Development of a New Silicone-Base Transdermal Therapeutic System. II. Study of Trifunctional Ingredients

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Received 12 October 2000; accepted 5 January 2001

ABSTRACT: The effect of two trifunctional silicon compounds was investigated on the polarity behavior of silicone elastomers by investigating the swelling properties in solvents of various polarity. The properties of the silicone elastomer were also influenced by methyltrimethoxysilane (MTS) and *N*-[(aminoethyl)aminopropyl]trimethoxysilane (GF-91) if they were used together with the networking agent. The cooperative effect of the polar liquid ingredients [glycerol, ethylene glycol, propylene glycol, poly(ethylene glycol) 400] and GF-91 as well as the dissolution of the liquid ingredients from the silicone elastomer were studied. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 82: 1187–1194, 2001

Key words: polydimethylsiloxane; trifunctional ingredients; liquid additives; swelling properties; polarity

INTRODUCTION

In the 1970s a new pharmaceutical form, the transdermal therapeutic system (TTS), appeared on the market. This new drug type releases its active ingredient through the patient's skin, providing a uniform blood level. In addition, since the active ingredient moves with the blood stream directly into the targeted organ, the effective dose can be lower than that in the traditional drug types. During the last years TTS has been developed on a silicone basis as well. In order to modify the drug uptake different ingredients were added, having substantial influence on the properties of the silicone matrices.

In our previous works,[1,2] the influence of several ingredients on the properties of the silicone matrices was investigated. In the present work we investigated silicone elastomers containing different trifunctional ingredients. The interaction between the liquid additives and the basic material as well as the trifunctional silicon ingredients was investigated. The interaction between the matrix and the ingredients was monitored by investigating the swelling properties of the polymers in different matrices.

EXPERIMENTAL

The polydimethylsiloxane-α,ω-diols, (oligomers R-5, R-18) and the polydimethylsiloxane oil M 350 (the number used in the product codes indicates the viscosity of the oligomer in terms of Pa s) used were products of Szilor Kft (Budapest, Hungary). The gelling agent used was the catalyst T-47 (Wacker Chemie GmbH, Munich, Germany). It contains poly(alkoxy silane) as the gelling compound and an organic tin compound as the crosslinking initiator. T-47 was mixed in a quantity of 5% into the oli-

Contract grant sponsor: OTKA Foundation; contract grant numbers: T 013053; T 022417.

Journal of Applied Polymer Science, Vol. 82, 1187–1194 (2001)

gomer and/or oligomer-additive mixtures; then, the mixtures were gelled at 25°C by spreading them on Teflon plates at a thickness of 1 mm. The trifunctional silicon compounds were methyltrimethoxysilane and *N*-[(aminoethyl)aminopropyl]trimethoxysilane GF-91 (Wacker GmbH, Munich, Germany). The dry glycerol and propylene glycol used were of Ph Hg VII degree, the ethylene glycol was of analytical purity (Reanal Finechemical Factory, Budapest, Hungary), and the poly(ethylene glycol) (PEG 400) was PLURIOL E 400 (BASF, Ludwigshafen, Germany). For the tests, films of 1 mm thickness were prepared, and after an aging period of 7 days, discs with a diameter of 2 cm and a surface area of 3.14 mm^2 were cut out. Each test was made with five parallel samples. Following a mass measurement with a four-decimal-point accuracy using an analytical balance, the samples were placed into solvents with different polarity—toluene, ethyl acetate, *n*-butanol, ethanol (analytical purity, Reanal Finechemical Factory, Budapest, Hungary), and distilled water—and their mass was measured after 24, 48, and 72 h. The volume of the absorbed solvent was calculated using eq. (1):

$$V = \frac{m_{sw} - m_d}{V_d \delta_s} \times 100 \qquad (1)$$

where V is the relative volume of the solvent uptake (i.e., the percentage increase in volume of the sample compared to that of the initial sample); m_{sw}, the mass of the sample in a given solvent after soaking; m_d, the mass of the "dry" sample; δ_s, the density of a given solvent; and V_d, the volume of the "dry" sample.

The data of the parallel samples were averaged, and these averaged data are shown below. Deviation of the parallel samples did not, in a single case, exceeded 3%. For study of the repeated solvent uptake, we cut 1-mm-thick samples with a 25-mm diameter from elastomers made with the polar ingredients [glycerol, ethylene glycol, propylene glycol, poly(ethylene glycol)]. The dimensions of the samples were increased for a better observation of the water uptake by mass determination. We studied three parallel samples from all matrix types. The mass change was measured after 72 h. During 24 h, the samples were dried at 25ºC in 60 relative water vapor and were measured subsequently. This process was repeated once more. The results showed the amount of the water the samples could uptake and evaporate from them. Furthermore, it is possible to conclude how far the water could penetrate into the matrix framework and how much polar solvent the penetrating water could dissolve. The diameter and thickness of the samples increased significantly after 72 h, but after 24 h drying, their original dimensions were recovered.

RESULTS AND DISCUSSION

Study of the Effect of the Trifunctional Networking Agents

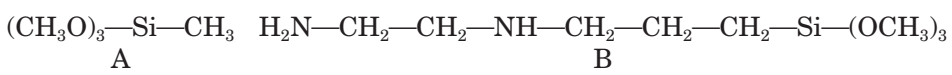
As the result of pharmaceutical technology research, a new drug type, the Transdermal Therapeutic System (TTS), emerged in pharmaceutical technology in the early 1970s. This new drug type releases its active ingredient through the patient's skin, providing a uniform blood level. In addition, since the active ingredient moves with the blood stream directly into the targeted organ, the effective dose can be lower than that in the traditional drug types.[3–5] Several forms of TTSs have been developed in recent years,[6–8] which may be divided into two major groups: In the first case, the optimal degree of release of the active ingredient is provided by the plaster base and the plaster structure together and, in the second case, by a special microporous or nonporous membrane. In our previous work,[2] the objective was to select silicon rubber base materials that will allow the development of a new TTS with optimal characteristics. Several publications have dealt with the characteristics of silicon membranes or with the testing of material diffusion through membranes[9–17]; however, commercially available silicon rubber films or factory kits used for manufacturing silicon rubber were used in these studies and, unfortunately, it is very difficult to establish what additives they really contain. Since the additives used change fundamentally the characteristics of the base materials, therefore, general conclusions from these results can only be drawn with difficulty and with reservations.

In our previous work,[2] we examined the effect of some polar and apolar solvents ("ingredients") commonly used in the pharmaceutical praxis for the silicone elastomer matrixes. We established that the ingredients can influence the behavior of the silicone elastomer in solvents having various polarity. In what follows, we examine the effect of

Table I Solvent Uptake of R-5 Elastomers Containing 3, 5, and 10% MTS in Solvents Having Various Polarity

Sample	Swelling Time (h)	Increase of Sample Volume (%) In Toluene	In Ethyl Acetate	In *n*-Butanol	In Ethanol	In Distilled Water
R-5 + 3% MTS	24	198.6	106	7.6	2.8	0
	48	204	106	7	2.8	0
	72	207.7	112	6.8	2.5	0
R-5 + 5% MTS	24	198	107.6	5.3	1.7	0
	48	204	109	7.1	1.9	0
	72	206	114	7.1	1.8	0
R-5 + 10% MTS	24	167	100	7.3	2	0
	48	185.6	104.6	7.7	2	0
	72	188	110	9.1	1.7	0

the tetrafunctional gelling agent and that of the trifunctional silicon compound on the behavior of the silicone elastomers. In our previous work, we demonstrated the presence of free Si—OH groups in the matrix after the gelling process. Since the trifunctional silicon compounds mixed with the silicone oligomers before the gelling process can bind to the free Si—OH groups built into the matrix framework, we expected that the structure of the polymer is looser and more flexible than that of the usual polymer. We studied the effect of two trifunctional compounds, namely, of (A) methyltrimethoxysilane and of (B) *N*-[(aminoethyl)aminopropyl]trimethoxysilane:



A B

These compounds were added to the oligomer–T-47 mixture in a quantity of 3, 5, and 10%, and the solvent uptake of these matrices was measured. The results can be seen in Tables I–IV. The results show the large difference between the effects of the two silicon compounds.

The presence of methyltrimethoxysilane decreased the solvent uptake in apolar solvents in

Table II Solvent Uptake of R-18 Elastomers Containing 3, 5, and 10% MTS in Solvents Having Various Polarity

Sample	Swelling Time (h)	Increase of Sample Volume (%) In Toluene	In Ethyl Acetate	In *n*-Butanol	In Ethanol	In Distilled Water
R-18 + 3% MTS	24	227.7	106.6	7.9	3.2	0
	48	239.8	111	5.6	3.6	0
	72	246	113	4.5	3.4	0
R-18 + 5% MTS	24	234.6	111	7.7	2.7	0
	48	245.8	122	7.1	2	0
	72	253.6	126.5	8.2	2.5	0
R-18 + 10% MTS	24	205.6	128	8.8	2.7	0
	48	210	128	8.9	2.7	0
	72	212.4	128.7	10.1	2.1	0

Table III Solvent Uptake of R-5 Elastomers Containing 3, 5, and 10% GF-91 in Solvents Having Various Polarity

Sample	Swelling Time (h)	Increase of Sample Volume (%)				
		In Toluene	In Ethyl Acetate	In *n*-Butanol	In Ethanol	In Distilled Water
R-5 + 3% GF 91	24	267	128.5	7.9	2	3.5
	48	283.6	131	8.3	1.8	4.9
	72	294.4	131	7.4	2.5	6.7
R-5 + 5% GF 91	24	270	125	9.5	2	3.3
	48	293	128	8.5	2	3.4
	72	344	134.4	9.2	2	6.5
R-5 + 10% GF 91	24	376	176	17.5	10	24.2
	48	404	174	18.6	14	38.8
	72	411	172	19.2	20	87

both types of oligomers, but in polar solvents, it is hard to see any difference in comparison with the base elastomers. The building-in of the trifunctional silicon compound did not loosen the matrix structure; to the contrary, the binding of free silanol groups caused a more rigid matrix structure in accordance with our preliminary expectations.

The polar group having an *N*-(aminoethyl)-aminopropyl chain loosened the internal structure of the elastomer, presumably due to repulsion with the apolar surrounding. Thus, these processes have resulted in a silicone elastomer having a more flexible structure than that of the elastomers made with the usual procedure. This matrix has a different appearance from that of the other elastomers: It is opalic, white, and soft and has a velvetlike touch. The great solvent uptake of this matrix experienced in the apolar solvents demonstrates the looser structure. The increasing solvent uptake observed in distilled water shows the polar character of the *N*-(aminoethyl)aminopropyl chain. The matrix structure and the fixed network are completely built; therefore, no decrease of mass could be observed in any of the solvents investigated.

Cooperative Effects of Liquid Ingredients and GF-91

For the experiments, we made elastomers having 10% liquid ingredients and 5% GF-91. The GF-91 helps the distribution of the polar ingredients in the framework of the matrix; thus, this elastomer can have a glycerol content up to 40% inside the

Table IV Solvent Uptake of R-18 Elastomers Containing 3, 5, and 10% GF-91 in Solvents Having Various Polarity

Sample	Swelling Time (h)	Increase of Sample Volume (%)				
		In Toluene	In Ethyl Acetate	In *n*-Butanol	In Ethanol	In Distilled Water
R-18 + 3% GF 91	24	243	126.7	8.8	2.4	2.9
	48	268	140.8	9	2.7	5.4
	72	283.7	146.8	9.4	2.5	7.4
R-18 + 5% GF 91	24	259.5	142	9.5	2	2.5
	48	268	143	10.6	2	4
	72	278	149	10	2.2	4.5
R-18 + 10% GF 91	24	531	248	19	13.5	8
	48	611	205	24	18	18
	72	638	179	26	23	3

Table V Solvent Uptake of R-5 Elastomers Containing 5% GF-91 and 10% Liquid Ingredients in Solvents Having Various Polarity

Sample	Swelling Time (h)	Increase of Sample Volume (%) In Toluene	In Ethyl Acetate	In *n*-Butanol	In Ethanol	In Distilled Water
R-5 + 5%	24	195	106	33.5	95	35.4
GF91 + 10%	48	202	108	17	84	52.2
glycerol	72	208	108	9.7	82	73
R-5 + 5%	24	196	78.6	25	127.7	40
GF91 + 10%	48	213	79.5	17	112	68
propylene glycol	72	226	80.4	13.2	95.8	92
R-5 + 5%	24	251	96	28.8	47	18
GF91 + 10%	48	289	98	9.3	38	26
ethylene glycol	72	325	100	5.6	32	32
R-5 + 5%	24	183.5	93	78	74.4	18.7
GF91 + 10%	48	196	96.3	84.4	96	36.4
PEG 400	72	207.7	98.4	83	109.6	51.7
R-5 + 5%	24	228	117	6.3	3	4
GF91 + 10%	48	243	114	5.6	3.1	4.5
M350	72	259	105	5.6	3.1	5.3

matrix. The experiments were carried out as discussed before. The results can be seen in the Tables V and VI.

In making the elastomer from R-5 with 5% GF-91 by addition of any polar ingredient in toluene, we observed the largest solvent uptake when the ingredient was ethylene glycol. GF-91 and ethylene glycol were built into the matrix structure. The residual polar ingredient, ethylene glycol, is associated with those polar chains built into the matrix. This latter part of ethylene glycol can be dissolved partially with the aliphatic alco-

Table VI Solvent Uptake of R-18 Elastomers Containing 5% GF-91 and 10% Liquid Ingredients in Solvents Having Various Polarity

Sample	Swelling Time (h)	Increase of Sample Volume (%) In Toluene	In Ethyl Acetate	In *n*-Butanol	In Ethanol	In Distilled Water
R-18 + 5%	24	210.6	111.7	9.4	80	36.7
GF 91 + 10%	48	228.6	115	33	61	60
glycerol	72	249.4	115	16	57	88
R-18 + 5%	24	225	116	69	93	36
GF 91 + 10%	48	252	119	87	117	58
propylene glycol	72	277	120	88	130	77
R-18 + 5%	24	287	114	55	50	15
GF 91 + 10%	48	352	116	46	58	22
ethylene glycol	72	425	120	38	59	22
R-18 + 5%	24	225	100	69.6	63.6	17.3
GF 91 + 10%	48	244.5	105	95	92	26.7
PEG 400	72	265	106	108	118	35.7
R-18 + 5%	24	455	184	7	3.6	6
GF 91 + 10%	48	501	170	6.7	3.2	11
M350	72	545	164	6.5	3.6	16

Table VII Repeated Water-uptake Study of Silicone Elastomers Containing Variable Ingredients Made from R-5 or R-18 Oligomers

	Water Uptake of R-5 (%)				Water Uptake of R-18 (%)			
Content of Liquid Ingredients	72 h in Water	24 h on Air	72 h in Water	24 h on Air	72 h in Water	24 h on Air	72 h in Water	24 h on Air
3% glycerol	8.8	−0.3	8.1	−0.3	10	−0.3	8.7	−0.3
5% glycerol	16.5	−0.7	14.5	−0.7	15.3	−0.7	13.9	−0.5
10% glycerol	30	+1	27	−1	46.4	+0.6	40.5	−1.2
10% glycerol + 5% GF-91	73	+4.2	64.4	−1.9	88	5	79.3	−1.6
3% propylene glycol	7.8	−0.1	0.2	−0.3	2	−0.1	2.1	−0.3
5% propylene glycol	8.3	−1.2	−0.6	−0.7	7.4	+0.8	8.6	−1.6
10% propylene glycol	8.4	−3.6	−1	−9	7.8	+0.8	4.8	−7.4
10% propylene glycol + 5% GF-91	92	+18.5	82.2	+1.3	77	0	99.6	−3.8
3% ethylene glycol	1.4	−0.2	0.4	−0.3	4	−0.2	0	−3.5
5% ethylene glycol	8	−0.1	8	−0.3	10	−0.3	0.9	−1.2
10% ethylene glycol	20	+1	9	−11.3	16	+5.2	11.2	−5.2
10% ethylene glycol + 5% GF-91	32	+1.7	7.4	−7	27	+3.2	13.3	−2.9
3% PEG 400	10.7	−0.9	20.3	−1	7.3	−0.6	11	−1
5% PEG 400	17	−1.4	32.6	−1.37	7.5	−0.3	11.5	−1.5
10% PEG 400	34	−2.2	67.1	−2.4	23.6	+0.6	35	−2.8
10% PEG + 5% GF-91	51.7	−1.2	98.2	−2	35.7	+3.5	56.7	−0.3

hols. The water, which is less moveable in an apolar environment, penetrates heavily into the matrix and residues near the polar groups. The apolar alkyl groups of propylene glycol seems to be built into the matrix structure to a lesser extent than is ethylene glycol, since the toluene uptake is not so large as in the previous case. In water, this matrix swells 10 times larger than does the basic R-5 polymer.

These data show coordination of the polar OH groups to the polar group of GF-91 and to the polar water while the apolar alkyl groups coordinate to the apolar matrix framework. This process seems to provide the most appropriate environment for the polar solvent.

The water uptake decreased when glycerol was used, but it is still twice larger than for the basic polymer. When the polar ingredient is PEG 400, the water uptake is 11/2 times larger than in case of the base elastomers. Thus, the use of polar ingredients with the application of GF-91 makes the R-5 framework structure looser and increases the matrix's internal polarity, stabilizing the incorporated polar liquid phase of the ingredients. We observed the same results when using the R-18 oligomer as the base. The solvent uptake was similar to that of the R-5 case.

It is interesting to note that, using GF-91 and polydimethylsiloxane oil, the samples swelled in water (by 5.3 and 16 %, respectively). This fact shows that when the framework structure is looser the apolar liquid phase can arrange in the matrix so that the polar groups will be approachable for the polar solvent.

Dissolution of Polar Ingredients

The previous experiments showed the changes of the matrix structure when using trifunctional silicon compounds. In the following, we studied the dissolvation of the incorporated polar ingredients [glycerol, ethylene glycol, propylene glycol, poly(ethylene glycol)]. We made samples with polar ingredients and GF-91 and also studied the above processes with these samples. The results can be seen in Table VI. Based on these experiments, we can state that the greatest water uptake was shown by the glycerol or PEG 400 having the R-5 matrix, and the solvent uptake is nearly equal in both cases (30 and 34%). The samples containing

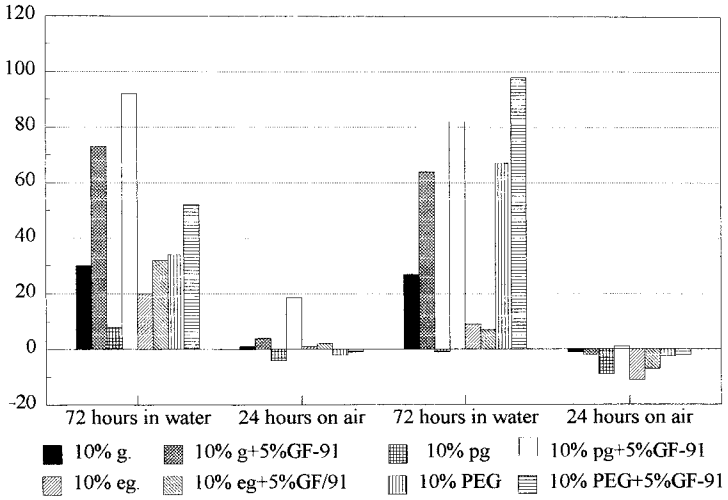


Figure 1 Effect of GF-91 on the repeated water uptake of R-5 elastomers containing10% liquid ingredients (g, glycerol, e.g., ethylene glycol; pg, propylene glycol).

propylene glycol swelled to a lesser extent than did the others and the water uptake was relatively independent of the quantity of the ingredients. The effect of ethylene glycol depends on the quantity of the ingredients, but the degree of swelling in water is only 60% of the PEG 400's effect. We observed a mass increase in all cases except by the 10% glycerol or ethylene glycol containing elastomers. These elastomers contain the polar ingredients in a high degree; therefore, the water penetrated in the matrix remains in a bounded form in the polar liquid phase.

The results obtained by the second 72-h swelling support the previous results. Only the mass of the membranes containing PEG 400 showed a further increase during the second 72-h swelling. The elastomers containing glycerol and ethylene glycol swelled to a 90 and 50% degree only, in comparison with the first swelling process. The elastomer containing propylene glycol showed the mass loss expressly. These data correlate with those given in the second drying. The highest mass loss can be given by the elastomers containing 10% glycerol or propylene glycol. On the basis

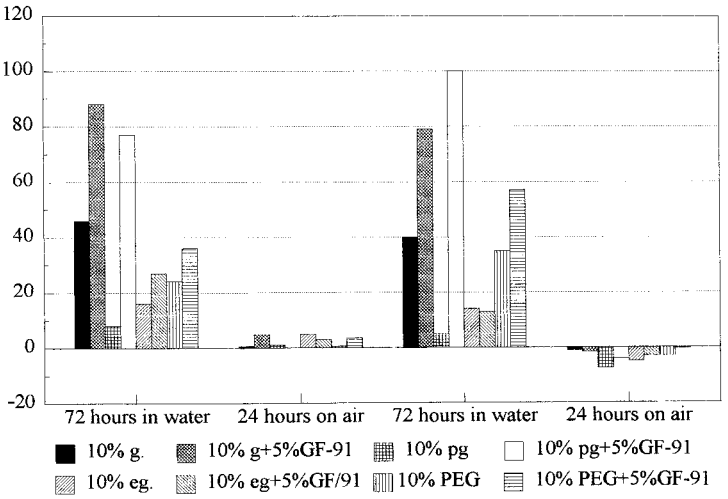


Figure 2 Effect of GF-91 on the repeated water uptake of R-18 elastomers containing 10% liquid ingredients (g, glycerol, e.g., ethylene glycol; pg, propylene glycol.)

of these results, only a few percent of PEG 400—closed in the compact structure of the R-5 matrix—can be delivered from the elastomer. Thus, the membrane channels containing the polar macromolecule can bind a considerable amount of water. This water-binding property is a reversible process; moreover, the structure was loosened by the first swelling. Thus, higher water uptake was observed in the second swelling. The 1% mass loss observed by the elastomers containing glycerol show that the polar ingredient is not only physically bound in the silicone elastomer. This is a little molecule and it would have been dissolved by water penetrating into the matrix. This, however, did not happen, because the glycerol is in a partially bound form. The other two diols can be dissolved from the silicone elastomer. The effect of GF-91 on the repeated water uptake of the 10% liquid ingredient containing the elastomers can be seen in Figures 1 and 2.

CONCLUSIONS

The result in the case of the R-18 oligomer is similar to the previous results, except for the high water uptake observed by the elastomer containing glycerol. This matrix has a looser structure than that of R-5; thus, the polar ingredients can move in the matrix framework more easily. Thus, during the gelling process, some substructures having only a few cross bonds have formed. These substructures have a rather flexible structure and the polar ingredient diffuses to these points to form associates and colloidal drops.

The matrix channels become poor in the liquid phase to account for the formation of these associates; thus, the solvent uptake is smaller than in the case of the R-5 elastomers. The water penetrated in the matrix blends with the polar ingredient; thus, during drying, it cannot go away. Therefore, the mass loss is less than in the case of the R-5 elastomers, and the elastomers have a large solvent uptake in the secondary swelling. Similarly, the mass loss is less in the secondary drying than in the case of the R-5 oligomers.

The results are completely different when the polar ingredients and GF-91 were used together. The building-in of the polar group in the matrix structure changed the binding of the polar ingredient to the matrix structure completely. The apolar methyl group of propylene glycol binds to the methyl groups of the siloxane chain and the polar OH groups of propylene glycol are bound to the —NH_2 group of the *N*-(aminoethyl)aminopropyl chain. Thus, the polar solvent is in a fixed form in the matrix structure, but it does not form a hydrogen bond between the diol and water. Glycerol has a similar effect; therefore, this elastomer has a larger water uptake than that of the elastomer containing glycerol only. GF-91 bound the residual Si—OH groups; thus, glycerol cannot build into the matrix structure and, therefore, it can be dissolved from the elastomer. Among the two OH— groups of ethylene glycol, only one is bound to the polymer; therefore, it can bound less water than can glycerol and propylene glycol. This ingredient dissolved from the matrix in a greater degree than did the another two. In the case of PEG 400, we also observed increased solvent uptake. A thermoanalytical study of membranes support these results.[18]

This work was supported by the OTKA Foundation (T 013053; T 022417) of the Government of Hungary.

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