International Journal of Pharmaceutics, 6 (1980) 333–337

A STUDY ON PARTICULATE FORMATION OF SILICONE-COATED GLASS SURFACES

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(Received March 25th, 1980)
(Revised version received August 25th, 1980)
(Accepted August 28th, 1980)

SUMMARY

Silicone-coated glass surfaces produced by two different siliconization procedures were exposed to an extreme and rapid temperature change (−70°C to +25°C). The extent of the formation of particulate (>25 μm) and the integrity of silicone-film were evaluated with respect to siliconization procedure and curing cycle. In all instances, the silicone-film integrity test showed that the integrity of the silicone-film was damaged when the coated surface was exposed to an extreme change of temperature. Furthermore, it was shown that in both siliconization procedures the formation of silicone particles (>25 μm) was reduced to a minimum when 0.5% (w/v) siliconizing fluid was used, and the coated surface was cured at 250°C for 3 h or at 300°C for 2 h. Under these conditions, a silicone coat relatively more resistant to extreme temperature change was obtained.

INTRODUCTION

The use of silicones for coating glass surfaces has become a widespread practice in drug industry (Gancberg, 1963). Frequently, the primary containers for parenteral products such as glass vials and amplules are siliconized in order to render the glass surface inert. and thus minimize the adsorption on the glass surface of active ingredients such as hormones, radionuclide-labeled chemicals and biologicals, to avoid denaturing sensitive biological injectables such as radionuclide-labeled firbrinogen, to improve recovery in certain analytical procedures (Bhargava, 1977), to allow uniform withdrawal of the vial's contents, and to improve the esthetics (Riffkin, 1968).

The siliconization of glass surfaces is achieved by dipping into or by spraying the glass

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surface with a solution of silicone and then by curing the coated surface in an oven under certain temperature and time conditions. These conditions directly affect the quality of the silicone coat. Since siliconized glass bottles, vials and ampules are used as primary containers in certain parenteral injectable products, it is important to determine the optimum curing conditions that will yield a durable silicone coat which will shed the least number of particles when it is exposed to temperature changes during the filling, packaging, shipping and storage conditions or due to the fact that the nature of preparation itself requires application of such temperature extremes.

In this study, the effect of the silicone concentration, curing temperature and time with respect to the formation of silicone particulate larger than 25 μm, and the integrity of the silicone-film after a freeze–thaw cycle was studied. The rationale for selecting the number of particles larger than 25 μm as criterion for evaluating the performance of the silicone coating when subjected to a freeze–thaw cycle was based on the following: (a) large numbers of such particles (>25 μm) are unacceptable in large volume parenteral (LVP) solutions (USP XX); and (b) the curing conditions that produced the silicone coating which when subjected to a freeze–thaw cycle shed the least number of particles larger than 25 μm were the proper conditions of siliconization for the intended use of the vials.

MATERIALS AND METHODS

Chemicals. Bovine serum albumin (BSA), silver nitrate, methyl ethyl ketone, conc. NH_4OH, formaldehyde 37% (v/v), bromophenol blue, medical grade 360 silicone fluid 1000 cS from Dow Corning.

Reagents. (a) BSA 6.0% (w/v) in saline; (b) $AgNO_3$, 4% (w/v); (c) bromophenol blue 0.2% (w/v) in 20% (v/v) ethanol solution; (d) medical grade 360 silicone fluid 1000 cS (0.5% (w/v) in methyl ethyl ketone; (e) NH_4OH 1% (v/v); (f) modified Tollen's reagent; NH_4OH 1% (v/v) was added drop by drop to 12 ml of 4% (w/v) $AgNO_3$ until the precipitate dissolved; excess of NH_4OH was avoided. This solution was freshly prepared.

Siliconization of glass surface. The glass vials (Type I, Wheaton) were washed in Cozzolli washer and then were rinsed with 95% (v/v) ethanol solution and dried. The vials were siliconized by dipping them into a methyl ethyl ketone solution of silicone for 5 min. The vials were then inverted and placed on a stainless steel screen and were left to drain for at least 15 min at an angle of 45°. Alternatively, the siliconization process by spraying involved injection of a silicone solution in methyl ethyl ketone into each vial through a nozzle tip. The spray cycle lasted for 2 s, delivering approximately 3--4 ml of solution. The vials were left to drain. The vials, 140 per lot, were placed in a stainless steel container and cured in a sterilization oven (Grieve). The following concentrations of silicone fluid in methyl ethyl ketone were used: 0.5, 1, 1.5, 2.0, 2.5, 3.0 and 3.5%. The cured vials from each lot were filled with 1 ml of double-distilled water in a laminar flow hood (Grieve) and capped with a 192 red, Teflon-coated stopper septum (West) and an overseal. One-half of the vials from each lot were dipped in acetone/CO_2 for 10 min and then were left to thaw. The other half of the vials from each lot was not exposed to temperature change and it was used as control.

Determination of particle size and count. The content of the vial was filtered through a 0.45 μm membrane filter and the silicone particles > 25 μm were observed and counted

through a dark-field microscope (Hohmann et al., 1973). The control vials were rinsed twice with double-distilled water (1 ml) and the washings were filtered through a 0.45-μm membrane filter.

Silicone-film integrity test. The integrity of the silicone film was evaluated by two qualitative tests. *Test A*: bovine serum albumin, 6.0% (w/v) in saline (1.6 ml), was injected through the stopper septum with a syringe. The vial was rotated on a vortex mixer so that the albumin solution was spread over the whole interior surface of the vial. Then 3 ml of acetone were injected into the liquid and 0.05 ml of bromophenol solution. The vial was placed in a water bath at 30–40°C for 30–40 s. During warming the vial was agitated until the albumin was denatured and coalesced into a mass. The vial was vortexed again and then it was inspected for the presence of firmly adhering denatured albumin particles on the glass wall. *Test B*: one ml of Tollen's reagent was injected into the vial and then two drops of a 37 (v/v) HCHO was added. The vial was agitated so that the liquid wetted the entire internal surface. Then, the surface was examined for silver metal deposited on the glass surface.

In both tests A and B, 10 randomly selected vials from each lot were tested for silicone-film integrity. A lot passed the silicone-film integrity test A or B if none of the 10 vials had firmly adhering denatured albumin particles or clear silver metal deposits on the walls. A lot failed the test A or B if only one vial out of 10 had visible denatured albumin particles or silver metal deposits on the vial's walls.

RESULTS AND DISCUSSION

The effect of the silicone concentration in the formation of silicone particulate is shown in Fig. 1. It is evident that the number of silicone particles (>25 μm) shed from the walls of the vials, after a freeze–thaw cycle (–70°C to +25°C), increased with increasing concentrations of siliconizing fluid. Furthermore, prolongation of the curing time at constant temperature (300°C) had the same effect at concentrations of silicone fluid

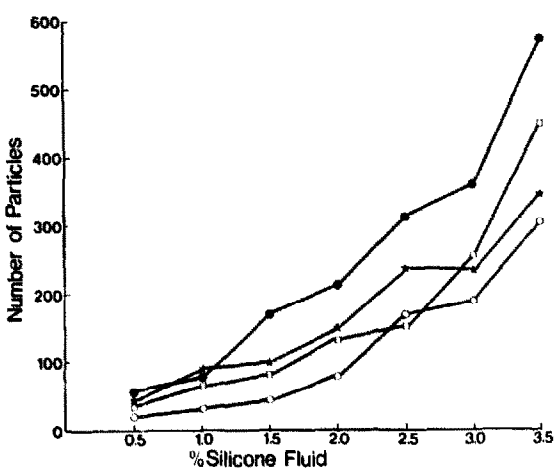

Fig. 1. Number of particles larger than 25 μm in 5 vials. Dipped vials cured for 6.0 h (●———●); sprayed vials cured for 6.0 h (★———★); dipped vials cured for 4 h (□———□); sprayed vials cured for 4 h (○———○). All vials cured at 300°C.

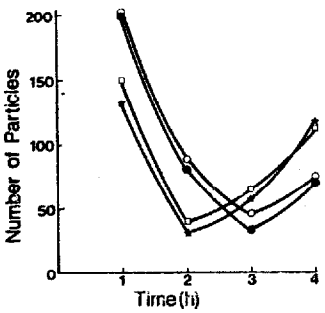

Fig. 2. Number of particles larger than 25 μm in 10 vials sprayed with or dipped in silicone fluid 0.5%. Sprayed vials cured at 250°C (●———●); and 300°C (□———□); dipped vials cured at 250°C (○———○); and at 300°C (★———★).

higher than 1.5%. The optimum silicone concentration for both siliconization procedures and cure cycles was 0.5% (w/v). The siliconization procedure by dipping produced more particles than the spraying procedure. The effect of the curing temperature and time on the formation of particulate (>25 μm) after the vials were subjected to a freeze–thaw cycle (–70°C to +25°C) is shown in Fig. 2. It is apparent that the curing-cycle conditions that produced the silicone film which shed the least number of particles (>25 μm) upon challenge with a freeze–thaw cycle, were either 2 h at 300°C or 3 h at 250°C. The controls for each lot which were not subjected to a freeze–thaw cycle had 3–7 silicone particles (>25 μm) per 10 vials (Table 1). All the control vials passed the silicone-film integ-

TABLE 1

PARTICULATE FORMATION IN SILICONE-COATED VIALS

Curing cycle	Sprayed vials						Dipped vials					
	C	A	B	F/T	A	B	C	A	B	F/T	A	B
1 h, 250°C	4 [a]	+	+	200 [a]	–	–	3 [a]	+	–	207 [a]	–	–
1 h, 300°C	3	+	+	150	–	–	5	+	+	133	–	–
2 h, 250°C	6	+	+	80	–	–	4	+	+	87	–	–
2 h, 300°C	6	+	–	41	–	–	3	+	+	29	–	–
3 h, 250°C	3	+	+	32	–	–	7	+	–	47	–	–
3 h, 300°C	5	+	+	65	–	–	4	+	+	55	–	–
4 h, 250°C	3	+	+	69	–	–	4	+	+	75	–	–
4 h, 300°C	3	+	+	116	–	–	5	+	+	120	–	–

C: control vials, not subjected to freeze–thaw cycle (–70°C to +25°C).
F/T: vials subjected to freeze–thaw cycle (–70°C to +25°C).
A: silicone-film integrity test A, 10 vials tested.
B: silicone-film integrity test B, 10 vials tested.
+: all 10 vials passed the test.
–: at least one vial failed the test.
[a] Particles > 25 μm, in 10 vials.

rity test A, but all the lots of vials subjected to the freeze–thaw cycle failed this test. The silicone-film integrity test B failed some of the controls and every lot of vials subjected to freeze–thaw cycle.

In conclusion, the present study has shown that silicone-coated glass surfaces shed particles when they were exposed to temperature extremes. However, under certain conditions of siliconization, more resistant silicone-film was produced which when subjected to temperature extremes shed the least number of particles larger than 25 μm. This particularly concerns situations where injectables and sensitive to glass biologicals are shipped within silicone-coated glass containers.

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