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KINETICS AND THERMODYNAMICS OF DRUG PERMEATION THROUGH SILICONE ELASTOMERS (II) EFFECT OF PENETRANT LIPOPHILICITY

Ying Sun, Kakuji Tojo and Yie W. Chien

Controlled Drug Delivery Research Center
Rutgers University
College of Pharmacy
P. O. Box 789, Busch Campus
Piscataway, New Jersey 08854

SUMMARY

The permeation of testosterone analogs through silicone membranes was studied. The variation in the lipophilicity of testosterone molecules was accomplished by the addition or elimination of methyl group and the formation of ester. Furthermore, the effects of replacing one of the CH_3 groups on the dimethylsiloxane unit in the silicone polymer chains by a polar $CH_2CH_2CF_3$ group, which changes polymer characteristics and thus affects the membrane permeability, was investigated as well. It was found that

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potential which might prevent flocculation altogether. This can lead to caking. The lowest concentration effective in preventing coagulum formation should be used.

Suspensions made from a fluid aluminum hydroxide concentration were easy to redisperse after six weeks of storage. The sedimentation volume was 0.64. Addition of 0.2% xanthan gum raised the sedimentation volume to a value of 1.0. There was no evidence of coagulum formation in this system.

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REFERENCES

1. J. S. Tempio and J. L. Zatz, J. Pharm. Sci., 69, 1209 (1980).
2. J. S. Tempio and J. L. Zatz, J. Pharm. Sci., 70, 554, (1981).
3. J. L. Zatz, P. Sarpotdar, G. Gergich and A. Wong, Int. J. Pharm., 9, 315 (1981).
4. A. Heyd and D. J. Dhabhar, J. Pharm. Sci., 64, 1697 (1975).

elastomer to steroids has been widely applied to the development of drug-filled silicone capsules (6) and drug-dispersed silicone matrices (7) for long-acting hormonal contraception. Although a number of investigations have been initiated to study the permeation of various steroids, including testosterone, across the silicone membrane (8) under various conditions, a review of the literature has revealed that no systemic study has been initiated to quantitate the effects of steroidal structure and polymer composition on the kinetics and thermodynamics of membrane permeation.

One of the objectives for this series of studies is to establish the quantitative relationship among membrane permeability, steroidal structure and polymer composition. In this second report, both the kinetics and thermodynamics for the membrane permeation of testosterone derivatives will be analyzed quantitatively.

EXPERIMENTAL

Materials

Testosterone[1], 19-nortestosterone[1], 17 α -methyltestosterone[1], testosterone acetate[1], testosterone propionate[1], testosterone pentanoate[2], testosterone heptanoate[1], testosterone cyclohexanoate[2], testosterone cypionate[1], testosterone benzoate[1], polyethylene glycol (PEG) 400[3] and silicone fluid[4] were used as received. Silicone (polydimethylsiloxane, polytrifluoropropylmethylsiloxane) membranes were custom prepared[4].

Determination of Solubility

The solubility of testosterone and its analogs in either 40% aqueous PEG 400 solution or silicone fluid was determined by equilibrating an excess amount of a steroid in each medium at a specific temperature with constant shaking for 48 hours. The sample was then withdrawn from each medium using

a preheated syringe equipped with 0.45 μm filter. The steroid concentration in the filtrate was then determined by UV spectrophotometry[5] from the peak absorbance at 245 nm. For the samples from the silicone fluid, the filtrates were first extracted with methanol and then assayed by UV spectrophotometric measurements.

Permeation through Silicone Membrane

To study the membrane permeation kinetics of testosterone and its analogs, a hydrodynamically well-calibrated Ghannam-Chien membrane permeation system (9) was used. After assembling the silicone membrane between the donor and receptor compartments, a suspension of steroid in 40% aqueous PEG 400 solution was added into the donor compartment and the aqueous medium (with no drug) was filled into the receptor compartment. At each predetermined interval, 10 ml of receptor solution was sampled and replaced with the same volume of fresh, drug-free PEG solution. The steroid concentration in the sample was analyzed by UV spectrophotometry from the peak absorbance at 245 nm.

THEORETICAL CONSIDERATIONS

The physical model for membrane permeation process is shown in Figure 1. Assuming a pseudosteady-state is achieved and sink condition is maintained, the apparent rate of permeation thus can be represented by:

$$\frac{dQ}{dt} = k_D(C_s - C_1) = \frac{D_p}{\ell}(K_1C_1 - K_2C_2) = k_R(C_2 - C_o) = k_RC_2 \qquad (1)$$

where D_p = Diffusivity of the drug through the polymeric membrane

K_1 = Partition coefficient between the donor phase and the membrane

K_2 = Partition coefficient between the receptor phase and the membrane

k_D = Mass transfer coefficient in the donor-side boundary layer

k_R = Mass transfer coefficient in the receptor-side boundary layer

and ℓ = Thickness of the polymeric membrane.

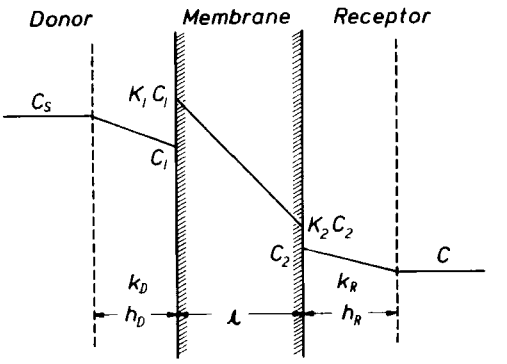


Figure 1: Physical model for the permeation across a polymeric membrane sandwiched between two aqueous diffusion layers.

Rearranging Eqn (1) yields:

$$\frac{dQ}{dt} = \frac{K_1 C_s}{\frac{K_1}{k_D} + \frac{\ell}{D_p} + \frac{K_2}{k_R}} \tag{2}$$

where K_1/k_D, ℓ/D_p and K_2/k_R denote the resistances due to the donor-side boundary layer, membrane and receptor-side boundary layer, respectively.

If the agitation of the solution medium is so vigorous that the diffusional resistance in the boundary layers on both donor and receptor sides of the polymeric membrane becomes negligible, Eqn (2) can be reduced to:

$$\left(\frac{dQ}{dt}\right)_\infty = \frac{K_1 C_s}{\ell/D_p} = \frac{K_1 D_p}{\ell} C_s \tag{3}$$

The correction factor (γ) for the calculation of the intrinsic permeation rate $(dQ/dt)_\infty$, which is defined as the permeation rate through a membrane with negligibly thin thickness of diffusional boundary layer, can be determined from the experimental data of apparent permeation rate (dQ/dt)obtained under non-ideal mixing condition:

$$\gamma = \frac{(dQ/dt)}{(dQ/dt)_\infty} = 1 - \frac{(\alpha-\beta)(dQ/dt)}{Sh_R D_s} \quad (4)$$

where $\alpha = k_R/k_D$, $\beta = K_2/K_1$, the Sherwood number (Sh_R) is a dimensionless parameter which characterizes the hydrodynamics of the membrane permeation system and d is the characteristic diameter of the stirrer used. D_s is diffusivity of the drug in the aqueous medium.

For the special case when the same aqueous medium and same agitation speed are used in the donor and receptor compartments, Eqn. (4) can be simplified to:

$$\gamma = 1 - \frac{2(dQ/dt)}{Sh_R D_s C_s/d} \quad (5)$$

The intrinsic rate of membrane permeation, $(dQ/dt)_\infty$, is thus obtained by:

$$\left(\frac{dQ}{dt}\right)_\infty = \frac{(dQ/dt)}{\gamma} \quad (6)$$

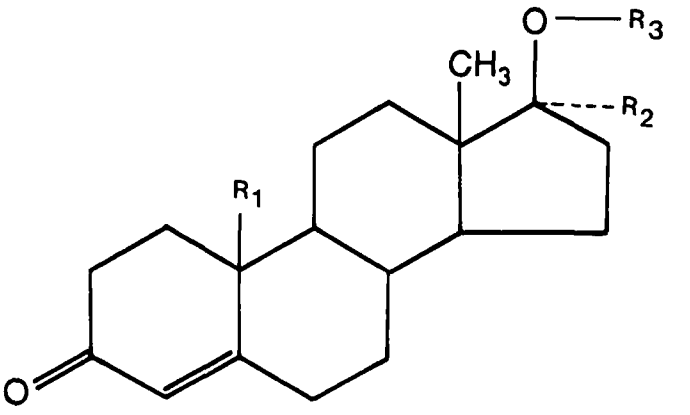
where (dQ/dt) is the apparent permeation rate obtained in the experiment.

RESULTS AND DISCUSSION

Effect of Steroidal Structure Modification on Lipophilicity

The structures of testosterone and its analogs used in the investigation are shown in Table I. It has been known that the chemical modification of steroid readily results in the change of physical properties (10). Esterification of the 17-OH group in testosterone molecule was reported to increase the lipophilicity of the steroids and to decrease the solubility in aqueous medium (11). Also, the alkyl chain length of ester was noted to have a profound influence on the physicochemical properties of steroids and, thus, affect their permeation. Table II summarizes the experimental observations on the structure-dependent variations in the solubility and partition coefficient of testosterone and its derivatives. The results indicate that ester derivatives of testosterone have lower solubility in either water or 40% aqueous PEG 400 solution than testosterone; the longer

Table I - Chemical Structure of Testosterone Analogs and the Arrangement of Various Side Chains



	R_1	R_2	R_3
19-Nortestosterone	H	H	H
Testosterone (T)	CH_3	H	H
17α-methyl testosterone	CH_3	CH_3	H
T-Acetate	CH_3	H	CH_3CO
T-Propionate	CH_3	H	CH_3CH_2CO
T-Pentanoate	CH_3	H	$CH_3(CH_2)_3CO$
T-Heptanoate	CH_3	H	$CH_3(CH_2)_5CO$
T-Cyclohexanoate	CH_3	H	$C_6H_{11}CO$
T-Benzoate	CH_3	H	C_6H_5CO
T-Cypionate	CH_3	H	$C_5H_9(CH_2)_2CO$

Table II - Physical Properties of Testosterone and Its Derivatives

Steroids	Solubility (μg/ml)*			K	C#
	Water	40% PEG 400	Silicone Fluid		
19-Nortestosterone	268.0	1270	132	0.10	-1
Testosterone	40.3	508	156	0.30	0
17α-methyltestosterone	37.7	559	240	0.42	1
Testosterone acetate	5.8	137	511	3.73	2
Testosterone propionate	3.7	115	590	5.13	3
Testosterone pentanoate	3.6	54	471	8.77	6
Testosterone heptanoate	3.1	47	443	9.42	7
Testosterone cyclohexanoate	3.7	47	443	9.42	7
Testosterone benzoate	3.1	23	103	4.47	7
Testosterone cypionate	10.2	60	650	10.83	8

*Measured at 37°C and each data point is a mean of triplicate determinations.

the ester chain length, the lower the aqeuous solubility. On the other hand, the increase in ester chain length, which enhances the steroidal solubility in silicone fluid, elevates the value of partition coefficient. The partition coefficient (K) for the interfacial partitioning between silicone membrane and aqueous medium is defined by:

$$K = \frac{C_p}{C_s} \tag{7}$$

where C_p and C_s are the solubililties in polymeric membrane and aqueous medium, respectively. It was also noted that the aqueous solubility for testosterone analogs in aqueous medium was enhanced 5 to 31 times when 40% PEG 400 was added into the water, i.e. the water-miscible PEG 400 served as a good cosolvent to enhance the aqueous solubility of steroids. Therefore, aqueous 40% v/v PEG 400 solution was used as the solution medium in both donor and receptor compartments to maintain the system under the sink condition. In this investigation silicone fluid, which is polydimethylsiloxane with low molecular weight, was used to determine the steroidal solubility in polymer. The partition coefficient determined from the ratio of solubility in silicone fluid over that in 40% PEG 400 solution was found to increase as increasing alkyl chain length, as a consequence of the decrease in aqueous solubility and the increase in the polymer solubility.

Effect of Steroidal Structure Modification on Permeation

It has been reported (12) that the aqueous solubility of each member of a homolog series can usually be related to alkyl chain length by:

$$\log C_{s,n} = \log C_{s,o} - \delta n \tag{8}$$

where $C_{s,o}$ and $C_{s,n}$ are the solubilities of the reference congener and the nth linear alkyl homolog of the series, respectively; δ is a constant factor as the series ascended (13). The relationship between the partition

coefficient (K_n) and the alkyl chain length for the nth compound in a series can be expressed by:

$$\log K_n = \log K_o + \pi n \tag{9}$$

where K_o is the partition coefficient of the reference congener and π is a constant, whose value depends upon the nature of the two immiscible partitioning phases (14). The intrinsic permeation rate, $(dQ/dt)_\infty$, as a function of steroidal structure thus can be obtained by substituting Eqn (8) and Eqn (9) into Eqn (3) and is shown as follows:

$$\left(\frac{dQ}{dt}\right)_\infty = \frac{D_p K_n C_{s,n}}{\ell} = \frac{D_p K_o C_{s,o}}{\ell} \cdot 10^{(\pi-\delta)n} \tag{10}$$

or,

$$\log \left(\frac{dQ}{dt}\right)_\infty = \log \left(\frac{D_p \cdot K_o \cdot C_{s,o}}{\ell}\right) + (\pi - \delta)n \tag{11}$$

The permeation profiles of testosterone and its derivatives across the polydimethylsiloxane (PDMS) membrane are shown in Figure 2. The linearity of these permeation profiles indicates that Fickian diffusion is followed. From the slope of the linear Q vs. t relationship the apparent rate of membrane permeation (Q/t) can be calculated for each compound. Using Eqn (6), the intrinsic rate of permeation can be determined and also shown in Figure 2 as dashed lines. The result in Figure 3 shows that, as indicated by Eqn (11), the intrinsic rate of permeation is first linearly increasing with n for the homologs with $n \leq 3$ and then decreasing as $n > 3$. The direction of change is dependent upon the relative magnitude of π and δ values. If π is greater than δ, the intrinsic permeation rate will be enhanced as the number (n) of carbon atoms in the side chains increases, with the exception of 19-nortestosterone. This unusual behavior was postulated by the authors in a previous work that the removal of 19-methyl group might increase the flexibility of steroidal conformation, which, therefore, yields the observation of exceptionally high permeability (15).

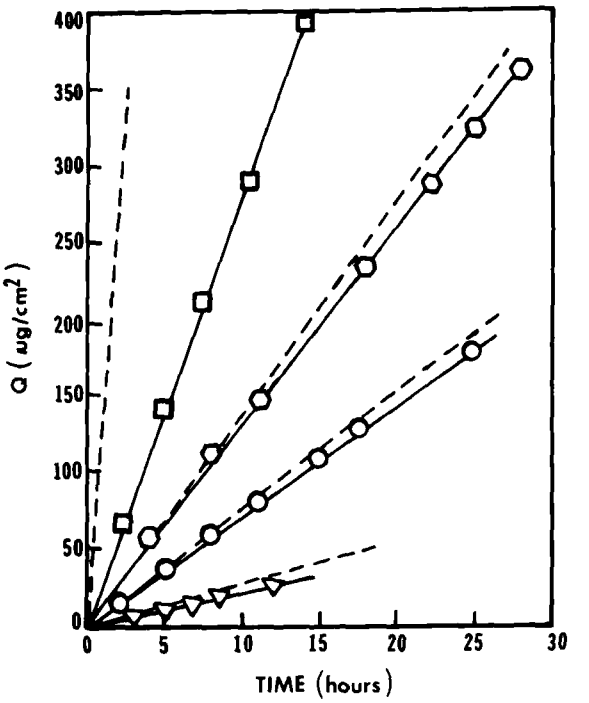


Figure 2: Permeation profiles of testosterone and its derivatives through PDMS membrane:
Key: testosterone (◯), 17 α - methyltestosterone (⬡), testosterone propionate (□), testosterone enanthate (▽).

When π is smaller than δ , as for the case where $n > 3$, a decrease in the intrinsic rate of permeation will be observed when additional carbon atoms are incorporated into the ester chain. According to Eqn (8), the aqueous solubilities of testosterone and its derivatives should be exponentially decreased with the number (n) of carbon atoms in the side chains. The result in Figure 4 demonstrates reasonably well this linear relationship for the aqueous solubility with a slope (δ) of 0.168 ($r = 0.94$). The dependency of partition coefficient data on the number of carbon atoms in testosterone side chains is shown in Figure 5. As suggested by Eqn (9), the value of log K increases as increasing the carbon number in the

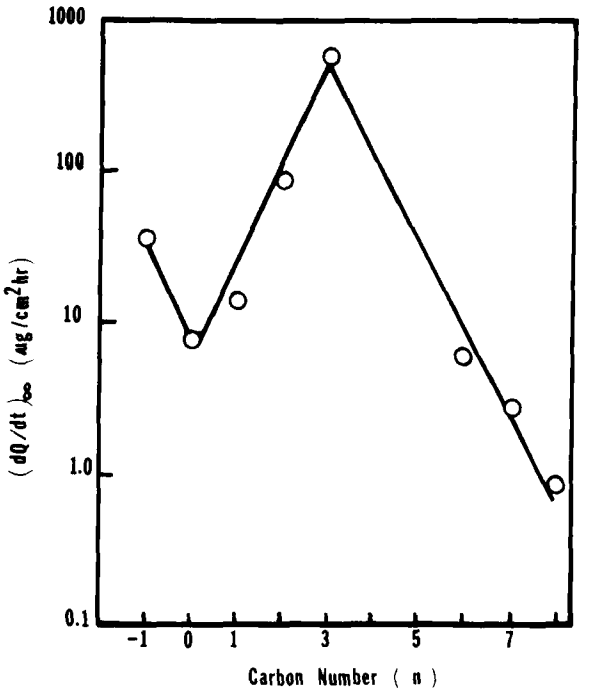


Figure 3: Dependency of intrinsic permeation rate across PDMS membrane on the number of carbon atoms in the side chains.

side chains. The data indicate that the partition coefficient shows a biphasic dependency on the alkly chain length with a breaking point occuring at $n \simeq 3$. This observation could possibly be attributed to the impact of structure bulkiness of long alkyl chain in the region with $n>3$. In the first region, the value of the incremental lipophilicity per methyl group is 0.479 (π_1). And in the second region where n is greater than 3, the incremental lipophilicity is reduced by almost 7 folds ($\pi_2 = 0.0711$). This reduction in the incremental lipophilicity apparently affects the dependency of intrinsic permeation rate on carbon number and thus produces the result observed earlier in Figure 3. Therefore, the data points determined experimentally show a good agreement with the theoretical line constructed from Eqn (11) using the values of π and δ obtained at two different regions.

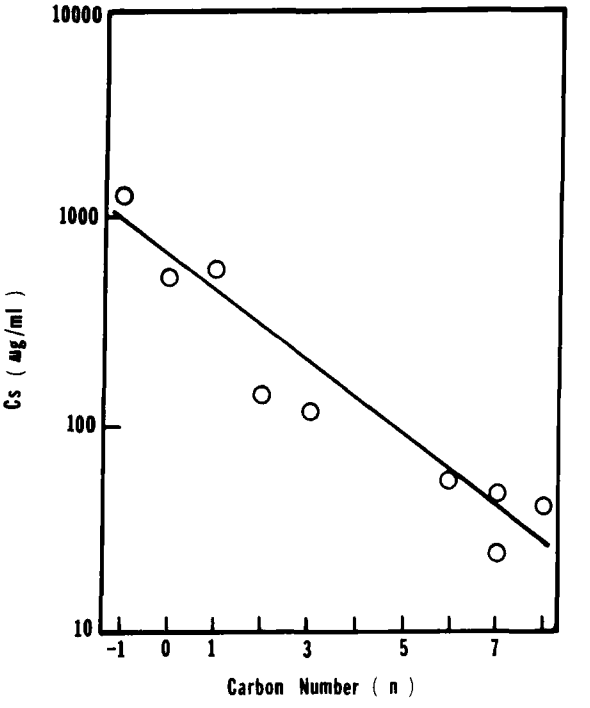


Figure 4: Semilogarithmic relationship between the solubility and the number of carbon atoms in the side chains.

Effect of Membrane Composition on Permeation

The permeation across a polymeric membrane is determined by the polymer chain segmental mobility. The local segmental mobility or chain stiffness may be affected by the interaction between neighboring polymer chains as the result of hydrogen bonding, polar interactions, or simple Van der Waals interactions. Polytrifluoropropylmethylsiloxane (PFMS) membrane, with the substitution of one CH_3 by a more polar, bulkier $CH_2CH_2CF_3$ in the polydimethylsiloxane backbone, is more polar and stiffer than PDMS membrane. The electro-negative characteristics of fluorine atoms could promote the polar interactions between polymer chains. Consequently, the increase in polymer chain polarity and polymer backbone stiffness will produce a greater resistance to the membrane permeation of the lipophilic testosterone

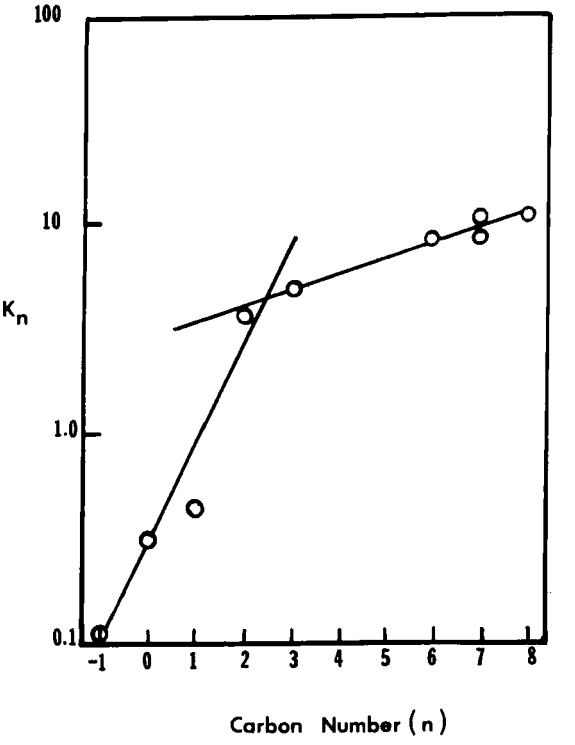


Figure 5: Biphasic dependency of partition coefficient on the number of carbon atoms in the side chains.

analogs. The data in Figure 6 show the reduction in permeation rate of testosterone and its derivatives across PFMS membrane as compared to PDMS membrane. The extent of reduction in permeation rate was observed to be greater for those analogs with higher permeability. The results imply that molecules with higher permeability are more susceptible to the variation in membrane polarity or membrane composition. However, the intrinsic rate of permeation across the PFMS membrane basically showed the same trend of dependency on the number of carbon atoms in the side chains of testosterone analogs.

The results in Figure 7 show that the presence of filler in the membrane also remarkably decreases the permeability of testosterone analogs. It

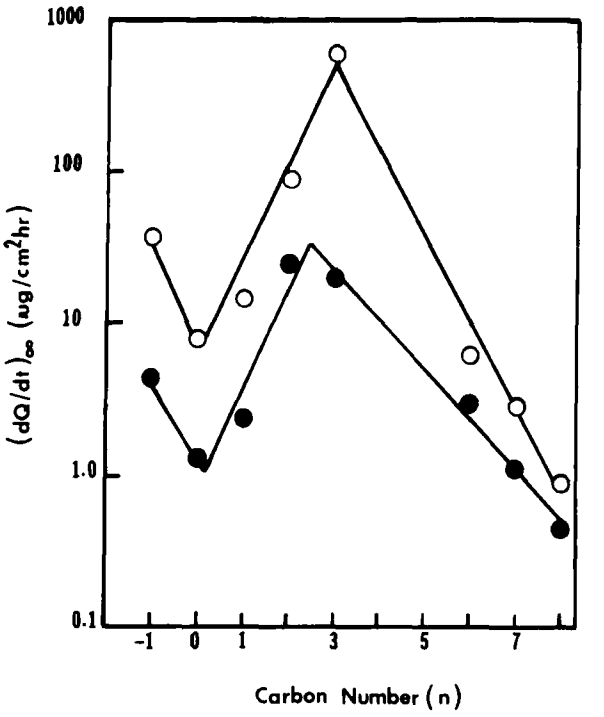


Figure 6: Effect of polymer composition on the relationship between the intrinsic permeation rate and the number of carbon atoms in the side chains.
Key: PDMS (◯), PFMS (●).

may be attributed to the decrease in the volume fraction of continuous phase and the increase in the tortuosity of diffusion path. The former one may account for most of the reduction in permeation rate according to some earlier investigations (16). However, the intrinsic rate of permeation across the PDMS membrane with filler basically showed the same trend of dependency on the number of carbon atoms in the side chains of testosterone analogs as the fillerless membrane. It is interesting to point out that the presence of an easily polarizable benzene group in the ester renders the steroid to be adsorbed extensively by the filler.

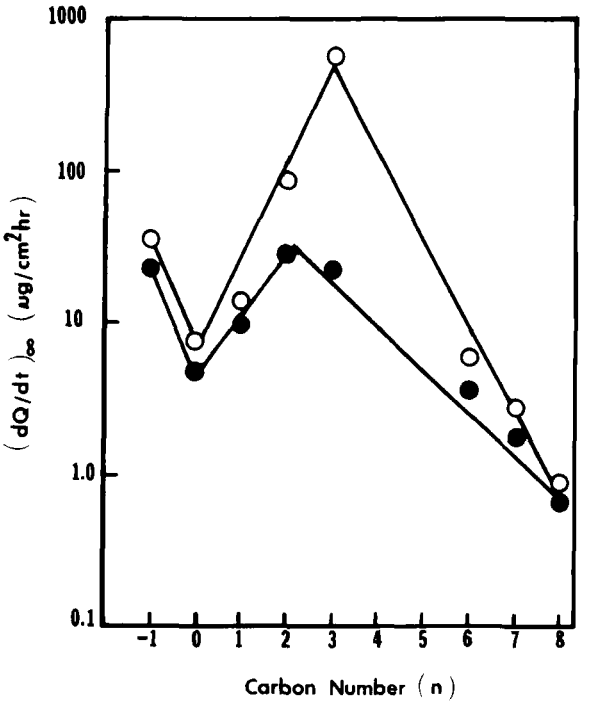


Figure 7: Effect of filler on the relationship between the intrinsic permeation rate of steroids and the number of carbon atoms in the side chains. Key: PDMS with filler (●) and PDMS without filler (○).

Thermodynamics of Permeation

Permeation of steroids across a polymeric membrane requires energy to facilitate the mass transfer of steroid molecules through the matrix of polymer barrier. The Arrhenius relationship for the intrinsic membrane permeation process can be written as:

$$\log (dQ/dt)_\infty = \text{constant} - \frac{(E_p + \Delta H_p)}{2.303\ R} \cdot \frac{1}{T} \qquad (12)$$

where $(E_p + \Delta H_p)$ is the total energy required for the permeation through the membrane and is equal to the sum of activation energy for polymer

diffusion (E_p) and the energy for the solvation of the steroid in the polymer media (ΔH_p). It can be easily derived from Eqn (3):

$$(dQ/dt)_\infty = \frac{D_p K_1}{\ell} C_s = \frac{D_p}{\ell} C_p \quad (13)$$

$$D_p = D_p^o e^{-E_p/RT} \quad (14)$$

$$C_p = C_p^o e^{-\Delta H_p/RT} \quad (15)$$

$$\text{So,} \quad (dQ/dt)_\infty = (dQ/dt)_\infty^o e^{-(E_p + \Delta H_p)} \quad (16)$$

The total energy required for the membrane permeation of various steroids through the silicone polymers can be determined experimentally from the membrane permeation kinetics studies at various temperatures by using Eqn (12). The results in Table III indicate that the addition of a methyl group to 17α-position and the elimination of 19-methyl group from testosterone seems to minimize the total energy required, whereas the esterification slightly increased the energy requirement. On the other hand, the increase in the polarity of the membrane, such as PFMS, substantially raises the energy requirement due to the increase in polymer stiffness and the decrease in polymer chain mobility originated from hydrogen bonding and/or polar interaction between neighboring polymer chains.

However, presence of silica filler had little effect on the energy requirements for testosterone analogs except that for benzoate (Table IV). The greater energy requirement observed for the permeation of testosterone benzoate across the PDMS membrane with filler could be the result of adsorption of benzoate onto filler particles in the membrane.

Effect of Ring Structure in Ester Chain

The effect of saturated and unsaturated ring structures in the ester chain on the lipophilicity and the kinetics and thermodynamics of membrane permeation of testosterone analogs was studied using heptanoate,

Table III - Thermodynamics of Membrane Permeation:

Steroids	Energy Required for Permeation (Kcal/mole)		
	PDMS (Filler)	PDMS (Fillerless)	PFMS (Fillerless)
19-Nortestosterone	10.6	10.6	15.8
Testosterone	14.7	14.6	18.5
17α-Methyltestosterone	12.7	12.4	16.6
Testosterone acetate	15.4	15.6	23.8
Testosterone propionate	15.4	16.9	23.9
Testosterone pentanoate	15.7	17.1	24.9
Testosterone heptanoate	15.8	17.2	25.3
Testosterone cypionate	15.7	17.2	25.5

cyclohexanoate and benzoate, all of these three esters have the same number of carbon atoms (n=7) (Table I).

The results summarized in Table IV indicate that the presence of a saturated ring structure (e.g., cyclohexane ring) improves the lipophilicity of testosterone toward silicone polymer but significantly reduces the intrinsic rate of permeation across the PDMS membrane (with and without filler) and PFMS membrane (with no filler). However, the effect on the energy requirement for membrane permeation is insignificant.

On the other hand, the presence of an unsaturated ring structure (e.g., benzene ring) was found to substantially decrease the lipophilicity of testosterone toward silicone polymer and also the intrinsic rate of

Table IV - Effect of Saturated and Unsaturated Ring Structures on Partition Coefficient, Intrinsic Membrane Permeation Rate, and Energy Requirements

Testosterone Esters (n=7)	K	$(dQ/dt)_\infty$			$(E_p + \Delta H_p)$		
		PDMS		PFMS	PDMS		PFMS
		Filler	Fillerless	(Fillerless)	Filler	Fillerless	(Fillerless)
Heptanoate	9.42	1.74	2.70	1.03	15.8	17.2	25.3
Cyclohexanoate	12.30	1.12	1.16	0.71	15.8	16.1	25.1
Benzoate	4.47	0.27	1.06	0.38	19.6	12.6	24.8

permeation across the PDMS and PFMS membranes, especially the PDMS membrane with filler and the fillerless PFMS membrane. The energy required for membrane permeation became greater for filler-containing PDMS membrane as the result of filler adsorption and decreased for fillerless PDMS membrane, whereas the energy requirement for permeation across the polar PFMS membrane showed no difference from the ester with straight chained hydrocarbon or with saturated ring structure.

CONCLUSION

The results of this investigation demonstrate that the permeation of testosterone and its derivatives across the silicone membrane is dependent upon the lipophilicity of the steroids and the polarity of the membrane. Partition coefficient and solubility in the polymer phase are the two major factors that will determine the permeation behavior. The location and the type of alkyl side chains on the steroidal skeleton are additional factors affecting the kinetics and thermodynamics of membrane permeation.

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FOOTNOTES

1. Sigma Chemical Company, Saint Louis, Missouri 63718
2. Custom synthesis by Pioneer Laboratories Inc., San Francisco, California 94127
3. Fisher Scientific, Fairlawn, New Jersey 07410
4. Silicone polymer membranes, PDMS and PFMS with or without filler, and silicone medical fluid were provided by Dow Corning Corporation, Midland, Michigan 48640

5. Perkin-Elmer model 559A UV/VIS Spectrophotometer, Perkin-Elmer Corporation, Elmwood Park, New Jersey 07407

REFERENCES

1. T. J. Roseman; Release of steroids from a silicone polymer, J. Pharm. Sci., 61 (1972) 46-50.
2. R. E. Lacey and D. R. Cowsar; Factors affecting the release of steroids from silicones, in Controlled Release of Biologically Active Agents (A. C. Tanquary and R. E. Lacey, Eds.), Plenum Press, New York, 1974, Chap. 5.
3. R. M. Barrer, J. A. Barrie and N. K. Raman; Solution and diffusion in silicone rubber I - a comparison with natural rubber, Polymer, 3 (1962) 595-603.
4. H. J. Tatum, E. M. Coutinho, K. Adodato-Filho and A.R.A. Sant'Ana; Acceptability of long-term contraceptive steroid administration by subcutaneous Silastic capsules, Amer. J. Obstet. Gynecol., 105 (1969) 1139-1143.
5. B. Arkles; Look what you can make out of silicones, Chem. Tech., September (1983) 542-555.
6. Y. W. Chien; In vitro-vivo correlation on the subcutaneous release of progesterone from silicone capsules, Chem. Pharm. Bull., 24 (1976) 1471-1479.
7. T. J. Roseman and W. I. Higuchi; Release of medroxyprogesterone acetate from a silicone polymer, J. Pharm. Sci., 59 (1970) 353-357.
8. R. L. Shippy, S. Hwang and R. G. Bunge; Controlled release of testosterone using silicone rubber, J. Biomed. Mater. Res., 7 (1973) 95-110.
9. K. Tojo, Y. Sun, M. Ghannam and Y. W. Chien; Characterization of a membrane permeation system for controlled drug delivery studies, AIChE J., accepted for publication (1984).

10. E. Diczfalusy; A new class of long-acting steroid hormone esters, Acta Endocrinologica, 35 (1960) 59-68.

11. M. Kupchan, A. Casy and J. W. Swintosky; Synthesis and preliminary evaluation of testosterone derivatives, J. Pharm. Sci., 54 (1965) 514-524.

12. S. H. Yalkowsky, G. L. Flynn and T. G. Slunick; Importance of chain length on physicochemical and crystalline properties of organic homologs, 61 (1972) 852-857.

13. G. L. Flynn and S. H. Yalkowsky; Correlation and prediction of mass transport across membranes I: influence of alkyl chain length on flux-determining properties of barrier and diffusant, J. Pharm. Sci., 61 (1972) 838-852.

14. T. Higuchi and S. S. Davis; Thermodynamic analysis of structure-activity relationships of drugs: prediction of optimal structure, J. Pharm. Sci., 59 (1970) 1376-1383.

15. J. C. Liu, Y. Sun, K. Tojo, and Y. W. Chien; Membrane permeation kinetics of nortestosterone: Effect of methyl groups on thermodynamics, International J. Pharm., accepted for publication (1985).

16. F. C. Most; Some filler effects on diffusion in silicone rubber, J. Appl. Polym. Sci., 14 (1970) 1019-1036.