

A NEW TRANSDERMAL SYSTEM I.

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Abstract

With the aim of developing a new drug delivery system, the transdermal therapeutic system (TTS), the author has studied membranes prepared from polydimethylsiloxane- α , ω -diols with different viscosities. The solvent uptake of the membranes was studied using solvents of different polarities. The results of thermochemical investigations supported the differences found in the behaviour of the membranes.

Keywords: transdermal system, membranes, silicone polymers.

As a result of technological research, a new form of pharmaceutical appeared in the middle of the 1970s: the transdermal therapeutic system, TTS. In the case of transdermal drug delivery the drug penetrates the skin and causes a constant drug level in the blood. In addition to this the effective dose is lower than for traditional forms as the drug gets directly into the target tissue through the circulation system [1-3].

There are four basic types of TT systems [4-6] which can be divided into two groups based on the principle of operation. In the first group the drug and the adhesive together, in the second group a special non-porous or microporous membrane serve to ensure the optimum rate of drug delivery.

The aim of our work has been to select silicone rubber types which enable a new TT system to be produced with favourable properties. The properties of silicone membranes have been described in a number of papers, and diffusion across silicone membranes has been studied by many researchers. However, these studies were made on commercially available silicone rubber films or the films were prepared using kits purchased from manufacturers [7-8]. Unfortunately the exact composition of such films is usually unknown, especially in respect of the additives present. Since these may change the properties of the membrane, it is difficult to draw general conclusions from the results of measurements. Hence, we have studied films prepared from polydimethylsiloxane- α , ω -diols with characteristic viscosities, without using additives.

Chemicals

Polydimethylsiloxane- α,ω -diols type R-1, R-5, R-18 and R-38 were purchased from Fine Chemicals Co., Hungary, (the numbers refer to the viscosity of the oligomer in Pas). As a cross-linking catalyst a Wacker product, type T-47 was used which contained tetraalkoxysilane as cross-linking agent and an organotin compound as initiator. In the experiments 5 % catalyst was mixed with the oligomers of different viscosities, then the mixtures were spread over a teflon base in the required thickness and allowed to set at 25 °C.

Studies on the Solvent Uptake

It is known that silicone rubber films are hydrophobic and impermeable to ions. It is, however, important from the technological point of view to measure the differences in the polarity of different silicone rubber films as this may influence the rate of diffusion across the membrane. Hence, 1 mm thick membranes with 3.14 cm² area were prepared from the materials studied and after soaking in solvents of different polarities (toluene, ethylacetate, n-propanol, n-butanol, distilled water) they were weighed after 24, 48 and 72 hours. The data obtained are summarized in *Table 1*.

Table 1
Mass increase in silicone-caoutchouc specimen of the effect of various solvents

Sign	Time (hrs)	Mass increase in %				
		Toluene	Ethylacetate	n-Butanol	n-Propanol	Distilled water
s f	24	173.5	114.9	1.06	1.06	0
	48	202.7	114.1	1.06	1.05	0
	72	208.6	114.8	1.06	1.05	0
R-1	24	215.3	113.8	1.07	1.06	0
	48	227.0	113.8	1.07	1.06	0
	72	229.0	124.5	1.05	1.05	0
R-5	24	280.0	144.0	1.08	1.07	0
	48	300.0	154.4	1.06	1.06	0
	72	306.6	155.0	1.06	1.06	0
R-18	24	312.9	165.1	1.07	1.06	0
	48	343.1	169.9	1.05	1.05	0
	72	351.4	170.0	1.05	1.05	0
R-38	24	312.9	165.1	1.07	1.06	0
	48	343.1	169.9	1.05	1.05	0
	72	351.4	170.0	1.05	1.05	0

The polarity of the solvents was calculated using the following formula [9]:

$$P = \frac{\epsilon - 1}{2\epsilon + 1},$$

where ϵ is the dielectric constant. The increase in weight of the samples is shown in *Figs. 1-3* as function of the polarity of the solvent.

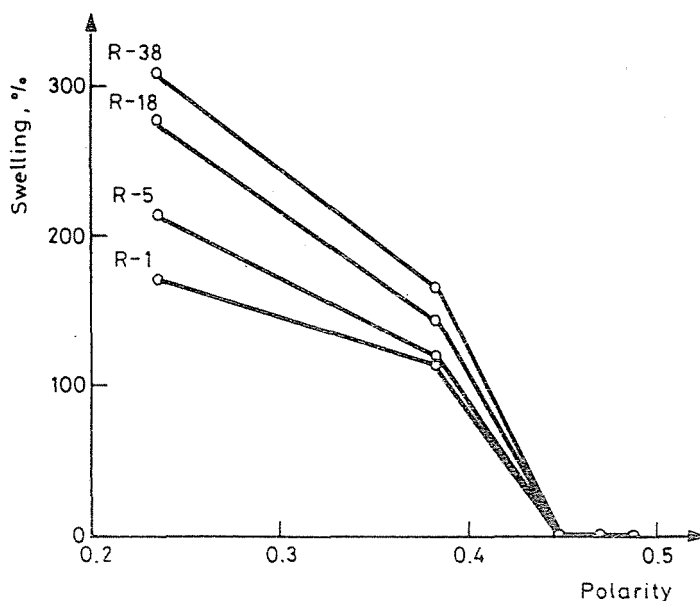


Fig. 1. The rate of swelling plotted against polarity during 24 hours

As the data in the figures show, there is a marked difference between the polymer films made of different oligomers. The apolar nature of the polymers becomes more pronounced as the viscosity of the oligomer increases. In the strongly apolar toluene the solvent uptake is significant as shown by the increase in weight and size of the specimens. The solvent uptake rapidly decreases as the polarity of the solvent increases. In butanol practically no solvent uptake is observed. It is, however, interesting that after soaking in butanol for 72 hours the polymer disintegrates. The different behaviour in toluene is the more striking as the dielectric constants of the oligomers, as given by the manufacturer, are very close, between 2.73 and 2.77, which is in turn very close to the dielectric constant of toluene, 2.38.

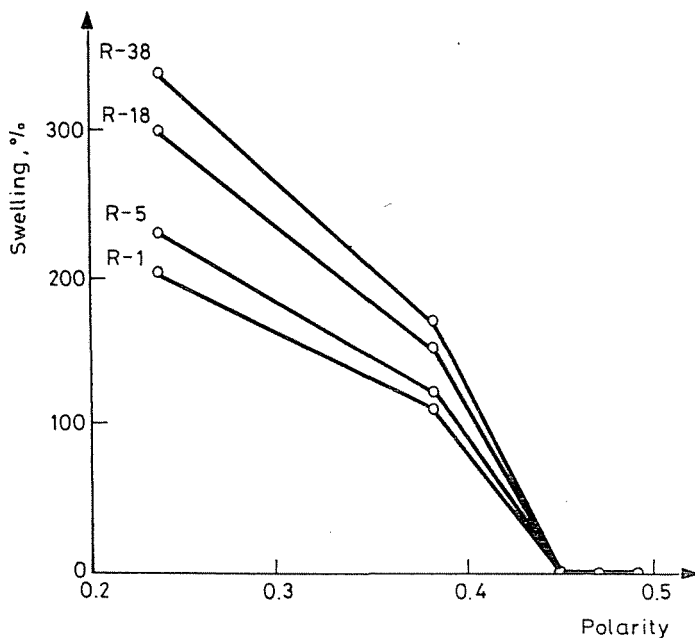


Fig. 2. The rate of swelling plotted against polarity during 48 hours

However, after soaking for 24 hours there appears a difference between the solvent uptake of oligomers with different degrees of cross-linking, and this difference remains practically unchanged until the end of 72 hour soaking. The comparison of data is presented in *Table 2*.

$$(\Delta = T\%_{R-38} - T\%_{R-x})$$

Based on the data we assumed that the structures of the silicone rubbers made from the R-1 and R-5 oligomer (and those from the R-18 and R-38 oligomer) are very similar, but differ markedly from the products made from oligomers of higher viscosity. To prove this assumption the thermal properties of the samples were also studied.

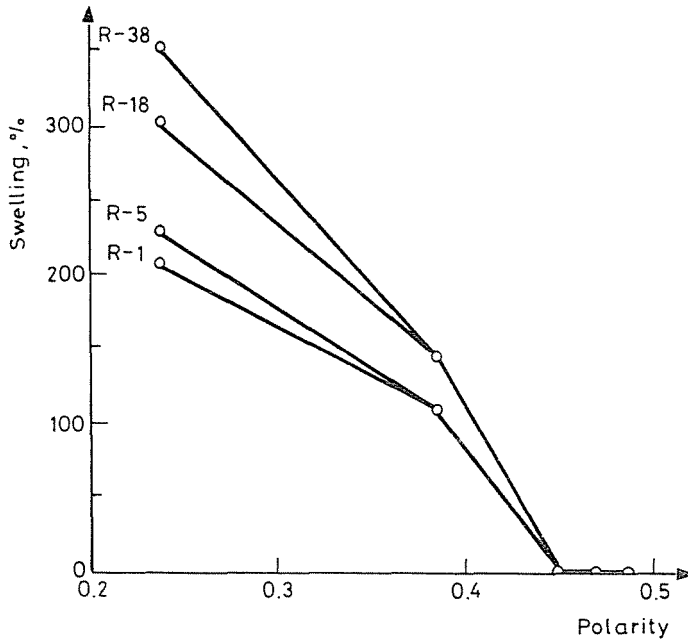


Fig. 3. The rate of swelling plotted against polarity during 72 hours

Table 2

Relative mass increase in silicone-caoutchouc specimen of the effect in toluene

Sign	24 hrs		48 hrs		72 hrs	
	Mass increase (%)	Δ	Mass increase (%)	Δ	Mass increase (%)	Δ
R-1	173.5	138.5	202.7	140.3	208.6	142.6
R-5	215.3	96.5	227.0	116.0	229.0	122.0
R-18	280.0	32.0	300.0	43.0	306.0	45.0
R-38	312.0		343.0		351.0	

Thermal Studies

The silicone rubber membranes were cut up into 1×1 mm particles. 100 mg of the sample were weighed into a platinum crucible and the thermal

curves were recorded with a Derivatograph type MOM OD 2 at a heating rate of 5 °C/min in air. The reference material was 100 mg α -Al₂O₃. The derivatograms of samples prepared from R-1 and R-5 are shown in *Fig. 4*, those made from R-18 and R-38 in *Fig. 5*.

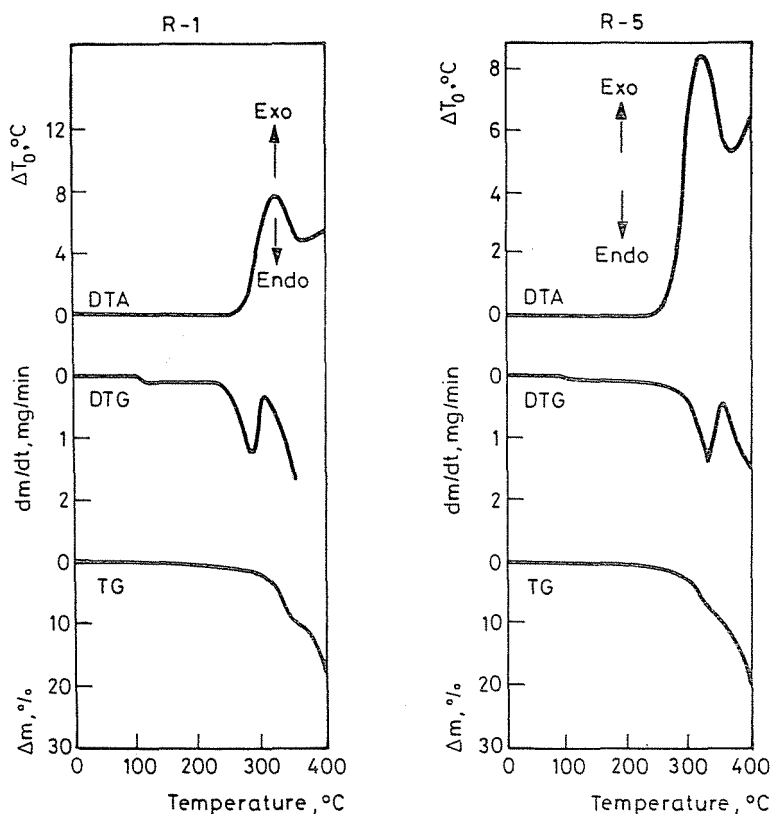


Fig. 4. Derivatogram of R-1 and R-5 samples

As the figures show, the thermal studies support the results of experiments on solvent uptake. Samples from R-1 and R-5 exhibit two exothermal decomposition peaks. The mass loss up to the first step is 2.55% due to the removal of volatile components adsorbed at the surface or contained in the matrix. A significant mass loss of 9.75% is observed at 295°C followed

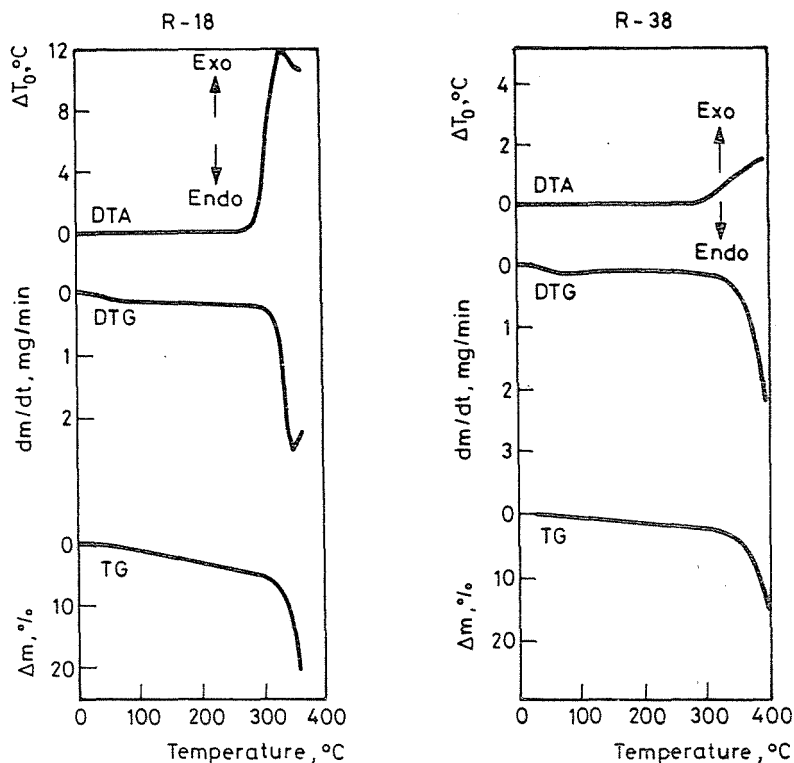


Fig. 5. Derivatogram of R-18 and R-38 samples

by the thermal degradation of the matrix at 350°C. In the derivatograms of the R-18 and R-38 samples only the continuous mass loss due to the evaporation of the volatile components is observed (5.75 and 4.25%, respectively), and the exothermal process at 364 and 360°C, respectively connected with a mass loss due to the decomposition of the matrix.

Based on these results we have assumed that in membranes made from low viscosity samples free Si-OH groups are left even after cross-linking, which reduce the apolar character of the membrane bulk. This and the different lengths of the chains forming the cross linkages may result in the different behaviour of the membranes.

The present work will be continued by studying the effect of auxiliary materials on the polarity of the silicone rubber matrix.

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