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RESEARCH ARTICLE

A drug-laden elastomer for surgical treatment of anal fistula

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Abstract Anal fistula is a common surgical problem with high incidence and causes suffering to patients. The management of high and complex anal fistula is challenging. The purpose of this work is to develop drug-laden elastomer not only to act as seton in the surgical management of anal fistula but also provide painkilling effect during the treatment. Elastic silicone bands were fabricated with different concentrations of lidocaine, with different in vitro drug release profiles. Muscle cutting experiment showed that the drug-laden elastic silicone bands were as effective as the surgical rubber bands in cutting function. Preliminary clinical trial indicated that the drug-laden silicone bands can be used as setons with analgesic effect in the treatment of anal fistula. The findings showed that the drug-laden elastic silicone bands are potentially useful as seton for surgical treatment of anal fistula.

Keywords Silicone elastomer · Elasticity · Local drug delivery · Seton · Anal fistula

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Abbreviations

ANOVA	Analysis of variance
BRS-6	6-Point Behavior Rating Scale
ETR	Enhanced tear resistant
LidoHCl	Lidocaine hydrochloride monohydrate
MTS	Mobile Traffic Solutions
UTS	Ultimate tensile stress
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

Introduction

Anal fistula is a common surgical disease. It is known to cause patient suffering and morbidity [1]. The incidence rate is 12.3 cases in men and 5.6 cases in women per 100,000 population. The disease occurs throughout adult life with the maximal incidence in the third and fourth decade of life [2]. A classic fistula is defined as an abnormal connection between two epithelium-lined surfaces. Anal fistula abnormally connects the anal canal to the skin surface. It may have different tracts and becomes complex. An anal fistula is the chronic phase of anorectal sepsis, which is the acute form of an abscess. Patients with anal fistula can present many different symptoms, such as chronic serosanguinous, purulent or fecal discharge, pain, intermittent swelling, and spontaneous drainage [3]. Anal fistula cause so much suffering to patients that their work, social life, and home life are seriously affected. The majority of anal fistulas is superficial and can be easily treated by fistulotomy. Because of the risk of incontinence and recurrence, the treatment of high and complicated anal fistula, however, remains a surgical challenge. Setons are the oldest of the surgical alternatives developed to address this challenge [4].

A seton is a thread of foreign material inserted through the fistulous track to aid the healing of fistula. It was used to treat anal fistula because it causes a chronic inflammatory reaction, stimulating fibrosis that fixes and prevents retraction and separation of sphincter muscle when it is divided in order to protect the sphincter continuity during the procedure [5]. A variety of materials have been used as seton: suture, stainless steel wire, herbal medicated thread, self-locking cable, silicone, thread, and rubber bands [5, 6]. However, the seton treatment is deemed cumbersome, too slow, and usually causes great pain to patient [7]. The seton treatment is usually performed under general anesthesia [8–11], local anesthesia, or oral medication [1, 4, 9, 12]. In some cases, when a seton was tightened or replaced, general anesthesia has to be given repeatedly [11, 13]. The average cut-out time varies from several days to several months, which depends on the tension on the seton, fistula complexity, and associated underlying pathology [6]. During the treatment, cutting setons can cause severe discomfort for the treated patients due to the tension on the seton and due to the long course of the treatment [14]. For some operations, patients were given oral pain medications following the operation [4]. However, during the operation, general anesthesia would cause certain side effects to patients while oral pain medication cannot last long. Thus, it is important to develop a local drug delivery system, which is able to relieve the pain of patients during the wound healing process.

An elastic band or rubber band is a commonly used seton [15, 16]. An elastic band used as seton has the advantage that it can cut slowly through the fistula tract while being used as drains too. The seton can be progressively tightened without replacement [17]. Figure 1a is the illustration of surgical technique that elastic band is used as a cutting seton in treating complex anal fistula [4]. An elastic band was passed through the fistulous tract and tightened by applying a silk thread to make a tie across it. The seton was then tightened to the desired tension at designated time. Drug-laden elastic bands combine the cutting function and analgesic effect, and the elasticity of the rubber bands can be compared to normal rubber bands used in clinical settings; however, such drug-laden elastic bands have never been reported to the best of our knowledge. One of the reasons is because the incorporation of drug into the rubber bands can compromise the elasticity of the rubber bands, so that such rubber bands were difficult to fabricate.

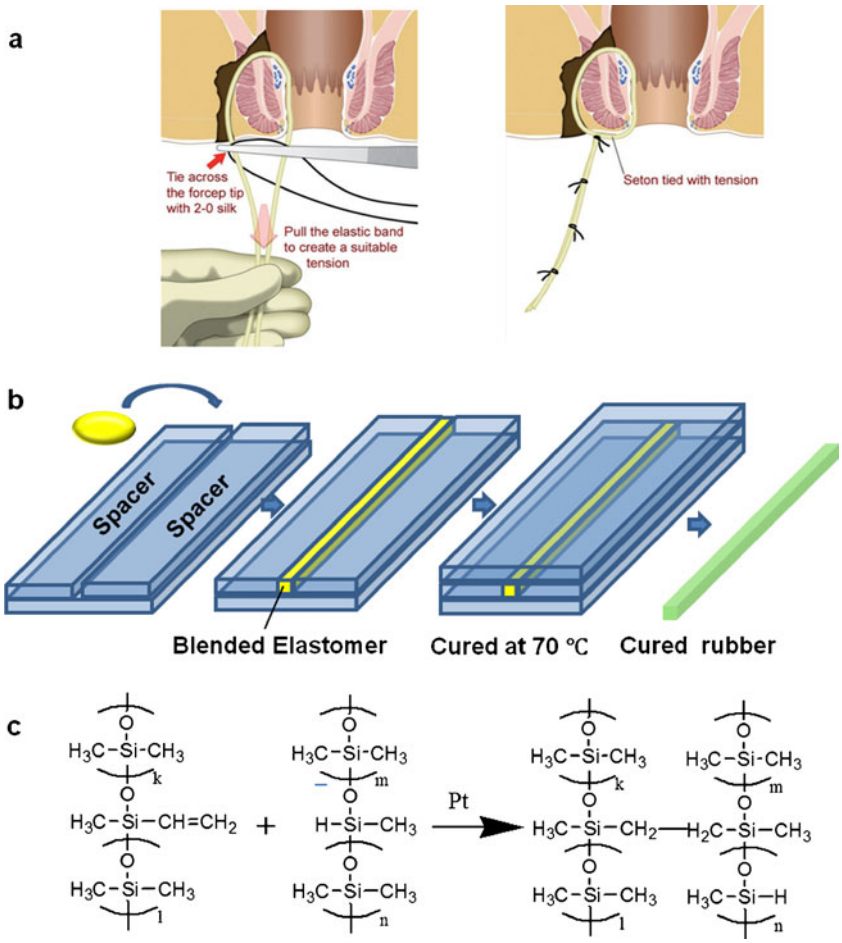

Fig. 1 **a** Illustration of an elastic band as seton in the treatment of anal fistula. Reprinted from reference [4], with permission from Elsevier. **b** Fabrication of drug-laden elastic silicon band; **c** silicone curing involving addition reaction. Reprinted from reference [27], with permission from Elsevier

In this study, we incorporated lidocaine into silicone elastomer to form elastic silicone bands for the surgical treatment of anal fistula, and lidocaine would be released from the elastic bands to relieve the pain of patients during the course of treatment. Silicone elastomer has been extensively used for many biomedical applications [18]. It has been reported as carriers for controlled release of water-soluble drugs, hydrophobic drugs, as well as protein drugs [19–22]. The method does not necessarily require the use of organic solvents or heating, and silicone formulations are chemically stable and do not change in vivo; therefore, they can be easily removed when the treatment has to be discontinued. Different silicone formulations have been reported, including injectable silicone implants for vaccine delivery, silicone elastomer vaginal rings for delivering HIV microbicide, anti-infective silicone central venous catheters [23–25]. Here, a drug-laden elastomer was used to fabricate elastic silicone bands. In vitro drug release from such elastic silicone bands was examined and muscle cutting experiment was conducted to predict its surgical applications. Moreover, preliminary clinical data was collected to better evaluate the drug-laden elastic silicone bands. The aim of our work is to develop painkilling elastic silicone bands as setons to provide some analgesic effect during the fistula treatment process.

Materials and methods

Silicone elastomer (SILASTIC® Biomedical Grade enhanced tear-resistant (ETR) Elastomer, Q7-4720) was a gift from Dow Corning (it has passed safety tests for being implanted in human for up to 29 days). Lidocaine Hydrochloride monohydrate (LidoHCl) was purchased from Sigma. All chemicals were used as supplied.

Fabrication of drug-laden elastic silicone bands

Silicone elastomer SILASTIC® Q7-4720 is supplied as a two-component kit (parts A and B). Part A contains a platinum catalyst and part B contains a cross-linker which has silicone hydride groups (Si–H). In order to obtain drug-laden rubber bands with best elasticity, different ratio of parts A and B (1:1, 2:1, 4:1, 10:1, 20:1) were tested together with different content of LidoHCl (0%, 1%, 5%, 10%) incorporated into the elastomer. Parts A, B, and LidoHCl were mixed by grinding until a homogeneous mixture was formed. The mixture was then molded in a groove mold (Fig. 1b) and heated at 70°C for about 18 h to allow the silicone elastomer to be completely cured. After the cured silicone bands were removed from the mold, residual elongation test was carried out to find out the optimal condition for the fabrication. Drug distribution inside the silicone bands was then evaluated by microscope imaging (Nikon Eclipse Ti).

Mechanical test

After being stretched and allowed to retract, the residual elongation of a specimen was tested to find the optimal fabrication conditions. The specimens were sectioned to about 60 mm and stretched, at an even rate, to a length three times that of the original. The specimen was held for 10 min by two clips, released quickly without it snapping back, and then the specimen was allowed to rest for 10 min. At the end of the 10-min resting period, distance was measured between the bench marks. The elongation was calculated as follows:

$$E = 100(L - L_o)/L_o$$

E is the elongation in percentage;
L is the observed distance between bench marks on the extended specimen;
L_o is the original distance between bench marks (use same units for L and L_o).

In addition to the residual elongation, other mechanical properties of silicone bands were also tested according to the American Society for Testing and Materials standard D638-10 specifications. Samples were first sectioned to 40 mm lengths, and a 20-mm section was marked in the middle of the sample with nondestructive ink. Precise measurement of the length was taken (L_o) to calculate the Strain. Width (W_o) and thickness (H_o) measurements were taken at three different points along the marked portion to get an averaged cross-section area for stress calculation. Specimens were clamped at each end up to demarcated margins using Mobile Traffic Solutions (MTS) Advantage™ 100/200-N capacity pneumatic grips and tested at 50 mm/min crosshead velocity. Specimens were tensile loaded to failure at a 20-Hz polling rate. Stress and strain values were obtained by using the MTS TestWorks 4 Application Software. Stress–strain graphs were generated separately in post-processing. Formulas included as follows:

Tensile strength (σ), also known as tensile stress, is the loading on the specimen per unit area.

$$\sigma = \text{Load}/\text{Cross} - \text{sectional area}$$

Strain (ε) is defined as the change in gauge length relative to the original gauge length.

$$\varepsilon = (L - L_o)/L_o$$

Ultimate tensile stress (UTS) is the maximum stress loading before material failure.

Young's Modulus is the modulus of elasticity, calculated by extending the initial linear segment of the stress- strain curve and deriving its gradient. Higher values indicate stiffer and more resistant to elastic deformation.

In vitro release study

Each sample was placed in a test-tube containing 10 ml of phosphate-buffered saline (pH 7.4), which was then placed in an incubator at 37°C. At designated times, the release test solutions were entirely replaced with fresh ones. Samples were analyzed with a ultraviolet spectrophotometer (Shimadzu UV-1800) at wavelength 216.5 nm to determine the concentration of released LidoHCl [26]. A series of different concentrations of LidoHCl in phosphate-buffered saline (pH 7.4) was prepared and determined to draft a calibration curve. To offset the presence of any degradation products of the silicone elastomer that could affect the spectrophotometric determination, blank silicone bands without LidoHCl were prepared and used in the in vitro release study together with drug-laden samples. After release testing, samples were taken out from release solution and dried at room temperature. Then the samples were subjected to the residual elongation test again.

Muscle cutting study

In order to evaluate the cutting function of the silicone bands, anal sphincter muscle was extracted from a pig. The seton was placed around the muscle and a thread was applied to make a tie across it, similar to the illustration of Fig. 1a. The seton was then tightened with tension and placed in sterile phosphate-buffered saline (pH 7.4) at 4°C for several days. The seton was cut and removed from the muscle at days 0 (immediately cut after tighten), 3, and 6. Pictures were taken and the thickness of the muscle was measured to evaluate cutting depth. Surgical rubber bands were used as a positive control. The muscle cutting was calculated as follows:

$$\text{Muscle cutting} = 100(l_o - l)/l_o$$

Muscle cutting	is the muscle cutting in percentage;
l	is the width of muscle after being tightened and cut;
l_o	is the original width of muscle (use same units for l and l_o).

Preliminary clinical trial

The preliminary clinical trial was approved by the ethical committee of Nanjing Municipal Hospital of T.C.M. Four male patients aged between 38 and 44 with anal fistula were involved in this preliminary clinical trial. Two patients in the control group were applied with surgical rubber bands as seton. The other two patients in the testing group were applied with 0.1% and 1% LidoHCl-laden silicone bands as seton, respectively. All the setons were loosely tied during the first few days, and then the setons were tightened at appropriate time. For the control group and the patient applied with 0.1% LidoHCl laden silicone band, intravenous tramadol hydrochloride was given at 2 ml/h on the first day after operation and the seton-tightening days. For the patient applied with the 1% LidoHCl laden silicone band, no extra analgesic was used.

Four different pain intensity rating methods were used to measure the pain during seton treatment. These included: (1) the Visual Analogue Scale (VAS), rating from 0 to 10; (2) the Verbal Rating Scale (VRS), rating from 0 to 3; (3) Wong-Baker face, rating from 0 to 6; (4) 6-point Behavior Rating Scale (BRS-6), rating from 1 to 6. In all these methods, the pain intensity increases with a higher number. Pain intensity was rated using these methods after the first 3 days of operation and on the seton tighten day and the day after it. Severe pain usually occurs especially on these chosen days.

Results

Fabrication of drug-laden silicone bands

When fabricated at parts A/B=1:1, which was recommended by the manufactures for non drug-laden elastomer applications, increased LidoHCl loading led to greater elongation of silicone band, and the silicone band became more fragile (Fig. 2a). If the silicone band is too fragile, it may be broken and difficult to cut the muscle when stretched in patients used as seton for anal fistula. Therefore, we need to make sure the elastic silicone bands are firm enough so that they will not break upon stretching. When the ratio of parts A/B was adjusted to 10:1, the residual elongation of LidoHCl-laden silicone bands was the least for every concentration of drug, which would be beneficial to clinical applications as cutting seton.

The stress–strain curves of silicone bands with different drug loading indicated their elastomeric and toughness properties (Fig. 3). The values of UTS and Young's modulus were showed in Table 1. Comparisons between groups were made using analysis of variance (ANOVA). A value of $p<0.05$ was considered significant. For UTS, there was significant difference between 10% LidoHCl and Blank/1%LidoHCl groups. It indicated that increased drug loading required less amount of stress for breakage and thus more fragile. For Young's Modulus, there was no significant

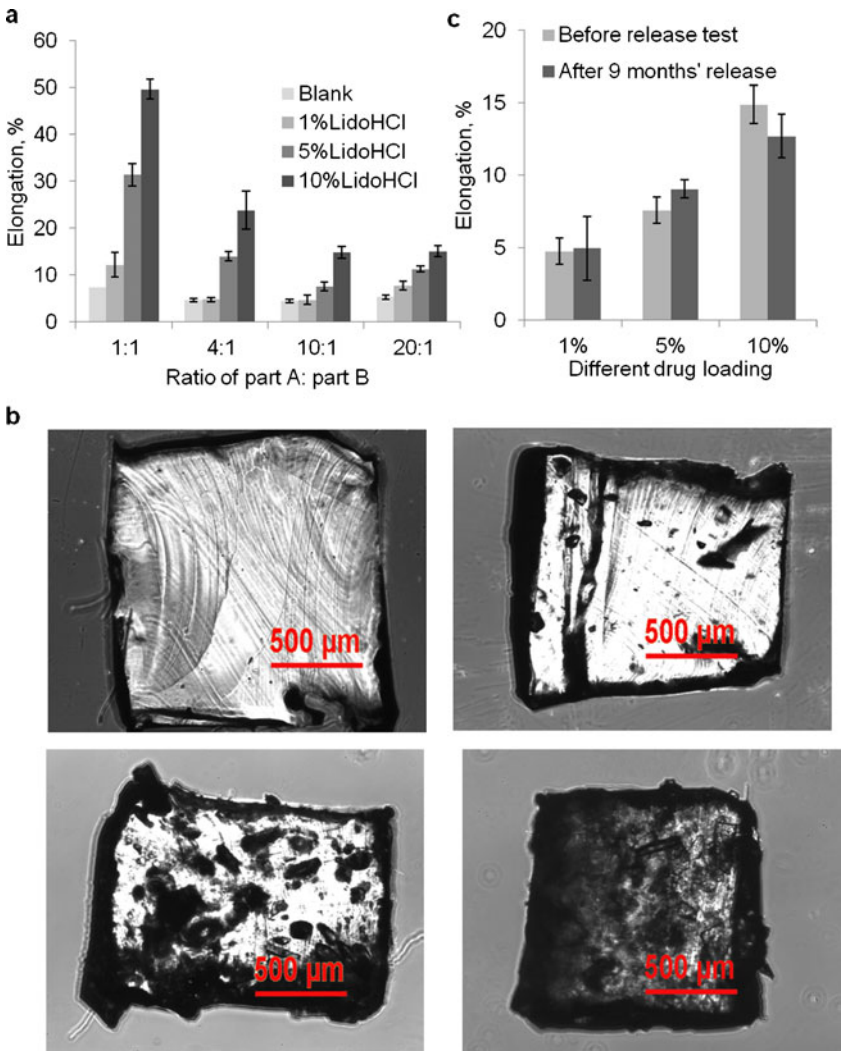

Fig. 2 **a** Results of residual elongation test of cured silicone bands. Each *point* represents mean±standard deviation of data from three independent samples. **b** Cross section of cured silicone bands via microscope imaging. *Upper left*, blank silicone band; *upper right*, 1% LidoHCl laden silicone band; *lower left*, 5% LidoHCl laden silicone band; *lower right*, 10% LidoHCl laden silicone band. **c** Residual elongation of silicone bands of different drug loading before and after 9 months' in vitro release test. Each *point* represents mean±standard deviation of data from three independent samples

difference among different groups, which showed the stiffness of different drug loading silicone bands was similar.

Figure 2b shows the cross section of silicone bands with different concentration of LidoHCl when fabricated at the optimal ratio of part A: part B via microscopy. For blank silicone band, it was more transparent, when increasing the LidoHCl loading in the silicone band, more black dots appeared, which showed the presence of LidoHCl crystals. The drug was uniformly distributed within the silicone band.

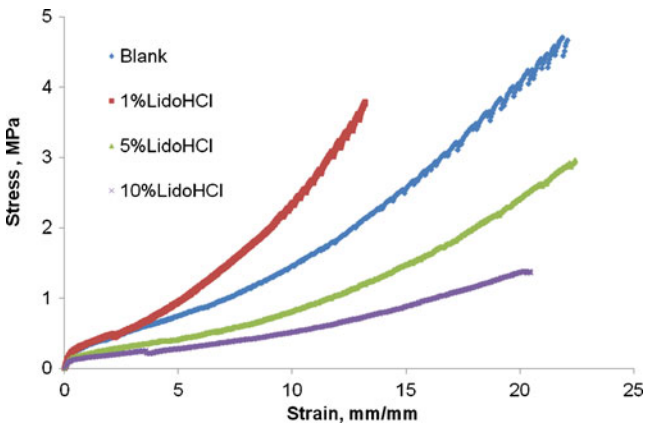

Fig. 3 Stress–strain curves of silicone bands with different drug loadings (From top: 1%, blank, 5% and 10%)

In vitro release study

A two-phase release profile was observed. There was a relatively rapid release in the first stage (about 30–40% of LidoHCl release in 24 h), followed by a sustained but slow release over prolonged time period, about 40–50% of the drug released in 4 weeks. For different LidoHCl concentration, the release profile was shown in Fig. 4a. In Fig. 4a (i), it was shown that the release rate had the tendency to increase with increased LidoHCl concentrations. The Fig. 4a (i) inset showed the systems had a burst release in the first few hours. The release amount can be adjusted by incorporating different amount of LidoHCl in the silicone band as shown in Fig. 4a (ii). When 5% LidoHCl-laden

Table 1 Mechanical properties of silicone bands with different drug loading (n=5, mean±standard deviation)

	Blank	1% LidoHCl	5% LidoHCl	10% LidoHCl
UTS (MPa)	4.5±1.0	4.4±1.2	2.5±0.6	1.3±0.5
Young's Modulus (MPa)	1.018±0.049	1.157±0.200	1.137±0.333	0.889±0.194

silicone bands were fabricated with different molds, i.e., thick mold and thin mold with the same length, the release profiles were shown in Fig. 4b. The release rate decreased slightly as the thickness of rubber increased. Thus different release profiles can also be achieved by adjusting the thickness of silicone bands.

When drugs were loaded into the silicone bands, their mechanical properties may change after the drugs released. So the residual elongation test was carried out after a period of 9 months' release. Figure 2c showed the residual elongation results. Without any breakage appearing, there was no significant difference between the two time points for each drug loading using t test. A value of $p<0.05$ was considered significant.

Muscle cutting study

To demonstrate that the drug-laden silicone bands are as effective as the normal rubber bands used in clinical surgery, muscle cutting experiment was conducted. Comparisons between groups were made using ANOVA. A value of $p<0.05$ was considered significant. From Fig. 5, we can see that there was no significant difference in muscle cutting effect among drug-laden silicone bands and the controls on days 0, 3, and 6.

Preliminary clinical trial

The setons were tightened on the seventh and eighth day after treatment for the two patients (C1 and C2 in Table 2,) in the control group, and on the sixth and ninth day for the patients applied with 0.1% LidoHCl laden silicone band (T1 in Table 2) and 1% LidoHCl laden silicone band (T2 in Table 2), respectively. The result of pain intensity for all the patients during seton treatment was shown in Table 2. Comparisons between the control group and T1/T2 were made using ANOVA for each pain rating method. A value of $p<0.05$ was considered significant. There was no significant difference between control group and T1 for all the pain rating methods. There was no significant difference between control group and T2 for all the pain methods except Wong-Baker face method. Wong-Baker face method showed the patient applied with 1% LidoHCl laden silicone band suffered less pain than the patients in control group ($p<0.05$). The result indicated that the drug-laden silicone band not only can be used as seton (T1) but

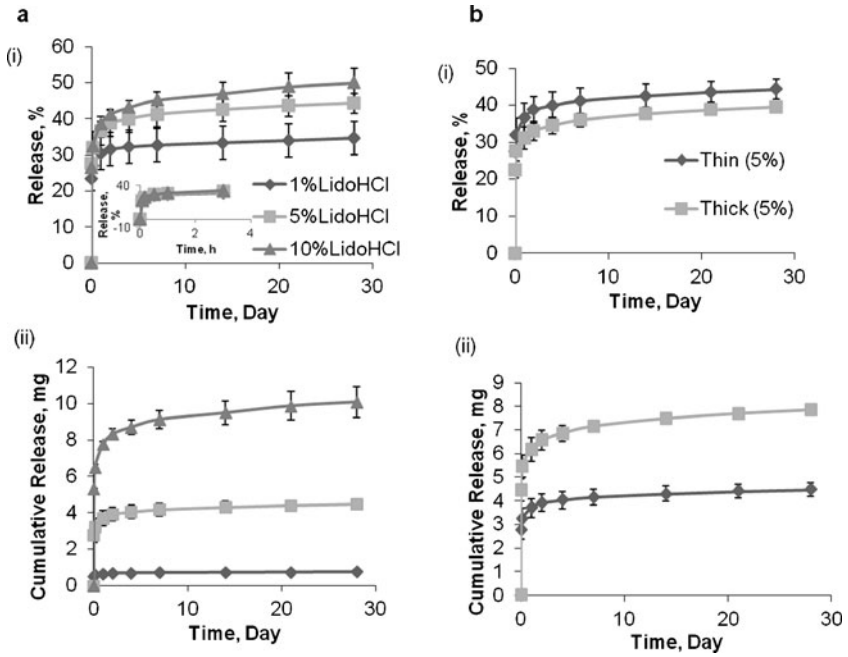

Fig. 4 In vitro release of drug-laden silicone bands. **a** silicone bands with different drug loading. **b** Thin and thick silicones bands with the same drug loading concentration. Data *points* represent mean±standard deviation of data from three independent samples

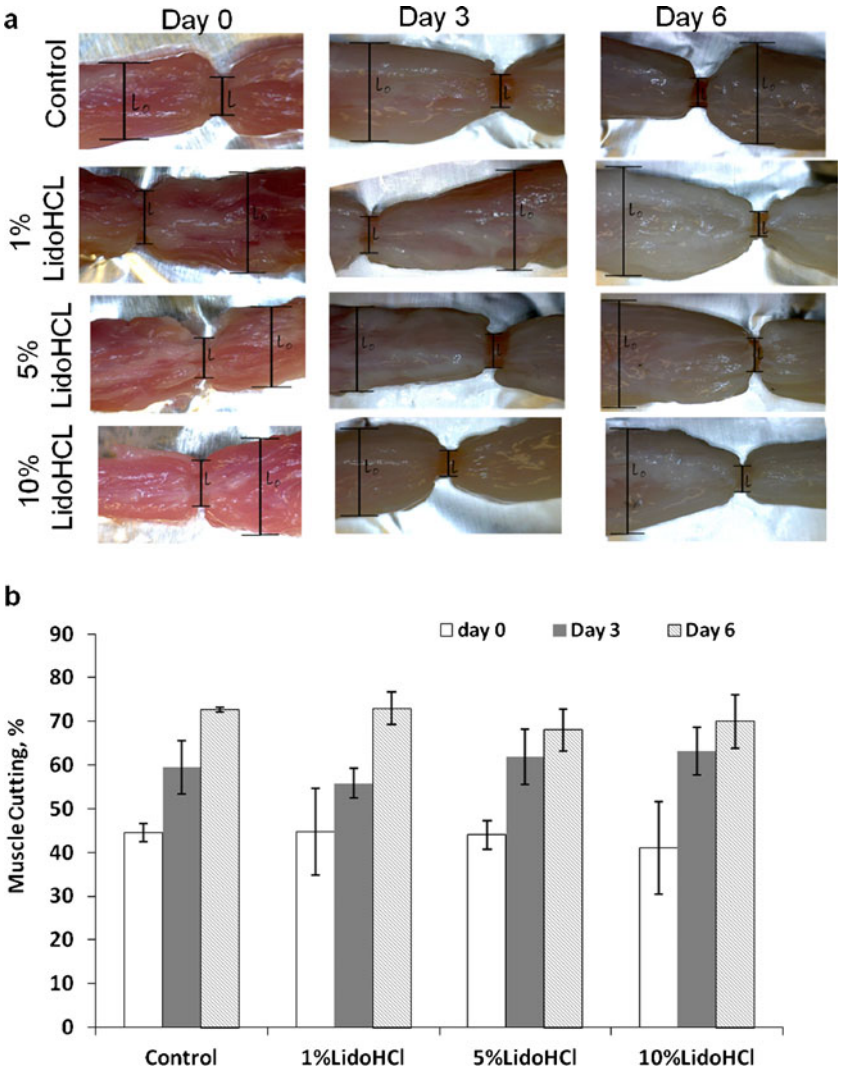

Fig. 5 Muscle cutting experiment. **a** images of muscles after applying silicone bands; **b** muscle cutting result in percentage. Each *point* represents mean± standard deviation of data from three independent samples

only can provide with analgesic effect (T2) in the treatment of anal fistula.

Discussion

Silicone elastomer SILASTIC® Q7-4720 was supplied as a two-component kit (parts A and B) that consists of dimethyl and methyvinyl siloxane copolymers and reinforcing silica. Besides, part A contains a platinum catalyst and part B contains a volatile inhibitor and a cross-linker which has silicone hydride groups (Si–H). When the two parts were mixed and the inhibitor was driven by heating, the curing reaction was catalyzed (Fig. 1c) [27]. When LidoHCl was mixed together with parts A and B, it seemed that LidoHCl would affect the curing process from Fig. 2.

Table 2 Pain intensity in the control group (C1 and C2) and the test group (T1 and T2) during seton treatment using different pain rating methods

Time	VAS				VRS				Wong-Baker face				BRS-6			
	C1	C2	T1	T2	C1	C2	T1	T2	C1	C2	T1	T2	C1	C2	T1	T2
Day 1	4	4	5	4	2	1	2	1	6	4	6	4	4	3	4	3
Day 2	4	6	4	4	2	2	1	1	4	6	4	4	3	5	3	3
Day 3	4	4	4	3	2	1	1	1	4	4	4	2	3	3	3	3
Tighten days	6	3	5	5	2	1	2	2	6	4	6	4	4	3	4	4
Second day after tightening	4	6	4	4	2	2	1	1	6	6	4	4	4	4	3	2

This is because the platinum catalyst used for hydrogenation is very susceptible to "poisoning", i.e., the curing process may be inhibited easily by certain chemicals [28]. Compounds containing basic nitrogen are one kind of these "poisonous" chemicals that have inhibiting effects on the platinum catalysts, due to their unshared pair of electrons. When the nitrogen atom is shielded by adding protic acids to the compounds, this inhibiting effect can be neutralized [29]. We had also tried to incorporate lidocaine base into the silicone rubber. However, the rubber was not cured at all when heating even for a week at 60°C, which is just below the melting point of lidocaine (66–69°C). When heated at a higher temperature more than the melting point, lidocaine would evaporate from the elastomer. For LidoHCl salt, part of the nitrogen atoms was shielded because of formation of salt, and the inhibiting effect is less than that of lidocaine base. However, the inhibiting effect increased with the increase of the concentration of LidoHCl when the ratio of parts A and B is 1:1. When the ratio of parts A/B increased from 1:1 to 10: 1, the absolute amount of part A increased thus the absolute amount of platinum increased, which can partly offset the inhibition effect of LidoHCl. However, when the ratio of parts A/B increased, the absolute amount of the cross-linker which is located in part B would decrease. If the cross-linker is not adequate, the cure process can also be inhibited, so the ratio of parts A/B cannot increase indefinitely. Besides, the ratio of parts A/B also has an effect on the network density of the cured silicone elastomer [18]. Less cross-linker may allow a higher density of the cured silicone on the condition that it is enough for the cross-linking process. This is because the cross-linkers usually contain more than one silicone hydride group (Si–H), and it can be linked to various silicone vinyl groups (Fig. 1c). Less cross-linker increases the possibility that one cross-linker will be linked to more silicone vinyl groups, thus obtains a higher density. The "poisoning" of platinum catalyst also reflects in the curing time, since the platinum catalyst acts as accelerator of the polymerization reaction. If no drug was added in the mixture of parts A and B, silicone band with constant elasticity was obtained in about 3 h at 70°C. However, when drug was introduced into the elastomer, longer curing time was needed. In this study, 18-h curing time was chosen, since it is long enough to obtain silicone bands with constant elasticity for all conditions.

The release profiles of LidoHCl from the silicone bands showed that our systems had a burst release, which may be beneficial to the treatment of anal fistula, since patients usually feel most painful at the initial treatment stage. The burst release may be due to the high solubility of LidoHCl in aqueous release solution, so that drugs on the surface dissolved quickly. After drug particles on the surface were dissolved, adjoining drug will dissolve and dissolution thus proceeded in succession. The amount release of 10% LidoHCl was faster than that of 1% LidoHCl and 5% LidoHCl (Fig. 4). Thus by controlling the content of LidoHCl loaded in the silicone band, the amount of LidoHCl released can be controlled (Fig. 4). In surgical practices, the duration of seton in place or cutting through the muscle varies between days and several months [4, 6]. In our in vitro experiment, LidoHCl can be released from the silicone bands continuously for at least 4 weeks. Though 10% LidoHCl-laden silicone band has a higher burst release, it would still be safe to patients, since the burst-released LidoHCl is less than 10 mg, which is far below the maximum recommended dose of lidocaine injection, 300 mg [30]. However, the amount released was limited after 24 h and it presented an issue if it is effective for painkilling after 24 h. In a recent study, 50 μg lidocaine released from lidocaine-coated microneedles was reported to be effective for local analgesia [31]. This indicated that when local high concentrations of lidocaine can be established, analgesic effects exist. Nonetheless, further research on modification of fabrication of the silicone bands should be done to better address this issue. One possible approach is to make silicone band with two layers. The outer later will act as release control layer and contain less drug than the inner layer which acts as a drug reservoir [25]. Ideally, the drug loaded in the silicone rubber can be released at a controllable rate. Another issue presented is that patients will feel extremely painful when the seton was re-tightened several days or several weeks later; however, the drug released at that time may be inadequate. To this end, pulsating drug release induced by tension may be explored.

Experiments were also conducted to evaluate the cutting function of the drug-laden silicone bands for anal fistula. As it was difficult to culture a big piece of muscle ex vivo, the experiment was conducted for only 6 days. Maximum tension was applied to the muscle for all groups. These silicone bands were not broken for 6 days. For clinical application, the tension could be adjusted according to the doctor's requirement. Figure 5 showed the effect of drug-laden silicone bands was similar to that of surgical rubber bands. These results demonstrated the effectiveness of the LidoHCl-laden silicone bands as cutting setons for clinical applications.

The preliminary clinical data showed the firmness of drug-laden silicone band used as seton and its effectiveness to provide analgesic effect. In this study, only low concentration (0.1% and 1%) of LidoHCl laden silicone bands were used. Higher concentrations (up to 10%) of LidoHCl can be introduced into the silicone bands with this fabrication method, which may provide a better analgesic effect during the anal fistula surgical treatment. However, more trials are needed to verify the results because of the limited patients in this study.

Conclusions

We developed a method to fabricate LidoHCl-laden elastic silicone bands, which not only provided a long-term drug vehicle but also made use of the elasticity of silicone. The drug release amount can be controlled by drug loading in the rubber band. In addition, the muscle cutting experiment indicated the drug-laden elastic silicone bands were as effective as the common surgical rubber band. The preliminary clinical trial demonstrated the effectiveness of the drug-laden silicone band used as seton with analgesic effect during the anal fistula treatment. These results indicate that the LidoHCl-laden elastic silicone band may be a novel cutting seton to treat anal fistula with painkilling effect.

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