

Poly(dimethylsiloxane) Coatings for Controlled Drug Release. I. Preparation and Characterization of Pharmaceutically Acceptable Materials

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ABSTRACT: The basic technology for forming crosslinked elastomers by the end linking of low molecular weight hydroxyl-terminated poly(dimethylsiloxane) (PDMS) with tetraethoxysilane (TEOS) was modified to make it suitable for preparing coatings for controlled drug release. The requirements for this application included establishing conditions for the end linking that did not require the usual toxic tin or platinum catalysts; preparation of emulsions of small PDMS network particles that had extensive shelf-lives and that could be coalesced into cohesive thin films or coatings; and the determination of the conditions to make such coatings pinhole free, mechanically robust, and of sufficient thermal stability for coating procedures at elevated temperatures. The approach taken consisted of preparing water-based emulsions of the PDMS with sodium lauryl sulfate and restriction of the pH of the system to the acidic range with HCl. Evaporation of water from the emulsions resulted in elastomeric free-standing films of the PDMS that were char-

acterized using stress-strain isotherms in elongation and equilibrium swelling in toluene, both at room temperature. The mechanical properties of the films were found to improve with an increasing molar ratio of HCl/TEOS and an increase in the amount of TEOS (giving increased degrees of crosslinking). Conditions for the optimization of the thermal stabilities as gauged by thermogravimetric analysis were established, including beneficial effects from the introduction of the crosslinks. Scanning electron microscopy showed that the predominant morphology was void-free films with very small, homogeneously dispersed silica particles from the hydrolysis of some of the TEOS. Additional work should be facilitated by the mechanisms for the crosslinking suggested by the experimental results. © 2003 Wiley Periodicals, Inc. *J Appl Polym Sci* 90: 658–666, 2003

Key words: silicones; latexes; elastomeric films and coatings; crosslinking; mechanical properties: drug release

INTRODUCTION

One of the most important goals of pharmaceutical coatings is to control drug release by the use of polymeric materials. Recent developments emphasize water-based coatings for environmental and toxicological reasons,¹ but such coatings are currently limited to latexes and pseudolatexes of cellulose derivatives and acrylate copolymers. However, there is at least one promising alternative, the polysiloxane or “silicone” elastomers.^{2,3}

These elastomers, which are frequently used elsewhere for their superb elastomeric properties, are highly promising because of their outstanding thermal and oxidative stability and biocompatibility. They have been the objects of toxicology studies with regard to their carcinogenic, reproductive, mutagenic, teratogenic, local, and general toxic effects.^{4–10} In addition to

their stability,¹¹ formulators can benefit from the fact that silicones have very low glass-transition temperatures. This allows economical manufacturing without the need for elevated temperatures or plasticizers, which are necessary for almost every other polymeric coating system presently available. Poly(dimethylsiloxane) (PDMS) [$-\text{Si}(\text{CH}_3)_2\text{O}-$] is by far the most used silicone polymer in both medicinal and nonmedicinal applications. For example, low molecular weight fluids are used as skin cream modifiers in cosmetics, antifoam agents in the food and chemical industries, and foam suppressors in antacid medications. In addition, the elastomeric properties of PDMS have been exploited in the medicinal field for several years. They have become an indispensable part of many controlled drug delivery devices, such as Norplant, and in devices such as foldable intraocular lenses, soft tissue implants, elastomeric toe and finger joints, infusion ports, shunts, and catheters.¹²

The use of PDMS as a pharmaceutical tablet coating in previous studies^{1,3,13–16} showed a potential for possible zero-order release (i.e., the highly desirable delivery of a constant amount of drug per unit of time). Drug release in these formulations was mainly depen-

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dent on the dispersion of domains of water-soluble substances such as low molecular weight polyethylene glycols within the PDMS films. Their dissolution provided channels for the release of the drug molecules, but a relatively large amount was necessary to assure connectivity of the paths thus generated. These studies, however, were limited to one particular polymer formulation and no commercial product was ever marketed. In addition, no information was reported on the stability of the coating dispersions with their low molecular weight additives.

Because PDMS chains are generally prepared so that they have functional groups at their ends, they are readily end linked with multifunctional reactants into the network structures required for elastomeric behavior. The standard reactant is tetraethoxysilane (TEOS) $[\text{Si}(\text{OC}_2\text{H}_5)_4]$, which is frequently used in the preparation of "model" networks for evaluating the molecular theories of rubberlike elasticity.¹⁷⁻¹⁹ The PDMS chains have also been used in some pharmaceutical coating materials,^{1,3,13-16,20} and there have been a number of relevant patents related to the preparation of PDMS elastomers and latexes.²¹⁻²³ However, very few of these uses are concerned with the PDMS crosslinking reaction. This is of particular importance here because such reactions generally require organic tin or platinum catalysts.²⁴⁻²⁶ Because such catalysts are toxic, they must be eliminated in products for oral administration.

In addition, the delivery system would have to be PDMS and TEOS in an oil/water emulsion suitable for use in a spray coating process. Such an emulsion needs to have particle sizes of $<5 \mu\text{m}$ and a viscosity $<60 \text{ MPa s}$,^{27,28} and the particles must be crosslinked while in the emulsified state. Also, it is necessary to have good stability and mechanical properties to produce coatings or films from drying such emulsions.

The objectives of the research undertaken can therefore be summarized as follows:

1. establish the conditions for end linking PDMS that do not require the usual toxic tin or platinum catalysts;
2. prepare emulsions of small PDMS network particles that have extensive shelf-lives and can be coalesced into cohesive thin films or coatings;
3. determine the conditions to make such coatings pinhole free, mechanically robust, and of sufficient thermal stability for coating procedures at elevated temperatures; and
4. correlate these preparative conditions with the resulting properties of the films to suggest crosslinking mechanisms that are useful in optimizing these materials in drug delivery applications.

TABLE I
Effects of Storage on Emulsion Particle Sizes and Viscosities

Emulsion Type	Particle Diameter ^a		Viscosity ^b	
	Median (μm)	Range (μm)	MPa s	SD
Freshly prepared	0.373	0.102–2.009	4.85	0.01
Stored for 3 months at				
25°C and 60% RH	0.377	0.088–1.149	3.52	0.01
40°C and 75% RH	0.380	0.129–1.177	2.93	0.02
Stored for 6 months at				
25°C and 60% RH	0.380	0.103–1.302	4.27	0.02
40°C and 75% RH	0.382	0.172–0.981	5.02	0.03
	Side peak at			
	1.385 ^c	0.988–2.48		

^a Average of four analyses.

^b Viscosity data obtained at 20 rpm at room temperature.

^c 1.62 vol %.

Experimental

Materials

Hydroxyl-terminated PDMS (Q1-3563; number-average molecular weight = $3 \times 10^3 \text{ g/mol}$) was kindly provided by the Dow Corning Corporation (Midland, MI). The emulsifier, sodium lauryl sulfate (SLS), was obtained from Fisher Scientific (Pittsburgh, PA). The TEOS, toluene, and methanol were purchased from Aldrich (Milwaukee, WI). All were used as received. Concentrated hydrochloric acid and ammonium hydroxide (both Aldrich) were diluted to 1M before use.

Preparation of emulsions

The emulsions or latexes were prepared by ultrasonic processing for 20 min at room temperature with 1% SLS as the surfactant. The specific emulsion characterized in the present investigation contained 30 wt % PDMS and had particle sizes around $0.4 \mu\text{m}$ and a viscosity of approximately 5.0 MPa s . The details are given in Table I.

Crosslinking of particles and characterization of particle sizes and emulsion viscosities

Crosslinking of the PDMS is necessary in order to achieve good film formation. Different degrees of crosslinking will have an impact on the characteristics of the resulting films and thus on the applicability of the material as a pharmaceutical coating. The required crosslinking was carried out by mixing the desired amounts of TEOS (0.5, 1, 1.5, and 2.5%) into the PDMS emulsion and then stirring it for 10 min at room temperature. Various molar ratios (R) of HCl/TEOS (0.1, 0.5, and 1) were used, giving a pH in the acidic range of 1–3. The mixtures were then stirred at room temperature for 10 h before collecting samples for analy-

sis. Similarly, ammonium hydroxide was used to adjust the pH to basic conditions (pH 10).

A particle size analyzer (Coulter LS230, Beckman Coulter Ind.) was used to measure the particle sizes in the emulsions. The emulsion viscosities were determined using a Brookfield digital viscometer (model DV-II+).

Stabilities of latexes

The stabilities of the resulting emulsions were characterized in terms of the effect of the storage time on the appearance, particle size, and viscosity. Specifically, the properties were compared directly after manufacture with those performed after 3- and 6-month storage under both long-term [25°C and 60% relative humidity (RH)] and accelerated conditions (40°C and 75% RH).

Phase separation of the emulsion would prevent use of the system for coating applications. Thus, the emulsions were monitored throughout the testing period of 6 months. No phase separation was visible at any time during the analysis.

In order to ensure the stability of the emulsions for an extended period of time, such as 1 year or longer, an upper particle size limit of 1 μm is desired.²⁷ In such emulsions, the thermal convection and Brownian motion of the particles are large enough to overcome the sedimentation tendency of the particles.

Preparation of free-standing films and characterization of their stabilities and morphologies

The PDMS latex (5 g) was cast into polyethylene dishes and dried for 7 days at room temperature. The resulting film was placed in an oven and dried at 60°C for 24 h prior to any characterization measurements. Because the particles were crosslinked, the integrity and associated mechanical properties of the dried films resulted from interpenetration of chains on the surfaces of contacting particles, hydrogen bonding from whatever hydroxyl groups might be available, completion of the crosslinking reactions, and bonding of chains onto the silica generated by hydrolysis of the TEOS that is not used up in the crosslinking.

A thermogravimetric analyzer (TGA 2050, TA Instruments) was used to investigate the thermal stabilities of the free-standing films under nitrogen from 25 to 600°C at a 10°C/min heating rate. Scanning electron microscopy (SEM) was carried out using a Philips XL30 ESEM microscope that was used to examine the film morphologies.

Gel content measurements

Emulsion samples were collected at various crosslinking reaction times (0, 1, 2, 3, 4, 6, 10 and 24 h), and then

weighed. The emulsions were broken using a 1:1 acetone–methanol mixture, and the oil or solid-gel phase was carefully separated from the solvent phase. Toluene was added to the oil or solid-gel phase and mixed and shaken for 2 min to dissolve the uncrosslinked portions. The solid-gel phase was separated from the toluene and dried under a vacuum at room temperature for 24 h before weighing. The gel contents, suitable for describing the degree of crosslinking, were calculated from the weights obtained.

Extractions of samples

Any noncrosslinked polymer was extracted from the films with toluene at room temperature until a constant weight was obtained. Films were then carefully deswollen in a series of toluene–methanol mixtures with an increasing content of the methanol nonsolvent.

Stress–strain measurements

Specimens having the approximate dimensions of 3.0 \times 0.5 \times 0.1 cm^3 were cut from each film, and the cross-sectional area (A^*) of each test sample in the unstretched state was measured using a cathetometer. The test apparatus was similar to those used in previous investigations on PDMS.^{17–19,29} Stress–strain isotherms for the test samples in elongation were determined at room temperature, and measurements were performed using a sequence of increasing values of the elongation or relative length ($\alpha = L/L_i$) of the sample. The value of the force (f) exhibited essentially immediately after the deformation was imposed was recorded as its initial value. The force was then monitored for at least 15 min until the rate of the slow relaxation became constant, and this force value was taken to approximate its equilibrium value. The nominal stress was computed from $f^* \equiv f/A^*$, and the reduced stress or modulus was computed from $[f^*] \equiv f^*/(\alpha - \alpha^{-2})$. All measurements were carried out to the rupture points of the samples.

Swelling equilibrium measurements

These measurements were carried out on weighed extracted samples, using toluene at room temperature, and the swollen weight was recorded after it became constant. The extent of swelling was characterized by the volume fraction of polymer in the network at equilibrium swelling (v_{2m}), which was calculated assuming additive volumes.³⁰

RESULTS AND DISCUSSION

Crosslinking reactions in emulsion

The degrees of crosslinking of the PDMS in emulsions were estimated from the gel contents that were pro-

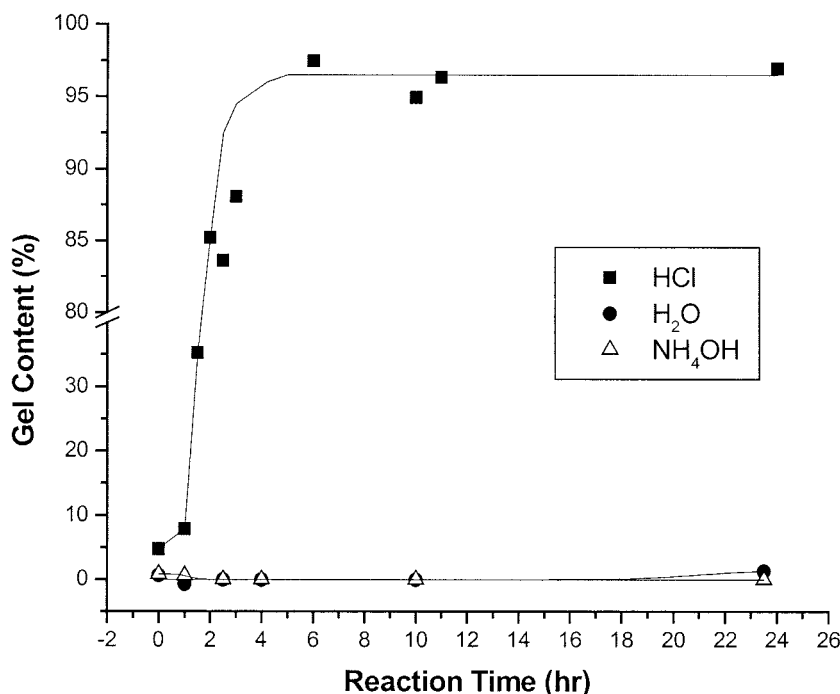


Figure 1 The gel content as a function of the reaction time for acidic, neutral, and basic conditions.

duced. The results parallel those in studies of crosslinked hydroxyl-terminated PDMS and TEOS in sol-gel processes and bulk reactions^{31,32} and in emulsions with organic tin catalysts.^{26,30} In this analysis of gel contents, no crosslinking was indicated by the PDMS of the broken emulsion forming a liquid, oily phase, which could be dissolved in the toluene. On the other hand, when crosslinking did occur, a solid gel was formed after breaking the emulsion; and it could not be dissolved in the toluene. The solid-gel contents obtained are shown in Figure 1. The three media that were examined employed the same amounts of PDMS and TEOS. During the first day no solid gel was produced when reactions were carried out in neutral or basic conditions in the absence of catalyst, and this situation persisted for at least 100 h. As expected, crosslinking did occur within 40 h under basic conditions when an organic tin catalyst was used.^{26,30} This demonstrates that the reaction between PDMS and TEOS could not be effectively carried out in neutral or basic conditions without the use of a catalyst. On the other hand, acidic conditions without a catalyst produced a gel within 30 min and the reaction proceeded to greater than 90% gel within 3 h. It was thus possible to identify conditions under which the uncatalyzed reaction between PDMS and TEOS was possible and essentially completed within a convenient period of time.

Stabilities of latexes

The analysis of the prepared emulsions showed unimodal particle size distributions with >90% of the

particles below 1.0 μm and 100% of the particles below 2.5 μm (Fig. 2). These materials are therefore suitable for applications in spray coating processes. No effects on film formation is expected so long as the particles are smaller than 5 μm and the amount of sediment is less than about 1% of the solid polymer, when stored at around 20°C.²⁷ The freshly prepared emulsions actually showed larger particle sizes than those after 3 or 6 months of storage. This minor effect may be due to losses of small amounts of volatile or soluble materials. In any case, more than 90% of the particles in the aged emulsions had diameters of less than 1 μm , and 100% of the diameters were less than 2.5 μm . After 3-month storage, the particle size did not change significantly with long-term or accelerated conditions (Table I). After 6-month storage, the stability of the long-term sample remained unaffected but a small side peak occurred under accelerated conditions, which was possibly due to unstable particle aggregates during this storage time. However, more than 90% of the particles still remained below 1 μm and no particles were larger than 5 μm . Thus, these emulsions can be safely considered to be stable over a period of 6 months under the described conditions.

The viscosities of dispersions or emulsions to be used in coatings cannot exceed a certain maximum value in order to be atomized and to allow for the created droplets to spread over the tablet surface; this value is mainly dependent on the equipment used, in particular, the type of spray nozzle.²⁸ The maximum viscosity for the spray nozzle used here was 60 MPa s. Determinations of the emulsion viscosity at baseline were slightly higher than after 3 months of storage and increased again when

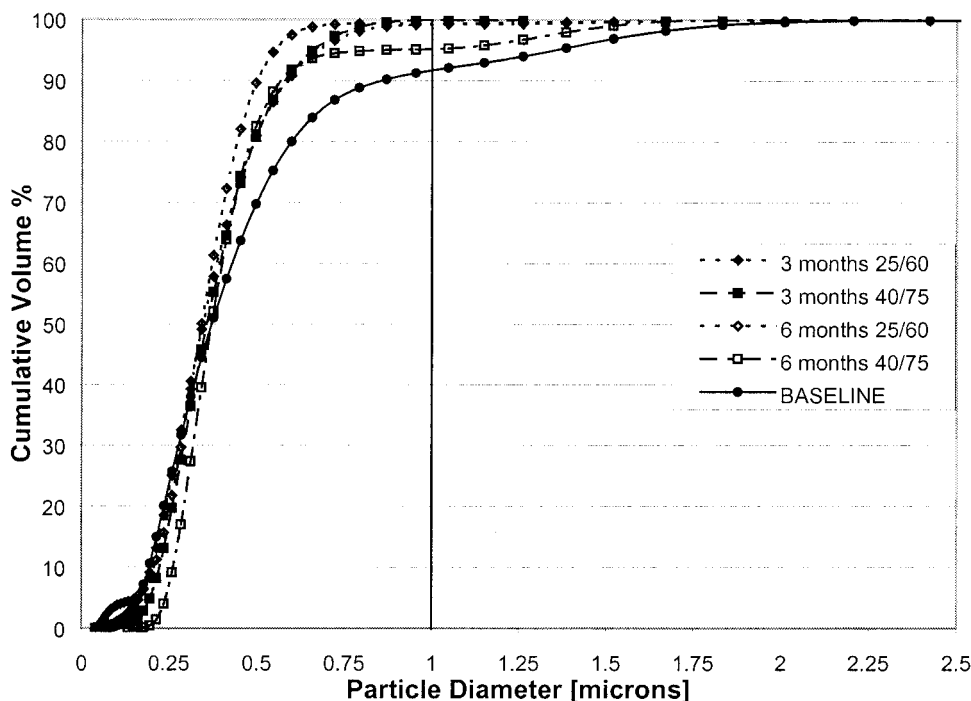


Figure 2 The effect of the storage time, temperature, and relative humidity on the particle size distribution.

tested after 6 months of storage (Table I). These findings were consistent with the results from the particle size determinations. Some possible small losses in components during the first few months of storage resulted in decreased emulsion viscosities, whereas after 6 months the viscosity slightly increased (possibly because of some coalescence of less stable particles). This increase, however, is still far below a critical value for spray applications and thus not significant with respect to the present preparative goals.

Properties of free films

Table II describes some of the mechanical properties of the free films prepared at various molar ratios of [HCl/TEOS] and amounts of TEOS. At a constant amount of TEOS, the reduced force or modulus at an

TABLE II
Mechanical Properties of Free-Standing Films at Various Molar HCl/TEOS (*R*) Ratios and Amounts of TEOS

		α_r^a	f_r^{*b}	$[f^{*c}]_r^c$
TEOS = 1% ^d	<i>R</i> = 0.05	2.24	0.099	0.048
	<i>R</i> = 0.50	1.98	0.222	0.129
	<i>R</i> = 1.0	1.70	0.189	0.139
<i>R</i> = 0.50	0.5% TEOS	1.64	0.060	0.047
	2.5% TEOS	2.84	0.562	0.207

The values are calculated as described in the text.

^a Elongation at rupture.

^b Nominal stress at rupture (MPa).

^c Reduced stress or modulus at rupture (MPa).

^d Amount of TEOS in the latex.

R value 1.0 was threefold larger than that for a value of 0.05. This indicated that the reduced pH resulted in improved mechanical properties of the free films. Similarly, at the same *R* value, the reduced force or modulus with 2.5% TEOS increased fivefold relative to that for 0.5% TEOS. Thus, the mechanical properties improved with the increase in the molar ratio and with the increase in the amount of TEOS.

Extraction and swelling equilibrium results for the same samples are shown in Figures 3 and 4. The soluble fraction of the polymer (S_f) and the volume fraction of the polymer at equilibrium swelling (v_{2m}) increased slightly with an increasing *R* value, but these changes were not significant (Fig. 3). However, the results show significant effects from the amount of TEOS on both S_f and v_{2m} (Fig. 4). Specifically, increased amounts of TEOS decreased the S_f but increased the v_{2m} .

Previous studies^{24,25,30} reported the mechanical properties and swelling results for PDMS films prepared in basic media with organic tin as the catalyst. The authors concluded that the dominant factor influencing the elastomer's mechanical properties was the extent to which the inorganic siliceous phase had precipitated onto the surfaces of the emulsion particles and into the interstices between them. This reinforcement occurred in much the same manner as that obtained from colloidal silica mechanically blended into silicone elastomers prior to curing. The present results are thus in agreement with earlier relevant studies. Because the mechanical properties and extent of swell-

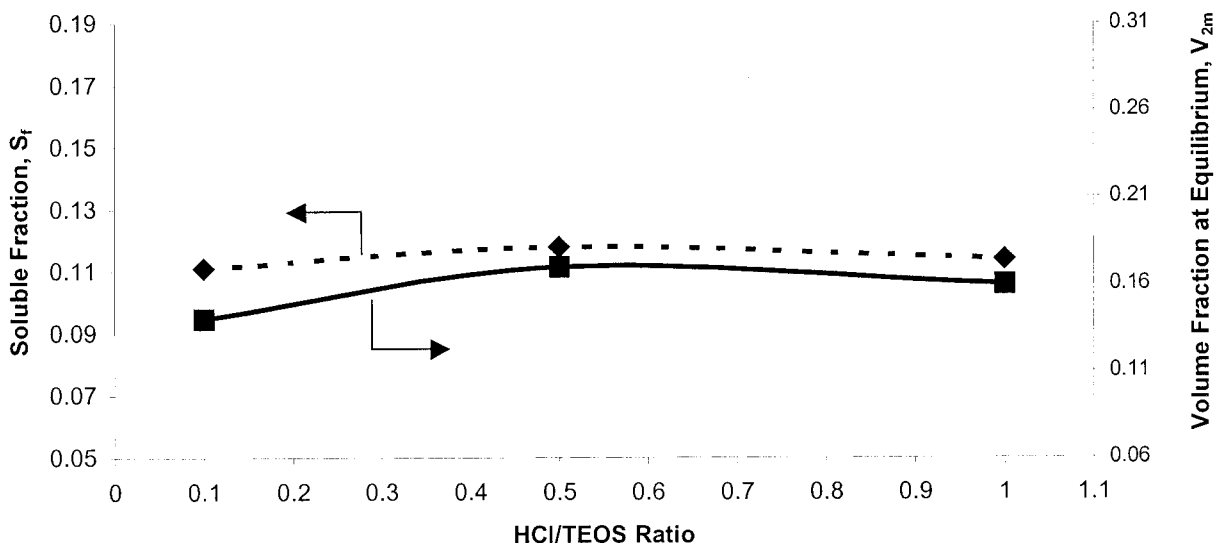


Figure 3 The dependence of the soluble fraction and volume fraction of the polymer present at swelling equilibrium of the films on the composition molar ratio.

ing can obviously depend on the nature of the crosslinking reaction, some possible mechanisms are discussed below.

Figure 5 illustrates the thermal stability results for PDMS. The results before and after crosslinking are illustrated. It can be seen that the main decomposition temperature was increased more than 150°C by the crosslinking. Prior to this main decomposition, there were approximately 8% weight losses, which were probably due to the decomposition of the low molecular weight surfactant and a small amount of uncrosslinked PDMS.

Mechanism of crosslinking reaction

The crosslinking reaction between hydroxyl-terminated PDMS and TEOS in emulsion usually involves

two steps. The first is hydrolysis of TEOS under acid or base catalysis. In the second step, the hydrolysis products are transported into the oily PDMS phase, followed by polycondensation between the terminal silanol groups of the PDMS and the OH groups of the partially hydrolyzed TEOS. It is this second step that would be facilitated by an organic tin catalyst.^{26,30}

As demonstrated, there was no crosslinking seen in basic or neutral media without the organic tin catalyst. Because the hydrolyzed TEOS is not transported into the oily PDMS phase, there was little chance for the reaction between PDMS and TEOS to occur. Moreover, the surfactants also prevent mixing of the two phases. Thus, it was somewhat surprising that the crosslinking reaction did occur under acidic conditions in the absence of any organic tin catalyst.

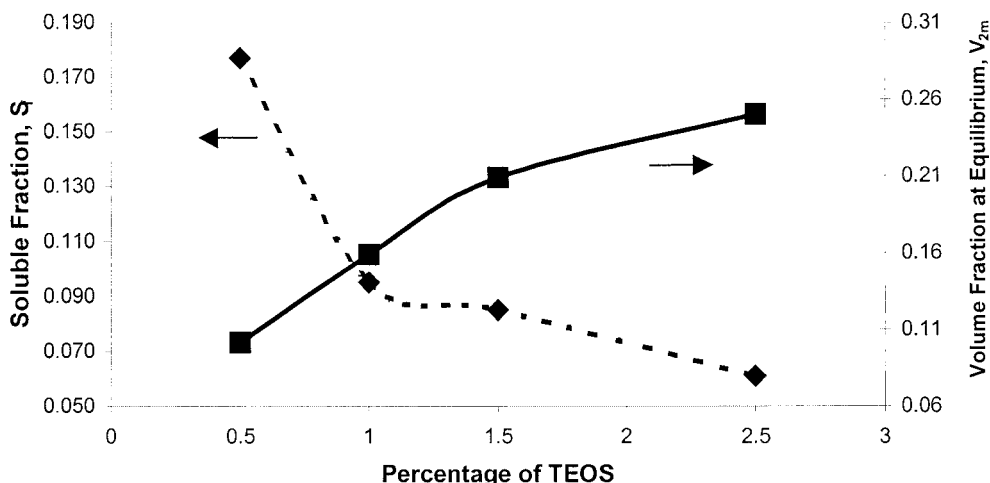


Figure 4 The dependence of the soluble fraction and volume fraction of the polymer present at swelling equilibrium of the films on the amount of TEOS.

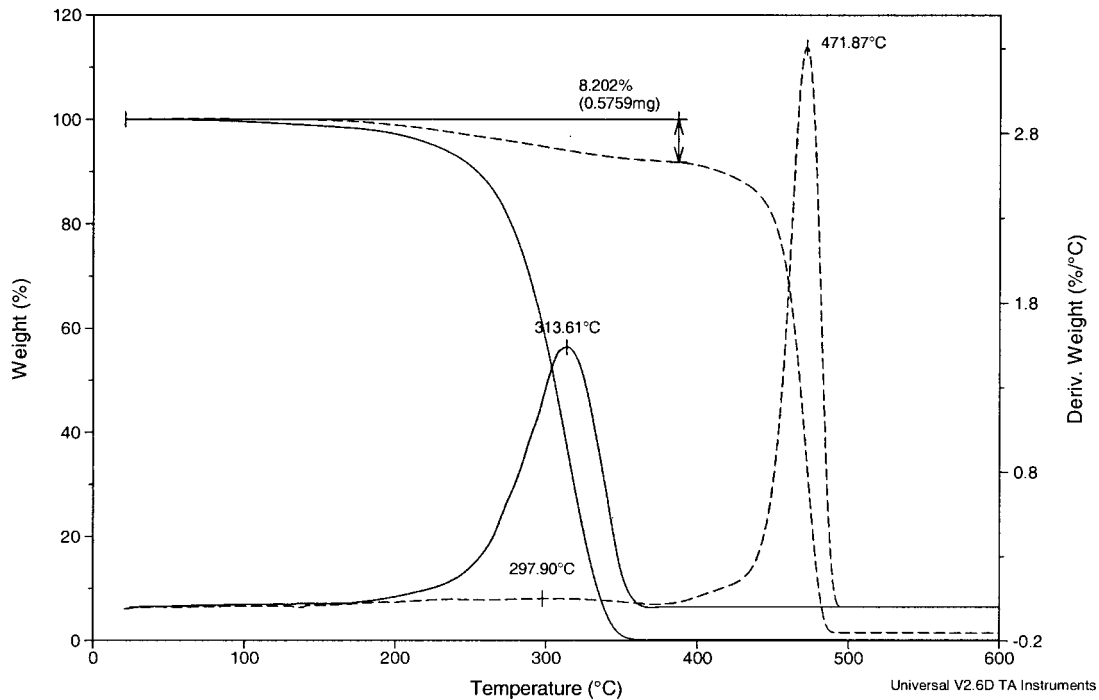


Figure 5 A comparison of the thermogravimetric analysis results for PDMS (—) before and (- - -) after crosslinking. The results are presented as the effects of temperature on both the weight and the weight change (derivative or slope, %/degree).

The results in this study suggested that the SLS surfactant in the interfaces between PDMS and water could help transport hydrolyzed TEOS into the PDMS phase under acidic conditions. This was supported by the observation that the molar ratio had relatively little affect on the network structure (as gauged by the values of S_f and v_{2m}). On the other hand, changing the amount of TEOS at a constant molar ratio did cause significant changes. This indicated that, although the acidity was critical for this mechanism, the variation of the pH within the acidic range had relatively little

affect on this possible transport. The effects of the R value on the mechanical properties of the films were caused by the pH dependence of the hydrolysis of TEOS. At higher TEOS concentrations, more TEOS was hydrolyzed and could be transported into the oil phase, giving higher crosslink densities and making S_f and v_{2m} change significantly. In addition, the higher the concentrations of hydrolyzed TEOS, the more readily it can condense to SiO_2 . The observed improvements in the mechanical properties with increasing TEOS concentration could therefore be due to

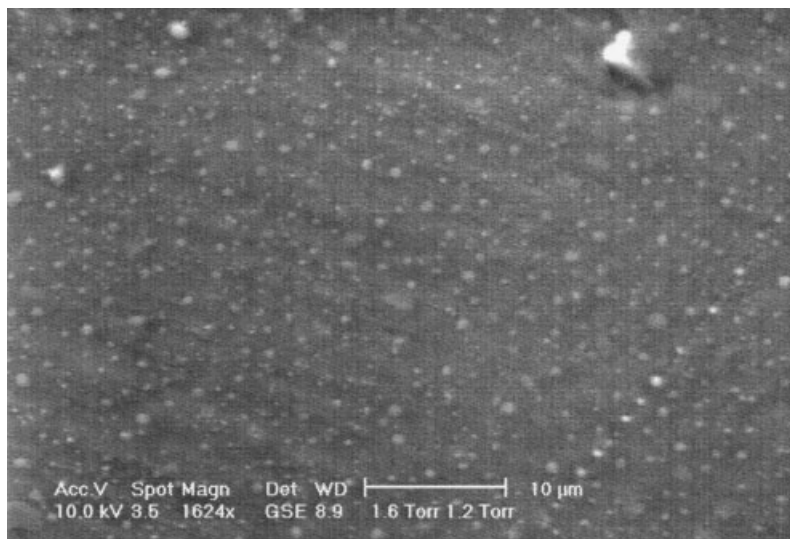


Figure 6 An illustrative scanning electron micrograph for a cross section of one of the films.

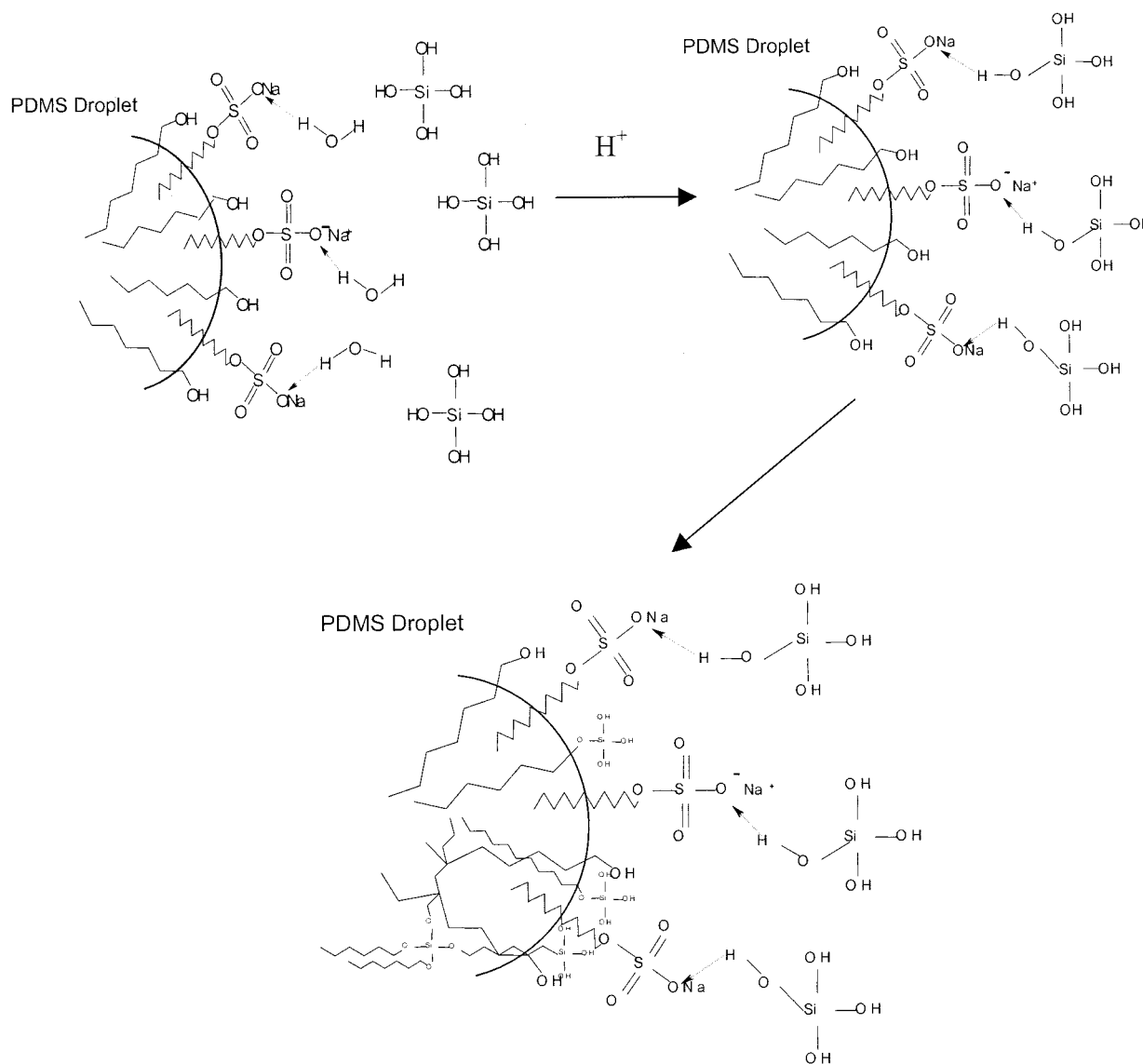


Figure 7 The possible mechanism for the PDMS crosslinking reaction in the emulsion.

higher degrees of crosslinking and the reinforcement provided by the SiO_2 particles.

The SEM results shown in Figure 6 appear to be consistent with these conclusions. The sample shown was prepared with 2.5 wt % TEOS at an R value of 0.50. The micrograph shows a cross section of a free film that was void free and contained some very small, homogeneously dispersed particles of SiO_2 (approximately 1–2 μm diameters). These fine SiO_2 particles were presumably produced by the condensation of hydrolyzed TEOS during the drying of the films. There was apparently less chance for condensed SiO_2 formation in the latex because no large particles were observed in the latex in the particle-size determinations.

On the basis of these conclusions, the possible mechanism of the crosslinking reaction in PDMS emulsions in acidic media is shown in Figure 7 and is described as follows. Under acidic conditions, the

TEOS first hydrolyzes to form silicic acid or water-soluble silicates. Then, the hydrolyzed TEOS may combine with the acidified SLS and be transported into the oily PDMS phase. The actual crosslinking reaction may then occur between the hydroxyl end groups of PDMS and the hydroxyl groups in the partially hydrolyzed TEOS.

The evaluation of such crosslinked PDMS films in applications requiring the absence of tin or platinum catalysts will be illustrated in the future using drug delivery systems, specifically in the spray coating of these formulations onto tablet surfaces to control drug release (unpublished results).

CONCLUSIONS

The crosslinking reaction between hydroxyl-terminated PDMS and TEOS in emulsions was carried out

in the absence of the usual organic tin catalysts only in the case of acidic media. SLS served not only as a surface active agent but also as a facilitator for this crosslinking reaction. Void-free, free-standing films were obtained by drying these latexes of crosslinked PDMS particles. The mechanical properties of the films increased with increased values of the molar composition ratio (HCl/TEOS) and the amounts of TEOS. This ratio had less effect on the network structure than the amount of TEOS. Finally, the thermal stability increased dramatically upon crosslinking the PDMS. The understanding of the fundamental mechanisms of the crosslinking reaction should provide valuable guidance in the use of these materials in a variety of applications, including formulation of latex coatings in controlled drug release systems.

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