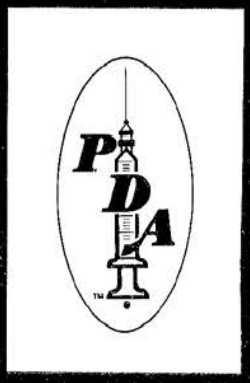
1988
SUPPLEMENT
Volume 42
Number 4S

Technical Report No. 12

Siliconization of Parenteral Drug Packaging Components

Journal of Parenteral Science and Technology



A publication of The Parenteral Drug Association

Siliconization of Parenteral Drug Packaging Components

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Siliconization of Parenteral Drug Packaging Components

Lubrication of Packaging Components Task Force

Contents

I. Scope

Most parenteral packaging components require the use of some form of lubrication in order to improve their processability and functionality. The Task Force on Lubrication of Packaging Components was formed because of an increasing number of questions about the use, measurement, and toxicity of lubricants.

The purpose for this publication is to present information. The publication reviews the common lubricants, the reasons for their use, methods of application and analytical measurement.

It is not the intent of this Task Force to recommend specific materials, methods of application, or analytical procedures, but rather to provide a source of information concerning the use of lubrication on pharmaceutical packaging components.

II. Introduction

One of the most commonly used lubricants for pharmaceutical packaging is polydimethylsiloxane fluid often referred to as silicone fluid. Siliconization of packaging components such as glass, elastomeric closures, plastic, and metal, places an invisible water repellant film on the surface of the components. This film can aid in the free-draining characteristics, processing and machinability of vials and elastomeric closures (1, 2). Silicone fluid is commonly applied to plastic syringe barrels and glass cartridges used as plunger barrels to facilitate easy movement of the plunger within the barrel (3). The application of a silicone film to hypodermic needles reduces the frictional drag and thus the pain associated with this drag as the coated needle passes through body tissue (4).

The term silicone was first used in the early 1900's in England as a generic designation for a family of polymers based on the element silicon. Siloxane is an acronym derived from silicon, oxygen, and methane (5). Commercially, the siloxanes which are most often used are the polydimethylsiloxanes. These materials are a class of chemical compounds composed of alternating silicon and oxygen atoms in a linear arrangement with two methyl (CH_3^-) groups attached to each silicon atom. The polymers can be end-blocked by a variety of chemical structures. When the trimethylsiloxy [$(CH_3)_3SiO—$] group is used, a series of linear silicone fluids is produced which possess the following general structure:

$$(CH_3)_3SiO\left[\begin{array}{c}CH_3\\SiO\\CH_3\end{array}\right]_x Si(CH_3)_3$$

The above formula represents molecules whose structures differ only in x, the number of dimethylsiloxane units; thus, as x increases the molecular weight and viscosity of the fluid increases. The relationship between the degree of polymerization (x), the molecular weight, and the viscosity of typical polydimethylsiloxane fluids appear in an article by S. Braley (6). A 350 centistoke polydimethylsiloxane fluid would have an approximate x value of 130 and an average molecular weight of 9780.

III. Reasons for Lubrication

A. Machinability

Machinability is greatly improved through the use of lubricated packaging components. Siliconization of rubber products reduces the friction present between the rubber closure and the metallic machinery. Lubrication helps eliminate clumping of parts as they are smoothly fed from hoppers to machine paths. These lubricated components then easily transverse down machine guides, reducing any possible problems, which are ultimately very costly in terms of lost production time.

B. Reduction of Insertion Force—Seating

After closures have been successfully transported to the vials, they must be inserted. Siliconization lowers the friction between the vial and the closure. This decrease in friction reduces the force necessary to insert vial stoppers properly.

C. Sealability

It has been observed in industrial manufacturing processes that the integrity of the closure/vial seal is improved by the siliconization of the closure.

D. Minimize Breakloose and Extrusion Force

As with stoppers, lubrication of syringe plungers through siliconization reduces the coefficient of friction on the surface of the plunger. This reduced friction minimizes the energy required to overcome the static force between the plunger and the barrel. Lubrication of the plunger also lowers the extrusion or dynamic forces needed to smoothly expel the drug product from the syringe. In order to keep potential functional problems to a minimum, breakloose and extrusion values should be low.

E. Syringe Barrel Lubrication

Syringe barrel lubrication is closely related to breakloose and extrusion values for plungers. Any lubricant present on the plunger or the barrel will greatly reduce the amount of friction between the two. The decrease in the friction will result in a reduction of force necessary to assure the proper operation. Siliconization of syringes will also aid in the initial insertion of the plunger into the syringe barrel during assembly.

F. Hypodermic Needle Lubrication

By utilizing a process of lubricating needles, a small residual amount of silicone is left on the surface. This silicone film on a hypodermic needle reduces frictional drag resulting in less pain during skin and muscle penetration (7). Lubrication of the needle surface also minimizes the force needed to pierce a rubber closure. In addition to enhanced penetration characteristics, siliconizing needles also improves the process of needle insertion into the protective sheath.

G. Drainage of Vial Contents

Siliconization of vials results in a thin water repellent film being applied to the inner surface of the vial. Aqueous

solutions tend to bead up on these surfaces since they do not wet the silicone film. This leads to characteristic improvements of the drainage of the vial (8). Siliconization of glass is also used to improve the handling of suspension products and to facilitate resuspension following storage.

IV. Compendial References

A. Medical Grade Silicone

The widely used term, Medical Grade Silicone, has no official compendial or regulatory status. The term Medical Grade was introduced by one manufacturer of silicone products. That producer, Dow Corning, attaches the following criteria to these products:

The biocompatibility of the material has been evaluated and a profile established. This profile is based on a series of tests performed by this manufacturer. Results of these tests are a part of the product information.

Medical Grade by this definition does not imply that the material has absolute biocompatibility or lack of toxicity—only that the level has been established by the tests. Further testing of the material by the user may be necessary to establish safety and efficiency for many specific uses.

B. USP XXI, NF XVI

The United States Pharmacopeia (USP) contains no monograph on polydimethylsiloxane fluids. However, the USP furnishes a Reference Standard Polydimethylsiloxane, catalog number 54630. This reference standard is referred to in the National Formulary (NF) Monograph on Dimethicone. The original NF monograph on Dimethicone has been supplemented more than once and the most current version is listed in the 5th Supplement of The United States Pharmacopeia Volume XXI and The National Formulary Volume XVI (9).

The NF has as its goal to provide monographs for those pharmaceutical ingredients, which are not included in the USP, as a means of characterizing their composition by providing tests and stating testing limits. While some polydimethylsiloxane manufacturers perform tests necessary to document their adherence to NF specifications, it is necessary for the pharmaceutical end-user of untested fluid to perform the necessary analyses.

C. Cosmetic, Toiletry, and Fragrance Association (CFTA)

The term "Dimethicone" is defined (10) as a mixture of fully methylated linear siloxane polymers containing repeating units of the formula [$(CH3)_2SIO$—], units. These fluids possess the following general structure:

$$(CH_3)_3SiO\left[\begin{array}{c}CH_3\\SiO\\CH_3\end{array}\right]_x Si(CH_3)_3$$

This definition is used by both the Cosmetic, Toiletry and Fragrance Association (CTFA) and by the National Formulary (NF). There is however, a different intent associated with these two systems of nomenclature.

The CTFA has adopted names for cosmetic ingredients, many taken from the USP or NF nomenclature system, to assist this industry in standardizing the labeling of these ingredients. The CTFA names do not, however, imply standards or grades of purity, strict chemical equality, or interchangeability of ingredients.

The difference between the CTFA and NF nomenclature concepts is one of compositional testing and stated testing limits. When the designation NF is used in conjunction with an official name, such as "Dimethicone, NF," it indicates that the product is in compliance with the NF standards. No such compliance testing or testing limits are associated with a CTFA product name, such as "Dimethicone."

D. Code of Federal Regulations (CFR)

Polydimethylsiloxane fluids are listed in the Code of Federal Regulations, Title 21—Food and Drugs in 178.3570—Lubricants with Incidental Food Contact (a) (3). The specific listing is Dimethylsiloxane (viscosity greater than 300 cst).

V. Toxicity of Polydimethylsiloxane Fluids

A. Introduction

The linear and cyclic polydimethylsiloxanes (PDMS) are materials which are frequently used in cosmetic and pharmaceutical applications because of their stability, hydrophobicity, lubricity, and low toxicity. They are represented by the following structural formulas.

$$(CH_3)_3SiO\left[\begin{array}{c}CH_3\\SiO\\CH_3\end{array}\right]_x Si(CH_3)_3 \qquad \text{Linear polymers}$$

$$\left[\begin{array}{c}CH_3\\SiO\\CH_3\end{array}\right]_x \qquad \text{Cyclic polymers}$$

The value of x in the linear polymers can be 2 to several thousand while x for the cyclic species can be 3 to 14, with 4 and 5 being used most frequently. The materials are clear, colorless, oily liquids that are odorless, tasteless, and insoluble in water and highly water repellent. They are also stable at high and low temperatures and are highly resistant to changes due to heat or oxidation. The viscosity of these linear polymers can vary from 0.65 to 1,000,000 centistokes depending on the average chain length (11).

Selected polydimethylsiloxane compounds have been extensively studied to assess their suitability for use in cosmetic, pharmaceutical, and related applications. It is generally believed that data gathered from these selected polymers can be applied to all of the materials except for certain compounds of very low molecular weight.

There is no indication that toxicity would be related to molecular weight or viscosity of these fluids. Calandra et al. have summarized their review of the health and environmental aspects of polydimethylsiloxane fluids by stating: "The polydimethylsiloxanes, in a very extensive bat-

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