Nicotine Base Permeation through Silicone Elastomers: Comparison of Dimethylpolysiloxane and Trifluoropropylmethylpolysiloxane Systems

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Abstract □ The rate of release of nicotine base from several silicone polymer systems was studied relative to diffusivity and solubility characteristics. Tubes composed of dimethylpolysiloxane released nicotine base rapidly: >75% in 4 hr. The same tubing with two external fluorosilicone laminations reduced release to about 40% in 4 hr. Tubes made of the silicone derivative trifluoropropylmethylpolysiloxane caused a substantial reduction in transmission of nicotine base. Drug permeability through dimethylpolysiloxane was >20 times more rapid than through the trifluoropropylmethylpolysiloxane system. Solubility of nicotine base in the dimethylpolysiloxane and trifluoropropylmethyl derivative membranes was estimated to be 201.4 and 112.9 mg/ml, respectively. The decreased permeability through the trifluoropropylmethylpolysiloxane polymer appears to be due to reduced diffusivity and solubility. The lower diffusivity cannot be explained on the basis of an increased effective diffusional path length since tortuosity values of about 1.0 were calculated for both polymers. Drug adsorption to filler and greater molecule–polymer interaction within the free volume matrix of the trifluoropropylmethylpolysiloxane polymer appear to be the predominant factors retarding the efflux of the nicotine. The release process was found to obey first-order kinetics by utilizing sigma-minus plots. It appears that the dimethylpolysiloxane membrane is much less suitable than the trifluoropropylmethyl derivative if one wishes to use nicotine experimentally as a timed-release preparation. Of major import is that, for other small molecules having physical–chemical characteristics similar to nicotine base, trifluoropropylmethylpolysiloxane polymers may be the most suitable drug vehicles if timed release is desirable.

Keyphrases □ Silicone elastomers—nicotine base permeation, comparison of dimethylpolysiloxane and trifluoropropylmethylpolysiloxane systems, diffusivity and solubility characteristics, application to timed-release preparations □ Nicotine base—permeation, comparison of dimethylpolysiloxane and trifluoropropylmethylpolysiloxane systems, timed-release formulation implications, diffusivity and solubility characteristics □ Dimethylpolysiloxane—nicotine base permeation, compared to trifluoropropylmethylpolysiloxane, diffusivity and solubility characteristics, timed-release formulations considered □ Trifluoropropylmethylpolysiloxane—nicotine base permeation, compared to dimethylpolysiloxane, diffusivity and solubility characteristics, timed-release formulations considered □ Timed-release formulations—comparison of dimethylpolysiloxane and trifluoropropylmethylpolysiloxane as vehicles, nicotine base permeation

In 1962, Ballard and Nelson (1) discussed the processes controlling the release of solid drugs from pellets used as subcutaneous implants. More recent research in this area has revolved around newer drug delivery systems, such as those prepared from silicone polymers, since these can provide timed release of many types of drugs (2–7). An added advantage of the use of silicone materials is that they produce minimal adverse tissue reactions when surgically implanted (8).

Higuchi (9) presented theoretical considerations for the timed release of solid drugs in matrixes. Steroid drugs can be incorporated into silicone matrixes and are then slowly released (3). Contrary to this, a small molecule like nicotine base diffuses through these membranes very rapidly (10). Most studies involving silicone membrane materials utilized the dimethylpolysiloxane elastomer.

Several other derivatives of polysiloxane are available and these exhibit differential permeability characteristics relative to various permeant molecules. For example, trifluoropropylmethylpolysiloxane membranes have been found to be less permeable than dimethylpolysiloxane to some steroids (11), thus reducing their release rate. Membranes composed of this type of material might be expected to reduce the release rate of a drug like nicotine similarly.

The studies reported here evaluate the potential for polysiloxane polymer membranes, prepared as tubes, to release nicotine base at a predictable rate over an extended period. Such tubes are easy to implant in animals and could be used to study chronic effects of nicotine and other drugs on biochemical and physiological functions.

EXPERIMENTAL

General Considerations—Transmission of a drug through a given synthetic membrane is dependent upon several factors. One important factor is the concentration gradient across the membrane, since diffusion through these membranes appears to follow Fick's law for various types of drugs (12–15). Permeability *(P)* through a *planar* silicone membrane can be described in terms of diffusion and solubility by Eq. 1 for the case where pure drug is initially in contact with the membrane:

$$P = D \times S \qquad \text{(Eq. 1)}$$

Here D is the apparent diffusivity (diffusion coefficient) in units of square centimeters per second, and S is the solubility of the permeant substance in the membrane phase. Units of milligrams per centimeter per second are usually given to the permeability. Diffusivity is a property of the permeant molecular size and temperature (16), in addition to the type and structure of the polymer membrane used (17, 18). Diffusivity and solubility are parameters that can be obtained experimentally and then used to estimate permeability values.

The diffusivity of a permeant molecule through a *hollow cylinder* of a silicone polymer can be calculated from Eq. 2 (19, 20):

$$D = \frac{(b^2 - a^2) + [(a^2 + b^2)] \ln a/b}{4L(\ln a/b)} \qquad \text{(Eq. 2)}$$

The designations a and b are the internal and external radii (centimeters) of the cylinder, respectively; L is the lag time (seconds) before steady-state diffusion is reached. A value for L can be obtained graphically by extrapolation of the tangent to the curve of the amount of permeant diffused *versus* time to the time *(x)* intercept (20).

If one assumes that at any given point along the inside cylinder wall a single permeant molecule "sees" the surface it enters as being planar, then a simplified expression (21) may be applied to calculate the diffusivity:

$$D = \frac{h^2}{6L} \qquad \text{(Eq. 3)}$$

where D is again the diffusivity (square centimeters per second), h is the membrane thickness (centimeters), and L is the lag time (seconds) before steady-state diffusion is reached. It will be shown later that diffusivities calculated from either Eq. 2 or 3 agree with one another very well.

Solubility of the permeant in the membrane also plays a significant part in the overall permeation process (13, 22). For polar or unsaturated molecules, an accurate value for this parameter is not easily determined, since commercial silicone rubbers generally contain porous fillers that may adsorb or sequester permeant molecules (23). An apparent solubility may be estimated by equilibration of the given membrane material (without filler) with a solution of the permeant.

Samples of the solution can be assayed over time and a solubility value can be obtained at equilibrium and used with diffusivity to calculate permeation through the matrix. In filled membranes, corrections for the volume fraction of filler and the adsorptive capacity also can be applied if the filler is known and is available in pure form.

Materials—The following three types of heat-vulcanized tubings were studied[1]: *(a)* dimethylpolysiloxane, *(b)* dimethylpolysiloxane with two external fluorosilicone laminations, and *(c)* trifluoropropylmethylpolysiloxane. Nicotine base[2] (grade 1, 99% pure) was constituted with *N*-methyl-^{14}C-nicotine base[3] (26 mCi/mmole) prior to incorporation into the silicone tubes. The aqueous desorbing medium (pH 7.4) was composed of 0.022 *M* $NaH_2PO_4 \cdot H_2O$ and 0.104 *M* Na_2HPO_4.

Methods—Dimethylpolysiloxane tubings, with and without two external fluorosilicone laminates, were prepared in lengths of 3 cm containing 25 μl (25.24 mg = 0.155 mmole) of the liquid ^{14}C-nicotine base (specific activity of 1.61 mCi/mmole). The ends were sealed with steel plugs immediately prior to suspension in the desorbing solution. Tubes of trifluoropropylmethylpolysiloxane were prepared[4] by heat vulcanization in special molds; one end of the tube was sealed in this process. These tubes were filled with 50 μl (50.48 mg = 0.310 mmole) of ^{14}C-nicotine base, and the open end was sealed with special room temperature vulcanizing silicone cement[5].

After preparation, each tube was suspended with silk thread into a 125-ml flask containing 100 ml of the pH 7.4 desorbing buffer. Flasks were maintained at 37° and shaken (about 70 oscillations/min) in an incubator[6]. Duplicate 100-μl samples were taken from the desorbing solution at specific time intervals and counted in a liquid scintillation spectrometer[7] using a commercial scintillation fluid[8] suitable for aqueous samples. All counts per minute were corrected to disintegrations per minute by internal standardization with ^{14}C-toluene (70–75% efficiency). The percent of nicotine base released at any given time was calculated from the total nicotine activity initially within the tube and the values obtained at sampling times.

Ionized compounds are known not to permeate silicone membranes (12, 13). Nicotine base has pK values of 3.10 and 8.01 at 25° (24). Therefore, nicotine entering the desorbing solution at pH 7.4 would be primarily in the form of the monovalent pyrrolidinium cation and thus unable to pass back through the membrane effectively *via* retrograde diffusion. In addition, factors such as the large volume (100 ml) of desorbing medium relative to the amount (25–50 mg) and the solubility (>1 g/ml) of nicotine base in the buffer indicate that sink conditions could be assumed to exist.

For determination of the solubility of nicotine in the polymers studied, standard pieces of dimethylpolysiloxane and trifluoropropylmethylpolysiloxane were cut from specially prepared *fillerless* sheets of uniform thickness. Each piece was placed in a glass scintillation vial and covered completely with pure nicotine base. Duplicate vials for each polymer were prepared in this manner.

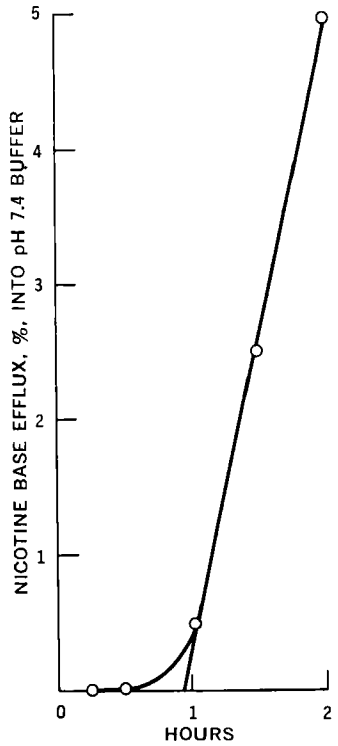

Figure 1—*Plot of steady-state portion of diffusion curve for nicotine base release from trifluoropropylmethylpolysiloxane tubing into pH 7.4 buffer at 37°. The intercept on the time axis is the lag time, estimated to be 55 min.*

The vials were shaken in an incubator[6] at 37°; they were removed periodically, blotted dry, and weighed until constant weight was obtained (about 8 days). The specific gravity of each polymer was determined by water displacement, and the solubility of nicotine was calculated (expressed as per milliliter of polymer volume and as per gram of polymer mass).

RESULTS

Diffusivity and Permeability—Lag times were estimated by extrapolation of linear portions of percent release *versus* time curves, according to the method of Barrer (21). Nicotine base permeated the plain (unlaminated) dimethylpolysiloxane membrane very rapidly, with an estimated lag time of only 2 min. An extrapolated value of about 26 min was obtained for the fluorosilicone-laminated membrane. The trifluoropropylmethyl derivative membrane delayed initial release most effectively and had an estimated lag time of 55 min (Fig. 1 and Table I).

Apparent diffusivity values were calculated for the three types of tubings using Eqs. 2 and 3. Diffusivity decreased in the fluorosilicone-laminated membrane compared to unlaminated dimethylpolysiloxane and decreased still further in the trifluoropropylmethyl polymer. Agreement between values calculated with Eqs. 2 and 3 was good (Table I), thus establishing the validity for application of either equation to determine nicotine base diffusivity under the present experimental conditions.

Perhaps more precise diffusivity values might have been calculated if fillerless tubings had been available for these studies; Most (23) claimed that filled materials may yield less "true" values when the lag time method is utilized. However, the tubings contained approximately equal amounts of filler so that comparisons between the tubings under these conditions are valid.

For calculation of diffusivities using Eq. 2, the internal *(a)* and external *(b)* radii of the tubings were used to determine the D_1 values shown in Table I. These radii were (in centimeters): a = 0.075 and b = 0.125 for dimethylpolysiloxane, a = 0.060 and b = 0.180 for fluorosilicone-laminated dimethylpolysiloxane, and a = 0.119 and b = 0.193 for the trifluoropropylmethylpolysiloxane tubing.

Solubility of nicotine base in the dimethylpolysiloxane and the trifluoropropylmethylpolysiloxane membranes (cured without filler) was determined to be 201.40 (194.60) and 112.90 mg/ml (88.90 mg/g) at 37°, respectively. The specific gravity of each type of

[1] All silicone membrane materials used were gifts from Dow Corning Corp., Midland, Mich.
[2] Sigma Chemical Co., St. Louis, Mo.
[3] International Chemical and Nuclear Corp., Cleveland, OH 44128
[4] At the Dow Corning Corp.
[5] Due to the small surface area of the sealed ends of the trifluoropropylmethylpolysiloxane tubes relative to total surface area, diffusion of drug through the ends was considered negligible.
[6] Dubnoff.
[7] Packard 2002, Packard Instruments, Downers Grove, Ill.
[8] Insta-Gel, Packard Instruments, Downers Grove, Ill.

Table I—Comparison of Apparent Nicotine Base Diffusivity at 37° in Three Types of Silicone Elastomeric Tubings

Tubing Type	Wall Thickness, cm	Lag Time, sec	D_1, cm²/sec[a]	D_2, cm²/sec[b]	Difference[c], %	Permeability, mg/cm/sec[d]
Dimethylpolysiloxane	0.050	120	3.47×10^{-6}	3.42×10^{-6}	1.44	6.95×10^{-4}
Dimethylpolysiloxane + fluorosilicone laminates	0.120	1560	1.54×10^{-6}	1.57×10^{-6}	1.95	3.14×10^{-4}
Trifluoropropylmethyl-polysiloxane	0.074	3300	2.69×10^{-7}	2.78×10^{-7}	3.34	3.09×10^{-5}

[a] D_1 is the apparent diffusivity calculated from Eq. 2 (19). [b] D_2 is the apparent diffusivity calculated from Eq. 3 (20). [c] $(D_1 - D_2)/D_1 \times 100$. [d] Calculated using the mean value, $(D_1 + D_2)/2$.

cured polymer was determined to be 0.966 and 1.270 g/ml for the dimethylpolysiloxane and trifluoropropylmethyl polymers, respectively. The assumption was made that the solubility of nicotine in the dimethylpolysiloxane polymer could be used for calculation of the permeability parameter in the case of the dimethylpolysiloxane fluorosilicone-laminated system.

Permeability values for each system were estimated with Eq. 1 from the experimentally determined solubilities and the *mean* diffusivity ($D_1 + D_2/2$) values (Table I). The mean values used in the calculation were: dimethylpolysiloxane = 3.45×10^{-6} cm²/sec, fluorosilicone laminated = 1.56×10^{-6} cm²/sec, and trifluoropropylmethylpolysiloxane = 2.74×10^{-7} cm²/sec.

There was a considerable reduction in permeability through the trifluoropropylmethyl derivative membrane compared to dimethylpolysiloxane: 3.09×10^{-5} *versus* 6.95×10^{-4} mg/cm/sec. The fluorosilicone-laminated tubing gave an intermediate permeability value of 3.14×10^{-4} mg/cm/sec (Table I).

First-Order Release Characteristics—In addition to studying the physical parameters of diffusivity and permeability, the release kinetics of nicotine base from these systems were determined. Initially, plotting the cumulative percent of nicotine base released *versus* time for the dimethylpolysiloxane and the laminated systems illustrated that the laminated tubing released only about 65% of the nicotine after 16 hr compared to about 92% from the plain dimethylpolysiloxane system over the same period (Fig. 2).

Further analysis was attempted by graphing data for the trifluoropropylmethylpolysiloxane system as a sigma-minus plot (26, 27). In this type of plot, the log of the amount of nicotine base remaining to be released at any given time $(A^\infty - A)$ is plotted as a linear regression on time in days (Fig. 3). An excellent linear relationship was obtained ($r = -0.999$) for release into pH 7.4 buffer. From this plot, an apparent rate constant (K) was calculated from the relation $K = 2.303 \times$ slope. The K value derived in this manner was used to calculate the amount of nicotine released at specific times, assuming first-order kinetic processes and using the following standard expression:

$$A = A^\infty[1 - e^{-Kt}] \qquad \text{(Eq. 4)}$$

Here A is the cumulative amount of nicotine base released at any time t, and A^∞ is the total amount released from the system. A plot of values calculated according to this first-order relationship gave essentially the same curve as that generated experimentally (Fig. 4). A first-order rate constant of 0.357 day^{-1} was obtained for the release from the trifluoropropylmethylpolysiloxane tubing. Therefore, nicotine base release from this system appears to obey first-order rate kinetics.

In a separate experiment the efflux of nicotine base from the trifluoropropylmethyl polymer system into *n*-octanol was studied and analyzed in the same manner. In this case, there was again excellent agreement between the experimental values and those calculated assuming first-order release kinetics (Fig. 5).

DISCUSSION

Nicotine base is an oily liquid at room temperature and was present in this form in the tubings used. This compound has a substantial ability to dissolve directly in the silicone polymer membranes discussed. Some steroid derivatives such as medroxyprogesterone acetate are released slowly when the solid form is incorporated into dimethylpolysiloxane membrane systems (25). In the case of solid drugs, the permeation process is thought to be dissolution rate controlled rather than diffusion controlled (22). Unlike steroids, the permeation rate for nicotine base was rapid; this apparently is due to its good solubility and high diffusivity within the dimethylpolysiloxane polymer. Thus, release of this small molecule in its liquid state appears to be diffusion controlled.

External fluorosilicone lamination of the dimethylpolysiloxane

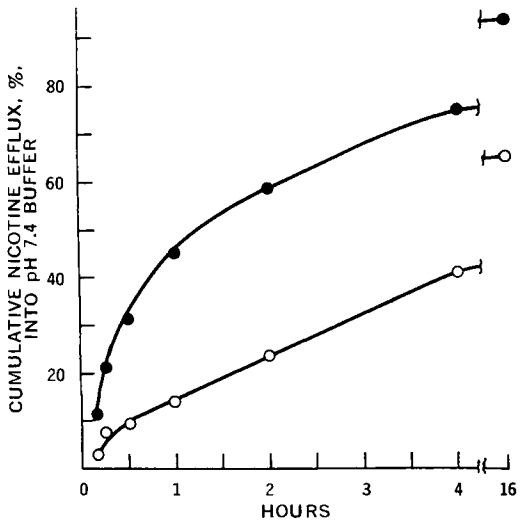

Figure 2—*Plot of the cumulative amount of nicotine base released from unlaminated dimethylpolysiloxane* (●) *and dimethylpolysiloxane + fluorosilicone-laminated polysiloxane* (○) *tubings into pH 7.4 buffer at 37°.*

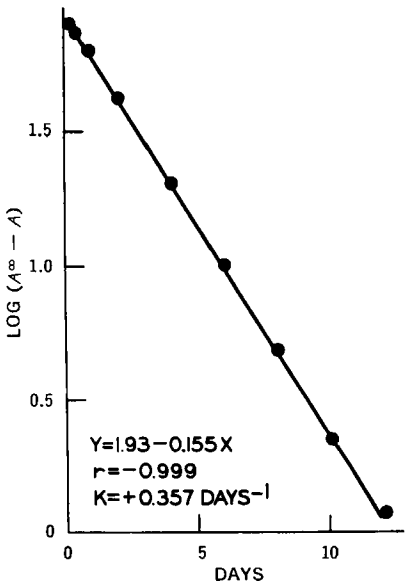

Figure 3—*Sigma-minus plot of the percent of nicotine base remaining to be released from trifluoropropylmethylpolysiloxane tubing into pH 7.4 buffer at 37°* ($A^\infty = 97\%$).

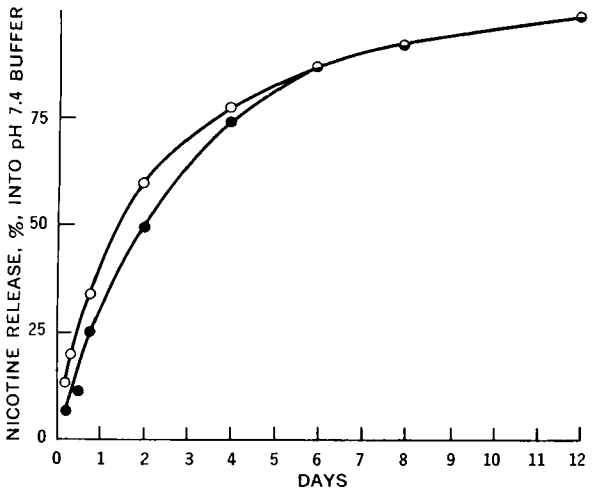

Figure 4—*Comparison of experimentally determined (actual) release* (○) *of nicotine base from trifluoropropylmethylpolysiloxane into pH 7.4 buffer with theoretical release* (●) *calculated with Eq. 4 (see text).*

membrane reduced permeability. It is not clear from these experiments whether the fluorosilicone layers retarded permeation by decreasing the diffusivity of nicotine or by acting as a final barrier in which the nicotine base was less soluble compared to the bulk membrane. The laminations comprise only a minor component of the overall membrane thickness, as reflected by the relatively small reduction in permeability.

A considerable reduction in permeability was obtained with the trifluoropropylmethyl derivative of polysiloxane. The permeability value for transport through the trifluoropropylmethylpolysiloxane membrane was less than 5% of that through the dimethylpolysiloxane system. A similar reduction in release of nicotine from the trifluoropropylmethylpolysiloxane compared to dimethylpolysiloxane tubes was recently shown *in vivo* after subcutaneous dimethylpolysiloxane implantation (28).

Various interactions within the membrane determine the overall release rate of a given drug. For nicotine, the reduction in permeation through the trifluoropropylmethylpolysiloxane membrane appears to be derived from reductions in both diffusivity and solubility. Reduced diffusivity may arise from greater molecular interaction of the nicotine with the trifluoropropyl or the methyl side-chain moieties of the polysiloxane matrix.

Filler effects may also be responsible for reduced diffusivity (23). The filler in these tubings was present in approximately equal amounts (±5%) in each type of membrane studied, but further details as to the exact filler type, particle size, exact quantity incorporated, and specific catalyst used in preparation were not

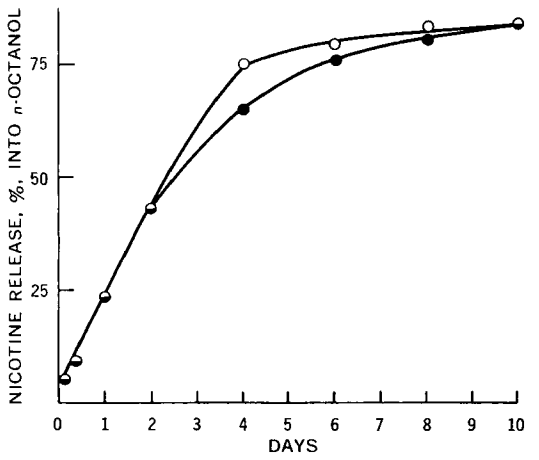

Figure 5—*Comparison of experimentally observed release* (○) *of nicotine base from trifluoropropylmethylpolysiloxane into n-octanol at 37° with theoretical release* (●) *calculated with Eq. 4 (see text).*

available. Flynn and Roseman (29) have given an expression for estimation of lag times in heterogeneous dimethylpolysiloxane barriers when filler effects may be operative. Their expression (Eq. 5) includes a tortuosity term, τ, which reflects an apparent "increased average diffusional path" for a permeant:

$$L = \frac{\tau^2 h^2}{6D} \qquad \text{(Eq. 5)}$$

Rearrangement gives the expression for calculating tortuosity:

$$\tau = \left(\frac{L6D}{h^2}\right)^{1/2} \qquad \text{(Eq. 6)}$$

By using this equation, tortuosity values of 0.970 and 1.01 were calculated for the dimethylpolysiloxane and trifluoropropylmethylpolysiloxane membranes, respectively. A value of $\tau = 1.00$ indicates that the diffusional path length is not effectively reduced within the matrix; thus the reduced diffusivity of nicotine could be due to adsorption by the filler. However, since the tubings contained about the same quantity of filler, the reduced diffusivity in the trifluoropropylmethyl polymer system may be due more to molecule–polymer interactions in the free volume phase of the matrix.

Sigma-minus plots to show first-order release kinetics are useful for obtaining rate constants. These K values may then be used to estimate the rate of permeation through silicone membrane systems more directly, without determining diffusivities, solubilities, and permeabilities. When comparing release into pH 7.4 buffer and *n*-octanol, it was noted that there was a slightly reduced rate of efflux into the *n*-octanol and a lesser maximum value was attained. These rate differences were minor, but the diminished values for the *n*-octanol case may be related to a change in sink conditions, *i.e.*, from the aqueous to the lipoidal external phase. Some retrograde partitioning (and diffusion) of *uncharged* nicotine could also have been occurring between this lipoid-desorbing medium and the nonpolar siloxane membrane.

Analysis of permeation based on diffusivity and first-order release indicates that the dimethylpolysiloxane membrane material is not suitable for prolonging the release of nicotine base or perhaps other small molecules having similar physical–chemical characteristics. The trifluoropropylmethylpolysiloxane membrane, however, does delay release of this compound effectively. By altering membrane thickness and length of this type of tubing, liquid nicotine may be administered over prolonged periods from subdermal implants.

Other salt forms of nicotine may also be of use if they can be shown to be released from silicone membrane systems. Copermeants may similarly be useful to modify transport through such membranes, since these can exert various influences by complexation externally or within the polymer phase (30, 31).

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Charge-Transfer Complexes in Alkaloid Assay

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Abstract □ The intense charge-transfer UV bands in the spectra of molecular complexes of iodine with amines were utilized in a sensitive spectrophotometric assay of alkaloids. Solutions of the alkaloids in chloroform or carbon tetrachloride when mixed with iodine in the same solvent exhibited blue-shifted iodine bands in the 270–305-nm range. Owing to the high molar absorptivities of the complexes, significant increases in sensitivity, accuracy, and precision were observed upon quantitation. The method is directly applicable to the purified alkaloid-containing chloroform fractions obtained in pharmacopeial assays or isolated from plant extracts and drug formulations in the general concentration range of 10^{-5}–10^{-6} M with a relative standard deviation of 0.015. The method is particularly recommended for assaying the tropane alkaloids and other weak UV-absorbing alkaloids such as ephedrine, codeine, and sparteine.

Keyphrases □ Alkaloids—spectrophotometric assay, charge-transfer complexes □ Charge-transfer complexes—alkaloid spectrophotometric assay □ Complexes, charge transfer—alkaloid spectrophotometric assay □ Spectrophotometry—alkaloid assay, charge-transfer complexes

The decolorization of bromine and iodine by many alkaloids is well known (1–4), and colorimetric methods based upon the residual color on adding excess reagent have been developed (4). In some cases, decolorization is due to iodination of the ring, *e.g.*, epinephrine and isoproterenol (4). However, the true nature of this more general reaction as a charge-transfer complex formation between the nitrogen of the alkaloid as the n-donor and the halogen molecule as the σ-acceptor was not recognized by early investigators.

The formation of complexes between electron donors and acceptors is an important phenomenon. Many molecular complexes are colored and give rise to new absorption bands in the electronic spectra. Although a new absorption band in the UV spectra of iodine and benzene solutions was recognized early as characteristic of the molecular complex between benzene and iodine (5), only after Mulliken (6) propounded the charge-transfer theory could the various features of the spectra and other properties of such molecular complexes be understood fully.

Amines are excellent n-donors, and charge-transfer complexes of these compounds with halogens and pseudohalogens have been reported (7–11). However, emphasis was placed on the study of the complexes by various physical methods and the determination of thermodynamic constants rather than on quantitative implications. Furthermore, recent comprehensive monographs on charge-transfer complexes (10, 11) are devoid of explicit reference to alkaloid–halogen complexes.

This work is a preliminary report on charge-transfer complexes of iodine with alkaloids and their utilization in a sensitive assay of many alkaloids, particularly those with very low original absorptivities. The determination of equilibrium constants for some selected alkaloids is also described.

EXPERIMENTAL[1]

Alkaloids—Analytical reagent or pharmaceutical grade alkaloids and alkaloidal salts, which passed compendial limits and possessed the correct physical constants, were used.

[1] A constant-temperature water bath was used in the determination of equilibrium constants. Spectra were made on SP 8000 Pye-Unicam spectrophotometer.