Korean J. Chem. Eng., 34(6), 1600-1603 (2017)
DOI: 10.1007/s11814-017-0069-2
pISSN: 0256-1115
eISSN: 1975-7220

RAPID COMMUNICATION

Controlled drug release in silicone adhesive utilizing particulate additives

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(*Received 17 August 2016 • accepted 13 March 2017*)

Abstract−Polydimethylsiloxane (PDMS) based adhesives were prepared by cross-linking tetraethoxyorthosilicate (TEOS) while controlling stoichiometry with PDMS, acid catalyst, and water. Particulate additives, alginate and bentonite, were added during the cross-linking process. Cationic drug lidocaine was incorporated into the adhesive with or without additive, and the time-dependent drug release profile was evaluated in phosphate buffered saline and ethanol, respectively. According to kinetic fitting to power function and parabolic diffusion, both solvent and additive type influenced drug release. In particular, particulate additives were found to suppress or facilitate drug release in water or ethanol, respectively.

Keywords: Silicone Adhesive, Particulate Additives, Lidocaine, Release Media, Release Kinetic

INTRODUCTION

Transdermal drug delivery system (TDDS), which provides painless administration, has attracted increasing interest in the drug delivery field [1,2]. Such a system is designed to be applied to skin and to provide drugs continuously. For effective adhesion to skin, adhesives, one of the layers in a patch, are designed as pressure sensitive adhesive (PSA) [3], which is possible with silicones like polydimethylsiloxane (PDMS). While traditional PSA require basic functions such as adhesivity and biocompatibility, the current one necessitates a drug reservoir and release properties in one system [4]. In this regard, two approaches are available: i) to control the cross-linking degree among polymer chains [5], and ii) to insert additives or membranes for controlled release [6]. However, there are only a limited number of studies on the drug release properties of PSA utilizing additives.

Inspired by controlled drug release of particles, we hypothesized that particulate additives with specific affinity to drugs can control its release property. In this study, we used particulate additives, alginate and bentonite, to control the release of a model drug from silicone. The δ^- sites in the sugar of alginate and negatively charged bentonite can interact with cationic drugs like lidocaine, and these additives can effectively introduce solvent into silicone matrix, resulting in controlled drug release. Furthermore, selected additives are highly biocompatible, as shown in Materials Safety Data Sheet (oral acute LD50 of alginate >5,000 mg/kg), and wide utility in the cosmetic application (e.g., bentonite based mud-pack).

To realize additive containing adhesive, PDMS, which is already verified to be biologically safe [7-9], was cross-linked with tetraethoxyorthosilicate (TEOS); the additives were inserted during the cross-linking. Lidocaine was incorporated into synthesized adhesives as a cationic model drug, and time-dependent release in phosphate buffered saline (PBS) and ethanol (EtOH) was investigated. The effect of additive on drug release was evaluated by kinetic model fitting.

MATERIALS AND METHODS

1. Materials

Hydroxyl terminated PDMS (70 cSt viscosity), TEOS, alginic acid sodium salt, bentonite, and lidocaine (99.999%) were obtained from Sigma-Aldrich Co. LLC. (St. Louis, USA). Nitric acid (64.0-66.0%) was purchased from Duksan Company (Ansan, Korea). PBS (Lonza, Walkersville, MD), tetrahydrofuran (THF, 99.8%, SK chemicals Co. Ltd., Suwon, Korea), and EtOH (99.8%, Honeywell Burdick & Jackson® Research Chemicals, Muskegon, USA) were used as received.

2. Preparation of Silicone Adhesive

To obtain adhesive silicones, stoichiometries of PDMS, TEOS, water, HNO_3, and additive were varied (Table 1). For example, S1 was prepared as follows: PDMS (5.8 g) and THF (24 g) were mixed for 10 min, and TEOS (0.23 g), deionized water (0.009 g), nitric acid (0.014 g) were added simultaneously. After stirring for 18 h, THF was removed under vacuum, followed by aging for seven days. Unreacted monomer was removed by soaking in ethanol for 12 h. For additive insertion, designated amount of additive (Table 1) was added to PDMS/THF mixture. Silicones with additives were named SA or SB for alginate or bentonite, respectively.

3. Lidocaine Loading and Release Testing

To incorporate drugs, the silicone adhesive (diameter 5.5 cm× thickness 1.0 cm) was soaked in lidocaine solution (15,000 ppm) for 24 h and washed thoroughly with EtOH. For release test, sample was placed in 30 mL media (PBS or EtOH), and 1 mL aliquots

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Table 1. Weight ratio among reactants

Sample	PDMS	TEOS	H_2O	HNO_3	Additive		Form of product
					Alginate	Bentonite	
S1*	25	1	0.04	0.06			Elastic adhesive
S2	25	1	0.09	0.06			Hard plastic
S3	5	1	0.04	0.06			Oily liquid
S4	5	1	0.09	0.06			Oily liquid
SA1	25	1	0.09	0.06	2.6		Elastic adhesive
SA2	25	1	0.09	0.06	3.9		Oily liquid
SA3*	25	1	0.09	0.12	3.9		Elastic adhesive
SB1	25	1	0.09	0.06		0.3	Elastic adhesive
SB2	25	1	0.09	0.06		1.3	Elastic adhesive
SB3*	25	1	0.09	0.12		1.7	Elastic adhesive

*Samples were subjected to drug release testing

were removed at designated times (0, 0.5, 2, 4, 8, 16, 32, 64, 128, 256 min). Lidocaine was quantified with high performance liquid chromatograph (Younglin Instrument Co., YL 9100) equipped with C18 column and UV detector at 210 nm, eluting with 50 mM sodium phosphate/water : methanol=3 : 7. Each experiment was repeated three times.

4. Kinetic Model Fitting

Time-dependent drug release was analyzed with following kinetic models:

(1) Parabolic diffusion [10]; $Q_t=Q_o+Rt^{0.5}$

R: diffusion rate constant $[(mgkg^{-1})^{-0.5}]$

(2) Power function [10]; $Q_t=at^b$

a: initial desorption rate constant $(mgkg^{-1}min^{-1})^b$, *b*: desorption rate coefficient $[(mgkg^{-1})^{-1}]$

RESULTS

As shown in Table 1, elastic adhesive was obtained with a certain weight ratio among reactants. Increasing PDMS:TEOS ratio negatively affected cross-linking, while high amount of water resulted in a hard plastic.

For additive containing silicone adhesives, higher ratio of water (0.09) than silicone itself (water ratio=0.06) was used, considering water absorption by additives. Properties of final silicone adhesives were affected by the amount of additive. For alginate and bentonite, respective PDMS : TEOS : H_2O : HNO_3 : additive ratio of 25 : 1 : 0.09 : 0.12 : 3.9 and 25 : 1 : 0.09 : 0.12 : 1.7 was optimal for elastic silicone that incorporated the greatest amount of additive among tested ratio. Scanning electron microscopic images showed that the obtained silicone adhesive had high degree of cross-linking without exhibiting network-like morphology (Fig. S1). Additives such as alginate bead or bentonite nanolayers were determined to be embedded in the dense silicone.

In drug release tests, adhesives S1, SA3, and SB3, which contained 85.3, 154.6 and 88.8 mg of lidocaine, respectively, were utilized. As shown in Fig. 1, time-dependent lidocaine release was highly dependent on media type and additive. Cumulative releases of lidocaine in PBS after 256 min were 2.16%, 1.28%, and 0.63% for S, SA, and SB, respectively (S>SA>SB). Three adhesives showed enhanced lidocaine release in EtOH, of which the cumulative amounts after 256 min were 6.67%, 10.90%, and 5.37%, respectively, for S, SA, and SB (SA>S>SB).

Release kinetics was fit to parabolic diffusion and power function (Fig. 2). Release patterns in PBS were well fit to power function, while in EtOH, kinetics was matched to both parabolic diffusion and the power function. According to kinetic constants (Table 2), additives decreased the value of *a* (initial desorption rate constant) and increased *b* (desorption rate coefficient) for power function in

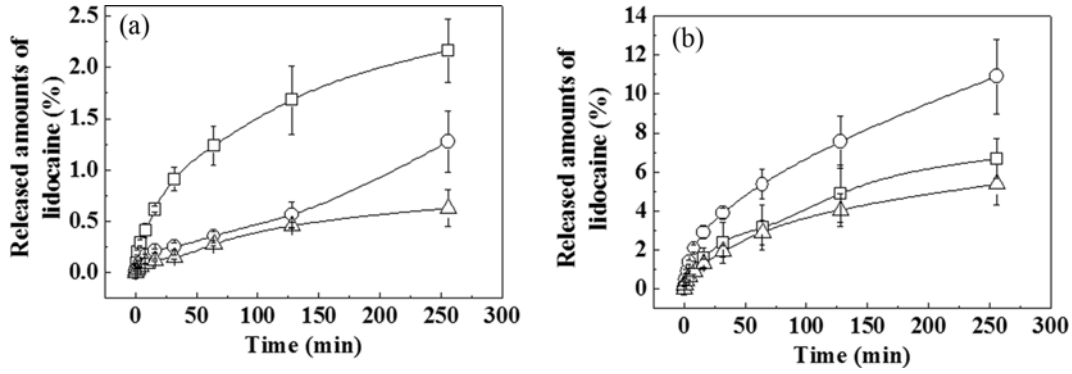

Fig. 1. Time-dependent lidocaine release from S, SA, and SB in PBS (a) and EtOH (b). S (□), SA (○), SB (△).

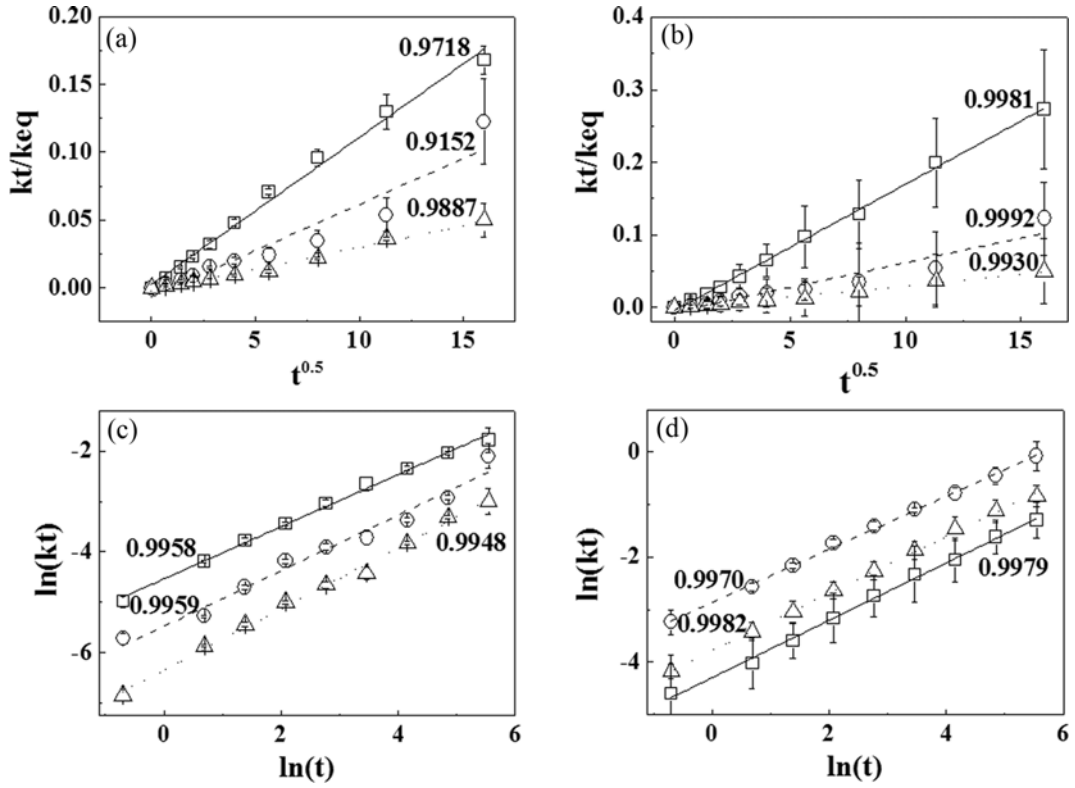

Fig. 2. Linear regression results for kinetics. (a) PBS, parabolic diffusion, (b) PBS, power function, (c) EtOH, parabolic diffusion, (d) EtOH, power function (inset figures are r^2 values.). S (□), SA (○), SB (△).

Table 2. Fitted kinetic constants of lidocaine release profile

Medium	Sample	Kinetic model	Constants		
			a $(mgkg^{-1}min^{-1})^b$	b $[(mgkg^{-1})^{-1}]$	R $[(mgkg^{-1})^{-0.5}]$
PBS	S	Power function	0.1377	0.5190	-
	SA		0.0436	0.5519	-
	SB		0.0218	0.6083	-
EtOH	S	Parabolic diffusion	-	-	0.0043
	SA		-	-	0.0068
	SB		-	-	0.0035
	S	Power function	0.3333	0.5464	-
	SA		0.6726	0.5048	-
	SB		0.2853	0.5402	-

PBS; bentonite showed a greater effect on modifying kinetic constants than alginate. On the other hand, in EtOH, additives increased the value of *a* and decreased *b*, with alginate exhibiting a greater influence than bentonite. Parabolic diffusion (in EtOH) rate constant *R* was smallest for the silicone adhesive without additive, and increased in the presence of additives, giving a higher value with alginate than bentonite.

DISCUSSION

We found that the property of silicone adhesive was dependent on the stoichiometry of reactants. A high TEOS : PDMS ratio facilitated self-condensation of TEOS rather than cross-linking of PDMS, resulting in oily liquid (S3 and S4). Thus, PDMS : TEOS ratio was set at 25 : 1. A higher water content increased the hydrolysis of TEOS, resulting in stiffening of the material (S1 and S2). Different from the silicone adhesive (S1), we controlled the amount of HNO_3 catalyst for additive containing silicones, as the catalytic reaction constructed cross-linkages between PDMS and additives. As too slow reaction could interrupt effective cross-linking between additives and silicone, we could obtain additive incorporated adhesive by controlling the amount of HNO_3.

As shown in Fig. 1, all the adhesives showed highly suppressed and prolonged drug release. While other reported sustained release

systems showed 10-90% (Eudragit) [11] and ~20% (polyvinylpyrrolidone:ethyl celluose) [12], our adhesive showed less than 10% of release. In terms of the solvent effect, drug release in EtOH was higher than in PBS. All of samples consisted mainly of silicone; thus, drug release was primarily governed by the chemical nature of silicone in each medium. The differing degrees of silicone swelling in water (0.45%) and EtOH (2.1%) [13] imply that more solvent is introduced into the silicone adhesive in EtOH than in water, resulting in effective solvation of lidocaine in EtOH. Furthermore, the higher solubility of lidocaine in EtOH than in water also facilitated drug release in EtOH.

Kinetic fitting of the drug release provided comprehensive explanation for the media and additive effects. All of release patterns showed high r^2 values for both the power function and parabolic diffusion (Fig. 2). Although both models have similar rate process mechanisms describing drug release from the matrices [10], the former emphasizes desorption and the latter emphasizes diffusion.

Lidocaine release in PBS was better fit to power function than parabolic diffusion, indicating that the release was mainly governed by desorption. Only a small amount of PBS could penetrate the silicone matrix, reducing the possibility of diffusion; however, abundant anions in PBS enabled desorption of lidocaine (power function). On the other hand, in EtOH, the silicone matrix absorbed sufficient solvent to effectively solvate the drug for desorption (power function) and secured diffusion pathways inside the silicone adhesive (parabolic diffusion).

The initial release rates (constant *a*) for S, SA, and SB in PBS clearly showed the role of the additives in modifying drug release. The *a* values were significantly lower in the presence of additives. The δ^- sites in alginate could trap lidocaine through dipole-charge interaction, suppressing initial release. Bentonite, whose surface is negatively charged, could strongly interact with lidocaine through charge-charge interaction, giving rise to more suppressed initial desorption than with alginate.

Drug release in EtOH followed both the power function and parabolic diffusion models, indicating both desorption and diffusion similarly regulated lidocaine release. In terms of desorption-governed release, the discussion of the PBS environment could be applied. Both additives efficiently absorbed EtOH; alginate and bentonite swell more than 40% in EtOH. Once absorbed, EtOH in the silicone would be concentrated around additive particles to solvate lidocaine molecules, resulting in fast initial desorption. Without additive, solvent molecules would be distributed throughout the silicone matrix, reducing the possibility of drug solvation. In parabolic diffusion, the absorbed solvent might secure sufficient diffusion pathway, as shown by the high diffusion constant *R* in the presence of additive.

CONCLUSION

Silicone adhesives were prepared through cross-linking of PDMS with or without additive, which had an affinity toward lidocaine. Drug release from silicone was found to depend on the type of solvent and additive. The amount of drug release was higher in EtOH than in PBS. Additives suppressed initial drug desorption in PBS but facilitated both initial desorption and diffusion in EtOH. Affinity between additive and drug was theorized to affect drug release kinetics.

ACKNOWLEDGEMENT

This paper is based upon work supported by the Ministry of Trade, Industry & Energy (MOTIE, Korea) under Industrial Technology Innovation Program. No. 10062252, 'Development of anti-biofouling functional tracheostomy tube component for critical patients'.

SUPPORTING INFORMATION

Additional information as noted in the text. This information is available via the Internet at http://www.springer.com/chemistry/journal/11814.

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Supporting Information

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(*Received 17 August 2016 • accepted 13 March 2017*)

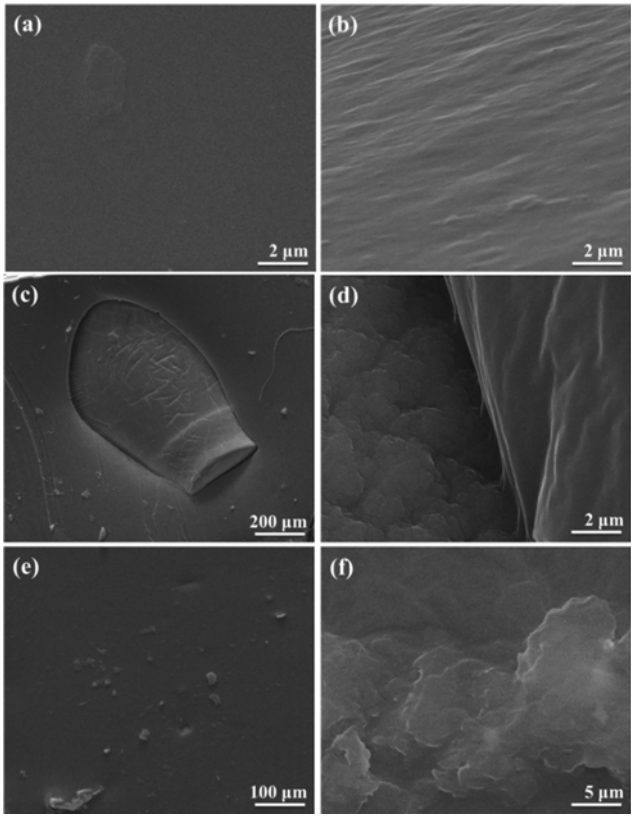

Fig. S1. SEM images for (a) surface of S1, (b) cross-section of S1 (c), (d) SA3 and (e), (f) SB3.

In order to verify the framework of silicone adhesive and morphology of additives in the silicone patch, SEM images were obtained (Fig. S1). The dense silicone surface was observed in the figure (a) and (b). In figure (c)-(f), we verified that alginate bead or bentonite nanolayers were well embedded in the dense silicone.