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CURE BEHAVIOR OF NEAT AND DRUG-LOADED POLY(ORTHO ESTER) BIOERODIBLE IMPLANTS

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The crosslinking behavior of a ketene acetal-terminated poly(ortho ester) prepolymer with a triol has been studied using differential scanning calorimetry (DSC) and dynamic mechanical analysis (DMA). DSC results at 70°C indicate that the cure is virtually complete in about 100 min, while DMA results indicate that the cure is essentially complete in about 180 min. When levonorgestrel and $Mg(OH)_2$ are incorporated into the prepolymer and the mixture then cured, about 16 h are required for complete cure. The increase in cure time is very likely due to the basic nature of $Mg(OH)_2$ which inhibits the acid-catalyzed reaction between ketene acetal and hydroxyl groups.

I. INTRODUCTION

In previous papers [1-4] we have described the preparation and properties of crosslinked poly(ortho esters) designed for use as bioerodible implants for the systemic release of the contraceptive steroid levonorgestrel. The crosslinked materials are prepared by first synthesizing a linear, ketene acetal-terminated prepolymer and then reacting the prepolymer with a triol.

Because polymer erosion and consequent levonorgestrel release is affected by the ultimate structure of the polymer network, it is important to establish reaction conditions under which the cure is complete in order to ensure that devices having reproducible erosion and drug release behavior can be routinely prepared.

In this manuscript we describe a characterization of the crosslinking reaction using differential scanning calorimetry and dynamic mechanical techniques in order to define conditions for complete cure. Long-term erosion and levonorgestrel release studies using completely cured devices are currently in progress and will be reported when concluded.

II. EXPERIMENTAL

Preparation of crosslinked devices

Ketene acetal-terminated prepolymers were prepared by reacting 30 g (141.3 mmol) of 3,9-bis(ethylidene-2,4,8,10-tetraoxaspiro[5,5]undecane), 7.102 g (60.1 mmol) of 3-methyl-1,5-pentanediol, 1.592 g (10.6 mmol) of triethylene glycol, and 28 mg (0.088 mmol) of 9,10-dihydroxystearic acid in 200 ml of distilled tetrahydrofuran (THF) following the procedures described previously [2]. The reaction was catalyzed by the addition of 0.3 ml of *p*-toluenesulfonic acid in THF (10 mg/ml) (see Scheme 1). After the reaction is complete, THF was removed from the prepolymer, first on a rotary evaporator and then under reduced pressure at

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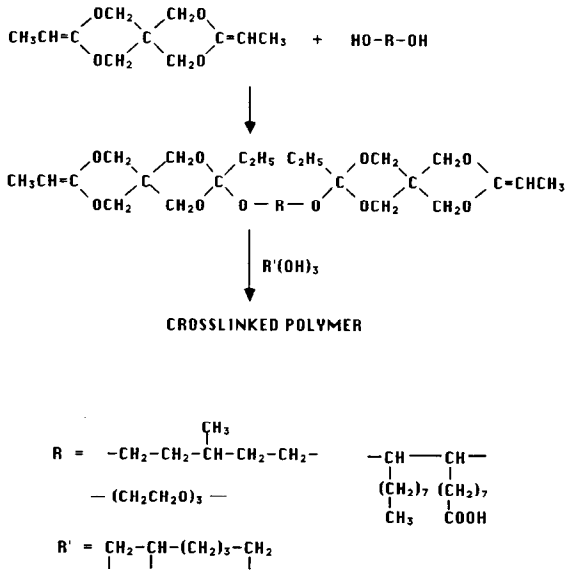

Scheme 1.

40°C for 16 hours. The prepolymer was immediately stored under anhydrous conditions at −20°C.

Crosslinking was carried out with 1,2,6-hexanetriol at a 1:1.3 molar ratio of ketene acetal to hydroxyl groups. A 30 mol% excess of hydroxyl groups was chosen to ensure that no unreacted ketene acetal groups remain in the crosslinked network. Materials based on equimolar amounts of ketene acetal and hydroxyl groups were also prepared.

For controlled release applications, 10 wt% levonorgestrel and 7 wt% $Mg(OH)_2$, both micronized, were blended uniformly into the prepolymers using an Atlantic 2CV reactor.

Thermal analysis

A DuPont 1090 thermal analyzer and a DuPont 910 differential scanning calorimetry (DSC) module were used to measure thermal properties of the crosslinking poly(ortho esters). The temperature of the DSC cell was calibrated using indium and tin. High-purity argon was used to purge the cell, and sealed DSC pans with sample size ranging from 15 to 30 mg were used in all measurements.

DSC samples were prepared immediately after the prepolymers were mixed with the triol and the samples stored at −20°C until use to minimize reactions at ambient temperatures. Unused samples were discarded after five days.

The crosslinking reaction was initiated by increasing sample temperature from 30°C to the cure temperature of either 70 or 90°C at a rate of 3°C/min followed by an isothermal cure. The glass transition temperature, T_g, of the crosslinked polymer was determined by DSC using a temperature scan of 10°C/min from −40 to 70°C.

Dynamic mechanical analysis

A Rheometrics mechanical spectrometer RMS-605 was used to monitor the increase in the dynamic moduli of the crosslinked polymer. Rheological functions obtained are the storage modulus (G'), the loss modulus (G''), and the loss tangent (tan $\delta = G''/G'$). Because poly(ortho esters) are hydrolytically labile, a modified cone-and-plate fixture was used for all dynamic mechanical analysis (DMA) experiments to protect the sample from atmospheric moisture during cure. The fixture, shown schematically in Fig. 1, contains a concentric shielding ring for each of the cone and the plate fixtures such that high temperature silicone oil can be used to isolate the sample from the outside environment. The diameter of the cone and plate was 25 mm and the cone angle was 0.1 rad.

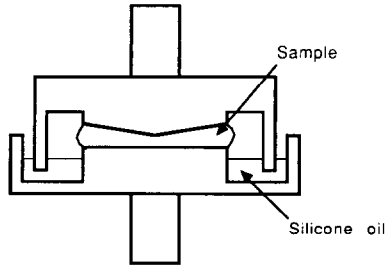

Fig. 1. Modified cone-and-plate with moisture seal.

During the curing reaction, the dynamic modulus of the crosslinking polymer increases by several orders of magnitude. Consequently, the strain setting for the dynamic measurements needs to be decreased with reaction time and the auto-strain feature of the rheometer was used to control the percent strain throughout the reaction. In a typical run at 1.0 rad/s, the strain was initially set at 100% and dropped to 5% at the end of the experiment.

The temperature program used for DMA measurements was similar to that used for DSC analysis. The sample temperature was ramped from 30°C to the final cure temperature at a rate of 3°C/min, and isothermal conditions were maintained until the end of the run.

III. RESULTS AND DISCUSSION

Figure 2 shows a DSC thermogram of the poly(ortho ester) crosslinking reaction with a ketene acetal to hydroxyl ratio of 1:1.3. The cure temperature was 70°C, reached from 30°C at a rate of 3°C/min. The reaction between ketene acetal and hydroxyl groups is exothermic, and the release of heat levels off in less than 60 min.

Figure 3 illustrates a series of dynamic DSC scans of the crosslinking polymer showing changes in T_g with reaction time. The increase in T_g is very significant in the first 30 min of the reaction, but further increase becomes virtually undetectable after about 100 min. These results are in good agreement with those shown in Fig. 2 and indicate that most of the functional groups have reacted in the first 60 min. However, as shown in Fig. 3, the second-order transition of the crosslinking poly(ortho ester) is quite broad, making an accurate determination of T_g difficult. Table 1 summarizes the T_g values determined as the half-height value between two intercepts (T_1, T_2) with the baselines before and after the transition at various reaction times. The accuracy of these values is ±2°C. These measurements indicate that virtually complete cure is achieved after about 100 min.

Figure 4 shows DMA data of a crosslinking poly(ortho ester) as a function of reaction time obtained at a strain frequency of 1 rad/s. The temperature program for curing was similar to the one used for the DSC study. In such studies

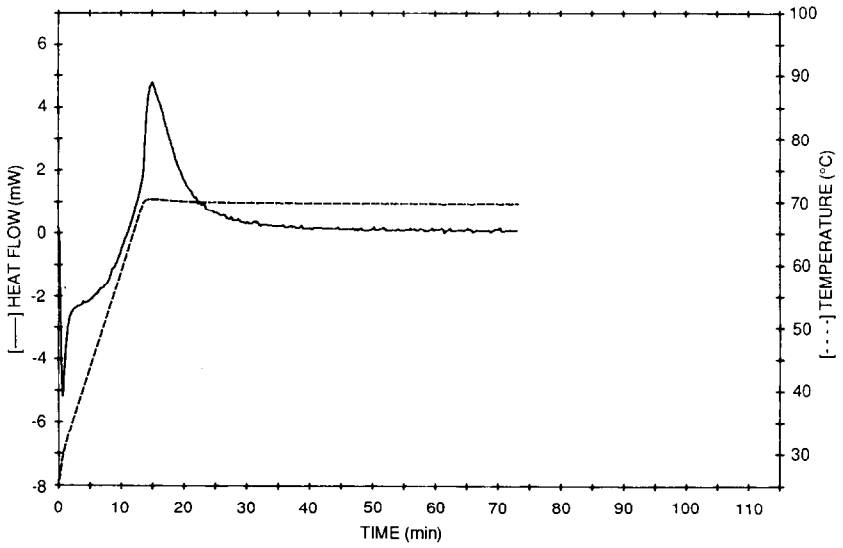

Fig. 2. DSC thermogram showing the thermal behavior of neat poly(ortho ester) at 70°C cure.

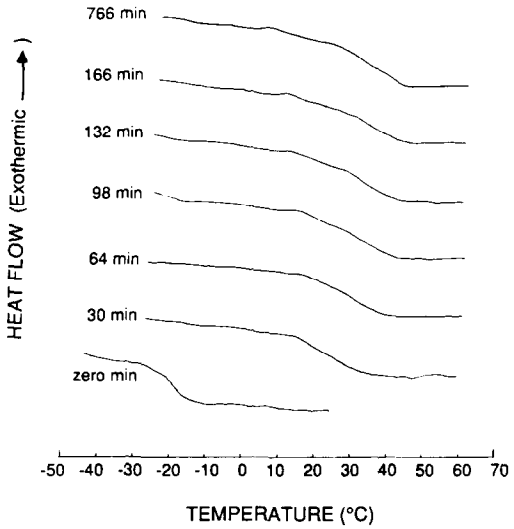

Fig. 3. DSC scans of crosslinking poly(ortho ester) illustrating the change in glass transition temperature as a function of reaction time at 70°C.

TABLE 1

Glass transition of crosslinking poly(ortho ester) with 30% excess hydroxyl groups at 70°C cure

Cure time (min)	T_g (°C)	T_1 (°C)	T_2 (°C)
0	−20	−26	−13
30	24	14	34
64	28	17	38
98	30	16	43
132	30	16	44
166	31	18	46
766	32	16	48

DMA can monitor cure reaction from gelation to the completion of the reaction because the elastic modulus in the rubbery state at constant temperature is a measure of the crosslink density [5]. During cure, both G' and G'' increase sharply near the gel point and gradually level off when complete cure is achieved while loss tangent decreases asymptotically to its final value. Thus, DMA results show that complete cure requires about 180 min, where change in G' with time can no longer be detected. These

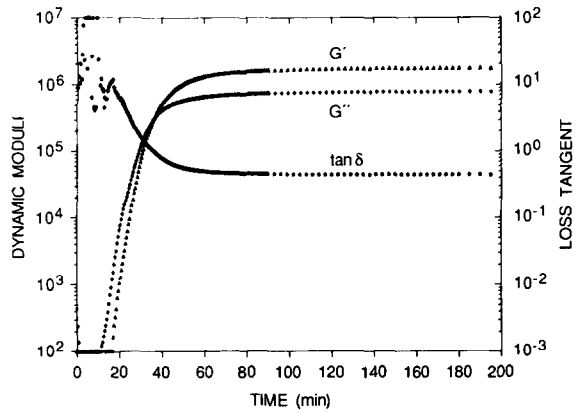

Fig. 4. Dynamic moduli and loss tangent of crosslinking poly(ortho ester) as a function of reaction time at 70°C and 1 rad/s strain frequency.

results show that DMA is somewhat more sensitive than DSC for detecting complete cure.

Effects of frequency on the DMA measurements

In dynamic mechanical analysis, the dynamic moduli are dependent on the frequency of the applied strain because polymer chains or segments having various relaxation times respond differently to different mechanical frequencies. In general, lower frequency measurements are more sensitive to changes in crosslink density, especially near completion of cure, because chain segments with longer relaxation times will also contribute to the response signal. However, the frequency should not be so low that the sampling rate is not fast enough to capture the rapid changes that occur near gelation.

Figure 5 shows DMA results as a function of reaction time of a crosslinking poly(ortho ester) at a frequency of 10 rad/s. The dynamic moduli assume the same characteristic shape as those at 1 rad/s shown in Fig. 4. However, G' and G'' level off at an earlier time (about 100 min) when compared to those determined at the lower frequency. As expected, the higher frequency measurements are less sensitive near

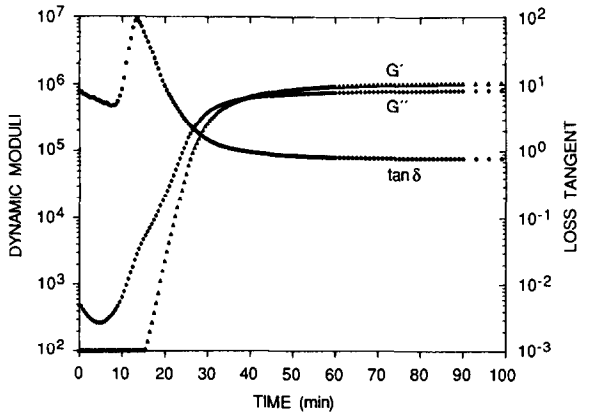

Fig. 5. Dynamic moduli and loss tangent of crosslinking poly(ortho ester) as a function of reaction time at 70°C and 10 rad/s strain frequency.

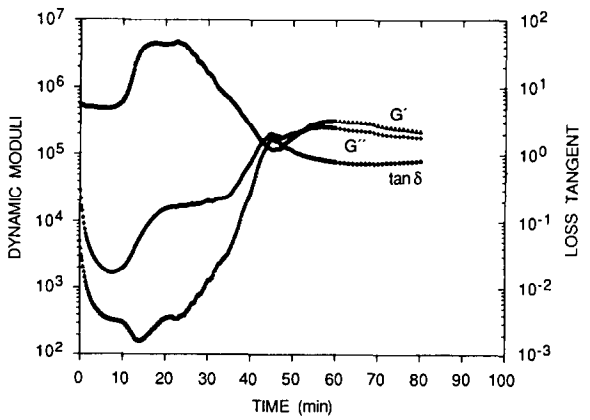

Fig. 6. Dynamic moduli and loss tangent of crosslinking poly(ortho ester) as a function of reaction time at 70°C and 100 rad/s strain frequency.

complete cure because chain segments with slower response times cannot respond to the higher strain frequency.

At both frequencies, G' and G'' cross over following the sharply changing part of the cure curve. Previous studies [6,7] have attributed this crossover point to the gelation point, although recent reports [8] demonstrated that this is not necessarily true for all crosslinking reactions. We have found that the crossover in G' and G'' ($\tan \delta = 1$) is quite insensitive to the applied frequency. It occurs at 36.2 min at 1 rad/s and 38.5 min at 10 rad/s.

When the strain frequency is increased to 100 rad/s, the cure curves exhibit a drastically different appearance as shown in Fig. 6 and the rheological functions G' and G'' no longer increase monotonically after the initial minimum. Since G' is related to the crosslink density in the elastic network, we attribute the observed peculiar cure feature to a mechanical cleavage of polymer chains or crosslinking network by the high frequency strain. In this case, the data are no longer meaningful because the probe used for studying the cure behavior is influencing the cure reaction.

Effects of cure temperature

Vitrification of the growing chains or network, a phenomenon distinct from gelation, may occur at any stage during cure. This transformation from a viscous liquid or elastic gel to a glass occurs when the T_g of the growing chains or network becomes coincidental with the cure temperature. Since curing in the glassy state is extremely slow, for all practical purposes, vitrification brings curing reactions to a halt [9,10].

The cure reaction can also be affected when the final T_g of the network is close to, but not coincidental, with the cure temperature since cure rate would significantly slow down as T_g approaches the cure temperature.

To investigate the effects of cure temperature on the crosslinking behavior of poly(ortho esters), we have performed a set of DSC experiments at the higher temperature of 90°C. Table 2 tabulates results of the 90°C cure. As compared with the 70°C cure, the reaction at 90°C appears to be faster and produces a narrower transition with higher half-height values. The narrower transition could indicate a more even distribution in the crosslink density. No significant thermal degradation was detected at 90°C even after 795 min.

TABLE 2

Glass transition of crosslinking poly(ortho ester) with 30% excess hydroxyl groups at 90°C cure

Cure time (min)	T_g (°C)	T_1 (°C)	T_1 (°C)
0	−22	−29	−14
30	34	19	41
51	35	22	42
72	34	20	43
93	34	19	43
129	36	31	42
195	35	28	42
795	35	30	40

TABLE 3

Glass transition of crosslinking poly(ortho ester) with stoichiometric ratio at 70°C cure

Cure time (min)	T_g (°C)	T_1 (°C)	T_2 (°C)
0	−20	−26	−14
30	22	13	34
64	27	21	34
98	29	22	37
132	32	22	44
766	42	30	55

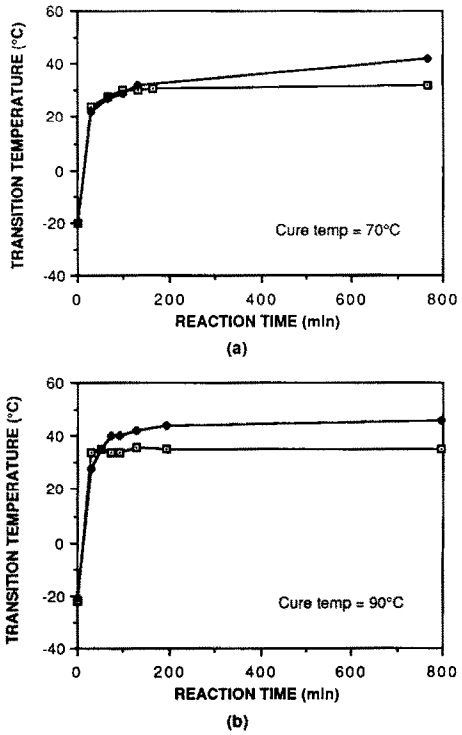

Fig. 7. Change in T_g as a function of reaction time for poly(ortho ester) with 30% excess hydroxyl groups (□) and stoichiometric ratio (♦). (a) 70°C cure temperature (b) 90°C cure temperature.

Effects of ratio of ketene acetal to hydroxyl groups

In all cure experiments discussed thus far, the ketene acetal to hydroxyl group ratio was 1:1.3. We also studied cure behavior when the ratio was stoichiometric. Table 3 tabulates results obtained at 70°C cure when DSC was used to monitor the change in T_g. When compared to data shown in Table 1, the initial increase in T_g for the stoichiometric mixture appears to be more gradual, and the ultimate T_g is higher. The comparison is shown graphically in Fig. 7(a). This behavior is probably due to the higher reactivities of the two primary hydroxyl groups in 1,2,6-hexanetriol relative to the secondary one. Thus, when hydroxyl groups are in excess, the more reactive primary hydroxyl groups are favored early in the crosslinking reaction, resulting in higher reaction rates. Involvement of the less reactive secondary hydroxyl groups becomes important at longer reaction times, but by that time the number of remaining unreacted ketene acetal groups has significantly decreased. This results in the formation of a less tightly crosslinked network which will have a lower final T_g value.

Table 4 tabulates T_g values measured for a stoichiometric mixture cured at 90°C and Fig. 7(b) graphically shows the comparison with cure data at the same temperature using a 30% excess hydroxyl groups (Table 2). Qualitatively, the effect of varying ketene acetal to hydroxyl group ratio is the same as for the 70°C cure. Further, as with the 70°C cure, the 90°C cure of a stoichiometric mixture also yields a

TABLE 4

Glass transition of crosslinking poly(ortho ester) with stoichiometric ratio at 90°C cure

Cure time (min)	T_g (°C)	T_1 (°C)	T_2 (°C)
0	−21	−25	−17
30	28	18	39
51	35	24	46
72	40	30	48
93	40	32	48
129	42	32	51
195	44	36	54
795	46	43	49

narrower transition temperature and a higher final T_g.

Effects of drug and excipient loading

Cure time for a poly(ortho ester) loaded with 10 wt% levonorgestrel and 7 wt% $Mg(OH)_2$ is significantly longer than that for the neat polymer alone. Figure 8 is a DSC thermogram showing cure behavior of the drug-loaded mixture, with a ketene acetal to hydroxyl group ratio of 1:1.3, at 70°C carried out for 960 min (16 h). As shown, changes in thermal properties were undetectable after about 600 min (10 h).

When the T_g of the matrix was used to monitor the state of cure, we have found that T_g increased slowly well after 10 h of cure at 70°C as is shown in Table 5. To confirm results of thermal analysis, we have carried out DMA measurements at 1 rad/s strain frequency up to 16 h of cure. Figure 9 shows plots of the storage (G') and loss (G'') moduli of the drug-loaded poly(ortho ester) as a function of cure time. The minimal changes in both moduli at the end of the 16 h period confirm that for all practical purposes by that time cure at 70°C is complete. The G' and G'' crossover point occurs at a later time (81.5 min), and the final values for G' and G'' are higher than those of the neat polymers. The higher moduli can be attributed to the fillers which act as a reinforcement to the matrix polymer.

Results of the 90°C cure of the loaded poly(ortho ester) are summarized in Table 6. Changes in T_g up to 48 h of cure time at 90°C appear to be comparable to those of the 70°C cure, although the breadth of the transition is again narrower at the higher cure temperature as was the case for the neat polymers.

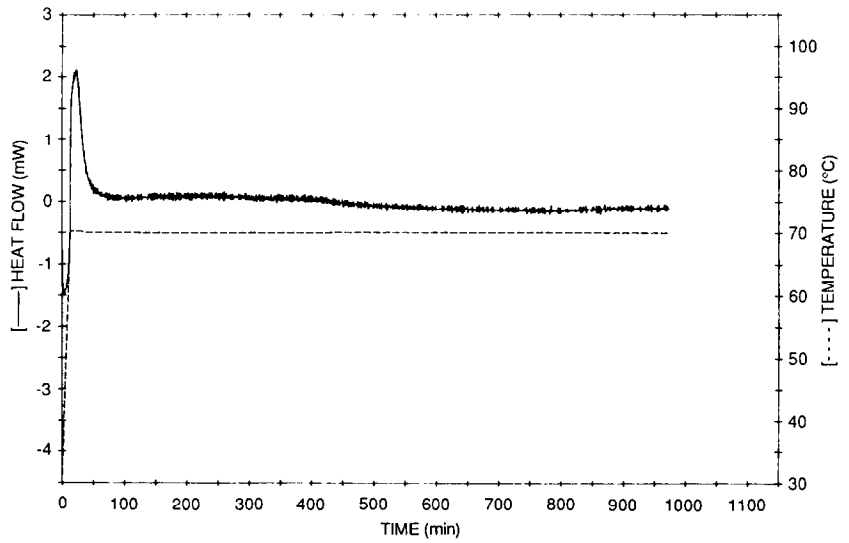

Fig. 8. DSC thermogram showing the thermal behavior of loaded poly(ortho ester) at 70°C cure.

TABLE 5

Glass transition of crosslinking drug-loaded poly(ortho ester) with 30% excess hydroxyl groups at 70°C cure

Cure time (h)	T_g (°C)	T_1 (°C)	T_2 (°C)
0	−20	−25	−17
4	24	15	32
8	27	15	40
16	30	15	44
24	31	17	45
48	31	17	45

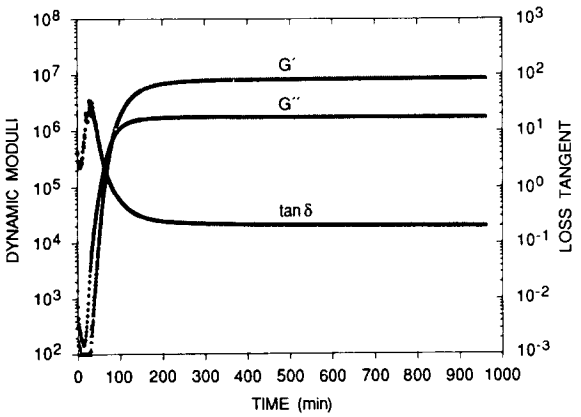

Fig. 9. Dynamic moduli and loss tangent of crosslinking poly(ortho ester), loaded with drug and excipient, as a function of reaction time at 70°C and 1 rad/s strain frequency.

TABLE 6

Glass transition of crosslinking drug-loaded poly(ortho ester) with 30% excess hydroxyl groups at 90°C cure

Cure time (h)	T_g (°C)	T_1 (°C)	T_2 (°C)
0	−20	−25	−17
3	26	12	39
8	28	16	39
16	31	19	44
48	34	27	42

The one order of magnitude reduction of cure rate caused by the addition of levonorgestrel and $Mg(OH)_2$ is undoubtedly due to the basicity of $Mg(OH)_2$ which retards the acid-catalyzed reaction between ketene acetals and hydroxyl groups. The alternate explanation that the reduced cure rate is due to a reduction in molecular mobility of the reactive species caused by the incorporated solid materials is unlikely because it has been reported that the addition of up to 40 wt% glass microsphere fillers had only a minor effect on cure kinetics of epoxy resins [11].

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