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Study of diffusional properties of silicone matrices for drug bioavailability modulation

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Modified silicone elastomers were synthesized by grafting an organic pendent segment (allylglycidylether) along polydimethylsiloxane chains. The effects of the degree of grafting were evaluated with respect to drug solubility, diffusivity and elastomer properties. It was found that this elastomer modification led to a high increase in solubility for a lipophilic steroid (progesterone) and a more hydrophilic drug (metronidazole). Drug diffusivities were not highly reduced; permeability and release properties of these modified silicone networks could also be widely improved not only for steroids but also for more hydrophilic drugs.

1. Introduction

Silicone elastomers are extensively used for drug delivery systems because of their high permeability and physiological inertness [1–3]. The hydrophobic nature of silicone materials explains why they are particularly suitable for the controlled delivery of lipophilic drugs such as steroids compared to other polymers [4, 5]. However, different steroids have been shown to have markedly different delivery rates through silicone elastomers because of their different polymer solubilities [6]; and a correlation has been established between drug hydrophilicity or lipophilicity and its permeation [7, 8].

Much research has been carried out to alter the permeation rates of steroids or to extend the use of silicone to the delivery of more hydrophilic drugs [9]. Thus, oil- or water-soluble additives can be co-formulated with silicone polymers allowing the enhancement of drug release rates [10, 11]. Recently, much interest has been focused on relationships between silicone polymer structure and drug permeation. Previously, Friedman *et al.* [12] demonstrated that functional groups of silicone membranes could influence steroid permeation rates. Lee *et al.* [13, 14] reported the effects of alkyl substituents on silicone and the incorporation of alkylene or arylene substituents along the siloxane backbone. These polymer modifications increased lipophilic steroid permeabilities more than those of hydrophilic steroids. Polydimethylsiloxane (PDMS)/poly(ethylene oxide) (PEO) block and graft copolymers have also been investigated [15, 16] and an important increase in hydrophilic steroid permeability has been obtained compared to a pure PDMS system. The graft copolymer approach has been shown to be more effective than the block copolymer approach.

In our work, other chemical modifications of silicone elastomers have been realized and their effects on drug solubility, diffusivity and elastomer properties have been evaluated. The chemical modifications consisted in grafting various organic pendent segments along PDMS chains. After vulcanization, modified elastomers have been tested using progesterone, which is commonly used as a diffusing molecule for silicone network evaluation, and metronidazole, a more hydrophilic model drug. In this paper, we report results for only one chemical modification of the silicone network: the grafting of allylglycidylether.

2. Materials and methods

2.1. Diffusing molecules

Progesterone and metronidazole were used as-received. Labelled solutes, (^{14}C) progesterone and (^{14}C) metronidazole, were also used for diffusion investigations and were added into silicones to a known quantity of unlabelled molecule.

Preliminary studies showed that these drugs had no inhibiting effect on vulcanization of elastomers. These solutes have quite different aqueous solubilities. Progesterone: 0.01 $g l^{-1}$; metronidazole: 10 $g l^{-1}$.

2.2. Elastomers investigated

All matrices were prepared from a room-temperature vulcanizing system (RTV) based upon a cross-linking

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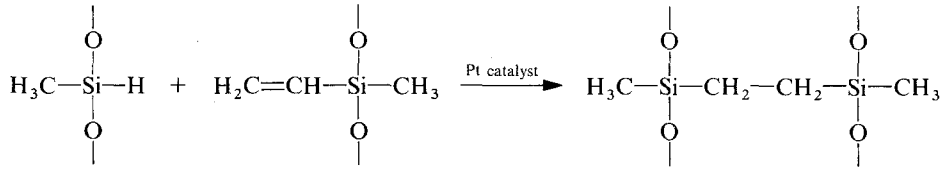


(1)

reaction between a silane oil and a vinyl oil according to the scheme shown above. The catalyst rate required for vulcanization is classically 5×10^{-4} mol mol^{-1}.

In order to achieve a good dissolution of diffusing molecules within elastomers, they were initially incorporated into oils before vulcanization.

PDMS oils used to prepare studied elastomers had the following general structures:

$$Me_3SiO(MeHSiO)_a(MeRSiO)_b(Me_2SiO)_cSiMe_3$$

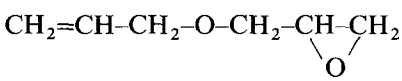
for silane oils and

$$Me_3SiO(MeCH_2CHSiO)_x(MeRSiO)_y(Me_2SiO)_zSiMe_3$$

for vinyl oils, where Me is a methyl group, R the grafted organic pendent segment and $a + b + c = 150$, $x + y + z = 300$.

All PDMS oils had the same number of silane or vinyl units ($a = 10$, $x = 8$); therefore, all elastomers had the same theoretical mesh size. The chemical structures are illustrated in Table I.

The segment studied here was the 1-allyloxy-2,3-epoxypropane (allylglycidylether)



Allylglycidylether grafted oils were prepared by a platinum-catalysed reaction (hydrosilylation) between the vinyl function segment and the silane units of the oils [17, 18]. Both silane and vinyl oils were modified in order to preserve their compatibility during vulcanization.

Three elastomers were prepared by varying the number of pendent segments along PDMS chains. They were 0 (as control), 5 and 15 wt % modified.

2.3. Characterization of PDMS oils and elastomers

The molecular weight distribution of the oils was measured by gel permeation chromatography (GPC).

TABLE I Chemical structures of experimented silicone elastomers. Key: see general structure of modified PDMS oils

	Elastomer theoretical wt % modification					
	0		5		15	
Silane oil	A	$a = 10$ $b = 0$ $c = 140$	C	$a = 10$ $b = 10$ $c = 130$	E	$a = 10$ $b = 25$ $c = 115$
Vinyl oil	B	$x = 8$ $y = 0$ $z = 292$	D	$x = 8$ $y = 9$ $z = 283$	F	$x = 8$ $y = 35$ $z = 257$

Vinyl and silane rates were evaluated by proton nuclear magnetic resonance (^{1}H NMR) and the volumetric titration of hydrogen released by reaction between silane units and potassium hydroxyde, respectively.

Quantitation of grafted organic segments was carried out by titration with bromhydric acid which reacts with the epoxy-1,2 functions of the pendent chains. Equivalence is observed with a coloured indicator.

Differential scanning calorimetry (DSC) was also employed to determine the glass transition temperature (T_g) of the oils.

Elastomers were characterized by their swelling rate and free chains rate (PDMS chains which are not cross-linked): every sample was soaked in methylcyclohexane at 20 °C during 48 h. The swelling rate was expressed as the ratio of solvent volume absorbed to dried sample volume. The ratio of weight lost by the sample to initial weight was the free chains rate. All experiments were run in triplicate.

Elongation at break was also determined with an Instron dynamometer (5 mm min^{-1}, 23 °C, $n = 10$).

2.4. Determination of drug solubility

An excess amount of the studied molecule was incorporated (constant stirring, 37 °C) in a silicone oil with the same functionality rate (wt %) as the elastomer investigated. After filtration, a part of the saturated oil was dissolved in dichloromethane and then the solubility was determined spectrophotometrically at 320 nm (metronidazole) or 239 nm (progesterone). Measurements were repeated three times.

2.5. Determination of drug diffusivity

Diffusion coefficients were measured by a method described previously [19, 20]. This method, using a radiotracer, is based on obtaining the concentration profile of the diffusing molecule within the elastomer where a concentration gradient has been initially determined. The concentration profiles as a function of time are evaluated with a high-resolution linear radioactivity counter. Two methods of interpretation of their evolution in time allows calculation of the intrinsic diffusion coefficient of the molecule in the elastomer.

All experiments were carried out in triplicate at 37 °C. The initial diffusing molecule concentration in the elastomer (labelled and unlabelled molecule) was about 80% of its solubility in the unmodified system.

TABLE II Characterization of silane PDMS oils

		PDMS oil		
		A	C	E
Molecular weight	Expected	11 122	12 122	13 622
	GPC M_n	9600	7760	21 600
	GPC M_w	16 900	30 440	58 710
Silane rate (% wt/wt)	Expected	0.090	0.083	0.073
	Volumetric method	0.083	0.078	0.072
	^{1}H NMR	0.086	0.066	0.073
Modification rate (% wt/wt)	Expected	0	9.4	20.9
	Titration		8.8	20.4
	^{1}H NMR		9.6	22.4
T_g(°C)		− 124	− 118	− 108

TABLE III Characterization of vinyl PDMS oils

		PDMS oil		
		B	D	F
Molecular weight	Expected	23 050	24 616	29 140
	GPC M_n	13 200	7860	9810
	GPC M_w	36 840	43 540	18 560
Vinyl rate (% wt/wt)	Expected	0.93	0.88	0.74
	^{1}H NMR	0.73	0.89	0.66
Modification rate (% wt/wt)	Expected	0	4.1	13.7
	Titration		4.1	14.1
	^{1}H NMR		1.5	7.7
T_g(°C)		− 123	− 119	− 112

3. Results and discussion

3.1. Oil characterizations

Analysis results, reported in Tables II and III, generally confirm the expected mean structure of the prepared oils.

Side reactions occur during the grafting of allylglycidylether on PDMS oils. Their difficult quantitation required the use of an excess amount of allylglycidylether. Therefore, the measured modification rates cannot be exactly the same as the theoretical ones.

The glass transition temperature (T_g) of the oils is very low for an unmodified PDMS oil (− 123 °C), due to a very high chain mobility. As shown in Tables II and III, T_g increases with the oil modification rate (until − 108 °C for oil E 20.9 wt % modified). The chemical modification studied here seems to reduce the mobility of PDMS chains by a decrease in free volumes induced by pendent segments.

3.2. Determination of vulcanization conditions

In order to determine the proportion of silane and vinyl oils yielding an optimal elastomer, two criteria were considered: the lowest free chains rate, and the highest elasticity. This study was carried out on the unmodified system. According to the results reported in Table IV, the best compromise between the two fixed criteria was obtained with the ratio SiVi/SiH = 2.

Vulcanization time and temperature were previously optimized: 100 °C, 2 h. However, the temperature had to be lowered to 50 °C to prevent drug damage.

3.3. Physical characterization of elastomers

The physical properties of the elastomers are reported in Table V. It appears that the free chains rate increases with the elastomer modification rate. Vulcanization seems to be more difficult as the modification extends. It can be due to a more difficult accessibility of reticulation units (silane and vinyl) because of their "intra-chains" position. This effect

TABLE IV Vulcanization conditions. Determination of the proportion of silane and vinyl oils in elastomers

	SiVi/SiH				
	$\frac{1}{2}$	$\frac{2}{3}$	1	$\frac{3}{2}$	2
Free chains rate (%)	8.5	7.8	7.0	9.1	7.5
Swelling rate	2.7	2.4	2.2	2.7	3.6
Elongation at break (%)	21.3	19.2	19.8	32.6	35.4

TABLE V Physical characteristics of the elastomers used ($n = 3$)

	Elastomer theoretical wt % modification		
	0	5	15
Elastomer real wt % modification	0	5.01	15.24
Free chains rate (%)	7.6 ± 0.4	15.5 ± 0.4	23.6 ± 0.5
Swelling rate	3.6 ± 0.3	3.6 ± 0.3	4.7 ± 0.2
Elongation at break (%)	35.4 ± 8.7	23.9 ± 4.8	22.7 ± 7.6

also involves an increasing swelling rate (4.7 for 15 wt % modified elastomer) and lower mechanical properties.

3.4. Solubility and diffusivity of solutes

Effects of silicone elastomer modifications on solubility and diffusivity of progesterone and metronidazole are given in Table VI.

The solubility of the two studied molecules is very significantly improved with the elastomer modification: 14 times for progesterone and 28 times for metronidazole in 15 wt % modified elastomer compared to the unmodified system. These solubilities are logically in relation to the aqueous solubilities: silicone elastomers are by nature hydrophobic materials; progesterone (a very lipophilic drug) is thus always more soluble than metronidazole. But, the increase in solubility by chemical modification is more important for metronidazole. Therefore, the compatibility between silicone elastomers and both lipophilic and hydrophilic drugs can be widely improved by the grafting of allylglycidylether on PDMS chains.

From a diffusional point of view, diffusivity of metronidazole within an unmodified elastomer is lower than that of progesterone. It can be correlated with a lower solubility as generally observed. For both solutes, the grafting of the organic pendent segment does not involve an important decrease in diffusion coefficient. For progesterone, as the modifications extend, a regular decrease is measured. The decrease in free volumes (increase in oil T_g) and the increase in free chains confined in networks can explain this evolution. For metronidazole, the same trend is observed in the 5 wt % modified system. But for higher modification rates, the very important increase in solubility leads to a partial increase in diffusivity.

In the aim of predicting characteristics of pharmaceutical implants, drug solubility and diffusivity can

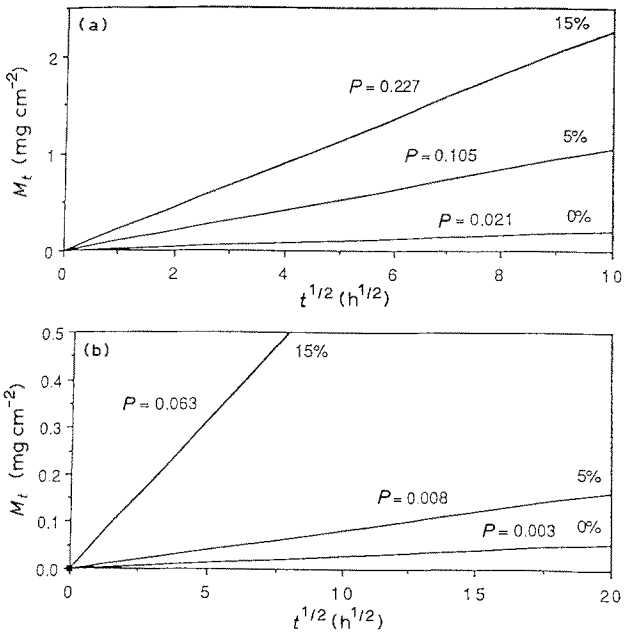


Figure 1 Effects of the degree of elastomers modification (0, 5 and 15 wt % modified) on their release properties. M_t (drug released quantity) versus square root of time for (a) progesterone and (b) metronidazole.

be studied together to evaluate release properties of matrices consisting of these different elastomers. Matrix release kinetics are of the $t^{1/2}$ type, according to the equation

$$M_t = 2C_s\left(\frac{D}{\pi}\right)^{1/2} t^{1/2} \quad (2)$$

where M_t is the drug released quantity, C_s the drug solubility in the matrice, D the drug diffusion coefficient in the elastomer and t the time. The evolution of M_t versus $t^{1/2}$ for progesterone and metronidazole for studied systems is shown in Fig. 1.

The decreasing diffusivity of progesterone is widely compensated by its increasing solubility. So, the release rate of a matrix consisting of the 15 wt % modified system is increased by a factor of 10 compared to an unmodified matrix. This effect is more important with metronidazole (increase by a factor of 20).

4. Conclusions

The effects of grafting allylglycidylether along PDMS chains of a RTV silicone elastomer were evaluated for

TABLE VI Progesterone and metronidazole solubility ($n = 3$) and diffusivity (37 °C, mean of six values) in tested modified elastomers

	Elastomer theoretical wt % modification		
	0	5	15
Progesterone			
Solubility (g kg^{-1})	0.385 ± 0.03	2.1 ± 0.1	5.5 ± 0.2
Diffusivity (10^7 cm^2 s^{-1})	6.6 ± 0.2	5.3 ± 0.2	3.7 ± 0.2
Metronidazole			
Solubility (g kg^{-1})	0.06 ± 0.01	0.23 ± 0.03	1.65 ± 0.06
Diffusivity (10^7 cm^2 s^{-1})	4.8 ± 0.3	2.7 ± 0.1	3.2 ± 0.1

solubility, diffusivity of a lipophilic steriod (progesterone) and a more hydrophilic drug (metronidazole). It was found that elastomer chemical modifications led to a high increase in solubility for both solutes and did not involve an important decrease in diffusivity. Thus, the permeability and release properties of these silicone networks can be widely improved not only for steroids but also for more hydrophilic drugs.

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