inlet pressure was 3 atm.abs. and the outlet pressure 2 atm.abs. The following temperature measurements were available: inlet, 600°C; 20% of coil length, 740°C; 80% of coil length, 812°C; outlet, 838°C. The following heat flux profile was generated from independent simulations of the heat transfer in the fire box: first tube, 22 kcal/m² s; second tube, 20; third, 18; fourth, 17; fifth, 15; sixth, 13; seventh, 11; eight, 8; ninth and tenth tube, 6. With this heat flux profile, the conversion, temperature, and total pressure profiles of Figure 13 were obtained. The agreement with the industrial data is really excellent. The use of the molecular reaction scheme of Table 8 also enabled the product distribution at the exit of the coil to be compared with the industrial data. This is done in Figure 14, which also shows an excellent agreement.


## ACKNOWLEDGMENT

The authors are grateful to the "Fonds voor Kollektief Fundamenteel Onderzoek" for support of Research Project nr. 919.


## NOTATION

$a$ = inhibition constant
$A$ = frequency factor, $s^{-1}$
$C$ = concentration, kmole/m³
$c_p$ = specific heat of gases, kcal/kmole °C
$d_t$ = internal tube diameter, m
$E$ = activation energy, kcal/kmole
$F_o$ = molar flow rate of propane at inlet, mole/s
$F_j$ = molar flow rate of component $j$, kmole/s
$G$ = mass flow velocity, kg/m² s
$\Delta H$ = heat of reaction, kcal/kmole
$k$ = rate coefficient, $s^{-1}$ or $\text{kmole}^{-(n-1)}\text{m}^{3n-3}\text{s}^{-1}$
$k_o$ = rate coefficient at zero conversion, $s^{-1}$ or $\text{kmole}^{-(n-1)}\text{m}^{3n-3}\text{s}^{-1}$
$n$ = order of reaction
$P$ = total pressure, atm. abs.
$P_R$ = reference totai pressure, atm. abs.
$Q(z)$ = heat flux, kcal/m² s
$R$ = gas constant, 1.987 kcal/kmole °C or 0.082 $\frac{\text{m}^3 \text{ atm.}}{\text{kmole °K}}$ in (16)
$r$ = rate of reaction, kmole/m³s
$r_b$ = radius of bend of the coil, m
$S_{ij}$ = stoichiometric coefficients of component $j$ in equation $i$
$T$ = temperature, °K or °C
$T_R$ = reference temperature, °K
$V_E$ = equivalent reactor volume, m³
$x$ = conversion
$Z$ = distance along the coil, m

$\delta$ = dilution ratio, kmole steam/kmole propane at inlet
$\epsilon$ = expansion factor, kmole products/kmole propane cracked
$\phi$ = inhibition function
$\Omega$ = cross sectional area of coil, m²

**Subscripts**

$i$ = $i^{\text{th}}$ stoichiometric equation
$j$ = component

## LITERATURE CITED


Buekens, A. G., and G. F. Froment, "Thermal Cracking of Propane," *Ind. Eng. Chem. Process Design and Develop.*, **7**, 435 (1968).

Davis, H. G., and T. J. Farrel, "Relative and Absolute Rates of Decomposition of Light Paraffins under Practical Operating Conditions," *ibid.*, **12**, 171 (1973).

Froment, G. F., H. Pijcke, and G. Goethals, "Thermal Cracking of Acetone—I & II," *Chem. Eng. Sci.*, **13**, 173 (1961); **13**, 180 (1961).

Herriott, G. E., K. E. Eckert, and L. F. Albright, "Kinetics of Propane Pyrolysis," *AIChE J.*, **18**, 84 (1972).

Illes, V., "The Pyrolysis of Gaseous Hydrocarbons III," *Acta. Chim. Acad. Sci. Hung.*, **67**, 41 (1971).

Kershenbaum, L. S., and J. J. Martin, "Kinetics of the Non-isothermal Pyrolysis of Propane," *AIChE J.*, **13**, 148 (1967).

Kunugi, T., K. Soma, and T. Sakai, "Thermal Cracking of Propylene," *Ind. Eng. Chem. Fundamentals*, **9**, 319 (1970).

Laidler, K. J., N. H. Sagert, and B. W. Wojciechowski, "Kinetics and Mechanisms of the Thermal Decomposition of Propane," *Proc. Roy. Soc.*, **A270**, 242 (1962).

Lichtenstein, L., "Design Cracking Furnaces by Computer," *Chem. Eng. Progr.*, **60**, No. 12, 64 (1964).

Martin, R., M. Dzierzynski, and M. Niclause, "La Décomposition Thermique du Propane," *J. Chim. Phys.*, **61**, 286 (1964).

Robinson, K. K., and E. Weger, "High Temperature Pyrolysis of Propylene-Propane Mixtures," *Ind. Eng. Chem. Fundamentals*, **10**, 198 (1971).

Shah, M. J., "Computer Control of Ethylene Production," *Ind. Eng. Chem.*, **59**, 70 (1967).



*Manuscript received March 7, 1975; revision received June 24, and accepted June 25, 1975.*


# A Thermodynamic Method of Predicting the Transport of Steroids in Polymer Matrices


**Application of Hildebrand's theory of the solubility of microsolutes in ordinary solvents, and of the Flory-Huggins theory to the solubility of steroids in polymers, has permitted the derivation of a predictive correlation between polymer permeability and steroid crystalline melting temperature, other correlating parameters being the entropy of fusion of the steroid and the (computed) solubility parameters of steroid and polymer. The correlation permits prediction of the permeability of any steroid in any polymer with reasonable accuracy.**



**A. S. MICHAELS, P. S. L. WONG, R. PRATHER, and R. M. GALE**

**ALZA Corporation**
***Palo Alto, California 94304***

## SCOPE

In recent years, considerable attention has been directed to the development of implantable, intrauterine, or intravaginal systems or devices providing prolonged and controlled administration to the body of steroid hormones, for both control of fertility and treatment of certain hormone deficiency diseases. Many of these delivery system concepts rely upon the use of synthetic polymeric membranes which are drug permeable as means for controlling the rate of release of hormones to the body. Since the steroid hormones of interest for these applications cover a wide range of physicochemical properties and potency, and since the polymeric materials of potential utility for systems fabrication differ markedly in their capacity to permeate and absorb the various steroids, the design of a particular delivery system may necessitate a rather protracted and tedious screening program to select a specific steroid/polymer pair which will satisfy the required delivery rate and *in vivo* life criteria. Obviously, the development of a predictive method or correlation which would allow one to estimate with reasonable accuracy the permeability of specific polymer to a specific steroid hormone from a knowledge of certain parameters characteristic of the steroid alone, on the one hand, and polymer alone, on the other, would be of significant value. Inasmuch as correlations of this nature have already been developed for predicting the permeability of a wide variety of polymers to large numbers of gases and vapors (Michaels and Bixler, 1968), the probability that a useful correlation for steroids might be found seemed to us to be reasonably high. The object of this paper is to propose such a correlation, to present its theoretical basis, and to test its utility as a predictive tool. Beyond its utility in therapeutic system design, such a correlation, if sufficiently general, should be very helpful in predicting the rate of permeation of any solid substance through a polymer.

## CONCLUSIONS AND SIGNIFICANCE

The solubility theories of Hildebrand and Scott (1964), Flory (1953), and Huggins (1942) as applied to a series of eleven steroid hormones in six rubbery polymers provide a useful basis for the prediction and correlation of the permeability (at 37°C) of polymers to steroids, via a semilogarithmic linear relationship of the form

$$\ln [J_{max} l \cdot \exp (1 + \chi)] \cong -X(T_M/T - 1) + \ln (0.03\rho_A D)$$

where $(X)$ is a constant very nearly equal to $(\Delta S_f/R)$, and $\Delta S_f$ is the mean entropy of fusion of the steroid series. This correlation permits the estimation (within a factor of 2) of the permeability of a given steroid through a given polymer from a knowledge of the melting temperature of the crystalline steroid, without recourse to direct experimental measurement of solubilities for the particular polymer/penetrant pair. Since measured permeabilities vary as much as 10000 fold between steroids in a given polymer, and 400 fold between polymers for a given steroid, the correlation is regarded as unexpectedly good.

The thermodynamic principles utilized in developing this correlation are not confined to steroid hormones but are generally applicable to crystalline solid penetrant/polymer systems obeying regular solution equilibrium relationships. It is thus likely that this approach can be used successfully for correlating and predicting permeation of other families of crystalline solid substances through polymers, including not only other families of drugs, but also such substances as stabilizers, antioxidants, pesticides, herbicides, catalyst and monomer residues, etc., whose rates of permeation through polymers are becoming of increasing industrial and social concern and importance.

---

### THEORETICAL TREATMENT

We begin by assuming that transport of a steroid hormone through a polymer takes place by the simple process of molecular dissolution and diffusion and that at steady state the transport flux $J$ can be represented by Fick's first law:

$$J = -D \frac{dC_A}{dx} \tag{1}$$

where $D$ is the diffusivity of the steroid in the polymer and $C_A$ its concentration.

Furthermore, if the steroid is but sparingly soluble in the polymer, $D \neq f(C)$, and for a film of thickness $(l)$

$$J = \frac{D [C_A(0) - C_A(l)]}{l} \tag{2}$$

Since most steroids exist as crystalline solids at physiologic temperatures, and since the body in most instances constitutes an infinite sink with respect to a membrane moderated drug delivery system, the maximum attainable flux of steroid through a membrane of thickness $(l)$ is given by

$$J_{max} = D C_A^*/l \tag{3}$$

where $C_A^*$ is the concentration of steroid in solution in the polymer at equilibrium with crystalline solid steroid (or with a saturated solution of that steroid in a solvent).

The product $(J_{max} l)$ we shall call the *normalized flux* of steroid through a particular polymer; this product is, of course, equal to the product $(D\ C_A^*)$. Both $(D)$ and $(C_A^*)$ are intensive properties of a specific steroid/polymer pair. The diffusivity $D$ should be uniquely determined by the molecular size and configuration of the steroid and the chain segmental compliance of the polymer. The saturation solubility of steroid in the polymer $C_A^*$ should be determined by the partial molar free energy change accompanying transfer of a steroid molecule from a position in the steroid crystal lattice to a position within the polymer matrix.

Virtually all steroid hormones share the common ring structure shown in Figure 1. Variations among steroids involve substitutions of rather small groups (for example, methyl, hydroxyl, carboxyl, hydrogen, halogen) at various points around the ring structure. While these substitutions would be expected to, and indeed do, have a profound effect upon the physicochemical properties and biological activity of these substances, they do not significantly alter the molecular weight or configuration of the molecule because of the dominant influence of the central steroid nucleus. Hence, one might predict that, with respect to

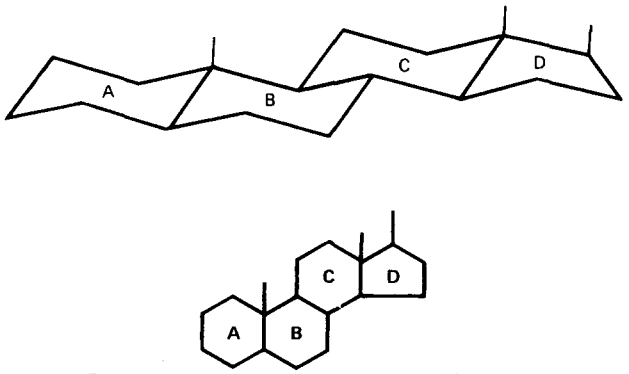


Fig. 1. Common ring-structure of steroid hormones.

a particular polymer, the diffusivities of different steroids should show little variability. Were this to be the case, then we might rewrite Equation (3) as

$$[J_{\max} l/D] = C_A^*;\ [J_{\max} l] \propto C_A^* \qquad (4)$$

whereupon the normalized flux for any particular steroid in a given polymer should be directly proportional to its limiting solubility in that polymer. It would, therefore, be convenient to find a means for predicting the solubility of a crystalline steroid in a polymer, since this may provide a basis for predicting its permeability.

Consider a pure crystalline solid substance $A$ of melting point $T_M$ (°K), and heat of fusion $\Delta H_f$($K$ cal/mole); the condition for equilibrium between that compound and its saturated solution in a polymer at temperature $T$ is represented by

$$A(S, T) \rightleftarrows A(C_A^*, T)$$

For this process, the free energy change per mole of solute $A$ transferred between phases is zero, and the chemical potential (hence, the fugacity) of the solute is the same in both phases:

$$\text{or} \quad f_{A_{(S)}} = f_{A_{(C_A^*)}} \quad \text{at} \quad T \qquad (5)$$

The fugacity of solute $A$ in the polymer when present at concentration $C_A$ can be represented by

$$f_{A_{(C_A)}} = \Gamma_A\, \phi_A\, f_A^0 \qquad (6)$$

where $\phi_A$ is the volume fraction of solute in the polymer corresponding to its concentration ($C_A$); $\Gamma_A$ is the (volume fraction normalized) activity coefficient of the solute, defined by the relation $a_A = \Gamma_A\, \phi_A$; and $f_A^0$ is the fugacity of (hypothetical) pure liquid $A$ at temperature $T$. [Note that if $C_A$ is expressed in grams per cubic centimeter, and if $\phi_A \cong 0$, then $\phi_A \cong C_A(V_A/M_A)$, where $V_A$ is the molar volume of the solute in the polymer, and $M_A$ is its molecular weight.] To a first approximation, $M_A/V_A \cong \rho_A$, the mass density of the pure solute in grams per cubic centimeter. For most crystalline steroids at 37°C, $\rho_A \cong 1.2$ g/cm$^3$.

For the condition of saturation equilibrium between the polymer and pure crystalline solute, Equation (6) becomes

$$f_{A_{(C_A^*)}} = \Gamma_A^*\, \phi_A^*\, f_A^0 \qquad (6a)$$

Combining Equations (5) and (6$a$), we obtain

$$\Gamma_A^*\, \phi_A^* = f_{A(S)}/f_A^0 = a_A^* \qquad (7)$$

For the change of state

$$A(s, T) \rightarrow A(l, T)$$

The change in molar free energy $\Delta G_{s\rightarrow l}$ is given by

$$\Delta G_{(s\rightarrow l)T} = RT \ln f_A^0/f_{A(s)} \qquad (8)$$

Since, however

$$\Delta G_{(s\rightarrow l)} = \Delta H_{(S\rightarrow l)} - T\Delta S_{(s\rightarrow l)} \qquad (9)$$

and since, at $T = T_M$, $\Delta G_{(S\rightarrow l)} = 0$, if $(T)$ is not far removed from $(T_M)$ and/or the heat capacities of the solute in the crystalline and liquid states are not far different, we can write

$$\Delta G_{(s\rightarrow l)T} = \Delta H_f[1 - T/T_M] = RT \ln f_A^0/f_{A(s)} \qquad (10)$$

Combining (10) with (7), we find

$$\ln a_A^* = \ln \Gamma_A^*\, \phi_A^* = -\Delta H_f/R\,[1/T - 1/T_M] \qquad (11)$$

Let us define, as the standard state of the solute $(A)$ at $T$, the pure liquid phase. In this state, the activity of $(A)$, $a_A^0[a_A = (f_A/f_A^0)]$ is unity. For the process of dissolution of $A$ from the pure liquid state into the polymer where its concentration is $C_A^*$ or its volume fraction, $\phi_A^*$ $[A(l, T) \rightarrow A\ (\phi_A^*, T)]$, the partial molar free energy change for this process is

$$\Delta\overline{G}_{A_{(l\rightarrow P)}} = \Delta\overline{G}_A^0 = RT \ln a_A/a_A^0$$

$$= RT \ln a_A^* = RT \ln (\Gamma_A^*\phi_A^*) \qquad (12)$$

However, this free energy change is also the free energy change of mixing and dilution of pure liquid $(A)$ with the polymer; this process is precisely that dealt with by Flory (1953) and by Huggins (1942), for which the partial molar free energy change for component $(A)$ is approximated by

$$\Delta\overline{G}_{A_{(l\rightarrow P)}} \cong RT\,[\ln \phi_A + (1 - 1/\overline{x})\phi_P + \chi_{AP}\phi_P^2] \qquad (13)$$

where $\phi_A$ is the volume fraction of $A$ in the mixture, $\phi_P$ the volume fraction of polymer, $\overline{x}$ the number average degree of polymerization of the polymer, and $\chi_{AP}$ the polymer solvent interaction parameter related to the heat of mixing of polymer and solute. Of principal interest to us in this analysis are polymers of relatively high molecular weight ($1/\overline{x} << 1$) and penetrants of but sparing solubility in the polymer ($\phi_A \rightarrow 0$; $\phi_P \rightarrow 1.0$), whence Equation (13) reduces to

$$\Delta\overline{G}_{A_{(l\rightarrow P)}} \cong RT\,[\ln \phi_A + (1 + \chi_{AP})] \qquad (14)$$

For the condition where $\phi_A = \phi_A^*$, $\Delta\overline{G}_{A_{(l\rightarrow P)}} = \Delta\overline{G}_A^0$, simultaneous solution of (12) and (14) yields

$$RT \ln (\Gamma_A^*\phi_A^*) = RT\,[\ln \phi_A^* + (1 + \chi_{AP})] \qquad (15)$$

or

$$\ln \Gamma_A^* \cong (1 + \chi_{AP}) \qquad (15a)$$

For solvent/solute interactions, where the dissolution process is endothermic and involves solely London dispersion and other Van der Waals interactions between molecules, Hildebrand and Scott (1964) have shown that, to a first approximation

$$\chi_{AP} \cong V_A/RT\,(\delta_A - \delta_P)^2 \qquad (16)$$

where $V_A$ is the molar volume of pure liquid $(A)$, and $\delta_A$ and $\delta_P$ are the solubility parameter (square root of the cohesive energy density) of solute and polymer, respec-

tively. Combining (15$a$) and (16), we have

$$\ln \Gamma_A = 1 + V_A/RT\ (\delta_A - \delta_P)^2 = 1 + \chi_{AP} \quad (17)$$

or

$$\Gamma_A = \exp\ (1 + \chi_{AP}) = \exp\ [1 + V_A/RT\ (\delta_A - \delta_P)^2] \quad (17a)$$

It should be noted that for dilute solutions of microsolutes in polymers

$$\Gamma_A \phi_A \equiv \gamma_A X_A \cong \gamma_A, \quad \text{since} \quad X_A \cong 1.0$$

Combining with Equation (17$a$),

$$\gamma_A = \phi_A \exp\ (1 + \chi_{AP})$$

and if polymer/solvent interaction is athermal, we get

$$\chi_{AP} = 0, \quad \Gamma_A = e, \quad \text{and} \quad \gamma_A = e\phi_A$$

This result differs from that of Hildebrand's general relation for the activity coefficient of microsolute ($A$) in solution of a low molecular weight solvent ($B$):

$$\ln \Gamma_A \cong (1 - V_A/V_B) + \chi_{AB}, \quad \text{if} \quad \phi_B \to 1.0$$

where

$$\Gamma_A \cong \exp\ [(1 - V_A/V_B) + \chi_{AB}] \quad (18)$$

or

$$\gamma_A = \Gamma_A \frac{\phi_A}{\chi_A} \cong V_A/V_B \exp\ [(1 - V_A/V_B) + \chi_{AB}] \quad (18a)$$

If

$$\chi_{AB} = 0, \quad \Gamma_A = \exp\ (1 - V_A/V_B)$$

and

$$\gamma_A = V_A/V_B \exp\ (1 - V_A/V_B)$$

Equations (18) and (17$a$) become identical for the case where $V_A/V_B = 0$ (as must be the case for solutions in polymers of high molecular weight). For mixtures of molecules of equal size ($V_A = V_B$), Equation (18$a$) becomes

$$\gamma_A = \Gamma_A = \exp \chi_{AB}$$

and for athermal mixing interactions ($\chi_{AB} = 0$), the solutions must be ideal ($\gamma_A \equiv \Gamma_A = 1.0$). Hence the minimum value for $\Gamma_A$ in a polymer must be $\Gamma_A = e$, while that in a micromolecular solvent is $[\exp(1 - V_A/V_B)]$.

Combining (17) and (11), we obtain

$$\ln \phi_A^\circ + [1 + V_A/RT\ (\delta_A - \delta_P)^2] = -\Delta H_f/R\ (1/T - 1/T_M) \quad (19)$$

or

$$\ln\ (C_A^\circ\ V_A/M_A) + [1 + V_A/RT\ (\delta_A - \delta_P)^2] = -\Delta H_f/R\ (1/T - 1/T_M) \quad (20)$$

where

$$\ln [J_{max} l \cdot \exp\ (1 + \chi_{AP})] = \ln [J_{max} l \cdot \exp\ (1 + (V_A/RT)\ (\delta_A - \delta_P)^2)] = -\Delta H_f/R\ (1/T - 1/T_M) + \ln \rho_A D = -\Delta S_f/R\ (T_M/T - 1) + \ln \rho_A D \quad (21)$$

For a series of steroid hormones in a given polymer, the last term on the right of (21) should be virtually constant and independent of the choice of compound, since neither $D$ nor $\rho_A$ vary significantly among compounds. The solubility parameters for both steroid ($\delta_A$) and polymer ($\delta_P$) can be roughly estimated by group contribution methods proposed by Small (1953), Gardon (1965), and others, where ($\chi$) can be computed via Equation (16). Both $T_M$ and $\Delta H_f$ can be experimentally determined with relative ease and accuracy for the pure steroids via techniques of differential thermal analysis of scanning colorimetry. If either the enthalpy of fusion ($\Delta H_f$) varies little among steroids, or, alternatively, the entropy of fusion ($\Delta S_f = \Delta H_f/T_M$) is nearly constant for the series, then Equation (21) is of the linear form $Y = MX + B$ for all steroids in any polymer, where $X = (1/T - 1/T_M)$ if $\Delta H_f \cong$ constant or $X = (T_M/T - 1)$ if $\Delta S_f \cong$ constant. As will be shown below, the entropy of fusion varies somewhat less from steroid to steroid than does the enthalpy of fusion, so that the temperature function $(T_M/T - 1)$ should be the more successful correlating parameter. That the entropy of fusion should be less variable from steroid to steroid than the enthalpy of fusion is perhaps not surprising, since the major contribution to the entropy change on melting is probably the configurational entropy gain upon loss of crystalline order. Since the lattice arrangements of steroid molecules in their crystalline states are probably all quite similar, so should be the configurational entropy change on melting.

The foregoing analysis leads to the following promising basis for correlation and prediction of the permeability of steroids through polymers; namely, a semilogarithmic plot of the permeability function $\Sigma = J_{max} l \cdot \exp(1 + \chi_{AP})$ vs. the melting temperature function $(T_M/T - 1)$ for a series of steroids in any given polymer should yield a straight line of slope $-(\Delta S_f/R)$ and intercept on the ordinate of $(\rho_A D)$. Since $(\Delta S_f)$ is a property solely of the penetrants (steroids), the slope of the line should be the same for all polymers and (since $\rho_A$ varies but little among steroids) the ordinate intercepts directly proportional to the diffusivity of steroids in the specific polymers. Thus, if the permeability and diffusivity of one steroid in a given polymer are experimentally measured, and the melting temperature of that steroid is known, then the permeability of any steroid in that polymer can be predicted from knowledge only of its melting temperature. Furthermore, if the diffusivity of a steroid molecule in a given polymer can be estimated by interpolation and extrapolation of a diffusivity vs. molecular size correlation for that polymer, it may even be possible to predict the permeability of any steroid in that polymer, even in the complete absence of experimental data relating to steroid permeation in the material. The potential success and utility of this correlation will be tested experimentally below.

## EXPERIMENTAL

The permeation rates of several steroids through various polymer films were measured in diffusion cells consisting of two identical horizontal glass chambers each containing about 20 cm$^3$ of water, separated by the membrane under study. The cell was submerged in a thermostatted water bath permitting temperature control to $\pm 0.1$°C. The membrane (exposed transport area 4.9 cm$^2$) was secured between the chambers by clamps. Small glass paddles rotating at 1000 rev./min. were mounted in each chamber close to the membrane surfaces.

By maintaining a saturated solution of steroid in contact with one surface of the membrane, by contacting the opposite surface with virtually pure solvent (water), and by measuring (by radiochemical or spectrophotometric means) the time rate of change of steroid in concentration in the downstream compartment, it was possible to determine the total flux of steroid between compartments:

$$J_T = V_d/A_m\ dC_d/dt \quad (22)$$

where $V_d$ is the volume of liquid in the downstream compartment, $C_d$ is the steroid concentration in that compartment at time t, and $A_m$ is the cross-sectional area of membrane exposed to solution.

Because of the low solubility of steroids in water, a significant resistance to transport of steroid between cell compartments is offered by the liquid phase boundary layers on both membrane surfaces; this resistance must be determined and corrected for if the true permeability of the membrane to steroid is to be obtained.

The principle of additivity of series resistances to mass transport can be employed to permit the correction, since it can be shown that (under steady state flux conditions)

$$1/J_T = 1/J_M + 1/J_B \qquad (23)$$

where $J_T$ is the experimentally measured flux, $J_M$ is the transmembrane flux which would be measured if the boundary layer resistances were eliminated, and $J_B$ is the flux which would take place across the boundary layers were the membrane infinitely permeable. Since the flux $J_M$ is inversely proportional to membrane thickness ($l$), Equation (23) can be rewritten

$$1/J_T l = 1/J_M l + 1/l\ (1/J_B) \qquad (24)$$

where $(J_M l)$ = a constant, and $J_B \neq f(l)$. Hence, a plot of $(1/J_T l)$ as a function of reciprocal membrane thickness $(1/l)$ should yield a straight line of intercept $(1/J_M l)$ and slope $(1/J_B)$.

Alternatively, the boundary layer resistance correction can be made by recognizing that the resistance to steroid mass transfer through the liquid films bounding the membrane must be inversely proportional to the limiting solubility of the steroid in the liquid phase. Since steroids are highly insoluble in water, but are orders of magnitude more soluble in ethanol, the presence of quite low concentrations of ethanol in water usually raises the steroid solubility substantially (without significant changes in solution viscosity or density). Hence, by measuring the intercompartment flux $J_T$ for a given steroid and membrane, and its variation with steroid solubility effected by addition of ethanol to the aqueous solutions in both compartments, we find that

$$1/J_T = 1/J_M + 1/J_B = 1/J_M + K/C_S \qquad (25)$$

where $C_S$ is the solubility of steroid in the solution phase, and $K$ is a cell constant. Hence, a plot of $(1/J_T)$ vs. $(1/C_S)$ yields a straight line of slope $(K)$ and intercept $(1/J_M)$. We have found for our cells that

$$1/J_B \cong 1320/C_S \text{ cm}^2 \text{ sec}/\mu\text{g} \qquad (26)$$

where $C_S$ is in units of micrograms per cubic centimeter. $J_B$ as determined by Equation (26) was found to be substantially identical to the value determined by Equation (24), confirming the validity of the two relationships and the hypotheses underlying their derivation. It is appropriate to note that the quantity (1320) in Equation (26) has the units of seconds per centimeter and represents the ratio of the effective thickness of the stagnant liquid boundary layer to the molecular diffusivity of steroid in the solution phase. Since the diffusivities of all steroids in water are virtually identical, it follows that the boundary-layer resistance of the permeation cell to each steroid studied can be computed from Equation (26), if we know the water solubility of the steroid in question. This correction was applied to the measured fluxes of all steroids examined to permit calculation of the true transmembrane flux $J_M$.

Initially, the upstream cell chamber is filled with a suspension of crystalline solid steroid in distilled water, and the downstream chamber is filled with distilled water. At certain intervals of time, a 10 cm$^3$ sample is automatically withdrawn from the downstream compartment (which is always maintained at less than 10% of saturation) and measured by UV spectrophotometry; hence, the steady state Fick's equation can be written as

$$J = KD\ [C^* - C_l]/l \cong KD\ C^*/l = DC_A^*/l \qquad (27)$$

where $C^*$ and $C_l$ are the average drug concentrations in the upstream and downstream solutions, respectively, and $K$ is the partition coefficient of steroid between polymer and solution. Since experimental measurement of $C^*$ is much easier than $C_A^*$, the normalized flux $(Jl)$ divided by $(C^*)$ yields the quantity $(KD)$, which can be regarded as the specific permeability coefficient of membrane to a given steroid when the contacting solutions are aqueous solutions.

The diffusivity of the drug in the membrane can also be estimated from measurement of the amount of drug transferred into the downstream cell compartment prior to the establishment of steady state permeation. As shown by Daynes (1920) and by Barrer (1955), solution of Fick's second law for the initial conditions of contacting a penetrant free membrane with a constant activity penetrant source upstream and zero penetrant downstream yields (for large time)

$$M_t = \frac{A_m D C_A^*}{l}\left[t - (l^2/6D)\right] \qquad (28)$$

Table 1. Steroid Properties and Parameters

| Reference number | Compound | Molecular weight | Crystalline density at 25°C g/cm$^3$ ($\rho_A$) | Molar volume, cm$^3$/mole ($V_A$) | Crystalline melting point, °K | Heat of fusion, K cal/g mole ($\Delta H_f$) | Entropy of fusion, cal/g mole °K $\Delta S_f$ | Solubility parameter, (cal/cm$^3$)$^{1/2}$ ($\delta_A$) |
|---|---|---|---|---|---|---|---|---|
| I | 4, 9 Pregnadiene-17$\alpha$ methyl-3, 20 dione | 313 | 1.15 | 272 | 378 | 4.3 | 11.4 | 8.4 |
| II | Progesterone | 315 | 1.17 | 269 | 402 | 6.7 | 16.7 | 8.6 |
| III | 19-Nor Progesterone | 281 | 1.18 | 238 | 419 | — | — | 8.4 |
| IV | Testosterone | 288 | 1.20 | 240 | 428 | 6.9 | 16.1 | 8.9 |
| V | 4, 9, 11 Pregnatriene-18 methyl, 17$\alpha$ ethinyl, 17$\beta$ acetate | 351 | 1.21 | 290 | 438 | 5.4 | 12.3 | 8.6 |
| VI | Estradiol | 272 | 1.24 | 219 | 445 | 9.7 | 21.8 | 10.3 |
| VII | Norgestrel | 325 | 1.24 | 262 | 470 | — | — | 9.6 |
| VIII | Norethindrone | 298 | 1.24 | 240 | 480 | 9.6 | 20.0 | 10.0 |
| IX | Cortisol | 333 | 1.24 | 269 | 487 | 8.1 | 16.6 | 10.4 |
| X | Prednisolone | 361 | 1.26 | 287 | 515 | — | — | 10.2 |
| XI | Estriol | 288 | 1.27 | 227 | 555 | 10.2 | 18.4 | 11.1 |
| | | | | | | 7.6 ± 2.2 (avg) | 16.7 ±3.5 (avg) | |

where $M_t$ is the amount of penetrant present in the downstream compartment at time $t$. If $M_t$ is plotted vs. $t$, the intercept of the limiting straight line extrapolated to $M_t = 0$ yields the so called *lag-time*

$$L = l^2/6D \qquad (29)$$

from which the diffusivity $D$ is readily calculated. Values of D determined in this fashion for certain of the steroid hormones in selected polymers are presented in Table 3.

## STEROID SOLUBILITY IN *n*-HEXANE

In order further to test the thermodynamic basis for correlating steroid permeability with intensive properties of steroid (for example, melting point, heat of fusion), the solubilities (at 37°C) of several steroids in *n*-hexane [$\delta_B = 7.3$ (cal/cm$^3$)$^{1/2}$] were measured by UV spectrophotometry. These results are presented in Table 2; according to Hildebrand (6), the relationship between solubility and steroid properties should (if $\phi_A^* \cong 0$) be approximated by

$$\ln \phi_A^* \Gamma_A^* = \ln \phi_A^* \exp\left[(1 - V_A/V_B) + \chi_{AB}\right]$$

$$= \frac{-\Delta H_f}{RT_M}(T_M/T - 1) \qquad (30)$$

where

$$\chi_{AB} = V_A/RT\,(\delta_A - \delta_B)^2$$

For steroids in hexane, $V_A/V_B \cong 2$, when $\Gamma_A^* \cong 0.37 \exp \chi_{AB}$. The data are plotted according to Equation (30) in Figure 2 and will be discussed below.

## RESULTS AND CONCLUSIONS

Table 1 enumerates the important intensive properties of the eleven steroid hormones examined in this study. The range of melting temperatures represented by the series is quite wide (the spread is nearly 200°C), and, as expected, the variation in mass density and molar volume is small (the mean value of $V_A$ is 255.6 ± 24.0 cm$^3$/mole). Solubility parameter values [calculated by the method of Small, Equations (5) and (6)] tend to show a consistent increase with steroid melting temperature. Experimentally measured values of the heats of fusion ($\Delta H_f$), with one exception, lie between about 5 and 10 k

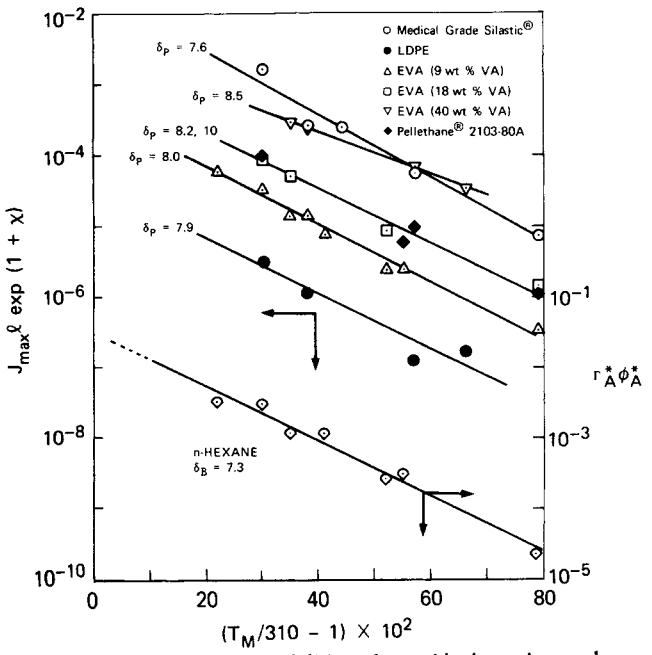


Fig. 2. Correlation of permeabilities of steroids in various polymers with steroid melting temperature.

TABLE 2. STEROID PERMEABILITY/SOLUBILITY DATA AND CORRELATING FACTORS

| Steroids | $\frac{TM}{310} - 1$ | Silastic ($\delta = 7.6$) | | | LDPE ($\delta = 7.9$) | | | 9% EVA ($\delta = 8.0$) | | | 18% EVA ($\delta = 8.2$) | | | 40% EVA ($\delta = 8.5$) | | | Pellethane ($\delta = 10$) | | | *N*-Hexane ($\delta = 7.3$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $J_{max}\ell$ | $\chi$ | $\Sigma$ | $J_{max}\ell$ | $\chi$ | $\Sigma$ | $J_{max}\ell$ | $\chi$ | $\Sigma$ | $J_{max}\ell$ | $\chi$ | $\Sigma$ | $J_{max}\ell$ | $\chi$ | $\Sigma$ | $J_{max}\ell$ | $\chi$ | $\Sigma$ | $\phi_A^*$ | $\Gamma_A^*$ | $\Gamma_A^*\phi_A^*$ |
| I | 0.22 | | | | | | | 20 | 0.07 | 58 | | | | | | | | | | 4.6 | 0.63 | 2.9 |
| II | 0.30 | 395 | 0.44 | 1,700 | 1.0 | 0.21 | 3.4 | 9.8 | 0.16 | 31 | 31 | 0.07 | 90 | | | | 15.8 | 0.86 | 100 | 3.4 | 0.78 | 2.7 |
| III | 0.35 | | | | | | | 4.9 | 0.06 | 14 | 18 | 0.02 | 50 | 105 | 0.004 | 290 | | | | 1.8 | 0.59 | 1.1 |
| IV | 0.38 | 51 | 0.66 | 270 | 0.27 | 0.39 | 1.1 | 4.0 | 0.32 | 15 | | | | 88 | 0.06 | 250 | | | | | | |
| V | 0.41 | | | | | | | 2.7 | 0.17 | 8.7 | | | | | | | | | | 1.3 | 0.81 | 1.1 |
| VI | 0.44 | 7.0 | 2.6 | 260 | | | | | | | | | | | | | | | | | | |
| VII | 0.52 | | | | | | | 0.41 | 1.1 | 3.4 | 1.4 | 0.83 | 8.7 | | | | | | | 0.065 | 3.7 | 0.24 |
| VIII | 0.55 | | | | | | | 0.27 | 1.6 | 3.6 | | | | | | | 2.2 | 0 | 6.0 | 0.046 | 5.9 | 0.27 |
| IX | 0.57 | 0.70 | 3.4 | 57 | 0.003 | 2.7 | 0.12 | | | | | | | 5.3 | 1.6 | 71 | 1.8 | 0.07 | 9.9 | | | |
| X | 0.66 | | | | 0.0055 | 2.5 | 0.18 | | | | | | | 3.3 | 1.3 | 33 | | | | | | |
| XI | 0.79 | 0.029 | 4.5 | 7.1 | | | | 0.0048 | 3.5 | 0.43 | 0.025 | 3.1 | 1.5 | | | | 0.28 | 0.45 | 1.2 | 2.7(10)$^{-4}$ | 74 | 0.02 |

$J_{max}\ell$, in $\mu$g/cm $s \times 10^6$.
$\chi = V_A/RT\,(\delta_A - \delta_B)^2$.
$\Sigma = (J_{max}\ell)\exp(1 + \chi)$, $\mu$g/cm $s \times 10^6$.
$\phi_A^*$, cm$^3$ solute/cm$^3$ solution $\times 10^3$.
$\Gamma_A^* = \exp[V_A/RT\,(\delta_A - \delta_B)^2]$.
$\Gamma_A^*\phi_A^*$ = cm$^3$ solute/cm$^3$ solution $\times 10^3$.

cal/mole; the average value for the series is 7.6 ± 2.2 k cal/mole. There is, however, a detectable trend toward increasing $\Delta H_f$ with increasing melting temperature, suggesting that the entropy of fusion ($\Delta S_f = \Delta H_f/T_M$) is more nearly constant for the steroid series than the enthalpy of fusion. The average value of $\Delta S_f$ is 16.6 ± 3.4 cal/(mole) (°K).

Hence, a semilogarithmic plot of the argument ($\Sigma$) vs. ($T_M/T - 1$) should be a straight line of slope ($-\Delta S_f/R$) and intercept ($\rho_A D$).

The observed parallel trends of melting points, heats of fusion, and solubility parameters among the steroids studied are consistent with the concomitant increase in polarity of the steroid molecules with their melting temperatures. This is particularly evident in the sequence progesterone < testosterone < estradiol < estriol, which have virtually identical structures but for their hydroxyl substitutions, which are, respectively 0, 1, 2, and 3 per molecule. It is thus apparent that dipolar and/or hydrogen bonding interactions between steroid molecules contribute not only to molar cohesion in the liquid state (as reflected in the solubility parameter) but also to the thermal stability of the crystal lattice in the normal solid state.

Table 2 summarizes the experimentally determined normalized fluxes ($J_{max}l$) of the various steroids in the polymers studied ($T = 310$°K) and computed values of $\chi_{AP}$, $[J_{max}l \cdot \exp(1 + \chi_{AP})]$, and ($T_M/T - 1$) for each steroid/polymer pair. These latter parameters are used to test the applicability of Equation (21) to the experimental data. Also included in Table 2 are the experimentally determined solubilities (310°K) of the various steroids in *n*-hexane and corresponding estimated values of the activity coefficients ($\Gamma_A$) and activities ($\Gamma_A\phi_A$) of the steroids in these solutions as determined by Equation (18*a*):

$$\Gamma_A \cong \exp\,[V_A/RT\,(\delta_A - \delta_B)^2], \quad \text{for} \quad \phi_A \sim 0, \quad V_A = 2V_B$$

The polymers studied (in order of increasing solubility parameter) were as follows:

Poly(dimethylsiloxane) ($\delta_P = 7.6$): Dow-Corning Medical Grade Silastic with silica fillers.

Low density polyethylene ($\delta_P = 7.9$): Petrothene NA 254, manufactured by USI; density (20°C) 0.929 g/cc; crystallinity approximately 53%.

Poly(co ethylene-vinyl acetate) containing 9% vinyl acetate by weight ($\delta_P = 8.0$: UE 637 (USI); density 0.928 g/cc; crystallinity approximately 47%.

Poly(co ethylene-vinyl acetate) containing 18% vinyl acetate by weight ($\delta_P = 8.2$): UE 630 (USI); density 0.936 g/cc; crystallinity approximately 31%.

Poly(co ethylene-vinyl acetate) containing 40% vinyl acetate by weight ($\delta_P = 8.5$): Elvax 40 (Du Pont); crystallinity approximately zero.

Poly (co polytetramethylene ether glycol-diphenylmethane di-isocyanate); ($\delta_P = 10.0$): Pellethane 2103-80A (Upjohn).

Figure 2 plots for each polymer studied the permeability function defined by Equation (21) and computed from experimentally measured permeability values for each steroid studied, as a function of ($T_M/T - 1$), where $T_M$ is the measured (or reported) melting point of each steroid ($T = 310$°K). Also plotted in this figure, vs. the same temperature function, are the activities of various steroids in *n*-hexane at 310°K, which are defined by Equation (30), employing measured values of steroid solubilities in hexane.

The data for each polymer are indeed well approximated by straight lines, whose slopes do not differ markedly, as shown in Table 3. The mean value of the slope for the six polymers is 8.6 ± 1.1, remarkably close to the value predicted from the mean entropy of fusion (8.43 ± 1.8). The slope of the activity vs. melting temperature line for steroids in *n*-hexane (8.8) is also close to the predicted value, thus lending support to the applicability of the thermodynamic model for predicting solubilities. Extrapolation of the n-hexane line to ($T_M/T - 1$) = 0 does not, however, correspond to unit activity (that is, $\phi_A^* \Gamma_A^* = 1.0$) as Equation (30) predicts but rather to an activity of about 0.03. This suggests the existence of an additional (solute independent) contribution to the entropy of mixing of the order of magnitude of $-R \ln 30 = -6.8$ cal/mole°K, which depresses steroid solubility by over an order of magnitude below that predicted from heat of mixing and ideal entropy of dilution considerations alone. If this correction applies to the solubility of steroids in the polymers as well as in *n*-hexane, then the intercepts determined by extrapolation of the permeability functions to ($T_M/T - 1$) = 0 will be about one-thirtieth the value of $\rho_A D$ rather than equal to $\rho_A D$ as predicted by Equation (21).

In Table 3 we have calculated values of the line intercepts for each polymer studied and from their values estimated the diffusivities of the steroids in the various polymers. The values so determined are quite reasonable for molecules of the dimensions of steroids in flexible-chain polymer matrices; indeed, for Silastic and low-density polyethylene (which ethylene/vinyl acetate copolymers of low ester content may be considered to resemble), correlations of penetrant diffusivity with penetrant molecular diameter (2) predict values for steroids (whose effective diameter is estimated to be about 11Å) surprisingly close to those estimated from the line intercepts of Figure 2, as Table 3 illustrates.

TABLE 3. CORRELATING PARAMETERS FROM FIGURE 1 [SEE EQUATION (21) AND (29)]

| Polymer | $\Delta S_f/R$ From slope of best line | $\Delta S_f/R$ Experimental | Difference, % | $\Sigma_0$ (from intercept) $\mu$/cm s | $D_{app} \cong 30$ $\Sigma_0/\rho_A$, cm²/s | $D$ (experimental) cm²/s | $D$ Predicted* assuming diameter of the steroid = 11A cm²/s |
|---|---|---|---|---|---|---|---|
| Silastic® | 10.1 | | 20% | $2.1\,(10)^{-2}$ | $5.4\,(10)^{-7}$ | $6\,(10)^{-7}$ | $2\,(10)^{-7}$ |
| LDPE | 9.0 | | 7% | $4\,(10)^{-5}$ | $1\,(10)^{-9}$ | $1\,(10)^{-9}$ | $3\,(10)^{-9}$ |
| EVA (9% VA) | 9.3 | 8.43 | 10% | $4.3\,(10)^{-4}$ | $1.1\,(10)^{-8}$ | $4\,(10)^{-9}$ | $3\,(10)^{-9}$ |
| EVA (18% VA) | 8.2 | ±1.8 | 3% | $1.2\,(10)^{-3}$ | $3\,(10)^{-8}$ | $3\,(10)^{-9}$ | $3\,(10)^{-9}$ |
| EVA (40% VA) | 7.0 | | 17% | $2.1\,(10)^{-3}$ | $5.4\,(10)^{-8}$ | $5\,(10)^{-9}$ | $3\,(10)^{-9}$ |
| Pellethane® 2103-80A | 8.2 | | 3% | $1.2\,(10)^{-3}$ | $3\,(10)^{-8}$ | $9\,(10)^{-10}$ | — |
| *N*-Hexane | 8.84 | 8.43 ± 1.8 | 5% | | | | |

* From published data on variations of diffusivity of gaseous penetrants in polymers with molecular diameter.

## ACKNOWLEDGMENT

The assistance of M. Baugh and K. Smith in the generation of the experimental data reported herein is gratefully acknowledged. The authors also wish to thank Professor J. M. Prausnitz for his generous assistance and enthusiastic encouragement in the development of the thermodynamic treatment.


## NOTATION

$a_A$, $a_A^*$ = activity and activity in saturated solution of solute $A$, respectively
$A_m$ = diffusional area of the membrane, cm$^2$
$C$, $C^*$ = concentration and saturation concentration of solute in liquid, respectively, $\mu$g/cm$^3$
$C_A$, $C_A^*$ = concentration and saturation concentration of solute $A$ in polymer, respectively, $\mu$g/cm$^3$
$C_d$ = solute concentration in the downstream compartment, $\mu$g/cm$^3$
$C_s$ = solubility of solute in liquid, $\mu$g/cm$^3$
$D$ = diffusivity, cm$^2$/s
$f_A$ = fugacity of solute, $A$
$\Delta G$, $\Delta\overline{G}$ = the change in molar and partial molar free energy respectively
$\Delta H_f$ = heat of fusion, K cal/mole
$J$ = steady state flux, $\mu$g/cm$^2$ s
$K$ = partition coefficient of solute between polymer and solution, or permeation cell constant
$l$ = membrane thickness, cm
$L$ = lag-time of the diffusion experiment
$M_A$ = molecular weight of solute, $A$
$M_t$ = amount of penetrant present in the downstream compartment at time, $t$
$R$ = gas constant, cal/mole °K
$\Delta S_f$ = entropy of fusion, cal/mole °K
$T_M$ = melting point of crystalline solid, °K
$T$ = absolute temperature, °K
$V_A$, $V_B$ = molar volume of solute $A$ and solvent $B$, respectively, cm$^3$/mole
$V_d$ = volume of liquid in the downstream compartment of the permeation cell
$X_A$, $X_B$ = mole fraction of solute $A$ and solvent $B$, respectively

### Greek Letters

$\Gamma_A$, $\Gamma_A^*$ = volume fraction normalized activity coefficient of solute $A$ and the activity coefficient at saturation, respectively
$\gamma_A$, $\gamma_A^*$ = mole fraction normalized activity coefficient of solute $A$ and at saturation, respectively
$\delta_A$, $\delta_P$ = solubility parameters of solute $A$ and of polymer respectively, [cal/cm$^3$]$^{1/2}$
$\rho_A$ = density of solute, g/cm$^3$
$\phi_A$, $\phi_A^*$ = volume fraction of solute $A$ in solution and the saturated volume fraction, respectively
$\phi_P$, $\phi_P^*$ = volume fraction of polymer in solution and the saturated volume fraction, respectively
$\chi_{AP}$, $\chi_{AB}$ = interaction parameter between solute $A$ with polymer and with solvent, respectively

## LITERATURE CITED


Barrer, R. M., Diffusion in and through Solids, Cambridge University Press, England (1955).
Daynes, H. A., *Proc. Roy. Soc.*, **A97**, 286 (1920).
Flory, P. J., *Principles of Polymer Chemistry*, pp. 513-514, Cornell University Press, Ithaca, N. Y. (1953).
Gardon, J. L., "Cohesive Energy Density," *Encyclopedia of Polymer Science and Technology*, Vol. 3, p. 884, Wiley, New York (1965).
Hildebrand, J. H., and R. L. Scott, *The Solubility of Nonelectrolytes*, 3 ed., Dover Publications, New York (1964).
Huggins, M. L., *J. Phys. Chem.*, **46**, 151 (1942).
Michaels, A. S., and H. J. Bixler, "Membrane Permeation: Theory and Practice," in *Progress in Separation and Purification*, E. S. Perry, ed., Vol. I, pp. 143-186, Interscience, New York (1968).
Small, P. A., *J. Appl. Chem.*, 3, 71 (1953).



*Manuscript received April 17, 1975; revision received May 30, and accepted June 2, 1975.*


# Flooding Rates and Holdup in Packed Liquid-Liquid Extraction Columns


**Countercurrent flow of liquids in columns packed with Raschig rings was studied with fluids having a wide range of physical properties. These results, along with data reported previously from other studies, were used to develop a correlation for predicting flooding rates in packed columns that is significantly better than previous correlations. Dispersed phase holdup in packed columns can be estimated over a wide range of flow rates or flow ratio by assuming a constant slip velocity between the two phases which is dependent on the properties of the fluids and packing used. Although the slip velocity is thus essentially constant at flow rates below flooding, the flooding rate correlation indicates that this term is not necessarily constant at flooding conditions.**



**J. S. WATSON, L. E. McNEESE, JOHN DAY, and P. A. CARROAD**

**Oak Ridge National Laboratory**
**Oak Ridge, Tennessee 37830**

John Day is with IRECO Chemicals, Salt Lake City, Utah. P. A. Carroad is at the University of California at Berkeley, Berkeley, California.