

**Silicones in New Pharmaceutical Developments
from formulations to
manufacturing processes**

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This article was originally published in
PharmaChem, 46-49, Oct. 2005
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published by  srl
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 20123 Milano (Italy)
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 www.b5srl.com

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INTRODUCTION

Silicones are synthetic polymers containing Si-O siloxane bonds. Their synthesis, properties and analysis have been described

elsewhere (1-3). The most common polymers are polydimethylsiloxanes (PDMS) of the structure shown in Figure 1, where the strongly polar backbone of Si-O bonds is shielded by organic methyl groups. This

gives PDMS some unique properties due to the very low level of intermolecular interactions between methyl groups like low viscosity, low surface tension or high permeability.

Silicones have long been used in a wide range of pharmaceutical products. Looking at various compendia such as PDR (USA), Rote Liste (Germany) and Vidal® (France), they can currently be found in the formulations of more than 350 registered drug products as actives or excipients (Table I).

The FDA "Inactive Ingredient Guide" also provides an interesting view as it lists silicone used as excipients in currently marketed products and relates them to dosage forms and route of administration.

As actives, silicones are used as an antifoam in various antacid or antflatulent drug formulations, particularly as blends of PDMS polymer with silica, known in Pharmacopoeia as Simethicone. Their mode of action is physical (2), and they are not metabolized but excreted (5). As excipients, they

are used in many more applications. As fluids, they are used in various topical products (see below). They are used as adhesives in transdermal patches because of their permeability to drugs and because

they allow long wear time. Silicone elastomers are used in inserts or implants, again because of their permeability to drugs but also their biocompatibility.

Silicones are also used as "process aids": for example, as fluids to lubricate needle and

syringe parts or as elastomers in tubing during transfer and filling operations (6).

The purpose of this article is to review some recent applications where silicones are contributing to innovation and to discuss how these applications relate to the physico-chemical properties of silicones. Analytical science will not be ignored as progress here has allowed more sophisticated characterizations.

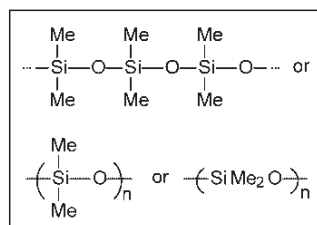


Figure 1 – PDMS structure

ABSTRACT

Silicones are currently used in many different pharmaceutical registered products or as process aids to manufacture such products. Silicones offer a unique set of physico-chemical properties such as low surface tension, non greasy touch, high permeability to drugs, and high stability during sterilization. This explains why they have been used, and are used, as active ingredients in antacid formulations or as excipients in applications as diverse as topical creams, drug-loaded controlled release pharmaceutical devices or as tubing in pharmaceutical transport and filling operations. This article reviews more recent examples where silicones contribute to innovative solutions, as well as the contributions of modern analytical techniques to their characterization.

Table I – Distribution of the 358 dosage forms identified to contain silicones, per physical type of silicone used (4)

| Dosage forms with silicone as: | Number of dosage forms, % of total | Physical type of silicone used in dosage forms | % |
|--------------------------------|------------------------------------|--|----|
| Active ingredients | 24 | Simethicone | 13 |
| | | Dimethicone | 11 |
| Excipients | 70 | Simethicone | 14 |
| | | Simethicone emulsion | 11 |
| | | Dimethicone | 10 |
| | | Elastomer | 6 |
| | | Silicone Oil | 5 |
| | | Silicone Polymer | 5 |
| Others | 19 | | |
| Unknown | 6 | | |

SILICONES AS NOVEL TOPICAL EXCIPIENTS

Silicones are used in many topical products, in particular trimethylsilyloxy endblocked polydimethylsiloxanes of specific viscosity, or Dimethicone as defined in various Pharmacopoeia and of the structure: $\text{Me}_3\text{SiO}-(\text{SiMe}_2\text{O})_n-\text{SiMe}_3$.

In the US, NF grade Dimethicone is recognized as an OTC active for **skin protectancy** (7), most likely because of its high hydrophobicity and the relative protection it can offer to nonmiscible water-based aggressions. Such silicone polymers are recognized as good emollients, not so much for their lubricity but for their high capability to spread due to their low surface tension which is also lower than their critical surface tension of wetting (2,8).

Other silicone polymers have been considered in various topical products. Low mol. wt. PDMS cyclic oligomers, such as Cyclomethicone NF or $(\text{SiMe}_2\text{O})_n$ where $n = 4$ or 5 , are disclosed in some cream formulations (e.g., against acne and psoriasis) (4). Low mol. wt. linear PDMS oligomers (e.g., hexamethyl-disiloxane or HMDS or $\text{Me}_3\text{SiOSiMe}_3$), have also been suggested as a **volatile solvent carrier** instead of other propellants. HMDS has a reasonable boiling point ($\text{bp} = 100^\circ\text{C}$), but a very low heat of evaporation if compared to water (30.11 kJ/mol for HMDS (9) or 0.19 kJ/g vs. 43.99 kJ/mol for water (10) or 2.44 kJ/g). HMDS is hydrophobic. It is also reported that HMDS does not sting on the skin compared to ethanol, although this is not substantiated by controlled clinical trials. All this explains why the use of HMDS has been suggested in anhydrous antifungal spray compositions (11,12).

At the other end, high mol. wt. siloxanes are also of interest. High mol. wt. PDMS polymers, or silicone gums, considering their honey-like but liquid appearance, have been shown to **improve the substantivity of actives** on the skin (e.g., in the case of ketoprofen) (13). Such high mol. wt. PDMS polymers are already widely used in personal care products to improve the efficacy of various UV absorbers, as these siloxanes are resistant to washing and can protect the UV absorbers from wash-off thus leading to "swimming resistant sun creams". These high mol. wt. PDMS polymers form interesting **nonvisible films** on the skin, which are highly hydrophobic yet highly **permeable to moisture** or gases, and therefore nonocclusive and "**pleasant**" to wear. Aesthetics should not be ignored in topical products, as sensory characteristics may be critical to patient compliance when dealing with chronic diseases that require repetitive product use, as recently noted (14).

Recently, combinations of HMDS with silicone gums have been described in patents about spray formulations that contain active pharmaceutical ingredients (API) such as a vitamin D derivative or clobetasol 17-propionate (Table II) (15,16).

The above sprayable silicone-based formulations show active delivery penetrations similar to those noted in the references.

Evaluation of product aesthetics by patients (15 psoriasis subjects – formulation C) leads to interesting results (16). The silicone-based sprayable formulation, when compared to a cream or a lotion, was perceived as significantly easier to apply, drying more rapidly, less greasy, less tacky and allowing clothes to be rapidly put back (16). Such good aesthetic results also have been observed for other silicone formulations when compared to a petrolatum-based commercial product (17).

NOVEL USE OF SILICONES IN HEAD LICE TREATMENT

Head lice infestation is common in all communities and apparently more related to the differing modes of social interaction and communication of boys versus girls than to any socioeconomic factors. For example, young girls have a greater tendency toward "ear-to-ear" communication, potentially increasing their susceptibility for infestation and the likelihood of acting as vectors within their family (18). Prevalence seems to be on the increase since 1995, attributed to treatment failures due to insecticide resistance (19). Current products are not without other concerns, e.g. their toxicological profile. Numerous alternatives have been sought and proposed, such as plant extract-based products. However, the efficacy of these alternatives is not always supported by clinical data.

Details and results from a randomized controlled equivalence clinical trial (214 young people and 39 adults with active head lice infestation) using a novel silicone topical lotion to treat head lice have been published (19). The clear and odorless silicone topical lotion is made of 4% high mol. wt. PDMS polymer and 96% low mol. wt. PDMS volatile cyclomethicone (20). The former is a higher mol. wt. version of silicone polymer currently recognized as Dimethicone in various Pharmacopoeia. The latter appears

Table II – Formulations and total quantity of active penetration into human skin (sums of quantities within the skin layers plus in the receptor compartment) with silicone-based formulations compared to references

| Formulation (15): | A % | Reference cream |
|--|---------------------------------|---------------------------------|
| Vitamin D derivative | 0.3 | 0.3 % |
| Hexamethyldisiloxane | 59.4 | |
| Silicone gum | 0.6 | |
| Paraffin oil | 10.0 | |
| Ethanol absolute | qsp 100% | |
| Penetration after 16 hr, μg | 2.64\pm0.50 | 0.63\pm0.14 |

| Formulation (16): | B % | C % | Reference Temovate® |
|--|---------------------------------|---------------------------------|---------------------------------|
| Clobetasol 17-propionate | 0.05 | 0.05 | 0.05% |
| Hexamethyldisiloxane | 60.0 | 59.4 | |
| Silicone gum | 0 | 0.6 | |
| Paraffin oil | 10.0 | 10.0 | |
| Ethanol absolute | qsp 100% | qsp 100% | |
| Penetration after 16 hr, μg | 1.35\pm0.45 | 1.31\pm0.35 | 0.67\pm0.08 |

in the US National Formulary. This formulation, made by a combination of the two siloxanes, is interesting. Silicones with their low surface tension are among the best materials to wet any surfaces. The above lotion associates good wetting (better than with most organic oils) and low viscosity, but yet, after evaporation of the volatile cyclomethicone, leaves a film of nonvolatile high mol. wt. PDMS polymer.

This silicone topical lotion was evaluated against a phenothrin-based commercial product as reference, both products tested in two applications seven days apart, each application being left for 8 or 12 hours/overnight. The results indicate that per protocol analysis (19):

- 84 out of 121 participants (69%) in the study were cured with the silicone topical lotion vs. 90 out of 116 participants (78%) with the reference product; the activities of the silicone and phenothrin products were found to be equivalent;
- There were significantly less irritation reactions with the silicone topical lotion compared to the reference product (3 cases/127 vs. 11 cases/125).

The authors of the above study also found during *in vitro* studies that this silicone lotion "immobilized head lice by coating the insect" and so potentially "disrupting their ability to manage water" (19). Other lotions containing no neurotoxin are known in the field: for example, oil-based mixtures such as mayonnaise, but their efficacy is poorly substantiated. Some organic solvents (e.g. alcohols of different chain lengths) also containing no neurotoxin have shown some efficacy in lab trials against both susceptible and permethrin-resistant lice (21).



Figure 2 – A transdermal drug delivery patch using a silicone pressure sensitive adhesive.

Photo courtesy of S. Postiaux, Dow Corning SA

The authors conclude that the above silicone topical lotion cures head lice, seems less irritating and that the silicone topical lotion has a physical action that should not be affected by a resistant breed of head lice (19).

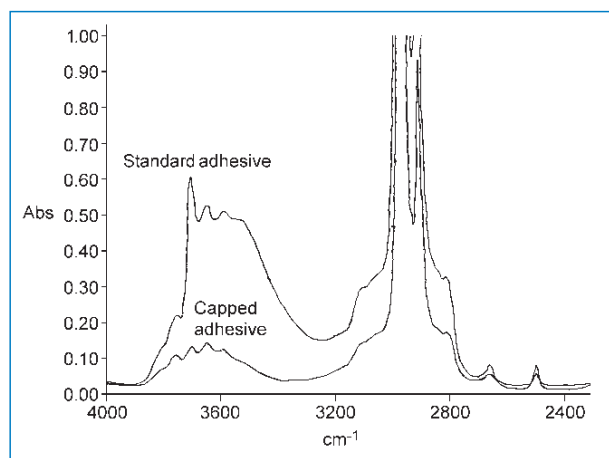


Figure 3 – IR spectra of a standard silicone pressure sensitive adhesive and a silylated (capped) amine-resistant pressure sensitive adhesive (23)

ADVANCES IN ANALYTICAL CHARACTERIZATION OF TDDS SILICONE PRESSURE SENSITIVE ADHESIVES

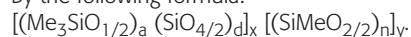
Today, progress in analytical techniques is allowing more in-depth characterisation of complex silicone materials such as silicone pressure sensitive adhesives. The structure of silicone can be analysed by conventional techniques such as IR spectroscopy but also, in more detail, by NMR of the ^{29}Si ($I = 1/2$) because of its high relative abundance (4.7%). The interpretation is eased by large chemical shifts. This allows identifying and studying the distribution of various siloxane groups within a copolymer.

Silicone pressure sensitive adhesives are used as skin adhesives in various transdermal drug delivery system (TDDS) or patches for the controlled release of actives including among others, nitroglycerine for the treatment of angina pectoris (*Nitroderm TTS*[®], Novartis), estradiol for HRT

(*Vivelle dot*[®], Novartis) or Fentanyl for pain management (*Duragesic*[®], Janssen-Cilag) (Figure 2).

The silicone in these adhesives is a copolymer made of partially-silylated silicate resin domains linked by long PDMS polymer chains. These adhesives are obtained by condensation of silanol groups, SiOH, from a partially-silylated silicate resin containing silanol groups, $[(\text{Me}_3\text{SiO}_{1/2})_a (\text{SiO}_{4/2})_b (\text{HOSiO}_{3/2})_c]$ and a silanol end-blocked polymer $\text{HO}(\text{SiMe}_2\text{O}_{2/2})_n\text{H}$. For ease of ^{29}Si NMR peaks attribution hereafter, Noll's notation convention is used here (1).

After condensation between silanol groups, these adhesives can be described by the following formula:



The resin (x) acts as a reinforcing agent and contributes to the elastic

component of the adhesive, while the long PDMS (y) polymer chain contributes to the spreading and wetting by the adhesive and to the viscous component of the viscoelastic behavior. The ratio between the resin and the polymer (x/y) determines much of the rheology of these standard adhesives and properties such as tack, peel strength, and shear strength (22).

Yet the above structure is only an approximation as it does not account for the presence of various residual silanol groups remaining after condensation between the resin and the polymer. Residual silanols remain on the resin, as not all the silicate resin silanols were condensed with the silanols of the polymer, and residual silanols remain on the polymer because not all polymer ends reacted. When used as adhesives, this is not a problem with most API. Yet with some API, in particular basic API containing amine groups, the API can act as a catalyst for further silanol/silanol condensation within the adhesive during storage of the finished patch, leading to further cross-linking within these standard adhesives and loss of adhesive properties. To counter this, the bulk standard silicone pressure adhesives can be silylated to reduce the overall concentration of residual silanols giving

adhesives that are not prone to further condensation (22). These adhesives are known as amine-resistant pressure sensitive adhesives. The reduction in the concentration of silanols after silylation is well observed via IR spectroscopy in the SiOH absorbing region around 3600 cm^{-1} (Figure 3).

Yet this technique is not able to indicate unambiguously if polymer silanols are treated too, as their reactivity is expected to be lower, their concentration is low, and their absorption band possibly enlarged by hydrogen bonding with the large excess of silanols coming from the resin.

^{29}Si NMR has proven a unique analytical technique to assess where silylation actually occurs during manufacturing of such amine-resistant pressure sensitive adhesives. It has been shown that not only the residual silanols on the resin are being treated (Figure 4, a and b). But that there is strong evidence that the less reactive residual polymer silanols are also being silylated as shown by the disappearance of the signal at -10.5 ppm corresponding to $-\text{O}_{1/2}\text{SiMe}_2\text{OH}$ polymer end groups (Figure 5, a and b).

So, amine-resistant pressure sensitive adhesives can therefore be best described as $[(\text{Me}_3\text{SiO}_{1/2})_e (\text{SiO}_{4/2})_d]_x [(\text{SiMe}_2\text{O}_{2/2})_n]_y [(\text{SiMe}_2\text{O}_{2/2})_n (\text{SiMe}_3\text{O}_{1/2})_w]$ and ^{29}Si NMR is proving to be an invaluable tool to characterize such materials.

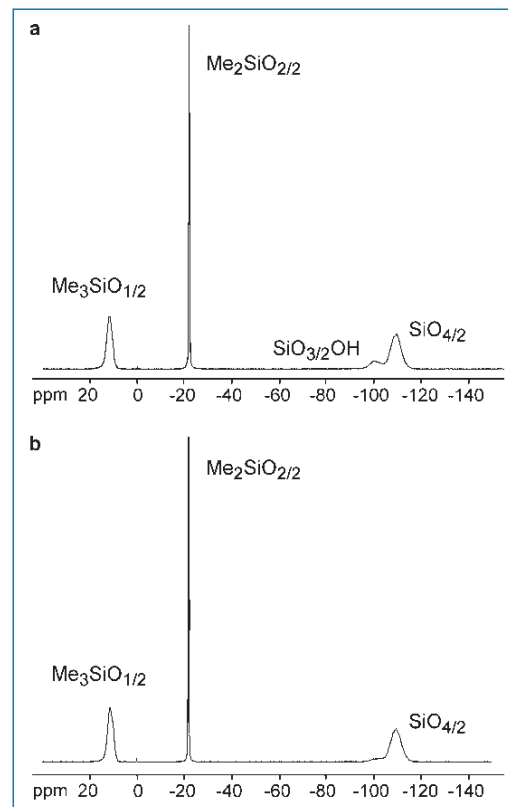


Figure 4 – ^{29}Si NMR spectra of a standard silicone pressure sensitive adhesive (a), and of an amine-resistant silicone pressure sensitive adhesive (silylated version) (b), showing the reduction of $\text{SiO}_{3/2}\text{OH}$ groups at -100 ppm (24)

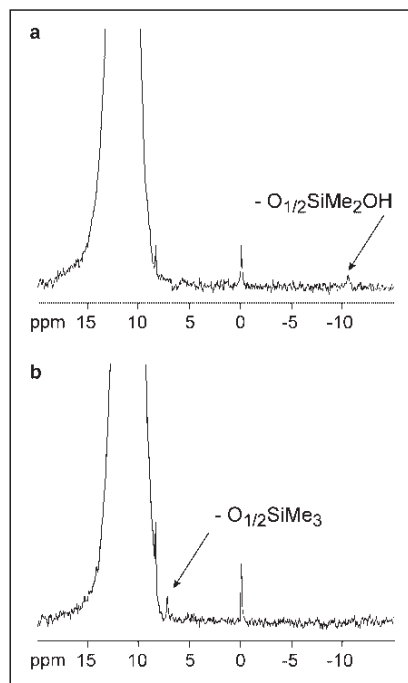


Figure 5 – Enlarged ^{29}Si NMR spectra of a standard silicone pressure sensitive adhesive (a), and of an amine-resistant silicone pressure sensitive adhesive (silylated version) (b), showing the disappearance of the $-\text{O}_{1/2}\text{SiMe}_2\text{OH}$ polymer hydroxyl end groups at -10.5 ppm, with the corresponding appearance at $+7.2$ ppm of $-\text{O}_{1/2}\text{SiMe}_3$ groups in alpha of $\text{Me}_2\text{SiO}_{2/2}$ polymer end groups (24)

NEW INSIGHTS TO SELECT ADEQUATE SILICONE TUBING FOR YOUR PROCESS

Here, tubing, while not present in the final drug product, is yet part of the manufacturing process and in certain countries such “process aids” could be required to follow critical GMPs principles for certain applications (6). Silicone elastomer tubing is used today in many drug manufacturing processes, including transfer or filling operations, because of its purity profile and ease of sterilization (6). Cross-linked silicone polymers remain elastomers at room temperature without the use of any plasticizers because of the low T_g of the PDMS polymer (2). Silicones are also able to withstand sterilization without major effects on their properties (6).

Various in-use properties relating to process design and performance have been recently further investigated.

Low spallation or low particle generation has been confirmed for peroxide cured (or rather, peroxide initiated) tubing when compared to standard Platinum (Pt)

cured tubing, while low hysteresis Pt cured tubing indicates improvement over standard Pt cured tubing. The advantage of the low hysteresis Pt cured tubing is confirmed in pump life trials indicating time to failure similar to that found with peroxide tubing (Table III).

Kink resistance also has been further investigated. Kinking is blockage occurring when tubing is submitted to situations where bend radius is too short. Such situations can not only reduce transfer rates but, worse, lead to pressure surges and tubing burst. Methods such as ASTM E290 appear to have limitations for assessing the performance of this tubing because the test was developed for stiffer materials (25).

A new test method is being developed to measure kink resistance. The tubing, through which water is allowed to flow (to correlate with actual in-use situations), is wrapped around mandrels of decreasing diameter and the change in pressure difference between the tubing inlet and outlet is measured. The mandrel size, at which a significant pressure difference change occurs, is recorded as the minimum bend radius acceptable for the tubing.

In general, and as expected, the highest resistance to kinking or lowest bend radii are measured for tubing of small internal diameter and of high hardness. Yet, it has been shown that silicone tubing is not as prone to kinking as suggested by bend radius data published in commercial literature when the presence of a fluid, and the internal pressure it creates, is taken into consideration (25).

CONCLUSIONS

Silicones are currently used in many pharmaceutical registered products because of their distinctive physicochemical properties. These include low surface tension, nongreasy touch, high skin substantivity and high permeability to drugs in various controlled release drug-loaded pharmaceutical devices. In addition, because of their purity profiles and stability during sterilization, silicones may also be used in various manufacturing processes. Progress in analytical techniques, including ^{29}Si NMR, has led to more detailed characterization of complex copolymer structures. Recent application examples indicate that silicones can contribute to

drug delivery system innovations, novel treatments and manufacturing process improvements.

ACKNOWLEDGEMENTS

The authors express their thanks to C. Moss and to the following Dow Corning colleagues for their contributions: A. Labrosse (IR data interpretation), A. Kretschmer (^{29}Si NMR data interpretation) and B. Van Roy (insightful editorial comments).

NOTE: *Temovate* (GSK), *Nitriderm TTS* and *Vivelle dot* (Novartis), *Duragesic* (Janssen-Cilag) are registered trade marks.

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Table III – Spallation and peristaltic pump life of different types of silicone tubing type as measured with water (26)

| | Spallation g particle / g tubing / hr x 10 ⁶ | Pump life (without back pressure) hour to fail at max. speed |
|----------------------------------|---|--|
| Pt cured tubing | 12 | 33 |
| Pt cured tubing - low hysteresis | 6 | 188 |
| Peroxide initiated tubing | 2 | 183 |

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