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Mechanism of diffusion of compounds through ethylene vinyl acetate copolymers I. Kinetics of diffusion of 1-chloro-4-nitrobenzene, 3,4-dimethylphenol and 4-hexylresorcinol

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Summary

The mechanism of diffusion of drugs through ethylene–vinyl acetate (EVA) copolymers has been studied. The observed permeability coefficients for the phenols, 4-hexylresorcinol and 3,4-dimethylphenol, increase in a non-linear fashion with increasing vinyl acetate content in the copolymer.

Furthermore, their partition coefficients vary in a non-linear manner with increasing vinyl acetate content, while the partition coefficient of a non-phenolic compound, 1-chloro-4-nitrobenzene, increases in a linear manner.

Since the diffusion coefficients for the two phenols are shown to be independent of vinyl acetate content, the permeability of phenols in EVA membranes depends almost entirely on the partition coefficient.

The non-linear partitioning behavior of the phenolic compounds can be attributed to the formation of vinyl acetate–phenol complexes. The linear increase in partition coefficient for 1-chloro-4-nitrobenzene is attributed to a straightforward solubility enhancement.

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Introduction

In recent years, the utilization of membrane-controlled diffusion devices for the controlled delivery of drug substances has received increasing attention in the literature. One such membrane, currently being used in devices releasing pilocarpine or progesterone, is an ethylene–vinyl acetate (EVA) copolymer. EVA copolymers have been found to be biocompatible, stable and heat-sealable and to possess optimal diffusional properties for such applications. Although EVA copolymers are being used extensively, very little information is available regarding the actual mechanism of diffusion of drugs through these membranes (Hsieh et al., 1983).

Since EVA consists of a polyethylene portion and a vinyl acetate portion, and can be obtained with vinyl acetate contents ranging from 8 to 60%, a study was undertaken to examine the effect of vinyl acetate content on the permeability of certain drugs through EVA membranes. The compounds chosen for this study were 4-hexylresorcinol, 3,4-dimethylphenol and 1-chloro-4-nitrobenzene. These compounds were chosen based on a previous study in which the solubility of the diphenol, 4-hexylresorcinol, in the non-polar solvent, hexane, was shown to increase in a non-linear fashion with the addition of increasing amounts of the esters ethyl acetate, ethyl pivalate and ethyl myristate (Akaho et al., 1981). The solubility of the monophenol, 3,4-dimethylphenol, however, increased linearly with added ester content. It has also been shown that the solubility and release rate characteristics of these two phenols in white petrolatum increase with increasing amounts of added ethyl myristate (Iga et al., 1981). These observations were rationalized on the basis of the formation of a 1 : 1 phenol–ester complex for the monophenol and both 1 : 1 and 1 : 2 phenol–ester complexes for 4-hexylresorcinol. Therefore, the possibility that the permeability of phenols through EVA membranes might be influenced by the formation of similar complexes between the phenols and the vinyl acetate portion of the membrane was investigated.

Materials and Methods

Materials

4-Hexylresorcinol [1] and 3,4-dimethylphenol [2] were recrystallized from a 4 : 1 mixture of *n*-hexane–benzene. 1-Chloro-4-nitrobenzene [2] and all other materials were of reagent grade and used without further purification. Ethylene–vinyl acetate copolymers [3] were obtained as pellets and characterized by IR [4]. An accurately known weight of EVA (usually ~ 300 mg) was dissolved in 25 ml toluene, the IR spectrum obtained and the intensity of absorption bands due to C–H stretching (2850 cm^{-1}) and C–O stretching (1740 cm^{-1}) were compared. Since each molecule

[1] Curtin-Matheson Scientific, Cincinnati, OH.
[2] Aldrich Chemicals, Milwaukee, WI.
[3] E.I. DuPont, Wilmington, DE.
[4] Model 567, Perkin-Elmer, Norwalk, CT.

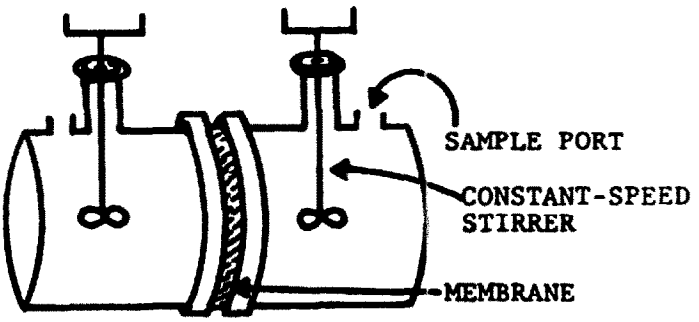


Fig. 1. Schematic representation of the cell employed in the diffusion studies.

of vinyl acetate monomer, A, yields one $-CH_2-$ group and one C=O group, and one molecule of ethylene monomer, E, yields two $-CH_2-$ groups in the copolymer, theoretical C–O/C–H ratios were calculated from A/(2E + A). The points on a plot of the observed IR peak ratios versus A/(2E + A) values for copolymers containing 12, 33, 38 and 40% (w/w) vinyl acetate were found to lie on a straight line described by:

$$\text{observed ratio} = 28.1\left[\frac{A}{2E + A}\right] - 0.062 \quad (r = 0.984)$$

EVA pellets were compressed into thin (~ 0.6 mm) membranes prior to inclusion in the studies.

Diffusion cell and studies

The rates of diffusion of 4-hexylresorcinol and 3,4-dimethylphenol were determined by fastening EVA membranes between the compartments of a diffusion cell. (The membranes were pre-saturated by maintaining them at 37°C for 72 h in flasks containing suspensions of the phenols in oxygen-free phosphate buffer (0.02 M, pH 7.4).) The cylindrical diffusion cell, shown in Fig. 1, was fabricated of stainless steel. The internal diameter of the cell was 3.51 cm so that the volume of each compartment was 68 ml and the total surface area of membrane in contact with donor or receptor solutions was 9.7 cm^2. The stirrers were operated at 60 rpm by constant-speed electric motors [5].

As soon as the membrane was in place, the donor compartment was filled with a suspension of the phenol [6] in buffer and the receptor compartment with buffer only. The complete assembly was maintained at 37°C by immersion in a water bath. The entire contents of the receptor compartment were periodically removed for analysis and replaced with fresh buffer. At the end of each experiment, the cell was disassembled and the membrane thickness determined with a micrometer.

[5] Tyle KYC 24A2, Bodine Electric, Chicago, IL.

[6] The suspension was used in order to maintain a constant concentration gradient across the membrane.

Under the conditions employed in this study (C receptor compartment ~ 0), the amount of drug permeated, Q, is given by Eqn. 1:

$$Q = \frac{PAC}{h} \cdot t \quad (1)$$

where P is the permeability, A is the surface area of the membrane, C is the concentration of drug in the donor compartment, h is the membrane thickness and t is time. Following an appropriate lag time, permeability values were obtained from the slopes of Q versus t plots.

Partitioning study

Four-hundred mg of 4-hexylresorcinol and 200 mg of 3,4-dimethylphenol and 1-chloro-4-nitrobenzene were each dissolved in 1 liter of oxygen-free phosphate buffer (0.02 M, pH 7.4) and 25 ml portions of each solution were added to flasks containing sections of the copolymer membranes. The weight of each membrane section was accurately known and was usually ~ 200 mg. The flasks were sealed and placed in a shaking water-bath [7] at 37°C for 72 h. Partition coefficients (PC) were calculated from the change in UV [8] absorbance (277.5, 277.0 and 278.0 nm for 4-hexylresorcinol, 3,4-dimethylphenol and 1-chloro-4-nitrobenzene, respectively) of the buffer solutions before and after the partition.

Release rate study

EVA membranes were cut into discs 1.9 cm in diameter, weighed and placed in oxygen-free phosphate buffer (0.02 M, pH 7.4) solutions of 4-hexylresorcinol and 3,4-dimethylphenol as described in the partitioning study above. After 72 h, the discs were removed, blotted on a tissue and placed in another flask containing 50 ml of drug-free buffer. These flasks were then maintained at 37°C in a water-bath. At convenient intervals, the membrane discs were transferred to additional flasks containing fresh 50 ml portions of drug-free buffer. The amount of phenol released during each interval was determined by measuring the UV absorbance of the solutions.

Results and Discussion

The mean permeability values for 4-hexylresorcinol and 3,4-dimethylphenol through EVA copolymer membranes of various vinyl acetate content were obtained from the slopes of the linear portions of Q versus t plots (as shown for the 12% vinyl acetate copolymer in Figs. 2 and 3) and are given in Table 1. As shown in Table 1, the permeability coefficients do not increase in a linear fashion with increasing vinyl

[7] Fisher Model 27, Fisher Scientific, Fairlawn, NJ.
[8] Cary 118, Varian Associates, Palo Alto, CA.

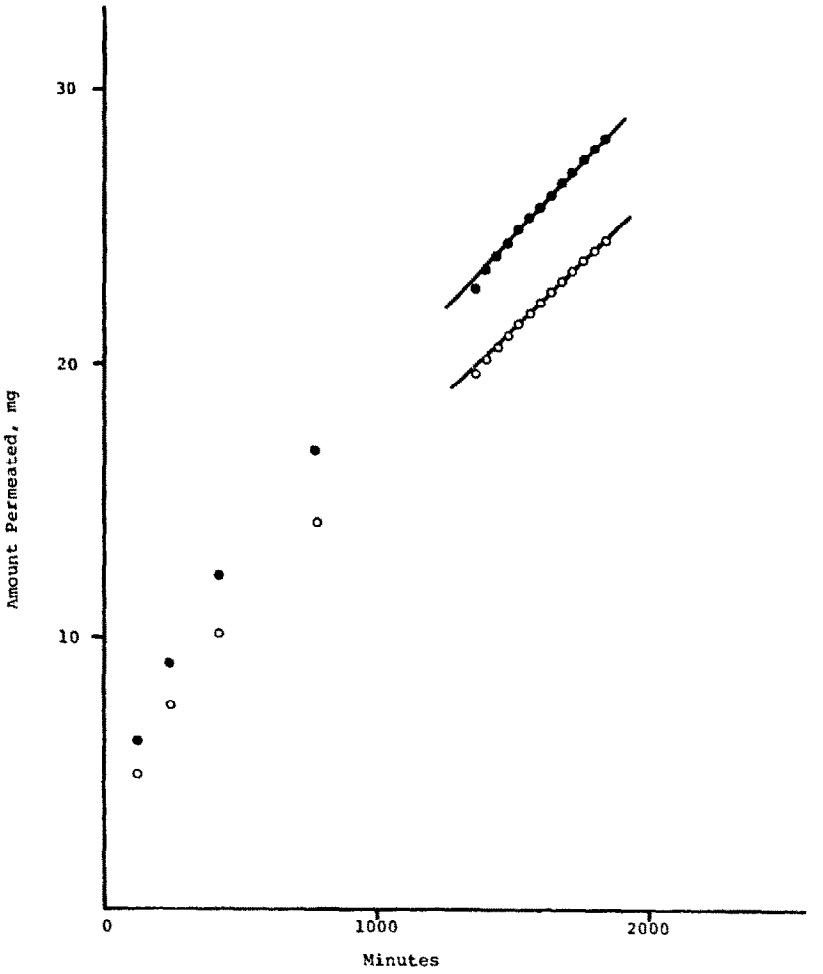


Fig. 2. Q, the amount of drug permeating a 12% VA membrane versus time for 4-hexylresorcinol. The open and closed symbols represent duplicate determinations.

acetate content. Since P is the product of the partition coefficient and the diffusion coefficient, the observed non-linearity could be the result of non-linear behavior by PC and/or D.

The partition coefficients observed for these two phenols as well as the non-phenol, 1-chloro-4-nitrobenzene, between aqueous buffer and EVA copolymers of various vinyl acetate content are shown in Fig. 4. The partition coefficient of 1-chloro-4-nitrobenzene increases in a linear fashion with increasing vinyl acetate in the copolymer, whereas the partition coefficients of the phenolic compounds exhibit definite non-linear dependency.

Diffusion coefficients for the two phenols as determined from the release rate study are shown in Table 2. Release rates of the compounds were found to lie on straight lines when plotted as the amount of drug released, Q, versus the square-root of time. This behavior is consistent with that predicted by the Higuchi equation (Higuchi, 1961) as modified for cases where the total drug present in the matrix is

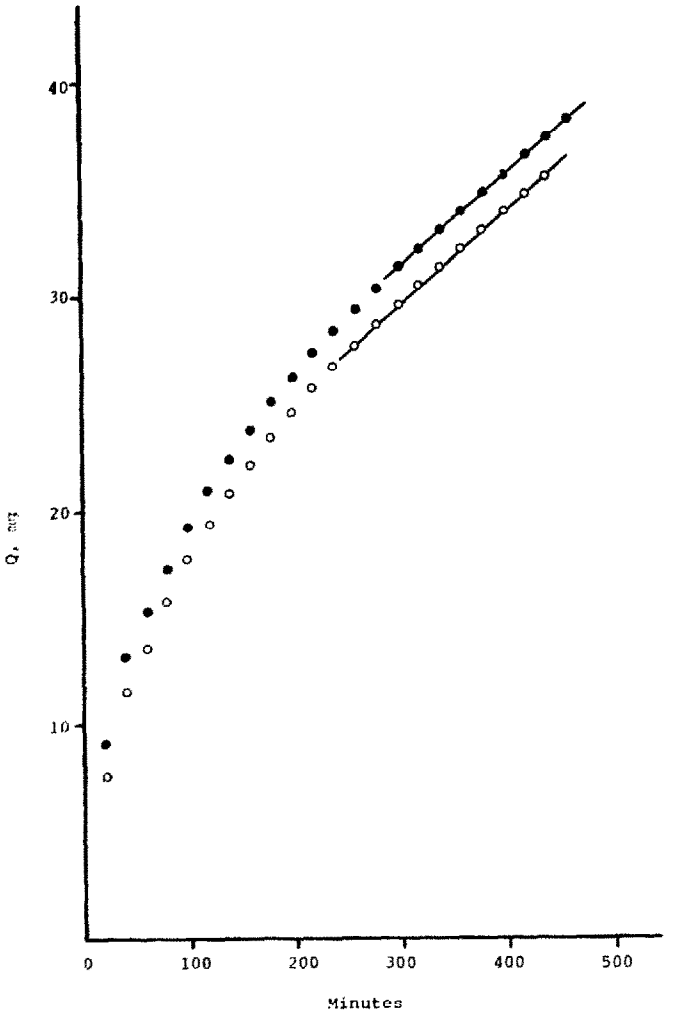


Fig. 3. Q, the amount of drug permeating a 12% VA membrane versus time for 3,4-dimethylphenol. The open and closed symbols represent duplicate determinations.

TABLE I

PERMEABILITY CONSTANTS FOR 4-HEXYLRESORCINOL AND 3,4-DIMETHYLPHENOL

% VA	Permeability constants (cm^2/s)	
	4-Hexylresorcinol	3,4-Dimethylphenol
7.5	9.98×10^{-8}	1.22×10^{-7}
12	5.08×10^{-7}	5.33×10^{-7}
28	4.12×10^{-6}	3.00×10^{-6}
33	4.65×10^{-6}	5.13×10^{-6}

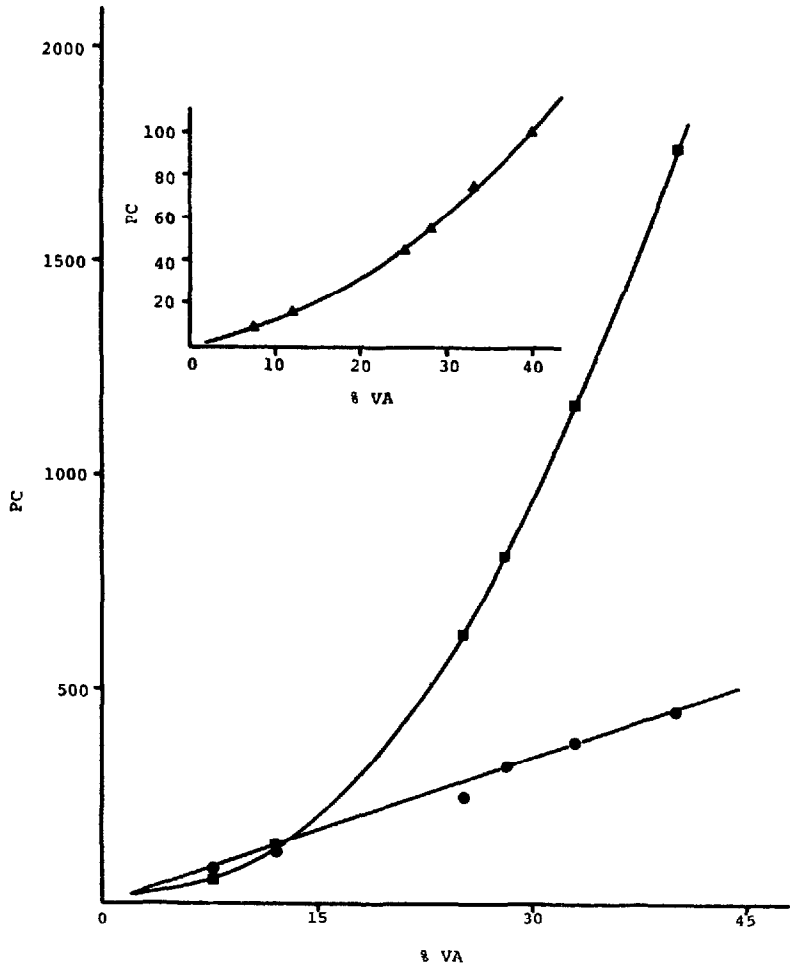


Fig. 4. The observed aqueous/EVA copolymer partition coefficient versus vinyl acetate content for: 4-hexylresorcinol, ■; 3,4-dimethylphenol, ▲; and 1-chloro-4-nitrobenzene, ●.

less than the solubility of that drug (Fessi et al., 1982):

$$Q = AD^{1/2}t^{1/2} \tag{2}$$

where A is the amount of drug in the matrix and D is the diffusion coefficient. The slopes of these lines permit estimates of the diffusion coefficients. The values of the slopes, intercepts and correlation coefficients obtained by least-squares fitting of the data are also shown in Table 2. As shown in Table 2, the diffusion coefficients for those copolymers with vinyl acetate content greater than 7.5%, are, for practical purposes, the same. This independence of diffusion coefficient and vinyl acetate content was further demonstrated for 4-hexylresorcinol by plotting $Q/\sqrt{t}$ versus the total drug in matrix for the 12% and the 28% copolymers. The slopes of the resulting lines are $D^{1/2}$ and were found to change very little for more than a two-fold increase in vinyl acetate content ($D^{1/2} = 5.83 \times 10^{-5}$ and 5.80×10^{-5} cm · $s^{-1/2}$ for the 12 and 28% copolymers, respectively).

TABLE 2

THE VALUES OBTAINED BY LEAST-SQUARES FITTING OF THE RELEASE RATE DATA TO EQN. 2 AND THE DIFFUSION COEFFICIENTS DETERMINED FROM THE RELEASE RATE STUDY AND THE DIFFUSION STUDY

Compound	% VA in the copolymer	Slope ($mg \cdot min^{-0.5}$)	Intercept	Correlation coefficient	Diffusion coefficient ($cm^2 \cdot s^{-1}$)	
					From release rate study	From diffusion study
4-Hexylresorcinol	7.5	3.94×10^{-2}	-8.43×10^{-3}	0.9958	2.05×10^{-9}	1.80×10^{-9}
	12	1.12×10^{-1}	-4.46×10^{-2}	0.9999	3.63×10^{-9}	3.72×10^{-9}
	28	2.30×10^{-1}	-4.97×10^{-1}	0.9998	3.40×10^{-9}	5.05×10^{-9}
	33	2.69×10^{-1}	-6.73×10^{-1}	0.9997	3.72×10^{-9}	3.98×10^{-9}
3,4-Dimethylphenol	7.5	3.99×10^{-1}	-1.72×10^{-1}	0.9998	2.73×10^{-8}	1.35×10^{-8}
	12	7.56×10^{-1}	-3.49×10^{-1}	0.9994	3.92×10^{-8}	3.30×10^{-8}
	28	2.195	-7.53×10^{-1}	0.9999	3.73×10^{-8}	5.40×10^{-8}
	33	2.922	-1.544	0.9999	4.47×10^{-8}	6.92×10^{-8}

Finally, in order to verify these results, diffusion coefficients for the phenols were calculated from the permeability data obtained in the diffusion cell study. Since P = (PC)D, substitution of the PC values from Fig. 5 gave the diffusion coefficients shown in the final column of Table 2. It is evident from these data that diffusion coefficients can be considered independent of the vinyl acetate content of EVA copolymers. Thus, the permeability of phenols through EVA membranes is almost entirely a function of the partition coefficient.

Unusual partitioning behavior has been observed for phenolic compounds in hexane–water systems as a function of added ester content, and has been rationalized (Akaho et al., 1981) on the basis of complex formation between the phenolic hydroxyl group and the ester. If similar complexation were influencing the partitioning in the present case, the system could be described mathematically by equations in which, for the purpose of derivation, EVA is considered to be a solution of acetate moieties in the copolymer. The complexation reactions would be described by:

$$C_m + V \rightleftharpoons C_mV \tag{3}$$

$$K_{1:1} = \frac{[C_mV]}{C_m[V]} \tag{4}$$

$$C_m + 2V \rightleftharpoons C_mV_2 \tag{5}$$

$$K_{1\,2} = \frac{[C_mV_2]}{C_m[V]^2} \tag{6}$$

$$C_T = C_m + C_mV + C_mV_2$$

$$= C_m\left(1 + K_{1:1}[V] + K_{1:2}[V]^2\right) \tag{7}$$

where C_m, V, C_mV, $K_{1:1}$, C_mV_2, $K_{1:2}$ and C_T represent the concentration of free drug in the membrane, the concentration of free acetate in the membrane, the 1 : 1 complex, the 1 : 1 formation constant, the 1 : 2 complex, the 1 : 2 formation constant and the total drug concentration in the membrane, respectively.

Since the partitioning study was carried out in dilute aqueous solutions, the concentration of complex would be small compared to the concentration of free acetate in the membrane. Thus [V] in Eqn. 7 can be replaced by $[V_T]$, the total acetate concentration:

$$C_T = C_m\left(1 + K_{1:1}[V_T] + K_{1:2}[V_T]^2\right) \tag{8}$$

Furthermore, the compounds studied were all found to be insoluble in polyethylene (vinyl acetate = 0%) so that the drug in the membrane is considered to lie in the vinyl acetate portion. The concentration of drug in that portion, C_{VA}, would be given by:

$$C_{VA} = \frac{C_m}{F} \tag{9}$$

where C_n is as defined above and F is the fraction of vinyl acetate in the membrane. The true partition coefficient between the vinyl acetate portion and the surrounding aqueous buffer is:

$$K = C_{VA}/C_{H_2O} \tag{10}$$

Combining Eqns. 9 and 10 gives:

$$C_m = KFC_{H_2O} \tag{11}$$

Substituting Eqn. 11 into Eqn. 8 gives:

$$C_T = KFC_{H_2O}\left(1 + K_{1:1}[V_T] + K_{1:2}[V_T]^2\right) \tag{12}$$

Since the observed partition coefficient, PC, is C_T/C_{H_2O}, Eqn. 12 can be written as:

$$PC = KF\left(1 + K_{1:1}[V_T] + K_{1:2}[V_T]^2\right) \tag{13}$$

The fractional term in Eqn. 13 can be put into concentration terms by the use of Eqn. 14:

$$V_T = \frac{1000Fd}{M} \tag{14}$$

where d and M are the density of the EVA membrane and the molecular weight of the vinyl acetate monomer, respectively. Combining Eqns. 13 and 14 gives:

$$\frac{PC}{V_T} = \frac{KM}{1000 \cdot d}\left(1 + K_{1:1}[V_T] + K_{1:2}[V_T]^2\right) \tag{15}$$

Eqn. 15 predicts that in the absence of complexing ($K_{1:1} = K_{1:2} = 0$) PC/V_T values would be constant and equal to $KM/1000 \cdot d$ as shown for 1-chloro-4-nitrobenzene in Table 3. If only a 1 : 1 complex were forming, Eqn. 15 predicts that a plot of PC/V_T versus V_T would result in a straight line with a slope of $KMK_{1:1}/(1000 \cdot d)$ and an intercept of $KM/1000 \cdot d$. This result is consistent with the data obtained for the monophenol, least-squares fitting resulting in $KMK_{1:1}/(1000 \cdot d) = 3.082$ and $KM/1000 \cdot d = 8.387$ ($r = 0.997$). In the case of higher-order complex formation, a plot of PC/V_T versus V_T would exhibit curvature due to the higher order V_T term. The values of K, $K_{1:1}$ and $K_{1:2}$ in Eqn. 15 were estimated for 4-hexylresorcinol by least-squares fitting of the polynomial $y = A + Bx + Cx^2$ employing a curve-fitting computer program [9] where y is $(PC/V_T)/(1000 \cdot d/M)$, x is V_T and A, B and C are

[9] 'Scientific Plotter', Interactive Microware, State College, Pennsylvania.

TABLE 3

THE PARTITION COEFFICIENT (PC) VALUES OBSERVED, THE CALCULATED INITIAL LOADS AND THE TRUE PARTITION COEFFICIENT (K) VALUES CALCULATED FROM EQN. 15 FOR THE EVA COPOLYMERS STUDIED

V_T(M)	PC	$\frac{PC}{V_T}(=\frac{KM}{1000d})$	K	'Load' (mg)
0.81	79.9	98.6	1088	80.443
1.3	123	94.6	1044	101.758
2.8	249	88.9	981	135.418
3.1	320	103.2	1139	145.869
3.7	376	101.6	1121	151.996
4.5	446	99.1	1094	157.946

$\bar{K} = 1078$
$S = 57.4$

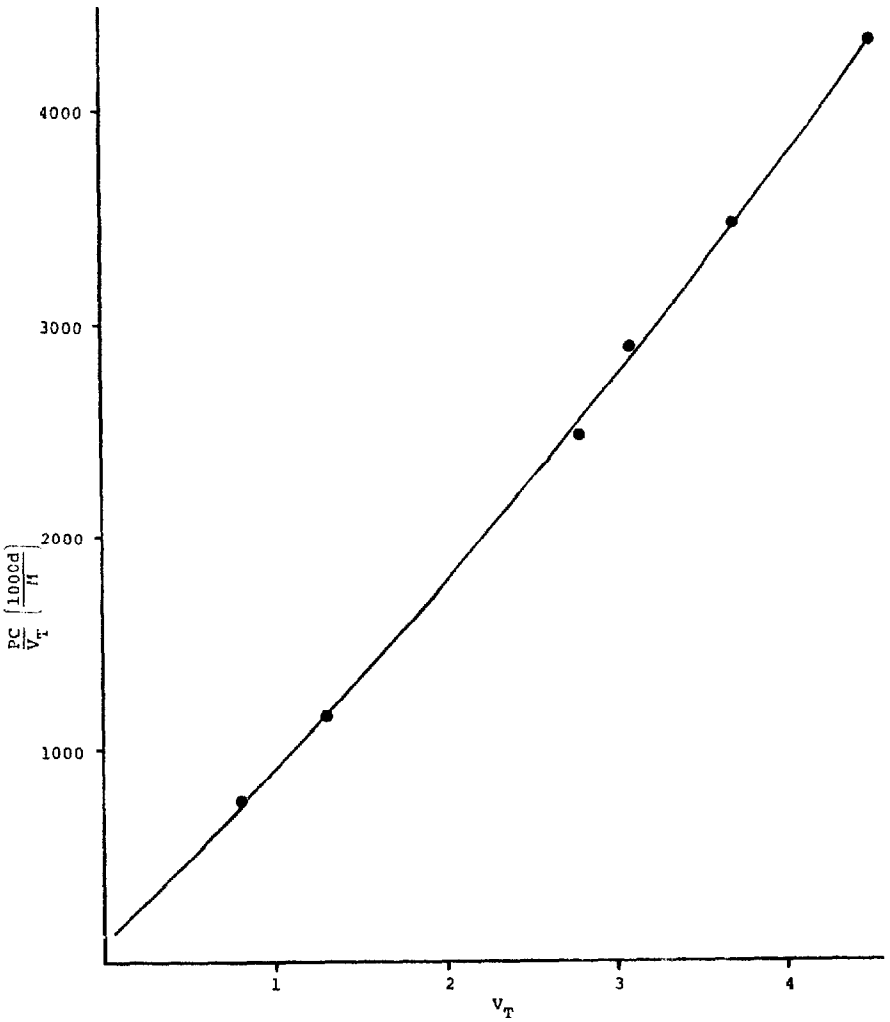


Fig. 5. $(PC/V_T)(1000 \cdot d/M)$ versus V_T for 4-hexylresorcinol. The points are experimental and the line is that generated by the computer.

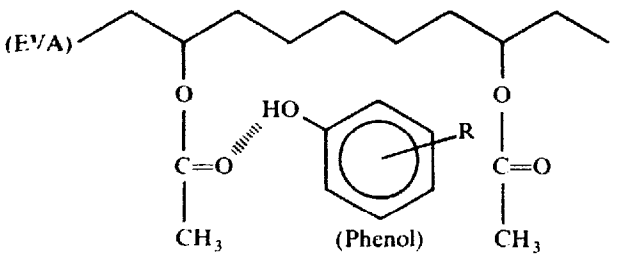
TABLE 4

THE STABILITY CONSTANTS FOR EVA ... ...EXES WITH 1-CHLORO-4-NITROBENZENE, 3,4-DIMETHYLPHENOL AND 4-HEXYLRESORCINOL

	K, $K_{1:1}$ and $K_{1:2}$ values		
	4-Hexyl-resorcinol	3,4-Dimethyl-phenol	1-Chloro-4-nitrobenzene
K $[M]^{-1}$	114	92.6	1078
$K_{1:1}$ $[M]^{-1}$	6.6	0.37	
$K_{1:2}$ $[M]^{-2}$	0.36		

K, $KK_{1:1}$ and $KK_{1:2}$, respectively. The result of this fitting is shown in Fig. 5 where the symbols are the experimental points and the line is that generated by the program. The values obtained for K, $K_{1:1}$ and/or $K_{1:2}$ for the compounds studied are shown in Table 4.

The data presented suggest that the non-linear permeability and partition coefficients observed for phenols and EVA membranes of various vinyl acetate content are due to complex formation. The complexes are probably formed between the phenolic hydroxyl groups and the vinyl acetate carbonyl function as shown in Scheme 1 below. The linear increase in the partition coefficient of the non-phenolic 1-chloro-4-nitrobenzene is primarily due to a straightforward solubility enhancement by vinyl acetate.



Scheme 1. The formation of phenol–ester complexes in EVA membranes.

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