Silicones for medical use

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1. Physical chemistry of the silicones

1.1 Nomenclature of the silicones

So great is the contribution of silicon to the development of advanced technologies that every single material derived from silicon chemistry seems extremely modern. Silicon occurs naturally in sand and rocks, generally in the form of silica and silicate, and is the second most abundant element on earth after oxygen. Only crystalline silicon and the silanes and organosiloxanes are truly modern products: they do not occur freely in nature, but are entirely the product of human invention. Table l outlines the terminology relating to the most common silicon derivatives.
In the medical industry, the term "silicone" refers to polydimethylsiloxane derivatives and to those compounds of which they are the principal constituents.

Table 1: *Classification of silicones*

Common name	**Chemical Terminology**
Silicon	Silicon Si
Silica	Silicon dioxide SiO_2
Silicate	Derivative of silicate anion $[SiO_4]^{4-}$
Organo-, chloro-, ... silane	Derivative of silane SiH_4
Silicone resin	Derivative of silsesquioxane $(RSiO_{3/2})$
Polydimethylsiloxane	Macromolecule with repeating dimethylsiloxane units $-(MeSiO)-_n$
Silicone	Derivative or compound with a polysiloxane or silsesquioxane base

1.2 Preparation of silicones

Sand, the starting material in silicon chemistry, is transformed into polydimethylsiloxanes by a series of syntheses and distillations (Table 2) [1,2]. The key intermediate is the dichlorodimethylsilane (Me_2SiCl_2), the main product of a blend of chlorosilanes. The latter are obtained by alkylation of silicon with methyl chloride, previously prepared from methanol and hydrochloric acid. The dichlorodimethylsilane is purified by distillation, which ensures the purity of the polydimethylsiloxanes. It is subsequently hydrolysed by water to dimethysilanediol, $Me_2Si(OH)_2$, which is highly reactive and condenses spontaneously to yield hydrochloric acid and monocyclic or linear dimethylsiloxane oligomers. The latter are purified and all traces of chlorine removed. The hydrochloric acid is then recycled in the production of methyl chloride.

Polydimethylsiloxanes are prepared by hydrolysis and condensation polymerisation of purified octamethylcyclotetrasiloxane using base or acid catalysts, which are subsequently neutralised and removed by filtration. The condensation polymerisation process incorporates an equilibration step and yields a mixture of high-molecular-weight polymers and low-molecular-weight products. The latter, essentially polydimethylcyclosiloxanes, are removed by distillation. The addition of functional siloxane groups during condensation or during subsequent re-equilibration allows methyl groups to be substituted by reactive groups which confer specific properties, e.g. vinyl, hydrogen, phenyl.

The very high purity of the chlorosilanes and the absence of synthesis-related contamination ensure extremely pure polydimethylsiloxanes which are practically free from organic impurities and heavy metals.

The physical form of the resulting polydimethylsiloxanes range from liquids of varying viscosity to gums and resins. More complex structures such as elastomers are obtained by formulation and cross-linking. Vinyl hydrosilylation using platinum as a catalyst is the most widely used reaction in the production of thermosetting silicones for medical use: no secondary products are released during this process, which takes place at low temperatures, involves very small quantities of catalyst, and provides a very high yield (Table 2).

Table 2: *Synthesis and purification of silicones*

Synthesis of silicon

high-temperature reduction of sand: $SiO_2 + 2\,C \rightarrow Si + 2\,CO$

Synthesis of dimethyldichlorosilane by alkylation of silicon

$$Si + MeCl \xrightarrow[\text{fluidized-bed}]{300\,^\circ C/1\text{-}5\ bar} \underset{\substack{x+y\leq 4\\ \text{mixture of chlorosilanes}}}{Me_xH_ySiCl_{4-x-y}} \xrightarrow{\text{distillation}} Me_2SiCl_2$$

Synthesis of polydimethylcyclosiloxanes

$$Me_2SiCl_2 \xrightarrow[\substack{-HCl\\ \text{hydrolysis}}]{+H_2O} \underset{\text{highly reactive}}{\left[Me_2Si(OH)_2\right]} \xrightarrow[\text{2) distillation}]{\text{1) condensation}} \underset{\substack{\text{(monocyclic,}\\ m = 3 \text{ or } 4)}}{(Me_2SiO)_m}$$

Synthesis of polydimethylsiloxanes by condensation of polydimethylcyclosiloxanes

$$\underset{\text{monocyclic}}{(Me_2SiO)_4} \underset{\text{condensation}}{\overset{KOH}{\rightleftharpoons}} \underset{\text{linear}}{-(Me_2SiO)_n} + \underset{\text{cyclic}}{(Me_2SiO)_m} \xrightarrow[\text{2) distillation}]{\text{1) neutralisation}} \underset{n > 50}{-(Me_2SiO)_n}$$

Cross-linking of polydimethylsiloxanes by vinyl hydrosilylation

$$\sim\!\!\sim OMe_2Si - \mathbf{CH=CH_2} + \mathbf{H} - Si\equiv \xrightarrow[\text{catalyst}]{\text{platinum}} \sim\!\!\sim OMe_2Si - \mathbf{CH_2-CH_2} - Si\equiv$$

$\equiv$ represents the other valences of silicon and $\sim\!\!\sim$ represents the remainder of the siloxane chain

1.3 Physico-chemical properties of the silicones

Silicones, in the form of polydimethylsiloxanes, have become essential over the latter half of this century, and are indeed irreplaceable in many different medical applications. Their exceptional and versatile properties (e.g. both adhesive and anti-adhesive) are a direct result of the unique physico-chemical characteristics of their semi-organic molecular structure (tables 3 and 4) [2, 3].

The polysiloxane chain forms an extremely flexible backbone, which is mobile and very open, and allows symmetrical substitution of methyl groups. The exceptional flexibility and mobility of this macromolecular structure is the result of a very open Si — O — Si bond angle, large interatomic distances, practically zero rotational energy for Si — O, and limited steric hindrance due to the divalency of oxygen. The electronegativity of the oxygen atom confers a degree of polarity on each siloxane bond, and the bond energy of Si — O is relatively high.

The methyl side-groups form a regular non-polar arrangement, and the mobility of the siloxane skeleton allows ready and preferential orientation, according to the molecular interaction to which the polydimethylsiloxane is subjected. When facing outwards, methyl groups confer hydrophobicity and unique surface properties on silicone. At the molecular level, this non-polarity results in extremely weak inter- and intra-molecular interactions. In terms of chemical resistance, silicone has greater thermal and oxidative stability than organic molecules, but it is susceptible to hydrolysis in the presence of acid or base catalysts. Finally, the reactivity, surface energy, thermal stability, hydrophilicity and other characteristics of silicone may be modified by substituting some of the methyl groups with suitable molecular groups, either along the siloxane chain or at the end, e.g. hydrogen, hydroxyl, vinyl, phenyl, alkoxy, fluoroalkyl, polyethylene glycol.

Table 3: *Molecular characteristics of the silicones*

Rotational energy	Si — O	polydimethylsiloxane	∿ 0 kJ / mol
	C — C	polystyrene	13,8 kJ / mol
	C — C	polytetrafluoroethylene	19,7 kJ / mol
Bond energy	Si — O	444 kJ / mol	
	Si — C	314 kJ / mol	
	C — C	356 kJ / mol	
Interatomic distance	Si — O	hexamethyldisiloxane	0,163 nm
	C — O	dimethyl ether	0,142 nm
	C — C	propane	0,154 nm
Bond angle	Si — O — Si	hexamethyldisiloxane	130°
	Si — O — Si	organosiloxane	105° to 180°
	C — C — C	propane	112°
	C — O — C	dimethyl ether	111°

Table 4: *Relationships between molecular characteristics, physico-chemical properties and biocompatibility*

Molecular characteristics	**Physico-chemical properties**	**Consequences for biocompatibility**
Flexibility and mobility of the siloxane chain Very open structure Regular arrangement of methyl side-chains Substitution of non-polar methyl groups Very slight molecular interaction	Very low surface tension - γ_{liquid} = *20,4 mN/m (20° C)* - $\gamma_{c\ wetting}$ = *24 mN/m* Flow properties Wetting and film-forming properties Lubricant, antifoaming, anti-adhesive, water-repellent properties Very low vitreous transition - T_g = *146 K polydimethylsiloxane* Rubber-like behaviour Ready intra-intermolecular reaction Very high permeability to gases Stable physical properties over a wide temperature range Excellent dielectric properties	Decreased molecular and cellular adhesion Permeability to steam Decreased tissue stress with soft, elastic materials
Homolytic stability of Si — O Stability of Si — C Absorption of methyls < 300 nm	Thermal and oxidative stability Transparency Stability to light	Stable in biological media Readily sterilisable

2. Safety of silicones

2.1 Applications

Silicones are used in pharmaceutical preparations and medico-surgical devices, as well as in other applications involving direct contact with the human body, in cosmetic preparations or as aids in food manufacturing. The biocompatibility of silicone polymers is in general due to their chemical stability, their low surface energy and their hydrophobicity.

The quantities of silicone used in these applications are very small, and low concentrations are thus introduced into our various ecosystems following their use. It is therefore important to understand their toxicological profile and their ultimate fate in the environment.

2.2 Toxicology

The most commonly used silicones are the polydimethylsiloxanes, $Me_3SiO(Me_2SiO)_nSiMe_3$, which have a viscosity of 10 to 100 000 mPa.s. The toxicity of these compounds is extremely low when they are given by the principal routes of administration [4]: when taken orally, they are not absorbed but are excreted unchanged, nor are they absorbed through the skin. Repeat dose studies involving oral, cutaneous and pulmonary administration in various species have shown no effects. *In vitro* studies have not indicated any mutagenic effects. It is for these reasons that silicones are used in numerous applications involving contact with the human body.

3. The impact of silicones on the environment

3.1 Water

The most common silicones are very poorly soluble in water. Their insolubility and low surface tension mean that they are very rapidly adsorbed onto the sludge in sewerage plants, although they do not impair the efficacy of such plants [5]. Several studies have shown that more than 99.99% of silicones are thus retained in sludge, and only very small quantities (< 0.01%) leave the sewerage plants with effluents in surface water, after which they quickly settle [5,6].

3.2 Soil

When the sludge is spread, the polymeric silicones are adsorbed by clays which act as a catalyst, and they are decomposed to oligomeric and finally monomeric silanols, which are volatile, water-soluble molecules. This process has been confirmed in a number of soil types from different geographic locations, and which are known to enhance degradation of chemical substances [7]. Thereafter, the monomeric silanols undergo biodegradation, although they are eliminated chiefly through evaporation into the atmosphere, followed by photodegradation. Together then, these processes result in complete mineralisation of the silicones in the environment [8,9].

3.3 Air

In the atmosphere, and in the presence of short-wave ultraviolet rays (at high altitudes), the volatile silicones are rapidly decomposed but do not give rise to any compounds that interfere with the ozone layer, and they play no part in global warming. This photolysis process leads to the formation of amorphous silica, carbon dioxide and water [10]. The same degradation products are found after incineration of silicones from household or hospital waste (there is no emission of chlorinated compounds).

A European directive is currently being prepared to regulate levels of free volatile compounds in the air, in particular pollutants which contribute to the formation of low-altitude (troposphere) ozone, and these have already been defined by laws and pronouncements by authorities such as the Environmental Protection Agency (EPA) in the United States on Volatile Organic Compounds (VOC). The latter are carbonaceous products with a partial pressure greater than 0.1 mmHg at 20°C and which are more reactive in air than methane.
At the instigation of Dow Corning, the linear and cyclic silicones $HO(Me_2SiO)_xH$ and $(Me_2SiO)_y$ (respectively) were studied in chambers simulating an urban atmosphere and containing nitrogen oxides and reactive organic vapours in order to determine their potential role in ozone formation. These studies demonstrated that the volatile silicones do not contribute to the formation of ozone vapours. On the basis of these results, these silicones have been granted an exemption, and they do not figure on the EPA's list of volatile compounds [11].

3.4 Recycling

Although they are generally disposed of on refuse tips or by incineration, the silicones can be recycled. Silicone elastomers can be milled and then used as fillers in new elastomers; silicone fluids can be depolymerised by means of a catalyst to yield cyclic silicones. In this way, the quantity of silicone introduced into the environment can be reduced.

4. Silicones and bioperformance

4.1 The notion of biocompatibility

The ideal biomaterial would not engender any thrombotic, immunological, toxic, inflammatory or allergenic reactions whatsoever, would not induce the destruction of cell components, and would not produce change in proteins or plasma enzymes.

To date, there is no biomaterial which fully meets these criteria, and it is important to bear in mind that unlike chemical properties, the property of absolute biocompatibility does not exist for any single material. It therefore seems more appropriate to define biocompatibility as "the ability of a given material to perform with an appropriate host response in a specific situation".

Before outlining the relationship between physico-chemical properties, biocompatibility and applications, it is important to recall the key parameters which may be used to describe this ability in order to formulate a more accurate definition.

First, the vast majority of chemical or biological reactions between a given material and an organic medium occur at the interface. One should consider at this level a number of highly complex interactions which may be grouped under four phases of increasing order of magnitude; each phase corresponds to a biological response of an intensity which correlates directly with the degree of biocompatibility of the material concerned:

a. initial physical, chemical and biochemical reaction between the surface of the biomaterial and the biological system;

b. modification by the biological environment of certain physico-chemical properties of the surface of the material;

c. development of a local biological response in the immediate vicinity of the biomaterial;

d. dissemination of this local response throughout the entire body.

4.2 Biocompatibility of silicones

The biocompatibility of silicones is a direct consequence of the molecular structure of dimethylsiloxane (table 4). From a toxicological standpoint, the dimethylsiloxane chain is non-cytotoxic. This is a major advantage for the silicones, since their purity, acquired during synthesis, is not compromised by the use of additives (plasticisers, anti-oxidants). Their relative chemical inertia and thermal stability render them non-biodegradable, and they may thus be readily sterilised with ethylene oxide or steam. Their very open molecular structure enhances permeability to numerous molecules, in particular to oxygen and steam. Their low surface energy reduces molecular and cellular adhesion, and their hydrophobic nature limits absorption of water. The elasticity of the elastomers reduces tissue stress.

4.3 Regulatory background to biomaterials

4.3.1 Biocompatibility testing

The existing directives chiefly comprise two officially recognised documents: ISO 10993-1 and Tripartite Guidance. To these may be added the pharmacopoeial tests of USP XXIII as well as some tests recommended by the ASTM (American Society for Testing and Materials).

a. ISO 10993-1
This is an international standard developed in 1992 by the International Organisation for Standardisation (ISO). It comprises of a basic document entitled "Guidance to Selection of Tests". This document constitutes a single section of a total of eighteen parts describing tests relating to various biological fields.

The ISO standard divides medical devices into three classes according to the type of contact with the human body: surface, externally communicating, or implantable. These first three classes are subdivided into three further categories according to duration of contact: limited (< 24 hours), prolonged (between 24 hours and 30 days), and permanent (>30 days).

b. Tripartite Guidance
This American standard is a guideline developed in 1986 by the Tripartite Subcommittee for Medical Devices, representing the regulatory bodies of the United States, Canada and the United Kingdom.

Like the ISO, the Tripartite Guidance distinguishes three kinds of contact: external, externally communicating, and internal. Devices are also classified into three categories according to duration of contact: transient (< 5 minutes), short-term (between 5 minutes and 29 days), and long-term (≥ 30 days).

Although the Tripartite Guidance provides a more extensive series of tests than that of the ISO, both documents are quite similar. They comprise of guidelines for a given application which can then be adapted according to the legislation of the country concerned. Protocols themselves are to be drawn up by the supplier of the starting material or by the final user.

c. USP XXIII
The main interest of the USP is that it provides a set of protocols which are recognised as references, with a series of tests allowing a classification of materials into six different categories.

d. ASTM
As with the USP, the tests described by the ASTM have been developed consensually, and for this reason they are often used as references. These tests generally concern the physical properties of the materials used, but certain biochemical tests are also described.

4.3.2 European directive concerning medical devices (93/42/EEC)

The objective of this directive is to harmonise conditions for marketing and use of medical devices so as to ensure the protection of the user on the same basis throughout the European Community.

Appendix IX of the directive classifies medical devices according to various potential risk factors: invasive or non-invasive, active or non-active, implantable or non-implantable. As a function of the combination of these factors, devices are divided into four classes (I, IIa, IIb and III) which correspond to increasing degrees of exposure.

Class-I devices can be placed on the market under the sole responsibility of the manufacturer, following assessment of their conformity. The other three classes require various types of notification procedures regarding the regulatory bodies.

4.4 Review of existing biomaterials applications

4.4.1 Biomaterials applications

Examination of the classification introduced by the ISO and Tripartite Guidance standards reveals the versatility of silicones, which are present in all categories:
- direct contact with healthy skin (oxygen masks, teats for babies' bottles);
- temporary contact with body fluids (tubes for extracorporeal circulation [ECC] in heart surgery and dialysis, drains and catheters);
- prolonged or permanent contact with the body (joint prostheses, contact lens, insulation coating for leads and circuits, and protective sheaths for pacemakers).

4.4.2 Pharmaceutical applications

The diversity of the existing silicone products allows them to be used in most areas of pharmacology:
- manufacturing aids (lubricants, tubing for transfer of liquids);
- inert pharmaceutical excipient (glidants for powders, soft capsule shells);
- active pharmaceutical excipient (development of sustained-release formulations);
- active principle (antiflatulent fluids or emulsions, both with and without antacids).

4.5 The notion of bioperformance

As previously stated, every biomaterial is potentially perfectible, even when the target use is a specific and recognised application. This is even truer where responses critical to the well-being of the beneficiary are involved; a host response induced by the biomaterial will be more readily accepted by users when there is a high benefit-risk ratio.

Moreover, the regulatory framework concerning evaluation of the biocompatibility of a biomaterial comprises only recommendations on the selection of types of tests for which no precise protocols have been drawn up. Consequently, a number of materials recognised as "biocompatible" for a specific usage and marketed as such may nevertheless have very different biocompatibilities, notably as regards clinical consequences. There is thus a place for biomaterials whose "bioperformance" might still be improved in at least two ways:

- suitability for use in widely divergent biological applications while still maintaining biocompatibility: the silicones provide an interesting response to this first criterion, as discussed in paragraph 4.4.
- further reduction of the body's response in terms of "pure biocompatibility" in a given situation, resulting in improved patient comfort.

In order to demonstrate bioperformance as encapsulated in this latter criterion, Dow Corning recently carried out a comparative study of the following four types of tubing, each representing materials currently used for ECC during heart surgery: platinum-catalysed silicone, silicone produced with initial peroxide catalysis, a PVC and a heparinated PVC.

The evaluation methodology used in this study included static and dynamic *in vitro* tests, as well as *in vivo* tests, in order to determine whether there were any clinically discernible and correlated differences (12). To this end, pertinent biological parameters were selected for each of the blood systems known to be involved in the inflammatory syndrome commonly occurring in patients following ECC during heart surgery. The biological fields studied were: the coagulation and fibrinolysis cascades, the complement system and the kinin-kallikrein system. After interpretation, the results were as follows [13,14,15,16,17]:

4.5.1 Leukocyte activation

Under static *in vitro* conditions, a leukocyte adhesion test revealed decreased cellular adhesion after five and fifteen minutes, indicating a lower degree of leukocyte activation for platinum-catalysed silicone. Under *in vivo* conditions, expression of membrane receptors CD11 and CD18 was less marked with the two types of silicone tubing than with the PVC ones.

4.5.2 Coagulation and fibrinolysis cascades

Under dynamic *in vitro* conditions, the adhesion of fibrinogen to the surface of the material was significantly less rapid for the two silicones. Under *in vivo* conditions, increase in platelets and in $\alpha 2$ antiplasmin, both indicators of inflammatory syndrome, was significantly lower for the two types of silicone tubing three days post surgery.

4.5.3 The complement system

Under *in vitro* conditions, the decrease in CH_{50}, an overall indicator of activation of the complement system, was significantly lower for the two silicone tube after two hours.

The main conclusion of this study is that the use of silicone tubes for ECC in heart surgery results in less marked inflammatory syndrome in patients during the post-operative period.

5. Conclusion

By virtue of their structure, the polydimethylsiloxanes exhibit unique properties, especially at the surface and the interface levels. Moreover, their intrinsic purity and favourable toxicological profile make them the candidates of choice for many different medical applications. Regarding the environment, current data indicates that the silicones do not accumulate in our environment, and that their decomposition does not result in toxic waste. Finally, as regards comparative biocompatibility which takes into account patient comfort, the silicones offer substantial benefits, as demonstrated by the study of tubings used during heart surgery.

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