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Controlled Release of Testosterone Using Silicone Rubber

RONALD L. SHIPPY, SUN-TAK HWANG, and RAYMOND G. BUNGE, *Departments of Chemical Engineering and Urology, University of Iowa, Colleges of Engineering and Medicine, Iowa City, Iowa 52240*

Summary

This study was undertaken to find a means for a long lasting and uniform release of the male hormone, testosterone. The rate of release of testosterone was determined over periods up to 4 months. The factors which affect the rate of testosterone release were studied and a mechanism for the release of testosterone was proposed.

The first means providing a constant release of testosterone was the use of silicone rubber membrane around testosterone cylinders. It was found that a constant rate of release was reached after an initial unsteady state period ranging from 1 to 2 weeks.

It was theorized that a water layer had formed between the membrane and testosterone cylinder. This layer caused the concentration inside the capsule to be that of saturated water.

Several testosterone cylinders were coated with especially prepared membranes. These membranes were made by dissolving testosterone and silicone rubber in a mixture of tetrahydrofurane and toluene. It was hoped that an amount of testosterone might be incorporated into the silicone rubber matrix. The samples were run and the permeabilities determined. The permeability showed little or no increase over the range of 10–30% testosterone.

Next, a membrane was prepared by mechanically mixing testosterone and silicone rubber. The amount of testosterone ranged between 5 and 20% by weight. A definite increase in the permeability was observed with an increase in the percentage of testosterone.

The second method of obtaining a uniform rate of release of testosterone was by mechanically mixing testosterone and silicone rubber and molding a sheet. After an initial unsteady state a constant rate of release was obtained and such rate of release increased with higher percentages of testosterone in the sheets.

INTRODUCTION

There has been much recent interest in the use of polymeric membranes as a means of providing a uniform and long lasting adequate dosage form for nutrients and drugs. This study was undertaken to investigate the use of silicone rubber as such an aid for the male hormone, testosterone. The parameters which produced the most uniform and long lasting therapeutic levels were studied.

Many researchers have shown that a great number of drugs and hormones are highly permeable to silicone rubber.[1–3] Silicone rubber has been shown to be a useful carrier for various drugs in both in vivo and in vitro systems.[4] Its usefulness lies in the fact that large quantities of drugs can be encapsulated in the silicone rubber and then released slowly over long periods of time.

Silicone rubber has been shown to be 100 to 1000 times as permeable to a similar hormone, progesterone, as to other common polymeric membranes.[5] Moon and Bunge[6] compared the growth rates of the ventral prostate, the dorsolateral prostate, the coagulating glands, and the empty seminal vesicles in noncastrated and castrated rats with 50 mg of testosterone in silastic capsules implanted subcutaneously. Evidence was obtained that testosterone passed through the silastic capsule and maintained a slightly inferior growth rate of the target organs. The silastic capsules used were much thicker than the silastic used in this study.

Kincl, Benagiano, and Angee[5] studied the diffusion of various hormones, including testosterone, but they reported only unnormalized "diffusion rates." They also used silastic tubes manufactured by Dow Corning and their minimum thickness was at least twice that used in this study. No correlation was found between the diffusion of various steroids and their molecular weight, indicating that silicone rubber acts as a homogenous membrane towards steroids.

The present study was undertaken to determine the means for providing a uniform, long-lasting dosage form. This study deals with the relationship of steady-state permeability of testosterone with respect to membrane thickness, membrane surface area, temperature, membrane structure, composition, and effects of boundary layers.

Each of these parameters is studied with the use of encapsulated testosterone, with solid testosterone-silicone rubber mixtures, and with silicone rubber membranes.

Hwang et al.[7] have reported a study of the steady-state permeability of testosterone through silicone rubber membranes in a previous publication.

In vivo tests are now being performed on dogs at the University of Iowa Department of Urology. Preliminary tests show that a constant amount of testosterone is released into the system of a castrated dog. Further data and publications will be released in the future.

EXPERIMENTS

All of the membranes used in this study were constructed by the authors. Medical grade silastic brand adhesive (Silicone Type A) was obtained from Dow Corning. Distilled water was the solvent used throughout the entire experiment.

Membranes Around Testosterone Cylinders

In the first phase of the experiment, membranes were placed around solid cylinders of crystalline testosterone. These cylinders were constructed by a press and set of dies. Each of these cylinders was labeled appropriately with radioactive testosterone to yield at least a 1000 cmp count rate at the counting time. The membrances were placed around the solid testosterone cylinders using one of the following techniques: (a) Pure silicone rubber adhesive and mechanical mixtures of testosterone and silicone rubber adhesive were placed around cylinders of labeled testosterone. The testosterone incorporated into the membranes was not labeled.

(b) A solvent made of a mixture of 60% tetrahydrofurane and 40% toluene by volume was prepared. Both testosterone and silicone rubber adhesive were soluble in the solvent, although the mixture appeared to be only a plasticizer for the silicone rubber adhesive. Then solutions containing silicone rubber adhesive and testosterone and silicone rubber together could be prepared. A simple dipping of the cylinder into the solution produced a cylinder coated with approximately 1 mil of silicone rubber.

Cylinders with differing thicknesses of silicone rubber coatings were prepared. Also coatings with various concentrations of silicone rubber and testosterone (0–30% testosterone by weight) were prepared with the same thicknesses.

The cylinders were first placed in a diffusion "cell" shown in Fig. 1. The cylinder was allowed to remain in the cell for exactly 1 day. At

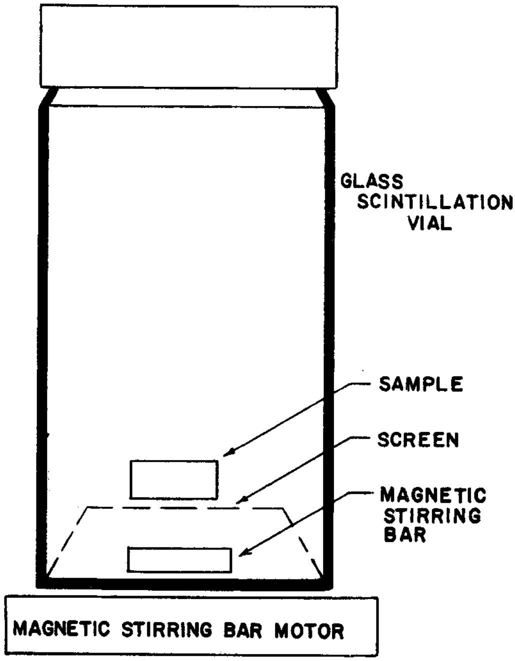

Fig. 1. Unsteady state diffusion cell.

this time the cylinder was removed and placed in a similar cell containing fresh solvent. The distilled water in the first cell was dried, scintillation fluid added, and the radioactivity counted. This sequence was repeated for a period of up to 4 months. At that time the cylinder was removed and quickly transferred to a diffusion "cell" shown in Fig. 2. In this cell the steady state permeability could be measured by maintaining a steady flow rate of solvent by means of a constant head of fluid.

The second cell was allowed at least 48 hr to equilibrate and the solvent flow was checked during this period. When steady state was reached, a sample was collected for a specified time, the solvent evaporated, and the radioactivity of the residue was counted in the Packard Tri-Carb liquid scintillator spectrometer Model 3380 which had an efficiency between 56 and 59%.

Both cells were immersed in a constant temperature bath held at 37°C. The bath could also be adjusted to range from 0 to 60°C.

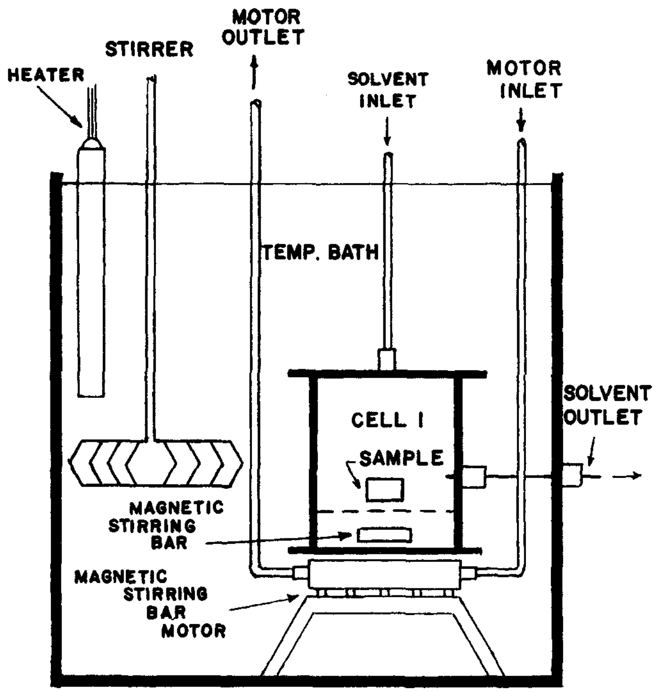

Fig. 2. Steady state diffusion cell number 1.

Solid Sheets of Testosterone and Silicone Rubber

Silicone rubber adhesive and labeled testosterone were mechanically mixed. The silicone rubber was then allowed to cure. Mixtures of from 19.57% up to 69.20% testosterone (by weight) were prepared. The sheets of testosterone and silicone rubber were placed in the diffusion "cell" shown in Fig. 1. Once again the solvent was changed every 24 hr and the radioactivity counted. In this way a rate of release vs. time could be studied.

Membranes With Known Concentration of Testosterone On Both Sides

This section of the experiment was carried out using pure silicone rubber membranes 2.1, 5.2, and 9.8 ml in thickness prepared by the authors. The steady state permeability was measured by means of a diffusion "cell" shown in Fig. 3. A saturated solution of testos-

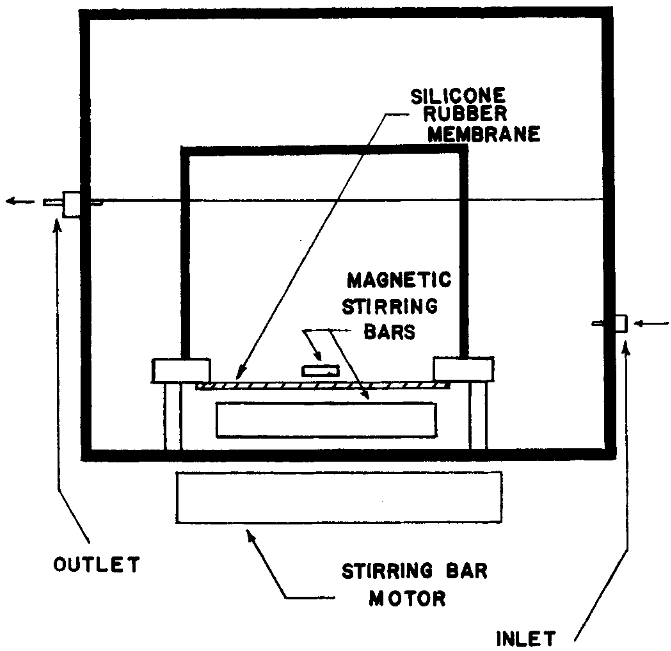

Fig. 3. Steady state diffusion cell number 2.

terone mixed with a known amount of tritium labeled testosterone in 2.0–4.0 ml of distilled water was placed inside the cell. Extra crystals of the hormone in the cell assured that the solution remained at a constant concentration. Solvent was fed into, and withdrawn from, the system at a constant rate, by means of capillary tubes, maintaining the concentration of testosterone outside the cell at a constant level. Magnetic stirrers maintained good agitation and the sealed lid prevented evaporation of volatile solvents.

Three membranes were prepared with an approximately 5.2 ml thickness. These membranes contained 22.0, 35.7, and 51.4% testosterone by weight incorporated into the membrane. This testosterone was added to the membranes by mechanically mixing labeled testosterone and silicone rubber adhesive and then forming a membrane.

The steady state permeability was determined using the technique adopted for the pure membranes.

RESULTS AND DISCUSSIONS

The experimental permeability can be easily determined under the steady state conditions. Fick's first equation can be written as:

$$F = -DA(C_2 - C_1)/X \tag{1}$$

where C_1 and C_2 are the concentrations of the diffusing species at both sides of the membrane surfaces. If Henry's law is applied,

$$C_1 = SC_1^* \tag{2}$$

$$C_2 = SC_2^* \tag{3}$$

where C_1^* and C_2^* are the concentrations of bulk solutions. Hence,

$$F = -PA(C_2^* - C_1^*)/X \tag{4}$$

where the experimentally measured permeability is a product of the diffusivity and the solubility.

$$P = DS \tag{5}$$

The Eq. (5) is not true in general. If the rate of diffusion is fast or the thickness of membrane is very thin, the resistances of the boundary layers should be taken into account. The presence of boundary layers will reduce the available driving force for diffusion inside the membrane. Hwang et al.[8] derived the following equation, where r_1 and r_2 are the boundary layer resistances, to show the influence of the boundary layers.

$$P = \frac{DSL}{PS(r_1 + r_2) + L} \tag{6}$$

The lack of variation of the permeability coefficient in Fig. 5 with respect to membrane thickness denotes that the immobile boundary layer does not add significant resistance to the flow of the solute. If this is the case, then the film resistance simply becomes zero, and Eq. (6) reduces to the familiar form Eq. (5).

The maximum solubility of testosterone in water as a function of temperature was determined. Our previous study[7] reported a solubility of testosterone in water at 37°C of 0.059 ± 0.003 mg per cm^3, as opposed to a value of about 0.061 ± 0.04 mg per cm^3 determined here. Sundaram and Kincl[9] reported a solubility at 37°C of 0.025 ml per cm^3. The value in the present study represents 10 separate determinations.

Results for Capsules

The rate of testosterone release vs. time for different thicknesses of membrane at 37°C showed a marked difference in rate of release as shown in Fig. 4.

Assuming the inside concentration of the capsule to be that of saturated solution of testosterone, the experimental permeability was determined for different thicknesses of pure silicone rubber coated capsules. From Fig. 5 it can be seen that the steady state permeability remains essentially constant as the membrane thickness varies from 1.1 mils to 11.2 mils. The thinner membranes showed the largest amounts of deviation. This could possibly be due to irregularities in the membranes themselves and the difficulty in measuring the membrane thickness accurately.

The permeabilities of testosterone for three capsules were measured at various temperatures. Figure 6 shows good agreement with the Arrhenius equation but for the thin membranes the curve was deviated from the first two.

Figure 7 shows the relationship of permeability to percentage of testosterone by weight in membranes made with solvent, silicone rubber adhesive, and unlabeled testosterone. The curve shows no

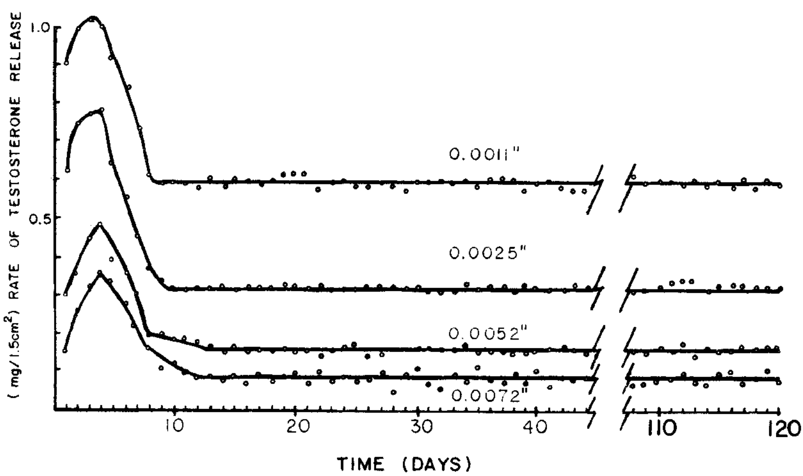

Fig. 4. Rate of testosterone release vs. time for capsules with different thicknesses of membrane at 37°C.

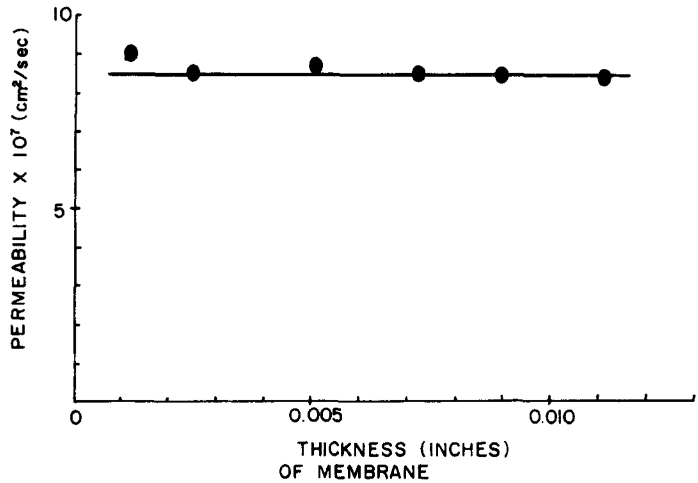

Fig. 5. Permeability vs. thickness for pure silicone rubber coated capsules.

increase in permeability with increasing percentage of testosterone. This might be explained by the fact that the solvent seemed to concentrate the testosterone on the surface of the membrane. Hence the concentration in the inside of the membrane might only be the maximum solubility of testosterone in the membrane.

Figure 8 shows the relationship of permeability to percentage of testosterone for membranes made by mechanically mixing testosterone and silicone rubber adhesive. The curve shows a definite increase in the permeability with increasing percentage of testosterone. The increased testosterone percentage may increase the porosity and completely change the membrane structure. This could account for the increase of permeability.

Inside Concentration for Silicone Rubber Coated Cylinders

It is basic to all calculations of the capsules to know the concentration on the inside of all the samples. One might assume that concentration is very large because of the intimate contact between the crystalline testosterone and the membrane. But it is our hypothesis that water permeates to the inside of each capsule and forms a layer of water between the crystalline testosterone and the membrane, thus providing a saturated solution. This water layer gives a steady

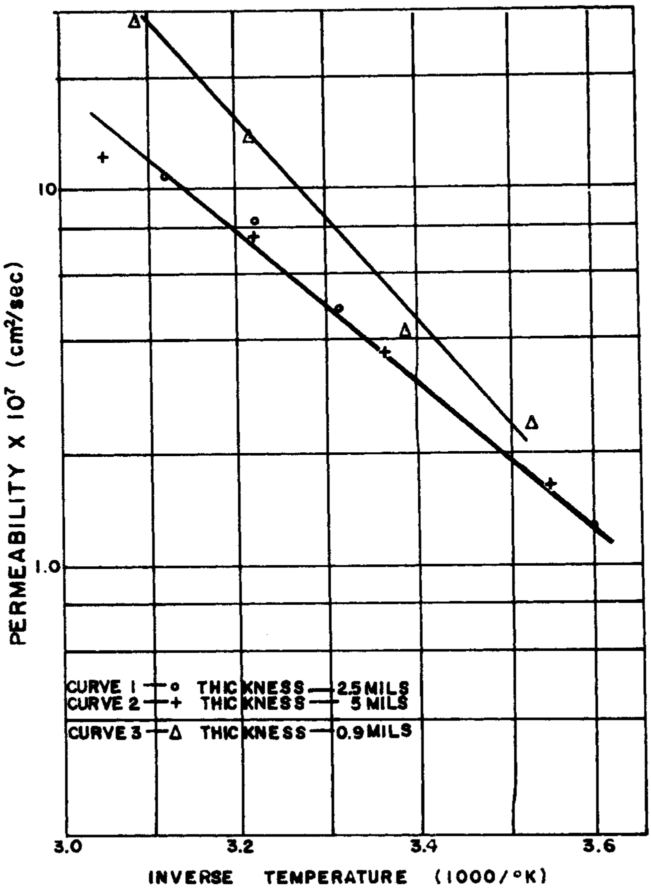

Fig. 6. Permeability vs. temperature for pure silicone rubber coated capsules.

concentration, at the system's temperature, for as long as testosterone remains in the inner cavity of the capsule. For all calculations performed on the encapsulated system in this study it was assumed that a saturated solution of testosterone on one side of the membrane was always present.

Reasons for Assuming Water Layer

There were four reasons for assuming that a layer of water was present between the testosterone and the membrane: First, the rate

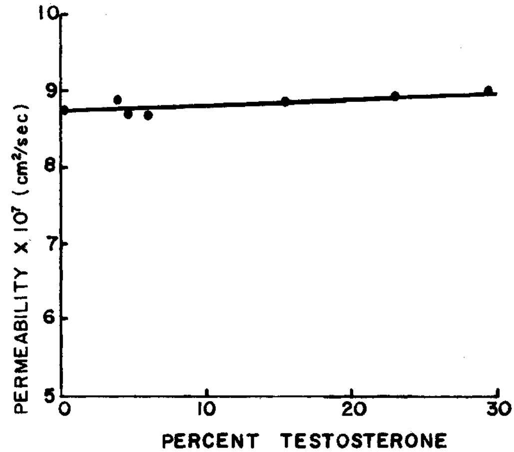

Fig. 7. Permeability vs. % testosterone for membrane made with solvent (37°C).

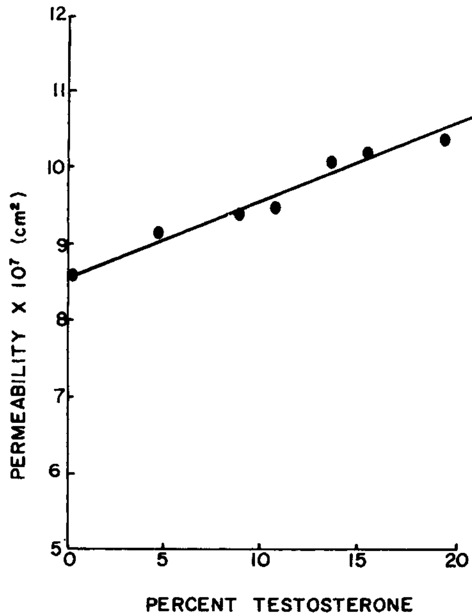

Fig. 8. Permeability vs. % testosterone for membrane made by mechanically mixing.

of release vs. time curve, Fig. 4, shows a distinct peak for the first 9 or 10 days and then levels off to a steady state of release. If the contact between testosterone and membrane was always good, one would assume that there would be a constant rate of release from the start. Since this did not occur some change in the contact could be suspected. Second, six capsules which were allowed to run in the diffusion cells for a period of 62 days were removed and carefully dried with a cloth. Then the samples were weighed and dried in an oven at 40°C for 2 days. This temperature is well below the decomposition temperature of silicone rubber or testosterone. All of the samples lost weight in the drying process. It is assumed that this loss of weight was due to the evaporation of water, since only water was in contact with the capsules. The third reason in support of the proposed water layer is the observation of Crank and Park[10] that good permeation of water vapor through silicone rubber occurred. It is an accepted fact that silicone rubber is highly permeable to water. The last evidence in support of the water layer mechanism is that the permeability coefficients, using saturated water as one concentration with the other concentration being the observed values, closely agreed with values determined using a steady state system with water on both sides of the membrane. Table I for capsules assuming an internal saturated solution of testosterone, agrees favorably with Table II, for the steady state membranes.

Results for Solid Sheets

The rate of release of testosterone from the mechanically prepared sheets of labeled testosterone and silicone rubber can be seen in Figs.

TABLE I

Capsules with Pure Silicone Rubber Membranes (37°C)

Membrane	Thickness (in.)	Permeability $\times 10^7$ cm^2/sec
1	0.0009	9.06
2	0.0022	8.97
3	0.0046	8.21
4	0.0078	8.06
5	0.0111	8.63
6	0.0150	8.59

TABLE II

Pure Silicone Rubber Membranes (37°C)

Membrane	Thickness (in.)	Area cm^2	Permeability $\times 10^7$ cm^2/sec
1	0.0021	9.63	9.08
2	0.0052	9.63	8.89
3	0.0098	9.63	8.63

9 and 10. The rate of testosterone release increased as the percentage of testosterone was increased from 19 to 69% by weight.

Figure 11 shows the steady rate of release which was obtained by six different sheets of the labeled testosterone-silicone rubber adhesive mixture. An almost linear relationship is in evidence. A 70% by weight testosterone sheet released approximately 0.72 mg of testosterone per day from a 5 cm^2 surface area of sheet.

Results for Membranes Between Solutions

Using the cell shown in Fig. 3 with the membrane between the two water solutions the steady state experimental permeabilities were

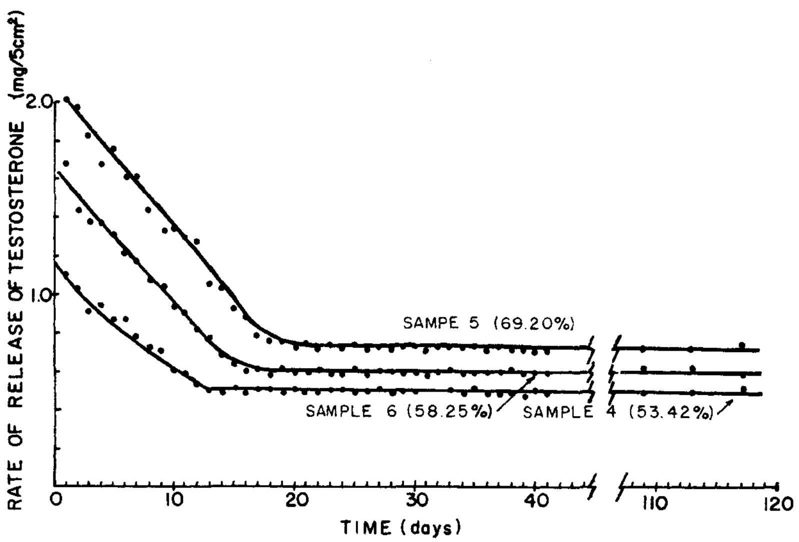

Fig. 9. Rate of testostrone release from silicone rubber–testosterone mixed sheets (37°C).

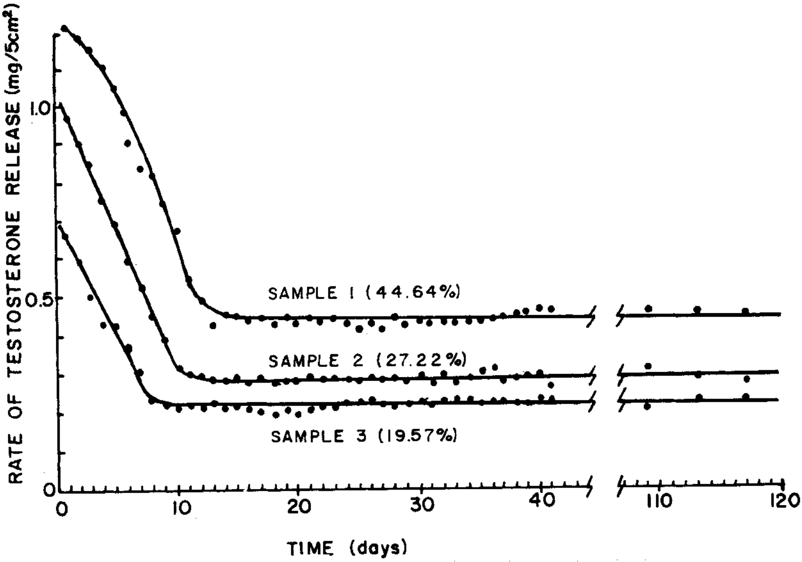

Fig. 10. Rate of testosterone release from silicone rubber–testosterone mixed sheets (37°C).

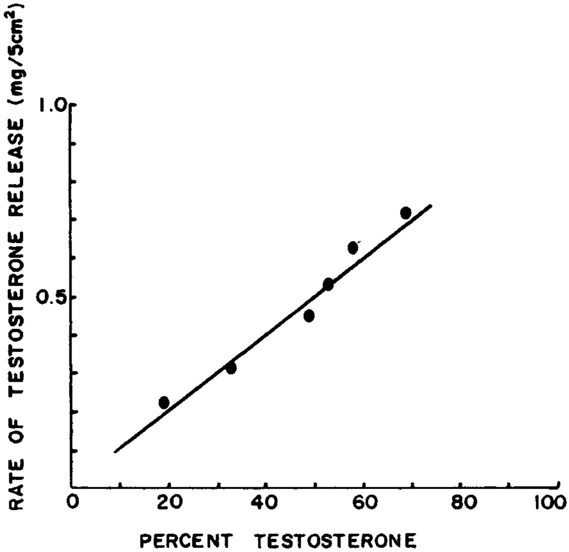

Fig. 11. Steady state rate of testosterone release vs. % testosterone in sheets at 37°C.

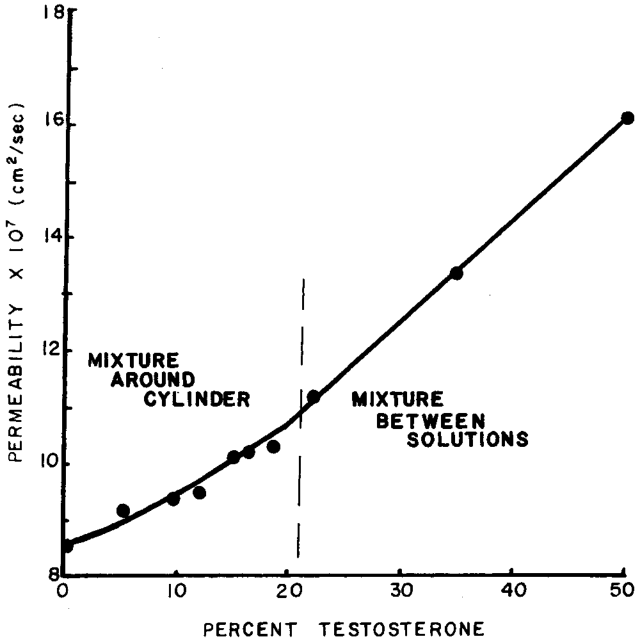

Fig. 12. Permeability vs. % testosterone for membrane around capsule and membrane between solutions.

determined. Table II gives the permeabilities that were determined using pure silicone rubber membranes.

These values are close to the values obtained with the capsules using the assumed saturated inner concentration.

Three membranes were constructed by mechanically mixing testosterone and silicone rubber adhesive. The right portion of Fig. 12 shows the permeabilities obtained for differing percentages of testosterone by weight. The left portion of the curve represents the permeabilities obtained for similar membranes placed around testosterone cylinders. The agreement is fairly good. No membrane of a concentration of testosterone above 20% could be placed around the cylinders.

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