Effect of the Incorporation of Hydroxy-Terminated Liquid Silicones on the Cure Characteristics, Morphology, and Release of a Model Protein from Silicone Elastomer-Covered Rods

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ABSTRACT: Silicone elastomer systems have previously been shown to offer potential for the sustained release of protein therapeutics. However, the general requirement for the incorporation of large amounts of release enhancing solid excipients to achieve therapeutically effective release rates from these otherwise hydrophobic polymer systems can detrimentally affect the viscosity of the precure silicone elastomer mixture and its curing characteristics. The increase in viscosity necessitates the use of higher operating pressures in manufacture, resulting in higher shear stresses that are often detrimental to the structural integrity of the incorporated protein. The addition of liquid silicones increases the initial tan δ value and the tan δ values in the early stages of curing by increasing the liquid character (G'') of the silicone elastomer system and reducing its elastic character (G'), thereby reducing the shear stress placed on the formulation during manufacture and minimizing the potential for protein degradation. However, SEM analysis has demonstrated that if the liquid character of the silicone elastomer is too high, the formulation will be unable to fill the mold during manufacture. This study demonstrates that incorporation of liquid hydroxy-terminated polydimethylsiloxanes into addition-cure silicone elastomer-covered rod formulations can both effectively lower the viscosity of the precured silicone elastomer and enhance the release rate of the model therapeutic protein bovine serum albumin. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 124: 805–812, 2012

Key words: silicone elastomer; liquid silicone; oscillatory rheology; protein delivery; sustained release; scanning electron microscope

INTRODUCTION

Silicone elastomers are already well-established for the fabrication of various marketed medical and sustained release drug delivery devices (e.g., Norplant®, Estring®, Femring®, and Compudose®), and there is considerable current interest in developing new devices to extend their role into other clinical indications (e.g., vaginal rings for sustained release of HIV microbicides). However, the highly hydrophobic nature of conventional medical-grade silicone elastomer systems, which are invariably based on polydimethylsiloxane, significantly limits their use in drug delivery applications, because only therapeutic agents having appreciable solubility and diffusivity in the elastomer can permeate through the elastomer and achieve therapeutically effective release rates.[1–4] These physicochemical constraints clearly preclude the release of water-soluble macromolecular therapeutics, such as peptides, proteins, and nucleic acids. It has been demonstrated that the inclusion of solid hydrophilic excipients, such as glycine and bovine serum albumin (BSA), into matrix and covered rod silicone elastomer devices can significantly increase the release rates of hydrophilic drugs.[5–22]

A rod insert vaginal ring (RIVR) for the sustained delivery of proteins and other biological macromolecules has recently been developed by our group and combines both the concepts of a vaginal ring device and a covered rod formulation (Patent Application No. 20090004246). In this device, the vaginal ring acts as a physical holder for the matrix rod insert containing the therapeutic agent. This "rod-in-ring" device essentially mimics the form and function of a covered rod (Fig. 1), with the added benefit of providing long-term retention in the vaginal tract for sustained mucosal drug administration. From a

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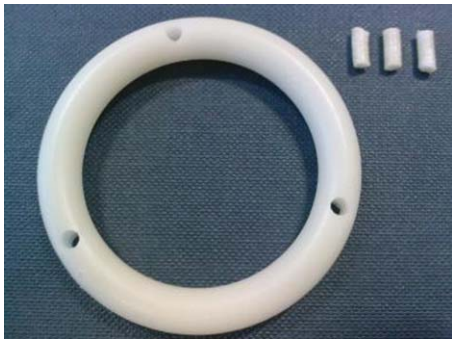

Figure 1 Rod inserted vaginal ring (RIVR) with three rod inserts. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

manufacturing perspective, the ring body and the rod inserts are produced in different steps. The ring body containing one or more cavities through its cross section is fabricated in a single-step elevated temperature reaction injection-molding process; the insert rods containing the therapeutic agent and accompanying excipients are manufactured by continuous room temperature reaction extrusion. The rods are then cut to length and inserted into the cavities within the ring body.

Previous studies have advocated the use of high loadings of solid excipients to enhance the release of hydrophilic and/or macromolecular therapeutics from polydimethylsiloxane elastomers.[5–22] However, we have recently shown that such high excipient loadings adversely affect the viscosity of the precured silicone elastomer systems[23] leading to the requirement for use of higher processing pressures during manufacture. The resulting high shear stresses experienced during the low temperature reaction extrusion process are not conducive to protein stability.

The inclusion of small quantities of liquid silicones is already used in the manufacture of commercial silicone elastomer devices, including vaginal rings, for the purpose of aiding removal of the device from the injection mold after curing is completed. The inclusion of larger quantities of liquid silicones in solid excipient-loaded silicone elastomer systems may serve to facilitate ease of processing (by decreasing the viscosity of the silicone elastomer mix) and simultaneously modify the release of incorporated therapeutic proteins from the device. Here, we evaluate the effect of incorporation of hydroxy-terminated liquid silicones and glycine on the rheological, release, and morphological characteristics of various BSA-loaded silicone elastomer formulations, where BSA is acting as a model therapeutic protein.

EXPERIMENTAL

Materials

Medical-grade, low-consistency poly(dimethylsiloxane) elastomer systems (MED2-4220 and LSR90-9508-30) from NuSil Technology (Carpinteria, CA) were purchased from Polymer Systems Technology (High Wycombe, UK). Glycine was supplied by Sigma-Aldrich (Dorset, England). α,ω-Dihydroxy polydimethylsiloxanes (hereafter referred to as "liquid silicones"; viscosity grades 50, 200, and 1000 cSt) were purchased from Sigma-Aldrich (Dorset, England). BSA fraction V lyophilized was supplied by Kraeber GMBH (Schleswig-Holstein, Germany). The BSA, which was originally in flake form, was milled using an automatic mortar grinder and then sieved. The fraction of BSA with a particle size from 65 to 250 μm was used for the preparation of all subsequent silicone elastomer formulations.

Preparation of silicone elastomer mixes

Addition-cure silicone elastomer mixes (3.0 g) were prepared for rheological evaluation by adding Part A and Part B of the silicone elastomer systems (1 : 1 ratio) and optionally the required amount of glycine, BSA, and liquid silicone to a sealed plastic container. Part B of the silicone elastomer was added last so as not to induce premature curing. The contents of the container were mixed for 30 s at 3500 rpm using a Speed Mixer DAC 15FVZ-K (Synergy Devices).

Oscillatory rheology

Each silicone elastomer mix was placed onto the lower parallel plate of a TA Instruments AR2000 Rheometer using a disposable plastic syringe. The upper 40-mm diameter crosshatch parallel plate was lowered to produce a 1000-μm plate gap, and the excess silicone mix was removed before the oscillation experiment was started. The linear viscoelastic region was determined for each silicone by performing a stress sweep on part A of each elastomer. The stress, for subsequent cure analysis experiments (270 Pa for MED2-4220 and 8.7 Pa for LSR90-9508-30), was selected from the midpoint of the horizontal portion of a stress sweep. A frequency of 1 Hz was used in all analyses, representative of the typical frequency that a device might be subjected to *in vivo*. Triplicate rheological evaluations of MED2-4220 and LSR90-9508-30 formulations were performed at 40 and 80°C, respectively.

Manufacture of BSA-loaded covered rods

Covered rod devices comprising 1% w/w BSA and various loadings of the release enhancing excipient glycine (0 and 50% w/w) and a liquid silicone (0 and 10% w/w) were prepared using the medical-grade, addition-cured, low-consistency platinum-catalyzed silicone elastomer system LSR9-9508-30. The silicone elastomer formulations were prepared by

mixing the part A and part B silicone elastomer components along with the appropriate amounts of BSA, glycine, and liquid silicone to give a 5.0-g total mix weight. The mix was injected into silicone tubing (3 mm ID and 6.35 mm OD) using a disposable plastic syringe and cured overnight at room temperature. The tubing was cut into 1.5 cm lengths to produce the BSA-loaded covered rods.

In vitro release experiments

Each silicone elastomer covered rod ($n = 4$) was placed into a glass vial containing 10 mL of HPLC grade water adjusted to pH 4.5 (mimicking vaginal pH). The vials were placed in an orbital shaking incubator (Unitron HT infors) at 37°C and 60 rpm, with daily sampling and complete replacement of the release medium over 14 days. BSA concentrations were determined by HPLC-UV.

Morphological evaluation of covered rods using scanning electron microscopy

Scanning electron microscopy (SEM; Jeol 6500F FEG) was used to characterize the changes in morphology occurring at the ends of the covered rods during the release experiments. Thin sections were cut from the end of covered rod formulations and attached to aluminum discs using acrylic glue before being sputter-coated with gold leaf.

HPLC methodology

Quantification of BSA release was performed using HPLC with UV detection. The instrument set-up was as follows: isocratic pump (Model-1515, Waters); autosampler (Model-717plus, Waters); dual wavelength absorbance detector (Model-2487, Waters); BioSep-SEC-S 3000 column (300 × 7.8 mm I.D., 5-μm particle size); mobile phase—50 m*M* ammonium acetate pH 6.8 buffer; 1.0 mL/min flow rate; 280 nm wavelength of detection; 100-μL sample injection volume.

Statistical analysis

The effect of liquid silicone viscosity and loading on the rheological cure characteristics of medical grade silicone elastomer systems and the release of BSA from these elastomers was statistically compared using a two-way analysis of variance (ANOVA) (GraphPad Prism version 5.02 for Windows, GraphPad Software, San Diego, CA). *Post hoc* comparisons of the means were performed using the Bonferroni correction. A one-way ANOVA (GraphPad Prism version 5.02 for Windows, GraphPad Software) was used to statistically evaluate the release of BSA (on days 1, 7, and 14) from these elastomers. *Post hoc* comparisons of the means were performed using Tukey's honestly significance difference test. A significance level of $P < 0.05$ was accepted to denote significance in all cases.

RESULTS

Rheological assessment of silicone elastomer systems loaded with liquid silicones

Table I summarizes the following pre- and postcure rheological character for the MED2-4220 and LSR9-9508-30 silicone elastomer systems containing different viscosity grades (50, 200, and 1000 cSt) and concentrations (0, 10, 30, and 50% w/w) of the liquid silicones: the initial tan δ value (a measure of the relative liquid/elastic character) of the precured silicone elastomer mix; the final G' value (storage modulus) of the cured system; time to reach a tan δ value of 0.2 (indicative of a cured system).[23] Whereas Figures 2 and 3 show the respective tan δ rheograms for each of the silicone elastomers containing varying loadings of each of the different grades of liquid silicone. In general, increasing the liquid silicone concentrations in the precured silicone systems results in increased initial tan δ values, consistent with increased liquid character. The elastic character of the systems postcure significantly decreases with increasing liquid concentration, as evidenced by decreasing final G' values (Table I). A two-way ANOVA demonstrates that the increase in the precure tan δ values is attributed to the liquid silicone concentration within the system ($P < 0.0001$) and not the viscosity grade of the incorporated liquid silicone ($P = 0.05$). A similar observation is made for the decrease in the postcure G' ($P = <0.0001$ and 0.41). Figures 2 and 3 further demonstrate that higher loadings of either grade of liquid silicone result in higher tan δ values early in the curing process, with tan δ decreasing over time as the silicone begins to cure. In the MED2-4220 silicone elastomer system (Fig. 2), the inclusion of 50% of either grade of liquid silicone results in significantly higher tan δ values compared to the 0, 10, and 30% loadings ($P < 0.0001$). Whereas a 10% loading of the 50 and 200 cSt grade liquid silicones actually lowered the tan δ value (an increase in the elastomer characteristic of the system), in the early stages of the curing process ($P = 0.03$ and 0.04) compared to the 0% loading, while a 10% loading of the 1000 cSt grade liquid silicone had no significant effect on the tan δ values ($P = 0.32$). In the case of the LSR9-9508-30 silicone elastomer system (Fig. 3), the majority of the loadings of the different grades of liquid silicones resulted in an increase in the tan δ during the early stages of cure (P values < 0.05). A 10% loading

TABLE I
The Effect of Liquid Silicones on the Initial Tan δ Value, the Final G′ Value, and the Time to Reach Tan δ 0.2 for the Silicone Elastomers MED2–4220 (at 40°C) and LSR9–9508–30 (at 80°C)

Silicone elastomer system	Liquid silicone viscosity (cSt)	Liquid silicone loading (%)	Initial tan δ	Final G' (Pa)	Time to reach tan δ 0.2 (min)
		0	4.3 (*0.1*)	5.2 (*0.0*)	5.7 (*0.2*)
	50	10	3.2 (*0.2*)	5.2 (*0.0*)	5.7 (*0.2*)
		30	6.2 (*0.9*)	5.0 (*0.2*)	6.8 (*0.2*)
		50	11.7 (*0.7*)	4.4 (*0.1*)	9.2 (*0.2*)
MED2–4220	200	10	3.2 (*0.5*)	5.2 (*0.2*)	5.8 (*0.1*)
		30	5.7 (*0.0*)	4.8 (*0.0*)	6.5 (*0.3*)
		50	13.9 (*1.2*)	4.4 (*0.1*)	8.8 (*0.2*)
	1000	10	4.3 (*0.0*)	5.1 (*0.0*)	5.8 (*0.2*)
		30	6.8 (*0.2*)	4.8 (*0.0*)	6.8 (*0.2*)
		50	12.5 (*0.7*)	4.5 (*0.0*)	8.2 (*0.1*)
		0	3.9 (*1.0*)	5.6 (*0.0*)	3.2 (*0.2*)
	50	10	4.7 (*0.4*)	5.4 (*0.0*)	3.3 (*0.1*)
		30	6.9 (*0.4*)	5.0 (*0.0*)	3.3 (*0.3*)
		50	10.0 (*0.9*)	4.5 (*0.0*)	4.2 (*0.2*)
LSR90–9508–30	200	10	4.3 (*1.9*)	5.4 (*0.0*)	3.7 (*0.1*)
		30	7.1 (*0.8*)	5.0 (*0.0*)	3.7 (*0.2*)
		50	9.0 (*1.3*)	4.5 (*0.0*)	4.5 (*0.2*)
	1000	10	5.3 (*0.2*)	5.4 (*0.0*)	3.2 (*0.2*)
		30	6.8 (*0.2*)	5.0 (*0.1*)	3.2 (*0.3*)
		50	11.0 (*0.8*)	4.6 (*0.0*)	4.7 (*0.2*)

of the 50 and 200 cSt liquid silicones showed no significant difference in the initial tan δ value (Table I) when compared with the 0% loading (P values $>$ 0.05). However, the 50 cSt liquid silicone had a higher tan δ value directly after the initial reading compared to the 0% loading, whereas the 200 cSt liquid silicone required up to 1 min into the curing process to show a higher tan δ value than the 0% loading.

For MED2-4220, the time to reach tan $\delta = 0.2$ (when the formulation is deemed sufficiently cured to be handled) increases significantly with increasing liquid silicone concentration. In the LSR9-9508-30 system, only the 50% liquid silicone concentrations significantly influenced this parameter ($P = 0.01$).

Rheological assessment of silicone elastomer systems loaded with both liquid silicones and glycine

It has been demonstrated that to increase the release rate of proteins from silicone elastomer devices, it has been necessary to incorporate solid hydrophilic excipients into the silicone elastomer, such as glycine.[6–22] The excipient provides the means by which aqueous fluid is absorbed into the device and the protein solubilized and released. As the excipient dissolves in the aqueous fluid, it leaves pores and channels in the elastomer, which allow the aqueous fluid to imbibe into the covered rod and thus solubilize and release the protein [Fig. 6(B)]. However, the inclusion of solid excipients, particularly at high loadings, adversely affects the precure viscosity of these silicone elastomer systems.[23] Therefore, the effect of liquid silicones on the precure viscosity of silicone elatomers modified with the solid excipient glycine was evaluated. The initial tan δ value, the final G' value, and the time to reach a tan δ value of 0.2 for the silicone elastomers MED2-4220 and LSR90-9508-30 with varying loadings (0, 10, 30, and 40% w/w) of liquid silicones (50, 200, and 1000 cSt viscosities) and glycine (10, 20, 40, and 50% w/w) are presented in Table II. Increasing the concentration of liquid silicone in the formulation increased the initial tan δ values significantly (P values = <0.05) while the final G' values were decreased (P values = <0.05). Figures 4 and 5 contain representative rheograms for the silicone elastomers MED2-4220 and LSR90-9508-30 with varying loadings of liquid silicone and glycine. All the silicone elastomer systems have the same trend of decreasing tan δ values with an increase in time. The MED2-4220 silicone elastomer systems containing 40% w/w of either of the liquid silicones and 10% w/w of glycine had significantly higher tan δ values in the early stages of the curing process than any other of the MED2-4220 systems (P values < 0.05). The 30% w/w liquid silicone 20% w/w glycine systems also had higher tan δ values during the early stages of curing compared to the silicone elastomer alone. However, the other formulations (10% w/w liquid silicone 40% glycine and 40% w/w glycine only) have tan δ values that are equal to or lower than the silicone elastomer alone. Similar trends are also seen

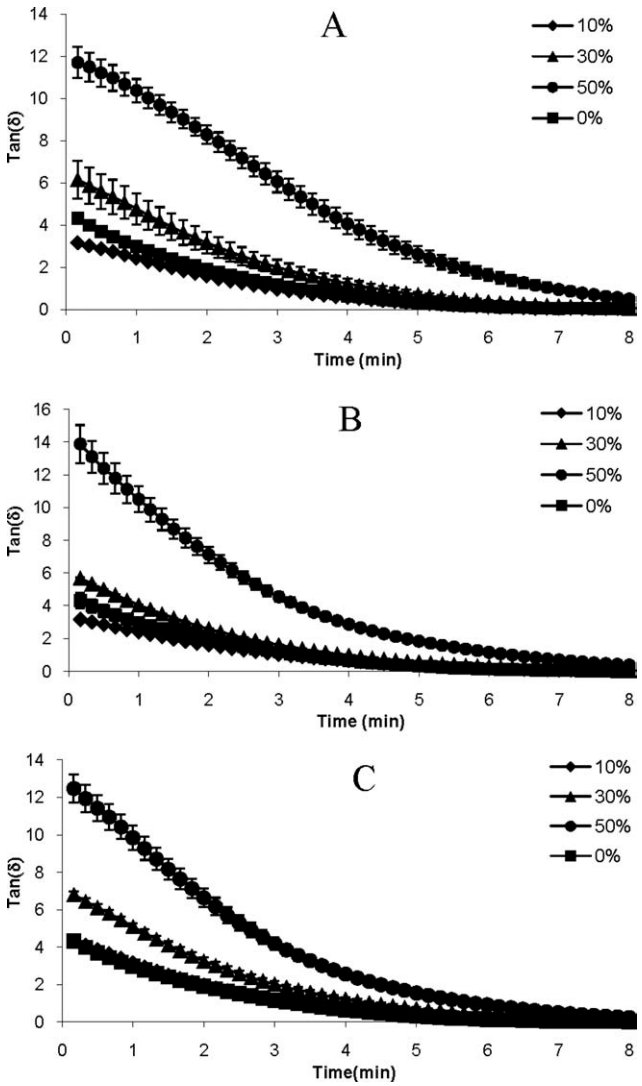

Figure 2 The effect of various loadings of liquid silicones [50 (A), 200 (B), and 1000 cSt (C)] on the tan δ value of the silicone elastomer MED2-4220.

for the silicone elatomer LSR90-9508-30. However, the 40% liquid silicone 10% glycine and the 30% liquid silicone 20% glycine systems have similar tan δ values, which are higher than all of the other systems for all grades of liquid silicone. Furthermore, for this silicone elastomer, the 10% w/w liquid silicone and the 40% glycine systems have lower tan δ values in the early stage of cure when compared with the silicone elastomer alone.

Morphological evaluation of covered rods using SEM

A representative SEM image of the end cross section of a covered rod containing 30% 200 cSt liquid silicone, 20% glycine, and 50% of the silicone elastomer LSR90-9508-30, which has an initial tan δ value of 6.5, is shown in Figure 6(A). It demonstrates that the initial viscosity of this formulation is so low (high initial tan δ value) that it is unable to fill the silicone tubing. A gap is clearly visible between the active core and the surrounding sheath of the aforementioned covered rod formulation. However, a covered rod containing 50% glycine and 50% of the silicone elastomer LSR90-9508-30 with an initial tan δ of 4.3 is capable of filling the silicone tubing [Fig. 6(B)]. This data demonstrates the importance of the precured viscosity of the formulation on manufacture. If the formulation has a high initial tan δ (low precured viscosity), like the example, in Figure 6(A), then it will be unable to take the shape of the mold during manufacture. Furthermore, if the initial tan δ values are too low (high precured viscosity), then higher processing pressures are required during

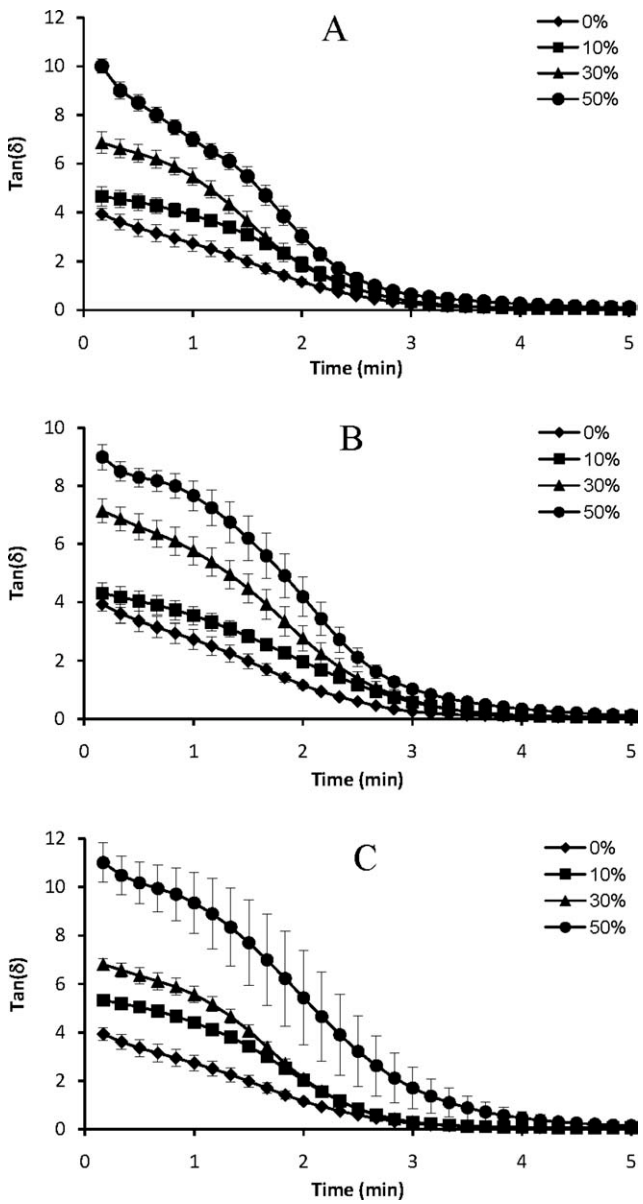

Figure 3 The effect of various loadings of liquid silicones [50 (A), 200 (B), and 1000 cSt (C)] on the tan δ value of the silicone elastomer LSR90-9508-30.

TABLE II
The Effect of Liquid Silicone and Glycine Loading on the Initial Tan δ Value, the Final G′ Value and the Time to Reach Tan δ for the Silicone Elastomers MED2–4220 (at 40°C) and LSR9–9508–30 (at 80°C)

Silicone elastomer system	Liquid silicone viscosity (cSt)	Liquid silicone/glycine loading (%)	Initial tan δ[a]	Final G′	Time to reach tan δ 0.2 (min)
MED2–4220		0	4.3[b]	5.2	5.7
		50	3.1[b]	6.1	5.7
	50	10/40	3.0[b]	5.6	5.7
		30/20	8.0	5.0	6.8
		40/10	11.3	4.7	8.0
	200	10/40	2.0[b]	5.7	5.3
		30/20	6.5[b]	5.0	6.8
		40/10	10.7	4.7	7.5
	1000	10/40	3.7[b]	5.6	5.5
		30/20	6.9	5.0	6.8
		40/10	9.7	4.7	7.5
LSR90–9508–30		0	4.5[b]	5.4	3.8
		40	0.9	6.0	1.8
	50	10/40	3.8[b]	5.8	2.7
		30/20	6.9	5.0	3.2
		40/10	8.1	4.7	3.5
	200	10/40	4.2[b]	5.9	2.7
		30/20	7.6	5.0	3.8
		40/10	8.6	4.7	4.0
	1000	10/40	2.4[b]	5.8	2.5
		30/20	7.3	5.0	3.7
		40/10	8.7	4.8	3.7

[a] A limit of 0.9–2.0 was set for the initial tan δ.
[b] Within the initial limits set for the tan δ.

manufacture. The resulting high shear stresses experienced during the low temperature reaction manufacturing process are not conducive to protein stability.

In vitro release of BSA from LSR90-9508-30 silicone elastomer-covered rods

Figure 7 demonstrates the effect of adding 10% w/w of a liquid silicone (200 cSt) to a silicone elastomer (LSR90-9508-30) modified with 50% w/w of the release enhancing excipient glycine on the release of BSA from a 1% w/w BSA-loaded covered rod. The figure shows that the addition of 50% w/w glycine only significantly enhances the release of BSA from 92.9 μg (∼ 4.6% of the total BSA content) for the silicone elastomer with no glycine or liquid silicone (P value < 0.01) to 1357.6 μg (∼ 67.9% of the total BSA content) over 14 days. The addition of 10% w/w of the 200 cSt liquid silicone to the elastomer modified with 50% w/w glycine further enhanced the release of BSA to 1802.8 μg (∼ 90.1% of the total BSA content) over 14 days (P value < 0.01).

DISCUSSION

The tan δ value was used to evaluate the effects of glycine and liquid silicone loading on the rheological character of the precured silicone elastomer formulations. Tan $\delta = G''/G'$ where G'' is a measure of the energy dissipated as heat and is associated with the liquid character of the system, and G' is a measure of the elastic character of the system. Therefore, a higher tan δ value means that G'' is greater than G', and so the silicone elastomer formulation has predominantly more liquid than elastomer character at the beginning of cure and should therefore have a lower viscosity. The final storage modulus (final G') was used to evaluate the rheological character of the final formulations. A high-final storage modulus would suggest that the cured silicone elastomer formulations would have limited flexibility, making them to brittle for insertion into the RIVR. All the formulations are considered cured when they reach tan $\delta = 0.2$. Therefore, to ensure short manufacturing times, the time to reach tan $\delta = 0.2$ was also reported.

The addition of liquid silicones increases the initial tan δ value (Table I) and the tan δ values in the early stages of curing (Figs. 2 and 3) by increasing the liquid character (G'') of the silicone elastomer system and reducing its elastic character (G'). The decrease in final G' (Table I) is attributed to the influence of the liquid silicone in reducing the elastic character of the cured silicone elastomer. Furthermore, the

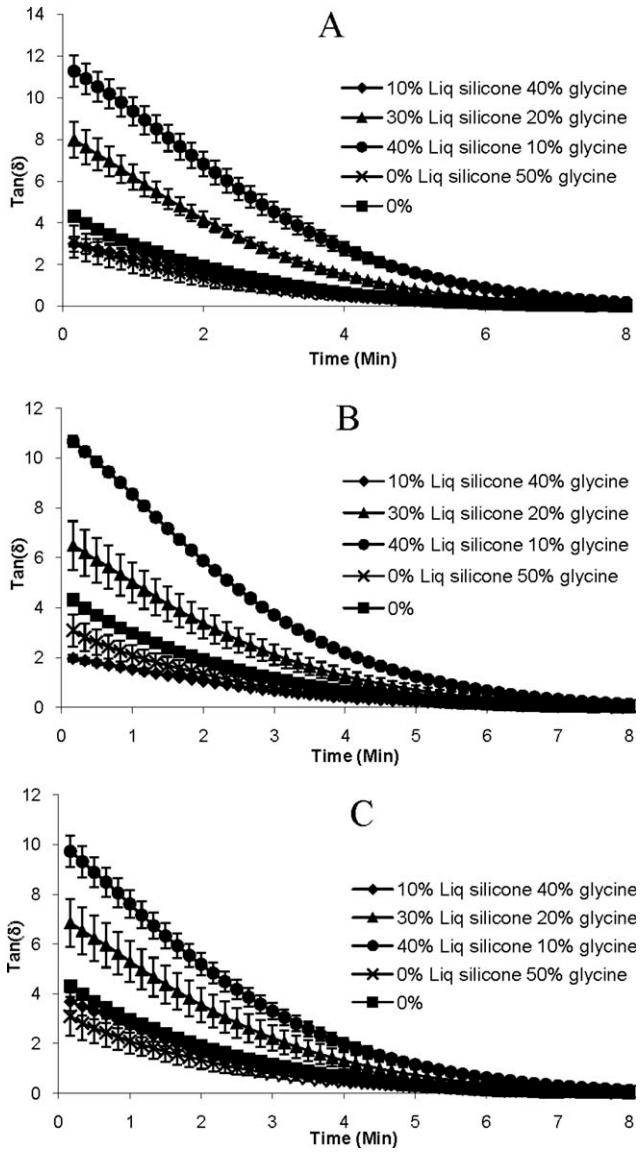

Figure 4 The effect of various loadings of liquid silicones [50 (A), 200 (B), and 1000 cSt (C)] and glycine on the tan δ value of the silicone elastomer MED2-4220.

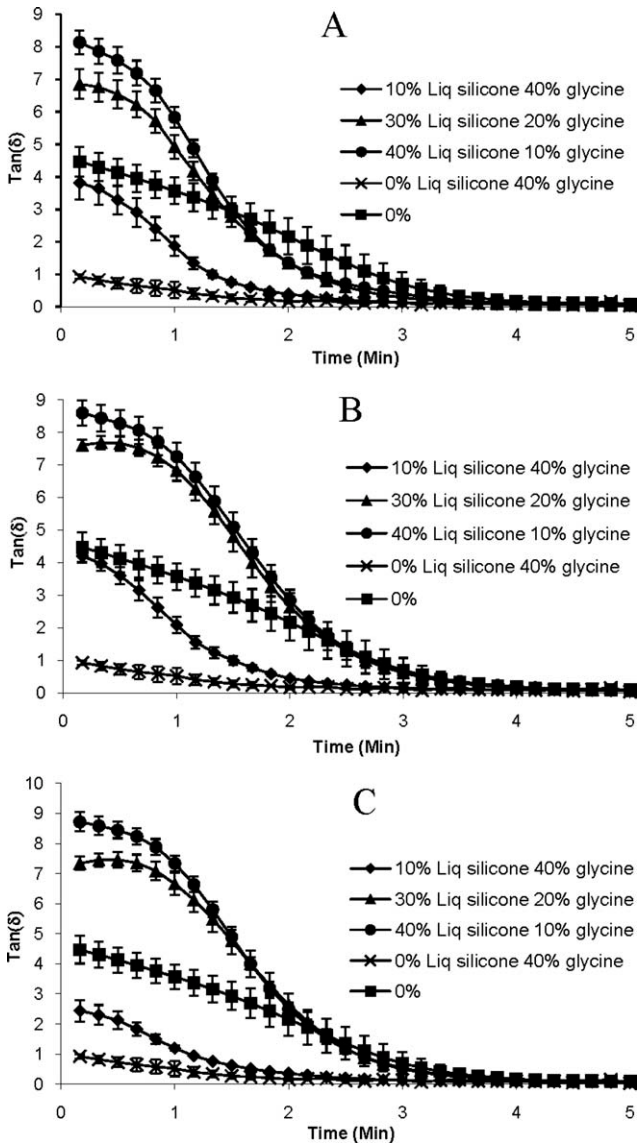

Figure 5 The effect of various loadings of liquid silicones [50 (A), 200 (B), and 1000 cSt (C)] and glycine on the tan δ value of the silicone elastomer LSR90-9508-30.

addition of liquid silicones to either grade of silicone elastomer did not increase the cure time enough to cause problems during manufacture.

It has been demonstrated that the inclusion of solid excipients, particularly at high loadings, adversely affects the precure viscosity of silicone

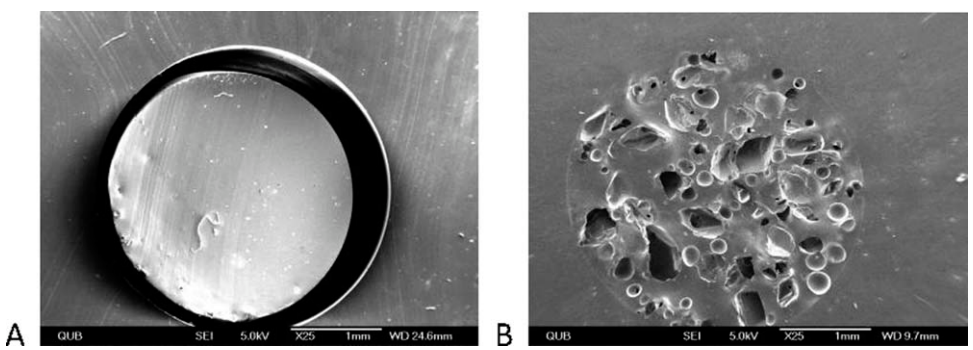

Figure 6 SEM images of the end of a postcured covered rod containing a 50% w/w loading of liquid silicone (A) and a 50% w/w loading of glycine (B) after 14 days on release.

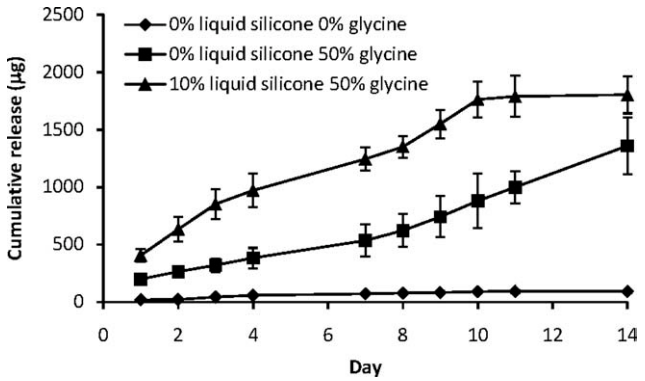

Figure 7 The effect of liquid silicone (200 cSt) and glycine on the release of BSA from LSR90-9508-30 covered rods.

elastomer systems.[23] Therefore, the effect of liquid silicones on the cure characteristics and release of BSA from silicone elastomers modified with glycine was evaluated. To ensure any changes in the cure, characteristics was a factor of the liquid silicone, and glycine loading the elastomer content of each formulation was kept at 50% and the ratio of liquid silicone to glycine adjusted.

Increasing the concentration of liquid silicone in the formulation increases the initial tan δ values and decreases the final G' values significantly (Table II), while Figures 4 and 5 demonstrate that the increase in tan δ value with the increase in liquid silicone content continues through the early stages of cure. These observations are a result of the liquid silicones increasing the liquid character (G'') of the silicone elastomer in the early stages of cure, which is represented by a higher tan δ value. However, Figure 6(A) demonstrates that if the initial tan δ of the formulation is too high (6.5), it is unable to fill the silicone tubing and thus will be unable to fill a mold during manufacture.

The release data presented in Figure 7 demonstrates that not only does the addition of a 10% w/w of the 200 cSt liquid silicone to the silicone elastomer LSR90-9508-30 modified with 50% w/w glycine reduce the precured viscosity and thus ease manufacture; it also enhances the release of BSA from the formulation. This enhancement of release can be attributed to the addition of the liquid silicone resulting in a more open elastomer network (demonstrated by lower final G' values). This, in turn, allowed more release media to imbibe into the silicone elastomer and more BSA to diffuse out.

CONCLUSIONS

This work has demonstrated that the inclusion of a liquid silicone into silicone elastomer formulations serves to lower the initial tan δ values of the precured mix, thereby reducing the shear stress placed on the formulation during manufacture and minimizing the potential for protein degradation.[24] The inclusion of liquid silicones in the formulation also provides greater scope for incorporating release-enhancing excipients (or therapeutic protein) facilitating increased release rates.

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