRESSURE ON THE RELEASE RATES AND CORRESPONDING TORTUOSITIES OF THE SALICYLIC ACID–POLYETHYLENE SYSTEM IN WATER

Net Pressure, p.s.i.	$Q/t^{1/2} \times 10^5$ Gm./sec.$^{1/2}$	τ
0	0.53	107
10	0.90	37.1
15	0.98	31.3
20	1.36	16.2
25	1.90	8.3
30	2.10	6.8
40	2.50	4.8

TABLE VI—COMPARISON OF THE EFFECTS OF PRESSURE ON THE RELEASE RATES OF THE SALICYLIC ACID–POLYETHYLENE SYSTEM AS A FUNCTION OF SOLUBILITY IN WATER

Net Pressure, p.s.i.	Exptl. Slope $\times 10^5$ Gm./sec.$^{1/2}$ 0 M 0.26[a]	0.05 M 1.00[a]	0.10 M 1.60[a]	0.25 M 3.72[a]
0	0.53	1.28	1.32	1.22
10	0.90	...	1.38	...
15	0.98	1.18	1.30	1.36
20	1.36	1.69	2.14	2.80
25	1.90	2.75	3.50	4.15
30	2.10	2.90	4.30	5.92
40	2.50	3.43	4.05	6.70

[a] Solubility in Gm./ml. $\times 10^2$.

suggest that at higher pressures a solubility effect should be observed.

This was substantiated by obtaining the release rates of salicylic acid in a series of release media at 40 p.s.i. external pressure. Data presented in the lowest row of Table VI show that the rate is increased with an increasing concentration of dibasic potassium phosphate, and thereby show that the solubility dependence is observed when 40 p.s.i. is applied to the aqueous system but is not observed at atmospheric pressure (Table I).

At this point it may be worthwhile to try to delineate the role played by solvent penetration in eliminating the solubility effect in terms of a hypothetical model utilizing an increasing net permeation pressure. This net permeation pressure, P_n, is defined as

$$P_n = P_p - P_i \qquad \text{(Eq. 1)}$$

where P_i is the internal pressure resisting solvent penetration, P_p is the permeability pressure $= P_w + P_e$; P_w is the pressure due to wetting, and P_e is the external pressure applied to the system.

In this model, the net permeation pressure is initially negative. This can be done by applying vacuum to a system previously loaded with solvent under atmospheric pressure. The entrapped air then causes an internal pressure which pushes solvent out of the matrix. This prevents solvent penetration and yields no drug release (see Fig. 3, top left).

This condition will persist until the net pressure is positive, at which point solvent will begin to penetrate (Fig. 3, bottom left). At low positive net pressures, however, the solvent rate of contact with solid drug is slower than the rate of drug diffusion, resulting in a subsaturated solution at the moving solvent boundary. As long as this condition persists, the release rate of the drug will

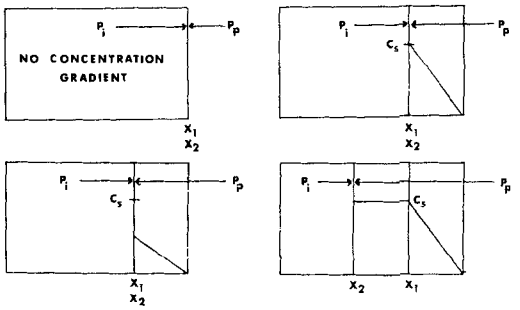

Fig. 3—Hypothetical model describing the conditions existing under a varying net pressure on the system.

be independent of the solubility. As the net positive pressure is further increased, the condition will be reached when the solvent rate of contact with solid drug becomes equal to the rate of drug diffusion (Fig. 3, top right). At this point no further increase in the rate of drug release will occur with further increase in net pressure. The solvent front, however, must continue to penetrate the matrix at a proportionally higher rate (Fig. 3, bottom right). This means that two boundaries must exist at net pressures above the minimum critical value—a solvent boundary, and a solid drug boundary, enclosing a region containing a saturated solution in equilibrium with its solid drug.

This model can be further clarified by exploiting the expression for the steady state at the solid drug–liquid interface, as the rate of drug solution must be equivalent to the rate of drug diffusion. The rate of solution is given by the amount of drug per unit volume of tablet, A, times the rate of the solid drug–liquid boundary movement, dx_1/dt. The rate of diffusion is given by the effective diffusion coefficient, $D\epsilon/\tau$, times the concentration gradient, dC/dx or Cx_1/x_1, where Cx_1 is the concentration of drug at the solid drug boundary. Then:

$$A \frac{dx_1}{dt} = \frac{D\epsilon}{\tau} \frac{Cx_1}{x_1}$$

(See Fig. 3, bottom right.) For the diffusion model to be operative the rate of permeation of the solvent must be equal to or greater than the rate of solid drug boundary movement, and permit a buildup of Cx_1 to the solubility level. The above equation can be rearranged to yield:

$$\frac{dx_1}{dt} = \frac{D\epsilon}{A\tau} \cdot \frac{Cs}{x_1} = \text{min. solvent permeation rate} \qquad \text{(Eq. 2)}$$

This shows that the minimum rate of penetration must increase as the porosity, the diffusion coefficient, or solubility of drug is increased, but it may permeate more slowly with a higher tortuosity, higher percentage of drug embedded in the matrix, and as penetration proceeds.

In an effort to verify the requirements of an increasing permeation rate with increasing solubility, the experiment conducted at 40 p.s.i. was repeated as a function of lower pressures, and the results are tabulated in Table VI and plotted in Fig. 4. Each curve seems to support the previous discussion as the rates of drug release appear to increase and

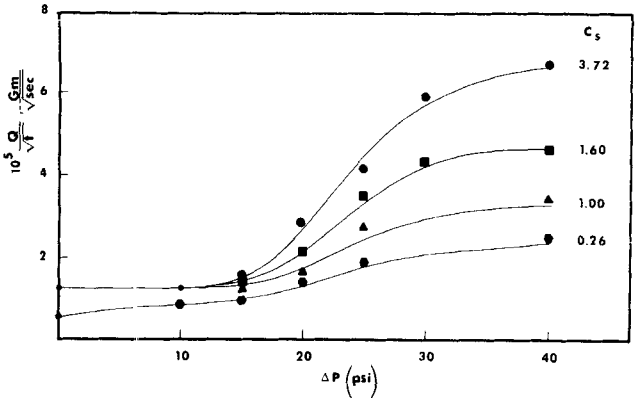

Fig. 4—Comparison of the effect of pressure on the release rates of the salicylic acid–polyethylene system as a function of solubility in water. Solubility is expressed in Gm./ml. × 10^2. (See Table VI.)

then plateau with an increased rate of solvent penetration. Furthermore, the plateau appears to require a higher rate of solvent penetration as drug solubility increases.

The family of curves in Fig. 4, however, also displays characteristics not predicted by the previous discussion. The rates of drug release do not increase with increasing solvent penetration rates until a net pressure of about 15 p.s.i. is reached, although the previous discussion indicated that this should begin at 0 p.s.i. This implies that an all-or-nothing effect is predominant below 15 p.s.i., but that above 15 p.s.i. the rate of penetration is controlling.

Pore Size Distribution—The initial plateau region of Fig. 4 displaying the all-or-nothing pressure effect can be explained if one includes the pore size distribution in the proposed model. This can be done by using the Washburn equation (5) which relates pore diameter to the solvent pressure required to initiate its penetration. Then,

$$P_i = -\left(\frac{4}{d_i}\right)\gamma \cos\theta \qquad \text{(Eq. 3)}$$

where P_i is the minimum net pressure required to achieve penetration, γ is the surface tension of the solvent, θ is the contact angle of the solid–solvent interface, and d_i is the minimum pore diameter penetrated by solvent at pressure P_i.

The above equation is valid only for contact angles greater than 90° (which is true of the system under consideration) and indicates that the all-or-nothing effect may be due to solvent impenetrability of certain pores present in the matrix which are below minimum diameter. This equation indicates that the pressure opposing solvent penetration is proportional to the product of the surface tension and the cosine of the wetting angle. Examination of this product, listed in Table I, indicates that all solutions are under the influence of a force opposing solvent penetration. Examination of Table II shows, however, that there is a positive permeation force manifested. More enlightening, on the other hand, is a re-examination of Table III, which shows that the above product ranges from an opposing penetration force to one of strong permeation. The plot in Fig. 2 strongly suggests the possibility that the presence of a restrictive pore distribution is operative in Fig. 4.

Figure 4 shows that the range of critical pressures begins at 20 p.s.i. and continues to a point past 40 p.s.i., indicating that there is a range of pore size which are not penetrated at a lower pressure. The distribution of pore sizes limiting penetration corresponding to the above range of critical pressures was calculated using the Washburn equation and found to range from 0.32 μ down to a value less than 0.12 μ. The average pore size of the above distribution was estimated to be 0.24 μ, using 25 p.s.i. as its critical pressure, which corresponds to the average point of inflection on the rising portions of all Fig. 4 curves. Porosimeter (6) data were obtained and indicated that the pore size distribution ranged from 40 μ down to below 0.06 μ. There was, however, a sharp peak beginning at 2 μ extending to 0.3 μ with its maximum at 0.8 μ. It was felt that this was in very good agreement with the hypothesis, if one considers that first, the porosimeter yields essentially data at equilibrium, whereas the pressure studies are rate data. One would therefore expect that the critical pressure would be increased, and therefore its apparent pore size distribution would be exhibited at lower pore sizes. Second, there may be distortion of the pores due to compression of preceding empty lumen occurring with the porosimeter at the higher pressures used. Last, the effective diameter (7) of a tortuous pipe will be less than the true diameter when considering hydraulic flow.

To further investigate the phenomenon, 0.005% polysorbate was added to the release media and release studies were again made as a function of the pressure. The contact angle for this system decreased from 98° to 93°, and the surface tension from 59 dynes/cm. to 44 dynes/cm. This means that the critical pressure should be lowered by a large factor of 0.6 (from the Washburn equation). The results of these studies are presented in Table VII and Fig. 5, and a large shift is seen supporting

Table VII—Comparison of the Effects of Pressure on the Release Rates of the Salicylic Acid–Polyethylene System as a Function of Solubility in 0.005% Polysorbate 80 Solution

Net Pressure, p.s.i.	Exptl. Slope × 10^5 Gm./sec.$^{1/2}$ 0 M 0.26[a]	0.05 M 1.00[a]	0.10 M 1.62[a]	0.25 M 3.74[a]
0	1.64	2.05	1.94	2.32
5	2.50	3.52	4.10	4.92
10	2.76	4.10	5.20	6.40
15	2.70	4.10	5.05	7.60

[a] Solubility in Gm./ml. × 10^2.

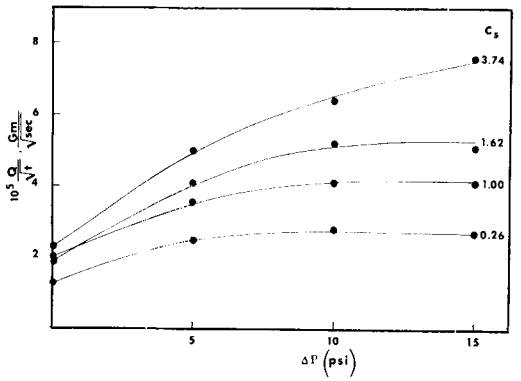

Fig. 5—Comparison of the effects of pressure on the release rates of the salicylic acid–polyethylene system as a function of solubility in 0.005% polysorbate solutions. Solubility is expressed in Gm./ml. × 10^2. (See Table VII.)

the previous discussion. Comparable release rates are seen in Figs. 4 and 5, although for the system containing polysorbate they occur at about 15 p.s.i. lower than in the absence of polysorbate. This implies that the addition of 0.005% polysorbate is equivalent to an application of 15 p.s.i.

This above observation can be quantitated by using the Washburn equation (Eq. 3) to determine the external pressure required for penetration under both water and surfactant conditions. Obviously, the difference will yield the contribution due to the addition of 0.005% polysorbate to the solution. Then,

$$P_{\text{polysorbate contribution}} = P_{\text{polysorbate}} - P_{\text{water}} = -\frac{4}{d}(\gamma_{PSO}\cos\theta_{PSO} - \gamma_{H_2O}\cos\theta_{H_2O})$$

and this yields a value of 10 p.s.i., which agrees very well with the above value.

The degree of the solubility dependence as a function of the pressure exhibited in Figs. 4 and 5 prior to the maximum plateau can be determined from a plot of the rate of drug release *versus* the square root of solubility. For better comparison, however, the ordinate and abscissa can be normalized by using the release rates and the corresponding solubility value in 0.25 *M* K_2HPO_4 solution for each pressure. Ideally, all curves should be superimposable with a slope of one, as the effect of all other factors (such as porosity, tortuosity, drug percent, and diffusion coefficient) are eliminated by taking a ratio, yet Figs. 6 and 7 show that the slopes are less than one and increase with an increasing rate of solvent penetration. Drug unavailability cannot be used to explain the results as the total amount of drug released showed that there was enough drug present to produce a saturated solution in the matrix. This indicates that there are complicating kinetic factors involved.

The Effect of Pressure Variation Under Wetting Conditions—If these factors are not dynamic in nature, there should not be pressure dependence of the release rates exhibited under wetting conditions. To test this point, two series of experiments were performed, one at a relatively high constant solubility level, 1.62 Gm./100 ml. (0.1 *M* K_2HPO_4), using a varying concentration of polysorbate solutions; and another at a relatively low constant solubility level, 0.26 Gm./100 ml. (H_2O), using a varying concentration of AOT solutions. The results of these experiments are tabulated in Tables VIII and IX, and are plotted in Figs. 8 and 9, respectively.

Both curves show that the release rates are not independent of pressure under these conditions. In addition, the application of external pressure and the permeation pressure due to wetting are evidently complementary, since with an increase in the permeation pressure (by increasing the wetting power of the release medium), less external pressure must be applied to achieve the maximum rate. In fact, the release rates no longer are dependent on the external pressure if the wetting power is sufficiently increased. The persistent pressure effect, even under wetting conditions, strongly reinforces the possibility that the partial solublity. dependence is due to complicating kinetic factiors These kinetic factors can be brought about by the presence of a complex distribution of pore sizes of which porosimeter data only showed two distri-

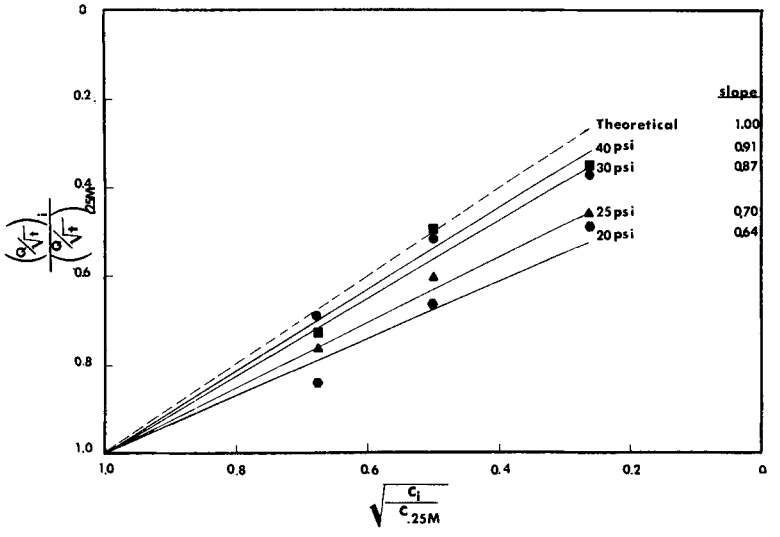

Fig. 6—Effect of increasing pressure on the observed solubility dependence for the same set of experiments as in Fig. 4, using 0.25 M as reference.

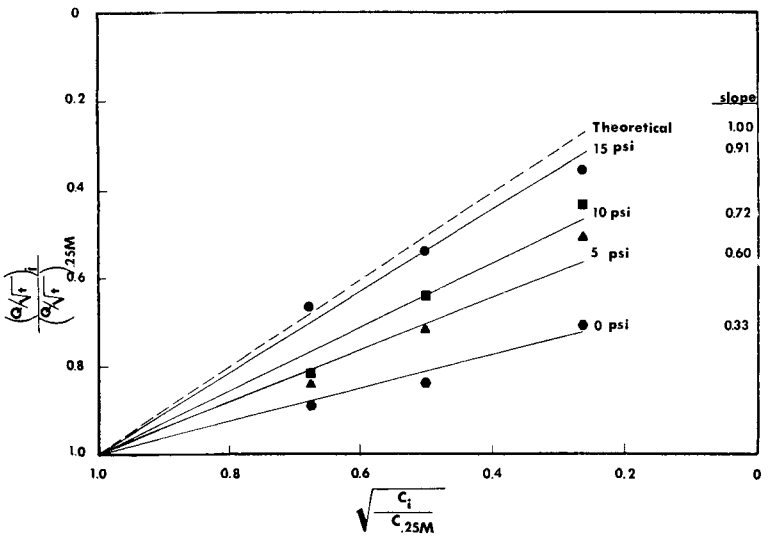

Fig. 7—Effect of increasing pressure on the observed solubility dependence for the same set of experiments as in Fig. 5, using 0.25 M *as reference.*

TABLE VIII—COMPARISON OF THE EFFECTS OF PRESSURE ON THE RELEASE RATES OF THE SALICYLIC ACID–POLYETHYLENE SYSTEM AS A FUNCTION OF THE CONTACT ANGLE IN POLYSORBATE SOLUTIONS

Net Pressure, p.s.i.	Exptl. Slope[a] × 10^5 Gm./sec.$^{1/2}$				
	0%[b]	0.005%[b]	0.01%[b]	0.05%[b]	0.10%[b]
0	1.32	1.90	2.22	3.80	5.20
5	1.36	4.10	4.54	5.20	6.00
10	1.38	5.20	5.50	5.95	5.90
15	1.30	5.05	5.50	5.95	5.95
Contact angle, $\theta°$	98	93	87	58	46
$\cos\theta$	−0.156	−0.070	0.052	0.530	0.695
γ, dynes/cm.	59.0	44.0	38.4	38.2	40.0
$\gamma\cos\theta$	−9.204	−3.080	1.997	20.246	27.800

[a] The solubility was maintained at 1.62×10^{-2} Gm./ml. [b] Percent polysorbate.

TABLE IX—COMPARISON OF THE EFFECTS OF PRESSURE ON THE RELEASE RATES OF THE SALICYLIC ACID–POLYETHYLENE SYSTEM AS A FUNCTION OF THE CONTACT ANGLE IN AOT SOLUTIONS

Net Pressure, p.s.i.	Exptl. Slope[a] × 10^5 Gm./sec.$^{1/2}$			
	0%[b]	0.005%[b]	0.01%[b]	0.05%[b]
0	0.53	1.00	1.08	3.00
15	0.98	1.63	2.30	2.92
30	2.10	2.40	2.60	...
40	2.50	2.67	2.76	...
Contact angle, $\theta°$	92	76	56	0
$\cos\theta$	−0.052	0.242	0.559	1.00
γ, dynes/cm.	60.4	42.0	38.1	30.4
$\gamma\cos\theta$	−3.141	10.164	21.298	30.400

[a] The solubility was maintained at 2.6×10^{-3} Gm./ml. [b] Percent AOT.

butions. Since all of the porosity was not accounted for, it is very likely that the unaccounted for porosity is composed of pores whose size distribution is so small it would require prohibitive pressures to detect. The higher resistance of these pores to flow, however, can greatly affect the rates of permeation and diffusion. These rates can also be complicated by other factors such as microenvironmental heterogeneities and contact angles which can exist throughout the matrix porosity.

Model Defining the Role of Solvent Penetration—It would be useful at this time to review the techniques and concepts that have been developed in this study, and show how they may be used to characterize various matrix systems.

It would appear, first of all, that one must consider kinetic as well as static factors. These include the degree of possible penetration which can range from matrix impermeability to one of complete permeability. The rate of permeation, on the other hand, can also be very important, and can be rate determining if too slow.

If one wishes to apply the results of this investigation to a particular inert matrix, however, one must be able to characterize each system, so that the variables can be identified which must be altered to obtain a desired drug release profile. The following discussion considers the different systems that can exist with the above in mind.

If incomplete penetration of the matrix occurs, the porosities used in the theoretical equations will obviously be too large, and consequently will yield

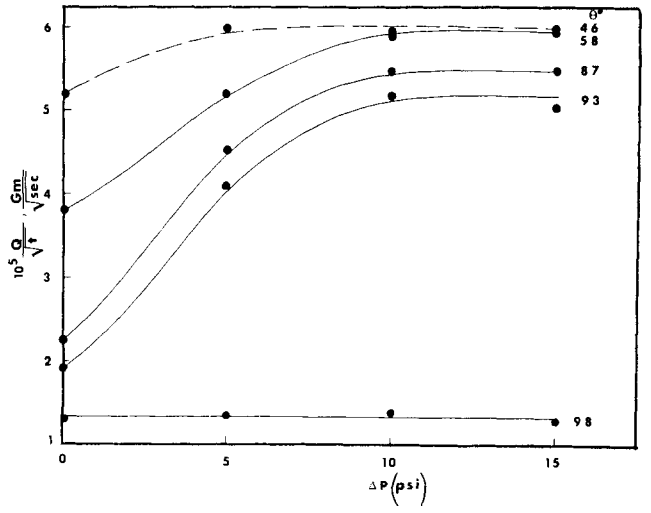

Fig. 8—Comparison of the effects of pressure on the release rates of the salicylic acid–polyethylene system as a function of the contact angle in polysorbate solutions. Solubility maintained constant at 1.6 × 10^{-2} Gm./ml. (See Table VIII.)

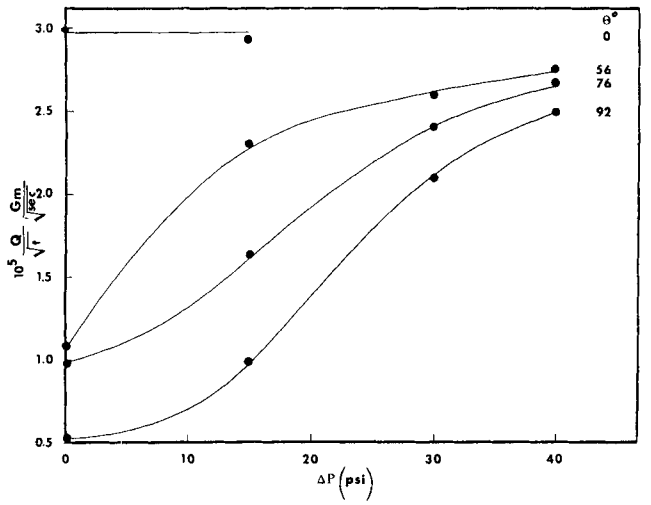

Fig. 9—Comparison of the effects of pressure in the release rates of the salicylic acid–polyethylene system as a function of the contact angle in AOT solutions. Solubility maintained constant at 2.6 × 10^{-3} Gm./ml. (See Table IX.)

abnormally high tortuosities. The rate of solvent penetration will strongly influence the characteristics exhibited by this system. For example, if the permeation rate is too slow, the release rate will be increased by either an increase in pressure or on addition of surfactant. The effect of pressure, however, may not be evident until a critical pressure is applied. This system is also characterized by an absence of a solubility dependence effect. These characteristics describe the salicylic acid release in water as shown by the effects of pressure and surfactant, tabulated in Tables II, III, V, and VI, and the solubility effect shown in Table I.

If the permeation rates, on the other hand, are sufficiently rapid, a solubility dependence will be exhibited. There also will be a concomitant decrease in the apparent tortuosity to an intermediate value. The pressure and surfactant studies will reveal the same behavior as the first case. These characteristics describe the salicylic acid release in 0.005% polysorbate solution as shown by the effects of pressure and surfactant in Table VIII and the solubility effect in Table VII. The appplication of a critical pressure was not necessary in this system.

If complete penetration of the matrix is accomplished, needless to say, only the rate of permeation of the solvent can be limiting. If it is too slow, no solubility dependence is found, both pressure and surfactant effects can be observed, and high apparent tortuosities will be present. This condition can be achieved if one utilizes a highly soluble drug in too low a percent in the tablet.

The rate of permeation, however, can be sufficiently rapid to manifest a solubility dependence, but not rapid enough to demonstrate it to the maximum. This system will be characterized by pressure and surfactant effects with intermediate values of apparent tortuosities. This description would appear to describe the salicylic acid release in 0.005% polysorbate solution, but this possibility is easily eliminated due to the high nonwetting contact angle. These characteristics, however, can be used to describe the release of salicylic acid in 0.005% AOT. The pressure and surfactant effects are shown in Table IX. The solubility dependence was not determined for this system, but examination of Fig. 9 leaves little doubt that a partial solubility dependence would be observed.

The ideal situation of complete penetration and

sufficiently rapid permeation rates, needless to say, will exhibit no pressure or surfactant effects, and yield a maximum solubility dependence with low tortuosities. These characteristics apply very well to salicylic acid release in 0.05% AOT as shown by Table II and Fig. 9.

It appears that the techniques developed and presented here lend themselves very well to a definitive description and characterization of the particular matrix system one is dealing with, and in particular, permit the selection of the proper variables to alter in order to remedy nonideal matrix systems to provide the desired release profiles.

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Keyphrases

Drug release rates
Matrices–inert
Wetting effect–drug release
Surfactant effect–wetting
Contact angle measurements
Pressure effect–drug release
Diffusion coefficients
Permeation rates–solvent

Use of the Overturn End Point for the Estimation of Absorption and Elimination Kinetics in Goldfish

By MILO GIBALDI and CHARLES H. NIGHTINGALE

The advantages of overturn time as a pharmacologic end point for studies of biologic membrane permeation in goldfish are presented. Studies with both pentobarbital and ethanol showed good reproducibility. Redeterminations of overturn time after 18 hr. provided excellent agreement with initial determinations with both drugs. Evidence is presented to suggest a complex mechanism of action of ethanol in goldfish. A kinetic model is derived which relates overturn time and recovery time and permits the estimation of an elimination rate constant from pharmacologic response data alone.

Fish, particularly goldfish, have been used since 1867 as test animals for determining the toxicity of various substances, and a number of techniques have been developed for this purpose (1). A useful approach has been measurement of the time required to produce a well-marked stage of toxicity such as death.

Powers (2), after an extensive series of experiments with goldfish using a variety of drugs and chemicals, concluded that for every toxic substance, over a certain concentration range, the survival time is inversely related to the concentration. For many years the idea prevailed that the magnitude of the slope of a reciprocal time of death-concentration plot was indicative of intrinsic toxicity (1). Recently, Levy and Gucinski (3) have demonstrated that the slope of such a plot is actually a complex function of both the intrinsic toxicity and the absorption rate of the drug. Furthermore, these workers proposed that the reciprocal time of occurrence of any suitable pharmacologic response for a given drug will be directly proportional to the absorption rate of the drug under certain specified conditions (*viz.*, absorption occurs by passive diffusion, drug concentration gradient across the absorbing membranes remains essentially constant, drug metabolism in the fish is negligible, and the pharmacologic end point occurs without significant delay after a given amount of drug is absorbed). Knowledge of the amount of drug in the goldfish body required to induce a pharmacologic response permits the calculation of the absorption rate constant from reciprocal time of response-concentration plots. Even in the absence of such knowledge, relative absorption rates of a single drug under different experimental conditions may be assessed from the slopes of reciprocal time-concentration plots (3).

Another apparently well-marked pharmaco-

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