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Research paper

Development of a long-acting therapeutic system: part I: a method to produce silicon rubbers with well-defined microstructures

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Abstract

Based on the free-volume theory of diffusion in rubbers it is shown that the diffusion coefficient D of a permeating drug can be written as the product of two probabilities $D \sim w_1 w_2$. The polymer chains in a rubber are subject to thermal vibrations. Hence collisions between vibrating polymer segments and permeating drug molecules can occur. w_1 describes the probability that by such a collision a drug molecule experiences an energy exchange which is large enough to overcome its interactions with its neighborhood. w_2 describes the probability that a permeating drug molecule will find in its immediate neighborhood a free volume being equal or larger than its own volume. Diffusion takes place if the drug molecule experiences a sufficiently large exchange of momentum and finds at the same time a sufficiently large free volume. As both events are independent their overall probability is given by the product of the two probabilities. For a given rubber and a given species of drug molecules in a first approximation w_1 can be considered as constant. This means the diffusion coefficient is mainly determined by w_2. This probability, however, is strongly determined by the microstructure of the rubber. In this study a procedure is developed allowing for a straightforward synthesis of silicone rubbers with defined network density.

Keywords: Diffusion; Polymers; Therapeutic systems; Silicon rubbers; Controlled release; Response surfaces

1. Introduction

During the development of the first contraceptives there was a fear that the safety of hormonal contraception would suffer from a non-regular intake of the pills. As ovulation inhibition could also be achieved by a dose of hormones administered continuously, Zaffaroni from Syntex Inc., initiated the development of dosage forms which should be able to release highly potent drugs over periods longer than 24 h by a zero order kinetic. He called this kind of dosage forms as 'therapeutic systems'.

In his pioneering work [1–3], Zaffaroni showed that only by diffusion across membranes a constant release of active ingredients can be achieved. As drug depots he always used highly concentrated drug suspensions. However, in practice the development of therapeutic systems was always limited by an insufficient availability of appropriate membranes. In consequence systems characterized by a constant drug release can be found only in the form of transdermal systems. In these systems the amount of drug to be released is determined by the permeation properties of a given membrane and the diffusional cross-section adopted accordingly. Sometimes it reaches 15 cm^2 and more.

In order to allow for an administration of therapeutic systems beyond the transdermal use one must be able to develop membranes with well-defined permeation properties in a straightforward manner.

2. Theory

Two different types of therapeutic systems are described in the pharmaceutical literature: systems with a matrix-controlled release of drug and systems with a membrane-controlled release of active ingredients.

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In the first type of therapeutic systems the highly dispersed active ingredient is suspended in a polymer which is then cross-linked in order to form a solid polymer matrix. The drug is released by diffusion. As shown by many authors [4,5] at the beginning of the drug release from a polymer matrix only the drug substance directly adjacent to the boundary of matrix and acceptor phase diffuses out of the depot. In consequence a drug gradient is formed in the polymer matrix. At the beginning of the release the zone of depletion is very thin. But with progressing release time its thickness increases. This means the distance the molecules have to overcome in order to be released from the polymer increases continuously. When plotted over the time the total amount of drug released until the time t follows a square-root-relationship [8]. This means a constant release of drug substance from monolithic matrix controlled system cannot be achieved.

In systems with membrane-controlled drug release the two functions, depot of drug substance and control of drug release, are well separated. The depot is formed by a highly concentrated suspension of the drug substance. A membrane controlling the drug release separates the depot from the acceptor medium. During storage after the manufacture of such a therapeutic system the drug diffuses out of the depot into the membrane until a Nernst distribution equilibrium is reached. As soon as the therapeutic system comes into contact with an acceptor the drug substance diffuses out of the membrane into the acceptor. In consequence a constant gradient in the concentration of the drug substance across the membrane is formed. According to Ficks first law the rate of drug release remains constant as long as this gradient remains constant. This condition is fulfilled as long as suspended drug substance is available in the depot. The amount of drug substance released per time unit is proportional to the slope of the concentration gradient of the drug substance across the membrane. Systems with a membrane controlled drug release allow to achieve a zero order drug release.

The amount of drug substance to be stored in the depot results from the intended duration of application. In any case it is a large multiple of the required daily dose. In all systems with membrane-controlled drug release the risk of an immediate, non-controlled release of the total drug substance stored in the depot in case of a damage of the release controlling membrane is inherent. According to its nature a system with matrix-controlled drug release does not bear this risk. It was the aim of this study to develop a therapeutic system which on one hand offers the safety of a system with matrix-controlled drug release but which on the other hand releases the drug substance with a zero order kinetic.

2.1. Diffusion in rubbers

The release of drug substance from therapeutic systems is always controlled by diffusion. In the manufacture of therapeutic systems rubber membranes are used. In consequence diffusion through such membranes can be treated according to the theory of diffusion in rubbery polymers.

Diffusion in gas or liquid phases can be described by Fick's laws. They are based on the homogeneity of the diffusion media which results in location independent probabilities of displacement of a diffusing molecule [6,7]. In polymers below T_g the homogeneity in time is not given. In partially crystalline polymers there is no homogeneity in space. Therefore Fick's laws are not valid in these cases.

If diffusion can be described by Fick's laws the amount of drug released per unit time across a unit area is primarily determined by the diffusion coefficient of the system. The theory of free volume allows for a mechanistic explanation of the phenomenological parameter 'diffusion coefficient' [9–16]. Above the glass transition temperature T_g the thermal expansion coefficient α of cross-linked polymers is significantly higher than below T_g. In consequence above T_g an increase in temperature results in a greater increase in volume than below T_g. As the van-der-Waals volume occupied by the polymer chains is almost independent from temperature any increase in the total volume V associated with raising temperatures results in the formation of voids within the rubber. The total of all these voids is called the free-volume V_f. The size distribution of the voids is described by their distribution density $f(V_f)$. The free-volume formed by the voids can be redistributed within the rubber without changes in total energy.

A drug molecule within a silicone rubber 'sees' its immediate neighborhood as a network formed by cross-linked siloprene chains. The network density of a rubber is described by the average molecular weight M_c (number average) of the cross-linked units. At temperatures above T_g the siloprene chains are continuously changing their configurations. During these rearrangements chain segments can collide with drug molecules dissolved in the rubber. In consequence momentum is exchanged between the collision partners. The extent of the exchanged momentum follows a statistical distribution and is described by the distribution density $f(E)$. In consequence of such a collision the drug molecule is moved from its equilibrium position in the network. If the energy transferred by such a collision on to the drug molecule is high enough to overcome the interactions with its environment the drug molecule can leave its place and jump into another adjacent non-occupied void, a free volume, being large enough to take it up. The minimum size of the free-volume required for such a change in place (jump) is called the critical hole free-volume v^*. The corresponding minimum energy is given by E^*.

For a given drug molecule the probability to find an adjacent free-volume being large enough to take it up is given by

$$w_1 = \int_{v^*}^{\infty} f(V_\mathrm{f})\mathrm{d}V_\mathrm{f} \tag{2.1}$$

Accordingly the probability w_2 that a drug molecule will obtain an energy greater than E^* is given by

$$w_2 = \int_{E^*}^{\infty} f(E)\mathrm{d}E \tag{2.2}$$

The two probabilities w_1 and w_2 are stochastically independent. Hence the total probability for a change in place is given by the product of these two probabilities. Without going deeper into the theory of free-volume the diffusion coefficient can be written as

$$D \sim w_1 w_2 \tag{2.3}$$

This means the diffusion coefficient D is a function of the activation energy E and of the free-volume V_f.

As long as the same drug substance as well as the same polymer system is considered, in a first approximation the probability w_2 can be assumed to be constant. In this case the diffusion coefficient is mainly a function of the free-volume

$$D \sim w_1 \sim f(V_\mathrm{f}) \tag{2.4}$$

As shown by the theory of rubber elasticity [17] in a rubber the flexibility of the polymer chains increases with increasing length of the cross-linked unit, i.e. network chain length (NCL). The longer the NCL the higher the number of potential configurations of the chain [18] and hence the possibilities to redistribute the free-volume. Large NCLs allow for less dense packing resulting in larger voids.

Hence it should be possible to control the permeability of membranes by the manufacture of rubbers with well-defined NCLs.

2.2. Synthesis of rubbers

As can be learned from textbooks of polymer chemistry [19] any linking of bifunctional polymers results in an increase in chain length only. In order to allow for cross-linking and hence for the development of three-dimensional structures, molecules carrying at least three functional groups must take part in the cross-linking reaction. The higher the concentration of polyfunctional molecules in the polymer mixture to be cross-linked the higher the achievable degree φ of cross-linking. φ is defined by the ratio of the mole number of cross-linked units of starting material to the mole number of all units of starting material contained in the polymer mixture to be cross-linked. In order to characterize the rubbers synthesized in the course of this study the average NCL was determined by swelling measurements.

3. Materials and methods

High molecular, non-cross-linked silicones and silicone rubbers are used in plastical and aesthetic as well as in prosthetic surgery. The cross-linked materials are characterized by a good tissue compatibility [20,30]. For the experiments performed in this study the Siloprene system of Bayer AG (Leverkusen, Germany) was used. After their characterization the polymers were used as supplied by Bayer AG. The composition of the polymers changes from batch to batch. Therefore each batch has to be analyzed carefully.

3.1. Vinyl-terminated polydimethylsiloxanes (Vinyl-PDMS) of the types U1, U10 and U165

These polydimethylsiloprenes have the general structure shown in Fig. 1.

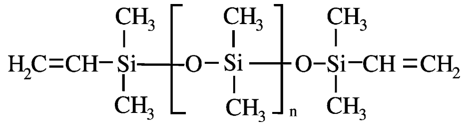
They differ in chain length and hence in viscosity. A number is used to characterize the various types. If this number is multiplied by 1000 the viscosity of the polymer in mPa s is obtained.

After the synthesis of Vinyl-PDMS its viscosity is adjusted by mixing Vinyl-PDMS chains of different molecular weight. As a given viscosity can be obtained by mixtures of different composition each batch of these polymers has to be further analyzed. For this purpose the weight as well as the number averages of the molecular weight, $\bar{M}_\mathrm{w}$ and $\bar{M}_\mathrm{n}$, respectively, and the concentration of vinyl groups were determined. From the weight and the number averages of the molecular weight the heterogeneity $\bar{M}_\mathrm{w}/\bar{M}_\mathrm{n}$ is calculated. The greater the heterogeneity numbers the wider the scattering of the molecular weights. In case of a polymer with uniform molecular weight the heterogeneity has the value 1.

3.2. Cross-linker Silopren® (SiH-PDMS)

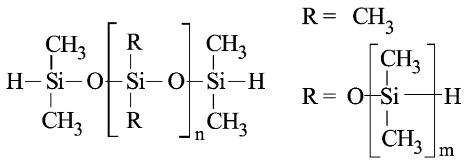
Branched polydimethylsiloxanes are used as cross-linkers. They carry different terminal groups, Fig. 2, among them the reactive SiH-groups.

The cross-linker molecules are of a relatively low molecular weight. Accordingly their viscosity is rather low. For the further characterization the weight and the number averages of the molecular weight of these polymers, the heterogeneity as well as the concentration of SiH-groups of each batch were determined.



$$\mathrm{H_2C{=}CH{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}\left[O{-}\overset{CH_3}{\underset{CH_3}{Si}}\right]_n{-}O{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}CH{=}CH_2}$$

Fig. 1. General structure of polydimethylsiloxanes of the types U1, U10 and U165 (Vinyl-PDMS).



$$H-\mathrm{Si}(CH_3)_2-O-\left[\mathrm{Si}(R)_2-O\right]_n-\mathrm{Si}(CH_3)_2-H \qquad R = CH_3 \qquad R = O-\left[\mathrm{Si}(CH_3)_2\right]_m-H$$

Fig. 2. General structure of the cross-linkers SiH-polydimethylsiloxane (SiH-PDMS).

3.3. Tetramethyl-tetravinyl-cyclotetrasiloxane (Vinyl-D4)

Tetramethyl-tetravinyl-cyclotetrasiloxane, Fig. 3, is a well-defined molecule carrying four reactive groups. Due to its functionality it strongly influences the network density achievable by cross-linking.

The higher the content of this compound in the polymer mixture to be cross-linked the longer the vulcanization time.

3.4. Silopren® U catalyst Pt/S

The addition reaction of the vinyl and the SiH groups is catalyzed by platinum. In the catalyst solutions the platinum atom is complexed with Vinyl-D4 molecules, Fig. 4. The platinum complex Pt/S is diluted with Vinyl-D4 as a solvent to obtain a platinum concentration of 20%.

3.5. Methods for the additional characterization of the polymers in use

3.5.1. Determination of the molecular weight by means of light scattering

The molecular weights (weight and number averages) of the starting polymers as well as their distributions were determined by means of an HPLC-LALLS (Low Angle Laser Light Scattering) coupling.

By means of an appropriate HPLC system (column, eluent and its flow rate) the molecules of a polymer sample can be separated according to their hydrodynamic properties. In an HPLC-LALLS-coupling a LALLS-photometer, a detector sensitive to the molecular weight (Chromatix, Inc., Sunnyvale, CA), is directly followed by a differential refractometer (Knauer, Berlin) used for the determination of polymer concentration. Such a coupling allows for the determination of absolute molecular weights.

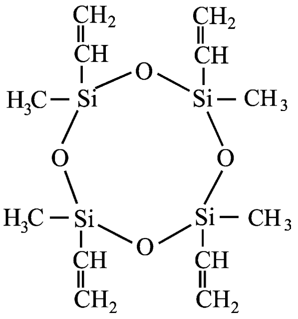


Fig. 3. Structure of tetramethyl-tetravinyl-cyclotetrasiloxane (Vinyl-D4).

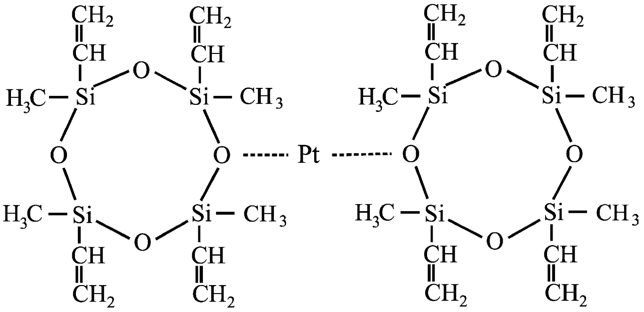


Fig. 4. Structure of the Silopren® U catalyst Pt/S.

From the signals of the two detectors the Rayleigh coefficient, the concentration as well as the molecular weight of the various polymer fractions can be calculated. The evaluation is performed according to Jordan [21].

In order to achieve a sufficient separation of the polymers, Lichrosphere 100 columns (250×4 mm) and Lichrosphere 500 Diol (10 nm) (Merck, Darmstadt, Germany) were combined. Toluol p.a. (Merck, Darmstadt, Germany) was used for the elution which was performed at a pressure of 1×10^7 Pa and a flux rate of 0.70 ± 0.01 ml/min, HPLC pump type 52 (Knauer, Berlin). A 1.8 mW He/Ne-Laser (Chromatix, Inc., Sunnyvale, CA) with a wavelength of 633 nm and a scattering angle of 4.85° was used as light source in the LALLS system. After passing an aperture with a diameter of 0.15 mm the light crossed a flow-through cell with a path width of 5 mm and a scattering volume of 0.1 μl.

3.5.2. Determination of the content of functional groups

For the quantitative determination of the functional groups in the various PDMS according to Harzdorf [22] a gas-volumetric procedure was used. The methods were validated by means of test substances supplied by Bayer AG. For the validation of the determination of the content of SiH-groups Baysilon-oil MH15 (test substance 457, Bayer AG, Leverkusen, Germany) with a concentration of 15.45 mMole/g was used. The method used for the determination of the content of vinyl-groups was validated by means of methyl-vinyl-D4 (test substance 456, Bayer AG, Leverkusen, Germany) with a content of 11.52 mMole vinyl/g.

3.5.3. Cross-linking method

For the manufacture of model networks the components Vinyl-PDMS, SiH-PDMS, Vinyl-D4 and the platinum catalyst were mixed up in well-defined stoichiometric amounts. In order to achieve their homogeneous distribution they were added sequentially. In a first step the catalyst dissolved in Vinyl-D4 was diluted with toluene to obtain a platinum concentration of 1 mg Pt/ml. This procedure enabled an exact dosing of the very small amounts of catalyst. In a second step the required stoichiometric amounts of the Pt/toluene mixture and of Vinyl-D4 were added to the corresponding amount of Vinyl-PDMS.

In a third step which was performed immediately before the start of cross-linking the required amount of SiH-PDMS was added to the mixture obtained from step two. This reactive mixture was evacuated in an exsiccator at room temperature in order to remove gas bubbles. By means of a single use syringe the mixture was injected into the molds preheated to the cross-linking temperature.

The mixing in the various steps was done by means of blade mixers. Vulcanization was performed in polyacrylate molds with the shape of the testing dumbbells according to ASTM. The molds were surrounded with a water jacket which allowed to maintain and control their temperature.

3.5.4. Method for rubber characterization

According to the theory of rubber elasticity [17] the molecular weight M_C of the cross-linking unit is related to the swelling ratio (SR) u of a rubber by

$$M_C = \frac{\rho V(0.5u - \sqrt[3]{u})}{\ln(1-u) + u + \chi u^2} \tag{3.1}$$

ρ is the density of the rubber and V the molar volume of the swelling liquid (969,697 cm^3 for tetrachloromethane at 25 °C [31]). χ stands for the so-called Flory–Huggins parameter. It measures the interaction between the swelling liquid and the rubber. For the system tetrachloromethane/PDMS $\chi = 0.45$ [17]. In order to obtain an illustrative measure for the length of the cross-linking units their molecular weight M_C was divided by 74.15, the molecular weight of a $SiO(CH_3)_2$-unit. The number obtained by this way is called NCL. Its value corresponds to the average number of $SiO(CH_3)_2$-units per cross-linking unit.

3.5.4.1. Determination of the rubber density. The density of the rubbers was determined by means of an immersion method. If a test specimen is completely immersed in a liquid of the density ρ_1 its true weight G_w is reduced by the buoyancy A. In consequence only a virtual weight G_s will be measured

$$A = G_w - G_s \tag{3.2}$$

The density ρ_2 of the test specimen is calculated as

$$\rho_2 = \frac{\rho_1 G_w}{G_w - G_s} \tag{3.3}$$

All weights are determined with an accuracy of four decimals. In order to determine the virtual weight G_s the sample pendulum of an analytical balance (Mettler, H10W, Giessen, Germany) is replaced by a small basket. In a first step the virtual weight of the empty basket is determined by its full immersion into the test liquid. In the next step the virtual weight G_s of the rubber sample having the true weight G_w is determined in the same way. Water is used as test liquid as it does not swell silicone rubbers in the short time.

3.5.4.2. Swelling measurements. A test specimen with a precisely (at least four decimals) determined weight (Mettler, H10W, Giessen, Germany) is stored for 48 h at 25 °C in tetrachloromethane p.a. (Merck, Darmstadt, Germany). Depending on the expected SR it should have a weight of 0.5–1 g. After removal from the swelling liquid the excess liquid is whipped up by means of a Kleenex towel. For weighing the sample it is transferred into a weighing bottle of well-known tare weight.

The extent of swelling is described by the SR. It is defined by the ratio of the volume V_0 of the non-swollen sample to the volume V_s of the swollen sample. The volume of the swollen sample is given by

$$V_s = V_0 + V_L + V_{Ex} \tag{3.4}$$

V_L is the volume of the swelling liquid absorbed by the sample, V_{Ex} being the increase in sample volume due to the interaction of the swelling liquid with the polymer chains. As a rule V_{Ex} is rather small. Therefore it is neglected when determining the SR. The SR is then given by

$$\mathrm{SR} = \frac{V_0}{V_0 + V_L} \tag{3.5}$$

Considering that $V_0 = m_0/\rho_0$ and $V_L = m_L/\rho_L$, respectively, m_0 and ρ_0 being the mass and the density of the non-swollen sample, m_L and ρ_L stand for the mass and the density of the swelling liquid, it follows

$$\mathrm{SR} = \frac{1}{1+q} \tag{3.6}$$

q is defined by

$$q = \frac{\rho_0 m_L}{\rho_L m_0} \tag{3.7}$$

The density of tetrachloromethane at 25 °C is given as 1.5848 g cm^{-3} [31].

3.5.5. Response surface technique

When carefully planned there is a functional relationship between the parameters and the results of an experiment. The 'response surface' technique is a procedure which allows to identify and to visualize this relation on the basis of a limited number of experiments. This technique which has already been used in the optimization of chemical syntheses [23–25] shall be applied to allow for a straightforward synthesis of rubbers with well-defined microstructures.

y_i stands for the result of an experiment, its response, with the parameters x_{i1} and x_{i2}. Then we have: $y_i = f(x_{i1}, x_{i2})$. The set of all experimental results y_i defines a hypersurface above the region of the experiment defined by the different values of the parameters x_1 and x_2. This hypersurface that represents all experimental results (responses) being possible above the experimental region is the so-called response surface. The function f projecting the parameters x_1 and x_2 into the response surface is assumed to be

Table 1
Molecular weights and concentrations of functional groups of various PDMS batches

Polymer	Batch No.	$\bar{M}_n$	$\bar{M}_w$	$\bar{M}_w/\bar{M}_n$	SiH (mMole/g)	Vinyl (mMole/g)
Silopren U1	003	15177	29132	1.92		0.119
	004	12417	24552	1.98		0.130
Silopren U10	003	35645	68610	1.92		0.045
	004	24874	58800	2.36		0.060
	005	30111	67853	2.25		0.058
Silopren U165	001	68945	148632	2.16		0.038
	003	68235	141846	2.08		0.021
Silopren SiH	001	2068	3054	1.48	7.90	
	002	1660	–	–	10.00	
	003	1854	–	–	8.61	
	004	2001	3460	1.73	7.80	
Vinyl-D4	005					11.45
	007					11.14
	008					11.17

continuous. According to the Taylor theorem continuous functions can be expanded in series

$$y = \alpha_0 + \alpha_1 x_1 + \alpha_2 x_1^2 + \cdots + \beta_1 x_2 + \beta_2 x_2^2 + \cdots \qquad (3.8)$$

This means it is possible to approximate the response surface by a polynomial of the experimental parameters x_1 and x_2. In most cases only a small part of the response surface is experimentally relevant. In consequence the expansion can be limited to a few terms

$$y = \hat{\alpha}_0 + \hat{\alpha}_1 x_1 + \hat{\alpha}_2 x_1^2 + \hat{\beta}_1 x_2 + \hat{\beta}_2 x_2^2 + \varepsilon = f(x_1, x_2) \qquad (3.9)$$

As the number of experimental results is limited the true function f can only be approximated by a function $\tilde{f}$.

$$\tilde{f} = a_0 + a_1 x_1 + a_2 x_1^2 + \cdots + b_1 x_2 + b_2 x_2^2 + \cdots \qquad (3.10)$$

The least-squares method is used to approximate the true function f, which is represented by the experimental results, by the function $\tilde{f}$.

In the course of a least squares method different types of sums of squares (SS) can be calculated [27,28]. The type III SS sometimes referred to as partial SS, are of special interest. They measure the contribution of a given effect in explaining the total variance. This means they directly measure the influence of a given effect on the response.

4. Results

4.1. Characterization of the starting polymers

The molecular weights of the different PDMS batches used in the experiments are given in Table 1. The number and the weight averages of the molecular weight of the various Silopren U types are significantly different (Table 2). Hence the inhomogeneities are also rather different. The number and weight averages of the molecular weight of the low molecular Silopren SiH do not differ so much. However, with two batches we have been unable to determine the weight average of the molecular weight. In the case of Vinyl-D4 which is chemically well-defined the differences in the concentrations of the vinyl groups has to be attributed to the analytical error.

4.2. Correlation between the composition of the mixtures of starting polymers and the properties of their cross-linking products

In a series of preliminary experiments the different polymer types Vinyl-PDMS U1, U10 and U165 were mixed with various amounts of SiH-PDSM and Vinyl-D4. The mixtures were cross-linked at the temperatures of $T = 100$ and 120 °C.

Table 2
Virtual molecular weights of the various Silopren-types

Polymer	Batch No.	Vinyl (mMole/g)	SiH (mMole/g)	$\bar{M}_n$	Virtual molecular weight
Silopren U1	003	0.119		15177	16806
	004	0.130		12417	15384
Silopren U10	003	0.045		35645	44444
	004	0.060		24874	33333
	005	0.058		30111	34483
Silopren U165	001	0.038		68945	52632
	003	0.021		68235	95238
Silopren SiH	001		7.90	2068	2025
	002		10.00	1660	1600
	003		8.61	1854	1858
	004		7.80	2001	2051

4.2.1. Qualitative findings

Depending on the stoichiometric ratio of the content of vinyl groups to the content of SiH-groups from recipes containing merely linear Vinyl-PDMS, SiH-PDMS and catalyst only sticky rubbers of low tensile strength were obtained. At a ratio Vinyl/SiH = 1 no rubber was obtained. With increasing content of SiH, this means with decreasing values of the ratio Vinyl/SiH, the cross-linking improved. However, all testing dumbbells showed no tensile strength even at very small strains. With pure polymer mixtures containing no Vinyl-D4 cross-linking is only observed if the content of SiH-PDMS is significantly higher than the content of vinyl groups. Obviously only a part of the SiH-groups of the SiH-PDMS molecules is involved in the cross-linking reaction.

Polymer mixtures containing Vinyl-PDMS U1, Vinyl-D4 and SiH-PDMS result in rubbers which are difficult to take out of the molds. If the slightest strain is applied the testing dumbbells immediately start to crumble. This clearly indicates very short NCLs. The tendency to crumble decreases with increasing amounts of Vinyl-D4, this means with increasing network density. However, a sizeable tensile strength cannot be achieved.

Depending on the contents in functional groups, polymer mixtures consisting of Vinyl-PDMS U10, Vinyl-D4 and SiH-PDMS result in a large variety of rubbers. The curing time increases with increasing amount of Vinyl-D4. Polymer mixtures with a molar ratio of the content of vinyl groups from Vinyl-PDMS to the content of vinyl groups from Vinyl-D4 in the range from 0.4 to 3.8 result in rubbers, which can easily be taken out of the molds. The tensile strength was significantly higher than in the case of the rubbers described above.

Even at very high concentrations of Vinyl-D4 polymer mixtures containing Vinyl-PDMS U165, Vinyl-D4 and SiH-PDMS result in rather soft rubbers which are difficult to be taken out of the molds. The curing times are higher than in corresponding mixtures containing Vinyl-PDMS U1 or U10.

Polymer mixtures containing various parts of Vinyl-PDMS U1 and U10 in addition to Vinyl-D4 and SiH-PDMS result in rubbers which can easily be taken out of the molds. Also in these cases the curing time increases with increasing content of Vinyl-D4.

From recipes containing various amounts of Vinyl-PDMS U1 and U165 in addition to Vinyl-D4 and SiH-PDMS even at high contents of Vinyl-D4 rubbers are obtained which are difficult to be taken out of the molds.

4.2.2. Quantitative correlation between the composition of the mixtures of starting polymers and the properties of their cross-linking products

The qualitative findings as well as the knowledge of the reactions between SiH-PDMS, Vinyl-PDMS and Vinyl-D4 give strong indications on how the parameters representing these groups interact during the cross-linking. Nevertheless it was studied very systematically which parameters and which representation of the parameters allowed for the best quantitative description of the correlation between the composition of the polymer mixtures and the properties of the rubbers obtained from their cross-linking.

As the functional groups react in a stoichiometric way the composition of the recipes is given by the molar content in functional groups. All figures given below refer to a constant batch weight of 100 g.

It was intended to describe the correlation between the composition of the different recipes and the NCLs of the resulting rubbers by means of a polynomial. The NCL is a dimensionless number. As mathematical equations have to be homogeneous in their dimensions, dimensionless numbers have to be identified allowing for correct description of the recipes composition. On the basis of stoichiometric considerations the ratio of the total amount of vinyl groups, this means the contributions from Vinyl-PDMS and from Vinyl-D4, divided by the total amount of SiH-groups in the mixture seems to be a meaningful dimensionless number. The reaction of the SiH-groups of the cross-linker SiH-PDMS with the vinyl-groups of the Vinyl-PDMS results in network chains whose maximum length is determined by the molecular weight of the Vinyl-PDMS chains. The reaction of Vinyl-D4 with SiH-groups of the cross-linker can result in a variety of different rather compact structures. Some of these reactions may increase the NCLs. It is also conceivable that by the reaction of several Vinyl-D4

Table 3
Composition of various polymer mixtures on the basis of Vinyl-PDMS U1 and the network chain lengths of the resulting rubbers (concentration of catalyst: 30 ppm)

Exp.	Vinyl-PDMS U1 # 004 (mMole)	SiH-PDMS # 001 (mMole)	Vinyl-D4 # 007 (mMole)	Vinyl lin./cycl.	Total vinyl/SiH	Network chain length (NCL)
1	10.826	104.474	38.964	0.278	0.477	14.96, 15.82, 15.63, 15.31, 15.68
2	11.525	73.117	23.307	0.494	0.476	31.04, 31.95, 28.21, 25.58, 31.85
3	12.320	37.434	5.489	2.244	0.476	71.79, 71.59, 67.19, 70.11, 67.55
4	10.732	109.013	40.657	0.264	0.471	15.36, 15.08, 15.31, 15.25, 14.44
5	11.456	76.508	24.388	0.470	0.468	30.59, 33.08, 32.62, 33.00, 33.12
6	12.286	39.296	5.762	2.132	0.459	70.50, 70.01, 64.95, 63.90, 70.97
7	10.629	113.964	42.504	0.250	0.466	14.30, 13.66, 13.52, 13.11, 14.19
8	11.381	80.230	25.574	0.445	0.461	26.66, 23.97, 28.32, 28.16, 28.51
9	12.249	41.353	6.064	2.020	0.443	51.26, 51.39, 51.40, 50.47, 51.23

Table 4
Coefficients of the polynomial given by Eq. (4.1)

Parameter	Coefficient	F-value	Type III SS
a_0	−7143.5076	–	
a_1	92.4415	4748.27	1413.92
a_2	−25.8432	78.83	721.24
b_1	30378.8375	151.59	584.42
b_2	−32329.2950	150.16	566.00

Correlation coefficient $r^2=0.992$.

molecules with one cross-linker molecule rather compact structures are formed which then may prevent the network chains from a full expansion. Obviously the two types of vinyl-groups can have at least a partial opposite effect on the network formation. Therefore the ratio of the molar amount of vinyl-groups from the Vinyl-PDMS (lin. vinyl) divided by the amount of vinyl-groups from Vinyl-D4 (cycl. vinyl) in the mixture seems to be another meaningful dimensionless number, (Vinyl lin./cycl.). The composition of formulations based on Vinyl-PDMS U1 as well as the network chains lengths of the corresponding rubbers are given in Table 3. At a cross-linking temperature of 100 °C a curing time of 2 min was needed.

The functional correlation between the NCLs obtained by cross-linking the mixtures summarized in Table 3 is given by Eq. (4.1).

$$\mathrm{NCL} = a_0 + a_1x_1 + a_2x_1^2 + b_1x_2 + b_2x_2^2 \tag{4.1}$$

x_1 represents the dimensionless variable 'vinyl lin./cycl.' whereas x_2 stands for the second dimensionless variable 'total vinyl/SiH'. Its coefficients are summarized in Table 4. The correlation coefficient is given by $r^2=0.992$. From tables of the F-distribution for $k=2$ and n-k-$1=42$ [26] the 0.99% point, $f_{0.99}\sim 5.1$, can be found. This means that all effects are statistically significant. The analysis of the type III SS shows that x_1 and x_1^2 contribute mostly to the explanation of the total variance. This means that the ratio 'vinyl lin./cycl.' has the greatest influence on the NCL.

Table 5 shows the composition of formulations containing the Vinyl-PDMS U10 instead of Vinyl-PDMS U1 with its short polymer chains. As expected the NCLs obtained by the cross-linking of the various formulations are longer than those obtained with Vinyl-PDMS U1. They cover a range from 40 up to 150 SiO-monomer units per NCL. As mentioned already the tensile strength of these rubbers is significantly higher than that obtained in experiments using Vinyl-PDMS U1.

If the dimensionless variables 'x_1=vinyl lin./cycl.' and 'x_2=total vinyl/SiH' are used to describe the composition of the formulations there is no longer a need to calibrate the total weight of each of the various formulation to 100 g. When calculating the dimensionless numbers the calibration factors are canceled.

The response surface describing the correlation between the compositions of the mixtures summarized in Table 5 and the NCLs of the rubbers obtained by their cross-linking is given by the following polynomial, Eq. (4.2)

$$\mathrm{NCL} = a_0 + a_1x_1 + a_2x_1^2 + b_1x_2 + b_2x_2^2 + c_1x_1x_2 + c_2x_1^2x_2 \tag{4.2}$$

The coefficients of the polynomial are summarized in Table 6. The correlation coefficient is given by $r^2=0.992$. From tables of the F-distribution for $k=2$ and n-k-$1=42$ [26] the 0.99% point, $f_{0.99}\sim 5.15$, can be found. This means all effects described by the coefficient of the polynomial are statistically significant. This is in good agreement with the analysis of the type III SS. It indicates that the factor x_2 has the strongest influence on the NCL. Obviously the increase in chain length of the linear Vinyl-PDMS U10 results in a stronger influence of the Vinyl-D4 on the achieved network density.

On the basis of the formulations summarized in the Tables 3 and 5 rubbers with NCLs in the range from 15 up to 150 SiO-monomer units could be obtained. However, as mentioned above the rubbers made from Vinyl-PDMS U1 show a tendency to scrumble. In addition their tensile strength is rather low.

Table 5
Composition of various polymer mixtures on the basis of Vinyl-PDMS U10 and the network chain lengths of the resulting rubbers (concentration of catalyst: 30 ppm)

Exp.	Vinyl-PDMS U10 # 004 (mMole)	SiH-PDMS # 001 (mMole)	Vinyl-D4 # 007 (mMole)	Vinyl lin./cycl.	Total vinyl/SiH	Network chain length (NCL)
1	5.895	13.154	0.662	8.797	0.493	146.76, 151.13, 148.37, 157.31, 138.43
2	5.873	15.418	1.290	4.555	0.465	134.16, 134.87, 134.78, 134.81, 135.85
3	5.879	15.349	2.026	2.910	0.514	126.21, 127.78, 124.21, 130.22, 129.89
4	5.696	32.855	9.487	0.601	0.462	105.70, 119.64, 114.58, 118.66, 110.48
5	5.634	38.740	12.486	0.452	0.468	102.48, 101.25, 98.78, 101.86, 101.79
6	5.574	44.418	15.563	0.358	0.476	88.47, 89.51, 89.48, 89.60, 89.12
7	5.391	63.213	25.100	0.215	0.482	59.01, 59.95, 58.87, 58.28, 58.54
8	5.307	70.916	29.104	0.182	0.485	47.55, 47.71, 48.03, 47.69, 47.63
9	5.227	77.634	32.719	0.160	0.489	41.21, 40.38, 40.86, 40.15, 40.14

Table 6
Coefficients of the polynomial given by Eq. (4.2)

Parameter	Coefficient	*F*-value	Type III SS
a_0	−29861.2835		
a_1	2150.9806	2958.35	134.42
a_2	−615.4866	218.26	206.28
b_1	124269.9703	672.24	356.23
b_2	−129191.3212	267.14	377.48
c_1	−4089.0492	267.14	124.11
c_2	1221.0715	16.33	202.22

Correlation coefficient $r^2 = 0.992$.

Therefore formulations were studied in which mixtures of Vinyl-PDMS U1 and Vinyl-PDMS U10 are used as Vinyl-PDMS component. It was the hope by this way to obtain rubbers with a relatively wide range of NCLs and appropriate tensile strengths. According to Flory [29] a mixture of polymers with the number averages of the molecular weight of $\bar{M}_{n1}$ and $\bar{M}_{n2}$ will have a number average of the molecular weight $\bar{M}_n$ given by Eq. (4.3).

$$\bar{M}_n = \frac{1}{w_1/\bar{M}_{n1} + w_2/\bar{M}_{n2}} \tag{4.3}$$

w_i stands for the weight fraction and $\bar{M}_{ni}$ for the number average of the molecular weight of the polymer component *i*. For the weight fractions we have: $\sum w_i = 1$.

As the molecules contained in the mixture are of a well-defined functionality it is possible to calculate their virtual molecular weight M_G from the content v_i of vinyl-groups and the weight fraction w_i of the two components of the mixture

$$M_G = \frac{\text{functionality}}{w_1 v_1 + w_2 v_2} \tag{4.4}$$

The 'virtual molecular weight' of a polymer mixture is a fictitious number. Nevertheless it is more illustrative than the number average of the molecular weight $\bar{M}_n$ when discussing the NCLs obtainable by curing of such polymer mixtures. For the description of formulations containing mixtures of Vinyl-PDMS U1 and of U10 the dimensionless virtual molecular weight of this mixture was used as third variable x_3 in addition to the other two dimensionless variables 'x_1 = vinyl lin./cycl.' and 'x_2 = total vinyl/SiH'.

Table 7 summarizes the composition of formulations containing mixtures of Vinyl-PDMS U1 and U10. In addition the NCLs measured in the corresponding rubbers are given. The cross-linker SiH-PDMS 1905 is characterized by a content of SiH-groups of 4.2 mMole/g. With respect to other properties the two cross-linkers are exchangeable.

Table 7
Recipes containing mixtures of Vinyl-PDMs U1 and U10 as well as the network chain length of the resulting rubbers

Exp.	Vinyl-PDMS		SiH-PDMS (mMole)	Vinyl-D4 (mMole)	Vinyl lin./cycl.	Total vinyl/SiH	Virtual molecular weight	Network chain length (NCL)
	U1 (mMole)	U10 (mMole)						
1	11.335	10.385	60.152	5.57	3.899	0.454	23966	133.38, 132.72, 133.09, 133.18, 127.44
2	11.335	10.385	66.839	5.57	3.899	0.408	23966	150.93, 157.58, 157.07, 153.31, 156.13
3	11.335	10.385	77.525	5.57	3.899	0.371	23966	158.46, 159.78, 160.93, 161.49,159.16
4	5.529	5.066	124.715	55.70	0.190	0.532	23966	64,55, 66.21, 66.79, 67.60, 66.63
5	5.529	5.066	138.571	55.70	0.190	0.478	23966	62.58, 70.06, 66.35, 69.64, 68.43
6	5.529	5.066	152.426	55.70	0.190	0.435	23966	76.95, 77.50, 78.30, 76.76, 78.25
7	2.834	2.597	112.795	55.70	0.098	0.542	23966	25.27, 25.48, 26.48, 26.52, 26.01
8	2.834	2.597	125.328	55.70	0.098	0.488	23966	29.07, 29.11, 29.48, 29.43, 29.51
9	2.834	2.597	138.520	55.70	0.098	0.441	23966	30.47, 31.07, 30.98, 31.37, 31.59
10	34.488	5.506	60.152	5.57	7.18	0.757	17856	180.61, 175.34, 178.21, 170.99,179.38
11	34.488	5.506	66.839	5.57	7.18	0.682	17856	176.40, 176.63, 184.59, 182.38, 175.99
12	34.488	5.505	73.525	5.57	7.18	0.620	17856	190.15, 187.61, 185.33, 193.18, 186.754
13	16.823	2.686	124.715	55.70	0.350	0.603	17856	140.38, 140.65, 141.29, 141.10, 140.74
14	16.823	2.686	138.571	55.70	0.350	0.543	17856	145.64, 146.01, 146.74, 147.76, 150.86
15	16.823	2.686	152.426	55.70	0.350	0.493	17856	149.42, 150.25, 153.68, 155.14, 154.64
16	8.623	1.377	112.795	55.70	0.180	0.582	17856	187.04, 188.85, 184.49, 185.61, 185.82
17	8.623	1.377	125.328	55.70	0.180	0.520	17856	184.34, 192.95, 191.65, 198.97, 189.98
18	8.623	1.377	138.520	55.70	0.180	0.412	17856	205.44, 202.86, 200.78, 201.85, 209.68
19	51.523	1.928	60.152	5.57	9.956	0.981	16032	214.58, 213.43, 211.59, 212.88, 211.58
20	51.523	1.928	66.839	5.57	9.956	0.883	16032	216.37, 216.60, 215.92, 217.23, 217.76
21	51.523	1.928	73.525	5.57	9.956	0.803	16032	223.24, 223.09, 223.60, 226.00,223.91
22	25.132	0.941	124.715	55.70	0.468	0.656	16032	97.03, 97.42, 100.03, 94.03, 95.58
23	25.132	0.941	138.571	55.70	0.468	0.590	16032	113.22, 112.77, 112.97, 115.12, 114.34
24	25.132	0.941	152.426	55.70	0.468	0.536	16032	117.07, 119.79, 118.65, 117.95, 120.01
25	12.882	0.482	112.795	55.70	0.240	0.612	16031	145.68, 148.75, 146.47, 147.76, 146.91
26	12.882	0.482	125.328	55.70	0.240	0.551	16032	154.76, 157.61, 155.59, 157.32, 156.70
27	12.882	0.482	138.520	55.70	0.240	0.474	16032	166.86, 167,47, 153.73, 168.14, 168.02

The response surface describing the correlation between the composition of the various formulation given in Table 7 and the NCLs measured in the corresponding rubbers is given by Eq. (4.5)

$$\begin{aligned}\mathrm{NCL} = {} & a_0 + a_1x_1 + a_2x_1^2 + b_1x_2 + b_2x_2^2 + c_1x_1x_3 \\ & + c_2x_2x_3 + d_1x_1x_3^2 + d_2x_2x_3^2 + d_3x_1^2x_3 \\ & + d_4x_2^2x_3 + e_1x_1^2x_3^2 + e_2x_2^2x_3^2 \end{aligned} \qquad (4.5)$$

The coefficients of the polynomial are summarized in Table 8. The correlation coefficient is given by $r^2=0.997$. From tables of the F-distribution for $k=3$ and n-k-$1=131$ [26] the 0.99% point, $f_{0.99} \sim 3.93$ can be found. Except from b_2 all effects represented by the coefficients are statistically significant. This is in agreement with the analysis of the type III SS where also b_2 shows the smallest influence.

After having identified the importance of the 'virtual molecular weight' as a third dimensionless variable to describe the composition of formulations it became evident that the formulations given in the Tables 3 and 5 are subsets of the experimental region defined by the parameters '$x_1=$ vinyl lin./cycl.', '$x_2=$total vinyl/SiH' and '$x_3=$virtual molecular weight'. In each of these subsets the parameter 'virtual molecular weight' was constant. Therefore it was not considered explicitly in the determination of the 'response surface'. Constant effects have an impact only on the coefficient a_0. If the virtual molecular weights of Vinyl-PDMS U1 and U10 are considered explicitly all experiments using the same cross-linker can be described by one polynomial only.

The polynomials given by Eqs. (4.1), (4.2) and (4.5) allow to calculate which amounts of the various starting polymers are required to obtain a rubber with a defined network chain density. Table 9 shows the excellent agreement between the NCLs used to calculate the composition of the mixture of the starting polymers and the NCLs determined experimentally in the rubbers obtained by curing these polymer mixtures.

Table 8
Coefficients of the polynomial given by Eq. (4.5)

Parameter	Coefficient	F-value	Type III SS
a_0	321.31658	–	
a_1	6601.99989	13952.20	4080.69
a_2	−1359.42102	90.88	9555.12
b_1	−9178.07549	16.13	5387.21
b_2	7743.37291	2.86	1739.06
c_1	−0.76252	495.13	5100.95
c_2	1.00939	15013.31	5948.67
d_1	0.00002	4116.82	6219.10
d_2	−0.00003	1888.76	7620.91
d_3	0.15463	301.81	10936.58
d_4	−0.88548	508.64	2097.75
e_1	−0.000004	847.37	12315.09
e_2	−0.000026	237.08	2810.28

Correlation coefficient $r^2=0.997$.

Table 9
Comparison between the network chain lengths (NCL's) as used for the calculation of the compositions of the polymer mixtures and the NCL's determined experimentally in the rubbers obtained from these mixtures (in $Si(CH_3)_2O$-units)

NCL's used for the calculation of the composition of the polymer mixtures	NCL's determined experimentally	
24.00	19.69	$\bar{x}=24.27$
	25.54	
	25.59	
	24.63	
	25.90	
27.00	27.90	$\bar{x}=26.80$
	26.78	
	27.01	
	26.78	
	26.52	
49.00	49.29	$\bar{x}=48.55$
	48.91	
	47.59	
	48.89	
	48.38	
160.00	160.75	$\bar{x}=160.05$
	159.92	
	159.81	
	159.41	
	160.55	

5. Discussion and summary

In this study it was shown that in the case of diffusion of small molecules in a rubber the diffusion coefficient D can be written as a product of two probabilities, $D \sim w_1w_2$. The probability w_2 describes the probability that by the collision with polymer chains performing thermal vibrations a drug molecule experiences an energy exchange which is large enough to overcome the interactions with its immediate neighborhood. This is one prerequisite, which has to be given to allow the molecule to leave its place. The other prerequisite is the molecule has to find in its immediate neighborhood a free-volume being large enough to take it up. This probability is described by w_1. The product of the two probabilities reflects that both events have to happen at the same time.

As long as the same system rubber/drug species is studied, in a first approximation the influence of the probability w_2 can be considered as constant. This means the diffusion coefficient D is mainly determined by the probability w_1 which is determined by the distribution of the free-volume in the rubber. This distribution, however, depends on its microstructure, this means on its network density.

With components of the Silopren® system of Bayer AG we tried on the basis of commercially available polymers to synthesize rubbers with defined NCLs. The Silopren® system of Bayer AG consists of the following components:

- Vinyl-PDMS: this component consists of linear bifunctional molecules carrying vinyl groups at both ends of the polydimethylsiloxane chains. There are three types of this polymer Vinyl-PDMS U1, U10 and U165. They differ in their viscosity and hence in their average chain length.
- SiH-PDMS: depending on their functionality these branched polydimethylsiloxanes carry SiH groups at some of its side chains. In an addition reaction these groups can react with the vinyl groups, e.g. of Vinyl-PDMS. These class of molecules often is addressed as cross-linker.
- Vinyl-D4: this is a well-defined small molecule, tetramethyl-tetravinyl-tetracyclosiloxane. Due to its high functionality it strongly contributes to the cross-linking. An increase of its concentration in the reaction mixture increases the curing time.
- Pt catalyst: the addition reaction is catalyzed by platinum. Platinum is complexed with Vinyl-D4.

By means of the ‘response surface’ technique a mathematical function was identified describing in a quantitative way the correlation between the NCLs of rubbers and the amounts of the various starting materials in the polymer mixture required to obtain a given average NCL. The proper selection of the parameters, which can be used to describe the composition of the mixture of starting materials, was a key problem. As the dependent variable ‘NCL’ is dimensionless it follows that the independent variables which stand only in an additive relation have to be dimensionless too in order to comply with the requirement that a mathematical equation has to be homogeneous in its dimensions. Considering the mechanism of the cross-linking reaction the variables ‘total vinyl/SiH’ and ‘vinyl lin./cycl.’ were identified as two dimensionless variables. The first one is defined by the ratio of concentration of all vinyl groups, from Vinyl-PDMS and from Vinyl-D4, in the reaction mixture divided by the concentration of all SiH groups in the reaction mixture. The second one describes the ratio of the concentration of vinyl groups from Vinyl-PDMS divided by the concentration of the vinyl groups from Vinyl-D4 in the reaction mixture. Experiments in which mixtures consisting of Vinyl-PDMS U1 and U10 were used as linear bifunctional polymers showed that the variable ‘virtual molecular weight’ of the Vinyl-PDMS component is appropriate to describe the influence of the various Vinyl-PDMS types. This variable is dimensionless too.

A careful evaluation of all experiments performed in the course of this study revealed that as long as the same cross-linker is used, one response surface is able to describe the correlation between the composition of the various polymer mixtures and the NCLs in the rubbers obtained by their cross-linking. The type of Vinyl-PDMS is considered by its virtual molecular weight. The polynomials describing the response surfaces can be used to calculate the composition of a mixture of starting materials resulting in a desired network density.

In a paper to follow we will report how this know-how on how to synthesize membranes with defined permeabilities is applied to develop a long-acting therapeutic system with zero order drug release.

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