



# **Silicones in Pharmaceutical Applications**

André Colas, Dow Corning

***DOW CORNING***



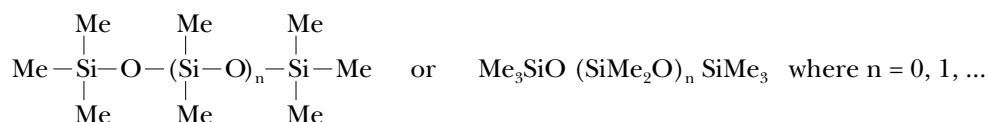


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## 1. Introduction

The name silicone encompasses a large number of compounds based on polydialkylsiloxanes; amongst them, the most common are the trimethylsilyloxy-terminated polydimethylsiloxanes of the structure:



These are linear polymers, liquid even at very high molecular weights.

Numerous other structures can easily be obtained, either by substitution of methyl groups by other groups like  $-\text{CH}=\text{CH}_2$ ,  $-\text{H}$ ,  $-\text{CH}_2\text{CH}_2\text{CF}_3$  or by replacing some of the  $\text{Me}_2\text{SiO}_{2/2}$  chain units with  $\text{MeSiO}_{3/2}$  or  $\text{SiO}_{4/2}$  units where the silicon is substituted with 3 or 4 oxygens to give non-linear branched structures <sup>(1)</sup>. The preferred polymers for pharmaceutical applications are the ones essentially substituted by methyl groups.

## 2. Silicone Preparation

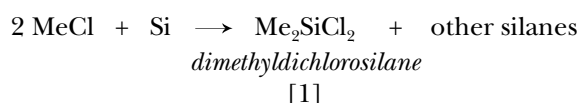
The silicones used in pharmaceutical applications are of 3 kinds: polymers, elastomers or pressure sensitive adhesives.

### 2.1 Polymers synthesis

Polydimethylsiloxanes polymers are prepared by the following 3 steps synthesis <sup>(1)</sup>.

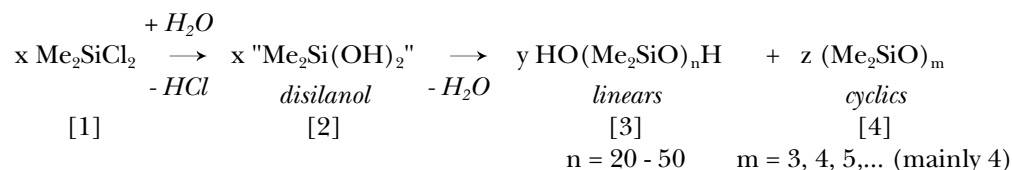
#### 2.1.1 Dimethyldichlorosilane synthesis

The dimethyldichlorosilane is isolated by distillation after the reaction between methyl chloride with silicon:



#### 2.1.2 Dimethyldichlorosilane hydrolysis

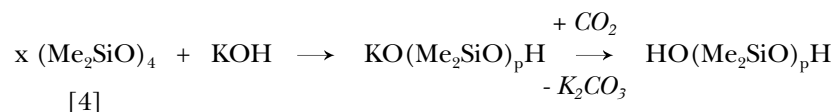
The Si-Cl bond is highly polarised and prone to nucleophilic attack. In presence of water, the attack of the 2 Si-Cl bonds in the dimethyldichlorosilane [1] leads to the formation of a dimethyldisilanol [2], which is unstable and readily condenses, intermolecularly, to give linear oligomers [3]. Small linears can also condense intramolecularly to give cyclic oligomers [4]:



Note that the HCl released is recycled by reaction with methanol to produce the methyl chloride used in the first step.

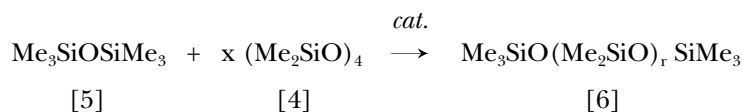
### 2.1.3 Octamethyltetracyclosiloxane polymerisation

Silicone polymers for pharmaceutical applications are preferably manufactured from cyclic oligomers, e.g. the octamethyltetracyclosiloxane  $(\text{Me}_2\text{SiO})_4$  [4] rather than linear, as the octamethyltetracyclosiloxane can be isolated by distillation and therefore with a high level of purity. The ring opening polymerisation is catalysed by bases e.g. KOH which is neutralised at the end of the reaction with  $\text{CO}_2$ . The  $\text{K}_2\text{CO}_3$  formed can be eliminated by filtration:

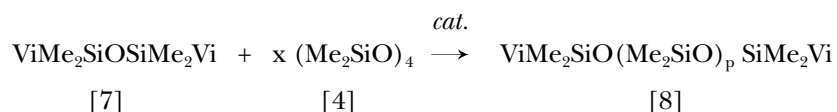


to give hydroxy terminated polydimethylsiloxanes.

This polymerisation can be conducted in presence of hexamethyldisiloxane [5], which will act as a chain endblocker to give trimethylsilyloxy terminated polymers [6]:



or in presence of divinyltetramethyldisiloxane [7] to give vinyl dimethylsilyloxy terminated polymers [8]:

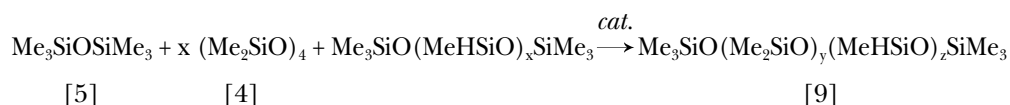


which will be used to prepare silicone elastomers.

The above polymers display a distribution of molecular weight around an average mass, depending on the amount of chain endblocker. Moreover, all these reactions are equilibrium reactions during which a certain quantity of oligomers, e.g. cyclics, is formed. The most volatiles will essentially be removed under vacuum at elevated temperatures. This explains why all silicones contain a certain amount of residual volatile oligomers.

The synthesis of silicone polymers is characterised by the high level of purity, which can be achieved in their preparation. The starting monomer, the dimethyldichlorosilane [1], is purified by distillation and is extremely reactive (strictly speaking, there is no residual monomer); after hydrolysis, the octamethyltetracyclosiloxane [4] is isolated by distillation before further polymerisation; the reactions used do not involve organic solvents or heavy metals; the catalysts used are strong bases or strong acids which are easily eliminated thanks to the high hydrophobicity of silicones. These advantages allow maximising the purity of silicones.

Using oligomers that are substituted by groups other than methyl, it is possible to prepare copolymers such as:



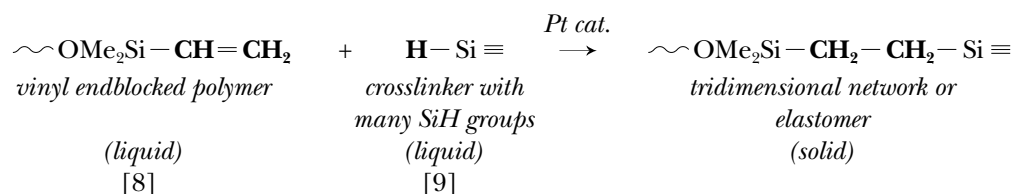
or polydimethyl-methylhydrogensiloxane [9], which can be used to prepare silicone elastomers (see further).

## 2.2 Elastomer manufacture

The polydimethylsiloxanes, very flexible with a very low glass transition temperature ( $T_g = 146 \text{ K}$ )<sup>(2)</sup>, are easily crosslinked into 3-dimensional networks or elastomers by the formation of covalent bonds between adjacent chains<sup>(1)</sup>.

Different crosslinking reactions can be used: condensation with the liberation of a by-product; initiation with a peroxide with the formation of peroxide by-products.

For pharmaceutical applications, crosslinking by addition is preferred using vinyl endblocked polymers [8] and polymers (or crosslinkers) carrying many SiH groups [9] as shown below:



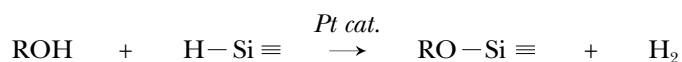
where  $\sim$  represents the remaining part of the polymer and  $\equiv$  the other Si valences.

This addition reaction requires very low levels of a platinum complex as catalyst (5 - 20 ppm as Pt) and does not generate any by-products, hence its advantages in pharmaceutical applications<sup>(3)</sup>. Using a polymer carrying many SiH groups, many vinyl endblocked chains can be crosslinked together. A large number of commercial products are available as ready-to-use 2-part elastomers. Usually, the part A contains the vinyl endblocked polymer and the platinum catalyst and the part B contains the vinyl endblocked polymer and the polymer carrying the SiH groups. These 2 parts are stored separately before use and the crosslinking reaction will only start upon mixing the parts A and B in a defined ratio, usually 50:50. The reaction can take place at room temperature or be heat accelerated to crosslink the elastomer in a few minutes after extrusion, injection or moulding. Heat curable 1-part materials have also appeared recently on the market; yet if this eases the handling prior to use (no mixing), these 1-part materials have a very limited shelf life.

Some precautions are required with this addition reaction as platinum catalysts can be poisoned by many nucleophilic substances possibly present as contaminants like amines or sulphur compounds (containers, gloves, ...) and which can form with the platinum catalyst more stable complexes, inactive as catalyst. This leads to an inhibition of the addition crosslinking reaction.

Silicone elastomer properties are strongly dependent of the structure of the polymer and crosslinker used. Hard elastomers will be obtained when the crosslinking density is high. On the contrary, a low crosslinking density will lead to soft and more plastic elastomers. An amorphous silica with a high specific surface area is normally included in the formulation of silicone elastomers to improve their mechanical properties.

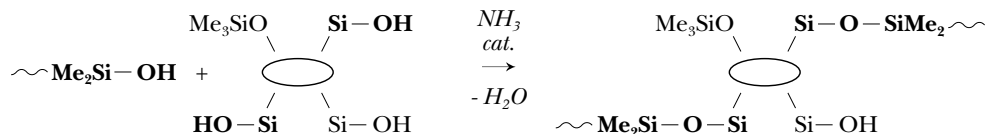
Other ingredients can also be used, like an alcohol capable to react with SiH groups to liberate hydrogen according to:




This reaction is catalysed by the same platinum complex as the addition reaction: as the hydrogen is evolved at the same time as the crosslinking take place, this leads to silicone elastomeric foams<sup>(4)</sup>. This is used to cast a silicone foam dressing in deep cavity wounds.

### 2.3 Pressure sensitive adhesives preparation

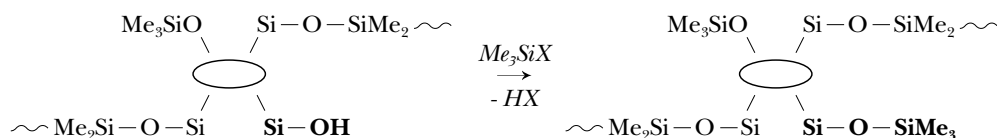
All the above polymers are linear but it is also possible to prepare branched silicone structures which behave as pressure sensitive adhesives (PSA). These are prepared from silylated polysilicate resins like  $(\text{Me}_3\text{SiO}_{1/2})_x(\text{SiO}_{4/2})_y$ , a silicate with trimethylsilyloxy groups and usually containing some silanol groups. These silanol groups can be condensed with hydroxy terminated polydimethylsiloxanes in presence of ammonia as catalyst according to <sup>(5)</sup>:



where  represents the polysilicate part,  $(\text{SiO}_{4/2})_x$ , of the resin.

The reaction product is made of a distribution of chains linked to resin particles and exhibits a pressure sensitive adhesive behaviour as a function of the relative ratio between the amount of polymer and resin. The polymer chains ensure wetting of the substrate surface because of their low surface tension (see further) whilst the resin will dictate the visco-elastic behaviour.

However, after condensation, the product still contains some residual SiOH groups. These are susceptible to further condensation, particularly in presence of a basic active drug, e.g. when the latter contains amine functions. To avoid this reaction, which would completely crosslink the PSA and reduce its adhesive properties, the residual SiOH groups are silylated <sup>(5)</sup> to prepare "amine resistant" PSA:



## 3. Physico-Chemical Properties

### 3.1 Intramolecular interactions

Polydimethylsiloxanes are characterised by strong chemical bonds, not easily broken by homolytic scission because of their polarity <sup>(1)</sup>. Only strong acids or strong bases are capable to depolymerise the siloxane chain. As a result, the polydimethylsiloxanes are not very susceptible to oxidation or thermal degradation and they can be sterilised by heat.

While the siloxane backbone is made of very polar Si-O-Si bonds, the polydimethylsiloxanes are actually very hydrophobic as the methyl groups shield the polar backbone, a feature enhanced by the very low energy of rotation around a  $\text{Me}_2\text{Si}-\text{O}$  bond (rotation barrier = 3.3 kJ/mol) which allow polydimethylsiloxanes to reduce their surface energy and their surface tension by exposing a maximum number of methyl groups <sup>(2)</sup>. The polydimethylsiloxane low surface tension property is used to prepare antifoam agents.

### 3.2 Intermolecular interactions

Because of its low rigidity, the siloxane backbone allows the methyl groups to be easily exposed to the outside and as a result, the polydimethylsiloxanes are characterised by low intermolecular interactions. This is demonstrated in several ways:

- even at high molecular weight, the polydimethylsiloxanes are liquid;

- the polydimethylsiloxanes properties are not very temperature dependent;
- the polydimethylsiloxanes, compared to other polymers, are very permeable to the diffusion of various substances, gases or active drugs (table 1).

**Table 1:** Comparison of the polydimethylsiloxane permeability with other polymers (6, 7, 8).

Type	Permeability to O <sub>2</sub> (cm <sup>3</sup> .cm)/(s.cm <sup>2</sup> .kPa) x 10 <sup>-7</sup>	Permeability to CO <sub>2</sub> (cm <sup>3</sup> .cm)/(s.cm <sup>2</sup> .kPa) x 10 <sup>-7</sup>	Relative permeability to Progesterone
Polydimethylsiloxane	79	405	100
Polyethylene	0.002	0.007	0.1
Polytetrafluoroethylene	0.001	0.003	0.1

## 4. Silicone Analysis

Among the many analytical methods used to characterise silicones, only a few and the more relevant to pharmaceutical applications will be presented here:

### 4.1 The Pharmacopoeia

Silicones appear in many compendia (table 2).

**Table 2:** The silicones in the European Pharmacopoeia (EP), United States Pharmacopoeia (USP®) and United States National Formulary (NF).

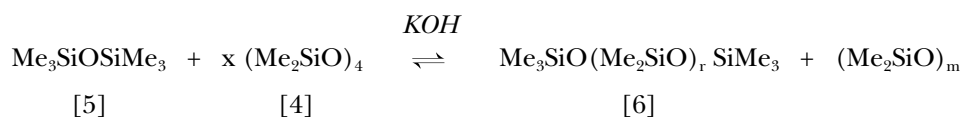
Compound	Typical applications	References
Dimethicone	Anti-foam, anti-flatulent	EP, NF
Simethicone*	Anti-foam, anti-flatulent	EP, USP
Simethicone emulsion	Anti-foam, anti-flatulent	USP
Cyclomethicone	Volatile carrier	NF
Silicone oil as lubricant	Lubricant	EP
Silicone elastomer for closures and tubing's	Closures, tubing's	EP

(\*) a blend of Dimethicone and silicon dioxide.

For silicone elastomers, the European Pharmacopoeia analytical methods include, amongst others, a product identification by IR spectroscopy and an evaluation of their purity. Yet, beside the heavy metal quantification, the proposed methods like the “substances soluble in hexane” or the “volatiles” provide for an overall quantification, but not for a specific measure of the low molecular weight residual impurities, like the different types of polydimethylcyclsiloxanes [4] remaining after polymerisation.

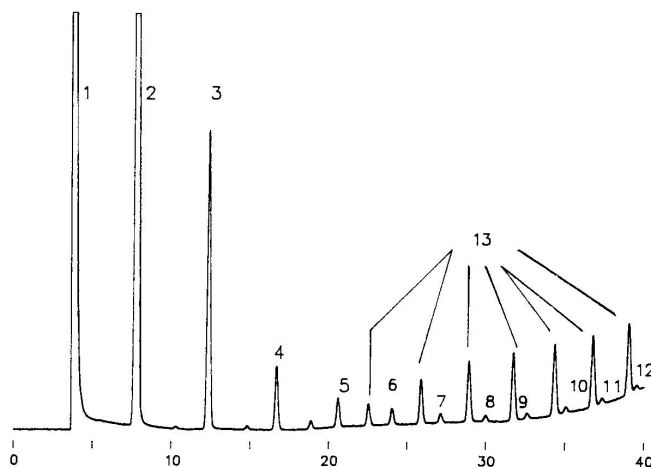
### 4.2 Polymer composition analysis

Because of their low intermolecular interactions and their high thermal stability, silicone polymers are easily analysed by chromatography, possibly after silylation if hydroxy groups are present. This allows quantifying the low molecular weight oligomers, which are always present in silicone polymers. As mentioned above, polymerisation reactions lead to the formation of two molecular weight distributions, polymers around a degree of polymerisation *r* and cyclics around a degree of polymerisation *m*, the lowest molecular weight species being eliminated by “stripping” under vacuum at elevated temperature:

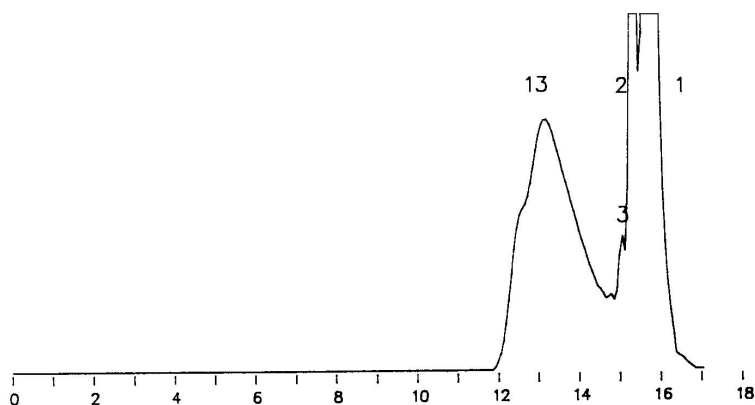


Various techniques can be used to evaluate the polymers and to identify and quantify the lowest molecular weight species present: GC, GPC or SFC (figure 1).

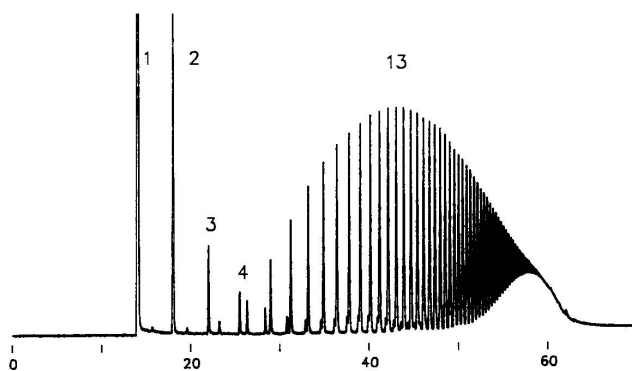
**GC**



**GPC**



**SFC**



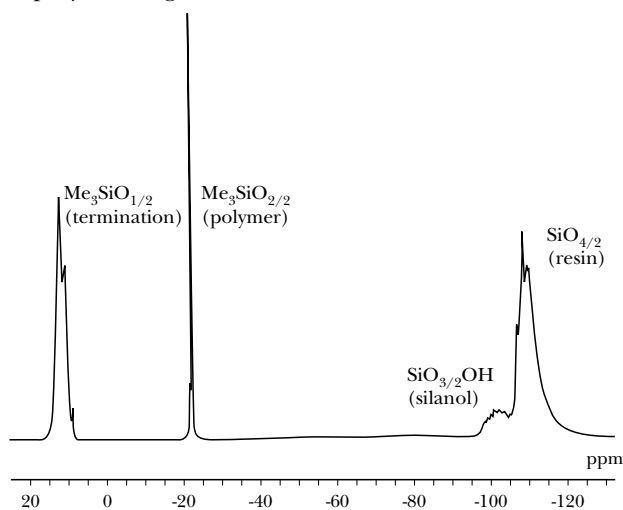
**Figure 1:** Comparison between different chromatographic techniques with a trimethylsilyloxy terminated polydimethylsiloxane<sup>(9)</sup>: peak 1 to 12 = cyclics [4] ( $m = 4$  to 15) and peak 13 = polymer [6].

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### 4.3 Polymer structural analysis

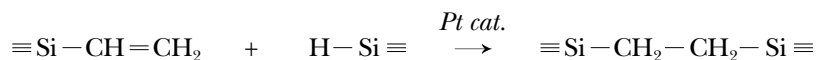
Because of its high relative abundance, the  $^{29}\text{Si}$  ( $I=1/2$ ; 4,7 %) allows the study of the structure of silicone polymers by NMR analysis. The interpretation is eased by large chemical shifts. This allows identifying and studying the distribution of various groups within a copolymer (figure 2).



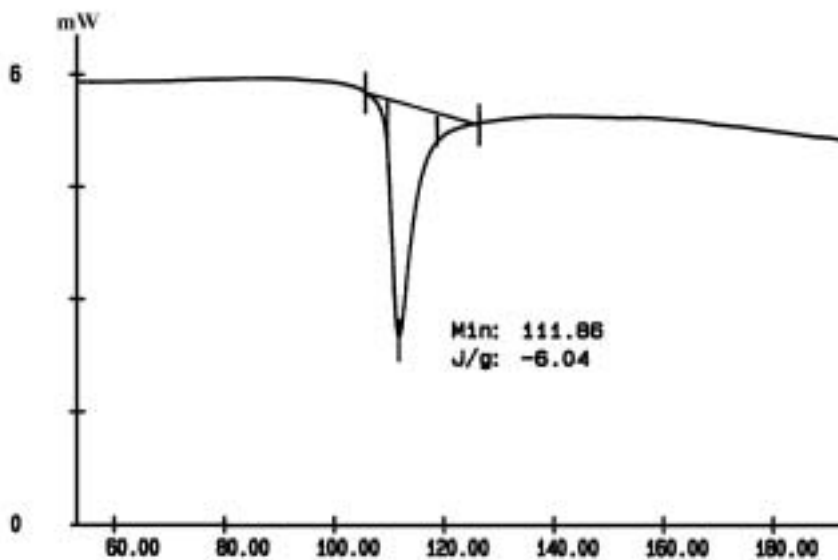
**Figure 2:**  $^{29}\text{Si}$  NMR spectrum of a pressure sensitive adhesive (PSA) <sup>(10)</sup>.

### 4.4 Thermal analysis

The addition reaction used to crosslink silicone elastomers:



is characterised by an exotherm ( $-\Delta H = 120 - 170 \text{ kJ/mol}$ ). This allows the use of the differential scanning calorimetry to characterise the crosslinking and optimise the elastomer formulation based on the temperatures corresponding to the onset of cure or the maximum cure rate (figure 3).



**Figure 3:** Differential scanning calorimetry of the reaction between polymers with SiVi groups [8] and with SiH [9] groups in presence of a Pt catalyst <sup>(11)</sup>.

## 5. Toxicology and Biocompatibility

The most widely used silicones are the polydimethylsiloxanes,  $\text{Me}_3\text{SiO}(\text{SiMe}_2\text{O})_n\text{SiMe}_3$  [6], with viscosities between 10 to 100,000 mPa.s. These have not shown toxicity during administration via typical exposure routes. Due to their high molecular weight, they are not absorbed in the G.I. tract and are excreted without modification, nor are they absorbed through the skin <sup>(12)</sup>. In vitro studies have not indicated mutagenic effects <sup>(12)</sup>. Repeated oral or cutaneous dosages have not indicated effects on different species <sup>(12)</sup>. Inhalation of aerosols of oily or fatty-type materials, including silicones, into alveolar regions of the lung may result in physical disturbances of the lining of the lung with associated effects <sup>(13)</sup>.

Lower molecular weight siloxanes are frequently used due their volatility and generally dry skin feel. These can include linear as well as cyclic siloxanes.

The lowest molecular weight linear material is hexamethyldisiloxane,  $(\text{Me})_3\text{SiOSi}(\text{Me})_3$  (HMDS) [5], which has a viscosity of 0.48 mPa.s. HMDS has generally shown little effects toxicologically, though recent data has indicated slightly earlier incidence of testicular tumors in male rats exposed to high levels of material via inhalation; the relevance of this effect to humans is not yet known <sup>(14)</sup>. Other linear molecules of three, four, or five siloxane units [6] do not exhibit toxic effects though the data is limited for long-term exposure <sup>(15)</sup>. The materials have very limited absorption via typical exposure routes. Like the higher molecular weight polymers, the low molecular weight linears are not mutagenic, irritating, or acutely toxic.

Cyclic siloxanes,  $(\text{SiMe}_2\text{O})_n$  [4] are widely used in skin care products, in particular the four ( $n = 4$ ) and five ( $n = 5$ ) members cyclics. None of these materials have exhibited toxicity except for the four members cyclic ( $n = 4$ ), which has shown a reduction in litter size with a reduction of implantation sites in the uterus of exposed female rats; this effect is not expected to occur in humans <sup>(16, 17)</sup>. These effects were not measured in the five ( $n = 5$ ) members or other cyclic siloxanes <sup>(18)</sup>.

The innocuity of silicones explains their numerous applications where a prolonged contact with the human body is involved: on textile fabrics, in cosmetics, in contact with food and in medical applications. Silicone elastomers are used in many class II or III medical devices regulated by the European Medical Devices Directive such as tubing for extra-corporeal circulation used during cardiac surgery, hydrocephalic shunts or pacemakers leads. Their excellent biocompatibility is partly due to the low chemical reactivity displayed by silicones, their low surface energy and their hydrophobicity <sup>(2)</sup>.

## 6. Epidemiology

While the legal controversy regarding silicone gel-filled implants continues in the United States (US), these medical devices are widely available worldwide and are available with some restriction in the US where they have been used since the early 1960's. The controversy in the 1990's initially involved breast cancer, then evolved to autoimmune connective tissue disease, and continued to evolve to the frequency of local or surgical complications such as rupture, infection or capsular contracture. Epidemiology studies have consistently found no association between breast implants and cancer, including breast cancer <sup>(19-24)</sup>. In fact, some studies suggest that women with implants may have decreased risk of breast cancer <sup>(23, 24)</sup>. The research on autoimmune or connective tissue disease has also been remarkably consistent and concludes there is no causal association between breast implants and connective tissue disease <sup>(25-30)</sup>.

## 7. Silicones and the Environment

High molecular weight polydimethylsiloxanes are used in many pharmaceutical applications but in relatively small quantities compared to the amounts used in other industrial applications. Silicone polymers in anti-flatulents and silicone elastomers in

tubings to transport various fluids are probably the largest pharmaceutical applications for polydimethylsiloxanes. The environmental fate and effect of silicones will depend to a large extent on the physical form of the material.

Silicone elastomers (solid) in the form of tubings have a negligible impact on the environment. For safety reasons, they are incinerated as other clinical wastes. Incineration converts polydimethylsiloxane elastomers to inorganic constituents, carbon dioxide, water and amorphous silica<sup>(31)</sup>. As the polydimethylsiloxanes contain no halogens, no toxic halogenated species, such as chloro- or bromodibenzodioxins are formed.

Silicone polymers (liquid) used in anti-flatulents will ultimately become part of the liquid waste discharged to municipal treatment plants. Even high concentrations of polydimethylsiloxanes in effluent cause no observed effects on waste water treatment processes; extensive studies show that more than 95 % silicones are removed from effluents by adsorption onto the sludge and that the silicone concentration in these effluent streams is reduced to a very low level, at or below the level of detection (5 µg/l)<sup>(32, 33)</sup>. Adsorption is favoured by the low water solubility of polydimethylsiloxanes.

The subsequent fate of the silicones will depend on the fate of the sludge. If incinerated, the silicones degrade as indicated previously. The other principal outlet for sludge is use as a soil conditioner or amendment. In mesocosm studies, the application of sludge-bound polydimethylsiloxane to soil caused no observed adverse effects on crop growth or soil organisms<sup>(34)</sup>. With radio-labelled compounds, little or no uptake of radioactivity into the plants was observed, which is consistent with animal studies, which show that high molecular weight polydimethylsiloxanes are too large to pass through biological membranes into either crops or animals. Extensive studies ranging from small scale laboratory tests<sup>(35, 36)</sup> to mesocosm<sup>(34, 37)</sup> show that sewage-sludge bound polydimethylsiloxanes degrade in soils as a result of contact with clay minerals. These clays will act as catalysts to depolymerise the siloxane backbone<sup>(35)</sup>, a reaction favoured by the polarity of the molecular chain  $(-\text{SiO})_n-$  and its susceptibility to heterolytic scission<sup>(1)</sup>. The primary degradation product, regardless of the polydimethylsiloxane molecular weight is dimethylsilanol,  $\text{Me}_2\text{Si}(\text{OH})_2$ <sup>(36)</sup>. Depending on the soil type, this undergoes further degradation either in the soil via biodegradation<sup>(38)</sup> or evaporates into the atmosphere<sup>(39)</sup> where, by analogy to trimethylsilanol, it is expected to be degraded by oxidation via reaction with hydroxyl radicals<sup>(40)</sup>. In both cases, there is conversion to inorganic constituents, carbon dioxide, water and amorphous silica.

Low molecular weight silicones display a different environmental profile. As a consequence of their very high volatility, they readily evaporate into the air, where they degrade as a result of reaction with hydroxyl radicals in the presence of sunlight. They are not however biodegradable, and as a consequence of this, and the fact that in a sealed system, they have the potential to bio accumulate, the Oslo Paris Commission (OSPAR), which is concerned with the discharge of man-made substances into the marine environment, have identified hexamethylsiloxane (HMDS) as a potential "Priority Hazardous Substance". The European Silicone Industry Association (CES) is therefore conducting a risk assessment on HMDS using the EU model (EUSES). However as both modelling data and environmental monitoring do not indicate any significant inputs into the marine environment, the European Silicone Industry is confident of a favourable outcome from the risk assessment.

## 8. Silicones in Pharmaceutical Formulations

More than 358 registered products containing silicones could be retrieved using CD Rom or internet databases such as the *PDR*<sup>®</sup> (USA), *Rote Liste*<sup>®</sup> and *Gelbe Liste* (Germany), *MediaVidal*<sup>®</sup> and *BIAM* (France), *BNF*<sup>®</sup> (UK), *Kompendium* (Switzerland) and *AGIM*<sup>®</sup> (Belgium). Searching was complex because silicones could be found in drug compositions under compendia's names (Dimethicone or Simethicone) as well

as under many other names like silicone, siloxane, methylsiloxane, polydimethylsiloxane or even trademarks such as *Silastic*<sup>®</sup>. In many instances silicone (a polymer) was also confused with silicon (a metal) or silica (an inorganic compound). Some databases were more friendly than others allowing for “word search” as in the *PDR* or for “list of non active substances” as in the *BIAM*. The presence of silicone was thus found in many registered drugs and noted in some very familiar ones like *Augmentin*<sup>®</sup>, *Maalox*<sup>®</sup>, *Prozac*<sup>®</sup>, *Tagamet*<sup>®</sup>, *Vicks VapoSteam*<sup>®</sup> to name but a few.

Silicones are used as actives, as Dimethicone or more often as Simethicone (a blend of Dimethicone and silicon dioxide), but surprisingly overall more often as excipients (table 3).

**Table 3:** Silicone occurrence as actives or excipients and physical form in registered drugs expressed as percentage of the 358 products identified in above databases <sup>(41)</sup>.

Silicone in composition	%	Form	%
As active	24	Simethicone	13
		Dimethicone	11
As excipient	70	Simethicone	14
		Simethicone emulsion	11
		Dimethicone	10
		Elastomer	6
		Silicone Oil	5
		Silicone Polymer	5
		Others	19
Unknown	6		

While the purpose of the silicones as actives is well documented as antifoam in anti-gas or anti-acid formulations, the purpose of silicones as excipients is more difficult to determine. Information on excipients is still limited as of today and, in some cases, it was not even possible to identify the physical form of the silicone used. Some information could yet be collected indicating that silicones are used as excipients in pharmaceutical formulations for siliconisation (lubrication of syringe barrels, pistons, needles or lubrication of stoppers), as skin adhesives (drug permeable), as elastomers (drug release control membrane), as release liner coatings for transdermal patch (release coating), and, in skin topicals, as polymers, volatiles or not, or as copolymers to carry actives or to improve spreading and aesthetic qualities. The latter is not surprising as silicones are widely used in Personal Care products, with around 60 % of today’s skin care products containing silicones <sup>(42)</sup> where they are recognised as safe, and known to provide for a pleasant “silky touch” non-greasy and non-staining feel.

It is also worth noting that a substantial number of registered products contain silicones that are not described in any Compendia, e.g. methylpolysiloxane, silicone for powder treatment, silicone or fluoro silicone for polyester film coating, silicone copolyol, HMDS, *Silastic*<sup>®</sup>, silicone wax, ...: in these registered product formulations, the benefits brought by silicones were obviously offsetting the regulatory hurdle to file a drug formulation with a new excipient.

## 9. Silicones as Antifoams in Pharmaceutical Formulations

Dimethicones and Simethicones are declared as actives and used as antifoams in numerous anti-flatulent or anti-acid formulations, even if their efficacy has been questioned in some indications <sup>(43)</sup>. Overall, this is the largest single application for silicones in registered products (64 registered products or 16 % of the ones retrieved in the above databases): among them *Maalox*<sup>®</sup>, *Mylanta*<sup>®</sup> and *Gel de Polysilane-Midy*<sup>®</sup>.

Silicones in these products help to suppress the formation of foam in the stomach without modifying the gastric pH <sup>(44)</sup>. This is not surprising as silicones, with their low surface tension (and in particular when compounded with silicon dioxide) are known to

destroy foams in many applications, e.g. in petrol, paper pulp or food processing. In pharmaceutical formulations, while considered as actives, the mode of action is physical as the polydimethylsiloxanes are not metabolised but excreted as such <sup>(12)</sup>. Silicones are often compounded with other anti-acid actives such as Al or Mg hydroxides, Mg or Ca carbonates. Simethicones and Dimethicones also appear in many other anti-acid or anti-flatulant formulations yet where the silicones are only declared as excipients and not as actives. Also declared as excipients, silicones appear in many liquid formulations like syrups as well as in effervescent tablets formulations, most likely either to control foaming during processing and filling operations or during use.

As actives, silicones are also used in diagnostic formulations to eliminate foam in the stomach during endoscopy or, in conjunction with barium sulphate, during X-Ray examination <sup>(45)</sup>.

## 10. Silicones as Excipients in Topical Formulations

After their use as antifoams (see above), the next largest application for silicones is in topical formulations. In the above databases, 36 products (10 % of the retrieved registered products) could be identified where silicones are used as excipients in topicals. Silicones were also declared as actives against acne in one product and for the prevention of skin ulceration around stoma in another, in the latter case possibly because NF grade Dimethicone is recognized as an active protecting the skin in OTC products (FDA tentative monograph 21 CFR Part 347).

The largest indication is for skin diseases, mainly as creams followed by gels and lotions for the treatment of acne, fungal diseases or psoriasis. The non-comedogenic nature of silicone probably accounts for their use in anti-acne formulations <sup>(45)</sup>. Other topical applications include contact with fragile mucosa in the treatment of haemorrhoids, anal dermatoses or itch relief as well as for the delivery of antibiotics in gynaecological capsules or creams.

When considering the type of silicones used, Dimethicones and Simethicones account for most of the occurrences yet some other specific silicones used as excipients could be retrieved in registered products using the above databases:

- Cyclomethicones [4], registered in *Diprolene*<sup>®</sup> (Schering Plough) or as decamethylpentacyclosiloxane (Me<sub>2</sub>SiO)<sub>5</sub> in the formulation *Dexeryl Crème*<sup>®</sup> (Pierre Fabre Santé); the exact purpose is not known, as for many excipients, but cyclomethicones are widely used in personal care because of their volatility, “aesthetic” and safety profile;
- Hexamethyldisiloxane [5]; recent work <sup>(46)</sup> shows that the hexamethyldisiloxane, Me<sub>3</sub>SiOSiMe<sub>3</sub> (Bp. = 100 °C), can be used as a volatile excipient in spray pump systems for topical applications, e.g. in combination with fungicides and was registered in *Pevaryl*<sup>®</sup> (Janssen-Cilag). The low surface tension of this disiloxane improves the coverage of the skin and possibly increases the bio-availability of the active drug. The advantage of this disiloxane, despite its flammability, is its very low heat of vaporisation, which, despite its rather high boiling point, allows the film to dry quickly;
- Stearyloxytrimethylsilane, CH<sub>3</sub>(CH<sub>2</sub>)<sub>17</sub>OSiMe<sub>3</sub>, a wax with occlusive properties but still with a pleasant silky feel as normally associated with silicones, registered in *Retinova*<sup>®</sup> (Roc - Johnson and Johnson);
- Dimethicone copolyol used in conjunction with Cyclomethicones in *Retin-A Micro*<sup>®</sup> (Ortho Dermatological - Johnson and Johnson), yet the exact structure of this silicone glycol copolymer cannot be determined from the databases used.

While the above silicones have certainly been used because of their biocompatibility and probably because of their aesthetic benefits, which is well known in personal care formulations, it is just becoming evident that silicones may also affect the bio-availability of actives.

The substantivity of actives on the skin can be increased by adding high molecular weight silicone polymers, linear or branched, which will allow a better cohesion of the formed film. These substantive agents can be combined with volatile silicones, such as hexamethyldisiloxane or cyclomethicones, reducing the blend viscosity and possibly leading to over-saturated solutions. Improved substantivity has been demonstrated for cosmetics products by attenuated total reflectance FTIR spectroscopy where it was shown that the substantivity of UV sunscreens on the skin was increased in presence of polydimethylsiloxane gums of very high molecular weight ( $M_w = 700,000$ ): the diving resistant sun cream <sup>(47)</sup>! It has now been shown that the use of high molecular weight silicone gum can also improve the substantivity on the skin of a pharmaceutical active, Ketoprofen, when dispensed from a silicone volatile-based spray <sup>(48)</sup>. After 8 hours, the presence of Ketoprofen could still be detected on the skin surface with formulations containing a silicone gum, while without it detection was not possible anymore after 6 hours. It is not clear yet if this occurred because abrasion resistance was improved or because the gum had an influence of the skin penetration rate, e.g. acting as a reservoir delaying penetration. Abrasion resistance was certainly improved: consecutive attempts, immediately after spraying, to remove the film from the skin with an adhesive tape indicated that the presence of gum made this more difficult and that the drug loaded film was more resistant to removal <sup>(48)</sup>. It is also known that the silicone gum on its own is very substantive: more than 25 % of it can still be quantified on the skin after 8 hours <sup>(49)</sup>. Interesting to note is that the improved substantivity was observed even at very low concentrations of silicone gum (1 to 3 % by weight) which allowed the viscosity to remain low enough to allow easy application by spraying without increasing the drying time unreasonably <sup>(48)</sup>.

Using different actives, trials on rat skin have indicated that the skin penetration rates and the compartmental distributions between the stratum corneum, the epidermis and the dermis can be affected by the presence of silicone gum in the applied formulation although too few actives have been evaluated so far to rationalise the results (table 4 and 5).

**Table 4:** Comparison of the penetration rates of different actives through hairless rat skin in Franz diffusion cells from silicone gum (2 % by weight) in silicone volatile formulations versus commercial products (without silicone) <sup>(49)</sup>.

Active	Cumulative amount after 24 h without silicone ( $\mu\text{g}/\text{cm}^2$ )	Cumulative amount after 24 h with silicone ( $\mu\text{g}/\text{cm}^2$ )
Ibuprofen	80	180
Econazole nitrate	0.7	0.5
Hydrocortisone	0.4	0.4

**Table 5:** Comparison of the compartmental distribution in hairless rat skin of different actives after 24 h from silicone gum (2 % by weight) in silicone volatile formulations versus commercial products (without silicone) <sup>(49)</sup>.

Active	Drug distribution for formulations without silicone (in % of initial drug load)			Drug distribution for formulations with silicone (in % of initial drug load)		
	str. corn.	epidermis	dermis	str. corn.	epidermis	dermis
Ibuprofen	1	0.2	0.3	1	0.2	1.5
Econazole nitrate	3.5	1	1	4	1	1
Hydrocortisone	0.2	2.5	0.5	7	2	0.8

While most silicones are hydrophobic and often used to formulate lipophilic drugs, low molecular weight OH endblocked fluids,  $\text{HO}-(\text{SiMe}_2\text{O})_n\text{-H}$  ( $n \sim 12$ ) [3], have been shown to dissolve hydrophilic actives like polyethyleneoxyalkylphenols, e.g. for the preparation of spermicidal condom lubricants <sup>(50)</sup>.

While polydimethylsiloxanes are highly permeable to moisture, some silicones display occlusive properties like the stearyloxytrimethylsilane wax (partially silylated stearyl alcohol) and yet retain the silky touch feel usually associated with silicones (table 6).

**Table 6:** Comparison of the occlusivity of oil-in-water emulsion made from Vaseline and/or stearyloxytrimethylsilane wax assessed by gravimetry of the water loss through gelatine membranes using the following formulations: oily ingredient: 20 %; silicone glycol copolymer emulsifier: 2 %; HMDS 10 %; EtOH: 10 %; water + 2 % NaCl: qsp<sup>(49)</sup>.

Oily ingredient	Occlusivity Power (%)
Vaseline emulsion	93.4
Vaseline / silicone wax 50 - 50 emulsion	84.7
Silicone wax emulsion	72.9

While silicone elastomers are solids, it is possible to prepare paste like products if the polymer crosslinking is carried out in the presence of a large amount of a non-reactive fluid, e.g. a volatile silicone. These products can be applied to the skin in large quantities while maintaining an exceptional feel. They are widely used in Personal Care products and it has recently been shown that they can be used as carrier for the release of actives<sup>(51)</sup>.

## 11. Silicones as Excipients in Controlled Release Devices

The controlled release of active drugs with polydimethylsiloxane goes back to the 60's. Today different registered products using silicone elastomers or silicone PSA's are commercialised:

- implants like the *Norplant*<sup>®</sup> (Leiras), a sub-cutaneous contraceptive implant releasing levonorgestrel for contraception over a 5 years period<sup>(52)</sup>;
- inserts like the *Estring*<sup>®</sup> (Pharmacia and Upjohn), a vaginal insert releasing 17- $\beta$  estradiol and used for the treatment of menopause symptoms<sup>(53)</sup>, or the *Mirena*<sup>®</sup> (Schering), an IUD releasing levonorgestrel for contraception;
- transdermal patches, like Nitriderm (Novartis), releasing nitroglycerine for the treatment of angina pectoris, *Durogesic*<sup>®</sup> (Janssen-Cilag) releasing Fentanyl for the treatment of chronic pain or *Vivelle-Dot*<sup>®</sup> (Novartis) releasing Estradiol for the treatment of menopause symptoms (HRT).

Not surprising, the actives involved in the above examples are all very potent at low doses so to allow delivery over a long period of time without having to design an oversized device.

In these devices, the active drug release is controlled by its diffusion through the silicone network which is possible thanks to the very high permeability of silicones to various actives, particularly when these are lipophilic and of low to medium molecular weight. Implants are particularly attractive when a low dose of the active is to be administered over a long period of time, that is when the drug is active at low concentrations and the need is chronic.

Compared to oral dosages, the degradation in the GI tract or by the liver is avoided with such controlled release devices. They also allow for a better treatment compliance and more comfort to the patient. Silicones are preferred in such applications, not only because of the simplicity to shape them by extrusion, injection or moulding and their crosslinking at low temperatures without by-products but also because of their stability and their outstanding biocompatibility.

There are 2 types of diffusion controlled release devices:

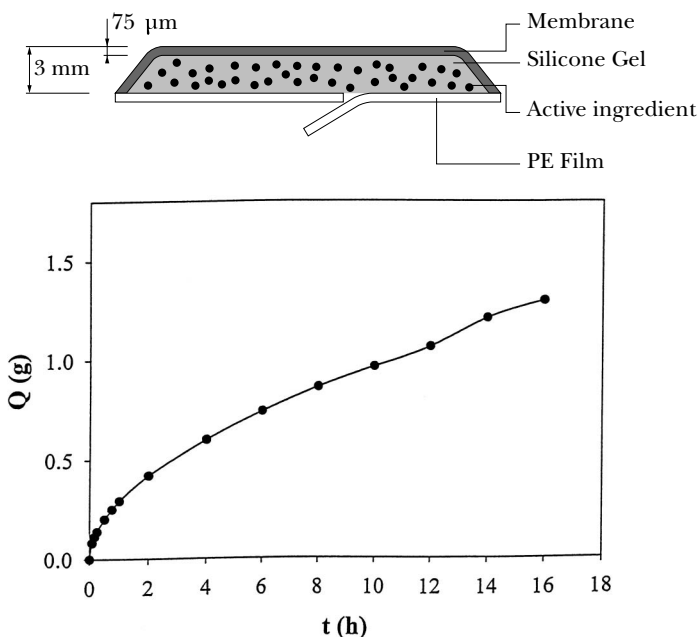
- matrix type devices, where the active is homogeneously distributed within the whole of the polymer making the matrix;

- reservoir devices (capsules) where the active is located in the centre of the device, creating a reservoir, and separated from the delivery location by a silicone membrane.

Both the matrix and the reservoir device contain an excess of active, e.g. as a solid, to ensure a release over a long period of time; yet they differ by the kind of associated release kinetic.

### 11.1 Matrix devices

In matrix devices, the active drug is homogeneously distributed in the whole of the device and will slowly be exhausted starting from the device's external surface, the surface which is in contact with the tissues. The release rate will slowly decrease with time, the active having to make a longer journey by diffusion to reach the external surface and the release location. This design has been developed for a topical dressing with an anti-inflammatory drug dispersed in a soft silicone adhesive elastomer: the dressing is extremely comfortable to wear and, because of the relatively high moisture vapour permeability of silicone, it does not create skin maceration (figure 4).



**Figure 4:** Matrix dressing in silicone adhesive elastomer loaded with an anti-inflammatory active and in-vitro release profile <sup>(54)</sup>.

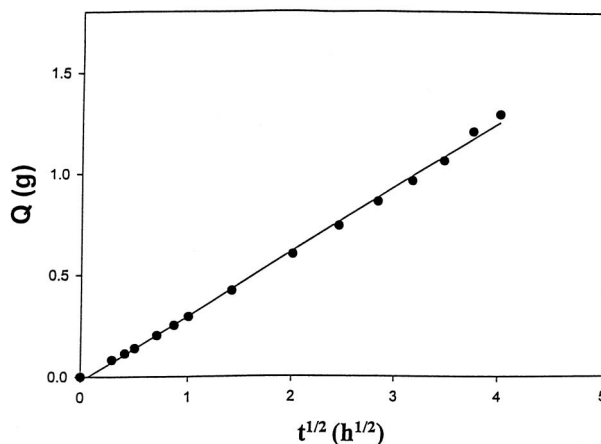
Applying Fick's law and assuming that the active does not build-up on the device external surface but is immediately taken away by the tissues (sink conditions), e.g. that it is weakly soluble in the polymer but highly soluble in solution, the quantity of released active is described by the following equation <sup>(55)</sup>:

$$Q = [ ( 2A - C_p ) C_p D_p t ]^{1/2}$$

- where:
- Q amount of active drug released per unit area;
  - A initial amount of active drug formulated into the polymer;
  - C<sub>p</sub> solubility of the active drug in the polymer;
  - D<sub>p</sub> diffusion coefficient of the active drug in the polymer.

In such device, the released amount is function of the active, its initial loading and its diffusion coefficient; the rate of release will slowly decrease with time: the kinetic order is one.





**Figure 5:** *In-vitro* release kinetic for an anti-inflammatory from a matrix dressing in silicone adhesive elastomer <sup>(54)</sup>.

The matrix type devices are interesting because of the simplicity of their design and ease of manufacturing but they are limited if a rigorous control of the active release rate is required.

## 11.2 Reservoir devices

In reservoir devices, the active is separated from the tissue by a silicone membrane, as in the vaginal ring (figure 6).

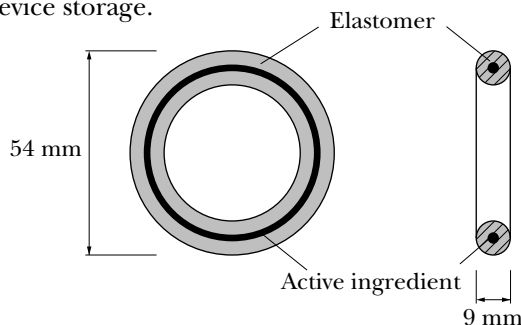
Applying Fick's law, and providing sink conditions are maintained, the amount of active drug released is described by the following equation <sup>(55)</sup>:

$$Q = (C_p K D_s D_p t) / (K D_s \delta_p + D_p \delta_d)$$

where:

- Q amount of active drug released per unit area;
- $C_p$  solubility of the active drug in the polymer;
- K active drug partition between solution/polymer;
- $D_s$  diffusion coefficient of the active drug in the solution;
- $D_p$  diffusion coefficient of the active drug in the polymer.
- $\delta_p$  membrane thickness;
- $\delta_d$  thickness of the hydrodynamic layer.

In such a reservoir device, the release rate is constant if the concentration on either sides of the membrane are maintained constant (constant gradient): active drug present in excess inside the device e.g. as a solid, rapid uptake by the tissue in contact with the device assuming no hydrodynamic layer is formed around the device. In such conditions, the release rate is constant versus time until exhaustion of the active drug excess: the kinetic order is zero (figure 7). To be noted, the release starts with a burst or peak corresponding to the release of the drug which has dissolved in the membrane during the device storage.



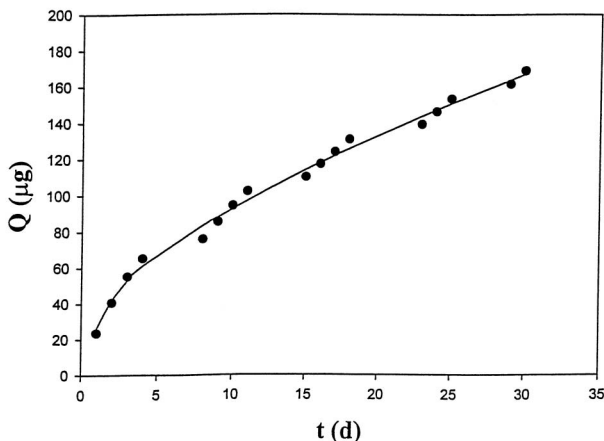


Figure 6: Vaginal ring reservoir loaded with a hormone and in-vitro release profile <sup>(54, 56)</sup>.

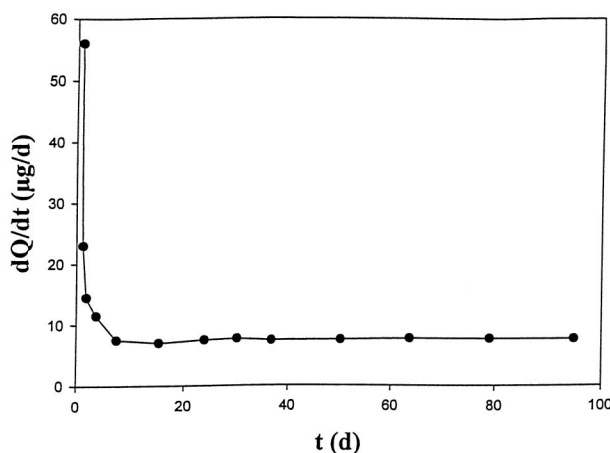


Figure 7: In-vivo release kinetic of a hormone from a vaginal ring reservoir; reproduced from ref. 53 with the permission of S. Karger AG, Basel.

In a reservoir device, and when the membrane is the determining factor, the release rate of the active drug increase with its solubility  $C_p$  in the membrane (figure 8) and decreases with the thickness  $\delta_p$  of the membrane (figure 9).

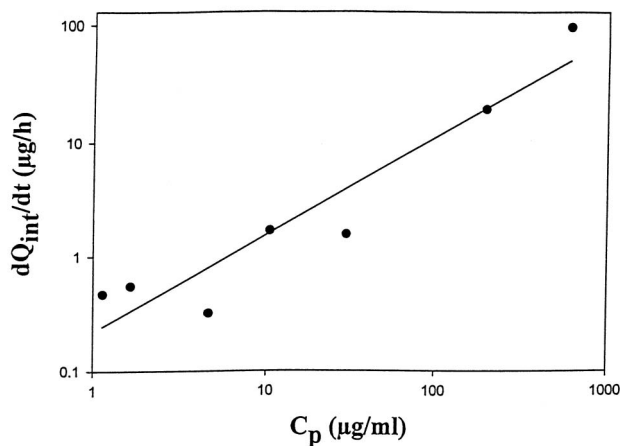
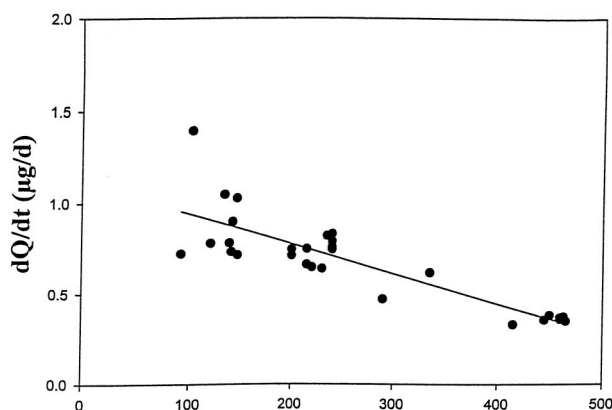


Figure 8: Influence of the solubility in silicone of different progesterone derivatives ( $C_p$ ) on the intrinsic release rate ( $dQ_{int}/dt$ ) measure in-vitro in diffusion cells; reproduced with permission of the © Controlled Release Society, Inc. <sup>(57)</sup>.



**Figure 9:** Influence of the membrane thickness  $\delta_p$  in a cylindrical reservoir device on the in-vitro release rate of an active drug<sup>(58)</sup>.

Silicone pressure sensitive adhesives are also used in reservoir devices like the *Transdermal-Nitro*<sup>®</sup> releasing nitroglycerine for the prevention of angina pectoris. Here, the silicone contributes with the ethylenevinylacetate copolymer membrane to the control of the active drug release whilst also providing adhesion of the patch to the skin. A silicone adhesive is used here because of its very high permeability to the active drug. Silicone PSA's are also used in matrix devices where the PSA acts as both the matrix for the active drug and as the patch adhesive<sup>(59)</sup>. Silicone PSA's are used for 1-day patches but longer wearing times are possible (2 or more days).

Contrary to organic adhesives, silicone PSA's are formulated without anti-oxidant and without organic tackifying resins. Silicone PSA's have been extensively tested on humans: they do not induce skin irritation neither allergenicity, they are non-toxic, they are used in prolonged therapies using successive patches and can be removed without pain<sup>(59)</sup>.

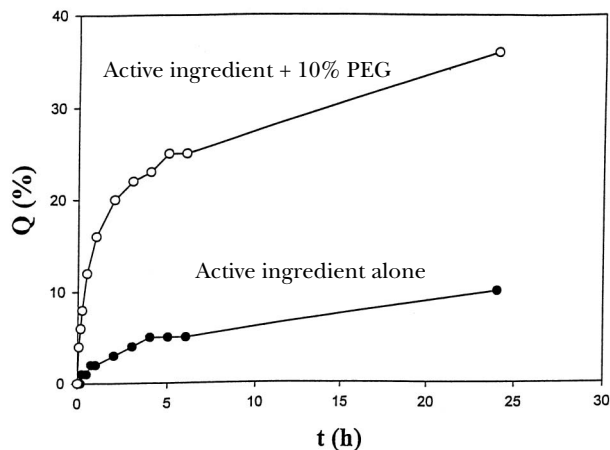
### 11.3 Controlled release device formulation and manufacturing process

The above examples highlight the importance of the choice made by the pharmacist between matrix and reservoir designs. Yet, other variables are to be considered like the silicone formulation or the intended production process.

#### 11.3.1. Formulation

As mentioned above, most silicone elastomers contain amorphous silica to improve their mechanical properties but this will also reduce their permeability, usually by a factor proportional to the volume fraction of this silica. Yet, in presence of identical amount of silica, the release of some active drugs seems more or less affected<sup>(55)</sup>. This suggests that mechanisms other than the diffusion through the silicone phase of the elastomer are involved in the permeability. Involvement of the silica in the permeability has been proposed for the release of the 17- $\beta$  estradiol from reservoir rings where the burst occurring at the beginning of the release is influenced by storage at various room humidity levels. The presence of silica increases the moisture content in the elastomer, which would affect the initial release of the active drug<sup>(60)</sup>.

Hydrophilic species may also be compounded with the elastomer to improve the compatibility and solubility of hydrophilic active drugs with the very hydrophobic silicone polymers<sup>(61)</sup>. Co-formulating silicone elastomers with polyglycols or carboxymethylcellulose allows to create pores within the elastomer to release the hydrophilic active drug<sup>(62)</sup>. This approach has been used to liberate active drugs having very low solubility in silicone elastomers e.g. using polyethylene glycols in adhesive silicone elastomers (figure 10).



**Figure 10:** In-vitro release of an active drug from a topical matrix dressing in adhesive silicone elastomer with or without polyethylene glycol <sup>(58)</sup>.

### 11.3.2. Manufacturing processes

The manufacturing processes of controlled release devices cannot be underestimated as thousands, possibly millions, of rather small objects may have to be produced and this with stringent tolerances. Dimensions, e.g. the external surface area or the membrane thickness, are indeed critical to the release rate control of the active.

How to process silicones is well known because of their numerous industrial applications. Silicone PSA's are easily coated in thin films from solution in organic solvents or directly when using hot melt versions; 2-part elastomers are easily shaped by extrusion, injection or moulding. However, in pharmaceutical production, these processes must be adapted to take into account the active drug compatibility and stability with the silicone, while still maintaining production rates that are commercially acceptable.

Reservoir devices are the most challenging for the formulation pharmacist, particularly the control of the membrane thickness. For cylindrical shaped devices, rather than filling and sealing individual capsules with the active drug <sup>(63)</sup>, a co-extrusion process allows to automate the manufacturing process by simultaneously extruding and subsequently crosslinking a core made of a drug loaded 2-part elastomer surrounded by a drug free 2-part elastomer acting as the membrane. Such a process has been demonstrated for the manufacturing of vaginal rings (figure 6). Another approach suggests the use of a sequential co-extrusion process to prepare a continuous external body made from a 2-part silicone elastomer and comprising enclosures of a drug loaded 2-part silicone elastomer: this method allows to manufacture drug loaded implants with no open ends in one single step <sup>(64)</sup>.

Some active drugs can interfere with the addition reaction used to crosslink 2-part elastomers, particularly actives containing amine functionality capable of strongly complexing the platinum catalyst (inhibition - see above). Moreover, some active drugs are unstable at the temperatures required for the crosslinking of these 2-part elastomers, even when conducted at low temperatures (60 - 80 °C). In such cases, a reservoir device may still be a viable option. Hollow structures can be produced and cured at elevated temperatures and subsequently filled at room temperature with a solution of the active drug. This could be done by injection with a needle, the silicone elastomer acting as a septum or seal. Various methods can be used to manufacture such hollow structures <sup>(65)</sup>.

## 12. Silicones in Pharmaceuticals Manufacturing

### 12.1 Siliconisation

Siliconisation encompasses the surface treatment with of many parenteral packaging components with silicones <sup>(66)</sup>. It is probably one of the oldest applications for silicone in the pharmaceutical field: treating glass vials with a film of polydimethylsiloxane was already mentioned in 1949 <sup>(67)</sup>. This allows the reduction of the glass surface energy and stops the surface being wet out by the pharmaceutical solution, reducing wastes and allowing better dosage with complete drainage from the vial <sup>(67)</sup>. Polydimethylsiloxanes (Dimethicone, Silicone Oil) are also used as lubricants on stoppers to ease machine ability <sup>(68)</sup>, in syringes to ease the piston movement <sup>(69)</sup> or on syringe needles to reduce pain when entering the skin. The surface treatment is done on clean surfaces by, at low concentrations, spraying, wiping or dipping with either a solvent solution or an emulsion of Dimethicone followed by air-drying and/or heat treatment <sup>(70)</sup>. The film coating is helped by the low surface tension of the polydimethylsiloxanes and on glass a subsequent heat treatment improves the adhesion of the film on the surface. Quantification is not easy as the amount applied on the considered surface is very low: some techniques exist e.g. using Atomic Absorption after removal with alcoholic potassium hydroxide <sup>(71)</sup> but often users rely on a functional test, e.g. contact angle or coefficient of friction measurements to determine the efficacy or effectiveness of the coating. The silicones stability and their low reactivity allow sterilisation by steam autoclaving, dry heat or with ethylene oxide.

### 12.2 Silicone antifoam

Because of their antifoam properties, silicones (Dimethicone, Simethicone or Simethicone emulsion) are used as additives in the manufacture of pharmaceuticals e.g. in fermentation processes, in mixing or filling operations: they are efficacious at very low levels, 1 to 50 ppm.

### 12.3 Silicone tubings

Silicone tubings are largely used in pharmaceutical manufacturing operations for the transfer between reactors e.g. for the production of vaccines, in peristaltic pumps, or in filling equipment lines. These tubings are made by extruding heat curable silicone elastomers and supplied in various dimensions (diameter and wall thickness) and hardness, the most popular being the 50 Shore A hardness. Both peroxide and Pt cured tubings are used but the Pt cured tubings are recommended as the peroxide cured tubings contain peroxide by-products, including PCB's, susceptible to be released to contaminate the transferred product. Other criteria to consider when selecting silicone tubings are: compatibility (chemical resistance, lack of absorption and contamination), preparation (cleaning and sterilisation), pressure resistance, resilience (pump life), kinking resistance, and regulatory status (compliance to Pharmacopoeia and supplier's quality system: product traceability, extrusion conditions and manufacturing site registration). In most cases, the users prefer to limit the usage of these tubings to a single operation rather than to validate difficult cleaning procedures for multiple re-use operations. Silicone tubings are preferred in these applications because of their purity (no plasticisers), flexibility, and ease of use.

## 13. Conclusions

Silicones have found many uses in healthcare applications, in the construction of medical devices, as non-metabolised active in gastro-enterology (antifoam) or as excipient in pharmaceutical formulations. As excipients, many of the unique properties of the polydimethylsiloxanes can be associated in controlled release drug delivery systems: chemical stability, high level of purity (absence of organic solvent or heavy metal contamination; low level of residual polydimethylcyclsiloxanes), ease of use to manufacture devices of different designs, very high permeability to many active drugs.

As a result, polydimethylsiloxanes are used in many anti-acid/anti-gas drugs, in transdermal systems (patches), in inserts or implants or in topical drugs. None of these

applications would be possible without the outstanding biocompatibility shown by the polydimethylsiloxanes, which is also the basis for their use in medical devices like hydrocephalic shunts or pacemaker leads.

Silicones will also help to improve patient comfort: controlled release devices allow for a simpler administration and a better compliance as demonstrated for inserts or implants; in topicals. Silicones are recognized to bring outstanding aesthetic.

Different parameters are available to the pharmaceutical formulator (silicone type, device type, device size) to allow the use of these polymers for the desired purposes.

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