Influence of network characteristics on diffusion in silicone elastomer

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Owing to their excellent biocompatibility, silicone elastomers are very often studied to prepare controlled-release systems of therapeutic molecules. In order to produce a loaded matrix, the influence of the physical properties of elastomers on molecule diffusion has to be characterized. In this work the influence of the mesh size on progesterone diffusion was analysed. The results show a very important evolution of the diffusion coefficient, *D*, in the smallest meshes. On the other hand, in the largest meshes, an increase in the mesh size involves a very slight increase in *D*, approaching an asymptotic value. In addition to the size, the mesh form has a significant effect on molecule diffusion. Moreover, in the case of a mesh size dispersion the smallest meshes of the network have a fundamental action on the diffusion coefficient of the progesterone.

1. Introduction

Silicone elastomers, by their physical, chemical and biological inertness and their biocompatibility, have been used since 1963 to prepare controlled-release systems. For about 10 years commercial realizations have appeared (Norplant, Progestasert, Transderm Nitro, Compudose, etc.) [1–4]. Duncan and Kalkwarf [5] showed that a steroid amount dispersed within a silicone elastomer implant is much more bioavailable than the same quantity dispensed by an oral or parenteral route. Therefore, it seems interesting to modulate the diffusion within the elastomers.

A few possible modulations have been proposed: by chemical modifications on the elastomer [6, 7], by modifications of the diffusing molecule [8–10] and by adding a solvent within the elastomer [11–13].

The influence of the physical properties of a silicone elastomer has not been studied much. By working on some particular systems, Bogner *et al.* [14] came to the conclusion that the influence of the network cross-link rate is not significant.

In this paper the influence of the mesh size of the silicone polymer is analysed. The high diffusitivity of progesterone in such a system is well known [15–17] and this should allow the relative variations from one system to another to be seen easily. On the other hand, the aim of this study was to characterize directly the diffusion into elastomer networks by using radiolabelled tracer molecules, as opposed to classical methods (film permeability, release in liquid phase, etc.) superposing diffusion and solubility effects, corrected approximately by experimental artefacts (nosink conditions, boundary layers, etc.).

2. Materials

2.1. Polymers

For this study, two component silicone elastomers, vulcanized at room temperature, were used. These were obtained by reacting a polydimethylsiloxane (PDMS) oil carrying groups of silanes within the chain (SiH oil) with a PDMS oil carrying vinyl groups at each end of the chain (SiVi oil).

The hydrosilation reaction (100 °C for 1 h), catalysed by Pt, leads to cross-links by the formation of covalent bonds. The network formed can be characterized by the mesh size, which is defined by the number of silicons, dividing statistically two neighbouring SiH groups, and by the number of the silicons in the SiVi chains. The various networks used here were obtained by reacting two SiH oils with three SiVi oils.

The SiH oils employed were $MD'_{12}D_{15}M$ and $MD'_{15}D_{95}M$, where M represents a terminal block with three methyl groups, D is an SiO group with two methyl groups and D' an SiO group with one methyl and one H. The SiH oil with 12 SiH groups and 29 Si is denoted α. The other SiH oil with 14 SiH groups and 110 Si is denoted β. The three SiVi oils had 200, 400 and 600 Si and are called, respectively, A, B and C. The mixing of oil C with the $HD_{12}H$ oil gives a longer SiVi oil denoted C_{al}.

In order to determine the free diffusion coefficient, an unreticulated mixture (termed system G) of different PDMS oils with similar molecular mass was used. All of these oils were supplied by Rhône-Poulenc (CRC, Saint Fons, France).

The networks are designated by the juxtaposition of the letters of their component oils, e.g. αA (Table I).

2.2. Diffusing molecule

To study the diffusion of the progesterone molecule, we used the unlabelled (Coger, France) and the radiolabelled form (CEA, France) with specific activity 62.4 mCi mmol^{-1}.

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3. Methods

3.1. Characterization of the networks

We measured the free chains rate (F) and the swelling rate (Q) of each network. In these networks, the free chains can be oils that are not cross-linked, carrying SiH or SiVi groups. Hexane is used as a swelling solvent and solvent for chains that are not cross-linked.

The F and Q were calculated from

$$F = (m_1 - m_2)/m_1$$

$$Q = \left(\frac{m_3 - m_2}{\rho_{hexane}} + \frac{m_2}{\rho_{elastomer}} \right) \frac{\rho_{elastomer}}{m_2}$$

where m_1 is the mass of the cross-linked sample, m_2 is the mass of the dry sample after elution in hexane, m_3 is the mass of the swollen sample and ρ is the density ($\rho_{hexane} = 0.66$ g cm^{-3} and $\rho_{elastomer} = 0.98$ g cm^{-3}).

Q is an indication of the network mesh size. The greater the mesh size is, the greater the hexane volume swelling the elastomer. For each network Q and F were obtained by averaging for ten samples.

3.2. Diffusion study

The diffusion coefficient of progesterone in silicone elastomers was obtained by using the method described by Couarraze *et al.* [18] and Conrath *et al.* [19].

The labelled solute was initially placed in the central part of a silicone matrix. It diffused into neighbouring parts, initially unloaded. With the help of a linear radioactivity multichannel counter, we obtained the concentration profiles of the diffusing molecule at different times.

TABLE I Constitutive oils and nomenclature of the networks studied: D, $-Si(CH_3)_2-O-$; D', $-Si(CH_3)H-O-$; and M, $-Si(CH_3)_3$

	$MD'_{12}D_{15}M$	$MD'_{15}D_{95}M$
$ViD_{200}Vi$	αA	βA
$ViD_{400}Vi$	αB	βB
$ViD_{600}Vi$	αC	βC
$ViD_{600}Vi + HD_{12}H$		βC_{al}
$ViD_{200}Vi + ViD_{600}Vi$	αAC	

Analysis of the changes in the area under the curves and of the peak heights with time led to a determination of the diffusion coefficient of the solute within the elastomer. The diffusion coefficient of progesterone in each network was obtained by taking the average of the observed values with both methods and three different cells.

4. Results

4.1. Influence of the mesh size

In order to determine the influence of the mesh size, the αA, αB and αC networks, and the unreticulated system (G), were used.

Table II gives F, Q, the cross-link density (ν) and the diffusion coefficient (D) for each system. ν was calculated from the Flory relationship

$$\nu = -\frac{\ln(1 - V_2) + V_2 + \chi_{rs} V_2^2}{V_1 (V_2^{1/3} - V_2/2)}$$

where V_1 is the molar volume of hexane (130.6 cm^3 mol^{-1}), V_2 the molar fraction of the swollen polymer in hexane and χ_{rs} the solvent–polymer interaction parameter (for hexane–silicone rubber $\chi_{rs} = 0.40$).

F varies slightly from one system to another and is always small ($< 5\%$). Its weak variation can produce a secondary effect on the variation in D. We did not take this effect into account in this study.

Q effectively increases with the mesh size. For the systems constituted from SiH oil α, Q increased from 3.9 to 5.9 when the vinyl chain was extended from 200 to 600 Si.

The D-values of progesterone showed that the diffusion increases with Q. The greater the network mesh size is, the higher the diffusion of progesterone.

As far as the αA network is concerned, its progesterone diffusion coefficient was very small: only 0.33×10^{-7} cm^2 s^{-1}. It seems that this condition is probably close to the diffusion hindrance of the progesterone molecule in the network. In fact, the size of the progesterone molecule (about 1.0 nm) is about the same as that of the smallest meshes of the network. In this case the progesterone molecule will probably diffuse with much difficulty.

We can note that this diffusional limitation is due to the existence of a steric blockage and not due to the modified mobility of the segments. Actually, the T_g of the PDMS chains varies little with the width (about 2 °C between the T_g of the 5Si oil and that of the 200Si

TABLE II Swelling rate (Q), free chains rate (F), cross-link density (ν) and diffusion coefficient (D) for the networks αA, αB and αC, and the unreticulated system G

System	Q (with hexane)	ν (mol cm^{-3})	F [% (w/w)]	D ($\times 10^{-7}$ cm^2 s^{-1})
Reticulated				
αA	3.9 ± 0.1	2.0×10^{-4}	3.4 ± 0.6	0.33 ± 0.03
αB	5.2 ± 0.1	1.1×10^{-4}	3.9 ± 0.3	0.70 ± 0.10
αC	5.9 ± 0.1	0.77×10^{-4}	4.5 ± 0.2	1.7 ± 0.5
Unreticulated				
G				8.1 ± 0.3

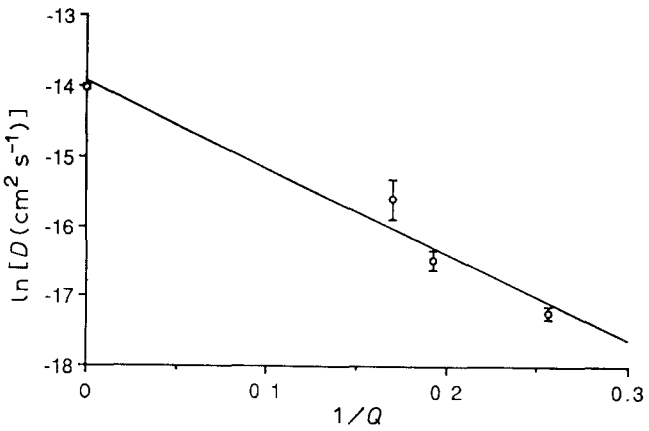

Figure 1 Plot of ln D versus $1/Q$ for three networks constituted with silane oil α and the three vinyl oils A, B and C, and the unreticulated system G.

oil). We can consider that the mobility of the chains is practically always the same in our diverse networks.

A correlation research between D, Q and ν values was considered. The best correlation was obtained considering $\ln D$ versus $1/Q$. This correlation is in accordance with the free volume theory [20]. In fact, this theory foresees an exponential decrease in D with the decrease in the free volume. The plot of ln D versus $1/Q$ appears as a straight line (Fig. 1). This figure shows the strong modulation possibility of D with the mesh size: an increase of the vinyl chain length from 200 to 600 Si leads to an increase in D by a factor of 5.2.

This study was completed by an analysis of the progesterone diffusion coefficient within networks having a different mesh form. For this, the β oil having more-spaced SiH groups was used. In this way the βA, βB and βC networks were constituted. The F, Q and D of the progesterone within these networks are given in Table III.

In this case, F was still small and its effects could not be taken into account.

The first remark is that Q has an approximately similar evolution as for the α oil component networks.

D still increases with Q, but this evolution is much less strong than in the former study (Fig. 2). It can be seen that the increase in the SiVi chain length from 200 to 600 Si only provides an increase from 6.0×10^{-7} to 7.4×10^{-7} cm^2 s^{-1}. This points to the fact that when the mesh size increases, comparatively with the size of the diffusant molecule, the effect of the mesh size has a very small influence on the diffusion.

On the other hand, we verified that there was no absolute correlation between D and Q. The βB and αB systems had the same Q, but the ratio of their diffusion coefficients was equal to 9. In the same way, the ratio between the βC and αC networks, having the same Q, was 4.

Consequently, we must conclude that there is a mesh form factor which modulates the steric diffusion hindrance of the network, related to Q. With our example, we can see that the internodal distance of the networks composed of α oil was more restrictive for the diffusion than for the one composed of β oil.

With the largest mesh sizes we established the slight relative variation of D. This proves the existence of an asymptotic value of D, beyond which we cannot obtain the values for D when the mesh size increases continuously.

This interpretation was confirmed by the value of D in the unreticulated system (G), found to be 8.1×10^{-7} cm^2 s^{-1}. This value is very close to the maximum values for the networks (7.4×10^{-7} cm^2 s^{-1}).

TABLE III Swelling rate (Q), free chains rate (F) and diffusion coefficient (D) for the networks βA, βB and βC, and the unreticulated system G

System	Q (with hexane)	F [% (w/w)]	D ($\times 10^{-7}$ cm^2 s^{-1})
Reticulated			
βA	4.9 ± 0.1	4.6 ± 0.4	6.0 ± 0.8
βB	5.2 ± 0.1	2.8 ± 0.5	6.5 ± 0.6
βC	5.9 ± 0.1	4.0 ± 0.2	7.4 ± 0.5
Unreticulated			
G			8.1 ± 0.3

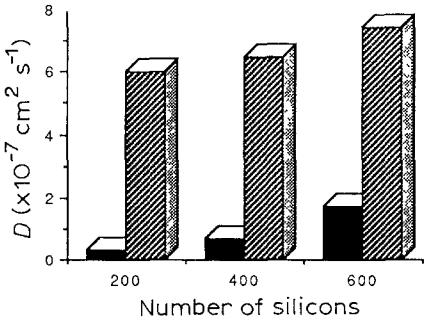

Figure 2 Evolution of the progesterone diffusion coefficient with the silicon number of the SiVi oil: (■) network α and (▨) network β.

4.2. Influence of the mesh size dispersion

The oils used to compose the network were not monodisperse. In the same way the SiH and SiVi groups were distributed at random around a mean value. These two effects lead to a dispersion of the mesh size. It therefore seems of interest to know the influence of such a dispersion on solute diffusion. In other words,

do the smallest meshes of the network selectively determine the diffusion properties of a solute, or do all of the meshes together involve the mean value of D?

In order to conclude, we created a network containing oils with different lengths: a molecule $HD_{12}H$ with a silane group at each end, incorporated into the vinyl oil C, allowed a longer SiVi oil to be obtained. The $HD_{12}H$ molecule allowed two SiVi molecules to be linked. Then, with the initial SiVi oil C and 30% (w/w) $HD_{12}H$, assuming that the more probable creation is the 1200 Si oil, the system should be constituted with 57% 600 Si chains and 43% 1200 Si chains.

This transformation of the basic system βC yields an increase in Q of the new network (βC_{al} $Q = 6.5 \pm 0.1$) in comparison with that of the βC network. This is the result of the increase of the network average mesh size.

If the smallest meshes are not highly restrictive towards the solute diffusion, we should observe an increase of the progesterone diffusion coefficient compared with the βC network. In fact, we obtained the same value for the progesterone diffusion coefficient [βC_{al} $D = (7.4 \pm 0.2) \times 10^{-7}$ cm^2 s^{-1}] for both networks, which should prove that the smallest mesh sizes of the network determine selectively the D of the solute.

Nevertheless, this value is close to the free diffusion value (8.1×10^{-7} cm^2 s^{-1}). Then, an increase in D should be necessarily limited and is perhaps not significant towards the measurement error and we cannot come to a definite conclusion.

In order to distinguish between these two interpretations, another system with two types of SiVi oils was created to obtain a diffusion coefficient sharply distinct from the free diffusion coefficient. For this purpose, the same number of A and C SiVi chains was used. The network was obtained by reticulation of these chains with α oil.

The Q of this network, denoted αAC, was 5.1 ± 0.1, which is very close to that of the αB network. The result is consistent with the mean mesh size of both networks. Conversely, the progesterone diffusion coefficient value of the αAC network, which was (0.4 ± 0.03) $\times 10^{-7}$ cm^2 s^{-1}, is significantly different from that observed for the αB network. It is in the same range of values as the progesterone diffusion coefficient in the αA network, however. Hence, we can objectively conclude that the smallest meshes have a fundamental action on the solute diffusion coefficient.

5. Conclusion

The diffusion coefficient of the progesterone in our polymer silicone increased with the length of the SiVi oil. The modulation of the increase is even more sensitive to the increase of the distance between two SiH groups, this distance being the smallest length of mesh for our networks. Furthermore, the smallest meshes of the elastomer silicone network had a strong influence on the progesterone diffusion coefficient. A large modulation of the progesterone diffusion coefficient in silicone elastomers can be obtained by variations in the mesh dimensions; the coefficient of diffusion can fluctuate from a very low value up to the free diffusion value.

To use these elastomers as biomaterials, this diffusion modulation coefficient allows the permeation properties of the membrane or the matrices' release also to be modelled. In fact, the structural transformations of the polymers have little effect on the solubility of the diffusing molecule. This is also how the solubility of progesterone in component silicones of the several elastomers analysed was measured, at a mean value of 650 ± 30 mg l^{-1} independent of the physical chemistry characterization of the various silicone chains utilized.

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