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Controlled drug release of silicone-based adhesive-containing cross-linked siloxane powders as a reservoir

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ABSTRACT: We prepared pressure-sensitive adhesive (PSA)-containing cross-linked siloxane powders (CS) as a reservoir for a transdermal drug delivery system (TDDS) and evaluated their sustained drug-release properties. PSA, as a patch-type adhesive, was synthesized by a hydrosilylation reaction of vinyl-terminated polysiloxanes with hydrogen-terminated polydimethylsiloxanes. CS was also prepared via a hydrosilylation process with vinyl-terminated polydimethylsiloxane, 1,3,5,7-tetramethyl-1,3,5,7-tetravinyltetracyclosiloxane (D_4^{Vi}), hydrogen-terminated polydimethylsiloxane, and dimethylhydrogenmethyl oligomeric siloxane copolymer. The results of release performances using ascorbic acid as a model drug showed a cumulative linear slope over a week, indicating a constant release performance. Our data suggest that this siloxane TDDS could be useful for constant drug release over a long period. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42154.

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INTRODUCTION

Transdermal drug delivery systems (TDDS) have been studied for decades in a variety of research and industrial fields including biology, pharmaceutics, chemistry, and materials science. The early approach to drug reservoirs focused on the maintenance of drug levels, within an efficient range, *in vivo* by controlling the dissolution of orally administered drugs in physiological systems.[1,2] Recent progress in molecular, supramolecular, polymeric, and nanomaterial sciences has enabled researchers to fabricate materials with specific physicochemical properties for their own application, and thus, strategies for TDDS have reached a turning point.[3,4] Indeed, the recent decade of TDDS study has been devoted to developing different approaches, such as targeted drug reservoirs to specific lesions, or to exploiting alternative administration routes for increased convenience of patients.

In this context, the most attractive research topic in drug reservoirs is the development of TDDS. Compared with traditional means of administration, such as oral or parenteral routes, TDDS has many advantages, including easy administration, reduction in patient pain, and continuous drug supplementation with a single administration; thus, it is considered one of the most advanced drug-delivery methods. Many research groups and pharmaceutical companies are developing TDDS, and some patch-type products,[5,6] such as Minivelle® (an estradiol transdermal system from Noven Therapeutics LLC), are now commercially available.[7]

TDDS patches are generally composed of several heterogeneous components, including backing materials, a drug reservoir, drug-releasing membrane, and contact adhesive, each of which is currently confined to a single functionality. Combining two or more of these heterogeneous components while preserving each functionality might confer the advantage of a simplified manufacturing process.[8] For example, if the contact adhesive maintains its adhesive properties while possessing drug reservoir and controlled-release functionality,[9–12] the TDDS patch system would be greatly simplified. However, the discrepancy in the chemical nature of pressure-sensitive adhesives (PSAs) and the other patch components has hindered such combinations.[13,14] Polysiloxanes, often referred to as silicones, are often used as contact adhesives because of their PSA property. However, it is very difficult to establish polysiloxane as a drug reservoir because interactions among side chains of polysiloxanes are not easily controlled or appropriate for drug release.[15,16]

Additional Supporting Information may be found in the online version of this article.

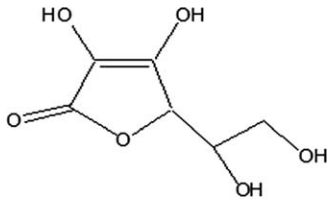
In this study, we prepared a polysiloxane PSA with drug-reservoir functionalities by the introduction of polysiloxane resin-type moieties, which act as a drug reservoir and release controller for PSA materials.[17–23] In general, polymerization in silicone chemistry involves dehydrative condensation between silanols, but it is difficult to control the degree of condensation or to modify side-chain functionality. We exploited cross-link coupling through the hydrosilylation process between vinyl and hydrogen moieties, by which the degree of polymerization and interaction between side chains can be manipulated. Through controlled interchain interaction, siloxane polymers prepared by this method can contain small cavities and grooves on the surface with hierarchical structures that might act as molecular reservoirs and release modulators.[24,25] Furthermore, such cross-linked-moiety-containing siloxanes are easily miscible with PSA materials in a nanoscale because of their similar chemical nature, resulting in a PSA with drug reservoir and release controlling properties.[26] We evaluated the drug release property of patch-type materials prepared by this method using ascorbic acid as a model drug in the TDDS system. The release rate for CS-PAA showed a cumulative linear slope over a week. Thus, this system might be applicable for constant-concentration-releasing systems over a given long period.

MATERIALS AND METHODS

The prepared reservoirs were characterized and analyzed by HPLC [Model YL9100 HPLC system, YL9130 Column compartment, YL9170 RI Detector Unison, UK-Amino (250 × 4.6 mm), Product No. UKA06, 3 μm, Imtakt column], NMR (Bruker Avance II$^+$ BBO 400 MHz S1 spectrometer), FT-IR, and SEM (Model Quanta 250FEG).

Materials

1. Synthesis of base gel (patch): vinyl-terminated polydimethylsiloxanes (200 cSt. 1,000 cSt. 10,000 cSt. Tairen, Taiwan, and 5,000 cSt. KCC, Korea), and hydrogen-terminated polydimethylsiloxane (30 cSt. Tairen) were used to synthesize the polysiloxane patch gel (base media).
2. Synthesis of cross-linked siloxane resin powders (CS): vinyl-terminated polydimethylsiloxane (100 cSt., Tairen), 1,3,5,7-tetramethyl-1,3,5,7-tetravinyltetracyclosiloxane (D_4^{Vi}, SKC, Korea), hydrogen-terminated dimethylhydrogenmethyl oligomeric siloxane copolymer (20 cSt. Shin-Etsu Silicone, Japan), and hydrogen-terminated polydimethylsiloxane (30 cSt. Tairen) were used to synthesize the cross-linked siloxane (CS) resin powder.
3. Synthesis of highly cross-linked comparative powder (HCP): 1,3,5,7-tetramethyl-1,3,5,7-tetravinyltetracyclosiloxane (D_4^{Vi}, SKC, Korea) and 1,3,5,7-tetrahydrogen-1,3,5,7-tetramethyltetracyclosiloxane (D_4^{H}, SKC) were used to synthesize the highly cross-linked comparative powder (HCP).
4. Pt Cat. (Karstedt's catalyst, CALS, Korea) was used for the hydrosilylation reaction.
5. Solution of L–ascorbic acid (AA): L–ascorbic acid (A5960-25G, Sigma-Aldrich, Figure 1), tetrahydrofuran (THF, Sigma-Aldrich), and methanol (HPLC grade reagent, Duksan Pure Chemical, Korea) were used to prepare the L–ascorbic acid solution (AA).
6. Releasing solvent: methanol (HPLC grade reagent, Duksan Pure Chemical) was used as both HPLC and releasing solvent to minimize analytical errors.



L-ascorbic acid, $C_6H_8O_6$

Figure 1. Structure of model drug, L–ascorbic acid, $C_6H_8O_6$.

Preparation of the Gel Base Material for TDDS Patch

Siloxane polymers of industrial grade were used to prepare the gel. The base of the gel (gel part A) was prepared with 40 g of vinyl-terminated polydimethylsiloxane (200 cSt. Tairen), 40 g of vinyl-terminated polydimethylsiloxane (1000 cSt. Tairen), 10 g of vinyl-terminated polydimethylsiloxane (5000 cSt. KCC), 10 g of vinyl-terminated polydimethylsiloxane (10,000 cSt. Tairen), and 0.070 g of Karstedt's catalyst.

The curing agent part of the gel (gel part B) was prepared with 39 g of vinyl-terminated polydimethylsiloxane (200 cSt. Tairen), 39 g of vinyl-terminated polydimethylsiloxane (1000 cSt. Tairen), 9 g of vinyl-terminated polydimethylsiloxane (5000 cSt. KCC), 9 g of vinyl-terminated polydimethylsiloxane (10,000 cSt, Tairen), and 4 g of hydrogen-terminated polydimethylsiloxane (30 cSt. Tairen).

Sticky gel (the patch) was prepared by mixing gel part A and gel part B in a 1 : 1 mixing ratio and curing at 120°C for 60 min. The two gel components were mixed homogeneously and used for the patch base material.

Preparation of Cross-Linked Siloxane Resin Powder

Cross-linked siloxane resin powder (CS), which contains multiple nanocavities and grooves, was synthesized through hydrosilylation with 30 g of vinyl-terminated polydimethylsiloxane (100 cSt. Tairen), 12 g of 1,3,5,7-tetramethyl-1,3,5,7-tetravinyltetracyclosiloxane (D_4^{Vi}, SKC), 10 g of hydrogen-terminated dimethylhydrogenmethyl oligomeric siloxane copolymer, (20 cSt. Shin-Etsu Silicone), 10 g of hydrogen-terminated polydimethylsiloxane (30 cSt. Tairen), and 0.070 g of Karstedt's catalyst. The CS was cured at 120°C for 60 min, ground to a powder in a mortar, and sieved through 60 stainless mesh before use.

Preparation of Highly Cross-Linked Comparative Powder

Very hard Highly Cross-Linked Comparative Powder (HCP) resin was synthesized with 34.4 g of 1,3,5,7-tetramethyl-1,3,5,7-tetravinyltetracyclosiloxane (D_4^{Vi}) and 24 of 1,3,5,7-tetrahydrogen-1,3,5,7-tetramethyltetracyclosiloxane (D_4^{H}) in the presence of 0.030 g of Karstedt's catalyst at 35–45°C for 30 min and post cured at 120°C for 60 min. The cured HCP was ground to a powder in a mortar, and then sieved through #60 stainless mesh before use.

It should be noted that the reaction of HCP preparation was very explosive and combustible above a temperature of 50°C.

Preparation of L–Ascorbic Acid Solution

To prepare L–Ascorbic Acid Solution (AA), 0.50 g of L–ascorbic acid (A5960-25G, Sigma-Aldrich) was diluted in 3 g of tetrahydrofuran (THF) and 9.5 g of methanol at room temperature. The prepared concentration of L–ascorbic acid solution was 3.8 wt %.

Preparation of CS-AA- and HCP-AA-Containing L–Ascorbic Acid on the Powdered CS and HCP Surfaces

CS-AA powder was prepared by immersing 10 g of sieved CS powder in 10 g of AA solution for 10 min at room temperature. CS-AA was dried at 90°C for 2 h, ground to a powder in a mortar, dried at 90°C for another 2 h, and then ground again and sieved through #60 stainless mesh before use.

HCP-AA powder was prepared by immersing 10 g of sieved HCP powder in 10 g of L–ascorbic acid solution for 10 min at room temperature. HCP-AA was dried at 90°C for 2 h, ground to a powder in a mortar, dried at 90°C for another 2 h, and then ground again and sieved through #60 stainless mesh before use.

Preparation of Releasing Samples

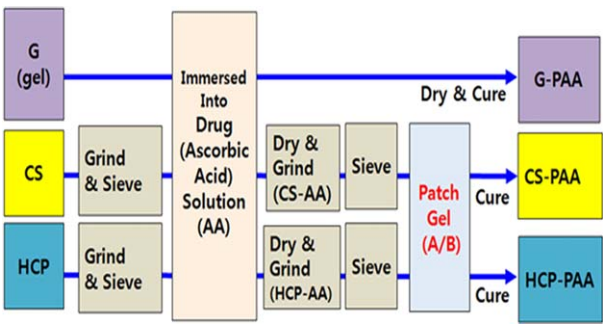
The procedure of sample preparation is summarized in Diagram 1.

Sample G-PAA: 9.50 g of gel part A, 9.50 g of gel part B, and 1 g of L–ascorbic acid solution were mixed well; 2 g of the mixture were transferred into a 20 mL glass vial (22 mm inner diameter, 60 mm height including screw part) and cured at 90°C for 90 min.

Sample CS-PAA: 4.75 g of gel part A, 4.75 g of gel part B, and 1.50 g of sieved CS-AA powder were mixed to homogeneity; 2 grams of the mixture were transferred to a 20 mL vial and cured at 90°C for 90 min.

Sample HCP-PAA: 4.75 g of gel part A, 4.75 g of gel part B, and 1.50 g of sieved HCP-AA were mixed to homogeneity; 2 g of the mixture were transferred to a 20 mL vial and cured at 90°C for 90 min.

The formulations of the samples are described in Table I and Supporting Information Table S1.



Dia 1. Summaries of the procedures for sample preparation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table I. Formulation of Each Sample

Item	Gel part A (g)	Gel part B (g)	Powder-AA (g)	Powder (%)	Sieving
G-PAA	9.75	9.75	-	-	No
CS-PAA	4.75	4.75	1.50	13.6	Yes
HCP-PAA	4.75	4.75	1.50	13.6	Yes

Characterization

Measurement of Concentration. To measure the concentrations of released L–ascorbic acid, analysis using high-performance liquid chromatography (HPLC) was performed, as follows, for all samples: column, [Unison UK-Amino (250 × 4.6 mm), Product No. UKA06, 3 μm, Imtakt]; carrier solvent, methanol (HPLC reagent grade, Samchun Pure Chemical, Korea, CAS No. 67-56-1); flow rate, 0.8 mL/min; total flow time of measurement, 40 min. Concentrations of released L–ascorbic acid were monitored each day (24 h elution period at room temperature) for a week, and each 4 g sample of releasing solvent was replaced by same weight (4 g) of fresh solvent.

Confirmation of Resin Structures. We performed FT-IR, NMR, and SEM to confirm the resin functionalities in the structure of CS and HCP. In FT-IR analysis of each reaction, the reactants yielded strong peaks: D_4^H (Si—H) and D_4^{Vi} (Si—CH=CH_2) gave quite clear and strong peaks at 3017.06, 3056.22 cm^{-1} and 1007.87, 950.53 cm^{-1}. In analysis of the product, the D_4^H and D_4^{Vi} peaks should have disappeared or minimized.

To confirm the reaction structure for the gel, CS, and HCP, ^{1}H NMRand ^{29}Si NMR spectra of reactants and products were obtained using an NMR spectrometer. The chemical shifts were referenced to internal $CDCl_3$ (^{1}H and ^{13}C NMR) or external tetramethylsilane (^{29}Si NMR). To compare differences in surface morphologies of the gel, CS, and HCP, we used SEM to scan the surfaces of the samples with different magnification ratios (Supporting Information Figures S5–S7).

RESULTS AND DISCUSSION

Release Performance Analysis

The release concentration of CS-PAA increased 22.2% on the 2nd day, 15.2% on the 3rd day, 7.2% on the 4th day, and 10.7% on the 5th day, and decreased 6.4% on the 6th day, as assessed by peak area compared to the released concentration on the 1st day. Contrast the release of CS-PAA with the release of HCP-PAA; HCP-PAA decreased constantly (22.1% on the 2nd day, 32.2% on the 3rd day, 52.3% on the 4th day, 72.7% on the 5th day, and 48.4% on the 6th day, by peak area compared to the concentration on the 1st day). The concentration of G-PAA (no addition of powder) similarly decreased each day: 24.3% on the 2nd day, 49.5% on the 3rd day, 58.1% on the 4th day, 50.3% on the 5th day, and 62.4% on the 6th day, by peak area compared to the released concentration of 1st day. (Supporting Information Figures S1–S4, S8)

The decrease or increase in concentration was calculated by the following equation:

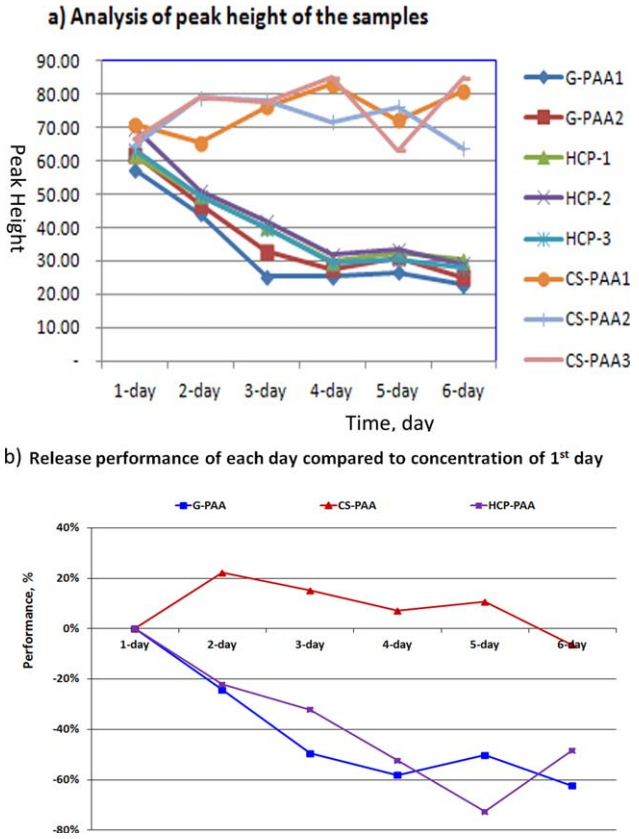


Figure 2. (a) Analysis of peak height of the samples. (b) Release performance of each day compared to the concentration of 1st day. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$$RC_{(day)} = 100\left[\left(C_{(day)}/C_{(1^{st}day)}\right) - 1\right] \quad (1)$$

where $RC_{(day)}$ was calculated as the release concentration of the test day, and $C_{(day)}$ and $C_{(1^{st}day)}$ are real detected concentrations by peak area of the test day and the 1st day.

In spite of 6 days of continuous elution, the released concentration on the 6th day of CS-PAA was only decreased 6.4% compared to the 1st day, but the released concentration on the 6th day of HCP-PAA decreased 48.4% compared to the 1st day (almost half of the concentration of the 1st day; 1085.84 to 560.17 by peak area) and the released concentration on the 6th day of G-PAA (with no addition of powder) also decreased 62.4% by peak area compared to the 1st day (Figure 2).

The cumulated concentration of CS-PAA showed a linear slope whereas G-PAA and HCP-PAA showed nonlinear slopes, the differences between CS-PAA and others are compared in Figure 3.

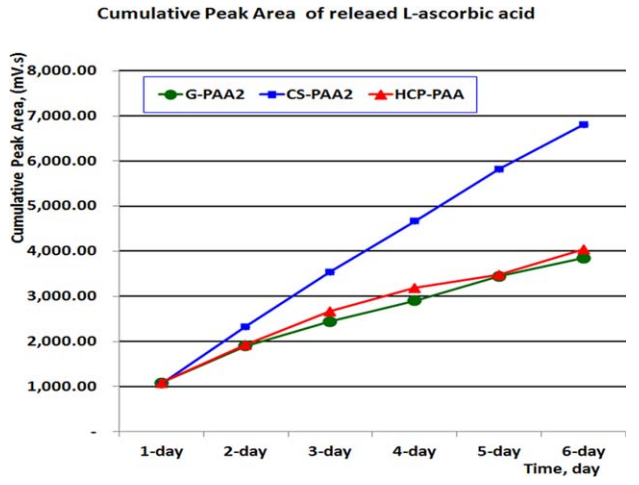


Figure 3. Cumulated peak area of released L–ascorbic acid. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Confirmation of the Results for Resin Structures

The functionality changes through the reaction of the HCP powder preparation were confirmed by FT-IR. The reactants showed strong peaks for their functional group: the D_4^H (Si—H) peak appeared very strongly at 2175.97 cm^{-1}, and D_4^{Vi} appeared quite clearly with strong peaks at 3017.06, 3056.22 cm^{-1} and 1007.87, 950.53 cm^{-1}. After the hydrosilylation reaction, these peaks were almost completely absent in the product HCP (Figure 4).

The estimated structures of CS powder and HCP powder are shown in Figures 5 and 6. The HCP structure contained very small and unique nanocavities and grooves, caused by alternating cross links between D_4^H and D_4^H (Figure 6), compared to CS (Figure 5) powder, which has nonunique cavities and grooves that are dependent on the random linkage of the siloxane reaction between cyclic and linear linkages (oligomeric siloxane copolymer also gives a random linkages in the three-dimensional network). These cavities and grooves may act as an excellent drug reservoir through polarities, hydrogen-bonding chemisorptions, etc. and effectively release a constant concentration over several days.

The reactants and products of CS and HCP were confirmed by ^1H NMR and ^{29}Si NMR spectrometer. The chemical shifts were referenced to internal $CDCl_3$ (^1H and ^{13}C NMR) or external tetramethylsilane (^{29}Si NMR). The shifts were divided very clearly into SiH, $SiCH{=}CH_2$, and $SiCH_3$. For ^1H NMR (400 MHz, $CDCl_3$, δ): 6.056 to 5.782 ($SiCH{=}CH_2$), 4.699 (SiH), 0.485 to 0.084 ($SiCH_3$), 1.526, 0.944, 0.210 ($SiCH_2CH_2Si$). For ^{29}Si NMR

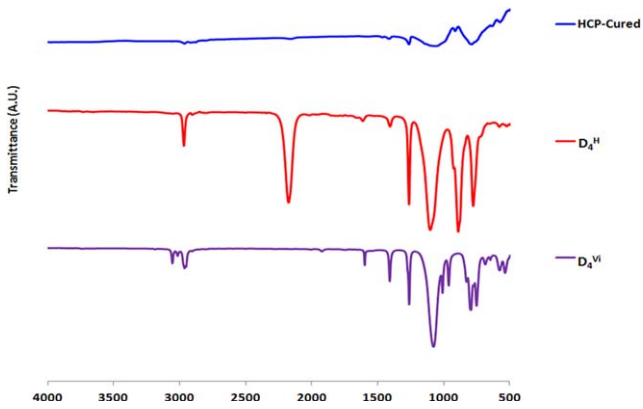


Figure 4. Confirmation of reactants and product of HCP reaction by FT-IR. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

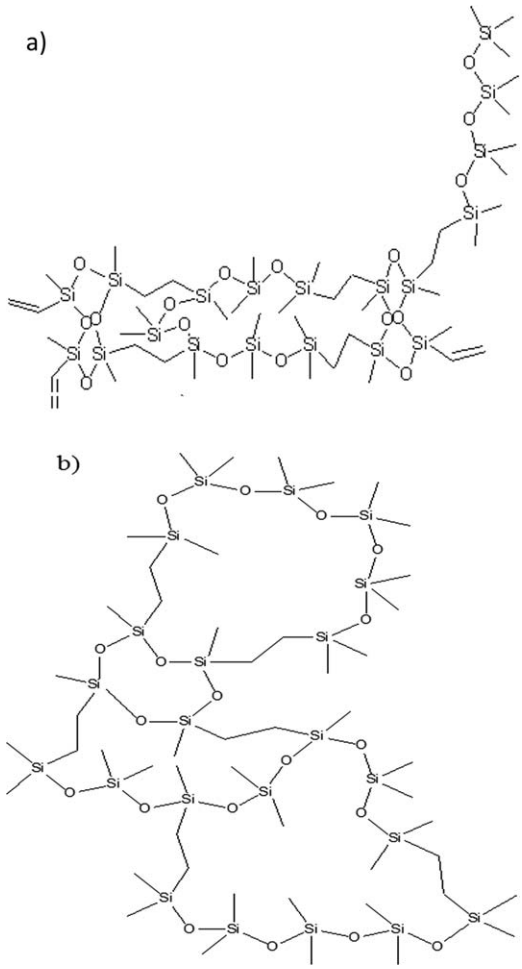


Figure 5. Estimated structure of CS. (a) Proposed structure for two molecules of tetramethyltetravinyltetracyclosiloxane (D_4^{Vi}), one molecule of hydrogen-terminated polydimethylsiloxane and one molecule of hydrogen-terminated polydimethylhydrogenmethyl oligomeric siloxane copolymer. (b) Proposed structure of one molecule of hydrogen-terminated polydimethylhydrogenmethyl oligomeric siloxane copolymer, one molecule of tetramethyltetravinyltetracyclosiloxane (D_4^{Vi}), and two molecules of hydrogen-terminated polydimethylsiloxane.

[400 MHz, $Si(CH_3)_4$, δ]: 32.46 [$(CH_3)_2SiOSi(CH_3)_2$], 3.20 to 32.82 (D_4^H), 32.50 to 32.61 $(CH_2{=}CH)CH_3SiO)_4$.

The morphology of the surfaces for the CS resin block and HCP resin block, which were smoothly cut from the surface of cured resin before powdering, was examined by SEM. The HCP resin block contained very fine discrete cavities and grooves on the entire surface, whereas the CS resin block contained several long hollow lines (cavities and grooves) on the surface (Figure 7).

The fine cavities and grooves of the HCP resin block were observed only at 100,000× magnification. At the other magnification levels, the surfaces appeared flat because the cavities and grooves are well ordered and nanosized.

The hollow line cavities and grooves of the CS resin block were observed at only 10,000× magnification. At the other magnification levels, we observed very rough surfaces because the cavities and grooves are irregular with different sizes (Figures 8–10).

The cavities and grooves were very similar to the estimated structures of CS and HCP generated by oligomeric cross-linking between linear siloxane (vinyl-terminated polydimethyl siloxane and hydrogen-terminated polydimethylsiloxane) and 1,3,5,7-tetramethyl-1,3,5,7-tetravinyltetracyclosiloxane (D_4^{Vi}) or hydrogen-terminated dimethylhydrogenmethyl oligomeric siloxane copolymer units.

Stickiness Performance

In general, the stickiness of the patch is considered an important characteristic. The reservoirs of TDDS, such as silica, clay, bentonite, or alginate, have been evaluated many times to improve drug-release performance and increase their percentage of the gel volume. However, porous fillers cannot constitute more than 10% weight of the base gels because they can block the sticky character of the patch gels.

The results of this work showed that CS did not block the sticky gel character; even though it composed more than 18% of the weight of the gel, it did not affect the stickiness of the patch gel.

Differences Between this Work and Other Studies that Used Several Different Reservoirs in TDDS are as Follows:

1. All of the chemicals used in this work for the gel, CS, and HCP were siloxanes with Si—O—Si backbones.
2. The siloxanes do not have any special functional group except a small number of Si–H and $SiCH{=}CH_2$ groups,

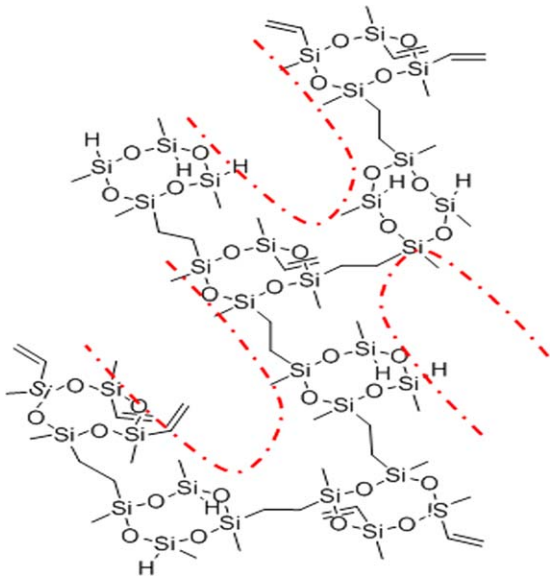


Figure 6. Estimated structure of cavities and grooves in HCP; the proposed structure shows that four molecules of 1,3,5,7-tetrahydrogen-1,3,5,7-tetramethyltetracyclosiloxane (D_4^H) and four molecules of 1,3,5,7-tetramethyl-1,3,5,7-tetravinyltetracyclosiloxane (D_4^{Vi}) are alternately cross-linked and generate multiple, very unique, and fine nanocavities and grooves on the surface. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

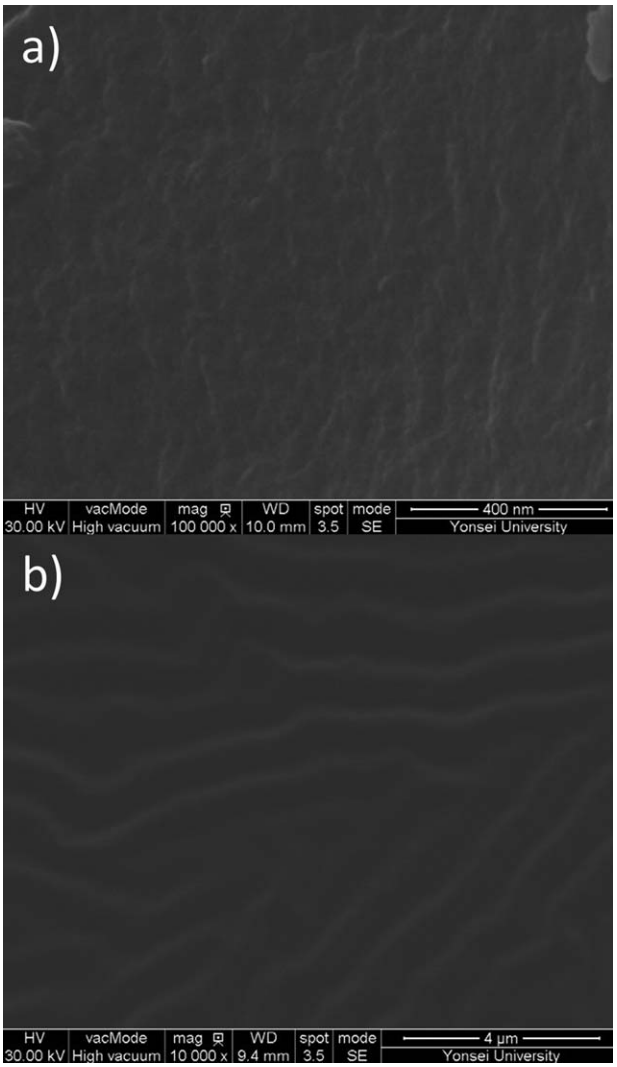


Figure 7. SEM analysis of each sample. (a) Smoothly cut surface of HCP resin block, ×100,000. (b) Smoothly cut surface of CS resin block, ×10,000.

which are chemically inert compared to hydroxyl or amine functional groups.

3. The siloxanes have biocompatibility with human skin, and the hydrosilylation reaction does not generate any byproducts during curing.
4. These reservoirs are nonbleeding siloxanes[27,28] because they do not contain any plasticizer to improve their flexibility and softness.
5. The base gel and filler (CS or HCP) have similar specific gravity, around 1.03 ± 0.02, and are therefore, easily mixed without separation.
6. Patch material can contain about 18% of reservoir (CS-PAA) without blocking the gel-like adhesive characters for a long period of time.
7. These reservoirs have a wide range of curing temperatures, from room temperature to 150°C, so they could be useful for various temperature-dependent TDDS.

Caution: The curing step of HCP powder synthesis was very dangerous (combustible and explosive), even though it was performed at 50°C, whereas CS powder was synthesized very easily. Therefore, we recommend CS synthesis procedure instead of HCP synthesis, based on safety considerations.

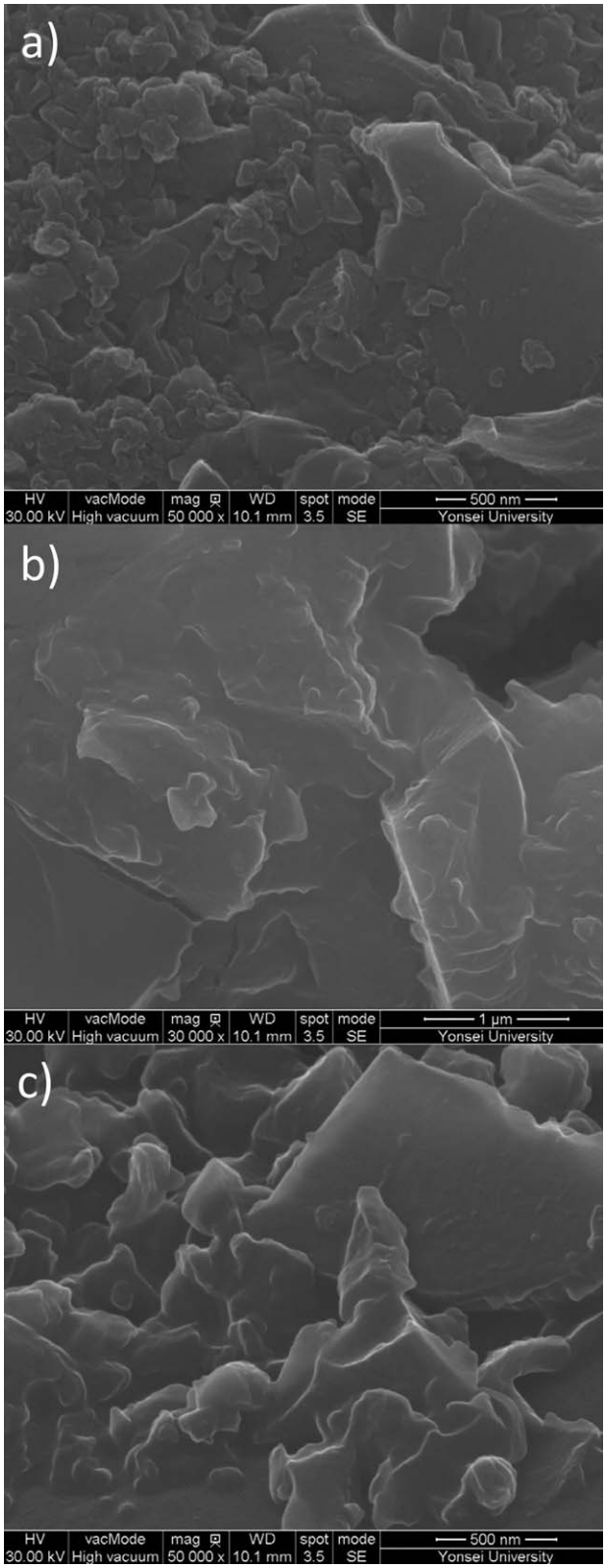


Figure 8. SEM scans of (a) highly cross-linked siloxane powder and (b) HCP powder surface ×30,000 and (c) HCP powder surface ×50,000.

CONCLUSIONS

CS-PAA was prepared by a hydrosilylation process involving the three components gel part A, gel part B, and CS-AA, and the model drug (L–ascorbic acid). CS-PAA showed excellent releasing performance with a cumulative linear slope over a week, and a 4-fold greater release than G-PAA and HCP-PAA. CS-PAA

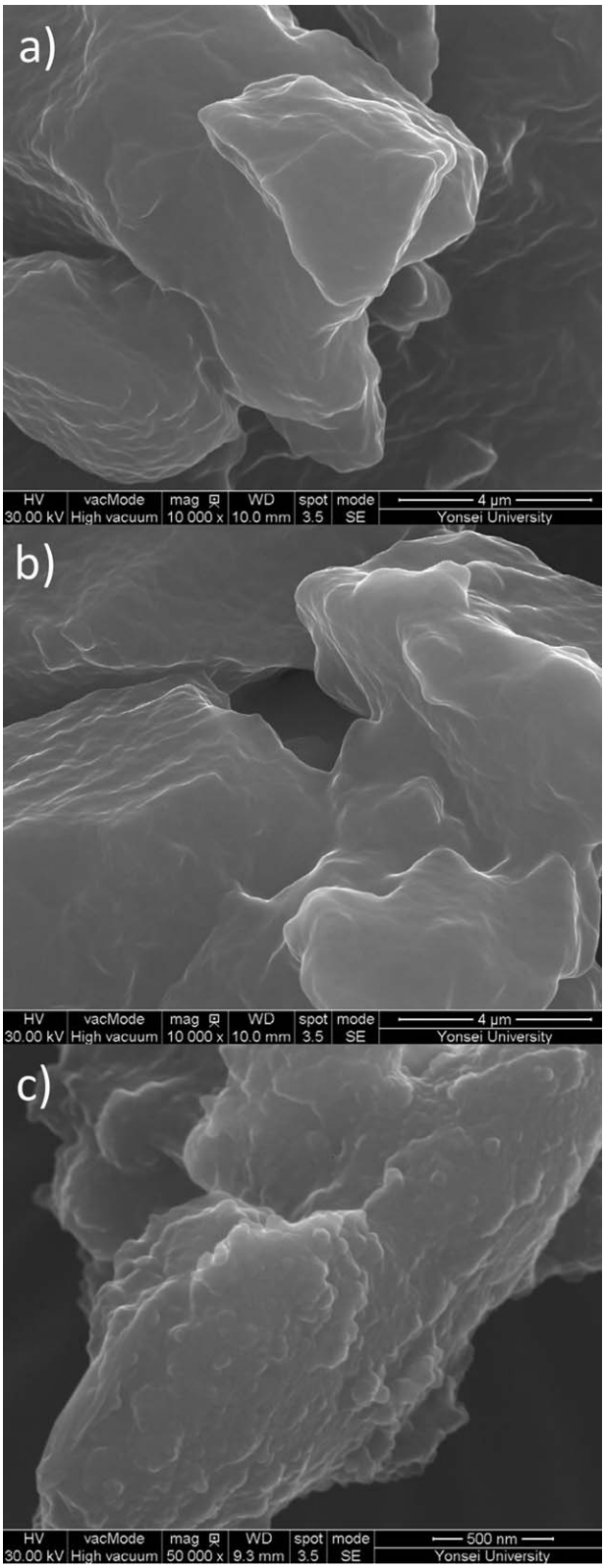


Figure 9. SEM images of CS powder. (a) CS powder surface ×10,000. (b) CS powder surface ×10,000 (another view). (c) CS powder surface ×50,000.

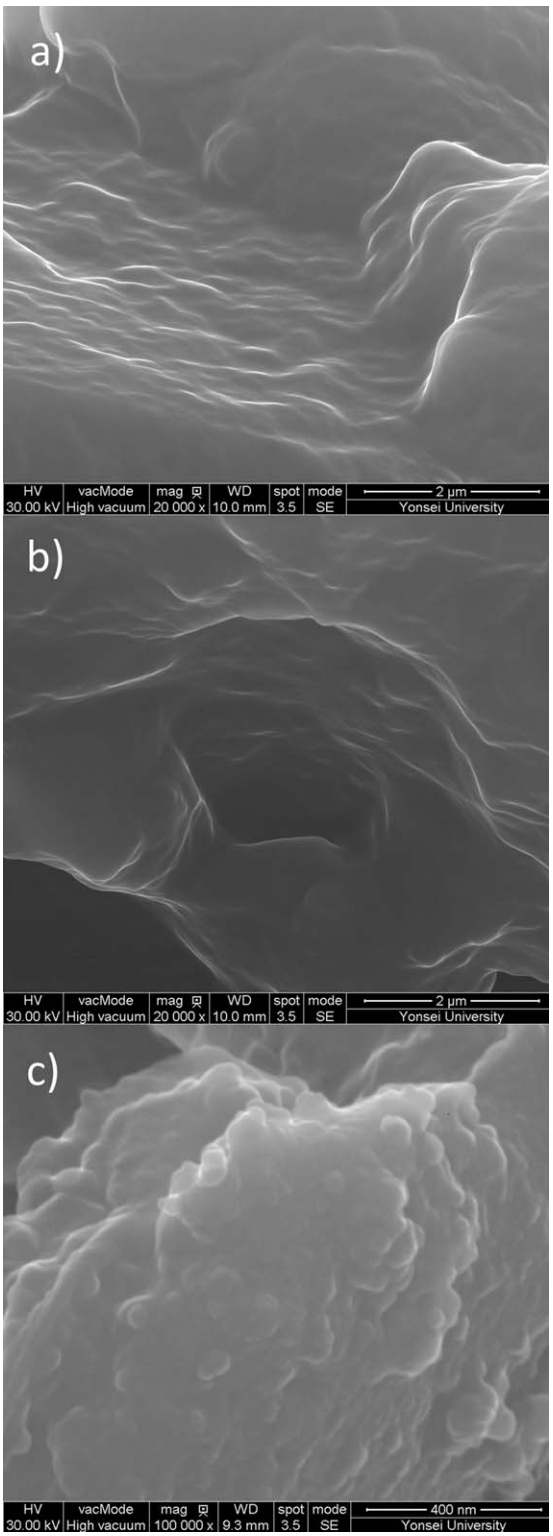


Figure 10. SEM images of cavities and grooves on the CS powder surface. (a) Grooves on the surface of CS powder ×20,000. (b) Cavities on the surface of CS powder ×20,000. (c) Irregular surface of CS powder ×100,000.

was characterized by FT-IR, NMR and SEM. One possible explanation for the improved release performance is that the grooves and cavities on the surface of CS play an important role in AA-adsorption through polarity, and AA-chemisorption, such as hydrogen bonding, resulting in filling of the cavities and controlled release. Based on the results described above, we suggest that the CS-PAA drug reservoir system could be applied for constant-concentration release of drugs over a long period of time.

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