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Using a drug to structure its release matrix and release profile

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ABSTRACT

Silicone elastomers have proven to be useful implantable release matrices for hydrophobic drugs. However, their utility for the release of hydrophilic materials is less well developed and, even with the addition of polar excipients such as poly(ethylene oxide) (PEO), burst release profiles are often observed—achieving longer term release is more challenging. We report that linoleic acid, initially used to solubilize polar, cationic nicotine in silicone precursors, additionally acted to change the internal morphology of resulting silicone + PEO elastomers. The unexpected consequence of this change was a change in the distribution of hydrophilic domains of PEO/drug within the silicone and the ability to control the rate of release of the drug in vitro. The relationship between excipients, silicone morphology, and release profile is examined.

1. Introduction

The advantages offered by implantable, biomaterials-based drug delivery systems for long-term systemic delivery of drugs are well documented (Di Colo, 1992). Much recent research has focused on biodegradable implantable materials (Commandeur et al., 2006). However, certain advantages accrue from non-degradable biomaterials, including their ready removal should have adverse effects arisen from the drug.

Silicone polymers have excellent biomaterials properties, and are widely used in a variety of biomedical devices including intraocular lenses, pacemaker leads and breast implants (Ratner et al., 1996). Silicones are intrinsically hydrophobic; they are among the lowest surface energy polymers known, exceeded only by fluorocarbon-based polymers (Owen, 1990, 1993). Non-degradable silicone (polydimethylsiloxane, PDMS) elastomers have thus been utilized in the delivery of lipophilic drugs such as steroidal hormones. For example, Norplant®, an implantable silicone drug delivery system used for sustained release of levonorgestrel over extended periods of time (5 years), and Compudose®, a long-term delivery system for 17-β-estradiol, both reached the market (Di Colo, 1992).

The utility of silicone elastomers to deliver lipid soluble drugs does not directly extend to hydrophilic drugs. Although some success has been achieved with polar molecules (Woolfson et al., 2003), it is normally necessary to add hydrophilic moieties to the elastomer. These may be covalently grafted, as is the case with currently available soft contact lenses—silicone hydrogels possess hydrophilic surfaces and greater permeability to hydrophilic molecules, such as nutrients, but retain the beneficial properties of silicones (e.g., oxygen transmission). Alternatively, hydrophilic excipients can be added to the preformed polymer. Ratner used this approach to deliver Tranilast from silicone elastomers containing poly(ethylene oxide) (PEO) (Ratner et al., 2003); the release consisted of a burst followed by sustained release over a short period of time.

As part of a project devoted to the study of nicotine on the fetal development of rats, an alternative drug delivery method to daily injection was sought. Topical delivery nicotine patches are widely utilized as protocols to facilitate smoking cessation (Gora, 1993; Thomas and Finnin, 2004; Fang et al., 1999). Initially, the possibility that such materials could also be used to deliver nicotine internally as implantable devices was investigated. However, duration and release profiles into saline of commercially available nicotine patches were found to be unacceptable for our purposes (data not shown). The biocompatibility of these materials as formulated in vivo is unclear.

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In light of their acceptability as internal drug depots, the use of silicone elastomers as implantable depots for nicotine delivery was examined. Previous research in our group has exploited the combination of silicones and hydrophilic polymers such as starch for drug delivery, for example as oral vaccines (Heritage et al., 1998; McDermott et al., 1996). Carelli and coworkers combined silicones with crosslinked poly(ethylene oxide) to deliver a variety of drugs; the nature of the drug was not a determinant in release rates (Carelli et al., 1995). Improved diffusion of water into, and drugs out of, the copolymer was realized using carboxylate-functionalized materials which swell at higher pH (Carelli et al., 1999). Note that similar silicone materials can be used as coatings (an active membrane layer) to retard drug release, depending on the balance between hydrophobic and hydrophilic constituents (Dahl and Sue, 1992). In this report, we examine the delivery of the nicotine from silicone elastomers designed to be implanted. PEO was used in various molecular weights and amounts to provide internal hydrophilic domains from which nicotine could be delivered. Initially poor results were improved when linoleic acid was added to increase nicotine solubility in silicone. Unexpectedly, the combination of the nicotine and linoleic acid also led to completely different internal morphologies of the silicone elastomer. The strategy of using a drug to manipulate its own release profile is described.

2. Experimental

2.1. Materials

Nicotine-(*N*-methyl-d_3) was purchased from CDN Isotopes Inc., isopropanol from Caledon (IPA), poly(ethylene oxide) (MW = 1000), (−)-nicotine hydrogen tartrate, linoleic acid, dibutyltin dilaurate and $Si(OEt)_4$ (TEOS) from Aldrich, and hydroxy-terminated silicone (PDMS-OH, $HO(Me_2SiO)_nH$, $n \sim 485$, 2200 cS, MW = 36,000) and aminopropyl-terminated PDMS (PDMS-NH_2) $(H_2N(CH_2)_3Me_2Si(OSiMe_2)_nOMe_2Si(CH_2)_3NH_2$, n = 8–9, 10–15 cS, MW ∼ 900) were obtained from Gelest. All compounds were used as received.

2.2. Characterization

Confocal microscopy was performed using a Zeiss LSM-510 confocal microscope with 24.6 mM fluorescein in DMSO/water 1:2. Incubation period was 48 h. UV–vis spectroscopy was performed using a Beckman DU-640 Coulter spectrophotometer.

2.3. Fabrication of silicone elastomers

Silicone elastomers were fabricated by combining the polymer matrix constituents, PDMS-OH and TEOS in a 20 mL glass vial with the catalyst aminopropyl-terminated PDMS. A separate vial with quantities of (−)-nicotine hydrogen tartrate, linoleic acid and PEO were combined with 0.5 mL IPA and homogenized by sonication and heated to approximately 60 °C for 5 min. The homogenous mixture was then combined with the polymer matrix constituents and mixed vigorously for 5 min. The mixture was poured into a 30 mm × 15 mm Petri dish, sufficiently covered to prevent exposure to dust, but sufficiently open to permit ingress of water vapor and egress of solvents, and allowed to cure at room temperature for 4 days. Each formulation contained varying amounts of nicotine, linoleic acid, PEO, H_2N-PDMS and PDMS (Table 1). After the silicone elastomer was cured (2–4 days), pellets were stamped out from the film using a metal coring device such that each pellets had dimensions of 6.0 mm × 2.0 mm (diameter × thickness). These pellets were transferred to a glass vials and marked according to their series number and stored for future analysis.

The properties of the pellets depended on PEO content. In the absence of PEO, the elastomer was translucent. The presence of 5% or 10% PEO gave an opaque material with lower elasticity. The 20% was hygroscopic and was no longer very elastomeric—it was a malleable gum.

2.4. Drug release in saline

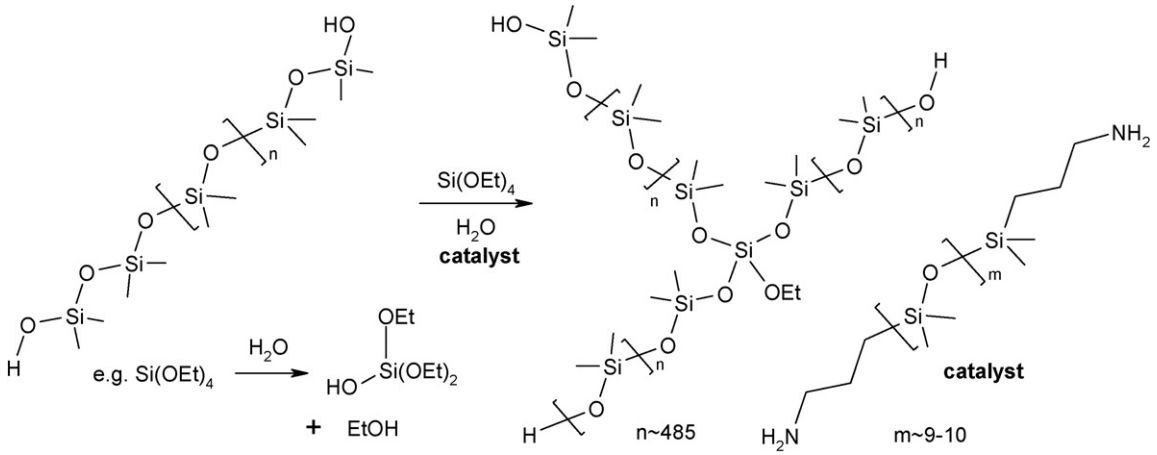
Nicotine release profiles were constructed using formulations of the silicone elastomer in triplicate (Table 1). Three pellets from each series were transferred into saline (0.9%, 2 mL) at room temperature in a sealed Falcon tube. The solutions were withdrawn for analysis and replenished with fresh saline at pre-selected intervals for the first 3 days. Subsequently, pellets were incubated with fresh saline at 37 °C, contents withdrawn and analyzed every 2 days for up to 28 days.

The pellets with 0, 5 and 10% PEO held their shape during this protocol. By contrast, the 20% PEO sample underwent visible swelling, then cracking; the solutions became turbid. Thus, the material had very little structural integrity and, shortly after swelling with water, underwent sufficient physical degradation that the entire drug bolus was released.

Table 1
Formulations of PEO–silicone elastomers with compositions listed per 5 g of silicone rubber[a]

Code	Nicotine (g)	PEO (g)	%	PEO MW	IPA (mL)	Linoleic acid (g)	PDMS (g)	%	TEOS (g)	%	NH_2-PDMS (g)	%	Sn catalyst (g)
A-A	0.26	0.52	10	200	1.1	0.86	3.53	68	0.52	10	0.58	11	–
A-B	0.25	0.50	10	4,600	0.9	0.84	3.52	69	0.51	10	0.53	11	–
A-C	0.26	0.50	10	10,000	1	0.86	3.53	69	0.52	10	0.54	11	–
B-A	0.25	0.51	11	1,000	0.5	0.84	3.56	78	0.50	11	0.00	0	0.21
B-B	0.25	0.52	11	1,000	0.5	0.41	3.52	77	0.52	11	0.00	0	0.31
C-A	0.25	0.50	10	1,000	0.5	0.40	3.67	71	0.51	10	0.51	10	–
C-B	0.25	0.50	10	1,000	0.5	1.15	3.55	70	0.50	10	0.50	10	–
C-C	0.25	0.52	10	1,000	0.5	2.00	3.59	70	0.50	10	0.51	10	–
C-D	0.26	0.51	10	1,000	0.5	0.00	3.53	70	0.52	10	0.52	10	–
A-BB	0.25	0.50	10	8,000	0.5	0.84	3.51	70	0.52	10	0.51	10	–
B-BB	0.25	0.51	10	1,000	0.5	0.40	3.99	80	0.51	10	0.00	0	0.02
C-BB	0.25	0.52	10	1,000	0.5	1.14	3.51	70	0.50	10	0.51	10	–
D-A	0.25	0.51	10	200	0.5	0.00	3.52	70	0.51	10	0.53	10	–
1A	0.06	0.00	0	1,000	0.5	0.20	4.00	80	0.50	10	0.50	10	–
1B	0.06	0.25	5	1,000	0.5	0.20	3.75	75	0.50	10	0.50	10	–
1C	0.06	0.50	10	1,000	0.5	0.20	3.50	70	0.50	10	0.50	10	–
1D	0.06	1.00	20	1,000	0.5	0.20	3.00	60	0.50	10	0.50	10	–
2A	0.25	0.25	5	1,000	0.5	0.83	3.75	75	0.50	10	0.50	10	–
2B	0.25	0.50	10	1,000	0.5	0.83	3.50	70	0.50	10	0.50	10	–

[a] H_2N-PDMS: $H_2N(CH_2)_3Me_2Si(OSiMe_2)_nOMe_2Si(CH_2)_3NH_2$, n = 8–9, PDMS-OH $(HO(SiMe_2O)_n)H$, MW = 36,000).



Scheme 1.

2.5. UV–vis spectrophotometry

Nicotine released into saline was quantified using UV–vis spectrometry; the absorbance of the solution at 259 nm ($\varepsilon_{259} = 929\ M^{-1}\ cm^{-1}$) was measured. Each measured absorbance was converted to a quantity of nicotine using a previously constructed calibration curve that was linear over the concentration range studied. The data reported on the graphs reflects the mean of three measurements with the error bars shown as the standard deviation.

3. Results

3.1. Formulation studies

Silicone elastomer pellets containing nicotine were prepared using a standard hydroxy-terminated silicone polymer that was crosslinked with tetraethoxysilane (TEOS, $Si(OEt)_4$) in a room temperature vulcanization process (RTV, Scheme 1). To avoid the presence of organometallic or metal oxide moieties in the material (organotin complexes (Ratner et al., 2003) or titanium alkoxides are typically used to catalyze RTV processes (Brook, 2000)), aminopropyl-terminated silicone polymers were used both as constituents of the elastomer and as catalysts for cure (Gill et al., 1998; Ragheb et al., 2005). These constituents were combined, poured into a Petri dish and allowed to cure for 2–4 days at ambient temperature. When nicotine and other excipients were also incorporated into the elastomer, they were first diluted with isopropanol and heated to form clear solutions that could be distributed with reasonable efficiency throughout the silicone before cure; as noted below, the specific morphology of the final polymers was very dependent on the specific ingredients used, particularly PEO and linoleic acid.

Primary amines are not very effective condensation catalysts for silicon, and long cure times were necessary as a result. Nicotine may also be an RTV catalyst, but its presence is not required for elastomer cure. For purposes of comparison, the conventional RTV catalyst, $Bu_2Sn(O_2CC_{11}H_{23})_2$ was examined with representative formulations.

Elastomer disks of 6 mm in diameter and 2 mm thick were cut from the sample and the release of nicotine was measured into saline. Calibration was performed with UV–vis spectroscopy for the saline samples.

Polar and, in the case of nicotine, ionic species, neither effectively disperse within nor diffuse through hydrophobic silicone elastomer matrixes. For example, a series of attempts to disperse nicotine hydrogen tartrate in the silicone as a dry powder, or a solution in isopropanol – a good solvent for silicones – were generally unsuccessful. Rather than a homogeneous dispersion of the drug within the polymer matrix, large domains of aggregated nicotine formed. This was an obstacle for two reasons. First, without a homogeneous mixture, the quantity of nicotine within each pellet could not be effectively controlled. Second, the formation of distinct domains of nicotine within the silicone elastomer prevented controlled release; the materials were subsequently shown to have very inconsistent release profiles that generally consisted of a single burst.

The use of silicone elastomers doped with hydrophilic polymers, rather than pure silicones, was anticipated to improve the ability to homogenously distribute nicotine throughout the matrix. Therefore, the biocompatible polymer PEO[1] $H(OCH_2CH_2)_nOH$ (Kelner and Schacht, 2005; Chen et al., 2005a,b) was also added to the silicone prepolymer. The nicotine was, as a consequence of the presence of PEO, more readily dispersible in the silicone. However, the subsequent release profile was unacceptable. Unlike the case of silicone/PEO polymers used for delivering amide/carboxylic acid drug Tranilast (Ratner et al., 2003), there was no subsequent sustained delivery; only a burst was observed.

The dispersion of nicotine in an organic oil has previously been facilitated by the addition of oleic acid, a non-toxic, monounsaturated fatty acid (Casanova et al., 2002). We reasoned that linoleic acid, an essential fatty acid and thus a viable excipient, could similarly be used to facilitate a more uniform distribution of nicotine throughout the silicone elastomer. A systematic study was therefore undertaken to relate the rate and profile of nicotine release from silicone elastomers to a wide set of parameters including PEO molecular weight and weight fraction in the elastomer, the concentrations of nicotine, linoleic acid and the crosslinker $Si(OEt)_4$ (Table 1) and, most importantly, the resulting morphology of the resulting biphasic silicone/PEO elastomers.

3.2. Physical characteristics: effect of PEO concentration

PEO weight fractions in the silicone were varied from 0 to 50%, and molecular weights from about 200–100,000 were examined. Irrespective of PEO molecular weight, high weight fractions of PEO in the silicone led to friable, fragile solids that could not be easily handled, and/or which disintegrated after exposure to aqueous

[1] We note that some of the lower ethylene oxide polymers are more correctly named poly(ethylene glycol) (PEG).

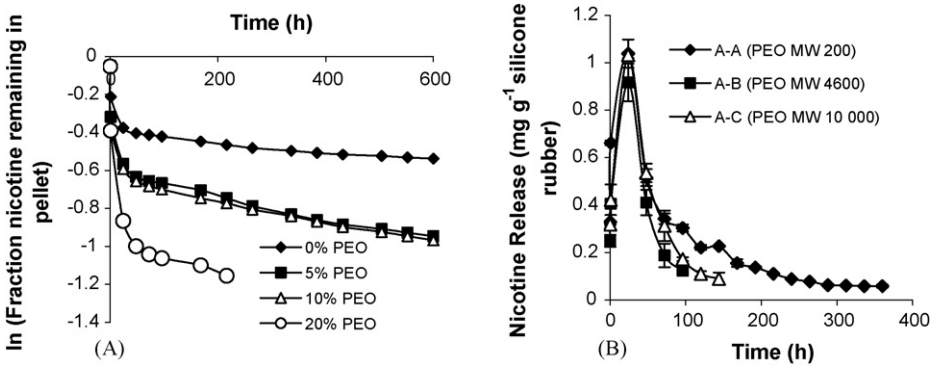


Fig. 1. (A) Plot of ln[remaining nicotine] vs. time for elastomers with different PEG concentrations: 0% PEO (■), 5% PEO (△), 10% PEO (♦) and 20% PEO (○). (B) Nicotine release profile (mg g^{-1} silicone rubber) as a function of PEO MW. Each data point is represented as the mean ± S.D. of three independent samples.

solutions. Although it was possible to make materials with up to 20 wt% PEO, convenient polymer properties resulted from materials with 5 or 10 wt% of PEO, respectively, and these materials were therefore studied in detail. They exhibited a high degree of pliability and retained structural integrity after deformation, properties that are necessary for materials to be used for implantation.

3.3. Release profiles

In the absence of PEO, the silicone matrix delivered a burst into saline but after about 40% of release of the entrained nicotine, release essentially ceased. When 5–10% PEO was present in the matrix, a burst of nicotine release was also observed, which was followed by an approximate first order release over extended periods of time (a plot of ln[nicotine remaining] vs. t was reasonably linear $R^2 = 0.94$) (Fig. 1A). With additional PEO (20%), all the nicotine was released as a burst within about 1 day. Note that the latter matrix was very unstable in water, and spontaneously broke into small fragments, which was accompanied by the burst release.

The rate of sustained release, for a given quantity of nicotine, was dependent upon the amount of PEO in the matrix. Thus, at 10 days the measured release rate from a matrix containing 5% 1000 MW PEO was 0.006 mg h^{-1}, whereas the rate for the material containing 10% of the same PEO was 0.009 mg h^{-1} (in both cases, the samples contained ~50 mg nicotine per gram of polymer matrix and the samples possessed the same dimensions, a 6-mm disk of thickness 2 mm; the rates were obtained from the slope (after linear regression) of Fig. 1A between 168 and 600 h, Table 1).

There was very little effect of the PEO molecular weight on the release profile. With the exception of the low MW weight (MW 200) materials that exhibited higher release rates, the burst occurred over a similar time period and the overall release after that point was comparable for samples containing the same weight% PEO (Fig. 1B). The low molecular weight materials likely have higher mobility within the silicone elastomer, leading to an effective PEO-facilitated release.

3.4. Effect of linoleic acid

As noted above, linoleic acid was added to facilitate nicotine delivery from the elastomer. Based on the reported study (Casanova et al., 2002), the mechanism of action involves exchange of tartrate salts of nicotine with the fatty acid, leading to more hydrophobic materials (e.g., $H_{31}C_{17}COO^{-}\cdot$nicotine^{+}) that will be more soluble in silicones. Three kinds of amines are present in the silicone elastomer matrix: two on nicotine – an aromatic and a tertiary amine – and primary amino groups on the aminopropyl-terminated silicone catalyst. The formulations used for the release profiles shown in Fig. 2A contain approximately a total of 4.2 mmol of amine groups (per 5 g of polymer matrix), that were titrated with 0 (0 g), 1.4 (0.40 g), 4.1 (1.14 g) and 7.1 (2.00) mmol of linoleic acid, respectively. The silicone matrix containing no linoleic acid exhibited a rapid

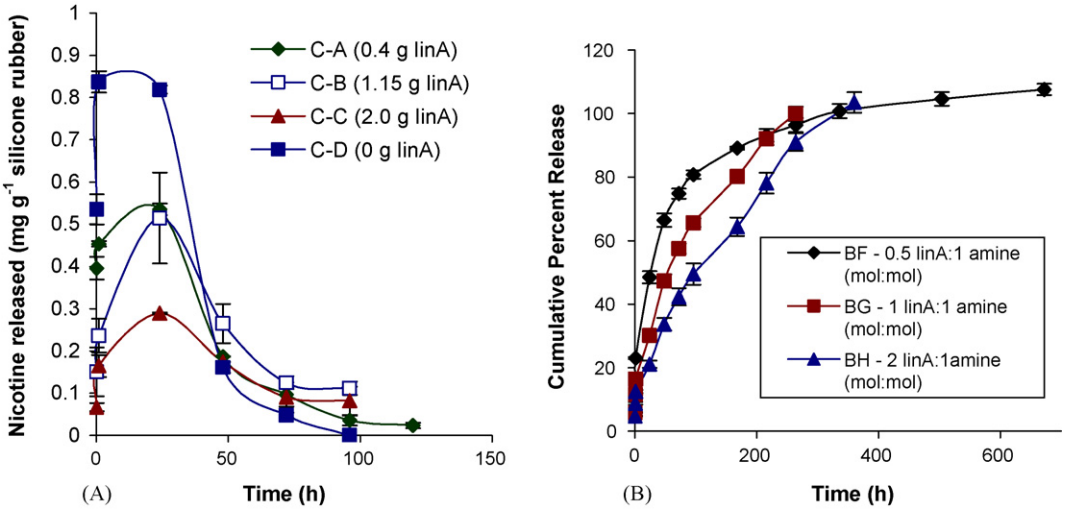


Fig. 2. Nicotine release profile: (A) nicotine release (mg g^{-1} silicone rubber) as a function of linoleic acid concentration (nicotine load ~250 mg and H_2N-PDMS ~500 mg) and (B) cumulative release as a function of linoleic acid/amine ratio (amines from catalyst and nicotine).

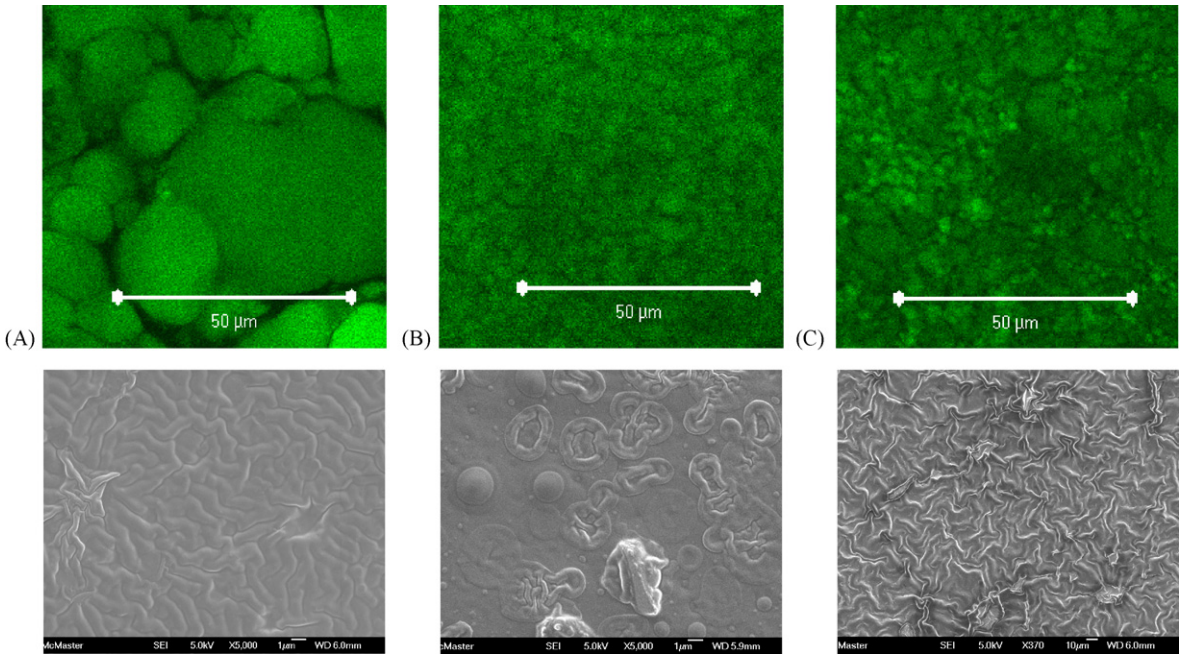


Fig. 3. (Top) Confocal internal and (bottom) SEM surface micrographs of silicone elastomers swollen with DMSO/water solutions of fluorescein: (A) no linoleic acid, 5% nicotine, 10% PEO1000 (formula CD); (B) 10% nicotine, 5% PEO1000 (formula N); (C) 5% nicotine, 10%PEO1000 (formula AA). (For interpretation of the references to color in the text, the reader is referred to the web version of the article.)

and large burst of drug (in this formulation, about 80% of the total present in the matrix). There was no subsequent sustained delivery. The remaining samples follow two different release profiles. In both, a burst is followed by sustained release, but the magnitude of the burst is lower, and length and quantity of sustained release is longer, when a molar excess of linoleic acid (2000 mg) is added. A secondary analysis was undertaken in which the amine groups in the formulation were titrated with less than, equal to, or greater than stoichiometric quantities of linoleic acid, respectively. The release profiles were observed to be more sustained with an increase in linoleic acid (Fig. 2B).

In addition to increased solubility in silicone, nicotine linoleate, a zwitterionic material bearing long chain hydrophobes, is surface active. It can thus act to stabilize the interface present between PEO (essentially insoluble in silicone) and silicone in the cured matrix. This effect was examined by comparing the morphology of silicone elastomers prepared with different amine/linoleic acid ratios. The materials, after swelling with fluorescein in DMSO/water, were examined using confocal microscopy and by SEM micrographs of the surface. In the absence of linoleic acid, the silicone matrix consisted of very large, occasionally connected, hydrophilic (PEO) domains formed in a mixed open/closed cell foam structure (Fig. 3A). With added linoleic acid, however, the hydrophilic domain size (green areas) decreased significantly, although a mixed open/closed cell structure remained (Fig. 3B); the number of pores and total internal surface area significantly increased. Higher quantities of PEO, while holding the linoleic acid fraction constant, led to the formation of even smaller domains (Fig. 3C). The consequence of these morphological changes is a modified nicotine release profile with more sustained release associated higher surface areas and smaller pore sizes.

4. Discussion

When observing the effects of increasing PEO content on the rate of nicotine release, it was seen that higher PEO content led to a higher rate of nicotine release (Fig. 1). Similar results were seen by Maeda et al. (2003) who incorporated polyethylene glycol 4000, a higher molecular weight PEO, into formulations of silicone elastomers and observed the changed release profile of ivermectin, a hydrophobic drug. The authors argued that PEO functions as both a pore-former and a compatibilizer (Walline, 2004) that can facilitate release by controlling the pore size and frequency within the matrix.

Although PEO permits release of nicotine from silicone matrices, when used as the sole excipient in silicone elastomers described above, a burst release profile was obtained without subsequent sustained release. Since the ability of polar materials such as nicotine to diffuse through hydrophobic materials such as silicones is exceptionally low, only nicotine in proximity to the external surface underwent release, with the remaining nicotine cached inside the matrix.

The key observation of this research is the ability of added linoleic acid to suppress the magnitude of the nicotine burst release, which has previously been a challenge in implantable systems releasing an anionic drug. The origins of this effect stem from the cationic nature of the drug that was being delivered, and to the constitution of the silicone elastomer which utilizes aminopropyl-terminated silicones as condensation catalysts rather than tin or titanium derivatives.

As amino groups are titrated with fatty acid, surface-active salts are formed. One direct result of their presence is the significantly higher internal surface area of the resulting silicone elastomers, as shown by the increased number of pores, and their smaller size (Fig. 3). At the same time, such interactions lead to a modified drug, which can interact with, and modify the interface, as shown schematically 1, 2 in Fig. 4. Improved pore necking and channeling between pores accompanies these interfacial modifications, as a greater fraction of the drug is ultimately delivered when more linoleic acid is present (Figs. 2 and 4). More importantly, the kinetic profile for delivery is changed such that the magnitude of the burst diminishes; either less drug is exposed at the external surface, or less of the drug present at the external surface is able to escape during the burst phase.

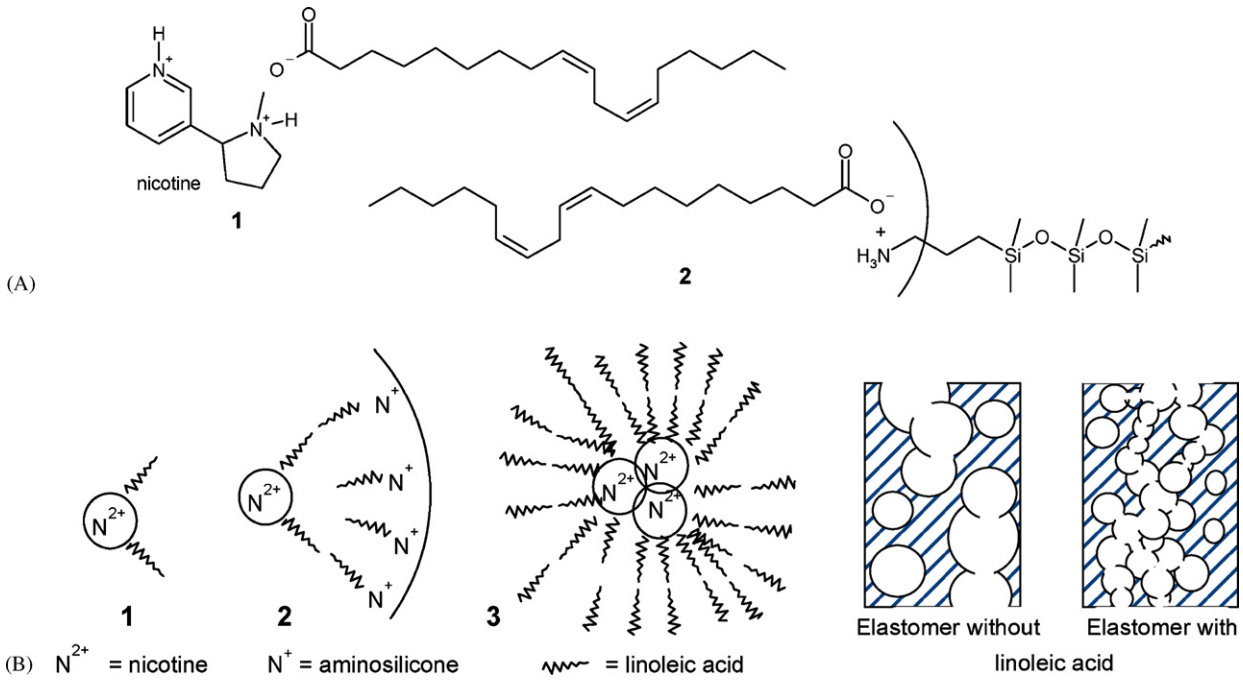


Fig. 4. Model interactions between nicotine, aminopropylsilicone leading to higher internal surface area silicone hydrogels.

At very high levels of linoleic acid, the burst is further suppressed. This can be ascribed to further structuring of the drug into micelles or vesicles, shown as a model 3 in Fig. 4. A more distributed network of smaller, linked pores (Fig. 3C) leads to more tortuous routes of migration for the drug. These changes account both for the lower burst, and the extended slow release of complexed nicotine. Thus, the cationic drug in combination with the carboxylate is responsible for the regulation of its own delivery. Judicious balancing of the interfacial characteristics of the silicone elastomer, the amount of hydrophilic materials (PEO) present, and the surface activity of the drug as modified by linoleic acid, therefore permits the formulator to simultaneously manipulate the morphology of the implantable silicone elastomer, and the profile of drug release. Extension and optimization of this strategy to delivery of other ionic species is currently ongoing.

5. Conclusion

Silicone elastomers with controlled internal morphologies were readily prepared by metal free, room temperature, amine-catalyzed crosslinking of silicone elastomers in the presence of PEO. All materials prepared exhibited a rapid burst release upon exposure to saline. However, sustained release was facilitated by more efficient dispersion of nicotine in a silicone/PEO elastomer comprised of an open cell structure, with small cell sizes. This morphology results from the addition of linoleic acid to the formulations. The fatty acid facilitates the control of diffusion of the ionic drug species, and also leads to changes in the internal morphology of the device, leading to smaller and better-connected pores within the elastomer, which correlated with the sustained release profile. When the surface-active acid is present in larger stoichiometric quantities than the amino groups in the matrix, the magnitude of the burst was further suppressed, and overall higher release rates over sustained periods were observed. Thus, the key finding is that linoleic acid, when used appropriately with functional silicone/PEO elastomers, changes the internal morphology of the elastomers, and can be used to tune the relative magnitude of the burst and sustained release phases of a cationic drug delivery.

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