Polymer Systems Technology Limited

Understanding the Role of Silicones in Controlled Release Applications

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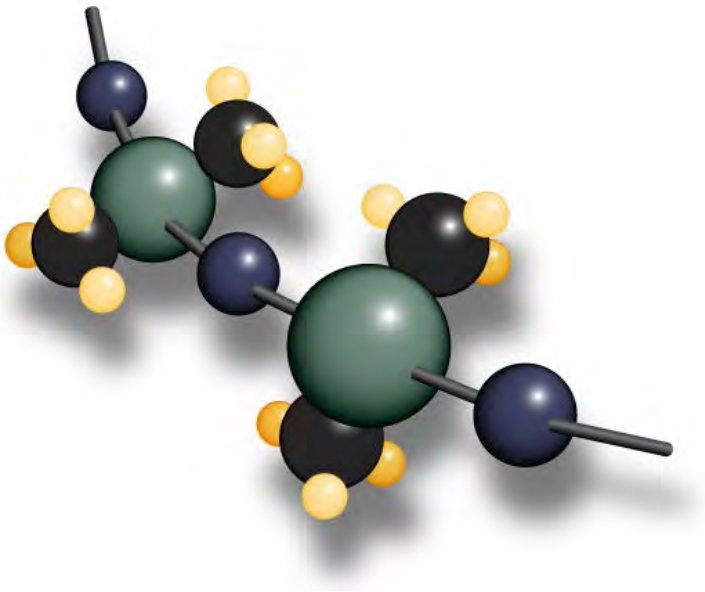
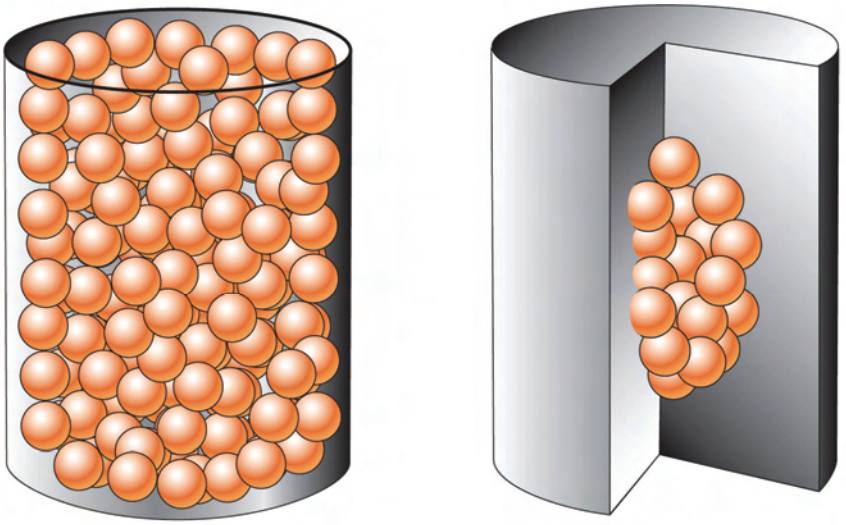


As one of the most widely researched biomaterials to date, silicone has an approximate 50-year legacy of use in the healthcare industry. This history of biocompatibility has made silicone a material of choice for both long and short-term implantable device applications. The last twenty years have seen the emergence of targeted release and combination product applications. These technologies evolved as the result of pharmaceutical and medical device manufacturers seeking novel ways to achieve their therapies. So, raw materials that were formerly chosen for their performance capabilities in medical device applications are now tasked with maintaining those requirements but also with meeting a host of new performance expectations that are specific to drug delivery applications. Faced with these new challenges few raw materials have succeeded in transitioning quite as well as silicone. This is because silicones possess certain dynamic characteristics which allow them to be compounded in with a host of actives. These same unique characteristics also allow them to release those actives from a molded/extruded device in a predictable way – whether that application is for transdermal, transmucosal, short or long-term human implantation. This article will highlight key attributes of certain silicones as well as key considerations when selecting a silicone.

When designing a drug delivery application with silicone, the first question to be answered relates to the product's basic design. Generally speaking there are two configurations to choose from: matrix and reservoir.



Matrix Configuration

Reservoir Configuration

A matrix design is where the active is mixed homogenously into the silicone and then molded, extruded, etc. into the desired geometry. A good example of this might be a central venous catheter impregnated with actives intended to combat infection.

Reservoir configurations are the other primary device design. A reservoir device is one where an active is concentrated in a void in the center of a molded silicone part. A good example of this would be several early-generation contraceptive devices that were

implanted just under the skin; small silicone tubes were molded or extruded, cured, filled with active and then sealed with silicone adhesives.

It's important to understand the impact that the design of a part or device has on how the active will be released. Generally speaking, matrix designs release the most active initially and then the release rate tapers off whereas reservoir devices will exhibit an initial spike and then normalize into a lower but consistent release rate.

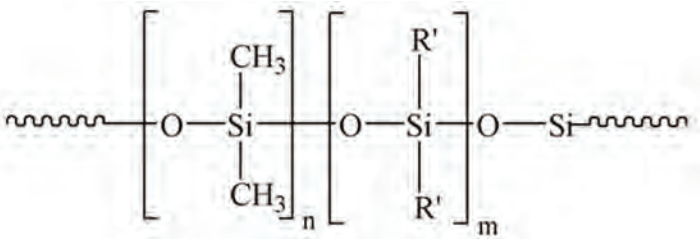
If it is decided that a matrix design is ideal, there are a number of considerations that must be evaluated. The first order of business is to establish that the active in question is appropriately soluble in silicone. As most silicones are hydrophobic in nature it is important to either know or establish the extent to which the active in question is hydrophobic/lipophilic. If an active is extremely polar and, subsequently, hydrophilic, it will not readily dissolve into most traditional silicone formulations. As a direct result of insolubility a matrix design would no longer be an option.

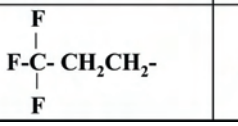
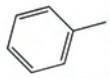
Once solubility is established the next question has to do with how one wishes to process the part/device in question. If the design relies upon heat curing the molded or extruded silicone part then the matrix design may not be an option if the active in question is heat sensitive. Here again, understanding the chemical characteristics of the API is key and the specific temperature threshold must be determined.

Perhaps the desire is to mold a matrix design and the drug is found to be robust relative to temperature, there still remains the potential that the platinum catalyzed, heat accelerated silicone will be inhibited by the active in question; it has been observed that some actives common to combination products are chemically very similar to an inhibitor often used to control the work time (pot life) of platinum systems. This can result in excessive work times or even failure of a part to cure. In such instances one option is to mold with rapidly curing moisture sensitive cure chemistries. However, it's important to note that these concerns are specific to matrix designs and not reservoir.

All this having been said it's understandable to wonder how an active moves (or diffuses) through a cured silicone medium at all. To better understand this phenomenon it is necessary to cover some basics of silicone chemistry.

To start with, silicone is an inorganic polymer, having no carbon atoms in its backbone. However, because the pendant groups off this backbone do contain carbon atoms it is fair to classify silicone as an "organo-polysiloxane". It is these organic pendant groups that make silicone hydrophobic. A typical silicone polymer structure is shown below.



R' Group	Methyl	Trifluoropropyl	Phenyl
Chemical Structure	CH_3-		

The constituent groups on the backbone of the polymer and the end-blocking units determine if the polymer is functional or non-functional. If a polymer only contains non-functional pendant groups (methyl, fluoro and/or phenyl), the polymer is essentially nonreactive, not easily crosslinked and generally only used as a fluid. While non-functional silicone fluids can be used as excipients to facilitate the diffusivity and ultimate elution of certain APIs through a device or part molded from a silicone elastomer, this article limits its scope to drug delivery applications relying simply on curable silicone chemistry.

Accordingly a closer look will now be taken at silicone gels, liquid silicone rubber elastomers (LSRs) and high consistency rubber elastomers (HCRs).

Silicone gels are polymers – similar to fluids – except that they contain reactive groups, which allow the polymers to crosslink. Because the degree of crosslinking (or crosslink density) tends to be minimal and because these materials tend to have little or no filler (silica, resin, diatomaceous earth, etc.) silicone gels cure into a soft and compliant gel-like rubber. Typical applications include tissue simulation.

Liquid silicone rubbers, or LSR's, are elastomers containing medium viscosity polymers and moderate amounts of silica. They tend to have an uncured consistency like that of petroleum jelly and the cured elastomers have good physical properties. These materials can be molded into parts and require the use of liquid injection molding equipment.

High consistency elastomers typically contain high viscosity polymers and sometimes contain higher levels of reinforcing silica. These materials are clay-like in consistency in their uncured state, and offer good physical properties when vulcanized. High consistency materials can be molded into parts by compression or transfer molding and are most commonly used for extrusion to yield tubing configurations.

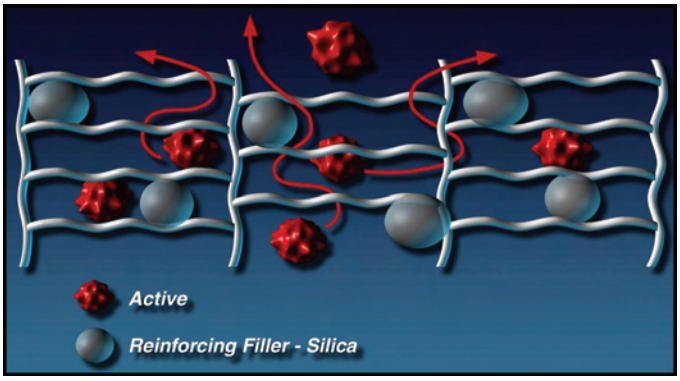
All of the above silicones rely upon the same basic repeating siloxane polymer and for each the pendant groups may be customized. Gels are loosely crosslinked, with little or no filler. LSRs have more crosslinking and more filler. Lastly, HCRs, are basically the same as LSRs except their polymers are of a much higher molecular weight.

Due to the fact that all of the above rely on the same basic siloxane polymer they all benefit from a unique characteristic that is inherent to these polymers – a lot of empty space. Specifically, the large atomic volume of the silicon atom, as well as the size and position of the applicable pendant groups, result in bond angles that yield a high degree of free volume. This free volume then provides what may be considered "microporous

pathways" for liquids and gasses (including water vapor) to migrate through a cured silicone medium.

Now that the means by which actives can move through silicone have been established, a closer look will be taken at the factors that control their diffusivity and rate of release. While we've talked briefly about how matrix and reservoir designs impact release rates, there are other factors to be considered in how an active will move throughout a cured silicone system and release into or onto the body. When considering diffusivity, one must realize that variables associated with both the active and the silicone medium have a part to play. On a very basic level the molecular weight and/or the molecular volume (or spatial dimensions) of an active will have an impact on how readily it migrates through a cured silicone. The bulkier the molecule the slower the progress. Similarly, the amount of crosslinking that a given silicone formula provides will impact diffusion and release. The more functional groups on the polymer (and often the lower the molecular weight of the polymer) will yield a greater crosslink density and, in effect a denser web through which to pass.

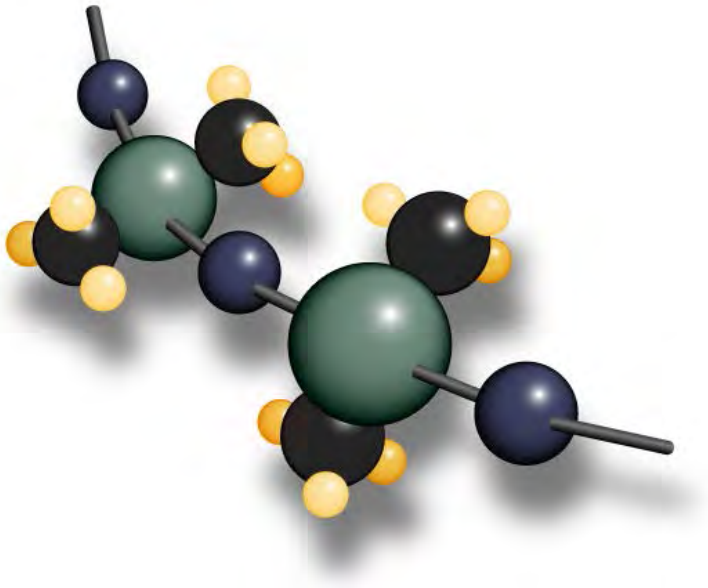
Then there are also filler levels to consider. Silicone elastomers are most commonly filled with silica, which provides the mechanical, rubber-like strength of an elastomer, as opposed to the soft and easily torn consistency of a silicone gel. The greater the loading of a reinforcing filler such as silica, the greater the steric hindrance to slow down the active. However, it's not simply the steric hindrance of the reinforcing filler; the pendant groups coming off the backbone of the polymers themselves will also impact the progress of an active. Moreover, very large groups such as diphenyl, will provide a much greater degree of hindrance than smaller groups such as dimethyl. Lastly, there is the polarity of the pendant groups versus the polarity of the active to be considered. Slight inconsistencies in polarity may result in further slowing of the active through the silicone.



All of the above variables may be controlled through custom formulation to optimize the diffusivity and permeability of an active through a silicone.

Silicones are well established as the elastomeric biomaterials of choice for long-term implants, and are also ideal for use as platforms for drug delivery. As indicated above, a host of APIs are soluble in silicones. Additionally, the material's inherent microporous structure provides a means of transporting soluble APIs through the cured material and

delivering them to their targeted location. Lastly, silicone chemistry offers a variety of methods by which to control permeation and elution rates. Taken as a whole, these characteristics distinguish silicone as a versatile raw material that is tailor-made to facilitate the needs of the emerging targeted-release and combination product markets.



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