Rheological Evaluation of the Isothermal Cure Characteristics of Medical Grade Silicone Elastomers

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ABSTRACT: Silicone elastomer systems have been shown to offer potential for the fabrication of medical devices and sustained release drug delivery devices comprising low molecular weight drugs and protein therapeutics. For drug delivery systems in particular, there is often no clear rationale for selection of the silicone elastomer grade, particularly in respect of optimizing the manufacturing conditions to ensure thermal stability of the active agent and short cycle times. In this study, the cure characteristics of a range of addition-cure and condensation-cure, low-consistency, implant-grade silicone elastomers, either as supplied or loaded with the model protein bovine serum albumin (BSA) and the model hydrophilic excipient glycine, were investigated using oscillatory rheology with a view to better understanding the isothermal cure characteristics. The results demonstrate the influence of elastomer type, cure temperature, protein loading, and glycine loading on isothermal cure properties. By measuring the cure time required to achieve tan delta values representative of early and late-stage cure conditions, a ratio t_1/t_2 was defined that allowed the cure characteristics of the various systems to be compared. Sustained *in vitro* release of BSA from glycine-loaded silicone elastomer covered rod devices was also demonstrated over 14 days. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 116: 2320–2327, 2010

Key words: silicone elastomer; cure characteristics; oscillatory rheology; protein delivery; sustained-release

INTRODUCTION

Silicone elastomers have been widely used in commercial polymeric medical devices (e.g., catheters, tubing, valves, implants) and drug delivery devices (e.g., Norplant®, Estring®, Femring®, Compudose®) owing to their ease and versatility of manufacture, excellent biocompatibility and sustained drug release characteristics. However, the highly hydrophobic nature of conventional medical-grade silicone elastomer systems, which are based almost exclusively on poly(dimethylsiloxane) (PDMS), has significantly limited their use in drug delivery applications. Therapeutically effective release rates are generally only attainable for drug molecules that have sufficient hydrophobic character to permit appreciable solvation in the elastomer and small molecular volume to permit subsequent molecular diffusion through the elastomer network. Representative molecules include steroids and HIV nonnucleoside reverse transcriptase inhibitors.[1–4] Such physicochemical constraints clearly preclude the release of water-soluble macromolecular therapeutics, including small-molecule actives, peptides, proteins and nucleic acids. The use of novel chemically-modified silicone elastomers incorporating hydrophilic moieties could provide enhanced delivery rates for such biomolecules.[5] However, the requirement for extensive and costly testing of new polymeric materials intended for use in medical devices and drug delivery systems seriously limits the short-term practicality of this approach. An alternative strategy that has been applied to silicone elastomers is to modify their physicochemical characteristics by incorporating approved pharmaceutical excipients into the elastomer system.[6–22] These excipients, which may be liquid or solid in nature, are substances that have been appropriately evaluated for safety and are included in the drug delivery system to perform one or more specific functions. For example, the incorporation of hydrophilic excipients into PDMS elastomers has been shown to permit significantly enhanced release of hydrophilic drug molecules, including proteins.[16–21] Although the incorporation of active therapeutic agents and excipients into pre-cured silicone elastomer systems is anticipated to affect the cure and mechanical characteristics, factors which are of paramount importance in terms of overall product development and manufacture, no such studies have been reported.

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TABLE I
Description of Silicone Elastomer Systems

Silicone elastomer	Mix ratio by weight A : B[a]	Viscosity (cP) A, B[b]	Mean viscosity (cP)[c]	Shore hardness[d]	Stress (Pa)[e]	Time (min) to tan δ = **1.0**, *0.2*[f] Cure temperature (°C) 100	80	60	40	20
MED-4011	10 : 1	110K, 1.5K	100K	30	270	**2.6 ± 0.0** *3.4 ± 0.0*	**6.8 ± 0.9** *9.8 ± 1.3*	**26.2 ± 2.1** *40.8 ± 3.3*		
MED-4044	10 : 1	115K, 250	105K	40	270	**3.0 ± 0.6** *8.7 ± 1.2*	**7.3 ± 0.8** *27.5 ± 3.4*			
MED-4210	10 : 1	90K, 5K	82K	20	8.5	**2.3 ± 0.2** *5.5 ± 0.4*	**3.9 ± 0.4** *12.0 ± 1.3*	**16.3 ± 0.5** *52.0 ± 0.6*		
MED2-4220	1 : 1	20K, 15K	18K	25	270		**0.2 ± 0.0** *0.8 ± 0.2*	**0.8 ± 0.2** *1.5 ± 0.3*	**3.3 ± 0.2** *5.7 ± 0.2*	**23.7 ± 0.2** *38.3 ± 0.6*
MED-6010	1 : 1	18K, 12K	15K	45	50	**3.2 ± 0.2** *4.5 ± 0.2*	**6.0 ± 0.9** *9.8 ± 2.6*			
MED-6015	10 : 1	6K, 100	5K	45	116	**2.7 ± 0.7** *3.6 ± 0.6*	**4.5 ± 0.4** *6.7 ± 0.6*	**8.2 ± 1.1** *18.2 ± 1.5*		
MED-6033	1 : 1	80K, 60K	70K	50	30	**4.3 ± 0.4** *7.0 ± 1.1*	**9.7 ± 0.7** *17.7 ± 1.3*	**46.5 ± 11.7** *111 ± 12.9*		
MED8-6382	22% filler	40K		45	15		**1.7 ± 0.4** *4.4 ± 0.2*	**3.1 ± 0.3** *5.5 ± 0.3*	**3.7 ± 0.1** *7.1 ± 0.1*	
MED10-6382	10% filler	na	na		10.5		**0.4 ± 0.2** *2.8 ± 1.1*	**0.7 ± 0.5** *2.6 ± 0.5*	**2.0 ± 0.1** *5.7 ± 0.8*	
LSR90-9508-30	1 : 1	45K, 60K	52K	25	8.5		**2.8 ± 0.3** *3.6 ± 0.2*	**6.5 ± 0.6** *9.5 ± 0.2*	**28.6 ± 0.1** *47.2 ± 1.1*	

[a] The addition cure silicone elastomers mixes are supplied as two-part systems, comprising Part A and Part B, that are required to be mixed to effect cure.
[b] Viscosity data for parts A and B, as supplied by the manufacturer.
[c] The theoretical mean viscosity of the mixture of Parts A and B, based on the weight-averaged mean of the viscosity of the individual parts.
[d] Shore hardness value of the cured silicone elastomer, as supplied by the manufacturer.
[e] The rheometer stress value used to monitor the curing reaction, based on determination of the linear viscoelastic region.
[f] Determined from the tan δ vs. *t* plots, according to the method detailed in Figure 2 and the accompanying text.

The increase in viscosity that accompanies the conversion of a reactive silicone mixture into an elastomer matrix may be readily followed by rheological analysis.[23–27] In this study, we evaluate the isothermal curing characteristics of a range of medical grade silicone elastomer systems using non-destructive oscillatory rheometry. The influence on curing and *in vitro* release of loading the silicone systems with the model protein bovine serum albumin (BSA) and the model release-enhancing/protein stabilizing excipient glycine is also evaluated.

EXPERIMENTAL SECTION

Materials

A range of medical-grade, low-consistency PDMS elastomer systems from NuSil Technology (Carpinteria, CA) was purchased through Polymer Systems Technology (High Wycombe) (Table I). Glycine was purchased from Sigma, and bovine serum albumin (BSA, fraction V lyophilized) from GBH. The supplied BSA was milled using an automated mortar grinder (Retsch RM100, 10 mins), and sieved using a 65/250 micron sieve assembly. The 65–250 micron particle size fraction was used in all subsequent experiments. All other materials were used as supplied.

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 systems (and optionally the required amount of glycine and BSA) to a sealed plastic container and mixing for 30 sec at 3500 rpm (SpeedMixer™ DAC 15FVZ-K, Synergy Devices). For the condensation-cure silicone elastomers, MED8-6382 (22% w/w filler) and MED10-6382 (10% w/w filler), the silicone base was mixed with the crosslinking agent tetrapropoxysilane in ratios of 25 : 1 and 16.4 : 1, respectively, followed by addition of 0.5% w/w stannous octoate catalyst and mixing in the SpeedMixer™.

Oscillatory rheology

Oscillatory rheology was performed on a TA Instruments AR2000 rotational rheometer. Following

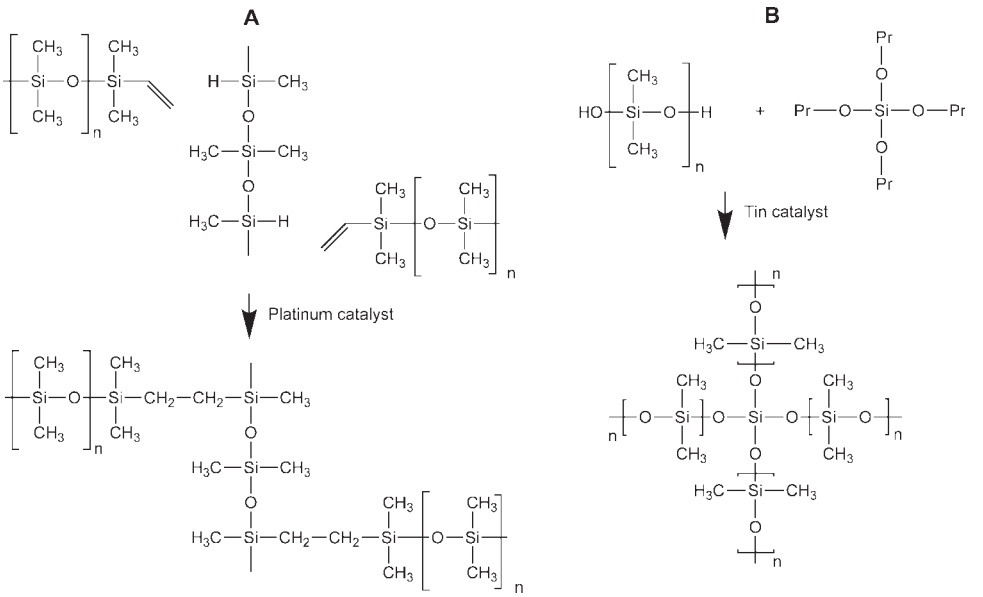

Figure 1 Platinum-catalyzed hydrosilyation reaction (A) and Tin-catalyzed condensation-type reaction (B) for the preparation of chemically-crosslinked silicone elastomers.

mixing, the silicone mixes were immediately placed onto the lower stationary plate of the rheometer using a disposable plastic syringe, and the upper plate (40 mm cross-hatch plate) was lowered to produce a gap between the plates of 1000 μm. Excess silicone mix was removed before the oscillation experiment was initiated. The time taken from loading of the sample and commencement of the experiment was typically less than 30 sec. The linear viscoelastic region (LVR) was determined for each mix, from which a nondestructive stress was selected for subsequent cure analysis experiments (Table I). A frequency of 1 Hz was used in all analyzes, representative of the frequency range to which a device might typically be subjected to *in vivo*.

Preparation and *in vitro* release testing of BSA-loaded covered rod formulations

Silicone elastomer covered-rod formulations containing a core loaded with 1.0% w/w BSA and between 0 and 50% w/w glycine were prepared by injecting via plastic disposable syringe 3.0 g of silicone elastomer base LSR90-9508-30/BSA/glycine mix into a 10 cm length of medical-grade silicone tubing (SFM3-3650, SF Medical, 3.17 mm internal diameter, 6.35 mm outer diameter). The covered rods were cured overnight at ambient temperature before being cut into 15 mm lengths. Individual rods were placed in sealed glass flasks containing 10.0 mL water adjusted to pH 5.5, and the flasks stored in a constant temperature (37°C) shaking orbital incubator (Unitron Infors, 60 rpm; throw diameter 2.5 cm). The release medium was sampled daily with complete replacement of the release medium so as to maintain sink conditions. Samples of the release medium were periodically analyzed using a Micro BCA™ Protein Assay Kit (Pierce) to quantify BSA concentrations.

Statistical analysis

The effect of temperature and protein/excipient loading on the rheological cure characteristics of medical grade silicone elastomer systems were statistically compared using a one-way ANOVA (Statview, Abacus Concepts, CA). 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 AND DISCUSSION

All of the silicone elastomers used in the study were medical grade low-consistency rubbers with restricted healthcare use suitable for short-term human implantation. The addition-type silicone elastomer systems cure according to a platinum-catalyzed hydrosilyation reaction between the silicon-hydride functional groups in one polydimethylsiloxane molecule and vinyl-silicon moieties in another, as detailed in Figure 1(A). The condensation-type silicone elastomer systems are prepared via the tin-catalyzed condensation reaction between hydroxy-terminated PDMS molecules and the tetrapropoxysilane crosslinking agent, described in Figure 1(B). For drug delivery applications, condensation-cure silicone elastomer systems are often the preferred choice, since certain chemical functionalities,

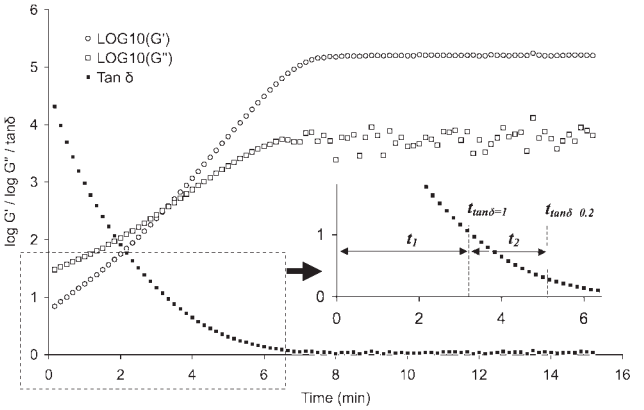

Figure 2 Representative oscillatory rheogram for the isothermal cure (40°C) of silicone elastomer MED2-4220 showing the trend in storage modulus (G'), loss modulus (G'') and tan δ ($= G''/G'$) as a function of cure time.

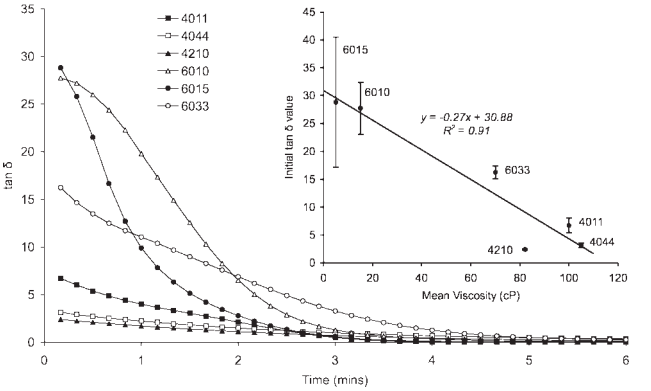

Figure 3 Tan δ versus time oscillatory rheograms for silicone elastomer systems cured at 100°C.

including unsaturated moieties and certain amine groups and thiols, are known to inhibit the addition-cure crosslinking reaction. However, an important feature of the addition-cure system is that no by-products are formed; a volatile alcohol is formed as a by-product of the condensation-cure reaction, which may lead to redistribution of the active agent within the drug delivery device and lead to an initial burst release phenomenon.

A representative rheogram, describing the isothermal silicone elastomer curing reaction (40°C) in terms of changes in the storage modulus (G'), loss modulus (G'') and tan delta ($=G''/G'$) as a function of cure time, is presented in Figure 2 for the addition-cure silicone elastomer MED2-4220. Initially, G'', which is a measure of the energy dissipated as heat and associated with the viscous character of the system, is larger than the G', which is a measure of the elastic character, a reflection of the predominantly liquid nature of the silicone rubbers before and during the initial stages of curing. As the crosslinking reaction proceeds, both G' and G'' are observed to increase, although the rate of increase of G' is greater than that for G'', such that a crossover point reflecting the transition between viscous and elastic behavior is attained (tan $\delta = 1$, $G' = G''$), after which the elastic character of the system predominates. All the silicone systems under investigation showed similar rheological trends. Given the interdependence of the G', G'' and tan δ rheological parameters, we have selected to present only tan δ data. Figures 3 and 4 show mean tan δ ($n = 3$) versus time isothermal cure rheograms for each of the ten silicone elastomer systems of the study, at representative temperatures of either 100°C (Fig. 3) or 40°C (Fig. 4). Each of the silicone elastomer systems has been formulated to provide significantly different initial viscosities, cure rates and postcure mechanical properties to meet a range of applications needs. For example, it was not possible to accurately monitor the 100°C curing reaction for the fast-cure silicone elastomer system MED2-4220 since it cured within seconds of application to the rheometer plate. The faster cure rate of MED2-4220 is a result of less inhibitor and more catalyst in the system. Also, the base vinyl-terminated polydimethylsiloxane chains have a lower molecular weight compared to the other silicone systems, thereby increasing chemical functionality. The tan δ values were observed to decrease with time for each silicone system as a result of the formation of a chemically-crosslinked elastomer network. The differences in the magnitude of the initial mean tan δ values at the beginning of the curing process (Fig. 3, $t = 10$ sec) reflect the differences in viscosity of the pre-cured silicone formulations and correlated well with the theoretical mean viscosities calculated based on the individual viscosities of the constituent parts of the elastomer systems (see Table I and Fig. 3 inset).

To better compare the curing characteristics for the silicone elastomer systems at different cure temperatures, the times required to obtain mean tan δ values of 1 and 0.2 ($t_{\tan\delta=1}$ and $t_{\tan\delta=0.2}$, respectively, approximating pre- and postgel point cure

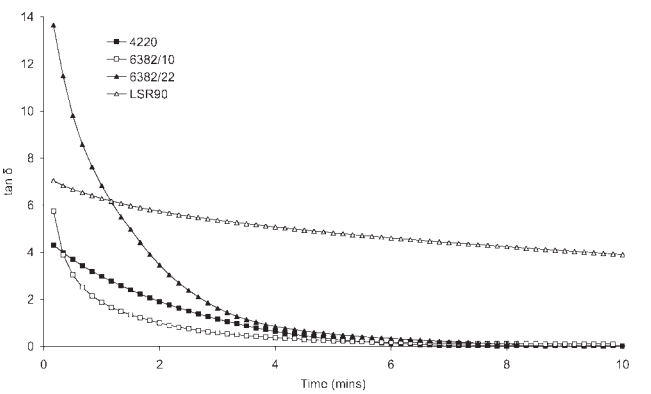

Figure 4 Tan δ versus time oscillatory rheograms for silicone elastomer systems cured at 40°C.

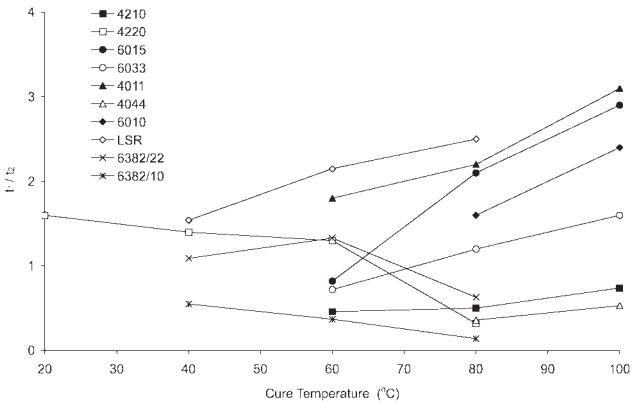

Figure 5 Influence of cure temperature and silicone elastomer type on the t_1/t_2 ratio.

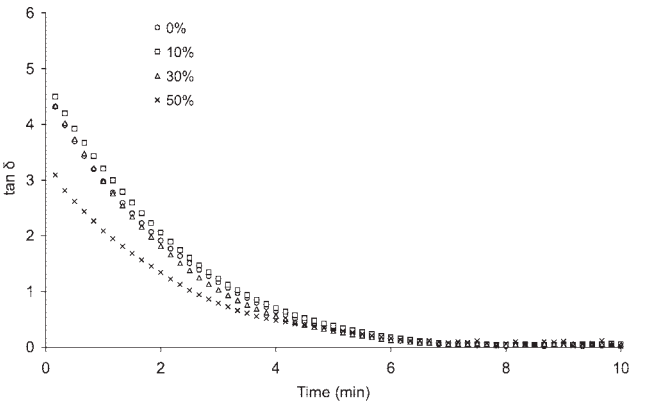

Figure 6 Oscillatory rheograms showing the influence of glycine loading on the silicone cure characteristics of MED2-4220.

characteristics and illustrated pictorially in the inset of Fig. 2) are presented in Table I for cure temperatures in the range of 20–100°C. In general, three different cure temperatures within this range were investigated for each silicone system. The cure temperatures were selected to reflect the differing thermal cure characteristics of each system—lower cure temperatures were selected for fast cure systems, and higher temperatures for slow cure systems. The results demonstrate the temperature dependence of the curing process (temperature had a significant effect on all values of time to tan $\delta = 1$ and 0.2, $p < 0.05$), with all silicone systems displaying significantly faster cure times at higher temperatures. The $t_{\tan\delta=1}$ and $t_{\tan\delta=0.2}$ parameters also permit direct comparison of the various silicone systems; for example, fast-cure MED2-4220 reaches the gel point (approximated as tan $\delta = 1$) at 40°C in 3.3 min, a similar time to MED-4044 at 100°C (3.0 min). By any measure, the addition-cure MED2-4220 is the fastest curing silicone elastomer system, followed by the condensation-cure MED-6382 systems, while the slowest cure behavior is exhibited by MED-6033. The information is of considerable use in selecting the appropriate grade of silicone elastomer for a given application.

A simple numerical parameter, the ratio t_1/t_2, was used to compare the silicone elastomer cure kinetics at different cure times (Fig. 5), where $t_1 = t_{\tan\delta=1}$ and $t_2 = (t_{\tan\delta=0.2} - t_{\tan\delta=1})$ (Fig. 2). Most of the silicone elastomer systems show an increasing t_1/t_2 ratio with increasing cure temperature. Given that the values of t_1 and t_2 decrease with increasing cure temperature (in accordance with Arrhenius considerations), it is the differential rates of decrease in the t_1 and t_2 values that produce the generally observed temperature-dependent increase in the t_1/t_2 ratio (Fig. 5). That is, the relative rate of cure pre-gel point is slower than that observed after the gel point as the cure temperature is increased. Interestingly, those elastomer systems classified as "fast-cure" (addition cure MED2-4220 and the two MED-6382 condensation-cure systems) show the opposite trend, with t_1/t_2 ratios decreasing with increasing cure temperature (Fig. 5), a consequence of their specific chemical compositions which promote faster pre-gel point cure rate.

Careful evaluation of the silicone elastomer cure characteristics are particularly important in developing systems for sustained-release of drugs. For protein therapeutics in particular, the stability and activity of the protein will be significantly influenced by the temperature and time duration of the injection molding manufacturing process. Clearly, many of the silicone systems investigated in this study would have limited use in the manufacture of protein delivery systems since their slow cure characteristics at temperatures conducive to protein stability would lead to excessively long manufacturing cycles.

It is widely recognized that large hydrophilic protein molecules do not have sufficient permeability in conventional silicone elastomers to achieve therapeutically useful release rates over prolonged periods of

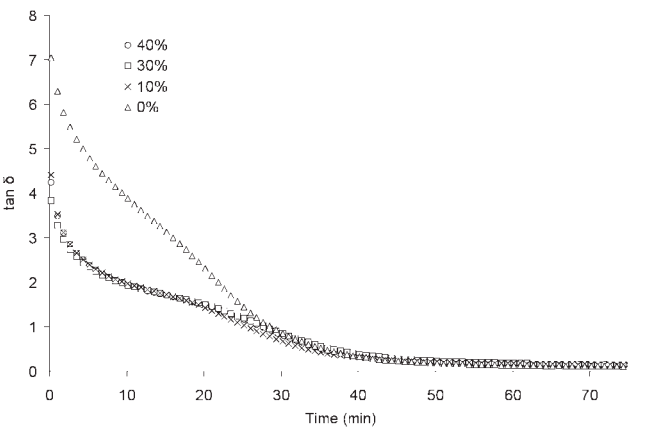

Figure 7 Oscillatory rheograms showing the influence of glycine loading on the silicone cure characteristics of LSR9-9508-30.

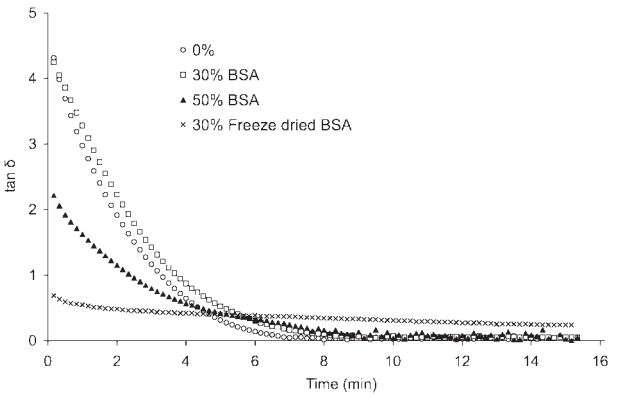

Figure 8 Oscillatory rheograms showing the influence of BSA loading on the silicone cure characteristics of MED2-4220.

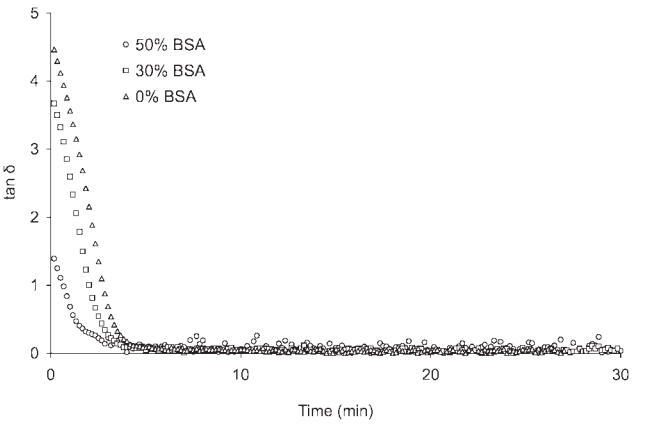

Figure 9 Oscillatory rheograms showing the influence of BSA loading on the silicone cure characteristics of LSR9-9508-30.

time, attributed to the poor solubility and limited molecular diffusion of protein molecules within the silicone elastomer network.[1] Therefore, to achieve significant protein release, it is necessary to either incorporate relatively high loadings of the protein into the silicone, or use low protein loadings in combination with the incorporation of release-enhancing hydrophilic excipients.[16–20] Ultimately, both of these methods depend upon aqueous fluid uptake by the high protein/excipient loading within the silicone elastomer matrix, and the subsequent formation of aqueous channels which facilitate protein dissolution and release.[4,6,8,13–15] For example, glycine has been reported to significantly enhance the release of human serum albumin and interferon from silicone matrices and covered rods.[16,17] The effect of glycine incorporation (10–50% w/w) on the isothermal (40°C) cure profiles for MED2-4220 and LSR9-9508-30 systems containing 1.0% w/w of the model protein BSA is demonstrated in Figures 6 and 7, respectively, and in Table II. For the fast-cure MED2-4220 silicone elastomer system, the tan δ versus time plots are similar for the 0, 10 and 30% w/w glycine loadings, while the 50% w/w glycine profile shows significantly decreased tan δ values during the initial stages of cure. By comparison, the incorporation of 10, 30, and 40% w/w glycine into the slower curing LSR9-9508-30 system containing 1.0% w/w BSA produces tan δ versus time profiles that are very similar, yet significantly different from that of the elastomer without any glycine. (It was not possible to incorporate 50% w/w glycine into the LSR9-9508-30 system, due to viscosity constraints).

The tan δ versus time plots are also influenced by the BSA loadings (Figs. 8 and 9, MED2-4220 and LSR9-9508-30, respectively, and in Table II), with higher BSA loadings producing decreased tan δ values during the early cure period as a result of an increase in the solid content of the elastomer system. There is no indication that the incorporation of BSA has any intrinsic effect on the kinetics of the silicone curing reaction; rather, the effect observed is analogous to that exerted by incorporation of a mechanical filler within a polymeric material. However, very significant differences in the tan δ versus time profile are provided by incorporating 30% lyophilized BSA into the silicone elastomer (Fig. 8), resulting in a flat tan δ profile having much lower tan δ values, compared to the non-freeze dried BSA system, during the early cure period, and higher tan δ values in the later stages of the cure, possibly indicating inhibition of cure. Investigation of the effect of using lyophilized protein is warranted due to the fact that many protein materials are supplied in aqueous buffers; removal of the water is required for incorporation into silicone elastomer systems, which are unable to accommodate large quantities of water.

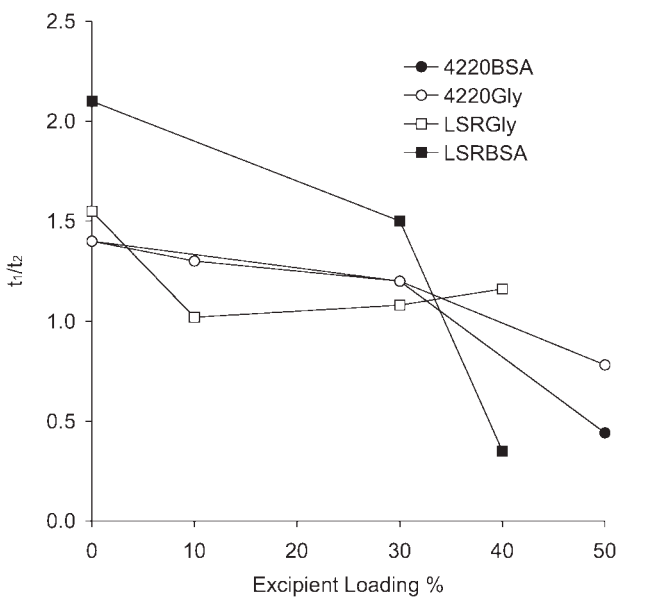

Figure 10 Influence of silicone elastomer type, excipient and BSA loading on the t_1/t_2 ratio.

Overall, the effect of increasing the loading of BSA and glycine in these silicone formulations results in a significant decrease in the value of the t_1/t_2 ratio, as summarized in Figure 10.

Both the glycine and BSA components are present predominantly as solid dispersions within these silicone systems. The relatively high loading of water-soluble glycine permits the uptake of aqueous fluid when placed into an *in vitro* release medium or a biological environment, leading to the formation of aqueous pathways through the silicone elastomer and the subsequent dissolution and release of an incorporated protein molecule. Of course, an entirely similar mechanism would also operate in silicone systems containing high BSA loadings, except that the process would be mediated by the high concentration of the protein rather than a hydrophilic release-enhancing agent. Although BSA is being employed here as a model for a therapeutic protein, it is worth noting that albumins could themselves be used as release enhancing agents for the sustained release of other therapeutic proteins. However, the expense of therapeutic proteins limits the practicality of this high protein loading approach. From the perspective of developing a sustained-release protein delivery system, a more effective and economical approach is to combine a low protein loading (<5% w/w) with a high loading of a hydrophilic release-enhancing excipient, as exemplified by the 1.0% BSA/ 50% glycine system whose BSA cumulative release versus time profile is shown in Figure 11 and which provides for a mean daily release rate of ~70 μg/day (day 1 burst excepted). It will be apparent that the lower glycine loadings (0–30% w/w) provided release rates an order of magnitude smaller than the 50% w/w loading, suggesting that the predominance of the silicone elastomer component in these systems restricts the extent of fluid uptake and ultimately protein release.

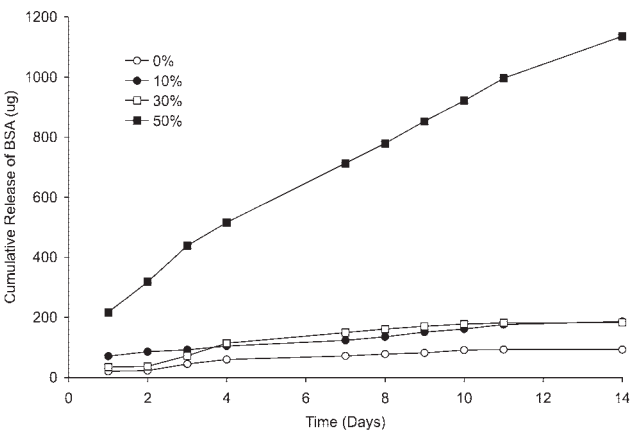

Figure 11 Cumulative release versus time profiles for LSR9-9508-30 silicone elastomer systems containing 1% BSA and various loadings (0, 10, 30, 50%) of glycine.

TABLE II
Time to Reach tan δ = 1 and tan δ = 0.2

Silicone elastomer	Time to tan δ = **1,** *0.2* (Std. dev.)
MED2-440	
0% glycine/BSA	**3.3** (*+0.2*), *5.7* (*+0.2*)
10% glycine	**3.3** (*+0.2*), *5.8* (*+0.4*)
30% glycine	**3.0** (*+0.3*), *5.5* (*+0.4*)
50% glycine	**2.5** (*+0.4*), *5.7* (*+0.2*)
30% BSA	**3.7** (*+0.7*), *6.8* (*+0.9*)
50% BSA	**2.3** (*+0.2*), *7.5* (*+0.3*)
30% FD BSA	**NA,** *17.2* (*+2.4*)
LSR90	
0% glycine	**28.7** (*+0.1*), *47.2* (*+1.1*)
10% glycine	**25.7** (*+0.7*), *51.0* (*+1.2*)
30% glycine	**28.0** (*+0.7*), *53.8* (*+2.2*)
40% glycine	**27.5** (*+0.6*), *51.2* (*+0.3*)
0% BSA	**2.7** (*+0.3*), *4.0* (*+0.2*)*
30% BSA	**2.0** (*+0.7*), *3.3* (*+0.7*)*
50% BSA	**0.7** (*+0.2*), *2.7* (*+0.1*)*

All data obtained at 40°C, except **"*"** at 80°C.

CONCLUSIONS

Sustained-release strategies for protein-based therapeutics are of considerable interest in a wide range of clinical applications. Although the development of new materials for construction of the delivery system and control of the protein release rate are important, there is also considerable scope for optimizing well-established polymeric biomaterials, such as silicone elastomer systems. In this study, the isothermal cure characteristics of a wide range of silicone elastomer systems were evaluated at different temperatures with a view to selecting systems which cure rapidly at relatively low temperatures to minimize potential thermal degradation of incorporated proteins during manufacture. The addition-cure silicone elastomer systems MED2-4220 and LSR90-9508-30 were selected for further study, and the influence of glycine and BSA loading on the silicone cure characteristics was evaluated. Although the incorporation of clinically relevant protein molecules into sustained release silicone elastomer systems may highlight formulations/stability problems relevant to that protein, it is suggested that MED2-4220 and LSR90-9508-30 materials may serve as a useful starting point for formulation development, particularly given their low temperature cure characteristics.

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