DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(6&7), 1411-1432 (1985)

ENHANCED RELEASE OF DRUGS FROM SILICONE ELASTOMERS (II): INDUCTION OF SWELLING AND CHANGES IN MICROSTRUCTURE

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ABSTRACT

Incorporation of glycerol into silicone elastomers was found to enhance the release of hydrophilic drugs as well as to cause the polymeric device to swell as a result of water uptake. There are similarities between the kinetics of drug release from the matrix of silicone elastomers and the kinetics of swelling, water uptake, and leaching of tritiated glycerol, in that they all follow a matrix diffusion-controlled mechanism. The results of absorption, desorption, and resorption kinetic studies suggest that the two processes of swelling and water uptake are reversible. The amount of glycerol which leached out from devices containing up to 20% glycerol was only 4×10^{-4} to 6×10^{-4}% of the amount of

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glycerol that had been originally incorporated into the device. A scanning electron microscopic examination of a silicone device containing glycerol revealed a microstructure in which glycerol vesicles are dispersed. In contrast to this, the matrix of a silicone device containing no glycerol was shown to be a continuous network. The microstructure of a glycerol-containing silicone device became more "spongy" after leaching than it was before leaching.

INTRODUCTION

Since silicone elastomers are physiologically inert and biomedically compatible, they have been used as the biomedical engineering materials for plastic surgery (1) and in the fabrication of controlled-release drug delivery systems for the prolonged administration of pharmaceuticals and veterinary drugs (2-4). These polymers are a family of unique synthetic polymers, the backbone of which is made up of alternating silicon and oxygen atoms, rather than a carbon-to-carbon linkage. The silicon atoms each have one or more attached organic side groups, usually either phenyl, methyl, or vinyl groups. Other groups, such as alky, aryl, and reactive organic groups, may also be added to the silicon atom. These organic side chains impart certain characteristics to the silicone elastomers, such as solvent resistance, lubricity, compatibility, and reactivity with organic chemicals and other polymers. Since silicone elastomers are hydrophobic (lipophilic) in nature, they are useful for the delivery of lipophilic and low molecular weight compounds (5). The first report in this series of investigations showed that the

incorporation of co-solvents, such as glycerol, into silicone elastomers changes the physical properties of the polymer matrix and makes it capable of delivering hydrophilic, low molecular weight compounds, such as melatonin (6), and high molecular weight compounds, such as bovine albumin (7). During the course of these and other investigations (8, 9), the silicone elastomer devices have swelled in response to the sorption of water during drug release studies.

The objectives of this paper are to investigate the swelling phenomenon of silicone elastomers, which is activated by the addition of glycerol, as well as to analyze the microstructure of the matrices, both before and after the leaching studies.

EXPERIMENTAL

A. Swelling of Silicone Elastomers by Addition of Glycerol

Polymer discs were prepared from polydimethylsiloxanes (*1) containing up to 20% w/w of glycerol (*2). After mixing well, the polymer/co-solvent mixture was spread evenly between two glass plates (8" by 8") with 1 mm-thick spacers. The plates were compressed and cured overnight at 50°C to form a polymer sheet. Polymer discs (2 cm in diameter) were cut from the polymer sheet and soaked in an aqueous solution containing 20% polyethylene glycol (PEG) 400 (*3). The changes in the dimensions and the weight of the polymer discs were measured at various time intervals. Four discs were run for each formulation. After soaking for 250 hours, the specimens were withdrawn and photographed so that comparisons could be made.

B. Reversibility Studies of the Swelling Phenomenon

1. Preparation of Indomethacin-releasing silicone implants - One percent (w/w) of Indomethacin (*4) was incorporated into silicone elastomer (*5) containing 0, 10, or 20% glycerol. The same fabrication procedures used previously (6) were followed.

2. Absorption - Silicone implants (with length of 3.0 cm and diameter of 0.32 cm) were soaked in 20% w/w aqueous PEG 400 solution in a shaking water-bath (*6) at 37°C. The uptake of water was monitored by measuring the weight gain, using a balance (*7), and the change in dimensions (both length and width), using a caliper (*8), until equilibrium was reached. Four implants were run for each experiment.

3. Desorption - After the absorption studies above, the implants were placed in a dessicator, which was evacuated for five minutes under a mild vacuum (about 200 torrs) (*9). The implants were removed from the dessicator every 24 hours and the amount of weight loss and the change in dimensions were immediately measured. This procedure was repeated regularly until equilibrium was reached.

4. Resorption - Following the desorption studies, the implants were again soaked in aqueous media containing 20% w/w PEG 400. The uptake of water and the changes in weight and in the dimensions were measured according to the method outlined above.

C. Leaching of Tritiated Glycerol from the Implants

In order to measure the amount of glycerol leached out from the silicone implants, tritiated glycerol was incorporated into silicone elastomers, resulting in implants containing 10%

glycerol. First, the ethanolic solution of 5% w/w tritiated glycerol (*10) was diluted with cold glycerol in the ratio of 1 to 99 (w/w). One-half (0.5) gram of this glycerol (hot and cold) mixture was dispersed well into 4.5 grams of silicone elastomer in a laboratory mixer. Next, a curing agent was mixed into the combination. The glycerol/polymer combination was then extruded into sections of Tygon tubing and cured in situ, following the same method reported previously (6). Silicone implants containing 20% w/w of glycerol were also prepared by the same procedure, but contain 1 gram of glycerol (hot and cold) in 4 grams of silicone elastomer.

Leaching studies were conducted by soaking the implants (3 cm in length and 0.32 cm in diameter) in 20% w/w aqueous PEG 400 solution maintained at 37°C in a shaking waterbath. Four implants were run for each experiment. They were transferred into new aqueous media every 24 hours.

The amount of glycerol leached out from the silicone implants was determined by measuring the radioactivity in the aqueous PEG 400 solution. Half of a ml of the aqueous media was collected at each sampling interval during the leaching studies and was diluted with 10 ml of the scintillation counting cocktail (*11). After mixing well, the radioactivity of the samples was measured in a liquid scintillation counter (*12).

D. Microstructural Analysis

The methods previously used to investigate silicone-protein matrices (7) were also utilized to investigate the microstructure of the glycerol-containing implants. Implants

containing 1% w/w of Indomethacin and up to 30% w/w of glycerol, similar to those used in the aforementioned studies of the reversibility of swelling, were subjected to a complete leaching. Two types of control implants were also used, implants containing no glycerol and implants containing glycerol but not subjected to the leaching studies. All samples, both before and after leaching, were quickly frozen in Freon® and then in liquid nitrogen. The samples were fractured, thawed in alcohol, and then subjected to critical-point drying procedures. The samples were sputter-coated with 200 Å of gold-palladium and then examined using an EMRAY 1200 scanning electron microscope (*13) at 15 kv.

RESULTS

A. Swelling of Silicone Elastomers by Addition of Glycerol

The polymer discs were fabricated from silicone elastomers, which contain 0, 10, or 20% w/w of glycerol, and were all the same size before they were soaked in aqueous media. After soaking for 250 hours, the silicone discs containing no glycerol did not change in size, whereas the silicone discs containing 10 or 20% w/w of glycerol became larger in diameter and heavier in weight (Figure 1). The uptake of water by the silicone discs containing glycerol was found to be time-dependent (Figure 2). After 250 hours of soaking, the weight of the silicone discs containing 10 and 20% glycerol increased by 62 and 152%, respectively, when compared with the initial weights before soaking. Similarly, the volume increased by 73 and 190% for silicone discs having 10 and 20% w/w glycerol (Figure 2). In contrast, both the weight and the

SILICONE DISC AFTER SOAKING:			
GLYCSEROL CONTENT: (%)	0	10	20
WEIGHT AFTER SOAKING: (Mg)	376	779	1034

Figure 1. Photographs of silicone discs having 0, 10, or 20% w/w of glycerol, after 250 hours of soaking in 20% v/v aqueous PEG 400 solution.

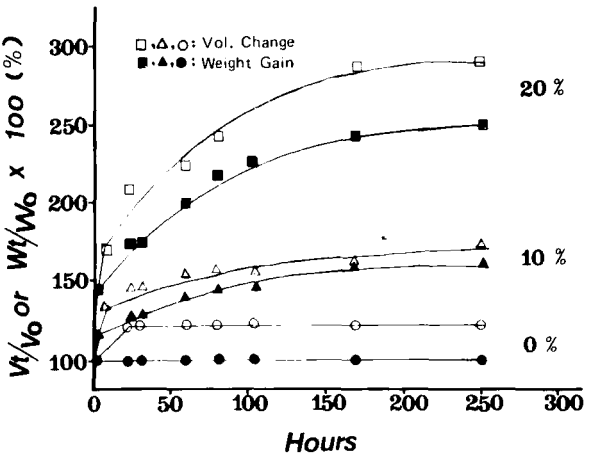

Figure 2. Time-dependent swelling of silicone discs having glycerol.

Key:

Silicone discs containing 20% w/w of glycerol:

□ volume expansion

■ weight gain

Silicone discs containing 10% w/w of glycerol:

△ volume expansion

▲ weight gain

Silicone discs containing no glycerol:

○ volume expansion

● weight gain

volume of the control discs (containing no glycerol) remained very much the same, except for an initial 20% increase in volume. This abrupt increase in volume occurred only in the initial stage of soaking, which may be due to the change in temperature from room temperature to 37° C. The same phenomenon was also noted in the glycerol-containing silicone discs. The swelling phenomenon was observed in the silicone elastomers with a polydimethylsiloxane backbone containing either a hydroxyl end block, such as silicone medical-grade elastomer 382, or a vinyl end block, such as silicone elastomer MDX 4-4210.

B. Reversibility of the Swelling Phenomenon

Figures 3A and 3B show the course for the changes in the volume and the weight of silicone implants over time, during the three phases of the sorption process: absorption, desorption, and resorption. During the absorption process, the volume expansion and weight gain of glycerol-containing silicone implants were observed to increase at a profile which can be described by a linear Q vs. $t^{1/2}$ relationship. Similar to the release of drugs from a matrix-type polymeric device, the observed Q vs. $t^{1/2}$ linearity suggests that the kinetics of volume expansion and weight gain are also matrix-controlled. After a month of soaking, the silicone implants containing 20% w/w of glycerol had an increase in volume to 297% of the original volume and a gain in weight to 235% of the original weight, while the silicone implants having 10% w/w of glycerol showed increases to 200 and 163% of the original volume and weight, respectively. The control implants (containing no

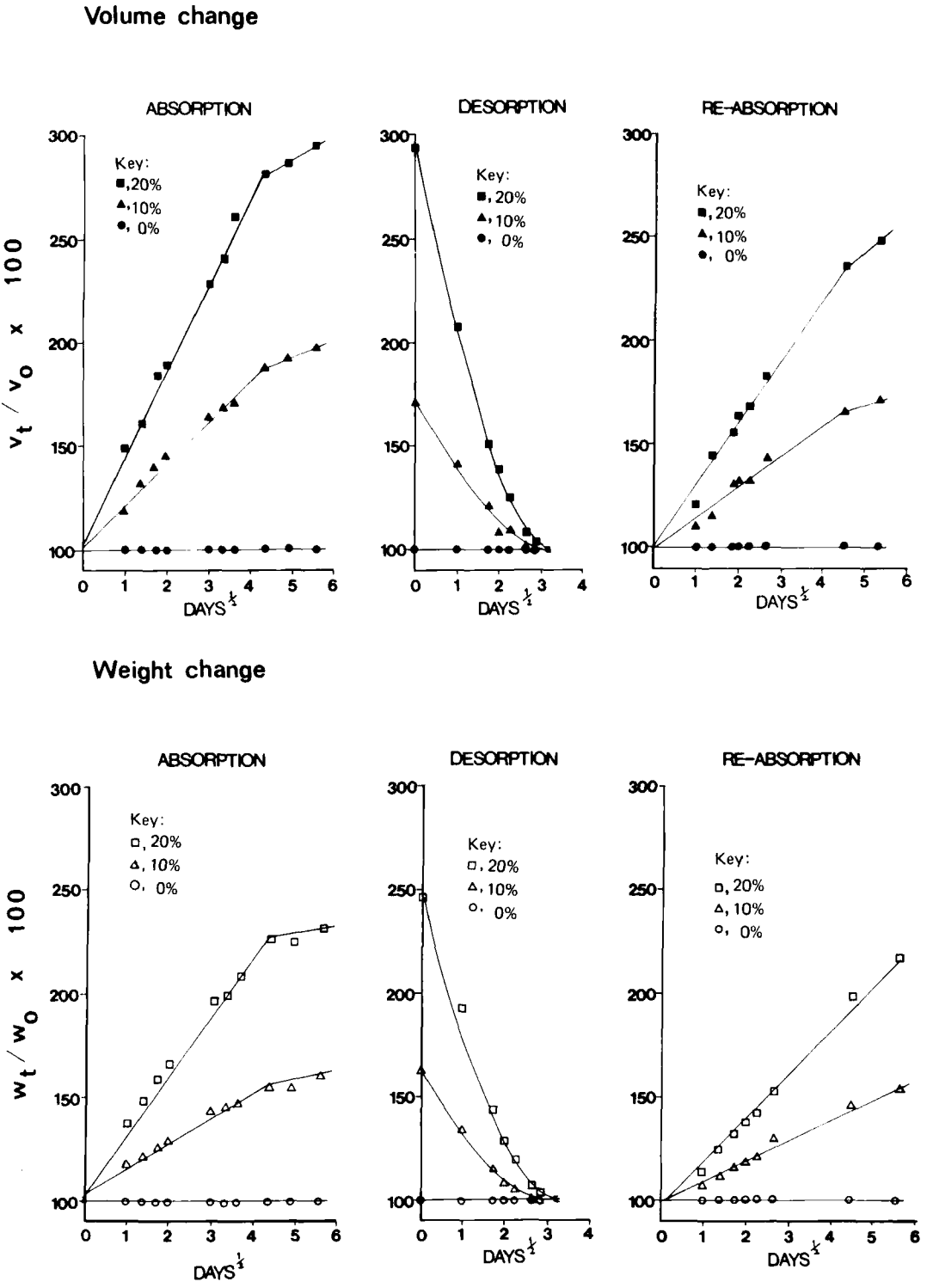

Figure 3. Time courses for the volume and weight changes of glycerol-containing silicone devices during absorption, desorption, and resorption studies.

glycerol) showed no significant changes in either volume or weight.

During the desorption process in a dessicator under a mild vacuum for 10 days, the glycerol-containing silicone implants decreased in volume and reduced in water content, as a function of the duration of desorption. They eventually returned to the initial weight and size of the implants before the absorption experiments (Figures 3a and 3b).

When the desorbed implants were subjected to resorption, the volume and the weight increased for the silicone implants containing glycerol. It was found that this increase also followed the same linear Q vs. $t^{\frac{1}{2}}$ relationship as that for the absorption and drug release studies. After soaking for a month in the aqueous media, the silicone implants containing 20% w/w of glycerol were noted to increase in volume to 250% of the orginal volume and in weight to 218% of the original weight, as compared to the 297 and 235% of the original volume and weight, respectively obtained in the absorption studies. The increases in volume and weight produced in the resorption studies represent an 84.2% regain in volume and a 92.8% regain in weight, when compared with the fully swollen silicone implants during the absorption process. Similarly, for silicone implants containing 10% w/w glycerol, the resorption process yielded an increase in volume to 173% of the original volume and in weight to 155% of the original weight. This represents an 86.5% regain in volume and a 95.1% regain in weight when compared with fully swollen silicone implants.

Table I summarizes the rate profiles for the changes in the volume and the weight of silicone implants during

Table I. Rate Profiles for the Changes in Volume and Weight of Silicone Implants During Absorption and Resorption

	% Glycerol	Volume Change (% per day$^{1/2}$) Slope	Intercept	Corr	Weight Change (% per day$^{1/2}$) Slope	Intercept	Corr
Absorption	0	-	-	-	-	-	-
	10	0.183	1.067	0.989	0.108	1.082	0.977
	20	0.366	1.150	0.985	0.242	1.159	0.975
Resorption	0	-	-	-	-	-	-
	10	0.144	1.027	0.971	0.106	0.998	0.993
	20	0.292	1.027	0.994	0.236	0.938	0.996

absorption and resorption. Due to the difference in experimental conditions and resultant difference in rate profiles between the desorption studies and the absorption and resorption studies, comparisons will be made mainly on the absorption and resorption processes. For the silicone implants having 10% w/w of glycerol, the rate of weight gain was 0.106% per day$^{\frac{1}{2}}$ during the resorption process, which was very much the same as the 0.108% per day$^{\frac{1}{2}}$ obtained in the absorption process. Similarly, for the silicone implants containing 20% w/w of glycerol, the rate of weight gain was again in fairly good agreement, i.e. 0.242% per day$^{\frac{1}{2}}$ for absorption and 0.236% per day$^{\frac{1}{2}}$ for resorption.

On the other hand, for the silicone implants having 10% w/w of glycerol, the rate of volume increase was 0.183% per day$^{\frac{1}{2}}$ for the absorption studies and 0.144% per day$^{\frac{1}{2}}$ for the resorption studies, i.e., a 21%-reduction in volume increase capacity. For the silicone implants containing 20% w/w of glycerol, the rate of volume increase was 0.366% per day$^{\frac{1}{2}}$ for the absorption studies and 0.292% per day$^{\frac{1}{2}}$ for the resorption studies, indicating also a 20%-reduction in the capacity of volume expansion after the desorption process.

C. Leaching of Tritiated Glycerol from the Implants

Figure 4 shows the time course for the increase in radioactivity in the aqueous media as a result of the leaching out of the tritiated glycerol from the glycerol-containing silicone implants. Interestingly, a linear relationship was also observed between the cumulative amount of tritiated glycerol leached out and the square root of leaching time. For the silicone implants containing 10% w/w of glycerol, the

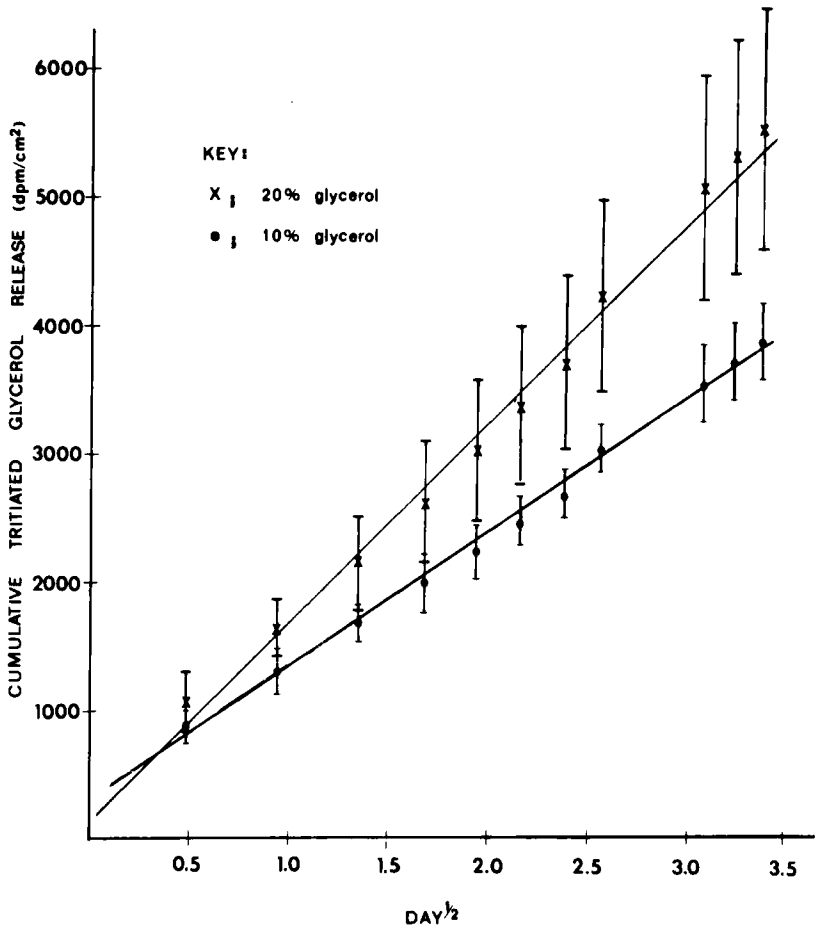

Figure 4. Leaching of tritiated glycerol from silicone devices having glycerol.

Key:

● 10% w/w of glycerol,

✕ 20% w/w of glycerol.

slope, after a linear regression analysis, was calculated to be 214 dpm/cm^2/hr^{½}, with a correlation coefficient of 0.997 and an intercept equal to 262 dpm/cm^2. For the silicone implants containing 20% w/w of glycerol, a slope of 322 dpm/cm^2 /hr^{½}, with a correlation coefficient of 0.996 and an intercept of 71

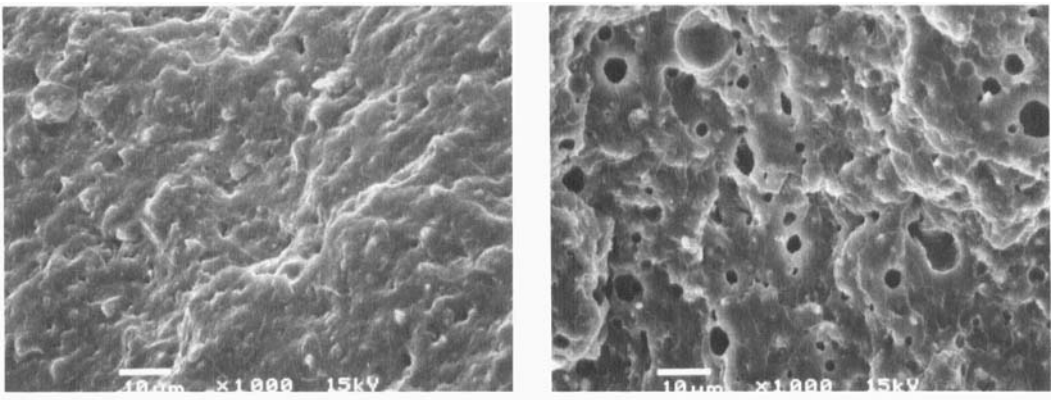

Figure 5. Photomicrographs of silicone devices before and after leaching.

Figure 5a: Silicone device containing no glycerol

Figure 5b: Silicone device containing 10% w/w of glycerol

Figure 5c: Silicone device containing 1% w/w of Indomethacin (after leaching)

Figure 5d: Silicone device containing 1% w/w of Indomethacin and 20% w/w of glycerol (before leaching)

Figure 5e: The same device as in Figure 5d, but after leaching

dpm/cm^2, was determined. The coefficient of variation, which can be calculated from the ratio of the standard deviation over the cumulative radioactivity of tritiated glycerol at each time point, has an average value of 9% for the silicone implants containing 10% w/w of glycerol, and 17.4% for the implants having 20% w/w of glycerol.

The radioactivity determined in the leaching media may be translated into the total quantity of glycerol leached out from

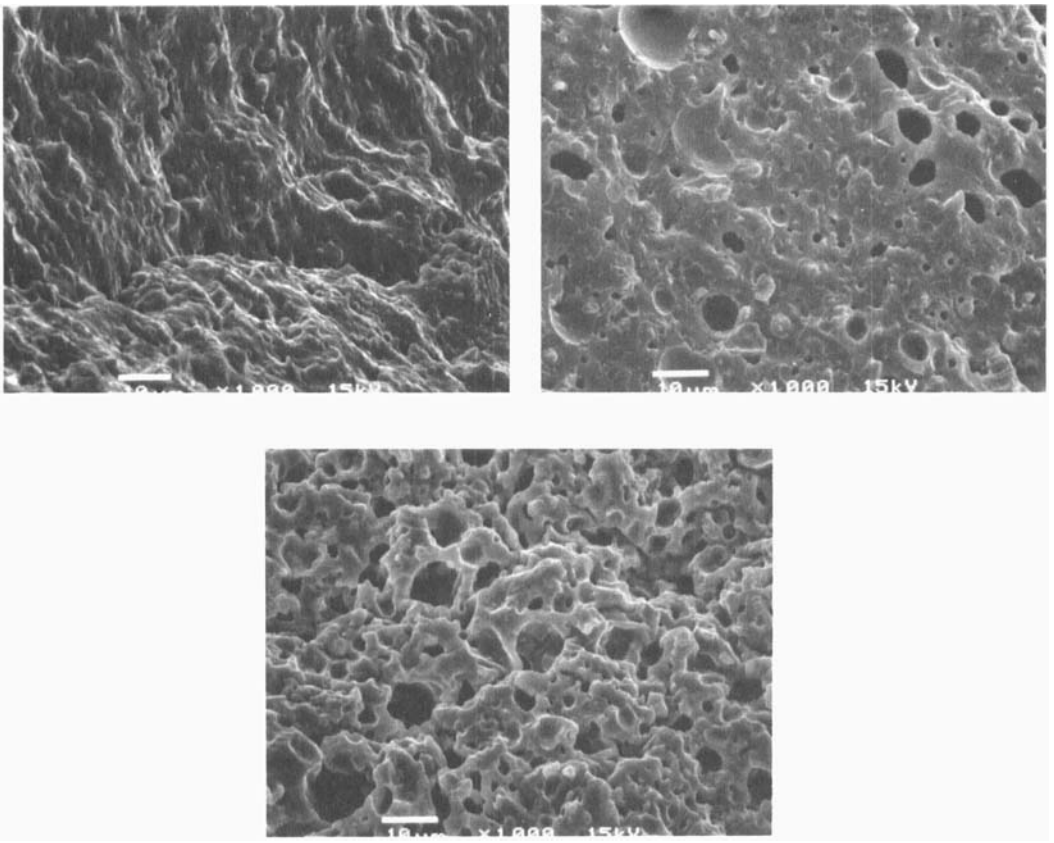

Figure 5 (Continued)

silicone implants, after taking into account the specific activity of tritiated glycerol and the dilution factors. By using the following formula:

$$\text{Amount of Glycerol} = \left(\text{Cumulative amount of radioactivity (dpm)} \Big/ \text{Specific Activity} \right) \times \text{Dilution Factor}$$

the amount of glycerol leached out from the silicone implants having 10% w/w of glycerol was only 1.55×10^{-4} μg, or 6×10^{-4} % of the total glycerol content originally incorporated into the silicone implants, and was 2.18×10^{-4} μg, or 4×10^{-4} % of the

total glycerol content initially incorporated into the silicone implants with 20% w/w of glycerol. The results obtained suggest that the leaching of glycerol is negligibly small.

D. Microstructural Analysis

Figures 5a to 5e are the scanning electron micrographs of silicone elastomers containing up to 20% w/w of glycerol. The polymeric implants prepared from the silicone elastomers containing no glycerol show a continuous network, with no vesicles or cavities (Figure 5a). Incorporation of glycerol into the silicone elastomers "generates" numerous vesicles within the silicone matrix (Figure 5b), while the addition of indomethacin (1% w/w) into silicone elastomer (without glycerol) does not change the continuous network of silicone elastomer (Figure 5c). However, once glycerol is incorporated into the Indomethacin-containing silicone elastomers, vesicles are generated (Figure 5d). After leaching in aqueous media, the silicone network appears to be more "spongy" than it was before leaching, although the silicone network was not disrupted during leaching (Figure 5e). Similar microstructural changes were also observed in other silicone implants containing either 10 or 30% w/w of glycerol.

DISCUSSION AND CONCLUSIONS

In the previous reports of this series, it was shown that the release of hydrophilic compounds, such as melatonin (6), and high molecular weight compounds, such as proteins (7), can be remarkably enhanced by incorporation of water-miscible co-solvents, such as glycerol, into silicone elastomers. This

phenomenon appears to be universal regardless of what kind of drug is used. In order to evaluate the possible mechanism(s) leading to the enhanced release of hydrophilic drugs from lipophilic silicone devices by the addition of glycerol, this study investigated the swelling phenomenon, because both the swelling of the devices and the enhanced release of hydrophilic drugs from the same devices occurred simultaneously.

It is interesting to note that, similar to the matrix diffusion-controlled release of drugs, the kinetics of swelling and uptake of water by the glycerol-containing silicone devices also follow the same linear Q vs. $t^{\frac{1}{2}}$ relationship as expected from the matrix diffusion-controlled mechanism (Figures 3 and 4). The volume expands, as a result of the uptake of water, to two to three times the size of the original device. Since the equilibrium solubility of water for the commonly used polymers, such as vulcanized rubber, ranges from about 0.02 to 0.2% by weight (10), the incorporated glycerol is apparently the predominant factor responsible for the uptake of water and the swelling of the silicone devices. This large amount of water taken up by the device may facilitate the transport of hydrophilic drugs in the polymer matrix, leading to an enhanced release of drugs out of the silicone devices to the surrounding media.

Fedors (10) studied the absorption of liquids by polymers which contain solid additives, such as NaCl and Na_2SO_4. He suggested that the equilibrium uptake of liquid can be calculated if the properties of the additive, such as the solubility, as well as the modulus of the polymer are known. The additive investigated in this study is glycerol, which results in the formation of vesicles. The vesicles are

different from the solid particles of NaCl used in the Fedors experiment. Although the two systems are somewhat different, the sequence of events during the uptake of water by the solid vulcanized silicone elastomer is rather similar. On the microscopic level, the process can be described in the following way: The initial inclusion, or glycerol vesicle (Figure 6), is, for the sake of simplification, assumed to be spherical in shape (with a radius of r_o). This assumption is derived from the photomicrographs shown in Figure 5. Water diffuses into the elastomer at an initial rate which depends upon the geometry of the test specimen and the chemical nature of the elastomer. After some time, the water molecules come into contact with the glycerol vesicle and begin to dissolve the glycerol molecules. Since glycerol is hygroscopic in nature, it accumulates the water molecules around the vesicle, which results in an increase in the volume of the vesicle. The outer boundary of the vesicle is a moving boundary. The radius of the undissolved portion of the vesicle becomes r(t), while the radius of the whole vesicle becomes R(t).

There is an osmotic pressure, with a magnitude of $\pi(t)$, associated with the solution, which acts radially outwards around the vesicle boundary. Simultaneously, the silicone elastomer itself exerts a retractive pressure P(t), acting radially inwards on the boundary. When these two pressures are equal, the vesicle ceases to grow. At this point, the osmotic pressure $\pi(\infty)$ of the vesicle equals the retractive pressure $P(\infty)$ of the polymer, and the vesicle reaches an equilibrium radius of $R(\infty)$. Macroscopically, a spherical matrix will behave in the same way.

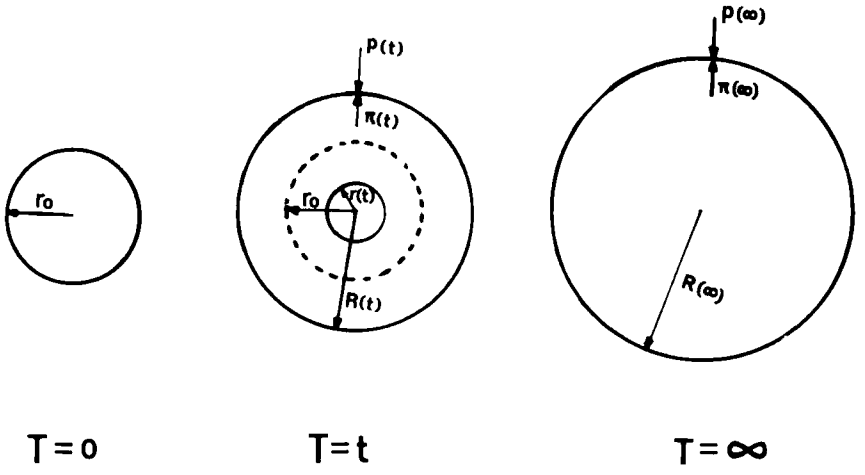

Figure 6. Schematic diagram for the growth of a glycerol vesicle in the polymer matrix during soaking (redrawn from Fedors, 1980).

From the leaching experiment of tritiated glycerol from silicone devices having up to 20% w/w of glycerol, it becomes clear that the amount of glycerol leached out is very minute, only from 4×10^{-4} to 6×10^{-4} % of the original amount of glycerol incorporated into the silicone elastomer. The results suggest that glycerol is essentially retained in the polymer matrix. One or more of the three hydroxy groups in the glycerol molecule may be covalently bound with the polydimethylsiloxane backbone during the curing process.

During the resorption process, the rate of water uptake by silicone devices containing 10-20% w/w of glycerol is identical to the rate of water uptake obtained in the absorption process, because glycerol, a hygroscopic agent, is still retained in the silicone device, even after the desorption treatment (Table I). However, the change in the volume is smaller (20-21%) during resorption process than in the absorption process. This may be

due to a microstructural change which occurs during the absorption-desorption cycle. This hypothesis has yet to be proved. However, experimental evidence for this hypothesis is found in the microstructural analysis of Figure 5e, which indicates a change in the silicone network after leaching.

In conclusion, a close correlation was established between enhanced release of hydrophilic drugs and the uptake of water and swelling of the silicone devices, triggered by the incorporation of glycerol in the polymer curing process. The enhancement of drug release could be caused by the osmotic effect during the water uptake by the glycerol vesicles in the polymer matrix. Although the polymer devices significantly expanded in volume, the leaching of glycerol from them was negligible. It was found experimentally that the kinetics of swelling, water-uptake, and leaching all follow a matrix diffusion-controlled process, similar to the process which controls the release of the drug from the matrix-type polymeric device.

Footnotes

1. MDX 4-4210, Dow Corning Co., Midland, MI.
2. USP Grade, Fisher Chemical Co., Fair Lawn, NJ.
3. Fisher Chemical Co., Fair Lawn, NJ.
4. Sigma Chemical Co., St. Louis, MO.
5. Silicone elastomer 382, Dow Corning Co., Midland, MI.
6. Model 127, Fisher Scientific Co., Fair Lawn, NJ.
7. Ainsworth®, Denver, CO.
8. Ralmike's®, So. Plainfield, NJ.
9. Cole Parmer, Co., Chicago, IL.

10. NET-022H, New England Nuclear, Boston, MA.
11. Hydroflour®, National Diagnostics, Somerville, NJ.
12. 6881 Liquid Scintillation System, Mark III, Tracor Analytic Co., Elk Grove Village, IL.
13. SEM photomicrographs were taken by Mr. Markus Meyenhofer at the University of Medicine and Dentistry of New Jersey, Newark, NJ.

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10. R.F. Fedors, Polymer 21 207 (1980).